Stereotactic Radiosurgery (SRS) using a gamma ray or linear accelerator (LINAC) unit may be considered **medically necessary** for any of the following indications:

- Acoustic neuromas
- Arteriovenous malformations
- Craniopharyngiomas
- Glomus jugulare tumors
- Mesial temporal lobe epilepsy refractory to medical management when standard alternative surgery is not an option
- Nonresectable, residual, or recurrent meningiomas
- Pituitary adenomas
- Malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas)
- Solitary or multiple brain metastases in patients having good performance status and no active systemic disease (defined as extracranial disease that is stable or in remission) (see Policy Guidelines section)
- Trigeminal neuralgia refractory to medical management
- Uveal melanoma

Stereotactic body radiotherapy (SBRT) may be considered **medically necessary** for any of the following indications:

- Patients with stage T1 or T2a non-small-cell lung cancer (not greater than 5 cm) showing no nodal or distant disease and who are not candidates for surgical resection
- Spinal or vertebral body tumors (metastatic or primary) in patients who have received prior spinal radiotherapy
- Spinal or vertebral metastases that are radioresistant (e.g., renal cell carcinoma, melanoma, sarcoma)
- Patients with low or favorable intermediate risk prostate cancer (see Policy Guidelines section)
- Pancreatic carcinoma, in 3 to 5 fractions, with total doses of 30 to 45 Gray (Gy) in patients with either of the following conditions:
  - Unresectable or locally advanced disease
  - Recurrent disease to the pancreatic bed
- Primary or metastatic tumors of the liver as an alternative locoregional treatment for patients with inoperable primary or metastatic lesions
- Primary renal cell carcinoma in patients who are not good surgical candidates or metastatic renal cell carcinoma
- Oligometastases involving lung, adrenal glands and bone (other than spine or vertebral body)

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

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

Stereotactic body radiotherapy is considered **investigational** for primary and metastatic tumors of the liver, kidney, adrenal glands, prostate and other conditions except as outlined in the policy statements above.
Stereotactic body radiotherapy is considered *investigational* for *any* of the following for the treatment of pancreatic adenocarcinoma:
- As neoadjuvant therapy in resectable or borderline resectable tumors
- As adjuvant therapy in resected disease (i.e., treatment to the tumor bed)
- For palliative treatment
- If there is direct invasion of the bowel or stomach

**Policy Guidelines**

**Radiation Source**

This evidence review 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 in Blue Shield of California Medical Policy: Charged-Particle (Proton or Helium Ion) Radiotherapy for Neoplastic Conditions.

**Number of Lesions**

A 1995 Blue Cross Blue Shield Association Technology Evaluation Center (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.

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

**Fractionation**

Fractionated SRS refers to SRS or SBRT performed more than once on a specific site.

SRS is most often single-fraction treatment; however, multiple fractions may be necessary when lesions are near critical structures.

SBRT is commonly delivered over 3 to 5 fractions.

**Prostate Cancer Gleason Score**

Low risk prostate cancer is defined as: Gleason score less than or equal to 6, prostate specific antigen less than 10 ng/mL and stage T1c or less.

Favorable intermediate risk prostate cancer is defined as predominantly Gleason grade 3 (i.e., Gleason score 3+4=7), percentage of positive biopsy cores less than 50% and no more than one NCCN intermediate risk factor (Clinical tumor stage T2b or T2c, Gleason score of 7, Prostate specific antigen level of 10 to 20 ng/mL).

The regimen used for stereotactic radiotherapy of the prostate hasn’t been clearly defined, but is usually between 33.5 and 38 Gray administered over 4 to 5 fractions.

**Note:** Gray (Gy) is a derived unit of ionizing radiation dose in the International System of Units (SI). It is defined as the absorption of one joule of radiation energy per kilogram of matter.
### Criteria Defining Resectability Status

<table>
<thead>
<tr>
<th>Resectability Status</th>
<th>Arterial</th>
<th>Venous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resectable</strong></td>
<td>No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).</td>
<td>No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.</td>
</tr>
</tbody>
</table>
| **Borderline Resectable** | Pancreatic head/uncinate process:  
- Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction.  
- Solid tumor contact with the SMA of ≤180°  
- Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present as it may affect surgical planning.  
  
Pancreatic body/tail:  
- Solid tumor contact with the CA of ≤180°  
- Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some members prefer this criteria to be in the unresectable category]. | Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction.  
- Solid tumor contact with the inferior vena cava (IVC). |
| **Unresectable**     |  
- Distant metastasis (including non-regional lymph node metastasis)  
  Head/uncinate process:  
- Solid tumor contact with SMA >180°  
- Solid tumor contact with the CA >180°  
- Solid tumor contact with the first jejunal SMA branch  
  Body and tail:  
- Solid tumor contact of >180° with the SMA or CA  
- Solid tumor contact with the CA and aortic involvement | Head/uncinate process:  
- Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)  
- Contact with most proximal draining jejunal branch into SMV  
  Body and tail:  
- Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) |

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**Coding**

Coding for SRS typically consists of a series of CPT codes describing the individual steps required (e.g., medical radiation physics, clinical treatment planning, attachment of stereotactic head...
frame, treatment delivery, and clinical treatment management). The following CPT codes have been used:

**Medical Radiation Physics**
- **77399**: Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services

**Clinical Treatment Planning**
- **77299**: Unlisted procedure, therapeutic radiology clinical treatment planning

**Attachment of Head Frame**
- **61800**: Application of stereotactic head frame for stereotactic radiosurgery (List separately in addition to code for primary procedure)

**Clinical Treatment Management**
- **77432**: Stereotactic radiation treatment management of cranial lesion(s) (complete course of treatment consisting of 1 session)
  - OR: **61796-61799** for stereotactic radiosurgery of cranial lesions
  - OR: **63620-63621** for stereotactic radiosurgery of spinal lesions

These surgical CPT codes (61796-61799 and 63620-63621) are typically used by the neurosurgeon, while the concurrent treatment management performed by the radiation oncologist would be coded as 77432. The SRS surgical CPT codes are reported per lesion not to exceed 5 lesions in the cranial SRS coding or 3 lesions in the spinal SRS coding per course of treatment.

**Treatment Delivery**
The codes used for treatment delivery will depend on the energy source used, typically either photons or protons.

**Note**: Codes for treatment delivery primarily reflect the costs related to the energy source used; and not physician work.

There are 2 CPT codes specific to stereotactic radiotherapy treatment delivery:
- **77371**: Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; multi-source Cobalt 60 based
- **77372**: Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; linear accelerator based

There are also two codes specific to stereotactic body radiotherapy:
- **77373**: Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions
- **77435**: Stereotactic body radiation therapy, treatment management, per treatment course, to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions

If treatment devices such as blocks, wedges, etc. are designed and used for the procedure, CPT codes **77332-77334** will be used.

The following code is used for the medical/surgical physician's component of thoracic stereotactic body radiotherapy planning:
- **32701**: Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (photon or particle beam), entire course of treatment
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.

Related Policies

- Charged-Particle (Proton or Helium Ion) Radiotherapy for Neoplastic Conditions
- Intensity-Modulated Radiotherapy of the Breast and Lung
- Intensity-Modulated Radiotherapy of the Prostate
- Intensity-Modulated Radiotherapy: Abdomen and Pelvis
- Intensity-Modulated Radiotherapy: Central Nervous System Tumors
- Intracavitary Balloon Catheter Brain Brachytherapy for Malignant Gliomas or Metastasis to the Brain

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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 1999, is the Gamma Knife® (Elekta; 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 the FDA through the 510(k) process. Examples include the Novalis Tx® (Novalis); the TrueBeam STx (Varian Medical Systems; approved 2012; FDA product code IYE); and the CyberKnife® Robotic Radiosurgery System (Accuray; approved 1998; FDA product code MUJ). LINAC-based devices may be used for intracranial and extracranial lesions.

Rationale

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 one 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 (e.g., 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 assessment that encompasses all potential uses is beyond the scope of this evidence review. Thus, a brief introduction follows for common applications of SRS and SBRT for which published evidence has been identified in database searches.

**Literature Review**

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 and Stereotactic Body Radiotherapy

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 (i.e., 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 (e.g., 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 Randomized 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. 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 radiotherapy alone, 31 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. 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. 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. 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. Starke et al (2016) reported on 2236 patients with any AVM treated by Gamma Knife surgery, with a mean follow-up of 7 years. 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. 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. 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. 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. 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. 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. 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. 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...
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. 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 cm³ (range, 0.1-27.1 cm³), 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, e.g., 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 (i.e., 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.\textsuperscript{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 (e.g., 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 (e.g., 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. 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>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbaro (2018); ROSE</td>
<td>US, UK, India</td>
<td>14</td>
<td>2009-2015</td>
<td>Pharmaco-resistant unilateral MTLE.</td>
<td>31 SRS^3</td>
</tr>
</tbody>
</table>

ATL: anterior temporal lobectomy; MTLE: mesial temporal lobe epilepsy; RCT: randomized controlled trial; SRS: stereotactic radiosurgery;
Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

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 cm² 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Seizure Remission²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbaro (2018)</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>58</td>
</tr>
<tr>
<td>SRS</td>
<td>16/31 (52)</td>
</tr>
<tr>
<td>ATL</td>
<td>21/27 (78)</td>
</tr>
</tbody>
</table>

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. 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, 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 Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment Special Report (1998) cited 2 small studies using radiosurgery to treat epilepsy.

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. 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. 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. 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 (e.g., 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 (i.e., 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 (e.g., 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
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. 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. 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. 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. 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 one patient (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. 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. Among patients with a parkinsonian tremor, at latest follow-up...
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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. 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 1999 Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment identified 2 small reports evaluating radiosurgical thalamotomy for chronic pain.

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 (e.g., 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 (i.e., 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 (e.g., 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. 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.

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. 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. 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. 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).

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 no 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 (>70 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. 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. 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. 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. 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 cm³ (median, 3.3 cm³). 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. 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 5.18 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. 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. 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. 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 (i.e., 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 (e.g., 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. 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). 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. 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. 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. 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. 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. 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. 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). 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.

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. 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. 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. 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). 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. 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. 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. 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. 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 (e.g., >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 has 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 (e.g., brachytherapy, proton beam) were identified.

Reynolds et al (2017) retrospectively analyzed outcomes for patients undergoing Gamma Knife radiosurgery for uveal melanoma and intraocular metastases. 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. 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). 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. 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%. 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. 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.

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 (i.e., benign, metastatic, single, or multiple lesions), in a variety of locations (i.e., cervical, thoracic, lumbar, sacral), who were treated with the CyberKnife in a single-session. 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. 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. 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. 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. 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. 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=0.001), 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 FEV₁ 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 initiated—the STARS and ROSEL trials—both 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). 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. 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. 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. 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. 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.

**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. 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), 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. 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, FEV1 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. 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. 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. 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 (i.e., 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, 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 post radiation. 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.

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. 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. 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. 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. The patients who had SBRT alone either refused TACE or had hepatic arteriovenous fistulas precluding TACE.
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 (i.e., 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 cm³ (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. 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. 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 cm³ vs ≥32 cm³, 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. 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. 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. 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. 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Participants</th>
<th>Tumor Type</th>
<th>Treatment Delivery</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yuan et al (2014)</td>
<td>1 site in China</td>
<td>57 patients</td>
<td>Mixed⁴</td>
<td>Median total dose, 42 Gy (range, 39-54 Gy) in 3 fractions (range, 3-7 fractions)</td>
<td>2006-2011, Median FU, 20.5 mo (range, 1-4 mo)</td>
</tr>
<tr>
<td>Lanciano et al (2012)</td>
<td>1 site in U.S.</td>
<td>30 patients</td>
<td>Mixed⁵</td>
<td>&gt;79.2 Gy10 or &lt;79.2 Gy10⁶</td>
<td>2007-2009, Median FU, 22 mo (range, 10-40 mo)</td>
</tr>
<tr>
<td>Chang et al (2011)</td>
<td>3 sites in U.S.</td>
<td>65 patients</td>
<td>CRC</td>
<td>Median total dose, 41.7 Gy (range, 22-60 Gy) in 6 fractions (range, 1-6 fractions)</td>
<td>2003-2009, Median FU, 1.2 y (range, 0.3-5.2 y)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Overall Survival, %</th>
<th>Post-SBRT Chemotherapy ≥2 Regimens, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>12 Months</td>
<td>18 Months</td>
</tr>
<tr>
<td>Yuan et al (2014)</td>
<td>Median total dose, 42 Gy (range, 39-54 Gy) in 3 fractions (range, 3-7 fractions)</td>
<td>68.65</td>
<td>NR</td>
</tr>
<tr>
<td>Lanciano et al (2012)</td>
<td>&gt;79.2 Gy10 or &lt;79.2 Gy10</td>
<td>73</td>
<td>NR</td>
</tr>
<tr>
<td>Chang et al (2011)</td>
<td>Median total dose, 41.7 Gy (range, 22-60 Gy) in 6 fractions (range, 1-6 fractions)</td>
<td>72</td>
<td>55%</td>
</tr>
</tbody>
</table>

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. 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Review Period</th>
<th>Treatments</th>
<th>Participants, n</th>
<th>Obtained OLT, %</th>
<th>1-Year Survival From Time of Transplant, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sapisochin et al (2017)</td>
<td>2004-2014</td>
<td>TACE, SBRT, RFA</td>
<td>36, 99, 244</td>
<td>83, 79.9, 83.2</td>
<td>83, 75, 75</td>
</tr>
<tr>
<td>Mannina et al (2017)</td>
<td>NR</td>
<td>SBRT</td>
<td>38</td>
<td>100</td>
<td>77*</td>
</tr>
</tbody>
</table>

NR: not reported; OLT: orthotopic liver transplantation; RFA: radiofrequency ablation; SBRT: stereotactic body radiotherapy; TACE: transcatheter arterial chemoembolization.

* 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=5381) 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>
<thead>
<tr>
<th>Study (Year)</th>
<th>Review Period</th>
<th>Sites</th>
<th>Patients</th>
<th>Risk Stage</th>
<th>Dose (Gy) by Fractions</th>
<th>Outcome (95% CI), %</th>
<th>Toxicity, n (%)</th>
<th>Follow-Up Duration (Actu times)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freeman et al (2011)</td>
<td>2003-2005</td>
<td>2</td>
<td>41</td>
<td>Low</td>
<td>35-36.25/5</td>
<td>bPFS = 92.7 (84.7 to 100)</td>
<td>No grade 4</td>
<td>5 y</td>
</tr>
<tr>
<td>King et al (2012)</td>
<td>2003-2009</td>
<td>2</td>
<td>67</td>
<td>Low</td>
<td>36.25/5</td>
<td>bPFS = 94 (85 to 102)</td>
<td>No grade 4</td>
<td>4 y</td>
</tr>
<tr>
<td>McBride et al (2011)</td>
<td>2006-2008</td>
<td>4</td>
<td>45</td>
<td>Low</td>
<td>35-36.25/5</td>
<td>3-y bPFS = 97.7 (NR)</td>
<td>7 (17) late grade 2 urinary toxicities</td>
<td>44.5 mo (range, 0-62 mo)</td>
</tr>
</tbody>
</table>

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.

Boike et al (2011) evaluated the tolerability of escalating doses of SBRT in the treatment of localized prostate cancer. Eligible patients included those with a prostate size of 60 cm³ 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). 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 ≥6 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
Sixty-one. 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). 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. 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. 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, rectal tolerance, and health-related QOL outcomes.

**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 sufficient 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. 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. 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 cm³ (range, 10.1-118 cm³) 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. 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. 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 sufficient 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. 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. 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. 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. 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. 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. 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>
<thead>
<tr>
<th>Study (Year)</th>
<th>Patients</th>
<th>Lesions</th>
<th>Histology</th>
<th>Dose (Gy) by Fractions</th>
<th>Local Control, %</th>
<th>Follow-Up Duration (Actuatsimes, mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sohn et al (2014)</td>
<td>13</td>
<td>13</td>
<td>RCC</td>
<td>38 (marginal dose) / 1-5</td>
<td>83.0</td>
<td>12</td>
</tr>
<tr>
<td>Thibault et al (2014)</td>
<td>37</td>
<td>71</td>
<td>RCC</td>
<td>24/2</td>
<td>83.0</td>
<td>12</td>
</tr>
<tr>
<td>Balagamwala et al (2012)</td>
<td>57</td>
<td>88</td>
<td>RCC</td>
<td>15/1</td>
<td>71.2</td>
<td>12</td>
</tr>
<tr>
<td>Zelefsky et al (2012)</td>
<td>45</td>
<td>45</td>
<td>RCC</td>
<td>24/1</td>
<td>88.0</td>
<td>36</td>
</tr>
<tr>
<td>Wang et al (2012)</td>
<td>149</td>
<td>166</td>
<td>Mixed</td>
<td>27-30/3</td>
<td>80.5</td>
<td>12</td>
</tr>
<tr>
<td>Yamada et al (2008)</td>
<td>93</td>
<td>103</td>
<td>Mixed</td>
<td>24/1</td>
<td>90.0</td>
<td>15</td>
</tr>
<tr>
<td>Gerszten et al (2007)</td>
<td>393</td>
<td>500</td>
<td>Mixed</td>
<td>20 (mean)/1</td>
<td>88.0</td>
<td>21 (median)</td>
</tr>
<tr>
<td>Gerszten et al (2005)</td>
<td>48</td>
<td>60</td>
<td>RCC</td>
<td>20 (mean)/1</td>
<td>89.0</td>
<td>37 (median)</td>
</tr>
</tbody>
</table>

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 differences 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. 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. 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. A retrospective review of 30 patients who had undergone SBRT for a 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. 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.
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
The following conclusions are based on a review of the evidence, including, but not limited to, published evidence and clinical expert opinion solicited via BCBSA’s Clinical Input Process.

Stereotactic Radiosurgery
For individuals who have non-neoplastic intracranial conditions (e.g., arteriovenous malformations, trigeminal neuralgia), non-neoplastic neurologic conditions (e.g., epilepsy, tremor and movement disorders, chronic pain), benign neoplastic intracranial lesion(s) (e.g., acoustic neuromas, pituitary adenoma, meningiomas, craniopharyngioma, glomus jugulare tumors), and malignant neoplastic intracranial lesion(s) (e.g., 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) (e.g., gliomas, astrocytomas)
- 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 transcatheter 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 sufficient 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 sufficient 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 confirm clinically 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

Objective

In 2018, clinical input was sought to help determine whether the use of either stereotactic radiosurgery or stereotactic body radiotherapy for a select set of populations would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice.

Respondents

Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- American Society for Radiation Oncology (ASTRO)
- American Society for Stereotactic and Functional Neurosurgery (ASSFN) and American Association of Neurological Surgeons / Congress of Neurological Surgeons (AANS/CNS)
- David B. Shultz, MD, Ph.D., Radiation Oncology, identified by American Society of Clinical Oncology (ASCO) and Princess Margaret Cancer Centre
- Anonymous, MD, Neurology, Epilepsy, identified by American Academy of Neurology (AAN)
- Anonymous, MD, Neurosurgery, identified by an academic medical center

่อ Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by a specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the Blue Cross Blue Shield Association (BCBSA) Evidence Street® clinical input process provide review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a specialty society and/or physician member designated by a specialty society or health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA or any Blue Plan.

Clinical Input Responses

** Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Additional Comments

Individuals with epilepsy who receive stereotactic radiosurgery:

- “Radiosurgery has been shown to be of value in terms of improving epilepsy in patients with hypothalamic hamartomas, cavernomas, and other structural abnormalities such as intracranial arteriovenous malformations... In addition, in patients with mesial temporal lobe epilepsy, SRS is an accepted and worthwhile treatment option for achieving seizure remission. In addition, there may be less verbal memory impairment with SRS compared to open surgical techniques in the treatment of mesial temporal lobe epilepsy.” (ASSFN, AANS/CNS)
- “The purpose of SRS is to use a focused radiotherapy technique to ablate epileptogenic foci when seizures have become drug-resistant or medication adverse events are intolerable and to potentially avoid complications associated with surgical intervention.” (Anonymous, Neurology, Epilepsy, identified by AAN)

Individuals with tremor and movement disorders who receive stereotactic radiosurgery (SRS):

- “There have been a number of studies demonstrating the safety and efficacy of SRS for tremor and movement disorders. In a recent review by Martinez-Moreno et al (2018), tremor reductions were reported in a mean of 88% of patients in a review of more than 34 different studies (PMID 29473775). In a study spanning a 19 year experience of 73 patients treated with SRS for intractable tremor, 93.2% of patient had improvement (PMID
In a prospective trial of tremor patients, Witjas et al (2015; PMID 26446066) noted 54.2% upper limb tremor score on blinded assessment and ADL improvement of 72.2%.” (ASSFN, AANS/CNS)

- “We do not use radiosurgery to treat patients with movement disorders because we feel other methods (e.g. DBS) are more effective and safer.” (Anonymous, Neurosurgery, identified by an academic medical center)

Individuals with chronic pain or other non-neoplastic neurologic disorders other than epilepsy or tremor/movement disorder who receive SRS:

- “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 adverse events are intolerable as an alternative to other surgical interventions.” (Anonymous, Neurology, Epilepsy, identified by AAN)
- “In our practice we do not view these conditions as being indications for radiosurgery.” (Anonymous, Neurosurgery, identified by an academic medical center)

Individuals with benign neoplastic intracranial lesion(s) (craniopharyngioma, glomus jugulare tumors) who receive SRS:

- “SRS has been shown to yield excellent long term tumor control in most patients with craniopharyngiomas and glomus tumors. In a recent study by Patel et al (2018; PMID 29652232), they demonstrated 98% 5-year progression free survival of glomus tumor patients treated with SRS. This was with an acceptable toxicity profile which is important given the potential lower cranial nerve dysfunction associated with open surgical treatment of these lesions. In an international multicenter study, tumor control following SRS was achieved in 93% of glomus tumor patients (Sheehan et al, 2012; PMID 22680240). 5 year progression free survival in craniopharyngioma patients was achieved in 91.6% following SRS (PMID 20005637). In another study of 137 craniopharyngioma patients treated with SRS, progression free survival was 70% at 5 years (PMID 25434950).” (ASSFN, AANS/CNS)
- “For other benign tumors, such as craniopharyngiomas, the role for SRS is less established. Several retrospective series suggest that treatment can be delivered safely and that it is effective, likely for carefully selected patients and small tumors. In reality, almost all craniopharyngiomas undergo surgery as the primary treatment, usually more than once. Local recurrences in this setting are difficult targets for SRS given the lack of a discrete target and the proximity to sensitive structures such as the optic chiasm. On the other hand, fractionated radiotherapy carries risks, such as secondary malignancies and cognitive toxicities, which are particularly relevant for this patient population. Fractionated SRS of the type referred to in Coombs et al (2007) is fundamentally different than single or limited fraction SRS; it far more common radiotherapy used for treating craniopharyngiomas. Although I do not have any experience treating glomus tumors with SRS, there appears to be greater clinical experience with that, including several meta-analyses in addition that cited in the section summary (Shapiro, 2018; Guss, 2011); however there are no prospective studies or comparative studies of this practice that I am aware of.” (Dr. Shultz, Radiation Oncology, identified by ASCO)
- “The purpose of SRS is to use a focused radiotherapy technique to treat intracranial and other brain lesions that are relatively inaccessible surgically and which are often located in proximity to eloquent or radio-sensitive areas.” (Anonymous, Neurology, Epilepsy, identified by AAN)
- “We would consider these indications on a case-by-case basis. In some circumstances radiosurgery might be the best treatment option.” (Anonymous, Neurosurgery, identified by an academic medical center)

Individuals with malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas) who receive SRS:

- “Radiosurgery has been shown to be of therapeutic value for patients with high and low grade gliomas. In a study by Cuneo et al (PMID 21489708), concurrent radiosurgery and...
Avastin resulted in median overall survival of 10 months in recurrent malignant glioma patients. In another study of radiosurgery for glioblastoma patients, 30% of patients had an overall survival of 2 years (PMID 25594327). In a study of SRS for pilocytic astrocytomas (Trifiletti et al, 2017; PMID 28567590), SRS resulted in durable tumor control of 93% of patients treated. (ASSFN, AANS/CNS)

“I have limited experience treating malignant gliomas with stereotactic radiosurgery (SRS). With regard to grade I gliomas, the primary treatment should be surgery if the lesion is accessible. For tumors that are inaccessible, SRS is likely a reasonable treatment, however there is no high-level evidence to support that management strategy. For grade 2 or higher gliomas, SRS has mainly been used as salvage therapy. Recurrent grade II tumors often recur as a higher grade; glioblastomas (grade IV) universally recur. When these tumors recur in patients who have previously undergone large field conventional radiotherapy, SRS targeting the recurrent lesion within that prior field or outside of if it has been reported in both retrospective and prospective studies, with favorable results, albeit without a comparator arm. Such a strategy is likely beneficial in instances where the recurrence is small, well defined, and where several months have passed since the initial chemoradiotherapy. At least one trial has used SRS for the upfront treatment of glioblastomas (Pollom, 2017), but that strategy should only be employed in the context of a clinical trial.” (Dr. Shultz, Radiation Oncology, identified by ASCO)

“We use conventional radiation delivery approaches for these patients, rather than radiosurgery. The one exception would be if there was a highly localized recurrence that could be treated with radiosurgery.” (Anonymous, Neurosurgery, identified by an academic medical center)

Individuals with uveal melanoma who receive SRS:

“I have no experience treating uveal melanoma with stereotactic radiosurgery (SRS) and a review of the published literature does not reveal any findings that would lead me to a conclusion that is different from that of the evidence summary except to say that, in comparison to brachytherapy, SRS is non-invasive. In comparison to conventionally fractionated radiotherapy, SRS requires far fewer treatment visits. From these perspectives, SRS may provide more value and better quality of life for patients, but that remains untested to date as far as I am aware.” (Dr. Shultz, Radiation Oncology, identified by ASCO)

Individuals with primary or metastatic spinal or vertebral body tumors who have received prior radiotherapy who receive SBRT:

“Patients who have previous radiotherapy to the spine will not be able to receive a second course of radiotherapy using conventional technique as the risk of radiation myelopathy will be substantial. Stereotactic body radiation therapy (SBRT) is the only means by which an adequate dose of radiation can be delivered to prevent future neurologic complications from progressive disease. A pooled analysis and a systematic review showed good local control with low toxicities which would not have been possible with any other therapy. Based on the ACR Appropriateness Criteria Expert Panel in Bone Metastasis guideline in recurrent spinal metastasis and spinal cord compression, SBRT with or without surgery is regarded as one of the most appropriate treatments.” (ASTRO)

“Spinal radiosurgery has been shown to be safe and effective for patients with various types of spinal tumors. In a study of 145 consecutive spinal metastasis patients, SRS afforded local control at 1 year in 90.3% of treated spinal metastases (Tseng et al, 2018; PMID 30003994). In another systematic review of the literature, spinal radiosurgery was
shown to yield significant local control and improvement in pain in patients treated with spinal metastasis from renal cell carcinoma (Smith et al, 2017; PMID 29038086). In that study, pain relief improvements ranged from 41-95%. In addition, radiosurgery in many instances is superior to conventional radiation therapy in that tumors once considered “radioreistant” can be successfully treated with high dose conformal stereotactic xrt with an acceptable side effect profile (PMID 28577828 and 29280455)” (ASSFN, AANS/CNS)

- “I have extensive experience treating metastatic spinal tumors with stereotactic body radiotherapy (SBRT) and consider SBRT is an extremely important tool for the treatment of patients whose spinal tumors have had prior radiotherapy because of the ability to spare the spinal cord and dose escalate tumor. The key to any type of SBRT, especially with regard to metastatic lesions, is patient selection. Spine tumors that have recurred following prior radiation carry a high risk of spinal cord compression and SBRT can be used to delay or prevent that outcome. Patients who will most benefit from spine SBRT are those with greater than 3 months expected survival. The conclusion of this evidence summary is that most literature addresses metastases that have recurred after prior radiotherapy - this is not accurate. Most retrospective and prospective series have focused on SBRT as first line treatment for spine metastases, where it also has an important role. Two randomized phase III trials are currently ongoing that compare SBRT to conventional radiotherapy for the treatment of metastatic spine tumors (RTOG 0631 and CCTG SC.24). A randomized phase II trial evaluating pain response following SBRT compared to conventional radiotherapy was published this year (Sprave, 2018), reporting faster and more robust responses from SBRT.” (Dr. Shultz, Radiation Oncology, identified by ASCO)

Individuals with non-small-cell lung cancer stage T1 or T2a who are not candidates for surgical resection who receive SBRT:

- “Multiple phase II trials and studies in the US, Japan and Europe have showed that SBRT has yielded superior local control and survival with low toxicities compared to conventional radiotherapy for medically inoperable early stage non-small cell lung carcinoma. Most recently, the TROG 09.02 CHISEL, a randomized phase III trial from Australia showed that for patients with early stage lung cancer SBRT was more effective in controlling cancer growth, resulting in longer life expectancy and is just as safe as traditional radiotherapy. ASTRO guideline also establish SBRT as the standard therapy for medically inoperable early stage non-small cell lung cancer.” (ASTRO)

- “I have extensive experience treating non-small cell lung cancer with stereotactic body radiotherapy (SBRT) and consider SBRT is an extremely important tool for the treatment of patients are poor surgical candidates or do not wish to undergo surgery. There is extensive evidence that supports SBRT as resulting in equivalent outcomes to surgery, despite the fact that operable patients are almost always much healthier in general than patients treated with SBRT. Unfortunately, randomized trials have failed to accrue and there is thus no level I evidence of an advantage of one modality over the other.” (Dr. Shultz, Radiation Oncology, identified by ASCO)

Individuals with primary or metastatic tumors of the liver who receive SBRT:

- “For metastases: Mahadevan et al ‘Stereotactic Body Radiotherapy (SBRT) for liver metastasis - clinical outcomes from the international multi-institutional RSSearch® Patient Registry’ PMID 29439707 supports higher dose SBRT as having better outcomes in liver metastases.” (ASTRO)

- “For primary HCC: NCCN Hepatobiliary v3.2018 HCC-E 2 of 3 supports the use of SBRT for patients with 1 to 3 primary liver tumors, but also states is can be considered for larger lesions or more extensive disease if there is sufficient uninvolved liver.” (ASTRO)

- “I have very limited experience using stereotactic body radiotherapy for the treatment of hepatocellular carcinoma or to oligometastatic lesions. What I do know is the liver SBRT is safe and largely effective as a local therapy. It appears from the studies cited that liver SBRT for localized HCC is associated with very high rates of local control and overall survival appears limited by metastatic disease and comorbid conditions. Liver
Individuals with primary pancreatic cancer who receive SBRT:
- “NCCN Pancreas v2.2018 PANC-F 5 of 9 supports it.” (ASTRO)

Individuals with primary or metastatic renal cell carcinoma who receive stereotactic body radiotherapy
- “Patients with primary renal cell carcinoma who are not surgical candidates or with a solitary kidney are left with limited options including partial nephrectomy, probe based therapy, and stereotactic body radiotherapy (SBRT). Recent pooled data from around the globe showed that SBRT for primary renal cell carcinoma was associated with excellent local control and low toxicities. Most recently, the Japanese Ministry of Health approved SBRT for renal cell carcinoma as one of the standard treatments as of April 1, 2018 (personal communication with Professor Hiroshi Onishi from University of Yamanashi). Compared to partial nephrectomy and probe based therapy, SBRT is the most non-invasive therapy with equivalent efficacy.” (ASTRO)
- “The treatment of primary RCC with SBRT is uncommon and is currently most often performed in the context of prospective trials for inoperable patients (Siva_2018). It is experimental in comparison to, for example, the treatment of SBRT for early stage lung cancer.” (Dr. Shultz, Radiation Oncology, identified by ASCO)

Individuals with metastatic adrenal cancer who receive SBRT:
- “Plichta et al. 'SBRT to adrenal metastases provides high local control with minimal toxicity’ PMID 29204525 is one of the more recent reports that also summarizes other studies showing high local control with SBRT.” (ASTRO)
- “I have limited experience using stereotactic body radiotherapy (SBRT) for the treatment of adrenal metastases. Although several retrospective case series have been published, there are no series that have included a comparative analysis to other common forms of local therapy such as surgery or radiofrequency ablation (RFA). Undoubtedly, SBRT represents 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. The adrenal gland is sometimes a challenging target for RFA or SBRT due to its proximity to small bowel.” (Dr. Shultz, Radiation Oncology, identified by ASCO)

Individuals with primary prostate carcinoma who receive SBRT:
- ASTRO supplied the following supporting references:
  - “I have no experience using stereotactic body radiotherapy for the treatment of prostate cancer and am not an expert in the field. Level I evidence with long term follow
up will inevitably be required to determine the relative efficacy and safety of SBRT for this indication.” (Dr. Shultz, Radiation Oncology, identified by ASCO)

Individuals with oligometastases who receive SBRT:

- “With the advent of systemic targeted therapy/immunotherapy, the survival of patients with metastatic carcinoma has dramatically prolonged. In patients with limited metastases (oligometastases) or isolate progression (oligoprogression), SBRT is used to provide local control which can potentially improve survival. When SBRT is used to tackle oligoprogression, it is possible to maintain the patient on the same line of systemic therapy, delaying the need for another line of therapy which is likely to be less effective.” (ASTRO)

- “I have extensive experience using stereotactic body radiotherapy (SBRT) to treat oligometastatic disease throughout the body, particularly to the brain, bones, and lung. SBRT is an essential tool for this purpose, however the benefit of ablative therapy in the setting of oligometastatic disease is to date unproven save for specific clinical scenarios, such as lung metastasectomy in sarcoma. Many clinical trials are ongoing that will provide prospective data, including phase II randomized trials comparing SBRT to standard of care treatment (Radwan, 2017; Palma, 2012). I am aware that one of these trials will be presented in the fall of 2018 with survival data that supports the use of SBRT, but this is not yet publically available, and in the absence of that, the use of SBRT to treat oligometastatic disease is supported most strongly by phase II single arm studies (Collen, 2014; Sutera 2018) showing promising progression-free and overall survival. In the absence of level I data, patient selection is key: performance status, expected survival, availability of effective systemic treatments, and potential or expected toxicity are all important factors to consider. Ultimately, I support the use of SBRT in instances where I believe durable tumor or pain control will significantly benefit the patient.” (Dr. Shultz, Radiation Oncology, identified by ASCO)

See Appendix 1 and 2 for details.

Supplemental Information

Clinical Input 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 from Blue Cross Blue Shield Association, input was received from 3 physician specialty societies (6 reviewers) and 6 academic medical centers, for a total of 12 reviewers, in 2013. Input was provided on content related to both SRS and SBRT. 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 from Blue Cross Blue Shield Association, input was received from 6 physician specialty societies (8 reviewers) and 4 academic medical centers, for a total of 12 reviewers in 2011. Input was provided on content related to both SRS and SBRT. 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 support for the use of SBRT in spinal tumors and early-stage non-small-cell lung cancer; there was also support to expand the use of SBRT 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 from Blue Cross Blue Shield Association, input was received from 2 physician specialty societies and 4 academic medical centers in 2008. Input uniformly supported the use of this technology in the treatment of non-small-cell lung cancer 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. The statement concludes that the available literature supports the use of stereotactic radiosurgery for small- to moderate-volume brain AVMs that are generally 12 cm³ or less in volume or located in deep or eloquent regions of the brain.

National Comprehensive Cancer Network Guidelines
The National Comprehensive Cancer Network provides guidelines for cancer treatment by site that include the use of stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) for certain cancers. Guidelines addressing SRS and SBRT are summarized in Table 8.

Table 8. Recommendations for SRS and SBRT

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Tumor Type</th>
<th>Recommendation</th>
<th>Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>Chondrosarcoma</td>
<td>Consider SRS to allow high-dose therapy while maximizing normal tissue sparing (category 2A)</td>
<td>1.2019</td>
</tr>
<tr>
<td></td>
<td>Chordoma</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Progressive Ewing sarcoma</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Unresectable giant cell tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Osteosarcoma with positive margins or relapsed progressive disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>Adult low-grade infiltrative supratentorial astrocytoma/oligodendroglioma</td>
<td>Principles of RT including consideration of SRS or SBRT are applied to each of the listed tumors (category 2A)</td>
<td>1.2018</td>
</tr>
<tr>
<td></td>
<td>Anaplastic gliomas/glioblastomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adult intracranial ependymoma</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Adult medulloblastoma</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Primary CNS lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary spinal cord tumors</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Meningiomas</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Limited brain metastases</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Extensive brain metastases</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Leptomeningeal metastases</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Metastatic spine tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>Oligometastases to liver or lung</td>
<td>Resection is preferred over locally ablative treatment. However, IGRT and SBRT may be considered.</td>
<td>4.2018</td>
</tr>
</tbody>
</table>
### Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Tumor Type</th>
<th>Recommendation</th>
<th>Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>• Hepatocellular carcinoma • Gallbladder Cancer</td>
<td>• Principles of locoregional therapy includes recommendations for SBRT</td>
<td>4.2018</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• SBRT (also known as SABR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Principles of RT including consideration of SBRT/SABR are applied to multiple NSCLC stages (category 2A)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• SBRT should be avoided if direct invasion of the bowel or stomach is identified on CT, MRI, and endoscopy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Definitive therapy option for locally advanced:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>+chemoradiation or SBRT in selected patients not candidates for combination therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>+induction chemotherapy followed by chemoradiation or SBRT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• SBRT may be utilized in isolated recurrence:</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>• Pancreatic adenocarcinoma</td>
<td>• Principles of RT identifies SBRT as acceptable in practices with appropriate technology, physics, and clinical expertise</td>
<td>4.2018</td>
</tr>
<tr>
<td>Prostate</td>
<td>• Prostate cancer</td>
<td>• Principles of RT identifies SBRT as acceptable in practices with appropriate technology, physics, and clinical expertise</td>
<td>4.2018</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>• Non-clear cell and clear cell renal carcinoma</td>
<td>• Relapse or Stage IV: Metastasectomy or SBRT or ablative techniques for oligometastatic disease</td>
<td>2.2019</td>
</tr>
<tr>
<td>Melanoma</td>
<td>• Intact extracranial metastases</td>
<td>Principles of RT include recommendations for use of SBRT</td>
<td>3.2018</td>
</tr>
<tr>
<td>Uveal melanoma</td>
<td></td>
<td>• SRS is the least often used and nonpreferred form of definitive RT for primary and recurrent intraocular tumors</td>
<td>1.2018</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>• Extremity/superficial trunk/head and neck • Retroperitoneal/intra-abdominal</td>
<td>• If disseminated metastases: SBRT as a palliative option (category 2A)</td>
<td>2.2018</td>
</tr>
<tr>
<td>Thyroid</td>
<td></td>
<td>• Consider resection of distant metastases and/or EBR1/EBRT/IMRT/other local therapies when available for progressive and/or symptomatic metastatic lesions</td>
<td>1.2018</td>
</tr>
</tbody>
</table>


**U.S. Preventive Services Task Force Recommendations**

Not applicable.
Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing stereotactic radiosurgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Central nervous system neoplasms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acoustic neuroma (vestibular schwannoma)</strong></td>
<td></td>
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<tr>
<td>NCT00377156</td>
<td>Phase III Randomized Trial of the Role of Whole Brain Radiation Therapy in Addition to Radiosurgery in Patients with One to Three Cerebral Metastases</td>
<td>213</td>
<td>Oct 2014 (ongoing)</td>
</tr>
<tr>
<td>NCT02055859</td>
<td>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</td>
<td>102</td>
<td>Nov 2021</td>
</tr>
<tr>
<td><strong>Brain metastases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01592968</td>
<td>A Prospective Phase III Randomized Trial to Compare Stereotactic Radiosurgery Versus Whole Brain Radiation Therapy for &gt; = 4 Newly Diagnosed Non-Melanoma Brain Metastases</td>
<td>100</td>
<td>Aug 2019</td>
</tr>
<tr>
<td>NCT02147028</td>
<td>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</td>
<td>84</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>NCT00950001</td>
<td>Efficacy of Post-Surgical Stereotactic Radiosurgery for Metastatic Brain Disease: A Randomized Trial</td>
<td>132</td>
<td>Aug 2020</td>
</tr>
<tr>
<td>NCT01644591</td>
<td>A Phase II Trial to Determine Local Control and Neurocognitive Preservation after Initial Treatment with Stereotactic Radiosurgery (SRS) for Patients with &gt; 3 Melanoma Brain Metastases</td>
<td>49</td>
<td>Aug 2020</td>
</tr>
<tr>
<td>NCT01372774</td>
<td>Stereotactic Radiosurgery or Whole-Brain Radiation Therapy in Treating Patients With Brain Metastases That Have Been Removed by Surgery</td>
<td>194</td>
<td>Nov 2020</td>
</tr>
<tr>
<td>NCT01503828</td>
<td>Whole Brain Radiotherapy Following Local Treatment of Intracranial Metastases of Melanoma - A Randomized Phase III Trial</td>
<td>200</td>
<td>Jun 2021</td>
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<tr>
<td><strong>Glioma</strong></td>
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<tr>
<td>NCT02085304</td>
<td>Phase I/II Randomized Prospective Trial for Newly Diagnosed GBM, with Upfront Gross Total Resection, Gliadel®, Followed by Temodar® with Concurrent IMRT Versus GK</td>
<td>80</td>
<td>Dec 2017 (ongoing)</td>
</tr>
<tr>
<td>NCT01464177</td>
<td>Prospective Randomized Phase II Trial of Hypofractionated Stereotactic Radiotherapy in Recurrent Glioblastoma Multiforme</td>
<td>40</td>
<td>Oct 2021</td>
</tr>
<tr>
<td><strong>Unpublished stereotactic radiosurgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02145910</td>
<td>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</td>
<td>36</td>
<td>Jun 2019 (withdrawn)</td>
</tr>
<tr>
<td>NCT01731704</td>
<td>A Randomized Controlled Study of Neurocognitive Outcomes in Patients with Five or More Brain Metastases Treated with Radiosurgery or Whole-Brain Radiotherapy</td>
<td>0</td>
<td>Dec 2018 (withdrawn)</td>
</tr>
<tr>
<td>NCT01535209</td>
<td>Phase 3 Study of Stereotactic Radiotherapy of the Postoperative Resection Cavity Versus Whole-Brain</td>
<td>100</td>
<td>Oct 2014 (unknown)</td>
</tr>
<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
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</tr>
<tr>
<td>NCT00280475</td>
<td>Irradiation after Surgical Resection of Single Brain Metastasis</td>
<td></td>
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<tr>
<td>NCT00280475</td>
<td>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 Risk Study (JCOG 0504)</td>
<td>270</td>
<td>Jan 2013 (completed)</td>
</tr>
</tbody>
</table>

**Ongoing stereotactic body radiotherapy**

**Non-small-cell lung cancer**

- **NCT01968941**
  - A Randomized Trial of Medically-Inoperable Stage 1 Non-small Cell Lung Cancer Patients Comparing Stereotactic Body Radiotherapy Versus Conventional Radiotherapy
  - Planned Enrollment: 324
  - Completion Date: 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)
  - Planned Enrollment: 420
  - Completion Date: 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
  - Planned Enrollment: 94
  - Completion Date: 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)
  - Planned Enrollment: 96
  - Completion Date: 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
  - Planned Enrollment: 98
  - Completion Date: Apr 2020

- **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
  - Planned Enrollment: 29
  - Completion Date: Dec 2020

- **NCT01014130**
  - A Randomized 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)
  - Planned Enrollment: 101
  - Completion Date: Dec 2020

**Hepatocellular carcinoma**

- **NCT01730937**
  - Randomized Phase III Study of Sorafenib Versus Stereotactic Body Radiation Therapy Followed by Sorafenib in Hepatocellular Carcinoma
  - Planned Enrollment: 368
  - Completion Date: Jun 2020

**Prostate cancer**

- **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.
  - Planned Enrollment: 29
  - Completion Date: Oct 2018

- **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.
  - Planned Enrollment: 350
  - Completion Date: Dec 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
  - Planned Enrollment: 30
  - Completion Date: Dec 2020

- **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
  - Planned Enrollment: 160
  - Completion Date: Dec 2021
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<td>A Randomized Study of Radiation Hypofractionation Via Extended Versus Accelerated Therapy (HEAT) For Prostate Cancer</td>
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<td>NCT02470897</td>
<td>A Phase I/II Study of Stereotactic Body Radiotherapy (SBRT) for Prostate Cancer Using Simultaneous Integrated Boost and Urethral-Sparing IMRT Planning</td>
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<td>NCT01764646</td>
<td>Stereotactic Body Radiation Therapy for cT1c - cT3a Prostate Cancer with a Low Risk of Nodal Metastases (≤ 20%, Roach Index); a NovoStim Circle Phase II Prospective Randomized Trial</td>
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<td>NCT01985828</td>
<td>Prospective Evaluation of CyberKnife® as Monotherapy or Boost Stereotactic Body Radiotherapy for Intermediate or High Risk Localized Prostate Cancer</td>
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<td>NCT03367702</td>
<td>Phase III IGRT and SBRT vs IGRT and Hypofractionated IMRT for Localized Intermediate Risk Prostate Cancer</td>
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**Kidney cancer**

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<td>NCT02138578</td>
<td>A Phase II Randomized Trial Comparing Stereotactic Body Radiation Therapy to Radiofrequency Ablation for the Treatment of Localized Renal Cell Carcinoma (RCC)</td>
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**Breast cancer**

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<td>NCT02089100</td>
<td>Multicentric Phase III Trial of Superiority of Stereotactic Body Radiation Therapy in Patients with Metastatic Breast Cancer in First-line Treatment</td>
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**Melanoma**

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<td>NCT01416831</td>
<td>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</td>
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**Oligometastases**

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<td>NCT01849510</td>
<td>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</td>
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<td>NCT01965223</td>
<td>Stereotactic Ablative Fractionated Radiotherapy Versus Radiosurgery for Oligometastatic Neoplasia to the Lung: A Randomized Phase II Trial</td>
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**Unpublished stereotactic body radiotherapy**

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<td>NCT01511081</td>
<td>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</td>
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<td>NCT02070419</td>
<td>Trans-Arterial Chemo-Embolization (TACE) vs TACE Plus Stereotactic Body Radio Therapy (SBRT) in the Treatment of Hepatocellular Carcinoma (HCC)</td>
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<td>Radiation Therapy for Colorectal Liver Metastases: A Randomized Trial</td>
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NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

References


60. Roos D. What is the randomised evidence for surgery and stereotactic radiosurgery for patients with solitary (or few) brain metastases? Int J Evid Based Healthc. Mar 2011;9(1):61-66. PMID 21332664


6.01.10 Stereotactic Radiosurgery and Stereotactic Body Radiotherapy
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Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Comorbidities
  - Activity and functional limitations
  - Family history if applicable
  - Reason for procedure/test/device, when applicable
  - Pertinent past procedural and surgical history
  - Past and present diagnostic testing and results
  - Prior conservative treatments, duration, and response
  - Treatment plan (i.e., surgical intervention)
- Consultation and medical clearance report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT, discogram)
- Laboratory results
- Other pertinent multidisciplinary notes/reports: (e.g., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management) when applicable

Post Service

- Results/reports of tests performed
- Procedure report(s)
**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

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<td>Image guided robotic linear accelerator-based stereotactic radiosurgery, complete course of therapy in one session or first session of fractionated treatment</td>
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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national...
guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.