Medical Policy

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Title: Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

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Populations	Interventions	Comparators	Outcomes
Individuals: • With non-neoplastic intracranial conditions (eg, arteriovenous malformations)	Interventions of interest are: • Stereotactic radiosurgery	Comparators of interest are: • Medical therapy	Relevant outcomes include: • Overall survival • Symptoms • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With non-neoplastic intracranial conditions (eg, trigeminal neuralgia refractory to medical management)	Interventions of interest are: • Stereotactic radiosurgery	Comparators of interest are: • Medical therapy	Relevant outcomes include: • Overall survival • Symptoms • Treatment-related morbidity
Individuals: • With non-neoplastic neurologic disorders (eg, epilepsy primary or secondary tumor-related)	Interventions of interest are: • Stereotactic radiosurgery	Comparators of interest are: • Surgery • Medical therapy	Relevant outcomes include: • Symptoms • Treatment-related morbidity
Individuals: • With non-neoplastic neurologic disorders: mesial temporal epilepsy refractory to medical management	Interventions of interest are: • Stereotactic radiosurgery	Comparators of interest are: • Surgery • Medical therapy	Relevant outcomes include: • Symptoms • Treatment-related morbidity
Individuals: • With non-neoplastic neurologic disorders: tremor and movement disorders	Interventions of interest are: • Stereotactic radiosurgery	Comparators of interest are: • Medical therapy	Relevant outcomes include: • Overall survival • Symptoms Treatment-related morbidity
Individuals: • With non-neoplastic neurologic disorders: (eg, chronic pain)	Interventions of interest are: • Stereotactic radiosurgery	Comparators of interest are: • Medical or surgical therapy	Relevant outcomes include: • Overall survival • Symptoms • Treatment-related morbidity
Individuals: • With benign neoplastic intracranial lesion(s) (eg, acoustic neuromas, pituitary adenoma, nonresectable residual or recurrent meningiomas)	Interventions of interest are: • Stereotactic radiosurgery	Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of other forms of radiotherapy, surgery, or chemotherapy	Relevant outcomes include: • Overall survival • Symptoms • Treatment-related morbidity
Individuals: • With benign neoplastic intracranial lesion(s) (craniopharyngioma, glomus jugulare tumors)	Interventions of interest are: • Stereotactic radiosurgery	Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of other forms of radiotherapy, surgery, or chemotherapy	Relevant outcomes include: • Overall survival • Symptoms • Treatment-related morbidity
Individuals: • With malignant neoplastic intracranial lesion(s) (eg, gliomas, astrocytomas)	Interventions of interest are: • Stereotactic radiosurgery	Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of other forms of radiotherapy, surgery, or chemotherapy	Relevant outcomes include: • Overall survival • Symptoms • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With malignant neoplastic intracranial lesion(s) (eg, brain metastases)	Interventions of interest are: • Stereotactic radiosurgery	Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of other forms of radiotherapy, surgery, or chemotherapy	Relevant outcomes include: • Overall survival • Symptoms • Treatment-related morbidity
Individuals: • With uveal melanoma	Interventions of interest are: • Stereotactic radiosurgery	Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of other forms of radiotherapy, surgery, or chemotherapy	Relevant outcomes include: • Overall survival • Symptoms • Treatment-related morbidity
Individuals: • With primary and metastatic spinal or vertebral body tumors who have received prior spinal radiotherapy	Interventions of interest are: • Stereotactic body radiotherapy	Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of other forms of radiotherapy, surgery, or chemotherapy	Relevant outcomes include: • Overall survival • Symptoms • Treatment-related morbidity
Individuals: • With stage T1 or T2A non-small cell lung cancer who are not candidates for surgical resection	Interventions of interest are: • Stereotactic body radiotherapy	Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of radiotherapy, surgery, or chemotherapy	Relevant outcomes include: • Overall survival • Symptoms • Treatment-related morbidity
Individuals: • With primary or metastatic tumor of the liver that is considered inoperable	Interventions of interest are: • Stereotactic body radiotherapy	Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of other forms of radiotherapy, surgery, or chemotherapy	Relevant outcomes include: • Overall survival • Symptoms • Treatment-related morbidity
Individuals: • With primary prostate carcinoma	Interventions of interest are: • Stereotactic body radiotherapy	Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of other forms of radiotherapy, surgery, or chemotherapy	Relevant outcomes include: • Overall survival • Symptoms • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With pancreatic adenocarcinoma	Interventions of interest are: • Stereotactic body radiotherapy	Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of other forms of radiotherapy, surgery, or chemotherapy	Relevant outcomes include: • Overall survival • Symptoms • Treatment-related morbidity
Individuals: • With primary or metastatic renal cell carcinoma who are not good surgical candidates	Interventions of interest are: • Stereotactic body radiotherapy	Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of other forms of radiotherapy, surgery, or chemotherapy	Relevant outcomes include: • Overall survival • Symptoms • Treatment-related morbidity
Individuals: • With oligometastases involving lung, adrenal glands, or bone (other than spine or vertebral body)	Interventions of interest are: • Stereotactic body radiotherapy	Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of other forms of radiotherapy, surgery, or chemotherapy	Relevant outcomes include: • Overall survival • Symptoms • Treatment-related morbidity

DESCRIPTION

Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) are 3-dimensional conformal radiotherapy methods that deliver highly focused, convergent radiotherapy beams on a target that is defined with 3-dimensional imaging techniques with the ability to spare adjacent radiosensitive structures. SRS primarily refers to such radiotherapy applied to intracranial lesions. SBRT refers to therapy generally applied to other areas of the body. Both techniques differ from conventional external beam radiotherapy which involves exposing large areas of tissue to relatively broad fields of radiation over multiple sessions.

OBJECTIVE

The objective of this policy is to determine whether the use of stereotactic radiosurgery to treat benign or malignant intracranial lesions and use of stereotactic body radiotherapy to treat primary and metastatic extracranial tumors improve the net health outcome.

BACKGROUND

Conformal Radiotherapy

Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) are techniques that use highly focused, conformal radiation beams to treat both neoplastic and non-neoplastic conditions. Although SRS and SBRT may be completed with 1 session

(single-fraction), SRS typically refers to a single-session procedure to ablate the target lesion. However, either technique may require additional sessions (typically not >5) over a course of days, referred to as fractionated radiotherapy.

Platforms available for SRS and SBRT are distinguished by their source of radiation; they include gamma radiation from cobalt 60 sources; high-energy photons from linear accelerator (LINAC) systems; and particle beams (eg, protons). Particle beam therapy is not covered in this evidence review.

SRS and SBRT have been used for a range of malignant and nonmalignant conditions. A comprehensive review that encompasses all potential uses is beyond the scope of this evidence review. Thus, a brief introduction follows of common applications of SRS and SBRT for which published evidence has been identified in database searches.

REGULATORY STATUS

Several devices that use cobalt 60 radiation (gamma ray devices) for SRS have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. The most commonly used gamma ray device, approved in May 1999, is the Gamma Knife® (Elekta, Stockholm; product code IWB), which is a fixed device used only for intracranial lesions. Gamma ray emitting devices that use cobalt 60 degradation are also regulated through the U.S. Nuclear Regulatory Commission.

A number of LINAC movable platforms that generate high-energy photons have been cleared for marketing by FDA through the 510(k) process. Examples include the Novalis Tx® (Novalis, Westchester, IL); the TrueBeam STx (Varian Medical Systems, approved 2012; FDA product code IYE); and the CyberKnife® Robotic Radiosurgery System (Accuray, approved; product code MUJ). LINAC-based devices may be used for intracranial and extracranial lesions.

POLICY

A. Stereotactic radiosurgery using a gamma ray or linear accelerator (LINAC) unit may be considered **medically necessary** for the following indications:
    1. Arteriovenous malformations;
    2. Acoustic neuromas;
    3. Pituitary adenomas;
    4. Non-resectable, residual, or recurrent meningiomas;
    5. Solitary or multiple brain metastases in patients having good performance status and indolent or no active systemic disease (defined as extracranial disease that is stable or in remission) (see Policy Guidelines);
    6. Malignant neoplastic intracranial lesion(s) (eg, gliomas, astrocytomas);
    7. Trigeminal neuralgia refractory to medical management;
    8. Craniopharyngiomas;

9. Glomus jugulare tumors;
10. Mesial temporal lobe epilepsy refractory to medical management when standard alternative surgery is not an option.

B. Stereotactic body radiotherapy may be considered **medically necessary** for the following indications:
   1. Patients with stage T1 or T2 non-small-cell lung cancer (not >7 cm) showing no nodal or distant disease and who are not candidates for surgical resection;
   2. Spinal or vertebral body tumors (metastatic or primary) in patients who have received prior radiotherapy;
   3. Spinal or vertebral metastases that are radioresistant (eg, renal cell carcinoma, melanoma, sarcoma);
   4. As a palliative treatment for individuals with specific liver-related symptoms due to tumor bulk (eg, pain) from any primary or metastatic hepatic tumor;
   5. Primary or metastatic tumors of the liver as an alternative locoregional treatment for patients with inoperable primary or metastatic lesions;
   6. Primary renal cell carcinoma in patients who are not good surgical candidates or metastatic renal cell carcinoma;
   7. Oligometastasis involving lung, adrenal glands, and bone (other than spine or vertebral body).
   8. Patients with low or intermediate risk prostate cancer (see Policy Guidelines).

C. When stereotactic radiosurgery or stereotactic body radiotherapy are performed using fractionation (defined in Policy Guidelines) for the medically necessary indications described above, it may be considered **medically necessary**.

D. Stereotactic radiosurgery is considered **experimental / investigational** for other applications including, but not limited to, the treatment of chronic pain, tremor, and the treatment of functional disorders other than trigeminal neuralgia.

E. Stereotactic body radiotherapy is **experimental / investigational** for pancreatic adenocarcinoma, prostate cancer, and other conditions except as outlined in the policy statements above.

Policy Guidelines

1. Radiation Source
   This policy addresses the use of stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) delivered by gamma ray or high-energy photons generated by a linear accelerator (LINAC) unit. The use of charged particle (proton on helium ion) radiotherapies is addressed separately.
2. Number of Lesions
   a) A 1995 TEC Assessment on SRS for multiple brain metastases found that evidence was sufficient to show that radiosurgery improved health outcome for up to 3 metastases in the presence of good performance status and no active

systemic disease. While evidence continues to demonstrate the importance of good performance status and absence of active systemic disease, it appears that the number of metastases may not be as predictive of outcome (see Rationale section). Thus, patients with more than 3 metastases who otherwise have good performance status and no evidence of active systemic disease may still benefit from SRS.

b) Many patients with brain metastases can either receive whole brain radiotherapy along with SRS, or whole brain radiotherapy may be delayed for use as salvage therapy for recurrent intracranial disease.

3. Fractionation
   a) Fractionated SRS refers to SRS or SBRT performed more than once on a specific site.
   b) SBRT is commonly delivered over 3 to 5 fractions.
   c) SRS is most often single-fraction treatment; however, multiple fractions may be necessary when lesions are near critical structures.
4. Prostate Cancer Characteristics
   a) NCCN defines low risk prostate cancer as Gleason score ≤6, prostate specific antigen <10 ng/mL, and clinical stage T1 to T2a.
   b) NCCN defines intermediate risk prostate cancer as predominantly Gleason grade group 2-3, clinical tumor stage T2b or T2c, or prostate specific antigen level of between 10 and 20 ng/mL.
   c) The regimen used for SBRT of the prostate hasn't been clearly defined, but is usually between 33.5 and 38 Gray administered over 4 to 5 fractions.

RATIONALE

This evidence review was created in 1995 and has been updated annually with a search of the MEDLINE database, most recently through November 15, 2018.

The following is based on a view of the evidence, including, but not limited to, published evidence and, clinical expert opinion solicited via BCBSA's Clinical Input Process.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function - including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and

confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Evidence on the use of stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) consists primarily of case series, registry data, and early phase trials, with a limited number of RCTs and nonrandomized comparative trials.

The delivery of SRS and SBRT is complex and individualized, requiring selection of the device, radiation dose, and the size and shape of treatment margins, all of which depend on the location, shape, and radiosensitivity of the target tissue and the function and radiosensitivity of the surrounding tissue. Several ongoing questions exist in the evaluation of SRS and SBRT, related to the most appropriate choices of:

- Radiotherapy delivery device based on the size and shape of the target lesion
- Dose fractionation
- Methods to reduce toxicity.

Trials that would allow direct comparison of all possible variables involved in selecting specific SRS and SBRT methods do not currently exist. Therefore, the available evidence is inadequate to permit conclusions about specific radiation planning and delivery techniques, including the specific number of fractions and methods of dose escalation or toxicity reduction. Therefore, the following review groups several different techniques for delivering SRS and SBRT and does not compare specific radiation planning and delivery techniques.

Stereotactic Radiosurgery for Non-Neoplastic Conditions: Arteriovenous Malformations

Clinical Context and Test Purpose

The purpose of SRS is to use a focused radiotherapy technique to treat intracranial and other brain lesions that are relatively inaccessible surgically and that are often located near eloquent or radiosensitive areas.

The question addressed in this evidence review is: Does the use of SRS for treatment of the non-neoplastic intracranial conditions (ie, arteriovenous malformation [AVMs]) result in changes in management and improvement in health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are patients with AVMs who have not yet experienced a significant hemorrhagic complication. An AVM comprises a tangled network of vessels in which blood passes from arteries to veins without intervening capillaries. AVMs range in size from small, barely detectable lesions to large lesions that can occupy an entire hemisphere.

Interventions

The intervention of interest is SRS prior to significant hemorrhage. SRS incites an inflammatory response in the vessels, which results in ongoing fibrosis with eventual complete obliteration of

the lesion over the course of months to years. In contrast, surgical excision provides an immediate effect on the risk of hemorrhage.

Comparators
The following therapies are currently being used to treat AVMs: conservative therapies (eg, surveillance, medical therapy) and surgical intervention. Total surgical extirpation of the lesion, if possible, is the desired form of therapy to avoid future hemorrhage. However, a small subset of AVMs, because of their size or location, cannot be excised without serious neurologic sequelae.

Outcomes
The outcomes of interest are overall survival (OS), symptom improvement, and treatment-related morbidity.

Timing
SRS is typically used during the latency period when a patient has not experienced a significant hemorrhage. This latency period is variable and typically is years in duration, depending on the size of the AVM and the dose distribution of the radiosurgery. During this latency period, an ongoing but declining risk of hemorrhage is present.

Setting
SRS is provided in a tertiary care setting.

Randomized Controlled Trials
Mohr et al (2014) reported results of the ARUBA (A Randomised trial of Unruptured Brain AVMs) trial, a randomized, multicenter study comparing medical therapy with medical therapy plus interventional therapy (including any neurosurgical, endovascular, or SRS procedure) in patients with unruptured AVMs.[1,] Two hundred twenty-six patients were enrolled and randomized, 116 to interventional therapy and 110 to medical management. Among those randomized to interventional therapy, 91 received interventional therapy; 5 with neurosurgery alone, 30 with embolization alone, 31 with radiotherapy alone, 12 with embolization and neurosurgery, 15 with embolization and radiotherapy, and 1 with all 3. The trial was stopped early after an interim analysis demonstrated the superiority of medical management; after outcomes were available for 223 patients with a mean follow-up time of 33.3 months. The risk of death or stroke was lower in the medical management group than in the interventional therapy group (hazard ratio [HR], 0.27; 95% confidence interval [CI], 0.14 to 0.54). Had the trial continued, the patients would have been followed to determine whether differences in outcomes persisted. Although a high proportion of patients randomized to interventional therapy (40.5%) received at least some radiotherapy, outcomes were not reported by therapy type, making it difficult to assess the comparative effectiveness of SRS in AVM treatment.

The results of the ARUBA trial have been the subject of controversy; specifically, whether the results are generalizable to all individuals with an unruptured AVM. There have been no publications on outcomes since the trial was stopped and the registry for comparator arm medical therapy alone participants was not developed.

Systematic Reviews
Magro et al (2017) published a systematic review of French- and English-language citations specifically reviewing the results of the ARUBA study.[2,] The most salient and recurring critique

was that the planned 5-year follow-up preferentially exposed problems with short- and long-term procedure results, and therefore did not detect the longer-term benefits of prophylactic interventions.

Mau et al (2016) published a systematic review examining the rate of hemorrhage following SRS in patients with high-grade AVMs, defined as a Pollock-Flickinger score greater than 2.[3,] Nine evaluating 673 patients were published in the English language, reported adequate data to calculate AVM score, and presented outcome data on hemorrhage following radiosurgery. The average length of follow-up in these studies was 4.6 years. There was a cumulative hemorrhage risk of 15.2% among all patients, and the mortality rate for patients with hemorrhage was 40.1%. The annual risk of hemorrhage varied among studies, ranging from 0.75% to 14.9%. The cumulative annual risk of hemorrhage was 3.3% (95% CI, 2.7% to 4.0%). This hemorrhage rate did not differ from the hemorrhage rates reported for untreated high-grade AVMs, which ranged from 5.9% to 18.0%.

Single-Arm Studies

There are many single-arm studies on SRS for AVMs.[4,5,6,7,8,9,10,11,12,13,14,15,] These studies have reported outcomes in different patient populations with AVMs and different protocols for SRS. Absent a control group, these studies offer limited evidence on treatment outcomes related to SRS. Some representative studies are discussed below.

Two larger single-arm studies were multicenter studies from 8 institutions participating in the International Gamma Knife Research Foundation.[11,15,] Starke et al (2016) reported on 2236 patients with any AVM treated by Gamma Knife surgery, with a mean follow-up of 7 years.[15,]Complete obliteration of the AVM was achieved in 64.7% of patients and favorable outcome, defined as complete obliteration with no hemorrhage or significant radiation adverse events, was achieved in 60.3% of patients. Hemorrhage occurred in 7.4% (165/2236) of patients, with an annual rate of hemorrhage of 1.1%. Permanent neurologic deficits due to radiation injury occurred in 2.7% of patients.

Ding et al (2016) was a second multicenter study of 891 patients with small, unruptured AVMs who were treated with Gamma Knife surgery and had at least 12 months of follow-up.[11,] The estimated complete obliteration rate was 63% at 5 years and 78% at 10 years. Optimal outcome, defined as complete obliteration of AVM without hemorrhage or significant radiation-induced adverse events, was achieved in 56% of patients. The annual rate of hemorrhage was 1.2%, and the rate of permanent neurologic deficits was 4%.

Paul et al (2014) conducted a retrospective cohort study that included 697 SRS treatments in 662 patients treated with SRS for brain AVMs at a single-institution.[8,] The obliteration rate after a single or multiple SRS procedures was 69.3% and 75%, respectively. The obliteration rates were significantly associated with AVMs that were compact (odds ratio [OR], 3.16; 95% CI, 1.92 to 5.22), with undilated feeders (OR=0.36; 95% CI, 0.23 to 0.57), with smaller volume (OR=0.95; 95% CI, 0.92 to 0.99), and treated with higher marginal dose (OR=1.16; 95% CI, 1.06 to 1.27).

Bowden et al (2014) reported outcomes from a retrospective cohort of patients with cerebellar AVM treated with SRS at a single-institution.[4,] Sixty-four patients were included, 73% of whom had presented with intracranial hemorrhage, and 19% of whom had undergone prior embolization. Total obliteration was achieved at 3, 4, and 5 to 10 years in 52%, 69%, and 75%,

respectively, of subjects. Obliteration was more likely in smaller AVMs but less likely in patients who had undergone prior embolization. Symptomatic adverse radiation events, defined by magnetic resonance imaging (MRI) changes and new neurologic deficits in the absence of hemorrhage, occurred in three patients.

Matsuo et al (2014) reported on outcomes from a cohort of 51 patients with intracranial AVMs treated with SRS at a single-institution.[7,] Rates of obliteration after a single SRS at 3, 5, 10, and 15 years were 46.9%, 54.%, 64%, and 68%, respectively; rates of obliteration after multiple SRS sessions at 3, 5, 10, and 15 years were 46.9%, 61.3%, 74.2%, and 90.3%, respectively. The adverse radiation events occurred in 9 (17.6%) cases, with 4 cases (3 symptomatic cysts, 1 intracranial hemorrhage) not occurring until 10 years after the SRS treatment.

Fokas et al (2013) reported long-term follow-up on a cohort of patients who underwent SRS for cerebral AVMs at a single-institution.[5,] One hundred sixty-four patients were identified, with a median follow-up of 93 months (range, 12-140 months). Thirty-nine percent of subjects had experienced a prior intracranial hemorrhage, and 43.3% and 8.0%, respectively, had undergone prior embolization or neurosurgical procedures. Complete obliteration was seen in 61% of patients at a median time of 29 months. Complete obliteration was achieved at 3 and 5 years in 61% and 88%, respectively. In multivariable models, higher radiation dosage and smaller target volumes were associated with higher rates of complete obliteration. The annual bleeding risk was 1.3% per year during follow-up.

Kano et al (2012) studied long-term outcomes and risks of AVM management using 2 or more stages of SRS for symptomatic large-volume lesions unsuitable for surgery.[6,] Forty-seven patients with such AVMs underwent volume-staged SRS. Eighteen (38%) patients had a prior hemorrhage and 21 (45%) patients had undergone prior embolization. In 17 patients, AVM obliteration was confirmed after 2 to 4 SRS procedures at a median follow-up of 87 months (range, 0.4-209 months). Five patients had near-total obliteration (volume reduction >75% but residual AVM). The actutimes rates of total obliteration after 2-stage SRS were 7%, 20%, 28%, and 36% at 3, 4, 5, and 10 years, respectively. The 5-year total obliteration rate after the initial staged volumetric SRS was 62% (p=0.001). Sixteen patients underwent additional SRS at a median interval of 61 months (range, 33-113 months) after the initial 2-stage SRS. The overall rates of total obliteration after staged and repeat SRS were 18%, 45%, and 56% at 5, 7, and 10 years, respectively. Ten patients sustained hemorrhage after staged SRS, and five of these patients died. Three of 16 patients who underwent repeat SRS sustained hemorrhage after the procedure and died. Based on Kaplan-Meier analysis (excluding the second hemorrhage in the patient who had 2 hemorrhages), the cumulative rates of AVM hemorrhage after SRS were 4.3%, 8.6%, 13.5%, and 36.0% at 1, 2, 5, and 10 years, respectively, corresponding to annual hemorrhage risks of 4.3%, 2.3%, and 5.6% for years 0 to 1, 1 to 5, and 5 to 10 after SRS. Multiple hemorrhages before SRS correlated with a significantly higher risk of hemorrhage after SRS. Symptomatic adverse radiation effects were detected in 13% of patients. The authors concluded that volume-staged SRS for large AVMs unsuitable for surgery has potential benefit, but often requires more than 2 procedures to complete the obliteration process and that, in the future, prospective volume-staged SRS followed by embolization (to reduce flow, obliterate fistulas, and occlude associated aneurysms) may improve obliteration results and further reduce the risk of hemorrhage after SRS.

In children, surgical resection of an AVM remains the reference standard of care. However, because the diagnosis is often made after rupture has occurred, evidence for the utility of SRS is limited. SRS to further obliterate the AVM is often preceded by embolization to control intracranial hemorrhage.[16,] Potts et al (2014) summarized outcomes for 80 children treated with SRS for intracranial AVMs, most of whom (56%) had an intracranial hemorrhage at the time of presentation.[9,] Among the 47% of subjects with available angiograms 3 years after treatment, AVM obliteration occurred in 52% of patients treated with higher dose SRS (18-20 gray [Gy]) and in 16% treated with lower dose SRS (<18 Gy).

Rupture of an AVM is a leading, nonobstetric cause of intracranial hemorrhage in pregnancy and the postpartum period. Therefore, interventions are typically emergent. El-Ghanem et al (2016) reported a single-institution retrospective analysis of authors' experience with Gamma Knife SRS from 1987 to 2012.[17,] During this time, 253 women of childbearing age (median age, 30 years; range, 15-40 years) underwent SRS for intracranial AVM. The median target volume was 3.9 cm^3 (range, 0.1-27.1 cm^3), and the median marginal dose was 20 Gy (range, 14-38 Gy). For all patients, the date of AVM obliteration was recorded, and the latency interval was calculated. Information about subsequent pregnancies and/or bleeding events during the latency interval was retrieved from the medical records and supplemented by telephone contact. AVM obliteration was confirmed by MRI or angiography at a median follow-up time of 39.3 months (range, 10-174 months). There were 828.7 patient-years of follow-up within the latency interval between SRS and the date of confirmed AVM obliteration. Among nonpregnant women, 20 hemorrhages occurred before AVM obliteration, yielding an annual hemorrhage rate of 2.5% for pregnant women during the latency interval. Among women who became pregnant during the latency interval, 2 hemorrhages occurred over the course of 18 pregnancies, yielding an annual hemorrhage rate of 11.1% for women who become pregnant during the latency interval. For the 2 pregnant patients who experienced hemorrhage, the bleeding occurred during the first trimester of pregnancy.

Section Summary: Arteriovenous Malformations

The evidence on the use of SRS for unruptured AVM consists primarily of noncomparative cohort studies, which reported relatively high rates of complete obliteration of AVM after SRS, in the range of 40% to 70%. Isolating the effect of SRS therapy in and of itself can be challenging, because many patients are treated with more than one therapy, including endovascular treatments and surgery. Recently, an RCT that compared medical therapy with various interventions in the treatment for AVM showed no significant improvement in outcomes with interventional therapy. However, given that the interventional studies included a variety of therapies, it is difficult to assess whether a particular component of the intervention has or lacks benefit. Several important aspects of management of AVM with or without SRS remain the subject of inquiry. Patient selection factors such as agreement on the exact definition of "unruptured" (no prior evidence of intracranial hemorrhage or mild intracranial hemorrhage associated with, eg, seizure leading to investigation and diagnosis), size, and location of lesions (eloquent areas) remain the subject of debate and impact potential candidacy for medical management vs intervention. The differentiation of focal neurologic deficits presumably due to limited intracranial hemorrhage from postintervention effects is under study. The evidence for the management of special populations (pediatrics and pregnant women) is limited to case reports.

SRS for Non-Neoplastic Conditions: Trigeminal Neuralgia

Clinical Context and Test Purpose

The purpose of SRS is to use a focused radiotherapy technique to treat trigeminal neuralgia when conservative therapy and medical treatment have failed and to potentially avoid complications associated with surgical intervention.

The question addressed in this evidence review is: Does the use of SRS for treatment of trigeminal neuralgia result in changes in management, avoidance of harms, and improvement in health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients

The population of interest are patients with trigeminal neuralgia who have failed conservative therapy and medical treatment. Trigeminal neuralgia is a disorder of the fifth cranial (ie, trigeminal) nerve that causes episodes of intense, stabbing pain in the face. The International Classification of Headache Disorders has defined classical trigeminal neuralgia as both idiopathic and related to vascular compression. Painful trigeminal neuropathy is also caused by other conditions, including postherpetic neuralgia and posttraumatic neuralgia, secondary to multiple sclerosis plaque or a space occupying lesion.[18,]

Interventions

The intervention of interest is SRS as an alternative to surgical intervention. Although trigeminal neuralgia is initially treated medically, in a substantial number of cases, pharmacologic treatment is either ineffective or the adverse events become intolerable. SRS of the proximal trigeminal nerve root has been investigated as an alternative to neurosurgical treatments.

Comparators

The following therapies are currently being used to treat trigeminal neuralgia: conservative therapies (eg, continued medical therapy) and surgical intervention. Neurosurgical options include microvascular decompression, which involves craniotomy, peripheral neurectomy, or rhizotomy. Rhizotomy is a technique to percutaneously isolate and ablate the nerve, with techniques such as balloon compression, radiofrequency ablation or chemical injection.

Outcomes

The outcomes of interest are overall survival, symptom improvement, and treatment-related morbidity.

Timing

SRS is typically used after conservative therapy and medical treatment have failed. There is a latency period of approximately one month for the effect to be observed.

Setting

SRS is provided in a tertiary care setting.

Systematic Reviews

A Cochrane review by Zakrzewska et al (2011) assessing 11 trials of neurosurgical interventions for trigeminal neuralgia found that there is very low-quality evidence for the efficacy of most

neurosurgical procedures for trigeminal neuralgia because of the poor quality of the trials.[19,]All procedures produced variable pain relief, but many resulted in sensory side effects. There were no studies of microvascular decompression which observational data would suggest gives the longest pain relief. Only one study was identified that used radiosurgery. The trial was intended to determine if increasing the nerve length within the SRS treatment volume would change outcomes. The study was stopped before accrual was completed, and it was noted that pain measurements using validated scales were not made before or after surgery.

Yen et al (2011) reviewed the literature on the use of SRS for trigeminal neuralgia.[20,] Reviewers concluded that patients with typical facial pain would achieve relief following radiosurgery.

Dhople et al (2009) reported on long-term outcomes of SRS for classical trigeminal neuralgia in 112 patients treated between 1996 and 2001.[21,] Of these, 67% had no prior invasive operations for trigeminal neuralgia prior to SRS, 13% had 1, 4% had 2, and 16% had 3 or more. The right side was affected in 56% of cases, predominantly involving V2 (26%), V3 (24%), or a combination of both (18%) branches. The median age at diagnosis was 56 years, and the median age at SRS was 64 years. The median prescription dose of 75 Gy (range, 70-80 Gy) was delivered to the involved trigeminal nerve root entry zone. Reviewers assessed the degree of pain before and after SRS using the Barrow Neurological Institute (BNI) pain scale. In total, 102 patients took the survey at least once (response rate, 91%). Although not found to alter the conclusions of this study, 7 cases of atypical trigeminal neuralgia were found, and these patients were removed, for a total of 95 cases analyzed. The median follow-up was 5.6 years (range, 13-115 months). Before Gamma Knife surgery, 88% of patients categorized their pain as BNI IV (inadequate control on medication) or V (severe pain on medication), whereas the remainder described their pain as BNI III (some pain but controlled on medication). After Gamma Knife surgery, 64% reported a BNI score of I (no pain, no medications), 5% had BNI II (no pain, still on medication), 12% had BNI III, and 19% reported a BNI score of IV or V. Median time to response was 2 weeks (range, 0-12 weeks), and median response duration was 32 months (range, 0-112 months). Eighty-one percent reported initial pain relief, and actutimes rates of freedom from treatment failure at 1, 3, 5, and 7 years were 60%, 41%, 34%, and 22%, respectively. Response duration was significantly better for those who had no prior invasive treatment vs those in whom a previous surgical intervention had failed (32 months vs 21 months, $p<0.02$). New facial numbness was reported in 6% of cases.

Section Summary: Trigeminal Neuralgia
Case series identify improvements in pain related to trigeminal neuralgia after treatment with SRS. Comparative studies that evaluated the use of SRS compared with alternative treatments for trigeminal neuralgia were reviewed in a systematic review without meta-analysis and were judged to be of poor quality. Only one study specifically addressed the use of radiosurgery, and it was stopped before accrual was completed.

SRS for Non-Neoplastic Neurologic Disorders: Epilepsy
Clinical Context and Test Purpose
The purpose of SRS is to use a focused radiotherapy technique to ablate epileptogenic foci when seizures have become drug-resistant or medication-related adverse events are intolerable and to potentially avoid complications associated with surgical intervention.

The question addressed in this evidence review is: Does the use of SRS for treatment of drug-resistant or medication-intolerant epilepsy result in changes in management, avoidance of harms, and improvement in health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients
The population of interest are patients with drug-resistant or medication-intolerant epilepsy. Epilepsy is diagnosed when an individual has unprovoked seizures. Primary seizure disorders include multiple subtypes which are recognizable by the degree and type of impairment of consciousness and motor capacity. Seizure disorders may be secondary to brain tumors or other space-occupying intracranial lesions. Mesial temporal lobe epilepsy (MTLE) also known as complex partial seizures is a focal epilepsy syndrome. The epileptogenic foci are in the hippocampus, amygdala and the parahippocampal gyrus. The most common non-traumatic or non-infectious etiology of MTLE is hippocampal sclerosis. The associated neuronal loss is a partial explanation for the difficulties in achieving satisfactory seizure control with antiepileptic medication.

Interventions
The intervention of interest is SRS as an alternative to surgical intervention. SRS is typically delivered in a single outpatient session. Dose to target protocols vary and the effect on seizure remission is gradual.

Comparators
The following therapies are currently being used to treat epilepsy: conservative therapies (eg, continued medical therapy) and surgical intervention. Seizure disorders are initially treated medically and may require more than one pharmacologic agent. Surgical treatment is only considered in those instances when the seizures have proven refractory to all attempts at aggressive medical management, when the frequency and severity of the seizures significantly diminish the quality of life, and when the seizure focus can be localized to a focal lesion in a region of the brain accessible to resection. When surgery is required the clinical standard of care is anterior temporal lobectomy (ATL).

Outcomes
Outcomes of interest are overall survival, symptom improvement, and treatment-related morbidity.

Timing
SRS is typically used after conservative therapy and medical treatment have failed. Follow-up for assessment of the effect of the procedure should be approximately 36 months and is related to the known latency of effect for seizure reduction or remission after SRS.

Setting
SRS is provided in a tertiary care setting.

Randomized Controlled Trials
Barbaro et al (2018) published the results of the only randomized controlled trial comparing SRS for the treatment of pharmacoresistant unilateral mesial temporal lobe epilepsy

to anterior temporal lobectomy (ATL) which is currently considered the clinical standard of care.[22,] The study was sponsored by the National Institute of Neurological Disorders and Stroke. The study was initially designed to have a 3- year recruitment period followed by a 3 year follow-up period. The sponsor stopped recruitment at 58 participants due to slow accrual resulting in a power of 41% for the primary hypothesis that SRS would be noninferior to ATL with respect to the seizure-free rate between 25 and 36 months with a noninferiority margin of 15%. A total of 37 (64%) patients achieved seizure remission, with 16 (52%) in SRS and 21 (78%) in ATL. The difference between ATL and SRS was 26%, with the upper bound of the 1-sided 95% CI at 46%. Because the upper bound exceeded the noninferiority margin of 15% (P-value was.82), noninferiority of SRS compared to ATL was not demonstrated. The corresponding 2-sided 90% CI for the difference in seizure-free rates between ATL and SRS ranged from 6% to 46%.

Other clinical outcomes were studied. SRS did not confer sparing of verbal memory deficits compared to ATL as measured by the long delay free recall score of the California Verbal Learning Test (CVLT) and the delayed recall score of the Logical Memory subtest from the Wechsler Memory Scale-Third Edition (WMS) for English speakers. Quality of life was assessed with the Quality of Life in Epilepsy (QOLIE-89) for English and Spanish speakers measured at baseline and 12, 24, and 36 months. In the SRS group, QOL scores improved significantly at 24 months and remained steady at 36 months, in contrast to the ATL group in whom the QOL score improvement was immediately noticeable at 12 months.

Adverse events were anticipated cerebral edema and related symptoms for some SRS patients, and cerebritis, subdural hematoma, and others for ATL patients. These all resolved with appropriate protocol-specified interventions.

The key characteristics and primary outcome results are summarized in Table 1 and Table 2 below.

Table 1. Summary of Key RCT Characteristics: SRS to Treat MTLE

Study; Trial	Countries	Sites	Dates	Participants[2]	Interventions[1]	
					Active N	Comparator N
Barbaro (2018); ROSE	US, UK, India	14	2009-2015	Pharmaco-resistant unilateral MTLE.	31 SRS[3]	27 ATL[4]

ATL: anterior temporal lobectomy; MTLE: mesial temporal lobe epilepsy; RCT: randomized controlled trial; SRS: stereotactic radiosurgery;
[1] Number randomized; intervention; mode of delivery; dose (frequency/duration).
[2] ≥18 years old, documented 3 months during which at least 3 focal-onset seizures with impairment of consciousness occurred during stable anticonvulsant administration, and lacked neurological or visual deficits.
[3] outpatient single session 24-Gy dose delivered to a 50% isodose volume between 5.5 and 7.5 cm 2 comprising the amygdala, anterior 2 cm of hippocampus, and parahippocampal gyrus.
[4] inpatient resection of 1-2 cm of the anterior superior temporal gyrus and 3 cm of the anterior middle and inferior temporal gyri, the temporal portion of the amygdala, the anterior 2-3 cm of the hippocampus, and adjacent entorhinal cortex. Participating neurosurgeons were documented to have performed at least 25 ATLs.

Table 2. Summary of Key RCT Results

Study		Seizure Remission[1]
Barbaro (2018)	N	58

Study	Seizure Remission[1]
SRS	16/31 (52)
ATL	21/27 (78)

ATL: anterior temporal lobectomy RCT: randomized controlled trial; SRS: stereotactic radiosurgery.
[1] seizure-free rate between 25 and 36 months

Systematic Reviews

Feng et al (2016) published a systematic review and meta-analysis of data from 13 studies on the use of SRS to treat mesial temporal lobe epilepsy.[23,] They calculated that approximately half of the patients were seizure-free over a follow-up period, which ranged from 6 months to 9 years (pooled estimate, 50.9%; 95% CI, 38.1% to 63.6%), with an average of 14 months to seizure cessation (pooled estimate, 14.08 months; 95% CI, 11.95 to 12.22 months). Nine of 13 included studies reported data for adverse events, which included visual field deficits and headache (the two most common adverse events), verbal memory impairment, psychosis, psychogenic nonepileptic seizures, and dysphasia. Patients in the individual studies experienced adverse events at rates that ranged from 8%, for nonepileptic seizures, to 85%, for headache.

A TEC Special Report (1998) cited 2 small studies using radiosurgery to treat epilepsy.[24,]

Single-Arm Studies

Regis et al (2000) selected 25 patients with mesial temporal lobe epilepsy, 16 of whom provided a minimum 2-year follow-up.[25,] Seizure-free status was achieved in 13 patients, 2 patients were improved, and 3 patients had radiosurgery-related visual field defects. A study by Schrottner et al (1998) included 26 patients with tumor-related epilepsy, associated mainly with low-grade astrocytomas.[26,] Mean follow-up among 24 available patients was 2.25 years. Tumor location varied across patients. Seizures were simple partial in 6 (3 with generalization) and complex partial in 18 (5 with generalization, 1 gelastic). Seizures were eliminated or nearly so in 13 patients. Little improvement was observed in 4 patients and none in seven. Whang and Kwon (1996) performed radiosurgery in 31 patients with epilepsy associated with nonprogressive lesions.[27,] A minimum of 1-year follow-up was available in 23 patients, 12 of whom were seizure-free (3 of whom had antiseizure medications discontinued), 2 had seizures reduced in frequency, and 9 experienced no change. While the Regis et al (2000) series selected a fairly homogeneous clinical sample, the other 2 studies were heterogeneous. No confirmatory evidence is available on mesial temporal lobe epilepsy. The available evidence from patients with epileptic lesions of various sizes and locations is insufficient to show what factors are associated with a favorable outcome.

Section Summary: Epilepsy

For individuals with epilepsy refractory to medical management, the evidence on the use of SRS as a treatment for epilepsy includes case reports in primary epileptic disorders and case reports for tumor-related epilepsy. For mesial temporal lobe epilepsy, there is a pilot prospective non-comparative intervention and a single RCT comparing SRS to anterior temporal lobectomy (ATL). Relevant outcomes are symptoms and treatment-related morbidity. The RCT did not meet participant accrual targets and, thus, did not demonstrate noninferiority of SRS to ATL. Seizure remission rates between 25 and 36 months were reported on a total of 58 patients (31 in SRS arm and 27 in ATL arm). Seizure remission rates suggest that ATL (78%) has an advantage over SRS (52%) in terms of proportion with seizure remission. The published evidence for SRS in epilepsy is insufficient. However, clinical expert opinion input reported that the less invasive

nature of SRS with acceptable seizure remission rates over time may be appropriate for a subpopulation of patients with mesial temporal epilepsy refractory to medical management when the standard alternative treatments are not an option. Thus, for this specific subpopulation, SRS would provide a clinically meaningful improvement in net health outcome.

SRS for Non-Neoplastic Neurologic Disorders: Tremor and Movement Disorders

Clinical Context and Test Purpose

The purpose of SRS is to use a focused radiotherapy technique to ablate brain nuclei foci associated with movement disorders (eg, essential tremor, parkinsonian disorders) when the conditions have become drug-resistant or medication-related adverse events are intolerable and to potentially avoid complications associated with surgical intervention.

The question addressed in this evidence review is: Does the use of SRS for treatment of drug-resistant, or medication-intolerant tremor and movement disorders result in changes in management, avoidance of harms, and improvement in health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients

The population of interest are patients with drug-resistant or medication-intolerant movement disorders including essential tremor and other forms of tremor (ie, secondary to Parkinson disease, multiple sclerosis, or other neurologic conditions).

Interventions

The intervention of interest is SRS of the thalamus (thalamotomy) as an alternative to surgical intervention.

Comparators

The following therapies are currently being used to treat movement disorders: conservative therapies (eg, continued medical therapy) and surgical intervention.

Outcomes

The outcomes of interest are overall survival, symptom improvement, and treatment-related morbidity.

Timing

SRS is typically used after conservative therapy and medical treatment have failed. The duration of follow-up to assess treatment effect varies.

Setting

SRS is provided in a tertiary care setting.

Nonrandomized Observational Studies

Niranjan et al (2017) reported a retrospective analysis of 73 patients who underwent Gamma Knife thalamotomy for intractable essential tremor during a 19-year period (1996-2015).[28,] A median central dose of 140 Gy (range, 130-150 Gy) was delivered to the nucleus ventralis intermedius through a single 4-mm isocenter. The median time to the last follow-up was 28 months (range, 6-152 months). Improvement in tremor occurred in 93.2% of patients as

demonstrated with changes in the Fahn-Tolosa-Marin Tremor Rating Scale to score tremor, handwriting, drawing, and ability to drink fluids. Three (4%) patients experienced temporary adverse radiation events.

Witjas et al (2015) reported on outcomes of a French prospective single-blind study of Gamma Knife thalamotomy for tremor.[29,] Fifty patients (mean age, 74.5 years; 32 men) with severe refractory tremor (36 essential, 14 parkinsonian) were treated with unilateral Gamma Knife thalamotomy at a prescription dose of 130 Gy. Neurologic and neuropsychological assessments including a single-blinded video assessment of the tremor severity performed by a movement disorders neurologist from another center were performed before and 12 months after treatment. The upper-limb tremor score improved by 54.2% on the blinded assessment ($p<0.001$). All tremor components (rest, postural, intention) were improved. Activities of daily living were improved by 72.2%. Cognitive functions remained unchanged. Following Gamma Knife thalamotomy, the median delay of improvement was 5.3 months (range, 1-12 months). The only side effect was a transient hemiparesis associated with excessive edema around the thalamotomy in one patient.

Kooshkabadi et al (2013) reported on outcomes for 86 patients with tremor treated over a 15-year period, including 48 with essential tremor, 27 with Parkinson disease, and 11 with multiple sclerosis.[30,] Fahn-Tolosa-Marin Tremor Rating Scale scores were used to compare symptoms pre- and post-procedure: the mean tremor score improved from 3.28 (pre-SRS) to 1.81 (post-SRS; $p<0.000$), the mean handwriting score improved from 2.78 (pre-SRS) to 1.62 (post-SRS; $p<0.000$), and the mean drinking score improved from 3.14 (pre-SRS) to 1.8 (post-SRS, $p<0.000$). Complications included temporary hemiparesis in two patients, dysphagia in one patient, and sustained facial sensory loss in one patient.

Ohye et al (2012) conducted a prospective study of SRS for tremor that included 72 (59 with Parkinson disease, 13 with essential tremor) patients.[31,] Among 52 patients who had follow-up at 24 months, tremor scores measured using the Unified Parkinson's Disease Rating Scale changed from 1.5 at baseline to 0.75 at 24-month follow-up ($p<0.001$; score decrease extrapolated from the graph).

Lim et al (2010) reported on outcomes for a small cohort of 18 patients who underwent SRS treatment for essential tremor.[32,] For the 14 patients with videotaped evaluations allowing blinded evaluation of tremor severity and at least 6 months of follow-up (11 with essential tremor, 3 with Parkinson disease), Fahn-Tolosa-Marin Tremor Rating Scale activities of daily living scores improved significantly after SRS (mean change score, 2.7 points; $p=0.03$). However, there was no significant improvement in other Fahn-Tolosa-Marin Tremor Rating Scale items ($p=0.53$ for resting tremor, $p=0.24$ for postural tremor, $p=0.62$ for action tremor, $p=0.40$ for drawing, $p>0.99$ for pouring water, $p=0.89$ for head tremor). Mild neurologic complications occurred in two patients (lip and finger numbness), and severe neurologic complications occurred in onepatient (edema surrounding thalamic lesion with subsequent hemorrhage at the lesion site, with speech difficulty and hemiparesis.)

Kondziolka et al (2008) reported on outcomes for 31 patients who underwent SRS thalamotomy for disabling essential tremor.[33,] Among 26 patients with follow-up data available, score on the Fahn-Tolosa-Marin Tremor Rating Scale score improved from 3.7 (pre-SRS [baseline]) to 1.7 (post-SRS; $p<0.000$) and score on the Fahn-Tolosa-Marin handwriting score improved from 2.8

(pre-SRS [baseline]) to 1.7 (post-SRS; p<0.000). One patient developed transient mild right hemiparesis and dysphagia, and one patient developed mild right hemiparesis and speech impairment.

Young et al (2000) reported on outcomes for a cohort of 158 patients with tremor who underwent SRS, including 102 patients with Parkinson disease, 52 with essential tremor, and 4 with tremor due to other conditions.[34,] Among patients with a parkinsonian tremor, at latest follow-up (mean, 47 months), blinded assessments on Unified Parkinson's Disease Rating Scale demonstrated improvements in several specific items, including overall tremor (from 3.3 pretreatment to 1.2 at last follow-up; p<0.05) and action tremor (from 2.3 pretreatment to 1.3 at last follow-up; p<0.05). Among patients with essential tremor, blinded assessments were conducted using the Fahn-Tolosa-Marin Tremor Rating Scale. At 1-year of follow-up, 92.1% of patients with essential tremor were completely or nearly tremor-free. Improvements were reported for components of the Fahn-Tolosa-Marin Tremor Rating Scale, but statistical comparisons were not presented. Three patients developed new neurologic symptoms attributed to the SRS.

Section Summary: Tremor and Movement Disorders
The evidence related to the use of SRS for tremor includes uncontrolled cohort studies, many of which reported outcomes from the treatment of tremor of varying etiologies. There is a retrospective analysis of a single-center experience. Most studies report improvements in standardized tremor scores, although few studies used a blinded evaluation of tremor score, allowing for bias in assessment. No studies comparing SRS with alternative methods of treatment or a control group were identified. Limited long-term follow-up is available, making the long-term risk-benefit ratio of an invasive therapy uncertain. Clinical input reported systematic reviews of retrospective studies that reported a reduction in tremors after SRS but confirmed that alternative approaches to thalamotomy are appropriate. The evidence is insufficient to determine the effects of the technology on health outcomes.

SRS for Non-Neoplastic Neurologic Disorders: Chronic Pain
Clinical Context and Test Purpose
The purpose of SRS is to use a focused radiotherapy technique to ablate intracranial neuronal foci of chronic pain that have become drug-resistant or when medication-related adverse events are intolerable as an alternative to other surgical interventions.

The question addressed in this evidence review is: Does the use of SRS for treatment of chronic pain syndromes result in changes in management, avoidance of harms, and improvement in health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients
The population of interest is patients with chronic pain syndromes refractory to standard medical and psychological treatments.

Interventions
The intervention of interest is SRS as an alternative to open neurosurgical intervention.

Comparators
The following therapies are currently being used to treat chronic pain syndromes: conservative therapies (eg, continued medical therapy) and surgical intervention. Neurodestructive procedures include cordotomy, myelotomy, and dorsal root entry zone lesions.

Outcomes
The outcomes of interest are overall survival, symptom improvement, and treatment-related morbidity.

Timing
SRS is typically used as an alternative to open neurosurgical intervention.

Setting
SRS is provided in a tertiary care setting.

Systematic Reviews
Roberts and Pouratian (2017) reported the results of a systematic review of the data in 6 studies (total n=113 patients) of SRS as an intervention for chronic pain.[35,] Outcomes were reported on the basis of the radiation target (pituitary or thalamus) and pain etiology (malignant or nonmalignant). Clinical success was reported to be achieved in 51% of pituitary SRS, at least 23% of thalamic SRS, 39% of nonmalignant, and at least 33% of malignant pain patients. Adverse events were noted in 21% of patients; the majority related to hormonal deficits from pituitary SRS.

A TEC Assessment (1999) identified 2 small reports evaluating radiosurgical thalamotomy for chronic pain.[24,]

Section Summary: Chronic Pain Syndromes
For individuals with chronic pain syndromes refractory to standard medical and psychological treatments, the evidence includes a systematic review of noncomparative studies. Relevant outcomes are symptoms and treatment-related morbidity. Clinical expert opinion input reported that intracranial SRS for treatment of chronic pain (other than associated with trigeminal neuralgia) was not an appropriate alternative to other surgical interventions. The evidence is insufficient to determine the effects of the technology on health outcomes.

SRS for Benign Neoplastic Intracranial Lesions
Clinical Context and Test Purpose
The purpose of SRS is to use a focused radiotherapy technique to treat intracranial and other brain lesions that are relatively inaccessible surgically and that are often near eloquent or radiosensitive areas.

The question addressed in this evidence review is: Does the use of SRS for treatment of the benign neoplastic intracranial conditions (eg, acoustic neuroma, pituitary adenoma, craniopharyngioma, glomus jugulare tumor) result in changes in management and improvement in health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients
The populations of interest are patients with symptomatic acoustic neuroma, pituitary adenoma, craniopharyngioma, and glomus jugulare tumor. Acoustic neuromas, also called vestibular schwannomas, are benign tumors originating on the eighth cranial nerve, sometimes associated with neurofibromatosis, which can be linked to significant morbidity and even death if their growth compresses vital structures. The tumors arise from the Schwann cell sheath surrounding the vestibular or cochlear branches of the eighth cranial nerve.

Pituitary adenomas are benign tumors with symptoms related to hormone production (ie, functioning adenomas) or neurologic symptoms due to tumor impingement on surrounding neural structures.

Craniopharyngiomas are benign tumors that arise from pituitary embryonic tissue at the base of the gland. However, because of their proximity to the optic pathways, pituitary gland, and hypothalamus, these tumors may cause severe and permanent damage to these critical structures and can be life-threatening.

A glomus jugulare tumor is a rare, benign tumor arising in the skull temporal bone that involves middle and inner ear structure.

Interventions
The intervention of interest is SRS. For acoustic neuromas, radiosurgery has been used as a primary treatment or as a treatment for recurrence after incomplete surgical resection. For pituitary adenomas, SRS has been used as primary treatment.

Comparators
The comparators are conservative therapies (eg, surveillance, medical therapy), radiotherapy, and surgical intervention. For acoustic neuromas, treatment options include complete surgical excision using microsurgical techniques.

For pituitary adenomas, surgical excision is typically offered to patients with functioning adenomas because complete removal of the adenoma leads to more rapid control of autonomous hormone production. In patients with nonfunctioning adenomas, the treatment goal is to control growth; complete removal of the adenoma is not necessary. Conventional radiotherapy has been for nonfunctioning adenomas with an approximate 90% success rate and few complications.

For craniopharyngiomas, total surgical resection is often difficult.

For glomus jugulare tumors, no consensus exists on optimal management to control tumor burden while minimizing treatment-related morbidity.

Outcomes
The outcomes of interest are overall survival, symptom improvement, and treatment-related morbidity.

Timing
SRS is typically used when conservative medical treatment has failed and as an alternative to open neurosurgical intervention. The effects of SRS on hormone production associated with pituitary adenomas may be delayed or incomplete.

Setting
SRS is provided in a tertiary care setting.

Acoustic Neuromas
Systematic Reviews
A systematic review by Persson et al (2017) reported on SRS vs fractionated radiotherapy for tumor control in vestibular schwannoma patients.[36,] Patients with unilateral vestibular schwannoma treated with radiosurgery were compared with patients treated using fractionated SRS. A meta-analysis was not performed because all identified studies were case series. Rates of adverse events were calculated; the risk for facial nerve deterioration was 3.6% for SRS and 11.2% for fractionated SRS, and the risk for trigeminal nerve deterioration was 6.0% for SRS and 8.4% for fractionated SRS.

A Cochrane review by Muzevic et al (2014) did not identify any RCTs that evaluated the efficacy of SRS compared with observation alone, microsurgical resection, or other possible treatment or combinations of treatments in patients with a cerebellopontine angle tumor up to 3 cm in diameter, presumed to be a vestibular schwannoma.[37,]

Case Series
Case series have reported generally high rates of local control. Badakhshi et al (2014) reported a 3-year local tumor control rate of 88.9% in 250 patients with vestibular schwannoma who underwent SRS or fractionated SRS.[38,] Williams et al (2013) reported rates of tumor progression-free survival (PFS) for patients with large vestibular schwannomas treated with SRS of 95.2% and 81.8% at 3 and 5 years, respectively.[39,] For patients with small vestibular schwannomas treated with SRS, tumor PFS was 97% and 90% at 3 and 5 years, respectively. In a retrospective case series of 93 patients with vestibular schwannomas treated with SRS, 83 of whom had long-term follow-up, Woolf et al (2013) reported an overall control rate of 92% at a median follow-up of 5.7 years.[40,] Pollock et al (2006) compared microsurgical resection (n=36) with SRS (n=46) for the management of small (<3 cm) vestibular schwannomas and showed better hearing preservation at last follow-up in the SRS group ($p<0.01$) and no difference in tumor control rates between groups (100% vs 96%, $p=0.50$).[41,]

In the treatment of acoustic neuromas, the most significant adverse events include loss of function of facial and auditory nerves. For example, Chang et al (2005) reported that 74% of 61 patients with acoustic neuromas treated with CyberKnife using staged treatment maintained serviceable hearing during at least 36 months of follow-up.[42,] Chung et al (2004) reported on the results of a single-institution case series of 72 patients with acoustic neuromas, 45 of whom received single-fraction therapy and 27 who received fractionated therapy.[43,] Patients receiving single-fraction treatment were functionally deaf, while those receiving fractionated therapy had useful hearing in the affected ear. After a median follow-up of 26 months, there was no tumor recurrence in either group. In a single-institution study, Meijer et al (2003) reported on the outcomes of single-fraction vs fractionated linear accelerator (LINAC)–based SRS in 129 patients with acoustic neuromas.[44,] Among these patients, 49 were edentate and thus could not be fitted

with a relocatable head frame that relies on dental impressions. This group was treated with a single-fraction, while the remaining 80 patients were treated with a fractionated schedule. With an average follow-up of 33 months, there was no difference in outcome in terms of local tumor control, facial nerve preservation, or hearing preservation.

Section Summary: Acoustic Neuromas
The evidence for the use of SRS for acoustic neuroma (vestibular schwannoma) consists primarily of case series and cohort studies, which has reported high rates of freedom from tumor progression generally using fractionated SRS. Given that vestibular schwannoma is a slow-growing tumor with symptoms most often related to local compression, demonstration of slowing of progression is a valid outcome. A single comparative study was identified that demonstrated comparable tumor control outcomes between SRS and surgical therapy for small vestibular schwannomas. A Cochrane review did not identify any RCTs.

Pituitary Adenoma
Systematic Reviews
Chen et al (2013) reported on the results of a systematic review and meta-analysis evaluating studies of SRS (specifically Gamma Knife surgery) for the treatment of nonfunctioning pituitary adenoma that included a volumetric classification.[45,] Seventeen studies met the inclusion criteria, including 7 prospective cohort studies and 10 retrospective cohort studies, with 925 patients included in the meta-analysis. Reported outcomes were related to the rate of tumor control, the rate of radiosurgery-induced optic neuropathy injury, and the rate of radiosurgery-induced endocrinologic deficits. In patients with tumor volume less than 2 mL, the rate of tumor control was 99% (95% CI, 96% to 100%), the rate of radiosurgery-induced optic neuropathy injury was 1% (95% CI, 0% to 4%), and the rate of radiosurgery-induced endocrinologic deficits was 1% (95% CI, 0% to 4%). In patients with volumes of 2 to 4 mL, the comparable rates were 96% (95% CI, 92% to 99%), 0% (95% CI, 0% to 2%), and 7% (95% CI, 2% to 14%), respectively, and in patients with volumes larger than 4 mL, the rates were 91% (95% CI, 89% to 94%), 2% (95% 0% to 5%), and 22% (95% CI, 14% to 31%), respectively. The rates of tumor control and radiosurgery-induced optic neuropathy injury differed significantly across the 3 groups.

Nonrandomized Observational Studies
Lee et al (2014) retrospectively reported on outcomes for 41 patients treated with SRS from a cohort of 569 patients treated for nonfunctioning pituitary adenomas at 3 institutions.[46,] Neuroimaging at a median follow-up of 48 months showed 34 (82.9%) patients had a decrease in tumor volume, 4 (9.8%) patients had tumor stability, and 3 (7.3%) patients had a tumor increase. PFS rates were 94% at 5 years and 85% at 10 years post-SRS. New onset or worsened pituitary deficiencies were found in 10 (24.4%) patients at a median follow-up of 52 months. The authors concluded that initial treatment with SRS for nonfunctioning pituitary adenomas might be appropriate in certain clinical settings, such as in older patients (³70 years); in patients with multiple comorbidities in whom surgery would involve high-risk; in patients with clear neuroimaging and neuroendocrine evidence of nonfunctioning adenomas, no mass effect on the optic apparatus, and progressive tumor on neuroimaging follow-up; or in patients who want to avoid resection.

Sheehan et al (2013) reported on results from a multicenter registry of 512 patients who underwent SRS for nonfunctional pituitary adenomas.[47,] Four hundred seventy-nine (93.6%) had undergone prior resection, and 34 (6.6%) had undergone prior external-beam radiotherapy

(EBRT). Median follow-up was 36 months. At last follow-up, 31 (6.6%) of 469 patients with available follow-up had tumor progression, leading to actutimes PFS rates of 98%, 95%, 91%, and 85% at 3, 5, 8, and 10 years post-SRS, respectively. Forty-one (9.3%) of 442 patients had worsened or new central nervous system deficits, more commonly in patients with tumor progression (p=0.038).

Section Summary: Pituitary Adenoma
Noncomparative studies have demonstrated high rates of tumor control (³85%) for pituitary adenomas with SRS treatment, with better tumor control with smaller lesions. Comparative studies evaluating the treatment of pituitary adenomas with SRS vs surgery or traditional radiotherapy do not exist.

Craniopharyngioma
Nonrandomized Observational Studies
Lee et al (2014) reported on a 20-year (1993-2012) experience of using Gamma Knife surgery to treat recurrent or residual craniopharyngiomas.[48,] A total of 137 consecutive patients underwent 162 sessions in a Veterans hospital. The median radiation dose was 12 Gy (range, 9.5-16.0 Gy) at a median isodose line of 55% (range, 50%-78%). At a median imaging follow-up of 45.7 months after Gamma Knife surgery, the rates of tumor control were 72.7%, 73.9%, and 66.3% for the solid, cystic, and mixed tumors, respectively. There were no unanticipated adverse events on visual fields or pituitary function.

Hashizume et al (2010) evaluated the use of SRS in 10 patients with craniopharyngioma adjacent to optic pathways.[49,] Ten patients (6 men, 4 women) with craniopharyngioma and the median age of 56.5 years (range, 10-74 years) were treated from 2006 through 2009. Median volume of tumor was 7.9 mL (range, 1.1-21 mL). A total dose of 30 to 39 Gy in 10 to 15 fractions (median, 33 Gy) was delivered to the target. Ten patients were followed for 9 to 36 months (median, 25.5 months). The response rate was 80% (8/10), and the control rate was 100%. Improvement of neurologic symptoms was observed in five patients. No serious complications due to SRS were found.

Hasegawa et al (2010) determined the limiting dose to the optic apparatus in single-fraction irradiation in patients with craniopharyngioma treated with Gamma Knife radiosurgery.[50,] One hundred patients with 109 craniopharyngiomas treated with radiosurgery were evaluated with a median follow-up period of 68 months. Tumor volume varied from 0.1 to 36.0 cm (median, 3.3 cm). The actutimes 5- and 10-year overall rates of survival after radiosurgery were 93% and 88%, respectively. The actutimes 5- and 10-year PFS rates were 62% and 52%, respectively. Among 94 patients in whom visual function was evaluable, only 3 patients developed radiation-induced optic neuropathy, indicating an overall Kaplan-Meier radiation-induced optic neuropathy rate of 5%.

Combs et al (2007) evaluated long-term outcomes in patients treated with fractionated SRS.[51,] Forty patients with craniopharyngiomas were treated between 1989 and 2006. Most patients were treated for tumor progression after surgery. A median target dose of 52.2 Gy (range, 50.4-56 Gy) was applied in a median conventional fractionation of 5´1.8 Gy per week. Follow-up examinations included a thorough clinical assessment, as well as contrast-enhanced MRI scans. After a median follow-up of 98 months (range, 3-326 months), local control was 100% at both 5 and 10 years. Overall survival (OS) rates at 5 and 10 years were 97% and 89%,

respectively. A complete response was observed in 4 patients, and partial responses were noted in 25 patients. Eleven patients presented with stable disease during follow-up. Acute toxicity was mild in all patients. Long-term toxicity included enlargement of cysts requiring drainage 3 months after fractionated SRS. No visual impairment, radionecrosis, or development of secondary malignancies was observed. The results would suggest that long-term outcomes of fractionated radiosurgery for craniopharyngiomas are associated with good local control and, acceptable treatment-related side effects.

Section Summary: Craniopharyngioma
The evidence related to the use of fractionated SRS for craniopharyngioma consists primarily of case series and cohort studies, which report high rates of OS.

Glomus Jugulare Tumors
Systematic Reviews
Ivan et al (2011) conducted a meta-analysis of tumor control and treatment-related mortality rates for patients with glomus jugulare tumors.[52,] In this meta-analysis, reviewers assessed published data collected from patients with glomus jugulare tumors to identify treatment variables that impacted clinical outcomes and tumor control rates. A comprehensive search of the English language literature identified 109 related studies. Univariate comparisons of demographic information between treatment cohorts were performed to detect differences in the sex distribution, age, and Fisch class of tumors among various treatment modalities. Meta-analyses were performed on calculated rates of recurrence and cranial neuropathy after subtotal resection (STR), gross total resection, STR with adjuvant postoperative SRS (STR plus SRS), and SRS alone. Reviewers identified 869 patients who met inclusion criteria. In these studies, the length of follow-up ranged from 6 to 256 months. Patients treated with STR were observed for 72 months and had a tumor control rate of 69% (95% CI, 57% to 82%). Those who underwent gross total resection had a follow-up of 88 months and a tumor control rate of 86% (95% CI, 81% to 91%). Those treated with STR plus SRS were observed for 96 months and had a tumor control rate of 71% (95% CI, 53% to 83%). Patients undergoing SRS alone had a follow-up of 71 months and a tumor control rate of 95% (95% CI, 92% to 99%). Reviewers' analysis indicated that patients undergoing SRS had the lowest rates of recurrence of these 4 cohorts and, therefore, experienced the most favorable tumor control rates ($p<0.01$). Patients who underwent gross total resection sustained worse rates of cranial nerve deficits with regard to cranial nerves IX, X, and XI than those who underwent SRS alone; however, the rates of cranial nerve XII deficits were comparable.

Case Series
Wakefield et al (2017), published a report from an academic medical center that included 17 patients (median age, 64 years) treated between 1996 and 2013 with SRS for glomus jugulare tumors.[53,] Gamma Knife surgery was delivered with definitive treatment intent in 8 (47%) patients and salvage treatment in 9 (53%) patients. Overall neurologic deficit improved by 53%, stabilized in 41%, and worsened in 6% of patients. Overall cause-specific survival was 100%, and actutimes local control was 94%. Eighty-eight percent of patients without prior resection experienced neurologic deficit improvement, while 25% of patients with prior resection experienced neurologic improvement. Ibrahim et al (2017) reported a U.K. referral center experience with 75 patients who had glomus jugulare tumors treated with SRS between 1994 and 2010.[54,]Gamma Knife radiosurgery was the primary treatment modality in 47 (63%) patients. The overall tumor control rate was 93.4% with low cranial nerve injury. Reduction of preexisting

deficits was noted in 15 (20%) patients. A stationary clinical course and no progression of symptoms were noted in 48 (64%) patients. Twelve (16%) patients had new symptoms or progression of their preexisting symptoms.

Section Summary: Glomus Jugulare Tumors
The evidence related to the use of SRS for glomus jugulare tumors includes a large meta-analysis and recently published case series, which has suggested that SRS is associated with improved patient outcomes.

Section Summary: Benign Neoplastic Intracranial Lesions
The published evidence for the use of SRS to treat a subgroup of uncommon benign neoplastic intracranial lesions (acoustic neuroma, pituitary adenoma, craniopharyngioma, and glomus jugulare tumors) remains limited to systematic reviews of nonrandomized observational studies, other nonrandomized observational studies, and case series. These reports would suggest that long-term outcomes of fractionated radiosurgery for these benign neoplasms are associated with good local control and, acceptable treatment-related side effects. The likelihood of high quality systematically acquired evidence is low due to the rarity of the conditions. Clinical input continues to support an individualized approach to the use of SRS for these tumors with recognition that outcomes are affected by factors such as location of the tumor and type of SRS used (hypofractionated, fractionated or single session treatment). Thus, for the subpopulation of patients with uncommon benign neoplastic intracranial tumors (acoustic neuroma, pituitary adenoma craniopharyngioma, and glomus jugulare tumors) SRS would provide a clinically meaningful improvement in net health outcome.

SRS for Malignant Neoplastic Intracranial Lesion(s)
Clinical Context and Test Purpose
The purpose of SRS is to use a focused radiotherapy technique to treat certain primary and metastatic intracranial malignant tumors that are relatively inaccessible surgically and which are often located in proximity to eloquent or radiosensitive areas.

The question addressed in this evidence review is: Does the use of SRS for treatment of certain primary and metastatic intracranial malignant tumors result in changes in management, avoidance of harms, and improvement in health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients
The population of interest are patients with certain primary and metastatic intracranial malignant tumors; including gliomas, malignant meningiomas, and primitive neuroectodermal tumors (ie, medulloblastoma, pineoblastoma). Treatment of primary brain tumors such as gliomas is more challenging, due to their generally larger size and infiltrative borders. Intracranial metastases tend to have a smaller spherical size and noninfiltrative borders. Brain metastases occur frequently, seen in 25% to 30% of all patients with cancer, particularly in those with cancer of the lung, breast, colon cancer, melanoma, and kidney.

Interventions
The intervention of interest is SRS as an alternative to open neurosurgical intervention. SRS may be added to whole-brain radiotherapy (WBRT) in selected patients.

Comparators
The comparators are conservative therapies (eg, continued medical therapy, surgical intervention). WBRT is considered the standard of care in the treatment of brain metastases.

Outcomes
The outcomes of interest are OS, symptom improvement, and treatment-related morbidity.

Timing
SRS is typically used as an alternative to open neurosurgical intervention. SRS offers the additional ability to treat tumors with relative sparing of normal brain tissue in a single-fraction.

Setting
SRS is provided in a tertiary care setting.

Primary or Recurrent Gliomas and Astrocytomas
Nonrandomized Observational Studies
El-Shehaby et al (2015), reported on a single-arm study of 11 patients with tectal gliomas who were treated with Gamma Knife SRS between 2002 and 2011.[55,] Tectal gliomas are present in a location that makes surgical resection difficult and are also commonly associated with aqueduct obstruction and consequently hydrocephalus. This necessitates some form of cerebrospinal fluid diversion procedure before radiosurgery. Five patients had pilocytic astrocytomas, and six had nonpilocytic astrocytomas. Ten patients presented with hydrocephalus and underwent a cerebrospinal fluid diversion procedure prior to SRS. The tumor volume ranged between 1.2 mL and 14.7 mL (median, 4.5 mL). The prescription dose was 11 to 14 Gy (median, 12 Gy). Patients were followed for a median of 40 months (range, 13-114 months). Tumor control after radiosurgery was seen in 100% of cases. In 6 (55%) of 11 cases, the tumors eventually disappeared after treatment. Peritumoral edema developed in 45% of cases at onset of 3 to 6 months after treatment. Transient tumor swelling was observed in 4 cases. Four patients developed cysts after treatment. One of these cases required aspiration and eventually disappeared, one became smaller spontaneously, and two remained stable.

Clark et al (2014), retrospectively reviewed 21 patients with recurrent malignant glioma (18 glioblastoma, 3, World Health Organization [WHO] grade 3 glioma), treated at initial diagnosis with surgery and standard chemoradiation, received concurrent bevacizumab with hypofractionated SRS (30 Gy in 5 fractions) with or without concurrent chemotherapy (temozolomide or lomustine).[56,] The median patient age was 54 years, median Karnofsky Performance Status was 80, and median target size was 4.3 mL (range, 3.4-7.5 mL). Eleven (52%) patients had previously failed bevacizumab. One patient had grade 3 toxicities (seizures, dysphasia), which resolved with inpatient admission and intravenous steroids and antiepileptics. Treatment-related toxicities were grade 3 (n=1), grade 2 (n=9), and grade 0-1 (n=11). Kaplan-Meier median PFS and OS estimates (calculated from the start of SRS) for glioblastoma patients (n=18) were 11.0 and 12.5 months, respectively.

Dodoo et al (2014) reported on results for 55 consecutive patients with 68 high-grade gliomas (WHO grade 3 and 4) were treated with SRS (Gamma Knife) for local recurrences between 2001 and 2007.[57,] All patients previously had microsurgery and radiochemotherapy. Complete follow-up was available in all patients, with a median follow-up of 17 months (range, 2.5-114.2 months). Median tumor volume was 5.2 mL, the prescription dose was 20 Gy (range, 14-22 Gy), and the

median maximal dose was 45 Gy (range, 30-77.3 Gy). Patients with WHO grade 3 tumors initially showed a median survival of about 50 months, with a 2-year OS rate of 90%; however, after SRS for tumor recurrences, those same patients showed a median survival of 24 months and a 2-year OS rate of 50%. Patients with WHO grade 4 tumors had an initial median survival of 24 months, with a 2-year OS rate of 51%; after tumor recurrence and SRS, the median survival was 11 months, and 2-year survival was 23%.

Cabrera et al (2013), prospectively treated 15 patients with recurrent malignant glioma lesions less than 3 cm in diameter were treated with SRS in a single fraction. Those with lesions 3 to 5 cm in diameter received five 5 Gy fractions; bevacizumab was administered immediately before SRS and two weeks later.[58,] At initial diagnosis, patients were treated with surgery and adjuvant radiotherapy plus temozolomide and then at least one salvage chemotherapy regimen. The primary endpoint was central nervous system toxicity. Secondary endpoints included survival, quality of life (QOL), microvascular properties as measured by MRI, steroid usage, and performance status. One grade 3 (severe headache) and two grade 2 central nervous system toxicity events were observed. No patients experienced grade 4 or 5 toxicity or intracranial hemorrhage. Neurocognition, QOL, and Karnofsky Performance Status did not change significantly with treatment. MRI results suggested a significant decline in tumor perfusion and permeability one week after SRS and further decline by two months.

Cuneo et al (2012) reported on a retrospective analysis of patients with recurrent malignant gliomas treated with salvage SRS from 2002 to 2010.[59,] All patients had experienced tumor progression after treatment with temozolomide and radiotherapy. Salvage SRS was typically administered only after multiple post chemoradiation salvage systemic therapies had failed. Among 63 patients treated with SRS for recurrent high-grade glioma, 49 patients had WHO grade 4 disease. Median follow-up was 31 months from primary diagnosis and 7 months from SRS. Median OS from primary diagnosis was 41 months for all patients. Median PFS and OS from SRS were 6 and 10 months for all patients, respectively. The 1-year OS rates after SRS for patients with grade 4 glioma who received adjuvant (concurrent with or after SRS) bevacizumab was 50% vs 22% for patients not receiving adjuvant bevacizumab (p=0.005). Median PFS for patients with WHO grade 4 glioma who received adjuvant bevacizumab was 5.2 months and 2.1 months for patients who did not receive adjuvant bevacizumab (p=0.014). Treatment-related grade 3 or 4 toxicity events for patients who did or did not receive adjuvant bevacizumab was 10% and 14%, respectively (p=0.58). On multivariate analysis, the relative risk of death and progression with adjuvant bevacizumab was 0.37 (95% CI, 0.17 to 0.82) and 0.45 (95% CI, 0.21 to 0.97), respectively. A Karnofsky Performance Status score greater than 70 and age less than 50 years were significantly associated with improved survival. The combination of salvage radiosurgery and bevacizumab to treat recurrent malignant gliomas was well tolerated and seemed to be associated with improved outcomes. Prospective multi-institutional studies are required to determine the efficacy and long-term toxicity with this approach.

Section Summary: Primary or Recurrent Gliomas and Astrocytomas

Direct evidence is not available to compare radiotherapy methods for primary or recurrent gliomas or astrocytomas. Evidence from heterogeneous observational studies has demonstrated local control using SRS in combination with chemotherapy to treat gliomas in the primary and recurrent setting. The tumors are very aggressive and there are limited treatment options. In 2018, clinical input continued to support that SRS for the treatment of recurrent glioma may be appropriate, although there is not an anticipated impact on overall survival. The standard of care

for initial therapy of primary glioma after surgical resection is chemoradiation with temozolomide and conventional radiotherapy.

Brain Metastases

Systematic Reviews

Roos (2011) conducted a systematic review to examine the evidence for treating brain metastases.[60,] MEDLINE, EMBASE, and Cochrane databases were searched for published articles and abstracts on relevant randomized trials; 14 randomized trials were identified: 11 final reports and 3 abstracts, investigating various combinations of surgery, SRS, and WBRT. Most trials had significant limitations. Surgery and SRS improved local control, maintenance of performance status, and survival for favorable prognosis patients with solitary brain metastases relative to WBRT alone, although the absolute survival benefit for the majority was modest. Limited evidence suggests similar outcomes from surgery and SRS, but few patients were truly suitable for both options. For multiple (2-4) brain metastases, SRS improved local control and functional outcome but not survival. Adjuvant WBRT also improved intracranial control but not survival; the neurocognitive risk-benefit ratio of WBRT was controversial. QOL data were limited.

Park et al (2011) reviewed the use of SRS for brain metastases discussed 2 randomized trials demonstrating that the addition of single-dose SRS to WBRT improves local tumor control and maintenance of functional status for patients.[61,] Also reviewed were 3 randomized trials comparing the outcomes for SRS alone with SRS plus WBRT for limited brain metastases. All 3 trials indicated a lack of detriment in neurocognition or QOL with the omission of WBRT, despite significantly worsened intracranial tumor control that would require additional salvage therapy in almost all patients.

A Cochrane review by Patil et al (2010) addressed the role of SRS and WBRT in patients with few metastatic lesions (generally ≤3 or 4 lesions) and, recommended, given the unclear risk of bias in the included studies, interpreting the results cautiously.[62,] The analysis of all included patients (3 trials) indicated that SRS plus WBRT did not show a survival benefit over WBRT alone; however, performance status and local control were significantly better in the SRS plus WBRT group.

This Cochrane review was updated by Patil et al (2012).[63,] No new studies were identified that met the inclusion criteria. Thus, the original findings were confirmed.

Randomized Controlled Trials

Chang et al (2009) conducted an RCT and concluded that patients treated with SRS plus WBRT were at a greater risk of a significant decline in learning and memory function by 4 months than the group that received SRS alone.[64,]

Some studies have suggested that use of radiosurgery for brain metastases should be limited to patients with three or fewer lesions. A randomized trial by Kondziolka et al (1999) compared WBRT with WBRT plus radiosurgery boost to metastatic foci.[65,] Results suggested that the significant advantage of radiosurgery boost over WBRT alone in terms of freedom from local failure did not differ among patients with 2, 3, or 4 metastases. Survival also did not depend on the number of metastases. As the number of metastases rises, so does the total volume of tissue receiving high-dose radiation; thus, the morbidity risk of radiation necrosis associated with radiosurgery is likely to increase. For a large number of metastases, and for large volumes of tissue, this risk may be high enough to negate the advantage of radiosurgery plus WBRT over

WBRT alone seen in patients with four or fewer metastases. SRS centers commonly exclude patients with more than 5 metastases from undergoing radiosurgery.[66,67,] It is difficult to identify a specific limit on the number of metastases for which SRS is advantageous. A large number of very small metastases may respond to radiosurgery, as well as a small number of larger metastases.

Aoyama et al (2006) reported on a randomized trial of SRS plus WBRT vs SRS alone for treatment of patients with 1 to 4 brain metastases.[68,] They found a 12-month intracranial tumor recurrence rate of 46.8% in the SRS plus WBRT group compared with 76.4% in the group that only received SRS. However, median survival times did not differ at 7.5 and 8.0 months, respectively. They also found no differences in neurologic functional preservation.

Nonrandomized Comparative Studies

Tian et al (2013) reported on results from a retrospective, single-institution cohort study comparing neurosurgical resection with SRS for solitary brain metastases from non-small-cell lung cancer (NSCLC).[69,] Seventy-six patients were included, 38 of whom underwent neurosurgery. Median survival was 14.2 months for the SRS group and 10.7 months for the neurosurgery group. In multivariable analysis, treatment mode was not significantly associated with differences in OS.

Noncomparative Studies

Noncomparative studies continue to evaluate the use of SRS without WBRT for the management of brain metastases and the role of SRS for the management of larger numbers of brain metastases. Yamamoto et al (2014) conducted a prospective observational study to evaluate primary SRS in patients with 1 to 10 newly diagnosed brain metastases.[70,] Inclusion criteria were largest tumor volume less than 10 mL and less than 3 cm in the longest diameter, a total cumulative volume of 15 mL or less, and a Karnofsky Performance Status score of 70 or higher. Among 1194 patients, the median OS after SRS was 13.9 months (95% CI, 12.0 to 15.6 months) in the 455 patients with 1 tumor, 10.8 months (95% CI, 9.4 to 12.4 months) in the 531 patients with 2 to 4 tumors, and 10.8 months (95% CI, 9.1 to 12.7 months) in the 208 patients with 5 to 10 tumors.

Yomo and Hayashi (2014) reported on outcomes for 41 consecutive patients with 10 or fewer brain metastases from NSCLC who received SRS as primary treatment.[71,] The study reported 1- and 2-year OS rates of 44% and 17%, respectively, with a median survival time of 8.1 months. Distant brain metastases occurred in 44% by 1 year, with 18 patients requiring repeat SRS, 7 requiring WBRT, and 1 requiring microsurgery.

Rava et al (2013), in a cohort study including 53 patients with at least 10 brain metastases, assessed the feasibility of SRS treatment.[72,] Median survival was 6.5 months in this cohort. Raldow et al (2013), in a cohort of 103 patients with at least 5 brain metastases treated with SRS alone, reported a median OS of 8.3 months, compared with historical controls.[73,] OS was similar for patients with 5 to 9 (7.6 months) and with at least 10 (8.3 months) metastases.

Section Summary: Brain Metastases

For brain metastases, evidence from RCTs and systematic reviews have indicated that SRS improves outcomes in the treatment of brain metastases. SRS appears to be feasible in the treatment of larger numbers (eg, >10) of brain metastases, and outcomes after SRS treatment

do not appear to be worse for patients with larger numbers of metastases, at least for patients with ten or fewer metastases.

SRS for Uveal Melanoma

Clinical Context and Test Purpose

The purpose of SRS is to use a focused radiotherapy technique to treat certain malignant tumors that are relatively inaccessible surgically and that are often located near eloquent or radiosensitive areas.

The question addressed in this evidence review is: Does the use of SRS for treatment of uveal melanoma result in changes in management, avoidance of harms, and improvement in health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients

The population of interest is patients with uveal melanoma. Melanoma of the uvea (choroid, ciliary body, and iris) is the most common, primary, malignant, intraocular tumor in adults. Uveal melanoma is diagnosed mostly at older ages, with a progressively rising, age-specific, incidence rate that peaks near the age of 70 years.

Uveal melanomas can arise in the anterior (iris) or the posterior (ciliary body or choroid) uveal tract. Melanomas of the posterior uveal tract generally have a more malignant, histologic appearance; are detected later; and metastasize more frequently than iris melanomas.

A number of factors influence prognosis. The most important factors include the following: cell type, tumor size, location of the anterior margin of the tumor, degree of ciliary body involvement, presence of secondary glaucoma and extraocular extension. Extraocular extension, recurrence, and metastasis are associated with an extremely poor prognosis, and long-term survival is limited. The 5-year mortality rate associated with metastasis from ciliary body or choroidal melanoma is approximately 30%, compared with a rate of 2% to 3% for iris melanomas.

Interventions

The intervention of interest is SRS as an alternative to enucleation of the eye.

Comparators

The following therapies are currently being used to treat uveal melanoma: established treatment modalities include enucleation, local resection, brachytherapy, and proton beam radiotherapy. Photodynamic therapy with verteporfin as also been used as primary treatment for choroidal melanoma.

Outcomes

The outcomes of interest are overall survival, symptom improvement, and treatment-related morbidity. The main objectives of treating the tumor are twofold: (1) to reduce the risk of metastatic spread; and (2) to salvage the eye with useful vision (if feasible). Treatment selection depends on tumor size and location, associated ocular findings, the status of the other eye, as

well as other individual factors, including age, life expectancy, quality of life issues, concurrent systemic diseases, and patient expectations.

Timing
SRS may be used as an alternative to enucleation of the eye.

Setting
SRS is provided in a tertiary care setting.

Case Series
The literature on the use of SRS for uveal melanoma consists of case series; no studies directly comparing SRS with other accepted radiation modalities used to treat uveal melanoma (eg, brachytherapy, proton beam) were identified.

Reynolds et al (2017) retrospectively analyzed outcomes for patients undergoing Gamma Knife radiosurgery for uveal melanoma and intraocular metastases.[74,] Eleven (11 eyes) patients had uveal melanoma while 7 patients (7 eyes) had intraocular metastases. Patients with uveal melanoma were followed for a median of 19.74 months, and 1 patient required enucleation. There were no metastases in this group during the observation period. Patients with intraocular metastases were followed for a median of 6.03 months, and one patient required enucleation.

Eibl-Lindner et al (2016) reported on a prospective case-control study conducted at a single ophthalmic specialty institution using frameless, single-session, image-guided robotic radiosurgery.[75,] Of the 242 patients, 217 were included in the analysis (25 were excluded because of short follow-up). Radiosurgery was indicated either because the size and location of the tumor were not amenable for brachytherapy or because the patient wanted to avoid primary enucleation. Two patients had undergone prior unsuccessful brachytherapy for the targeted lesion. Mean follow-up was 29.6 months (range, 5.9-84.0 months; median, 26.4 months). Sixty-seven (30.6%) patients were followed for at least 3 years after treatment. Actutimes eye retention was 86.7% (95% CI, 79.9% to 91.3%) at 3 years and 73.0% (95% CI, 58.1% to 83.3%) at 5 years. Radiation-induced retinopathy was observed in 29 patients at the end of follow-up and treatment-induced glaucoma developed in 33 patients at a median time of 20.8 months (range, 5.8-54.0 months) after treatment.

Wackernagel et al (2014) reported on outcomes for 189 patients with choroidal melanoma treated with SRS (Gamma Knife).[76,] All patients with choroidal melanoma at the authors' institution were offered SRS as an alternative to enucleation if they wanted to retain their eye; other globe-preserving treatment options were not feasible because of tumor size or location or the patient's general health. Sixty-six (37.3%) patients, all treated before 2003, received high-dose SRS (35-80 Gy); subsequently, all patients received low-dose SRS (30 Gy in 87 patients, 25 Gy in 24 patients). Median overall follow-up was 39.5 months. During follow-up, local tumor control was achieved in 167 (94.4%) patients. Enucleation was required in 25 patients, 7 were due to tumor recurrence and 18 were due to radiation-induced adverse events. OS and distant metastasis rates were not reported.

Furdova et al (2014) reported on outcomes for a cohort of 96 patients who underwent SRS at a single-center in Slovakia for stage T2 or T3 uveal melanoma.[77,] Local tumor control occurred in 95% of patients at 3-year follow-up and in 85% of patients at 5-year follow-up. Eleven (11.5%)

patients required secondary enucleation between 3- and 5-years post-SRS, due to radiation neuropathy or secondary glaucoma.

Zehetmayer (2012) reviewed the literature on the use of SRS for uveal melanoma, with long-term tumor control rates using the Gamma Knife reported to be around 90%.[78,] Initial studies using SRS for uveal melanoma reported secondary adverse events from radiation to be common; however, more recent studies have reported lower incidences with lower total radiation doses.

Dunavoelgyi et al (2011) reported on a 10-year study of 212 patients with choroidal melanoma, who were not suitable for brachytherapy or resection.[79,] Patients in the study received different doses of radiation, ranging from 50 to 70 Gy, in 5 fractions over 7 days. Ophthalmologic examination was performed at baseline and every 3 months in the first 2 years, every 6 months until 5 years, and once annually to 10 years after SRS. The study measured tumor dimension and height using standardized methods, assessed visual acuity, and included routine ophthalmologic examinations. Local tumor control was 96% at 5 years and 93% at 10 years. Thirty-two patients developed metastases, 22 of whom died during the follow-up period. Median visual acuity decreased from 0.55 at baseline to hand motion ($p<0.001$). The authors concluded that SRS was sufficient to achieve excellent local tumor control in patients with melanoma of the choroid and that disease outcome and vision were comparable to that achieved with proton beam radiotherapy.

Additional case series using SRS to treat uveal melanoma have suggested that SRS is a possible eye-sparing option for patients, with outcomes comparable to enucleation or other radiation modalities.[80,81,82,]

Section Summary: Uveal Melanoma
The evidence for use of SRS to treat uveal melanoma is limited to case series. The published literature is insufficient to demonstrate improved outcomes with SRS over other accepted radiation modalities in the treatment of uveal melanoma. The condition is rare with poor clinical outcomes and treatment options. There are currently no active clinical trials to evaluate SRS to treat uveal melanoma and, therefore, there are limited prospects for accumulating additional high quality data. The evidence from published literature is insufficient to determine the effect on net health outcomes. However, clinical input reported that the use of SRS to treat uveal melanoma could provide patients with low-risk disease (based on tumor size using the Collaborative Ocular Melanoma Study (COMS) definition of small and medium) an option to avoid or postpone enucleation with preservation of some visual acuity and functional abilities.

Stereotactic Body Radiotherapy

Clinical Context and Test Purpose
The purpose of SBRT is to use a focused radiotherapy technique to treat certain primary and metastatic extracranial tumors that are relatively inaccessible surgically and that are often located in proximity to radiosensitive organs at risk.

The question addressed in this evidence review is: Does the use of SBRT for treatment of certain primary and metastatic extracranial tumors result in changes in management, avoidance of harms, and improvement in health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients
The population of interest are patients with primary and metastatic spinal or vertebral tumors.

Interventions
The intervention of interest is SBRT as an alternative to open surgical intervention, other forms of radiation therapy or as an adjunct to systemic therapy.

Comparators
The following therapies are currently being used to treat primary and metastatic spinal and vertebral tumors: other forms of radiation therapy, surgical interventions and/or continued systemic medical therapy.

Outcomes
The outcomes of interest are OS, symptom improvement, and treatment-related morbidity.

Timing
Follow-up of weeks to months is required to determine the effect of SBRT on local toxicity and months to years to determine the effect on tumor control.

Setting
SBRT is provided in a tertiary care setting.

Primary and Metastatic Spinal Tumors
Nonrandomized Observational Studies
Gerszten et al (2014) reported on the outcomes for 115 patients with spinal tumors of varying etiologies (ie, benign, metastatic, single, or multiple lesions), in a variety of locations (ie, cervical, thoracic, lumbar, sacral), who were treated with the CyberKnife in a single-session.[83,] Most patients were treated for pain control and also had prior EBRT. The authors pointed out that radiotherapy of the spinal cord is limited by its low tolerance and that, if a radiation dose could be targeted more accurately at the lesions, higher doses could be delivered in a single-fraction. They further pointed out that conventional methods for delivering intensity-modulated radiotherapy (IMRT) are limited due to lack of target immobilization. Axial and radicular pain improved in 74 of the 79 symptomatic patients. There was no acute radiation toxicity or new neurologic deficits. Conventional EBRT typically is delivered over 10 to 20 fractions. In contrast, in this study, only one CyberKnife treatment was given. In a study, Degen et al (2005) reported on the outcomes of 51 patients with 72 spinal lesions who were treated with the CyberKnife.[84] Patients underwent a median of three treatments. Patients reported reductions in pain as measured on the visual analog scale; QOL was maintained during the 1-year study period.

Sahgal et al (2013) evaluated rates of vertebral compression fractures after SBRT in 252 patients with 410 spinal segments treated with SBRT.[85,] Fifty-seven (13.9% of spinal segments treated) fractures were observed, with 27 de novo fractures and 30 cases of existing fracture progression. Most fractures occurred relatively early posttreatment, with a median and mean time to fracture of 2.46 months and 6.33 months, respectively. Radiation dose per fraction, baseline vertebral compression fracture, lytic tumor, and baseline spinal misalignment were predictive of fracture risk.

Gerszten et al (2007) published the results of a series of 500 cases from a single-institution (334 tumors had previously undergone EBRT) using the CyberKnife system.[86,] In this series, the maximum intratumoral dose ranged from 12.5 to 25 Gy (mean, 20 Gy). Long-term pain improved in 290 (86%) of 336 cases. Long-term radiographic tumor control was demonstrated in 90% of lesions treated with radiosurgery as a primary treatment modality. Twenty-seven (84%) of 32 cases with a progressive neurologic deficit prior to treatment experienced at least some clinical improvement. Chang et al (2007) reported on phase 1/2 results of SBRT used to treat 74 spinal lesions in 63 (55% had prior irradiation) patients with cancer.[87,] The actutimes 1-year tumor progression-free incidence was 84%. Pattern-of-failure analysis showed two primary mechanisms of failure: recurrence in the bone adjacent to the site of previous treatment and recurrence in the epidural space adjacent to the spinal cord. The authors concluded that data analysis supported the safety and effectiveness of SBRT in cases of metastatic spinal tumors. They added that it would be prudent to routinely treat the pedicles and posterior elements using a wide bone margin posterior to the diseased vertebrae because of the possible direct extension into these structures and for patients without a history of radiotherapy, to use more liberal spinal cord dose constraints than those they used.

Section Summary: Spinal Tumors
SBRT has been shown to improve outcomes (reduce pain) in patients with spinal (vertebral) tumors. Repeat administration of conventional radiation therapy increases the risk of treatment-related myelopathies. For individuals with primary and metastatic spinal or vertebral body tumors who have received prior radiotherapy who are treated with SBRT the observational literature primarily addresses metastases that recur after prior radiotherapy. Repeat administration of conventional radiation therapy increases the risk of treatment-related myelopathies. Nonrandomized study results are sufficient to determine that SBRT improves outcomes (reduce pain) in patients with spinal (vertebral) tumors. In addition, in 2018, clinical expert opinion input reported that SBRT is an important treatment option for patients whose spinal tumors have had prior radiotherapy because of the ability to spare the spinal cord and escalate tumor dose. Thus, for individuals with primary or metastatic spinal or vertebral body tumors in patients who have received prior spinal radiotherapy, SBRT would provide a clinically meaningful improvement in net health outcome.

Clinical input reported that SRS is an important treatment option for patients whose spinal tumors have had prior radiotherapy because of the ability to spare the spinal cord and dose escalate tumor. Thus, for individuals with primary or metastatic spinal or vertebral body tumors in patients who have received prior spinal radiotherapy, SBRT would provide a clinically meaningful improvement in net health outcome

Non-Small-Cell Lung Cancer
The following PICOTS were used to select literature to inform this review.

Patients
The population of interest are patients with non-small cell lung cancer (NSCLC).

Interventions
The intervention of interest is SBRT as an alternative to open surgical intervention, other forms of radiation therapy or as an adjunct to systemic therapy.

Comparators
The following therapies are currently being used to treat primary and metastatic NSCLC: other forms of radiation therapy, surgical interventions and/or continued systemic medical therapy.

Outcomes
The outcomes of interest are OS, symptom improvement, and treatment-related morbidity.

Timing
Follow-up of weeks to months is required to determine the effect of SBRT on local toxicity and months to years to determine the effect on tumor control.

Setting
SBRT is provided in a tertiary care setting.

Inoperable NSCLC
Systematic Reviews
Solda et al (2013) assessed the efficacy of stereotactic ablative radiotherapy (SABR) vs surgery for the treatment of NSCLC in a systematic review of all relevant publications from 2006 to 2013.[88,] Data were analyzed from studies of 20 or more stage I NSCLC patients treated with SABR and a median follow-up of 1 year (minimum). The data were compared with the outcome of surgery obtained from a matched control population from the International Association for the Study of Lung Cancer database. Forty-five reports containing 3771 patients treated with SABR for NSCLC were identified that fulfilled the selection criteria; both survival and staging data were reported in 3171 patients. The 2-year survival of rate the 3201 patients with localized stage I NSCLC treated with SABR was 70% (95% CI, 67% to 72%), with a 2-year local control rate of 91% (95% CI, 90% to 93%). This was compared with a 68% (95% CI, 66% to 70%) 2-year survival rate for 2038 stage I NSCLC patients treated with surgery. There was no survival or local PFS difference with different radiotherapy technologies used for SABR. The reviewer concluded that selection bias could not be assessed from the published reports and treatment-related morbidity data was limited.

Nonrandomized Comparative Studies
Harkenrider et al (2014) reported on outcomes after SBRT for 34 patients with unbiopsied lung cancer, with estimated rates of 2-year regional control, distant control, and OS of 80%, 85%, and 85%, respectively.[89,]

Jeppesen et al (2013) compared SBRT with conventional radiotherapy for patients with medically inoperable NSCLC (T1-2N0M0).[90,] The study included 100 subjects treated with SBRT and 32 treated with conventional radiotherapy. At baseline, the SBRT-treated patients had smaller tumor volume, lower forced expiratory volume in 1 second (FEV_1), and a greater proportion of stage T1 disease. Median OS was 36.1 months for SBRT and 24.4 months for conventional radiotherapy (p=0.015). Local failure-free survival rates at 1 year were 93% in the SBRT group and 89% in the conventional radiotherapy group; and, at 5 years, 69% and 66%, respectively (p=0.99).

In a prospective evaluation of 185 medically inoperable patients with early (T1-T2N0M0) NSCLC treated with SBRT, Allibhai et al (2013) evaluated the influence of tumor size on outcomes.[91,] Over a median follow-up of 15.2 months, tumor size (maximum gross tumor diameter) was not associated with local failure but was associated with regional failure (p=0.011)

and distant failure (p=0.021). Poorer OS (p=0.001), disease-free survival (DFS; p=9.001), and cause-specific survival (p=0.005) were significantly associated with tumor volume.

Hof et al (2007) reported on outcomes (median follow-up, 15 months) for 42 patients with stages I and II lung cancer who were not suitable for surgery and who were treated with SBRT.[92,] In this series, at 12 months, the OS rate was 75%, and the DFS rate was 70%. Better local control was noted with higher doses of radiation.

Noncomparative Studies

The Radiation Therapy Oncology Group (RTOG) 0236 trial was a phase 2 North American multicenter, cooperative group study (2010) to assess SBRT in treating medically inoperable patients with early-stage NSCLC. Patients had biopsy-proven peripheral T1-T2N0M0 non-small cell tumors less than 5 cm in diameter and medical conditions precluding surgical treatment. The prescription dose was 18 Gy per fraction given in 3 fractions (54 Gy total) delivered over 1.5 to 2 weeks. The study opened in 2004 and closed in 2006; data were analyzed through August 2009.[93,]

The three year results were reported. The primary endpoint was primary tumor control with OS, DFS, adverse events, involved lobe, regional, and disseminated recurrence as secondary endpoints. Prior to enrollment, "operability" of patients was evaluated by an experienced thoracic surgeon or pulmonologist. Standard indicators defining a patient to be "medically inoperable" included baseline FEV_1 less than 40% predicted, carbon monoxide diffusing capacity less than 40% predicted, baseline hypoxemia or hypercapnia, pulmonary hypertension, diabetes with end-organ damage, and/or severe cardiovascular or peripheral vascular disease.

Fifty-nine patients accrued, of which 55 were evaluable (44 T1 and 11 T2 tumors) with a median follow-up of 34.4 months (range, 4.8-49.9 months). Only 1 patient had a primary tumor failure; the estimated 3-year primary tumor control rate was 97.6% (95% CI, 84.3% to 99.7%). Three patients had a recurrence within the involved lobe; the 3-year primary tumor and involved lobe (local) control rate was 90.6% (95% CI, 76.0% to 96.5%). Two patients experienced regional failure; the locoregional control rate was 87.2% (95% CI, 71.0% to 94.7%). Eleven patients experienced disseminated recurrence; the 3-year rate of disseminated failure was 22.1% (95% CI, 12.3% to 37.8%). The rates of DFS and OS at 3 years were 48.3% (95% CI, 34.4% to 60.8%) and 55.8% (95% CI, 41.6% to 67.9%), respectively. The median OS was 48.1 months (95% CI, 29.6% to not reached). Five-year results have only been presented in abstract form.

Stanic et al (2014) reported an additional analysis of pulmonary toxicity in RTOG 0236 participants.[94,] During 2-year follow-up pulmonary function test results were collected. Mean percentage of predicted FEV_1 and DLCO declined 5.8% and 6.3%, respectively. There was no significant decline in oxygen saturation. Baseline pulmonary function testing was not predictive of any pulmonary toxicity following SBRT. Whole lung V5, V10, V20 and mean dose to the whole lung were almost identical between patients who developed pneumonitis and patients who were pneumonitis-free. Poor baseline pulmonary function testing did not predict decreased OS. Patients with poor baseline pulmonary function testing as a reason for medical inoperability had a higher median and OS than patients with normal baseline pulmonary function testing but with cardiac morbidity.

Operable NSCLC

Randomized Controlled Trials

Two RCTs were planned and initiated¾the STARS and ROSEL trials¾both of which were intended to compare SRS with surgery for operable early-stage NSCLC. However, both closed early due to slow enrollment. A pooled analysis of the available data from these 2 trials was published by Chang et al (2015).[95,] Fifty-eight patients enrolled and randomized (31 to SRS, 27 to surgery), with a mean follow-up of 40.2 months. OS favored the SRS group, but there were wide confidence intervals that crossed the threshold for statistical significance (HR=0.14; 95% CI, 0.02 to 1.2). Complications were less in the SRS group. The rate of grade 3 or 4 adverse events was 10% in the SRS group compared with 44% in the surgery group (statistics not reported).

An additional RCT, the American College of Surgeons Oncology Group trial Z4099 was opened for accrual in 2011.[96,] It was a phase 3 randomized study comparing SBRT with sublobar resection (with or without brachytherapy) for high-risk operable patients with NSCLC. In 2013, the study was closed due to slow accrual.

Systematic Reviews

Zheng et al (2014) reported results from a systematic review and meta-analysis comparing survival after SBRT with survival after surgical resection for the treatment of stage I NSCLC.[97,] Reviewers included 40 studies reporting outcomes from SBRT, including 4850 patients; 23 studies reported outcomes after surgery published in the same time period, including 7071 patients. For patients treated with SBRT, the mean unadjusted OS rates at 1, 3, and 5 years were 83.4%, 56.6%, and 41.2%, respectively. Mean unadjusted OS rates at 1, 3, and 5 years were 92.5%, 77.9%, and 66.1%, respectively, with lobectomy, and 93.2%, 80.7%, and 71.7%, with limited lung resections. After adjustment for surgical eligibility (for the 27 SBRT studies that reported surgical eligibility) and age, in a multivariable regression model, the treatment modality (SBRT vs surgical therapy) was not significantly associated with OS (p=0.36).

Nguyen et al (2008) cite a number of studies of SBRT for early-stage lung cancer receiving a biologically equivalent dose of 100 Gy or more.[98,] Three studies reported 5-year survival that ranged from 30% to 83%; in the largest series of 257 patients, the 5-year survival was 42%. Koto et al (2007) reported on a phase 2 study of 31 patients with stage I NSCLC.[99,] Patients received 45 Gy in 3 fractions, but those with tumors close to an organ at risk received 60 Gy in 8 fractions. With a median follow-up of 32 months, the 3-year OS rate was 72%, while the DFS rate was 84%. Five patients developed grade 2 or greater pulmonary toxicity. While comparative studies were not identified, older studies have reported 3-year disease-specific survival rates of 49% for those with stage I disease.[100,]

Nonrandomized Comparative Studies

Numerous nonrandomized, comparative studies have compared SBRT with surgery for NSCLC. A few of them used matching and are therefore are the strongest methodologically of this group.

Two matched analyses used the Surveillance, Epidemiology, and End Results database to identify patients. Yu et al (2015) identified elderly patients with stage I NSCLC who received either SBRT or surgery from 2007 to 2009.[101,] Propensity matching was used to select 2 surgery patients for each SRS patient. A total of 367 SBRT patients were matched with 711 surgery patients. Early mortality at 3 months was significantly better for the SBRT group compared with the surgery group (2.2% vs 6.1%, p=0.005). However, late mortality at 24 months was significantly worse

for the SBRT group (40.1%) compared with the surgery group (22.3%; p<0.001). Across the 24-month follow-up, patients in the SBRT group had fewer complications (incidence rate ratio, 0.74; 95% CI, 0.64 to 0.87). A similar study was performed by Ezer et al(2015),[102,] and the 2 studies likely had overlapping populations. A total of 362 patients with stage I or II NSCLC and negative lymph nodes were matched with patients who received limited resection. There was no difference in OS for the SBRT patients compared with the surgery patients (HR=1.19; 95% CI, 0.97 to 1.47). Complications were less common in patients undergoing SBRT (14% of total) compared with patients undergoing resection (28%; p<0.001).

In a matched-cohort study design, Crabtree et al (2014) retrospectively compared outcomes between SBRT and surgical therapy in patients with stage I NSCLC.[103,] Four hundred fifty-eight patients underwent primary surgical resection, and 151 were treated with SBRT. Surgical and SBRT patients differed significantly on several baseline clinical and demographic characteristics, with SBRT patients having an older mean age, higher comorbidity scores, a greater proportion of peripheral tumors, and worse lung function at baseline. For the surgical group, 3-year OS and DFS rates were 78% and 72%, respectively. Of note, among the 458 patients with stage I lung cancer, 14.8% (68/458) were upstaged at surgery and found to have occult N1 or N2 disease. For patients with occult nodal disease, 3- and 5-year OS rates were 66% and 43%, respectively. For patients without occult nodal disease, 3- and 5-year OS rates were 80% and 68%, respectively. For the SBRT group, 3-year OS and DFS rates were 47% and 42%, respectively.

In a propensity score-matched analysis, 56 patients were matched based on clinical characteristics, including age, tumor size, Adult Co-Morbidity Evaluation score, FEV_1 percent, and tumor location (central vs peripheral). In the final matched comparison, 3-year OS was 52% for SBRT and 68% for surgery (p=0.05), while DFS was 47% vs 65% (p=0.01), respectively. Two-, 3-, 4-, and 5-year local recurrence-free survival rates were 91%, 91%, 81%, and 40% for SBRT, respectively, and 98%, 92%, 92%, and 92% for surgery (p=0.07).

Port et al (2014) compared SBRT with wedge resection for patients with clinical stage IA NSCLC using data from a prospectively maintained database.[104,] One hundred sixty-four patients were identified, 99 of whom were matched based on age, sex, and tumor histology. Thirty-eight patients underwent a wedge resection only, 38 patients underwent a wedge resection with brachytherapy, and 23 patients had SBRT. SBRT patients were more likely to have local or distant recurrences than surgically treated patients (9% vs 30%, p=0.016), but there were no differences between the groups in 3-year DFS rates (77% for wedge resection vs 59% for SBRT, p=0.066).

Varlotto et al (2013) compared surgical therapy (132 with lobectomy, 48 with sublobar resection) with SBRT (n=137) in the treatment of stage I NSCLC.[105,] Mortality was 54% in the SBRT group, 27.1% in the sublobar resection group, and 20.4% in the lobar resection group. After matching for pathology, age, sex, tumor diameter, aspirin use, and Charlson Comorbidity Index, patients with SBRT had lower OS than patients treated with either wedge resection (p=0.003) or lobectomy (p<0.000).

Noncomparative Studies

Timmerman et al (2007) evaluated the toxicity and efficacy of SBRT in high-risk patients with early-stage (but medically inoperable) lung cancer.[106,] In a phase 2 North American multicenter study of patients aged 18 years or older with biopsy-proven peripheral T1-T2N0M0 non-small-cell

tumors (<5 cm in diameter) and medical conditions precluding surgical treatment. The prescription dose was 18 Gy in 3 fractions (54 Gy total), with the entire treatment lasting between 1.5 weeks and 2 weeks. The primary endpoint was 2-year actutimes primary tumor control; secondary endpoints were DFS (ie, primary tumor, involved lobe, regional, and disseminated recurrence), treatment-related toxicity, and OS. A total of 59 patients accrued, 55 of whom were evaluable (44 patients with T1 tumors, 11 patients with T2 tumors) with a median follow-up of 34.4 months (range, 4.8-49.9 months). Only 1 patient had primary tumor failure; the estimated 3-year primary tumor control rate was 97.6% (95% CI, 84.3% to 99.7%). Three patients had a recurrence within the involved lobe; the 3-year primary tumor and involved lobe (local) control rate was 90.6% (95% CI, 76.0% to 96.5%). Two patients experienced regional failure; the locoregional control rate was 87.2% (95% CI, 71.0% to 94.7%). Eleven patients experienced disseminated recurrence; the 3-year rate of disseminated failure was 22.1% (95% CI, 12.3% to 37.8%). The rates for DFS and OS at 3 years were 48.3% (95% CI, 34.4% to 60.8%) and 55.8% (95% CI, 41.6% to 67.9%), respectively. The median OS was 48.1 months (95% CI, 29.6 months to not reached). Protocol-specified treatment-related grade 3 adverse events were reported in 7 (12.7%) patients; grade 4 adverse events were reported in 2 (3.6%) patients. No grade 5 adverse events were reported. The authors concluded that patients with inoperable NSCLC who received SBRT had a survival rate of 55.8% at 3 years, high rates of local tumor control, and moderate treatment-related morbidity.

Section Summary: Non-Small-Cell Lung Cancer
Although no direct comparative evidence is available, evidence suggests that survival rates may be similar for SBRT and surgical resection for patients with stage T1 and T2a NSCLC tumor (not >5 cm in diameter) who show no nodal or distant disease and who are not candidates for surgical resection because of comorbid conditions. The published evidence is insufficient to determine the effect on net health outcomes. However, observational data and safety and efficacy results of an Australian randomized phase III trial of SBRT for patients with early-stage lung cancer (reported in abstract form) indicate that survival rates may be similar for these patients and those who are not candidates for surgical resection because of comorbid conditions. In 2018, clinical expert opinion input continued to support that SBRT is an important treatment option for patients who are poor surgical candidates or who do not wish to undergo surgery. Thus, for this specific subpopulation, SBRT would provide a clinically meaningful improvement in net health outcome.

Primary and Metastatic Hepatic Cancer
Hepatocellular Carcinoma
The following PICOTS were used to select literature to inform this review.

Patients
The population of interest are patients with primary and metastatic hepatocellular carcinoma (HCC).

Interventions
The intervention of interest is SBRT as an alternative to open surgical intervention, other forms of radiation therapy, liver-directed therapies or as an adjunct to systemic therapy. The use of SBRT for treatment of primary HCC has generally been directed toward locally advanced disease or metastatic lesions for which surgical resection or results with other liver-directed therapies would be suboptimal due to lesion size, number, or location. SBRT can deliver high doses of radiation in

a smaller number of fractions than conventional radiotherapy and is associated with a high degree of accuracy for the lesion target delineation. The most common SBRT fractionation protocols are 3 fractions at 10 to 20 Gy, 4 to 6 fractions at 8 to 10 Gy, and 10 fractions at 5 to 5.5 Gy[107,] and each of the 8 different liver segments may exhibit different tolerances. Some reports have included patients with intrahepatic cholangiocarcinoma for which there are for treatment options.

Comparators
The following therapies are currently being used to treat primary and metastatic HCC: other forms of radiation therapy, surgical interventions and/or continued systemic medical therapy. Surgical resection is the preferred treatment of HCC-although, at the time of diagnosis, less than 20% of patients are amenable to definitive surgical management due to advanced local disease or comorbidities. These patients may be candidates for local ablative therapies, including radiofrequency ablation and chemoembolization. Radiation may be considered as an alternative to local ablative/embolization therapies or if these therapies fail.

Radiation-induced liver disease is an important complication of radiotherapy and is secondary to endothelial injury and thrombotic sequelae. The disease typically occurs 4 to 8 weeks after completion of radiotherapy but has been described as early as 2 weeks and as late as 7 months postradiation. It is a major factor that limits radiation dose escalation and reirradiation for tumors situated proximate to the liver. The whole-liver tolerance for radiotherapy with a 5% risk of radiation-induced liver disease had been reported at whole-liver doses of 30 to 35 Gy in 2 Gy per fraction.[108,109,]

Outcomes
The outcomes of interest are OS, symptom improvement, and treatment-related morbidity.

Timing
Follow-up of weeks to months is required to determine the effect of SBRT on local toxicity and months to years to determine the effect on tumor control.

Setting
SBRT is provided in a tertiary care setting.

Systematic Reviews
A systematic review by Tao and Yang (2012) assessed the efficacy and safety of SBRT for treating primary and secondary hepatic neoplasms.[110,] Reviewers included prospective nonrandomized clinical trials published in English. Fifteen studies involving 158 patients with primary tumors and 341 patients with metastases to the liver were included between 2004 and 2011. Treatment was performed in 1 to 10 fractions to total doses of 18 to 60 Gy. Most studies included reported outcomes for patients with both primary (including primary cholangiocarcinoma) and metastatic disease, without separating the outcome data for primary tumors only. Most patients in the studies had metastatic tumors (n=341). In patients unable or unwilling to undergo surgical resection or other local therapy, SBRT was associated with 1-year local control rates ranging from 50% to 100%, and OS rates ranging from 33% to 100%.

Nonrandomized Comparative Studies

SBRT has been used in conjunction with other liver-directed therapies for the treatment of locally advanced HCC; either as a planned adjunct or after incomplete ablation with the other treatment. All studies identified for review were retrospective reports.

Wahl et al (2016) reported on single U.S. site experience with 224 patients with nonmetastatic HCC accumulated between 2004 and 2012.[111,] Radiofrequency ablation (RFA) was used to treat 161 patients and 249 lesions with a freedom from local progression (FFLP) rate at 1 year of 83.6%, and 2 years of 80.2%. SBRT was used to treat 63 patients with 83 lesions with an FFLP rate at 1 year of 97.4%, and 2 years of 83.8%.

The effect of SBRT in conjunction with transarterial chemoembolization (TACE) was reported in 3 retrospective studies. Jacob et al (2015) evaluated HCC lesions 3 cm or more and compared TACE alone (n=124) with TACE plus SBRT (n=37) from 2008 to 2013.[112] Sorafenib, a tyrosine kinase inhibitor, was used by 36.1% of the TACE alone group and 41.9% in the combination therapy group. Both groups had received before and after chemotherapy. Local recurrence was significantly decreased in the TACE plus SBRT group (10.8%) compared with the TACE-only group (25.8%) (CI, not reported, p=0.04). After censoring for liver transplantation, OS was significantly increased in the TACE plus SBRT group (33 months) compared with the TACE-only group (20 months; CI, not reported, p=0.02). Chronic hepatitis C virus (HCV) infection was the cause of HCC in most patients in both groups.

Su et al (2016) reported on a single-site experience with 77 HCC lesions greater than 5 cm treated with SBRT followed by TACE and 50 patients who had SBRT alone.[113] The patients who had SBRT alone either refused TACE or had hepatic arteriovenous fistulas precluding TACE. The median follow-up was 20.5 months and median tumor size was 8.5 cm (range, 5.1-21.0 cm). The PFS and local relapse-free survival did not differ significantly between groups.

Zhong et al (2014) reported on a single-site experience with 72 of 1086 HCC patients consecutively treated with SBRT between 2006 and 2012.[114] These patients had lesions 10 cm or larger and incomplete ablation with prior TACE. The median total dose of 35.6 Gy was delivered over 12 to 14 days with a fractional dose of 2.6 to 3.0 Gy at 6 fractions per week. A complete response achieved in 6 (8.3%), partial response in 51 (70.8%), stable disease in 9 (12.5%) and progressive disease in 6 patients (8.3%) within a median follow-up of 18 months.

Noncomparative Studies

Bujold et al (2013) reported on sequential phase 1 and 2 trials of SBRT for locally advanced HCC.[115,] Two trials of SBRT for patients with HCC considered unsuitable for standard locoregional therapies were conducted from 2004 to 2010. All patients had Child-Turcotte-Pugh (CTP) class A disease. The primary endpoints were toxicity and local control at 1 year, defined as no progressive disease of irradiated HCC by Response Evaluation Criteria in Solid Tumors (RECIST). A total of 102 patients were evaluable (n=50 in trial 1 from 2004-2007; n=52 in trial 2 from 2007-2010). The underlying liver disease was hepatitis B in 38% of patients, hepatitis C in 38%, alcohol-related in 25%, other in 14%, and none in 7%. Fifty-two percent received prior therapies (excluding sorafenib). The TNM stage was III in 66% of patients and 61% had multiple lesions. Median gross tumor volume was 117.0 mL (range, 1.3-1913.4 mL). Tumor vascular thrombosis (TVT) was present in 55%, and 12% of patients had extrahepatic disease. Local control at 1 year was 87% (95% CI, 78% to 93%). Toxicity of grade 3 or higher was seen in 30% of patients. In

7 patients (2 with TVT and progressive disease), death was possibly related to treatment (1.1-7.7 months after SBRT). Median OS was 17.0 months (95% CI, 10.4 to 21.3 months).

Yoon et al (2013) reported on outcomes for 93 patients with primary nonmetastatic HCC treated with SBRT at a single institution.[116,] Median follow-up was 25.6 months. OS rates at 1 and 3 years were 86% and 53.8%, respectively. The main cause of treatment failure was intrahepatic (ie, out-of-field) metastases. At 1 and 3 years, local control rates were 94.8% and 92.1%, respectively, and distant metastasis-free survival rates were 87.9% and 72.2%, respectively. However, intrahepatic recurrence-free survival rates at 1 and 3 years were 51.9% and 32.4%, respectively.

Jung et al (2013) reported on rates of radiation-induced liver disease in patients with HCC treated with SBRT for small (<6 cm), nonmetastatic HCC that was not amenable to surgery or percutaneous ablative therapy.[117,] Ninety-two patients were included, 17 (18.5%) of whom developed grade 2 or worse radiation-induced liver disease within 3 months of SBRT. In multivariable analysis, Child-Pugh class was the only significant predictor of radiation-induced liver injury. The 1- and 3-year survival rates were 86.9% and 54.4%, respectively (median survival, 53.6 months). The presence of radiation-induced liver disease was not associated with survival.

Ibarra et al (2012) evaluated tumor response to SBRT in a combined multicenter database.[118,] Patients with advanced HCC (n=21) or intrahepatic cholangiocarcinoma (n=11) treated with SBRT from 4 academic medical centers were entered into a common database. Statistical analyses were performed for FFLP and patient survival. Overall FFLP for advanced HCC was 63% at a median follow-up of 12.9 months. Median tumor volume decreased from 334.2 to 135 cm^3 ($p<0.004$). The median time-to-local progression was 6.3 months. The 1- and 2-year OS rates were 87% and 55%, respectively. The incidence of grade 1 to 2 toxicities, mostly nausea and fatigue, was 39.5%. Grade 3 and 4 toxicities were present in two and one patients, respectively.

Price et al (2012) reported on the results of a phase 1/2 trial that evaluated the radiologic response in 26 patients with HCC who were not surgical candidates and were treated with SBRT between 2005 and 2008.[119,] Eligibility criteria included solitary tumors of 6 cm or less or up to 3 lesions with cumulative diameters of 6 cm or less, and well-compensated cirrhosis. All patients had imaging before, at 1 to 3 months, and every 3 to 6 months after SBRT. Patients received 3 to 5 fractions of SBRT. Median SBRT dose was 42 Gy (range, 24-48 Gy). Median follow-up was 13 months. Per RECIST, 4 patients had a complete response, 15 had a partial response, and 7 achieved stable disease at 12 months. One patient with stable disease experienced progression marginal to the treated area. The overall best response rate (complete response plus partial response) was 73%. In comparison, using the European Association for the Study of the Liver criteria, 18 of 26 patients had 50% or more nonenhancement at 12 months. Thirteen of 18 demonstrated 100% nonenhancement, being greater than 50% in 5 patients. Kaplan-Meier 1- and 2-year survival estimates were 77% and 60%, respectively. SBRT is an effective therapy for patients with HCC with an overall best response rate (complete response plus partial response) of 73%.

Andolino et al (2011) evaluated the safety and efficacy of SBRT for the treatment of primary HCC.[120,] From 2005 to 2009, 60 patients with liver-confined HCC were treated with SBRT (36 CTP

class A, 24 CTP class B). Median number of fractions, dose per fraction, and total dose were 3 Gy, 14 Gy, and 44 Gy, respectively, for those with CPT class A cirrhosis and 5 Gy, 8 Gy, and 40 Gy, respectively, for those with CPT class B. All patients' records were reviewed, and treatment response was scored according to RECIST v.1.1. Toxicity was graded using the Common Terminology Criteria for Adverse Events v.4.0. Local control, time to progression, PFS, and OS were calculated according to the Kaplan-Meier method. Median follow-up time was 27 months, and median tumor diameter was 3.2 cm. The 2-year local control, PFS, and OS rates were 90%, 48%, and 67%, respectively, with a median time to progression of 47.8 months. Subsequently, 23 patients underwent a transplant, with a median time to transplant of 7 months. There were no nonhematologic toxicities at grade 3 or higher. Thirteen percent of patients experienced an increase in hematologic/hepatic dysfunction greater than 1 grade, and 20% experienced progression in CTP class within 3 months of treatment. The authors concluded that SBRT is a safe, effective, noninvasive option for patients with HCC of 6 cm or less and that SBRT should be considered when bridging to transplant, or as definitive therapy for patients ineligible for transplant.

Kwon et al (2010) evaluated the long-term effect of SBRT for primary HCC in 42 patients ineligible for local ablation therapy or surgical resection.[121,] Median tumor volume was 15.4 mL, and the median follow-up duration was about 29 months. Complete response for the in-field lesion was initially achieved in 59.6% and partial response in 26.2% of patients. Hepatic out-of-field progression occurred in 18 (42.9%) patients and distant metastasis developed in 12 (28.6%) patients. One- and 3-year OS rates were 92.9% and 58.6%, respectively. In-field PFS at 1 and 3 years was 72.0% and 67.5%, respectively. Patients with smaller tumors had better in-field PFS and OS rates (<32 cm^3 vs ≥ 32 cm^3, $p<0.05$). No major toxicity was encountered, but 1 patient died with extrahepatic metastasis and radiation-induced hepatic failure.

Liver Oligometastases

The liver is the most common site of metastatic spread of colorectal cancer. Evidence has shown that surgical resection of limited liver metastases can result in long-term survival in select patients. However, only 10% to 20% of patients with metastatic colorectal cancer to the liver are surgical candidates. In patients who are not candidates for surgery, a variety of locally ablative techniques have been developed, the most common of which are RFA and TACE.

Noncomparative Studies

The RSSearch® Patient Registry is an international multi-platform research and data sharing registry aimed at generating peer-reviewed publications and increasing collaboration among the diverse clinical specialties, hospitals, and industries participating in SRS and SBRT. The registry is organized and managed by the Radiosurgery Society® which is a multi-disciplinary non-profit organization of surgeons, radiation oncologists, physicists, and allied professionals. Mahadevan et al (2018) reported on patients with liver metastases treated with SBRT identified in the registry.[122,] A total of 427 patients with 568 liver metastases from 25 academic and community-based centers were included. Median age was 67 years (31-91 years). Colorectal adenocarcinoma (CRC) was the most common primary cancer and 73% of patients received prior chemotherapy. Median tumor volume was 40 cm3 (1.6-877 cm3), median SBRT dose was 45 Gy (12-60 Gy) delivered in a median of 3 fractions. Smaller tumor volumes (< 40 cm3) and higher radiation dose were correlated with improved local control and OS. At a median follow-up of 14 months (1-91 months), the median OS was 22 months. Median OS differed on the basis of the primary malignancy; it was greater for patients with CRC (27 months), breast (21 months) and

gynecological (25 months) metastases compared to lung (10 months), other gastrointestinal (18 months) and pancreatic (6 months) primaries ($p < 0.0001$). Local control was not affected by tumor histology.

Case Series

There are three relatively large series reporting on SBRT and liver metastases. Yuan et al (2014) reported on the single-site experience of a cohort of patients with liver metastases from multiple primary sites; 56% of whom had received prior systemic therapy.[123,] Patients were considered to have a favorable prognosis with primary tumors originating from the colon, breast, or stomach, as well as sarcomas. In this group, the median OS was not reached and the 1-year and 2-year OS rates were 89.6% and 72.2%, respectively. Tables 3 and 4 summarize the characteristics and key results of these studies. Lanciano et al (2012) reported on the single-center experience with SBRT to treat patients with metastases from multiple primary sites.[124,] The patients were heavily pretreated with 87% having had prior systemic chemotherapy for treatment of liver metastases or liver tumor and 37% having had prior liver-directed therapy. These therapies included surgical resection, chemoembolization, RFA, photodynamic therapy, or previous EBRT. Four patients had more than one prior liver-directed treatment. Chang et al(2011) studied outcomes of SBRT in a pooled patient cohort from 3 institutions with colorectal liver metastases.[125,] Patients were included if they had 1 to 4 lesions and 27 (43%) had been treated with 2 or more chemotherapy regimens prior to SBRT.

Table 3. Characteristics of Case Series Assessing SBRT for Liver Metastases

Study	Country	Participants	Tumor Type	Treatment Delivery	FU
Yuan et al (2014)[123,]	1 site in China	57 patients (80 lesions)	Mixed[d]	Median total dose, 42 Gy (range, 39-54 Gy) in 3 fractions (range, 3-7 fractions)	2006-2011 Median FU, 20.5 mo (range, 1-4 mo)
Lanciano et al (2012)[124,]	1 site in U.S.	30 patients[a] (41 lesions)	Mixed[b]	>79.2 Gy10 or <79.2 Gy10[c]	2007-2009 Median FU, 22 mo (range, 10-40 mo)
Chang et al (2011)[125,]	3 sites in U.S. and Canada	65 patients (102 lesions)	CRC	Median total dose, 41.7 Gy (range, 22-60 Gy) in 6 fractions (range, 1-6 fractions)	2003-2009 Median FU, 1.2 y (range, 0.3-5.2 y)

CRC: colorectal cancer; FU: follow-up; Gy: gray; SBRT: stereotactic body radiotherapy.
[a] Twenty-three of 30 patients had metastatic disease.
[b] CRC, breast, esophageal, gastrointestinal stromal tumor, pancreatic, non-small-cell lung cancer.
[c] Gy10: alpha/beta (a/b) ratio is a theoretical measure of a tissue's predicted response to a dose of radiation, relative to the size of the dose delivered per fraction.
[d] CRC, breast, esophageal, pancreatic, lung, ovarian, renal, sarcoma, hepatocellular, gallbladder, stomach, olfactory neuroblastoma.

Table 4. Results of Case Series Assessing SBRT for Liver Metastases

Study	Treatment	Overall Survival, %			Post-SBRT Chemotherapy ≥2 Regimens, n (%)
		12 Months	18 Months	24 Months	
Yuan et al (2014)[123,]	Median total dose, 42 Gy (range, 39-54 Gy) in 3 fractions (range, 3-7 fractions)	68.65	NR	55.9	
Lanciano et al (2012)[124,]	>79.2 Gy10 or <79.2 Gy10	73	NR	31	NR
Chang et al (2011)[125,]	Median total dose, 41.7 Gy (range, 22-60 Gy) in 6 fractions (range, 1-6 fractions)	72	55%	38	9 (14)

Gy: gray; NR: not reported; SBRT: stereotactic body radiotherapy.

These studies had relatively short follow-up times were also limited by differences in pre- and post-SBRT treatments, which might have affected treatment outcomes.

Bridge to Transplantation

The increasing prevalence of chronic liver conditions progressing to HCC such as hepatitis C virus (HCV) infection and alcoholic cirrhosis has led to an interest in the use of SBRT and other liver-directed therapies as bridge therapy to transplantation for persons who are on organ waitlists.

Mazloom et al (2014) reported on a single case of HCV-related HCC with a complex series of liver-directed therapy pre- and post-transplantation.[126,] The patient was initially treated with TACE and while awaiting transplant had recurrent disease treated with SBRT. The extirpated liver showed no signs of residual tumor at the time of transplantation. The patient subsequently developed recurrent HCC and was treated with SBRT with no clinical or imaging evidence of residual disease at 1 year after SBRT.

Table 5 summarized various case reports using SBRT alone or in combination with other therapies as a bridge to transplant.

Table 5. Case Series Assessing SBRT as Bridge to Transplant

Study	Review Period	Treatments	Participants, n	Obtained OLT, %	1-Year Survival From Time of Transplant, %
Sapisochin et al (2017)[127,]	2004-2014	· TACE · SBRT · RFA	· 36 · 99 · 244	· 83 · 79.9 · 83.2	· 83 · 75 · 75
Mannina et al (2017)[128,]	NR	· SBRT	· 38	· 100	· 77[a]
Jacob et al (2015)[112]	2008-2013	· TACE · TACE plus SBRT	· 124 · 37	· 15.5 · 12.1	· NR

NR: not reported; OLT: orthotopic liver transplantation; RFA: radiofrequency ablation; SBRT: stereotactic body radiotherapy; TACE: transcatheter arterial chemoembolization.
[a] Kaplan-Meier estimate of 3-year survival.

Section Summary: Hepatocellular Carcinoma

There are no RCTs reported on the use of SBRT for HCC. Studies have used heterogeneous treatment schedules, treatment planning techniques, patient populations, and outcome measures. The optimal dose and fractionation scheme are unknown. Although promising local control rates of 71% to 100% at 1 year have been reported, there is only retrospective reporting on the use of SBRT in conjunction with or as an alternative to established treatment modalities, including systemic therapy, RFA, and TACE. Similar short-term lesion-control rates have been reported for metastatic liver disease. Palliative treatment, including for larger lesions (>3 cm), has also been reported. The use of SBRT, either alone or in conjunction with other liver-directed therapies, is emerging as a bridge to transplant. Overall, the evidence from published literature is insufficient to determine the effect on net health outcomes. In 2018, clinical expert opinion input confirmed the lack of RCTs and reported on nonrandomized observational studies that support the use of SBRT as an alternative locoregional treatment for patients with inoperable primary hepatocellular carcinoma or metastatic lesions. Clinical input also referred to national guidelines that have rendered the same recommendation. Thus, for this specific subpopulation, SBRT would provide a clinically meaningful improvement in net health outcome.

Prostate Cancer
The following PICOTS were used to select literature to inform this review.

Patients
The population of interest are patients with primary prostate cancer.

Interventions
The intervention of interest is SBRT as an alternative to open surgical intervention, other forms of radiation therapy or as an adjunct to systemic therapy.

Comparators
The following therapies are currently being used to treat primary prostate cancer: other forms of radiation therapy, surgical interventions and/or continued systemic medical therapy.

Outcomes
The outcomes of interest are OS, symptom improvement, and treatment-related morbidity.

Timing
Follow-up of weeks to months is required to determine the effect of SBRT on local toxicity and months to years to determine the effect on tumor control.

Setting
SBRT is provided in a tertiary care setting.

Low-Risk Prostate Cancer
Nonrandomized Comparative Studies
Yu et al (2014) assessed toxicities after treatment between SBRT (n=1335) and IMRT (n=2670) as primary treatment for prostate cancer, using claims data for Medicare beneficiaries.[129,] The authors identified early-stage prostate cancer patients (age range, 66-94 years) treated from 2008 to 2011 who received IMRT (n=53841) or SBRT (n=1335) as primary treatment. SBRT patients were matched in a 2:1 manner based on potential confounders. SBRT was associated with higher rates of genitourinary (GU) toxicity. By 6 months after treatment initiation, 15.6% of SBRT patients had a claim indicative of treatment-related GU toxicity vs 12.6% of IMRT patients (OR=1.29; 95% CI, 1.05 to 1.53; p=0.009). By 12 months posttreatment, 27.1% of SBRT vs 23.2% of IMRT patients had a claim indicative of GU toxicity (OR=1.23; 95% CI, 1.03 to 1.43; p=0.01), and by 24 months after treatment initiation, 43.9% of SBRT vs 36.3% of IMRT patients had a claim indicative of GU toxicity (OR=1.38; 95% CI, 1.12 to 1.63; p=0.001). At 6 months posttreatment, there was increased gastrointestinal (GI) toxicity for patients treated with SBRT, with 5.8% of SBRT patients having had a claim indicative of GI toxicity vs 4.1% of IMRT patients (OR=1.42; 95% CI, 1.00 to 1.85; p=0.02); but at 12 and 24 months, posttreatment, there were no significant differences in GI toxicity between groups.

Katz et al (2012) examined QOL after either radical prostatectomy (n=123) or SBRT (n=216) in patients with early-stage prostate cancer.[130,] Using the Expanded Prostate Cancer Index Composite (EPIC), QOL was assessed in the following areas: urinary, sexual, and bowel function. The EPIC data from the SBRT group were compared at baseline, 3 weeks, 5, 11, 24, and 36 months with the surgery group at baseline, 1, 6, 12, 24, and 36 months. The largest differences in QOL occurred 1 to 6 months after treatment, with larger declines in urinary and sexual QOL

occurring in the surgery group, but a larger decline in bowel QOL after SBRT. The long-term urinary and sexual QOL declines remained clinically significantly lower for patients who underwent prostatectomy but not for SBRT patients.

Noncomparative Studies

Multiple cohort studies have reported outcomes for patients treated with a standard dose of SBRT or for groups of patients treated with SBRT at escalating doses.

Studies that evaluated low-risk patients treated with SBRT are summarized in Table 6.

Table 6. Select Noncomparative Cohort Series Assessing SBRT in Prostate Cancer

Study	Review Period	Sites	Patients	Risk Stage	Dose (Gy) by Fractions	bPFS % (95% CI)	Toxicity, n (%)	Follow-Up Duration (Actutimes)
King et al (2012)[131,]	2003-2009	2 in U.S.	67	Low	36.25/5	94 (85 to 102)	No grade 4	4 y
Freeman and King (2011)[132,]	2003-2005	2 in U.S.	41	Low[a]	35-36.25/5	92.7 (84.7 to 100)	No grade 4	5 y
McBride et al (2011)[133,]	2006-2008	4 in U.S.	45	Low	35-36.25/5	3-y=97.7 (NR)	7 (17) late grade 2 urinary toxicities	44.5 mo (range, 0-62 mo)

bPFS: biochemical progression-free survival; CI: confidence interval; Gy: gray; NR: not reported; PSA: prostate-specific antigen; SBRT: stereotactic body radiotherapy; TNM: tumor, node, metastasis.
[a] Low risk generally defined by TNM (T1c-T2a), PSA ≤10 ng/mL, and Gleason score 2-6.

Boike et al (2011) evaluated the tolerability of escalating doses of SBRT in the treatment of localized prostate cancer.[134,] Eligible patients included those with a prostate size of 60 cm^3 or less, and American Urological Association score 15 or less. Dose-limiting toxicity was defined as grade 3 or worse GI/GU toxicity by Common Terminology Criteria of Adverse Events (v.3). Patients completed QOL questionnaires at defined intervals. Groups of 15 patients received 45 Gy, 47.5 Gy, and 50 Gy in 5 fractions (45 total patients). Median follow-up was 30 months (range, 3-36 months), 18 months (range, 0-30 months), and 12 months (range, 3-18 months) for the 45 Gy, 47.5 Gy, and 50 Gy groups, respectively. For all patients, GI grade of 2 or more and grade 3 or more toxicity occurred in 18% and 2%, respectively, and GU grade 2 or more and grade 3 or more toxicity occurred in 31% and 4%, respectively. Mean American Urological Association scores increased significantly from baseline in the 47.5-Gy dose level (p=0.002) compared with the other dose levels, where mean values returned to baseline. Rectal QOL scores (EPIC) fell from baseline up to 12 months but trended back at 18 months. In all patients, PSA control was 100% by the nadir +2 ng/mL failure definition.

High-Risk and Mixed Population Prostate Cancer

Bolzicco et al (2013) reported outcomes from 100 patients treated with SBRT for localized prostate cancer, 41 of whom were low-risk (PSA ≤10 ng/mL or Gleason score ≤6 or tumor category T1c-T2a), 42 were intermediate-risk (PSA 10-20 ng/mL or Gleason score 7 or tumor category T2c), and 17 were high-risk (PSA >20 ng/mL or Gleason score >7 or 2 median risk factors).[135,] Twenty-seven patients received androgen deprivation therapy at the discretion of their treating urologist. Sixty-two patients had acute toxicity (within the first 1-2 weeks after

treatment): 34% had grade 1 and 12% grade 2 urinary toxicity; 27% had grade 1 and 18% grade 2 GI toxicity. Late urinary toxicity, primarily urgency, and frequency (at ³6 months posttreatment) occurred in 8% of the patients: 4% grade 1, 3% grade 2, and 1% grade 3. The 3-year biochemical PFS rate was 94.4% (95% CI, 85.3% to 97.9%).

Jabbari et al (2012) reported PSA nadir and acute and late toxicities with SBRT as monotherapy and a post-EBRT boost for prostate cancer using high-dose rate (HDR) brachytherapy fractionation.[136,] Thirty-eight patients had been treated with SBRT with a minimum follow-up of 12 months. Twenty of 38 patients were treated with SBRT monotherapy (9.5 Gy in 4 fractions), and 18 were treated with SBRT boost (9.5 Gy in 2 fractions) post-EBRT and androgen deprivation therapy. Forty-four HDR brachytherapy boost patients with disease characteristics similar to the SBRT boost cohort had their PSA nadir levels analyzed as a descriptive comparison; SBRT was well tolerated. With a median follow-up of 18.3 months (range, 12.6-43.5 months), 42% and 11% of patients had acute grade 2 GU and GI toxicity, respectively, with no grade 3 or higher acute toxicity. Two patients experienced late grade 3 GU toxicity. All patients were without evidence of biochemical or clinical progression, and favorably low PSA nadirs were observed with a current median PSA nadir of 0.35 ng/mL (range, <0.01-2.1 ng/mL) for all patients (0.47 ng/mL; range, 0.2-2.1 ng/mL, for the monotherapy cohort; 0.10 ng/mL; range, 0.01-0.5 ng/mL, for the boost cohort). With a median follow-up of 48.6 months (range, 16.4-87.8 months), the comparable HDR brachytherapy boost cohort achieved a median PSA nadir of 0.09 ng/mL (range, 0.0-3.3 ng/mL). The authors concluded that early results with SBRT monotherapy and a post-EBRT boost for prostate cancer demonstrated acceptable PSA response and minimal toxicity; PSA nadir with SBRT boost appeared comparable to those achieved with HDR brachytherapy boost.

Katz et al (2010) performed SBRT on 304 patients with clinically localized prostate cancer (211 with high-risk disease, 81 with intermediate-risk, 12 with low-risk disease): Fifty received 7 Gy in 5 fractions (total dose, 35 Gy) and 254 received 7.25 Gy in 5 fractions (total dose, 36.25 Gy).[137,] At a median 30-month (range, 26-37 months) follow-up, there were no biochemical failures for the 35-Gy dose group. Acute grade 2 urinary and rectal toxicities occurred in 4% of patients with no higher grade, acute toxicities. At a median 17-month follow-up (range, 8-27 months), the 36.25-Gy dose group had 2 low- and 2 high-risk patients fail biochemically (biopsy showed 2 low- and 1 high-risk patients were disease-free in the gland). Acute grade II urinary and rectal toxicities occurred in 4.7% and 3.6% of patients, respectively.

At 6-year follow-up, late urinary grade 2 complications were seen in 4% of patients treated with 35 Gy and 9% of patients treated with 36.25 Gy.[138,] Five late grade 3 urinary toxicities occurred in patients treated with 36.25 Gy. Late grade 2 rectal complications were seen in 2% and 5% of patients treated with 35 Gy and 36.25 Gy, respectively. Initially, bowel and urinary QOL scores decreased but returned to baseline levels. There was an overall 20% decrease in the sexual QOL score. For patients who were potent prior to SBRT, 75% remained potent. Actutimes 5-year biochemical recurrence-free survival was 97% for patients with low-risk disease, 90.7% with intermediate-risk, and 74.1% with high-risk disease.

Evaluation of Toxicity and Adverse Events

Wiegner and King (2010) published the results of the phase 2 trial (King et al [2012]) reported on sexual function in a subset of patients.[139,] A literature review for other radiation modalities assessed by patient self-reported questionnaires served as a historical comparison. Using the EPIC-validated QOL questionnaire, the sexual function of 32 consecutive patients was analyzed at

median times of 4, 12, 20, and 50 months after treatment. Median follow-up was 35.5 months (range, 12-62 months). The authors concluded that the rates of erectile dysfunction after treatment for prostate cancer with SBRT were comparable to those reported for other modalities of radiotherapy. Other noncomparative studies have reported on specific outcomes after SBRT for prostate cancer, including rates of patient-reported urinary incontinence,[140,] rectal tolerance,[141,] and health-related QOL outcomes.[142,]

Section Summary: Prostate Cancer
Evidence on the use of SBRT in prostate cancer consists primarily of single-arm assessments of acute and late toxicity and early PSA outcome data retrospectively compared with historical controls. Studies have shown promising initial results on the use of SBRT in prostate cancer with seemingly low toxicity rates. One comparative study of IMRT and SBRT from 2014 suggested higher GI and GU complication rates after SBRT; while this study had a large number of patients and attempted to control for bias using matching on observed variables, it was subject to limitations deriving outcome measures from claims data. There are no published randomized controlled trials. Longer-term follow-up would be needed to assess the effect on long-term toxicities, cancer control, and patient survival. Limited clinical input reported that the use of SBRT to treat primary prostate cancer provides biochemical control of disease (prostate specific antigen (PSA) surveillance), preserved quality of life (primarily focused on erectile dysfunction) and acceptable short-term urinary tract toxicity posttreatment. This input did not differentiate candidate patients on the basis of guideline-based risk stratification for localized prostate cancer. The evidence is insufficient to determine the effect on net health outcomes.

Pancreatic Adenocarcinoma
The following PICOTS were used to select literature to inform this review.

Patients
The population of interest are patients with pancreatic adenocarcinoma.

Interventions
The intervention of interest is SBRT as an alternative to open surgical intervention, other forms of radiation therapy or as an adjunct to systemic therapy.

Comparators
The following therapies are currently being used to treat pancreatic adenocarcinoma: other forms of radiation therapy, surgical interventions and/or continued systemic medical therapy. Radiation may be part of the treatment plan for pancreatic cancer, resectable or unresectable disease, and may be used in the adjuvant or neoadjuvant setting.

Outcomes
The outcomes of interest are OS, symptom improvement, and treatment-related morbidity.

Timing
Follow-up of weeks to months is required to determine the effect of SBRT on local toxicity and months to years to determine the effect on tumor control.

Setting
SBRT is provided in a tertiary care setting.

Zhong et al (2017) published a retrospective database analysis comparing conventional fractionated radiotherapy (CFRT) with SBRT for locally advanced primary pancreatic carcinoma.[143] Using a large hospital-based registry, the National Cancer Data Base, clinical outcomes were described in 10,534 cases (CFRT in 7819, SBRT in 631) diagnosed and treated between 2004 and 2012. To minimize the treatment selection bias, a propensity score matching method was used. A logistic regression model predicting CFRT treatment vs SBRT treatment was used to calculate propensity scores for covariates of interest. The covariates chosen were ones found to be significant in the multivariate analysis or ones thought to be clinically significant and included the following: patient age, American Joint Committee on Cancer clinical T and N staging, chemotherapy use, Charlson-Deyo Comorbidity Index score, year of diagnosis, and receipt of definitive surgery. In the multivariate analysis, treatment with SBRT was associated with significantly improved OS (HR=0.84; 95% CI, 0.75 to 0.93; p<0.001). With matched propensity score analysis, a total of 988 patients were analyzed, with 494 patients in each cohort. The median follow-up time was 26 months. After propensity matching, SBRT usage continued to be associated with significantly improved OS with a median survival of 13.9 months vs 11.6 months (p<0.001). Kaplan-Meier curves for the propensity-matched groups demonstrate a significantly better OS curve for the SBRT cohort (p=0.001) with 2-year OS rates of 21.7% and 16.5% for the SBRT and CFRT groups, respectively (p=0.001).

Goyal et al (2012) reported outcomes with SBRT in patients with pancreatic adenocarcinoma who were not candidates for surgical resection.[144,] A prospective database of the first 20 consecutive patients receiving SBRT for unresectable pancreatic adenocarcinomas and a neuroendocrine tumor was reviewed. Mean radiation dose was 25 Gy (range, 22-30 Gy) delivered over 1 to 3 fractions. Chemotherapy was given to 68% of patients in various schedules and timing. Patients had a mean gross tumor volume of 57.2 cm^3 (range, 10.1-118 cm^3) before SBRT. The mean total gross tumor volume reduction at 3 and 6 months after SBRT were 21% and 38%, respectively (p<0.05). Median follow-up was 14.57 months (range, 5-23 months). The overall rates of FFLP at 6 and 12 months were 88% and 65%, respectively. The probabilities of OS at 6 and 12 months were 89% and 56%, respectively. No patient had a complication related to fiducial markers placement regardless of modality. Rates of radiation-induced adverse events were: 11% for grade 1 to 2 and 16% for grade 3. No grade 4 or 5 adverse events were reported.

Rwigema et al (2011) assessed the feasibility and safety of SBRT in patients with advanced pancreatic adenocarcinoma.[145,] The outcomes of 71 patients treated with SBRT for pancreatic cancer between 2004 and 2009 were reviewed. Forty (56%) patients had locally unresectable disease, 11 (16%) patients had a local recurrence following surgical resection, 8 (11%) patients had metastatic disease, and 12 (17%) patients received adjuvant SBRT for positive margins. Median dose was 24 Gy (18-25 Gy), given in single-fraction SBRT (n=67) or fractionated SBRT (n=4). Kaplan-Meyer survival analyses were used to estimate FFLP and OS rates. Median follow-up among surviving patients was 12.7 months (4-26 months). Median tumor volume was 17 mL (range, 5.1-249 mL). Overall FFLP rates at 6 months and 1 year were 71.7% and 48.5%, respectively. Among those with macroscopic disease, FFLP was achieved in 77.3% of patients with tumor size less than 15 mL (n=22), and 59.5% for tumor size of 15 mL or more (n=37) (p=0.02). FFLP was achieved in 73% following 24 to 25 Gy and 45% with 18 to 22 Gy (p=0.004). Median OS was 10.3 months, with 6-month to 1-year OS rates of 65.3% to 41%, respectively. Grade 1 and 2 acute and late GI toxicity were seen in 39.5% of patients. Three patients experienced acute grade 3 toxicities. SBRT is feasible, with minimal grade 3 or more toxicity. The overall FFLP rate for all patients was 64.8%, comparable to rates with EBRT.

Chang et al (2009) reported on the local control and toxicity of SBRT for patients with unresectable pancreatic adenocarcinoma.[64,] Seventy-seven patients with unresectable adenocarcinoma of the pancreas received 25 Gy in 1 fraction. Forty-five (58%) patients had locally advanced disease, 11 (14%) patients had medically inoperable disease, 15 (19%) patients had metastatic disease, and 6 (8%) patients had locally recurrent disease. Nine (12%) patients had received prior chemoradiotherapy. Sixteen (21%) patients received between 45 and 54 Gy of fractionated radiotherapy and SBRT. Various gemcitabine-based chemotherapy regimens were received by 74 (96%) patients, but 3 (4%) patients did not receive chemotherapy until they had distant failure. Median follow-up was 6 months (range, 3-31 months) and, among surviving patients, it was 12 months (range, 3-31 months). Overall rates of FFLP at 6 months and 12 months were 91% and 84%, respectively. The 6- and 12-month isolated local recurrence rates were 5% and 5%, respectively. There was no difference in the 12-month FFLP rate based on tumor location (head/uncinate, 91% vs body/tail, 86%; p=0.52). The PFS rates at 6 and 12 months were 26% and 9%, respectively. The PFS rate at 6 months was superior for patients who had nonmetastatic disease vs patients who had metastatic disease (28% vs 15%; p=0.05). OS rates at 6 and 12 months from SBRT were 56% and 21%, respectively. Four (5%) patients experienced grade 2 or greater acute toxicity. Three (4%) patients experienced grade 2 late toxicity, and 7 (9%) patients experienced grade 3 or greater late toxicity. At 6 and 12 months, the rates of grade 2 or greater late toxicity were 11% and 25%, respectively.

Section Summary: Pancreatic Cancer
Combined chemoradiotherapy plays a significant role in the treatment of locally advanced pancreatic cancer. Noncomparative observational and retrospective studies of SBRT have reported increased patient survival compared with historical data. Acute grade 3 toxicities have been reported. Limited clinical expert opinion input reported that the use of SBRT for inoperable pancreatic adenocarcinoma also referred to guideline-based recommendations for use in localized disease. The evidence is insufficient to determine the effects of the technology on health outcomes.

Primary and Metastatic Renal Cell Carcinoma
The following PICOTS were used to select literature to inform this review.

Patients
The population of interest are patients with primary and metastatic renal cell carcinoma (RCC).

Interventions
The intervention of interest is SBRT as an alternative to open surgical intervention, other forms of radiation therapy or as an adjunct to systemic therapy.

Comparators
The following therapies are currently being used to treat primary and metastatic RCC: other forms of radiation therapy, surgical interventions and/or continued systemic medical therapy. Localized renal cell carcinoma (RCC) is conventionally treated surgically. Primary RCC is treated with partial or total nephrectomy when surgery is feasible. Patients may also receive systemic therapy with tyrosine kinase inhibitor therapy and supportive care. Local ablative methods may also be an option. RCC has been considered relatively radioresistant. However, the renal parenchyma, vasculature, and collecting system are considered radiosensitive.

Outcomes
The outcomes of interest are OS, symptom improvement, and treatment-related morbidity.

Timing
Follow-up of weeks to months is required to determine the effect of SBRT on local toxicity and months to years to determine the effect on tumor control.

Setting
SBRT is provided in a tertiary care setting.

Systematic Reviews
Taunk et al (2015) reported on a systematic review and clinical opinion on the use of SBRT for spinal metastases from RCC.[146,] Important clinical outcomes discussed include the rates of vertebral compression fracture which ranged from 11% to 39% from heterogeneous studies. Preexisting mechanical instability of the spine and prior radiotherapy may be risk factors for fracture. Table 7 summarizes the series described in the systematic review.

Siva et al (2012) performed a systematic review that identified 126 patients worldwide who had been treated with SBRT for primary RCC.[147,] There were 10 studies (7 retrospective studies, 3 prospective studies) that used a wide range of techniques, doses, and dose fractionation schedules. Median or mean follow-up ranged from 9 to 57.5 months. Local control was reported as 93.9% (range, 84%-100%) and the rate of severe grade 3 or higher adverse events was 3.8% (range, 0%-19%). The systematic review concluded that SBRT for RCC could be delivered with good rates of local control and acceptable toxicity, but that evidence was insufficient to recommend a consensus for dose fractionation or technique.

Nonrandomized Studies
Yamamoto et al (2016) reported on 14 patients (11 males, 3 females) who received SBRT for RCC at a single-site between 2010 and 2014.[148] The dose constraints for planning organ at risk volume of 10-fraction SBRT were 30 Gy for patients who retained both kidneys and 26 Gy in patients with single kidneys. Significant renal atrophic change was observed at a median observation interval of 16.9 months (range, 12.0-21.8 months). No patient experienced worsening of hypertension or required hemodialysis.

Verma et al (2013) retrospectively reviewed patients receiving different radiotherapy modalities for brain metastases with or without tyrosine kinase inhibitor therapy.[149,] Among 34 patients (89 lesions), those receiving SRS and tyrosine kinase inhibitors had 6-month local control rates of 94.7% vs 73.7% in the group who received SRS without tyrosine kinase inhibitors. The difference was not statistically significant (p=0.09).

Ranck et al (2013) reported on outcomes for 18 patients with RCC with limited metastases who were treated with SBRT.[150,] The most common metastatic sites were osseous (n=11), abdominal lymph nodes (n = 10), mediastinal lymph nodes (n=7), and lung nodules (n=4). Twelve patients underwent treatment for all sites of known disease. For patients with 5 or fewer metastatic lesions, all lesions were treated; in patients with greater than 5 lesions, rapidly growing lesions or those close to vital organs were treated. In all, 39 metastatic lesions were treated, with a median of 2 lesions per patient. The 2-year lesion-control rate was 91.4% in the 12 patients who underwent treatment for all metastases, over a median follow-up of 21.3 months. However, in

these patients, 2-year freedom from new metastases was 35.7%. The OS rate was 85% at 2 years. There were no patient deaths in those who received treatment on all lesions.

Beitler et al (2004) reported outcomes in 9 patients with nonmetastatic RCC, 2 of whom had bilateral RCC.[151,] Patients were treated definitively with 40 Gy in 5 fractions using SBRT. At a median follow-up of 26.7 months, 4 of the 9 patients were alive. Survivors had a minimum follow-up of 48 months. At presentation, all 4 survivors had tumors of 3.4 cm or less in largest dimension, had clinically negative lymph nodes, and presented no clinical evidence of penetration of Gerota fascia or renal vein extension.

Table 7 summarizes additional case series evaluating SBRT for RCC-related spinal metastases.

Table 7. Selected Series Assessing SBRT for Spinal Metastases in RCC and Mixed Histologies

Study	Patients	Lesions	Histology	Dose (Gy) by Fractions	Local Control, %	Follow-Up Duration (Actutimes), mo
Sohn et al (2014)[152,]	13	13	RCC	38 (marginal dose)/1-5	83.0	12
Thibault et al (2014)[153,]	37	71	RCC	24/2	83.0	12
Balagamwala et al (2012)[154,]	57	88	RCC	15/1	71.2	12
Zelefsky et al (2012)[155,]	45	45	RCC	24/1	88.0	36
Wang et al (2012)[156,]	149	166	Mixed	27-30/3	80.5	12
Yamada et al (2008)[157,]	93	103	Mixed	24/1	90.0	15
Gerszten et al (2007)[86,]	393	500	Mixed	20 (mean)/1	88.0	21 (median)
Gerszten et al (2005)[158,]	48	60	RCC	20 (mean)/1	89.0	37 (median)

Gy: gray; RCC: renal cell carcinoma; SBRT: stereotactic body radiotherapy.

Section Summary: Renal Cell Carcinoma

The literature on the use of SBRT for RCC consists of small case series, a systematic review of case series and retrospective reviews. Generally, high rates of local control have been reported for primary RCC. Adverse effects include nephron loss and kidney shrinkage, however, avoidance of nephrectomy in patients with hypertension or solitary kidney may be desirable. Renal cell carcinoma is considered to be relatively radioresistant. Case series have reported good local control in patients with spinal metastases. There are no RCTs that have evaluated SBRT for primary RCC or metastatic lesions to the brain or spine that permit comparisons between SBRT and currently established treatment modalities for RCC. The evidence is insufficient to determine the effect on net health outcomes. Limited clinical input reported that SBRT may be appropriate for patients with primary renal cell carcinoma who are not good surgical candidates and, for relapsed or stage IV disease referred to guideline-based recommendations. Thus, for this specific subpopulation, SBRT would provide a clinically meaningful improvement in net health outcome.

Oligometastases

Brain, spinal and liver metastases have been reviewed in prior sections of the policy update. The following PICOTS were used to select literature to inform this review.

Patients
The population of interest are patients with oligometastases in the lung, adrenal glands, and bone.

Interventions
The intervention of interest is SBRT as an alternative to open surgical intervention, other forms of radiation therapy or as an adjunct to systemic therapy.

Comparators
The following therapies are currently being used to treat oligometastases in the lung, adrenal glands, and bone: other forms of radiation therapy, surgical interventions and/or continued systemic medical therapy.

Outcomes
The outcomes of interest are OS, symptom improvement, and treatment-related morbidity.

Timing
Follow-up of weeks to months is required to determine the effect of SBRT on local toxicity and months to years to determine the effect on tumor control.

Setting
SBRT is provided in a tertiary care setting.

Multiple 2012 and 2013 reviews on the use of SBRT for oligometastases summarize data on local tumor control, and in a limited subset of patients, survival, for various anatomic sites.[159,160,161,]

A long-term follow-up of a prospective study by Milano et al (2012) reported on oligometastases treated with SBRT.[162,] The authors prospectively analyzed the long-term survival, tumor control outcomes, and freedom from widespread distant metastases (FFDM) after SBRT in 121 patients with 5 or fewer clinically detectable metastases, from any primary site, metastatic to 1 to 3 organ sites, and treated with SBRT. For patients with breast cancer, median follow-up was 4.5 years (7.1 years for 16/39 patients alive at the last follow-up visit). The 2-year OS, FFDM, and local control rates were 74%, 52%, and 87%, respectively. Six-year OS, FFDM, and local control rates were 47%, 36%, and 87%, respectively. From the multivariate analyses, the variables of bone metastases (p=0.057) and 1 vs more than 1 metastasis (p=0.055) were associated with a 4-fold and 3-fold reduced hazard of death, respectively. None of the 17 bone lesions from breast cancer recurred after SBRT vs 10 of 68 lesions from other organs (p=0.095). For patients post–breast cancer, median follow-up was 1.7 years (7.3 years for 7/82 patients alive at the last follow-up visit). Two-year OS, FFDM, and local control rates were 39%, 28%, and 74%, respectively, and 6-year OS, FFDM, and local control rates were 9%, 13%, and 65%, respectively. For non–breast cancers, a greater SBRT target volume was significantly adverse for OS (p=0.012) and lesion local control (p<0.001). Patients, whose metastatic lesions demonstrated radiographic progression after systemic therapy but before SBRT, experienced significantly worse OS compared with patients with stable or regressing disease. The authors concluded that select patients with limited metastases treated with SBRT are long-term survivors.

Lung Oligometastases

For isolated or a few lung metastases (including <3 or <5, according to different selection criteria), the local control probability at 1 year has been reported in the range of 70% to 100%.[159,] In most series, the most common clinical presentation is a single lung metastasis. It is difficult to accurately evaluate survival estimates and clinical outcomes using SBRT for lung metastases due to the absence of randomized trials and because most phase 1 and 2 trials included heterogeneous patient populations.[159,]

It is also difficult to compare OS evidence from SBRT with that of historical surgical metastasectomy series, mainly because of difference in the clinical characteristics of patients (most referred for SBRT are felt to be inoperable due to medical comorbidities that affect OS outcomes).[159,] Data from the International Registry of Lung Metastases reported OS rates of 70% at 2 years and 36% at 5 years in patients with a single metastasis who underwent surgical metastasectomy.[163,]

Systematic Reviews

A systematic review by Siva et al (2010) on the use of SBRT for pulmonary oligometastases estimated from the largest studies included in the review a 2-year weighted OS rate of 54.5%,[164,] ranging from higher rates (84%) in a study by Norihisa et al (2008)[165,] to lower rates (39%) reported from a 2009 multi-institutional trial.[166,]

Prospective Studies

Since the publication of the Siva et al (2010) review, Osti et al (2013) reported outcomes from a prospective cohort study of SBRT for lung oligometastases.[167,] Sixty-six patients with lung oligometastases were included, most (61%) with a single pulmonary nodule. For the primary endpoint of local control, over a median follow-up of 14 months, local control rates at 1 and 2 years were 89.1% and 82.1%, respectively. OS rates at 1 and 2 years were 76.4% and 31.2%, respectively, while PFS rates at 1 and 2 years were 53.9% and 22%, respectively. Two cases of grade 3 toxicity (pneumonitis) occurred.

Adrenal Gland Oligometastases

The most frequent primary tumor that metastasizes to the adrenal glands is NSCLC. Longer OS times have been reported with resection of clinically isolated adrenal metastases compared with nonsurgical therapy, which has included locally ablative techniques, embolization, and EBRT. Few studies on the use of SBRT in adrenal metastases have been published. Local control rates at 1 year ranging from 55% to 90% have been reported, and 1-year OS rates ranging from 40% to 56% and 2-year OS ranging from 14% to 33% have been reported.[159,]

Ahmed et al (2013) reported outcomes from a single-center's experience with SBRT for treatment of metastases to the adrenal glands.[168,] Thirteen patients were included, most with lung primary tumors (n=9), with the remainder with kidney (n=2), skin (n=2), bladder (n=1), colon (n=1), and liver (n=1) as primary sites. Eleven (84.6%) patients had received prior chemotherapy since being diagnosed with metastatic disease, and 1 patient had undergone previous SBRT to bilateral psoas muscle metastases before adrenal SBRT. At the time of analysis, 8 of 13 patients were alive. Median follow-up time for living patients was 12.3 months (range, 3.1-18 months). Median survival for the 5 patients who died was 6.9 months (range, 2.1-15.2 months). Of the 12 patients evaluated for local control and distant control, 11 (91.6%) had some local response to therapy, but distant failure occurred in 6 patients at a median of 2.5 months posttreatment, leading to a

1-year distant control estimate of 55%. In an exploratory analysis, there was no difference between lung primary tumor and other primary tumor sites in terms of OS or distant control. Acute toxicity included grade 2 nausea in 2 patients, grade 2 abdominal pain in 1 patient, grade 1 fatigue in 5 patients, and grade 1 diarrhea in 1 patient.

Scorsetti et al (2012) described the feasibility, tolerability, and clinical outcomes of SBRT in the treatment of adrenal metastases in consecutive cancer patients.[169,] Between 2004 and 2010, 34 patients, accounting for 36 adrenal metastatic lesions, were treated with SBRT. All 34 patients were clinically and radiologically evaluated during and after completion of SBRT. The following outcomes were taken into account: best clinical response at any time, local control, time-to-systemic progression, time-to-local progression, OS, and toxicity. The Kaplan-Meier method was used to estimate survival; factors that could potentially affect outcomes were analyzed with Cox regression analysis. No cases of grade 3 or greater toxicity were recorded. At a median follow-up of 41 months (range, 12-75 months), 22 patients were alive. Eleven percent of lesions showed complete remission, 46% partial remission, 36% stable disease, and 7% progressed in the treated area. Local failure was observed in 13 cases and actutimes local control rates at 1 and 2 years were 66% and 32%, respectively. The median time-to-local progression was 19 months, and median survival was 22 months.

Casamassima et al (2012) retrospectively evaluated a single-institution's outcomes after hypofractionated SBRT for adrenal metastases.[170,] Between 2002 and 2009, 48 patients were treated with SBRT for adrenal metastases. Eight patients were treated with single-fraction SBRT and 40 patients with multifraction. Median follow-up was 16.2 months (range, 3-63 months). At the time of analysis, 20 of 48 patients were alive. One- and 2-year actutimes OS rates were 39.7% and 14.5%, respectively. Median interval to local failure was 4.9 months. The actutimes 1-year disease control rate was 9%; the actutimes 1- and 2-year local control rates were both 90%.

Holy et al (2011) presented initial institutional experiences with SBRT for adrenal gland metastases.[171,] Between 2002 and 2009, 18 patients with NSCLC and adrenal metastases received SBRT for the metastatic disease. Metastases were isolated in 13 patients and multiple in 5 patients. A median PFS of 4.2 months was seen in the entire patient group, with an increased PFS of 12 months in the 13 patients with isolated metastasis. After a median follow-up of 21 months, 77% of the patients with isolated adrenal metastasis achieved local control. In these patients, median OS was 23 months.

Chawla et al (2009) investigated the dosimetry and outcomes of patients undergoing SBRT for metastases to the adrenal glands.[172,] A retrospective review of 30 patients who had undergone SBRT for adrenal metastases from various primary sites, including lung (n=20), liver (n=3), breast (n=3), melanoma (n=1), pancreas (n=1), head and neck (n=1), and unknown primary (n=1), was performed. Of the 30 patients, 14 with 5 or fewer metastatic lesions (including adrenal) underwent SBRT, with the intent of controlling all known sites of metastatic disease. Sixteen patients underwent SBRT for palliation or prophylactic palliation of bulky adrenal metastases. Twenty-four patients had more than 3 months of follow-up with serial computed tomography. Of these 24 patients, 1 achieved complete remission, 15 achieved partial remission, 4 had stable disease, and 4 developed progressive disease. No patients developed symptomatic progression of their adrenal metastases. Local control was poor, and most patients developed widespread metastases shortly after treatment, with 1-year survival, local control, and distant

control rates of 44%, 55%, and 13%, respectively. No patient developed grade 2 or greater toxicity.

Bone Oligometastases

Napieralska et al (2014) reported on a series 48 cases of prostate cancer–related bone metastases (in 32 patients) treated with SBRT primarily for pain control.[173,] The size of the treated lesions ranged from 0.7 to 5.5 cm (mean, 3 cm), and 31 (65%) of the treated metastases were located in the spine. At 3-month follow-up, 17 patients had complete pain relief, 2 had partial pain relief, and 2 had no pain reduction. At the end of the follow-up period, complete pain relief was observed in 28 patients and partial pain relief in 16 patients.

Section Summary: Oligometastases

The evidence related to the use of SBRT for the management of oligometastases to multiple sites, including the lungs, adrenal glands, and bones (other than spine) consists of relatively small, noncomparative studies that confirm clinically important rates of local control. Systemic therapy is most frequently the preferred therapy for patients with metastatic disease of these selected tumor types. Published evidence is insufficient to determine the effect on net health outcomes. Limited clinical input reported that given the emergence of highly effective systemic therapies; SBRT used to treat oligoprogression has the potential for a patient to be maintained on the same line of systemic therapy, delaying the need for another line of therapy that is likely to be less effective. Clinical input also reported that SBRT may represent the singular option for some patients with oligometastatic disease that includes one or both adrenal glands in patients who are poor surgical and RFA candidates. Thus, for this specific subpopulation, SBRT would provide a clinically meaningful improvement in net health outcome.

SUMMARY OF EVIDENCE

Stereotactic Radiosurgery

For individuals who have non-neoplastic intracranial conditions (eg, arteriovenous malformations, trigeminal neuralgia), non-neoplastic neurologic conditions (eg, epilepsy, tremor and movement disorders, chronic pain), benign neoplastic intracranial lesion(s) (eg, acoustic neuromas, pituitary adenoma, meningiomas, craniopharyngioma, glomus jugulare tumors), and malignant neoplastic intracranial lesion(s) (eg, gliomas, astrocytomas, brain metastases), or uveal melanoma who receive SRS, the evidence includes randomized controlled trials (RCTs), nonrandomized retrospective cohort studies, and observational studies or case series. Relevant outcomes are overall survival (OS), symptoms, and treatment-related morbidity. General limitations of the body of evidence include a lack of trials that directly compare SRS with comparators, patient heterogeneity within and between studies, and failure to use standardized methods to collect and report outcomes (benefits and harms). There are several contextual factors to consider, such as SRS offers a noninvasive, highly precise radiotherapy alternative to surgery (particularly important for patients unable to undergo resection due to the presence of underlying comorbidities), intracranial lesions often are difficult to access surgically (and may be associated with a high-risk for devastating adverse sequelae), intracranial lesions typically are located adjacent to vital organs and structures that are highly susceptible to radiation toxicities, and the accuracy and precision of SRS in this context make this technique a viable alternative to standard, nonconformal external-beam radiotherapy. Finally, given the rarity of many of the conditions under review, direct comparative trials are unlikely.

The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome for patients with:

- arteriovenous malformations;
- trigeminal neuralgia refractory to medical management;
- acoustic neuromas;
- pituitary adenomas;
- nonresectable residual or recurrent meningiomas;
- malignant neoplastic intracranial lesion(s) (eg, gliomas, astrocytomas); and
- solitary or multiple brain metastases.

For individuals with epilepsy (primary or secondary tumor-related), the evidence for the use of SRS as a treatment for epilepsy includes case reports in primary epileptic disorders and case reports for tumor-related epilepsy. Relevant outcomes are symptoms and treatment-related morbidity. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with mesial temporal lobe epilepsy refractory to medical management, the published evidence for the use of SRS includes a pilot prospective noncomparative intervention and a single RCT comparing SRS to anterior temporal lobectomy (ATL). Relevant outcomes are symptoms and treatment-related morbidity. The RCT did not meet participant accrual targets and, thus, did not demonstrate noninferiority of SRS to ATL. Seizure remission rates between 25 and 36 months were reported on a total of 58 patients (31 in SRS arm and 27 in ATL arm). Seizure remission rates suggest that ATL (78%) has an advantage over SRS (52%) in terms of proportion with seizure remission. The published evidence for SRS in mesial temporal lobe epilepsy is insufficient. However, in 2018, clinical expert opinion input reported the less invasive nature of SRS with acceptable seizure remission rates over time may be appropriate for the specific subpopulation of patients with mesial temporal epilepsy refractory to medical management when the standard alternative treatments are not an option. Thus, for this specific subpopulation, SRS would provide a clinically meaningful improvement in net health outcome. The evidence is sufficient to determine the impact of the technology results in a meaningful improvement in the net health outcome.

For individuals with tremor and movement disorder, the evidence related to the use of SRS includes uncontrolled cohort studies, many of which reported outcomes from the treatment of tremor of varying etiologies. There is a retrospective analysis of a single-center experience. Relevant outcomes are symptoms and treatment-related morbidity. Most studies report improvements in standardized tremor scores, although few studies used a blinded evaluation of tremor score, allowing for bias in assessment. No studies comparing SRS with alternative methods of treatment or a control group were identified. Limited long-term follow-up is available, making the long-term risk-benefit ratio of an invasive therapy uncertain. Clinical expert opinion input reported systematic reviews of retrospective studies that reported a reduction in tremors after SRS but confirmed that alternative approaches to thalamotomy are appropriate. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with chronic pain syndromes refractory to standard medical and psychological treatments, the evidence includes a systematic review of noncomparative studies. Relevant outcomes are symptoms and treatment-related morbidity. Clinical expert opinion input reported that intracranial SRS for treatment of chronic pain (other than associated with trigeminal

neuralgia) was not an appropriate alternative to other surgical interventions. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals in the subgroup of uncommon benign neoplastic intracranial lesions (acoustic neuroma, pituitary adenoma, craniopharyngioma, and glomus jugulare tumors) the published evidence for the use of SRS remains limited to systematic reviews of nonrandomized observational studies, other nonrandomized observational studies, and case series. Relevant outcomes are symptoms and treatment-related morbidity. These reports would suggest that long-term outcomes of fractionated radiosurgery for these benign neoplasms are associated with good local control and, acceptable treatment-related side effects. The likelihood of high-quality systematically acquired evidence is low due to the rarity of the conditions and the published evidence is insufficient to determine the effects of the technology on health outcomes. However, in 2018, clinical expert opinion input continues to support an individualized approach to the use of SRS for these tumors with the recognition that outcomes are affected by factors such as the location of the tumor and type of SRS used (hypofractionated, fractionated or single-session treatment). Thus, for the subpopulation of patients with uncommon benign neoplastic intracranial tumors (acoustic neuroma, pituitary adenoma craniopharyngioma, and glomus jugulare tumors), SRS would provide a clinically meaningful improvement in net health outcome. The evidence is sufficient to determine the impact of the technology results in a meaningful improvement in the net health outcome.

For individuals with uveal melanoma, evidence for use of SRS is limited to case series. Relevant outcomes are overall survival, symptoms, and treatment-related morbidity. The published literature is insufficient to demonstrate improved outcomes with SRS over other accepted radiation modalities in the treatment of uveal melanoma. The condition is rare with poor clinical outcomes and treatment options. There are currently no active clinical trials to evaluate SRS to treat uveal melanoma and, therefore, there are limited prospects for accumulating additional high quality data. In 2018, clinical expert opinion input reported that the use of SRS to treat uveal melanoma could provide patients with low-risk disease (based on tumor size using the Collaborative Ocular Melanoma Study (COMS) definition of small and medium) an option to avoid or postpone enucleation with preservation of some visual acuity and functional abilities. Thus, for individuals with uveal melanoma, SRS would provide a clinically meaningful improvement in net health outcome. The evidence is sufficient to determine the impact of the technology results in a meaningful improvement in the net health outcome.

Stereotactic Body Radiotherapy

For individuals with primary and metastatic spinal or vertebral body tumors who have received prior radiotherapy who are treated with SBRT, the observational literature primarily addresses metastases that recur after prior radiotherapy. Relevant outcomes are overall survival, symptoms, and treatment-related morbidity. Repeat administration of conventional radiation therapy increases the risk of treatment-related myelopathies. Nonrandomized study results are sufficient to determine that SBRT improves outcomes (reduce pain) in patients with spinal (vertebral) tumors. In addition, in 2018, clinical expert opinion input reported that SBRT is an important treatment option for patients whose spinal tumors have had prior radiotherapy because of the ability to spare the spinal cord and escalate tumor dose. Thus, for individuals with primary or metastatic spinal or vertebral body tumors in patients who have received prior spinal radiotherapy, SBRT would provide a clinically meaningful improvement in net health outcome.

The evidence is sufficient to determine the impact of the technology results in a meaningful improvement in the net health outcome.

For individuals with non-small cell lung cancer (NSCLC) there is no direct comparative evidence for the use of SBRT compared to surgical resection in patients with stage T1 and T2a without nodal or distant disease. Relevant outcomes are overall survival, symptoms, and treatment-related morbidity. The published evidence is insufficient to determine the effect on net health outcomes. However, observational data and safety and efficacy results of an Australian randomized phase III trial of SBRT for patients with early-stage lung cancer (reported in abstract form) indicate that survival rates may be similar for these patients and those who are not candidates for surgical resection because of comorbid conditions. In 2018, clinical expert opinion input continued to support that SBRT is an important treatment option for patients who are poor surgical candidates or who do not wish to undergo surgery. Thus, for this specific subpopulation, SBRT would provide a clinically meaningful improvement in net health outcome. The evidence is sufficient to determine the impact of the technology results in a meaningful improvement in the net health outcome.

For individuals with primary hepatocellular carcinoma (HCC), there are no RCTs reported on the use of SBRT for HCC. Relevant outcomes are overall survival, symptoms, and treatment-related morbidity. Studies have used heterogeneous treatment schedules, treatment planning techniques, patient populations, and outcome measures. The optimal dose and fractionation scheme are unknown. Although promising local control rates of 71% to 100% at 1 year have been reported, there is only retrospective study reporting on the use of SBRT in conjunction with or as an alternative to established treatment modalities, including systemic therapy, radiofrequency ablation, and transarterial chemoembolization. Similar short-term lesion-control rates have been reported for metastatic liver disease. Palliative treatment, including for larger lesions (>3 cm), has also been reported. The use of SBRT, either alone or in conjunction with other liver-directed therapies, is emerging as a bridge to transplant. Overall, the evidence from published literature is insufficient to determine the effect on net health outcomes. However, clinical expert opinion input confirmed the lack of RCTs and reported on nonrandomized observational studies that support the use of SBRT as an alternative locoregional treatment for patients with inoperable primary hepatocellular carcinoma or metastatic lesions. Clinical input also referred to national guidelines that have rendered the same recommendation. Thus, for this specific subpopulation including primary or metastatic tumor of the liver that is considered inoperable, SBRT would provide a clinically meaningful improvement in net health outcome. The evidence is sufficient to determine the impact of the technology results in a meaningful improvement in the net health outcome.

For individuals with primary prostate carcinoma, the evidence on the use of SBRT consists primarily of single-arm assessments of acute and late toxicity and early prostate-specific antigen outcome data retrospectively compared with historical controls. Relevant outcomes are overall survival, symptoms, and treatment-related morbidity. Studies have shown promising initial results on the use of SBRT in prostate cancer with seemingly low toxicity rates. One comparative study of intensity-modulated radiotherapy and SBRT from 2014 suggested higher gastrointestinal and genitourinary complication rates after SBRT; while this study had a large number of patients and attempted to control for bias using matching on observed variables, it was subject to limitations deriving outcome measures from claims data. There are no published randomized controlled trials. Longer term follow-up would be needed to assess the effect on long-term toxicities, cancer

control, and patient survival. Limited clinical expert opinion input reported that the use of SBRT to treat primary prostate cancer provides biochemical control of disease (prostate-specific antigen surveillance), preserved quality of life (primarily focused on erectile dysfunction) and acceptable short-term urinary tract toxicity posttreatment. This input did not differentiate candidate patients on the basis of guideline-based risk stratification for localized prostate cancer. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with pancreatic adenocarcinoma combined chemoradiotherapy plays a significant role in the treatment of locally advanced pancreatic cancer. Relevant outcomes are overall survival, symptoms, and treatment-related morbidity. Noncomparative observational and retrospective studies of SBRT have reported increased patient survival compared with historical data. Acute, grade 3 toxicities have been reported. Limited clinical expert opinion input reported that the use of SBRT for inoperable pancreatic adenocarcinoma also referred to guideline-based recommendations for use in localized disease. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with renal cell carcinoma (RCC), the evidence for the use of SBRT consists of small case series, a systematic review of case series and retrospective reviews. Relevant outcomes are overall survival, symptoms, and treatment-related morbidity. Generally, high rates of local control have been reported for primary RCC. Adverse effects include nephron loss and kidney shrinkage, however, avoidance of nephrectomy in patients with hypertension or solitary kidney may be desirable. RCC is considered to be relatively radioresistant. Case series have reported good local control in patients with spinal metastases. There are no RCTs that have evaluated SBRT for primary RCC or metastatic lesions to the brain or spine that permit comparisons between SBRT and currently established treatment modalities for RCC. The published evidence is insufficient to determine that the impact of the technology results in an improvement in the net health outcome. Limited clinical expert opinion input reported that SBRT may be appropriate for patients with primary renal cell carcinoma who are not good surgical candidates and, for relapsed or stage IV disease referred to guideline-based recommendations. Thus, for this specific subpopulation, SBRT would provide a clinically meaningful improvement in net health outcome. The evidence is sufficient to determine the impact of the technology results in a meaningful improvement in the net health outcome.

For individuals with oligometastatic disease, the evidence for the use of SBRT for the management of oligometastases at multiple sites, including the lungs, adrenal glands, and bones (other than spine or vertebral body) consists of relatively small, noncomparative studies that confirmclinically important rates of local control. Relevant outcomes are overall survival, symptoms, and treatment-related morbidity. Systemic therapy is most frequently the preferred therapy for patients with metastatic disease of these selected tumor types. The published evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome. Limited clinical expert opinion input reported that given the emergence of highly effective systemic therapies; SBRT used to treat oligoprogression maintains the patient on the same line of systemic therapy, delaying the need for another line of therapy that is likely to be less effective. Clinical input also reported that SBRT may represent the singular option for some patients with oligometastatic disease that includes one or both adrenal glands in patients who are poor surgical and RFA candidates. Thus, for this specific subpopulation, SBRT would provide a clinically meaningful improvement in net health outcome. The evidence is sufficient to

determine the impact of the technology results in a meaningful improvement in the net health outcome.

CLINICAL INPUT RECEIVED FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2018 Input

In response to requests, clinical input on stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) was received from 5 respondents, including 2 specialty society-level responses, one of which included multiple specialty societies, and 3 physician-level responses either identified by specialty societies or an academic medical center, while this policy was under review in 2018.

Evidence from clinical input is integrated within the Rationale section summaries and the Summary of Evidence.

2013 Input

In response to requests, input was received from 3 physician specialty societies (6 reviewers) and 6 academic medical centers, for a total of 12 reviewers, while this policy was under review for September 2013. Support for the use of SBRT for hepatocellular carcinoma, prostate cancer, and oligometastases, and the use of SRS for uveal melanoma was mixed.

2011 Input

In response to requests, input was received from 6 physician specialty societies (8 reviewers) and 4 academic medical centers, for a total of 12 reviewers, while this policy was under review for October 2011. There was general agreement with the policy statements for the use of SRS in treating the neoplasms/conditions listed in the policy statements. In addition, there was support to expand the policy statements on the use of SRS to include craniopharyngiomas and glomus jugulare tumors.

There was general support for the use of SBRT in spinal tumors and early stage non-small-cell lung cancer (NSCLC) and support to expand the use in the spine to include metastatic radioresistant tumors. Support for the use in primary and metastatic lesions of the liver, pancreas, adrenal, and kidney was mixed. There was little support for the use of SBRT in prostate cancer.

2008 Input

In response to requests, input was received from 2 physician specialty societies and 4 academic medical centers while this policy was under review for December 2008. The input uniformly supported use of this technology in the treatment of NSCLC and spinal tumors after prior radiotherapy. There was also support for use in some patients with liver (metastatic and primary) cancer and as first-line treatment of spinal tumors. There was little support for its use in cases of prostate cancer.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Heart Association Scientific Statement

The American Heart Association and American Stroke Association (2017) published a scientific statement on the management of brain arteriovenous malformations.[174,] The statement concludes that the available literature supports the use of stereotactic radiosurgery for small- to moderate-volume brain AVMs that are generally 12 cm^3 or less in volume or located in deep or eloquent regions of the brain.

National Comprehensive Cancer Network (NCCN) Guidelines

National Comprehensive Cancer Network (NCCN) provides guidelines for cancer treatment by site that include the use of SRS and SBRT for certain cancers.[175] Guidelines addressing SRS and SBRT are summarized in Table 8.

Table 8. Recommendations for SRS and SBRT

Cancer Site	Tumor Type	Recommendation	Version
Bone	· Chondrosarcoma · Chordoma · Progressive Ewing sarcoma · Unresectable giant cell tumor · Osteosarcoma with positive margins or relapsed progressive disease	• Consider SRS to allow high-dose therapy while maximizing normal tissue sparing (category 2A)	1.2019
CNS	· Adult low-grade infiltrative supratentorial astrocytoma/oligodendroglioma · Anaplastic gliomas/glioblastomas · Adult intracranial ependymoma · Adult medulloblastoma · Primary CNS lymphoma · Primary spinal cord tumors · Meningiomas · Limited brain metastases · Extensive brain metastases · Leptomeningeal metastases · Metastatic spine tumors	• Principles of RT including consideration of SRS or SBRT are applied to each of the listed tumors (category 2A)	1.2018
Colon	· Oligometastases to liver or lung	• Resection is preferred over locally ablative treatment. However, IGRT and SBRT may be considered.	4.2018
Head and neck		• Palliative conformal RT, IMRT, SBRT should be considered in the advanced cancer care setting when curative-intent treatment is not appropriate.	2.2018
Hepatobiliary	· Hepatocellular carcinoma · Gallbladder Cancer	• Principles of locoregional therapy includes recommendations for SBRT	4.2018
Lung	· NSCLC	• SBRT (also known as SABR) • Principles of RT including consideration of SBRT/SABR are applied to multiple NSCLC stages (category 2A)	1.2019
Pancreas	· Pancreatic adenocarcinoma	• SBRT should be avoided if direct invasion of the bowel or stomach is identified on CT, MRI, and endoscopy • Definitive therapy option for locally advanced: +chemoradiation or SBRT in selected patients not candidates for combination therapy	1.2019

Cancer Site	Tumor Type	Recommendation	Version
		+induction chemotherapy followed by chemoradiation or SBRT • SBRT may be utilized in isolated recurrence:	
Prostate	· Prostate cancer	• Principles of RT identifies SBRT as acceptable in practices with appropriate technology, physics, and clinical expertise	4.2018
Kidney cancer	· Non-clear cell and clear cell renal carcinoma	• Relapse or Stage IV: Metastasectomy or SBRT or ablative techniques for oligometastatic disease	2.2019
Melanoma	· Intact extracranial metastases	Principles of RT include recommendations for use of SBRT	3.2018
Uveal melanoma		• SRS is the least often used and nonpreferred form of definitive RT for primary and recurrent intraocular tumors	1.2018
Soft tissue sarcoma	· Extremity/superficial trunk/head and neck · Retroperitoneal/intra-abdominal	• If disseminated metastases: SBRT as a palliative option (category 2A) • No recommendation identified for SBRT	2.2018
Thyroid		• Consider resection of distant metastases and/or EBRT/SBRT/IMRT/other local therapies when available for progressive and/or symptomatic metastatic lesions	1.2018

CNS: central nervous system; CT: computed tomography; EBRT: external-beam radiotherapy; IGRT: image-guided radiotherapy; IMRT: intensity-modulated radiotherapy; MRI: magnetic resonance imaging; NSCLC: non-small-cell lung cancer; RT: radiotherapy; SABR: stereotactic ablative radiotherapy; SBRT: stereotactic body radiotherapy; SRS: stereotactic radiosurgery.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 9.

Table 9. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing stereotactic radiosurgery			
Central nervous system neoplasms			
Acoustic neuroma (vestibular schwannoma)			
NCT00377156	Phase III Randomized Trial of the Role of Whole Brain Radiation Therapy in Addition to Radiosurgery in Patients With One to Three Cerebral Metastases	213	Oct 2014 (ongoing)
NCT02055859	Randomized Phase II Study Comparing Stereotactic Body Radiotherapy (SBRT) With Stereotactic Body Proton Therapy (SBPT) for Centrally Located Stage I, Selected Stage II and Recurrent Non-Small Cell Lung Cancer	102	Nov 2021
Brain metastases			
NCT01372774	Stereotactic Radiosurgery or Whole-Brain Radiation Therapy in Treating Patients With Brain Metastases That Have Been Removed by Surgery	194	Nov 2020
NCT00950001	Efficacy of Post-Surgical Stereotactic Radiosurgery for Metastatic Brain Disease: A Randomized Trial	132	Aug 2020
NCT01592968	A Prospective Phase III Randomized Trial to Compare Stereotactic Radiosurgery Versus Whole Brain Radiation Therapy for >/= 4 Newly Diagnosed Non-Melanoma Brain Metastases	100	Aug 2019
NCT01644591	A Phase II Trial to Determine Local Control and Neurocognitive Preservation After Initial Treatment With Stereotactic Radiosurgery (SRS) for Patients With >3 Melanoma Brain Metastases	49	Aug 2020

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02147028	A Randomized Phase II Trial of Hippocampal Sparing Versus Conventional Whole Brain Radiotherapy After Surgical Resection or Radiosurgery in Favourable Prognosis Patients With 1-4 Brain Metastases	84	Dec 2019
NCT01503827	Whole Brain Radiotherapy Following Local Treatment of Intracranial Metastases of Melanoma - A Randomised Phase III Trial	200	Jun 2021
Glioma			
NCT02085304	Phase I/II Randomized Prospective Trial for Newly Diagnosed GBM, With Upfront Gross Total Resection, Gliadel®, Followed by Temodar® With Concurrent IMRT Versus GK	80	Dec 2017 (ongoing)
NCT01464177	Prospective Randomized Phase II Trial of Hypofractionated Stereotactic Radiotherapy in Recurrent Glioblastoma Multiforme	40	Oct 2021
Unpublished stereotactic radiosurgery			
Central nervous system neoplasms			
Brain metastases			
NCT00280475	Randomized Phase III Trial of Postoperative Whole Brain Radiation Therapy Compared With Salvage Stereotactic Radiosurgery in Patients With One to Four Brain Metastasis: Japan Clinical Oncology Group Study (JCOG 0504)	270	Jan 2013 (completed)
NCT01535209	Phase 3 Study of Stereotactic Radiotherapy of the Postoperative Resection Cavity Versus Whole-Brain Irradiation After Surgical Resection of Single Brain Metastasis	100	Oct 2014 (unknown)
NCT02145910	Phase I Study of Vemurafenib Combined With Whole Brain Radiation Therapy (WBRT) or Radiosurgery (SRS) for Melanoma Patients With BRAF Mutation Presented With Brain Metastases	36	Jun 2019 (withdrawn)
NCT01731704	A Randomized Controlled Study of Neurocognitive Outcomes In Patients With Five Or More Brain Metastases Treatment With Radiosurgery Or Whole-Brain Radiotherapy	0	Dec 2018 (withdrawn)
Ongoing stereotactic body radiotherapy			
Non-small-cell lung cancer			
NCT02045446	Maintenance Chemotherapy Versus Consolidative Stereotactic Body Radiation Therapy (SBRT) Plus Maintenance Chemotherapy for Stage IV Non-Small Cell Lung Cancer (NSCLC): A Randomized Phase II Trial	29	Dec 2020
NCT01014130	A Randomised Phase III Trial of Highly Conformal Hypofractionated Image Guided ("Stereotactic") Radiotherapy (HypoRT) Versus Conventionally Fractionated Radiotherapy (ConRT) for Inoperable Early Stage I Non-small Cell Lung Cancer (CHISEL)	101	Dec 2020
NCT01968941	A Randomized Trial of Medically-Inoperable Stage 1 Non-small Cell Lung Cancer Patients Comparing Stereotactic Body Radiotherapy Versus Conventional Radiotherapy	324	Apr 2019
NCT01336894	A Randomized Phase III Study of Sublobar Resection (+/- Brachytherapy) Versus Stereotactic Body Radiation Therapy in High Risk Patients With Stage I Non-Small Cell Lung Cancer (NSCLC)	420	Aug 2019
NCT01725165	A Randomized Phase II Study Assessing the Efficacy of Local Consolidative Therapy for Non-Small Cell Lung Cancer Patients With Oligometastatic Disease	94	Nov 2019
NCT01622621	Randomized Phase II Trial of Stereotactic Body Radiotherapy (SBRT) Versus Sublobar Resection for High-Risk Patients With Early Stage Non-Small Lung Cancer (NSCLC)	96	Mar 2020
NCT00843726	A Phase II Randomized Study of 2 Stereotactic Body Radiation Therapy (SBRT) Regimens for Medically Inoperable Patients With Node Negative, Peripheral Non-Small Cell Lung Cancer	98	Apr 2020
Hepatocellular carcinoma			

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT01730937	Randomized Phase III Study of Sorafenib Versus Stereotactic Body Radiation Therapy Followed by Sorafenib in Hepatocellular Carcinoma	368	Jun 2020
Prostate cancer			
NCT01794403	A Randomized Study of Radiation Hypofractionation Via Extended Versus Accelerated Therapy (HEAT) For Prostate Cancer	456	Mar 2023
NCT01839994	Phase III Clinical Trial on Conventionally Fractionated Conformal Radiotherapy (CF-CRT) Versus CF-CRT Combined With High-dose-rate Brachytherapy or Stereotactic Body Radiotherapy for Intermediate and High-risk Prostate Cancer.	350	Dec 2018
NCT01737151	Study of 4-Fraction Split-Course Stereotactic Ablative Radiation Therapy of the Treatment of Patients With Low and Intermediate Risk Adenocarcinoma of the Prostate	160	Dec 2021
NCT01764646	Stereotactic Body Radiation Therapy for cT1c - cT3a Prostate Cancer With a Low Risk of Nodal Metastases (≤ 20%, Roach Index): a Novalis Circle Phase II Prospective Randomized Trial	152	Sep 2025
NCT02064036	Whole-Pelvic Radiotherapy With a Stereotactic Body Radiotherapy Boost and Long-Term Androgen Deprivation for Unfavorable-Intermediate and High Risk Localized Adenocarcinoma of the Prostate.	29	Oct 2018
NCT01508390	Phase II Study of Hypofractionated Stereotactic Body Radiation Therapy as a Boost to the Prostate for Treatment of Localized, Non-Metastatic, High Risk Prostate Cancer	30	Dec 2020
NCT02470897	A Phase I/II Study of Stereotactic Body Radiotherapy (SBRT) for Prostate Cancer Using Simultaneous Integrated Boost and Urethral-Sparing IMRT Planning	160	Dec 2024
NCT01985828	Prospective Evaluation of CyberKnife as Monotherapy or Boost Stereotactic Body Radiotherapy for Intermediate or High Risk Localized Prostate Cancer	72	Dec 2026
NCT03367702	Phase III IGRT and SBRT vs IGRT and Hypofractionated IMRT for Localized Intermediate Risk Prostate Cancer	606	Dec 2028
Kidney cancer			
NCT02138578	A Phase II Randomized Trial Comparing Stereotactic Body Radiation Therapy to Radiofrequency Ablation for the Treatment of Localized Renal Cell Carcinoma (RCC)	110	Feb 2019
Breast cancer			
NCT02089100	Multicentric Phase III Trial of Superiority of Stereotactic Body Radiation Therapy in Patients With Metastatic Breast Cancer in First-line Treatment	280	Feb 2020
Melanoma			
NCT01416831[a]	Phase II Randomized Study of High Dose Interleukin-2 Versus Stereotactic Body Radiation (SBRT) and High Dose Interleukin-2 (IL-2) in Patients With Metastatic Melanoma	43	Oct 2018 (ongoing)
Oligometastases			
NCT01429493	Biological Image Guided Antalgic Stereotactic Body Radiotherapy of Bone Metastases: a Randomized Phase II/III Trial	120	Dec 2015 (ongoing)
NCT00922974	Phase II/III Study of Image-Guided Radiosurgery/SBRT for Localized Spine Metastasis	339	Jan 2022
NCT01849510	Efficacy of Dose Intensified Radiotherapy of Spinal Metastases of Solid Tumors by Dose Increased, Homogeneous Radiation of Vertebral Body and Simultaneous Application of Stereotactic Boost	155	Apr 2019
NCT01965223	Stereotactic Ablative Fractionated Radiotherapy Versus Radiosurgery for Oligometastatic Neoplasia to the Lung: A Randomised Phase II Trial	84	Jan 2020
Unpublished stereotactic body radiotherapy			
NCT01511081	Randomized Phase II Study Comparing Stereotactic Body Radiotherapy (SBRT) With Stereotactic Body Proton Therapy	21	Oct 2016 (terminated)

NCT No.	Trial Name	Planned Enrollment	Completion Date
	(SBPT) for Centrally Located Stage I, Selected Stage II and Recurrent Non-Small Cell Lung Cancer		
NCT02070419	Trans-Arterial Chemo-Embolization (TACE) vs TACE Plus Stereotactic Body Radio Therapy (SBRT) in the Treatment of Hepatocellular Carcinoma (HCC)	0	Nov 2014 (withdrawn)
NCT01233544	The International Liver Tumor Group RAS-trial Radiofrequency Ablation Versus Stereotactic Body Radiation Therapy for Colorectal Liver Metastases: A Randomized Trial	300	Dec 2014 (terminated)
NCT02167633	A Randomized Trial of Stereotactic Radiosurgery Versus Decompressive Surgery Followed by Postoperative Radiotherapy in Metastatic Spinal Cord Compression	130	Dec 2017

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

32701	Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (photon or particle beam), entire course of treatment (Effective 01-01-2013)
61781	Stereotactic computer-assisted (navigational) procedure; cranial, intradural (List separately in addition to code for primary procedure)
61782	Stereotactic computer-assisted (navigational) procedure; cranial, extradural (List separately in addition to code for primary procedure)
61783	Stereotactic computer-assisted (navigational) procedure; spinal (List separately in addition to code for primary procedure)
61796	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 simple cranial lesion
61797	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, simple (List separately in addition to code for primary procedure)
61798	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 complex cranial lesion
61799	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, complex (List separately in addition to code for primary procedure)
61800	Application of stereotactic headframe for stereotactic radiosurgery (List separately in addition to code for primary procedure)
63620	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion
63621	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional spinal lesion (List separately in addition to code for primary procedure)

77371	Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cerebral lesion(s) consisting of 1 session; multi-source Cobalt 60 based
77372	Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cerebral lesion(s) consisting of 1 session; linear accelerator based
77373	Stereotactic body radiation therapy, treatment delivery per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions
77432	Stereotactic radiation treatment management of cerebral lesion(s) (complete course of treatment consisting of one session)
77435	Stereotactic body radiation therapy, treatment management, per treatment course, to one or more lesions, including image guidance, entire course not to exceed 5 fractions
G0339	Image-guided robotic linear accelerator-based stereotactic radiosurgery, complete course of therapy in one session or first session of fractionated treatment.
G0340	Image-guided robotic linear accelerator based stereotactic radiosurgery, delivery including collimator changes and custom plugging, fractionated treatment, all lesions, per session, second through fifth sessions; maximum five sessions per course of treatment.

ICD-10 Diagnoses

C22.0	Liver cell carcinoma
C22.1	Intrahepatic bile duct carcinoma
C22.2	Hepatoblastoma
C22.3	Angiosarcoma of liver
C22.4	Other sarcomas of liver
C22.7	Other specified carcinomas of liver
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
C47.0	Malignant neoplasm of peripheral nerves of head, face and neck
C49.0	Malignant neoplasm of connective and soft tissue of head, face and neck
C61	Malignant neoplasm of prostate
C69.01	Malignant neoplasm of right conjunctiva
C69.02	Malignant neoplasm of left conjunctiva
C69.11	Malignant neoplasm of right cornea
C69.12	Malignant neoplasm of left cornea
C69.21	Malignant neoplasm of right retina
C69.22	Malignant neoplasm of left retina
C69.31	Malignant neoplasm of right choroid
C69.32	Malignant neoplasm of left choroid
C69.41	Malignant neoplasm of right ciliary body
C69.42	Malignant neoplasm of left ciliary body

C69.51 Malignant neoplasm of right lacrimal gland and duct
C69.52 Malignant neoplasm of left lacrimal gland and duct
C69.61 Malignant neoplasm of right orbit
C69.62 Malignant neoplasm of left orbit
C69.81 Malignant neoplasm of overlapping sites of right eye and adnexa
C69.82 Malignant neoplasm of overlapping sites of left eye and adnexa
C69.91 Malignant neoplasm of unspecified site of right eye
C69.92 Malignant neoplasm of unspecified site of left eye
C70.0 Malignant neoplasm of cerebral meninges
C70.1 Malignant neoplasm of spinal meninges
C71.0 Malignant neoplasm of cerebrum, except lobes and ventricles
C71.1 Malignant neoplasm of frontal lobe
C71.2 Malignant neoplasm of temporal lobe
C71.3 Malignant neoplasm of parietal lobe
C71.4 Malignant neoplasm of occipital lobe
C71.5 Malignant neoplasm of cerebral ventricle
C71.6 Malignant neoplasm of cerebellum
C71.7 Malignant neoplasm of brain stem
C71.8 Malignant neoplasm of overlapping sites of brain
C71.9 Malignant neoplasm of brain, unspecified
C72.0 Malignant neoplasm of spinal cord
C72.1 Malignant neoplasm of cauda equina
C79.31 Secondary malignant neoplasm of brain
C79.32 Secondary malignant neoplasm of cerebral meninges
C79.49 Secondary malignant neoplasm of other parts of nervous system
D07.5 Carcinoma in situ of prostate
D32.0 Benign neoplasm of cerebral meninges
D32.1 Benign neoplasm of spinal meninges
D33.3 Benign neoplasm of cranial nerves
D33.4 Benign neoplasm of spinal cord
D35.2 Benign neoplasm of pituitary gland
D35.3 Benign neoplasm of craniopharyngeal duct
D40.0 Neoplasm of uncertain behavior of prostate
D42.0 Neoplasm of uncertain behavior of cerebral meninges
D42.1 Neoplasm of uncertain behavior of spinal meninges
D43.0 Neoplasm of uncertain behavior of brain, supratentorial
D43.1 Neoplasm of uncertain behavior of brain, infratentorial
D43.4 Neoplasm of uncertain behavior of spinal cord
E22.0 Acromegaly and pituitary gigantism
E24.0 Pituitary-dependent Cushing's disease
E24.2 Drug-induced Cushing's syndrome
E24.3 Ectopic ACTH syndrome
E24.8 Other Cushing's syndrome
E34.4 Constitutional tall stature
G50.0 Trigeminal neuralgia
Q28.2 Arteriovenous malformation of cerebral vessels
Q28.3 Other malformations of cerebral vessels

REVISIONS

09-25-2007	Created two policies from the one Stereotactic Radiosurgery policy entitled: 1. Stereotactic Radiosurgery other than CyberKnife ▪ Policy section the same as previous Stereotactic Radiosurgery policy 2. Stereotactic Radiosurgery and Radiotherapy – CyberKnife ▪ In Policy section added the following indication: 12. Pulmonary malignancies with at least one of the following characteristics: a. Medically inoperable early stage non-small cell lung cancer (T1 and T2) 5 cm or less in size b. Radioresistant histological subtypes that are not amenable to conventional radiation therapy c. Oligometastatic disease (no more than 5 metastases) deep in the parenchyma and not readily accessible by surgery d. Metastases near vital structures e. Focally persistent or recurrent stage II or III non-small cell lung cancer after prior chemoradiation
06-26-2008	Created one policy entitled Stereotactic Radiosurgery and Radiotherapy from two policies: 1. Stereotactic Radiosurgery other than CyberKnife, and 2. Stereotactic Radiosurgery and Radiotherapy – CyberKnife The policy language was combined into one policy.
01-01-2009	In Coding section: ▪ Removed CPT code 61793 as code was deleted by CPT for 2009. ▪ Added new 2009 CPT codes 61796, 61797, 61798, 61799, 61800, 63620, 63621.
06-16-2009	In Policy section: ▪ On #5 added "indolent or" to read, "Solitary or multiple brain metastases (initial treatment or treatment of recurrence for patients having good performance status and indolent or no active systemic disease)" ▪ On #12 removed "(e.g. CyberKnife)" In Coding section: ▪ Added CPT code 61795. ▪ Added Diagnosis codes 132.3, 162.4, 162.5, 162.8, 162.9
02-25-2011	In Coding section: ▪ Added CPT codes 61781, 61782, 61783 ▪ Removed CPT code 61795
01-15-2013	In the Coding section: ▪ Added CPT code 32701 (Effective 01-01-2013)
03-27-2014	Updated Description section.
	In Policy section: ▪ Removed Item A, 9, "Uveal melanoma" ▪ In Item B, added "treatment of uveal melanoma" to read "All other uses of stereotactic radiosurgery are considered experimental / investigational including, but not limited to, treatment of chronic pain, treatment of uveal melanoma,…"
	Added Rationale section.
	In Coding section: ▪ Added ICD-10 Diagnosis *(Effective October 1, 2014)*
	Updated Reference section.

01-21-2016	Title of policy revised; was previously entitled "Stereotactic Radiosurgery and Radiotherapy."
	Updated Description section.
	In Policy section: ▪ In Item A, removed "(single fraction) and/or stereotactic radiation therapy (multiple fractions) is a viable option for treatment of tumors up to about 5 cm in greatest dimension. There are a number of devices which are designed and licensed for this application. These include GammaKnife, CyberKnife, and radiosurgically configured linear accelerators. This technology is now applied to lesions throughout the body. The following is a current list of appropriate sites and diseases." and added "using a gamma ray or linear accelerator (LINAC) unit may be considered medically necessary for the following indications:" to read, "Stereotactic radiosurgery using a gamma ray or linear accelerator (LINAC) unit may be considered medically necessary for the following conditions:" ▪ In Item A 3, removed "(Cushing's disease or acromegaly)" ▪ In Item A 5, removed "(initial treatment or treatment of recurrence for patients" and added "in patients" and "defined as extracranial disease that is stable or in remission) (see Policy Guidelines)" to read, "Solitary or multiple brain metastases in patients having good performance status and indolent or no active systemic disease (defined as extracranial disease that is stable or in remission) (See Policy Guidelines);" ▪ Removed Items 8-11. ▪ Added Item A 12, "Craniopharyngiomas;" ▪ Added Item A 13, "Glomus jugulare tumors." ▪ Added Item B, "Stereotactic body radiotherapy may be considered medically necessary for the following indications: 1. Patients with stage T1 or T2a non-small-cell lung cancer (not >5 cm) showing no nodal or distant disease and who are not candidates for surgical resection; 2. Spinal or vertebral body tumors (metastatic or primary) in patients who have received prior radiotherapy; 3. Spinal or vertebral metastases that are radioresistant (e.g., renal cell carcinoma, melanoma, sarcoma)." ▪ Added Item C, "When stereotactic radiosurgery or stereotactic body radiotherapy are performed using fractionation (defined in Policy Guidelines) for the medically necessary indicates described above, it may be considered medically necessary." ▪ In Item D (previously Item B), removed "For these applications, there is a lack of studies regarding the safety and effectiveness of radiosurgery in comparison with standard therapies." and added "treatment of seizures," and "tremor," to read, "All other uses of stereotactic radiosurgery are considered experimental / investigational including, but not limited to, treatment of seizures, treatment of chronic pain, treatment of uveal melanoma, tremor, psychoneurosis, epilepsy, Parkinson's and other movement disorders, and the treatment of functional disorders other than trigeminal neuralgia." ▪ Added Item E, "Stereotactic body radiotherapy is experimental / investigational for primary and metastatic tumors of the liver, pancreas, kidney, adrenal glands, and prostate except as outlined in the policy statements above." ▪ Added Policy Guidelines.
	Updated Rationale section.
	In Coding section: ▪ Removed HCPCS codes G0173 and G0251.
	Updated References section.
12-20-2017	Updated Description section.
	In Policy section: ▪ Added Item B 4, "As a palliative treatment for individuals with specific liver-related symptoms due to tumor bulk (eg, pain) from any primary or metastatic hepatic tumor;"

	▪ Added Item B 5, "Patients with low or intermediate risk prostate cancer (see Policy Guidelines) ▪ In Policy Guidelines, added new Item 4.
	Updated Rationale section.
	In Coding section: ▪ Removed ICD-9 codes. ▪ Added ICD-10 codes: C22.0, C22.1, C22.2, C22.3, C22.4, C22.7, C61, D07.5, D40.0.
	Updated References section.
03-27-2019	Updated Description section.
	In Policy section: ▪ Removed Item A 6, "Primary malignancies of the central nervous system (CNS), including, but not limited to, high-grade gliomas (initial treatment or treatment of recurrence)" and replaced with "Malignant neoplastic intracranial lesion(s) (eg, gliomas, astrocytomas)". ▪ Added new Item A 10, "Mesial temporal lobe epilepsy refractory to medical management when standard alternative surgery is not an option." ▪ In Item B 1, removed "a" and "5" and added "7" to read, "Patients with stage T1 or T2 non-small-cell lung cancer (not >7 cm) showing no nodal or distant disease and who are not candidates for surgical resection". ▪ Added new Item B 5, "Primary or metastatic tumors of the liver as an alternative locoregional treatment for patients with inoperable primary or metastatic lesions". ▪ Added new Item B 6, "Primary renal cell carcinoma in patients who are not good surgical candidates or metastatic renal cell carcinoma". ▪ Added new Item B 7, "Oligometastasis involving lung, adrenal glands, and bone (other than spine or vertebral body)". ▪ In Item D, removed "All other uses of", "are", "seizures, treatment of", "treatment of uveal melanoma" and added "is", "for other applications", and "the" to read, "Stereotactic radiosurgery is considered experimental / investigational for other applications including, but not limited to, the treatment of chronic pain, tremor, and the treatment of functional disorders other than trigeminal neuralgia." ▪ In Item E, removed "primary and metastatic tumors of the liver", "kidney, adrenal glands, and" and added "adenocarcinoma" and "cancer, and other conditions" to read, "Stereotactic body radiotherapy is experimental / investigational for pancreatic adenocarcinoma, prostate cancer, and other conditions except as outlined in the policy statements above."
	Updated Rationale section.
	Updated References section.

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