Effective April 1, 2013 Policy Retired Refer to LCD L32973

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Stereotactic Radiosurgery

Policy #: 279
Category: Surgery

Latest Review Date: July 2012
Policy Grade: A

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Stereotactic radiosurgery (SRS) is a method of delivering high doses of ionizing radiation to small intracranial targets. The technique differs from conventional radiotherapy, which involves exposing large areas of intracranial tissue to relatively broad fields of radiation over a number of treatment sessions. Stereotactic radiosurgery entails delivering highly focused convergent beams in a single session, so that only the desired target is radiated, sparing adjacent structures.

Traditional external beam radiation therapy may involve daily treatments for a duration of six weeks or longer. The emerging trend in recent years has been toward shorter, more "hypofractionated" courses, such as with SRS and SBRT. 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. Fractionation has been made possible by the ability to duplicate the treatment plan from one session to the next. 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.

The main methods of this technology include gamma-ray radiosurgery (Gamma Knife®), most frequently used for intracranial lesions, and linear-accelerator radiosurgery or LINAC (e.g. CyberKnife®). 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), and positron emission tomography/computed tomography (PET/CT).

Applications of SRS and SBRT

SRS

The most common applications of SRS include treatment of intracranial malignancies, including primary and metastatic tumors, and benign intracranial tumors (i.e., meningiomas, pituitary adenomas, and acoustic neuromas). 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. Examples of functional disorders include chronic pain.

Acoustic neuromas are benign tumors originating on the eighth cranial nerve, and they can be seen in association with neurofibromatosis. Although these tumors are benign, they are 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. Acoustic neuromas were one of the first indications for SRS, dating back to 1969.

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.

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. Neurodestructive 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 neurodestructive procedures.

Intracranial metastases have been considered ideal targets for radiosurgery due to their small spherical size and non-infiltrative 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. The idea of deferring WBRT in order to avoid its effects on normal tissues and using SRS alone continues to generate significant discussion and interest. Several trials have been conducted to address this issue.

The treatment of primary brain tumors such as gliomas is more challenging, due to their generally larger size and infiltrative borders.

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.

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.

Metastases from non-small cell lung cancer (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.

Policy:

Effective April 1, 2013 this policy was replaced by LCD L32973.

Effective for dates of service on or after April 1,2013 please refer to LCD L32973 for codes 77371,77372, 77373,77432,77435, G0173,G0251, G0339 and G0340.

Effective for dates of service on or after July 16, 2012:

Blue Advantage will treat **stereotactic radiosurgery** performed with an FDA-approved gamma beam (gamma knife), CyberKnife®, linear accelerator (LINAC), or proton beam unit as a **covered** benefit 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.

Blue Advantage will treat **stereotactic Body Radiotherapy (SBRT)** as a **covered** benefit 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).

Blue Advantage will treat **stereotactic radiosurgery** as a **non-covered** benefit 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

*** 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.

Effective for dates of service on or after March 17, 2009 and prior to July 16, 2012:
Blue Advantage will treat **stereotactic radiosurgery** performed with an FDA-approved gamma beam (gamma knife), CyberKnife®, linear accelerator (LINAC), or proton beam unit as a **covered** benefit 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.

Blue Advantage will treat **stereotactic Body Radiotherapy (SBRT)** as a **covered** benefit 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.

Blue Advantage will treat **stereotactic radiosurgery** as a **non-covered** benefit for the following:

- Chronic pain
- Epilepsy
- Parkinson disease
- Extracranial oncologic indications not listed above including, but not limited to, tumors of the following:
    - Pancreas
    - Liver
    - Lung except as described above
    - Prostate
    - Retroperitoneum and pelvis

*** 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 90 80	Normal no complaints; no evidence of disease. Able to carry on normal activity; minor signs or symptoms of disease. 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 60 50	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 medial care.
Unable to care for self; Requires equivalent of institutional or hospital care; diseases may be progressing rapidly	40 30 20 10 0	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

Effective for dates of service June 8, 2007 through March 16, 2009:
Blue Advantage will treat **stereotactic radiosurgery** performed with an FDA-approved gamma beam (gamma knife), CyberKnife®, linear accelerator (LINAC), or proton beam unit as a **covered** benefit 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
- Primary malignancies of the CNS, generally under 5 cm
- Primary and secondary tumors involving the brain or spine 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

Blue Advantage will treat **stereotactic radiosurgery** as a **non-covered** benefit for the following:

- Chronic pain
- Epilepsy
- Parkinson disease
- Extracranial oncologic indications not listed above including, but not limited to, tumors of the following:
    - Pancreas
    - Liver
    - Lung
    - Prostate
    - Retroperitoneum and pelvis

*** 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 90 80	Normal no complaints; no evidence of disease. Able to carry on normal activity; minor signs or symptoms of disease. 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 60 50	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 medial care.
Unable to care for self; Requires equivalent of institutional or hospital care; diseases may be progressing rapidly	40 30 20 10 0	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

Blue Advantage 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 Advantage administers benefits based on the members' contract and 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:

Challenges to an Evidence-Based Approach to Rapidly Evolving Technologies in Radiation Oncology

This policy groups together several different techniques for delivering stereotactic radiosurgery (SRS), i.e., the Gamma Knife®, LINAC devices, and the CyberKnife® device. However, from an evidence-based approach, it is extremely difficult to compare these different devices to determine if one device is superior to another for a particular indication. A literature search in May 2006 failed to identify any controlled trials directly comparing different devices in homogeneous groups of patients. In addition, the field of radiation oncology is rapidly evolving, with a current intense interest in emerging image-guided technology. A limited number of

stereotactic radiosurgery options may be available in individual markets, and thus, the choice among devices may be dictated primarily by geography. The following summarizes different variables related to stereotactic radiosurgery and radiotherapy.

Size of Lesion
In terms of stereotactic radiosurgery, the superiority of one energy source over another depends primarily on the dose distribution capabilities, which in turn depend on the target's volume, location, and shape. For small lesions (i.e., less than 5 cm^3), the dose distributions produced by the gamma knife are essentially identical to those achievable with LINAC units. When the target lesion is nonspherical or of intermediate size (e.g., between five and 25 cm^3), LINAC units may have an advantage over Gamma Knife units, due to their ability to treat larger lesions without requiring multiple isocenters (which makes treatment planning difficult), and the ability to shape the dose using collimated fields. However, when targeting large volumes (i.e., greater than 25 cm^3), charged particle units that use a small fixed number of beams have the best ability to shape dose distributions and thus offer some advantages over both LINAC and Gamma Knife units.

Dose Fractionation
Standard radiobiologic principles suggest that fractionating radiation therapy (i.e., delivery in multiple sessions) will reduce both early and late toxicities to surrounding normal tissues. Radiosurgery (one treatment) or hypofractionation (limited number of treatments) may be considered when patient movement limits the use the use of conventional radiation therapy, or may be offered as a convenience to patients, particularly those that require rapid pain relief. These two clinical indications are also associated with different outcomes that must be considered as part of an evidence-based analysis. A more basic scientific issue is an underlying understanding of the radiosensitivity of surrounding normal tissues.

Dose Escalation
Novel forms of radiation therapy, for example, the Cyberknife® and proton beam therapy have been proposed as ways to provide dose escalation. In this setting, clinical questions include whether or not dose escalation provides improved tumor control, which depends on the dose response rate of individual tumor types, and whether an increased dose is associated with increased toxicity to surrounding tissues.

Decreased Toxicity
A variety of novel treatment planning and delivery are designed to reduce toxicity. The ability of the Cyberknife® to accommodate patient movement is a unique feature and a variety of applications have been suggested, including treatment of lung, prostate and pancreas cancer. In these settings, respiratory motion can limit the ability to deliver intense radiation, and thus in this setting the Cyberknife® may be considered an alternative to multileaf collimators, tomotherapy or the "step and shoot" technique. Evidence of reduced toxicity would require directly comparative studies. Many of the potential benefits of the Cyberknife® and other treatment delivery systems have been based on modeling studies, or studies with phantoms, and limited clinical experience.

In summary, the lack of comparative studies of different techniques of radiation planning and delivery in homogeneous groups of patients limits any scientific analysis regarding the relative safety and efficacy of different systems for different clinical situations (i.e., reduction of fractionation, dose escalation, reduced toxicity, or a combination of all three). Therefore the scientific evidence is inadequate to permit scientific conclusions regarding the superiority of one device over another. The following discussion focuses on different general applications of stereotactic applications in radiation therapy.

The following is a summary of the literature available through May 2012. Data on the use of SRS and SBRT consists primarily of case series, registry data and early phase trials.

Stereotactic Radiosurgery (SRS)

Non-neoplastic conditions

Arteriovenous malformations

Kano et al published a study to define long-term outcomes and risks of arteriovenous malformation (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. The median interval between the first- and second-stage SRS was 4.9 months (range 2.8-13.8 months). The median target volume was 11.5 cm^3 (range, 4.0-26 cm^3) in the first-stage SRS and 9.5 cm^3 in the second-stage SRS. In 17 patients, AVM obliteration was confirmed after two to four SRS procedures at a median follow-up of 87 months (range 0.4-209 months). Five patients had near-total obliteration (volume reduction >75% but residual AVM). The actuarial rates of total obliteration after 2-stage SRS were 7%, 20%, 28%, and 36% at three, four, five, and ten years, respectively. The 5-year total obliteration rate after the initial staged volumetric SRS was 62% (p=0.001). Sixteen patients underwent additional SRS at a median interval of 61 months (range 33-113 months) after the initial 2-stage SRS. The overall rates of total obliteration after staged and repeat SRS were 18%, 45%, and 56% at 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 2 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 0-1, 1-5, and 5-10 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, but no patient died as a result of an adverse radiation effect. 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.

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, 70-80 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, 13-115 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 2 weeks (range 0-12 weeks), and the median response duration was 32 months (range 0-112 months). Eighty-one percent reported initial pain relief, and actuarial rates of freedom from treatment failure at 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.

Epilepsy

A 1998 TEC Assessment cited two studies of 11 and 9 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 2-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 tumoral 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 1-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. There is inadequate reporting of complications associated with radiosurgery. The studies published to date are preliminary in nature. The 1998 TEC Assessment observed that evidence was insufficient to

permit conclusions about the effects of radiosurgery on epilepsy. Conclusions about the health outcome effects of radiosurgery await additional studies.

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

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.

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 10-74 years) were treated from 2006 through 2009. Median volume of tumor was 7.9 mL (range 1.1-21 mL). A total dose of 30-39 Gy in 10-15 fractions (median 33 Gy) was delivered to the target. Ten patients were followed up for 9-36 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 5- and 10-year overall rates of survival of tumor progression after radiosurgery were 93% and 88%, respectively. The actuarial 5- 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 50.4-56 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 3-326 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.

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 6 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]: 57-82%). Those who underwent GTR had a follow-up of 88 ± 5.0 months and a tumor control rate of 86% (95% CI: 81%-91%). Those treated with STR+SRS were observed for 96 ± 4.4 months and had a tumor control rate of 71% (95% CI: 53%-83%). Patients undergoing SRS alone had a follow-up of 71 ± 4.9 months and a tumor control rate of 95% (95% CI: 92%-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 CNs IX-XI than those who underwent SRS alone; however, the rates of CN XII deficits were comparable.

Brain Metastases

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, 11 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 (2-4) 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.

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 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. In a randomized trial of 58 patients published following the Cochrane review, 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.

Aoyama et al recently 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.

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.

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 1-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 25 Gy with a mean of 20 Gy. 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 1-year tumor progression-free incidence was 84%. Pattern-of-failure analysis showed two primary mechanisms of failure: recurrence in the bone adjacent to the site of previous treatment; and recurrence in the epidural space adjacent to the spinal cord. The authors concluded that 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.

Non-small cell lung cancer (NSCLC)
A review by Nguyen et al cites a number of studies of SBRT for early-stage lung cancer receiving a biologic equivalent dose of 100 Gy or more. Three of the studies cited reported 5-year survival that ranged from 30% to 83%; in the largest series of 257 patients, the 5-year survival was 42%. Koto et al reported on a Phase II study of 31 patients with stage 1 NSCLC. Patients received 45 Gy in three fractions, but those with tumors close to an organ at risk received 60 Gy in 8 fractions. With a median follow-up of 32 months, the 3-year 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 3-year disease-specific survival rates of 49% for those with Stage 1 disease.

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 2 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 18 Gy per fraction x 3 fractions (54 Gy total), with the entire treatment lasting between 1.5 to 2 weeks. The primary endpoint was 2-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 11 patients with T2 tumors) with a median follow-up of 34.4 months (range, 4.8-49.9 months). Only one patient had primary tumor failure; the estimated 3-year primary tumor control rate was 97.6% (95% confidence interval [CI]: 84.3-99.7%). Three patients had recurrence within the involved lobe; the 3-year primary tumor and involved lobe (local) control rate was 90.6% (95% CI: 76.0-96.5%). Two patients experienced regional failure; the local-regional control rate was 87.2% (95% CI: 71.0-94.7%). Eleven patients experienced disseminated recurrence; the 3-year rate of disseminated failure was 22.1% (95% CI: 12.3-37.8%). The rates for disease-free survival and overall survival at three years were 48.3% (95% CI: 34.4-60.8%) and 55.8% (95% CI: 41.6-67.9%), 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: 9.6-15.8%); Grade 4 adverse events were reported in two patients (3.6%; 95% CI: 2.7-4.5%). 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.

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 1-10 fractions to total doses of 18-60 Gy. 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, 1-3 lesions and cumulative tumor diameter ≤6 cm. Patients with CTP-A were treated in three fractions with the dose escalated from 12 to 16 Gy. For patients with CTP-B, the dose was modified to 5 fractions starting at 8 Gy 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 1,288 mL, range 1,008-1,815 mL) with no worse than CTP-A liver disease and without extrahepatic metastases The 4×8–10 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 50-100% and 33-100%, 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.

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, 14 Gy, and 44 Gy, respectively, for those with CTP Class A cirrhosis and 5, 8 , and 40 Gy, 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 2-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 ≥Grade 3 nonhematologic toxicities. Thirteen percent of patients experienced an increase in hematologic/hepatic dysfunction greater than 1 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 ≤6 cm 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 135 cm (3) ($p<0.004$). The median time to local progression was 6.3 months. The 1- and 2-year overall survival rates were 87% and 55%, respectively. The incidence of Grade 1-2 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 ≤6 cm or up to three lesions with sum diameters ≤6 cm, 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 24-48 Gy). 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 ≥50% nonenhancement at 12 months. Thirteen of 18 demonstrated 100% nonenhancement, being >50% in five patients. Kaplan-Meier 1- and 2-year survival estimates were 77% and 60%, respectively. SBRT is effective therapy for patients with HCC with an overall best response rate (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 45 Gy in three fractions of 15 Gy each was prescribed to the 80% isodose line (95% of the PTV received 45 Gy) and delivered to the target volume over 10-12 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 1- and 2-year local control rate was 95% (95% CI: 69-95%). At a median overall follow-up of 12.7 months (range, 1-24 months), six of the 25 (24%) patients have died. Overall actuarial survival at one and two years was 79% (95% CI: 52-92%) and 52% (95% CI: 19-78%), 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 15.4 cc (3.0-81.8), and the median follow-up duration was 28.7 months (8.4-49.1). 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 1-year and 3-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 cc vs. ≥32 cc, p<0.05). No major toxicity was encountered but one patient died with extrahepatic metastasis and radiation-induced hepatic failure.

Liver Metastases
A 2012 review by Mendez and Hoyer summarizes the literature on the use of SBRT for liver metastases. In general, the data are limited by the small numbers of patients in the studies, retrospective analyses, and the inclusion of mixed tumor types in the local control and survival analyses. In addition, differences in the systemic therapies administered after SBRT may have affected treatment outcomes. One of the largest studies included in the review is outlined below.

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 at least three months' post-treatment. Sixty-five patients with 102 lesions treated from 2003 to 2009 were retrospectively analyzed. Forty-seven (72%) patients had ≥1 chemotherapy regimen before stereotactic body radiotherapy, and 27 (42%) patients had ≥2 regimens. The median follow-up was 1.2 years (range, 0.3-5.2 years). The median dose was 42 gray (Gy; range, 22-60 Gy). One- and 2-year local control rates were 67% and 55%, respectively. One- and 2-year OS rates were 72% and 38%, respectively.

Prostate Cancer
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 1, 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 0-62 months). The bPFS rate at three years was 97.7%. The median PSA declined from 4.9 ng/mL at diagnosis to 0.2 ng/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 7.2-18.2 months), and the mean percentage PSA bounce was 1.07 ng/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, ≤T2b, prostate size ≤60 cm, and American Urological Association (AUA) score ≤15. Dose-limiting toxicity was defined as Grade 3 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 45 Gy, 47.5 Gy, and 50 Gy 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 45 Gy, 47.5 Gy, and 50 Gy 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 + 2 ng/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 35-36.25 Gy 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 which 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 (9.5 Gy × 4 fractions), and 18 were treated with SBRT boost (9.5 Gy × 2 fractions) post-EBRT and androgen deprivation therapy. PSA nadir to date for 44 HDR brachytherapy boost patients with disease characteristics similar to the SBRT boost cohort was also analyzed as a descriptive comparison. SBRT was well-tolerated. With a median follow-up of 18.3 months (range 12.6-43.5), 42% and 11% of patients had acute Grade 2 gastro-urinary 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 <0.01-2.1) for all patients (0.47 ng/mL, range 0.2-2.1 for the monotherapy cohort; 0.10 ng/mL, range, 0.01-0.5 for the boost cohort). With a median follow-up of 48.6 months (range 16.4-87.8), the comparable HDR brachytherapy boost cohort has achieved a median PSA nadir of 0.09 ng/mL (range 0.0-3.3). 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 10 ng/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 36.25 Gy in 5 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-75th percentile, 1.8-4.5 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 4-year PSA relapse-free survival was 94% (95% confidence interval [CI]: 85%-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 12-62 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: Fifty received five fractions of 7 Gy (total dose 35 Gy) and 254 received 5 fractions of 7.25 Gy (total dose 36.25 Gy). At a median 30-month (range 26-37 months) follow-up, there were no biochemical failures for the 35-Gy dose level. Acute Grade II urinary and rectal toxicities occurred in 4% of patients with no higher grade acute toxicities. At a median 17-month (range: 8-27 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.

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 25 Gray (Gy) (range 22-30 Gy) 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 57.2 cm^3 (range 10.1-118 cm^3) before SBRT. The mean total gross tumor volume reduction at 3 and 6 months after SBRT were 21% and 38%, respectively ($p<0.05$). Median follow-up was 14.57 months (range 5-23 months). The overall rate of freedom from local progression at 6 and 12 months were 88% and 65% respectively. The probability of overall survival at 6 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 24 Gy (18-25 Gy), given in a single-fraction SBRT (n=67) or fractionated SBRT (n=4). Kaplan-Meyer 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 17 mL (5.1-249 mL). 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 <15 mL (n=22), and 59.5% for ≥15 mL (n=37) (p=0.02). FFLP was achieved in 73% following 24 to 25 Gy, and 45% with 18 to 22 Gy (p=0.004). 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 25 gray (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 54 Gy 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 3-31 months) and, among surviving patients, it was 12 months (range 3-31 months). The overall rates of freedom from local progression (FFLP) at six months and 12 months were 91% and 84%, respectively. The 6- and 12-month isolated local recurrence rates were 5% and 5%, respectively. There was no difference in the 12-month FFLP rate based on tumor location (head/uncinate, 91% vs body/tail, 86%; p=0.52). The progression-free survival (PFS) rates at 6 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 6 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 6 months and 12 months, the rates of Grade ≥late toxicity were 11% and 25%, respectively.

Kidney cancer

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 40 Gy 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.

Adrenal metastases
Scorsetti et al described the feasibility, tolerability and clinical outcomes of SBRT in the treatment of adrenal metastases in 34 consecutive cancer patients. Between 2004 and 2010, a total of 34 consecutive 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. Survival was estimated by the Kaplan-Meier method and factor potentially affecting outcomes were analyzed with Cox regression analysis. Results: Total RT doses ranged from 20 Gy in four fractions to 45 Gy in 18 fractions (median dose: 32 Gy; median number of fractions: four). All doses were prescribed to the 95% isodose line. No cases of Grade ≥3 were reported. Three of 28 lesions (11%) showed complete response, 13/28 (46%) partial response, 10/28 (36%) stable disease and 2/28 (7%) progressed in the treated area. Local failure was observed in 13 cases. Actuarial local control rates at one and two years were 66% and 32%, respectively. Median time to local progression was 19 months. 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 a non-small cell lung cancer and adrenal metastasis received SBRT. An isolated adrenal metastasis was diagnosed in 13 patients, while five patients with multiple metastatic lesions had SBRT due to back pain. Depending on treatment intent and target size, the dose/fraction concept varied from 5 x 4 Gy to 5 x 8 Gy. Dose was given with an isotropic convergent beam technique to a median maximum dose of 132% to the target's central part. The mean clinical (CTV) and planning target volume (PTV) was 89 cm^3 (5-260 cm^3) and 176 cm^3 (20-422 cm^3), respectively. A median progression-free survival time (PFS) of 4.2 months was obtained for the entire patient group, with a markedly increased PFS of 12 months in 13 patients suffering from an isolated metastasis of the adrenal gland. After a median follow-up of 21 months, 10 of 13 patients (77%) with isolated adrenal metastasis achieved local control. In these patients, median overall survival (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. The median age of the patient population was 62.7 years (range 43-77 years). In the majority of patients, the prescription dose was 36 Gy in three fractions (70% isodose, 17.14 Gy per fraction at the isocenter). Eight patients were treated with single-fraction stereotactic radiosurgery and 40 patients with multi-fraction stereotactic radiotherapy. Overall, the series of patients was followed up for a median of 16.2 months (range 3-63 months). At the time of analysis, 20 patients were alive and 28 patients were dead. The 1- and 2-year actuarial overall survival rates were 39.7% and 14.5%, respectively. We recorded 48 distant failures and 2 local failures, with a median interval to local failure of 4.9 months. The actuarial 1-year disease control rate was 9%; the actuarial 1- and 2-year local control rate was 90%. Our retrospective study indicated that SBRT for the treatment of adrenal metastases represents a safe and effective option with a control rate of 90% at two years.

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, and 16 underwent SBRT for palliation or prophylactic palliation of bulky adrenal metastases. The prescribed dose ranged from 16 Gy in four fractions to 50 Gy in 10 fractions. The median dose was 40 Gy. Of the 30 patients, 24 had greater 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 patient developed symptomatic progression of their adrenal metastases. The 1-year survival, local control, and distant control rate was 44%, 55%, and 13%, respectively. No patient developed Radiation Therapy Oncology Group Grade 2 or greater toxicity. Local control was poor, and most patients developed widespread metastases shortly after treatment.

Summary

Stereotactic radiosurgery is an established safe and effective treatment modality for many benign and malignant intracranial tumors/conditions. Improved outcomes using stereotactic body radiation therapy have also been demonstrated in patients with early-stage non-small cell lung cancer 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.

There is insufficient evidence or clinical support for the use of stereotactic radiation therapy/stereotactic body radiation therapy to treat other conditions including, but not limited to, other extracranial tumors except for lung and spinal tumors as outlined above, and seizures.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN) Guidelines.

NCCN guidelines for the treatment of central nervous system tumors (v.1.2012) recommends, as category 2A, stereotactic radiosurgery for certain benign and malignant brain tumors, limited (one to three) metastatic lesions as category 2A if used alone; category 1 if with whole brain radiation for one metastasis, certain metastatic spinal tumors and primary spinal cord tumors if re-irradiating (category 2A).

For non-small cell lung cancer, NCCN guidelines (v3.2012) recommend SBRT for inoperable early-stage disease. (category 2A).

For prostate cancer, NCCN guidelines (v.3.2012) state that SBRT requires longer follow-up and prospective multi-institutional data to evaluate longer term results.

For hepatocellular carcinoma, NCCN guidelines (v.2.2012) state that radiation therapy (conformal or stereotactic) is one of the options to consider in patients with unresectable HCC with local disease (category 2B).

For colon cancer metastatic to the liver (colon cancer guidelines v3.2012), NCCN considers radiation in highly selected cases in which the patient has a limited number of metastases (category 3) or in the setting of a clinical trial.

For pancreatic adenocarcinoma (v2.2012), NCCN recommends that SBRT only be utilized as part of a clinical trial.

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:

CyberKnife received FDA approval July 27, 1999 for the non-invasive treatment of tumors and other conditions affecting the brain, head, neck, and cervico-thoracic spine. Gamma Knife received FDA approval in 1989 for the treatment of abnormal brain lesions.

Benefit Application:

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

Current Coding: (As of April,1 2013)

CPT Codes:	**32701**	Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (photon or particle beam), entire course of treatment
	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 bean, gamma ray, or linear accelerator); each additional spinal lesion (List separately in addition to code for primary procedure)
	77299	Unlisted procedure, therapeutic radiology clinical treatment planning
	77399	Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services
ICD-9 Procedure:	**92.30-92.39**	Stereotactic radiosurgery
	93.59	Other immobilization, pressure, and attention to wound (includes stereotactic head frame application)

Previous Coding:

61793	Stereotactic radiosurgery (particle beam, gamma ray or linear accelerator), one or more sessions **(Code deleted effective January 1, 2009)**
77371	Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cerebral lesion(s) consisting of 1 session; multi-source cobalt 60 based (**code moved to LCD L32973 April 1 2013**)
77372	; linear accelerator based (**code moved to LCD L32973 April 1 2013**)
77373	Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions (**code moved to LCD L32973 April 1 2013**)
77432	Stereotactic radiation treatment management of cerebral lesion(s) (complete course of treatment consisting of one session) (**code moved to LCD L32973 April 1 2013**)
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 (**code moved to LCD L32973 April 1 2013**)
G0173	Stereotactic radiosurgery, complete course of therapy in one session (**code moved to LCD L32973 April 1 2013**)
G0243	Multi-source photon stereotactic radiosurgery, delivery including Collimator changes and custom plugging complete course of treatment, all lesions **(deleted 12/31/06)**
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. (**code moved to LCD L32973 April 1 2013**)

G0339	Image guided robotic linear accelerator base stereotactic radiosurgery, complete course of therapy in one session, or first session of fractionated treatment (**code moved to LCD L32973 April 1 2013**)
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 (**code moved to LCD L32973 April 1 2013**)

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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.