Clinical Policy Bulletin: Stereotactic Radiosurgery

Number: 0083

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers stereotactic radiosurgery medically necessary according to the following selection criteria.

I. Cranial stereotactic radiosurgery with a Cyberknife, gamma knife, or linear accelerator (LINAC) is considered medically necessary when used for any of the following indications:

   A. For treatment of members with symptomatic, small (less than 3 cm) arterio-venous (AV) malformations, aneurysms, and benign tumors (acoustic neuromas (vestibular schwannomas), craniopharyngiomas, hemangiomas, meningiomas, pituitary adenomas, and neoplasms of the pineal gland) if the lesion is unresectable due to its deep intracranial location or if the member is unable to tolerate conventional operative intervention; or
   
   B. For members with trigeminal neuralgia that has not responded to other more conservative treatments (see CPB 0374 - Trigeminal Neuralgia: Treatments); or
   
   C. Severe essential tremor not adequately responsive to standard medical therapy (see CPB 0153 - Thalamotomy); or
   
   D. Disabling tremor in individuals with Parkinson’s disease (eg, thalamotomy) who meet medical necessity criteria for thalamotomy (see CPB 0153 - Thalamotomy) but are not candidates for surgery; or
   
   E. For treatment of brain malignancies (primary tumors and/or metastatic lesions) (see Appendix).

II. Stereotactic body radiation therapy with a Cyberknife, gamma knife, or linear accelerator (LINAC) is considered medically necessary for localized malignant conditions within the body where highly precise application of high-dose radiotherapy is required and clinically appropriate (see Appendix).

III. Fractionated stereotactic radiotherapy is considered medically necessary when criteria for stereotactic radiosurgery are met. Fractionated stereotactic radiotherapy is useful for treatment of tumors in hard-to-reach locations, tumors with very unusual shapes, or for tumors located in such close proximity to a vital structure (e.g., optic nerve or hypothalamus) that even a very accurate high-dose single fraction of stereotactic radiosurgery could not be tolerated.

IV. Stereotactic proton beam radiosurgery: please see CPB 0270 - Proton Beam and Neutron Beam Radiotherapy.

Aetna considers stereotactic radiosurgery experimental and investigational for all other indications because its effectiveness for these indications has not been established including (not an all-inclusive list):

- Cluster headaches
- Epilepsy (except when associated with treatment of AV malformations or brain tumors)
Background

With any external beam radiation therapy, the highest dose of radiation develops where multiple beams intersect. Thus, the fewer beams there are, the greater the dose reaching other areas traversed by the beams. For example, if only 2 beams are used, the highest dose would develop at the site where the beams intersect, but a significant portion of the dose would be distributed to fields anterior and posterior to the intersection.

Stereotactic radiosurgery (SRS) uses the above principle to deliver a highly focused ionizing beam so that the desired target is obliterated, leaving adjacent structures nearly unaffected. Guidance is provided by a variety of imaging techniques, including angiography, computerized tomography (CT), and magnetic resonance imaging (MRI). The key to SRS is immobilization of the patient so that targeting can be accurate and precise.

Stereotactic radiation is also used in extra-cranial sites, in a procedure called stereotactic body radiation therapy (SBRT). A body frame has been designed to immobilize patients for such treatment. In addition, frameless methods of administering SBRT to the body have been developed. These frameless systems rely on skeletal landmarks or implanted fiducial markers to locate and guide the therapy beam to treatment targets within the body.

Based upon professional opinion, a coding guide from the American Society for Therapeutic Radiation and Oncology (ASTRO, 2007) stated that SBRT is considered appropriate for the treatment of the following conditions:

- Lung or liver metastases not amenable to surgery
- Medically inoperable early stage lung cancer
- Primary liver cancer not amenable to surgery
- Recurrent lung cancer amenable to salvage therapy
- Recurrent pelvic tumors
- Retroperitoneal tumors
- Spinal and para-spinous tumors
- Other recurrent cancers or tumors.

The radioactive particles used in SRS and SBRT may come from various sources. The Gamma Knife uses Cobalt-60. Over 200 finely focused beams of gamma radiation simultaneously intersect at the precise location of the brain disorder. Proton beam radiosurgery derives its advantage from the so-called "Bragg peak", a term that describes the pattern of deposition of proton beam radiation. Protons decelerate as they travel though tissue, depositing disproportionately more radiation at greater depths. The protons deposit most of their energy at their depth of maximal penetration, resulting in a "peak" of radiation at that tissue depth. The depth of peak radiation can be precisely defined by the energy the cyclotron imparts to the proton beam.

A linear particle accelerator, or LINAC, creates photons by accelerating electrons along a linear path where they collide with a metal target. This produces a single, intense photon beam. To reduce the effect of the radiation on adjacent healthy tissues, a moving frame is used to target the abnormality with "arcs" from different directions. LINAC treatments may be given in multiple sessions over several days, which are referred to as fractionated radiotherapy. With fractionated radiotherapy, radiation is delivered to the tumor or lesion at different points in the cell division cycle. This may be the preferred form of treatment in some circumstances. Fractionated treatments may continue for up to 30 days. "Hypo-fractionated" treatments are given over 5 to 8 treatment days.

Precise stereotactic localization is necessary for treatment of intra-cranial structures, because of their deep location and because of the close proximity of vital structures in the brain. During radiotherapy administration, the cranium can be completely immobilized using a frame.
Fractionated stereotactic radiotherapy (FSRT) involves multiple low-dose radiation treatments. Fractionated stereotactic radiotherapy is used to treat tumors in hard-to-reach locations or with very unusual shapes. Fractionated stereotactic radiotherapy is also used to treat tumors which are located in close proximity to vital structures, such as the optic nerve or hypothalamus, where even a very accurate high-dose single fraction of stereotactic radiosurgery could not be tolerated.

For this procedure, patients are required to wear a special customized fiberglass helmet. (For other stereotactic radiation techniques of the head, the patient's head must be immobilized in a special head-ring frame, which is applied under local anesthetic.) After the patient undergoes the usual stereotactic imaging such as CT or MRI, small doses of radiation are accurately applied each day. The customized fiberglass helmet harnesses the patient while receiving low, daily doses. Fractionated stereotactic radiotherapy is also an excellent way to administer radiation treatments to infants or small children whose fast-growing brains cannot tolerate standard radiation. In the past, oncologists were limited to treating infants and small children with chemotherapy alone. This technique also shows great promise in the treatment of benign tumors such as pituitary adenomas or meningiomas. The use of fractionated stereotactic radiotherapy permits excellent control of the tumor but spares the brain from such cognitive side-effects as impaired cognition and memory that commonly occur with standard radiation treatment.

An assessment conducted by the Alberta Heritage Foundation for Medical Research (Hailey, 2002) concluded that there is limited evidence that fractionated stereotactic radiotherapy may have an advantage over stereotactic radiosurgery in treatment of acoustic neuromas and brain tumors.

There are clinical reports of the effectiveness of SBRT for radiosensitive CNS tumors invading the spine. SBRT is useful to treat surgically unresectable ependymomas and other radiosensitive primary central nervous system tumors if they are invading the spine and spinal cord. SBRT has not been as successful when used on metastatic tumors to the spine, because these metastatic lesions are not usually radiosensitive. SBRT of the spine has been performed using an immobilizing frame. In addition, frameless methods of administering SBRT to the spine are in development. These frameless systems rely on skeletal landmarks or implanted fiducial markers to locate and guide the therapy beam to treatment targets within the spine or spinal cord.

With the development of a stereotactic body frame analogous to the stereotactic head frames used for intra-cranial targets, stereotactic techniques have been used to treat tumors in extra-cranial sites other than the spine. Available evidence for SBRT is from dose analysis studies showing theoretical advantage to this form of treatment, and phase II studies evaluating local control and toxicity.

A number of studies have examined SBRT of primary lung cancer. Nyman et al (2005) from Finland reported experience of SBRT in 45 patients with stage I non-small cell lung cancer. The investigators reported 80 % 1-year survival and 30 % 5-year survival, and median survival of 39 months. Nagata et al (2005) reported on experience from Japan on SBRT in 45 patients with stage IA and IB lung cancer.

Sixteen percent of tumors showed complete response, and 84 % of tumors showed partial response. With a median follow-up of 30 months, no pulmonary complications greater than grade 3 were found and no other vascular, cardiac, esophageal or neurologic toxicities encountered. The investigators reported that, for stage IA lung cancer, the disease-free and overall survival rates after 1 and 3 years were 80 % and 72 %, and 92 % and 83 %, respectively, whereas for stage IB lung cancer, the disease-free survival and overall survival rates were 92 % and 71 %, and 82 % and 72 %, respectively. McGarry et al (2003) from Indiana University reported on a phase I dose escalation study of SBRT in 47 patients with inoperable stage I lung cancer. Dose-limiting toxicity included predominantly bronchitis, pericardial effusion, hypoxia, and pneumonitis. Local failure occurred in 4 of 19 T1 and 6 of 28 T2 patients. Local failures occurred between 3 and 31 months from treatment. Within the T1 group, 5 patients had distant or regional recurrence as an isolated group, whereas 3 patients had both distant and regional recurrence. Within the T2 group, 2 patients had solitary regional recurrences, and the 4 patients who failed distantly also failed regionally.

An earlier report from Indiana University details phase I trial experience with 37 patients with stage I non-small cell lung cancer treated with SBRT (Timmerman et al, 2003). Significant toxicity was limited to 1 case
of grade 3 pneumonitis and 1 case of hypoxia. Minor transient pulmonary function changes were commonly seen, and 1 case of asymptomatic pericardial effusion was noted. Twenty-seven patients had a complete response to treatment, and 60 % of patients had a partial response. After a median follow-up period of 15.2 months, 6 patients experienced local failure, all at lower dose levels than currently employed. A 2003 Korean study reported experience using SBRT in 28 patients with primary or metastatic lung tumors (Lee et al, 2003). A hypo-fractionated 3 or 4 treatment regimen was used. Thirty-nine percent complete and 43 % partial response rates were noted. Whyte et al (2003) from Stanford University reported on a phase I clinical trial of SBRT in 23 patients with lung cancer. Complete radiographic responses were seen in 2 patients, partial responses in 15 patients, and no response or progression in 6 patients. Three pneumothoraces resulted from fiducial placement. A 2001 Japanese report detailed a 5-year experience in treating 50 patients with stage I non-small cell lung cancer. In 18 of these patients, SBRT was boost treatment after conventional radiotherapy. With a median 36-month follow-up, 30 patients were alive and disease-free. The 3-year case-specific survival rate was 88 %. The Radiation Therapy Oncology Group has an ongoing clinical study of SBRT in patients with inoperable stage I/II non-small cell lung cancer.

There are studies of SBRT in body sites other than the spine and lung. Schefter et al (2001) reported on a phase I clinical trial of stereotactic body radiotherapy in 18 patients with metastatic liver cancer. The study was limited to patients with 1 to 3 liver metastases, tumor diameter less than 6 cm, and adequate liver function. These investigators reported that no patients experienced acute grade 3 liver or intestinal toxicity or any acute grade 4 toxicity.

Hoyer et al (2005) from Denmark reported on a phase II study of SBRT in pancreatic cancer. A total of 22 patients with locally advanced and surgically non-resectable, histological proven pancreatic carcinoma were included into the trial. The investigators reported that only 2 patients were found to have a partial response, and the remaining patients had no change or progression after treatment. Six patients had local tumor progression, but only 1 patient had an isolated local failure without simultaneous distant metastasis. The investigators reported that median time to local or distant progression was 4.8 months. Median survival time was 5.7 months and only 5 % of patients were alive 1 year after treatment. The investigators noted that acute toxicity reported 14 days after treatment was pronounced. The investigators stated that there was a significant deterioration of performance status, significantly more nausea and significantly more pain after 14 days compared with baseline. However, 8 of 12 patients improved in performance status, scored less nausea, pain, or needed less analgesic drugs at 3 months after treatment. Four patients suffered from severe mucositis or ulceration of the stomach or duodenum and one of the patients had a non-fatal ulcer perforation of the stomach. The investigators concluded that SBRT “was associated with poor outcome, unacceptable toxicity and questionable palliative effect and cannot be recommended for patients with advanced pancreatic carcinoma.”

Wersall et al (2005) from Sweden investigated the results of using SBRT in 58 patients with renal cell carcinomas. The investigators reported that tumor lesions regressed totally in 30 % of the patients at 3 to 36 months, whereas 60 % of the patients had a partial volume reduction or no change after a median follow-up of 37 months for censored and 13 months for uncensored patients. The investigators reported that side effects were generally mild. The investigators reported that 3 of 162 treated tumors recurred, yielding a local control rate of 90 to 98 %, considering the 8 % non-evaluable sites.

Hoyer and colleagues (2006) evaluated the effectiveness of SBRT in the treatment of inoperable patients with colorectal cancer metastases. Sixty-four patients with a total number of 141 colorectal cancer metastases in the liver (n = 44), lung (n = 12), lymph nodes (n = 3), suprarenal gland (n = 1) or 2 organs (n = 4) were treated with SBRT. After 2 years, actuarial local control was 86 % and 63 % in tumor and patient based analysis, respectively. Nineteen percent were without local or distant progression after 2 years and overall survival was 67, 38, 22, 13, and 13 % after 1, 2, 3, 4 and 5 years, respectively. The investigators reported that 1 patient died due to hepatic failure, 1 patient was operated for a colonic perforation and 2 patients were conservatively treated for duodenal ulcerations. In addition, moderate toxicities such as nausea, diarrhea and skin reactions were observed.

Tse and colleagues (2008) reported outcomes of a phase I study of individualized SBRT for unresectable hepatocellular carcinoma (HCC) and intra-hepatic cholangiocarcinoma (IHC). Patients with unresectable HCC or IHC, and who are not suitable for standard therapies, were eligible for 6-fraction SBRT during 2
weeks. Radiation dose was dependent on the volume of liver irradiated and the estimated risk of liver toxicity based on a normal tissue complication model. Toxicity risk was escalated from 5% to 10% and 20%, within 3 liver volume-irradiated strata, provided at least 3 patients were without toxicity at 3 months after SBRT. A total of 41 patients with unresectable Child-Pugh A HCC (n = 31) or IHC (n = 10) completed 6-fraction SBRT. Five patients (12%) had grade 3 liver enzymes at baseline. The median tumor size was 173 ml (9 to 1,913 ml). The median dose was 36.0 Gy (24.0 to 54.0 Gy). No radiation-induced liver disease or treatment-related grade 4/5 toxicity was seen within 3 months after SBRT. Grade 3 liver enzymes were seen in 5 patients (12%). Two patients (5%) with IHC developed transient biliary obstruction after the first few fractions. Seven patients (5 HCC, 2 IHC) had decline in liver function from Child-Pugh class A to B within 3 months after SBRT. Median survival of HCC and IHC patients was 11.7 months (95% confidence interval [CI]: 9.2 to 21.6 months) and 15.0 months (95% CI: 6.5 to 29.0 months), respectively. The authors concluded that individualized 6-fraction SBRT is a safe treatment for unresectable HCC and IHC.

Goodman et al (2010) performed a phase I dose-escalation study to explore the feasibility and safety of treating primary and metastatic liver tumors with single-fraction SBRT. Between February 2004 and February 2008, a total of 26 patients were treated for 40 identifiable lesions: 19 patients had hepatic metastases, 5 had IHC, and 2 had recurrent HCC. The prescribed radiation dose was escalated from 18 to 30 Gy at 4-Gy increments with a planned maximum dose of 30 Gy. Cumulative incidence functions accounted for competing risks to estimate local failure (LF) incidence over time under the competing risk of death. All patients tolerated the single-fraction SBRT well without developing a dose-limiting toxicity. Nine acute grade 1 toxicities, 1 acute grade 2 toxicity, and 2 late grade 2 gastrointestinal toxicities were observed. After a median of 17 months follow-up (range of 2 to 55 months), the cumulative risk of LF at 12 months was 23%. Fifteen patients have died: 11 treated for liver metastases and 4 with primary liver tumors died. The median survival was 28.6 months, and the 2-year actuarial overall survival was 50.4%. The authors concluded that it is feasible and safe to deliver single-fraction, high-dose SBRT to primary or metastatic liver malignancies measuring less than or equal to 5 cm. Moreover, single-fraction SBRT for liver lesions demonstrated promising local tumor control with minimal acute and long-term toxicity. Single-fraction SBRT appears to be a viable non-surgical option.

Kopek et al (2010) reported outcomes of a single institution study of SBRT for unresectable cholangiocarcinoma. The dose-volume dependency of the observed gastrointestinal toxicity was explored. A total of 27 patients with unresectable cholangiocarcinoma (IHC, n = 1; Klatskin tumors, n = 26) were treated by linac-based SBRT. The dose schedule was 45 Gy in 3 fractions prescribed to the isocenter. The median progression-free survival and overall survival were 6.7 and 10.6 months, respectively. With a median follow-up of 5.4 years, 6 patients had severe duodenal/pyloric ulceration and 3 patients developed duodenal stenosis. Duodenal radiation exposure was higher in patients developing moderate- to high-grade gastro-intestinal toxicity with the difference in mean maximum dose to 1 cm (3) of duodenum reaching statistical significance. A statistically significant association between grade 2 ulceration and volume of duodenum exposed to selected dose levels was not established. The authors concluded that the outcomes of SBRT for unresectable cholangiocarcinoma appear comparable to conventionally fractionated chemoradiotherapy with or without brachytherapy boost. The practical advantages of SBRT are of particular interest for such poor prognosis patients. Patient selection, however, is key in order to avoid compromising such practical gains with excessive gastrointestinal toxicity.

A structured evidence review by the Alberta Heritage Foundation for Medical Research (Hailey, 2002) concluded that "the place of SRS [stereotactic radiosurgery] in the treatment of Parkinson's disease does not appear to be established." In addition, the review concluded that "[the] efficacy of SRS in the management of epilepsy appears not to have been established, other than in association with its use in treatment for AVMs or brain tumors."

Bartolomei et al (2008) reported the effectiveness and tolerance of gamma knife (GK) radiosurgery in mesial temporal lobe epilepsy (MTLE) after a follow-up more than 5 years. Patients presenting with MTLE and treated with a marginal dose of 24 Gy were included in the study (n = 15) -- 8 were treated on the left side, and 7 were treated on the right. The mean follow-up was 8 years (range of 6 to 10 years). At the last follow-up, 9 of 16 patients (60%) were considered seizure-free (Engel Class I) (4/16 in Class IA, 5/16 in
Class IB). Seizure cessation occurred with a mean delay of 12 months (+/- 3) after GK radiosurgery, often preceded by a period of increasing aura or seizure occurrence (6/15 patients). The mean delay of appearance of the first neuroradiological changes was 12 months (+/- 4). Nine patients (60 %) experienced mild headache and were placed on corticosteroid treatment for a short period. All patients who were initially seizure-free experienced a relapse of isolated aura (10/15, 66 %) or complex partial seizures (10/15, 66 %) during anti-epileptic drug (AED) tapering. Restoration of treatment resulted in good control of seizures. The authors concluded that GK radiosurgery is an effective and safe treatment for MTLE. Results are maintained over time with no additional side effects. Long-term results compare well with those of conventional surgery. The authors also noted that the main disadvantage of this approach is the delay of seizure remission, often preceded by a period of increasing seizure frequency. Patients must also be warned that a long-lasting AED treatment must be maintained (usually at a lower dose) following the procedure.

In an editorial that accompanied the afore-mention article, Spencer (2008) stated that GK treatment in MTLE is still searching for a place; its disadvantages (slightly lower seizure response rate, delayed response, absolute requirement for continued medication, higher mortality) compared to anterior medial temporal resection seem to outweigh its non-invasive status, which so far does not appear to carry any clear benefits in terms of neurological or cognitive function, or seizure response. Furthermore, whether GK treatment should be considered for intractable epilepsy arising in other functional cortical regions that can not be treated with resection remains unexplored.

In a review on the application of SRS to disorders of the brain, Kondziolka et al (2008) noted that radiosurgery has had an impact on the management of patients with vascular malformations, all forms of cerebral neoplasia, and selected functional disorders such as trigeminal neuralgia and tremor. Epilepsy, behavioral disorders, and other novel indications are the topics of current investigation. This is in agreement with the observation of Quigg and Barbaro (2008) who stated that further studies are needed to ascertain if the effectiveness of SRS for treatment of epilepsy attains that of traditional surgery while offering a non-invasive technique with potentially lower morbidity.

Stereotactic radiosurgery is being investigated as a treatment for cluster headache. In a prospective open trial, Donnet et al (2005) examined the effectiveness of gamma knife radiosurgery of the trigeminal nerve in the treatment of patients with chronic cluster headache (CCH). A total of 10 patients (9 men, 1 woman; mean age of 49.8 years) were enrolled. They presented with severe and drug resistant CCH (mean duration of 9 years). The cisternal segment of the trigeminal nerve was targeted with a single 4-mm collimator (80 to 85 Gy max). The mean follow-up was 13.2 months. No improvement was observed in 2 patients, while 3 patients had no further attacks. Three patients showed dramatic improvement with a few attacks per month or very few attacks over the last 6 months. Two patients were pain-free for only 1 week and 2 weeks, respectively, and their headaches recurred with the same severity as before. Three patients developed paresthesia with no hypoesthesia, 1 developed hypoesthesia, and 1 developed de-afferentation pain. These investigators considered the morbidity to be significant for the low rate of pain cessation, making this procedure less attractive even for the more severely affected subgroup of patients.

In a phase I clinical trial, Boke et al (2011) evaluated the tolerability of escalating doses of stereotactic body radiation therapy in the treatment of localized prostate cancer. Eligible patients included those with Gleason score 2 to 6 with prostate-specific antigen (PSA) less than or equal to 20, Gleason score 7 with PSA less than or equal to 15, less than or equal to T2b, prostate size less than or equal to 60 cm(3), and American Urological Association (AUA) score less than or equal to 15. Pre-treatment preparation required an enema and placement of a rectal balloon. Dose-limiting toxicity (DLT) was defined as grade 3 or worse 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 5 fractions (45 total patients). The median follow-up is 30 months (range of 3 to 36 months), 18 months (range of 0 to 30 months), and 12 months (range of 3 to 18 months) for the 45 Gy, 47.5 Gy, and 50 Gy groups, respectively. For all patients, GI greater than or equal to 2 and grade greater than or equal to 3 toxicity occurred in 18 % and 2 %, respectively, and GU grade greater than or equal to 2 and grade greater than or equal to 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 is 100% by the nadir + 2 ng/ml failure definition. The authors concluded that dose escalation to 50 Gy has been completed without DLT. They stated that a multi-center phase II trial is underway treating patients to 50 Gy in 5 fractions to further evaluate this experimental therapy.

The Agency for Healthcare Research and Quality (AHRQ)'s Effective Health Care Program released a new technical brief (2011) that provides a broad overview of the current state of evidence on the use of stereotactic body radiation therapy for targeting solid malignant tumors. The brief, Stereotactic Body Radiation Therapy, identifies gaps in the scientific data regarding the theoretical advantages of stereotactic body radiation therapy over other radiotherapies in actual clinical use. While stereotactic body radiation therapy appears to be widely used for treatment of a variety of cancer types, none of the currently available studies includes comparison groups. The researchers noted that in order to assess fully the benefits and risks of stereotactic body radiation therapy, comparative studies are needed. These studies should preferably be randomized trials but, at a minimum, there is a need for trials with concurrent controls. The technical brief also provides a review of key research questions that remain unanswered and may be helpful to radiology researchers in prioritizing future research.

The Expert Panel on Radiation Oncology-Gynecology/American College of Radiology’s Appropriateness Criteria on “Definitive therapy for early stage cervical cancer” (Small et al, 2012) stated that “Stereotactic body RT (SBRT) has been shown to be a useful treatment option in other tumor sites, especially in early stage lung cancer. There are preliminary data on its use in treating cervical cancer, but, given target definition, tumor motion, and the proven track record of brachytherapy, SBRT should not be considered a substitute for brachytherapy”. Yamada et al (2013) stated that en bloc wide-margin excision significantly decreases the risk of chordoma recurrence. However, a wide surgical margin cannot be obtained in many chordomas because they arise primarily in the sacrum, clivus, and mobile spine. Furthermore, these tumors have shown resistance to fractionated photon radiation at conventional doses and numerous chemotherapies. These researchers analyzed the outcomes of single-fraction SRS in the treatment of chordomas of the mobile spine and sacrum. A total of 24 patients with chordoma of the sacrum and mobile spine were treated with high-dose single-fraction SRS (median dose of 2,400 cGy); 21 primary and 3 metastatic tumors were treated; 7 patients were treated for post-operative tumor recurrence. In 7 patients, SRS was administered as planned adjuvant therapy, and in 13 patients, SRS was administered as neoadjuvant therapy. All patients had serial magnetic resonance imaging follow-up. The overall median follow-up was 24 months. Of the 24 patients, 23 (95%) demonstrated stable or reduced tumor burden based on serial magnetic resonance imaging.

One patient had radiographic progression of tumor 11 months after SRS; 6 of 13 patients who underwent neoadjuvant SRS proceeded to surgery. This decision was based on the lack of radiographic progression and the patient’s preference. Complications were limited to 1 patient in whom sciatic neuropathy developed and 1 with vocal cord paralysis. The authors concluded that high-dose single-fraction SRS provides good tumor control with low treatment-related morbidity. Moreover, they stated that additional follow-up is needed to determine the long-term recurrence risk.

**Hepatocellular Carcinoma:**

Klein et al (2014) stated that although liver-directed therapies such as surgery or ablation can cure hepatocellular carcinoma (HCC), few patients are eligible due to advanced disease or medical co-morbidities. In advanced disease, systemic therapies have yielded only incremental survival benefits. Historically, RT for liver cancer was dismissed due to concerns over unacceptable toxicities from even moderate doses. Although implementation requires more resources than standard RT, SBRT can deliver reproducible, highly conformal ablative radiotherapy to tumors while minimizing doses to nearby critical structures. Trials of SBRT for HCC have demonstrated promising local control and survival results with low levels of toxicity in Child-Pugh class A patients. The authors reviewed the published literature and made recommendations for the future of this emerging modality.

Van De Voorde et al (2015) noted that stereotactic ablative body radiotherapy (SABR) is a non-invasive treatment option for inoperable patients or patients with unresectable liver tumors. Outcome and toxicity
were evaluated retrospectively in this single-institution patient cohort. Between 2010 and 2014, a total of 39 lesions were irradiated in 33 consecutive patients (18 males, 15 females, median age of 68 years). All the lesions were liver metastases (n = 34) or primary HCC (n = 5). The patients had undergone 4-dimensional respiration-correlated PET-CT for treatment simulation to capture tumor motion. These researchers analyzed local control with a focus on CT-based response at 3 months, 1 year and 2 years after treatment, looking at overall survival (OS) and the progression pattern. All patients were treated with hypo-fractionated image-guided SRS. The equivalent dose in 2 Gy fractions varied from 62.5 Gy to 150 Gy, delivered in 3 to 10 fractions (median dose of 93.8 Gy, alpha/beta = 10). The CT-based regression pattern 3 months after radiotherapy revealed partial regression in 72.7 % of patients with a complete remission in 27.3 % of the cases. The site of first progression was predominantly distant; 1-and 2-year OS rates were 85.4 % and 68.8 %, respectively. No toxicity of grade 2 or higher according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v4.0 was observed. The authors concluded that SABR is a safe and efficient treatment for selected inoperable patients or unresectable tumors of the liver. Moreover, they stated that future studies should combine SABR with systemic treatment acting in synergy with radiation, such as immunological interventions or hypoxic cell radio-sensitizers to prevent distant relapse.

Furthermore, National Comprehensive Cancer Network (NCCN)'s clinical practice guideline on "Hepatobiliary cancers" (Version 2.2015) does not mention SRS as a therapeutic option.

**Intramedullary Spinal Cord Tumors:**

Park and Chang (2013) stated that SRS represents an increasingly utilized modality in the treatment of intra-cranial and extra-cranial pathologies. Stereotactic spine radiosurgery (SSR) uses an alternative strategy to increase the probability of local control by delivering large cumulative doses of RT in only a few fractions. Stereotactic spine radiosurgery in the treatment of intramedullary lesions remains in its infancy. This review summarized the current literature regarding the use of SSR for treating intramedullary spinal lesions. Several studies have suggested that SSR should be guided by the principles of intra-cranial radiosurgery with radiation doses placed no further than 1 to 2 mm apart, thereby minimizing exposure to the surrounding spinal cord and allowing for delivery of higher radiation doses to target areas. Maximum dose-volume relationships and single-point doses with SSR for the spinal cord are currently under debate. Prior reports of SRS for intramedullary metastases, AVMs, ependymomas, and hemangioblastomas demonstrated favorable outcomes. The authors concluded that in the management of intramedullary spinal lesions, SSR appeared to provide a safe and effective treatment compared to conventional RT. They stated that SSR should likely be utilized for select patient-scenarios given the potential for radiation-induced myelopathy, though high-quality literature on SSR for intramedullary lesions remains limited.

Hernandez-Duran et al (2016) noted that advances in imaging technology and microsurgical techniques have made microsurgical resection the treatment of choice in cases of symptomatic intramedullary tumors. The use of SRS for spinal tumors is a recent development, and its application to intramedullary lesions is debated. These researchers conducted a literature search through PubMed's MeSH system, compiling information regarding intramedullary neoplasms treated by SRS. They compiled histology, tumor location and size, treatment modality, radiation dose, fractionation, radiation-induced complications, follow-up, and survival. A total of 10 papers on 52 patients with 70 tumors were identified. Metastatic lesions accounted for 33 %, while 67 % were primary ones. Tumor location was predominantly cervical (53 %), followed by thoracic (33 %). Mean volume was 0.55 cm3 (95 % CI: 0.26 to 0.83). Preferred treatment modality was CyberKnife (87 %), followed by Novalis (7 %) and LINAC (6 %). Mean radiation dose was 22.14 Gy (95 % CI: 20.75 to 23.53), with mean fractionation of 4 (95 % CI: 3 to 5); 3 hemangioblastomas showed cyst enlargement. Symptom improvement or stabilization was seen in all but 2 cases. Radionecrotic spots adjacent to treated areas were seen at autopsy in 4 lesions, without clinical manifestations. Overall, clinical and radiological outcomes were favorable. Although surgery remains the treatment of choice for symptomatic intramedullary lesions, SRS can be a safe and effective option in selected cases. The authors concluded that while the findings of this review suggested the overall safety and effectiveness of SRS in the management of intramedullary tumors, future studies need randomized, homogeneous patient populations followed over a longer period to provide more robust evidence in its favor.
Operable Non-Small-Cell Lung Cancer:

The American College of Chest Physicians’ evidence-based clinical practice guidelines on “Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer” (Howington et al, 2013) noted that surgical resection remains the primary and preferred approach to the treatment of stage I and II non-small-cell lung cancer (NSCLC). Lobectomy or greater resection remains the preferred approach to T1b and larger tumors. The use of sublobar resection for T1a tumors and the application of adjuvant radiation therapy in this group are being actively studied in large clinical trials. Every patient should have systematic mediastinal lymph node sampling at the time of curative intent surgical resection, and mediastinal lymphadenectomy can be performed without increased morbidity. Peri-operative morbidity and mortality are reduced and long-term survival is improved when surgical resection is performed by a board-certified thoracic surgeon. The use of adjuvant chemotherapy for stage II NSCLC is recommended and has shown benefit. The use of adjuvant radiation or chemoradiation therapy for stage I NSCLC is of unproven benefit. Primary radiation therapy remains the primary curative intent approach for patients who refuse surgical resection or are determined by a multi-disciplinary team to be inoperable. There is growing evidence that SBRT provides greater local control than standard RT for high-risk and medically inoperable patients with NSCLC. The authors concluded that the role of ablative therapies in the treatment of high-risk patients with stage I NSCLC is evolving. Radiofrequency ablation, the most studied of the ablative modalities, has been used effectively in medically inoperable patients with small (less than 3 cm) peripheral NSCLC that are clinical stage I.

In a systematic review and meta-analysis, Zhang et al (2014) compared the effectiveness of SBRT versus surgery for early-stage NSCLC. All the eligible studies were searched by PubMed, Medline, Embase, and the Cochrane Library. The meta-analysis was performed to compare odds ratios (OR) for OS, cancer-specific survival (CSS), disease-free survival (DFS), local control (LC), and distant control (DC). A total of 6 studies containing 864 matched patients were included in the meta-analysis. The surgery was associated with a better long-term OS in patients with early-stage NSCLC. The pooled OR and 95% CI for 1-year, 3-year OS were 1.31 [0.90 to 1.91] and 1.82 [1.38 to 2.40], respectively. However, the differences in 1-year and 3-year CSS, DFS, LC and DC were not significant. The authors concluded that the findings of this systematic review revealed a superior 3-year OS after surgery compared with SBRT, which supports the need to compare both treatments in large prospective, randomized, controlled clinical trials.

In a meta-analysis, Zheng et al (2014) compared treatment outcomes of SBRT with those of surgery in stage I NSCLC. Eligible studies of SBRT and surgery were retrieved through extensive searches of the PubMed, Medline, Embase, and Cochrane library databases from 2000 to 2012. Original English publications of stage I NSCLC with adequate sample sizes and adequate SBRT doses were included. A multi-variate random effects model was used to perform a meta-analysis to compare survival between treatments while adjusting for differences in patient characteristics. A total of 40 SBRT studies (4,850 patients) and 23 surgery studies (7,071 patients) published in the same period were eligible. The median age and follow-up duration were 74 years and 28.0 months for SBRT patients and 66 years and 37 months for surgery patients, respectively. The mean unadjusted OS rates at 1, 3, and 5 years with SBRT were 83.4 %, 56.6 %, and 41.2 % compared to 92.5 %, 77.9 %, and 66.1 % with lobectomy and 93.2 %, 80.7 %, and 71.7 % with limited lung resections. In SBRT studies, OS improved with increasing proportion of operable patients. After these researchers adjusted for proportion of operable patients and age, SBRT and surgery had similar estimated OS and DFS. The authors concluded that patients treated with SBRT differed substantially from patients treated with surgery in age and operability. After adjustment for these differences, OS and DFS did not differ significantly between SBRT and surgery in patients with operable stage I NSCLC. They stated that a randomized prospective trial is needed to compare the effectiveness of SBRT and surgery.

Chang et al (2015) stated that the standard of care for operable, stage I NSCLC is lobectomy with mediastinal lymph node dissection or sampling. Stereotactic ablative radiotherapy (SABR) for inoperable stage I NSCLC has shown promising results, but 2 independent, randomized, phase III clinical trials of SABR in patients with operable stage I NSCLC (STARS and ROSEL) closed early due to slow accrual. These investigators evaluated OS for SABR versus surgery by pooling data from these trials. Eligible patients in the STARS and ROSEL studies were those with clinical T1-2a (less than 4 cm), N0M0, operable
NSCLC. Patients were randomly assigned in a 1:1 ratio to SABR or lobectomy with mediastinal lymph node dissection or sampling. These investigators performed a pooled analysis in the intention-to-treat population using OS as the primary end-point. Both trials are registered with ClinicalTrials.gov (STARS: NCT00840749; ROSEL: NCT00687986). A total of 58 patients were enrolled and randomly assigned (31 to SABR and 27 to surgery). Median follow-up was 40.2 months (IQR 23.0 to 47.3) for the SABR group and 35.4 months (18.9 to 40.7) for the surgery group; 6 patients in the surgery group died compared with 1 patient in the SABR group. Estimated OS at 3 years was 95 % (95 % CI: 85 to 100) in the SABR group compared with 79 % (64 to 97) in the surgery group (hazard ratio [HR] 0.14 [95 % CI: 0.017 to 1.190], log-rank p = 0.037). Recurrence-free survival at 3 years was 86 % (95 % CI: 74 to 100) in the SABR group and 80 % (65 to 97) in the surgery group (HR 0.69 [95 % CI: 0.21 to 2.29], log-rank p = 0.54). In the surgery group, 1 patient had regional nodal recurrence and 2 had distant metastases; in the SABR group, 1 patient had local recurrence, 4 had regional nodal recurrence, and 1 had distant metastases. Three (10 %) patients in the SABR group had grade 3 treatment-related adverse events (3 [10 %] chest wall pain, 2 [6 %] dyspnea or cough, and 1 [3 %] fatigue and rib fracture). No patients given SABR had grade 4 events or treatment-related death. In the surgery group, 1 (4 %) patient died of surgical complications and 12 (44 %) patients had grade 3 to 4 treatment-related adverse events. Grade 3 events occurring in more than 1 patient in the surgery group were dyspnea (4 [15 %] patients), chest pain (4 [15 %] patients), and lung infections (2 [7 %]). The authors concluded that SABR could be an option for treating operable stage I NSCLC. Moreover, they stated that because of the small patient sample size and short follow-up, additional randomized studies comparing SABR with surgery in operable patients are needed.

Furthermore, NCCN’s clinical practice guideline on “Non-small cell lung cancer” (Version 1.2016) lists SRS only as a therapeutic option of brain metastases of NSCLC.

Pancreatic Adenocarcinoma:

In a phase II, multi-institutional, clinical trial, Herman et al (2015) examined if gemcitabine (GEM) with fractionated SBRT results in acceptable late grade 2 to 4 gastro-intestinal (GI) toxicity when compared with a prior trial of GEM with single-fraction SBRT in patients with locally advanced pancreatic cancer (LAPC). A total of 49 patients with LAPC received up to 3 doses of GEM (1,000 mg/m²) followed by a 1-week break and SBRT (33.0 gray [Gy] in 5 fractions). After SBRT, patients continued to receive GEM until disease progression or toxicity. Toxicity was assessed using the NCI Common Terminology Criteria for Adverse Events [version 4.0] and the Radiation Therapy Oncology Group radiation morbidity scoring criteria.

Patients completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) and pancreatic cancer-specific QLQ-PAN26 module before SBRT and at 4 weeks and 4 months after SBRT. The median follow-up was 13.9 months (range of 3.9 to 45.2 months). The median age of the patients was 67 years and 84 % had tumors of the pancreatic head. Rates of acute and late (primary end-point) grade greater than or equal to 2 gastritis, fistula, enteritis, or ulcer toxicities were 2 % and 11 %, respectively. QLQ-C30 global quality of life scores remained stable from baseline to after SBRT (67 at baseline, median change of 0 at both follow-ups; p > 0.05 for both). Patients reported a significant improvement in pancreatic pain (p = 0.001) 4 weeks after SBRT on the QLQ-PAN26 questionnaire. The median plasma carbohydrate antigen 19-9 (CA 19-9) level was reduced after SBRT (median time after SBRT, 4.2 weeks; 220 U/ml versus 62 U/ml [p < 0.001]). The median OS was 13.9 months (95 % CI: 10.2 months to 16.7 months). Freedom from local disease progression at 1 year was 78 %; 4 patients (8 %) underwent margin-negative and lymph node-negative surgical resections. The authors concluded that fractionated SBRT with GEM resulted in minimal acute and late GI toxicity. They stated that future studies should incorporate SBRT with more aggressive multi-agent chemotherapy.

Furthermore, NCCN’s clinical practice guideline on “Pancreatic adenocarcinoma” (Version 2.2015) does not mention SRS as a therapeutic option.

Appendix

Stereotactic radiosurgery for treatment of brain malignancies (primary tumors and/or metastatic lesions) is considered medically necessary in members with a good performance status (a score between 80 and 100 on the Karnofsky Performance Scale;1 [ie, at a minimum, able to perform normal activity with effort]), controlled systemic disease (defined as extracranial disease that is stable or in remission), and no more
than 4 metastatic lesions. For treatment to additional lesions, further clinical justification may be needed.

Stereotactic radiosurgery is considered medically necessary for ocular melanomas that are not amenable to surgical excision or other conventional forms of treatment.

Stereotactic body radiation therapy is considered medically necessary for localized malignant conditions within the body where highly precise application of high-dose radiotherapy is required and clinically appropriate, including:

- Hepatocellular carcinoma in individuals with unresectable disease that is considered to be extensive and not suitable for liver transplantation or for individuals with local disease only with a good performance status (a score between 80 and 100 on the Karnofsky Performance Scale2) but who are not amenable to surgery due to comorbidities;
- Prostate cancer in individuals with organ-confined prostate cancer with Gleason score less than or equal to eight and prostate-specific antigen (PSA) less than 20;
- Non-small cell lung cancer for inoperable stage I or II tumors;
- Inoperable primary spinal tumors with compression or intractable pain;
- Recurrent metastatic disease in a previously irradiated area
- Recurrent localized head and neck cancer
- Metastatic lesions to the liver when they are the sole site of disease and cannot be surgically resected or undergo accepted ablation techniques
- Metastatic disease to the lung when clinically appropriate and on a case-by-case basis

All other clinical sites or indications are considered experimental and investigational but will be considered on a case-by-case basis.

CPT Codes / HCPCS Codes / ICD-10 Codes

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+".*

CPT codes covered if selection criteria are met:

- **20660** Application of cranial tongs, caliper, or stereotactic frame, including removal (separate procedure)
- **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** each additional cranial lesion, simple (List separately in addition to code for primary procedure)
- **61798** 1 complex cranial lesion
- **+ 61799** each additional cranial lesion, complex (List separately in addition to code for primary procedure)
- **61800** Application of stereotactic headframe for stereotactic radiosurgery (List separately in addition to code for primary procedure)
- **63620** Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion
- **63621** each additional spinal lesion (List separately in addition to code for primary procedure)
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>77371</td>
<td>Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; multi-source Cobalt 60 based linear accelerator based</td>
</tr>
<tr>
<td>77373</td>
<td>Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions</td>
</tr>
<tr>
<td>77432</td>
<td>Stereotactic radiation treatment management of cranial lesion(s) (complete course of treatment consisting of 1 session)</td>
</tr>
<tr>
<td>77435</td>
<td>Stereotactic body radiation therapy, treatment management, per treatment course, to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions</td>
</tr>
</tbody>
</table>

**HCPCS codes covered if selection criteria are met:**

- **G0173** Linear accelerator based stereotactic radiosurgery, complete course of therapy in one session
- **G0251** Linear accelerator based stereotactic radiosurgery, delivery including collimator changes and custom plugging, fractionated treatment, all lesions, per session, maximum 5 sessions per course of treatment
- **G0339** Image guided robotic linear accelerator-based stereotactic radiosurgery, complete course of therapy in one session, or first session of fractionated treatment
- **G0340** Image guided robotic linear accelerator-based stereotactic radiosurgery, delivery including collimator changes and custom plugging, fractionated treatment, all lesions, per session, second through fifth sessions, maximum 5 sessions per course of treatment

**Other HCPCS codes related to the CPB:**

- **A4648** Tissue marker, implantable, any type, each
- **A4650** Implantable radiation dosimeter, each

**ICD-10 codes covered if selection criteria are met:**

- **C00 - C96** Malignant neoplasms
- **D33.0 - D33.2** Benign neoplasm of brain
- **G20** Parkinson’s disease
- **G21.0 - G21.9** Secondary parkinsonism
- **G25.0** Essential tremor
- **G50.0** Trigeminal neuralgia
- **I67.1** Cerebral aneurysm, nonruptured
- **Q28.2 - Q28.3** Other congenital malformations of circulatory system

**ICD-10 codes not covered for indications listed in the CPB:**

- **G40.001 - G40.919** Epilepsy and recurrent seizures
- **G44.001 - G44.099** Cluster headache and trigeminal autonomic cephalgias (TAC)
The above policy is based on the following references:

1070.


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0083
Stereotactic Radiosurgery

There are no amendments for Medicaid.