Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

Policy Number: 6.01.10  
Origination: 1/1989

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for stereotactic radiosurgery when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

Stereotactic radiosurgery using a gamma or LINAC unit may be considered medically necessary for the following indications:

- arteriovenous malformations;
- acoustic neuromas;
- pituitary adenomas;
- non-resectable, residual, or recurrent meningiomas;
- craniopharyngiomas;
- glomus jugulare tumors;
- 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);
- primary malignancies of the CNS, including but not limited to high-grade gliomas (initial treatment or treatment of recurrence);
- trigeminal neuralgia refractory to medical management.

Stereotactic Body Radiotherapy (SBRT) may be considered medically necessary for the following indications:

- patients with stage T1 or T2a non-small cell lung cancer (not larger 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 radiation therapy;
- spinal or vertebral metastases that are radioresistant (e.g., renal cell carcinoma, melanoma and sarcoma);
- low to intermediate risk prostate cancer when all of the following criteria are met:
- Gleason score equal to or less than 6 and prostate-specific antigen (PSA) less than 10 ng/mL; and
- Minimal disease defined as less than four cores positive; and
- No evidence of extraprostatic disease; and
- Life expectancy of greater than 10 years.

When stereotactic radiosurgery or stereotactic body radiation therapy are performed using fractionation (defined in the Considerations) for the medically necessary indications described above, it may be considered medically necessary.

**When Policy Topic is not covered**

Investigational applications of stereotactic radiosurgery include, but are not limited to, the treatment of seizures and functional disorders (other than trigeminal neuralgia), including chronic pain, tremor and the treatment of uveal melanoma.

Stereotactic body radiation therapy is investigational for primary and metastatic tumors of the liver, pancreas, kidney, adrenal glands and prostate, except as outlined in the policy statements above.

**Considerations**

**Radiation Source**

This policy addresses the use of SRS and SRBT 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 in a separate policy.

**Number of Lesions**

The 1995 TEC Assessment on SRS for multiple brain metastases found that the 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 radiation therapy (WBRT) along with SRS or the WBRT may be delayed for use as salvage therapy for recurrent intracranial disease.

**Fractionation**

Fractionated stereotactic radiotherapy refers to when SRS or SBRT is performed more than one time on a specific site.

SBRT is commonly delivered over 3-5 fractions.
SRS is most often single-fraction treatment; however, multiple fractions may be necessary when lesions are near critical structures.

### Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
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<tbody>
<tr>
<td><strong>Individuals:</strong> With non-neoplastic intracranial conditions (eg, arteriovenous malformations)</td>
<td>Interventions of interest are: • Stereotactic radiosurgery</td>
<td>Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of other forms of radiotherapy, surgery, or chemotherapy • Medical therapy</td>
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<td><strong>Individuals:</strong> With benign neoplastic neurologic disorders (eg, epilepsy, tremor and movement disorders, chronic pain)</td>
<td>Interventions of interest are: • Stereotactic radiosurgery</td>
<td>Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of other forms of radiotherapy, surgery, or chemotherapy • Medical therapy</td>
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<td><strong>Individuals:</strong> With benign neoplastic intracranial lesion(s) (eg, acoustic neuroma, pituitary adenoma, meningiomas)</td>
<td>Interventions of interest are: • Stereotactic radiosurgery</td>
<td>Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of other forms of radiotherapy, surgery, or chemotherapy • Medical therapy</td>
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<td><strong>Individuals:</strong> With benign neoplastic intracranial lesion(s) (craniopharyngioma, glomus jugulare tumors)</td>
<td>Interventions of interest are: • Stereotactic radiosurgery</td>
<td>Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of other forms of radiotherapy, surgery, or chemotherapy • Medical therapy</td>
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<td><strong>Individuals:</strong> With malignant neoplastic intracranial lesion(s) (eg, gliomas, astrocytomas)</td>
<td>Interventions of interest are: • Stereotactic radiosurgery</td>
<td>Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of other forms of radiotherapy, surgery, or chemotherapy • Medical therapy</td>
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<td><strong>Individuals:</strong> With malignant neoplastic intracranial lesion(s) (eg, brain metastases)</td>
<td>Interventions of interest are: • Stereotactic radiosurgery</td>
<td>Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of other forms of radiotherapy, surgery, or chemotherapy • Medical therapy</td>
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<td><strong>Individuals:</strong> With uveal melanoma</td>
<td>Interventions of interest are: • Stereotactic radiosurgery</td>
<td>Comparators of interest are: • Other forms of radiotherapy • Surgery • Combinations of other forms of radiotherapy, surgery, or chemotherapy • Medical therapy</td>
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Extracranial lesions include: primary and metastatic spinal or vertebral body tumors, non-small-cell lung cancer; primary and metastatic tumors of the liver; primary pancreatic cancer; primary and metastatic renal cell carcinoma; metastatic adrenal cancer; primary prostate carcinoma, and oligometastases.

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 ability to spare adjacent radiosensitive structures. SRS primarily refers to such radiotherapy applied to intracranial lesions and SBRT refers to therapy extracranial areas of the body including the spine. Both techniques differ from conventional external-beam radiotherapy (EBRT), which involves exposing large areas of tissue to relatively broad fields of radiation over multiple sessions.

**Stereotactic Radiosurgery**

For individuals who have benign and malignant intracranial lesions 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, symptoms, and treatment-related morbidity. General limitations of the body of evidence include a lack of trials that directly compare SRS and 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 EBRT. 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 of patients with:

- arteriovenous malformations;
- acoustic neuromas;
- pituitary adenomas, nonresectable;
- residual, or recurrent meningiomas;
• solitary or multiple brain metastases;
• primary malignancies of the central nervous system;
• trigeminal neuralgia refractory to medical management.

The evidence is insufficient to determine the effects of the technology on health outcomes in patients with:

• craniopharyngiomas;
• glomus jugulare tumors;
• epilepsy;
• functional disorders other than trigeminal neuralgia;
• tremors;
• chronic pain;
• uveal melanoma.

For individuals with craniopharyngiomas or glomus jugulare tumors, there was strong clinical support for SRS. Contextual factors considered included the rarity of these tumors, low likelihood of high-quality trials, and the potential for reduced harm compared with surgery.

**Stereotactic Body Radiotherapy**

For individuals who have benign or malignant extracranial lesion(s) who receive SBRT, the evidence includes a few RCTs, nonrandomized cohort studies and case series. Relevant outcomes are overall survival, symptoms, and treatment-related morbidity. Limitations of the evidence include a lack of comparative trials, heterogeneity between patients and treatment schedules and planning techniques, and failure to use standardized methods to collect and report outcomes. Based on the available trials survival rates may be similar for SBRT compared with surgical resection for patients with stage T1 and T2a non-small-cell lung cancer (NSCLC) who are not candidates for surgical resection because of comorbid conditions. SBRT has been shown to improve outcomes (reduce pain) in patients with spinal (vertebral) tumors.

The evidence is insufficient to determine the effects of the technology effects on health outcomes in patients with:

• stage T1 or T2a NSCLC tumors (not >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 radiotherapy;
• spinal or vertebral metastases that are radioresistant (eg, renal cell carcinoma, melanoma, sarcoma); and
• solid tumors, primary or metastatic, of the liver, pancreas, kidney, adrenal glands, prostate;
• oligometastases, except metastases to the spine.
There was strong clinical support for use of SBRT in patients with the conditions listed below. Contextual factors considered included the lack of alternatives in inoperable patients and the potential for reduced harm compared with surgery.

- stage T1 or T2a NSCLC tumors (not >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 radiotherapy; and
- spinal or vertebral metastases that are radioresistant (eg, renal cell carcinoma, melanoma, sarcoma).

**Background**

**CONFORMAL RADIOThERAPY**

Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) are techniques that use highly focused, conformal radiation beams to treat both neoplastic and non-neoplastic conditions. Although SRS and SBRT may be completed with 1 session (single fraction), SRS typically refers to a single-session procedure to ablate the target lesion. However, either technique may require additional sessions (typically not >5) over a course of days, referred to as fractionated radiotherapy.

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

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

**STEREOTACTIC RADIosURGERY**

**Non-Neoplastic Intracranial Conditions Treated With SRS**

**Arteriovenous Malformations**

An arteriovenous malformation (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. SRS incites an inflammatory response in the vessels, which results in ongoing fibrosis with eventual complete obliteration of the lesion over a course of months to years. This latency period is variable, 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. In contrast, surgical excision provides an immediate effect on the risk of hemorrhage. 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. SRS is an alternative in selected patients.

**Trigeminal Neuralgia**

Trigeminal neuralgia is a disorder of the fifth cranial (ie, trigeminal) nerve that causes episodes of intense, stabbing pain in the face. The International Classification of Headache Disorders has defined classical trigeminal neuralgia as both idiopathic and related to vascular compression. Painful trigeminal neuropathy is caused by other conditions; post herpetic, posttraumatic, secondary to multiple sclerosis plaque or a space occupying lesion.(1)

Although trigeminal neuralgia is initially treated medically, in a substantial number of cases, drug treatment is either ineffective or the adverse effects become intolerable. Neurosurgical options include microvascular decompression which involves craniotomy, peripheral neurectomy or rhizotomy. Rhizotomy is a technique to percutaneously isolate the nerve and apply ablation techniques such as balloon compression, radiofrequency ablation or chemical injection. SRS of the proximal trigeminal nerve root has been investigated as an alternative to these neurosurgical treatments. There is a latency period of approximately one month for effect to be observed.

**Other Neurologic Disorders**

Seizure disorders are initially treated medically. 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 are so frequent and severe as to significantly diminish quality of life, and when the seizure focus can be localized to a focal lesion in a region of the brain that is accessible to resection. SRS has been investigated as an alternative to neurosurgical resection. For chronic pain that is refractory to a variety of medical and psychological treatments, there are a variety of surgical alternatives. Neurodestructive procedures include cordotomy, myelotomy, dorsal root entry zone lesions, and stereotactic radiofrequency thalamotomy. SRS targeting the thalamus has been considered an investigative alternative to these neurodestructive procedures.

SRS for the destruction of the thalamic nuclei (thalamotomy) has been proposed for a treatment of essential tremor and other forms of tremor (ie, secondary to Parkinson disease, multiple sclerosis, or other neurologic conditions), as an alternative to medical therapy or surgical therapy in extreme cases.

**Neoplastic Conditions Treated With SRS**

**Primary Intracranial Tumors**

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 either the vestibular or cochlear branches of the eighth cranial
nerve. Treatment options include complete surgical excision using microsurgical techniques; radiosurgery has also been used extensively, either as a primary treatment or as a treatment of recurrence after incomplete surgical resection.

Pituitary adenomas are benign tumors with symptoms related to hormone production (ie, functioning adenomas) or to neurologic symptoms due to their impingement on surrounding neural structures. Surgical treatment options for pituitary adenomas include excision, conventional radiotherapy, or SRS. 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. The effects of SRS on hormone production are delayed or incomplete. In patients with nonfunctioning adenomas, the treatment goal is to control growth; complete removal of the adenoma is not necessary. Conventional radiotherapy has been used in this setting with an approximate 90% success rate with few complications.

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

A glomus jugulare tumor is a rare, benign tumor arising in the skull temporal bone that involves middle and inner ear structure. No consensus exists on optimal management to control tumor burden while minimizing treatment-related morbidity.

SRS has been used for the treatment of other primary brain tumors, including gliomas, meningiomas, and primitive neuroectodermal tumors (ie, medulloblastoma, pineoblastoma). Treatment of primary brain tumors such as gliomas is more challenging, due to their generally larger size and infiltrative borders.

Melanoma of the uvea (choroid, ciliary body, and iris) is the most common, primary, malignant, intraocular tumor in adults. Established treatment modalities include enucleation, local resection, brachytherapy, and proton beam radiotherapy. 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.

**Intracranial Metastatic Diseases**

Intracranial metastases are considered ideal targets for radiosurgery due to their small spherical size and noninfiltrative borders. Brain metastases are a frequent occurrence, seen in 25% to 30% of all patients with cancer, particularly in those with lung, breast, colon cancer, melanoma, and kidney. Whole brain radiotherapy
(WBRT) is considered the standard of care in the treatment of brain metastases, and the addition of SRS to WBRT has been shown to improve survival and local tumor control in selected patients. SRS offers the additional ability to treat tumors with relative sparing of normal brain tissue in a single fraction.

**STEREOTACTIC BODY RADIOTHERAPY**

**Extracranial Primary Tumors Treated With SBRT**

SBRT has been studied for the treatment of lung cancers, specifically non-small-cell lung cancer (NSCLC), with the greatest focus on inoperable stage I NSCLC.

Surgical resection is the preferred treatment of hepatocellular carcinoma, 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 may be part of the treatment plan for pancreatic cancer, resectable or unresectable disease, and may be used in the adjuvant or neoadjuvant setting.

Localized renal cell carcinoma is conventionally treated surgically; local ablative methods may also be an option. Preoperative and adjuvant external radiation have not improved survival. However, because renal cell cancer brain metastases—although radioresistant to conventional external radiation—have been responsive to radiosurgery, interest remains in the possibility of treating primary kidney cancer with SBRT.

**Extracranial Metastatic Tumors Treated With SBRT**

Oligometastases are defined as isolated sites of metastasis, with the entire burden of disease being recognized as a finite number of discrete lesions that can be potentially cured with local therapies.(2)

In general, the indications for SBRT for oligometastases are the same as for metastasectomy. Recently proposed specific criteria for the use of SBRT in patients with oligometastases include: a controlled primary, favorable histology, limited metastatic disease, metachronous appearance of metastases, young age, and good performance status.(2)

Management of metastatic solid tumors has historically focused on systemic treatment with palliative intent. However, surgical treatment of oligometastatic disease is now common practice in some clinical settings.(3) Although cure may be possible in some patients with oligometastatic disease, the aim of SBRT in this setting is mainly to achieve local control and delay progression, which also may postpone the need for further treatment.

Metastases from NSCLC to the adrenal gland are common, and systemic treatment is the most frequent therapeutic option. Nevertheless, in patients suffering from
an isolated adrenal metastasis, a survival benefit could be achieved after surgical resection.

**Spinal Primary and Metastatic Tumors Treated With SBRT**

Metastatic tumors to the spine have historically been treated with conventional radiotherapy. The need for retreatment is high due to morbidity from metastatic disease (e.g., pain, myelopathy, spinal cord compression), but radiotherapy to the spine is often limited due to concern for radiation myelopathy and other adverse radiation effects. SBRT to the spine has been most widely studied in patients requiring re-irradiation, but interest has also developed in the use of SBRT for the initial treatment of spinal tumors.

**REGULATORY STATUS**

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

A number of LINAC movable platforms that generate high-energy photons have been cleared for marketing by FDA through the 510(k) process. Examples include the Novalis Tx® (Novalis, Westchester, IL); the TrueBeam STx (Varian Medical Systems, Palo Alto, CA; approved December 2012; product code IYE); and the CyberKnife® Robotic Radiosurgery System (Accuray, Sunnyvale, CA; approved December 1998; product code MUJ). LINAC-based devices may be used for intracranial and extracranial lesions.

**Rationale**

This evidence review was created in January 1995 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through September 15, 2017.

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 randomized controlled trials (RCTs) and nonrandomized comparative trials.

The selection of variables used in 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 most appropriate choices of:

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

Assessment of efficacy for a therapeutic intervention involves a determination of whether an intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

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**

**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 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 the non-neoplastic intracranial conditions (ie, arteriovenous malformation [AVMs]) result in changes in management and improvement in health outcomes?

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

*Patients*

The relevant population of interest is patients with AVMs who have not yet experienced a significant hemorrhagic complication.

*Interventions*

The intervention of interest is SRS prior to significant hemorrhage.

*Comparators*

The comparators of interest are conservative therapies (eg, surveillance, medical therapy) as well as surgical intervention.
Outcomes
The outcomes of interest are overall survival, symptom improvement, and treatment-related morbidity.

Timing
SRS is typically used during the latency period when a patient has not experienced a significant hemorrhage.

Setting
SRS is provided in a tertiary care setting.

Randomized Controlled Trials
In 2014, Mohr et al reported results of the ARUBA trial, a randomized, multicenter study comparing medical therapy with medical therapy plus interventional therapy (including any neurosurgical, endovascular, or stereotactic radiotherapy 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 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 interim analysis demonstrated superiority of medical management, after outcomes were available for 223 patients with 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). Patients were to be followed to determine whether differences in outcomes persist. 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 study was stopped and the registry for comparator arm medical therapy alone participants was not developed.

Systematic Reviews
In 2017, Magro 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 thus 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. There were 9 studies with 673 patients included that were published in the English language, reported adequate data to calculate AVM score, and presented outcome data on hemorrhage following radiosurgery. Average
length of follow-up in these studies was approximately 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 rate of hemorrhage was not different from the rates of hemorrhage reported for untreated high-grade AVMs, which range from 5.9% to 18.0%.

**Single-Arm Studies**

There are many single-arm studies of SRS for AVMs.(7-18) 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 from SRS. Some representative studies are discussed below.

The 2 largest single-arm studies were multicenter studies from 8 institutions participating in the International Gamma Knife Research Foundation.(14,18) Starke et al (2016) reported on 2236 patients with any AVM treated by gamma knife surgery, with a mean follow-up of 7 years.(18) 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 effects, 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.

The second multicenter study (2016) was a publication of 891 patients with small, unruptured AVMs who were treated with gamma knife surgery and had at least 12 months of follow-up.(14) 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.(11) 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.(7) 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 3 patients.

Fokas et al (2013) reported long-term follow-up of a cohort of patients who underwent SRS for cerebral AVMs at a single institution.(8) 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.

Matsuo et al (2014) reported outcomes from a cohort of 51 patients with intracranial AVMs treated with SRS at a single institution.(10) 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.

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.(9) Forty-seven patients with such AVMs underwent volume-staged SRS. Eighteen (38%) patients had 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 actuarial 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 5 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.

Surgical resection of an AVM in children 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 intracranial hemorrhage at the time of presentation. 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 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. A single-institution retrospective analysis reviewed 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 demonstrate relatively high rates of complete obliteration of AVM after SRS, in the range of 40% to 70%. Isolating the effect of the SRS therapy in and of itself can be challenging, as many patients are treated with more than 1 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 therapies 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, for example, 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 management of special populations; pediatrics and pregnant women is limited to case reports.

**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 is patients with trigeminal neuralgia when conservative therapy and medical treatment have failed.

*Interventions*
The intervention of interest is SRS as an alternative to surgical intervention.

*Comparators*
The comparators of interest are conservative therapies (eg, continued medical therapy, 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.

*Setting*
SR is provided in a tertiary care setting.

A 2011 review article summarizes the literature on the use of SRS for trigeminal neuralgia.(21) Most patients with typical facial pain will achieve relief following radiosurgery.
Dhople et al. (2009) reported long-term outcomes of SRS for classical trigeminal neuralgia in 112 patients treated between 1996 and 2001. 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 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. The authors assessed the degree of pain before and after SRS by using the Barrow Neurological Institute (BNI) pain scale. In total, 102 patients took the survey at least once, for a response rate of 91%. Although not found to alter the conclusions of this study, 7 cases of atypical TN 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 actuarial 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.

A 2011 Cochrane review of 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. All procedures produced variable pain relief, but many resulted in sensory side effects. There were no studies of microvascular decompression which observational data suggests gives the longest pain relief. Only 1 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 either before or after surgery. (23)

**Section Summary: Trigeminal Neuralgia**

Case series identify improvements in pain related to trigeminal neuralgia after treatment with SRS. Comparative studies that evaluate 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 1 study specifically addressed the use of radiosurgery and it was stopped before accrual was completed.

**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 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 is patients with drug-resistant or medication-intolerant epilepsy.

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

Comparators
The comparators of interest are conservative therapies (eg, continued medical therapy, surgical intervention).

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.

Setting
SRS is provided in a tertiary care setting.

A 1998 TEC Special Report cited 2 studies of 11 and 9 patients, respectively, in which radiosurgery was used to treat epilepsy.(24)

In 2016, Feng published a systematic review and meta-analysis of data from 13 studies on the use of SRS to treat mesial temporal lobe epilepsy.(25) They calculated approximately half of the patients were seizure free over a follow-up period that ranged from 6 months to 9 years (pooled estimate, 50.9%; 95% CI, 38.1% to 63.6%), with an average of 14 months to seizure cessation (pooled estimate, 14.08 months; 95% CI, 11.95 to 12.22 months). Nine of 13 included studies reported data for adverse events, which included visual field deficits and headache (the two most common adverse events), verbal memory impairment, psychosis, psychogenic nonepileptic seizures, and dysphasia. Patients in the individual studies experienced adverse events at rates that ranged from 8%, for nonepileptic seizures, to 85%, for headache.
Additional literature includes 3 small studies on the use of radiosurgery for medically refractory epilepsy. Regis et al (2000) selected 25 patients with mesial temporal lobe epilepsy, 16 of whom provided minimum 2-year follow-up.(26) 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.(27) 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 7. Whang and Kwon (1996) performed radiosurgery in 31 patients with epilepsy associated with nonprogressive lesions.(28) 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 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 favorable outcome.

Section Summary: Epilepsy
The literature on the use of SRS as a treatment for epilepsy includes reports on primary epileptic disorders as well as tumor-related epilepsy. Evidence on the use of SRS for epilepsy treatment is limited by the lack of randomized controlled clinical trials comparing SRS to other therapies for epilepsy treatment.

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 such as essential tremor and parkinsonian disorders when the conditions have become drug-resistant or medication 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 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 is patients with drug-resistant or medication-intolerant movement disorders.
**Interventions**
The intervention of interest is SRS as an alternative to surgical intervention.

**Comparators**
The comparators are conservative therapies (e.g., continued medical therapy, 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.

**Setting**
SRS is provided in a tertiary care setting.

SRS has been used for the treatment of tremor through stereotactic radiofrequency thalamotomy.

In 2017, Niranjan reported a retrospective analysis of 73 patients who underwent gamma knife thalamotomy for intractable essential tremor during a 19-year period (1996-2015). A median central dose of 140 Gy (range, 130-150 Gy) was delivered to the nucleus ventralis intermedius through a single 4-mm isocenter. The median time to 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 clinical tremor rating scale to score tremor, handwriting, drawing, and ability to drink fluids. Three (4%) patients experienced temporary adverse radiation effects.

Additional literature includes uncontrolled cohort studies.

In 2015, Witjas, et al reported on outcomes of a French prospective single-blind study of Gamma Knife thalamotomy (GKT) for tremor. Fifty patients (mean age, 74.5 years; 32 men) with severe refractory tremor (36 essential, 14 parkinsonian) were treated with unilateral GKT 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 GKT, 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.
In 2008, Kondziolka et al reported 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 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 1 patient developed mild right hemiparesis and speech impairment.

Kooshkabadi et al (2013) reported 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 postprocedure: 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 2 patients, dysphagia in 1 patient, and sustained facial sensory loss in 1 patient.

Lim et al (2010) reported 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 2 patients (lip and finger numbness) and severe neurologic complications occurred in 1 patient (edema surrounding thalamic lesion with subsequent hemorrhage at the lesion site, with speech difficulty and hemiparesis.)

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 (\( p<0.001 \); approximate score decrease extrapolated from graph, 1.5 at baseline to 0.75 at 24-month follow-up).

Young et al (2000) reported 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 (mean, 47 months), blinded assessments on Unified Parkinson’s Disease Rating Scale demonstrated improvements in several specific items, including overall tremor (from 3.3 pretreatment to 1.2 at last follow-up; \( p<0.05 \)) and action tremor (from 2.3 pretreatment to 1.3 at last follow-up; \( p<0.05 \)). Among patients with Essential tremor, blinded assessments were conducted using the Fahn-Tolosa-Marin Tremor Rating Scale. At 1-year of follow-up, 92.1% of patients with essential tremor were
completely or nearly tremor-free. Improvements were reported for components of the Fahn-Tolosa-Marin Tremor Rating Scale, but statistical comparisons were not presented. Three patients developed new neurologic symptoms attributed to the SRS.

**Section Summary: Tremor**
The evidence related to the use of SRS for tremor includes uncontrolled cohort studies; many of which report outcomes from the treatment of tremor of varying etiologies. There is one report of a retrospective analysis of single center experience. Most studies report improvements in standardized tremor scores, although few studies used a blinded evaluation of tremor score, allowing for bias in assessment. No studies that compared 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.

**Chronic Pain**

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

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

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

*Patients*
The population of interest is patients with chronic pain syndromes.

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

*Comparators*
The comparators are conservative therapies (eg, continued medical therapy, surgical intervention).

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

*Timing*
SRS is typically used as an alternative to open neurosurgical intervention.
Setting
SRS is provided in a tertiary care setting.

The TEC Assessment from 1998 identified 2 reports, with 2 and 47 patients, respectively, who underwent radiosurgical thalamotomy for chronic pain.

In 2017, Roberts reported the results of a systematic review of the data in 6 studies (113 patients) of SRS as an intervention for chronic pain.(36) Outcomes were reported on the basis of 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.

This review does not alter the conclusions of the 1998 TEC Assessment.

Central Nervous System (Intracranial) Neoplasms: Benign

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 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 the benign neoplastic intracranial conditions (eg, acoustic neuroma, craniopharyngioma, glomus jugulare tumor, pituitary adenoma) 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, craniopharyngioma, glomus jugulare tumor, and pituitary adenoma AVMs.

Interventions
The intervention of interest is SRS.

Comparators
The comparators are conservative therapies (eg, surveillance, medical therapy) as well as surgical intervention.

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.
**Setting**
SRS is provided in a tertiary care setting.

**Acoustic Neuromas**
SRS is widely used to treat acoustic neuromas (vestibular schwannomas).

In 2017, a systematic review by Persson et al reported on SRS vs fractionated radiotherapy for tumor control in vestibular schwannoma (VS) patients. Patients with unilateral VS treated with radiosurgery were compared with patients treated using fractionated stereotactic radiotherapy (FSRT). A meta-analysis was not performed because all of the 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 FSRT and for trigeminal nerve deterioration 6.0% for SRS and 8.4% for FSRT.

A 2014 Cochrane review did not identify any RCTs that evaluated the efficacy of stereotactic radiotherapy compared with observation alone, microsurgical resection, or any other possible treatment or combination of treatments in patients with a cerebellopontine angle tumor up to 3 cm in diameter, presumed to be a vestibular schwannoma.

Case series have reported generally high rates of local control (LC). For example, Badakhshi et al (2014) reported a 3-year local tumor control rate of 88.9% in a study of 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. A small study from 2006 that compared microsurgical resection (n=36) with SRS (n=46) for the management of small (<3 cm) vestibular schwannomas showed better hearing preservation at last follow-up in the SRS group (p<0.01) and no difference in tumor control between the groups (100% vs 96%, p=0.50).

In the treatment of acoustic neuromas, the most significant adverse events is loss of function of facial and auditory nerves. For example, 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. 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. 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.(44) 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. Chang et al 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. (45)

Section Summary: Acoustic Neuromas
The evidence related to the use of SRS for acoustic neuroma (vestibular schwannoma) consists primarily of case series and cohort studies, which report 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.

Craniopharyngioma
Hashizume et al (2010) evaluated the use of SRS in 10 patients with craniopharyngioma adjacent to optic pathways. (46) Ten (6 men, 4 women) patients with craniopharyngioma and 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 control rate was 100%. Improvement of neurologic symptoms was observed in 5 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. (47) One hundred patients with 109 craniopharyngiomas treated with radiosurgery were evaluated with a median follow-up period of 68 months. Tumor volume varied from 0.1 to 36.0 cm (median, 3.3 cm). The actuarial 5- and 10-year overall rates of survival of tumor progression after radiosurgery were 93% and 88%, respectively. The actuarial 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. (48) Forty patients with craniopharyngiomas were treated between 1989 and 2006. Most patients were treated for tumor progression after surgery. A median target dose of 52.2 Gy (range, 50.4-56 Gy) was applied in a median conventional fractionation of 5×1.8 Gy per week. Follow-up examinations included thorough clinical assessment, as well as contrast-enhanced MRI scans.
After a median follow-up of 98 months (range, 3-326 months), LC 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 suggest that long-term outcomes of fractionated radiosurgery for craniopharyngiomas are excellent with regard to LC, and treatment-related side effects.

In 2014, Lee et al reported on a 20 year (1993-2012) experience of using GKS to treat recurrent or residual craniopharyngiomas.(49) A total of 137 consecutive patients underwent 162 sessions in the setting of 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 GKS, 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 effects on visual fields or pituitary function.

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
Ivan et al (2011) conducted a meta-analysis of tumor control rates and treatment-related mortality for patients with glomus jugulare tumors.(50) 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 studies that described outcomes for patients with glomus jugulare tumors. 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 (GTR), STR with adjuvant postoperative SRS (STR plus SRS), and SRS alone. The authors identified 869 patients who met inclusion criteria. In these studies, length of follow-up ranged from 6 to 256 months. Patients treated with STR were observed for 72±7.9 months and had a tumor control rate of 69% (95% CI, 57% to 82%). Those who underwent GTR 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%). Authors' analysis found that patients undergoing SRS had the lowest rates of recurrence of these 4 cohorts and, therefore, experienced the most favorable rates of tumor control (p<0.01). Patients who underwent GTR sustained worse rates of cranial nerve (CN) deficits with regard to
CNs IX-XI than those who underwent SRS alone; however, the rates of CN XII deficits were comparable.

In 2017, 2 retrospective case series reports were published on the use of SRS for treatment of glomus jugulare tumors over approximately comparable time periods. The report from an academic medical center included 17 patients with a median age of 64 years treated between 1996 and 2013. GKSRS was delivered with definitive treatment intent in 8 (47%) and salvage in 9 (53%) patients. Overall neurological deficit improved in 53%, stabilized in 41%, and worsened in 6% of patients. Overall cause-specific survival was 100%, and actuarial 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. A U.K. referral center had 75 patients treated 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. Improvement 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 suggest that SRS treatment is associated with improved patient outcomes.

**Pituitary Adenoma**
In 2013, Chen et al reported results from a systematic review and meta-analysis of studies evaluating SRS (specifically Gamma Knife surgery) for the treatment of nonfunctioning pituitary adenoma that included a volumetric classification. 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, 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 was 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.

In 2014, Lee et al retrospectively reported outcomes for 41 patients treated with SRS from a cohort of 569 patients treated for nonfunctioning pituitary adenomas at 3 institutions. Neuroimaging at a median follow-up of 48 months showed 34 (82.9%) patients had a decrease in tumor volume, 4 (9.8%) patients had tumor...
stability, and 3 (7.3%) patients had a tumor increase. PFS was 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 may be appropriate in certain clinical settings, such as in older patients (>70 years); in patients with multiple comorbidities in whom surgery would involve a high risk; in patients with clear neuroimaging and neuroendocrine evidence of an 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 results from a multicenter registry of 512 patients who underwent SRS for nonfunctional pituitary adenomas.(55) 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 an actuarial PFS 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 (CNS) deficits, more commonly in patients with tumor progression (p=0.038).

Section Summary: Pituitary Adenoma
Noncomparative studies demonstrate high rates of tumor control (>85%) 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.

Central Nervous System (Intracranial) Neoplasms: Malignant

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 is patients with certain primary and metastatic intracranial malignant tumors.

Interventions
The intervention of interest is SRS as an alternative to open neurosurgical intervention.
Comparators
The comparators are conservative therapies (eg, continued medical therapy, surgical intervention).

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

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

Setting
SRS is provided in a tertiary care setting.

Primary or Recurrent Gliomas and Astrocytomas
In a single-arm study (2015), 11 patients with tectal gliomas were treated with Gamma Knife SRS between October 2002 and May 2011.(56) 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 (CSF) diversion procedure before radiosurgery. Five patients had pilocytic astrocytomas and 6 had nonpilocytic astrocytomas. Ten patients presented with hydrocephalus and underwent a CSF diversion procedure prior to SRS. The tumor volume ranged between 1.2 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 an 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 2 remained stable.

In a retrospective review (2014), 21 patients with recurrent malignant glioma (18 glioblastoma, 3 World Health Organization [WHO] grade III 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 CCNU).(57) 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 start of SRS) for glioblastoma patients (n=18) were 11.0 and 12.5 months, respectively.

In a prospective study (2013), 15 patients with recurrent malignant glioma lesions less than 3 cm in diameter were treated with SRS in a single fraction, whereas
those with lesions 3 to 5 cm in diameter received five 5-Gy fractions; bevacizumab was administered immediately before SRS and 2 weeks later. At initial diagnosis, patients were treated with surgery and adjuvant radiotherapy plus temozolomide and then at least 1 salvage chemotherapy regimen. The primary end point was CNS toxicity. Secondary end points included survival, quality of life (QOL), microvascular properties as measured by MRI, steroid usage, and performance status. One grade 3 (severe headache) and 2 grade 2 CNS toxicities were observed. No patients experienced grade 4/5 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 1 week after SRS and further decline by 2 months.

A retrospective analysis (2012) was performed on patients with recurrent malignant gliomas treated with salvage SRS from September 2002 to March 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 IV 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 SRS for patients with grade IV 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 IV 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 3/4 toxicity for patients who received 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 efficacy and long-term toxicity with this approach.

Fifty-five consecutive patients with high-grade glioma comprising 68 WHO grade III and IV 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, 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 III tumors initially showed a median survival of about 50 months, with a 2-year OS of 90%. After SRS of the recurrences, these patients showed a median survival of 24 months and a 2-year survival of 50%. Patients with WHO grade IV tumors had an
initial median survival of 24 months, with a 2-year survival of 51%; after the recurrence was treated with SRS, the median survival was 11 months and 2-year survival was 23%.

**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 demonstrates high rates of local control and survival using SRS to treat gliomas in the primary and recurrent setting.

**Uveal Melanoma**
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 (brachytherapy, proton beam) were identified.

A 2012 review article summarized 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%.(61) Initial studies using SRS for uveal melanoma reported secondary adverse effects from radiation to be common; however, more recent studies have reported lower incidences with lower total radiation doses.(61)

In 2016, a single ophthalmic specialty institution reported on the experience of a prospective case-control study and treated with frameless, single-session, image-guided robotic radiosurgery.(62) Of the 242 patients, 217 were included in the analysis and 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 wished 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. Actuarial 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.

In 2017, Reynolds et al retrospectively analyzed outcomes for patients undergoing gamma knife radiosurgery for uveal melanoma and intraocular metastases.(63) Eleven (11 eyes) patients had UM while seven 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 1 patient required enucleation.

A large 10-year study (2011) included 212 patients with choroidal melanoma, who were not suitable for brachytherapy or resection.(64) 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 until 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.

Since publication of the 2012 review, several studies have reported outcomes from SRS for intraocular melanoma. Wackernagel et al (2014) reported outcomes for 189 patients with choroidal melanoma treated with SRS (Gamma Knife).(65) 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 due to tumor recurrence and 18 due to radiation-induced adverse effects. OS and distant metastasis rates were not reported.

Furdova et al (2014) reported outcomes for a cohort of 96 patients who underwent SRS at a single center in Slovakia for stage T2 or T3 uveal melanoma.(66) 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.

Additional case series using SRS for uveal melanoma have suggested that SRS is a possible eye-sparing option for patients, with outcomes comparable to enucleation or other radiation modalities.(67-69)

Section Summary: Uveal Melanoma
The evidence for 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.

Brain Metastases

Systematic Reviews
In a 2011 systematic review, Roos examined the randomized evidence for treating brain metastases.(70) A search of MEDLINE, EMBASE, and Cochrane databases for published articles and abstracts on relevant randomized trials was undertaken.
Fourteen randomized trials were identified, 11 final reports and 3 abstracts, investigating various combinations of surgery, SRS and whole brain radiotherapy (WBRT). Most trials had significant limitations. Surgery and SRS improved LC, 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 LC 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.

A 2011 review by Park et al on the use of SRS for brain metastases discussed the 2 randomized trials demonstrating that the addition of single-dose SRS to WBRT improves local tumor control and maintenance of functional status for patients.(71) Also reviewed are 3 recent randomized trials comparing the outcomes for SRS alone vs 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 2010 analysis, a Cochrane review,(72) which addressed the role for SRS and WBRT in patients with few metastatic lesions (generally no >3 or 4 lesions), noted that, given the unclear risk of bias in the included studies, the results need to be interpreted 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 LC were significantly better in the SRS plus WBRT group.

This Cochrane review was updated in 2012.(73) No new studies were found that met the inclusion criteria. Analysis of all included patients, 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.

**Randomized Controlled Trials**

Chang et al (2009) 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.(74)

Some studies have suggested that use of radiosurgery for brain metastases should be limited to patients with 3 or fewer lesions. A randomized trial compared WBRT with WBRT plus radiosurgery boost to metastatic foci.(75) Results stated 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 4 or fewer metastases. SRS centers commonly exclude patients with more than 5 metastases from undergoing radiosurgery.\(^{(76,77)}\) 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.

In 2006, Aoyama et al reported on a randomized trial of SRS plus WBRT vs SRS alone for treatment of patients with 1 to 4 brain metastases.\(^{(78)}\) 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. In an accompanying editorial, Raizer commented that either treatment approach is a reasonable first step, recognizing that those who select SRS alone are more likely to need subsequent salvage radiation treatments.\(^{(79)}\)

**Nonrandomized Comparative Studies**

Tian et al (2013) reported results from a retrospective, single-institution cohort study comparing neurosurgical resection with SRS for solitary brain metastases from non-small-cell lung cancer (NSCLC).\(^{(80)}\) 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.\(^{(81)}\) 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 total 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.

Rava et al (2013), in a cohort study including 53 patients with at least 10 brain metastases, assessed the feasibility of SRS treatment.\(^{(82)}\) 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, demonstrated a median OS of 8.3 months, comparable to historical controls.\(^{(83)}\) OS was similar for patients with 5 to 9 and with at least 10 metastases (7.6 months and 8.3 months, respectively).

Yomo and Hayashi (2014) reported 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.

Section Summary: Brain Metastases
For brain metastases, evidence from RCTs and systematic reviews indicates 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 10 or fewer metastases.

STEREOTACTIC BODY RADIOTHERAPY
Assessment of efficacy for a therapeutic intervention involves a determination of whether the intervention improves health outcomes. The optimal study design for this purpose is an RCT that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

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.

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 which 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 populations of interest are patients with certain primary and metastatic extracranial tumors; primary and metastatic spinal tumors, primary non-small-cell lung cancer (NSCLC), primary hepatocellular carcinoma (HCC), metastatic liver carcinomas, primary pancreatic carcinomas, primary and metastatic renal cell carcinomas, metastatic adrenal gland tumors, and primary prostate carcinoma.
**Interventions**
The intervention of interest is SBRT as an alternative to open surgical intervention, other liver-directed therapies, and/or as an adjunct to systemic therapy.

**Comparators**
The comparators are surgical interventions and/or continued systemic medical therapy.

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

**Timing**
SBRT is typically used as an alternative to open surgical intervention and/or adjunct to systemic medical therapy.

**Setting**
SBRT is provided in a tertiary care setting.

**Primary and Metastatic Spinal Tumors**
In 2004, Gerszten et al reported on the outcomes for 115 patients with spinal tumors of varying etiologies (ie, benign, metastatic, single, or multiple lesions), in a variety of locations (ie, cervical, thoracic, lumbar, sacral), who were treated with the CyberKnife in a single session.(85) 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 a course of 10 to 20 fractions. In contrast, in this study, only 1 CyberKnife treatment was given. In a 2005 study, Degen et al reported on the outcomes of 51 patients with 72 spinal lesions who were treated with the CyberKnife.(86) Patients underwent a median of 3 treatments. Pain was improved, as measured by declining mean visual analog scale score, and QOL was maintained during the 1-year study period.

In 2007, Gerszten et al published results on a series of 500 cases from a single institution (334 tumors had previously undergone external-beam irradiation) using the CyberKnife system.(87) 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 in 74 spinal lesions in 63 (55% had prior irradiation) patients with
The actuarial 1-year tumor progression-free incidence was 84%. Pattern-of-failure analysis showed 2 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.

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.

Section Summary: Spinal Tumors
SBRT has been shown to improve outcomes (reduce pain) in patients with spinal (vertebral) tumors. Most of the literature addresses metastases that recur after prior radiotherapy.

Non-Small-Cell Lung Cancer

SBRT in Inoperable NSCLC

Systematic Reviews
Solda assessed the efficacy of stereotactic ablative radiotherapy (SABR) for the treatment of NSCLC through a systematic review of all relevant publications from 2006 to the present compared to controls treated with surgery. Patient data from populations of 20 or more stage I NSCLC patients treated with SABR with a median follow up of minimum of 1 year. 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 (IASLC) 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 the 3201 patients with localized stage I NSCLC treated with SABR was 70% (95% CI, 67% to 72%) with a 2 year local control of 91% (95% CI, 90% to 93%). This was compared with a 68% (95% CI, 66% to 70%) 2-year survival of 2038 stage I NSCLC patients treated with surgery. There was no survival or local PFS difference with different radiotherapy technologies used for SABR. The review concluded that selection bias could not be assessed from the published reports and treatment related morbidity data was limited.
Nonrandomized Comparative Studies
Jeppersen et al (2013) compared SBRT with conventional radiotherapy for patients with medically inoperable NSCLC (T1-2N0M0).(91) 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 expiatory volume in 1 second (FEV1), and a greater proportion of T1 stage disease. Median OS was 36.1 months and 24.4 months for SBRT and conventional radiotherapy, respectively (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).

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, OS was 75% and DFS was 70%. Better local control was noted with higher doses of radiation.

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.(93) 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), DFS (p=9.001), and cause-specific survival (p=0.005) were significantly associated with tumor volume.

Harkenrider et al (2014) reported 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.(94)

Noncomparative Studies
The Radiation Therapy Oncology Group (RTOG) 0236 trial was a phase 2 North American multicenter, cooperative group study to test SBRT in treating medically inoperable patients with early-stage NSCLC. Patients had biopsy-proven peripheral T1-T2, N0, M0 non-small cell tumors less than 5 cm in diameter and medical conditions precluding surgical treatment. The prescription dose was 18 Gy per fraction times 3 fractions (54 Gy total) delivered over 1.5 to 2 weeks. The study opened in May 2004, and closed in October 2006; data were analyzed through August 2009.(95)

The 3-year results were reported. The primary endpoint was primary tumor control with OS, DFS, adverse events, involved lobe, regional, and disseminated recurrence as secondary end points. 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 FEV1 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 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 local-regional 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.

In 2014, Stanic reported additional analysis of pulmonary toxicity in RTOG 0236 participants. During 2-year follow-up pulmonary function test results were collected. Mean percentage of predicted FEV1 and DLCO declines were 5.8% and 6.3%, respectively. There was no significant decline of 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 overall survival. Patients with poor baseline pulmonary function testing as a reason for medical inoperability had higher median and overall survivals than patients with normal baseline pulmonary function testing but with cardiac morbidity.(96)

**SBRT in Operable NSCLC**

**Randomized Controlled Trials**

There were 2 RCTs that 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 in 2015.(97) 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 to 44% in the surgery group (statistics not reported).

An additional RCT, American College of Surgeons Oncology Group (ACOSOG) trial Z4099 was opened for accrual in May 2011. It was a phase 3 randomized study comparing SBRT and sublobar resection (with or without brachytherapy) for high-risk operable patients with NSCLC.(98) In May 2013, the study was closed due to slow accrual.
Systematic Reviews
In 2014, Zheng et al 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).

A 2008 review by Nguyen et al cites 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 1 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 was 72%, while DFS 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 SEER (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 to 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. (105) 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 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 were 66% and 43%, respectively. For patients without occult nodal disease, 3- and 5-year OS were 80% and 68%, respectively. For the SBRT group, 3-year OS and DFS 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% vs 68% for SBRT and surgery, respectively (p=0.05), while DFS was 47% vs 65% (p=0.01). Two-, 3-, 4-, and 5-year local recurrence-free survival was 91%, 91%, 81%, and 40% for SBRT, respectively, vs 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. (106) 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 (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. (107) 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 a high-risk population of patients with early stage but medically inoperable lung cancer. (108) 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 end point was 2-year actuarial
primary tumor control; secondary end points were DFS (ie, primary tumor, involved lobe, regional, and disseminated recurrence), treatment-related toxicity, and OS. A total of 59 patients accrued, 55 of whom were evaluable (44 patients with T1 tumors, 11 patients with T2 tumors) with a median follow-up of 34.4 months (range, 4.8-49.9 months). Only 1 patient had primary tumor failure; the estimated 3-year primary tumor control rate was 97.6% (95% CI, 84.3% to 99.7%). Three patients had 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 (95% CI, 9.6% to 15.8%); grade 4 adverse events were reported in 2 (3.6%) patients (95% CI, 2.7% to 4.5%). 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 (not >5 cm in diameter) who show no nodal or distant disease and who are not candidates for surgical resection because of comorbid conditions.

**Primary and Metastatic Hepatic Cancer**

**Hepatocellular Carcinoma**

Radiation induced liver disease (RILD) is one of the important complications of radiotherapy. RILD typically occurs 4–8 weeks after completion of radiotherapy but has been described as early as 2 weeks and as late as 7 months after radiation. It is a major factor that limits radiation dose escalation and re-irradiation for tumors that are situated in the close vicinity of the liver. The whole-liver tolerance for radiotherapy with a 5% risk of RILD had been reported at whole-liver doses of 30 to 35 Gy in 2 Gy per fraction.(109,110) Endothelial injury leads to thrombosis.

The use of SBRT for treatment of primary HCC has been generally directed toward locally advanced disease or metastatic lesions for which surgical resection or results with other liver directed therapies would be suboptimal due to size, number or location of the lesions. 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 $3 \times 10-20$ Gy, $4-6 \times 8-10$ Gy, and $10 \times 5-5.5$ Gy(111) and each of the 8 different liver segments may exhibit different tolerances. Some
reports have included patients with intrahepatic cholangiocarcinoma for which there are limited treatment options.

**Systematic Reviews**
A 2012 systematic review conducted by Tao and Yang, assessed the efficacy and safety of SBRT for treating primary and secondary hepatic neoplasms. (112) The review included prospective non-randomized 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 out 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 an incomplete ablation with the other treatment.

All studies identified for review were retrospective reports.

In 2016, Wahl, et al reported on single U.S. site experience with 224 patients with nonmetastatic HCC accumulated between 2004 and 2012. (113) 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 a 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. In 2015, Jacob et al evaluated HCC lesions 3 cm or more and compared TACE alone (n=124) with TACE plus SBRT (n=37) from 2008 to 2013. (114) Sorafenib, the tyrosine kinase inhibitor (TKI), was used by 36.1% of the TACE alone group and 41.9% in the combination therapy group. Both groups had received pre- and posttreatment chemotherapy. Local recurrence was significantly decreased in the TACE plus SBRT group (10.8%) in comparison with the TACE-only group (25.8%) (CI, not reported, p=0.04). After censoring for liver transplantation, OS was found to be 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 HCV infection was the cause of HCC in most patients in both groups.

In 2016, Su et al, 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. (115) The patients who had SBRT alone either refused TACE or had hepatic arteriovenous fistulas precluding TACE. The median follow-up was 20.5 months.
and median tumor size was 8.5 cm (range, 5.1-21.0 cm). The PFS and local relapse-free survival did not differ significantly between groups.

In 2014, Zhong et al reported on a single-site experience with 72 of 1086 HCC patients consecutively treated with SBRT between 2006 and 2012.(116) 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 (CR) achieved in 6 (8.3%), partial response (PR) in 51 (70.8%), stable disease (SD) in 9 (12.5%) and progressive disease (PD) in 6 patients (8.3%) within a median follow-up of 18 months.

**Noncomparative Studies**

In 2013, Bujold et al reported on sequential phase 1 and 2 trials of SBRT for locally advanced HCC.(117) 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 class A disease. The primary end points were toxicity and LC at 1 year, defined as no progressive disease of irradiated HCC by RECIST (Response Evaluation Criteria in Solid Tumors). A total of 102 patients were evaluable (n=50 in trial 1 from 2004-2007; n=52 in trial 2 from 2007-2010). 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). 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. LC 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).

In 2013, Yoon et al reported outcomes for 93 patients with primary nonmetastatic HCC treated with SBRT at a single institution.(118) Median follow-up was 25.6 months. OS rates at 1 and 3 years were 86% and 53.8%, respectively. The main cause of treatment failure was intrahepatic (ie, out-of-field) metastases. At 1 and 3 years, LC 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.

In 2012, Ibarra et al evaluated tumor response to SBRT in a combined multicenter database.(119) Patients with advanced HCC (n=21) or intrahepatic cholangiocarcinoma (ICC; n=11) treated with SBRT from 4 academic medical centers were entered into a common database. Statistical analyses were performed for freedom from local progression (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 2 and 1 patients, respectively.

In 2012, Price et al reported 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. 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 European Association for the Study of the Liver (EASL) 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 effective therapy for patients with HCC with an overall best response rate (complete response plus partial response) of 73%.

In 2010, Kwon et al 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 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 cc vs ≥32 cc, p<0.05). No major toxicity was encountered, but 1 patient died with extrahepatic metastasis and radiation-induced hepatic failure.

In 2013, Jung et al reported 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. 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.

In 2011, Andolino et al 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 Child-Turcotte-Pugh class A and 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 Child-Turcotte-Pugh class A cirrhosis and 5
Gy, 8 Gy, and 40 Gy, respectively, for those with Child-Turcotte-Pugh 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. LC, time to progression (TTP), PFS, and OS were calculated according to Kaplan-Meier method. Median follow-up time was 27 months, and median tumor diameter was 3.2 cm. The 2-year LC, PFS, and OS rates were 90%, 48%, and 67%, respectively, with median TTP of 47.8 months. Subsequently, 23 patients underwent transplant, with a median time to transplant of 7 months. There were no grade 3 or higher nonhematologic toxicities. Thirteen percent of patients experienced an increase in hematologic/hepatic dysfunction greater than 1 grade, and 20% experienced progression in Child-Turcotte-Pugh 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 those ineligible for transplant.

Liver Oligometastases

The liver is the most common site of metastatic spread of colorectal cancer (CRC). 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 CRC 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.

There are 3 relatively large series reporting on SBRT and liver metastases. In 201, Chang et al 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. In 2012, Lanciano et al 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 external-beam radiation. There were 4 patients who had more than 1 prior liver-directed treatment. In 2014, Yuan et al 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 overall survival was not reached and the 1-year and 2-year overall survival rates were 89.6% and 72.2%, respectively. Tables 1 and 2 summarize the characteristics and key results of these studies.

Table 1. Summary of Key Case Series Characteristics –SBRT for Liver Metastases

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Country</th>
<th>Participants</th>
<th>Tumor Type</th>
<th>Treatment Delivery</th>
<th>Follow-Up</th>
</tr>
</thead>
</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 2. Summary of Key Case Series Results

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Treatment</th>
<th>12-Month OS, %</th>
<th>18-Month OS, %</th>
<th>24-Month OS, %</th>
<th>Post-SBRT Chemotherapy ≥2 Regimens, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang (2011)124</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>
<td>38%</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Lanciano (2012)125</td>
<td>&gt;79.2 Gy10 or &lt;79.2 Gy10</td>
<td>73%</td>
<td>NR</td>
<td>31%</td>
<td>NR</td>
</tr>
<tr>
<td>Yuan (2014)126</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>
<td>55.9%</td>
<td></td>
</tr>
</tbody>
</table>

NR: not reported; OS: overall survival; SBRT: stereotactic body radiotherapy.

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

**Bridge to Transplantation**

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

In 2014, Mazloom et al reported a single case of HCV-related HCC with a complex series of liver-directed therapy pre- and posttransplantation. 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 3 is a summary of various case reports using SBRT alone or in combination with other therapies as a bridge to transplant.

### Table 3. Summary of Key Case Series SBRT as Bridge to Transplant

<table>
<thead>
<tr>
<th>Author</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>Jacob (2015)114</td>
<td>2008-2013</td>
<td>• TACE</td>
<td>124</td>
<td>15.5%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• TACE plus SBRT</td>
<td>37</td>
<td>12.1%</td>
<td></td>
</tr>
<tr>
<td>Sapisochin (2017)128</td>
<td>2004-2014</td>
<td>• TACE</td>
<td>36</td>
<td>83%</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• SBRT</td>
<td>99</td>
<td>79.9%</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• RFA</td>
<td>244</td>
<td>83.2%</td>
<td>75%</td>
</tr>
<tr>
<td>Mannina (2017)129</td>
<td>NR</td>
<td>• SBRT</td>
<td>38</td>
<td>100%</td>
<td>77%a</td>
</tr>
</tbody>
</table>

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

### Section Summary: Hepatocellular Carcinoma

There are no RCTs reported on the use of SBRT for HCC. Studies have used heterogeneous treatment schedules, treatment planning techniques, patient populations and outcome measures. The optimal dose and fractionation scheme are unknown. Although promising local control rates of 71% to 100% at 1 year have been reported, there is only retrospective reporting on the use of SBRT in conjunction with or as an alternative to established treatment modalities, including systemic therapy, RFA, and TACE. Similar short-term lesion control rates have been reported for metastatic liver disease. Palliative treatment, including for larger lesions (>3 cm), has also been reported. The use of SBRT, either alone or in conjunction with other liver-directed therapies, is emerging as a bridge to transplant.

### Prostate Cancer

**Low-Risk Prostate Cancer**
Nonrandomized Comparative Studies
Katz et al (2012) examined QOL after either radical prostatectomy (n=123) or SBRT (n=216) in patients with early-stage prostate cancer. QOL was assessed using the Expanded Prostate Cancer Index Composite (EPIC), addressing urinary, sexual, and bowel function. The EPIC data from the SBRT group was compared with the surgery group at baseline, 3 weeks, 5, 11, 24, and 36 months (SBRT group) and baseline, 1, 6, 12, 24, and 36 months (surgery group). 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.

In 2014, Yu et al assessed toxicities after treatment between SBRT (n=1335) and IMRT (n=2670) as primary treatment for prostate cancer, using claims data for Medicare beneficiaries. The authors identified early-stage prostate cancer patients (age range, 66-94 years) treated from January 2008 to June 2011 who received either IMRT (n=53,841) 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.

Noncomparative Studies
Multiple cohort studies report 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 (as defined by the National Comprehensive Cancer Network as: TNM [T1c-T2a], prostate-specific antigen level of ≤10 ng/mL, and Gleason score 2-6) treated with SBRT are summarized in Table 4.

Table 4. Selected Noncomparative Cohort Series for SBRT in Prostate Cancer

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Review Period</th>
<th>Sites</th>
<th>Patients</th>
<th>Risk Stage</th>
<th>Dose (Gy)/Treatment Fractions</th>
<th>Outcome (95% CI)</th>
<th>Toxicity, n (%)</th>
<th>Follow-Up Duration (Actuarial)</th>
</tr>
</thead>
</table>
Boike et al (2011) evaluated the tolerability of escalating doses of SBRT in the treatment of localized prostate cancer. Eligible patients included those with prostate size of 60 cm³ or less, and American Urological Association (AUA) 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 AUA 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 (Expanded Prostate Cancer Index Composite) 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**

**Noncomparative Studies**

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 5 fractions of 7 Gy (total dose, 35 Gy) and 254 received 5 fractions of 7.25 Gy (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 level. Acute grade II 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 level 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. The authors concluded that the low toxicity was
encouraging and that additional follow-up is needed to determine long-term biochemical control and maintenance of low toxicity.

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. (134) 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. Actuarial 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.

Bolzicco et al (2013) reported outcomes from 100 patients treated with SBRT for localized prostate cancer, 41 of whom were low risk (PSA ≤10 ng/mL or Gleason score ≤6 or tumor category T1c-T2a), 42 were intermediate risk (PSA 10-20 ng/mL or Gleason score 7 or tumor category T2c), and 17 were high risk (PSA >20 ng/mL or Gleason score >7 or 2 median risk factors). (135) Twenty-seven patients received androgen deprivation therapy at the discretion of their treating urologist. Sixty-two patients had acute toxicity (within the first 1-2 weeks after treatment): 34% had grade 1 and 12% grade 2 urinary toxicity; 27% had grade 1 and 18% grade 2 GI toxicity. Late urinary toxicity, primarily urgency and frequency (at ≥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 post-EBRT boost for prostate cancer using high-dose rate (HDR) brachytherapy fractionation. (136) Thirty-eight patients had been treated with SBRT with a minimum follow-up of 12 months. Twenty of 38 patients were treated with SBRT monotherapy (9.5 Gy x 4 fractions), and 18 were treated with SBRT boost (9.5 Gy x 2 fractions) post-EBRT and androgen deprivation therapy. PSA nadir to date for 44 HDR brachytherapy boost patients with disease characteristics similar to the SBRT boost cohort was also 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 to date. 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 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.
Evaluation of Toxicity and Adverse Events
In 2010, Wiegner et al published results of the phase 2 trial (King 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 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 is subject to limitations deriving outcome measures from claims data. Longer term follow-up is needed to assess the effect on long-term toxicities, cancer control, and patient survival.

Pancreatic Cancer
In 2017, Zhong et al 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 (NCDB), 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, AJCC clinical T and N staging, chemotherapy use, Charlson-Deyo comorbidity score, year of diagnosis, and receipt of definitive surgery. In the multivariate analysis, treatment with SBRT was associated with significantly improved overall survival (OS) with a hazard ratio of 0.84 (95% CI, 0.75 to 0.93; p<.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 as described above, 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).

In 2012, Goyal et al reported outcomes with SBRT in patients with pancreatic adenocarcinoma who were not candidates for surgical resection.(142) 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/timing. Patients had a mean gross tumor volume (GTV) of 57.2 cm3 (range, 10.1-118 cm3) before SBRT. The mean total GTV 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 freedom from local progression 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 4/5 adverse events were reported.

In 2011, Rwigema et al assessed the feasibility and safety of SBRT in patients with advanced pancreatic adenocarcinoma.(143) 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 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/1 year were 71.7% to 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/1 year OS rates of 65.3% to 41%, respectively. Grade 1/2 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.

In 2009, Chang et al reported on the local control and toxicity of SBRT for patients with unresectable pancreatic adenocarcinoma.(74) 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. The role of SBRT as a radiation technique for pancreatic tumors has not been established, and it is not clear which patients would most likely benefit. Although studies have shown promising local control rates, there is limited information on significant changes in patient survival compared with historical data, and some studies have shown acute grade 3 toxicities.

**Primary and Metastatic Renal Cell Carcinoma**
Primary renal cell carcinoma (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. RCC has been considered relatively radioresistant. However, the renal parenchyma, vasculature, and collecting system is considered radiosensitive.

A 2012 systematic review by Siva et al on the use of SBRT for primary renal cell carcinoma (RCC) identified a total of 126 patients worldwide who had been treated using this modality at the time of publication. (144) Ten studies (7 retrospective studies, 3 prospective studies) that used a wide range of techniques, doses, and dose fractionation schedules were identified. Median or mean follow-up ranged from 9 to 57.5 months. Local control (LC) 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 can be delivered with good rates of LC and acceptable toxicity, but that evidence was insufficient to recommend a consensus for dose fractionation or technique.

In 2004, Beitler et al reported outcomes in 9 patients with nonmetastatic RCC, 2 of whom had bilateral RCCs. (145) 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.

In 2016, Yamamoto, et al reported on 14 patients (11 males, 3 females) who received SBRT for RCC at a single site between April 2010 and February 2014. (146) 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.

In 2013, Verma et al retrospectively reviewed patients receiving different radiotherapy modalities for brain metastases with or without tyrosine kinase inhibitor (TKI) therapy. (147) Among 34 patients (89 lesions) those receiving SRS and TKIs had 6-month local control rates of 94.7% vs 73.7% in the group who received SRS without TKIs. The difference was not statistically significant (p=0.09).

In 2015, Taunk et al reported a systematic review and clinical opinion on the use of SBRT for spinal metastases from RCC. (148) 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 radiation therapy may be risk factors for fracture. Table 5 summarizes the series described in the systematic review.

### Table 5. Selected Series for Spine SBRT in RCC and Mixed Histologies

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Patients</th>
<th>Lesions</th>
<th>Histology</th>
<th>Dose (Gy)/Treatment Fractions</th>
<th>Local Control, %</th>
<th>Follow-Up Duration (Actuarial), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balagamwala (2012)149</td>
<td>57</td>
<td>88</td>
<td>RCC</td>
<td>15/1</td>
<td>71.2</td>
<td>12</td>
</tr>
<tr>
<td>Gerszten (2005)150</td>
<td>48</td>
<td>60</td>
<td>RCC</td>
<td>20 (mean)/1</td>
<td>89.0</td>
<td>37 (median)</td>
</tr>
<tr>
<td>Gerszten (2007)87</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>Sohn (2014)151</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 (2014)152</td>
<td>37</td>
<td>71</td>
<td>RCC</td>
<td>24/2</td>
<td>83.0</td>
<td>12</td>
</tr>
<tr>
<td>Wang (2012)153</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 (2008)154</td>
<td>93</td>
<td>103</td>
<td>Mixed</td>
<td>24/1</td>
<td>90.0</td>
<td>15</td>
</tr>
<tr>
<td>Zelefsky (2012)155</td>
<td>45</td>
<td>45</td>
<td>RCC</td>
<td>24/1</td>
<td>88.0</td>
<td>36</td>
</tr>
</tbody>
</table>

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

In 2013, Ranck et al reported outcomes for 18 patients with RCC with limited metastases who were treated with SBRT. (156) 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. No patients who underwent treatment at all lesion sites died.

Section Summary: Renal Cell Carcinoma
The literature on the use of SBRT for RCC consists of small case series and systematic review of case series, which generally report high rates of local control which may be particularly important for brain and spinal metastases. However, the impact of SBRT on patient outcomes cannot conclusively be derived from this evidence. There are no RCTs that have evaluated SBRT for primary RCC or metastatic lesions to the brain or spine that allow comparisons to be made between SBRT and current established treatment modalities for RCC.

Oligometastases
The 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.(2,3,157)

A 2012 long-term follow-up of a prospective study was reported on oligometastases treated with SBRT.(158) 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 LC rates were 74%, 52%, and 87%, respectively. Six-year OS, FFDM, and LC 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 LC rates were 39%, 28%, and 74%, respectively, and 6-year OS, FFDM, and LC 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 LC (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 LC probability at 1 year has been reported in the range of 70% to 100%.(2) 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.(2)

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

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%,(160) ranging from higher rates (84%) in a study by Norihisa et al (2008) (161) to lower rates (39%) reported from a multi-institutional trial.(162)

Since publication of the Siva’s systematic review, Osti et al (2013) reported outcomes from a prospective cohort study of SBRT for lung oligometastases.(163) Sixty-six patients with lung oligometastases were included, most (61%) with a single pulmonary nodule. For the primary end point of LC, over a median follow-up of 14 months, LC at 1 and 2 years was 89.1% and 82.1%, respectively. OS at 1 and 2 years was 76.4% and 31.2%, respectively, while PFS at 1 and 2 years was 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. LC 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.(2)

Scorsetti et al (2012) described the feasibility, tolerability, and clinical outcomes of SBRT in the treatment of adrenal metastases in consecutive cancer patients.(164) Between 2004 and 2010, a total of 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, LC, 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 actuarial local control rates at 1 and 2 years were 66% and 32%, respectively. Median time-to-local progression was 19 months and median survival was 22 months.

Holy et al (201‘) presented initial institutional experiences with SBRT for adrenal gland metastases.(165) 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 time 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 LC. In these patients, median OS was 23 months.

Casamassima et al (2011) retrospectively evaluated a single institution’s outcomes after hypofractionated SBRT for adrenal metastases.(166) 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 time of analysis, 20 of 48 patients were alive. One- and 2-year actuarial OS rates were 39.7% and 14.5%, respectively. Median interval to local failure was 4.9 months. The actuarial 1-year disease control rate was 9%; the actuarial 1- and 2-year LC rates were both 90%.

Chawla et al (2009) investigated the dosimetry and outcomes of patients undergoing SBRT for metastases to the adrenal glands.(167) A retrospective review of 30 patients who had undergone SBRT for adrenal metastases from various primary sites, including lung (n=20), liver (n=3), breast (n=3), melanoma (n=1), pancreas (n=1), head and neck (n=1), and unknown primary (n=1), was performed. Of the 30 patients, 14 with 5 or fewer metastatic lesions (including adrenal) underwent SBRT, with the intent of controlling all known sites of metastatic disease. Sixteen patients underwent SBRT for palliation or prophylactic palliation of bulky adrenal metastases. Twenty-four patients had more than 3 months of follow-up with serial computed tomography. Of these 24 patients, 1 achieved complete remission, 15 achieved partial remission, 4 had stable disease, and 4 developed progressive disease. No patients developed symptomatic progression of their adrenal metastases. LC was poor, and most patients developed widespread metastases shortly after treatment, with 1-year survival, LC, and distant control rates of 44%, 55%, and 13%, respectively. No patient developed grade 2 or greater toxicity.

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 LC 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 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.

**Bone Oligometastases**

Napieralska et al (2014) reported 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. Systemic therapy is most frequently the preferred therapy for patients with liver metastases, but surgical excision or local tumor ablation strategies are often considered for patients with limited disease.

**SUMMARY OF EVIDENCE**

**Stereotactic Radiosurgery**

For individuals who have benign and malignant intracranial lesions 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, symptoms, and treatment-related morbidity. General limitations of the body of evidence include a lack of trials that directly compare SRS and 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 EBRT. 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 of patients with:

- arteriovenous malformations;
- acoustic neuromas;
- pituitary adenomas, nonresectable;
- residual, or recurrent meningiomas;
- solitary or multiple brain metastases;
- primary malignancies of the central nervous system;
- trigeminal neuralgia refractory to medical management.

The evidence is insufficient to determine the effects of the technology on health outcomes in patients with:

- craniopharyngiomas;
- glomus jugulare tumors;
- epilepsy;
- functional disorders other than trigeminal neuralgia;
- tremors;
- chronic pain;
- uveal melanoma.

For individuals with craniopharyngiomas or glomus jugulare tumors, there was strong clinical support for SRS. Contextual factors considered included the rarity of these tumors, low likelihood of high-quality trials, and the potential for reduced harm compared with surgery.

**Stereotactic Body Radiotherapy**

For individuals who have benign or malignant extracranial lesion(s) who receive SBRT, the evidence includes a few RCTs, nonrandomized cohort studies and case series. Relevant outcomes are overall survival, symptoms, and treatment-related morbidity. Limitations of the evidence include a lack of comparative trials, heterogeneity between patients and treatment schedules and planning techniques, and failure to use standardized methods to collect and report outcomes. Based on the available trials survival rates may be similar for SBRT compared with surgical resection for patients with stage T1 and T2a non-small-cell lung cancer (NSCLC) who are not candidates for surgical resection because of comorbid conditions. SBRT has been shown to improve outcomes (reduce pain) in patients with spinal (vertebral) tumors.

The evidence is insufficient to determine the effects of the technology effects on health outcomes in patients with:

- stage T1 or T2a NSCLC tumors (not >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 radiotherapy;
spinal or vertebral metastases that are radioresistant (eg, renal cell carcinoma, melanoma, sarcoma); and
solid tumors, primary or metastatic, of the liver, pancreas, kidney, adrenal glands, prostate;
oligometastases, except metastases to the spine.

There was strong clinical support for use of SBRT in patients with the conditions listed below. Contextual factors considered included the lack of alternatives in inoperable patients and the potential for reduced harm compared with surgery.

stage T1 or T2a NSCLC tumors (not >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 radiotherapy; and
spinal or vertebral metastases that are radioresistant (eg, renal cell carcinoma, melanoma, sarcoma).

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.

2013 Input
In response to requests, input was received from 3 physician specialty societies (6 reviewers) and 6 academic medical centers, for a total of 12 reviewers, while this policy was under review in 2013. Input was provided on content related to both stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (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, input was received from 6 physician specialty societies (8 reviewers) and 4 academic medical centers, for a total of 12 reviewers, while this policy was under review 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 general support for the use of SBRT in spinal tumors and early stage non-small-cell lung cancer (NSCLC) and support to expand the use in the spine to
include metastatic radioresistant tumors. Support for the use in primary and metastatic lesions of the liver, pancreas, adrenal, and kidney was mixed. There was little support for the use of SBRT in prostate cancer.

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

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Heart Association Scientific Statement
In 2001, the American Heart Association issues a scientific statement with recommendations for the management of intracranial arteriovenous malformations (AVMs).(170) Radiosurgery could be considered in lesions thought to be at high risk from a surgical or endovascular standpoint. The statement notes:

“The overall efficacy of radiosurgery is higher for small lesions, and therefore, this modality may be considered as a primary treatment for smaller as opposed to larger lesions. However, size is not the only factor in the final determination of treatment. The exact location, patient age, symptoms, and angiographic anatomy must be considered in this decision process. For small, surgically accessible lesions (Spetzler-Martin grade I or II), surgery has fewer risks than radiosurgery.

Radiosurgery may be considered in larger lesions (Spetzler-Martin grade II through V) only if the overall goal is complete obliteration of the lesion. Partial treatment of a larger lesion with radiosurgery or embolization subjects the patient to the risks of the procedure without eliminating the risk of hemorrhage.”

National Comprehensive Cancer Network Guidelines
National Comprehensive Cancer Network (NCCN) provides guidelines for cancer treatment by site that include the use of stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) for certain cancers.(171) Guidelines addressing SRS and SBRT are summarized in Table 7.

Table 7: 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>Osteosarcoma – metastatic disease</td>
<td>▪ Consider SRS, especially for oligometastases (category 2A)</td>
<td>2.2017</td>
</tr>
<tr>
<td>CNS</td>
<td>Adult intracranial and spinal ependymoma – spine or brain reoccurrence</td>
<td>▪ Resection with limited RT if no prior RT; consider use of SRS if geometrically favorable (category 2A) ▪ If unresectable, RT if no prior</td>
<td>1.2016</td>
</tr>
</tbody>
</table>
### CNS

**Adult medulloblastoma and supratentorial PNET – recurrent disease**
- If progression, RT; consider SRS if geometrically favorable (category 2A)

**Primary spinal cord tumors**
- If recurrence, RT including SRS if surgery is not possible (category 2A)

**Meningiomas – asymptomatic and small (<30 mm)**
- If potential neurologic consequences and accessible, surgery followed by RT (external beam or SRS) if WHO grade 3; consider RT if WHO grade 2 (category 2A)
- If potential neurologic consequences from surgery, RT (external beam or SRS) (category 2A)

**Meningiomas – asymptomatic and large (≥30 mm)**
- If accessible, surgery followed by RT (external beam or SRS) if WHO grade 3 or RT (external beam or SRS) (category 2A)

**Meningiomas – symptomatic and small (<30 mm)**
- If accessible, surgery followed by RT (external beam or SRS) if WHO grade 3 or RT (external beam or SRS) (category 2A)

**Meningiomas – symptomatic and large (≥30 mm)**
- If accessible, surgery followed by RT (external beam or SRS) if WHO grade 3; consider for resected or incompletely resected WHO grade II or incompletely resected WHO grade I (category 2A)

**Metastatic disease – 1-3 lesions, primary treatment**
- If resectable, surgical resection followed by WBRT (category 1) or SRS (category 2B), OR SRS and WBRT (category 1 for 1 metastasis), OR SRS alone (category 2A)
- If unresectable, WBRT or SRS (category 2A)

**Metastatic disease – 1-3 lesions, recurrence**
- If local recurrence and previous surgery only, surgery, single-dose or fractionated SRS, or WBRT (category 2A)
- If local recurrence and previous WBRT or SRS, surgery or single-dose (category 2B) or fractionated SRS (category 2A)
- If distant brain recurrence and 1-3 lesions, surgery, single-dose or
<table>
<thead>
<tr>
<th>Tumor Site</th>
<th>Metastatic Condition</th>
<th>Treatment Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Metastatic disease – &gt;3 lesions, primary treatment</td>
<td>- WBRT or SRS (category 2A). SRS can be considered for patients with good performance status and low overall tumor volume.</td>
</tr>
<tr>
<td>CNS</td>
<td>Metastatic spine tumors</td>
<td>- For recurrence of spine tumors, re-resection or RT or re-irradiation (include SRS), if surgery not possible or chemotherapy if further surgery or RT not possible (category 2A) - For recurrence or progressive disease previously treated with RT or surgery and RT, consider surgery or SRS (category 2A) - For metastatic spine tumors, recommend SRS if oligometastases and radioresistant (category 2A)</td>
</tr>
<tr>
<td>Colon</td>
<td>Metastatic to liver or lung</td>
<td>- In highly selected cases 3-D conformal RT, IMRT, or SBRT to the metastatic site can be considered in highly selected cases or in the setting of a clinical trial. RT should not be used in place of surgical resection.</td>
</tr>
<tr>
<td>Head and neck</td>
<td></td>
<td>- Either IMRT or 3-D conformal RT is recommended for initial RT treatment of head and neck cancers. - Guidelines are provided for reirradiation with 3-D conformal RT, SBRT, PBT, or IMRT.</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>Hepatocellular carcinoma</td>
<td>- If potentially resectable and Child-Pugh class A or B, no portal hypertension, suitable tumor location, adequate liver reserve, and suitable liver remnant, consider IMRT (conformal or stereotactic) (category 2B) - All tumors irrespective of the location may be amenable to EBRT (SBRT), IMRT OR 3-dimensional conformal RT - If unresectable and not eligible for liver transplant, consider EBRT (conformal or stereotactic) (category 2B) - If inoperable by performance status or comorbidity and local disease with minimal or no extrahepatic disease, consider EBRT (conformal or stereotactic)</td>
</tr>
<tr>
<td>Organ</td>
<td>Diagnosis</td>
<td>Recommendations</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>Unresectable Gallbladder Cancer</td>
<td>- All tumors irrespective of the location may be amenable to RT (3D conformal RT, IMRT, or SBRT) (category 2A)</td>
</tr>
<tr>
<td>Lung</td>
<td>Initial treatment for inoperable non-small-cell lung cancer</td>
<td>- Patients with medically inoperable disease may be candidates for SABR, also known as SBRT (category 2A)</td>
</tr>
<tr>
<td>Lung</td>
<td>Non-small-cell lung cancer – Stage IA</td>
<td>- If negative mediastinal lymph nodes and inoperable, definitive RT (stereotactic ablative radiotherapy) (category 2A)</td>
</tr>
</tbody>
</table>
| Lung                  | Non-small-cell lung cancer – Stage IV, metastatic disease to single site, brain or adrenal. | - Brain metastasis: Surgical resection followed by WBRT or SRS (category 2A), or SRS and WBRT (category 1 for 1 metastasis), or SRS alone (category 2A)  
  - If brain or adrenal metastasis and T1-2, N0-1 or T3, N0 disease: consider stereotactic ablative radiotherapy of lung lesion (category 2A) |
| Pancreas              | Pancreatic adenocarcinoma          | - SBRT is recommended only as part of a clinical trial (category 2B) |
| Prostate              | Prostate cancer                    | - SBRT may be considered as an alternative to conventional fractionated RT at clinics with appropriate technology and expertise |
| Renal Cell Carcinoma  | Renal Cell Carcinoma               | - Stage 1 selected patients: ablative techniques (eg, cryotherapy, RFA)  
  - Stage 4 potentially resectable primary with oligometastatic sites “Ablative techniques of metastases in selected patients who are not candidates for surgery”  
  - Stage 4 unresectable: SBRT option for solitary brain metastases or oligometastatic lesions |
| Melanoma              | Brain metastases (see NCCN guidelines for CNS cancers) | - SRS as primary treatment  
  - SRS as adjuvant treatment |
| Soft tissue sarcoma – extremity, superficial trunk, head/neck | Sarcoma – synchronous stage IV | ▪ If single organ and limited tumor bulk that are amenable to local therapy: consider SBRT (category 2A)  
▪ If disseminated metastases: SBRT as a palliative option (category 2A) | 2.2017 |
| Soft tissue sarcoma – extremity, superficial trunk, head/neck | Sarcoma – recurrent disease with metastases | ▪ If single organ and limited tumor bulk that are amenable to local therapy: consider SBRT (category 2A)  
▪ If disseminated metastases: SBRT as a palliative option (category 2A)  
▪ If isolated regional disease or nodes: consider SBRT (category 2A) | 2.2017 |
| Thyroid | Papillary, follicular, or Hürthle cell carcinoma – structurally persistent/recurrent locoregional or distant metastatic disease not amenable to radioactive iodine | ▪ CNS metastases: for solitary lesions either neurosurgical resection of SRS is preferred (category 2A) | 2.2017 |


**American Society for Radiation Oncology**
The American Society for Radiation Oncology (ASTRO) has guidelines for the treatment of a number of conditions, several of which include SRS or SBRT.

For brain metastases, ASTRO makes the following recommendations related to the use of SRS(172):

- For single brain metastases (initial management):
  - If good prognosis (expected survival ≥3 months) and complete resection possible:
    - If brain metastasis ≤3-4 cm, options include SRS and WBRT (level of evidence: I), SRS alone (level of evidence: 1), and surgery with SRS/radiation boost with or without WBRT (level of evidence: 3)
    - If brain metastasis >3-4 cm, treatment options include surgery with SRS/radiation boost with or without WBRT (level of evidence: 3)
  - If good prognosis and not resectable:
    - If brain metastasis ≤3-4 cm, options include SRS and WBRT (level of evidence: I), SRS alone (level of evidence: 1).
- For multiple brain metastases (initial management)
  - If good prognosis (expected survival ≥3 months) and brain metastasis ≤3-4 cm, options include SRS and WBRT (level of evidence: I), SRS alone (level of evidence: 1)
For palliative therapy for bone metastases, ASTRO made recommendations in 2011 and in a 2017 update(173,174):

- “Advanced RT techniques such as SBRT as the primary treatment for painful spine bone lesions or for spinal compression should be considered in the setting of a clinical trial or with data collected in a registry given that insufficient data are available to routinely support this treatment currently.”
- “Advanced radiation techniques such as SBRT retreatment for recurrent pain in spine bone lesions may be feasible, effective, and safe, but the panel recommends that this approach should be limited to clinical trial participation or on a registry given limited data supporting routine use.”

For glioblastoma, ASTRO makes the following guideline statement(175):

- “In younger patients with good performance status, focal reirradiation (eg, stereotactic radiosurgery, hypofractionated stereotactic radiotherapy, brachytherapy) for recurrent glioblastoma may improve outcomes compared with supportive care or systemic therapy alone (LQE). Tumor size and location should be taken into account when deciding whether reirradiation would be safe (93% agreement, Low Quality Evidence; Weak recommendation).”

ASTRO recommendations for the use of SBRT for NSCLC, ASTRO are summarized in Table 8(176):

<table>
<thead>
<tr>
<th>Table 8. Summary of NSCLC SBRT Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSCLC Stage</strong></td>
</tr>
<tr>
<td>T1-2, N0 NSCLC medically operable</td>
</tr>
<tr>
<td>T1-2, N0 NSCLC medically inoperable</td>
</tr>
<tr>
<td>Centrally located tumors</td>
</tr>
<tr>
<td>- tumors &gt;5 cm</td>
</tr>
<tr>
<td>- synchronous primary or multifocal tumors</td>
</tr>
<tr>
<td>- post-pneumonectomy with new tumor in residual lung</td>
</tr>
<tr>
<td>- proximity/involvement of mediastinal structures</td>
</tr>
<tr>
<td>- abuts or invades chest wall</td>
</tr>
<tr>
<td>Appropriate</td>
</tr>
<tr>
<td>Appropriate</td>
</tr>
<tr>
<td>Appropriate</td>
</tr>
<tr>
<td>Recurrent lung cancer medically inoperable</td>
</tr>
<tr>
<td>- post conventional fractionated RT</td>
</tr>
<tr>
<td>- previous SBRT</td>
</tr>
<tr>
<td>- post sublobar resection</td>
</tr>
</tbody>
</table>

N: node; NSCLC: non-small cell lung cancer; RT: radiotherapy; SBRT: stereotactic body radiotherapy; T: tumor.

**International RadioSurgery Association Guidelines**

The International RadioSurgery Association published consensus-based guidelines on the treatment of brain or dural AVMs.(177) The guidelines included a clinical
pathway that incorporates patients’ choice, AVM location and volume, and presence of residual AVM after repeat treatment to guide decisions about SRS use.

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>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<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>238</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>120</td>
<td>Aug 2017</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>192</td>
<td>Aug 2016 (ongoing)</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 2017</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 2018</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 2018</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>120</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT02147028</td>
<td>A Randomized Phase II Trial of Hippocampal</td>
<td>84</td>
<td>Dec 2019</td>
</tr>
</tbody>
</table>
Sparing Versus Conventional Whole Brain Radiotherapy After Surgical Resection or Radiosurgery in Favourable Prognosis Patients With 1-4 Brain Metastases  

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Description</th>
<th>Patients</th>
<th>Start Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01503827</td>
<td>Whole Brain Radiotherapy Following Local Treatment of Intracranial Metastases of Melanoma - A Randomised Phase III Trial</td>
<td>200</td>
<td>Jun 2021</td>
</tr>
</tbody>
</table>

**Glioma**

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Description</th>
<th>Patients</th>
<th>Start Date</th>
</tr>
</thead>
<tbody>
<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 Radiation Therapy</td>
<td>80</td>
<td>Dec 2016</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>
</tbody>
</table>

**Unpublished stereotactic radiosurgery**

**Central nervous system neoplasms**

**Brain metastases**

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Description</th>
<th>Patients</th>
<th>Start Date</th>
</tr>
</thead>
<tbody>
<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 Study (JCOG 0504)</td>
<td>270</td>
<td>Jan 2013</td>
</tr>
<tr>
<td>NCT01535209</td>
<td>Phase 3 Study of Stereotactic Radiotherapy of the Postoperative Resection Cavity Versus Whole-Brain Irradiation After Surgical Resection of Single Brain Metastasis</td>
<td>100</td>
<td>Oct 2014</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</td>
</tr>
</tbody>
</table>

**Ongoing stereotactic body radiotherapy**

**Non-small-cell lung cancer**

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Description</th>
<th>Patients</th>
<th>Start Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02045446</td>
<td>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</td>
<td>36</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT01014130</td>
<td>A Randomised Phase III Trial of Highly Conformal Hypofractionated Image Guided (&quot;Stereotactic&quot;) Radiotherapy (HypoRT) Versus Conventionally Fractionated Radiotherapy (ConRT) for Inoperable Early Stage I Non-small Cell Lung Cancer (CHISEL)</td>
<td>100</td>
<td>Jun 2018</td>
</tr>
<tr>
<td>NCT01968941</td>
<td>A Randomized Trial of Medically-Inoperable Stage I Non-small Cell Lung Cancer Patients Comparing Stereotactic Body Radiotherapy Versus Conventional Radiotherapy</td>
<td>324</td>
<td>Apr 2019</td>
</tr>
<tr>
<td>NCT01336894</td>
<td>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)</td>
<td>420</td>
<td>Aug 2019</td>
</tr>
<tr>
<td>NCT Number</td>
<td>Study Title</td>
<td>Tag</td>
<td>Date</td>
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</tr>
<tr>
<td>NCT01725165</td>
<td>A Randomized Phase II Study Assessing the Efficacy of Local Consolidative Therapy for Non-Small Cell Lung Cancer Patients With Oligometastatic Disease</td>
<td>94</td>
<td>Nov 2019</td>
</tr>
<tr>
<td>NCT01622621</td>
<td>Randomized Phase II Trial of Stereotactic Body Radiotherapy (SBRT) Versus Sublobar Resection for High-Risk Patients With Early Stage Non-Small Lung Cancer (NSCLC)</td>
<td>96</td>
<td>Mar 2020</td>
</tr>
<tr>
<td>NCT00843726</td>
<td>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</td>
<td>98</td>
<td>Apr 2020</td>
</tr>
<tr>
<td><strong>Hepatocellular carcinoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01730937</td>
<td>Randomized Phase III Study of Sorafenib Versus Stereotactic Body Radiation Therapy Followed by Sorafenib in Hepatocellular Carcinoma</td>
<td>368</td>
<td>Jun 2020</td>
</tr>
<tr>
<td><strong>Prostate cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01794403</td>
<td>A Randomized Study of Radiation Hypofractionation Via Extended Versus Accelerated Therapy (HEAT) For Prostate Cancer</td>
<td>75</td>
<td>Feb 2018</td>
</tr>
<tr>
<td>NCT01839994</td>
<td>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.</td>
<td>350</td>
<td>Dec 2018</td>
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<tr>
<td>NCT01737151</td>
<td>Study of 4-Fraction Split-Course Stereotactic Ablative Radiation Therapy of the Treatment of Patients With Low and Intermediate Risk Adenocarcinoma of the Prostate</td>
<td>160</td>
<td>Dec 2021</td>
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<tr>
<td>NCT01764646</td>
<td>Stereotactic Body Radiation Therapy for cT1c - cT3a Prostate Cancer With a Low Risk of Nodal Metastases (≤ 20%, Roach Index): a Novalis Circle Phase II Prospective Randomized Trial</td>
<td>152</td>
<td>Sep 2025</td>
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<tr>
<td><strong>Kidney cancer</strong></td>
<td></td>
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<tr>
<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>
<td>110</td>
<td>Feb 2019</td>
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<tr>
<td><strong>Breast cancer</strong></td>
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<tr>
<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>
<td>280</td>
<td>Feb 2020</td>
</tr>
<tr>
<td><strong>Melanoma</strong></td>
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<td>NCT01416831a</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>
<td>44</td>
<td>Oct 2018</td>
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<tr>
<td><strong>Oligometastases</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT01429493</td>
<td>Biological Image Guided Antalgic</td>
<td>120</td>
<td>Dec 2015</td>
</tr>
<tr>
<td>NCT</td>
<td>Study Title</td>
<td>Start Date</td>
<td>End Date</td>
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<tr>
<td>NCT00922974</td>
<td>Stereotactic Body Radiotherapy of Bone Metastases: a Randomized Phase II/III Trial</td>
<td>(ongoing)</td>
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<tr>
<td>NCT02167633</td>
<td>Phase II/III Study of Image-Guided Radiosurgery/SBRT for Localized Spine Metastasis</td>
<td>352</td>
<td>Nov 2017</td>
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<tr>
<td>NCT01849510</td>
<td>A Randomized Trial of Stereotactic Radiosurgery Versus Decompressive Surgery Followed by Postoperative Radiotherapy in Metastatic Spinal Cord Compression</td>
<td>130</td>
<td>Dec 2017</td>
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<td>NCT01965223</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>
<td>155</td>
<td>Apr 2019</td>
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<tr>
<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>
<td>21</td>
<td>Aug 2017     (terminated)</td>
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<tr>
<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>
<td>0</td>
<td>Nov 2014 (withdrawn)</td>
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<tr>
<td>NCT01833544</td>
<td>The International Liver Tumor Group RAS-trial Radiofrequency Ablation Versus Stereotactic Body Radiation Therapy for Colorectal Liver Metastases: A Randomized Trial</td>
<td>300</td>
<td>Dec 2014 (terminated)</td>
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</table>

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

### Unpublished stereotactic body radiotherapy

**Non-small-cell lung cancer**

<table>
<thead>
<tr>
<th>NCT</th>
<th>Study Title</th>
<th>Start Date</th>
<th>End Date</th>
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<tbody>
<tr>
<td>NCT01511081</td>
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<td>21</td>
<td>Aug 2017 (terminated)</td>
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**Hepatocellular carcinoma**

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**Oligometastases**

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<tr>
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<td>300</td>
<td>Dec 2014 (terminated)</td>
</tr>
</tbody>
</table>

References:


70. 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


79. Raizer J. Radiosurgery and whole-brain radiation therapy for brain metastases: either or both as the optimal treatment. *JAMA.* Jun 7 2006;295(21):2535-2536. PMID 16757726


**Billing Coding/Physician Documentation Information**

**32701** Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (photon or particle beam), entire course of treatment.

**61781** Stereotactic computer-assisted (navigational) procedure; cranial, intradural (List separately in addition to code for primary procedure)

**61782** Stereotactic computer-assisted (navigational) procedure; cranial, extradural (List separately in addition to code for primary procedure)

**61783** Stereotactic computer-assisted (navigational) procedure; spinal (List separately in addition to code for primary procedure)

**61796** Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 simple cranial lesion

**61797** Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, simple (List separately in addition to code for primary procedure)

**61798** Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 complex cranial lesion

**61799** Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, complex (List separately in addition to code for primary procedure)

**61800** Application of stereotactic headframe for stereotactic radiosurgery (List separately in addition to code for primary procedure)
Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion

Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional spinal lesion (List separately in addition to code for primary procedure)

Unlisted procedure, therapeutic radiology clinical treatment planning

Treatment devices, design and construction; simple (simple block, simple bolus)

Treatment devices, design and construction; intermediate (multiple blocks, stents, bite blocks, special bolus)

Treatment devices, design and construction; complex (irregular blocks, special shields, compensators, wedges, molds or casts)

Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cerebral lesions(s) consisting of 1 session; multi-source Cobalt 60 based

Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cerebral lesions(s) consisting of 1 session; linear accelerator based

Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions

Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services

Radiation treatment delivery, single treatment area, single port or parallel opposed ports, simple blocks or no blocks; up to 5 MeV

Radiation treatment delivery, =>1 MeV; intermediate

Radiation treatment delivery, =>1 MeV; complex

Stereotactic radiation treatment management of cerebral lesion(s) (complete course of treatment consisting of one session)

Stereotactic body radiation therapy, treatment management, per treatment course, to one or more lesions, including image guidance, entire course not to exceed 5 fractions

Proton treatment delivery; simple, without compensation

Proton treatment delivery; simple, with compensation

Proton treatment delivery; intermediate

Proton treatment delivery; complex

Image guided robotic linear accelerator base stereotactic radiosurgery, complete course of therapy in one session, or first session of fractionated treatment

Image guided robotic linear accelerator based stereotactic radiosurgery, delivery including collimator changes and custom plugging, fractionated treatment, all lesions, per session, second through fifth sessions, maximum five sessions per course of treatment

ICD-10 Codes

C34.00- C34.92 Malignant neoplasm of bronchus and lung code range

C41.2 Malignant neoplasm of vertebral column
Malignant neoplasm of brain code range
Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system code range
Secondary malignant neoplasm of brain
Secondary malignant neoplasm of other parts of nervous system
Secondary malignant neoplasm of bone
Benign neoplasm of meninges, unspecified (includes meningo NOS)
Benign neoplasm of cranial nerves (includes acoustic neuroma)
Benign neoplasm of pituitary gland (includes pituitary adenoma)
Trigeminal neuralgia
Arteriovenous malformation of precerebral vessels
Arteriovenous malformation of cerebral vessels

Coding for stereotactic radiosurgery typically consists of a series of CPT codes describing the individual steps required; medical radiation physics, clinical treatment planning, attachment of stereotactic head frame, treatment delivery, and clinical treatment management.

Deleted Codes: (as of 1/1/2011): 61795
Deleted Codes: (as of 1/1/2015): 77403, 77404, 77406, 77408, 77409, 77411, 77413, 77414, 77416, G0173, G0251

Additional Policy Key Words
N/A

Policy Implementation/Update Information
11/1/89 New policy added to the surgery section.
11/1/00 No policy statement changes.
11/1/01 Policy statement revised to add fractionated radiotherapy as investigational. New codes added.
11/1/02 No policy statement changes. Added new codes. Added to the radiology section.
11/1/03 No policy statement changes. Added new codes.
5/1/05 Policy statement revised to include proton beam to the medically necessary procedures; removed fractionated radiotherapy from the policy, added robotically assisted stereotactic radiosurgery as investigational.
11/1/05 Policy statement revised to remove statement regarding robotically assisted stereotactic radiosurgery. Robotic assist procedures are discussed under a separate policy.
11/1/06 Policy statement revised to include extracranial sites as investigational. Change is effective 2/1/2007.
11/1/07 No policy statement changes.
11/1/08 No policy statement changes. Reference numbers 19 to 25 added. Title changed from Stereotactic Radiosurgery to Stereotactic Radiosurgery and Stereotactic Radiotherapy.
12/11/08 Interim update. Policy statements changed to indicate SBRT may be considered medically necessary in specific cases of both non-small cell lung cancer and spinal tumors. Policy title modified to include “Stereotactic Body Radiation Therapy.” CPT coding updated.

11/1/09 No policy statement changes.

11/1/10 No policy statement changes.

11/1/11 No policy statement changes.

1/1/12 Clarification to the policy statement regarding arteriovenous malformations (AVMs) that it is medically necessary only for intracranial AVMs.

11/1/12 Policy statements added that SRS may be considered medically necessary for craniopharyngiomas and glomus tumors, SBRT may be considered medically necessary for spinal or vertebral metastases that are radioresistant (e.g., renal cell carcinoma, melanoma and sarcoma), and that when stereotactic radiosurgery or stereotactic body radiation therapy are performed using fractionation for the medically necessary indications described, it is considered medically necessary. Policy statement added that SBRT is considered investigational for primary and metastatic tumors of the liver, pancreas, kidney, adrenal glands and prostate.

11/1/13 CPT code 32701 added. Policy statement added that SRS is investigational for uveal melanoma. Title revised to remove “Radiotherapy” and replace it with “Body Radiation Therapy.”

11/1/14 Tremor added to the list of investigational indications for SBRT. "except as outlined in the policy statements above." added to investigational statement.

11/1/15 Updated CPT codes. No policy statement changes.

11/1/16 No policy statement changes.

7/1/17 Added medically necessary indication for low to intermediate risk prostate cancer.

11/1/17 No policy statement changes.

12/1/17 No policy statement changes.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.