



BlueCross BlueShield
of Alabama

Effective for dates of service on or after May 1, 2015 refer to:
Blue Cross and Blue Shield of Alabama Radiation Therapy Management – RTM Policies

Name of Policy:

Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy

Policy #: 279
Category: Surgery

Latest Review Date: September 2014
Policy Grade: A

Background:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

- 1. The technology must have final approval from the appropriate government regulatory bodies;*
- 2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
- 3. The technology must improve the net health outcome;*
- 4. The technology must be as beneficial as any established alternatives;*
- 5. The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

- 1. In accordance with generally accepted standards of medical practice; and*
- 2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
- 3. Not primarily for the convenience of the patient, physician or other health care provider; and*
- 4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) are techniques that use highly focused radiation beams to treat both neoplastic and non-neoplastic conditions, in contrast to traditional external radiation beam therapy (EBRT), which involves the use of relatively broad fields of radiation over a number of sessions that may occur over weeks to months. SRS and SBRT rely on 3-dimensional imaging to localize the therapy target. Because they are more targeted than traditional EBRT, SRS and SBRT are often used for treatment at sites that are difficult to reach via surgery, located close to other vital structures, or subject to movement within the body.

Both SRS and SBRT may be completed with one session (single-fraction) or some may require additional sessions (typically no more than five) over a course of days, referred to as fractionated stereotactic radiotherapy. The fractionation used for SRS and SBRT is less than that used for conventional EBRT, thus, “hypo-fractionated.” Fractionation of stereotactic radiotherapy aims to optimize the therapeutic ratio; that is the ratio between tumor control and late effects on normal tissues. The main advantage of fractionation is that it allows higher total doses to be delivered to the tumor because of increased tolerance of the surrounding healthy tissues to each individual, fractionated dose. In addition, some lesions such as large arteriovenous malformations may require more than one procedure to complete the obliteration process.

SRS and SBRT can be administered by several types of devices that are distinguished by their source of radiation, including particle beams (proton), gamma rays from cobalt-60 sources, or high-energy photons from LINAC systems. The use of charged particle (proton beam) radiotherapies is addressed in a separate policy (medical policy #348 *Charged-particle (Proton or Helium Ion) Radiation Therapy*). The most commonly used gamma ray device is the Gamma Knife® (Elekta, Inc., Stockholm), which is a fixed device used for intracranial lesions, typically for smaller lesions. Several brands of LINAC devices are available, including the Novalis Tx® (Novalis, Westchester, IL), the TrueBeamSTx (Varian Medical Systems, Palo Alto, CA), and the CyberKnife® system (Accuray, Sunnyvale, CA).

The radiosurgical procedure using SRS or SBRT is preceded by a process of localizing the target with 3-dimensional imaging such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography/computed tomography (PET/CT), or a combination of modalities.

Applications of SRS and SBRT

SRS and SBRT have been used for a range of malignant and non-malignant conditions. A complete review of all of the indications is beyond the scope of this policy, but a brief discussion of common applications of SRS and SBRT is outlined next.

SRS

The most common applications of SRS include treatment of intracranial malignancies, including primary and metastatic tumors, and benign intracranial tumors such as meningiomas, pituitary adenomas, and acoustic neuromas (vestibular schwannomas). SRS has been used for trigeminal neuralgia that is resistant to other therapies. It is also an established treatment for arteriovenous

malformations (AVMs). More recently, SRS has been investigated as a treatment of functional disorders, which are defined as conditions having no detectable organic cause.

Non-Neoplastic Conditions Treated with SRS

Arteriovenous malformations consist of a tangled network of vessels in which blood passes from arteries to veins without intervening capillaries. They range in size from small, barely detectable lesions to huge 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, there is an ongoing but declining risk of hemorrhage. 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 important alternative in these patients.

Trigeminal neuralgia is a disorder of the fifth cranial (i.e., trigeminal) nerve that causes episodes of intense, stabbing pain in the face. 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, balloon compression, and rhizotomy. SRS has been investigated as an alternative to these neurosurgical treatments.

Seizure disorders are initially treated medically. Surgical treatment is only considered in those rare instances when the seizures have proven refractory to all attempts at aggressive medical management, when 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 amenable 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.

Neuro-destructive procedures include cordotomy, myelotomy, dorsal root entry zone (DREZ) lesions, and stereotactic radiofrequency thalamotomy. SRS targeting the thalamus has been considered an investigative alternative to these neuro-destructive procedures.

SRS, for the destruction of the thalamic nuclei (thalamotomy) has been proposed for a treatment of essential tremor and other forms of tremor (i.e., 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

SRS is used for primary intracranial tumors and tumors that have metastasized to the CNS.

Primary intracranial tumors

Acoustic neuromas, also called vestibular schwannomas, are benign tumors originating on the eighth cranial nerve, sometimes seen in association with neurofibromatosis, which can be

associated with significant morbidity and even death if their growth compresses vital structures. Treatment options include complete surgical excision using microsurgical techniques, but 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 that are related to hormone production (i.e., functioning adenomas) or to neurologic symptoms due to their impingement on surrounding neural structures. Treatment options for pituitary adenomas include surgical excision, conventional radiation therapy, or SRS. Surgical excision is typically offered to patients with functioning adenomas, since 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 radiation therapy has been used in this setting with an approximate 90% success rate with few complications.

Craniopharyngiomas are benign. However, because of proximity to the optic pathways, pituitary gland, and hypothalamus, may cause severe and permanent damage to such critical structures and can even be life-threatening. Total surgical resection is often difficult.

Because of the rarity of glomus jugulare tumors, a variety of treatment paradigms are currently used. There is no consensus regarding the 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 (i.e., medulloblastoma, pineoblastoma). The 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 to reduce the risk of metastatic spread and 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 disease

Intracranial metastases have been considered ideal targets for radiosurgery due to their small spherical size and noninfiltrative borders. Brain metastases are a frequent occurrence, seen in 25–30% of all patients with cancer, particularly in those with lung, breast, or colon cancer or melanoma. Whole brain radiation treatment (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. Stereotactic radiosurgery (SRS) offers the additional ability to treat tumors with relative sparing of normal brain tissue in a single fraction. Ongoing research addresses whether using SRS alone to avoid the adverse effects of WBRT on normal tissues.

SBRT

Studies are being conducted to evaluate SBRT for a number of extracranial sites. This approach is being studied to better target lesions (sparing surrounding normal structures) and to shorten the length of time needed to complete the treatments.

Extracranial primary tumors treated with SBRT

SBRT has been studied for the treatment of lung cancers – specifically NSCLC, with the greatest focus on inoperable Stage I NSCLC. Without the use of SBRT, local NSCLC would be treated with surgical resection, if possible, or conventional radiotherapy.

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 a 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, there is interest in the possibility of treating primary kidney cancer with SBRT.

Data 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 to historical controls. Studies have shown promising initial results on the use of SBRT in prostate cancer with seemingly low toxicity rates.

Extracranial metastatic tumors treated with SBRT

Oligometastasis 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.

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

The 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. 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.

Policy:

Effective for dates of service on or after May 1, 2015 refer to [Blue Cross and Blue Shield of Alabama Radiation Therapy Management – RTM Policies](#)

Effective for dates of service on or after November 1, 2014 and prior to May 1, 2015:

Stereotactic radiosurgery (SRS) using a gamma ray or linear accelerator (LINAC) unit meets Blue Cross and Blue Shield of Alabama’s medical criteria for the following indications:

- Arteriovenous malformations;
- Acoustic neuromas;
- Pituitary adenomas;
- Nonresectable, 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 central nervous system (CNS), including but not limited to, high-grade gliomas (initial treatment or treatment of recurrence);
- Trigeminal neuralgia refractory to medical management.

*** Karnofsky Performance Status (KPS)**

KPS is a standard way of measuring the ability of cancer patients to perform ordinary tasks. The Karnofsky Performance scores range from 0 to 100. A higher score means the patient is better able to carry out daily activities.

Definitions	Rating (%)	Criteria
Able to carry on normal activity and to work; No special care needed	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with efforts; some signs or symptoms of disease.

Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work. Requires occasional assistance, but is able to care for most of his personal needs. Requires considerable assistance and frequent medical care.
	60	
	50	
Unable to care for self; Requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance. Severely disabled; hospital admission is indicated although death not imminent. Very sick; hospital admission necessary; active supportive treatment necessary. Moribund; fatal processes progressing rapidly. Dead
	30	
	20	
	10	
	0	

Stereotactic body radiotherapy (SBRT) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the following indications:

- Patients with stage T1 or T2a non-small cell lung cancer (not larger than 5cm) 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).
- Prostate cancer when **ALL** of the following criteria are met:
 - Clinically localized disease as defined by:
 - Stage less than T3a; **and**
 - Gleason score (GS)<8; **and**
 - Prostate Specific Antigen (PSA)<20; **PLUS**
 - Negative bone scan within the last 6 months (**unless** patient is defined as low risk prostate cancer - PSA<10 plus GS<7 and stage 1c/2a - as bone scans not recommended for this subset)

When **stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) are performed using fractionation** for the medically necessary indications described above, it may be considered to meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage.

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

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

Stereotactic radiosurgery (SRS) does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational** for applications including, but not limited to, the treatment of seizures, functional disorders other than trigeminal neuralgia, including chronic pain, and uveal melanoma.

Stereotactic body radiation therapy (SBRT) does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational for applications including, but not limited to, the treatment of primary and metastatic tumors of the liver, pancreas, kidney, and adrenal glands.

Effective for dates of service on or after December 1, 2013 through October 31, 2014:
Stereotactic radiosurgery using a gamma ray or linear accelerator (LINAC) unit meets Blue Cross and Blue Shield of Alabama’s medical criteria for the following indications:

- Arteriovenous malformations;
- Acoustic neuromas;
- Pituitary adenomas;
- Nonresectable, 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 central nervous system (CNS), including but not limited to, high-grade gliomas (initial treatment or treatment of recurrence);
- Trigeminal neuralgia refractory to medical management.

*** Karnofsky Performance Status (KPS)**

KPS is a standard way of measuring the ability of cancer patients to perform ordinary tasks. The Karnofsky Performance scores range from 0 to 100. A higher score means the patient is better able to carry out daily activities.

Definitions	Rating (%)	Criteria
<i>Able to carry on normal activity and to work; No special care needed</i>	100	<i>Normal no complaints; no evidence of disease.</i>
	90	<i>Able to carry on normal activity; minor signs or symptoms of disease.</i>
	80	<i>Normal activity with efforts; some signs or symptoms of disease.</i>
<i>Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.</i>	70	<i>Cares for self; unable to carry on normal activity or to do active work.</i>
	60	<i>Requires occasional assistance, but is able to care for most of his personal needs.</i>
	50	<i>Requires considerable assistance and frequent medical care.</i>

<i>Unable to care for self; Requires equivalent of institutional or hospital care; disease may be progressing rapidly</i>	40	<i>Disabled; requires special care and assistance.</i>
	30	<i>Severely disabled; hospital admission is indicated although death not imminent.</i>
	20	<i>Very sick; hospital admission necessary; active supportive treatment necessary.</i>
	10	<i>Moribund; fatal processes progressing rapidly.</i>
	0	<i>Dead</i>

Stereotactic body radiotherapy (SBRT) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the following indications:

- Patients with stage T1 or T2a non-small cell lung cancer (not larger than 5cm) 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).

When **stereotactic radiosurgery or stereotactic body radiation therapy** are performed **using fractionation** for the medically necessary indications described above, it may be considered to meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage.

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

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

Stereotactic radiosurgery does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational** for applications including, but not limited to, the treatment of seizures, functional disorders other than trigeminal neuralgia, ~~including~~ chronic pain, and uveal melanoma.

Stereotactic body radiation therapy does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational** for applications including, but not limited to, the treatment of primary and metastatic tumors of the liver, pancreas, kidney, adrenal glands and prostate.

Effective for dates of service July 16, 2012 through November 30, 2013:

Stereotactic radiosurgery performed with an FDA-approved gamma beam (gamma knife), CyberKnife®, linear accelerator (LINAC), or proton beam unit **meets** Blue Cross and Blue

Shield of Alabama's medical criteria for coverage when performed for **ANY** of the following indications:

- Cranial arteriovenous malformations and hemangiomas;
- Acoustic neuromas;
- Pituitary adenomas;
- Pineal Cystomas;
- Non-resectable, residual, or recurrent meningiomas;
- 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, generally under 5 cm;
- Primary and secondary tumors involving the brain parenchyma, meninges/dura or immediately adjacent bony structures;
 - Patients with metastases in these structures should have a limited number of lesions, with stable systemic disease, *Karnofsky Performance Status* 70 or greater (or expected to return to 70 or greater with treatment), and otherwise reasonable treatment expectations.
- Trigeminal neuralgia refractory to medical management;
- Other intracranial and spinal cord lesions;
- Nasopharyngeal tumors;
- Jugular Foramen Schwannomas;
- Uveal melanoma;
- Relapse in a previously irradiated cranial or spinal field where the additional stereotactic precision is required to avoid unacceptable vital tissue radiation;
- Glomus tumors of the base of skull;
- Hemangiopericytomas;
- Carotid-cavernous fistulas;
- Cavernous angiomas;
- Cerebral aneurysms;
- Craniopharyngiomas; glomus jugulare tumors.

Stereotactic Body Radiotherapy (SBRT) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the following indications:

- Patients with stage 1 non-small cell lung cancer showing no nodal or distant disease and who are not candidates for surgical resection; or
- 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).

Stereotactic radiosurgery does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the following:

- Chronic pain
- Epilepsy
- Parkinson disease

- Extracranial oncologic indications not listed above including, but not limited to, primary and metastatic tumors of the following:
 - Pancreas
 - Liver
 - Lung except as described above
 - Prostate
 - Retroperitoneum and pelvis
 - Adrenal glands
-

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Data on the use of SRS and 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 are lacking.

The selection of variables used in the delivery of stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (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.

Trials that would allow direct comparison of all of the possible variables involved in selecting specific SRS and SBRT methods do not currently exist. Therefore, the available evidence is inadequate to permit scientific 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 discussion groups together several different techniques for delivering SRS and SBRT and does not attempt to compare specific radiation planning and delivery techniques.

Stereotactic Radiosurgery (SRS)

Non-Neoplastic conditions

Arteriovenous malformations

In 2014, Mohr et al reported results of the ARUBA trial, a randomized, multicenter trial to compare medical therapy with medical therapy with interventional therapy (including any

neurosurgical, endovascular, or stereotactic radiotherapy procedure) in patients with unruptured arteriovenous malformations (AVM). 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, five with neurosurgery alone, 30 with embolization alone, 31 with radiotherapy alone, 12 with embolization and neurosurgery, 15 with embolization and radiotherapy, and one with all three. The trial was stopped early by its data and safety monitoring board 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 will continue 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 are not reported by therapy type, making it difficult to assess the comparative effectiveness of SRS in AVM treatment.

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

Bowden et al reported outcomes from a retrospective cohort study of patients with cerebellar AVM treated with SRS at a single institution. Sixty-four patients were included, 73% of whom had presented with intracranial hemorrhage and 19% of whom had undergone prior embolization. Total obliteration was achieved at three, four, and five to ten years in 52%, 69%, and 75%, respectively, of subjects. Obliteration was more likely in smaller AVMs but less likely in patients who had undergone prior embolization. Symptomatic adverse radiation events, defined by magnetic resonance imaging (MRI) changes and new neurologic deficits in the absence of hemorrhage, occurred in three patients.

Fokas et al reported long-term follow-up of a cohort of patients who underwent SRS for cerebral AVMs at a single institution. One hundred sixty-four patients were identified, with a median follow-up of 93 months (range, 12-140 months). Thirty-nine percent of subjects had experienced a prior intracranial hemorrhage, and 43.3% and 8.0%, respectively, had undergone prior embolization or neurosurgical procedures. Complete obliteration was seen in 61% of patients at a median time of 29 months. Complete obliteration was achieved at three and five 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 reported outcomes from a cohort of 51 patients with intracranial AVMs treated with SRS at a single institution. Rates of obliteration after a single SRS at three, five, ten, and 15 years were 46.9%, 54.%, 64%, and 68%, respectively; rates of obliteration after multiple SRS sessions at three, five, ten, and 15 years were 46.9%, 61.3%, 74.2%, and 90.3%, respectively.

The adverse radiation events occurred in nine cases (17.6%), with four cases (three symptomatic cysts and one intracranial hemorrhage) not occurring until ten years after the SRS treatment.

Potts et al 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 three 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).

Kano et al published a study to define long-term outcomes and risks of AVM management using two or more stages of stereotactic radiosurgery (SRS) for symptomatic large-volume lesions unsuitable for surgery. Forty-seven patients with such AVMs underwent volume-staged SRS. Eighteen patients (38%) had had a prior hemorrhage and 21 patients (45%) had undergone prior embolization. In 17 patients, AVM obliteration was confirmed after two to four SRS procedures at a median follow-up of 87 months (range 0.4 to 209 months). Five patients had near-total obliteration (volume reduction >75% but residual AVM). The actuarial rates of total obliteration after two-stage SRS were 7%, 20%, 28%, and 36% at three, four, five, and ten years, respectively. The five-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 to 113 months) after the initial two-stage SRS. The overall rates of total obliteration after staged and repeat SRS were 18%, 45%, and 56% at five, seven, and ten years, respectively. Ten patients sustained hemorrhage after staged SRS, and five of these patients died. Three of 16 patients who underwent repeat SRS sustained hemorrhage after the procedure and died. Based on Kaplan-Meier analysis (excluding the second hemorrhage in the patient who had two hemorrhages), the cumulative rates of AVM hemorrhage after SRS were 4.3%, 8.6%, 13.5%, and 36.0% at one, two, five, and ten 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 two 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.

The evidence related to the use of SRS for AVM consists primarily of non-comparative cohort studies, which demonstrate relatively high rates of complete obliteration of AVM after SRS, in the range of approximately 40% in some studies to greater than 70% in others. Isolating the effect of the SRS therapy in and of itself can be challenging, as many patients are treated with more than one therapy, including endovascular treatments and surgery. Recently, an RCT that compared medical therapy with a variety of 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 one particular component of the intervention has benefit or lacks benefit. Longer-term follow up will be forthcoming from this study.

Trigeminal Neuralgia

A 2011 review article summarizes the literature on the use of SRS for trigeminal neuralgia. The majority of patients with typical facial pain will achieve relief following radiosurgical treatment.

Dhople reports 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 one, 4% had two, and 16% had at least three. 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 to 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, seven cases of atypical TN were found, and these patients were removed, for a total of 95 cases herein analyzed. The median follow-up was 5.6 years (range, 13 to 115 months). Before gamma knife surgery (GKS), 88% of patients categorized their pain as BNI IV or V (inadequate control or severe pain on medication), whereas the remainder described their pain as BNI III (some pain, but controlled on medication). After GKS, 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. The median time to response was two weeks (range 0 to 12 weeks), and the median response duration was 32 months (range 0 to 112 months). Eighty-one percent reported initial pain relief, and actuarial rates of freedom from treatment failure at one, three, five, and seven years were 60, 41, 34, and 22%, respectively. Response duration was significantly better for those who had no prior invasive treatment versus those in whom a previous surgical intervention had failed (32 vs 21 months, $p < 0.02$). New facial numbness was reported in 6% of cases.

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 are lacking.

Epilepsy

A 1998 TEC Assessment cited two studies of 11 and nine patients, respectively, in which radiosurgery was used to treat epilepsy. The subsequent literature search revealed three small studies on the use of radiosurgery for medically refractory epilepsy. Regis et al selected 25 patients with mesial temporal lobe epilepsy, of which 16 provided minimum two-year follow-up. Seizure-free status was achieved in 13 patients, two patients were improved, and three patients had radiosurgery-related visual field defects. A study by Schrottner et al included 26 patients with tumor-related epilepsy, associated mainly with low-grade astrocytomas. Mean follow-up among 24 available patients was 2.25 years. Tumor location varied across patients. Seizures were simple partial in six (three with generalization) and complex partial in 18 (five with generalization, one gelastic). Seizures were eliminated or nearly so in 13 patients. Little improvement was observed in four patients and none in seven. Whang and Kwon performed radiosurgery in 31 patients with epilepsy associated with non-progressive lesions. A minimum of one-year follow-up was available in 23 patients, 12 of whom were seizure-free (and three of whom had antiseizure medications discontinued), two had seizures reduced in frequency, and

nine experienced no change. While the Regis series selected a fairly homogeneous clinical sample, the other two 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.

In the most recent 2014 literature review, no new comparative studies evaluating SRS for the treatment of epilepsy were identified.

The currently-available research related to the use of SRS for epilepsy treatment is preliminary. There is inadequate information to determine the risk: benefit ratio of SRS compared with other therapies for epilepsy treatment.

Tremor

SRS has been used for the treatment of tremor through stereotactic radiofrequency thalamotomy. 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 compared with baseline from 3.7 (pre-SRS) to 1.7 (post-SRS; $p < 0.000$) and score on the Fahn-Tolosa-Marin handwriting score improved compared with baseline from 2.8 (pre-SRS) to 1.7 (post-SRS; $p < 0.000$). One patient developed transient mild right hemiparesis and dysphagia and one patient developed mild right hemiparesis and speech impairment.

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

Lim et al 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 six months of follow-up (N=11 with essential tremor and N=3 with Parkinson disease), Fahn-Tolosa-Marin Tremor Rating Scale activities of daily living scores improved significantly after SRS (mean change score 2.7 points; $p = 0.03$). However, there was no significant improvement in other Fahn-Tolosa-Marin Tremor Rating Scale items ($p = 0.53$ for resting tremor, $p = 0.24$ for postural tremor, $p = 0.62$ for action tremor, $p = 0.40$ for drawing, $p > 0.99$ for pouring water, $p = 0.89$ for head tremor). Mild neurologic complications occurred in two patients (lip and finger numbness), and severe neurologic complications occurred in one patient (edema surrounding thalamic lesion with subsequent hemorrhage at the lesion site, with speech difficulty and hemiparesis).

Ohye et al conducted a prospective study of SRS for tremor that included 72 patients, 59 with Parkinson disease and 13 with essential tremor). 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 from 1.5 at baseline to 0.75 at 24 month follow-up).

Young et al reported outcomes for a cohort of 158 patients with tremor who underwent SRS, including 102 patients with Parkinson disease, 52 with essential tremor, and four 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 pre-treatment to 1.2 at last follow-up; $p < 0.05$) and action tremor (from 2.3 pre-treatment 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 one-year of follow-up, 92.1% of patients with essential tremor were completely or nearly tremor-free. Improvements were reported in components of the Fahn-Tolosa-Marin Tremor Rating Scale, but statistical comparisons are not presented. Three patients developed new neurologic symptoms attributed to the SRS.

The evidence related to the use of SRS for tremor consists of uncontrolled cohort studies, many of which report outcomes from the treatment of tremor of varying etiologies. 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

The TEC Assessment from 1998 identified two reports, with two and 47 patients, respectively, who underwent radiosurgical thalamotomy for chronic pain. No new studies were found in the search of recent literature. Thus, the conclusions of the 1998 TEC Assessment have not changed.

Central Nervous System Neoplasms

Acoustic neuromas

SRS is widely used for the treatment of acoustic neuromas (vestibular schwannomas). Case series report generally high rates of local control (LC). For example, Badahshi et al reported a three-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 reported rates of tumor progression-free survival (PFS) for patients with large vestibular schwannomas treated with SRS of 95.2% and 81.8% at three and five years, respectively. For patients with small vestibular schwannomas treated with SRS, tumor PFS was 97% and 90% at three and five 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 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 (<3cm) 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 side effect is functional preservation of the facial and auditory nerve. For example, in a single-institution study, Meijer et al reported on the outcomes of single fraction versus fractionated 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, and hearing preservation. Chung et al 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. 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 had serviceable hearing maintained during at least 36 months of follow-up.

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. Given that vestibular schwannoma is a slow-growing tumor with symptoms most often related to local compression, demonstration of slowing of progression is a reasonable outcome. A single comparative study was identified that demonstrated comparable tumor control outcomes between SRS and surgical therapy for small vestibular schwannomas.

Craniopharyngioma

Hashizume et al evaluated the results of the use of SRS in ten patients with craniopharyngioma adjacent to optic pathways. Ten patients (six men, four women) with craniopharyngioma and median age of 56.5 years (range 10 to 74 years) were treated from 2006 through 2009. Median volume of tumor was 7.9 mL (range 1.1 to 21 mL). A total dose of 30-39 Gy in 10 to 15 fractions (median 33 Gy) was delivered to the target. Ten patients were followed up 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 five patients. No serious complications due to SRS were found.

Hasegawa et al determined the limiting dose to the optic apparatus in single-fraction irradiation in patients with craniopharyngioma treated with gamma knife radiosurgery. One hundred patients with 109 craniopharyngiomas treated with radiosurgery were evaluated with a median follow-up period of 68 months. Tumor volume varied from 0.1 to 36.0 (median, 3.3) cm. The actuarial five and 10-year overall rates of survival of tumor progression after radiosurgery were 93% and 88%, respectively. The actuarial five and 10-year progression-free survival rates were 62% and 52%, respectively.

Among 94 patients in whom visual function was evaluable, only three patients developed radiation-induced optic neuropathy, indicating an overall Kaplan-Meier radiation-induced optic neuropathy rate of 5%.

Combs et al evaluated the long-term outcome in patients with craniopharyngiomas treated with fractionated stereotactic radiotherapy. A total of 40 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 grays (Gy) (range 50.4 to 56 Gy) was applied in a median conventional fractionation of 5 x 1.8 Gy per week. Follow-up examinations included thorough clinical assessment as well as contrast-enhanced magnetic resonance imaging (MRI) scans. After a median follow-up of 98 months (range 3 to 326 months), local control was 100% at both five years and ten years. Overall survival rates at five years and ten years were 97% and 89%, respectively. A complete response was observed in four 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 three months after fractionated stereotactic radiotherapy (FSRT). No visual impairment, radionecrosis, or developments of secondary malignancies were observed. The authors concluded that long-term outcome of fractionated radiosurgery for craniopharyngiomas is excellent with regard to local control, as well as treatment-related side effects.

The evidence related to the use of SRS for craniopharyngioma consists primarily of case series and cohort studies, which report high rates OS. There is a lack of comparative studies evaluating the treatment of pituitary adenomas with SRS versus surgery or traditional radiotherapy.

Glomus Jugulare Tumors

Ivan et al conducted a meta-analysis of tumor control rates and treatment-related mortality for patients with glomus jugulare tumors. In this study, the authors assessed data collected from 869 patients with glomus jugulare tumors from the published literature to identify treatment variables that impacted clinical outcomes and tumor control rates. A comprehensive search of the English language literature identified 109 studies that collectively 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 radiosurgery (STR+SRS), and stereotactic radiosurgery alone (SRS). The authors identified 869 patients who met their inclusion criteria. In these studies, the length of follow-up ranged from six to 256 months. Patients treated with STR were observed for 72 ± 7.9 months and had a tumor control rate of 69% (95% confidence interval [CI]: 57 to 82%). Those who underwent GTR had a follow-up of 88 ± 5.0 months and a tumor control rate of 86% (95% CI: 81% to 91%). Those treated with STR+SRS were observed for 96 ± 4.4 months and had a tumor control rate of 71% (95% CI: 53% to 83%). Patients undergoing SRS alone had a follow-up of 71 ± 4.9 months and a tumor control rate of 95% (95% CI: 92% to 99%). The authors' analysis found that patients undergoing SRS had the lowest rates of recurrence of these four cohorts, and therefore, these patients 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 CN IX to XI than those who underwent SRS alone; however, the rates of CN XII deficits were comparable.

The evidence review related to the use of SRS for glomus jugulare tumors identified includes a large meta-analysis, which suggested 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 seven prospective cohort studies and ten retrospective cohort studies, with 925 patients included in the meta-analysis. Outcomes were reported 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 2mL, 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 from 2 to 4mL, 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 4mL was 91% (95% CI, 89% to 94%), 2% (95% CI, 0% to 5%) and 22% (95% CI, 14% to 31%), respectively. The rates of tumor control and rates of radiosurgery-induced optic neuropathy injury differed significantly across the three groups.

In 2014, Lee et al retrospectively reported outcomes for 41 patients treated with SRS in a cohort of 569 patients treated for nonfunctioning pituitary adenomas at three institutions. At a median follow-up of 48 months, on neuroimaging 34 patients (82.9%) had a decrease in tumor volume, four patients had tumor stability (9.8%), and three patients had a tumor increase (7.3%). PFS was 94% at five years and 85% at ten years post-SRS. New onset or worsened pituitary deficiencies were found in ten patients (24.4%) at a median follow-up of 52 months. The authors conclude 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 an operation would involve a high risk; in patients with clear neuroimaging and neuro-endocrine evidence of an NFA, no mass effect on the optic apparatus, and progressive tumor on neuroimaging follow-up; or in patients who wish to avoid resection.

Sheehan et al reported results from a multicenter registry of 512 patients who underwent SRS for nonfunctional pituitary adenomas. Four hundred seventy-nine (93.6%) had undergone prior resection, and 34 (6.6%) had undergone prior external beam radiotherapy (EBRT). Median follow-up was 36 months. At last follow up, 31 of 469 patients with available follow-up (6.6%) had tumor progression, leading to an actuarial PFS of 98%, 95%, 91%, and 85% at three, five, eight, and ten years post-SRS, respectively. Forty-one (9.3%) of 442 patients had worsened or new CNS deficits, more commonly in patients with tumor progression (p=0.038).

Non-comparative studies demonstrate high rates of tumor control (85% and better) for pituitary adenomas with SRS treatment, with better tumor control with smaller lesions. There is a lack of comparative studies evaluating the treatment of pituitary adenomas with SRS versus surgery or traditional radiotherapy.

Brain Metastases

Systematic Reviews and Meta-Analyses

Roos et al examined the randomized evidence to treat brain metastases. A search of MEDLINE, EMBASE, and Cochrane databases for published papers and abstracts on relevant randomized trials was undertaken. Fourteen randomized trials were identified, eleven final reports and three abstracts, investigating various combinations of surgery, SRS and whole brain radiation therapy (WBRT). Most of the trials had significant limitations. Surgery and SRS improved local control, maintenance of performance status and survival for favorable prognosis patients with solitary brain metastases relative to WBRT alone, although the absolute survival benefit for the majority was modest. Limited data suggest similar outcomes from surgery and SRS, but few patients were truly suitable for both options. For multiple (two to four) brain metastases, SRS improved local control and functional outcome but not survival. Adjuvant WBRT also improved intracranial control but not survival; however, the neurocognitive risk:benefit ratio of WBRT was controversial. Quality of life data were limited.

A 2011 review by Park et al on the use of SRS for brain metastases discussed the two randomized trials that demonstrated that the addition of single-dose SRS to WBRT improves local tumor control and maintenance of functional status for patients. Also reviewed are three recent randomized trials comparing the outcomes for SRS alone versus SRS plus WBRT for limited brain metastases. All three trials indicated a lack of detriment in neurocognition or quality of life with the omission of WBRT, despite significantly worsened intracranial tumor control that would require additional salvage therapy in almost all patients.

In a 2010 analysis, a Cochrane review addressed the role for both SRS and whole-brain radiation therapy (WBRT) in patients with small numbers of metastatic lesions (generally no more than three or four lesions), noted that given the unclear risk of bias in the included studies, the results need to be interpreted with caution. The analysis of all included patients (three trials) indicated that SRS plus WBRT did not show a survival benefit over WBRT alone; however, performance status and local control were significantly better in the SRS plus WBRT group.

RCTs

Since publication of the systematic reviews, several RCTs have been published. Chang et al concluded that patients treated with SRS plus WBRT were at a greater risk of a significant decline in learning and memory function by four months compared with the group that received SRS alone.

Some studies have suggested that use of radiosurgery for brain metastases should be limited to patients with three or fewer lesions. A randomized trial compared whole-brain radiation therapy (WBRT) with WBRT plus radiosurgery boost to metastatic foci. It found that the significant advantage of radiosurgery boost over WBRT alone in terms of freedom from local failure did not differ among patients with two, three, or four metastases. Survival also did not depend on the number of metastases. As the number of metastases rises, so does the total volume of tissue receiving high-dose radiation, thus the morbidity risk of radiation necrosis associated with radiosurgery is likely to increase. For a large number of metastases, and for large volumes of tissue, this risk may be high enough to negate the advantage of radiosurgery plus WBRT over WBRT alone seen in patients with four or fewer metastases. Stereotactic radiosurgery centers

commonly exclude patients with more than five metastases from undergoing radiosurgery. It is difficult to identify a specific limit on the number of metastases for which the use of 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 versus SRS alone for treatment of patients with one to four brain metastases. They found a 12-month intracranial tumor recurrence rate of 46.8% in the SRS plus WBRT group compared to 76.4% in the group that only received SRS. However, median survival times were not different 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.

Nonrandomized, Comparative Studies

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

Non-comparative Studies

Non-comparative 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 conducted a prospective observational study to evaluate primary SRS in patients with one to ten newly-diagnosed brain metastases. Inclusion criteria included largest tumor volume less than 10mL and less than 3cm in the longest diameter, a total cumulative volume of 15mL or less, and a Karnofsky performance status score of 70 or higher. Among total 1194 patients, the median OS after SRS was 13.9 (95% CI, 12.0 to 15.6) in the 455 patients with one tumor, 10.8 months (95% CI, 9.4 to 12.4) in the 531 patients with two to four tumors, and 10.8 months (95% CI, 9.1 to 12.7) in the 208 patients with five to ten tumors.

Rava et al, in a cohort study including 53 patients with at least ten brain metastases, described the feasibility of SRS treatment. Median survival was 6.5 months in this cohort. Raldow et al, in a cohort of 103 patients with at least five brain metastases who were treated with SRS alone, demonstrated a median OS of 8.3 months, comparable with historical controls. OS was similar for patients with five to nine and with at least ten metastases (7.6 months and 8.3 months, respectively).

Yomo et al reported outcomes for 41 consecutive patients with ten or fewer brain metastases from NSCLC who received SRS as primary treatment. The study reported one- and two-year OS rates of 44% and 17%, respectively, with a median survival time of 8.1 months. Distant brain metastases occurred in 44% by one year, with 18 patients requiring repeat SRS, seven requiring WBRT, and one requiring microsurgery.

For cases of brain metastases, evidence from RCTs and systematic reviews indicates that the use of SRS improves outcomes in the treatment of brain metastases. SRS appears to be feasible in the treatment of larger numbers (e.g., >10) of brain metastases, and outcomes after SRS treatment do not appear to be worse for patients with larger numbers of metastases, at least for patients with ten or fewer metastases.

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) are identified.

A 2012 review article summarizes the literature on the use of SRS for uveal melanoma, with long-term tumor control rates using the Gamma Knife reported to be around 90%. Initial studies using SRS for uveal melanoma reported secondary side effects from radiation to be common; however, more recent studies have reported lower incidences with lower total radiation doses.

The largest study to date consisted of 212 patients with choroidal melanoma, who were not suitable for brachytherapy or resection. Patients in the study received different doses of radiation ranging from 50Gy to 70Gy, in five fractions over seven days. Ophthalmologic examination was performed at baseline and every three months in the first two years, every six months until five years, and once a year until ten years after SRS. The study included measurement of tumor dimension and height using standardized methods, assessment of visual acuity and routine ophthalmologic examinations. Local tumor control was 96% at five years, and 93% at ten years. Thirty-two patients developed metastases, and 22 of these patients 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 reported outcomes for 189 patients with choroidal melanoma treated with SRS (Gamma Knife). All patients with choroidal melanoma at the authors' institution were offered SRS as an alternative to enucleation if they wished to retain their eye, and other globe-preserving treatment options were not feasible because of tumor size or location or the patient's general health. Sixty-six patients (37.3%), all treated before 2003, received high-dose SRS (35-80Gy); subsequently, all patients received low-dose SRS (30Gy in 87 patients and 25Gy in 24 patients). The median overall follow-up was 39.5 months. During follow-up, local tumor control was achieved in 167 patients (94.4%). Enucleation was required in 25 patients, seven due to tumor recurrence and 18 due to radiation-induced adverse effects. OS and distant metastasis rates are not reported.

Furdova et al reported outcomes for a cohort of 96 patients who underwent SRS at a single center in Slovakia for stage T2/T3 uveal melanoma. Local tumor control occurred in 95% of patients at three years of follow-up and in 85% of patients at five years of follow up. Eleven patients (11.5%) required secondary enucleation between three and five year's post-SRS due to radiation neuropathy or secondary glaucoma.

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

The evidence related to SRS for the treatment of uveal melanoma is limited to case series. The published literature is insufficient to demonstrate improved outcomes with the use of stereotactic radiosurgery over other accepted radiation modalities in the treatment of uveal melanoma.

Stereotactic Body Radiation Therapy

Spinal tumors

Gerszten et al reported on the outcomes of 115 patients with spinal tumors of varying etiologies, i.e., benign, metastatic, single, or multiple lesions, in a variety of locations, i.e., cervical, thoracic, lumbar, sacral, who were treated with the CyberKnife in a single session. The majority of patients was treated for pain control and also had received prior external beam irradiation. The authors point out that radiation therapy 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 point out that conventional methods of delivering intensity-modulated radiation therapy (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 external beam radiation therapy (EBRT) typically is delivered over a course of 10 to 20 fractions. In contrast, in this study, only one CyberKnife treatment session was used. In a 2005 study, Degen et al reported on the outcomes of 51 patients with 72 spinal lesions who were treated with the CyberKnife. Patients underwent a median of three treatments. Pain was improved, as measured by declining mean visual analogue scale (VAS) score, and quality of life was maintained during the one-year study period.

Gerszten et al recently published results on a series of 500 cases from a single institution (334 tumors had previously undergone external beam irradiation) using the CyberKnife system. In this series, the maximum intratumoral dose ranged from 12.5 to 25Gy with a mean of 20Gy. Long-term pain improvement occurred in 290 of 336 cases (86%). Long-term radiographic tumor control was demonstrated in 90% of lesions treated with radiosurgery as a primary treatment modality. Twenty-seven of 32 cases (84%) with a progressive neurologic deficit before treatment experienced at least some clinical improvement. Chang et al reported on Phase I/II results of SBRT in 74 spinal lesions in 63 patients (55% had prior irradiation) with cancer. The actuarial one-year tumor progression-free incidence was 84%. Pattern-of-failure analysis showed two primary mechanisms of failure: recurrence in the bone adjacent to the site of previous treatment; and recurrence in the epidural space adjacent to the spinal cord. The authors concluded that analysis of the data obtained in their study supports the safety and effectiveness of SBRT in cases of metastatic spinal tumors. They add that they consider it 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, more liberal spinal cord dose constraints than those used in the study.

Sahgal et al evaluated rates of vertebral compression fractures after SBRT in 252 patients with 410 spinal segments treated with SBRT. Fifty-seven fractures were observed (13.9% of spinal segments treated), with 27 de novo fractures and 30 cases of existing fracture progression. Most fractures occurred relatively early post-treatment, 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.

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 (NSCLC)

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. The authors included 40 studies reporting outcomes from SBRT, including 4850 patients, and 23 studies reporting outcomes after surgery published in the same time period, including 7071 patients. For patients treated with SBRT, the mean unadjusted OS rates at one, three, and five years were 83.4%, 56.6%, and 41.2%, respectively. The mean unadjusted OS rates at one, three, and five 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 review by Nguyen et al cites a number of studies of SBRT for early-stage lung cancer receiving a biologic equivalent dose of 100Gy or more. Three of the studies cited reported five-year survival that ranged from 30% to 83%; in the largest series of 257 patients, the five-year survival was 42%. Koto et al reported on a Phase II study of 31 patients with Stage I NSCLC. Patients received 45Gy in three fractions, but those with tumors close to an organ at risk received 60Gy in eight fractions. With a median follow-up of 32 months, the three-year overall survival was 72%, while disease-free survival was 84%. Five patients developed Grade 2 or greater pulmonary toxicity. While comparative studies were not identified, older studies have reported three-year disease-specific survival rates of 49% for those with Stage I disease.

Nonrandomized, Comparative Studies

In a matched-cohort study design, Crabtree et al retrospectively compared outcomes between SBRT and surgical therapy in patients with Stage I NSCLC. Four hundred fifty-eight patients underwent primary surgical resection, and 151 were treated with SBRT. Surgical and SBRT patients differed significantly on several baseline clinical and demographic characteristics, with SBRT patients having an older mean age, higher comorbidity scores, a greater proportion of peripheral tumors, and worse lung function at baseline. For the surgical group, three-year OS and disease-free survival (DFS) were 78% and 72%, respectively. Of note, among the 458 patients with clinical 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, three-year and five-year OS were 66% and 43%, respectively. For patients without occult nodal disease, three- and five-

year OS were 80% and 68%, respectively. For the SBRT group, three-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, ACE comorbidity score, forced expiratory volume in one second percent (FEV1%), and tumor location (central versus peripheral). In the final matched comparison, three-year OS was 52% versus 68% for SBRT and surgery, respectively ($p=0.05$), while DFS was 47% versus 65% ($p=0.01$). Two-, three-, four-, and five-year local recurrence-free survival for SBRT was 91%, 91%, 81%, and 40%, respectively, versus 98%, 92%, 92%, and 92% for surgery ($p=0.07$).

Jepperson et al compared SBRT with conventional radiotherapy for patients with medically inoperable NSCLC (T1-2N0M0). 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 FEV1, and a greater proportion of T1 stage disease. Median OS was 36.1 months versus 24.4 months for SBRT and conventional radiotherapy, respectively ($p=0.015$). Local failure-free survival rates at one year were 93% in the SBRT group versus 89% in the conventional radiotherapy group and at five years 69% versus 66%, SBRT and conventional radiotherapy, respectively ($p=0.99$).

Port et al compared SBRT with wedge resection for patients with clinical stage 1A NSCLC using data from a prospectively maintained database. One hundred sixty-four patients were identified, 99 of who 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 disease-free three-year survival (77% for wedge resection vs 59% for SBRT, $p=0.066$).

Varlotta et al compared surgical therapy (N=132 with lobectomy and N=48 with sublobar resection) with SBRT (N=137) in the treatment of stage 1 NSCLC. Mortality was 54% in the SBRT group, 27.1% in the sublobar resection group, and 20.4% in the lobar resection group. After matching for pathology, age, sex, tumor diameter, aspirin use, and Charlson comorbidity index, patients with SBRT had lower OS than patients treated with either wedge resection ($p=0.003$) or lobectomy (<0.000).

Non-comparative Studies

Timmerman et al evaluated the toxicity and efficacy of stereotactic body radiation therapy in a high-risk population of patients with early stage but medically inoperable lung cancer. In a Phase II North American multicenter study of patients aged 18 years or older with biopsy-proven peripheral T1-T2N0M0 non-small cell tumors (measuring <5 cm in diameter) and medical conditions precluding surgical treatment. The prescription dose was 18Gy per fraction x 3 fractions (54Gy total), with the entire treatment lasting between 1.5 to 2 weeks. The primary endpoint was two-year actuarial primary tumor control; secondary endpoints were disease-free survival (i.e., primary tumor, involved lobe, regional, and disseminated recurrence), treatment-related toxicity, and overall survival. A total of 59 patients accrued, of which 55 were evaluable

(44 patients with T1 tumors and eleven patients with T2 tumors) with a median follow-up of 34.4 months (range, 4.8 to 49.9 months). Only one patient had primary tumor failure; the estimated three-year primary tumor control rate was 97.6% (95% confidence interval [CI]: 84.3 to 99.7%). Three patients had recurrence within the involved lobe; the three-year primary tumor and involved lobe (local) control rate was 90.6% (95% CI: 76.0-96.5%). 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 three-year rate of disseminated failure was 22.1% (95% CI: 12.3 to 37.8%). The rates for disease-free survival and overall survival at three years were 48.3% (95% CI: 34.4 to 60.8%) and 55.8% (95% CI: 41.6 to 67.9%), respectively. The median overall survival was 48.1 months (95% CI: 29.6 months to not reached). Protocol-specified treatment-related Grade 3 adverse events were reported in seven patients (12.7%; 95% CI: 9.6 to 15.8%); Grade 4 adverse events were reported in two patients (3.6%; 95% CI: 2.7 to 4.5%). No Grade 5 adverse events were reported. The authors concluded that patients with inoperable non-small cell lung cancer who received stereotactic body radiation therapy had a survival rate of 55.8% at three years, high rates of local tumor control, and moderate treatment-related morbidity.

Hof et al 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 stereotactic radiotherapy. In this series, at 12 months, overall survival was 75% and disease-free survival 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 evaluated the influence of tumor size on outcomes. 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 also significantly associated with tumor volume more significant than diameter.

Harkenrider et al reported outcomes after SBRT for 34 patients with un-biopsied lung cancer, with estimated rates of two-year regional control, distant control, and OS of 80%, 85%, and 85%, respectively.

Although no comparative data are available, studies have shown that SBRT for patients with Stage I NSCLC who are not candidates for surgical resection because of comorbid conditions or for those with early stage disease who refuse surgery, survival rates may be comparable with surgical resection. Therefore, SBRT may be considered medically necessary in patients with Stage T1 and T2a NSCLC (not larger than 5cm in diameter) showing no nodal or distant disease.

Hepatocellular Carcinoma (HCC)

Systematic Reviews and Meta-Analyses

Meng and colleagues conducted a systematic review and meta-analysis of transcatheter arterial chemoembolization (TACE) in combination with radiotherapy compared to TACE alone for unresectable HCC using meta-analysis of data from the literature involving available trials. Seventeen trials involving 1,476 patients were identified. Five were RCTs, and 12 non-

randomized studies were Graded C. Results showed that TACE plus RT significantly improved survival and tumor response over TACE alone. The authors concluded that considering the strength of the evidence, additional randomized controlled trials are needed before combination TACE and RT can be recommended routinely.

A 2012 systematic review conducted by Tao and Yang assessed the efficacy and safety of SBRT for treating primary and secondary hepatic neoplasms. The review included prospective clinical trials published in English. Fifteen studies involving 158 patients with primary tumors and 341 patients with metastases to the liver were included. Treatment was performed in one to ten fractions to total doses of 18 to 60Gy. Most studies that were included reported outcomes for patients with both primary and metastatic disease, without separating out outcome data for primary tumors only. In addition, some studies reporting on outcomes for primary liver tumors included cholangiocarcinomas. At Indiana University, in a Phase I study, Cardenes et al treated 17 HCC patients with Child-Turcotte-Pugh (CTP) CTP-A or CTP-B, one to three lesions and cumulative tumor diameter ≤ 6 cm. Patients with CTP-A were treated in three fractions with the dose escalated from 12 to 16Gy. For patients with CTP-B, the dose was modified to five fractions starting at 8Gy per fraction and was not escalated because two patients treated at 3×14 Gy developed Grade 3 hepatic toxicity. The one-year overall survival was 75%, and there were no local failures during the median 24 months of follow-up.

Building upon the Phase I study, 36 patients with CTP-A disease were treated with 3×18 Gy, and 24 patients with CTP-B disease were treated with 5×8 Gy. With this regimen, Andolino et al reported complete response, partial response, and stable disease for 30%, 40%, and 25% of tumors, respectively. Two-year local control, progression-free survival, and overall survival were 90%, 48%, and 67%, respectively, with a median progression-free survival of 20.4 months and overall survival of 44.4 months.

In an attempt to extend the use of SBRT to larger lesions, Shin et al treated six patients with large tumors (median tumor volume 1,288mL, range 1,008 to 1,815mL) with no worse than CTP-A liver disease and without extrahepatic metastases. The $4 \times 8-10$ Gy regimen was relatively safe with only one case of Grade 3 changes in transaminases. However, one-year overall survival was only 33%, in part due to advanced disease. One-year local control and overall survival rates were 50 to 100% and 33 to 100%, respectively. There were 13 cases of radiation-induced liver disease and four Grade 5, six Grade 4, and sixty-nine Grade 3 adverse events reported.

Non-comparative Studies

Bujold and colleagues reported on sequential Phase I and II trials of SBRT for locally advanced hepatocellular carcinoma. Two trials of SBRT for patients with HCC who were considered to be unsuitable for standard locoregional therapies were conducted from 2004 to 2010. All of the patients had Child-Turcotte-Pugh class A disease. The primary end points were toxicity and local control at one 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, 2004 to 2007; n=52 in Trial 2, 2007 to 2010). Underlying liver disease was hepatitis B in 38% of patients, hepatitis C in 38%, alcohol related in 25%, and 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 117.0mL (range, 1.3 to 1,913.4mL). Tumor vascular thrombosis (TVT) was present in 55% and 12% of patients had extrahepatic disease. Local control at one year was 87% (95% CI, 78% to 93%). Toxicity \geq grade # was seen on 30% of patients. In seven patients (two with TVT and progressive disease), death was possibly related to treatment (1.1 to 7.7 months after SBRT). Median overall survival was 17.0 months (95% CI, 10.4 to 21.3 months).

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 (CTP) Class A and 24 CTP Class B. The median number of fractions, dose per fraction, and total dose was three, 14Gy, and 44Gy, respectively, for those with CTP Class A cirrhosis and five, eight, and 40Gy, respectively, for those with CTP Class B. The records of all patients were reviewed, and treatment response was scored according to Response Evaluation Criteria in Solid Tumors v1.1. Toxicity was graded according to the Common Terminology Criteria for Adverse Events v4.0. Local control (LC), time to progression (TTP), progression-free survival (PFS), and overall survival (OS) were calculated according to the method of Kaplan and Meier. The median follow-up time was 27 months, and the median tumor diameter was 3.2 cm. The two-year LC, PFS, and OS 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 seven months. There were no \geq Grade 3 nonhematologic toxicities. Thirteen percent of patients experienced an increase in hematologic/hepatic dysfunction greater than one grade, and 20% experienced progression in CTP class within three months of treatment. The authors concluded that SBRT is a safe, effective, noninvasive option for patients with HCC \leq 6cm and that SBRT should be considered when bridging to transplant or as definitive therapy for those ineligible for transplant.

Ibarra et al evaluated tumor response to SBRT in a combined multicenter database. Patients with advanced HCC (n=21) or intrahepatic cholangiocarcinoma (ICC, n=11) treated with SBRT from four academic medical centers were entered into a common database. Statistical analyses were performed for freedom from local progression (FFLP) and patient survival. The overall FFLP for advanced HCC was 63% at a median follow-up of 12.9 months. Median tumor volume decreased from 334.2 to 135cm³ (p<0.004). The median time to local progression was 6.3 months. The one and two-year overall survival rates were 87% and 55%, respectively. The incidence of Grade 1 to 2 toxicities, mostly nausea and fatigue, was 39.5%. Grade 3 and 4 toxicities were present in two and one patients, respectively.

Price et al reported the results of a Phase 1/2 trial which 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 \leq 6cm or up to three lesions with sum diameters \leq 6cm, and well-compensated cirrhosis. All patients had imaging before, at one to three months, and every three to six months after SBRT. Patients received three to five fractions of SBRT. Median SBRT dose was 42 Gray (Gy) (range 24 to 48Gy). Median follow-up was 13 months. Per Response Evaluation Criteria in Solid Tumors (RECIST), four patients had a complete response (CR), 15 had a partial response (PR), and seven achieved stable disease (SD) at 12 months. One patient with SD experienced progression marginal to the treated area. The overall best response rate (CR + PR) was 73%. In comparison, by European Association for the

Study of the Liver (EASL) criteria, 18 of 26 patients had $\geq 50\%$ nonenhancement at 12 months. Thirteen of 18 demonstrated 100% nonenhancement, being $>50\%$ in five patients. Kaplan-Meier one and two-year survival estimates were 77% and 60%, respectively. SBRT is effective therapy for patients with HCC with an overall best response rate (CR + PR) of 73%.

Louis et al evaluated the feasibility, tolerance, and toxicity of SBRT in 25 HCC patients who were not eligible for other treatment modalities. All patients had liver cirrhosis with an Eastern Cooperative Oncology Group (ECOG) performance score of less than two and pre-treatment Child scores ranging from A5 to B9. A total dose of 45Gy in three fractions of 15Gy each was prescribed to the 80% isodose line (95% of the PTV received 45Gy) and delivered to the target volume over 10 to 12 days. Overall, the treatment was well-tolerated with two Grade 3 acute toxicities and no acute Grade 4 toxicities. Late toxicity was minimal; all observed late toxicities occurred within the first six months of follow-up. Three hepatic recurrences at a distance from the initial target were observed. The actuarial one and two-year local control rate was 95% (95% CI: 69 to 95%). At a median overall follow-up of 12.7 months (range, 1 to 24 months), six of the 25 (24%) patients have died. Overall actuarial survival at one and two years was 79% (95% CI: 52 to 92%) and 52% (95% CI: 19 to 78%), respectively.

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 15.4cc (3.0 to 81.8), and the median follow-up duration was 28.7 months (8.4 to 49.1). Complete response (CR) for the in-field lesion was initially achieved in 59.6% and partial response (PR) in 26.2% of patients. Hepatic out-of-field progression occurred in 18 patients (42.9%) and distant metastasis developed in 12 (28.6%) patients. Overall one-year and three-year survival rates were 92.9% and 58.6%, respectively. In-field progression-free survival at one and three years was 72.0% and 67.5%, respectively. Patients with smaller tumors had better in-field progression-free survival and overall survival rates ($<32\text{cc}$ vs. $\geq 32\text{cc}$, $p < 0.05$). No major toxicity was encountered but one patient died with extrahepatic metastasis and radiation-induced hepatic failure.

Yoon et al reported outcomes for 93 patients with primary nonmetastatic HCC treated with SBRT at a single institution. The median follow-up was 25.6 months. OS at one and three years was 86% and 53.8%, respectively. The main cause of treatment failure was intrahepatic (i.e., out-of-field) metastases. At one and three 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 one and three years were 51.9% and 32.4%, respectively.

Jung et al reported rates of radiation-induced liver disease in patients with HCC treated with SBRT for small ($<6\text{cm}$), nonmetastatic HCC that was not amenable to surgery or percutaneous ablative therapy. Ninety-two patients were included, 17 of whom (18.5%) developed Grade II or worse radiation-induced liver disease within three months of SBRT. In multivariable analysis, Child-Pugh class was the only significant predictor of radiation-induced liver injury. The one- and three-year survival rates were 86.9% and 54.4% respectively; with the median survival of 53.6 months. The presence of radiation-induced liver disease was not associated with survival.

Studies on the use of SBRT for HCC have consisted of heterogeneous treatment schedules, treatment planning techniques and patient populations. The optimal dose and fractionation scheme are unknown. Although promising LC rates of 71% to 100% have been reported, it is not clear how SBRT should be used considering the use of established treatment modalities, including systemic therapy, radiofrequency ablation (RFA), and chemoembolization. Therefore, the use of SBRT for HCC is considered investigational.

Prostate Cancer

Nonrandomized Comparative Studies

Katz et al compared quality of life (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, three weeks, five, eleven, 24 and 36 months (SBRT group) and baseline, one, six, 12, 24, and 36 months (surgery group). The largest differences in QOL occurred one to six 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 the patients who underwent prostatectomy but not for the SBRT patients.

In 2014, Yu et al compared toxicities after treatment with either SBRT (N=1335) or IMRT (N=2670) as primary treatment for prostate cancer, using claims data for Medicare beneficiaries. The authors identified early stage prostate cancer patients aged 66 to 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 six months after treatment initiation, 15.6% of SBRT patients had a claim indicative of treatment-related GU toxicity versus 12.6% of IMRT patients (odd ratio [OR]=1.29; 95% CI, 1.05 to 1.53; p=0.009). By 12 months post-treatment, 27.1% of SBRT versus 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 versus 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 six months post-treatment, 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 versus 4.1% of IMRT patients (OR=1.42; 95% CI, 1.00 to 1.85; p=0.02), but at 12 and 24 months post-treatment, there were no significant differences in GI toxicity between groups.

Non-comparative Studies

Multiple cohort studies report outcomes for patients treated with a standard dose of SRS, or for groups of patients treated with SRS at escalating doses.

McBride et al reported on a multi-institutional experience with SBRT for early-stage, low-risk prostate adenocarcinoma. A total of four centers and 45 patients were enrolled in a Phase I, multi-institutional trial. Thirty-four patients received 7.5 grays (Gy) delivered in five fractions, nine patients received 7.25 Gy delivered in five fractions, and two patients received other regimens. The variables evaluated were biochemical progression-free survival (bPFS), prostate-

specific antigen (PSA) bounce, and toxicities. Health-related quality of life was evaluated using the Sexual Health Inventory for Men (SHIM), American Urological Association (AUA), and Expanded Prostate Cancer Index Composite (EPIC) questionnaires. The median follow-up for surviving patients was 44.5 months (range 0 to 62 months). The bPFS rate at three years was 97.7%. The median PSA declined from 4.9ng/mL at diagnosis to 0.2ng/mL at last follow-up, and the median percentage PSA decline at 12 months was 80%. Nine patients experienced at least one PSA bounce ≥ 0.4 ng/mL, and four patients experienced two PSA bounces. The median time to first PSA bounce was 11.6 months (range 7.2 to 18.2 months), and the mean percentage PSA bounce was 1.07ng/mL. There was one episode of late Grade 3 urinary obstruction, and there were two episodes of late-Grade 3 proctitis. There was a significant late decline in SHIM and EPIC sexual scores and a small, late decline in the EPIC Bowel domain score.

Boike et al evaluated the tolerability of escalating doses of SBRT in the treatment of localized prostate cancer. Eligible patients included those with Gleason score 2 to 6 with prostate-specific antigen (PSA) ≤ 20 , Gleason score 7 with PSA ≤ 15 , $\leq T2b$, prostate size ≤ 60 cm, and American Urological Association (AUA) score ≤ 15 . Dose-limiting toxicity was defined as Grade III or worse gastrointestinal (GI)/genitourinary (GU) toxicity by Common Terminology Criteria of Adverse Events (version 3). Patients completed quality-of-life questionnaires at defined intervals. Groups of 15 patients received 45Gy, 47.5Gy, and 50Gy in five fractions (45 total patients). The median follow-up is 30 months (range, 3 to 36 months), 18 months (range 0 to 30 months), and 12 months (range 3 to 18 months) for the 45Gy, 47.5Gy, and 50Gy groups, respectively. For all patients, GI Grade ≥ 2 and Grade ≥ 3 toxicity occurred in 18% and 2%, respectively, and GU Grade ≥ 2 and Grade ≥ 3 toxicity occurred in 31% and 4%, respectively. Mean AUA scores increased significantly from baseline in the 47.5-Gy dose level ($P=0.002$), as compared with the other dose levels, where mean values returned to baseline. Rectal quality-of-life 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 + 2ng/mL failure definition.

Freeman and King presented the outcomes for low-risk prostate cancer patients with a median follow-up of five years after SBRT. Between 2003 and 2005, a pooled cohort of 41 consecutive patients from two institutions received SBRT for clinically localized, low-risk prostate cancer. Prescribed dose was 35 to 36.25Gy in five fractions. No patient received hormone therapy. Kaplan-Meier biochemical progression-free survival (defined using the Phoenix method) and Radiation Therapy Oncology Group (RTOG)-toxicity outcomes were assessed. At a median follow-up of five years, the biochemical progression-free survival was 93% (95% CI: 84.7% to 100%). Acute side effects resolved within one to three months of treatment completion. There were no Grade 4 toxicities. No late Grade 3 rectal toxicity occurred, and only one, late Grade 3 genitourinary toxicity occurred following repeated urologic instrumentation.

Jabbari et al reported PSA nadir and acute and late toxicities with SBRT as monotherapy and post-external beam radiation therapy (EBRT) boost for prostate cancer using high-dose rate (HDR) brachytherapy fractionation. 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 (9.5Gy \times 4 fractions), and 18 were treated with SBRT boost (9.5Gy \times 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 to 43.5), 42% and 11% of patients had acute Grade 2 gastrourinary and gastrointestinal toxicity, respectively, with no Grade 3 or higher acute toxicity noted at publication. Two patients experienced late Grade 3 GU toxicity. All patients are without evidence of biochemical or clinical progression to date, and favorably low PSA nadirs have been observed with a current median PSA nadir of 0.35 ng/mL (range <0.01 to 2.1) for all patients (0.47ng/mL, range 0.2 to 2.1 for the monotherapy cohort; 0.10ng/mL, range, 0.01-0.5 for the boost cohort). With a median follow-up of 48.6 months (range 16.4 to 87.8), the comparable HDR brachytherapy boost cohort has achieved a median PSA nadir of 0.09ng/mL (range 0.0 to 3.3). 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.

King et al reported the long-term outcomes of a Phase 2 prospective trial of SBRT for low-risk, biopsy-proven newly diagnosed prostate cancer in 67 patients enrolled between 2003 and 2009. Low-risk was defined as a prebiopsy prostate specific antigen (PSA) of 10ng/mL or less, a biopsy Gleason grade of 3+3 or 3+4, and a clinical stage T1c or T2a/b. Median patient age was 66 years. Treatment consisted of 36.25Gy in five fractions using SBRT with CyberKnife. Patients who had received prior therapy (e.g. hormonal therapy) were excluded. The endpoints were early and late bladder and rectal toxicities, which were patient self-reported and graded on the Radiation Therapy Oncology Group (RTOG) scale. At baseline, 92% of patients reported no urinary issues and 8% had minor issues. Baseline function for the bowel was 89% with no issues and 11% with minor issues. Median follow-up was 2.7 years (25th to 75th percentile, 1.8 to 4.5 years, and maximum 5.9 years). There were no Grade 4 toxicities. RTOG Grade 1, 2 and 3 bladder toxicities were seen in 23%, 5% and 3% of patients, respectively. The Grade 3 toxicities were attributed to dysuria exacerbated by urologic instrumentation. Grade 1, 2 and 3 rectal toxicities were seen in 12.5%, 2% and 0% of patients, respectively. There were two PSA, biopsy-proven failures with negative metastatic work-up. The four-year PSA relapse-free survival was 94% (95% confidence interval [CI]: 85% to 102%). The authors concluded that significant bladder and rectal toxicities from SBRT for prostate cancer were infrequent.

A separate publication from the same Phase 2 trial outlined above reported 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 Expanded Prostate Cancer Index Composite (EPIC)-validated quality-of-life questionnaire, the sexual function of 32 consecutive patients was analyzed at median times of 4, 12, 20 and 50 months after treatment. The median follow-up was 35.5 months (range 12 to 62 months). The authors concluded that the rates of erectile dysfunction after treatment of prostate cancer with SBRT were comparable to those reported for other modalities of radiotherapy.

Katz et al performed SBRT on 304 patients with clinically localized prostate cancer (211 with high-risk disease, 81 with intermediate-risk and 12 with low-risk disease). Fifty received five fractions of 7Gy (total dose 35Gy) and 254 received five fractions of 7.25Gy (total dose 36.25Gy). At a median 30-month (range 26 to 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 (range: 8 to 27 months) follow-up, the 36.25-Gy dose level had two low- and two high-risk patients fail biochemically (biopsy showed two low- and one 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 six years follow-up, late urinary Grade II complications were seen in 4% of patients treated with 35Gy and 9% of patients treated with 36.25Gy. Five late Grade III urinary toxicities occurred in patients treated with 36.25Gy. Late Grade II rectal complications were seen in 2% and 5% of patients treated with 35Gy and 36.25Gy, 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 that were potent prior to SBRT, 75% remained potent. Actuarial five-year biochemical recurrence-free survival was 97% for those with intermediate risk, and 74.1% for high-risk patients.

Bolzicco et al reported outcomes from 100 patients treated with SBRT for localized prostate cancer, 41 of whom were low risk (PSA \leq 10ng/mL or Gleason Score \leq 6; or tumor category T1c-T2a), 42 were intermediate risk (PSA 10-20ng/mL or Gleason Score 7 or tumor category T2c), and 17 were high risk (PSA >20ng/mL or Gleason Score >7 or two median risk factors). Twenty-seven patients received androgen deprivation therapy at the discretion of their treating urologist. Sixty-two patients had acute toxicity (within the first one to two weeks after treatment): 34% had Grade I and 12% Grade II urinary toxicity; 27% had Grade I and 18% Grade II GI toxicity. Late urinary toxicity, primarily urgency and frequency (at six months or later post-treatment) occurred in 8% of the patients: 4% Grade I, 3% Grade II and 1% Grade III. The three-year bPFS rate was 94.4% (95% CI, 85.3% to 97.9%)

Other non-comparative studies have reported on specific outcomes after SBRT for prostate cancer, including rates of patient-reported urinary incontinence and rectal tolerance and health-related QOL outcomes.

Data on the use of SBRT in prostate cancer consists primarily of a single arm assessments of acute and late toxicity and early PSA outcome data retrospectively compared to 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 versus 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 the limitation of 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. At least two ongoing randomized trials are comparing SBRT with accepted standard therapy.

The American Society for Radiation Oncology (ASTRO) consensus panel statement from April 2010 on the use of stereotactic body radiotherapy approached (five fractions or less) states, "...results, primarily available only in abstract form and consisting of reports of clinical experiences from single institutions, show that SBRT for the prostate is technically feasible, with little reported acute morbidity. Very early results of limited statistical power, suggest that

treatment will induce an initial PSA response of a magnitude equivalent to that seen with conventionally fractionated radiotherapy.” PSA relapse-free survival and acute and chronic toxicity are equivalent with those of conventional external beam radiation therapy or permanent brachytherapy, with follow-up beyond five years. Although late outcome and toxicity data beyond ten years are not yet available, SBRT for low and intermediate risk prostate cancer, in selected and well-informed patients, could be considered an acceptable option as first line treatment of prostate cancer.

Pancreatic cancer

Goyal et al reported outcomes with SBRT in patients with pancreatic adenocarcinoma who were found not to be candidates for surgical resection. A prospective database of the first 20 consecutive patients receiving SBRT for unresectable pancreatic adenocarcinomas and a neuroendocrine tumor was reviewed. Mean radiation dose was 25Gray (Gy) (range 22 to 30Gy) delivered over one to three fractions. Chemotherapy was given to 68% of patients in various schedules/timing. Patients had a mean gross tumor volume of 57.2cm³ (range 10.1 to 118cm³) before SBRT. The mean total gross tumor volume reduction at three and six months after SBRT were 21% and 38%, respectively (p<0.05). Median follow-up was 14.57 months (range 5 to 23 months). The overall rate of freedom from local progression at six and 12 months were 88% and 65% respectively. The probability of overall survival at six and 12 months were 89% and 56%, respectively. No patient had a complication related to fiducial markers placement regardless of modality. The rate of radiation-induced adverse events was: Grade 1-2 (11%) and Grade 3 (16%). There were no Grade 4/5 adverse events seen.

Rwigema et al assessed the feasibility and safety of SBRT in patients with advanced pancreatic adenocarcinoma. The outcomes of 71 patients treated with SBRT for pancreatic cancer between 2004 and 2009 were reviewed. Forty patients (56%) had locally unresectable disease, 11 patients (16%) had local recurrence following surgical resection, eight patients (11%) had metastatic disease, and 12 patients (17%) received adjuvant SBRT for positive margins. The median dose was 24Gy (18-25Gy), given in a single-fraction SBRT (n=67) or fractionated SBRT (n=4). Kaplan-Meier survival analyses were used to estimate freedom from local progression (FFLP) and overall survival (OS) rates. The median follow-up among surviving patients was 12.7 months (4-26 months). The median tumor volume was 17mL (5.1-249mL). The overall FFLP rates at six months/one year were 71.7%/48.5%, respectively. Among those with macroscopic disease, FFLP was achieved in 77.3% of patients with tumor size <15mL (n=22), and 59.5% for ≥15mL (n=37) (p=0.02). FFLP was achieved in 73% following 24 to 25Gy, and 45% with 18 to 22Gy (p=0.004). The median OS was 10.3 months, with six month/one year OS rates of 65.3%/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 toxicity. The overall FFLP rate for all patients was 64.8%, comparable to rates with external-beam radiotherapy.

Chang et al reported on the local control and toxicity of SBRT for patients with unresectable pancreatic adenocarcinoma. Seventy-seven patients with unresectable adenocarcinoma of the pancreas received 25Gray (Gy) in one fraction. Forty-five patients (58%) had locally advanced disease, 11 patients (14%) had medically inoperable disease, 15 patients (19%) had metastatic disease, and six patients (8%) had locally recurrent disease. Nine patients (12%) had received

prior chemoradiotherapy. Sixteen patients (21%) received between 45 to 54Gy of fractionated radiotherapy and SBRT. Various gemcitabine-based chemotherapy regimens were received by 74 patients (96%), but three patients (4%) did not receive chemotherapy until they had distant failure. The median follow-up was six months (range 3 to 31 months) and, among surviving patients, it was 12 months (range 3 to 31 months). The overall rates of freedom from local progression (FFLP) at six months and 12 months were 91% and 84%, respectively. The six 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 progression-free survival (PFS) rates at six months and 12 months were 26% and 9%, respectively. The PFS rate at six months was superior for patients who had nonmetastatic disease versus patients who had metastatic disease (28% vs 15%; $p=0.05$). The overall survival (OS) rates at six months and 12 months from SBRT were 56% and 21%, respectively. Four patients (5%) experienced Grade ≥ 2 acute toxicity. Three patients (4%) experienced Grade 2 late toxicity, and seven patients (9%) experienced Grade ≥ 3 late toxicity. At six months and 12 months, the rates of Grade \geq late toxicity were 11% and 25%, respectively.

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 LC rates, there have been no significant changes in patient survival compared with historical data, and some studies have shown unacceptable toxicity and questionable palliative effect. Therefore, the use of SBRT for pancreatic cancer is considered investigational.

Renal Cell Carcinoma

A 2012 systematic review on the use of stereotactic radiotherapy for primary renal cell carcinoma identified a total of 126 patients worldwide who had been treated using this modality. A systematic search performed in January 2012 identified seven retrospective studies and three prospective studies that used a wide range of techniques, doses, and dose fractionation schedules. Median or mean follow-up ranged from nine months to 57.5 months. Local control was reported as 93.9% (range 84% to 100%) and the rate of severe Grade 3 or higher adverse events was 3.8% (range 0% to 19%). The conclusions of the systematic review were that the current literature suggests that stereotactic radiotherapy for renal cell carcinoma can be delivered with good rates of local control and acceptable toxicity, but that there is insufficient evidence to recommend a consensus for dose fractionation or technique, and there is a need for further prospective studies.

Beitler et al reported outcomes in nine patients with nonmetastatic renal cell carcinoma, two of whom had bilateral renal cell cancers. Patients were treated definitively with 40Gy in five fractions using SBRT. With a median follow-up of 26.7 months, four of the nine patients were alive. The survivors had a minimum follow-up of 48 months. At presentation, all four of the survivors had tumors ≤ 3.4 cm in largest dimension, had clinically negative lymph nodes, and presented no clinical evidence of penetration of Gerota fascia or renal vein extension.

Ranck et al reported outcomes for 18 patients with RCC with limited metastases who were treated with SBRT. For patients with five or fewer metastatic lesions, all lesions were treated; in patients with greater than five lesions, rapidly-growing lesions or those close to vital organs were treated. In all, 39 metastatic lesions were treated, with a median of two lesions per patient. The

two-year lesion-control rate was reported as 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, two-year freedom from new metastases was 35.7%. OS was 85% at two years. No patients who underwent treatment at all lesion sites died.

The literature on the use of SBRT for RCC consists of very small case series, which generally report high rates of LC. However, little evidence about the and no impact on patient outcomes can be derived from these data, nor any comparison made between this treatment modality and more established treatment modalities for RCC. Therefore, the use of SBRT for kidney cancer is considered investigational.

Oligometastasis

2012 and 2013 reviews on the use of SBRT for oligometastasis summarize the data on local tumor control, and in a limited subset of patients, survival, for various anatomical sites.

A 2012 long-term follow-up of a prospective study was reported on oligometastasis treated with SBRT. The authors prospectively analyzed the long-term survival, tumor control outcomes and freedom from widespread distant metastases (FFDM) after SBRT in 121 patients with five or fewer clinically detectable metastases, from any primary site, metastatic to one to three organ sites, and treated with SBRT. For patients with breast cancer, the median follow-up was 4.5 years (7.1 years for 16 of 39 patients alive at the last follow-up visit). The two-year OS, FFDM and local control (LC) rate was 74%, 52%, and 87%, respectively. Six-year OS, FFDM, and LC rate were 47%, 36%, and 87%, respectively. From the multivariate analyses, the variables of bone metastases ($p=0.057$) and one versus more than one metastasis ($p=0.055$) were associated with a four-fold and three-fold reduced hazard of death, respectively. None of the 17 bone lesions that were from breast cancer recurred after SBRT versus ten of 68 lesions from other organs that recurred ($p=0.095$). For patients with non-breast cancers, the median follow-up was 1.7 years (7.3 years for seven of 82 patients alive at the last follow-up visit). Two-year OS, FFDM, and LC rate were 39%, 28%, and 74%, respectively, and six-year OS, FFDM, and LC rate 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 ($p<0.0001$). 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 conclude that select patients with limited metastases treated with SBRT are long-term survivors.

Lung Oligometastasis

For isolated or a few lung metastases (including less than three or less than five, according to different selection criteria), the local control probability at one year has been reported in the range of 70-100%. 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 an absence of randomized trials and because most Phase I and II trials included heterogeneous patient populations.

It is also difficult to compare OS data from SBRT with that of historical surgical metastasectomy series, mainly because of the different clinical characteristics of the patients, as most patients

referred for SBRT are felt to be inoperable due to medical comorbidities that affect OS outcomes. Data from the International Registry of Lung Metastases reported OS of 70% at two years and 36% at five years in patients with a single metastasis who underwent surgical metastasectomy.

A systematic review by Siva and colleagues on the use of SBRT for pulmonary oligometastasis estimated from the largest studies included in the review a two-year weighted OS rate of 54.5%, ranging from higher rates in a study by Norisha and colleagues of 84% (66) to lower rates, such as 39%, reported from a multi-institutional trial.

Since publication of the Siva et al systematic review, Osti et al reported outcomes from a prospective cohort study of SBRT for lung oligometastases. 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 one year and two years was 89.1% and 82.1%, respectively. OS at one and two years was 76.4% and 31.2%, respectively, while PFS at one and two years was 53.9% and 22%, respectively. Two cases of grade 3 toxicity (pneumonitis) occurred.

Liver Oligometastasis

The liver is the most common site of metastatic spread of colorectal cancer (CRC). Data show 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 considered to be candidates for surgery, a variety of locally ablative techniques have been developed, the most common of which are radiofrequency ablation (RFA) and transarterial chemoembolization. Retrospective analyses of RFA for liver metastases from CRC have shown wide variability in five-year OS rates, ranging from 14% to 55%.

Retrospective series on the use of SBRT has reported local control rates ranging from 57 to 100%.

Prospective studies have reported one-year OS rates ranging from 61 to 85% and two-year OS rates ranging from 30 to 62%.

One of the larger series that was reported by Chang et al studied outcomes of SBRT for colorectal liver metastases in a pooled patient cohort from three institutions with colorectal liver metastases. Patients were included if they had one to four lesions, received one to six fractions of SBRT, and had radiologic imaging three months or more post-treatment. Sixty-five patients with 102 lesions treated from 2003 to 2009 were retrospectively analyzed. Forty-seven (72%) patients had one or more chemotherapy regimens before stereotactic body radiotherapy, and 27 (42%) patients had two or more regimens. The median follow-up was 1.2 years (range, 0.3 to 5.2 years). The median dose was 42Gray (Gy; range, 22 to 60Gy). One- and two- year LC rates were 67% and 55%, respectively. One- and two-year OS rates were 72% and 38%, respectively.

These studies have had relatively short follow-up times, typically less than 18 months. They are also limited by relatively small numbers of patients in the studies and differences in the systemic therapies administered, which may have affected treatment outcomes.

Adrenal Gland Oligometastasis

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

Scorsetti et al described the feasibility, tolerability and clinical outcomes of SBRT in the treatment of adrenal metastases in consecutive cancer patients. 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, local control, time-to-systemic progression, time-to-local progression, overall survival and toxicity. The Kaplan-Meier method was used to estimate survival and 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 to 75 months), 22 patients were alive. Eleven percent of lesions showed complete response, 46% partial response, 36% stable disease and 7% progressed in the treated area. Local failure was observed in 13 cases and actuarial local control rates at one and two years were 66% and 32%, respectively. Median time-to-local progression was 19 months and median survival was 22 months.

Holy et al presented initial institutional experiences with SBRT for adrenal gland metastases. Between 2002 and 2009, 18 patients with non-small cell lung cancer and adrenal metastases received SBRT for the metastatic disease. Metastases were isolated in 13 patients and multiple in five patients. A median progression-free survival 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 local control. In these patients, median OS was 23 months.

Casamassima et al evaluated a retrospective single-institution outcome after hypofractionated SBRT for adrenal metastases. Between 2002 and 2009, 48 patients were treated with SBRT for adrenal metastases. Eight patients were treated with single-fraction SBRT and 40 patients with multi-fraction. Median follow-up was 16.2 months (range 3 to 63 months). At time of analysis, 20 patients were alive and 28 patients were dead. One- and two-year actuarial OS rates were 39.7% and 14.5%, respectively. The median interval to local failure was 4.9 months. The actuarial one-year disease control rate was 9%; the actuarial one- and two-year local control rates were both 90%.

Chawla et al investigated the dosimetry and outcomes of patients undergoing SBRT for metastases to the adrenal glands. A retrospective review of 30 patients who had undergone SBRT for 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 five 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 three months of follow-up with serial computed tomography. Of these 24 patients, one achieved a complete response, 15 achieved a partial response, four had stable disease, and four developed progressive disease. No patients developed symptomatic progression of their adrenal metastases. Local control was poor, and most patients developed widespread metastases shortly after treatment, with one-year survival, local control, and distant control rates of 44%, 55%, and 13%, respectively. No patient developed Grade 2 or greater toxicity.

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

Bone Oligometastases

Napieralska et al reported a series 48 cases of prostate cancer bone metastases (in 32 patients) treated with SBRT primarily for pain control. The size of the treated lesions ranged from 0.7 to 5.5cm (mean of 3 dimension), and 31 (65%) of the treated metastases were located in the spine. At three-month follow up, 17 patients had complete pain relief, two had partial pain relief, and two 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.

The evidence related to the use of SBRT for the management of oligometastases to multiple sites, including the lungs, liver, adrenal glands, and bones (other than spine) consists of relatively small, non-comparative studies. For liver metastases, 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. The role of SBRT in metastases to the liver is not clear. The optimal dose and fractionation is not known, nor is there consensus on the maximum size or number of lesions suitable to SBRT. The literature on the use of SBRT in liver metastases is limited by the small numbers of patients in the studies, retrospective analyses, and the inclusion of mixed tumor types in the LC and survival analyses. Therefore, the use of SBRT for hepatic metastases is considered investigational.

The evidence related to the use of SBRT for oligometastases to other locations, including the lungs, adrenal glands, and non-spinal bones is subject to similar limitations.

Summary

Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) are radiotherapy methods that entail delivering highly focused, convergent beams on a precise target that is defined with 3-dimensional imaging techniques, sparing adjacent structures. SRS refers to such radiotherapy applied to intracranial lesions, while SBRT refers to therapy applied to other areas of the body. The technique differs from conventional radiotherapy, which involves exposing large areas of tissue to relatively broad fields of radiation over a multiple sessions. It may offer a noninvasive alternative to invasive surgery, particularly for patients unable to undergo surgery or for lesions that are difficult to access surgically or are adjacent to vital organs.

SRS

Stereotactic radiosurgery SRS is an established safe and effective treatment modality for many benign and malignant intracranial tumors/conditions. The evidence, largely consisting of nonrandomized cohort studies, combined with clinical input, supports the use of SRS for the following conditions: intracranial arteriovenous malformations; acoustic neuromas (vestibular schwannomas); pituitary adenomas; nonresectable, residual, or recurrent meningiomas; craniopharyngiomas; glomus jugulare tumors; and primary malignancies of the central nervous system; and trigeminal neuralgia that is refractory to medical management. Evidence from several RCTs demonstrated the benefit of SRS for small numbers of brain metastases from a variety of tumor types. Evidence from nonrandomized studies suggests that outcomes from SRS for intracranial metastatic disease is not worse for larger numbers of metastases; therefore, SRS may be considered medically necessary for solitary or multiple brain metastases in patients who have otherwise good performance status.

For the treatment of uveal melanoma, no studies that directly compare patients treated with SRS with other radiotherapies were identified. Existing cohort studies generally report high rates of LC, but some have limited reporting about distant metastases and OS. Therefore, the evidence is insufficient to conclude that SRS for uveal melanoma is associated with improved outcomes.

For the treatment of tremor, non-comparative studies in heterogeneous patient populations generally report improvements in tremor scores from pre- to post-SRS. However, studies with longer-term follow-up are needed to determine the risk: benefit ratio. The evidence related to the use of SRS for the management of other intracranial conditions, including epilepsy and chronic pain, is limited. Therefore, SRS is considered investigational for these conditions.

SBRT

For the use of SBRT, improved outcomes following using stereotactic body radiation therapy SBRT have also been demonstrated in patients with early stage NSCLC who are not considered to be candidates for resection. The literature and input from clinical vetting support its use in spinal tumors that have been previously irradiated and in radioresistant metastases to the spine. Therefore, SBRT may be considered medically necessary for the treatment of early stage NSCLC and metastases to the spine in patients who meet appropriate criteria.

For the use of SBRT for HCC, a number of randomized and nonrandomized studies have been reported in two systematic reviews from 2009 and 2012. The conclusions that can be drawn overall about outcomes after SBRT for HCC are limited because studies have been heterogeneous treatment schedules, treatment planning techniques, and patient populations. Since the publication of the 2009 and 2012 systematic reviews, case series of patients with nonmetastatic HCC treated with SBRT report high rates of LC, but low rates of intrahepatic recurrence-free survival. The evidence for the use of SBRT for pancreatic cancer and RCC consists of small case series and does not permit conclusions about outcomes after SBRT compared with other therapies. The evidence related to the use of SBRT for the management of oligometastases to multiple sites, including the lungs, liver, adrenal glands, and bones (other than spine) consists of relatively small, non-comparative studies, and there is a lack of consensus about optimal dose, fractionation, and the size, number, and types of lesions amenable to SBRT. Clinical input was mixed regarding the use of SBRT for the treatment of hepatocellular cancer, prostate cancer, pancreatic cancer, RCC, and oligometastases. Given insufficient evidence from the published literature or clinical support, the use of SBRT to treat other conditions, including but not limited to HCC, RCC, pancreatic cancer, and oligometastases, except metastases to the brain and spine as previously outlined, is considered investigational.

The evidence for the use of SBRT in prostate cancer consists primarily of single-arm assessments of toxicity and PSA. Longer term follow-up is needed to assess the effect on long-term toxicities, cancer control, and patient survival. However, five-year data report that PSA relapse-free survival, and acute and chronic toxicity data are equivalent to those of conventional external beam radiation therapy and permanent brachytherapy, and may be considered an acceptable option for the treatment of prostate cancer.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN) Guidelines

National Comprehensive Cancer Network (NCCN) provides guidelines for cancer treatment Guidelines for Cancer by site that include the use of SRS and SBRT for certain cancers. Guidelines addressing SRS and SBRT are summarized in Table 1:

Table 1: NCCN Recommendations for SRS and SBRT

Cancer Site	Tumor Type	Recommendation	Version
Bone	Osteosarcoma – metastatic disease	<ul style="list-style-type: none"> Consider use of stereotactic radiotherapy, especially for oligometastases (category 2A) 	1.2014
CNS	Adult intracranial and spinal ependymoma – spine or brain reoccurrence	<ul style="list-style-type: none"> Resection with limited radiotherapy if no prior radiotherapy; consider use of SRS if geometrically favorable (category 2A). If unresectable, radiotherapy if no prior radiotherapy; consider use of SRS if geometrically favorable (category 2A). If progression, radiotherapy; consider use of SRS if 	1.2014

		geometrically favorable (category 2A).	
CNS	Adult medulloblastoma and supratentorial PNET – recurrent disease	<ul style="list-style-type: none"> If progression after localized recurrence and maximum safe progression, SRS if geometrically favorable (category 2A). 	1.2014
CNS	Primary spinal cord tumors	<ul style="list-style-type: none"> If recurrence, radiotherapy including SRS if surgery is not possible (category 2A) 	
CNS	Meningiomas – asymptomatic and small (<30 mm)	<ul style="list-style-type: none"> 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). 	1.2014
CNS	Meningiomas – asymptomatic and large (≥30 mm)	<ul style="list-style-type: none"> If accessible, surgery followed by RT (external beam or SRS) if WHO grade 3; consider RT if incompletely resected WHO grade 1-2 (category 2A). 	1.2014
CNS	Meningiomas – symptomatic and small (<30 mm)	<ul style="list-style-type: none"> If accessible, surgery followed by RT (external beam or SRS) if WHO grade 3 or RT (external beam or SRS) (category 2A). 	1.2014
CNS	Meningiomas – symptomatic and large (≥30 mm)	<ul style="list-style-type: none"> If accessible, surgery followed by RT (external beam or SRS) if WHO grade 3; consider RT if incompletely resected WHO grade 1-2 (category 2A). RT (external beam or SRS) as an alternative (category 2A). 	1.2014
CNS	Metastatic disease – 1-3 lesions, primary treatment	<ul style="list-style-type: none"> 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). 	1.2014
CNS	Metastatic disease – 1-3 lesions, recurrence	<ul style="list-style-type: none"> If local recurrence and previous surgery only, surgery, single dose or 	1.2014

		fractionated stereotactic RT, or WBRT (category 2A).	
		<ul style="list-style-type: none"> • 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 fractionated stereotactic RT, WBRT, or consider chemotherapy. 	
CNS	Metastatic disease – >3 lesions, primary treatment	<ul style="list-style-type: none"> • WBRT or SRS (category 2A). SRS can be considered for patients with good performance status and low overall tumor volume. 	1.2014
CNS	Metastatic spine tumors	<ul style="list-style-type: none"> • If no spinal cord compression, no fracture or spinal cord instability, consider surgery or stereotactic RT if deterioration during RT, intractable pain, or tumor progression during primary treatment (RT [preferred], chemotherapy, or surgery followed by RT) (category 2A). 	1.2014
Colon	Metastatic to liver or lung	<ul style="list-style-type: none"> • In highly selected cases in which patient is symptomatic, external beam radiation (including SBRT) can be considered (category 3, or in a clinical trial). 	3.2014
Hepatobiliary	Hepatocellular carcinoma	<ul style="list-style-type: none"> • If potentially resectable and Child-Pugh class A or B, no portal hypertension, suitable tumor location, adequate liver reserve, and suitable liver remnant, consider external beam radiation therapy (conformal or stereotactic) (category 2B). • If unresectable and not eligible for liver transplant, consider external beam radiation therapy (conformal or stereotactic) (category 2B) • If inoperable by performance status or comorbidity and local disease with minimal or no extrahepatic disease, consider external beam radiation therapy (conformal or stereotactic) (category 2B). 	2.2014

Lung	Non-small cell lung cancer – Stage IA	<ul style="list-style-type: none"> If negative mediastinal lymph nodes and inoperable, definitive RT (stereotactic ablative radiotherapy) (category 2A). 	4.2014
Lung	Non-small cell lung cancer – Stage IV, metastatic disease to single site, brain or adrenal.	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> SBRT is recommended only as part of a clinical trial. 	2.2014
Prostate	Prostate cancer	<ul style="list-style-type: none"> SBRT may be considered as an alternative to conventional fractionated RT at clinics with appropriate technology and expertise. 	2.2014
Skin	Melanoma – metastatic	<ul style="list-style-type: none"> Brain metastases: SRS or WBRT as primary treatment or following resection. 	4.2014
Soft tissue sarcoma – extremity, superficial trunk, head/neck	Sarcoma – synchronous stage IV	<ul style="list-style-type: none"> 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). 	2.2014
Soft tissue sarcoma – extremity, superficial trunk, head/neck	Sarcoma – recurrent disease with metastases	<ul style="list-style-type: none"> 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). 	2.2014
Thyroid	Papillary, follicular, or Hurthle cell carcinoma – structurally persistent/recurrent locoregional or distant metastatic disease not amenable to	<ul style="list-style-type: none"> CNS metastases: for solitary lesions, neurosurgical resection or SRS is preferred (category 2A). 	1.2014

radioactive iodine

CNS – central nervous system; PNET – primitive neuroectodermal tumor; RT – radiotherapy; SBRT – stereotactic body radiation therapy; SRS – stereotactic radiosurgery; WBRT – whole brain radiation therapy.

For the treatment of primary kidney cancer (v3.2014), NCCN guidelines do not address the use of SBRT.

American Society for Radiation Oncology Guidelines

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:

- For single brain metastases (initial management):
 - If good prognosis (expected survival three months or more) and complete resection possible:
 - If brain metastasis ≤ 3 -4cm, 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 -4cm, 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 -4cm, 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 or more) and brain metastasis ≤ 3 -4cm, options include SRS and WBRT (level of evidence: I), SRS alone (level of evidence: 1)

ASTRO has given the opinion “that data supporting the use of SBRT for prostate cancer have matured to a point where SBRT could be considered an appropriate alternative for select patients with low to intermediate risk disease.”

For palliative therapy for bone metastases, ASTRO makes the following recommendations related to the use of SRS:

- Patients with painful bone metastases should be treated with SBRT only in clinical trials and that SBRT should not be the primary treatment of vertebral bone lesions causing cord compression.
- For re-treatment of recurrent metastatic spine pain with SBRT, the Task Force states that the specifics of SBRT re-treatment dosing and target delineation are insufficiently defined to allow SBRT re-treatment outside of the clinical trial setting.

ASTRO radiation therapy guidelines for glioblastoma and locally advanced non-small cell lung cancer are under development.

International RadioSurgery Association Guidelines

The International RadioSurgery Association published consensus-based guidelines on the treatment of brain or dural AVMs. The guidelines include 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

SRS is not a preventive service.

Key Words:

CyberKnife, Gamma Knife, Helium Radiosurgery, LINAC Radiosurgery, Linear Accelerator Radiosurgery, Neutron Beam Radiosurgery, Proton Beam Radiosurgery, Stereotactic Radiosurgery, BrainLAB Novalis®, TomoTherapy®, LINAC with computerized tomography (CT)

Approved by Governing Bodies:

Several SRS and SBRT devices that use LINAC units to generate high-energy photons have been cleared for marketing by FDA through the 510(k) premarket notification process, including the CyberKnife® System for Stereotactic Radiosurgery/Radiotherapy (Accuray, Inc.; approved December 1998, product code MUJ) and the TrueBeam™ Radiotherapy Delivery System (Varian Medical Systems; approved December 2012; product code IYE). Several devices that use cobalt 60 degradation (gamma ray devices) for SRS have been cleared for marketing by FDA through the 510(k) process, including the Leksell GammaKnife® (Elekta; approved May 1999, product code IWB). Gamma ray emitting devices that use cobalt 60 degradation are also regulated through the U.S. Nuclear Regulatory Commission.

Benefit Application:

Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply

FEP contracts: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

77299	Unlisted procedure, therapeutic radiology clinical treatment planning
77332	Treatment devices, design and construction; simple (simple block, simple bolus)
77333	; intermediate (multiple blocks, stents, bite blocks, special bolus)

77334	;complex (irregular blocks, special shields, compensators, wedges, molds or casts)
77371	Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; multi-source cobalt 60 based
77372	Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; linear accelerator base
77373	Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions
77399	Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services
77432	Stereotactic radiation treatment management of cranial lesion(s) (complete course of treatment consisting of one session)
77435	Stereotactic body radiation therapy, treatment management, per treatment course, to one or more lesions, including image guidance, entire course not to exceed 5 fractions
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 head frame for stereotactic radiosurgery (List separately in addition to code for primary procedure)
63620	Stereotactic radiosurgery (particle beam, gamma ray or linear accelerator); 1 spinal lesion
63621	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional spinal lesion (List separately in addition to code for primary procedure)
32701	Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (photon or particle beam), entire course of treatment
HCPCS Codes:	
G0339	Image guided robotic linear accelerator base stereotactic radiosurgery, complete course of therapy in one session, or first session of fractionated treatment.
G0340	Image guided robotic linear accelerator based stereotactic radiosurgery, delivery including collimator changes and

custom plugging, fractionated treatment, all lesions, per session, second through fifth sessions, maximum five sessions per course of treatment

Previous Coding:

HCPCS Codes:

- | | |
|--------------|---|
| G0173 | Stereotactic radiosurgery, complete course of therapy in one session (Deleted 01/01/15) |
| G0251 | Linear accelerator based stereotactic radiosurgery, delivery including collimator changes and custom plugging, fractionated treatment, all lesions, per session, maximum five sessions per course of treatment. (Deleted 01/01/15) |

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Policy History:

Medical Policy Group, June 2006 (4)

Medical Review Committee, June 2006

Medical Policy Group, March 2007 (2)

Medical Policy Administration Committee, April 2007

Available for comment April 12-May 26, 2007

Medical Policy Group, December 2008 (2)

Medical Policy Administration Committee, February 2009

Available for comment February 6-March 23, 2009

Medical Policy Panel, September 2010

Medical Policy Group, November 2010 (2)

Medical Policy Group, July 2012 (2): Removed code 20660 – added to policy by mistake

Medical Policy Panel, June 2012

Medical Policy Group, July 2012 (2): Updated to add coverage indications for craniopharyngiomas, glomus jugulare tumors, radioresistant spinal or vertebral metastasis, non-coverage indication for adrenal glands, Key Points, References updated. Coding section corrected.

Available for comment July 26 through September 4, 2012

Medical Policy Group, November 2012 (2): 2013 Coding update – added 32701 effective 1/1/13

Medical Policy Panel, September 2013

Medical Policy Group, October 2013 (2): Policy statement added that SRS is investigational for uveal melanoma. Description, Key Points, References updated to support new policy statement and literature search. Codes 77332-77334 added

Medical Policy Group, October 2013 (2): Removed ICD-9 Procedure codes; no change to policy statement.

Medical Policy Administration Committee, October 2013

Available for comment October 16 through November 30, 2013

Medical Policy Group, June 2014 (3): Updated policy with link to CareCore National© medical policies effective August 1, 2014

Medical Policy Administration Committee, June 2014

Available for comment June 16 through July 31, 2014

Medical Policy Group, July 2014: Removed CareCore link. Transfer to CareCore is on hold until further notice. The policy has been returned to FINAL.

Medical Policy Panel, September 2014

Medical Policy Group, September 2014 (3): 2014 Updates including editing updates throughout entire policy; updated policy statement to include coverage criteria for prostate cancer

Available for comment November 11 through December 29, 2014

Medical Policy Group, December 2014: 2015 Annual Coding Update. Added Previous coding section to include HCPCS deleted codes G0173 and G0251.

Medical Policy Group, February 2015: Added Care Core Draft link

Available for comment February 12 through April 30, 2015

Medical Policy Group, May 2015: Changed RTM link from Draft to Current, removed Draft from header.

Medical Policy Group, October 2015: Added Draft & removed header, added new (removed) eviCore RTM draft link, added (removed) comment period.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.