Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy

Effective: March 1, 2018

Next Review: June 2018
Last Review: February 2018

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) are radiotherapy techniques that use highly focused radiation beams to treat both neoplastic and non-neoplastic conditions, in contrast to traditional external radiation beam therapy, which involves the use of relatively broad fields of radiation over a number of sessions that may occur over weeks to months.

MEDICAL POLICY CRITERIA

I. Stereotactic radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT), also known as Stereotactic Ablative Body Radiotherapy (SABR), may be considered medically necessary for initial treatment or treatment of recurrence for any of the following indications:

A. Intracranial sites:
   1. Primary neoplasms of the CNS (See Appendix I), including but not limited to low grade gliomas and high-grade gliomas
   2. Metastasis to CNS (solitary or multiple) in patients when both of the following are met:
a. Karnofsky performance score greater than or equal to 70 or an ECOG score less than or equal to 2 (See Policy Guidelines); and
b. Absent or stable extracranial disease.

3. Acoustic neuromas (Vestibular Schwannomas)
4. Arteriovenous malformations
5. Chordomas and chordrosarcomas of the skull base
6. Craniopharyngiomas
7. Hemangioblastoma
8. Hemangiopericytoma
9. Glomus jugulare and Glomus tympanicum tumors
10. Meningiomas, benign, atypical, or malignant
11. Pituitary adenomas
12. Spinal or paraspinal tumors (primary or metastatic)
13. Trigeminal neuralgia (tic douloureux) refractory to medical management
14. Uveal melanoma

B. Extracranial sites:

1. Hepatic tumor (primary or metastatic) as palliative or curative treatment when both of the following are met:
   a. Absence or minimal extra hepatic disease; and
   b. Karnofsky performance score greater than or equal to 70 or an ECOG score less than or equal to 2 (See Policy Guidelines).

2. Hepatocellular carcinoma when all of the following criteria are met:
   a. Five or fewer hepatic lesions; and
   b. Size of largest lesion is 6 cm diameter or less; and
   c. Karnofsky performance score greater than or equal to 70 or an ECOG score less than or equal to 2 (See Policy Guidelines).

3. Lung metastases when both of the following criteria are met:
   a. Five or fewer metastatic lung lesions; and
   b. Karnofsky performance score greater than or equal to 70 or an ECOG score less than or equal to 2 (See Policy Guidelines).

4. Non-small cell lung cancer (NSCLC), primary (node negative, tumor stage T1a, T1b, T2a, T2b)

5. Osteosarcoma, metastatic when all of the following criteria are met:
   a. Five or fewer metastatic lesions; and
   b. Karnofsky performance score greater than or equal to 70 or an ECOG score less than or equal to 2 (See Policy Guidelines).
6. Prostate cancer, low- to intermediate-risk (See Policy Guidelines) when all of the following criteria are met:
   a. Stage less than T3a; and
   b. PSA less than or equal to 20; and
   c. Gleason Score less than 8.

7. Spinal or paraspinal tumors (primary or metastatic)

II. Stereotactic radiosurgery and stereotactic body radiation therapy (also known as Stereotactic ablative body radiotherapy) are considered investigational for all other indications including but not limited to:
   A. Cavernous malformations
   B. Choroidal neovascularization (CNV)
   C. Chronic pain
   D. Epilepsy
   E. Functional disorders other than trigeminal neuralgia
   F. Refractory symptoms of essential tremor or Parkinson's disease
   G. Seizures
   H. Tumors, primary of the following sites or metastatic to the following sites:
      1. Cervix
      2. Endometrium
      3. Esophagus
      4. Hemangiomas
      5. Kidney
      6. Large bowel
      7. Ovaries
      8. Pancreas
      9. Rectum
     10. Small bowel

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History/Physical and Chart notes, including requirements as outlined by the policy criteria, as applicable to the indication for treatment.
- As applicable, documented ECOG score or Karnofsky performance score
For prostate cancer, PSA and Gleason score.

For the purposes of this policy, neoplasm is defined as “an abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Neoplasms may be benign (not cancer), or malignant (cancer).”[1]

**PERFORMANCE STATUS MEASUREMENT**

Performance status is frequently used in oncology practice as a variable in determining prognosis and management strategies. Either the Karnofsky Performance Status (KPS) or the Eastern Cooperative Oncology Group (ECOG) Performance Status scoring systems may be used.

**Karnofsky Performance Status**

<table>
<thead>
<tr>
<th>100</th>
<th>Normal, without symptoms</th>
</tr>
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<tbody>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some signs or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance; able to care for most personal needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalization is indicated</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; active support treatment is necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly</td>
</tr>
</tbody>
</table>

**ECOG Performance Status**

<table>
<thead>
<tr>
<th>0</th>
<th>Fully active, able to carry on all pre-disease performance without restriction.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
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</tbody>
</table>

**Prostate Cancer Risk**

The National Comprehensive Network (NCCN) Clinical Practice Guideline for Prostate Cancer defines low risk prostate cancer as T1-T2a, Gleason score less than or equal to six/Gleason grade one, and PSA less than 10ng/mL.[2] Intermediate risk is defined as T2b-T2c or Gleason score of seven/Gleason grade group two or three, or PSA 10-20ng/ml.

**FRACTIONATION**

Fractionated stereotactic radiotherapy refers to when SRS or SBRT are performed in 1-10 treatments focused upon a specific site. SRS is commonly delivered in 1-5 fractions and SBRT or SABR is commonly delivered in 1-5 fractions but may be delivered in as many as 10 fractions.
DOSE CONSTRAINT REFERENCES

Radiation Therapy Oncology Group (RTOG) Radiation Dose Constraints


Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC)


CROSS REFERENCES

1. [Charged Particle (Proton or Helium Ion) Radiation Therapy](https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity/Medicine/Policy_No. 49), Medicine, Policy No. 49
2. [Intraocular Radiation Therapy for Age-Related Macular Degeneration](https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity/Medicine/Policy_No. 134), Medicine, Policy No. 134
3. [Intensity Modulated Radiotherapy (IMRT) of the Thorax](https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity/Medicine/Policy_No. 136), Medicine, Policy No. 136
4. [Intensity Modulated Radiotherapy (IMRT) of the Prostate](https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity/Medicine/Policy_No. 137), Medicine, Policy No. 137
5. [Intensity Modulated Radiotherapy (IMRT) for Head and Neck Cancers and Thyroid Cancer](https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity/Medicine/Policy_No. 138), Medicine, Policy No. 138
6. [Intensity Modulated Radiotherapy (IMRT) of the Abdomen and Pelvis](https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity/Medicine/Policy_No. 139), Medicine, Policy No. 139
7. [Radioembolization for Primary and Metastatic Tumors of the Liver](https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity/Medicine/Policy_No. 140), Medicine, Policy No. 140
8. [Intensity Modulated Radiotherapy (IMRT): Central Nervous System (CNS) and Vertebral Tumors](https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity/Medicine/Policy_No. 147), Medicine, Policy No. 147

BACKGROUND

Stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) rely on three-dimensional imaging to localize the therapy target. SRS and SRBT have been used for a range of malignant and non-malignant conditions. Because they are more targeted than traditional external radiation therapy, SRS and SBRT are often used for treatment at sites that are difficult to reach via surgery, located close to other vital structures, or subject to movement within the body. The term SBRT will be used to describe treatment also referred to as stereotactic ablative body radiotherapy (SABR).

SRS and SBRT (or SABR) employ similar technological "stereotactic" sophistication with elements of advanced pretreatment imaging for localization of target(s), patient immobilization, control of breathing associated tumor movement, focally targeted treatment planning, and daily image guidance to ensure precise delivery of high daily doses of radiation. As commonly used in the medical literature, SRS refers to intracranial treatments and SBRT refers to extracranial treatments. Alternatively, SRS and SBRT may be defined independent of whether treatment is directed to intra or extra cranial tumors volumes. According to this definition, when such treatment is given as a single fraction, it may be referred to as SRS, and when it is delivered in 2-10 fractions it may be referred to as SBRT or SABR.

The fractionation used for SRS and SBRT is referred to as “hypofractionated” because it is fewer treatments than those used for conventional external beam radiotherapy.” Fractionation of stereotactic radiotherapy aims to optimize the therapeutic ratio; that is the ratio between tumor control and late effects on normal tissues. The main advantage of fractionation is that it allows higher total doses to be delivered to the tumor because of increased tolerance of the surrounding healthy tissues to each individual, fractionated dose. In addition, some lesions such as large arteriovenous malformations may require more than one procedure to complete the obliteration process.
SRS and SBRT can be administered by several types of devices that are distinguished by their source of radiation, including particle beams (e.g., proton), gamma radiation from cobalt-60 sources, or high-energy photons from linear accelerator (LINAC) systems. The Gamma Knife and linear accelerator systems (including the Cyberknife®) are similar in concept; both use multiple photon radiation beams that intersect at a stereotactically determined target, thus permitting higher doses of radiation delivery with sparing of surrounding normal tissues. The differences between the two relate to how the energy is produced (i.e., through decaying cobalt-60 in the gamma knife devices, or from x-rays in the linear accelerator system) and the number of energy sources used (i.e., multiple energy sources in the gamma knife versus one in the linear accelerator system).

IMAGE-GUIDED RADIOSURGERY OR RADIOTHERAPY

Image-guided radiosurgery or radiotherapy is a relatively new development collectively describing units with real-time image guidance systems. Examples include the Cyberknife® device, BrainLAB Novalis®, TomoTherapy®, and LINAC with computerized tomography (CT).

REGULATORY STATUS

Several devices that use cobalt 60 radiation (gamma ray devices) for SRS have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. The most commonly used gamma ray device is the GammaKnife (Elekta; approved May 1999). Gamma ray emitting devices that use cobalt 60 degradation are also regulated through the U.S. Nuclear Regulatory Commission.

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

Note: Particle radiation can also be used without stereotactic guidance. In this setting, the use of particles is referred to as proton, helium, or neutron radiation therapy. Proton or helium ion radiation therapies (RT), intraocular RT for age-related macular degeneration, and electromagnetic navigation bronchoscopy for placement of fiducial markers are considered in separate medical policies. See cross-reference section below.

EVIDENCE SUMMARY

The selection of variables used in the delivery of SRS and SBRT is complex and individualized, requiring selection of the device, radiation dose, and the size and shape of treatment margins. All of these variables depend on the location, shape, and radiosensitivity of the target tissue and the function and radiosensitivity of the surrounding tissue. Trials that allow direct comparison of all of the possible variables involved in selecting specific SRS and SBRT methods do not broadly exist making it difficult to draw comparative effectiveness conclusions. Further, for many rare conditions, large comparative studies are unlikely. The evidence below will focus on indications with criteria and investigational indications.

Please note that the evidence review below does not compare specific radiation planning and delivery techniques.
INTRACRANIAL INDICATIONS

Trigeminal Neuralgia

Dhople (2009) reported long-term outcomes of SRS for classical trigeminal neuralgia in 112 patients treated between 1996 and 2001.[3] Of these, 67% had no prior invasive operations for trigeminal neuralgia (TN) prior to SRS, 13% had one, 4% had two, and 16% had three or more. The right side was affected in 56% of cases, predominantly involving V2 (26%), V3 (24%), or a combination of both (18%) branches. The median age at diagnosis was 56 years, and median age at SRS was 64 years. The median prescription dose of 75 Gy (range, 70-80 Gy) was delivered to the involved trigeminal nerve root entry zone. The authors assessed the degree of pain before and after SRS by using the Barrow Neurological Institute (BNI) pain scale. In total, 102 patients took the survey at least once, for a response rate of 91%. Although not found to alter the conclusions of this study, 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 two 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 1, 3, 5, and 7 years were 60%, 41%, 34%, and 22%, respectively. Response duration was significantly better for those who had no prior invasive treatment 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.

Section Summary

Case series identify improvements in pain related to trigeminal neuralgia after treatment with SRS. Comparative studies that evaluate the use of SRS compared with alternative treatments for trigeminal neuralgia are lacking.

Epilepsy

A 1998 TEC Assessment[4] 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 (2000)[5] selected 25 patients with mesial temporal lobe epilepsy, 16 of whom provided minimum two-year follow-up. Seizure-free status was achieved in 13 patients, two patients were improved, and three patients had radiosurgery-related visual field defects.

A study by Schrottner (1998)[6] included 26 patients with tumor-related epilepsy, associated mainly with low-grade astrocytomas. Mean follow-up among 24 available patients was 2.25 years. Tumor location varied across patients. Seizures were simple partial in six (three with generalization) and complex partial in 18 (five with generalization, one gelastic). Seizures were eliminated or nearly so in 13 patients. Little improvement was observed in four patients and none in seven. Whang and Kwon (1996)[7] performed radiosurgery in 31 patients with epilepsy associated with nonprogressive lesions. A minimum of one-year follow-up was available in 23 patients, 12 of whom were seizure-free (and three of whom had antiseizure medications discontinued), two had seizures reduced in frequency, and nine experienced no change. While
the Regis series selected a fairly homogeneous clinical sample, the other two studies were heterogeneous. No confirmatory evidence is available on mesial temporal lobe epilepsy. The available evidence from patients with epileptic lesions of various sizes and locations is insufficient to show what factors are associated with favorable outcome.

In the most recent literature review (2017), no new comparative studies evaluating SRS for the treatment of epilepsy were identified.

**Section Summary**

The studies of SRS for treatment of epilepsy published to date are preliminary in nature, have very small study populations (less than 50 participants), short follow-up times, and/or contain heterogeneous study populations. In addition, the available evidence from patients with epileptic lesions of various sizes and locations is unable to adequately show what factors are associated with favorable outcomes following SRS treatment. There is inadequate information to determine the risk: benefit ratio of SRS compared with other therapies for epilepsy treatment.

**Tremor**

SRS has been used for the treatment of tremor through stereotactic radiofrequency thalamotomy. In 2008, Kondziolka (2008) reported outcomes for 31 patients who underwent SRS thalamotomy for disabling essential tremor. Among 26 patients with follow-up data available, score on the Fahn-Tolosa-Marin tremor score improved compared with baseline from 3.7 (pre-SRS) to 1.7 (post-SRS; p<0.000) and score on the Fahn-Tolosa-Marin handwriting score improved compared with baseline from 2.8 (pre-SRS) to 1.7 (post-SRS; p<0.000). One patient developed transient mild right hemiparesis and dysphagia and one patient developed mild right hemiparesis and speech impairment.

Kooshkabadi (2013) reported outcomes for 86 patients with tremor treated over a 15-year period, including 48 with essential tremor, 27 with Parkinson disease, and 11 with multiple sclerosis. Fahn-Tolosa-Marin tremor scores were used to compare symptoms pre- and post-procedure: the mean tremor score improved from 3.28 (pre-SRS) to 1.81 (post-SRS; p<0.0001), the mean handwriting score improved from 2.78 (pre-SRS) to 1.62 (post-SRS; p<0.0001), and the mean drinking score improved from 3.14 (pre-SRS) to 1.8 (post-SRS; p<0.0001). Complications included temporary hemiparesis in two patients, dysphagia in one patient, and sustained facial sensory loss in one patient.

Lim (2010) reported outcomes for a small cohort of 18 patients who underwent SRS treatment for essential tremor. For the 14 patients with videotaped evaluations allowing blinded evaluation of tremor severity and at least six months of follow-up (N=11 with essential tremor and N=3 with Parkinson disease), Fahn-Tolosa-Marin Tremor Rating Scale activities of daily living scores improved significantly after SRS (mean change score 2.7 points; p=0.03). However, there was no significant improvement in other Fahn-Tolosa-Marin Tremor Rating Scale items (p=0.53 for resting tremor, p=0.24 for postural tremor, p=0.62 for action tremor, p=0.40 for drawing, p>0.99 for pouring water, p=0.89 for head tremor). Mild neurologic complications occurred in two patients (lip and finger numbness), and severe neurologic complications occurred in one patient (edema surrounding thalamic lesion with subsequent hemorrhage at the lesion site, with speech difficulty and hemiparesis.)
Ohye (2012) conducted a prospective study of SRS for tremor that included 72 patients, 59 with Parkinson disease and 13 with essential tremor. Among 52 patients who had follow-up at 24 months, tremor scores measured using the unified Parkinson’s Disease Rating Scale (p<0.001; approximate score decrease extrapolated from graph from 1.5 at baseline to 0.75 at 24-month follow-up).

Young (2000) reported outcomes for a cohort of 158 patients with tremor who underwent SRS, including 102 patients with Parkinson disease, 52 with essential tremor, and four with tremor due to other conditions. Among patients with a parkinsonian tremor, at latest follow-up (mean, 47 months), blinded assessments on unified Parkinson’s Disease Rating Scale demonstrated improvements in several specific items, including overall tremor (from 3.3 pretreatment to 1.2 at last follow-up; p<0.05) and action tremor (from 2.3 pretreatment to 1.3 at last follow-up; p<0.05). Among patients with Essential tremor, blinded assessments were conducted using the Fahn-Tolosa-Marin Tremor Rating Scale. At one-year of follow-up, 92.1% of patients with essential tremor were completely or nearly tremor-free. Improvements were reported in components of the Fahn-Tolosa-Marin Tremor Rating Scale, but statistical comparisons are not presented. Three patients developed new neurologic symptoms attributed to the SRS.

Section Summary

The evidence related to the use of SRS for tremor consists of uncontrolled cohort studies, many of which report outcomes from the treatment of tremor of varying etiologies. Most studies report improvements in standardized tremor scores, although few studies used a blinded evaluation of tremor score, allowing for bias in assessment. No studies that compared SRS with alternative methods of treatment or a control group were identified. Limited long-term follow-up is available, making the long-term risk: benefit ratio of an invasive therapy uncertain. Due to inadequate evidence, conclusions cannot be drawn about the safety and effectiveness of SRS for these indications.

Chronic Pain

In 2017, Roberts and Pouratian performed a systematic review to evaluate the efficacy of SRS for chronic pain. They identified six articles with 113 patients that underwent SRS and had at least a three month follow-up for nonmalignant pain or at least a one month follow-up for malignant pain. At least 35% of patients reported having significant pain relief, but 21% of patients reported adverse events.

Section Summary

The evidence related to the use of SRS for chronic pain is limited and there remains a lack of comparative studies and long-term outcomes. This evidence is not sufficient to understand the safety and effectiveness of SBRT for the treatment of chronic pain or to adequately describe the subpopulation of patients with chronic pain most likely to benefit.

Acoustic Neuromas

SRS is widely used for the treatment of acoustic neuromas (vestibular schwannomas). Case series report generally high rates of local control (LC). For example, Badahshi (2014) reported a three-year local tumor control rate of 88.9% in a study of 250 patients with vestibular schwannoma who underwent SRS or fractionated SRS. Williams (2013) reported rates of tumor progression-free survival (PFS) for patients with large vestibular schwannomas treated
with SRS of 95.2% and 81.8% at three and five years, respectively.\cite{15} For patients with small vestibular schwannomas treated with SRS, tumor PFS was 97% and 90% at three and five years, respectively. In a retrospective case series of 93 patients with vestibular schwannomas treated with SRS, 83 of whom had long-term follow-up, Woolf reported an overall control rate of 92% at a median follow-up of 5.7 years. A small study from 2006 that compared microsurgical resection (N=36) with SRS (N=46) for the management of small (<3 cm) vestibular schwannomas showed better hearing preservation at last follow-up in the SRS group (p<0.01) and no difference in tumor control between the groups (100% vs 96%, p=0.50).\cite{16}

In the treatment of acoustic neuromas, the most significant adverse effect is loss of function of the facial and auditory nerve. For example, in a single-institution study, Meijer (2003) reported on the outcomes of single fraction versus fractionated linear accelerator (LINAC)-based SRS in 129 patients with acoustic neuromas.\cite{17} 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 (2004) reported on the results of a single-institution case series of 72 patients with acoustic neuromas, 45 of whom received single-fraction therapy and 27 who received fractionated therapy.\cite{18} 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 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.\cite{19}

**Section Summary**

The evidence related to the use of SRS for acoustic neuroma (vestibular schwannoma) consists primarily of case series and cohort studies, which report high rates of freedom from tumor progression. Given that vestibular schwannoma is a slow-growing tumor with symptoms most often related to local compression, demonstration of slowing of progression is a reasonable outcome. A single comparative study was identified that demonstrated comparable tumor control outcomes between SRS and surgical therapy for small vestibular schwannomas.

**Facial Nerve Schwannomas**

Sheehan (2015) published a multicenter case series study that evaluated 42 patients with facial nerve schwannomas undergoing SRS.\cite{20} Prior resection was performed in 36% of cases. At a median follow-up of 28 months, tumor control was achieved in 90% of patients. The study authors reported that most patients treated with SRS had neurological preservation. Smaller tumors treated with SRS had better outcomes for nerve function.

**Section Summary**

The evidence related to the use of SRS for facial nerve schwannomas consists of case series, which report high rates of tumor control and nerve preservation. However, there remains a lack of comparative studies that evaluate long term outcomes including overall survival.

**Primary or Recurrent Gliomas and Astrocytomas**
In a single-arm study, El-Shehaby (2015) reported on 11 patients with tectal gliomas treated with Gamma Knife SRS between October 2002 and May 2011.[21] Tectal gliomas are present in a critical location that makes surgical resection difficult, and are also commonly associated with aqueductal obstruction and consequently hydrocephalus. This necessitates some form of CSF diversion procedure before radiosurgery. Five patients had pilocytic astrocytomas and six nonpilocytic astrocytomas. Ten patients presented with hydrocephalus and underwent a CSF diversion procedure prior to SRS. The tumor volume ranged between 1.2 and 14.7 mL (median, 4.5 mL). The prescription dose was 11 to 14 Gy (median, 12 Gy). Patients were followed for a median of 40 months (range, 13-114 months). Tumor control after radiosurgery was seen in 100% of cases. In 6 of 11 cases (55%), the tumors eventually disappeared after treatment. Peritumoral edema developed in 45% of cases at an onset of 3 to 6 months after treatment. Transient tumor swelling was observed in four cases. Four patients developed cysts after treatment. One of these cases required aspiration and eventually disappeared, one became smaller spontaneously, and two remained stable.

In a retrospective review, Clark (2014) reported on 21 patients with recurrent malignant glioma (18 glioblastoma, three World Health Organization [WHO] grade III glioma), treated at initial diagnosis with surgery and standard chemoradiation, who received concurrent bevacizumab (BVZ) with hypofractionated SRS (30 Gy in five fractions) with or without concurrent chemotherapy (temozolomide or CCNU).[22] The median patient age was 54 years, median Karnofsky Performance Status was 80, and median target size was 4.3 mL (range, 3.4-7.5 mL). Eleven patients (52%) had previously failed BVZ. One patient had grade three toxicities (seizures, dysphasia), which resolved with inpatient admission and intravenous steroids/antiepileptics. Treatment-related toxicities were grade three (n=1), grade two (n=9), and grade 0-1 (n=11). Kaplan-Meier median PFS and OS estimates (calculated from start of SRS) for GBM patients (n=18) were 11.0 and 12.5 months, respectively.

In a prospective study from Cabrera (2013), 15 patients with recurrent malignant glioma lesions less than 3 cm in diameter were treated with SRS in a single fraction, whereas those three to 5 cm in diameter received five 5-Gy fractions; BVZ was administered immediately before SRS and two weeks later.[23] At initial diagnosis, patients were treated with surgery and adjuvant radiation therapy plus temozolomide and then at least one salvage chemotherapy regimen. The primary end point was central nervous system (CNS) toxicity. Secondary end points included survival, quality of life (QOL), microvascular properties as measured by MRI, steroid usage, and performance status. One grade three (severe headache) and two grade two CNS toxicities were observed. No patients experienced grade four to five toxicity or intracranial hemorrhage. Neurocognition, QOL, and Karnofsky Performance Status did not change significantly with treatment. MRI results suggested a significant decline in tumor perfusion and permeability one week after SRS and further decline by two months.

A retrospective analysis was performed by Cuneo (2013) on patients with recurrent malignant gliomas treated with salvage SRS from September 2002 to March 2010.[24] All patients had experienced progression after treatment with temozolomide and radiotherapy. Salvage SRS was typically administered only after multiple post chemoradiation salvage systemic therapies had failed. Among 63 patients treated with SRS for recurrent high-grade glioma, 49 patients had WHO grade IV disease. Median follow-up was 31 months from primary diagnosis and seven months from SRS. Median OS from primary diagnosis was 41 months for all patients. Median PFS and OS from SRS (OS-SRS) were 6 and 10 months for all patients, respectively. The one-year OS-SRS for patients with grade IV glioma who received adjuvant (concurrent with or after SRS) bevacizumab was 50% versus 22% for patients not receiving adjuvant
bevacizumab (p=0.005). Median PFS for patients with a WHO grade IV glioma who received adjuvant bevacizumab was 5.2 months versus 2.1 months for patients who did not receive adjuvant bevacizumab (p=0.014). Treatment related grade three or four toxicity for patients who receiving and did not receive adjuvant BVZ was 10% and 14%, respectively (p=0.58). On multivariate analysis, the relative risk of death and progression with adjuvant bevacizumab was 0.37 (95% CI, 0.17 to 0.82) and 0.45 (95%CI, 0.21 to 0.97). A Karnofsky Performance Status score greater than 70 and age less than 50 years were significantly associated with improved survival. The combination of salvage radiosurgery and bevacizumab to treat recurrent malignant gliomas is well tolerated and seems to be associated with improved outcomes. Prospective multiinstitutional studies are required to determine efficacy and long-term toxicity with this approach.

Dodoo (2014) reported on a total of 55 consecutive patients with high-grade glioma comprising 68 WHO grade III and WHO grade IV treated with SRS (Gamma Knife) for local recurrences between 2001 and 2007.[25] All patients had previously undergone microsurgery and radiochemotherapy. Complete follow-up was available in all patients, with a median follow-up of about 17 months (range, 2.5-114.2 months). Median tumor volume was 5.2 mL, prescription dose was 20 Gy (range, 14-22 Gy), and the median maximal dose was 45 Gy (range, 30-77.3 Gy). Patients with WHO grade III tumors initially showed a median survival of about 50 months, with a two-year OS of 90%. After SRS of the recurrences, these patients showed a median survival of 24 months and a two-year survival of 50%. The patients with WHO grade IV tumors had an initial median survival of 24 months with a two-year survival of 51%; after the recurrence was treated with SRS, the median survival was 11 months and two-year survival was 23%.

Section Summary

Direct evidence is not available to compare radiotherapy methods in the setting of primary or recurrent gliomas or astrocytomas. Evidence from heterogeneous observational studies demonstrates high rates of local control and survival with the use of SRS to treat gliomas in the primary and recurrent setting.

Brain Metastases

Systematic Reviews

In 2017, Ghidini conducted a systematic review on CNS metastases from esophageal and gastric cancer.[26] The authors analyzed data from 37 studies that met the criteria for inclusion. SRS was found to result in better OS, with the caveat that the studies examined included combination therapies that could cause an overestimate of survival.

Roos (2011) examined the randomized evidence to treat brain metastases.[27] 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 3 abstracts, investigating various combinations of surgery, SRS and WBRT. Most of the trials had significant limitations. Surgery and SRS improved LC, maintenance of performance status and survival for favorable prognosis patients with solitary brain metastases relative to WBRT alone, although the absolute survival benefit for the majority was modest. Limited data suggest similar outcomes from surgery and SRS, but few patients were truly suitable for both options. For multiple (two-four) brain metastases, SRS improved LC and functional outcome but not survival. Adjuvant WBRT also improved intracranial control but not survival; however,
the neurocognitive risk: benefit ratio of WBRT was controversial. Quality-of-life data were limited.

A 2011 review by Park (2011) 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.[28] 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.

A Cochrane systematic review by Patil (2010)[29] addressed the role for both SRS and 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 (3 trials) indicated that SRS plus WBRT did not show a survival benefit over WBRT alone; however, performance status and LC were significantly better in the SRS plus WBRT group.

**Randomized Controlled Trials**

Since publication of the systematic reviews, several RCTs have been published. Chang (2009) 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.[30]

Some studies have suggested that use of radiosurgery for brain metastases should be limited to patients with three or fewer lesions. A randomized trial from Kondziolka (1999) compared WBRT with WBRT plus radiosurgery boost to metastatic foci.[31] Results stated that the significant advantage of radiosurgery boost over WBRT alone in terms of freedom from local failure did not differ among patients with 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. SRS centers commonly exclude patients with more than five metastases from undergoing radiosurgery.[32,33] It is difficult to identify a specific limit on the number of metastases for which the use of SRS is advantageous. A large number of very small metastases may respond to radiosurgery, as well as a small number of larger metastases.

In 2006, Aoyama reported on a randomized trial of SRS plus WBRT versus SRS alone for treatment of patients with one to four brain metastases.[34] They found a 12-month intracranial tumor recurrence rate of 46.8% in the SRS plus WBRT group compared with 76.4% in the group that only received SRS. However, median survival times 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.[35]

**Nonrandomized Comparative Studies**
Tian (2013) reported results from a retrospective, single-institution cohort study comparing neurosurgical resection to SRS for solitary brain metastases from non-small-cell lung cancer (NSCLC). Seventy-six patients were included, 38 of whom underwent neurosurgery. Median survival was 14.2 months for the SRS group and 10.7 months for the neurosurgery group. In multivariable analysis, treatment mode was not significantly associated with differences in OS.

Noncomparative Studies

Noncomparative studies continue to evaluate the use of SRS without WBRT for the management of brain metastases and the role of SRS for the management of larger numbers of brain metastases. Yamamoto (2014) conducted a prospective observational study to evaluate primary SRS in patients with 1 to 10 newly diagnosed brain metastases. Inclusion criteria included largest tumor volume less than 10 mL and less than 3 cm in the longest diameter, a total cumulative volume of 15 mL or less, and a Karnofsky Performance Status score of 70 or higher. Among total 1194 patients, the median OS after SRS was 13.9 (95% CI, 12.0 to 15.6) in the 455 patients with one tumor, 10.8 months (95% CI, 9.4 to 12.4) in the 531 patients with two to four tumors, and 10.8 months (95% CI, 9.1 to 12.7) in the 208 patients with 5 to 10 tumors.

Rava (2013), in a cohort study including 53 patients with at least 10 brain metastases, described the feasibility of SRS treatment. Median survival was 6.5 months in this cohort. Raldow (2013), in a cohort of 103 patients with at least 5 brain metastases who were treated with SRS alone, demonstrated a median OS of 8.3 months, comparable with historical controls. OS was similar for patients with 5 to 9 and with at least 10 metastases (7.6 months and 8.3 months, respectively).

Yomo (2014) reported outcomes for 41 consecutive patients with 10 or fewer brain metastases from NSCLC who received SRS as primary treatment. The study reported one- and two-year OS rates of 44% and 17%, respectively, with a median survival time of 8.1 months. Distant brain metastases occurred in 44% by one year, with 18 patients requiring repeat SRS, 7 requiring WBRT, and one requiring microsurgery.

Section Summary

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

Cavernous Malformations

In 2017, Lopez-Serrano reported a case series of 95 patients treated with SRS for cavernous malformations (CMs). Patients, who had all experienced at least one bleeding incident before treatment, were followed for a median of 78 months after treatment. Hemorrhage rate was compared pretreatment (3.06%) to the first 3-year latency interval (1.4%) and to the remainder of the follow-up (0.16%). Adverse events reported were four patients with new location-dependent neurological deficits and three patients with edema-related headache. All patients recovered from these events fully.

A 2014 case series by Lee reported on 31 patients who were treated with SRS for CMs. Treatment followed a single symptomatic bleed in 31 patients (group A) and two or more
symptomatic bleeds in 18 patients (group B). The annual hemorrhage rate following SRS within the first two years and after two years (up to a mean follow-up of 64 months) was 7.06% and 2.03% for group A and 9.84% and 1.50% for group B, respectively. Pretreatment hemorrhage rate was 38.36% for group B. Adverse events were reported in four patients, one of which was did not resolve during the trial.

Park (2013) reported a case series of 21 patients treated with SRS for symptomatic brainstem intra-axial CMs.[43] Mean follow-up was 32 months. Excluding the first hemorrhage, the hemorrhage rate before SRS was 39.5%. The annual rate after SRS was 8.2% for the first two years. One adverse event, permanent paresthesia in one patient, was reported.

A case series of 30 patients treated with SRS for single or multiple CMs was reported by Huang in 2006.[44] For six patients, radiosurgery was for residual lesions identified following craniotomy. Mean follow-up was 59.9 months. Of the 13 patients presenting with seizures, following SRS eight were seizure-free, three had rare episodes of seizures, and two continued to have seizures. Hemorrhage rate pretreatment for the 22 patients presenting initially as acute hemorrhage was 1.9%. For all 30 patients, posttreatment hemorrhage rate was 1.9%. Posttreatment edema was observed in two patients.

In 2002, Kim reported a case series of 22 patients with symptomatic CMs treated with SRS.[45] Of these, 11 were treated with LINAC and 11 with Gamma knife. Twenty patients had experienced at least one episode of bleeding and two presented with seizure but did not have evidence of recent bleeding. Four of the patients that had incidence of bleeding underwent microsurgery prior to radiosurgery. Median follow-up was 38.3 months. The hemorrhage rate was 35.5% per year pretreatment and 1.55% per year posttreatment. Neurological deterioration was reported in six patients, and of those, persisted in two. Magnetic resonance images taken at the last follow-up showed that the lesion was decreased in eleven patients, increased in one, and unchanged in 10 cases.

Section Summary

The evidence related to the use of SRS for cavernous malformations consists of case series, which have reported improvements in hemorrhage rates. However, there remains a lack of comparative studies that evaluate long term outcomes.

EXTRACRANIAL INDICATIONS

Spinal Tumors

In 2017, Huo performed a systematic review of SRS for the spine. The authors found local control rates at a 12-18 months to be between 80.5 and 95%.[46] They found that with strict quality assurance, efficacious results can be obtained but that a number of contraindications to spine SBRT should be avoided, including spinal instability, poor performance status, and high-grade epidural disease.

Jawad (2016) evaluated 594 spinal tumors treated with SBRT at eight different institutions. 24% of cases had preexisting vertebral compression fractures.[47] At a median follow up of 10.1 months, 80% of patients had local tumor control. At the last imaging follow-up was (median 8.8 months after SBRT), 3% had new vertebral compression fractures and 2.7% had progressive vertebral compression fractures.
Sahgal (2013) evaluated rates of vertebral compression fractures after SBRT in 252 patients with 410 spinal segments treated with SBRT. Fifty-seven fractures were observed (13.9% of spinal segments treated), with 27 de novo fractures and 30 cases of existing fracture progression. Most fractures occurred relatively early posttreatment, with a median and mean time to fracture of 2.46 months and 6.33 months, respectively. Radiation dose per fraction, baseline vertebral compression fracture, lytic tumor, and baseline spinal misalignment were predictive of fracture risk.

Gerszten (2007) 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 Gy 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 (2007) reported on phase one/two results of SBRT in 74 spinal lesions in 63 patients (55% had prior irradiation) with cancer. The actuarial one-year tumor progression-free incidence was 84%. Pattern-of-failure analysis showed two primary mechanisms of failure: recurrence in the bone adjacent to the site of previous treatment and recurrence in the epidural space adjacent to the spinal cord. The authors concluded that analysis of the data obtained in their study supports the safety and effectiveness of SBRT in cases of metastatic spinal tumors. They add that they consider it prudent to routinely treat the pedicles and posterior elements using a wide bone margin posterior to the diseased vertebrae because of the possible direct extension into these structures and for patients without a history of radiotherapy, more liberal spinal cord dose constraints than those used in the study.

Gerszten (2004) 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. Most patients were treated for pain control and also had prior EBRT. The authors point out that radiotherapy of the spinal cord is limited by its low tolerance and that if a radiation dose could be targeted more accurately at the lesions, higher doses could be delivered in a single fraction. They further 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 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 (2005) reported on the outcomes of 51 patients with 72 spinal lesions who were treated with the CyberKnife. Patients underwent a median of three treatments. Pain was improved, as measured by declining mean visual analog scale (VAS) score, and quality of life was maintained during the one-year study period.

Section Summary

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

Non-Small-Cell Lung Cancer

Systematic Reviews
In 2014, Zheng reported results from a systematic review and meta-analysis comparing survival after SBRT with survival after surgical resection for the treatment of stage I NSCLC.[53] The authors included 40 studies reporting outcomes from SBRT, including 4850 patients, and 23 studies reporting outcomes after surgery published in the same time period, including 7071 patients. For patients treated with SBRT, the mean unadjusted OS rates at one, three, and five years were 83.4%, 56.6%, and 41.2%, respectively. The mean unadjusted OS rates at one, three, and five years were 92.5%, 77.9%, and 66.1%, respectively, with lobectomy, and 93.2%, 80.7%, and 71.7% with limited lung resections. After adjustment for surgical eligibility (for the 27 SBRT studies that reported surgical eligibility) and age, in a multivariable regression model, the treatment modality (SBRT vs surgical therapy) was not significantly associated with OS (p=0.36).

A review by Nguyen (2008)[54] 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 five-year survival was 42%. Koto reported on a phase two study of 31 patients with stage one NSCLC.[55] Patients received 45 Gy in 3 fractions, but those with tumors close to an organ at risk received 60 Gy in 8 fractions. With a median follow-up of 32 months, the three-year OS was 72%, while disease-free survival was 84%. Five patients developed grade two or greater pulmonary toxicity. While comparative studies were not identified, older studies have reported three-year disease-specific survival rates of 49% for those with stage one disease.[56]

Nonrandomized Comparative Studies

In a matched-cohort study design, Crabtree (2014) retrospectively compared outcomes between SBRT and surgical therapy in patients with stage one NSCLC.[57] Four hundred fifty-eight patients underwent primary surgical resection, and 151 were treated with SBRT. Surgical and SBRT patients differed significantly on several baseline clinical and demographic characteristics, with SBRT patients having an older mean age, higher comorbidity scores, a greater proportion of peripheral tumors, and worse lung function at baseline. For the surgical group, three-year OS and disease-free survival (DFS) were 78% and 72%, respectively. Of note, among the 458 patients with clinical stage I lung cancer, 14.8% (68/458) were upstaged at surgery and found to have occult N1 or N2 disease. For patients with occult nodal disease, three-year and five-year OS were 66% and 43%, respectively. For patients without occult nodal disease, 3- and 5-year OS were 80% and 68%, respectively. For the SBRT group, three-year OS and DFS were 47% and 42%, respectively.

In a propensity score-matched analysis, 56 patients were matched based on clinical characteristics, including age, tumor size, ACE comorbidity score, forced expiratory volume in one second (FEV$_1$) percent, and tumor location (central vs peripheral). In the final matched comparison, three-year OS was 52% versus 68% for SBRT and surgery, respectively (p=0.05), while DFS was 47% versus 65% (p=0.01). Two-, three-, four-, and five-year local recurrence-free survival for SBRT was 91%, 91%, 81%, and 40%, respectively, versus 98%, 92%, 92%, and 92% for surgery (p=0.07).

Jeppeson (2013) compared SBRT with conventional radiotherapy for patients with medically inoperable NSCLC (T1-2N0M0).[58] The study included 100 subjects treated with SBRT and 32 treated with conventional radiotherapy. At baseline, the SBRT-treated patients had smaller tumor volume, lower FEV$_1$, and a greater proportion of T1 stage disease. Median OS was 36.1 months versus 24.4 months for SBRT and conventional radiotherapy, respectively (p=0.015).
Local failure-free survival rates at one year were 93% in the SBRT group versus 89% in the conventional radiotherapy group and at 5 years 69% versus 66%, SBRT and conventional radiotherapy, respectively (p=0.99).

Port (2014) compared SBRT with wedge resection for patients with clinical stage IA NSCLC using data from a prospectively maintained database.[59] One hundred sixty-four patients were identified, 99 of whom were matched based on age, sex, and tumor histology. Thirty-eight patients underwent a wedge resection only, 38 patients underwent a wedge resection with brachytherapy, and 23 patients had SBRT. SBRT patients were more likely to have local or distant recurrences than surgically-treated patients (9% vs 30%, p=0.016), but there were no differences between the groups in disease-free three-year survival (77% for wedge resection vs 59% for SBRT, p=0.066).

Varlotta (2013) compared surgical therapy (n=132 with lobectomy, n=48 with sublobar resection) with SBRT (N=137) in the treatment of stage I NSCLC.[60] Mortality was 54% in the SBRT group, 27.1% in the sublobar resection group, and 20.4% in the lobar resection group. After matching for pathology, age, sex, tumor diameter, aspirin use, and Charlson Comorbidity Index, patients with SBRT had lower OS than patients treated with either wedge resection (p=0.003) or lobectomy (p<0.000).

Noncomparative Studies

In a 2015 multicenter study, Nagata evaluated SBRT with four fractions in patients (n=164) with T1N0M0 non-small cell lung cancer.[61] The median age of the study population was 78-years old. The three-year overall survival for the 100 inoperable patients was 59.9%. Grade three and four toxicities were observed in 10 and two patients, respectively. The three-year overall survival for the 64 operable patients was 76.5%. There were five patients with Grade three toxicities.

A retrospective database study (n=3,147) by Nanda (2015) evaluated patients aged 70 years or older with early stage (T1-T3N0M0) NSCLC for three years.[62] Overall survival was compared between stereotactic body radiotherapy alone and no treatment. SBRT was associated with improved survival in elderly patients who have concurrent comorbid conditions compared with no treatment.

Timmerman (2007) evaluated the toxicity and efficacy of SBRT in a high-risk population of patients with early stage but medically inoperable lung cancer.[63] in a phase two North American multicenter study of patients aged 18 years or older with biopsy-proven peripheral T1-T2N0M0 non-small-cell tumors (<5 cm in diameter) and medical conditions precluding surgical treatment. The prescription dose was 18 Gy per fraction × 3 fractions (54 Gy total), with the entire treatment lasting between 1.5 to two weeks. The primary end point was two-year actuarial primary tumor control; secondary end points were DFS (ie, primary tumor, involved lobe, regional, and disseminated recurrence), treatment-related toxicity, and OS. A total of 59 patients accrued, 55 of whom were evaluable (44 patients with T1 tumors, 11 patients with T2 tumors) with a median follow-up of 34.4 months (range, 4.8-49.9 months). Only one patient had primary tumor failure; the estimated three-year primary tumor control rate was 97.6% (95% CI, 84.3% to 99.7%). Three patients had recurrence within the involved lobe; the three-year primary tumor and involved lobe (local) control rate was 90.6% (95% CI, 76.0% to 96.5%). Two patients experienced regional failure; the local-regional control rate was 87.2% (95% CI, 71.0% to 94.7%). Eleven patients experienced disseminated recurrence; the three-year rate of disseminated failure was 22.1% (95% CI, 12.3% to 37.8%). The rates for DFS and
OS at three years were 48.3% (95% CI, 34.4% to 60.8%) and 55.8% (95% CI, 41.6% to 67.9%), respectively. The median OS was 48.1 months (95% CI, 29.6 months to not reached). Protocol-specified treatment-related grade three adverse events were reported in 7 patients (12.7%; 95% CI, 9.6% to 15.8%); grade four adverse events were reported in two patients (3.6%; 95% CI, 2.7% to 4.5%). No grade five adverse events were reported. The authors concluded that patients with inoperable NSCLC who received SBRT had a survival rate of 55.8% at three years, high rates of local tumor control, and moderate treatment-related morbidity.

Hof (2007) reported on outcomes (median follow-up, 15 months) for 42 patients with stages I and II lung cancer who were not suitable for surgery and who were treated with stereotactic radiotherapy.[64] In this series, at 12 months, OS was 75% and DFS was 70%. Better local control was noted with higher doses of radiation.

In a prospective evaluation of 185 medically inoperable patients with early (T1-T2N0M0) NSCLC treated with SBRT, Allibhai (2014) evaluated the influence of tumor size on outcomes.[65] Over a median follow-up of 15.2 months, tumor size (maximum gross tumor diameter) was not associated with local failure but was associated with regional failure (p=0.011) and distant failure (p=0.021). Poorer OS (p=0.001), DFS (p=9.001), and cause-specific survival (p=0.005) were also significantly associated with tumor volume more significant than diameter.

Harkenrider (2014) reported outcomes after SBRT for 34 patients with unbiopsied lung cancer, with estimated rates of two-year regional control, distant control, and OS of 80%, 85%, and 85%, respectively.[66]

Section Summary
Although no comparative data are available, studies have shown that SBRT for patients with stage one NSCLC who are not candidates for surgical resection because of comorbid conditions or for those with early stage disease who refuse surgery, survival rates may be comparable with surgical resection.

Hepatocellular Carcinoma

Systematic Reviews
Meng (2009) conducted a systematic review and meta-analysis of transcatheter arterial chemoembolization (TACE) in combination with radiotherapy compared with TACE alone for unresectable hepatocellular carcinoma (HCC) using meta-analysis of data from the literature involving available trials.[67] Seventeen trials involving 1476 patients were identified. Five were RCTs, and 12 were non-RCTs. In terms of quality, five RCTs were graded B, and the 12 nonrandomized studies were graded C. Results showed that TACE plus radiotherapy significantly improved survival and tumor response over TACE alone. The authors concluded that considering the strength of the evidence, additional RCTs are needed before combination TACE and radiotherapy can be routinely recommended.

A 2012 systematic review conducted by Tao and Yang, assessed the efficacy and safety of SBRT for treating primary and secondary hepatic neoplasms.[68] 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 to 10 fractions to total doses of 18 to 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 reported on outcomes for primary liver tumors including cholangiocarcinomas. At Indiana University, in a phase I study, Cardenes (2010) treated 17 HCC patients with Child-Turcotte-Pugh (CTP) CTP-A or CTP-B, one to three lesions and cumulative tumor diameter of 6 cm or less.\(^{[69]}\) 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 three hepatic toxicity. The one-year OS was 75%, and there were no local failures during the median 24 months of follow-up.

In an attempt to extend the use of SBRT to larger lesions, Shin (2010) treated 6 patients with large tumors (median tumor volume, 1288 mL; range, 1008-1815 mL) with no worse than CTP-A liver disease and without extrahepatic metastases.\(^{[70]}\) The 4 × 8–10 Gy regimen was relatively safe with only one case of grade three changes in transaminases. However, one-year OS was only 33%, in part due to advanced disease. One-year LC and OS rates were 50% to 100% and 33% to 100%, respectively. There were 13 cases of radiation-induced liver disease and four, grade five; six, grade four; and 69, grade three adverse events reported.

**Noncomparative Studies**

Scorsetti (2015) published a single center case series study with 43 patients (63 HCC lesions). Median follow-up was eight months (range 3-43 months).\(^{[71]}\) Median OS was 18 months +/-5.8 months. Actuarial local control was 64.4% +/-11.5% at 24 months. Overall survival was correlated with local control and gross tumor volume less than 5 cm. No radiation induced liver disease was reported. Several patients experienced significant toxicity ( ≥ Grade three).

Bujold (2013) reported on sequential phase one and two trials of SBRT for locally advanced HCC.\(^{[72]}\) Two trials of SBRT for patients with HCC who were considered to be unsuitable for standard locoregional therapies were conducted from 2004 to 2010. All of the patients had CTP class A disease. The primary end points were toxicity and LC at one year, defined as no progressive disease of irradiated HCC by Response Evaluation Criteria in Solid Tumors (RECIST). A total of 102 patients were evaluable (n=50 in trial one from 2004-2007; n=52 in trial two from 2007-2010). Underlying liver disease was hepatitis B in 38% of patients, hepatitis C in 38%, alcohol-related in 25%, and other in 14%, and none in 7%. Fifty-two percent received prior therapies (excluding sorafenib). TNM stage was III in 66% of patients, and 61% had multiple lesions. Median gross tumor volume was 117.0 mL (range, 1.3-1913.4 mL). Tumor vascular thrombosis (TVT) was present in 55% and 12% of patients had extrahepatic disease. LC at one year was 87% (95% CI, 78% to 93%). Toxicity of grade three or more was seen in 30% of patients. In 7 patients (two with TVT and progressive disease), death was possibly related to treatment (1.1-7.7 months after SBRT). Median OS was 17.0 months (95% CI, 10.4 to 21.3 months).

Andolino (2011) evaluated the safety and efficacy of SBRT for the treatment of primary HCC.\(^{[73]}\) From 2005 to 2009, 60 patients with liver-confined HCC were treated with SBRT: 36 CTP class A and 24 CTP class B. The median number of fractions, dose per fraction, and total dose was 3, 14 Gy, and 44 Gy, respectively, for those with CTP class A cirrhosis and 5, 8 Gy and 40 Gy, respectively, for those with CTP class B. The records of all patients were reviewed, and treatment response was scored according to RECIST v1.1. Toxicity was graded according to the Common Terminology Criteria for Adverse Events v4.0. LC, time to progression (TTP).
PFS, and OS were calculated according to Kaplan-Meier method. The median follow-up time was 27 months, and the median tumor diameter was 3.2 cm. The two-year LC, PFS, and OS were 90%, 48%, and 67%, respectively, with median TTP of 47.8 months. Subsequently, 23 patients underwent transplant, with a median time to transplant of 7 months. There were no grade three or greater nonhematologic toxicities. Thirteen percent of patients experienced an increase in hematologic/hepatic dysfunction greater than one grade, and 20% experienced progression in CTP class within three months of treatment. The authors concluded that SBRT is a safe, effective, noninvasive option for patients with HCC of 6 cm or less and that SBRT should be considered when bridging to transplant or as definitive therapy for those ineligible for transplant.

Ibarra (2012) 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 cm³ (p<0.004). The median time to local progression was 6.3 months. The one- and two-year OS rates were 87% and 55%, respectively. The incidence of grade one to two toxicities, mostly nausea and fatigue, was 39.5%. Grade three and four toxicities were present in two and one patients, respectively.

Price (2012) reported the results of a Phase one/two trial that evaluated the radiologic response in 26 patients with HCC who were not surgical candidates and were treated with SBRT between 2005 and 2008. Eligibility criteria included solitary tumors of 6 cm or less or up to three lesions with sum diameters of 6 cm or less, and well-compensated cirrhosis. All patients had imaging before, at one to three months, and every three to 6 months after SBRT. Patients received three to five fractions of SBRT. Median SBRT dose was 42 Gy (range, 24-48 Gy). Median follow-up was 13 months. Per RECIST, four patients had a complete response (CR), 15 had a partial response (PR), and 7 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% or more nonenhancement at 12 months. Thirteen of 18 demonstrated 100% nonenhancement, being greater than 50% in five patients. Kaplan-Meier one- and two-year survival estimates were 77% and 60%, respectively. SBRT is effective therapy for patients with HCC with an overall best response rate (CR + PR) of 73%.

Louis (2010) 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 performance score of less than two and pretreatment 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 planning target volume [PTV] received 45 Gy) and delivered to the target volume over 10 to 12 days. Overall, the treatment was well tolerated with two grade three acute toxicities and no acute grade four toxicities. Late toxicity was minimal; all observed late toxicities occurred within the first six months of follow-up. Three hepatic recurrences at a distance from the initial target were observed. The actuarial one- and two-year LC rate was 95% (95% CI, 69% to 95%). At a median overall follow-up of 12.7 months (range, 1-24 months), 6 of the 25 (24%) patients have died. Overall actuarial survival at one and two years was 79% (95% CI, 52% to 92%) and 52% (95% CI, 19% to 78%), respectively.
Kwon (2010) evaluated the long-term effect of SBRT for primary HCC in 42 patients ineligible for local ablation therapy or surgical resection.[77] 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). CR for the in-field lesion was initially achieved in 59.6% and partial response (PR) in 26.2% of patients. Hepatic out-of-field progression occurred in 18 patients (42.9%) and distant metastasis developed in 12 (28.6%) patients. Overall one-year and three-year survival rates were 92.9% and 58.6%, respectively. In-field PFS at one and three years was 72.0% and 67.5%, respectively. Patients with smaller tumors had better in-field PFS and OS rates (<32 cc vs ≥32 cc, p<0.05). No major toxicity was encountered, but one patient died with extrahepatic metastasis and radiation-induced hepatic failure.

Yoon (2013) reported outcomes for 93 patients with primary nonmetastatic HCC treated with SBRT at a single institution.[78] The median follow-up was 25.6 months. OS at one and three years was 86% and 53.8%, respectively. The main cause of treatment failure was intrahepatic (i.e., out-of-field) metastases. At one and three years, LC rates were 94.8% and 92.1%, respectively, and distant metastasis-free survival rates were 87.9% and 72.2%, respectively. However, intrahepatic recurrence-free survival rates at one and three years were 51.9% and 32.4%, respectively.

Jung (2013) reported rates of radiation-induced liver disease in patients with HCC treated with SBRT for small (<6 cm), nonmetastatic HCC that was not amenable to surgery or percutaneous ablative therapy.[79] Ninety-two patients were included, 17 of whom (18.5%) developed grade two or worse radiation-induced liver disease within three months of SBRT. In multivariable analysis, Child-Pugh class was the only significant predictor of radiation-induced liver injury. The one- and three-year survival rates were 86.9% and 54.4% respectively; with the median survival of 53.6 months. The presence of radiation-induced liver disease was not associated with survival.

Section Summary

The current evidence base is largely heterogenous and includes mostly prospective cohort studies that report outcomes for patients with HCC. Many of the studies were conducted on patients eligible for transplant or who were not eligible for other treatment modalities. Local control and overall survival among the study participants were generally over 70% at one-three-years follow-up. Studies reported a reduction in these outcomes after two-three years follow-up. Multiple studies reported better outcomes when tumors were 6 cm or less. It is important to note that multiple studies reported severe adverse events (≥ grade three) after SBRT for a small number of study participants.

Prostate Cancer

Nonrandomized Comparative Studies

In 2014, Yu (2014) compared toxicities after treatment with either SBRT (N=1335) or IMRT (N=2670) as primary treatment for prostate cancer, using claims data for Medicare beneficiaries.[80] The authors identified early stage prostate cancer patients aged 66 to 94 years treated from January 2008 to June 2011 who received either IMRT (N=53,841) or SBRT (N=1335) as primary treatment. SBRT patients were matched in a 2:1 manner based on potential confounders. SBRT was associated with higher rates of genitourinary (GU) toxicity. By six months after treatment initiation, 15.6% of SBRT patients had a claim indicative of treatment-related GU toxicity versus 12.6% of IMRT patients (odds ratio [OR]=1.29; 95% CI,
1.05 to 1.53; p=0.009). By 12 months posttreatment, 27.1% of SBRT versus 23.2% of IMRT patients had a claim indicative of GU toxicity (OR=1.23; 95% CI, 1.03 to 1.43; p=0.01), and by 24 months after treatment initiation, 43.9% of SBRT versus 36.3% of IMRT patients had a claim indicative of GU toxicity (OR=1.38;95% CI, 1.12 to 1.63; p=0.001). At six months posttreatment, there was increased gastrointestinal (GI) toxicity for patients treated with SBRT, with 5.8% of SBRT patients having had a claim indicative of GI toxicity versus 4.1% of IMRT patients (OR=1.42; 95% CI, 1.0 to 1.85; p=0.02), but at 12 and 24 months posttreatment, there were no significant differences in GI toxicity between groups.

Katz (2012) compared quality of life (QOL) after either radical prostatectomy (n=123) or SBRT (n=216) in patients with early stage prostate cancer.[81] QOL was assessed using the Expanded Prostate Cancer Index Composite (EPIC), addressing urinary, sexual and bowel function. The EPIC data from the SBRT group was compared with the surgery group at baseline, three weeks, 5, 11, 24 and 36 months (SBRT group) and baseline, 1, 6, 12, 24, and 36 months (surgery group). The largest differences in QOL occurred one to six months after treatment, with larger declines in urinary and sexual QOL occurring in the surgery group, but a larger decline in bowel QOL after SBRT. The long-term urinary and sexual QOL declines remained clinically significantly lower for the patients who underwent prostatectomy but not for the SBRT patients.

Noncomparative Studies

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

Boyer (2017) reported on a phase II study of SBRT for low to intermediate risk prostate cancer.[82] A total of 60 patients with a Gleason score of six and PSA less than or equal to 15 or a Gleason score of seven and PSA less than or equal to 10 were enrolled and treated with 37 Gy in five fractions. The study reported toxicity and quality of life measures. There were 10 reported late grade two or three toxicities. The median American Urological Association symptom score had a significant increase (from 4.5 to 11) during treatment but decreased to five at 36 months post-treatment. Both the Median International Index of Erectile Function and Expanded Prostate Cancer Index Composite Short Form sexual domain scores were significantly decreased at 36 months post-treatment. The authors concluded that SBRT is well tolerated when used to treat low to intermediate risk prostate cancer.

A retrospective study by Jeong (2015) evaluated SBRT for low- to intermediate-risk prostate adenocarcinoma.[83] The study included 39 patients with a median follow-up of 30 months. After five months, the median PSA was less than 2 ng/mL. In addition, the rate of overall three-year actuarial biochemical failure free survival was 93%.

King (2013) analyzed 1100 patients with clinically localized prostate cancer pooled from prospective phase two clinical trials of SBRT from eight institutions.[84] The median follow-up was 36 months, with 135 patients possessing a minimum of five-year follow-up. The five-year actuarial biochemical relapse free survival (bRFS) rate for all patients, including low-, medium-, and high-risk patients, was 93%. When broken down by risk, the 5-year actuarial bRFS rate was 95%, 84%, and 81% for low, intermediate, and high-risk patients, respectively.

McBride (2011) reported on a multi-institutional experience with SBRT for early stage, low-risk prostate adenocarcinoma.[85] A total of four centers and 45 patients were enrolled in a phase one, multi-institutional trial. Thirty-four patients received 7.5 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 PFS (bPFS), 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 of 0.4 ng/mL or more, 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 three urinary obstruction, and there were two episodes of late-grade three 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 (2011) evaluated the tolerability of escalating doses of SBRT in the treatment of localized prostate cancer. Eligible patients included those with Gleason score two to six with PSA 20 or less, Gleason score 7 with PSA 15 or less, T2b or less, prostate size 60 cm³ or less, and AUA score 15 or less. Dose-limiting toxicity was defined as grade three or worse GI/genitourinary (GU) toxicity by Common Terminology Criteria of Adverse Events (version three). Patients completed QOL questionnaires at defined intervals. Groups of 15 patients received 45 Gy, 47.5 Gy, and 50 Gy in 5 fractions (45 total patients). The median follow-up is 30 months (range, 3-36 months), 18 months (range, 0-30 months), and 12 months (range, 3-18 months) for the 45 Gy, 47.5 Gy, and 50 Gy groups, respectively. For all patients, GI grade of two or more and grade three or more toxicity occurred in 18% and 2%, respectively, and GU grade two or more and grade three or more toxicity occurred in 31% and 4%, respectively. Mean AUA scores increased significantly from baseline in the 47.5-Gy dose level (p=0.002), as compared with the other dose levels, where mean values returned to baseline. Rectal QOL scores (Expanded Prostate Cancer Index Composite) fell from baseline up to 12 months but trended back at 18 months. In all patients, PSA control was 100% by the nadir +2 ng/mL failure definition.

Freeman and King (2011) presented the outcomes for low-risk prostate cancer patients with a median follow-up of five years after SBRT. Between 2003 and 2005, a pooled cohort of 41 consecutive patients from two institutions received SBRT for clinically localized, low-risk prostate cancer. Prescribed dose was 35 to 36.25 Gy in five fractions. No patient received hormone therapy. Kaplan-Meier bPFS (defined using the Phoenix method) and Radiation Therapy Oncology Group (RTOG)-toxicity outcomes were assessed. At a median follow-up of five years, the bPFS was 93% (95% CI, 84.7% to 100%). Acute adverse effects resolved within one to three months of treatment completion. There were no grade four toxicities. No late grade three rectal toxicity occurred, and only one late grade three GU toxicity occurred following repeated urologic instrumentation.

Jabbari (2012) reported PSA nadir and acute and late toxicities with SBRT as monotherapy and post-EBRT boost for prostate cancer using high-dose rate (HDR) brachytherapy fractionation. 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 two GU and GI toxicity, respectively, with no grade three or higher acute toxicity to date. Two patients experienced late grade three GU toxicity. All patients were without evidence of biochemical or clinical progression at the date of publication, 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 with those achieved with HDR brachytherapy boost.

King (2012) reported the long-term outcomes of a phase two 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 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 five fractions using SBRT with CyberKnife. Patients who had received prior therapy (e.g., hormonal therapy) were excluded. The end points were early and late bladder and rectal toxicities, which were patient self-reported and graded on the 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; maximum, 5.9 years). There were no grade four toxicities. RTOG grade one, two, and three bladder toxicities were seen in 23%, 5% and 3% of patients, respectively. The grade three toxicities were attributed to dysuria exacerbated by urologic instrumentation. Grade one, two, and three rectal toxicities were seen in 12.5%, 2% and 0% of patients, respectively. There were two PSA, biopsy-proven failures with negative metastatic workup. The four-year PSA relapse-free survival was 94% (95% CI, 85% to 102%). The authors concluded that significant bladder and rectal toxicities from SBRT for prostate cancer were infrequent.

In a separate publication from the same phase two trial previously outlined, Weigner (2010) 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 EPIC-validated QOL questionnaire, the sexual function of 32 consecutive patients was analyzed at median times of 4, 12, 20, and 50 months after treatment. 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 with those reported for other modalities of radiotherapy.

Katz (2010) performed SBRT on 304 patients with clinically localized prostate cancer (211 with high-risk disease, 81 with intermediate-risk, 12 with low-risk disease). Fifty received 5 fractions of 7 Gy (total dose, 35 Gy) and 254 received 5 fractions of 7.25 Gy (total dose, 36.25 Gy). At a median 30-month (range, 26-37 months) follow-up, there were no biochemical failures for the 35-Gy dose level. Acute grade II urinary and rectal toxicities occurred in 4% of patients with no higher grade acute toxicities. At a median 17-month (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.
At six-year follow-up also performed by Katz, late urinary grade II complications were seen in 4% of patients treated with 35 Gy and 9% of patients treated with 36.25 Gy. [92] Five late grade III urinary toxicities occurred in patients treated with 36.25 Gy. Late grade II rectal complications were seen in 2% and 5% of patients treated with 35 Gy and 36.25 Gy, respectively. Initially, bowel and urinary QOL scores decreased but returned to baseline levels. There was an overall 20% decrease in the sexual QOL score. For patients who were potent prior to SBRT, 75% remained potent. Actuarial five-year biochemical recurrence-free survival was 97% for patients with low-risk disease, 90.7% for those with intermediate risk, and 74.1% for high-risk patients.

Bolzicco (2013) reported outcomes from 100 patients treated with SBRT for localized prostate cancer, 41 of whom were low risk (PSA ≤10 ng/mL or Gleason score ≤6; or tumor category T1c-T2a), 42 were intermediate risk (PSA 10-20 ng/mL or Gleason score seven or tumor category T2c), and 17 were high risk (PSA >20 ng/mL or Gleason score >7 or two median risk factors).[93] Twenty-seven patients received androgen deprivation therapy at the discretion of their treating urologist. Sixty-two patients had acute toxicity (within the first one to two weeks after treatment): 34% had grade one and 12% grade two urinary toxicity; 27% had grade one and 18% grade two GI toxicity. Late urinary toxicity, primarily urgency and frequency (at 6 months or later posttreatment) occurred in 8% of the patients: 4% grade one, 3% grade two and 1% grade three. The three-year bPFS rate was 94.4% (95% CI, 85.3% to 97.9%).

Other noncomparative studies have reported on specific outcomes after SBRT for prostate cancer, including rates of patient-reported urinary incontinence[94] and rectal tolerance[95] and health-related QOL outcomes.[96]

Section Summary

Data on the use of SBRT in prostate cancer consists primarily of single-arm assessments of acute and late toxicity and early PSA outcome data retrospectively compared with historical controls and a few looking at recurrence-free survival with a follow-up of three years or longer. Studies have shown promising initial results on the use of SBRT in prostate cancer with seemingly low toxicity rates and relatively high rates of biochemical recurrence-free survival.

Pancreatic Cancer

A 2017 systematic review from Petrelli evaluated the safety and efficacy of SBRT for the treatment of pancreatic cancer. Nineteen studies, with a total of 1009 patients, including nonrandomized and single-center series with mixed populations, were analyzed.[97] No publication bias was identified, but the heterogeneity among studies was substantial. A meta-analysis calculated the OS rate at one year and the median OS to be 51.6% and 17 months, respectively. The rate of acute severe toxicity ranged from 0% to 36%. The authors concluded that no evidence supports the claim that SBRT results in better outcomes than conventional RT, but there are benefits of SBRT, including shorter treatment time.

Goyal (2012) reported outcomes with SBRT in patients with pancreatic adenocarcinoma who were found not to be candidates for surgical resection.[98] A prospective database of the first 20 consecutive patients receiving SBRT for unresectable pancreatic adenocarcinomas and a neuroendocrine tumor was reviewed. Mean radiation dose was 25 Gy (range, 22-30 Gy) delivered over one to three fractions. Chemotherapy was given to 68% of patients in various schedules/timing. Patients had a mean gross tumor volume (GTV) of 57.2 cm³ (range, 10.1-118 cm³) before SBRT. The mean total GTV reduction at three and six 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 OS 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 one to two (11%) and grade three (16%). There were no grade four or five adverse events seen.

Rwigema (2011) assessed the feasibility and safety of SBRT in patients with advanced pancreatic adenocarcinoma.[99] 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, 8 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 FFLP and 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 6 months/one year were 71.7% to 48.5%, respectively. Among those with macroscopic disease, FFLP was achieved in 77.3% of patients with tumor size less than 15 mL (n=22), and 59.5% for tumor size of 15 mL or more (n=37) (p=0.02). FFLP was achieved in 73% following 24 to 25 Gy, and 45% with 18 to 22 Gy (p=0.004). The median OS was 10.3 months, with six month/one year OS rates of 65.3% to 41%, respectively. Grade one and two acute and late GI toxicity were seen in 39.5% of patients. Three patients experienced acute grade three toxicities. SBRT is feasible, with minimal grade three or more toxicity. The overall FFLP rate for all patients was 64.8%, comparable with rates with EBRT.

Chang (2009) reported on the local control and toxicity of SBRT for patients with unresectable pancreatic adenocarcinoma.[30] Seventy-seven patients with unresectable adenocarcinoma of the pancreas received 25 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 6 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 FFLP at 6 months and 12 months were 91% and 84%, respectively. The 6- and 12-month isolated local recurrence rates were 5% and 5%, respectively. There was no difference in the 12-month FFLP rate based on tumor location (head/uncinate, 91% vs body/tail, 86%; p=0.52). The PFS rates at 6 months and 12 months were 26% and 9%, respectively. The PFS rate at 6 months was superior for patients who had nonmetastatic disease versus patients who had metastatic disease (28% vs 15%; p=0.05). The OS rates at 6 months and 12 months from SBRT were 56% and 21%, respectively. Four patients (5%) experienced grade two or greater acute toxicity. Three patients (4%) experienced grade two late toxicity, and seven patients (9%) experienced grade three or greater late toxicity. At 6 months and 12 months, the rates of grade two or greater late toxicity were 11% and 25%, respectively.

Section Summary

Combined chemoradiotherapy plays a significant role in the treatment of locally advanced pancreatic cancer. The role of SBRT as a radiation technique for pancreatic tumors has not
been established, and it is not clear which patients would most likely benefit. Although studies have shown promising LC rates, there have been no significant changes in patient survival compared with historical data, and some studies have shown unacceptable toxicity and questionable palliative effect.

Renal Cell Carcinoma

A 2012 systematic review on the use of stereotactic radiotherapy for primary renal cell carcinoma (RCC) identified a total of 126 patients worldwide who had been treated using this modality. A systematic search performed in January 2012 identified seven retrospective studies and three prospective studies that used a wide range of techniques, doses and dose fractionation schedules. Median or mean follow-up ranged from 9 months to 57.5 months. LC was reported as 93.9% (range, 84%-100%) and the rate of severe grade three or higher adverse events was 3.8% (range, 0%-19%). The conclusions of the systematic review were that the current literature suggests that stereotactic radiotherapy for RCC can be delivered with good rates of LC and acceptable toxicity but that there is insufficient evidence to recommend a consensus for dose fractionation or technique, and there is a need for further prospective studies.

Beitler (2004) reported outcomes in nine patients with nonmetastatic RCC, two of whom had bilateral RCCs. Patients were treated definitively with 40 Gy in 5 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 of 3.4 cm or less in largest dimension, had clinically negative lymph nodes, and presented no clinical evidence of penetration of Gerota fascia or renal vein extension.

Ranck (2013) reported outcomes for 18 patients with RCC with limited metastases who were treated with SBRT. For patients with five or fewer metastatic lesions, all lesions were treated; in patients with greater than five lesions, rapidly-growing lesions or those close to vital organs were treated. In all, 39 metastatic lesions were treated, with a median of two lesions per patient. The two-year lesion-control rate was reported as 91.4% in the 12 patients who underwent treatment for all metastases, over a median follow-up of 21.3 months. However, in these patients, two-year freedom from new metastases was 35.7%. OS was 85% at two years. No patients who underwent treatment at all lesion sites died.

Section Summary

The literature on the use of SBRT for RCC consists of very small case series, which generally report high rates of LC. However, little evidence about the impact on patient outcomes can be derived from these data, nor any comparison made between this treatment modality and more established treatment modalities for RCC.

Oligometastases

The 2012 and 2013 reviews on the use of SBRT for oligometastases summarize the data on local tumor control, and in a limited subset of patients, survival, for various anatomic sites. The review conclusions are summarized below by type of oligometastases.

A 2012 long-term follow-up of a prospective study was reported by Milano (2012) on oligometastases treated with SBRT. The authors prospectively analyzed the long-term survival, tumor control outcomes, and freedom from widespread distant metastases (FFDM) after SBRT in 121 patients with 5 or fewer clinically detectable metastases, from any primary
site, metastatic to one to three organ sites, and treated with SBRT. For patients with breast cancer, the median follow-up was 4.5 years (7.1 years for 16/39 patients alive at the last follow-up visit). The two-year OS, FFDM and LC rate was 74%, 52%, and 87%, respectively. Six-year OS, FFDM, and LC rate were 47%, 36%, and 87%, respectively. From the multivariate analyses, the variables of bone metastases (p=0.057) and one versus more than one metastasis (p=0.055) were associated with a four-fold and three-fold reduced hazard of death, respectively. None of the 17 bone lesions that were from breast cancer recurred after SBRT versus 10 of 68 lesions from other organs that recurred (p=0.095). For patients with post breast cancers, the median follow-up was 1.7 years (7.3 years for 7 of 82 patients alive at the last follow-up visit). Two-year OS, FFDM, and LC rate were 39%, 28%, and 74%, respectively, and 6-year OS, FFDM, and LC rate were 9%, 13%, and 65%, respectively. For nonbreast cancers, a greater SBRT target volume was significantly adverse for OS (p=0.012) and lesion LC (p<0.001). Patients, whose metastatic lesions demonstrated radiographic progression after systemic therapy but before SBRT, experienced significantly worse OS compared with patients with stable or regressing disease. The authors conclude that select patients with limited metastases treated with SBRT are long-term survivors.

In 2015, Scorsetti published a case series with 82 elderly patients (111 total metastases) with oligometastases (16 localized to the abdomen, 50 liver, 45 lungs).[107] Median age was 79 years of age. The majority of patients (n=64) had a single lesion and 18 had two-four lesions. Local response was reported for 87 lesions and local progression was reported for 24 lesions. Two-year local control findings were 76.3% +/- 4.4% and overall survival was 72.0% +/- 5.6%. Disease-specific survival was 81.6% +/- 4.9% at two years. Treatment related Grade toxicity was reported. Grade two-three toxicity was reported in five patients, Grade one toxicity in seven patients, and no toxicity in 85.4% of patients.

Lung Oligometastases

For isolated or a few lung metastases (including <3 or <5, according to different selection criteria), the LC probability at one year has been reported in the range of 70% to 100%.[103] The overall survival varied widely after two-years (21%-84%) among the studies. In most case series, the most common clinical presentation is a single-lung metastasis. It is difficult to accurately evaluate survival estimates and clinical outcomes using SBRT for lung metastases due to an absence of randomized trials and because most phase one and two trials included heterogeneous patient populations.[103]

It is also difficult to compare OS data from SBRT with that of historical surgical metastasectomy series, mainly because of the different clinical characteristics of the patients, as most patients referred for SBRT are felt to be inoperable due to medical comorbidities that affect OS outcomes.[103] Data from the International Registry of Lung Metastases reported OS of 70% at two years and 36% at five years in patients with a single metastasis who underwent surgical metastasectomy.[108]

A systematic review by Siva (2010) on the use of SBRT for pulmonary oligometastases estimated from the largest studies included in the review a two-year weighted OS rate of 54.5%,[109] ranging from higher rates in a study by Norisha (2008) of 84%[110] to lower rates, such as 39%, reported from a multi-institutional trial.[111]

Since publication of the Siva systematic review, Osti (2013) reported outcomes from a prospective cohort study of SBRT for lung oligometastases.[112] Sixty-six patients with lung oligometastases were included, most (61%) with a single pulmonary nodule. For the primary
end point of LC, over a median follow-up of 14 months, LC at one year and two years was 89.1% and 82.1%, respectively. OS at one and two years was 76.4% and 31.2%, respectively, while PFS at one and two years was 53.9% and 22%, respectively. Two cases of grade three toxicity (pneumonitis) occurred.

Liver Oligometastases

The liver is the most common site of metastatic spread of colorectal cancer (CRC). Data show that surgical resection of limited liver metastases can result in long-term survival in select patients. However, only 10% to 20% of patients with metastatic CRC to the liver are surgical candidates. In patients who are not considered to be candidates for surgery, a variety of locally ablative techniques have been developed, the most common of which are RFA and transarterial chemoembolization. Retrospective analyses of RFA for liver metastases from CRC have shown wide variability in five-year OS rates, ranging from 14% to 55%.[103]

Retrospective series on the use of SBRT has reported LC rates ranging from 57% to 100% (median follow-up ranged 10 months – 4.3 years).[103] Prospective studies have reported one-year OS rates ranging from 61% to 85% and two-year OS rates ranging from 30% to 62%.[103] Another systematic review concluded similar findings evaluating similar studies.[105] In addition, the review concluded that the rate of adverse events was low with less than 5% of patients experiencing severe toxicity (grade three or more).

One of the larger series that was reported by Chang (2011) studied outcomes of SBRT for colorectal liver metastases in a pooled patient cohort from three institutions with colorectal liver metastases.[113] Patients were included if they had one to four lesions, received one to six fractions of SBRT, and had radiologic imaging three months or more posttreatment. Sixty-five patients with 102 lesions treated from 2003 to 2009 were retrospectively analyzed. Forty-seven (72%) patients had one or more chemotherapy regimens before stereotactic body radiotherapy, and 27 (42%) patients had two or more regimens. The median follow-up was 1.2 years (range, 0.3-5.2 years). The median dose was 42 Gy (range, 22-60 Gy). One- and two-year LC rates were 67% and 55%, respectively. One- and two-year OS rates were 72% and 38%, respectively.

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

Adrenal Gland Oligometastases

The most frequent primary tumor that metastasizes to the adrenal glands is NSCLC. Longer OS times have been reported with resection of clinically isolated adrenal metastases when compared with nonsurgical therapy, which has included locally ablative techniques, embolization and EBRT. LC rates at one year ranging from 55% to 90% have been reported, and one-year OS rates ranging from 40% to 56% and two-year OS ranging from 14% to 33%.[103]

Scorsetti (2012) described the feasibility, tolerability and clinical outcomes of SBRT in the treatment of adrenal metastases in consecutive cancer patients.[114] Between 2004 and 2010, a total of 34 patients, accounting for 36 adrenal metastatic lesions, were treated with SBRT. All 34 patients were clinically and radiologically evaluated during and after completion of SBRT. The following outcomes were taken into account: best clinical response at any time, LC, time-
to-systemic progression, time-to-local progression, OS and toxicity. The Kaplan-Meier method was used to estimate survival and factors that could potentially affect outcomes were analyzed with Cox regression analysis. No cases of grade three or greater toxicity were recorded. At a median follow-up of 41 months (range, 12-75 months), 22 patients were alive. Eleven percent of lesions showed CR, 46% PR, 36% SD, and 7% progressed in the treated area. Local failure was observed in 13 cases and actuarial local control rates at one and two years were 66% and 32%, respectively. Median time-to-local progression was 19 months and median survival was 22 months.

Holy (2011) presented initial institutional experiences with SBRT for adrenal gland metastases.[115] Between 2002 and 2009, 18 patients with NSCLC and adrenal metastases received SBRT for the metastatic disease. Metastases were isolated in 13 patients and multiple in five patients. A median PFS time of 4.2 months was seen in the entire patient group, with an increased PFS of 12 months in the 13 patients with isolated metastasis. After a median follow-up of 21 months, 77% of the patients with isolated adrenal metastasis achieved LC. In these patients, median OS was 23 months.

Casamassima (2012) retrospectively evaluated a single-institution’s outcomes after hypofractionated SBRT for adrenal metastases.[116] Between 2002 and 2009, 48 patients were treated with SBRT for adrenal metastases. Eight patients were treated with single-fraction SBRT and 40 patients with multifraction. Median follow-up was 16.2 months (range, 3-63 months). At time of analysis, 20 patients were alive and 28 patients were dead. One- and two-year actuarial OS rates were 39.7% and 14.5%, respectively. The median interval to local failure was 4.9 months. The actuarial one-year disease control rate was 9%; the actuarial one- and two-year LC rates were both 90%.

Chawla (2009) investigated the dosimetry and outcomes of patients undergoing SBRT for metastases to the adrenal glands.[117] A retrospective review of 30 patients who had undergone SBRT for adrenal metastases from various primary sites, including lung (n=20), liver (n=3), breast (n=3), melanoma (n=1), pancreas (n=1), head and neck (n=1), and unknown primary (n=1) was performed. Of the 30 patients, 14 with five or fewer metastatic lesions (including adrenal) underwent SBRT, with the intent of controlling all known sites of metastatic disease. Sixteen patients underwent SBRT for palliation or prophylactic palliation of bulky adrenal metastases. Twenty-four patients had more than three months of follow-up with serial computed tomography. Of these 24 patients, one achieved CR, 15 achieved PR, four had SD, and four developed progressive disease. No patients developed symptomatic progression of their adrenal metastases. LC was poor, and most patients developed widespread metastases shortly after treatment, with one-year survival, LC, and distant control rates of 44%, 55%, and 13%, respectively. No patient developed grade two or greater toxicity.

Ahmed (2013) reported outcomes from a single-center’s experience with SBRT for treatment of metastases to the adrenal glands.[118] Thirteen patients were included, most with lung primary tumors (n=9), with the remainder having kidney (n=2), skin (n=2), bladder (n=1), colon (n=1), and liver (n=1) as primary sites. Eleven patients (84.6%) had received prior chemotherapy since being diagnosed with metastatic disease, and one patient had undergone previous SBRT to bilateral psoas muscle metastases before adrenal SBRT. At the time of analysis, 8 of 13 patients were alive. The median follow-up time for living patients was 12.3 months (range, 3.1-18 months). Median survival for the five patients who died was 6.9 months (range, 2.1-15.2 months). Of the 12 patients who had evaluation for LC and distant control, 11 (91.6%) had some local response to therapy, but distant failure occurred in six patients at a
median of 2.5 months posttreatment, leading to a one-year distant control estimate of 55%. In exploratory analysis, there was no difference between lung primary tumor and other primary tumor sites in terms of OS or distant control. Acute toxicity included grade two nausea in two patients, grade two abdominal pain in one patient, grade one fatigue in five patients, and grade one diarrhea in one patient.

**Bone Oligometastases**

Napieralska (2014) reported a series 48 cases of prostate cancer bone metastases (in 32 patients) treated with SBRT primarily for pain control.[119] The size of the treated lesions ranged from 0.7 to 5.5 cm (mean, three dimension), and 31 (65%) of the treated metastases were located in the spine. At three-month follow-up, 17 patients had complete pain relief, two had partial pain relief, and two had no pain reduction. At the end of the follow-up period, complete pain relief was observed in 28 patients and partial pain relief in 16 patients.

**Spinal Oligometastases**

A small number of case series have been published evaluating the use of SBRT for the treatment of spinal metastases and are summarized in the included systematic reviews addressing oligometastases. The case series are heterogenous and some include studies with mixed primary sites. The studies consistently report local control rates of 77%-93% with a median follow-up ranging from 6-21 months. Data is lacking regarding longer-term follow-up and overall survival.[104,105]

**Section Summary**

The evidence for the use of SBRT to treat oligometastases is generally limited to case series with heterogenous study populations. However, the evidence consistently reports a high rate of tumor control for isolated or few metastases (≤ 3 or ≤ 5) for the liver and lung. The local tumor control is good and reported at one-year to be in the range of 70% to 100%. The overall survival varied widely after two-years (21%-84%) among the studies. Although some adverse events were reported, the overall rates for adverse events were low.

The evidence related to the use of SBRT for oligometastases for all other locations is heterogenous and limited to very small sample sizes, short-term follow-up, and retrospective, noncomparative analyses. More evidence is needed to establish the role of SBRT for the treatment of oligometastases for many of these locations.

### PRACTICE GUIDELINE SUMMARY

**NATIONAL COMPREHENSIVE CANCER NETWORK**

The National Comprehensive Network (NCCN) provides guidelines for cancer treatment by site that include the use of SRS and SBRT for certain cancers.[120]

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Tumor Type</th>
<th>Recommendation</th>
<th>Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>Osteosarcoma – metastatic disease</td>
<td>Consider use of stereotactic radiotherapy, especially for oligometastases (category 2A)</td>
<td>2.2017</td>
</tr>
<tr>
<td>CNS</td>
<td>Adult intracranial and spinal ependymoma – spine or brain reoccurrence</td>
<td>• Resection with limited radiotherapy if no prior radiotherapy; consider use of SRS if geometrically favorable (category 2A)</td>
<td>1.2016</td>
</tr>
<tr>
<td>Cancer Site</td>
<td>Tumor Type</td>
<td>Recommendation</td>
<td>Version</td>
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<tr>
<td>CNS</td>
<td>Adult medulloblastoma and supratentorial PNET – recurrent disease</td>
<td>• If unresectable, radiotherapy if no prior radiotherapy; consider use of SRS if geometrically favorable (category 2A) If progression, radiotherapy; consider use of SRS if geometrically favorable (category 2A)</td>
<td>1.2016</td>
</tr>
<tr>
<td>CNS</td>
<td>Primary spinal cord tumors</td>
<td>If progression after localized recurrence and maximum safe resection (category 2A)</td>
<td>1.2016</td>
</tr>
<tr>
<td>CNS</td>
<td>Meningiomas – asymptomatic</td>
<td>Observe (preferred for small tumors) or if accessible, surgery with or without RT (external beam or SRS). Recommendations based on WHO grade: Grade III – RT; Grade II with incomplete resection: RT; Grade I/II with complete resection – consider RT</td>
<td>1.2017</td>
</tr>
<tr>
<td>CNS</td>
<td>Meningiomas – symptomatic</td>
<td>If accessible, surgery with or without RT (external beam or SRS). Recommendations based on WHO grade: Grade III – RT; Grade II with incomplete resection: RT; Grade I/II with complete resection – consider RT</td>
<td>1.2017</td>
</tr>
<tr>
<td>CNS</td>
<td>Metastatic disease – 1-3 lesions, primary treatment</td>
<td>• If resectable, surgical resection followed by WBRT (category 1) or SRS (category 2B), OR SRS and WBRT (category 1 for 1 metastasis), OR SRS alone (category 2A) If unresectable, WBRT or SRS (category 2A)</td>
<td>1.2016</td>
</tr>
<tr>
<td>CNS</td>
<td>Metastatic disease – 1-3 lesions, recurrence</td>
<td>• If local recurrence and previous surgery only, surgery, single dose or fractionated stereotactic RT, or WBRT (category 2A) • If local recurrence and previous WBRT or SRS, surgery or single dose (category 2B) or fractionated SRS (category 2A) If distant brain recurrence and 1-3 lesions, surgery, single dose or fractionated stereotactic RT, WBRT, or consider chemotherapy</td>
<td>1.2016</td>
</tr>
<tr>
<td>CNS</td>
<td>Metastatic disease – &gt;3 lesions, primary treatment</td>
<td>WBRT or SRS (category 2A). SRS can be considered for patients with good performance status and low overall tumor volume.</td>
<td>1.2016</td>
</tr>
<tr>
<td>CNS</td>
<td>Metastatic spine tumors</td>
<td>• If no spinal cord compression, no fracture or spinal cord instability, consider surgical stabilization or vertebral augmentation followed by RT (recommend SRS if oligometastases and radioresistant) • If no spinal cord compression, no fracture or spinal instability, RT (preferred) or chemotherapy or surgery. Consider surgery or SRS if deterioration during RT, intractable pain, or tumor progression (recommend SRS if oligometastases and radioresistant) (category 2A). • If progressive disease or recurrent disease and if previously treated with RT or surgery and RT, consider surgery or SRS (recommend SRS if oligometastases and radioresistant). • If progressive disease or recurrent disease and previously treated with chemotherapy, consider</td>
<td>1.2016</td>
</tr>
<tr>
<td>Cancer Site</td>
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<td>Recommendation</td>
<td>Version</td>
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<tr>
<td>Colon</td>
<td>Metastatic to liver or lung</td>
<td>In patients with a limited number of liver or lung metastases, radiotherapy to the metastatic sites can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3-D conformal radiation therapy, IMRT, or SBRT.</td>
<td>2.2017</td>
</tr>
</tbody>
</table>
| Hepatobiliary | Hepatocellular carcinoma | • If potentially resectable or transplantable, operable by performance status or comorbidity, and Child-Pugh class A or B, no portal hypertension, suitable tumor location, adequate liver reserve, and suitable liver remnant, resection if feasible or external beam radiation therapy (category 2B)  
• If unresectable and not a liver transplant candidate, consider external beam radiation therapy among other options (category 2B)  
• If inoperable by performance status or comorbidity and local disease with minimal or no extrahepatic disease, consider external beam radiation therapy among other options (category 2B)  
SBRT may be considered as an alternative to the techniques listed above. Palliative EBRT is appropriate for symptom control and/or prevention of complications from metastatic HCC lesions, such as bone or brain metastases. | 2.2017 |
| Lung        | Non-small-cell lung cancer – Stage IA | If negative mediastinal nodes and medically inoperable, definitive RT including stereotactic ablative radiotherapy (category 2A) | 8.2017 |
| Lung        | Non-small-cell lung cancer – Stage IV, metastatic disease to single site, brain or adrenal. | • Brain metastasis: Surgical resection followed by WBRT or SRS (category 2A) or SRS alone (category 2A)  
If brain or adrenal metastasis and T1-2, N0-1 or T3, N0 disease: consider stereotactic ablative radiotherapy of lung lesion (category 2A) or chemotherapy followed by surgical resection of lung lesion or stereotactic ablative radiotherapy of lung lesion (category 2A) | 8.2017 |
| Pancreas    | Pancreatic adenocarcinoma | • If local recurrence in Pancreatic bed, consider induction chemotherapy followed by SBRT if radiation not previously done.  
• If good performance status, in selected patients, locally advanced without systemic metastases, induction chemotherapy followed by chemoradiation or SBRT | 2.2017 |
<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Tumor Type</th>
<th>Recommendation</th>
<th>Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>Prostate cancer</td>
<td>SBRT may be considered as a cautious alternative to conventionally fractionated RT at clinics with appropriate technology, physics, and clinical expertise</td>
<td>2.2017</td>
</tr>
<tr>
<td>Skin</td>
<td>Melanoma – metastatic</td>
<td>Brain metastases: SRS either as adjuvant or primary treatment or WBRT</td>
<td>2.2017</td>
</tr>
<tr>
<td>Soft tissue sarcoma – extremity, superficial trunk, head/neck</td>
<td>Sarcoma – synchronous stage IV</td>
<td>• If single organ and limited tumor bulk that are amenable to local therapy: consider SBRT (category 2A) &lt;br&gt;• If disseminated metastases: SBRT as a palliative option (category 2A)</td>
<td>2.2017</td>
</tr>
<tr>
<td>Soft tissue sarcoma – extremity, superficial trunk, head/neck</td>
<td>Sarcoma – recurrent disease with metastases</td>
<td>• If single organ and limited tumor bulk that are amenable to local therapy: consider SBRT (category 2A) &lt;br&gt;• If disseminated metastases: SBRT as a palliative option (category 2A) &lt;br&gt;• If isolated regional disease or nodes: consider SBRT (category 2A)</td>
<td>2.2017</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Papillary, follicular, or Hurthle cell carcinoma – structurally persistent/recurrent locoregional or distant metastatic disease not amenable to radioactive iodine</td>
<td>CNS metastases: for solitary lesions, either neurosurgical resection or SRS is preferred (category 2A)</td>
<td>2.2017</td>
</tr>
</tbody>
</table>

**NCCN Categories**
- **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
- **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

*All recommendations are category 2A unless otherwise noted.*

**AMERICAN COLLEGE OF CHEST PHYSICIANS**

**Non-Small-Cell Lung Cancer**

- In patients with stage I or II NSCLC with no medical contraindications to operative intervention, surgical resection is recommended (grade 1B-strong recommendation based on moderate evidence)[121]
- In patients with stage I NSCLC who cannot tolerate lobectomy or segmentectomy:[121]  
  - SBRT and wedge resection are recommended over no treatment (Grade 2C).  
  - SBRT is favored over wedge resection in these cases unless surgical resection may provide the benefit of definitive histologic analysis and nodal information that will result in a change in the patient’s management.  
  - SBRT is also favored in these patients if adequate surgical margin is unlikely with wedge resection.
• For high-risk stage I NSCLC tumors <5 cm, SBRT is preferred over conventional fractionated RT for definitive treatment when normal dose constraints can be respected. [122]
• For tumors within 2 cm of the proximal bronchial tree, a modified SBRT treatment schedule is suggested to decrease treatment-related toxicity. [122]
• For second primary lung cancer, SRS is an emerging technology, particularly when there is limited pulmonary reserve. [121]

Lung Cancer

• In lung cancer patients with 1-3 brain metastases, stereotactic radiosurgery (SRS) alone is the recommended initial therapy (Grade 1A). [123]

AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO)

Central Nervous System

• Brain Metastases: SRS is recommended for the following: [124]
  o Single brain metastases (initial management):
    ▪ If good prognosis (expected survival 3 months or more) and complete resection possible:
      • If brain metastasis ≤3-4 cm, options include SRS and WBRT (level of evidence: I), SRS alone (level of evidence: 1), and surgery with SRS/radiation boost with or without WBRT (level of evidence: 3)
      • If brain metastasis >3-4 cm, treatment options include surgery with SRS/radiation boost with or without WBRT (level of evidence: 3)
    ▪ If good prognosis and not resectable:
      • If brain metastasis ≤3-4 cm, options include SRS and WBRT (level of evidence: I), SRS alone (level of evidence: 1).
  o For multiple brain metastases (initial management):
    ▪ If good prognosis (expected survival 3 months or more) and brain metastasis ≤3-4 cm, options include SRS and WBRT (level of evidence: I), SRS alone (level of evidence: 1).
• Bone Metastases For palliative therapy for bone metastases, ASTRO makes the following recommendations related to the use of SBRT: [125]
  o Patients with painful bone metastases or spinal cord compression should be treated with SBRT only in clinical trials or with data collected in a registry.
  o For re-treatment of recurrent metastatic spine pain with SBRT, the Task Force states that the specifics of SBRT re-treatment dosing and target delineation are insufficiently defined to allow SBRT re-treatment outside of the clinical trial setting.

Non-Small-Cell Lung Cancer

• For patients with T1-2, N0 non-small cell lung cancer who are medically operable, ASTRO makes the following recommendations related to the use of SBRT: [126]
  o “For patients with “standard operative risk” (i.e., with anticipated operative mortality of <1.5%) and stage I NSCLC, SBRT is not recommended as an alternative to surgery outside of a clinical trial.”
  o “For patients with “high operative risk” (i.e., those who cannot tolerate lobectomy, but are candidates for sublobar resection) stage I NSCLC, discussions about SBRT as a potential alternative to surgery are encouraged. Patients should be informed that
while SBRG may have decreased risks from treatment in the short term, the longer-term outcomes >3 years are not well-established.

Glioblastoma

- “SRS and hypofractionated stereotactic RT appear to provide promising outcomes compared with chemotherapy, with median survival from reirradiation typically 8 to 12 months”.[127]

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

The ASCO guideline addresses the management of brain metastases for patients with human epidermal growth factor receptor 2 (HER2) -positive advanced breast cancer.[128] ASCO makes the following recommendations:

- For patients with a favorable prognosis for survival and a single brain metastasis, treatment options include surgery with postoperative radiation, stereotactic radiosurgery (SRS), whole-brain radiotherapy (WBRT; SRS), fractionated stereotactic radiotherapy (FSRT), and SRS (WBRT), depending on metastasis size, resectability, and symptoms. After treatment, serial imaging every 2 to 4 months may be used to monitor for local and distant brain failure.
- For patients with a favorable prognosis for survival and limited (two to four) metastases, treatment options include resection for large symptomatic lesion(s) plus postoperative radiotherapy, SRS for additional smaller lesions, WBRT (SRS), SRS (WBRT), and FSRT for metastases 3 to 4 cm.
- For metastases 3 to 4 cm, treatment options include resection with postoperative radiotherapy. In both cases, available options depend on resectability and symptoms.
- For patients with progressive intracranial metastases despite initial radiation therapy, options include SRS, surgery, WBRT, a trial of systemic therapy, or enrollment onto a clinical trial, depending on initial treatment. For patients in this group who also have diffuse recurrence, best supportive care is an additional option.

A 2016 ASCO guideline addresses the treatment of locally advanced, unresectable pancreatic cancer.[129] ASCO makes the following evidence-based recommendations:

- “Initial systemic therapy with combination regimens is recommended for most patients who meet the following criteria: Eastern Cooperative Oncology Group (ECOG) PS 0 or 1, a favorable comorbidity profile, and patient preference and a support system for aggressive medical therapy. There is no clear evidence to support one regimen over another, and physicians may offer therapy on the basis of extrapolation from data derived from studies in the metastatic setting. For some patients, conformal radiation therapy (CRT) or stereotactic body radiotherapy (SBRT) may be offered up front on the basis of patient and physician preference.” (evidence quality intermediate)
- “A short course of palliative radiotherapy (conventional RT or SBRT) may be offered to patients with LAPC who meet the following criteria: prominent local symptoms, such as abdominal pain and/or worsening jaundice and/or gastrointestinal (GI) bleeding; local infiltration into the GI tract causing impending gastric outlet or duodenal obstruction; and patient preference.” (evidence quality intermediate)

AMERICAN ACADEMY OF NEUROLOGY
The American Academy of Neurology published evidence-based recommendations in the
Treatment of Essential Tremor Practice Parameter in 2005 (updated in 2011).[130] It states
“There is insufficient evidence regarding the surgical treatment of head and voice tremor and
the use of gamma knife thalamotomy (Level U).”

SUMMARY

INTRACRANIAL INDICATIONS

There is enough research to show that use of stereotactic radiosurgery (SRS) and
stereotactic body radiation therapy (SBRT) for initial treatment or treatment of recurrence
improve health outcomes for the following intracranial conditions: primary neoplasms of the
central nervous system; metastasis to CNS with adequate performance score and absent or
stable extracranial disease; acoustic neuromas (vestibular schwannomas); arteriovenous
malformations; chordomas and chondrosarcomas of the skull base; craniopharyngiomas;
hemangioblastoma; hemangiopericytoma; glomus jugulare and glomus tympanicum tumors;
meningiomas; pituitary adenomas; trigeminal neuralgia that is refractory to medical
management; and uveal melanoma. In addition, clinical practice guidelines recommend the
use of SRS or SBRT for many these indications. Therefore, the use of SRS and SBRT may
be considered medically necessary when policy criteria are met for these indications.

EXTRACRANIAL INDICATIONS

Hepatic Tumors

There is enough evidence to show that stereotactic radiosurgery (SRS) and stereotactic
body radiation therapy (SBRT) improve health outcomes for patients with hepatic tumors.
Therefore, the use of SRS and SBRT for the treatment of hepatic tumors (primary or
metastatic) may be considered medically necessary when policy criteria are met.

For all other tumors or indications when policy criteria is not met, there is not enough
research to show improved health outcomes with stereotactic radiosurgery (SRS) or
stereotactic body radiation therapy (SBRT). Therefore, all other indications for the use of
SRS or SBRT for hepatic tumors are considered investigational.

Hepatocellular Cancer (HCC)

There is enough research to show that stereotactic radiosurgery (SRS) and stereotactic
body radiation therapy (SBRT) for HCC improve health outcomes in patients with less than
five tumors and less than 6 centimeters in diameter. Therefore, SRS and SBRT for the
treatment of HCC may be considered medically necessary when policy criteria are met.

There is not enough research to show that SRS or SBRT improves health outcomes for HCC
when the criteria are not met. Therefore, the use of SRS and SBRT for all other indications
for HCC is considered investigational.

Lung Metastases

There is enough research to show that stereotactic radiosurgery (SRS) and stereotactic
body radiation therapy (SBRT) improve health outcomes for people with lung metastases
(e.g., local control and acceptable treatment-related toxicity) in a select group of patients
with a limited number of metastases. Therefore, the use of SRS or SBRT for lung metastases may be considered medically necessary when policy criteria are met.

Outside this subgroup, there is not enough research to show that SRS or SBRT improves health outcomes for patients with lung metastases. Therefore SRS and SBRT of lung metastases are considered investigational when policy criteria are not met.

**Osteosarcoma**

There is enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT) may improve health outcomes for patients with osteosarcoma. Current clinical practice guidelines recommend SRS or SBRT as a treatment option for osteosarcoma metastatic disease. Therefore, SRS and SBRT for the treatment of osteosarcoma metastatic disease may be considered medically necessary when policy criteria are met.

For all other indications when policy criteria are not met, there is not enough research to show that SRS or SBRT improves health outcomes for patients with osteosarcoma. Therefore, the use of SRS and SBRT for osteosarcoma when policy criteria are not met are considered investigational.

**Primary Non-Small Cell Lung Cancer**

Non-comparative studies have consistently shown that stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) for patients with non-small cell lung cancer (NSCLC), node negative, tumor stage T1a, T1b, T2a, or T2b, have survival rates comparable to patients who have undergone surgical resection. In addition, clinical practice guidelines recommend the use of SRS or SBRT for NSCLC. Therefore, SRS and SBRT may be considered medically necessary for patients with NSCLC, when policy criteria are met.

For all other indications when policy criteria are not met, there is not enough research to show that SRS or SBRT improves health outcomes for patients with NSCLC. Therefore, SRS and SBRT for NSCLC are considered investigational when policy criteria are not met.

**Prostate Cancer**

There is enough research to show that stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) may improve health outcomes for people with prostate cancer. Clinical guidelines based on research cautiously recommend SRS or SBRT for people with prostate cancer. Therefore, the use of SRS or SBRT for prostate cancer may be considered medically necessary.

For all other indications when policy criteria are not met, there is not enough research to show that SRS or SBRT improves health outcomes for patients with prostate cancer. Therefore, SRS and SBRT for prostate cancer are considered investigational when policy criteria are not met.

**Spinal and Vertebral Body Tumors (Primary or Metastatic)**

There is enough research to show that stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) lead to improved net health outcomes in patients with spinal or vertebral body tumors and especially in patients that have received prior radiation therapy.
In addition, there is expert clinical consensus on the benefits of SBRT in this population. Therefore, SRS and SBRT may be considered medically necessary for the treatment of primary and salvage treatment of local recurrence after previous irradiation when policy criteria are met.

Adrenal Metastases

There is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for people with adrenal metastases. No clinical guidelines based on research recommend SRS or SBRT for people with adrenal metastases. Therefore, the use of SRS and SBRT for adrenal metastases is considered investigational.

Choroidal neovascularization (CNV)

There is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for people with choroidal neovascularization (CNV). No clinical guidelines based on research recommend SRS or SBRT for patients with CNV. Therefore, SRS or SBRT for CNV is considered investigational.

Chronic Pain

There is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for patients with chronic pain. No clinical guidelines based on research recommend SRS or SBRT for people with chronic pain. Therefore, the use of SRS or SBRT for chronic pain is considered investigational.

Epilepsy

There is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for patients with epilepsy. No clinical guidelines based on research recommend SRS or SBRT for people with epilepsy. Therefore, SRS or SBRT for epilepsy is considered investigational.

Kidney Cancer

There is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) improves health outcomes for patients with renal cell carcinoma. No clinical guidelines based on research recommend SRS or SBRT to treat patients with renal cell carcinoma. Therefore, the use of SRS or SBRT for kidney cancer are considered investigational.

Oligometastases

There is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT) improves health outcomes for people with oligometastases to locations not currently addressed as medically necessary in the policy criteria. Therefore, the use of SRS and SBRT for oligometastases not currently addressed as medically necessary in the policy criteria are considered investigational.

Pancreatic Cancer

There is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT) improves health outcomes for patients with pancreatic cancer. No clinical guidelines based on research recommend SRS or SBRT for patients with pancreatic cancer. Therefore, the use of SRS and SBRT for pancreatic cancer is considered investigational.
body radiation therapy (SBRT) improves health outcomes for people with pancreatic tumors. Therefore, the use of SRS or SBRT for pancreatic cancer is considered investigational.

Other Indications

For all other tumors or indications when policy criteria are not met, there is not enough research to show that stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT) leads to improved health outcomes. Therefore, SRS and SBRT are considered investigational when policy criteria are not met.

REFERENCES


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### CODES

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

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

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>32701</td>
<td>Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (photon or particle beam), entire course of treatment</td>
</tr>
<tr>
<td></td>
<td>77371</td>
<td>Radiation therapy delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; multi-source Cobalt 60 based</td>
</tr>
<tr>
<td></td>
<td>77372</td>
<td>Radiation therapy delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; linear accelerator based</td>
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<tr>
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<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 fraction</td>
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<tr>
<td></td>
<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>

**NOTE:** Codes for treatment delivery primarily reflects the cost related to the energy source used, and not physician work.

Clinical treatment management:

| CPT | 77432 | Stereotactic radiation treatment management of cerebral lesion(s) (complete course of treatment consisting of one session.) |
|     | 61796 | Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 simple cranial lesion |
|     | 61797 | Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, simple (List separately in addition to code for primary procedure) |
|     | 61798 | Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 complex cranial lesion |
|     | 61799 | Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, complex (List separately in addition to code for primary procedure) |
|     | 61800 | Application of stereotactic headframe for stereotactic radiosurgery (List separately in addition to code for primary procedure) |
|     | 63620 | Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion |
|     | 63621 | Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional spinal lesion (List separately in addition to code for primary procedure) |
| HCPCS | 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 five sessions per course of treatment |
## APPENDIX I: WHO Classification of Tumors of the Central Nervous System

<table>
<thead>
<tr>
<th>Diffuse astrocytic astrocytic and oligodendrogial tumors</th>
<th>Neuronal and mixed neuronal-glial tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse astrocytoma</td>
<td>Dysembryoplastic neuroepithelial tumor</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>Gangliocytoma</td>
</tr>
<tr>
<td>Diffuse midline glioma</td>
<td>Ganglioglioma</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>Anaplastic ganglioglioma</td>
</tr>
<tr>
<td><strong>Other astrocytic tumors</strong></td>
<td>Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)</td>
</tr>
<tr>
<td>Pilocytic astrocytoma</td>
<td>Desmoplastic infantile astrocytoma and ganglioglioma</td>
</tr>
<tr>
<td>Pilomyxoid astrocytoma</td>
<td>Papillary glioneuronal tumor</td>
</tr>
<tr>
<td>Subependymal giant cell astrocytoma</td>
<td>Rosette-forming glioneuronal tumor</td>
</tr>
<tr>
<td>Pleomorphic xanthoastrocytoma</td>
<td>Central neurocytoma</td>
</tr>
<tr>
<td>Anaplastic pleomorphic xanthoastrocytoma</td>
<td>Extraventricular neurocytoma</td>
</tr>
<tr>
<td><strong>Other gliomas</strong></td>
<td>Cerebellar liponeurocytoma</td>
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<tr>
<td>Choroid plexus papilloma</td>
<td>Paragangioma</td>
</tr>
<tr>
<td>Atypical choroid plexus papilloma</td>
<td><strong>Tumors of the pineal region</strong></td>
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<tr>
<td>Choroid plexus carcinoma</td>
<td>Pineocytoma</td>
</tr>
<tr>
<td>Milanotic schwannoma</td>
<td>Pineal parenchymal tumor of intermediate differentiation</td>
</tr>
<tr>
<td>Neurofibroma</td>
<td>Pineoblastoma</td>
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<tr>
<td>Atypical neurofibroma</td>
<td>Papillary tumor of the pineal region</td>
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<tr>
<td>Plexiform neurofibroma</td>
<td><strong>Embryonal tumors</strong></td>
</tr>
<tr>
<td>Perineurioma</td>
<td>Medulloblastomas</td>
</tr>
<tr>
<td>Hybrid nerve sheath tumors</td>
<td>Embryonal tumor with multilayered rosettes</td>
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<tr>
<td>Malignant peripheral nerve sheath tumor</td>
<td>Medulloepithelioma</td>
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<tr>
<td><strong>Meningiomas</strong></td>
<td>CNS neuroblastoma</td>
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<td>Meningioma</td>
<td>CNS ganglioneuroblastoma</td>
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<tr>
<td>Meningothelial meningioma</td>
<td>CNS embryonal tumor</td>
</tr>
<tr>
<td>Fibrous meningioma</td>
<td>Atypical teratoid/rhabdoid tumor</td>
</tr>
<tr>
<td>Transitional meningioma</td>
<td><strong>Tumors of the cranial and paraspinal nerves</strong></td>
</tr>
<tr>
<td>Psammomatous meningioma</td>
<td>Schwannoma</td>
</tr>
<tr>
<td>Angiomatous meningioma</td>
<td>Osteochondroma</td>
</tr>
<tr>
<td>Microcystic meningioma</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Secretory meningioma</td>
<td><strong>Melanocytic tumors</strong></td>
</tr>
<tr>
<td>Lymphoplasmacyte-rich meningioma</td>
<td>Meningeal melanocytosis</td>
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<tr>
<td><strong>APPENDIX I: WHO Classification of Tumors of the Central Nervous System</strong></td>
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<tr>
<td>Metaplastic meningioma</td>
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<td>Clear cell meningioma</td>
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<td>Atypical meningioma</td>
<td><strong>Lymphomas</strong></td>
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<td>Diffuse large B-cell lymphoma of the CNS</td>
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<tr>
<td>Rhabdoid meningioma</td>
<td>Immunodeficiency-associated CNS lymphomas</td>
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<td>Anaplastic (malignant) meningioma</td>
<td>Intravascular large B-cell lymphoma</td>
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<td><strong>Mesenchymal, non-meningothelial tumors</strong></td>
<td>T-cell and NK/T-cell lymphomas of the CNS</td>
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<td>Solitary fibrous tumor/hemangiopericytoma</td>
<td>Anaplastic large cell lymphoma</td>
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<tr>
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<td>MALT lymphoma of the dura</td>
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<tr>
<td>Hemangioma</td>
<td><strong>Histocytic tumors</strong></td>
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<td>Epithelioid hemangioendothelioma</td>
<td>Langerhans cell histiocytosis</td>
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<td>Erdheim-Chester disease</td>
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<tr>
<td>Kaposi sarcoma</td>
<td>Rosai-Dorfman disease</td>
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<td>Ewing sarcoma /PNET</td>
<td>Juvenile xanthogranuloma</td>
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<td><strong>Tumors of the sellar region</strong></td>
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</tbody>
</table>

Adapted from Louis (2016).[132]

*Date of Origin: January 1996*