6.01.10	Stereotactic Radiosurgery and Stereotactic Body Radiotherapy		
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Policy Statement

I. Stereotactic radiosurgery (SRS) using a gamma-ray or linear accelerator (LINAC) unit may be considered **medically necessary** for **any** of the following indications:
   A. Acoustic neuromas
   B. Arteriovenous malformations
   C. Craniopharyngiomas
   D. Glomus jugulare tumors
   E. Malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas)
   F. Mesial temporal lobe epilepsy refractory to medical management when standard alternative surgery is not an option
   G. Nonresectable, residual, or recurrent meningiomas
   H. Pituitary adenomas
   I. Solitary or multiple brain metastases in individuals having good performance status and no active systemic disease (defined as extracranial disease that is stable or in remission)
   J. Trigeminal neuralgia refractory to medical management
   K. Uveal melanoma

II. Stereotactic body radiotherapy (SBRT) may be considered **medically necessary** for **any** of the following indications:
   A. Primary or metastatic spinal or vertebral body tumors in individuals who have received prior spinal radiotherapy
   B. Spinal or vertebral metastases that are radioresistant (e.g., renal cell carcinoma, melanoma, sarcoma)
   C. Individuals with stage T1 or T2a non-small-cell lung cancer (not greater than 5 cm) showing no nodal or distant disease and who are not candidates for surgical resection
   D. Individuals with low or favorable intermediate risk prostate cancer
   E. Pancreatic carcinoma, in 3 to 5 fractions, with total doses of 30 to 45 Gray (Gy) in individuals with **either** of the following conditions:
      1. Unresectable or locally advanced disease
      2. Recurrent disease to the pancreatic bed
   F. Primary or metastatic tumors of the liver as an alternative locoregional treatment for individuals with inoperable primary or metastatic lesions
   D. Primary renal cell carcinoma in individuals who are not good surgical candidates or who have metastatic renal cell carcinoma;
   E. Oligometastases involving the lung, adrenal glands, and bone (other than spine or vertebral body)

III. When stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT) are performed using fractionation for the medically necessary indications described above, it may be considered **medically necessary**.

IV. Stereotactic radiosurgery (SRS) is **investigational** for other applications including, but not limited to, the treatment of seizures and functional disorders (other than trigeminal neuralgia), including chronic pain and tremor.

V. Stereotactic body radiotherapy (SBRT) is **investigational** for primary and metastatic tumors of the liver, kidney, adrenal glands, prostate and other conditions except as outlined in the policy statements above.

VI. Stereotactic body radiotherapy (SBRT) is **investigational** for **any** of the following for the treatment of pancreatic adenocarcinoma:
   A. As neoadjuvant therapy in resectable or borderline resectable tumors
   B. As adjuvant therapy in resected disease (i.e., treatment to the tumor bed)
   C. For palliative treatment
   D. If there is direct invasion of the bowel or stomach

See Policy Guidelines for allowable codes/number of units.

Image Guided Radiation Therapy (IGRT)

VII. IGRT may be considered **medically necessary** as an approach to delivering radiotherapy when combined with **any** of the following treatments (see Policy Guidelines):
   A. Intensity-modulated radiotherapy (IMRT)
   B. Stereotactic body radiation therapy (SBRT)
   C. Proton delivery

VIII. IGRT is **investigational** as an approach to delivering radiotherapy when combined with **any** of the following treatments:
   A. Conventional three-dimensional conformal radiation therapy (3D CRT) (see Policy Guidelines for considerations)
   B. Stereotactic radiosurgery (SRS)
   C. Electronic brachytherapy

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Radiation Source

This evidence review addresses the use of stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) delivered by gamma-ray or high-energy photons generated by a linear accelerator (LINAC) unit. The use of charged-particle (proton or helium ion) radiotherapies is addressed separately in Blue Shield of California Medical Policy: Charged-Particle (Proton or Helium Ion) Radiotherapy for Neoplastic Conditions.

Number of Lesions

A 1995 Blue Cross Blue Shield Association Technology Evaluation Center on SRS for multiple brain metastases found that evidence was sufficient to show that radiosurgery improved health outcomes for up to 3 metastases in the presence of good performance status and no active systemic disease. While evidence continues to demonstrate the importance of good performance status and absence of active systemic disease, it appears that the number of metastases may not be as predictive of outcome. Thus, individuals with more than 3 metastases who otherwise have good performance status and no evidence of active systemic disease may still benefit from SRS.

Many individuals with brain metastases can either receive whole-brain radiotherapy (WBRT) along with SRS, or WBRT may be delayed for use as salvage therapy for recurrent intracranial disease.

Fractionation

Fractionated SRS refers to SRS or SBRT performed more than once on a specific site.

SRS is most often single-fraction treatment; however, multiple fractions may be necessary when lesions are near critical structures.

SBRT is commonly delivered over 3 to 5 fractions.

Prostate Cancer Gleason Score

Low risk prostate cancer is defined as: Gleason score less than or equal to 6, prostate specific antigen less than 10 ng/mL and stage T1c or less.

Favorable intermediate risk prostate cancer is defined as predominantly Gleason grade 3 (i.e., Gleason score 3+4=7), percentage of positive biopsy cores less than 50% and no more than one NCCN intermediate risk factor (Clinical tumor stage T2b or T2c, Gleason score of 7, Prostate specific antigen level of 10 to 20 ng/mL).

The regimen used for stereotactic radiotherapy of the prostate hasn't been clearly defined, but is usually between 33.5 and 38 Gray administered over 4 to 5 fractions.

Note: Gray (Gy) is a derived unit of ionizing radiation dose in the International System of Units (SI). It is defined as the absorption of one joule of radiation energy per kilogram of matter.

Table A: National Comprehensive Cancer Network® Clinical Practice Guidelines (NCCN Guidelines®) for the treatment of Pancreatic Adenocarcinoma[175]

Criteria Defining Resectability Status[a]

Resectability Status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[b]	<u>Pancreatic head/uncinate process</u>: • Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be should be noted if present as it may affect surgical planning. <u>Pancreatic body/tail</u>: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some members prefer this criteria to be in the unresectable category].	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Unresectable[b]	• Distant metastasis (including non-regional lymph node metastasis) <u>Head/uncinate process</u>: • Solid tumor contact with SMA >180°	<u>Head/uncinate process</u> • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

Criteria Defining Resectability Status[a]		
	• Solid tumor contact with the CA >180° • Solid tumor contact with the first jejunal SMA branch <u>Body and tail</u> • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	• Contact with most proximal draining jejunal branch into SMV <u>Body and tail</u> • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

[a]Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014 Jan; 270(1):248-260.
[b]Solid tumor contact may be replaced with increased hazy density/stranding of the fat surrounding the peri-pancreatic vessels (typically seen following neoadjuvant therapy); this finding should be reported on the staging and follow-up scans. Decision on resectability status should be made in these patients, in consensus at multidisciplinary meetings/discussions.

Coding

Image Guided Radiation Therapy (IGRT) Considerations:

The following codes are for hospital outpatient IMRT/SBRT delivery use which includes image guidance in the delivery code for the facility (technical, or -TC modifier) component. However, the professional component (-26 modifier) is still allowed for payment.

- **77385**: Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple
- **77386**: Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; complex
- **77373**: Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions

Note: Proton delivery codes do not include image guidance, so IGRT codes for both TC and professional components can be billed separately when indicated. IGRT may be indicated for some conventional 3D CRT cases such as a morbidly obese patient with an abdominal target in which standard approaches for guidance are inadequate. Cases can be considered for approval on an individual basis

The Centers for Medicare & Medicaid Services (CMS) did not implement the above mentioned CPT codes (77385 & 77386) and instead created HCPCS G codes for freestanding outpatient centers. The following delivery codes may also be used for IMRT depending on the setting. They do not include image guidance, so both the technical and professional components are allowed when criteria are met.

- **G6015**: Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session
- **G6016**: Compensator-based beam modulation treatment delivery of inverse planned treatment using three or more high resolution (milled or cast) compensator, convergent beam modulated fields, per treatment session

The following codes are typical for IGRT. Up to one unit per session can be allowed (although balanced by additional radiation for the imaging, so IGRT may not take place with every treatment session).

- **77014**: Computed tomography guidance for placement of radiation therapy fields
- **G6001**: Ultrasonic guidance for placement of radiation therapy fields

- **G6002**: Stereoscopic x-ray guidance for localization of target volume for the delivery of radiation therapy

The following codes do not have a technical (facility) component but can be used for professional services only. Since there is no specific code for MRI guidance, 77387 can be considered for approval for professional services for MRI guidance when appropriate documentation is submitted, but can also be used for other types of guidance.

- **77387**: Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed
- **G6017**: Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3D positional tracking, gating, 3D surface tracking), each fraction of treatment

Note: G6017 does not have a technical (facility) component (usually done by a technician covered by the facility delivery fee), and intra-fraction tracking is unusual to involve physician guidance, so documentation of that service should be provided if billed for professional services.

Coding for SRS typically consists of a series of CPT codes describing the individual steps required (e.g., medical radiation physics, clinical treatment planning, attachment of stereotactic head frame, treatment delivery, and clinical treatment management). The following CPT codes have been used:

Attachment of Head Frame

- **61800**: Application of stereotactic headframe for stereotactic radiosurgery (List separately in addition to code for primary procedure).

Planning and Simulation:

The following codes may be used for this application:

- **77261**: Therapeutic radiology treatment planning; simple
- **77262**: Therapeutic radiology treatment planning; intermediate
- **77263**: Therapeutic radiology treatment planning; complex
- **77280** (may not be billed with 77301): Therapeutic radiology simulation-aided field setting; simple
- **77285** (may not be billed with 77301): Therapeutic radiology simulation-aided field setting; intermediate
- **77290** (may not be billed with 77301): Therapeutic radiology simulation-aided field setting; complex
- **77295**: 3-dimensional radiotherapy plan, including dose-volume histograms
- **77301** : Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications

Clinical Treatment Management

- **77432:** Stereotactic radiation treatment management of cranial lesion(s) (complete course of treatment consisting of 1 session).
- **77435**: Stereotactic body radiation therapy, treatment management, per treatment course, to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions

OR:

- **61796-61799:** for stereotactic radiosurgery of cranial lesions

OR:

- **63620-63621:** for stereotactic radiosurgery of spinal lesions.

These surgical Current Procedural Terminology (CPT) codes (61796-61799 and 63620-63621) are typically used by the neurosurgeon, while the concurrent treatment management performed by the

radiation oncologist would be coded as 77432. The SRS surgical CPT codes are reported per lesion not to exceed 5 lesions in the cranial SRS coding or 3 lesions in the spinal SRS coding per course of treatment. These codes include delivery, and can't be used concurrently with radiation oncology delivery codes (77371-77373).

Treatment Delivery

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

Note: Codes for treatment delivery primarily reflect the costs related to the energy source used-and not physician work.

There are 2 CPT codes specific to SRS delivery:

- **77371:** Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; multi-source Cobalt 60 based
- **77372:** Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; linear accelerator based

There are also 2 codes specific to SBRT:

- **77373:** Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions
- **77435:** Stereotactic body radiation therapy, treatment management, per treatment course, to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions.

If treatment devices such as blocks, wedges, etc. are designed and used for the procedure, CPT codes **77332-77334** will be used.

The following code is specific to medical/surgical physician's component of thoracic SBRT planning:

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

Table B: Allowable Codes and Frequencies for Stereotactic Brain and Body Radiotherapy

Description	Code	Maximum per course of treatment	Notes
For SBRT: IGRT (Image Guided Radiation Therapy)	77014 (CT) 77387 (any) G6001 (stereotactic) G6002 (US) G6017	Professional portion allowed for up to 1 unit for each delivery session when provided	Facility fee (TC) included with delivery codes 77385/ 77386/ 77373 for IMRT/ SBRT. 77387 and G6017 are for pro fee only. Others need -26 modifier for approval
Clinical Treatment Planning	77263	1	
Simulation	77280, 77285, 77290	1	May not be billed with 77301; usually 77290 will be used
Verification Simulation	77280	1	May not be billed with 77301
Respiratory Motion Management	77293	0	1 for breast, lung, and upper abdominal or thoracic cancer areas
3D CRT Plan	77295	1	May not be used with 77301
SRS Treatment Management, cranial	77432	1	May not be used with 77435, may not be billed by neurosurgeon with any of the following: 61781-61783, 61796-61800, 63620-63621.
SBRT Treatment Management, per course of therapy	77435	1	May not be used with 77432. May not be billed by neurosurgeon with any of the following: 61781-61783, 61796-61800, 63620-63621
IMRT Plan	77301	1	May not be used with 77295

Description	Code	Maximum per course of treatment	Notes
Basic Dosimetry	77300	4 up to a max of 10 with documentation	0 if billed with 77306, 77307, 77321, 0394T or 0395T
Treatment Devices, Designs, and Construction	77332, 77333, 77334	1, 5, or 10	-If billed w/ MLC (77338): 1 -If billed w/o MLC: 5 (any combination) -More may be allowed when documentation of medical necessity is provided (such as additional beams), maximum of 10
Multi-leaf Collimater	77338	1	(MLC may not be reported in conjunction with HCPCS G6016)
Special Radiation Physics Consult	77370	0	May allow x 1; documentation of medical necessity required
Special MD Consultation (Special Tx Procedure)	77470	0	May allow x 1; documentation of medical necessity required
Radiation Delivery, Single Dose (SRS)	G0339, 77371 or 77372	1	Gammaknife; either Cobalt-60 or linear accelerator. May allow 1 of either G0339, 77371 or 77372, not all.
Radiation Delivery, up to 5 fractions (SBRT)	77373, G0339, G0340	77373: 5 or G0339: 1/ G0340: 4	Cyberknife, per fraction up to 5, can't be billed with 77371 or 77372. May bill either 77373 or G0339/G0340, not both.
Radiation Delivery by neurosurgeon, computer-assisted	61781, 61782 or 61783	5	Cranial, computer-assisted; not to be billed with other delivery codes: 77371-77373, 61796-61799, 77432, 77435, G0339-G0340
Radiation Delivery by neurosurgeon, cranial	61796, 61797, 61798, 61799, 61781	5	Cranial; not to be billed with: 77371-77373, 77432, 77435, G0339-G0340.
Radiation Delivery by neurosurgeon, spine	63620, 63621	63620 x1 + 63621 x2	Spinal; not to be billed with: 77371-77373, 77432, 77435, G0339-G0340
Application of Stereotactic Headframe for Stereotactic Radiosurgery	61800	1	

See the Codes table for details.

Description

Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) are 3-dimensional conformal radiotherapy methods that deliver highly focused, convergent radiotherapy beams on a target that is defined with 3-dimensional imaging techniques with the ability to spare adjacent radiosensitive structures. SRS primarily refers to such radiotherapy applied to intracranial lesions. SBRT refers to therapy generally applied to other areas of the body. Both techniques differ from conventional external-beam radiotherapy, which involves exposing large areas of tissue to relatively broad fields of radiation over multiple sessions.

Summary of Evidence

Stereotactic Radiosurgery

For individuals with non-neoplastic intracranial conditions (e.g., arteriovenous malformations [AVMs]), the evidence includes noncomparative cohort studies, systematic reviews, and a single randomized controlled trial (RCT). Relevant outcomes are symptoms, treatment-related morbidity, and overall survival (OS). Observational studies have reported relatively high rates (40% to 70%) of complete obliteration of AVM after stereotactic radiosurgery (SRS). An RCT that compared medical

therapy with various interventions in the treatment for AVM showed no significant improvement in outcomes; however, given that the interventional studies included a variety of therapies, it is difficult to assess whether a particular component of the intervention has or lacks benefit. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with non-neoplastic intracranial conditions (e.g., trigeminal neuralgia refractory to medical management), the evidence includes systematic reviews and case series. Relevant outcomes are symptoms, treatment-related morbidity, and OS. A case series identified improvements in pain related to trigeminal neuralgia after treatment with SRS. Comparative studies that evaluated the use of SRS compared with alternative treatments for trigeminal neuralgia were reviewed in a systematic review without meta-analysis and were judged to be of poor quality. Only 1 study specifically addressed the use of radiosurgery, and it was stopped before accrual was completed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with epilepsy refractory to medical management, the evidence on the use of SRS as a treatment for epilepsy includes a case series in primary epileptic disorders and for tumor-related epilepsy. Relevant outcomes are symptoms, treatment-related morbidity, and quality of life (QOL). The available evidence from patients with epileptic lesions of various sizes and locations is insufficient to show what factors are associated with a favorable outcome. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with mesial temporal lobe epilepsy, the evidence includes a systematic review of data from 13 studies, a single RCT comparing SRS to anterior temporal lobectomy (ATL), and case series. Relevant outcomes include symptoms, treatment-related morbidity, and QOL. In the RCT, remission rates were reported for a total of 58 patients (31 in SRS arm and 27 in ATL arm). Seizure remission rates suggest that ATL (78%) has an advantage over SRS (52%) in terms of proportion with seizure remission. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with tremor and movement disorder, the evidence related to the use of SRS includes a systematic review and nonrandomized observational studies, many of which reported outcomes from the treatment of tremors of varying etiologies. Relevant outcomes include symptoms, treatment-related morbidity, and QOL. 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 comparing 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with chronic pain syndromes refractory to standard medical and psychological treatments, the evidence includes a systematic review of noncomparative studies. Relevant outcomes include OS, symptoms, and treatment-related morbidity. Although clinical success was reported in varying percentages of patients dependent upon the radiation target and pain etiology, the data are primarily from a period of time before the common use of other treatments for patients with chronic pain syndromes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals in the subgroup of uncommon benign neoplastic intracranial lesions (acoustic neuroma [i.e., vestibular schwannoma] and pituitary adenoma) the published evidence for the use of SRS remains limited to systematic reviews of nonrandomized observational studies, other nonrandomized observational studies, and case series. Relevant outcomes include OS, symptoms, and treatment-related morbidity. These reports would suggest that long-term outcomes of fractionated radiosurgery for these benign neoplasms are associated with good local control and acceptable treatment-related side effects. One systematic review found that SRS and microsurgery

are comparable treatments for primary management of small to medium (<3 cm) vestibular schwannomas with regard to hearing preservation at 65 months; microsurgery was favored over SRS for tumor control at 70 months (98% vs 92%), while SRS was favored over microsurgery for reducing the proportion of patients with facial nerve dysfunction at 12 months (2% vs 10%). The likelihood of high-quality systematically acquired evidence is low due to the rarity of the conditions. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals in the subgroup of uncommon benign neoplastic intracranial lesions (craniopharyngioma and glomus jugulare tumors) the published evidence for the use of SRS remains limited to systematic reviews of nonrandomized observational studies, other nonrandomized observational studies, and case series. Relevant outcomes include OS, symptoms, and treatment-related morbidity. These reports would suggest that long-term outcomes of fractionated radiosurgery for these benign neoplasms are associated with good local control and, acceptable treatment-related side effects. The likelihood of high-quality systematically acquired evidence is low due to the rarity of the conditions. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with malignant neoplastic intracranial conditions (e.g., gliomas, astrocytomas), the evidence on the use of SRS as a treatment for epilepsy includes a single systematic review and meta-analysis of case series with ≥5 patients and heterogeneous observational studies. Relevant outcomes are symptoms, treatment-related morbidity, and OS. Observational studies have demonstrated local control using SRS in combination with chemotherapy to treat gliomas in the primary and recurrent setting. These tumors are very aggressive and there are limited treatment options. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with malignant neoplastic intracranial conditions (e.g., brain metastases), the evidence includes systematic reviews, RCTs, and nonrandomized observational studies. Relevant outcomes are symptoms, treatment-related morbidity, and OS. The existing evidence body indicates that SRS improves outcomes in the treatment of brain metastases. Stereotactic radiosurgery appears to be feasible for 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 metastases. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with uveal melanoma, evidence for use of SRS is limited to a meta-analysis of case series and individual case series. Relevant outcomes include OS, symptoms, and treatment-related morbidity. The published literature is insufficient to demonstrate improved outcomes with SRS over other accepted radiation modalities in the treatment of uveal melanoma. The condition is rare with poor clinical outcomes and treatment options. There are currently no active clinical trials to evaluate SRS to treat uveal melanoma and, therefore, there are limited prospects for accumulating additional high-quality data. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Stereotactic Body Radiotherapy

For individuals with primary and metastatic spinal or vertebral body tumors who have received prior radiotherapy who are treated with stereotactic body radiotherapy (SBRT), the evidence includes a systematic review of RCTs that compared SBRT to external beam radiotherapy (EBRT) in patients with painful spinal metastasis and observational literature that primarily addresses metastases that recur after prior radiotherapy. Relevant outcomes are OS, progression-free survival (PFS), disease-free survival (DFS), symptoms, and treatment-related morbidity. In the comparative systematic review , SBRT was superior to EBRT for the achievement of a complete response from pain 3 months after radiotherapy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with stage T1 or T2A non-small cell lung cancer (NSCLC) there is no direct comparative evidence for the use of SBRT compared to surgical resection in patients with stage T1 and T2A cancer without nodal or distant disease. Relevant outcomes are OS, PFS, DFS, symptoms, and treatment-related morbidity. Although no direct comparative evidence is available, evidence suggests that survival rates may be similar for SBRT and surgical resection for patients with stage T1 and T2A NSCLC tumor (not >5 cm in diameter) who show no nodal or distant disease and who are not candidates for surgical resection because of comorbid conditions. Additionally, SBRT was associated with improved survival and a reduced risk of adverse events as compared to conventional radiotherapy and radiofrequency ablation (RFA) in inoperable NSCLC. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with primary HCC, s1 RCT reported on the use of SBRT for hepatocellular carcinoma (HCC) treatment, but findings are limited due to termination after slow accrual. Relevant outcomes are OS, PFS, DFS, symptoms, and treatment-related morbidity. Studies have used heterogeneous treatment schedules, treatment planning techniques, patient populations, and outcome measures. The optimal dose and fractionation scheme are unknown. Although promising local control rates of 71% to 100% at 1 year have been reported, there are only retrospective studies reporting on the use of SBRT in conjunction with or as an alternative to established treatment modalities, including systemic therapy, RFA, and transarterial chemoembolization. Similar short-term lesion-control rates have been reported for metastatic liver disease. Palliative treatment, including for larger lesions (>3 cm), has also been reported. The use of SBRT, either alone or in conjunction with other liver-directed therapies, is emerging as a bridge to transplant. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with primary prostate carcinoma, the evidence on the use of SBRT consists of systematic reviews, cohort studies, and RCTs s. Relevant outcomes are OS, PFS, DFS, symptoms, and treatment-related morbidity. Studies have shown promising initial results on the use of SBRT in prostate cancer with seemingly low toxicity rates; the PACE-B study demonstrated that SBRT does not increase the incidence of gastrointestinal or genitourinary acute toxicity compared to conventional treatment. One comparative study of intensity-modulated radiotherapy and SBRT suggested higher gastrointestinal (GI) and genitourinary (GU) complication rates after SBRT; while this study had a large number of patients and attempted to control for bias using matching on observed variables, it was subject to limitations deriving outcome measures from claims data. In the randomized ORIOLE study, SBRT was associated with a significant improvement in disease progression and median PFS as compared to observation in men with recurrent hormone-sensitive prostate cancer and 1 to 3 metastases with a similar toxicity profile. The HYPO-RT-PC trial found that ultra-hypofractionation was found to be non-inferior to conventional fractionation. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with pancreatic adenocarcinoma, the evidence for the use of SBRT consists of systematic reviews, retrospective comparative studies, and noncomparative studies. Relevant outcomes are OS, PFS, DFS, symptoms, and treatment-related morbidity. Combined chemo-radiotherapy plays a significant role in the treatment of locally advanced pancreatic cancer whereas re-resection demonstrates improved median OS outcomes for isolated local recurrence. Non-comparative observational studies of SBRT have reported increased patient survival compared with historical data. Acute, grade 3 toxicities have been reported. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with renal cell carcinoma (RCC), the evidence for the use of SBRT consists of small case series, systematic reviews, and other observational studies. Relevant outcomes are OS, PFS, DFS, symptoms, and treatment-related morbidity. Generally, high rates of local control have been reported for primary RCC. Adverse effects include nephron loss and kidney shrinkage, however, avoidance of nephrectomy in patients with hypertension or solitary kidney may be desirable. RCC is considered to be relatively radioresistant. Case series have reported good local control in patients

with spinal metastases. There are no RCTs that have evaluated SBRT for primary RCC or metastatic lesions to the brain or spine that permit comparisons between SBRT and currently established treatment modalities for RCC. Two observational studies demonstrated that SBRT extends the duration of ongoing systemic therapy by approximately 1 year in patients with metastatic RCC with fewer than 3 to 5 sites of progression. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with oligometastatic disease, the evidence for the use of SBRT for the management of oligometastases at multiple sites, including the lungs, adrenal glands, and bones (other than spine or vertebral body) primarily consists of relatively small, noncomparative studies that confirm clinically important rates of local control and 2 RCTs. Relevant outcomes are OS, PFS, DFS, symptoms, and treatment-related morbidity. In the randomized SABR-COMET trial that compared SBRT versus standard of care palliative treatment in patients with oligometastatic cancers, results revealed a significantly improved median OS in the SBRT group with grade 2 or worse adverse events occurring more frequently, including 3 treatment-related deaths versus 0 in the control group. In subsequent publications of long-term results of the SABR-COMET trial, the 5-year OS and 8-year OS rates were significantly improved with SBRT with no new grade 3 to 5 adverse events reported. The randomized CURB study compared SBRT to standard of care in patients with oligoprogressive metastatic breast cancer or NSCLC. The trial was prematurely terminated due to beneficial PFS findings with SBRT at interim analysis; however, the finding in the subgroup of patients with breast cancer were not significant. Systemic therapy is most frequently the preferred therapy for patients with metastatic disease of these selected tumor types. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with small cell lung cancer, the evidence for the use of SBRT consists of 1 systematic review and meta-analysis of retrospective cohort studies and 1 nonrandomized study. The meta-analysis (N=399; 7 studies) showed that SABR achieved high local control rates of 97.3% (95% CI: 92.3% to 99.8%) at 1 year, 95.7% (95% CI: 74.2% to 100.0%) at 2 years, and 93.6% (95% CI: 77.5% to 100.0%) at 3 years. Overall survival rates were 86.3% (95% CI: 74.4% to 94.9%) at 1 year, 63.7% (95% CI: 45.7% to 79.9%) at 2 years, and 55.2% (95% CI: 43.5% to 66.6%) at 3 years. Recurrence rates were 17.8% (95% CI: 7.5% to 31.2%) for nodal and 26.9% (95% CI: 7.4% to 53.0%) for distant recurrences. The meta-analysis was limited due to heterogeneity in patient selection, diagnostic protocols, and treatment regimens across studies, as well as the retrospective design of the studies. In the nonrandomized study (N=29) the median overall survival (OS) was 27 months (95% CI 20.2–33.8) and the median progression-free survival (PFS) was 12 months (95% CI 4.2–19.8). Larger randomized controlled trials are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

2018 Input

Clinical input was sought to help determine whether the use of SRS and SBRT for individuals with various neoplasms/conditions would provide a clinically meaningful improvement in the net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 5 respondents, including 2 specialty society-level responses, 1 of which included multiple specialty societies, and 3 physician-level responses either identified by specialty societies or an academic medical center, while this policy was under review.

Stereotactic Radiosurgery

For individuals who have mesial temporal lobe epilepsy who receive SRS, clinical input supports that this use provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected patients. Clinical input reported that the less invasive nature of SRS coupled with acceptable seizure remission rates over time may be appropriate for the specific subpopulation of patients with mesial

temporal lobe epilepsy refractory to medical management when standard alternative surgery is not an option.

For individuals who have tremor and movement disorders who receive SRS, clinical input does not support a clinically meaningful improvement in the net health outcome and does not indicate this use is consistent with generally accepted medical practice. Clinical input noted systematic reviews of retrospective studies reported a reduction in tremors after SRS, but confirmed that alternative approaches to thalamotomy are appropriate.

For individuals who have chronic pain syndromes refractory to standard medical and psychological treatments (other than associated with trigeminal neuralgia) who receive intracranial SRS, clinical input does not support a clinically meaningful improvement in the net health outcome and does not indicate this use is consistent with generally accepted medical practice.

For individuals who have uncommon benign neoplastic intracranial lesions (acoustic neuroma, pituitary adenoma, craniopharyngioma, and glomus jugulare tumors) who receive SRS, clinical input supports that this use provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice. Clinical input continues to support an individualized approach to the use of SRS for these tumors with the recognition that outcomes are affected by factors such as the location of the tumor and type of SRS used (hypofractionated, fractionated, or single-session treatment).

For individuals who have uveal melanoma, clinical input supports that this use provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice. Clinical input reported that the use of SRS to treat uveal melanoma could provide patients with low-risk disease (based on tumor size using the Collaborative Ocular Melanoma Study definition of small and medium) an option to avoid or postpone enucleation with preservation of some visual acuity and functional abilities.

Stereotactic Body Radiotherapy

For individuals who have primary and metastatic spinal or vertebral body tumors who have received prior radiotherapy who are treated with SBRT, clinical input supports that this use provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice. Clinical input reported that SBRT is an important treatment option for patients whose spinal tumors had prior radiotherapy because of the ability to spare the spinal cord and escalate tumor dose.

For individuals who have NSCLC, clinical input supports that this use provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected patients. The following patient selection criteria are based on clinical expert opinion from clinical study populations: patients with NSCLC who are poor surgical candidates or who do not wish to undergo surgery.

For individuals who have primary HCC, clinical input supports that this use provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected patients. Clinical input confirmed the lack of RCTs and reported on nonrandomized observational studies that support the use of SBRT as an alternative locoregional treatment for patients with inoperable primary HCC or metastatic lesions and referred to national guidelines that have rendered the same recommendation. The following patient selection criteria are based on clinical expert opinion from clinical study populations: patients with primary or metastatic tumor of the liver that is considered inoperable.

For individuals who have primary prostate carcinoma, limited clinical input reported that the use of SBRT to treat primary prostate cancer provides biochemical control of disease (based on prostate-

specific antigen surveillance), preserved quality of life (primarily focused on erectile dysfunction) and acceptable short-term urinary tract toxicity posttreatment. This input did not differentiate candidate patients using guideline-based risk stratification for localized prostate cancer.

For individuals who have pancreatic adenocarcinoma, limited clinical input reported that the use of SBRT for inoperable pancreatic adenocarcinoma also referred to guideline-based recommendations for use in localized disease.

For individuals who have RCC, clinical input supports that this use provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected patients. The following patient selection criteria are based on clinical expert opinion from clinical study populations: patients with primary RCC who are not good surgical candidates or for relapsed or stage IV disease.

For individuals who have oligometastatic disease, clinical input supports that this use provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected patients. The following patient selection criteria are based on clinical expert opinion from clinical study populations: patients with oligometastatic disease that includes 1 or both adrenal glands in patients who are poor surgical or radiofrequency ablation candidates.

Further details from clinical input are included in the Appendix.

Related Policies

- Intensity-Modulated Radiotherapy of the Breast and Lung
- Intensity-Modulated Radiotherapy of the Prostate
- Intensity-Modulated Radiotherapy: Abdomen, Pelvis and Chest
- Intensity-Modulated Radiotherapy: Central Nervous System Tumors
- Intracavitary Balloon Catheter Brain Brachytherapy for Malignant Gliomas or Metastasis to the Brain
- Radiation Oncology

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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

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

Rationale

Background

In the United States, certain racial/ethnic groups continue to be at an increased risk of developing or dying from particular cancers. Black men have the highest rate of new cancer diagnoses and Black men and women experience the highest rate of cancer-related death. American Indians and Alaska Natives are disproportionally affected by kidney cancer and also have higher death rates from this cancer when compared to other racial/ethnic groups.

Studies have demonstrated that there are socioeconomic disparities with regard to access to radiation therapy, particularly for patients in ethnic minority groups and those living in rural areas.

Conformal Radiotherapy

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

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

SRS and SBRT have been used for a range of malignant and nonmalignant conditions. A comprehensive assessment that encompasses all potential uses is beyond the scope of this evidence review.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function - including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be

used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

The delivery of stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) is complex and individualized, requiring selection of the device, radiation dose, and the size and shape of treatment margins, all of which depend on the location, shape, and radiosensitivity of the target tissue and the function and radiosensitivity of the surrounding tissue. Several ongoing questions exist in the evaluation of SRS and SBRT, related to the most appropriate choices of:

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

Trials that would allow direct comparison of all possible variables involved in selecting specific SRS and SBRT methods do not currently exist. Therefore, the available evidence is inadequate to permit conclusions about specific radiation planning and delivery techniques, including the specific number of fractions and methods of dose escalation or toxicity reduction. Therefore, the following review groups several different techniques for delivering SRS and SBRT and does not compare specific radiation planning and delivery techniques.

Stereotactic Radiosurgery for Non-Neoplastic Conditions: Arteriovenous Malformations

Clinical Context and Therapy Purpose

The purpose of SRS is to use a focused radiotherapy technique to treat intracranial and other brain lesions that are relatively inaccessible surgically and that are often located near eloquent or radiosensitive areas.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with arteriovenous malformations (AVMs) who have not yet experienced a significant hemorrhagic complication. An AVM comprises a tangled network of vessels in which blood passes from arteries to veins without intervening capillaries. AVMs range in size from small, barely detectable lesions to large lesions that can occupy an entire hemisphere.

Interventions

The therapy being considered is SRS prior to significant hemorrhage. SRS incites an inflammatory response in the vessels, which results in ongoing fibrosis with eventual complete obliteration of the lesion over the course of months to years. In contrast, surgical excision provides an immediate effect on the risk of hemorrhage.

Comparators

The following therapies are currently being used to treat AVMs: conservative therapies (e.g., surveillance, medical therapy) and surgical intervention. Total surgical extirpation of the lesion, if possible, is the desired form of therapy to avoid future hemorrhage. However, a small subset of AVMs, because of their size or location, cannot be excised without serious neurologic sequelae.

Outcomes

The outcomes of interest are overall survival (OS), symptom improvement, and treatment-related morbidity. SRS is typically used during the latency period when a patient has not experienced a significant hemorrhage. This latency period is variable and typically is years in duration, depending on the size of the AVM and the dose distribution of the radiosurgery. During this latency period, an ongoing but declining risk of hemorrhage is present.

Study Selection Criteria

Methodologically credible studies were selected for all SRS indications within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

The International Stereotactic Radiosurgery Society (2024) conducted a systematic review and meta-analysis to establish evidence-based guidelines for single-fraction stereotactic radiosurgery (SRS) in treating intracranial cavernous malformations.[1,] The meta-analysis included 32 studies (N=2672) and showed a decrease in annual hemorrhage rates post-treatment (RR: 0.17), in the first 2 year (RR: 0.29), and after 2 years (RR: 0.11). Hemorrhage rates differed before and after 2 years post-SRS (RR: 0.36). Among epileptic patients, 20.2% had epilepsy pretreatment, and 49.9% were seizure-free post-SRS, while 30.6% experienced reduced seizure frequency. Lesion volume changes showed a reduction in 46.9%, stability in 47.1%, and an increase in 6.7%. Symptomatic radiation effects occurred in 8% of patients, with symptomatic change rates of 6% at doses ≤13 Gy compared to 9% at doses >13 Gy. Permanent clinical deficits were rare (2%). The authors conclude SRS can be an effective intervention for intracranial cavernous malformations, reducing hemorrhage rates and improving seizure outcomes.

Ilyas et al (2022) published a meta-analysis to identify and evaluate studies of patients with AVM who met the eligibility criteria for A Randomised trial of Unruptured Brain AVMs study (ARUBA; Mohr et al [2014]) and underwent SRS, to indirectly compare results with those reported in the ARUBA study.[2,] Eight studies (N=1620) were included, and the mean follow-up duration for the studies was 80 months. Rates of radiologic, symptomatic, and permanent radiation-induced changes were 45%, 11%, and 2%, respectively; at last follow-up, the rates of obliteration, post-SRS hemorrhage, and mortality were 68%, 8%, and 2%, respectively. The ARUBA composite outcome (symptomatic stroke or death) occurred in 10% of patients. The authors concluded that SRS carries a favorable risk to benefit ratio for ARUBA-eligible patients and that the results of ARUBA do not necessarily reflect the real-world safety and efficacy of SRS for unruptured AVMs.

China et al (2022) published a systematic review examining the efficacy and safety of Gamma knife radiosurgery for cerebral AVMs.[3,] A total of 34 cohort studies (N=8673) with a median follow up of 60 months were identified. The studies included were at moderate risk of bias because none of them were randomized and none concealed treatment allocation. The pooled obliteration rate following single-session SRS for cerebral AVMs was 56.7% in 21 cohorts that confirmed obliteration by angiography alone and 67.8% in 29 cohorts that confirmed obliteration by either angiography or magnetic resonance imaging (MRI). For cohorts with a follow up of at least 2 years, the median obliteration rate was 63.5% and 70.85%, respectively, for obliteration confirmed by angiography or a selection of either angiography or MRI. The authors noted there is a risk of over-estimation of the true obliteration rate when MRI is used to confirm obliteration compared to angiography.

Magro et al (2017) published a systematic review of French- and English-language citations specifically reviewing the results of the ARUBA study, which is summarized in more detail in the section below.[4,] The most salient and recurring critique was that the planned 5-year follow-up preferentially exposed problems with short- and long-term procedure results, and therefore did not detect the longer-term benefits of prophylactic interventions.

Mau et al (2016) published a systematic review examining the rate of hemorrhage following SRS in patients with high-grade AVMs, defined as a Pollock-Flickinger score greater than 2.[5,] Nine studies evaluating 673 patients were published in the English language, reported adequate data to calculate AVM score, and presented outcome data on hemorrhage following radiosurgery. The average length of follow-up in these studies was 4.6 years. There was a cumulative hemorrhage risk of 15.2% among all patients, and the mortality rate for patients with hemorrhage was 40.1%. The annual risk of hemorrhage varied among studies, ranging from 0.75% to 14.9%. The cumulative annual risk of hemorrhage was 3.3% (95% confidence interval [CI], 2.7% to 4.0%). This hemorrhage rate did not differ from the hemorrhage rates reported for untreated high-grade AVMs, which ranged from 5.9% to 18.0%.

Randomized Controlled Trials

Mohr et al (2014) reported primary results of the ARUBA trial, a randomized, multicenter study comparing medical therapy with medical therapy plus interventional therapy (including any neurosurgical, endovascular, or SRS procedure) in patients with unruptured AVMs.[6,] Two hundred twenty-six patients were enrolled and randomized, 116 to interventional therapy and 110 to medical management. Among those randomized to interventional therapy, 91 received interventional therapy; 5 with neurosurgery alone, 30 with embolization alone, 31 with radiotherapy alone, 12 with embolization and neurosurgery, 15 with embolization and radiotherapy, and 1 with all 3 interventions. The trial was stopped early after an interim analysis demonstrated the superiority of medical management after outcomes were available for 223 patients with a mean follow-up time of 33.3 months. The risk of death or stroke was lower in the medical management group than in the interventional therapy group (hazard ratio [HR], 0.27; 95% CI, 0.14 to 0.54). Had the trial continued, the patients would have been followed to determine whether differences in outcomes persisted. Although a high proportion of patients randomized to interventional therapy (40.5%) received at least some radiotherapy, outcomes were not reported by therapy type, making it difficult to assess the comparative effectiveness of SRS in AVM treatment.

The results of the ARUBA trial have been the subject of controversy; specifically, whether the results are generalizable to all individuals with an unruptured AVM. There have been no publications on outcomes since the trial was stopped and a registry for comparator arm medical therapy alone participants was not developed.

Single-Arm Studies

There are many single-arm studies on SRS for AVMs.[7,8,9,10,11,12,13,14,15,16,17,18,18,] These studies have reported outcomes in different patient populations with AVMs and different protocols for SRS. Without a control group, these studies offer limited evidence on treatment outcomes related to SRS. Representative studies are discussed below.

Two larger single-arm studies were multicenter studies from 8 institutions participating in the International Gamma Knife Research Foundation.[14,18,] Starke et al (2016) reported on 2236 patients with any AVM treated by Gamma Knife surgery, with a mean follow-up of 7 years.[18,] Complete obliteration of the AVM was achieved in 64.7% of patients and favorable outcome, defined as complete obliteration with no hemorrhage or significant radiation adverse events, was achieved in 60.3% of patients. Hemorrhage occurred in 7.4% (165/2236) of patients, with an annual rate of hemorrhage of 1.1%. Permanent neurologic deficits due to radiation injury occurred in 2.7% of patients.

Ding et al (2016) published a multicenter study of 891 patients with small, unruptured AVMs who were treated with Gamma Knife surgery and had at least 12 months of follow-up.[14,] The estimated complete obliteration rate was 63% at 5 years and 78% at 10 years. The optimal outcome, defined as a complete obliteration of AVM without hemorrhage or significant radiation-induced adverse events, was achieved in 56% of patients. The annual rate of hemorrhage was 1.2%, and the rate of permanent neurologic deficits was 4%.

Paul et al (2014) conducted a retrospective cohort study that included 697 SRS treatments in 662 patients treated with SRS for brain AVMs at a single-institution.[11,] The obliteration rate after single or multiple SRS procedures was 69.3% and 75%, respectively. The obliteration rates were significantly associated with AVMs that were compact (odds ratio [OR], 3.16; 95% CI, 1.92 to 5.22), with undilated feeders (OR, 0.36; 95% CI, 0.23 to 0.57), with smaller volume (OR, 0.95; 95% CI, 0.92 to 0.99), and treated with higher marginal dose (OR, 1.16; 95% CI, 1.06 to 1.27).

Bowden et al (2014) reported outcomes from a retrospective cohort of patients with cerebellar AVM treated with SRS at a single-institution.[7,] Sixty-four patients were included, 73% of whom had presented with intracranial hemorrhage, and 19% of whom had undergone prior embolization. Total obliteration was achieved at 3, 4, and 5 to 10 years in 52%, 69%, and 75%, respectively, of subjects. Obliteration was more likely in smaller AVMs but less likely in patients who had undergone prior embolization. Symptomatic adverse radiation events, defined by MRI changes and new neurologic deficits in the absence of hemorrhage, occurred in 3 patients.

Matsuo et al (2014) reported on outcomes from a cohort of 51 patients with intracranial AVMs treated with SRS at a single-institution.[10,] Rates of obliteration after a single SRS at 3, 5, 10, and 15 years were 46.9%, 54%, 64%, and 68%, respectively; rates of obliteration after multiple SRS sessions at 3, 5, 10, and 15 years were 46.9%, 61.3%, 74.2%, and 90.3%, respectively. Adverse radiation events occurred in 9 (17.6%) cases, with 4 cases (3 symptomatic cysts, 1 intracranial hemorrhage) not occurring until 10 years after the SRS treatment.

Fokas et al (2013) reported long-term follow-up on a cohort of patients who underwent SRS for cerebral AVMs at a single-institution.[8,] One hundred sixty-four patients were identified, with a median follow-up of 93 months (range, 12 to 140 months). Thirty-nine percent of subjects had experienced a prior intracranial hemorrhage, and 43.3% and 8.0%, respectively, had undergone prior embolization or neurosurgical procedures. Complete obliteration was seen in 61% of patients at a median time of 29 months. Complete obliteration was achieved at 3 and 5 years in 61% and 88%, respectively. In multivariable models, higher radiation dosage and smaller target volumes were associated with higher rates of complete obliteration. The annual bleeding risk was 1.3% per year during follow-up.

Kano et al (2012) studied long-term outcomes and risks of AVM management using 2 or more stages of SRS for symptomatic large-volume lesions unsuitable for surgery.[9,] Forty-seven patients with such AVMs underwent volume-staged SRS. Eighteen (38%) patients had a prior hemorrhage and 21 (45%) patients had undergone prior embolization. In 17 patients, AVM obliteration was confirmed after 2 to 4 SRS procedures at a median follow-up of 87 months (range, 0.4 to 209 months). Five patients had near-total obliteration (volume reduction >75% but residual AVM). The actutimes rates of total obliteration after 2-stage SRS were 7%, 20%, 28%, and 36% at 3, 4, 5, and 10 years, respectively. The 5-year total obliteration rate after the initial staged volumetric SRS was 62% (p=.001). Sixteen patients underwent additional SRS at a median interval of 61 months (range, 33 to 113 months) after the initial 2-stage SRS. The overall rates of total obliteration after staged and repeat SRS were 18%, 45%, and 56% at 5, 7, and 10 years, respectively. Ten patients sustained hemorrhage after staged SRS, and 5 of these patients died. Three of 16 patients who underwent repeat SRS sustained hemorrhage after the procedure and died. Based on Kaplan-Meier analysis (excluding the second hemorrhage in the patient who had 2 hemorrhages), the cumulative rates of AVM hemorrhage after

SRS were 4.3%, 8.6%, 13.5%, and 36.0% at 1, 2, 5, and 10 years, respectively, corresponding to annual hemorrhage risks of 4.3%, 2.3%, and 5.6% for years 0 to 1, 1 to 5, and 5 to 10 after SRS. Multiple hemorrhages before SRS correlated with a significantly higher risk of hemorrhage after SRS. Symptomatic adverse radiation effects were detected in 13% of patients. The authors concluded that volume-staged SRS for large AVMs unsuitable for surgery has potential benefit, but often requires more than 2 procedures to complete the obliteration process and that, in the future, prospective volume-staged SRS followed by embolization (to reduce flow, obliterate fistulas, and occlude associated aneurysms) may improve obliteration results and further reduce the risk of hemorrhage after SRS.

In children, surgical resection of an AVM remains the reference standard of care. However, because the diagnosis is often made after the rupture has occurred, evidence for the utility of SRS is limited. SRS to further obliterate the AVM is often preceded by embolization to control intracranial hemorrhage.[19,] Potts et al (2014) summarized outcomes for 80 children treated with SRS for intracranial AVMs, most of whom (56%) had an intracranial hemorrhage at the time of presentation.[12,] Among the 47% of subjects with available angiograms 3 years after treatment, AVM obliteration occurred in 52% of patients treated with higher dose SRS (18 to 20 gray [Gy]) and in 16% treated with lower dose SRS (<18 Gy).

Rupture of an AVM is a leading, nonobstetric cause of intracranial hemorrhage in pregnancy and the postpartum period. Therefore, interventions are typically emergent. Tonetti et al (2014) reported a single-institution retrospective analysis of authors' experience with Gamma Knife SRS from 1987 to 2012.[20,] During this time, 253 women of childbearing age (median age, 30 years; range, 15 to 40 years) underwent SRS for intracranial AVM. The median target volume was 3.9 cm^3 (range, 0.1 to 27.1 cm^3), and the median marginal dose was 20 Gy (range, 14 to 38 Gy). For all patients, the date of AVM obliteration was recorded, and the latency interval was calculated. Information about subsequent pregnancies and/or bleeding events during the latency interval was retrieved from the medical records and supplemented by telephone contact. AVM obliteration was confirmed by MRI or angiography at a median follow-up time of 39.3 months (range, 10 to 174 months). There were 828.7 patient-years of follow-up within the latency interval between SRS and the date of confirmed AVM obliteration. Among nonpregnant women, 20 hemorrhages occurred before AVM obliteration, yielding an annual hemorrhage rate of 2.5% for pregnant women during the latency interval. Among women who became pregnant during the latency interval, 2 hemorrhages occurred over the course of 18 pregnancies, yielding an annual hemorrhage rate of 11.1% for women who become pregnant during the latency interval. For the 2 pregnant patients who experienced hemorrhage, the bleeding occurred during the first trimester of pregnancy.

Section Summary: Arteriovenous Malformation

The evidence on the use of SRS for unruptured AVM consists primarily of noncomparative cohort studies and systematic reviews, which reported relatively high rates of complete obliteration of AVM after SRS, in the range of 40% to 70%. Isolating the effect of SRS therapy in and of itself can be challenging, because many patients are treated with more than 1 therapy, including endovascular treatments and surgery. In 2014, an RCT that compared medical therapy with various interventions in the treatment for AVM showed no significant improvement in outcomes with interventional therapy. However, given that the interventional studies included a variety of therapies, it is difficult to assess whether a particular component of the intervention has or lacks benefit. Several important aspects of management of AVM with or without SRS remain the subject of inquiry. Patient selection factors such as agreement on the exact definition of "unruptured" (no prior evidence of intracranial hemorrhage or mild intracranial hemorrhage associated with, e.g., seizure leading to investigation and diagnosis), size, and location of lesions (eloquent areas) remain the subject of debate and impact potential candidacy for medical management versus intervention. The differentiation of focal neurologic deficits presumably due to limited intracranial hemorrhage from postintervention effects is under study. The evidence for the management of special populations (pediatrics and pregnant women) is limited to case reports.

Stereotactic Radiosurgery for Non-Neoplastic Conditions: Trigeminal Neuralgia

Clinical Context and Therapy Purpose

The purpose of SRS is to use a focused radiotherapy technique to treat trigeminal neuralgia and to potentially avoid complications associated with surgical intervention when conservative therapy and medical treatment have failed.

The following PICO was used to select literature to inform this review.

Populations

The population of interest is individuals with trigeminal neuralgia who have failed conservative therapy and medical treatment. Trigeminal neuralgia is a disorder of the fifth cranial (i.e., trigeminal) nerve that causes episodes of intense, stabbing pain in the face. The International Classification of Headache Disorders has defined classical trigeminal neuralgia as both idiopathic and related to vascular compression. Painful trigeminal neuropathy is also caused by other conditions, including postherpetic neuralgia and posttraumatic neuralgia, secondary to multiple sclerosis plaque or a space-occupying lesion.[21,]

Interventions

The therapy being considered is SRS as an alternative to surgical intervention. Although trigeminal neuralgia is initially treated medically, in a substantial number of cases, pharmacologic treatment is either ineffective or the adverse events become intolerable. SRS of the proximal trigeminal nerve root has been investigated as an alternative to neurosurgical treatments.

Comparators

The following therapies are currently being used to treat trigeminal neuralgia: conservative therapies (e.g., continued medical therapy) and surgical intervention. Neurosurgical options include microvascular decompression, which involves craniotomy, peripheral neurectomy, or rhizotomy. Rhizotomy is a technique to percutaneously isolate and ablate the nerve, with techniques such as balloon compression, radiofrequency ablation (RFA) or chemical injection.

Outcomes

The outcomes of interest are OS, symptom improvement, and treatment-related morbidity. SRS is typically used after conservative therapy and medical treatment has failed. There is a latency period of approximately 1 month for the effect to be observed.

Study Selection Criteria

Methodologically credible studies were selected for all SRS indications within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

A Cochrane review by Zakrzewska et al (2011) assessing 11 trials of neurosurgical interventions for trigeminal neuralgia found that there is very low-quality evidence for the efficacy of most neurosurgical procedures for trigeminal neuralgia because of the poor quality of trials.[22,] All procedures produced variable pain relief, but many resulted in sensory side effects. There were no studies of microvascular decompression, which observational data would suggest gives the longest

pain relief. Only 1 study was identified that used radiosurgery. The trial was intended to determine if increasing the nerve length within the SRS treatment volume would change outcomes. The study was stopped before accrual was completed, and it was noted that pain measurements using validated scales were not made before or after surgery.

Yen et al (2011) reviewed the literature on the use of SRS for trigeminal neuralgia.[23,] Reviewers concluded that patients with typical facial pain would achieve relief following radiosurgery.

Case Series

Dhople et al (2009) reported on the long-term outcomes of SRS for classical trigeminal neuralgia in 112 patients treated between 1996 and 2001.[24,] Of these, 67% had no prior invasive operations for trigeminal neuralgia prior to SRS, 13% had 1, 4% had 2, and 16% had 3 or more. The right side was affected in 56% of cases, predominantly involving V2 (26%), V3 (24%), or a combination of both (18%) branches. The median age at diagnosis was 56 years, and the median age at SRS was 64 years. The median prescription dose of 75 Gy (range, 70 to 80 Gy) was delivered to the involved trigeminal nerve root entry zone. Reviewers assessed the degree of pain before and after SRS using the Barrow Neurological Institute (BNI) pain scale. In total, 102 patients took the survey at least once (response rate, 91%). Although not found to alter the conclusions of this study, 7 cases of atypical trigeminal neuralgia were found, and these patients were removed, for a total of 95 cases analyzed. The median follow-up was 5.6 years (range, 13 to 115 months). Before Gamma Knife surgery, 88% of patients categorized their pain as BNI IV (inadequate control on medication) or V (severe pain on medication), whereas the remainder described their pain as BNI III (some pain but controlled on medication). After Gamma Knife surgery, 64% reported a BNI score of I (no pain, no medications), 5% had BNI II (no pain, still on medication), 12% had BNI III, and 19% reported a BNI score of IV or V. Median time to response was 2 weeks (range, 0 to 12 weeks), and median response duration was 32 months (range, 0 to 112 months). Eighty-one percent reported initial pain relief, and actutimes 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 months versus 21 months, p<.02). New facial numbness was reported in 6% of cases.

Section Summary: Trigeminal Neuralgia

A case series (N =112) identified improvements in pain related to trigeminal neuralgia after treatment with SRS. Comparative studies that evaluated the use of SRS compared with alternative treatments for trigeminal neuralgia were reviewed in a systematic review without meta-analysis and were judged to be of poor quality. Only 1 study specifically addressed the use of radiosurgery, and it was stopped before accrual was completed.

Stereotactic Radiosurgery for Non-Neoplastic Neurologic Disorders: Epilepsy

Clinical Context and Therapy Purpose

The purpose of SRS is to use a focused radiotherapy technique to ablate epileptogenic foci when seizures have become drug-resistant or medication-related adverse events are intolerable and to potentially avoid complications associated with surgical intervention.

The following PICO was used to select literature to inform this review.

Populations

The population of interest is individuals with drug-resistant or medication-intolerant epilepsy. Epilepsy is diagnosed when an individual has unprovoked seizures. Primary seizure disorders include multiple subtypes that are recognizable by the degree and type of impairment of consciousness and motor capacity. Seizure disorders may be secondary to brain tumors or other space- occupying intracranial lesions. Mesial temporal lobe epilepsy also known as complex partial seizures is a focal epilepsy syndrome. The epileptogenic foci are in the hippocampus, amygdala, and the parahippocampal gyrus. The most common non-traumatic or non-infectious etiology of mesial

temporal lobe epilepsy is hippocampal sclerosis. The associated neuronal loss is a partial explanation for the difficulties in achieving satisfactory seizure control with antiepileptic medication

Interventions
The therapy being considered is SRS as an alternative to surgical intervention. SRS is typically delivered in a single outpatient session. Dose to target protocols vary and the effect on seizure remission is gradual.

Comparators
The following therapies are currently being used to treat epilepsy: conservative therapies (e.g., continued medical therapy) and surgical intervention. Seizure disorders are initially treated medically and may require more than 1 pharmacologic agent. Surgical treatment is only considered in those instances when the seizures have proven refractory to all attempts at aggressive medical management, when the frequency and severity of the seizures significantly diminish the QOL, and when the seizure focus can be localized to a focal lesion in a region of the brain accessible to resection. When surgery is required the clinical standard of care is anterior temporal lobectomy (ATL).

Outcomes
Outcomes of interest are symptom improvement, treatment-related morbidity, and QOL. SRS is typically used after conservative therapy and medical treatment has failed. Follow-up for assessment of the effect of the procedure should be approximately 36 months and is related to the known latency of effect for seizure reduction or remission after SRS.

Study Selection Criteria
Methodologically credible studies were selected for all SRS indications within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Systematic Reviews
Feng et al (2016) published a systematic review and meta-analysis of data from 13 studies on the use of SRS to treat mesial temporal lobe epilepsy.[25,] The authors calculated that approximately half of the patients were seizure-free over a follow-up period, which ranged from 6 months to 9 years (pooled estimate, 50.9%; 95% CI, 38.1% to 63.6%), with an average of 14 months to seizure cessation (pooled estimate, 14.08 months; 95% CI, 11.95 to 12.22). Nine of 13 included studies reported data for adverse events, which included visual field deficits and headache (the 2 most common adverse events), verbal memory impairment, psychosis, psychogenic nonepileptic seizures, and dysphasia. Patients in the individual studies experienced adverse events at rates that ranged from 8% for nonepileptic seizures to 85% for headache.

Randomized Controlled Trials
Barbaro et al (2018) completed the Radiosurgery versus Open Surgery for mesial temporal lobe epilepsy (ROSE) trial, the only RCT comparing SRS for the treatment of pharmacoresistant unilateral mesial temporal lobe epilepsy to ATL, which is currently considered the clinical standard of care.[26,] The study was sponsored by the National Institute of Neurological Disorders and Stroke. The study was initially designed to have a 3 year recruitment period followed by a 3 year follow-up period. The sponsor stopped recruitment at 58 participants due to slow accrual resulting in a power of 41% for the primary hypothesis that SRS would be noninferior to ATL with respect to the seizure-free rate

between 25 and 36 months with a noninferiority margin of 15%. A total of 37 (64%) patients achieved seizure remission, with 16 (52%) in SRS and 21 (78%) in ATL. The difference between ATL and SRS was 26%, with the upper bound of the 1-sided 95% CI at 46%. Because the upper bound exceeded the noninferiority margin of 15% (p=.82), the noninferiority of SRS compared to ATL was not demonstrated. The corresponding 2-sided 90% CI for the difference in seizure-free rates between ATL and SRS ranged from 6% to 46%.

Other clinical outcomes were studied. SRS did not confer sparing of verbal memory deficits compared to ATL as measured by the long delay free recall score of the California Verbal Learning Test and the delayed recall score of the Logical Memory subtest from the Wechsler Memory Scale-Third Edition for English speakers. The QOL was assessed with the Quality of Life in Epilepsy for English and Spanish speakers measured at baseline and 12, 24, and 36 months. In the SRS group, QOL scores improved significantly at 24 months and remained steady at 36 months, in contrast to the ATL group in whom the QOL score improvement was immediately noticeable at 12 months. Adverse events were anticipated cerebral edema and related symptoms for some SRS patients, and cerebritis, subdural hematoma, and others for ATL patients. These all resolved with appropriate protocol-specified interventions.

The key characteristics and primary outcome results are summarized in Table 1 and Table 2.

Table 1. Summary of Key Randomized Controlled Trial Characteristics: Stereotactic Radiosurgery to Treat Mesial Temporal Lobe Epilepsy

Study; Trial	Countries	Sites	Dates	Participants[1]	Interventions[2]	
					SRS[3] n	ATL[4] n
Barbaro et al (2018); ROSE[26,]	US, UK, India	14	2009 to 2015	Pharmacoresistant unilateral MTLE	31	27

ATL: anterior temporal lobectomy; MTLE: mesial temporal lobe epilepsy; SRS: stereotactic radiosurgery; UK; United Kingdom; US: United States.
[1]≥18 years old, documented 3 months during which at least 3 focal-onset seizures with impairment of consciousness occurred during stable anticonvulsant administration and lacked neurological or visual deficits.
[2]Number randomized; intervention; mode of delivery; dose (frequency/duration).
[3]Outpatient single session 24-Gy dose delivered to a 50% isodose volume between 5.5 and 7.5 cm^2 comprising the amygdala, anterior 2 cm of hippocampus, and parahippocampal gyrus.
[4]Inpatient resection of 1 to 2 cm of the anterior superior temporal gyrus and 3 cm of the anterior middle and inferior temporal gyri, the temporal portion of the amygdala, the anterior 2 to 3 cm of the hippocampus, and adjacent entorhinal cortex. Participating neurosurgeons were documented to have performed at least 25 ATLs.

Table 2. Summary of Key Randomized Controlled Trial Results

Study; Trial	Seizure Remission[1] n (%)
Barbaro et al (2018); ROSE[26,]	N=58
SRS	16/31 (52)
ATL	21/27 (78)

ATL: anterior temporal lobectomy; RCT: randomized controlled trial; SRS: stereotactic radiosurgery.
[1]Seizure-free rate between 25 and 36 months.

Quigg et al (2018)[27,] published a follow-up report on visual field defects observed in patients treated during the ROSE trial. Out of 58 treated patients, 29/31 (93.5%) SRS patients and 25/27 (92.6%) ATL patients completed visual field testing. Ninety-three percent of patients treated with SRS reported visual field defects compared to 88% of patients treated with ATL (p=.65). Younger age at diagnosis correlated with worse outcomes; this significance was stronger in the SRS arm compared to the ATL arm (p=.04 and p=.20), but this difference was not significant upon multivariable regression. Presence or absence of visual field defects was not correlated with either seizure remission (p=.22 and p=1.00) or driving status (p=.53 and p=1.00) for the SRS or ATL treatment arms, respectively.

Case Series

Regis et al (2000) selected 25 patients with mesial temporal lobe epilepsy, 16 of whom provided a minimum 2-year follow-up.[28,] Seizure-free status was achieved in 13 patients, 2 patients were improved, and 3 patients had radiosurgery-related visual field defects.

A study by Schrottner et al (1998) included 26 patients with tumor-related epilepsy, associated mainly with low-grade astrocytomas.[29,] Mean follow-up among 24 available patients was 2.25 years. Tumor location varied across patients. Seizures were simple partial in 6 (3 with generalization) and complex partial in 18 (5 with generalization, 1 gelastic). Seizures were eliminated or nearly so in 13 patients. Little improvement was observed in 4 patients and none in 7.

Whang and Kwon (1996) performed radiosurgery in 31 patients with epilepsy associated with nonprogressive lesions.[30,] A minimum of 1-year follow-up was available in 23 patients, 12 of whom were seizure-free (3 of whom had antiseizure medications discontinued), 2 had seizures reduced in frequency, and 9 experienced no change. While the Regis et al (2000) series selected a fairly homogeneous clinical sample, the other 2 studies were heterogeneous. No confirmatory evidence is available on mesial temporal lobe epilepsy. The available evidence from patients with epileptic lesions of various sizes and locations is insufficient to show what factors are associated with a favorable outcome.

Section Summary: Epilepsy

For individuals with epilepsy refractory to medical management, the evidence on the use of SRS as a treatment for epilepsy includes a systematic review, a single RCT, and case reports in primary epileptic disorders and for tumor-related epilepsy. Overall, the available evidence from patients with epileptic lesions of various sizes and locations is insufficient to show what factors are associated with a favorable outcome. For mesial temporal lobe epilepsy, a systematic review of data from 13 studies and a single RCT comparing SRS to ATL comprise the majority of data. In the RCT, remission rates were reported for a total of 58 patients (31 in SRS arm and 27 in ATL arm). Seizure remission rates suggest that ATL (78%) has an advantage over SRS (52%) in terms of proportion of patients with seizure remission.

Stereotactic Radiosurgery for Non-Neoplastic Neurologic Disorders: Tremor and Movement Disorders

Clinical Context and Therapy Purpose

The purpose of SRS is to use a focused radiotherapy technique to ablate brain nuclei foci associated with movement disorders (e.g., essential tremor, parkinsonian disorders) when the conditions have become drug-resistant or medication-related adverse events are intolerable, and to potentially avoid complications associated with surgical intervention.

The following PICO was used to select literature to inform this review.

Populations

The population of interest is individuals with drug-resistant or medication-intolerant movement disorders including essential tremor and other forms of tremors (i.e., secondary to Parkinson disease, multiple sclerosis, or other neurologic conditions)

Interventions

The therapy being considered is SRS of the thalamus (thalamotomy) as an alternative to surgical intervention.

Comparators

The following therapies are currently being used to treat movement disorders: conservative therapies (e.g., continued medical therapy) and surgical intervention.

Outcomes

The outcomes of interest are OS, symptom improvement, treatment-related morbidity, and QOL. SRS is typically used after conservative therapy and medical treatment has failed. The duration of follow-up to assess the treatment effect varies.

Study Selection Criteria

Methodologically credible studies were selected for all SRS indications within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Dallapiazza et al (2018)[31,] conducted a systematic review comparing the outcomes of various surgical procedures for the treatment of refractory essential tremor, including deep brain stimulation, thalamotomy with radiofrequency, SRS, and focused ultrasound. Studies were pooled and graded for their overall level of evidence according to the Oxford Centre for Evidence-based Medicine standards. Measured outcomes included tremor control according to the Fahn-Tolosa-Marin rating scale, QOL improvements, and complication rates. Characteristics and results of the review are summarized in Table 3. Overall, while complication rates were generally lower for SRS compared to other interventions, alternative approaches presented higher control rates and QOL improvements at more robust tiers of evidence.

Table 3. Systematic Review: Comparison of Surgical Interventions for Essential Tremor[1]

Study	Surgical Intervention			
Dallapiazza et al (2018)[31,]	DBS	SRS	FUS	RF
Patients, n	1093	360	151	278
Years	Since 1998	Since 2007	Since 2013	Since 1986
LOE	Level 2	Level 4	Level 1	Levels 2 to 4
Tremor Control, 1 year	UL: 53.4 to 62.8% BL: 66 to 78%	UL: 48 to 63% BL: ND	UL: 35 to 75% BL: ND	UL: 74 to 90% BL: ND
Tremor Control, Long-term	UL: 60 to 75% BL: 75%	UL: 3 to 63% BL: ND	UL: 56% BL: ND	UL: 74 to 90% BL: ND
QOL Improvements	57.9 to 82%	65%	37 to 73%	47%
Adverse Events	UL, BL	UL	UL	UL
Dysarthria	11 to 39%, 22 to 75%	1 to 3%	3%	4.6 to 29%
Ataxia/gait	9 to 17%, 56 to 86%	0 to 17%	23%	5 to 27%
Paraesthesia	5%, 5.9%	1 to 9%	14 to 25%	6 to 42%
Hemiparesis	4.5%, 6.7%	0 to 8%	2 to 7%	0 to 34%

BL: bilateral; DBS: deep brain stimulation; FUS: focused ultrasound; LOE: level of evidence; ND: no data; QOL: quality of life; RF: radiofrequency; SRS: stereotactic radiosurgery; UL: unilateral.
[1]Adapted from Dallapiazza et al (2018).

Nonrandomized Observational Studies

Raju et al (2018)[32,] published a retrospective analysis of 15 patients with medically refractory multiple sclerosis-related tremors who were treated with Gamma Knife thalamotomy at a median maximum

dose of 140 Gy (range, 130 to 150 Gy) targeted to the posteroinferior region of the nucleus ventralis intermedius. The Fahn-Tolosa-Marin clinical rating scale was administered to rate tremor, handwriting, drawing, and drinking. Median time to follow up was 39 months. Seven patients reported excellent tremor improvement and 6 reported good tremor improvement. Four patients noted tremor arrest at a median of 4.5 months post-treatment. Four patients noted excellent functional improvement and 8 noted good functional improvement. Three patients reported diminished tremor relief at a median of 18 months post-treatment. Two patients experienced temporary adverse radiation effects. A third patient developed a large thalamic cyst, which was successfully managed with the placement of a reservoir.

Niranjan et al (2017) reported a retrospective analysis of 73 patients who underwent Gamma Knife thalamotomy for intractable essential tremor during a 19-year period (1996 to 2015).[33,] A median central dose of 140 Gy (range, 130 to 150 Gy) was delivered to the nucleus ventralis intermedius through a single 4-mm isocenter. The median time to the last follow-up was 28 months (range, 6 to 152 months). Improvement in tremor occurred in 93.2% of patients as demonstrated with changes in the Fahn-Tolosa-Marin Tremor Rating Scale to score tremor, handwriting, drawing, and ability to drink fluids. Three (4%) patients experienced temporary adverse radiation events.

Witjas et al (2015) reported on outcomes of a French prospective single-blind study of Gamma Knife thalamotomy for tremor.[34,] Fifty patients (mean age, 74.5 years; 32 men) with severe refractory tremor (36 essential, 14 parkinsonian) were treated with unilateral Gamma Knife thalamotomy at a prescription dose of 130 Gy. Neurologic and neuropsychological assessments including a single-blind video assessment of the tremor severity by a movement disorders neurologist from another center were performed before and 12 months after treatment. The upper-limb tremor score improved by 54.2% on the blinded assessment (p<.001). All tremor components (rest, postural, intention) were improved. Activities of daily living were improved by 72.2%. Cognitive functions remained unchanged. Following Gamma Knife thalamotomy, the median delay of improvement was 5.3 months (range, 1 to 12 months). The only side effect was a transient hemiparesis associated with excessive edema around the thalamotomy in 1 patient.

Kooshkabadi et al (2013) reported on 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.[35,] Fahn-Tolosa-Marin Tremor Rating Scale 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<.000), the mean handwriting score improved from 2.78 (pre-SRS) to 1.62 (post-SRS; p<.000), and the mean drinking score improved from 3.14 (pre-SRS) to 1.8 (post-SRS, p<.000). Complications included temporary hemiparesis in 2 patients, dysphagia in 1 patient, and sustained facial sensory loss in 1 patient.

Ohye et al (2012) conducted a prospective study of SRS for tremors that included 72 (59 with Parkinson disease, 13 with essential tremor) patients.[36,] Among 52 patients who had a follow-up at 24 months, tremor scores measured using the Unified Parkinson's Disease Rating Scale changed from 1.5 at baseline to 0.75 at 24-month follow-up (p<.001; score decrease extrapolated from the graph).

Lim et al (2010) reported on outcomes for a small cohort of 18 patients who underwent SRS treatment for essential tremor.[37,] For the 14 patients with videotaped evaluations allowing blinded evaluation of tremor severity and at least 6 months of follow-up (11 with essential tremor, 3 with Parkinson disease), Fahn-Tolosa-Marin Tremor Rating Scale activities of daily living scores improved significantly after SRS (mean change score, 2.7 points; p=.03). However, there was no significant improvement in other Fahn-Tolosa-Marin Tremor Rating Scale items (p=.53 for resting tremor, p=.24 for postural tremor, p=.62 for action tremor, p=.40 for drawing, p>.99 for pouring water, p=.89 for head tremor). Mild neurologic complications occurred in 2 patients (lip and finger numbness), and severe neurologic complications occurred in 1 patient (edema surrounding thalamic lesion with subsequent hemorrhage at the lesion site, with speech difficulty and hemiparesis).

Kondziolka et al (2008) reported on outcomes for 31 patients who underwent SRS thalamotomy for disabling essential tremor.[38,] Among 26 patients with follow-up data available, score on the Fahn-Tolosa-Marin Tremor Rating Scale score improved from 3.7 (pre-SRS [baseline]) to 1.7 (post-SRS; p<.000) and score on the Fahn-Tolosa-Marin handwriting score improved from 2.8 (pre-SRS [baseline]) to 1.7 (post-SRS; p<.000). One patient developed transient mild right hemiparesis and dysphagia, and 1 patient developed mild right hemiparesis and speech impairment.

Young et al (2000) reported on outcomes for a cohort of 158 patients with tremors who underwent SRS, including 102 patients with Parkinson disease, 52 with essential tremor, and 4 with tremors due to other conditions.[39,] 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<.05) and action tremor (from 2.3 pretreatment to 1.3 at last follow-up; p<.05). Among patients with essential tremor, blinded assessments were conducted using the Fahn-Tolosa-Marin Tremor Rating Scale. At 1-year of follow-up, 92.1% of patients with essential tremor were completely or nearly tremor-free. Improvements were reported for components of the Fahn-Tolosa-Marin Tremor Rating Scale, but statistical comparisons were not presented. Three patients developed new neurologic symptoms attributed to SRS.

Section Summary: Tremor and Movement Disorders

The evidence related to the use of SRS for tremors includes a systematic review and nonrandomized observational studies, many of which reported outcomes from the treatment of tremors 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 comparing 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.

Stereotactic Radiosurgery for Non-Neoplastic Neurologic Disorders: Chronic Pain

Clinical Context and Therapy Purpose

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

The following PICO was used to select literature to inform this review.

Populations

The population of interest is individuals with chronic pain syndromes refractory to standard medical and psychological treatments.

Interventions

The therapy being considered is SRS as an alternative to open neurosurgical intervention.

Comparators

The following therapies are currently being used to treat chronic pain syndromes: conservative therapies (e.g., continued medical therapy) and surgical intervention. Neurodestructive procedures include cordotomy, myelotomy, and dorsal root entry zone lesions.

Outcomes

The outcomes of interest are OS, symptom improvement, and treatment-related morbidity. SRS is typically used as an alternative to open neurosurgical intervention.

Study Selection Criteria

Methodologically credible studies were selected for all SRS indications within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Roberts and Pouratian (2017) reported the results of a systematic review of the data in 6 studies (N=113 patients) of SRS as an intervention for chronic pain.[40,] Outcomes were reported on the basis of the radiation target (pituitary or thalamus) and pain etiology (malignant or nonmalignant). Clinical success was reported to be achieved in 51% of pituitary SRS, at least 23% of thalamic SRS, 39% of nonmalignant pain patients, and at least 33% of malignant pain patients. Adverse events were noted in 21% of patients; the majority related to hormonal deficits from pituitary SRS. Because reports of SRS for pain largely stem from a period before the common use of neuromodulatory and intrathecal therapies, the efficacy in patients who fail such therapies remains unclear and requires further characterization.

Section Summary: Chronic Pain Syndromes

For individuals with chronic pain syndromes refractory to standard medical and psychological treatments, the evidence includes a systematic review of noncomparative studies. Although clinical success was reported in varying percentages of patients dependent upon the radiation target and pain etiology, the data are primarily from a period of time before the common use of other treatments for patients with chronic pain syndromes.

Stereotactic Radiosurgery for Benign Neoplastic Intracranial Lesions

Clinical Context and Therapy Purpose

The purpose of SRS is to use a focused radiotherapy technique to treat intracranial and other brain lesions that are relatively inaccessible surgically and that are often near eloquent or radiosensitive areas.

Acoustic neuromas, also called vestibular schwannomas, are benign tumors originating on the eighth cranial nerve, sometimes associated with neurofibromatosis, which can be linked to significant morbidity and even death if their growth compresses vital structures. The tumors arise from the Schwann cell sheath surrounding the vestibular or cochlear branches of the eighth cranial nerve.

Pituitary adenomas are benign tumors with symptoms related to hormone production (i.e., functioning adenomas) or neurologic symptoms due to tumor impingement on surrounding neural structures.

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

A glomus jugulare tumor is a rare, benign tumor arising in the skull temporal bone that involves middle and inner ear structures.

The following PICO was used to select literature to inform this review.

Populations
The population of interest is individuals with symptomatic acoustic neuroma, pituitary adenoma, craniopharyngioma, and glomus jugulare tumor.

Interventions
The therapy being considered is SRS.

Comparators
The following therapies are currently being used to treat benign neoplastic intracranial lesions: conservative therapies (e.g., surveillance, medical therapy), radiotherapy, and surgical intervention.

For acoustic neuromas, treatment options include complete surgical excision using microsurgical techniques.

For pituitary adenomas, surgical excision is typically offered to patients with functioning adenomas because complete removal of the adenoma leads to more rapid control of autonomous hormone production. In patients with nonfunctioning adenomas, the treatment goal is to control growth; complete removal of the adenoma is not necessary. Conventional radiotherapy has been typically offered for nonfunctioning adenomas with an approximate 90% success rate and few complications.

For craniopharyngiomas, total surgical resection is often difficult.

For glomus jugulare tumors, no consensus exists on optimal management to control tumor burden while minimizing treatment-related morbidity.

Outcomes
The outcomes of interest are OS, symptom improvement, and treatment-related morbidity. SRS is typically used when conservative medical treatment has failed and as an alternative to open neurosurgical intervention. The effects of SRS on hormone production associated with pituitary adenomas may be delayed or incomplete.

Study Selection Criteria
Methodologically credible studies were selected for all SRS indications within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Acoustic Neuromas

Systematic Reviews
Savardekar et al (2022) published a systematic review comparing SRS with microsurgery with regard to hearing preservation, tumor control, and facial nerve dysfunction in patients undergoing primary treatment for small to medium (<3 cm) sporadic vestibular Schwannomas.[41,] Characteristics of the review and results of the meta-analysis are summarized in Tables 4 and 5, respectively. A crosswalk of studies that included SRS is found in Table SR1 in the Appendix.

Table 4. SR & M-A Characteristics

Study	Dates	Studies	Participants	N, range	Design	Follow-up
Savardekar (2022)[41,]	Jan 2010 to Jun 2020	32 (MS, 10 studies; SRS, 23 studies; MS and SRS, 1 study)	Patients with small to medium (<3 cm) sporadic vestibular schwannomas	MS: 43 to 1006 SRS: 31 to 420 The proportion of included males across cohorts ranged from 40% to 61% (mean, 49%).	Observational (all except 2 were retrospective)	≥3 years

MA: meta-analysis; MS: microsurgery; SR: systematic review; SRS: stereotactic radiosurgery.

Table 5. SR & M-A Results

Study	Hearing preservation	Tumor control	Facial nerve dysfunction
Savardekar (2022)[41,]			
Total N	MS: 809 SRS: 1234	MS: 1635 SRS: 1234	MS: 1101 SRS: 2285
Follow up (months)	65	70	12
MS	56%	98%	10%
SRS	59%	92%	2%
P-value	.1527	<.0001	<.0001

MA: meta-analysis; MS: microsurgery; SR: systematic review; SRS: stereotactic radiosurgery

A systematic review by Persson et al (2017) reported on SRS versus fractionated radiotherapy for tumor control in vestibular schwannoma patients.[42,] Patients with unilateral vestibular schwannoma treated with radiosurgery were compared with patients treated with fractionated SRS. A meta-analysis was not performed because all identified studies were case series. Rates of adverse events were calculated; the risk for facial nerve deterioration was 3.6% for SRS and 11.2% for fractionated SRS, and the risk for trigeminal nerve deterioration was 6.0% for SRS and 8.4% for fractionated SRS.

A Cochrane review by Muzevic et al (2014) did not identify any RCTs that evaluated the efficacy of SRS compared with observation alone, microsurgical resection, or other possible treatment or combinations of treatments in patients with a cerebellopontine angle tumor up to 3 cm in diameter, presumed to be a vestibular schwannoma.[43,]

Case Series

Case series have reported generally high rates of local control. Badakhshi et al (2014) reported a 3-year local tumor control rate of 88.9% in 250 patients with vestibular schwannoma who underwent SRS or fractionated SRS.[44,]

Williams et al (2013) reported rates of tumor progression-free survival (PFS) for patients with large vestibular schwannomas treated with SRS of 95.2% and 81.8% at 3 and 5 years, respectively.[45,] For patients with small vestibular schwannomas treated with SRS, tumor PFS was 97% and 90% at 3 and 5 years, respectively.

In a retrospective case series of 93 patients with vestibular schwannomas treated with SRS, 83 of whom had long-term follow-up, Woolf et al (2013) reported an overall control rate of 92% at a median follow-up of 5.7 years.[46,]

Pollock et al (2006) compared microsurgical resection (n=36) with SRS (n=46) for the management of small (<3 cm) vestibular schwannomas and showed better hearing preservation at last follow-up in the SRS group (p<.01) and no difference in tumor control rates between groups (100% vs 96%, p=.50).[47,]

In the treatment of acoustic neuromas, the most significant adverse events include loss of function of facial and auditory nerves.

Chang et al (2005) reported that 74% of 61 patients with acoustic neuromas treated with CyberKnife using staged treatment maintained serviceable hearing during at least 36 months of follow-up.[48,]

Chung et al (2004) reported on the results of a single-institution case series of 72 patients with acoustic neuromas, 45 of whom received single-fraction therapy and 27 who received fractionated therapy.[49,] 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.

In a single-institution study, Meijer et al (2003) reported on the outcomes of single-fraction versus fractionated linear accelerator-based SRS in 129 patients with acoustic neuromas.[50,] Among these patients, 49 were edentate and thus could not be fitted with a relocatable head frame that relies on dental impressions. This group was treated with a single-fraction, while the remaining 80 patients were treated with a fractionated schedule. With an average follow-up of 33 months, there was no difference in outcome in terms of local tumor control, facial nerve preservation, or hearing preservation.

Sub-section Summary: Acoustic Neuromas

The evidence for the use of SRS for acoustic neuroma (vestibular schwannoma) consists primarily of systematic reviews and case series, which have reported high rates of freedom from tumor progression generally using fractionated SRS. One systematic review found that SRS and micro-surgery are comparable treatments for primary management of small to medium (<3 cm) vestibular schwannomas with regard to hearing preservation at 65 months; microsurgery was favored over SRS for tumor control at 70 months (98% vs 92%), while SRS was favored over microsurgery for reducing the proportion of patients with facial nerve dysfunction at 12 months (2% vs 10%). Given that vestibular schwannoma is a slow-growing tumor with symptoms most often related to local compression, demonstration of slowing of progression is a valid outcome. A Cochrane review did not identify any RCTs.

Pituitary Adenoma

Systematic Reviews

Chen et al (2013) reported on the results of a systematic review and meta-analysis evaluating studies of SRS (specifically Gamma Knife surgery) for the treatment of nonfunctioning pituitary adenoma that included a volumetric classification.[51,] Seventeen studies met the inclusion criteria, including 7 prospective cohort studies and 10 retrospective cohort studies, with 925 patients included in the meta-analysis. Reported outcomes were related to the rate of tumor control, the rate of radiosurgery induced optic neuropathy injury, and the rate of radiosurgery-induced endocrinologic deficits. In patients with a tumor volume less than 2 mL, the rate of tumor control was 99% (95% CI, 96% to 100%), the rate of radiosurgery-induced optic neuropathy injury was 1% (95% CI, 0% to 4%), and the rate of radiosurgery-induced endocrinologic deficits was 1% (95% CI, 0% to 4%). In patients with volumes of 2 to 4 mL, the comparable rates were 96% (95% CI, 92% to 99%), 0% (95% CI, 0% to 2%), and 7% (95% CI, 2% to 14%), respectively, and in patients with volumes larger than 4 mL, the rates were 91% (95% CI, 89% to 94%), 2% (95% CI, 0% to 5%), and 22% (95% CI, 14% to 31%), respectively. The rates of tumor control and radiosurgery-induced optic neuropathy injury differed significantly across the 3 groups.

Nonrandomized Observational Studies

Lee et al (2014) retrospectively reported on outcomes for 41 patients treated with SRS from a cohort of 569 patients treated for nonfunctioning pituitary adenomas at 3 institutions.[52,] Neuroimaging at a median follow-up of 48 months showed 34 (82.9%) patients had a decrease in tumor volume, 4 (9.8%) patients had tumor stability, and 3 (7.3%) patients had a tumor increase. PFS rates were 94% at 5

years and 85% at 10 years post-SRS. New onset or worsened pituitary deficiencies were found in 10 (24.4%) patients at a median follow-up of 52 months. The authors concluded that initial treatment with SRS for nonfunctioning pituitary adenomas might be appropriate in certain clinical settings, such as in older patients (≥70 years of age); in patients with multiple comorbidities in whom surgery would be high-risk; in patients with clear neuroimaging and neuroendocrine evidence of non-functioning adenomas, no mass effect on the optic apparatus, and progressive tumor on neuroimaging follow-up; or in patients who want to avoid resection.

Sheehan et al (2013) reported results from a multicenter registry of 512 patients who underwent SRS for nonfunctional pituitary adenomas.[53,] Four hundred seventy-nine (93.6%) had undergone prior resection, and 34 (6.6%) had undergone prior external-beam radiotherapy (EBRT). Median follow-up was 36 months. At last follow-up, 31 (6.6%) of 469 patients with available follow-up had tumor progression, leading to actutimes PFS rates of 98%, 95%, 91%, and 85% at 3, 5, 8, and 10 years post-SRS, respectively. Forty-one (9.3%) of 442 patients had worsened or new central nervous system deficits, more commonly in patients with tumor progression (p=.038).

Sub-section Summary: Pituitary Adenoma

Noncomparative studies have demonstrated high rates of tumor control (≥85%) for pituitary adenomas with SRS treatment, with better tumor control with smaller lesions. Comparative studies evaluating the treatment of pituitary adenomas with SRS versus surgery or traditional radiotherapy do not exist.

Craniopharyngioma

Nonrandomized Observational Studies

Lee et al (2014) reported on a 20-year (1993 to 2012) experience of using Gamma Knife surgery to treat recurrent or residual craniopharyngiomas.[54,] A total of 137 consecutive patients underwent 162 sessions in a Veterans hospital. The median radiation dose was 12 Gy (range, 9.5 to 16.0 Gy) at a median isodose line of 55% (range, 50% to 78%). At a median imaging follow-up of 45.7 months after Gamma Knife surgery, the rates of tumor control were 72.7%, 73.9%, and 66.3% for the solid, cystic, and mixed tumors, respectively. There were no unanticipated adverse events on visual fields or pituitary function.

Hashizume et al (2010) evaluated the use of SRS in 10 patients with craniopharyngioma adjacent to optic pathways.[55,] Ten patients (6 men, 4 women) with craniopharyngioma and the median age of 56.5 years (range, 10 to 74 years) were treated from 2006 through 2009. Median volume of the tumor was 7.9 mL (range, 1.1 to 21 mL). A total dose of 30 to 39 Gy in 10 to 15 fractions (median, 33 Gy) was delivered to the target. Ten patients were followed for 9 to 36 months (median, 25.5 months). The response rate was 80% (8/10), and the control rate was 100%. Improvement of neurologic symptoms was observed in 5 patients. No serious complications due to SRS were found.

Hasegawa et al (2010) determined the limiting dose to the optic apparatus in single-fraction irradiation in patients with craniopharyngioma treated with Gamma Knife radiosurgery.[56,] One hundred patients with 109 craniopharyngiomas treated with radiosurgery were evaluated with a median follow-up period of 68 months. Tumor volume varied from 0.1 to 36.0 cm (median, 3.3 cm). The actutimes 5- and 10-year overall rates of survival after radiosurgery were 93% and 88%, respectively. The actutimes 5- and 10-year PFS rates were 62% and 52%, respectively. Among 94 patients in whom the visual function was evaluable, only 3 patients developed radiation-induced optic neuropathy, indicating an overall Kaplan-Meier radiation-induced optic neuropathy rate of 5%.

Combs et al (2007) evaluated long-term outcomes in patients treated with fractionated SRS.[57,] Forty patients with craniopharyngiomas were treated between 1989 and 2006. Most patients were treated for tumor progression after surgery. A median target dose of 52.2 Gy (range, 50.4 to 56 Gy) was applied. Follow-up examinations included a thorough clinical assessment, as well as contrast-enhanced MRI scans. After a median follow-up of 98 months (range, 3 to 326 months), local control

was 100% at both 5 and 10 years. OS rates at 5 and 10 years were 97% and 89%, respectively. A complete response was observed in 4 patients, and partial responses were noted in 25 patients. Eleven patients presented with stable disease during follow-up. Acute toxicity was mild in all patients. Long-term toxicity included enlargement of cysts requiring drainage 3 months after fractionated SRS. No visual impairment, radionecrosis, or development of secondary malignancies was observed. The results would suggest that long-term outcomes of fractionated radiosurgery for craniopharyngiomas are associated with good local control and, acceptable treatment-related side effects.

Sub-section Summary: Craniopharyngioma

The evidence related to the use of fractionated SRS for craniopharyngioma consists primarily of nonrandomized observational studies, which report high rates of OS.

Glomus Jugulare Tumors

Systematic Reviews

Two systematic reviews evaluated SRS for patients with glomus jugulare tumors; neither review compared SRS to other treatment modalities.[58,59,]

Ong et al (2022) identified 23 studies (N=460).[58,] The average follow-up across studies was 47 months (range, 4 to 268 months). The pooled tumor control rate after SRS was 95% (95% CI, 93 to 97). Rates of tinnitus, hearing loss, and lower cranial nerve improvement after treatment were 54%, 28%, and 22%, respectively.

Ivan et al (2011) conducted a meta-analysis of tumor control and treatment-related mortality rates.[59,] In this meta-analysis, reviewers assessed published data collected from patients with glomus jugulare tumors to identify treatment variables that impacted clinical outcomes and tumor control rates. A comprehensive search of the English language literature identified 109 related studies. Univariate comparisons of demographic information between treatment cohorts were performed to detect differences in the sex distribution, age, and Fisch class of tumors among various treatment modalities. Meta-analyses were performed on calculated rates of recurrence and cranial neuropathy after subtotal resection (STR), gross total resection, STR with adjuvant postoperative SRS (STR plus SRS), and SRS alone. Reviewers identified 869 patients who met inclusion criteria. In these studies, the length of follow-up ranged from 6 to 256 months. Patients treated with STR were observed for 72 months and had a tumor control rate of 69% (95% CI, 57% to 82%). Those who underwent gross total resection had a follow-up of 88 months and a tumor control rate of 86% (95% CI, 81% to 91%). Those treated with STR plus SRS were observed for 96 months and had a tumor control rate of 71% (95% CI, 53% to 83%). Patients undergoing SRS alone had a follow-up of 71 months and a tumor control rate of 95% (95% CI, 92% to 99%). Reviewers' analysis indicated that patients undergoing SRS had the lowest rates of recurrence of these 4 cohorts and, therefore, experienced the most favorable tumor control rates ($p<.01$). Patients who underwent gross total resection sustained worse rates of cranial nerve deficits with regard to cranial nerves IX, X, and XI than those who underwent SRS alone; however, the rates of cranial nerve XII deficits were comparable.

Case Series

Wakefield et al (2017), published a report from an academic medical center that included 17 patients (median age, 64 years) treated between 1996 and 2013 with SRS for glomus jugulare tumors.[60,] Gamma Knife surgery was delivered with definitive treatment intent in 8 (47%) patients and salvage treatment in 9 (53%) patients. Overall neurologic deficit improved by 53%, stabilized in 41%, and worsened in 6% of patients. Overall cause-specific survival was 100%, and actutimes local control was 94%. Eighty-eight percent of patients without prior resection experienced neurologic deficit improvement, while 25% of patients with prior resection experienced neurologic improvement. Ibrahim et al (2017) reported a U.K. referral center experience with 75 patients who had glomus jugulare tumors treated with SRS between 1994 and 2010.[61,] Gamma Knife radiosurgery was the primary treatment modality in 47 (63%) patients. The overall tumor control rate was 93.4% with low

cranial nerve injury. Reduction of preexisting deficits was noted in 15 (20%) patients. A stationary clinical course and no progression of symptoms were noted in 48 (64%) patients. Twelve (16%) patients had new symptoms or progression of their preexisting symptoms.

Sub-section Summary: Glomus Jugulare Tumors

The evidence related to the use of SRS for glomus jugulare tumors includes 2 systematic reviews, neither of which compared SRS to other treatment modalities and recently published case series. Available data suggest that SRS is associated with improved patient outcomes.

Section Summary: Benign Neoplastic Intracranial Lesions.

The published evidence for the use of SRS to treat a subgroup of uncommon benign neoplastic intracranial lesions (acoustic neuroma, pituitary adenoma, craniopharyngioma, and glomus jugulare tumors) remains limited to systematic reviews of nonrandomized observational studies, other nonrandomized observational studies, and case series. These reports would suggest that long-term outcomes of fractionated radiosurgery for these benign neoplasms are associated with good local control and acceptable treatment-related side effects. The likelihood of high quality systematically acquired evidence is low due to the rarity of the conditions.

Stereotactic Radiosurgery for Malignant Neoplastic Intracranial Lesion(s)
Primary or Recurrent Gliomas and Astrocytomas

Clinical Context and Therapy Purpose

The purpose of SRS is to use a focused radiotherapy technique to treat certain primary intracranial malignant tumors that are relatively inaccessible surgically and which are often located in proximity to eloquent or radiosensitive areas.

The following PICO was used to select literature to inform this review.

Populations

The population of interest is individuals with certain primary intracranial malignant tumors; including gliomas, astrocytomas, malignant meningiomas, and primitive neuroectodermal tumors (i.e., medulloblastoma, pineoblastoma). Treatment of primary brain tumors such as gliomas is more challenging, due to their generally larger size and infiltrative borders.

Interventions

The therapy being considered is SRS as an alternative to open neurosurgical intervention. SRS may be added to whole-brain radiotherapy (WBRT) in selected patients.

Comparators

The following practice is currently being used to treat patients with certain primary and metastatic intracranial malignant tumors: conservative therapies (e.g., continued medical therapy, surgical intervention). WBRT is considered the standard of care in the treatment of brain metastases.

Outcomes

The outcomes of interest are OS, symptom improvement, and treatment-related morbidity. SRS is typically used as an alternative to open neurosurgical intervention. SRS offers the additional ability to treat tumors with relative sparing of normal brain tissue in a single-fraction.

Study Selection Criteria

Methodologically credible studies were selected for all SRS indications within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Review

De Maria et al (2021) conducted a systematic review and meta-analysis including case series with 5 or more patients who received CyberKnife SRS for treatment of recurrent World Health Organization (WHO) grade 3 and 4 gliomas of the brain.[62,] The meta-analysis included 13 studies (N=398); from the time of treatment with SRS, the median OS, time to progression, and PFS were 8.56 months (95% CI, 17.56 to 27.58 months), 6.68 months (95% CI, 2.13 to 11.22 months), and 7.05 months (95% CI, 1.30 to 12.79 months), respectively. Median OS for WHO grade 3 and 4 gliomas from the time of SRS was 8.4 months (95% CI, 6.35 to 10.45 months) and 11 months (95% CI, 5.12 to 16.88 months), respectively. Median OS was 9.52 months (95% CI, 7.78 to 11.25 months) for patients who underwent SRS plus chemotherapy, compared to 4.44 months (95% CI, 0 to 9.46 months) for patients who underwent SRS alone. Reported complications of SRS included acute neurologic adverse events (3.6%; 95% CI, 1.5 to 5.7), acute non-neurologic adverse events (13%; 95% CI, 0 to 26.1), corticosteroid dependency (18.8%; 95% CI, 10 to 27.6), and radiation necrosis (4.3%; 95% CI, 2.1 to 6.6).

Nonrandomized Observational Studies

El-Shehaby et al (2015), reported on a single-arm study of 11 patients with tectal gliomas who were treated with Gamma Knife SRS between 2002 and 2011.[63,] Tectal gliomas are present in a location that makes surgical resection difficult and are also commonly associated with aqueduct obstruction and consequently hydrocephalus. This necessitates some form of cerebrospinal fluid diversion procedure before radiosurgery. Five patients had pilocytic astrocytomas, and 6 had nonpilocytic astrocytomas. Ten patients presented with hydrocephalus and underwent a cerebrospinal fluid diversion procedure prior to SRS. The tumor volume ranged between 1.2 mL 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 to 114 months). Tumor control after radiosurgery was seen in 100% of cases. In 6 (55%) of 11 cases, the tumors eventually disappeared after treatment. Peritumoral edema developed in 45% of cases at the onset of 3 to 6 months after treatment. Transient tumor swelling was observed in 4 cases. Four patients developed cysts after treatment. One of these cases required aspiration and eventually disappeared, 1 became smaller spontaneously, and 2 remained stable.

Clark et al (2014), retrospectively reviewed 21 patients with recurrent malignant glioma (18 glioblastoma; 3, WHO grade 3 glioma), treated at initial diagnosis with surgery and standard chemoradiation, receiving concurrent bevacizumab with hypofractionated SRS (30 Gy in 5 fractions) with or without concurrent chemotherapy (temozolomide or lomustine).[64,] The median patient age was 54 years, median Karnofsky Performance Status (KPS) was 80, and the median target size was 4.3 mL (range, 3.4 to 7.5 mL). Eleven (52%) patients had previously failed bevacizumab. One patient had grade 3 toxicities (seizures, dysphasia), which resolved with inpatient admission and intravenous steroids and antiepileptics. Treatment-related toxicities were grade 3 (n=1), grade 2 (n=9), and grade 0 to 1 (n=11). Kaplan-Meier median PFS and OS estimates (calculated from the start of SRS) for glioblastoma patients (n=18) were 11.0 and 12.5 months, respectively.

Dodoo et al (2014) reported on results for 55 consecutive patients with 68 high-grade gliomas (WHO grade 3 and 4) who were treated with SRS (Gamma Knife) for local recurrences between 2001 and 2007.[65,] All patients previously had microsurgery and radiochemotherapy. Complete follow-up was available in all patients, with a median follow-up of 17 months (range, 2.5 to 114.2 months). Median tumor volume was 5.2 mL, the prescription dose was 20 Gy (range, 14 to 22 Gy), and the median maximal dose was 45 Gy (range, 30 to 77.3 Gy). Patients with WHO grade 3 tumors initially showed a median survival of about 50 months, with a 2-year OS rate of 90%; however, after SRS for tumor

recurrences, those same patients showed a median survival of 24 months and a 2-year OS rate of 50%. Patients with WHO grade 4 tumors had an initial median survival of 24 months, with a 2-year OS rate of 51%; after tumor recurrence and SRS, the median survival was 11 months, and 2-year survival was 23%.

Cabrera et al (2013), prospectively treated 15 patients with recurrent malignant glioma lesions less than 3 cm in diameter with SRS in a single fraction. Those with lesions 3 to 5 cm in diameter received five, 5 Gy fractions; bevacizumab was administered immediately before SRS and 2 weeks later.[66,] At initial diagnosis, patients were treated with surgery and adjuvant radiotherapy plus temozolomide and then at least 1 salvage chemotherapy regimen. The primary endpoint was central nervous system toxicity. Secondary endpoints included survival, QOL, microvascular properties as measured by MRI, steroid usage, and performance status. One grade 3 (severe headache) and 2 grade 2 central nervous system toxicity events were observed. No patients experienced grade 4 or 5 toxicity or intracranial hemorrhage. Neurocognition, QOL, and KPS did not change significantly with treatment. MRI results suggested a significant decline in tumor perfusion and permeability 1 week after SRS and further decline by 2 months.

Cuneo et al (2012) reported on a retrospective analysis of patients with recurrent malignant gliomas treated with salvage SRS from 2002 to 2010.[67,] All patients had experienced tumor progression after treatment with temozolomide and radiotherapy. Salvage SRS was typically administered only after multiple post chemoradiation salvage systemic therapies had failed. Among 63 patients treated with SRS for recurrent high-grade glioma, 49 patients had WHO grade 4 disease. Median follow-up was 31 months from primary diagnosis and 7 months from SRS. Median OS from primary diagnosis was 41 months for all patients. Median PFS and OS from SRS were 6 and 10 months for all patients, respectively. The 1-year OS rates after SRS for patients with grade 4 glioma who received adjuvant (concurrent with or after SRS) bevacizumab was 50% versus 22% for patients not receiving adjuvant bevacizumab (p=.005). Median PFS for patients with WHO grade 4 glioma who received adjuvant bevacizumab was 5.2 months and 2.1 months for patients who did not receive adjuvant bevacizumab (p=.014). Treatment-related grade 3 or 4 toxicity events for patients who did or did not receive adjuvant bevacizumab was 10% and 14%, respectively (p=.58). On multivariate analysis, the relative risk (RR) of death and progression with adjuvant bevacizumab was 0.37 (95% CI, 0.17 to 0.82) and 0.45 (95% CI, 0.21 to 0.97), respectively. A KPS score greater than 70 and age less than 50 years were significantly associated with improved survival. The combination of salvage radiosurgery and bevacizumab to treat recurrent malignant gliomas was well tolerated and seemed to be associated with improved outcomes. Prospective multi-institutional studies are required to determine the efficacy and long-term toxicity with this approach.

Section Summary: Primary or Recurrent Gliomas and Astrocytomas

Direct evidence is not available to compare radiotherapy methods for primary or recurrent gliomas or astrocytomas. Evidence from a single meta-analysis including case series with ≥5 patients and heterogeneous observational studies has demonstrated local control using SRS in combination with chemotherapy to treat gliomas in the primary and recurrent setting. The tumors are very aggressive and there are limited treatment options.

Brain Metastases

Clinical Context and Therapy Purpose

The purpose of SRS is to use a focused radiotherapy technique to treat certain metastatic intracranial malignant tumors that are relatively inaccessible surgically and which are often located in proximity to eloquent or radiosensitive areas.

The following PICO was used to select literature to inform this review.

Populations
The population of interest is individuals with cancer that has metastasized to the brain. Intracranial metastases tend to have a smaller spherical size and noninfiltrative borders. Brain metastases occur frequently, seen in 25% to 30% of all patients with cancer, particularly in those with cancer of the lung, breast, colon, melanoma, and kidney.

Interventions
The therapy being considered is SRS as an alternative to open neurosurgical intervention. SRS may be added to WBRT in selected patients.

Comparators
The following practice is currently being used to treat patients with brain metastases: WBRT is considered the standard of care.

Outcomes
The outcomes of interest are OS, symptom improvement, and treatment-related morbidity. SRS is typically used as an alternative to open neurosurgical intervention. SRS offers the additional ability to treat tumors with relative sparing of normal brain tissue in a single-fraction.

Study Selection Criteria
Methodologically credible studies were selected for all SRS indications within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Systematic Reviews
Garsa et al (2021) conducted a systematic review of available evidence comparing WBRT and SRS alone or in combination, as initial or postoperative treatment, with or without systemic therapy for adults with brain metastases due to lung cancer, breast cancer, or melanoma.[68,] Despite the identification of 97 studies, statistical analyses were limited due to heterogeneity across the available data. Based on pooled data from 4 RCTs, there was no statistically significant difference in OS when comparing SRS plus WBRT to SRS alone or to WBRT alone (HR, 1.09; 95% CI, 0.69 to 1.73). Based on pooled data from 3 RCTs, OS did not differ when comparing postsurgical WBRT to postsurgical SRS (HR, 1.17; 95% CI, 0.61 to 2.25). Lastly, pooled data from 4 RCTs did not show a significant difference in the risk of serious adverse events with WBRT plus SRS versus WBRT or SRS alone (RR, 1.05; 95% CI, 0.12 to 8.89).

Liu et al (2020) conducted a systematic review to compare SRS to surgical resection in the initial treatment of brain metastases.[69,] The review included 20 studies (18 retrospective cohorts; 2 RCTs) involving 1809 patients. Results revealed that SRS and surgical resection were comparable with regard to local control (HR, 1.02; 95% CI, 0.64 to 1.64; p=.92), distant intracranial control (HR, 0.78; 95% CI, 0.38 to 1.60; p=.49), and OS (HR, 0.91; 95% CI, 0.65 to 1.27; p=.57) in patients with single or solitary brain metastases. However, the authors noted that a prospective RCT with a larger patient population and a longer follow-up is necessary to confirm their findings.

Roos (2011) conducted a systematic review to examine the evidence for treating brain metastases.[70,] PubMed, EMBASE, and Cochrane databases were searched for published articles and abstracts on relevant randomized trials; 14 randomized trials were identified: 11 final reports and 3

abstracts, investigating various combinations of surgery, SRS, and WBRT. Most trials had significant limitations. Surgery and SRS improved local control, maintenance of performance status, and survival for favorable prognosis patients with solitary brain metastases relative to WBRT alone, although the absolute survival benefit for the majority was modest. Limited evidence suggests similar outcomes from surgery and SRS, but few patients were truly suitable for both options. For multiple (2 to 4) brain metastases, SRS improved local control and functional outcome but not survival. Adjuvant WBRT also improved intracranial control but not survival; the neurocognitive risk-benefit ratio of WBRT was controversial. The QOL data were limited.

Park et al (2011) reviewed the use of SRS for brain metastases and discussed 2 randomized trials demonstrating that the addition of single-dose SRS to WBRT improves local tumor control and maintenance of functional status for patients.[71,] Also reviewed were 3 randomized trials comparing the outcomes for SRS alone with SRS plus WBRT for limited brain metastases. All 3 trials indicated a lack of detriment in neurocognition or QOL with the omission of WBRT, despite significantly worsened intracranial tumor control that would require additional salvage therapy in almost all patients.

A Cochrane review by Patil et al (2010) addressed the role of SRS and WBRT in patients with few metastatic lesions (generally ≤3 or 4 lesions) and, recommended, given the unclear risk of bias in the included studies, interpreting the results cautiously.[72,] 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 local control were significantly better in the SRS plus WBRT group. This Cochrane review was updated by Patil et al (2012).[73,] No new studies were identified that met the inclusion criteria. Thus, the original findings were confirmed. In 2017, Patil et al updated this review with 1 new study; however, this study was not included in the meta-analysis due to lack of data from the original trial team and the conclusions were not changed.[74,]

Randomized Controlled Trials

Chang et al (2009) conducted an RCT and concluded that patients treated with SRS plus WBRT were at a greater risk of a significant decline in learning and memory function by 4 months than the group that received SRS alone.[75,]

Hartgerink et al (2021) conducted an RCT comparing WBRT to SRS in Dutch patients with 4 to 10 brain metastases.[76,] The study was prematurely stopped due to poor accrual, but prior to that, 15 patients were randomized to receive SRS and 14 patients to WBRT. The median number of lesions was 6 (range, 4 to 9). Results demonstrated a 1-year actutimes survival rate of 57% with SRS and 31% with WBRT (p=.52). The actutimes 1-year brain salvage-free survival rate was 50% with SRS and 78% with WBRT (p=.22). In a separate publication describing QOL outcomes in 20 patients 3 months post-treatment, SRS demonstrated favorable outcomes compared to WBRT for the following EuroQol- 5 Dimension domains: mobility (p=.041), self-care (p=.028), and alopecia (p=.014).[77,]

Some studies have suggested that the use of radiosurgery for brain metastases should be limited to patients with 3 or fewer lesions.

A randomized trial by Kondziolka et al (1999) compared WBRT with WBRT plus radiosurgery boost to metastatic foci.[78,] Results suggested that the significant advantage of radiosurgery boost over WBRT alone in terms of freedom from local failure did not differ among patients with 2, 3, or 4 metastases. Survival also did not depend on the number of metastases. As the number of metastases rises, so does the total volume of tissue receiving high-dose radiation; thus, the morbidity risk of radiation necrosis associated with radiosurgery is likely to increase. For a large number of metastases, and for large volumes of tissue, this risk may be high enough to negate the advantage of radiosurgery plus WBRT over WBRT alone seen in patients with 4 or fewer metastases. SRS centers commonly exclude patients with more than 5 metastases from undergoing radiosurgery.[79,80,] It is difficult to identify a

specific limit on the number of metastases for which SRS is advantageous. A large number of very small metastases may respond to radiosurgery, as well as a small number of larger metastases.

Aoyama et al (2006) reported on a randomized trial of SRS plus WBRT versus SRS alone for treatment of patients with 1 to 4 brain metastases.[81,] They found a 12-month intracranial tumor recurrence rate of 46.8% in the SRS plus WBRT group compared with 76.4% in the group that only received SRS. However, median survival times did not differ at 7.5 and 8.0 months, respectively. They also found no differences in neurologic functional preservation.

Nonrandomized Observational Studies

Tian et al (2013) reported on results from a retrospective, single-institution cohort study comparing neurosurgical resection with SRS for solitary brain metastases from non-small cell lung cancer (NSCLC).[82,] 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 continue to evaluate the use of SRS without WBRT for the management of brain metastases and the role of SRS for the management of larger numbers of brain metastases.

Yamamoto et al (2014) conducted a prospective observational study to evaluate primary SRS in patients with 1 to 10 newly diagnosed brain metastases.[83,] Inclusion criteria were the 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 KPS score of 70 or higher. Among 1194 patients, the median OS after SRS was 13.9 months (95% CI, 12.0 to 15.6) in the 455 patients with 1 tumor, 10.8 months (95% CI, 9.4 to 12.4) in the 531 patients with 2 to 4 tumors, and 10.8 months (95% CI, 9.1 to 12.7) in the 208 patients with 5 to 10 tumors.

Yomo and Hayashi (2014) reported on outcomes for 41 consecutive patients with 10 or fewer brain metastases from NSCLC who received SRS as primary treatment.[84,] The study reported 1- and 2-year OS rates of 44% and 17%, respectively, with a median survival time of 8.1 months. Distant brain metastases occurred in 44% by 1 year, with 18 patients requiring repeat SRS, 7 requiring WBRT, and 1 requiring microsurgery.

Rava et al (2013), in a cohort study including 53 patients with at least 10 brain metastases, assessed the feasibility of SRS treatment.[85,] Median survival was 6.5 months in this cohort.

Raldow et al (2013), in a cohort of 103 patients with at least 5 brain metastases treated with SRS alone, reported a median OS of 8.3 months, compared with historical controls.[86,] OS was similar for patients with 5 to 9 (7.6 months) and with at least 10 (8.3 months) metastases.

Section Summary: Brain Metastases

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

Stereotactic Radiosurgery for Uveal Melanoma

Clinical Context and Therapy Purpose

The purpose of SRS is to use a focused radiotherapy technique to treat certain malignant tumors that are relatively inaccessible surgically and that are often located near eloquent or radiosensitive areas.

The following PICO was used to select literature to inform this review.

Populations
The population of interest is individuals with uveal melanoma. Melanoma of the uvea (choroid, ciliary body, and iris) is the most common, primary, malignant, intraocular tumor in adults. Uveal melanoma is diagnosed mostly at older ages, with a progressively rising, age-specific, incidence rate that peaks near the age of 70 years.

Uveal melanomas can arise in the anterior (iris) or the posterior (ciliary body or choroid) uveal tract. Melanomas of the posterior uveal tract generally have a more malignant, histologic appearance; are detected later; and metastasize more frequently than iris melanomas.

A number of factors influence prognosis. The most important factors include the following: cell type, tumor size, location of the anterior margin of the tumor, degree of ciliary body involvement, presence of secondary glaucoma and extraocular extension. Extraocular extension, recurrence, and metastasis are associated with an extremely poor prognosis, and long-term survival is limited. The 5-year mortality rate associated with metastasis from the ciliary body or choroidal melanoma is approximately 30%, compared with a rate of 2% to 3% for iris melanomas.

Interventions
The therapy being considered is SRS as an alternative to enucleation of the eye.

Comparators
The following therapies are currently being used to treat uveal melanoma: established treatment modalities include enucleation, local resection, brachytherapy, and proton beam radiotherapy. Photodynamic therapy with verteporfin has also been used as a primary treatment for choroidal melanoma.

Outcomes
The outcomes of interest are OS, symptom improvement, and treatment-related morbidity. The main objectives of treating the tumor are 2-fold: (1) to reduce the risk of metastatic spread; and (2) to salvage the eye with useful vision (if feasible). Treatment selection depends on tumor size and location, associated ocular findings, the status of the other eye, as well as other individual factors, including age, life expectancy, QOL, concurrent systemic diseases, and patient expectations. SRS may be used as an alternative to enucleation of the eye.

Study Selection Criteria
Methodologically credible studies were selected for all SRS indications within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Systematic Review
Parker et al (2020) conducted a systematic review of 52 studies (mainly retrospective case series) including 1010 patients with uveal melanoma and 34 patients with metastases to the eye; meta-analysis was performed on 28 of those studies evaluating outcomes in patients with uveal melanomas and metastases treated with Gamma Knife radiosurgery.[87,] Doses of SRS ranged from 16 to 59 Gy (median dose 32 Gy). Pooled data from 19 studies (n=898) showed that 96% of patients treated with SRS had local tumor control (95% CI, 94% to 97%; I^2, 16%; p=.26) and 81% of patients from 16 studies (n=478) showed evidence of tumor regression (95% CI, 70% to 90%; I^2, 83%; p<.0001).

The most common adverse effects reported included glaucoma, radiation retinopathy, and vitreous hemorrhage. Since only 4 studies reported on SRS-induced complications, the ratio of the highest number of any reported complication from each of those studies was used to estimate the expected likelihood of radiation-induced complications overall; with this method, the authors estimated that 7% of patients would require enucleations due to treatment failure (95% CI, 4% to 12%; I^2, 66%; p=.0017). Pooled data showed an OS of 92.4% (95% CI, 79.9% to 99.5%; I^2, 92%, p<.0001) at 3 years and 76.3% (95% CI, 65.7% to 85.5%; I^2, 76%, p=.0004) at 5 years after SRS.

Case Series

The literature on the use of SRS for uveal melanoma consists of case series; no studies directly comparing SRS with other accepted radiation modalities used to treat uveal melanoma (e.g., brachytherapy, proton beam) were identified.

Guleser et al (2022) retrospectively evaluated patients with uveal melanoma who were treated with either brachytherapy (n=201) or Gamma knife radiosurgery (n=52) at a single center in Turkey.[88,] The median follow-up time was 45 months for the brachytherapy group and 56 months for the SRS group. The OS at 5 years was 88% and 89% for patients in the SRS and brachytherapy groups, respectively. Local recurrence occurred in 13% of patients in the SRS group and in 7% of patients in the brachytherapy group (p=.13). Eye retention was more likely with brachytherapy compared to SRS (95% vs 81%; p<.001) and vision loss was more likely with SRS compared to brachytherapy (60% vs 44%; p=.048).

Eibl-Lindner et al (2016) reported on a prospective case-control study conducted at a single ophthalmic specialty institution using frameless, single-session, image-guided robotic radiosurgery.[89,] Of the 242 patients, 217 were included in the analysis (25 were excluded because of short follow-up). Radiosurgery was indicated either because the size and location of the tumor were not amenable for brachytherapy or because the patient wanted to avoid primary enucleation. Two patients had undergone prior unsuccessful brachytherapy for the targeted lesion. Mean follow-up was 29.6 months (range, 5.9 to 84.0 months; median, 26.4 months). Sixty-seven (30.6%) patients were followed for at least 3 years after treatment. Actutimes eye retention was 86.7% (95% CI, 79.9 to 91.3) at 3 years and 73.0% (95% CI, 58.1 to 83.3) at 5 years. Radiation-induced retinopathy was observed in 29 patients at the end of follow-up and treatment-induced glaucoma developed in 33 patients at a median time of 20.8 months (range, 5.8 to 54.0 months) after treatment.

Furdova et al (2014) reported on outcomes for a cohort of 96 patients who underwent SRS at a single center in Slovakia for stage T2 or T3 uveal melanoma.[90,] Local tumor control occurred in 95% of patients at a 3-year follow-up and in 85% of patients at a 5-year follow-up. Eleven (11.5%) patients required secondary enucleation between 3- and 5-years post-SRS, due to radiation neuropathy or secondary glaucoma.

Zehetmayer (2012) reviewed the literature on the use of SRS for uveal melanoma, with long-term tumor control rates using the Gamma Knife reported to be around 90%.[91,] Initial studies using SRS for uveal melanoma reported secondary adverse events from radiation to be common; however, more recent studies have reported lower incidences with lower total radiation doses.

Dunavoelgyi et al (2011) reported on a 10-year study of 212 patients with choroidal melanoma, who were not suitable for brachytherapy or resection.[92,] Patients in the study received different doses of radiation, ranging from 50 to 70 Gy, in 5 fractions over 7 days. Ophthalmologic examination was performed at baseline and every 3 months in the first 2 years, every 6 months until 5 years, and once annually to 10 years after SRS. The study measured tumor dimension and height using standardized methods, assessed visual acuity, and included routine ophthalmologic examinations. Local tumor control was 96% at 5 years and 93% at 10 years. Thirty-two patients developed metastases, 22 of whom died during the follow-up period. Median visual acuity decreased from 0.55 at baseline to hand motion (p<.001). The authors concluded that SRS was sufficient to achieve excellent local tumor

control in patients with melanoma of the choroid and that disease outcome and vision were comparable to that achieved with proton beam radiotherapy.

Additional case series using SRS to treat uveal melanoma have suggested that SRS is a possible eye-sparing option for patients, with outcomes comparable to enucleation or other radiation modalities.[93,94,95,]

Section Summary: Uveal Melanoma

The evidence for the use of SRS to treat uveal melanoma is limited to a meta-analysis of case series and individual case series. While a meta-analysis suggests that SRS may lead to local tumor control and tumor regression, the condition is rare with poor clinical outcomes and treatment options. There are currently no active clinical trials to evaluate SRS to treat uveal melanoma and, therefore, there are limited prospects for accumulating additional high-quality data.

Stereotactic Body Radiotherapy
Primary and Metastatic Spinal Tumors

Clinical Context and Therapy Purpose

The purpose of SBRT is to use a focused radiotherapy technique to treat certain primary and metastatic extracranial tumors that are relatively inaccessible surgically and that are often located in proximity to radiosensitive organs at risk.

The following PICO was used to select literature to inform this review.

Populations

The population of interest is individuals with primary and metastatic spinal or vertebral tumors.

Interventions

The therapy being considered is SBRT as an alternative to open surgical intervention, other forms of radiation therapy, or as an adjunct to systemic therapy.

Comparators

The following therapies are currently being used to treat primary and metastatic spinal and vertebral tumors: other forms of radiation therapy, surgical interventions, and/or continued systemic medical therapy.

Outcomes

The outcomes of interest are OS, PFS, disease-free survival (DFS), symptom improvement, and treatment-related morbidity. Follow-up of weeks to months is required to determine the effect of SBRT on local toxicity and months to years to determine the effect on tumor control.

Study Selection Criteria

Methodologically credible studies were selected for all SBRT indications within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Spinal Tumors

Systematic Review
Wong et al (2024) compared SBRT and EBRT in a meta-analysis of 3 RCTs (N=642).[96,] Overall pain response at 3 months was similar between groups (risk ratio, 1.12; 95% CI, 0.74 to 1.70; p=.59). In the 2 studies evaluating complete pain response at 3 months, SBRT was superior to EBRT (risk ratio, 2.52; 95% CI, 1.58 to 4.01; p<.0001). Complete pain response with SBRT was also superior at 6 months (risk ratio, 2.48; 95% CI, 1.23 to 4.99; p=.01). Local progression and overall survival were similar between groups.

A systematic review by Guninski et al (2024) identified a total of 69 studies (14 prospective) evaluating SBRT for spinal metastases.[97,] Data on re-irradiation was excluded from analysis. A total of 5736 patients were analyzed with an overall pain response rate of 83% and a complete pain response of 36%; however, heterogeneity was high (I^2=86% to 93%). Adverse events were low with a pooled vertebral fracture rate of 9%, myelopathy rate of 0%, and a pain flare rate of 6%.

Randomized Controlled Trials
Sahgal et al (2021) compared complete response rates for pain after SBRT (n=114) or EBRT (n=115) in patients with painful spinal metastasis enrolled in an open-label, multicenter, RCT performed at 13 hospitals in Canada and 5 in Australia.[98,] Patients were eligible if they had painful (defined as ≥2 points with the Brief Pain Inventory) MRI-confirmed spinal metastasis, ≤3 consecutive vertebral segments to be included in the treatment volume, an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤2, and no neurologically symptomatic spinal cord or cauda equina compression. The primary endpoint was the proportion of patients with complete response for pain at 3 months after radiotherapy. At baseline, approximately 75% of enrolled patients were radio-sensitive and 25% were radioresistant. Results demonstrated that significantly more patients who received SBRT compared to EBRT achieved the primary endpoint (35% vs 14%; risk ratio, 1.33; 95% CI, 1.14 to 1.55; p=.0002).

Ryu et al (2023) randomized patients to SRS or ERBT in a 2:1 ratio.[99,] The primary end point was pain response at 3 months as defined by a 3-point improvement on the Numerical Rating Pain Scale. Pain response was significantly greater with EBRT than SRS (60.5% vs 41.3%; difference, -19%; 95% CI, -32.9 to -5.5; p=.01). However, the mean change from baseline in pain scores at the index site was similar between groups (-2.98 with SRS and -3.83 with EBRT; p=.07). By 12 months, pain response was similar between groups (57.6% vs 55.3%; p=.49). Survival rates at 12 and 24 months were 44.3% and 31.5% with SRS, and 53.1% and 31.5% for EBRT (HR, 0.91; 95% CI, 0.69 to 1.20; p=.51), Adverse events were similar between groups.

Guckenberger et al (2024) conducted a randomized, controlled phase 3 trial aimed to determine if dose-intensified stereotactic body radiotherapy (SBRT) for painful vertebral metastases results in increased pain improvement compared to conventional external beam radiotherapy (cEBRT) six months after treatment.[100,] Patients aged 18 or older with one or two painful vertebral metastases and a life expectancy of at least one year were included (N=63). Patients received either SBRT (48.5 Gy in 10 fractions or 40 Gy in five fractions) or cEBRT (30 Gy in 10 fractions or 20 Gy in five fractions). The primary endpoint was a pain score improvement of at least 2 points on a visual analog scale at six months. Out of 214 screened patients, 63 were randomized 1:1 between SBRT and cEBRT. The intention-to-treat analysis showed a higher proportion of patients with pain reduction in the SBRT group compared to the control group (69.4% versus 41.9%, p=.02). There were no significant differences in opioid intake, vertebral compression fractures, or adverse events between the groups. The study concluded that dose-intensified SBRT improved pain scores more effectively than cEBRT at six months. However, the trial was terminated early due to slow accrual and therefore was underpowered.

Nonrandomized Observational Studies

Ito et al (2022) reported on the outcomes for 33 patients with metastatic epidural spinal cord compression who underwent separation surgery and SBRT and were followed prospectively for a median duration of 15 months (range, 3 to 35 months).[101,] Approximately 25% of enrolled patients were treated with radiotherapy in the past. The 1-year local failure rate was 13% (95% CI, 4 to 27) and the 1-year OS rate was 79%. Complete or partial pain response at 1, 3, 6, 9, and 12 months was 82%, 92%, 80%, 74%, and 83%, respectively.

Gerszten et al (2014) reported on the outcomes for 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.[102,] Most patients were treated for pain control and also had prior EBRT. The authors pointed out that radiotherapy of the spinal cord is limited by its low tolerance and that, if a radiation dose could be targeted more accurately at the lesions, higher doses could be delivered in a single fraction. They further pointed out that conventional methods for delivering intensity-modulated radiotherapy (IMRT) are limited due to a 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 10 to 20 fractions. In contrast, in this study, only 1 CyberKnife treatment was given.

In a study, Degen et al (2005) reported on the outcomes of 51 patients with 72 spinal lesions who were treated with the CyberKnife.[103,] Patients underwent a median of 3 treatments. Patients reported reductions in pain as measured on the visual analog scale; QOL was maintained during the 1-year study period.

Sahgal et al (2013) evaluated rates of vertebral compression fractures after SBRT in 252 patients with 410 spinal segments treated with SBRT.[104,] Fifty-seven (13.9% of spinal segments treated) fractures were observed, with 27 de novo fractures and 30 cases of existing fracture progression. Most fractures occurred relatively early posttreatment, with a median and mean time to fracture of 2.46 months and 6.33 months, respectively. Radiation dose per fraction, baseline vertebral compression fracture, lytic tumor, and baseline spinal misalignment were predictive of fracture risk.

Gerszten et al (2007) published the results of a series of 500 cases from a single-institution (334 tumors had previously undergone EBRT) using the CyberKnife system.[105,] In this series, the maximum intratumoral dose ranged from 12.5 to 25 Gy (mean, 20 Gy). Long-term pain improved in 290 (86%) of 336 cases. Long-term radiographic tumor control was demonstrated in 90% of lesions treated with radiosurgery as a primary treatment modality. Twenty-seven (84%) of 32 cases with a progressive neurologic deficit prior to treatment experienced at least some clinical improvement.

Chang et al (2007) reported on phase 1/2 results of SBRT used to treat 74 spinal lesions in 63 (55% had prior irradiation) patients with cancer.[106,] The actutimes 1-year tumor progression-free incidence was 84%. Pattern-of-failure analysis showed 2 primary mechanisms of failure: recurrence in the bone adjacent to the site of previous treatment and recurrence in the epidural space adjacent to the spinal cord. The authors concluded that data analysis supported the safety and effectiveness of SBRT in cases of metastatic spinal tumors. The authors added that it would be prudent to routinely treat the pedicles and posterior elements using a wide bone margin posterior to the diseased vertebrae because of the possible direct extension into these structures and for patients without a history of radiotherapy, to use more liberal spinal cord dose constraints than those they used.

Section Summary: Spinal Tumors

SBRT has been shown to improve outcomes (reduce pain) in patients with spinal (vertebral) tumors in numerous observational trials and systematic reviews. Two large RCTs comparing CBRT and SBRT have shown inconsistent pain findings at 3 months with 1 trial favoring SBRT and another favoring EBRT. For individuals with primary and metastatic spinal or vertebral body tumors who have received prior radiotherapy who are treated with SBRT, the observational literature primarily addresses

metastases that recur after prior radiotherapy. Repeat administration of conventional radiation therapy increases the risk of treatment-related myelopathies. Nonrandomized study results are sufficient to determine that SBRT improves outcomes (reduces pain) in patients with spinal (vertebral) tumors.

Non-Small Cell Lung Cancer

Clinical Context and Therapy Purpose

The purpose of SBRT is to use a focused radiotherapy technique to treat certain primary and metastatic extracranial tumors that are relatively inaccessible surgically and that are often located in proximity to radiosensitive organs at risk.

The following PICO was used to select literature to inform this review.

Populations

The population of interest is individuals with stage T1 or T2A NSCLC who are not candidates for surgical resection.

Interventions

The therapy being considered is SBRT as an alternative to open surgical intervention, other forms of radiation therapy, or as an adjunct to systemic therapy.

Comparators

The following therapies are currently being used to treat primary and metastatic NSCLC: other forms of radiation therapy, surgical interventions, and/or continued systemic medical therapy.

Outcomes

The outcomes of interest are OS, PFS, DFS, symptom improvement, and treatment-related morbidity. Follow-up of weeks to months is required to determine the effect of SBRT on local toxicity and months to years to determine the effect on tumor control.

Study Selection Criteria

Methodologically credible studies were selected for all SBRT indications within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Inoperable Non-Small Cell Lung Cancer

Systematic Reviews

Zhang et al (2021) published a systematic review of 87 studies involving SBRT (n=12,811) and 18 studies involving RFA (n=1,535) for patients with inoperable stage I NSCLC.[107,] The local control rates with SBRT were 98%, 95%, 92%, and 92%, respectively, at 1, 2, 3, and 5 years; the local control rates for RFA were significantly lower (75%, 31%, 67%, and 41%, respectively, at 1, 2, 3, and 5 years; p<.01 for all comparisons). The OS rates were similar between SBRT and RFA at 1 year (87% vs 89%, respectively; p=.07) and 2 years (71% vs 69%, respectively; p=.42), whereas the OS was significantly improved with SBRT over RFA at 3 years (58% vs 48%; p<.01) and 5 years (39% vs 21%; p<.01). The most common complication of SBRT was radiation pneumonitis (9.1%), whereas pneumothorax was the most common complication of RFA (27.2%).

Li et al (2020) evaluated the efficacy and safety of SBRT versus conventional radiotherapy in inoperable stage I NSCLC via a meta-analysis of 17 articles involving 17973 patients.[108,] Results revealed that SBRT was associated with significantly improved OS (HR, 0.66; 95% CI, 0.62 to 0.70; p<.00001), lung cancer-specific survival (HR, 0.42; 95% CI, 0.35 to 0.50; p<.00001), and PFS (HR, 0.34; 95% CI, 0.25 to 0.48; p<.00001). SBRT was also associated with improved 4-year OS, 4-year lung cancer-specific survival, 3-year local control, and 5-year PFS rates as compared to conventional radiotherapy. A significantly reduced risk of dyspnea (RR, 0.77; 95% CI, 0.62 to 0.97; p=.02), radiation pneumonitis (RR, 0.52; 95% CI, 0.32 to 0,84; p=.0007), and esophagitis (RR, 0.30; 95% CI, 0.12 to 0.74; p=.009) was seen with SBRT versus conventional radiotherapy. The authors noted that several limitations existed in the meta-analysis including the potential for language bias, heterogeneity in the quality of included studies, and the types and treatment doses of conventional radiotherapy utilized in includes studies was quite diverse.

Solda et al (2013) assessed the efficacy of stereotactic ablative radiotherapy (SABR) versus surgery for the treatment of NSCLC in a systematic review of all relevant publications from 2006 to 2013.[109,] Data were analyzed from studies of 20 or more stage I NSCLC patients treated with SABR and a median follow-up of 1 year (minimum). The data were compared with the outcome of surgery obtained from a matched control population from the International Association for the Study of Lung Cancer database. Forty-five reports containing 3771 patients treated with SABR for NSCLC were identified that fulfilled the selection criteria; both survival and staging data were reported in 3171 patients. The 2-year survival rate of the 3201 patients with localized stage I NSCLC treated with SABR was 70% (95% CI, 67% to 72%), with a 2-year local control rate of 91% (95% CI, 90% to 93%). This was compared with a 68% (95% CI, 66% to 70%) 2-year survival rate for 2038 stage I NSCLC patients treated with surgery. There was no survival or local PFS difference with different radiotherapy technologies used for SABR. The reviewer concluded that selection bias could not be assessed from the published reports and treatment-related morbidity data was limited.

Randomized Controlled Trials

Swaminath et al (2024) conducted a phase 3 randomized clinical trial (RCT) aimed to compare the effectiveness of stereotactic body radiotherapy (SBRT) with hypofractionated conventional radiotherapy (CRT) in stage I medically inoperable non-small cell lung cancer (NSCLC) (N=233).[110,] Patients were randomized 2:1 to receive either SBRT (n=154) or CRT (n=79). The primary objective was to assess local control (LC) at 3 years, with secondary outcomes including event-free survival, overall survival, and toxic effects. The 3-year LC was 87.6% (95% CI: 81.9% to 93.4%) for SBRT and 81.2% (95% CI: 71.9% to 90.5%) for CRT, with a hazard ratio (HR) of 0.61 (95% CI: 0.31 to 1.20; p=.15). The HR for event-free survival was 1.02 (95% CI: 0.72 to 1.45; p=.87) and for overall survival was 1.18 (95% CI: 0.80 to 1.76; p=.40). Among those randomized to SBRT, late grade 3 or 4 toxic effects occurred in 5 of 45 (11%) with central NSCLC and 2 of 109 (1.8%) with peripheral NSCLC; and among those randomized to CRT, occurred in 1 of 19 (5%) with central NSCLC and 1 of 60 (2%) with peripheral NSCLC. One patient who received SBRT for an ultracentral lesion experienced a possible treatment-related grade 5 event (hemoptysis). The authors concluded that there was no significant difference in LC between SBRT and CRT, but further research is needed to determine the effectiveness of SBRT for peripheral and central NSCLC.

Nonrandomized Comparative Studies

Harkenrider et al (2014) reported on outcomes after SBRT for 34 patients with unbiopsied lung cancer, with estimated rates of 2-year regional control, distant control, and OS of 80%, 85%, and 85%, respectively.[111,]

In a prospective evaluation of 185 medically inoperable patients with early (T1-T2N0M0) NSCLC treated with SBRT, Allibhai et al (2013) evaluated the influence of tumor size on outcomes.[112,] 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=.011) and distant failure

(p=.021). Poorer OS (p=.001), DFS (p=.001), and cause-specific survival (p=.005) were significantly associated with tumor volume.

Hof et al (2007) reported on outcomes (median follow-up, 15 months) for 42 patients with stages I and II lung cancer who were not suitable for surgery and who were treated with SBRT.[113,] In this series, at 12 months, the OS rate was 75%, and the DFS rate was 70%. Better local control was noted with higher doses of radiation.

Noncomparative Studies

The Radiation Therapy Oncology Group (RTOG) 0236 trial was a phase 2 North American multicenter, cooperative group study (2010) to assess SBRT in treating medically inoperable patients with early-stage NSCLC. Patients had biopsy-proven peripheral T1-T2N0M0 non-small cell tumors less than 5 cm in diameter and medical conditions precluding surgical treatment. The prescription dose was 18 Gy per fraction given in 3 fractions (54 Gy total) delivered over 1.5 to 2 weeks. The study opened in 2004 and closed in 2006; data were analyzed through August 2009.[114,]

The 3-year results were reported. The primary endpoint was primary tumor control, with OS, DFS, adverse events, involved lobe, regional, and disseminated recurrence as secondary endpoints. Prior to enrollment, the "operability" of patients was evaluated by an experienced thoracic surgeon or pulmonologist. Standard indicators defining a patient to be "medically inoperable" included baseline forced expiratory volume in 1 second (FEV_1) less than 40% predicted, carbon monoxide diffusing capacity less than 40% predicted, baseline hypoxemia or hypercapnia, pulmonary hypertension, diabetes with end-organ damage, and/or severe cardiovascular or peripheral vascular disease.

Fifty-nine patients accrued, of which 55 were evaluable (44 T1 and 11 T2 tumors) with a median follow-up of 34.4 months (range, 4.8 to 49.9 months). Only 1 patient had a primary tumor failure; the estimated 3-year primary tumor control rate was 97.6% (95% CI, 84.3% to 99.7%). Three patients had a recurrence within the involved lobe; the 3-year primary tumor and involved lobe (local) control rate was 90.6% (95% CI, 76.0% to 96.5%). Two patients experienced regional failure; the locoregional control rate was 87.2% (95% CI, 71.0% to 94.7%). Eleven patients experienced disseminated recurrence; the 3-year rate of disseminated failure was 22.1% (95% CI, 12.3% to 37.8%). The rates of DFS and OS at 3 years were 48.3% (95% CI, 34.4% to 60.8%) and 55.8% (95% CI, 41.6% to 67.9%), respectively. The median OS was 48.1 months (95% CI, 29.6% to not reached).

Stanic et al (2014) reported an additional analysis of pulmonary toxicity in RTOG 0236 participants.[115,] During 2-year follow-up, pulmonary function test results were collected. Mean percentage of predicted FEV_1 and diffusing capacity for carbon monoxide (DL_{CO}) declined by 5.8% and 6.3%, respectively. There was no significant decline in oxygen saturation. Baseline pulmonary function testing was not predictive of any pulmonary toxicity following SBRT. Whole lung V5, V10, V20 and mean dose to the whole lung were almost identical between patients who developed pneumonitis and patients who were pneumonitis-free. Poor baseline pulmonary function testing did not predict decreased OS. Patients with poor baseline pulmonary function testing as a reason for medical inoperability had a higher median and OS than patients with normal baseline pulmonary function testing but with cardiac morbidity.

Timmerman et al (2007) evaluated the toxicity and efficacy of SBRT in high-risk patients with early-stage (but medically inoperable) lung cancer.[116,] In a phase 2 North American multicenter study of patients aged 18 years or older with biopsy-proven peripheral T1-T2N0M0 non-small-cell tumors (<5 cm in diameter) and medical conditions precluding surgical treatment. The prescription dose was 18 Gy in 3 fractions (54 Gy total), with the entire treatment lasting between 1.5 and 2 weeks. The primary endpoint was 2-year actutimes primary tumor control; secondary endpoints were DFS (i.e., 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 to 49.9 months). Only 1 patient had

primary tumor failure; the estimated 3-year primary tumor control rate was 97.6% (95% CI, 84.3% to 99.7%). Three patients had a recurrence within the involved lobe; the 3-year primary tumor and involved lobe (local) control rate was 90.6% (95% CI, 76.0% to 96.5%). Two patients experienced regional failure; the locoregional control rate was 87.2% (95% CI, 71.0% to 94.7%). Eleven patients experienced disseminated recurrence; the 3-year rate of disseminated failure was 22.1% (95% CI, 12.3% to 37.8%). The rates for DFS and OS at 3 years were 48.3% (95% CI, 34.4% to 60.8%) and 55.8% (95% CI, 41.6% to 67.9%), respectively. The median OS was 48.1 months (95% CI, 29.6 months to not reached). Protocol-specified treatment-related grade 3 adverse events were reported in 7 (12.7%) patients; grade 4 adverse events were reported in 2 (3.6%) patients. No grade 5 adverse events were reported. The authors concluded that patients with inoperable NSCLC who received SBRT had a survival rate of 55.8% at 3 years, high rates of local tumor control, and moderate treatment-related morbidity.

Operable Non-Small Cell Lung Cancer

Systematic Reviews

Ijsseldijk et al (2020) conducted a systematic review and meta-analysis comparing oncologic outcomes of surgery versus SBRT for patients with stage I NSCLC.[117,] The analysis included a total of 100 studies. Results revealed that long-term OS and DFS after lobar resection was better than SBRT in all comparisons, and for the majority of comparisons, sublobar resection was better than SBRT. Included studies were heterogeneous and of low quality; however, results remained essentially unchanged after many stratifications and sensitivity analyses.

Zheng et al (2014) 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.[118,] Reviewers included 40 studies reporting outcomes from SBRT, including 4850 patients; 23 studies reported outcomes after surgery published in the same time period, including 7071 patients. For patients treated with SBRT, the mean unadjusted OS rates at 1, 3, and 5 years were 83.4%, 56.6%, and 41.2%, respectively. Mean unadjusted OS rates at 1, 3, and 5 years were 92.5%, 77.9%, and 66.1%, respectively, with lobectomy, and 93.2%, 80.7%, and 71.7%, with limited lung resections. After adjustment for surgical eligibility (for the 27 SBRT studies that reported surgical eligibility) and age, in a multivariable regression model, the treatment modality (SBRT vs surgical therapy) was not significantly associated with OS (p=.36).

Nguyen et al (2008) cite a number of studies of SBRT for early-stage lung cancer receiving a biologically equivalent dose of 100 Gy or more.[119,] Three studies reported 5-year survival that ranged from 30% to 83%; in the largest series of 257 patients, the 5-year survival was 42%. Koto et al (2007) reported on a phase 2 study of 31 patients with stage I NSCLC.[120,] Patients received 45 Gy in 3 fractions, but those with tumors close to an organ at risk received 60 Gy in 8 fractions. With a median follow-up of 32 months, the 3-year OS rate was 72%, while the DFS rate was 84%. Five patients developed grade 2 or greater pulmonary toxicity. While comparative studies were not identified, older studies have reported 3-year disease-specific survival rates of 49% for those with stage I disease.[121,]

Randomized Controlled Trials

Two RCTs were planned and initiated, the STARS and ROSEL trials, both of which were intended to compare SABR with surgery for operable early-stage NSCLC. However, both closed early due to slow enrollment. A pooled analysis of the available data from these 2 trials was published by Chang et al (2015).[122,] Fifty-eight patients were enrolled and randomized (31 to SABR, 27 to surgery), with a mean follow-up of 40.2 months. OS favored the SABR group, but there were wide CIs that crossed the threshold for statistical significance (HR, 0.14; 95% CI, 0.02 to 1.2). Complications were less in the SABR group. The rate of grade 3 or 4 adverse events was 10% in the SABR group compared with 44% in the surgery group (statistics not reported).

Nonrandomized Comparative Studies

Numerous nonrandomized, comparative studies have compared SBRT with surgery for NSCLC. A few of them used matching and are therefore the strongest methodologically of this group.

Two matched analyses used the Surveillance, Epidemiology, and End Results database to identify patients. Yu et al (2015) identified elderly patients with stage I NSCLC who received either SBRT or surgery from 2007 to 2009.[123,] Propensity matching was used to select 2 surgery patients for each SBRT patient. A total of 367 SBRT patients were matched with 711 surgery patients. Early mortality at 3 months was significantly better for the SBRT group compared with the surgery group (2.2% vs 6.1%, p=.005). However, late mortality at 24 months was significantly worse for the SBRT group (40.1%) compared with the surgery group (22.3%; p<.001). Across the 24-month follow-up, patients in the SBRT group had fewer complications (incidence rate ratio, 0.74; 95% CI, 0.64 to 0.87). A similar study was performed by Ezer et al (2015),[124,] and the 2 studies likely had overlapping populations. A total of 362 patients with stage I or II NSCLC and negative lymph nodes were matched with patients who received limited resection. There was no difference in OS for the SBRT patients compared with the surgery patients (HR, 1.19; 95% CI, 0.97 to 1.47). Complications were less common in patients undergoing SBRT (14% of total) compared with patients undergoing resection (28%; p<.001).

In a matched-cohort study design, Crabtree et al (2014) retrospectively compared outcomes between SBRT and surgical therapy in patients with stage I NSCLC.[125,] Four hundred fifty-eight patients underwent primary surgical resection, and 151 were treated with SBRT. Surgical and SBRT patients differed significantly on several baseline clinical and demographic characteristics, with SBRT patients having an older mean age, higher comorbidity scores, a greater proportion of peripheral tumors, and worse lung function at baseline. For the surgical group, 3-year OS and DFS rates were 78% and 72%, respectively. Of note, among the 458 patients with stage I lung cancer, 14.8% (68/458) were upstaged at surgery and found to have occult N1 or N2 disease. For patients with occult nodal disease, 3- and 5-year OS rates were 66% and 43%, respectively. For patients without occult nodal disease, 3- and 5-year OS rates were 80% and 68%, respectively. For the SBRT group, 3-year OS and DFS rates were 47% and 42%, respectively.

In a propensity score-matched analysis, 56 patients were matched based on clinical characteristics, including age, tumor size, Adult Co-Morbidity Evaluation score, FEV_1 percent, and tumor location (central versus peripheral). In the final matched comparison, 3-year OS was 52% for SBRT and 68% for surgery (p=.05), while DFS was 47% versus 65% (p=.01), respectively. Two-, 3-, 4-, and 5-year local recurrence-free survival rates were 91%, 91%, 81%, and 40% for SBRT, respectively, and 98%, 92%, 92%, and 92% for surgery (p=.07).

Port et al (2014) compared SBRT with wedge resection for patients with clinical stage IA NSCLC using data from a prospectively maintained database.[126,] 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=.016), but there were no differences between the groups in 3-year DFS rates (77% for wedge resection vs 59% for SBRT, p=.066).

Varlotto et al (2013) compared surgical therapy (132 with lobectomy, 48 with sublobar resection) with SBRT (n=137) in the treatment of stage I NSCLC.[127,] 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=.003) or lobectomy (p<0.000).

Section Summary: Non-Small Cell Lung Cancer

Although no direct comparative evidence is available, evidence suggests that survival rates may be similar for SBRT and surgical resection for patients with stage T1 and T2A NSCLC tumor (not >5 cm in

diameter) who show no nodal or distant disease and who are not candidates for surgical resection because of comorbid conditions. Additionally, SBRT was associated with improved survival and a reduced risk of adverse events as compared to conventional radiotherapy and RFA in inoperable NSCLC. In patients with operable stage I NSCLC, long-term OS and DFS were improved with lobar resection as compared to SBRT and, for the majority of comparisons, sublobar resection was better than SBRT.

Primary and Metastatic Hepatic Cancer
Hepatocellular Carcinoma

Clinical Context and Therapy Purpose
The purpose of SBRT is to use a focused radiotherapy technique to treat certain primary and metastatic extracranial tumors that are relatively inaccessible surgically and that are often located in proximity to radiosensitive organs at risk.

Surgical resection is the preferred treatment of hepatocellular carcinoma (HCC) although, at the time of diagnosis, less than 20% of patients are amenable to definitive surgical management due to advanced local disease or comorbidities. These patients may be candidates for local ablative therapies, including RFA and chemoembolization. Radiation may be considered as an alternative to local ablative/embolization therapies or if these therapies fail.

Radiation-induced liver disease is an important complication of radiotherapy and is secondary to endothelial injury and thrombotic sequelae. The disease typically occurs 4 to 8 weeks after completion of radiotherapy but has been described as early as 2 weeks and as late as 7 months post-radiation. It is a major factor that limits radiation dose escalation and reirradiation for tumors situated proximate to the liver. The whole-liver tolerance for radiotherapy with a 5% risk of radiation-induced liver disease had been reported at whole-liver doses of 30 to 35 Gy in 2 Gy per fraction.[128,129,

The use of SBRT for treatment of primary HCC has generally been directed toward locally advanced disease or metastatic lesions for which surgical resection or results with other liver-directed therapies would be suboptimal due to lesion size, number, or location. SBRT can deliver high doses of radiation in a smaller number of fractions than conventional radiotherapy and is associated with a high degree of accuracy for the lesion target delineation. The most common SBRT fractionation protocols are 3 fractions at 10 to 20 Gy, 4 to 6 fractions at 8 to 10 Gy, and 10 fractions at 5 to 5.5 Gy[130,] and each of the 8 different liver segments may exhibit different tolerances. Some reports have included patients with intrahepatic cholangiocarcinoma for which there are treatment options.

The following PICO was used to select literature to inform this review.

Populations
The population of interest is individuals with primary and metastatic HCC.

Interventions
The therapy being considered is SBRT as an alternative to open surgical intervention, other forms of radiation therapy, liver-directed therapies or as an adjunct to systemic therapy.

Comparators
The following therapies are currently being used to treat primary and metastatic HCC: other forms of radiation therapy, surgical interventions and/or continued systemic medical therapy.

Outcomes
The outcomes of interest are OS, PFS, DFS, symptom improvement, and treatment-related morbidity. Follow-up of weeks to months is required to determine the effect of SBRT on local toxicity and months to years to determine the effect on tumor control.

Study Selection Criteria

Methodologically credible studies were selected for all SBRT indications within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Shanker et al (2021) conducted a meta-analysis of 48 cohort studies (mainly retrospective) assessing the rates of OS and local control in 2846 patients with primary HCC.[131,] Comparisons to other treatment modalitles were not made. Pooled 1-, 2- and 3-year OS rates were 78.4%, 61.3%, and 48.3%, respectively. Rates of local control rates at 1-, 2- and 3-years were 91.1%, 86.7%, and 84.2%, respectively.

Long et al (2021) conducted a meta-analysis of 14 observational (mainly retrospective) studies assessing OS and local control in 1238 patients with small HCC confined to the liver who received SBRT.[132,] Pooled rates for OS were 93% (95% CI, 62% to 79%) at 1 year (10 studies) and 72% (95% CI, 62% to 79%) at 3 years (6 studies). Pooled rates for local control were 96% (95% CI, 91% to 98%) at 1 year (10 studies) and 91% (95% CI, 85% to 95%) at 3 years (6 studies). Significant heterogeneity among studies was found for all results. Pooled subgroup analyses revealed that hepatic disease classified with a Child-Pugh class A rating was predictive for improved OS (p=.0001). Pooled rates for hepatic complications and radiation-induced liver disease (grade 3 or higher for both) were 4.0% (95% CI, 2% to 8%) and 15% (95% CI, 8% to 22%), respectively.

Lee et al (2020) evaluated the efficacy of SBRT versus RFA for the treatment of liver malignancies via a meta-analysis of 11 studies involving 2238 patients.[133,] Of the 11 studies, 8 involved treating patients for early HCC and 3 for liver metastases. Results revealed that the pooled 2-year local control rate was significantly improved in the SBRT versus RFA arm (83.8% vs 71.8%; p=.024). The pooled 2-year control rate was also significantly higher in the SBRT versus RFA arm among patients in the liver metastases studies only (83.6% vs 60%; p<.001) while no such significant difference was seen in HCC studies (84.5% vs 79.5%; p=.431). Pooled analysis of OS in HCC studies showed an OR of 1.43 (95% CI, 1.05 to 1.95; p=.023), favoring RFA. Only 2 liver metastases studies had comparative survival data; no significant difference was seen.

A systematic review by Tao and Yang (2012) assessed the efficacy and safety of SBRT for treating primary and secondary hepatic neoplasms.[134,] Reviewers included prospective nonrandomized clinical trials published in English. Fifteen studies involving 158 patients with primary tumors and 341 patients with metastases to the liver were included between 2004 and 2011. Treatment was performed in 1 to 10 fractions to total doses of 18 to 60 Gy. Most studies included reported outcomes for patients with both primary (including primary cholangiocarcinoma) and metastatic disease, without separating the outcome data for primary tumors only. Most patients in the studies had metastatic tumors (n=341). In patients unable or unwilling to undergo surgical resection or other local therapy, SBRT was associated with 1-year local control rates ranging from 50% to 100%, and OS rates ranging from 33% to 100%.

Randomized Controlled Trials

Méndez Romero et al (2023) conducted an RCT comparing transarterial chemoembolization delivered with drug eluting beads (TACE-DEB) with SBRT in patients with HCC.[135,] Accrual was slow,

and the study was prematurely terminated after the enrollment of only 30 patients. No significant differences were found between groups in median time to progression (12 months with TACE-DEB and 19 months with SBRT; p=.15), median local control (12 months for TACE-DEB and >40 months for SBRT; p=.075), or median OS (36.8 months with TACE-DEB and 44.1 with SBRT; p=.36); however, the small sample size limits generalizability of these findings.

Nonrandomized Comparative Studies

SBRT has been used in conjunction with other liver-directed therapies for the treatment of locally advanced HCC; either as a planned adjunct or after incomplete ablation with the other treatment. All studies identified for review were retrospective reports.

Ji et al (2021) compared SBRT to RFA in 60 patients with unresectable HCC at a single center in Japan.[136,] There were 22 cases treated by SBRT and 38 cases by RFA. The complete remission rate at 3 months was similar in both SBRT and RFA groups (81.8% and 89.4%, respectively), as was the local tumor control rate (90.9% and 94.7%, respectively). The 1-year and 2-year rates of OS were 88.2% and 85.7% in the SBRT group and 100% and 75% in the RFA group, respectively; the differences between treatment groups did not reach statistical significance. Extrahepatic recurrence occurred in 6 patients in the SBRT group and no patients in the RFA group (p<.001).

Bettinger et al (2018)[137,] reported on a multi-center retrospective comparative study of SBRT (n=122) or sorafenib (n=901), a tyrosine kinase inhibitor (TKI), for the treatment of advanced HCC. Unadjusted median OS was 18.1 months (95% CI, 10.3 to 25.9) for SBRT and 8.8 (95% CI, 8.2 to 9.5) for sorafenib. Adjusted median OS was 17.0 months (95% CI, 10.8 to 23.2) and 9.6 (95% CI, 8.6 to 10.7), respectively. No survival benefit was observed for patients with SBRT in patients with portal vein thrombosis. Over 80% of patients were male in each study arm. Patients in the sorafenib group had significantly worse ECOG PS scores (p<.001), were more frequently pre-treated with RFA (p<.001) or transarterial chemo-embolization (TACE) (p=.016), had a higher incidence of multifocal disease and extrahepatic metastases (p<.001), and had more advanced illness on the basis of the Barcelona Clinic Liver Cancer staging system (Grade B, intermediate and Grade C, advanced; p<.001). Although propensity score matching was utilized to adjust for differences in baseline characteristics, the data are limited by extensive heterogeneity in the respective treatment populations. Presently, the U.S. Food and Drug Administration indication for the use of sorafenib is for patients with unresectable HCC. Due to the inclusion of patients who had previously been treated by surgery and with early or intermediate stage disease on the basis of Barcelona Clinic Liver Cancer criteria, it is unclear whether some patients were candidates for re-resection, potentially limiting the relevance of this study.

Wahl et al (2016) reported on a single U.S. site experience with 224 patients with nonmetastatic HCC accumulated between 2004 and 2012.[138,] RFA was used to treat 161 patients and 249 lesions with a freedom from local progression (FFLP) rate at 1 year of 83.6%, and 2 years of 80.2%. SBRT was used to treat 63 patients with 83 lesions with an FFLP rate at 1 year of 97.4%, and 2 years of 83.8%.

The effect of SBRT in conjunction with TACE was reported in 3 retrospective studies. Jacob et al (2015) evaluated HCC lesions 3 cm or more and compared TACE alone (n=124) with TACE plus SBRT (n=37) from 2008 to 2013.[139,] Sorafenib was used by 36.1% of the TACE alone group and 41.9% in the combination therapy group. Local recurrence was significantly decreased in the TACE plus SBRT group (10.8%) compared with the TACE-only group (25.8%) (CI, not reported, p=.04). After censoring for liver transplantation, OS was significantly increased in the TACE plus SBRT group (33 months) compared with the TACE-only group (20 months; CI, not reported, p=.02). Chronic hepatitis C virus infection was the cause of HCC in most patients in both groups.

Zhong et al (2014) reported on a single-site experience with 72 of 1086 HCC patients consecutively treated with SBRT between 2006 and 2012.[140,] These patients had lesions 10 cm or larger and incomplete ablation with prior TACE. The median total dose of 35.6 Gy was delivered over 12 to 14 days with a fractional dose of 2.6 to 3.0 Gy at 6 fractions per week. A complete response was

achieved in 6 patients (8.3%), partial response in 51 (70.8%), stable disease in 9 (12.5%), and progressive disease in 6 (8.3%) within a median follow-up of 18 months.

Noncomparative Studies

Bujold et al (2013) reported on sequential phase 1 and 2 trials of SBRT for locally advanced HCC.[141,] Two trials of SBRT for patients with HCC considered unsuitable for standard locoregional therapies were conducted from 2004 to 2010. All patients had Child-Turcotte-Pugh (CTP) class A disease. The primary endpoints were toxicity and local control at 1 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 1 from 2004 to 2007; n=52 in trial 2 from 2007 to 2010). The underlying liver disease was hepatitis B in 38% of patients, hepatitis C in 38%, alcohol-related in 25%, other in 14%, and none in 7%. Fifty-two percent received prior therapies (excluding sorafenib). The TNM stage was III in 66% of patients and 61% had multiple lesions. Median gross tumor volume was 117.0 mL (range, 1.3 to 1913.4 mL). Tumor vascular thrombosis was present in 55%, and 12% of patients had extrahepatic disease. Local control at 1 year was 87% (95% CI, 78% to 93%). Toxicity of grade 3 or higher was seen in 30% of patients. In 7 patients (2 with tumor vascular thrombosis and progressive disease), death was possibly related to treatment (1.1 to 7.7 months after SBRT). Median OS was 17.0 months (95% CI, 10.4 to 21.3).

Ibarra et al (2012) evaluated tumor response to SBRT in a combined multicenter database.[142,] Patients with advanced HCC (n=21) or intrahepatic cholangiocarcinoma (n=11) treated with SBRT from 4 academic medical centers were entered into a common database. Statistical analyses were performed for FFLP and patient survival. Overall, FFLP for advanced HCC was 63% at a median follow-up of 12.9 months. Median tumor volume decreased from 334.2 to 135 cm^3 ($p<.004$). The median time-to-local progression was 6.3 months. The 1- and 2-year OS rates were 87% and 55%, respectively. The incidence of grade 1 to 2 toxicities, mostly nausea and fatigue, was 39.5%. Grade 3 and 4 toxicities were present in 2 and 1 patients, respectively.

Price et al (2012) reported on the results of a phase 1/2 trial that evaluated the radiologic response in 26 patients with HCC who were not surgical candidates and were treated with SBRT between 2005 and 2008.[143,] Eligibility criteria included solitary tumors of 6 cm or less or up to 3 lesions with cumulative diameters of 6 cm or less and well-compensated cirrhosis. All patients had imaging before, at 1 to 3 months, and every 3 to 6 months after SBRT. Patients received 3 to 5 fractions of SBRT. Median SBRT dose was 42 Gy (range, 24 to 48 Gy). Median follow-up was 13 months. Per RECIST, 4 patients had a complete response, 15 had a partial response, and 7 achieved stable disease at 12 months. One patient with stable disease experienced progression marginal to the treated area. The overall best response rate (complete response plus partial response) was 73%. In comparison, using the European Association for the Study of the Liver criteria, 18 of 26 patients had 50% or more nonenhancement at 12 months. Thirteen of 18 patients demonstrated 100% nonenhancement, being greater than 50% in 5 patients. Kaplan-Meier 1- and 2-year survival estimates were 77% and 60%, respectively. SBRT is an effective therapy for patients with HCC with an overall best response rate (complete response plus partial response) of 73%.

Andolino et al (2011) evaluated the safety and efficacy of SBRT for the treatment of primary HCC.[144,] From 2005 to 2009, 60 patients with liver-confined HCC were treated with SBRT (36 CTP class A, 24 CTP class B). Median number of fractions, dose per fraction, and total dose were 3 Gy, 14 Gy, and 44 Gy, respectively, for those with CPT class A cirrhosis and 5 Gy, 8 Gy, and 40 Gy, respectively, for those with CPT class B. All patients' records were reviewed, and treatment response was scored according to RECIST v.1.1. Toxicity was graded using the Common Terminology Criteria for Adverse Events v.4.0. Local control, time to progression, PFS, and OS were calculated according to the Kaplan-Meier method. Median follow-up time was 27 months, and the median tumor diameter was 3.2 cm. The 2-year local control, PFS, and OS rates were 90%, 48%, and 67%, respectively, with a median time to progression of 47.8 months. Subsequently, 23 patients underwent a transplant, with a median time to transplant of 7 months. There were no nonhematologic toxicities at grade 3 or

higher. Thirteen percent of patients experienced an increase in hematologic/hepatic dysfunction greater than 1 grade, and 20% experienced progression in CTP class within 3 months of treatment. The authors concluded that SBRT is a safe, effective, noninvasive option for patients with HCC of 6 cm or less and that SBRT should be considered when bridging to transplant, or as definitive therapy for patients ineligible for transplant.

Liver Oligometastases

The liver is the most common site of metastatic spread of colorectal cancer (CRC). Evidence has shown that surgical resection of limited liver metastases can result in long-term survival in select patients. However, only 10% to 20% of patients with metastatic CRC to the liver are surgical candidates. In patients who are not candidates for surgery, a variety of locally ablative techniques have been developed, the most common of which are RFA and TACE.

Noncomparative Studies

The RSSearch® Patient Registry is an international multi-platform research and data sharing registry aimed at generating peer-reviewed publications and increasing collaboration among the diverse clinical specialties, hospitals, and industries participating in SRS and SBRT. The registry is organized and managed by the Radiosurgery Society® which is a multi-disciplinary non-profit organization of surgeons, radiation oncologists, physicists, and allied professionals. Mahadevan et al (2018) reported on patients with liver metastases treated with SBRT identified in the registry.[145,] A total of 427 patients with 568 liver metastases from 25 academic and community-based centers were included. Median age was 67 years (range, 31 to 91 years). CRC was the most common primary cancer and 73% of patients received prior chemotherapy. Median tumor volume was 40 cm^3 (range, 1.6 to 877 cm^3), median SBRT dose was 45 Gy (range, 12 to 60 Gy) delivered in a median of 3 fractions. Smaller tumor volumes (<40 cm^3) and higher radiation dose were correlated with improved local control and OS. At a median follow-up of 14 months (range, 1 to 91 months), the median OS was 22 months. Median OS differed on the basis of the primary malignancy; it was greater for patients with CRC (27 months), breast (21 months), and gynecological (25 months) metastases, compared to lung (10 months), other gastrointestinal (GI; 18 months) and pancreatic (6 months) primaries (p<.0001). Local control was not affected by tumor histology.

Case Series

There are 3 relatively large series reporting on SBRT and liver metastases. Yuan et al (2014) reported on the single-site experience of a cohort of patients with liver metastases from multiple primary sites, 56% of whom had received prior systemic therapy.[146,] Patients were considered to have a favorable prognosis with primary tumors originating from the colon, breast, or stomach, as well as sarcomas. In this group, the median OS was not reached and the 1-year and 2-year OS rates were 89.6% and 72.2%, respectively. Tables 6 and 7 summarize the characteristics and key results of these studies. Lanciano et al (2012) reported on the single-center experience with SBRT to treat patients with metastases from multiple primary sites.[147,] The patients were heavily pretreated with 87% having had prior systemic chemotherapy for treatment of liver metastases or liver tumor and 37% having had prior liver-directed therapy. These therapies included surgical resection, chemoembolization, RFA, photodynamic therapy, or previous EBRT. Four patients had more than 1 prior liver-directed treatment. Chang et al (2011) studied outcomes of SBRT in a pooled patient cohort from 3 institutions with colorectal liver metastases.[148,] Patients were included if they had 1 to 4 lesions and 27 (43%) had been treated with 2 or more chemotherapy regimens prior to SBRT.

Table 6. Characteristics of Case Series Assessing Stereotactic Body Radiotherapy for Liver Metastases

Study	Country	Participants	Tumor Type	Treatment Delivery	FU
Yuan et al (2014)[146,]	1 site in China	57 patients (80 lesions)	Mixed[a]	Median total dose, 42 Gy (range, 39 to 54 Gy) in 3 fractions (range, 3 to 7 fractions)	2006 to 2011 Median FU, 20.5 mo (range, 1 to 4 mo)

Study	Country	Participants	Tumor Type	Treatment Delivery	FU
Lanciano et al (2012)[147,]	1 site in U.S.	30 patients[b] (41 lesions)	Mixed[c]	>79.2 Gy10 or <79.2 Gy10[d]	2007 to 2009 Median FU, 22 mo (range, 10 to 40 mo)
Chang et al (2011)[148,]	3 sites in U.S. and Canada	65 patients (102 lesions)	CRC	Median total dose, 41.7 Gy (range, 22 to 60 Gy) in 6 fractions (range, 1 to 6 fractions)	2003 to 2009 Median FU, 1.2 y (range, 0.3 to 5.2 y)

CRC: colorectal cancer; FU: follow-up; Gy: gray.
[a]CRC, breast, esophageal, pancreatic, lung, ovarian, renal, sarcoma, hepatocellular, gallbladder, stomach, olfactory neuroblastoma.
[b] Twenty-three of 30 patients had metastatic disease.
[c]CRC, breast, esophageal, gastrointestinal stromal tumor, pancreatic, non-small-cell lung cancer.
[d] Gy10: alpha/beta (a/b) ratio is a theoretical measure of a tissue's predicted response to a dose of radiation, relative to the size of the dose delivered per fraction.

Table 7. Results of Case Series Assessing Stereotactic Body Radiotherapy for Liver Metastases

Study	Treatment	OS, %			Post-SBRT Chemotherapy ≥2 Regimens, n (%)
		12 Months	*18 Months*	*24 Months*	
Yuan et al (2014)[146,]	Median total dose, 42 Gy (range, 39 to 54 Gy) in 3 fractions (range, 3 to 7 fractions)	68.65	NR	55.9	
Lanciano et al (2012)[147,]	>79.2 Gy10 or <79.2 Gy10	73	NR	31	NR
Chang et al (2011)[148,]	Median total dose, 41.7 Gy (range, 22 to 60 Gy) in 6 fractions (range, 1 to 6 fractions)	72	55%	38	9 (14)

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

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

Bridge to Transplantation

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

Mazloom et al (2014) reported on a single case of hepatitis C virus-related HCC with a complex series of liver-directed therapy pre- and post-transplantation.[149,] The patient was initially treated with TACE and while awaiting transplant had recurrent disease treated with SBRT. The extirpated liver showed no signs of residual tumor at the time of transplantation. The patient subsequently developed recurrent HCC and was treated with SBRT with no clinical or imaging evidence of residual disease at 1 year after SBRT.

Table 8 summarizes various case reports using SBRT alone or in combination with other therapies as a bridge to transplant.

Table 8. Case Series Assessing Stereotactic Body Radiotherapy as Bridge to Transplant

Study	Review Period	Treatments	Participants, n	Obtained OLT, %	1-Year Survival From Time of Transplant, %
Sapisochin et al (2017)[150,]	2004 to 2014	• TACE • SBRT • RFA	• 36 • 99 • 244	• 83 • 79.9 • 83.2	• 83 • 75 • 75

Study	Review Period	Treatments	Participants, n	Obtained OLT, %	1-Year Survival From Time of Transplant, %
Mannina et al (2017)[151],	NR	• SBRT	• 38	• 100	• 77[a]
Jacob et al (2015)[139],	2008 to 2013	• TACE • TACE plus SBRT	• 124 • 37	• 15.5 • 12.1	• NR

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

Section Summary: Hepatocellular Carcinoma

Only 1 RCT has evaluated SBRT for HCC, but the trial was terminated prematurely due to slow accrual. Studies have used heterogeneous treatment schedules, treatment planning techniques, patient populations, and outcome measures. The optimal dose and fractionation scheme are unknown. Although promising local control rates of 71% to 100% at 1 year have been reported, there are only retrospective cohorts reporting on the use of SBRT in conjunction with, or as an alternative to, established treatment modalities, including systemic therapy, RFA, and TACE. Similar short-term lesion-control rates have been reported for metastatic liver disease. Palliative treatment, including for larger lesions (>3 cm), has also been reported. The use of SBRT, either alone or in conjunction with other liver-directed therapies, is emerging as a bridge to transplant.

Prostate Cancer

Clinical Context and Therapy Purpose

The purpose of SBRT is to use a focused radiotherapy technique to treat certain primary and metastatic extracranial tumors that are relatively inaccessible surgically and that are often located in proximity to radiosensitive organs at risk.

The following PICO was used to select literature to inform this review.

Populations

The population of interest is individuals with primary prostate cancer.

Interventions

The therapy being considered is SBRT as an alternative to open surgical intervention, other forms of radiation therapy, or as an adjunct to systemic therapy.

Comparators

The following therapies are currently being used to treat primary prostate cancer: other forms of radiation therapy, surgical interventions, and/or continued systemic medical therapy.

Outcomes

The outcomes of interest are OS, PFS, DFS, symptom improvement, and treatment-related morbidity. Follow-up of weeks to months is required to determine the effect of SBRT on local toxicity and months to years to determine the effect on tumor control and late toxicities.

Study Selection Criteria

Methodologically credible studies were selected for all SBRT indications within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Systematic Reviews
Foerster et al (2021) conducted a systematic review of 18 studies (N=651; both prospective and retrospective data) to evaluate the safety and efficacy of SBRT among patients with high-risk prostate cancer.[152,] Five additional studies were included in data synthesis because they were deemed to include relevant information. Overall, there were 3 trials that assessed SBRT including pelvic nodes, 2 with elective nodal irradiation, and 1 with positive pelvic nodes only; all other studies assessed SBRT of only the prostate. Biochemical control rates ranged from 82% to 100% after 2 years and 56% to 100% after 3 years. Grade 2 or higher acute and chronic genitourinary (GU) toxicity rates ranged between 12% to 46.7% and 7% and 60%, respectively, in studies that included pelvic node irradiation and between 0% to 89% and 2% and 56.7% in studies, respectively, that evaluated SBRT for the prostate only. Grade 2 or higher acute and chronic GI toxicity rates ranged between 0% to 4% and 4% to 50%, respectively, for pelvic node irradiation studies and between 0% to 18% and 0% and 40%, respectively, in prostate only studies.

Jackson et al (2019)[153,] performed a systematic review and meta-analysis on prospective studies assessing SBRT for localized prostate cancer. Thirty-eight prospective studies between 1990 and 2018 were retrieved featuring low- (45%), intermediate- (47%), and high-risk (8%) patients (N=6116). The most common dose received was 7.25 Gy/fraction (range, 5 to 10 Gy) in a median of 5 fractions (range, 4 to 9 fractions). Five- and 7-year biochemical relapse-free survival rates were 95.3% (95% CI, 91.3 to 97.5; I^2, 87.96; Q value, 74.9, p<.001)) and 93.7% (95% CI, 91.4 to 95.5), respectively. Late grade 3 or higher GU or GI toxicity rates were 2.0% (95% CI, 1.4 to 2.8) and 1.1% (95% CI, 0.6 to 2.0), respectively. In 33 studies that reported on the use of androgen-deprivation therapy (ADT), 15% of patients received ADT alongside SBRT. The impact of ADT on pooled outcomes is unknown. Furthermore, studies did not stratify biochemical relapse-free survival rates by patient risk level, contributing to high heterogeneity in the results.

Kishan et al (2019)[154,] pooled long-term outcomes from 10 single-center and 2 multi-center prospective trials evaluating SBRT for the treatment of low-to-intermediate risk prostate cancer (N=2142). Doses of SBRT ranged from 33.5 to 40.0 Gy in 4 to 5 fractions. Overall, 115 patients (5.4%) received concurrent ADT. Mean overall follow-up duration was 6.9 years (interquartile range, 4.9 to 8.1 years). For patients with low, intermediate-favorable, and intermediate-unfavorable, and any intermediate risk level, biochemical recurrence rates were 4.5% (95% CI, 3.2 to 5.8), 8.6% (95% CI, 6.2 to 11.0), 14.9% (95% CI, 9.5 to 20.2), and 10.2% (95% CI, 8.0 to 12.5), respectively. Corresponding OS rates were 91.4% (95% CI, 89.4 to 93.0), 93.7% (95% CI, 91.0 to 95.6), 86.5% (95% CI, 80.6 to 90.7), and 91.7% (95% CI, 89.2 to 93.6), respectively. There were 13 (0.6%) and 2 (0.09%) reported cases of acute grade 3 or higher GU or GI toxicities. The incidence of late grade 3 or higher GU and GI toxicities was 2.4% (95% CI, 1.8 to 3.2) and 0.4% (95% CI, 0.2 to 0.8), respectively. The analysis was limited by heterogeneity in toxicity reporting and scoring criteria and a lack of comparative studies.

Low-Risk Prostate Cancer
Randomized Controlled Trials
van As et al (2024) conducted a phase 3, international, open-label, randomized controlled trial of men with stage T1 or T2 prostate cancer (N=874).[155,] Patients with stage T1 or T2 prostate cancer, a Gleason score of 3+4 or less, and a PSA level of no more than 20 ng per milliliter were included. Patients were randomly assigned to receive either SBRT (36.25 Gy in 5 fractions over 1 or 2 weeks) or control radiotherapy (CRT) (78 Gy in 39 fractions over 7.5 weeks or 62 Gy in 20 fractions over 4 weeks). The primary endpoint was freedom from biochemical or clinical failure, with a critical hazard ratio for noninferiority of 1.45. At a median follow-up of 74 months, the 5-year incidence of freedom from biochemical or clinical failure was 95.8% (95% CI: 93.3 to 97.4) in the SBRT group and 94.6% (95% CI:

91.9 to 96.4) in the CRT group (unadjusted hazard ratio for biochemical or clinical failure: 0.73; 90% CI: 0.48 to 1.12; p=.004 for noninferiority), indicating the noninferiority of SBRT. Up to 5 years, the cumulative incidence of late Radiation Therapy Oncology Group (RTOG) grade 2 or worse genitourinary toxic effects was higher with SBRT (26.9%; 95% CI: 22.8 to 31.5) compared to CRT (18.3%; 95% CI, 14.8 to 22.5; p<.001), and the cumulative incidence of late RTOG grade 2 or worse gastrointestinal toxic effects was similar between the groups, with 10.7% (95% CI: 8.1 to 14.2) for SBRT and 10.2% (95% CI: 7.7 to 13.5) for CRT (p=.94). The study concluded that five-fraction SBRT is noninferior to CRT in patients with low-to-intermediate-risk localized prostate cancer. Summary of this study and study characteristics are described in the Tables 9 through 12 below.

Vargas et al (2018) evaluated toxicity and QOL outcomes of hypofractionated proton therapy versus standard fractionated proton therapy for low-risk prostate cancer.[156,] This interim analysis of a phase 3 study included 75 patients; the primary outcome was the cumulative incidence of greater than or equal to Grade 2 adverse events. Secondary outcomes included QOL measures. Cumulative Grade 2 and above genitourinary toxicity was similar between groups. American Urological Association Symptom Index (AUASI) scores differed <5 points at 12 months, favoring the standard fractionation arm. Differences in AUASI score were not significant at ≥18 months. Expanded Prostate Index Composite (EPIC) urinary symptoms favored the standard fractionation arm at 12 months and 18 months; there were no significant differences found in EPIC domains of bowel or sexual symptoms. Summary of this study and study characteristics are described in the Tables 9 through 12 below.

Table 9. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants[2]	Interventions[1]	
					Active	Comparator
Vargas et al (2018)[156,]	United States	NR	2011-2014	Patients with low-risk prostate cancer (defined as clinical stage T1 to T2a, Gleason score 6, and prostate-specific antigen level <10 ng/mL)	Hypofractionation (38 Gy RBE over 5 fx); n=46	Standard fractionation (79.2 Gy RBE over 44 fx); n=29
van As et al (2024)[155,]	United Kingdom, Ireland, Canada	38	2012-2018	Patients ≥18 years with histologically confirmed prostate adenocarcinoma with T1 or T2 disease categorized based on NCCN criteria as low (Gleason 3+3 and PSA ≤10 ng/ml) or intermediate (at least one of the following factors: Gleason 3+4, PSA 10.1-20.0 ng/ml)	Stereotactic body radiotherapy (36.25 Gy in 5 fx); n=433	Control radiotherapy (78 Gy in 39 fx); n=441

fx: fractions; Gy: gray; NCCN: National Comprehensive Cancer Network; NR: not reported; RBE: relative biologic effectiveness; RCT: randomized controlled trial.
[1] Number randomized; intervention; mode of delivery; dose (frequency/duration).
[2] Key eligibility criteria

Table 10. Summary of Key RCT Results

Study	Overall cumulative incidence of ≥ Grade 2 AE	AUASI scores (12 month)	EPIC urinary scores (12 month; 18 month)
Vargas et al (2018)[156,]	N=75	N=61	N=59 (12 month); N=62 (18 month)

Study		Overall cumulative incidence of ≥ Grade 2 AE	AUASI scores (12 month)	EPIC urinary scores (12 month; 18 month)
		n, (%)	Mean (SD)	Mean (SD)
Hypofractionation		Urinary tract: 14 (30.4); Bowel: 9 (19.6)	8.58 (6.868)	12 month: 84.5 (13.800); 18 month: 85.3 (13.646)
Standard fractionation		Urinary tract: 10 (34.5); Bowel: 5 (17.2)	4.40 (3.218)	12 month: 92.3 (8.555); 18 month: 92.3 (10.874)
P value		Urinary tract: =.80; Bowel: >.99	=.002	12 month: =.009; 18 month: =.03
	Biochemical/clinical free rate (5 years)	RTOG grade ≥2 GU toxicity (to 5 years)	RTOG grade ≥2 GI toxicity (to 5 years)	EPIC urinary scores (5 years)
van As et al (2024)[155,]	N=874	N=874	N=874	N=874
	% (95% CI)	% (95% CI)	% (95% CI)	Median (IQR)
Stereotactic body radiotherapy (n=433)	95.6 (93.3 to 97.4)	26.9 (22.8 to 31.5)	10.7 8.1 to 14.2)	96.9 (73.0 to 100)
Control radiotherapy (n=441)	94.6 (91.9 to 96.4)	18.3 (14.8 to 22.5)	10.2 (7.7 to 13.5)	100 (79.3 to 100)
Unadjusted hazard ratio (90% CI)	.73 (.48 to 1.12)			
P value	.004	.11	.37	.45

AE: adverse event; AUASI: American Urological Association Symptom Index; EPIC: Expanded Prostate Index Composite; IQR: interquartile range; RCT: randomized controlled trial; RR: relative risk; RTOG: Radiation Therapy Oncology Group; SD: standard deviation.

Table 11. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Vargas et al (2018) [156,]	5. small sample size				
van As et al (2024)[155,]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 12. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Vargas et al (2018)[156,]		1. open-label				
van As et al (2024)[155,]		1. blinding not specified				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment

unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Nonrandomized Comparative Studies

Yu et al (2014) assessed toxicities after treatment between SBRT (n=1335) and IMRT (n=2670) as primary treatment for prostate cancer, using claims data for Medicare beneficiaries.[157,] The authors identified early-stage prostate cancer patients (age range, 66 to 94 years) treated from 2008 to 2011 who received IMRT (n=53841) 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 GU toxicity. By 6 months after treatment initiation, 15.6% of SBRT patients had a claim indicative of treatment-related GU toxicity versus 12.6% of IMRT patients (OR, 1.29; 95% CI, 1.05 to 1.53; p=.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=.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=.001). At 6 months posttreatment, there was increased GI toxicity for patients treated with SBRT, with 5.8% of SBRT patients having had a claim indicative of GI toxicity versus 4.1% of IMRT patients (OR, 1.42; 95% CI, 1.00 to 1.85; p=.02); but at 12 and 24 months posttreatment, there were no significant differences in GI toxicity between groups.

Katz et al (2012) examined QOL after either radical prostatectomy (n=123) or SBRT (n=216) in patients with early-stage prostate cancer.[158,] Using the EPIC scoring tool, QOL was assessed in the following areas: urinary, sexual, and bowel function. The EPIC data from the SBRT group were compared at baseline, 3 weeks, 5, 11, 24, and 36 months with the surgery group at baseline, 1, 6, 12, 24, and 36 months. The largest differences in QOL occurred 1 to 6 months after treatment, with larger declines in urinary and sexual QOL occurring in the surgery group, but a larger decline in bowel QOL after SBRT. The long-term urinary and sexual QOL declines remained clinically significantly lower for patients who underwent prostatectomy, but not for SBRT patients.

Noncomparative Studies

Multiple cohort studies have reported outcomes for patients treated with a standard dose of SBRT or for groups of patients treated with SBRT at escalating doses.

Studies that evaluated predominantly low-risk patients treated with SBRT are summarized in Table 13.

Table 13. Select Noncomparative Cohort Series Assessing Stereotactic Body Radiotherapy in Prostate Cancer

Study	Review Period	Sites	Patients	Risk Stage	Dose (Gy) by Fractions	bPFS or bF % (95% CI)	Toxicity, n (%)	Follow-Up Duration
Miszczyk et al (2019)[159,]	2011 to 2017	1 in Poland	500	Low; Intermediate[a]	36.25/5	3 (NR)[#]	1 (NR) G4; 3 (NR) G3	32.7 mo (NR)
Zelefsky et al (2019)[160,]	2012 to 2017	1 in U.S.	551	Low; Intermediate	37.5 to 40/5	2.1 (0.6 to 5.3)[#]	No G4	17 mo (IQR, 7 to 29)

Study	Review Period	Sites	Patients	Risk Stage	Dose (Gy) by Fractions	bPFS or bF % (95% CI)	Toxicity, n (%)	Follow-Up Duration
Fuller et al (2018)[161,]	2007 to 2012	18 in U.S.	259	Low; Intermediate	38/4	Low: 100 (NR); Intermediate: 88.5 (NR)	0.4% late G4 GU	60 mo (IQR, 37 to 85 mo)
King et al (2012)[162,]	2003 to 2009	2 in U.S.	67	Low	36.25/5	94 (85 to 102)	No G4	4 y (NR)
Freeman and King (2011)[163,]	2003 to 2005	2 in U.S.	41	Low[b]	35 to 36.25/5	92.7 (84.7 to 100)	No G4	5 y (NR)
McBride et al (2011)[164,]	2006 to 2008	4 in U.S.	45	Low	35 to 36.25/5	97.7 (NR)*	7 (17) late G2 GU	44.5 mo (range, 0 to 62 mo)

bF: biochemical failure; bPFS: biochemical progression-free survival; CI: confidence interval; G: grade; GU: genitourinary; Gy: gray; IQR: interquartile range; NR: not reported; PSA: prostate-specific antigen; TNM: tumor, node, metastasis.
* At 3 years.
[a] Low risk generally defined by TNM (T2a or lower) and Gleason score <7. Intermediate risk generally defined by TNM (T2b-T2c) and Gleason score 3+4 (Grade 2). Maximum PSA level was <20 ng/mL for all patients.
[b] Low risk generally defined by TNM (T1c-T2a), PSA <10 ng/mL, and Gleason score ≤6.
[c] Intermediate risk generally defined by TNM (T2b-T2c), PSA 10-20 ng/mL, and Gleason score 7.

Boike et al (2011) evaluated the tolerability of escalating doses of SBRT in the treatment of localized prostate cancer.[165,] Eligible patients included those with a prostate size of 60 cm^3 or less, and an American Urological Association score of 15 or less. Dose-limiting toxicity was defined as grade 3 or worse GI/GU toxicity by Common Terminology Criteria of Adverse Events (v.3). Patients completed QOL questionnaires at defined intervals. Groups of 15 patients received 45 Gy, 47.5 Gy, and 50 Gy in 5 fractions (45 total patients). Median follow-up was 30 months (range, 3 to 36 months), 18 months (range, 0 to 30 months), and 12 months (range, 3 to 18 months) for the 45 Gy, 47.5 Gy, and 50 Gy groups, respectively. For all patients, GI grade of 2 or more and grade 3 or more toxicity occurred in 18% and 2%, respectively, and GU grade 2 or more and grade 3 or more toxicity occurred in 31% and 4%, respectively. Mean American Urological Association scores increased significantly from baseline in the 47.5-Gy dose level (p=.002) compared with the other dose levels, where mean values returned to baseline. Rectal QOL scores (EPIC) fell from baseline up to 12 months but trended back at 18 months. In all patients, prostate-specific antigen (PSA) control was 100% by the nadir +2 ng/mL failure definition.

High-Risk and Mixed Population Prostate Cancer

Randomized Controlled Trials

In a phase 3, non-inferiority trial (HYPO-RT-PC trial), Widmark et al (2019) evaluated ultra-hypofractionated versus conventionally fractionated radiotherapy in patients with intermediate-to-high-risk prostate cancer.[166,] There were 1200 patients randomized to conventional fractionation (n=602) or ultra-hypofractionation (n=598). The primary outcome was time to biochemical or clinical failure, which was analyzed in the per-protocol population; the prespecified non-inferiority margin was 4% at 5 years. Estimated failure-free survival at 5 years was 84% (95% CI, 80 to 87) in both groups, with an adjusted HR of 1.002 (95% CI, 0.758 to 1.325; log-rank p=.99). Ultra-hypofractionation was found to be non-inferior to conventional fractionation. Summary of this study and study characteristics are described in the Tables 14 through 17 below.

Table 14. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Widmark et al (2019)[166,]	Sweden and Denmark	12	2005-2015	Patients with intermediate-to-high-risk prostate cancer	Ultra-hypofractionation(42.7 Gy in seven fractions); n=598	Conventional fractionation (78.0 Gy in 39 fractions); n=602

Study; Trial	Countries	Sites	Dates	Participants	Interventions
				(categorized according to the TNM classification system as T1c–T3a, Gleason score, and PSA level)	

Gy: gray; PSA: prostate-specific antigen; RCT: randomized controlled trial; TNM classification: describe the tumor (T), node (N), and metastasis (M) categories.

Table 15. Summary of Key RCT Results

Study	Estimated failure-free survival at 5 years	Frequency of ≧ Grade 2 urinary or bowel toxicity (5-year followup)
Widmark et al (2019)[166,]	N=1180	N=492
	% (95% CI)	%
Hypofractionation	84 (80 to 87)	Urinary: 5% (11/243); Bowel: 1% (3/244)
Conventional fractionation	84 (80 to 87)	Urinary 5% (12/249); Bowel: 4% (9/249)
log-rank p value	=.99	NR

CI: confidence interval; NR: not reported; RCT: randomized controlled trial.

Table 16. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Widmark et al (2019)[166,]	3. high-risk subgroup only comprises 11% of the study population				1,2: relatively short follow-up of 5 years

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 17. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Widmark et al (2019)[166,]		1. open-label				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Cohort Studies

Yasar et al (2024) reported the primary outcomes of the Stereotactic Prostate Augmented Radiotherapy with CyberKnife (SPARC) investigating simultaneous focal boost with stereotactic radiation therapy for localized intermediate- to high-risk prostate cancer (N=20).[167,] The study evaluated the toxicity and quality of life (QoL) associated with CyberKnife-based stereotactic body radiation therapy (SBRT) with a simultaneous integrated boost in patients with localized prostate cancer. Patients received 36.25 Gy in 5 fractions, with a boost up to 47.5 Gy to the dominant intraprostatic lesion (DIL). The primary outcome was acute grade 2+ genitourinary toxicity, which was observed in 25% of participants, while 30% experienced acute grade 2+ gastrointestinal toxicity. One patient developed acute grade 3 genitourinary toxicity (5%), but no late grade 3 genitourinary or gastrointestinal toxicity was reported. The median D95 dose to DIL was 47.43 Gy. Patient-reported outcomes showed no significant change in EQ-5D QoL scores at 12 weeks and 1 year, and there were no cases of biochemical relapse. Overall, the authors conclude the treatment was well tolerated, with toxicity rates comparable to other contemporary SBRT trials, however, the analysis was limited by its small sample size.

Bolzicco et al (2013) reported outcomes from 100 patients treated with SBRT for localized prostate cancer, 41 of whom were low-risk (PSA ≤10 ng/mL or Gleason score ≤6 or tumor category T1c to T2a), 42 were intermediate-risk (PSA 10 to 20 ng/mL or Gleason score 7 or tumor category T2c), and 17 were high-risk (PSA >20 ng/mL or Gleason score >7 or 2 median risk factors).[168,] Twenty-seven patients received ADT at the discretion of their treating urologist. Sixty-two patients had acute toxicity (within the first 1 to 2 weeks after treatment): 34% had grade 1 and 12% grade 2 urinary toxicity; 27% had grade 1 and 18% grade 2 GI toxicity. Late urinary toxicity, primarily urgency, and frequency (at ≥6 months posttreatment) occurred in 8% of the patients: 4% grade 1, 3% grade 2, and 1% grade 3. The 3-year biochemical PFS rate was 94.4% (95% CI, 85.3% to 97.9%)

Jabbari et al (2012) reported PSA nadir and acute and late toxicities with SBRT as monotherapy and a post-EBRT boost for prostate cancer using high-dose-rate (HDR) brachytherapy fractionation.[169,] 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 in 4 fractions), and 18 were treated with SBRT boost (9.5 Gy in 2 fractions) post-EBRT and ADT. Forty-four HDR brachytherapy boost patients with disease characteristics similar to the SBRT boost cohort had their PSA nadir levels analyzed as a descriptive comparison; SBRT was well tolerated. With a median follow-up of 18.3 months (range, 12.6 to 43.5 months), 42% and 11% of patients had acute grade 2 GU and GI toxicity, respectively, with no grade 3 or higher acute toxicity. Two patients experienced late grade 3 GU toxicity. All patients were without evidence of biochemical or clinical progression, and favorably low PSA nadirs were observed with a current median PSA nadir of 0.35 ng/mL (range, <0.01 to 2.1 ng/mL) for all patients (0.47 ng/mL; range, 0.2 to 2.1 ng/mL, for the monotherapy cohort; 0.10 ng/mL; range, 0.01 to 0.5 ng/mL, for the boost cohort). With a median follow-up of 48.6 months (range, 16.4 to 87.8 months), the comparable HDR brachytherapy boost cohort achieved a median PSA nadir of 0.09 ng/mL (range, 0.0 to 3.3 ng/mL). The authors concluded that early results with SBRT monotherapy and a post-EBRT boost for prostate cancer demonstrated acceptable PSA response and minimal toxicity; PSA nadir with SBRT boost appeared comparable to those achieved with HDR brachytherapy boost.

Katz et al (2010) performed SBRT on 304 patients with clinically localized prostate cancer (211 with high-risk disease, 81 with intermediate-risk disease, 12 with low-risk disease): Fifty patients received 7

Gy in 5 fractions (total dose, 35 Gy) and 254 patients received 7.25 Gy in 5 fractions (total dose, 36.25 Gy).[170,] At a median 30-month (range, 26 to 37 months) follow-up, there were no biochemical failures for the 35-Gy dose group. Acute grade 2 urinary and rectal toxicities occurred in 4% of patients with no higher grade, acute toxicities. At a median 17-month follow-up (range, 8 to 27 months), the 36.25-Gy dose group had 2 low- and 2 high-risk patients fail biochemically (biopsy showed 2 low- and 1 high-risk patients were disease-free in the gland). Acute grade II urinary and rectal toxicities occurred in 4.7% and 3.6% of patients, respectively.

At 6-year follow-up (Katz et al [2013]), late urinary grade 2 complications were seen in 4% of patients treated with 35 Gy and 9% of patients treated with 36.25 Gy.[171,] Five late grade 3 urinary toxicities occurred in patients treated with 36.25 Gy. Late grade 2 rectal complications were seen in 2% and 5% of patients treated with 35 Gy and 36.25 Gy, respectively. Initially, bowel and urinary QOL scores decreased but returned to baseline levels. There was an overall 20% decrease in the sexual QOL score. For patients who were potent prior to SBRT, 75% remained potent. Actutimes 5-year biochemical recurrence-free survival was 97% for patients with low-risk disease, 90.7% with intermediate-risk disease, and 74.1% with high-risk disease.

Evaluation of Toxicity and Adverse Events

Brand et al (2019) published a phase 3, non-inferiority trial (PACE-B) which evaluated acute toxicity findings of conventionally fractionated or moderately hypofractionated radiotherapy compared to SBRT in patients with low-risk to intermediate-risk localised prostate cancer.[172,] There were 874 patients randomized to either conventionally fractionated or moderately hypofractionated radiotherapy (n=441) or SBRT (n=433). Coprimary outcomes were Grade 2 or more severe RTOG GI or GU toxic effects score up to 12 weeks after radiotherapy. Acute RTOG GI effect toxicity proportions was similar between groups (difference -1.9 percentage points; 95% CI, -6.2 to 2.4; p=.38). Acute RTOG GU toxicity proportions were also similar between groups (difference -4.2 percentage points; 95% CI, -10.0 to 1.7; p=.16). There were no treatment-related deaths in either group.

Loi et al (2019)[173,] published a systematic review assessing sexual function in prostate cancer patients who had been treated with SBRT. A total of 12 studies representing 1221 patients who had not received ADT and were available at final follow-up were analyzed. Studies used varying definitions for erectile dysfunction; some were based on the Sexual Health Inventory for Men scale whereas others were based on the EPIC-26. At 60 months, erectile dysfunction was reported by 26% to 55% of previously sexually functioning patients in 5 of 12 studies.

Wiegner and King (2010) published the results of a phase 2 trial (King et al [2012]) that reported on sexual function in a subset of patients.[174,] A literature review for other radiation modalities assessed by patient self-reported questionnaires served as a historical comparison. Using the EPIC-validated QOL questionnaire, the sexual function of 32 consecutive patients was analyzed at median times of 4, 12, 20, and 50 months after treatment. Median follow-up was 35.5 months (range, 12 to 62 months). The authors concluded that the rates of erectile dysfunction after treatment for prostate cancer with SBRT were comparable to those reported for other modalities of radiotherapy. Other noncomparative studies have reported on specific outcomes after SBRT for prostate cancer, including rates of patient-reported urinary incontinence,[175,] rectal tolerance,[176,] and health-related QOL outcomes.[177,]

Oligometastatic Prostate Cancer

Systematic Review

Yan et al (2020) completed a systematic review of SBRT for oligometastatic prostate cancer involving 10 studies (6 observational cohorts; 1 phase I single arm prospective trial; 1 phase II single arm prospective trial; 2 phase II RCTs) with 653 patients and 1111 lesions.[178,] Results revealed an overall local control rate of 97% (95% CI, 94 to 100), median ADT-free survival of 24.7 months (95% CI, 20.1 to 29.2), 2-year biochemical free survival of 33% (95% CI, 11 to 55), 2-year PFS of 39% (95% CI, 24 to 54),

and 2-year ADT-free survival of 52% (95% CI, 41 to 62). Patients treated with SBRT were half as likely to experience PSA progression than those on observation when evaluating RCT data alone.

Comparative Studies

See et al (2024) conducted a 5-year analysis of the TRANSFORM trial, a prospective cohort of individuals (N=199) with oligometastatic prostate cancer (PCa) treated with stereotactic body radiotherapy (SBRT)-based metastasis-directed therapy (MDT).[179,] The primary endpoint, 5-year treatment escalation:free survival (TE:FS), was achieved by 21.7% (95% CI: 15.7% to 28.7%) of participants, with a higher rate of 25.4% (95% CI: 18.1% to 33.9%) in the hormone-naive subgroup. Subgroups with higher baseline prostate-specific antigen (PSA) (HR: 1.06, 95% CI: 1.03 to 1.09; p<.001), International Society of Urological Pathology Grade Groups 4 to 5 disease (HR: 1.48, 95% CI: 1.05 to 2.01; p=.026), and those who received prior androgen deprivation therapy (ADT) (HR: 2.13, 95% CI: 1.40 to 3.26; p<.001) were at greater risk of treatment escalation. At a median follow-up of 67.9 months, 18.9% (95% CI: 13.2% to 25.7%) of participants were free from treatment escalation, and 2 participants had undetectable PSA levels. No grade 3 or higher treatment-related adverse events were reported. Future randomized trials are needed to compare SBRT-based MDT with standard-of-care ADT-based approaches to evaluate the impact on survival.

Phillips et al (2020) conducted the phase 2, randomized Observation versus Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer (ORIOLE) study, which enrolled 54 men with recurrent hormone-sensitive prostate cancer and 1 to 3 metastases detectable by conventional imaging who had not received ADT within 6 months of enrollment or 3 or more years total.[180,] These men were randomly assigned to stereotactic ablative radiotherapy or observation in a 2:1 ratio; 36 to treatment and 18 to observation. Results revealed that progression at 6 months was observed significantly more frequently in patients in the observation group versus active treatment (61% vs 19%; p=.005). Stereotactic ablative radiotherapy was also associated with significant improvement in median PFS (not reached vs 5.8 months; HR, 0.30; 95% CI, 0.11 to 0.81; p=.002). No adverse effects of grade 3 or greater were reported.

De Bleser et al (2019)[181,] conducted a multi-institutional, retrospective analysis comparing SBRT (n=309) to elective nodal radiotherapy (ENRT) (n=197) for patients with hormone-sensitive nodal oligore current prostate cancer. Median follow-up duration was 36 months (interquartile range, 23 to 56 months). Patients could be administered a minimum of 5 Gy/fraction for up to 10 fractions for SBRT and ENRT was defined as a minimum dose of 45 Gy in up to 25 fractions with or without a simultaneous boost to the suspicious node(s). Importantly, the choice of utilizing radiotherapy was at the discretion of the treating physician, and treatments were not balanced over treatment centers. Three-year metastasis-free survival was 68% (95% CI, 61 to 73) for SBRT and 77% (95% CI, 69 to 82) for ENRT (p=.01). However, a significantly greater number of patients in the ENRT group were managed with ADT at the time of recurrence, limiting the interpretation of these findings. Early and late toxicities following ENRT were significantly higher than those following SBRT (p=.002 and p<.001, respectively). Five patients developed grade 3 to 4 toxicities.

Section Summary: Prostate Cancer

Evidence on the use of SBRT in prostate cancer consists of systematic reviews of prospective and retrospective studies, RCTs, and single-arm assessments of acute and late toxicity and early PSA outcome data retrospectively compared with historical controls. Studies have shown promising initial results on the use of SBRT in prostate cancer with seemingly low toxicity rates; the PACE-B study demonstrated that SBRT does not increase incidence of gastrointestinal or genitourinary acute toxicity compared to conventional treatment. One comparative study of IMRT and SBRT suggested higher GI and GU complication rates after SBRT; while this study had a large number of patients and attempted to control for bias using matching on observed variables, it was subject to limitations deriving outcome measures from claims data. In the ORIOLE study, SBRT was associated with a significant improvement in disease progression and median PFS as compared to observation in men with recurrent hormone-sensitive prostate cancer and 1 to 3 metastases with a similar toxicity profile.

The HYPO-RT-PC trial found that ultra-hypofractionation was found to be non-inferior to conventional fractionation.

Pancreatic Adenocarcinoma

Clinical Context and Therapy Purpose

The purpose of SBRT is to use a focused radiotherapy technique to treat certain primary and metastatic extracranial tumors that are relatively inaccessible surgically and that are often located in proximity to radiosensitive organs at risk.

The following PICO was used to select literature to inform this review.

Populations

The population of interest is individuals with pancreatic adenocarcinoma.

Interventions

The therapy being considered is SBRT as an alternative to open surgical intervention, other forms of radiation therapy, or as an adjunct to systemic therapy.

Comparators

The following therapies are currently being used to treat pancreatic adenocarcinoma: other forms of radiation therapy, surgical interventions, and/or continued systemic medical therapy. Radiation may be part of the treatment plan for pancreatic cancer, resectable or unresectable disease, and may be used in the adjuvant or neoadjuvant setting.

Outcomes

The outcomes of interest are OS, PFS, DFS, symptom improvement, and treatment-related morbidity. Follow-up of weeks to months is required to determine the effect of SBRT on local toxicity and months to years to determine the effect on tumor control.

Study Selection Criteria

Methodologically credible studies were selected for all SBRT indications within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Petrelli et al (2017)[182,] conducted a meta-analysis of 19 trials (N=1009) evaluating SBRT for patients with locally advanced pancreatic cancer and unresectable or borderline resectable disease. Studies evaluating regimens with or without concomitant chemotherapy were included. The mean follow-up period ranged from 6 to 21 months. The pooled 1-year OS from 13 trials (n=668) was 51.6% (95% CI, 41.4 to 61.7) with a median OS of 17 months (range, 5.7 to 47 months). The locoregional control rate at 1-year (n=889) was 72.3% (95% CI, 58.5 to 79; I^2=89%; p<.001). The rate of acute grade 3 to 4 toxicity ranged from 0% to 36%. Three studies reported grade 3 to 4 GI toxicity rates exceeding 10%. Late grade 3 to 4 toxicities did not exceed 11% (range, 0% to 11%). The analysis was limited by heterogeneity in the included study populations, variation in the treatment protocols and SBRT techniques, short follow-up duration, and lack of comparative studies.

Groot et al (2016)[183,] published a systematic review comparing outcomes from re-resection, chemoradiotherapy, and SBRT in patients with isolated local recurrence after initial curative-intent resection of primary pancreatic cancer. A total of 18 studies reporting on 313 patients was included for analysis, which included 4 retrospective case series (n=60) on SBRT. Morbidity and mortality were reported for re-resection (29% and 1%), chemoradiotherapy (54% and 0%), and SBRT (3% and 1%). Morbidity for re-resection was defined as the sum of surgical complications and non-surgical 30-day complications. For chemoradiotherapy and SBRT, it was defined as toxicities of grade 3 or higher as defined by the Common Terminology Criteria for Adverse Events v4.0 guidelines. Mortality was defined as death within 30 days post-intervention. Median survival post-treatment was 32 months (range, 16 to 32 months), 19 months (range, 16 to 19 months), and 16 months (range, 9 to 16 months) for re-resection, chemoradiotherapy, and SBRT, respectively. The disease-free interval for the re-resection group tended to be longer than for chemoradiotherapy or SBRT, a finding that is known to correlate with improved outcomes for patients with isolated local recurrence. Acute and late toxicity rates were reported for chemoradiotherapy (52% and 2%) and SBRT (3% and 2%), respectively. The analysis was limited by heterogeneity in treatments, including inconsistent use of combination systemic therapies.

Randomized Controlled Trials

Timmer et al (2024) reported results from the Crossatlantic Randomized Controlled Trial Comparing Outcome in Survival After Systemic Plus Focal Therapy for Inoperable Pancreatic Carcinoma: Radiotherapy Versus Irreversible Electroporation (CROSSFIRE) trial.[184,] The CROSSFIRE trial aimed to compare the efficacy and safety of MRI-guided stereotactic ablative body radiotherapy (SABR) versus CT-guided percutaneous irreversible electroporation in patients with stage III locally advanced pancreatic cancer following FOLFIRINOX chemotherapy. Patients were randomized (N=68) to either SABR (n=34) or irreversible electroporation (n=34). The primary endpoint was overall survival, with median survival of 16.1 months (95% CI: 12.1 to 19.4) in the SABR group versus 12.5 months (95% CI: 10.9 to 17.0) in the irreversible electroporation group (HR: 1.39; p=.21). Adverse events occurred in 20/32 (63%) SABR patients and in 19/32 (59%) of irreversible electroporation patients (p=.8), with grade 3 to 5 events in 5 (16%) of SABR patients and 8 (25%) of irreversible electroporation patients (p=.35). A limitation of the trial was that it was halted early due to futility. The authors conclude no significant difference in overall survival or adverse events was found between the two treatments.

Retrospective, Comparative Studies

Zhong et al (2017) published a retrospective database analysis comparing conventional fractionated radiotherapy (CFRT) with SBRT for locally advanced primary pancreatic carcinoma.[185,] Using a large hospital-based registry, the National Cancer Data Base, clinical outcomes were described in 10534 cases (CFRT in 7819, SBRT in 631) diagnosed and treated between 2004 and 2012. To minimize the treatment selection bias, a propensity score matching method was used. A logistic regression model predicting CFRT treatment versus SBRT treatment was used to calculate propensity scores for covariates of interest. The covariates chosen were ones found to be significant in the multivariate analysis or ones thought to be clinically significant and included the following: patient age, American Joint Committee on Cancer clinical T and N staging, chemotherapy use, Charlson-Deyo Comorbidity Index score, year of diagnosis, and receipt of definitive surgery. In the multivariate analysis, treatment with SBRT was associated with significantly improved OS (HR, 0.84; 95% CI, 0.75 to 0.93; p<.001). With matched propensity score analysis, a total of 988 patients were analyzed, with 494 patients in each cohort. The median follow-up time was 26 months. After propensity matching, SBRT usage continued to be associated with significantly improved OS with a median survival of 13.9 months versus 11.6 months (p<.001). Kaplan-Meier curves for the propensity-matched groups demonstrate a significantly better OS curve for the SBRT cohort (p=.001) with 2-year OS rates of 21.7% and 16.5% for the SBRT and CFRT groups, respectively (p=.001).

Noncomparative Studies

Weisz Ejlsmark et al (2024) evaluated the efficacy and toxicity of stereotactic body radiotherapy (SBRT) in patients with locally advanced pancreatic cancer (LAPC) after more than two months of

combination chemotherapy.[186,] Patients with histologically or cytologically proven adenocarcinoma of the pancreas were enrolled (N=28). They were prescribed 50-60 Gy in 5-8 fractions, initially treated on a standard linac (n=4), and then from 2019, patients were treated using online magnetic resonance (MR) image-guidance on a 1.5 T MRI-linac. The primary endpoint was resection rate. The median follow-up was 28.3 months (95% CI: 24.0 to not reported), with median progression-free survival of 7.8 months (95% CI: 5.0 to 14.8) and overall survival of 16.5 months (95% CI: 10.7 to 22.6). Six patients experienced grade 3 treatment-related adverse events, and 1 patient treated on a standard linac experienced a grade 4 perforation of the duodenum. Six patients (21%) underwent resection, and 1 additional patient was offered resection but declined. The authors concluded that SBRT was safe and well tolerated with limited severe toxicities. The authors note limitations, including the nonrandomized study design with no comparator and possible selection bias due to patients being diagnosed 6 months prior to being offered SBRT.

Goyal et al (2012) reported outcomes with SBRT in patients with pancreatic adenocarcinoma who were not candidates for surgical resection.[187,] 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 to 30 Gy) delivered over 1 to 3 fractions. Chemotherapy was given to 68% of patients in various schedules and timing. Patients had a mean gross tumor volume of 57.2 cm^3 (range, 10.1 to 118 cm^3) before SBRT. The mean total gross tumor volume reduction at 3 and 6 months after SBRT were 21% and 38%, respectively ($p<.05$). Median follow-up was 14.57 months (range, 5 to 23 months). The overall rates of FFLP at 6 and 12 months were 88% and 65%, respectively. The probabilities of OS at 6 and 12 months were 89% and 56%, respectively. No patient had a complication related to fiducial markers placement regardless of modality. Rates of radiation-induced adverse events were: 11% for grade 1 to 2 and 16% for grade 3. No grade 4 or 5 adverse events were reported.

Rwigema et al (2011) assessed the feasibility and safety of SBRT in patients with advanced pancreatic adenocarcinoma.[188,] The outcomes of 71 patients treated with SBRT for pancreatic cancer between 2004 and 2009 were reviewed. Forty (56%) patients had locally unresectable disease, 11 (16%) patients had a local recurrence following surgical resection, 8 (11%) patients had metastatic disease, and 12 (17%) patients received adjuvant SBRT for positive margins. Median dose was 24 Gy (range, 18 to 25 Gy), given in single-fraction SBRT (n=67) or fractionated SBRT (n=4). Kaplan-Meyer survival analyses were used to estimate FFLP and OS rates. Median follow-up among surviving patients was 12.7 months (range, 4 to 26 months). Median tumor volume was 17 mL (range, 5.1 to 249 mL). Overall FFLP rates at 6 months and 1 year were 71.7% and 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=.02). FFLP was achieved in 73% following 24 to 25 Gy and 45% with 18 to 22 Gy (p=.004). Median OS was 10.3 months, with 6-month to 1-year OS rates of 65.3% to 41%, respectively. Grade 1 and 2 acute and late GI toxicity were seen in 39.5% of patients. Three patients experienced acute grade 3 toxicities. SBRT is feasible, with minimal grade 3 or more toxicity. The overall FFLP rate for all patients was 64.8%, comparable to rates with EBRT.

Chang et al (2009) reported on the local control and toxicity of SBRT for patients with unresectable pancreatic adenocarcinoma.[75,] Seventy-seven patients with unresectable adenocarcinoma of the pancreas received 25 Gy in 1 fraction. Forty-five (58%) patients had locally advanced disease, 11 (14%) patients had a medically inoperable disease, 15 (19%) patients had metastatic disease, and 6 (8%) patients had locally recurrent disease. Nine (12%) patients had received prior chemoradiotherapy. Sixteen (21%) patients received between 45 and 54 Gy of fractionated radiotherapy and SBRT. Various gemcitabine-based chemotherapy regimens were received by 74 (96%) patients, but 3 (4%) patients did not receive chemotherapy until they had distant failure. Median follow-up was 6 months (range, 3 to 31 months) and, among surviving patients, it was 12 months (range, 3 to 31 months). Overall rates of FFLP at 6 months and 12 months were 91% and 84%, respectively. The 6- and 12-month isolated local recurrence rates were 5% and 5%, respectively. There was no difference in the 12-month FFLP rate based on tumor location (head/uncinate, 91% vs body/tail, 86%; p=.52). The PFS

rates at 6 and 12 months were 26% and 9%, respectively. The PFS rate at 6 months was superior for patients who had nonmetastatic disease versus patients who had metastatic disease (28% vs 15%; p=.05). OS rates at 6 and 12 months from SBRT were 56% and 21%, respectively. Four (5%) patients experienced grade 2 or greater acute toxicity. Three (4%) patients experienced grade 2 late toxicity, and 7 (9%) patients experienced grade 3 or greater late toxicity. At 6 and 12 months, the rates of grade 2 or greater late toxicity were 11% and 25%, respectively.

Section Summary: Pancreatic Cancer

Combined chemoradiotherapy plays a significant role in the treatment of locally advanced pancreatic cancer. Noncomparative observational and retrospective studies of SBRT have reported increased patient survival compared with historical data. Acute grade 3 toxicities have been reported.

Primary and Metastatic Renal Cell Carcinoma

Clinical Context and Therapy Purpose

The purpose of SBRT is to use a focused radiotherapy technique to treat certain primary and metastatic extracranial tumors that are relatively inaccessible surgically and that are often located in proximity to radiosensitive organs at risk.

The following PICO was used to select literature to inform this review.

Populations

The population of interest is individuals with primary and metastatic renal cell carcinoma (RCC).

Interventions

The therapy being considered is SBRT as an alternative to open surgical intervention, other forms of radiation therapy, or as an adjunct to systemic therapy.

Comparators

The following therapies are currently being used to treat primary and metastatic RCC: other forms of radiation therapy, surgical interventions, and/or continued systemic medical therapy. Localized RCC is conventionally treated surgically. Primary RCC is treated with partial or total nephrectomy when surgery is feasible. Patients may also receive systemic therapy with TKI therapy and supportive care. Local ablative methods may also be an option. RCC has been considered relatively radioresistant. However, the renal parenchyma, vasculature, and collecting system are considered radiosensitive.

Outcomes

The outcomes of interest are OS, PFS, DFS, symptom improvement, and treatment-related morbidity. Follow-up of weeks to months is required to determine the effect of SBRT on local toxicity and months to years to determine the effect on tumor control.

Study Selection Criteria

Methodologically credible studies were selected for all SBRT indications within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Taunk et al (2015) reported on a systematic review and clinical opinion on the use of SBRT for spinal metastases from RCC.[189,] Important clinical outcomes discussed include the rates of vertebral compression fracture, which ranged from 11% to 39% from heterogeneous studies. Preexisting mechanical instability of the spine and prior radiotherapy may be risk factors for fracture. Table 18 summarizes the series described in the systematic review.

Siva et al (2012) performed a systematic review that identified 126 patients worldwide who had been treated with SBRT for primary RCC.[190,] There were 10 studies (7 retrospective studies, 3 prospective studies) that used a wide range of techniques, doses, and dose fractionation schedules. Median or mean follow-up ranged from 9 to 57.5 months. Local control was reported as 93.9% (range, 84% to 100%) and the rate of severe grade 3 or higher adverse events was 3.8% (range, 0% to 19%).

Siva et al (2022) performed an individual patient data meta-analysis on 5-year outcomes after SABR of patients with primary RCC who were enrolled in the International Radiosurgery Consortium of the Kidney (IROCK).[191,] The analysis included 190 patients and the overall cumulative incidence of local failure at 5 years was 5.5% (95% CI, 2.8 to 9.5). Single-fraction SABR yielded fewer local failures than multi-fraction SABR (Gray's, p=.02). There were no grade 3 adverse events or treatment-related deaths reported; 1 patient developed a grade 4 acute duodenal ulcer and late grade 4 gastritis.

Nonrandomized Studies

Siva et al (2024) evaluated SABR for patients with primary RCC in a nonrandomized, multicenter study.[192,] A total of 70 patients were treated. All patients had local control at 12 months and there were no cancer-related deaths. Overall survival was 99% at 12 months and 82% at 36 months. Grade 3 treatment-related adverse events occurred in 10% of patients (nausea/vomiting [n=3], pain [n=4], colon obstruction [n=2], and diarrhea [n=1], and no patients had grade 4 events.

Hannan et al (2023) evaluated SABR in 16 patients with primary RCC.[193,] All tumors remained without progression at 1 year. At 36 months the disease control rate was 94%. There were no toxicities grade 2 or greater.

Hannan et al (2022) assessed the efficacy of SBRT in 20 patients with metastatic RCC who developed growth of 3 or fewer tumors while receiving first- to fourth-line systemic therapy.[194,] Results demonstrated a local control rate of 100%; the OS was not reached. At a median follow-up of 10.4 months, SBRT extended the duration of the ongoing systemic therapy by more than 6 months in 14 patients. The median time from SBRT to the onset of new systemic therapy or death was 11.1 months.

Cheung et al (2021) assessed the efficacy of SBRT in 37 patients with metastatic RCC who developed growth of 5 or fewer tumors while receiving oral TKI therapy for at least 3 months.[195,] Results demonstrated a 1-year local control rate of 93% after SBRT, a median PFS of 9.3 months (95% CI, 7.5 to 15.7), and a 1-year OS rate of 92% (95% CI, 82 to 100). The cumulative incidence of changing systemic therapy was 47%, with a median time to change in systemic therapy of 12.6 months.

Yamamoto et al (2016) reported on 14 patients (11 males, 3 females) who received SBRT for RCC at a single-site between 2010 and 2014.[196,] The dose constraints for planning organ at risk volume of 10-fraction SBRT were 30 Gy for patients who retained both kidneys and 26 Gy in patients with single kidneys. Significant renal atrophic change was observed at a median observation interval of 16.9 months (range, 12.0 to 21.8 months). No patient experienced worsening of hypertension or required hemodialysis.

Verma et al (2013) retrospectively reviewed patients receiving different radiotherapy modalities for brain metastases with or without TKI therapy.[197,] Among 34 patients (89 lesions), those receiving SRS

and TKIs had 6-month local control rates of 94.7% versus 73.7% in the group who received SRS without TKIs. The difference was not statistically significant (p=.09).

Ranck et al (2013) reported on outcomes for 18 patients with RCC with limited metastases who were treated with SBRT.[198,] The most common metastatic sites were osseous (n=11), abdominal lymph nodes (n = 10), mediastinal lymph nodes (n=7), and lung nodules (n=4). Twelve patients underwent treatment for all sites of a known disease. For patients with 5 or fewer metastatic lesions, all lesions were treated; in patients with greater than 5 lesions, rapidly growing lesions or those close to vital organs were treated. In all, 39 metastatic lesions were treated, with a median of 2 lesions per patient. The 2-year lesion-control rate was 91.4% in the 12 patients who underwent treatment for all metastases, over a median follow-up of 21.3 months. However, in these patients, 2-year freedom from new metastases was 35.7%. The OS rate was 85% at 2 years. There were no patient deaths in those who received treatment on all lesions.

Beitler et al (2004) reported outcomes in 9 patients with nonmetastatic RCC, 2 of whom had bilateral RCC.[199,] Patients were treated definitively with 40 Gy in 5 fractions using SBRT. At a median follow-up of 26.7 months, 4 of the 9 patients were alive. Survivors had a minimum follow-up of 48 months. At presentation, all 4 survivors had tumors of 3.4 cm or less in the largest dimension, had clinically negative lymph nodes, and presented no clinical evidence of penetration of Gerota fascia or renal vein extension.

Table 18 summarizes additional case series evaluating SBRT for RCC-related spinal metastases.

Table 18. Selected Series Assessing Stereotactic Body Radiotherapy for Spinal Metastases in Renal Cell Carcinoma and Mixed Histologies

Study	Patients	Lesions	Histology	Dose (Gy) by Fractions	Local Control, %	Follow-Up Duration(actutimes), mo
Sohn et al (2014)[200,]	13	13	RCC	38 (marginal dose)/1 to 5	83.0	12
Thibault et al (2014)[201,]	37	71	RCC	24/2	83.0	12
Balagamwala et al (2012)[202,]	57	88	RCC	15/1	71.2	12
Zelefsky et al (2012)[203,]	45	45	RCC	24/1	88.0	36
Wang et al (2012)[204,]	149	166	Mixed	27-30/3	80.5	12
Yamada et al (2008)[205,]	93	103	Mixed	24/1	90.0	15
Gerszten et al (2007)[105,]	393	500	Mixed	20 (mean)/1	88.0	21 (median)
Gerszten et al (2005)[206,]	48	60	RCC	20 (mean)/1	89.0	37 (median)

Gy: gray; RCC: renal cell carcinoma.

Section Summary: Renal Cell Carcinoma

The literature on the use of SBRT for RCC consists of small case series, a systematic reviews, and other observational studies. Generally, high rates of local control have been reported for primary RCC. Adverse effects include nephron loss and kidney shrinkage, however, avoidance of nephrectomy in patients with hypertension or solitary kidney may be desirable. RCC is considered to be relatively radioresistant. Case series have reported good local control in patients with spinal metastases. There are no RCTs that have evaluated SBRT for primary RCC or metastatic lesions to the brain or spine that permit comparisons between SBRT and currently established treatment modalities for RCC. Two observational studies demonstrated that SBRT extends the duration of ongoing systemic therapy by approximately 1 year in patients with metastatic RCC with fewer than 3 to 5 sites of progression.

Oligometastases

Clinical Context and Therapy Purpose

The purpose of SBRT is to use a focused radiotherapy technique to treat certain primary and metastatic extracranial tumors that are relatively inaccessible surgically and that are often located in proximity to radiosensitive organs at risk.

Brain, spinal, and liver metastases have been reviewed in prior sections of the policy update.

The following PICO was used to select literature to inform this review.

Populations

The population of interest is individuals with oligometastases in the lung, adrenal glands, and bone.

Interventions

The therapy being considered is SBRT as an alternative to open surgical intervention, other forms of radiation therapy, or as an adjunct to systemic therapy.

Comparators

The following therapies are currently being used to treat oligometastases in the lung, adrenal glands, and bone: other forms of radiation therapy, surgical interventions, and/or continued systemic medical therapy.

Outcomes

The outcomes of interest are OS, PFS, DFS, symptom improvement, and treatment-related morbidity. Follow-up of weeks to months is required to determine the effect of SBRT on local toxicity and months to years to determine the effect on tumor control.

Study Selection Criteria

Methodologically credible studies were selected for all SBRT indications within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Oligometastases

Multiple reviews on the use of SBRT for oligometastases summarize data on local tumor control, and in a limited subset of patients, survival, for various anatomic sites.[207,208,209,]

A long-term follow-up of a prospective study by Milano et al (2012) reported on oligometastases treated with SBRT.[210,] The authors prospectively analyzed the long-term survival, tumor control outcomes, and freedom from widespread distant metastases (FFDM) after SBRT in 121 patients with 5 or fewer clinically detectable metastases, from any primary site, metastatic to 1 to 3 organ sites, and treated with SBRT. For patients with breast cancer, the median follow-up was 4.5 years (7.1 years for 16/39 patients alive at the last follow-up visit). The 2-year OS, FFDM, and local control rates were 74%, 52%, and 87%, respectively. Six-year OS, FFDM, and local control rates were 47%, 36%, and 87%, respectively. From the multivariate analyses, the variables of bone metastases (p=.057) and 1 versus more than 1 metastasis (p=.055) were associated with a 4-fold and 3-fold reduced hazard of death, respectively. None of the 17 bone lesions from breast cancer recurred after SBRT versus 10 of 68 lesions from other organs (p=.095). For patients post-breast cancer, median follow-up was 1.7

years (7.3 years for 7/82 patients alive at the last follow-up visit). Two-year OS, FFDM, and local control rates were 39%, 28%, and 74%, respectively, and 6-year OS, FFDM, and local control rates were 9%, 13%, and 65%, respectively. For non-breast cancers, a greater SBRT target volume was significantly adverse for OS (p=.012) and lesion local control (p<.001). Patients, whose metastatic lesions demonstrated radiographic progression after systemic therapy but before SBRT, experienced significantly worse OS compared with patients with stable or regressing disease. The authors concluded that select patients with limited metastases treated with SBRT are long-term survivors.

Palma et al (2019) compared SBRT versus standard of care palliative treatment in patients with oligometastatic cancers in the randomized, phase 2, open-label Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases (SABR-COMET) trial.[211,] This multicenter study enrolled 99 adults with a controlled primary tumor and 1 to 5 metastatic lesions. After stratification by the number of metastases, patients were randomly assigned in a 1:2 ratio to either palliative standard of care or standard of care plus SBRT to all metastatic lesions. Results revealed a median OS of 28 months (95% CI, 19 to 33) in the control group versus 41 months (95% CI, 26 to not reached) in the SBRT group (HR, 0.57; 95% CI, 0.30 to 1.10; p=.09). Grade 2 or worse adverse events occurred more frequently in the SBRT group (29% vs 9%; p=.026) and treatment-related deaths were reported in 3 patients in the SBRT group versus 0 in the control group. In a subsequent publication of long-term results of the SABR-COMET trial, the 5-year OS rate was 17.7% in the standard of care arm versus 42.3% in the SBRT arm (p=.006).[212,] The 5-year PFS was not reached in the standard of care group but was 17.3% in the SBRT group (p=.001). No new grade 2 to 5 adverse events were reported and there were no differences in QOL between the groups. Extended long-term outcome results for up to 10 years for the SABR-COMET trial was published by Harrow et al (2022). [213,] Eight-year OS in the SABR arm was 27.2% versus 13.6% in the control arm (HR, 0.50; 95% CI, 0.30 to 0.84; p=.008), and 8-year PFS in the SABR arm was 21.3% versus 0.0% in the control arm (HR, 0.45; 95% CI, 0.28 to 0.72; p<.001). There were no new grade 3 or 5 adverse events, and incidence of grade 2 or higher adverse events was 30.3% in the SABR group compared to 9.1% in the control group (p=.019).

Tsai et al (2024) compared SBRT versus standard of care treatment in patients with oligoprogressive metastatic breast cancer or NSCLC in the randomized, phase 2, open-label Consolidative Use of Radiotherapy to Block (CURB) oligoprogression trial.[214,] A total of 106 patients were randomized, and the study was closed early because the primary endpoint was met at an interim analysis. The median PFS was 3.2 months (95% CI, 2.0 to 4.5) with standard of care and 7.2 months (95% CI, 4.5 to 10.0) with SBRT (HR, 0.53; 95% CI, 0.35 to 0.81; p=.0035). In a subgroup analysis, the PFS remained significantly improved with SBRT in patients with NSCLC (10.0 months vs 2.2 months; HR, 0.41; 95% CI, 0.22 to 0.75; p=.0039), but not those with breast cancer (4.4 months vs 4.2 months; HR, 0.78; 95% CI, 0.43 to 1.43; p=.43). Adverse events of grade 2 or greater were more common with SBRT (62% vs 41%). Further studies are needed in order to apply these findings to patients with particular cancer types.

Lung Oligometastases

For isolated or a few lung metastases (including <3 or <5, according to different selection criteria), the local control probability at 1 year has been reported in the range of 70% to 100%.[207,] In most series, the most common clinical presentation is a single lung metastasis. It is difficult to accurately evaluate survival estimates and clinical outcomes using SBRT for lung metastases due to the absence of randomized trials and because most phase 1 and 2 trials included heterogeneous patient populations.[207,]

It is also difficult to compare OS evidence from SBRT with that of historical surgical metastasectomy series, mainly because of differences in the clinical characteristics of patients (most referred for SBRT are felt to be inoperable due to medical comorbidities that affect OS outcomes).[207,] Data from the International Registry of Lung Metastases reported OS rates of 70% at 2 years and 36% at 5 years in patients with a single metastasis who underwent surgical metastasectomy.[215,]

Systematic Reviews

A systematic review by Siva et al (2010) on the use of SBRT for pulmonary oligometastases estimated, from the largest studies included in the review, a 2-year weighted OS rate of 54.5%,[216,] ranging from higher rates (84%) in a study by Norihisa et al (2008)[217,] to lower rates (39%) reported from a 2009 multi-institutional trial.[218,]

Tsao et al (2019) completed a systematic review of SBRT for extracranial oligometastatic NSCLC involving 4 prospective phase II randomized trials (N=188), 4 prospective nonrandomized studies (N=140), and 11 retrospective studies (N=1288).[219,] Results revealed a median OS ranging from 13.5 to 55 months and a PFS ranging from 4.4 to 14.7 months. The authors noted that results from mature phase III RCTs are needed to fully determine the benefits and risks of SBRT for oligometastatic NSCLC.

Londero et al (2020) compared surgery versus SBRT for the treatment of pulmonary metastases in a systematic review of 79 studies (61 on surgical treatment and 18 on SBRT).[220,] Results revealed no difference in short-term survival when comparing pulmonary metastasectomy and SBRT; however, survival rates were improved in the long-term among patients who underwent surgery. Mortality and morbidity after treatment were 0% to 4.7% and 0% to 23% for surgery and 0% to 2% and 4% to 31% for SBRT. The authors concluded that surgical metastasectomy remains the treatment of choice for pulmonary oligometastases.

Adrenal Gland Oligometastases

The most frequent primary tumor that metastasizes to the adrenal glands is NSCLC. Longer OS times have been reported with resection of clinically isolated adrenal metastases compared with nonsurgical therapy, which has included locally ablative techniques, embolization, and EBRT. Few studies on the use of SBRT in adrenal metastases have been published. Local control rates at 1 year ranging from 55% to 90% have been reported, and 1-year OS rates ranging from 40% to 56% and 2-year OS rates ranging from 14% to 33% have been reported.[207,]

Ahmed et al (2013) reported outcomes from a single center's experience with SBRT for the treatment of metastases to the adrenal glands.[221,] Thirteen patients were included, most with lung primary tumors (n=9), and the remainder with kidney (n=2), skin (n=2), bladder (n=1), colon (n=1), and liver (n=1) as primary sites. Eleven (84.6%) patients had received prior chemotherapy since being diagnosed with metastatic disease, and 1 patient had undergone previous SBRT to bilateral psoas muscle metastases before adrenal SBRT. At the time of analysis, 8 of 13 patients were alive. Median follow-up time for living patients was 12.3 months (range, 3.1 to 18 months). Median survival for the 5 patients who died was 6.9 months (range, 2.1 to 15.2 months). Of the 12 patients evaluated for local and distant control, 11 (91.6%) had some local response to therapy, but distant failure occurred in 6 patients at a median of 2.5 months posttreatment, leading to a 1-year distant control estimate of 55%. In an exploratory analysis, there was no difference between lung primary tumor and other primary tumor sites in terms of OS or distant control. Acute toxicity included grade 2 nausea in 2 patients, grade 2 abdominal pain in 1 patient, grade 1 fatigue in 5 patients, and grade 1 diarrhea in 1 patient.

Scorsetti et al (2012) described the feasibility, tolerability, and clinical outcomes of SBRT in the treatment of adrenal metastases in consecutive cancer patients.[222,] Between 2004 and 2010, 34 patients, accounting for 36 adrenal metastatic lesions, were treated with SBRT. All 34 patients were clinically and radiologically evaluated during and after completion of SBRT. The following outcomes were taken into account: best clinical response at any time, local control, time-to-systemic progression, time-to-local progression, OS, and toxicity. The Kaplan-Meier method was used to estimate survival; factors that could potentially affect outcomes were analyzed with Cox regression analysis. No cases of grade 3 or greater toxicity were recorded. At a median follow-up of 41 months (range, 12 to 75 months), 22 patients were alive. Eleven percent of lesions showed complete remission, 46% partial remission, 36% stable disease, and 7% progressed in the treated area. Local failure was observed in 13 cases and actutimes local control rates at 1 and 2 years were 66% and 32%,

respectively. The median time-to-local progression was 19 months, and the median survival was 22 months.

Casamassima et al (2012) retrospectively evaluated a single institution's outcomes after hypofractionated SBRT for adrenal metastases.[223,] 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 to 63 months). At the time of analysis, 20 of 48 patients were alive. One- and 2-year actutimes OS rates were 39.7% and 14.5%, respectively. Median interval to local failure was 4.9 months. The actutimes 1-year disease control rate was 9%; the actutimes 1- and 2-year local control rates were both 90%.

Holy et al (2011) presented initial institutional experiences with SBRT for adrenal gland metastases.[224,] Between 2002 and 2009, 18 patients with NSCLC and adrenal metastases received SBRT for metastatic disease. Metastases were isolated in 13 patients and multiple in 5 patients. A median PFS of 4.2 months was seen in the entire patient group, with an increased PFS of 12 months in the 13 patients with isolated metastasis. After a median follow-up of 21 months, 77% of the patients with isolated adrenal metastasis achieved local control. In these patients, the median OS was 23 months.

Chawla et al (2009) investigated the dosimetry and outcomes of patients undergoing SBRT for metastases to the adrenal glands.[225,] A retrospective review of 30 patients who had undergone SBRT for adrenal metastases from various primary sites, including lung (n=20), liver (n=3), breast (n=3), melanoma (n=1), pancreas (n=1), head and neck (n=1), and unknown primary (n=1), was performed. Of the 30 patients, 14 with 5 or fewer metastatic lesions (including adrenal) underwent SBRT, with the intent of controlling all known sites of metastatic disease. Sixteen patients underwent SBRT for palliation or prophylactic palliation of bulky adrenal metastases. Twenty-four patients had more than 3 months of follow-up with serial computed tomography. Of these 24 patients, 1 achieved complete remission, 15 achieved partial remission, 4 had stable disease, and 4 developed progressive disease. No patients developed symptomatic progression of their adrenal metastases. Local control was poor, and most patients developed widespread metastases shortly after treatment, with 1-year survival, local control, and distant control rates of 44%, 55%, and 13%, respectively. No patient developed grade 2 or greater toxicity.

Bone Oligometastases

Tariq et al (2024) conducted a systematic review and meta-analysis comparing stereotactic radiotherapy (SRT) and conventional radiation therapy (CRT) for pain management in metastatic bone cancer patients (N=1152).[226,] Results of the random-effects models showed significantly higher complete pain relief in the SRT group during both early and late follow-up (RR: 1.61; 95% CI: 1.17 to 2.23; p=.004; I^2: 0%). SRT also showed a non-significant increase in partial pain relief (RR: 1.07; 95% CI: 0.85 to 1.34; p=.56; I^2: 18%) and a significantly reduced risk of stationary pain (RR: 0.61; 95% CI: 0.48 to 0.76; p<.0001; I^2: 0). The incidence of progressive pain was non-significantly reduced with SRT (RR: 0.77; 95% CI: 0.50 to 1.17; p=.22; I^2: 0%). Secondary outcomes showed non-significant trends favoring SRT for dysphagia, esophagitis, pain, and radiodermatitis, with a non-significant increase in nausea, fatigue, and vertebral compression fracture. The authors conclude SRT is more effective in achieving complete pain relief and reducing stationary pain compared to CRT, but future research should address the risk of vertebral compression fracture.

Napieralska et al (2014) reported on a series of 48 cases of prostate cancer-related bone metastases (in 32 patients) treated with SBRT primarily for pain control.[227,] The size of the treated lesions ranged from 0.7 to 5.5 cm (mean, 3 cm), and 31 (65%) of the treated metastases were located in the spine. At a 3-month follow-up, 17 patients had complete pain relief, 2 had partial pain relief, and 2 had no pain reduction. At the end of the follow-up period, complete pain relief was observed in 28 patients and partial pain relief in 16 patients.

Section Summary: Oligometastases

The evidence related to the use of SBRT for the management of oligometastases to multiple sites, including the lungs, adrenal glands, and bones (other than spine) primarily consists of relatively small, noncomparative studies that confirm clinically important rates of local control and 2 RCTs. The randomized SABR-COMET trial that compared SBRT versus standard of care palliative treatment in patients with oligometastatic cancers revealed a significantly improved median OS in the SBRT group with grade 2 or worse adverse events occurring more frequently, including 3 treatment-related deaths versus 0 in the control group. In a subsequent publications of long-term results of the SABR-COMET trial, the 5-year OS and 8-year OS rateswere significantly improved with SBRT with no new grade 3 to 5 adverse events reported. The randomized CURB study compared SBRT to standard of care in patients with oligoprogressive metastatic breast cancer or NSCLC. The trial was prematurely terminated due to beneficial PFS findings with SBRT at interim analysis; however, the subgroup of patients with breast cancer did not have significantly improved PFS with SBRT. Systemic therapy is most frequently the preferred therapy for patients with metastatic disease of these selected tumor types.

Small Cell Lung Cancer

Clinical Context and Therapy Purpose

The purpose of SBRT is to use a focused radiotherapy technique to treat certain primary and metastatic extracranial tumors that are relatively inaccessible surgically and that are often located in proximity to radiosensitive organs at risk.

The following PICO was used to select literature to inform this review.

Populations

The population of interest is individuals with small cell lung cancer (SCLC).

Interventions

The therapy being considered is SBRT as an alternative to open surgical intervention, other forms of radiation therapy, or as an adjunct to systemic therapy.

Comparators

The following therapies are currently being used to treat SCLC: other forms of radiation therapy, surgical interventions, and/or continued systemic medical therapy.

Outcomes

The outcomes of interest are OS, PFS, DFS, symptom improvement, and treatment-related morbidity. Follow-up of weeks to months is required to determine the effect of SBRT on local toxicity and months to years to determine the effect on tumor control.

Study Selection Criteria

Methodologically credible studies were selected for all SBRT indications within this review using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Safavi et al (2021) conducted a systematic review and meta-analysis.[228,] This systematic review and meta-analysis evaluated the effectiveness of stereotactic ablative radiotherapy (SABR) for treating inoperable early-stage, node-negative small cell lung cancer (SCLC). The analysis included 7 studies (N=399), showing that SABR achieved high local control rates of 97.3% (95% CI: 92.3% to 99.8%) at 1 year, 95.7% (95% CI: 74.2% to 100.0%) at 2 years, and 93.6% (95% CI: 77.5% to 100.0%) at 3 years. Overall survival rates were 86.3% (95% CI: 74.4% to 94.9%) at 1 year, 63.7% (95% CI: 45.7% to 79.9%) at 2 years, and 55.2% (95% CI: 43.5% to 66.6%) at 3 years. Recurrence rates were 17.8% (95% CI: 7.5% to 31.2%) for nodal and 26.9% (95% CI: 7.4% to 53.0%) for distant recurrences. The treatment was well-tolerated, with low rates of grade 1 (12.6%; 95% CI: 6.7% to 19.9%), grade 2 (6.7%; 95% CI: 3.3% to 11.2%), and grade 3 (1.4%; 95% CI: 0.0% to 5.3%) toxicities, and no grade 4 or 5 events observed. The authors concluded that SABR is an effective and safe option for this patient population, though further prospective studies are needed to evaluate its role for patients at higher risk of toxicity with surgery or combined chemoradiation. The authors note the limits of the meta-analysis due to heterogeneity in patient selection, diagnostic protocols, and treatment regimens across studies, as well as the retrospective design of the studies. Included studies and characteristics are described in Tables 19 and 20. Results are summarized in Table 21.

Table 19. Comparison of Studies Included in Systematic Reviews and Meta-Analyses

Study	Safavi et al (2021)[228,]
Newman et al (2019)	●
Singh et al (2019)	●
Shioyama et al (2018)	●
Verma et al (2017)	●
Ly et al (2014)	●
Shioyama et al (2013)	●
Videtic et al (2013)	●

Table 20. Systematic Review and Meta-Analyses Characteristics

Study	Dates	Trials	Participants[1]	N (Range)	Design	Duration
Safavi et al (2021)[228,]	2013-2019	7	Patients with inoperable early-stage, node-negative small cell lung cancer	399 (6-239)	Retrospective cohort studies	11.9 to 32 months

[1] Key eligibility criteria.

Table 21. Systematic Review and Meta-Analyses Results

Study	Local control (3 years)	Overall survival (3 years)	Nodal recurrence	Distant recurrence	Grade 3 toxicity rate
Safavi et al (2021)[228,]					
SABR	N=399	N=399	N=399	N=399	N=399
Pooled effect (95% CI)	93.6% (77.5 % to 100.0%)	55.2% (43.5% to 66.6%)	17.8% (7.5% to 31.2%)	26.9% (7.4% to 53.0%)	1.4% (0.0% to 5.3%)
I^2 (p)	NR	NR	58.1% (.085)	86.4% (.001)	NR

CI: confidence interval; NR: not reported; SABR: stereotactic ablative radiotherapy.

Nonrandomized Studies

Li et al (2014) conducted a prospective phase 2 study of patients with limited stage small cell lung cancer (LS-SCLC) (N=29) receiving stereotactic body radiotherapy (SBRT) concurrently with cisplatin-based chemotherapeutic regimen.[229,] Patients were predominantly male (83%, 24/29), with a median age of 55 years (range 41–72). Most patients had a WHO performance status score of 1 (89.7%, 26/29). Lymphadenopathy was present in all patients, with involvement of the ipsilateral hilar (83%, 24/29), mediastinal (55%, 16/29), and ipsilateral supraclavicular lymph nodes (10%, 3/29). The stages of SCLC

among patients were: stage I (13.8%, 4/29), stage II (27.6%, 8/29), and stage III (58.6%, 17/29). The majority of tumors were centrally located (79%, 23/29) with a median size of 4.9±0.4 cm (range 1.0–10.0 cm). Patients were followed for a median duration of 19 months (range 10–85). The median overall survival (OS) was 27 months (95% CI 20.2–33.8), with estimated OS rates at 1 and 2 years of 79.3% and 47.7%, respectively. The median progression-free survival (PFS) was 12 months (95% CI 4.2–19.8), with estimated PFS rates at 1 and 2 years of 48.3% and 27.0%, respectively. At the time of final analysis, 44.8% (13/29) of patients were still alive, with 53.9% (7/13) showing no disease progression. The longest survival was 85 months in a patient who was still alive at the last follow-up. For the secondary endpoints, 31.0% (9/29) of patients achieved complete response (CR), 51.7% (15/29) achieved partial response (PR), and 17.2% (5/29) had progressive disease (PD). The estimated objective response rate was 82.8% after four cycles of chemotherapy. The mean tumor size reduced to 1.7 ± 0.3 cm (range 0.0–5.6 cm) from a baseline mean of 4.9 ± 2.1 cm (range 1.0–10.0 cm), with a median tumor shrinkage rate of 62.2%. Tumor recurrence occurred in 72.4% (21/29) of patients, with simple regional recurrence in 20.7% (6/29), simple distant metastasis in 27.6% (8/29), and both regional recurrence and distant metastasis in 24.1% (7/29). Treatment-related adverse events were relatively mild, with no grade 4 events. For treatment-related adverse events, grade 3 events occurred in 13.8% (5/29) of patients, including esophagitis in four patients, which resolved within 4 weeks, and neutropenia in six patients, with grade 3 neutropenia in one patient. No grade 4 events were reported. No discontinuations due to adverse events were reported, and no deaths occurred within 30 days of the last infusion. Grade 1 late pneumonitis was observed in 20.7% (6/29) of patients. The authors concluded while SBRT plus concurrent chemotherapy shows promise as a safe and effective treatment for LS-SCLC patients, further investigation with a larger patient cohort and different dose-fractionation regimens is needed to confirm its efficacy. Larger randomized controlled trials are also needed. Study characteristics are described in Table 22. Study results are summarized in Table 23.

Table 22. Summary of Key Nonrandomized Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up, median (range)
Li et al (2014)[229,]	Prospective	China	2004-2012	Patients with pathologically proven LS-SCLC	Stereotactic body radiotherapy (SBRT) concurrently with cisplatin-based chemotherapeutic regimen	19 months (10 to 85)

LS-SCLC: limited stage small cell lung cancer.

Table 23. Summary of Key Nonrandomized Study Results

Study	Overall survival	Progression-free survival	Complete response	Partial response	Progressive disease
Li et al (2014)[229,]	N=29	N=29	N=29	N=29	N=29
	Median (95% CI)	Median (95% CI)	n/n total (%)	n/n total (%)	n/n total (%)
SBRT	27 months (20.2 to 33.8)	12 months (4.2 to 19.8)	9/29 (31.0)	15/29 (51.7)	5/29 (17.2%)

CI: confidence interval; SBRT: stereotactic body radiotherapy.

Section Summary: Small Cell Lung Cancer

The evidence related to the use of SBRT for the treatment of small cell lung cancer consists of 1 systematic review and meta-analysis of retrospective cohort studies and 1 nonrandomized study. The meta-analysis (N=399; 7 studies) showed that SABR achieved high local control rates of 97.3% (95% CI: 92.3% to 99.8%) at 1 year, 95.7% (95% CI: 74.2% to 100.0%) at 2 years, and 93.6% (95% CI: 77.5% to 100.0%) at 3 years. Overall survival rates were 86.3% (95% CI: 74.4% to 94.9%) at 1 year, 63.7% (95% CI: 45.7% to 79.9%) at 2 years, and 55.2% (95% CI: 43.5% to 66.6%) at 3 years. Recurrence rates were

17.8% (95% CI: 7.5% to 31.2%) for nodal and 26.9% (95% CI: 7.4% to 53.0%) for distant recurrences. The meta-analysis was limited due to heterogeneity in patient selection, diagnostic protocols, and treatment regimens across studies, as well as the retrospective design of the studies. In the nonrandomized study (N=29) the median overall survival (OS) was 27 months (95% CI 20.2–33.8) and the median progression-free survival (PFS) was 12 months (95% CI 4.2–19.8). Larger randomized controlled trials are needed.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2018 Input

Clinical input was sought to help determine whether the use of stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) for individuals with various neoplasms/conditions would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 5 respondents, including 2 specialty society-level responses, 1 of which included multiple specialty societies, and 3 physician-level responses either identified by specialty societies or an academic medical center, while this policy was under review.

Stereotactic Radiosurgery

For individuals who have mesial temporal lobe epilepsy who receive SRS, clinical input supports that this use provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected patients. Clinical input reported that the less invasive nature of SRS coupled with acceptable seizure remission rates over time may be appropriate for the specific subpopulation of patients with mesial temporal lobe epilepsy refractory to medical management when standard alternative surgery is not an option.

For individuals who have tremor and movement disorders who receive SRS, clinical input does not support a clinically meaningful improvement in the net health outcome and does not indicate this use is consistent with generally accepted medical practice. Clinical input noted systematic reviews of retrospective studies reported a reduction in tremors after SRS, but confirmed that alternative approaches to thalamotomy are appropriate.

For individuals who have chronic pain syndromes refractory to standard medical and psychological treatments (other than those associated with trigeminal neuralgia) who receive intracranial SRS, clinical input does not support a clinically meaningful improvement in the net health outcome and does not indicate this use is consistent with generally accepted medical practice.

For individuals who have uncommon benign neoplastic intracranial lesions (acoustic neuroma, pituitary adenoma, craniopharyngioma, and glomus jugulare tumors) who receive SRS, clinical input supports that this use provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice. Clinical input continues to support an individualized approach to the use of SRS for these tumors with the recognition that outcomes are affected by factors such as the location of the tumor and type of SRS used (hypofractionated, fractionated, or single-session treatment).

For individuals who have uveal melanoma, clinical input supports that this use provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice. Clinical input reported that the use of SRS to treat uveal melanoma could provide patients with low-risk disease (based on tumor size using the Collaborative Ocular Melanoma Study definition of small and medium) an option to avoid or postpone enucleation with preservation of some visual acuity and functional abilities.

Stereotactic Body Radiotherapy

For individuals who have primary and metastatic spinal or vertebral body tumors who have received prior radiotherapy who are treated with SBRT, clinical input supports that this use provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice. Clinical input reported that SBRT is an important treatment option for patients whose spinal tumors had prior radiotherapy because of the ability to spare the spinal cord and escalate tumor dose.

For individuals who have non-small cell lung cancer (NSCLC), clinical input supports that this use provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected patients. The following patient selection criteria are based on clinical expert opinion from clinical study populations: patients with NSCLC who are poor surgical candidates or who do not wish to undergo surgery.

For individuals who have primary hepatocellular carcinoma (HCC), clinical input supports that this use provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected patients. Clinical input confirmed the lack of randomized controlled trials and reported on nonrandomized observational studies that support the use of SBRT as an alternative locoregional treatment for patients with inoperable primary HCC or metastatic lesions and referred to national guidelines that have rendered the same recommendation. The following patient selection criteria are based on clinical expert opinion from clinical study populations: patients including primary or metastatic tumor of the liver that is considered inoperable.

For individuals who have primary prostate carcinoma, limited clinical input reported that the use of SBRT to treat primary prostate cancer provides biochemical control of disease (based on prostate-specific antigen surveillance), preserved quality of life (primarily focused on erectile dysfunction) and acceptable short-term urinary tract toxicity posttreatment. This input did not differentiate candidate patients using guideline-based risk stratification for localized prostate cancer.

For individuals who have pancreatic adenocarcinoma, limited clinical input reported that the use of SBRT for inoperable pancreatic adenocarcinoma also referred to guideline-based recommendations for use in localized disease.

For individuals who have renal cell carcinoma (RCC), clinical input supports that this use provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected patients. The following patient selection criteria are based on clinical expert opinion from clinical study populations: patients with primary RCC who are not good surgical candidates or for relapsed or stage IV disease.

For individuals who have oligometastatic disease, clinical input supports that this use provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected patients. The following patient selection criteria are based on clinical expert opinion from clinical study populations: patients with oligometastatic disease that includes 1 or both adrenal glands in patients who are poor surgical or radiofrequency ablation candidates.

2013 Input

Clinical input was sought to help determine whether the use of SRS and SBRT for individuals with various neoplasms/conditions would provide a clinically meaningful improvement in the net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 3 physician specialty societies (6 reviewers) and 6 academic medical centers, for a total of 12 reviewers. Clinical input supported the use of SBRT for HCC, prostate cancer, and oligometastases, and the use of SRS for uveal melanoma was mixed.

2011 Input

Clinical input was sought to help determine whether the use of SRS and SBRT for individuals with various neoplasms/conditions would provide a clinically meaningful improvement in the net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, input was received from 6 physician specialty societies (8 reviewers) and 4 academic medical centers, for a total of 12 reviewers. There was general agreement with the policy statements for the use of SRS in treating the neoplasms/conditions listed in the policy statements. In addition, there was support to expand the policy statements on the use of SRS to include craniopharyngiomas and glomus jugulare tumors. There was support for the use of SBRT in spinal tumors and early-stage NSCLC; there was also support to expand the use of SBRT in the spine to include metastatic radioresistant tumors. Support for the use in primary and metastatic lesions of the liver, pancreas, adrenal, and kidney was mixed. There was little support for the use of SBRT in prostate cancer.

2008 Input

Clinical input was sought to help determine whether the use of SRS and SBRT for individuals with various neoplasms/conditions would provide a clinically meaningful improvement in the net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, input was received from 2 physician specialty societies and 4 academic medical centers while this policy was under review. Input uniformly supported the use of this technology in the treatment of NSCLC and spinal tumors after prior radiotherapy. There was also support for use in some patients with liver (metastatic and primary) cancer and as first-line treatment of spinal tumors. There was little support for its use in cases of prostate cancer.

Further details from clinical input are included in the Appendix.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Association for the Study of Liver Diseases

The 2023 American Association for the Study of Liver Disease guidelines for hepatocellular carcinoma consider external beam radiation therapy (including stereotactic body radiotherpy [SBRT] or proton beam therapy) as an alternative to thermal ablation for patients with BCLC [Barcelona Clinic Liver Cancer] stage A HCC who are not candidates for surgical resection, including those with tumors greater than 3 cm in size.[230,]

American Heart Association Scientific Statement

In 2017, the American Heart Association and American Stroke Association published a scientific statement on the management of brain arteriovenous malformations (AVMs).[231,] The statement concludes that the available literature supports the use of SRS for small- to moderate-volume brain AVMs that are generally 12 cm^3 or less in volume or located in deep or eloquent regions of the brain.

American Society of Clinical Oncology

In 2024, the American Society of Clinical Oncology (ASCO) published guidelines endorsing the American Society for Radiation Oncology (ASTRO) guidelines for radiation therapy for small cell lung cancer.[232,233,] The following recommendations regarding the use of SBRT in this population were made in these guidelines:

- "Recommendation 2.1. For patients with stage I or II node-negative LS-SCLC who are medically inoperable, either SBRT or conventional fractionation is recommended (Strength of recommendation: strong; Quality of evidence: moderate). Implementation Remarks: Ideally, the node-negative status should be confirmed by invasive nodal staging. Ultracentral tumors (ASCO clarifying comment: meaning those with the planning target volume touching or overlapping the proximal bronchial tree, esophagus, or trachea) may be more appropriately treated with conventional fractionation schema.
- Recommendation 2.2. For patients with stage I or II node-negative LS-SCLC receiving SBRT, chemotherapy should be delivered to patients in whom it is medically tolerated (Strength of recommendation: strong; Quality of evidence: moderate)."

In 2021, ASCO , Society for NeuroOncology (SNO), and ASTRO published a guideline that addresses the role of surgery, radiation therapy, and systemic therapy in the treatment of patients with brain metastases secondary to nonhematologic solid tumors.[234,] The following recommendations regarding the use of SRS in this population were made in this guideline:

- "SRS alone (as opposed to WBRT [whole brain radiotherapy] or combination of WBRT and SRS) should be offered to patients with one to four unresected brain metastases, excluding small-cell carcinoma."
    - "Qualifying Statement: The inclusion criteria of the randomized trials that underly this recommendation were generally tumors of less than 3 or 4 cm in diameter and did not include radioprotectant strategies of memantine or hippocampal avoidance"
- "SRS alone should be offered to patients with one to two resected brain metastases if the surgical cavity can be safely treated and considering the extent of remaining intracranial disease."
    - "Qualifying Statement: The randomized trials upon which this recommendation is based were of single-fraction SRS and conventional WBRT (without radioprotectant strategies of memantine or hippocampal avoidance)"
- "SRS, WBRT, and the combination of SRS plus WBRT are all reasonable options for patients with more than four unresected or more than two resected brain metastases and better performance status (e.g., [Karnofsky Performance Status] KPS ≧70). SRS may be preferred for patients with better prognosis or where systemic therapy that is known to be active in the CNS [central nervous system] is available."

In 2016, ASCO published a guideline that provided recommendations for the treatment of locally advanced, unresectable pancreatic cancer.[235,] The recommendations for SBRT are as follows:

- "For some patients, chemoradiotherapy (CRT) or stereotactic body radiation therapy (SBRT) may be offered up front, on the basis of patient and physician preference (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)."
- "If there is local disease progression after induction chemotherapy, but without evidence of systemic spread, then CRT or SBRT may be offered to patients who meet the following criteria: First-line chemotherapy treatment is completed or terminated because of progression or toxicity; ECOG PS ≦ 2; a comorbidity profile that is adequate, including adequate hepatic and renal function and hematologic status; and patient preference (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)."
- "CRT or SBRT may be offered to patients who have responded to an initial 6 months of chemotherapy or have stable disease but have developed unacceptable chemotherapy-

related toxicities or show a decline in performance status, as a consequence of chemotherapy toxicity (Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)."

- "If there is response or stable disease after 6 months of induction chemotherapy, CRT or SBRT may be offered as an alternative to continuing chemotherapy alone for any patient with LAPC [locally advanced, unresectable pancreatic cancer] (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)."
- "Clinicians may offer SBRT for treatment of patients with LAPC, although additional prospective and/or randomized trials are required to compare results of SBRT with chemotherapy alone and SBRT (Type: informal consensus, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation:moderate)."

American Society for Radiation Oncology

In 2017, the American Society for Radiation Oncology (ASTRO) published an evidence-based guideline on SBRT in patients with early-stage NSCLC.[236,] The guideline concluded that "SBRT has an important role to play in treating early-stage NSCLC, particularly for medically inoperable patients with limited other treatment options." Additionally, the document noted that "lower quality evidence led to conditional recommendations on use of SBRT for tumors >5 cm, patients with prior pneumonectomy, T3 tumors with chest wall invasion, synchronous multiple primary lung cancer, and as a salvage therapy after prior radiation therapy." Of note, the ASCO reviewed the ASTRO guideline in 2018 and determined that "the recommendations from the ASTRO guideline…are clear, thorough, and based on the most relevant scientific evidence."[237,]A 2023 ASTRO guideline for oligometastatic NSCLC recommends, "a patient-centered multidisciplinary discussion of the most appropriate local treatment strategy of RT [radiation therapy] and/or surgery either alone or in combination are recommended" where radiation therapy includes SBRT, hypofractionation, or conventional radiation therapy.[238,]

In 2022, ASTRO published an evidence-based guideline on indications and techniques for external beam radiation therapy (EBRT) in patients with primary liver cancers.[239,] SBRT (also referred to as ultrahypofractionation delivered in ≤5 fractions) was among the EBRT techniques discussed for patients with confirmed HCC and intrahepatic cholangiocarcinoma (IHC). The choice of regimen is based on tumor location, underlying liver function, and available technology.

In 2019, ASTRO published an evidence-based guideline on radiation therapy for pancreatic cancer.[240,]Recommendations are based on a ranking of evidence quality with a corresponding strength of recommendation rating scheme. Quality of evidence is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability. Recommendations about SBRT are detailed in Table 19 below.

In 2022, ASTRO published an evidence-based guideline on radiation therapy for brain metastases.[241,] Recommendations are based on a ranking of evidence quality with a corresponding strength of recommendation rating scheme. Quality of evidence is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability. Recommendations about SRS are detailed in Table 24 below.

Table 24. American Society for Radiation Oncology Stereotactic Radiosurgery Recommendations for Brain Metastases and Pancreatic Cancer

Recommendation	Strength of Recommendation	Quality of Evidence
Indications for SRS alone for intact brain metastases		
For patients with an ECOG performance status of 0-2 and up to 4 intact brain metastases, SRS is recommended	Strong	High

Recommendation	Strength of Recommendation	Quality of Evidence
For patients with an ECOG performance status of 0-2 and 5-10 intact brain metastases, SRS is conditionally recommended	Conditional	Low
For patients with intact brain metastases measuring <2 cm in diameter, single-fraction SRS with a dose of 2000-2400 cGy is recommended	Strong	Moderate
For patients with intact brain metastases measuring ≥2 to <3 cm in diameter, singlefraction SRS using 1800 cGy or multifraction SRS (e.g., 2700 cGy in 3 fractions or 3000 cGy in 5 fractions) is conditionally recommended	Conditional	Low
For patients with intact brain metastases measuring ≥3 to 4 cm in diameter, multifraction SRS (e.g., 2700 cGy in 3 fractions or 3000 cGy in 5 fractions) is conditionally recommended	Conditional	Low
For patients with intact brain metastases measuring >4 cm in diameter, surgery is conditionally recommended, and if not feasible, multifraction SRS is preferred over single-fraction SRS	Conditional	Low
Indications for observation, postoperative SRS, WBRT or preoperative SRS for brain metastases		
For patients with resected brain metastases, radiation therapy (SRS or WBRT) is recommended to improve intracranial disease control.	Strong	High
For patients with resected brain metastases and limited additional brain metastases, SRS is recommended over WBRT to preserve neurocognitive function and patient-reported QoL	Strong	Moderate
. For patients whose brain metastasis is planned for resection, preoperative SRS is conditionally recommended as a potential alternative to postoperative SRS	Conditional	Low
Indications for conventionally fractionated RT or SBRT for pancreatic cancer		
Following surgical resection of pancreatic cancer, adjuvant SBRT is only recommended on a clinical trial or multi-institutional registry.	Strong	Very low
For patients with borderline resectable pancreatic cancer and select locally advanced pancreatic cancer appropriate for downstaging prior to surgery, a neoadjuvant therapy regimen of systemic chemotherapy followed by multifraction SBRT is conditionally recommended	Conditional	Low
For patients with locally advanced pancreatic cancer not appropriate for downstaging to eventual surgery, a definitive therapy regimen of systemic chemotherapy followed by either (1) conventionally fractionated RT with chemotherapy, (2) dose-escalated chemoradiation, or (3) multifraction SBRT without chemotherapy is conditionally recommended	Conditional	Low
Recommendations for dose fractionation and target volumes for pancreatic cancer		
For patients with borderline resectable pancreatic cancer selected for SBRT, 3000-3300 cGy in 600-660 cGy fractions with a consideration for a simultaneous integrated boost of up to 4000 cGy to the tumor vessel interface is conditionally recommended	Conditional	Moderate

Recommendation	Strength of Recommendation	Quality of Evidence
For patients with locally advanced pancreatic cancer selected for SBRT, 3300- 4000 cGy in 660-800 cGy fractions is recommended	Strong	Moderate
For patients with borderline resectable pancreatic cancer selected for SBRT, a treatment volume including the gross tumor volume with a small margin is recommended	Strong	High
For patients with locally advanced pancreatic cancer selected for SBRT, a treatment volume including the gross tumor volume with a small margin is recommended	Strong	High

Abbreviation: CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; RT: radiation therapy; SRS: stereotactic radiosurgery; SBR: stereotactic body radiation therapy; QoL: quality of life; WBRT: whole brain radiation therapy.

Congress of Neurological Surgeons

In 2019, the Congress of Neurological Surgeons published evidence-based guidelines on the use of SRS in the treatment of adults with metastatic brain tumors.[242,] The Congress recommended the following regarding specific clinical questions:

1. Should patients with newly diagnosed metastatic brain tumors undergo SRS compared with other treatment modalities?

- SRS is recommended as an alternative to surgical resection in solitary metastases when surgical resection is likely to induce new neurological deficits and tumor volume and location are not likely to be associated with radiation-induced injury to surrounding structures
- SRS should be considered as a valid adjunctive therapy to supportive palliative care for some patients with brain metastases when it might be reasonably expected to relieve focal symptoms and improve quality of life in the short term if this is consistent with the overall goals of the patient.

2. What is the role of SRS after open surgical resection of brain metastases?

- After open surgical resection of a solitary brain metastasis, SRS should be used to decrease local recurrence rates.

3. What is the role of SRS alone in the management of patients with 1 to 4 brain metastases?

- For patients with solitary brain metastasis, SRS should be given to decrease the risk of local progression.
- For patients with 2 to 4 brain metastases, SRS is recommended for local tumor control, instead of whole brain irradiation therapy, when their cumulative volume is <7 mL.

4. What is the role of SRS alone in the management of patients with more than 4 brain metastases?

- The use of SRS alone is recommended to improve median overall survival for patients with >4 metastases having a cumulative volume <7 mL.

All of these recommendations are Level 3 - based on randomized studies with significant design flaws hampering interpretation and application to all patients, single institution case series, and comparative studies based on historical controls.

International Stereotactic Radiosurgery Society

The International Stereotactic Radiosurgery Society (ISRS) has published a variety of relevant clinical practice guidelines and practice opinions related to SRS. For select guidelines, recommendations are based on a ranking of evidence quality with a corresponding strength of recommendation rating scheme (Table 25).

Table 25. International Stereotactic Radiosurgery Society Guidelines: Rating Schemes for the Strength of the Evidence and Recommendations.

Strength of Evidence	Strength of Recommendation
Class I: • High quality randomized trial with statistically significant difference or no statistically significant difference but narrow confidence intervals • Systematic review of Class I RCTs (and study results were homogenous)	Level I: High degree of clinical certainty (Class I evidence or overwhelming Class II evidence)
Class II: • Lesser quality (e.g., <80% follow-up, no blinding, or improper randomization • Prospective comparative study • Systematic review of Class II studies or Class I studies with inconsistent results • Case control study • Retrospective comparative study	Level II: Clinical certainty (Class II evidence or a strong consensus of Class III evidence)
Class III: • Case series • Expert Opinion	Level III: Clinical uncertainty (Inconclusive or conflicting evidence or opinion)

RCT: randomized controlled trial.

Recommendations and conclusions from various ISRS guidelines and practice opinions include:

Intracranial noncavernous sinus benign meningioma: Current literature supporting SRS for this condition "lacks level I and II evidence. However, when summarizing the large number of level III studies, it is clear that SRS can be recommended as an effective evidence-based treatment option (recommendation level II) for grade 1 meningioma.[243,]

Non-functioning pituitary adenomas: SRS is an effective and safe treatment for patients with non-functioning pituitary adenomas via consensus opinion.[244,] The position paper states that "encouraging short-term data support hypofractionated stereotactic radiotherapy for select patients, and mature outcomes are needed before definitive recommendations can be made."

Benign (World Health Organization Grade I) cavernous sinus meningiomas: Current literature is "limited to level III evidence with respect to outcomes of SRS in patients with cavernous sinus meningiomas. Based on the observed results, SRS offers a favorable benefit to risk profile for patients with cavernous sinus meningioma."[245,]

Arteriovenous malformations: Current literature cautiously suggests that "SRS appears to be a safe, effective treatment for grade I to II arteriovenous malformation and may be considered a front-line treatment, particularly for lesions in deep or eloquent locations." However, the literature is "low quality, limiting interpretation."[246,]

Arteriovenous fistulas: SRS is recommended for patients with "complex dural arteriovenous fistula who are planned for embolization and are at high risk for not achieving complete obliteration with embolization alone; dural arteriovenous fistula who have received previous embolization without complete obliteration and have refractory symptoms; high-risk noncavernous sinus dural arteriovenous fistula or symptomatic cavernous sinus dural arteriovenous fistula who are not candidates for or have refused both embolization or microsurgery."[247,]

Epilepsy: Current literature states that "radiosurgery is an efficacious treatment to control seizures in mesial temporal lobe epilepsy, possibly resulting in superior neuropsychological outcomes and quality of life metrics in selected subjects compared to microsurgery."[248,]

Tremor: For medically refractory tremor, "SRS to the unilateral thalamic ventral intermediate nucleus, with a dose of 130 to 150 Gy, is a well-tolerated and effective treatment….and 1 that is recommended by the International Stereotactic Radiosurgery Society."[249,]

Trigeminal neuralgia: Current literature is "limited in its level of evidence, with only 1 comparative randomized trial reported to date. At present, 1 can conclude that stereotactic radiosurgery is a safe and effective therapy for drug-resistant trigeminal neuralgia."[250,]

Reirradiation for spinal metastases: Current literature suggests that "SBRT to previously irradiated spinal metastases is safe and effective with respect to both local control and pain relief. Although the evidence is limited to low-quality data, SBRT can be a recommended treatment option for reirradiation."[251,]

Postoperative spine malignancy: "Postoperative spine SBRT delivers a high 1-year local control with acceptably low toxicity. Patients who may benefit from this include those with oligometastatic disease, radioresistant histology, paraspinal masses, or those with a history of prior irradiation to the affected spinal segment…the ISRT recommends a minimum interval of 8 to 14 days after invasive surgery before simulation for SBRT, with initiation of radiation therapy within 4 weeks of surgery."[252,]

Postoperative brain metastases resection cavities: "After surgery for a brain metastasis, postoperative SRS is preferred over observation due to superior local control (recommendation level I)." "For patients with 1 resected brain metastasis, ECOG performance status of 0 to 2, and a resection cavity measuring <5 cm, postoperative SRS to the resection cavity is recommended to minimize cognitive toxicity compared with WBRT (recommendation level I)."[253,]

Secretory pituitary adenomas: "SRS is an effective option to control growth of GH-, ACTH-, & PRL-secreting residual or recurrent pituitary adenomas after prior surgical resection but offers lower rate of endocrine improvement or remission." "SRS could also be used as primary therapy for GH- and ACTH-secreting pituitary adenomas in patients deemed medically unfit for surgical resection, or as an alternative to surgical resection for PRL-secreting pituitary adenomas unresponsive to dopaminergic agonists." "Withdrawal of antisecretory medications is preferred, typically for 4 to 12 weeks prior to radiosurgery, if safely possible considering endocrinologic status of patient."[254,]

Vestibular schwannoma: Single-fraction radiosurgery and fractionated stereotactic radiation therapy is recommended for small newly diagnosed vestibular schwannoma without significant mass effect (Koos Grades I to III) and for growing vestibular schwannoma that is small to moderate in size without significant mass effect. [255,]

Small brain metastases (≤1 cm in diameter): Current literature suggests that "for small (1 cm) brain metastases can be safely performed on both Gamma Knife (GK) and CyberKnife (CK) as well as on modern LINACs, specifically tailored for radiosurgical procedures, however, considerable expertise and resources are required for a program based on the latest evidence for best practice". [256,]

Renal cell carcinoma: "The ideal candidates for SBRT are patients who are medically inoperable, technically not suited to surgery, or are at high risk of postoperative dialysis."[257,]

National Comprehensive Cancer Network Guidelines

The National Comprehensive Cancer Network provides guidelines for cancer treatment by site that include the use of SRS and SBRT for certain cancers (Table 26).

Table 26. National Comprehensive Cancer Network Recommendations for Stereotactic Radiosurgery and Stereotactic Body Radiotherapy[i,ii 258,]

Cancer Site	Tumor Type	Recommendation	Version
Bone	• Chondrosarcoma • Chordoma • Ewing sarcoma family of tumors • Giant cell tumor of the bone • Osteosarcoma	• Consider SRS to allow high-dose therapy while maximizing normal tissue sparing (category 2A) • Consider use of SRS/SBRT, especially for oligometastases	1.2025
CNS	• Adult low-grade glioma/pilocytic and infiltrative supratentorial astrocytoma/oligodendroglioma • Anaplastic gliomas/glioblastomas • Adult intracranial ependymoma • Adult medulloblastoma • Primary CNS lymphoma • Primary spinal cord tumors • Meningiomas • Limited brain metastases • Extensive brain metastases • Leptomeningeal metastases • Metastatic spine tumors	• Principles of RT including consideration of SRS or SBRT are applied to each of the listed tumors (category 2A)	3.2024
Colon	• Oligometastases to liver or lung	• Resection is preferred over locally ablative treatment. However, ablative radiotherapy may be considered in patients with a limited number of liver or lung metastases in highly selected cases or in the setting of a clinical trial. RT should not be used in place of surgical resection. • IMRT is preferred for unique clinical situations such as reirradiation of previously treated patients with recurrent disease or unique anatomical situations where IMRT facilitates the delivery of recommended target volume doses while respecting accepted normal tissue dose-volume constraints. • Consider SBRT for patients with oligometastatic disease • SBRT is a reasonable option for patients whose disease cannot be resected or ablated. Many patients, however, are not surgical candidates and/or have disease that cannot be ablated with clear margins or safely treated by SBRT	5.2024
Head and neck		• The panel acknowledged that SBRT might be beneficial in the setting of re-irradiation, palliation, or older adults.	1.2025

Cancer Site	Tumor Type	Recommendation	Version
Hepatobiliary	• Hepatocellular carcinoma • Biliary tract cancers	• Principles of locoregional therapy includes recommendations for SBRT • SBRT can be considered as an alternative to ablation/embolization techniques for HCC or when these therapies have failed or are contraindicated. SBRT (3 to 5 fractions) is often used for patients with 1 to 3 tumors. SBRT could be considered for larger lesions or more extensive disease, if there is sufficient uninvolved liver and liver radiation tolerance can be respected. There should be no extrahepatic disease or it should be minimal and addressed in a comprehensive management plan. • SBRT may be considered for patients with unresectable intrahepatic cholangiocarcinomas	1.2023
Lung	• NSCLC	• SBRT (also known as SABR) has achieved good primary tumor control rates and overall survival, higher than conventionally fractionated radiotherapy. Although SABR is not proven equivalent to lobectomy, some prospective series have demonstrated similar overall and cancer-specific survival (Stage 1, selected node-negative Stage IIA). • Close follow-up and salvage therapy for isolated local and/or locoregional recurrence after SABR have been shown to improve overall survival. • SABR is an appropriate option for patients with high surgical risk (e.g., age ≥75 years, poor lung function) • SABR is most commonly used for tumors up to 5 cm in size, though selected larger isolated tumors can be treated safely if normal tissue constraints are respected. • Definitive RT to limited oligometastases, particularly SABR, is an appropriate option when it can be delivered safely to the involved sites (Stage IV, advanced/metastatic) • SABR/SRS has been found in randomized clinical trials to produce better pain and tumor control of spine and non-spine bone metastases than	11.2024

Cancer Site	Tumor Type	Recommendation	Version
		conventionally fractionated palliative RT, and is appropriate especially for patients with longer expected survival.	
	• SCLC	• Selected patients with stage I–IIA (T1–2, N0, M0) SCLC who are medically inoperable or in whom a decision is made not to pursue surgery may be candidates for stereotactic ablative radiotherapy (SABR), also known as stereotactic body RT (SBRT), to the primary tumor followed by adjuvant systemic therapy.	3.2025

Pancreas	• Pancreatic adenocarcinoma	Locally advanced disease
		• SBRT should be avoided if direct invasion of the bowel or stomach is identified on CT, MRI, and/or endoscopy
		• Data are limited to support specific RT recommendations for locally advanced disease. Options may include:
		  ○ chemoradiation, SBRT, or hypofractionated RT in selected patients who are not candidates for combination chemotherapy
		  ○ induction chemotherapy followed by chemoradiation or SBRT in select patients (locally advanced without systemic metastases)
		• SBRT should be delivered at an experienced, high-volume center with technology that allows for image-guided RT or in a clinical trial
		Recurrent pancreatic cancer
		• Data are limited to support specific RT recommendations for locally recurrent disease. Options for patients with recurrent, unresectable disease may include:
		  ○ Induction chemotherpy followed by chemoradiation or SBRT (if not previously performed)
		  ○ Chemoradiation or SBRT in selected patients who are not candidates for induction chemotherapy
		• SBRT should be delivered at an experienced, high-volume center with technology that allows for
			3.2024

Cancer Site	Tumor Type	Recommendation	Version
		image-guided RT or in a clinical trial	
Prostate	• Prostate cancer	• SBRT is acceptable for treatment of primary prostate cancer across all risk groups and for locoregional and/or distant metastases in practices with appropriate technology and expertise • Based upon data for improved durability of disease control and pain reduction compared to historical palliative regimens, SBRT is recommended for metastasis-directed therapy in the following circumstances: ○ In a patient with limited metastatic disease (e.g., oligometastatic) when ablation is the goal ○ In a patient with limited progression (e.g., oligoprogression) or limited residual disease on otherwise effective systemic therapy (e.g., consolidation) where PFS is the goal ○ In a symptomatic patient where the lesion occurs in or immediately adjacent to a previously irradiated treatment field ○ At physician discretion for more durable control of pain than achieved with typical palliative regimens used in some randomized trial data, which should be considered particularly in prostate cancer where natural history of advanced disease can be very long • •	1.2025
Kidney cancer	• Non-clear cell and clear cell renal carcinoma	• SBRT may be considered for medically inoperable patients with stage 1 kidney cancer (category 2B) or stage II/III kidney cancer (both category 3) • Relapse or Stage IV: Metastasectomy or SBRT or ablative techniques for oligometastatic disease	2.2025
Cutaneous Melanoma	• Intact extracranial metastases	• Principles of RT include recommendations for use of SBRT	3.2024

Cancer Site	Tumor Type	Recommendation	Version
		• SBRT may be considered for selected patients with oligometastasis	
Uveal melanoma	• Primary and recurrent intraocular tumors	• SRS is the least often used form of definitive RT	1.2024
Soft tissue sarcoma	• Extremity/superficial trunk/head and neck • Retroperitoneal/intra-abdominal	• If disseminated metastases: SBRT as a palliative option (category 2A) • For Stage IV with oligometastases and limited tumor bulk that are amenable to local therapy: SBRT with or without chemotherapy as an option • For metastatic disease with isolated regional disease or nodes: SBRT as an option	4.2024
Thyroid	• Thyroid carcinoma	• Surgical excision, EBRT, SBRT, or other local therapies can be considered for symptomatic isolated skeletal metastases or those that are asymptomatic in weight-bearing sites	4.2024

ADT: androgen-deprivation therapy; CNS: central nervous system; CT: computed tomography; EBRT: external-beam radiotherapy; HCC: hepatocellular carcinoma; IGRT: image-guided radiotherapy; IMRT: intensity-modulated radiotherapy; MRI: magnetic resonance imaging; NCCN: National Comprehensive Cancer Network; NSCLC: non-small cell lung cancer; RT: radiotherapy; SABR: stereotactic ablative radiotherapy; SBRT: stereotactic body radiotherapy; SCLC: small cell lung cancer; SRS: stereotactic radiosurgery.
[i] Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®).
©National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed June 1, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org.
[ii] NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Currently ongoing and unpublished trials that might influence this review are listed in Table 27. These trials are merely representative of the numerous clinical trials involving SRS and SBRT for various conditions.

Table 27. Summary of Key Trials

NCT No.	Trial Name	Enrollment	Completion Date
Ongoing: Stereotactic radiosurgery			
Central nervous system neoplasms			
Acoustic neuroma (vestibular schwannoma)			
NCT02055859	Cyberknife Radiosurgery for Patients with Neurinomas	108	May 2025
Brain metastases			
NCT01592968	A Prospective Phase III Randomized Trial to Compare Stereotactic Radiosurgery Versus Whole Brain Radiation Therapy for >/= 4 Newly Diagnosed Non-Melanoma Brain Metastases	88	Sept 2025

NCT No.	Trial Name	Enrollment	Completion Date
NCT00950001	Efficacy of Post-Surgical Stereotactic Radiosurgery for Metastatic Brain Disease: A Randomized Trial	132	Apr 2025
NCT01644591	A Phase II Trial to Determine Local Control and Neurocognitive Preservation After Initial Treatment With Stereotactic Radiosurgery (SRS) for Patients With >3 Melanoma Brain Metastases	49	Aug 2025
NCT04891471	WHOle Brain Irradiation and STEreotactic Radiosurgery for Five or More Brain Metastases (WHOBI-STER): a Prospective Comparative Study of Neurocognitive Outcomes, Level of Autonomy in Daily Activities and Quality of Life	100	Sep 2025
Spinal metastases			
NCT02800551	Dose-intensified Image-guided Fractionated Stereotactic Body Radiation Therapy for Painful Spinal Metastases Versus Conventional Radiation Therapy: a Randomised Controlled Trial (DOSIS RCT)	219 (actual)	Jul 2024
Glioma			
NCT01464177	Prospective Randomized Phase II Trial of Hypofractionated Stereotactic Radiotherapy in Recurrent Glioblastoma Multiforme	40	Aug 2024
Ongoing: Stereotactic body radiotherapy			
Non-small cell lung cancer			
NCT05111197	Local Ablative Stereotactic Radiotherapy for Residual Hypermetabolic Lesion in Patients With Locally Advanced or Metastatic Non-small Cell Lung Cancer Long-term Responders to Immunotherapy : a Randomized, Multicenter, Open-label Phase III Study	112	Jan 2025
Hepatocellular carcinoma			
NCT01730937	Randomized Phase III Study of Sorafenib Versus Stereotactic Body Radiation Therapy Followed by Sorafenib in Hepatocellular Carcinoma	193	Jul 2027
Prostate cancer			
NCT01584258	International Randomised Study of Prostatectomy vs Stereotactic Body Radiotherapy (SBRT) and Conventionally Fractionated Radiotherapy vs SBRT for Organ-Confined Prostate Cancer	2205 (actual)	Dec 2027 (active, not recruiting)
NCT05209243	Phase III Study of Stereotactic BodyRadiation Therapy (SBRT) Plus Standard of Care in Castration Sensitive Oligometastatic Prostate Cancer Patients	266	Jan 2027
NCT04983095	Metastasis Directed Stereotactic Body Radiotherapy for Oligo Metastatic Hormone Sensitive Prostate Cancer	118	Dec 2031
NCT01508390	Phase II Study of Hypofractionated Stereotactic Body Radiation Therapy as a Boost to the Prostate for Treatment of Localized, Non-Metastatic, High Risk Prostate Cancer	35	Dec 2027
NCT01794403	A Randomized Study of Radiation Hypofractionation Via Extended Versus Accelerated Therapy (HEAT) For Prostate Cancer	456	Aug 2024
NCT02470897	A Phase I/II Study of Stereotactic Body Radiotherapy (SBRT) for Prostate Cancer Using Simultaneous Integrated Boost and Urethral-Sparing IMRT Planning	115	Aug 2025
NCT01764646	Stereotactic Body Radiation Therapy for cT1c - cT3a Prostate Cancer With a Low Risk of Nodal Metastases (≦ 20%, Roach Index): a Novalis Circle Phase II Prospective Randomized Trial	170	Sep 2025
NCT01985828	Prospective Evaluation of CyberKnife® as Monotherapy or Boost Stereotactic Body Radiotherapy for Intermediate or High Risk Localized Prostate Cancer	72	Dec 2026
NCT03367702	Phase III IGRT and SBRT vs IGRT and Hypofractionated IMRT for Localized Intermediate Risk Prostate Cancer	698	Dec 2030
Epilepsy			
NCT05182437	Precision Radiation Treatment for Epilepsy (PRECISION)	94	Jan 2028
Unpublished: Stereotactic Radiosurgery			
NCT02147028	A Randomized Phase II Trial of Hippocampal Sparing Versus Conventional Whole Brain Radiotherapy After Surgical Resection or Radiosurgery in Favourable Prognosis Patients With 1-4 Brain Metastases	23	Feb 2021

NCT No.	Trial Name	Enrollment	Completion Date
Unpublished: Stereotactic body radiotherapy			
NCT01839994	Phase III Clinical Trial on Conventionally Fractionated Conformal Radiotherapy (CF-CRT) Versus CF-CRT Combined With High-dose-rate Brachytherapy or Stereotactic Body Radiotherapy for Intermediate and High-risk Prostate Cancer.	350	Dec 2018 (unknown)
NCT01968941	A Randomized Trial of Medically-Inoperable Stage 1 Non-small Cell Lung Cancer Patients Comparing Stereotactic Body Radiotherapy Versus Conventional Radiotherapy	324	May 2022

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

Appendix 1

Appendix 1. Studies included in Systematic Reviews

Table SR1. Comparison of Trials/Studies Included in SR & M-A

Study	Savardekar (2022)[41,]
Han (2012)	●
Park (2012)	●
Roos (2012)	●
Varughese (2012)	●
Yomo (2012)	●
Carlson (2013)	●
Sager (2013)	●
Vivas (2013)	●
Boari (2014)	●
Carratalá (2014)	●
Combs (2015)	●
Ikonomidis (2015)	●
Golfinos (2016)	●
Horiba (2016)	●
Klijn (2016)	●
Watanabe (2016)	●
Bowden (2017)	●
Milner (2017)	●
Pan (2017)	●
Rueß (2017)	●
Chung (2018)	●
Hasegawa (2018)	●
Dzierzecki (2020)	●

M-A: meta-analysis; S-R: systematic review.

Appendix 2

2018 Input

Clinical input was sought to help determine whether the use of stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) for individuals with various neoplasms/conditions would provide a clinically meaningful improvement in the net health outcome and whether the use is consistent with generally accepted medical practice.

Respondants

Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- American Society for Radiation Oncology

- American Society for Stereotactic and Functional Neurosurgery and American Association of Neurological Surgeons / Congress of Neurological Surgeons
- David B. Shultz, MD, PhD, Radiation Oncology, identified by the American Society for Radiation Oncology
- Anonymous, MD, Neurology, Epilepsy, identified by the American Academy of Neurology
- Anonymous, MD, Neurosurgery, identified by an academic medical center

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by a specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the Evidence Street® clinical input process provide review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a specialty society and/or physician member designated by a specialty society or health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA or any Blue Plan.

Respondent Profile

Appendix Table 1. Respondent Profile

	Specialty Society				
No.	Name of Organization		Clinical Specialty		
1	American Society for Radiation Oncology		Radiation Oncology		
2	American Society for Stereotactic and Functional Neurosurgery and American Association of Neurological Surgeons / Congress of Neurological Surgeons		Neurosurgery; Stereotactic and Functional Neurosurgery		
	Physician				
No.	Name	Degree	Institutional Affiliation	Clinical Specialty	Board Certification and Fellowship Training
Identified by American Society of Clinical Oncology					
3	David B. Shultz	MD, PhD	Princess Margaret Cancer Centre	Radiation Oncology	Diplomate of the American Board of Radiology; Fellow of the Royal College of Physicians of Canada
Identified by American Academy of Neurology					
4	Anonymous	MD	Associate professor at an academic medical center	Neurology; Epilepsy	American Board of Psychiatry and Neurology; Adult Epilepsy
Identified by an academic medical center					
5	Anonymous	MD	Academic medical center	Neurosurgery	American Board of Neurological Surgery

Respondent Conflict of Interest Disclosure

Appendix Table 2. Respondent Conflict of Interest Disclosure

No.	1. Research support related to the topic where clinical input is being sought		2. Positions, paid or unpaid, related to the topic where clinical input is being sought		3. Reportable,more than $1000, healthcare-'related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought		4. Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	
	Yes/No	*Explanation*	*Yes/No*	*Explanation*	*Yes/No*	*Explanation*	*Yes/No*	*Explanation*
3	No		No		No		Yes	I have previously received travel

No.	1. Research support related to the topic where clinical input is being sought	2. Positions, paid or unpaid, related to the topic where clinical input is being sought	3. Reportable,more than $1000, healthcare-'related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	4. Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought
				reimbursements from Elekta. I have previously received money from AstraZeneca ($2000) for a lecture.
4	No	No	No	No
5	No	No	No	No

No.	Conflict of Interest Policy Statement
1	ASTRO's Payer Relations Committee provided input for the response. We do not have any conflicts.
2	Ad hoc committee. There are no conflicts of interest related to this topic among the Board of Directors of ASSFN or the ad hoc committee.

Individual physician respondents answered at individual level. Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response.

Responses

- We are seeking your opinion on whether using the interventions for the below indications provide a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience. Please address these points in your response:
  - Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
  - Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication;
  - Supporting evidence from the authoritative scientific literature (please include PMID).

No.	Indications	Rationale
1	Individuals with epilepsy who receive stereotactic radiosurgery	• Barajas MA, Ramirez-Guzman MG, Rodriguez-Vazquez C, et al. G. Gamma Knife surgery for hypothalamic hamartomas accompanied by medically intractable epilepsy and precocious puberty: experience in Mexico. *J Neurosurg*. 2005;102 Suppl:53-55. PMID 15662781. • Mathieu D, Kondziolka D, Niranjan A, et al. Gamma knife radiosurgery for refractory epilepsy caused by hypothalamic hamartomas. *Stereotact Funct Neurosurg*. 2006;84(2-3): 82-87. PMID 21121804 • Regis J, Scavarda D, Tamura M, et al. Epilepsy related to hypothalamic hamartomas: Surgical management with special reference to Gamma Knife surgery. Childs Nerv Syst. 2006; 22(8):881-895 • Barbaro NM, Quigg M, Broshek DK, et al. A multicenter, prospective pilot study of gamma knife radiosurgery for mesial temporal lobe epilepsy: seizure response, adverse events, and verbal memory. *Ann Neurol*. 2009;65(2):167-175. PMID 19243009 • Quigg M, Barbaro NM. Stereotactic radiosurgery for treatment of epilepsy. *Arch Neurol*. 2008;65(2):177-183. PMID 18268185

No.	Indications	Rationale
2	Individuals with epilepsy who receive stereotactic radiosurgery	Radiosurgery has been shown to be of value in terms of improving epilepsy in patients with hypothalamic hamartomas, cavernomas, and other structure abnormalities such as intracranial arteriovenous malformations. In a recent study by Bowden et al. (PMID 24926653), 53% of AVM patients achieved Engel Class I after radiosurgery. In another study by Ding et al. (PMID 26026628), seizure improvement and remission were seen in 57% and 20% of 229 AVM patients treated with SRS. In addition, in patients with mesial temporal lobe epilepsy, SRS is an accepted and worthwhile treatment option for achieving seizure remission. In addition, there may be less verbal memory impairment with SRS compared to open surgical techniques in the treatment of mesial temporal lobe epilepsy (PMID: 29600809). • Bowden G, Kano H, Tonetti D, et al. Stereotactic radiosurgery for sylvian fissure arteriovenous malformations with emphasis on hemorrhage risks and seizure outcomes. *J Neurosurg*. Sep 2014;121(3):637-44. PMID 24926653 • Ding D, Quigg M, Starke RM, et al. Cerebral Arteriovenous Malformations and Epilepsy, Part 2: Predictors of Seizure Outcomes Following Radiosurgery. World Neurosurg. 2015 Sep;84(3):653-62. PMID 26026628 • Barbaro NM, Quigg M, Ward MM, et al. Radiosurgery versus open surgery for mesial temporal lobe epilepsy: The randomized, controlled ROSE trial. *Epilepsia*. Jun 2018;59(1):119801207. PMID 29600809
3	Individuals with epilepsy who receive stereotactic radiosurgery	I do not have any clinical experience using stereotactic radiosurgery (SRS) to treat epilepsy and am not an expert on the subject. However, in addition to the reports cited in November 2017 evidence summary, and systematic reviews published in the past year (Eekers, 2018 and McGonigal, 2017), in 2018, results from a randomized trial of 58 patients comparing SRS to anterior temporal lobectomy for drug-resistant mesial temporal lobe epilepsy (MTLE) were published (Barbaro, 2018). In this report, 52% of patients treated with SRS achieved seizure remission compared to 78% in the surgery group. According to the study design, this study failed to show non-inferiority of SRS to surgery. However, it does provide higher level evidence that SRS is safe and effective in some seizure patients with MTLE, and is consistent with numerous retrospective reports. • Eekers DBP, Pijnappel EN, Schihns OEMG, et al. Evidence on the efficacy of primary radiosurgery or stereotactic radiotherapy for drug-resistant non-neoplastic focal epilepsy in adults: A systematic review. *Seizure*. Feb 2018;55:83-92. PMID 29414140 • McGonigal A, Sahgal A, De Salles A, et al. Radiosurgery for epilepsy: Systematic review and International Stereotactic Radiosurgery Society (ISRS) practice guideline. *Epilepsy Res.* Nov 2017; 137:123-131. PMID 28939289 • Barbaro NM, Quigg M, Ward MM, et al. Radiosurgery versus open surgery for mesial temporal lobe epilepsy: The randomized, controlled ROSE trial. *Epilepsia*. Jun 2018;59(1):119801207. PMID 29600809
4	Individuals with epilepsy who receive stereotactic radiosurgery	The background review in Evidence Street from 2017 was reviewed and this author agrees with the prior summary with the following additions below. The purpose of SRS is to use a focused radiotherapy technique to ablate epileptogenic foci when seizures have become drug-resistant or medication adverse events are intolerable and to potentially avoid complications associated with surgical intervention. Evidence on the use

No.	Indications	Rationale
		of SRS for epilepsy treatment is limited by the lack of RCTs comparing SRS with other therapies for epilepsy treatment. A systemic review by McGonigal in 2017, listed two indications of SRS for epilepsy, specifically mesial temporal lobe epilepsy (MTLE) and hypothalamic hamartoma (HH) as having level 2 evidence (prospective studies). Additional indications of corpus callosotomy as a palliative treatment and epilepsy related to cavernous malformations was level 4 (case reports, etc.). Consideration should be given to these specific situations especially when there is a contraindication to resective or ablative epilepsy surgery. PMID 28939289 • McGonigal A, Sahgal A, De Salles A, et al. Radiosurgery for epilepsy: Systematic review and International Stereotactic Radiosurgery Society (ISRS) practice guideline. *Epilepsy Res*. Nov 2017; 137:123-131. PMID 28939289
5	Individuals with epilepsy who receive stereotactic radiosurgery	I provide neurosurgical treatment for patients with medically refractory epilepsy. Our institution does not use radiosurgery to treat patients with this condition. We do not believe radiosurgery is superior to more standard alternative treatments.
1	Individuals with tremor and movements disorders who receive stereotactic radiosurgery	• Kondziolka D, Ong JG, Lee JY, et al. Gamma Knife thalamotomy for essential tremor. *J Neurosurg*. 2008;108(1):111-117. PMID 18173319 • Zesiewicz TA, Elble R, Louis ED, et al. Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2005;64(12):2008-2020. PMID 15972843 • Duma CM. Movement disorder radiosurgery--planning, physics and complication avoidance. *Prog Neurol Surg*. 2007; 20:249-266 PMID 17317994
2	Individuals with tremor and movements disorders who receive stereotactic radiosurgery	There have been a number of studies demonstrating the safety and efficacy of SRS for tremor and movement disorders. In a recent review by Martinez-Moreno et al. (2018), tremor reductions were reported in a mean of 88% of patients in a review of more than 34 different studies (PMID 29473775). In a study spanning a 19 year experience of 73 patients treated with SRS for intractable tremor, 93.2% of patient had improvement (PMID 28319282). In a prospective trial of tremor patients, Witjas et al. (2015; PMID 26446066) noted 54.2% upper limb tremor score on blinded assessment and ADL improvement of 72.2%. • Martinez-Moreno NE, Sahgal A, De Salles A, et al. Stereotactic radiosurgery for tremor: systematic review. *J Neurosurg*. Feb 2018:1-12 PMID 29473775 • Niranjan A, Raju SS, Kooshkabadi A, et al. Stereotactic radiosurgery for essential tremor: Retrospective analysis of a 19-year experience. *Mov Disord*. May 2017;32(5):769-777. PMID 28319282 • Witjas T, Carron R, Krack P, et al. A prospective single-blind study of Gamma Knife thalamotomy for tremor. *Neurology*. Nov 2015;85(18):1562-8. PMID 26446066
3	Individuals with tremor and movements disorders who receive stereotactic radiosurgery	I do not have any clinical experience using stereotactic radiosurgery (SRS) to treat tremor or movement disorders and am not an expert on the subject. My review of the current literature revealed one new systematic review (Martinez-Moreno, 2018). I concur with the section summary. I was able to identify one study that retrospectively compared deep brain stimulation, radiofrequency thermocoagulation, and SRS, reporting similar control rates from the 3 modalities but less toxicity and more durability from SRS. (Niranjan, 2000). In particular, there are a few studies that included a blinded evaluation and nearly all studies consistently show improvement with SRS. Studies

No.	Indications	Rationale
		assessing quality of life would be helpful in terms of understanding better what changes in rating scales means from a practical standpoint for patients. i.e. whether the improvements are clinically significant. Furthermore, there does appear to be a lack of long-term follow up. Nonetheless, my impression is that SRS provides meaningful benefit for the health outcome of patients treated for tremors or movement disorders. • Martinez-Moreno NE, Sahgal A, De Salles A, et al. Stereotactic radiosurgery for tremor: systematic review. *J Neurosurg.* Feb 2018:1-12 PMID 29473775 • Niranjan A, Kondziolka D, Baser S, et al. Functional outcomes after gamma knife thalamotomy for essential tremor and MS-related tremor. *Neurology.* Aug 2000;55(3):443-6. PMID 10932286
4	Individuals with tremor and movements disorders who receive stereotactic radiosurgery	The background review in Evidence Street from 2017 was reviewed and this author agrees with the prior summary with the following additions below. The purpose of SRS is to use a focused radiotherapy technique to ablate brain nuclei foci associated with movement disorders (e.g., essential tremor, parkinsonian disorders) when the conditions have become drug-resistant or medication adverse events are intolerable and to potentially avoid complications associated with surgical intervention. After review, no additional studies or evidence was found beyond which was already included in the 2017 report.
5	Individuals with tremor and movements disorders who receive stereotactic radiosurgery	As with epilepsy surgery (above) we do not use radiosurgery to treat patients with movement disorders because we feel other methods (e.g. DBS) are more effective and safer.
1	Individuals with chronic pain or other non-neoplastic neurologic disorders other than epilepsy or tremor / movement disorder who receive stereotactic radiosurgery	• Donnet A, Tamura M, Valade D, RJ. Trigeminal nerve radiosurgical treatment in intractable chronic cluster headache: unexpected high toxicity. *Neurosurgery.* 2006; 59(6):1252-1257. PMID 17277687
2	Individuals with chronic pain or other non-neoplastic neurologic disorders other than epilepsy or tremor / movement disorder who receive stereotactic radiosurgery	In a recent systematic review, trigeminal neuralgia was found to demonstrate substantial response to SRS (Tuleasca et al., 2018; PMID 29701555). In this study of 585 initially identified results from a literature review, median actutimes initial freedom from pain was achieved in 52.1% of trigeminal neuralgia patients treated with Gamma Knife radiosurgery. In another study of quality of life outcomes in trigeminal neuralgia patients treated with SRS, SF-36 quality of life indices improved significantly with SRS induced pain relief (Pan et al., 2010; PMID 21121802). In a recent practice guideline, the International Stereotactic Radiosurgery Society noted "better risk-benefit ratio for small hypothalamic hamartomas compared to surgical methods" when using SRS (McGonigal et al., 2017; PMID 28939289). • Tuleasca C, Regis J, Sahgal A, et al. Stereotactic radiosurgery for trigeminal neuralgia: a systematic review. *J Neurosurg.* Apr 2018;27:1-25. PMID 29701555 • Pan HC, Sheehan J, Huang CF, et al. Quality-of-life outcomes after Gamma Knife surgery for trigeminal neuralgia. *J Neurosurg*. Dec 2010;113 Suppl:191-8. PMID 21121802 • McGonigal A, Sahgal A, De Salles A, et al. Radiosurgery for epilepsy: Systematic review and International Stereotactic

No.	Indications	Rationale
		Radiosurgery Society (ISRS) practice guideline. *Epilepsy Res.* Nov 2017; 137:123-131. PMID 28939289
3	Individuals with chronic pain or other non-neoplastic neurologic disorders other than epilepsy or tremor / movement disorder who receive stereotactic radiosurgery	Trigeminal neuralgia (TG) is the pain syndrome for which SRS is used. There are numerous retrospective series reporting outcomes, primarily using Gamma Knife, for the treatment of TG. The largest are: Maesawa (2001), Brisman (2004), Kondziolka (2010), and Verheul (2010). These studies have median follow up ranging from 11-28 months. Collectively, these studies a reasonable rate of pain control at 1 year (64-91%) that diminishes over time (38%-78% at 5 years). Pain control is exceedingly difficult to measure due to lack of standardization in testing and reporting outcomes as well as subjectivity on the part of patients, so it is not surprising that this degree of variability exists. What is clear is that SRS used for this purpose has a low rate of toxicity (5-10% rate in these series, mostly mild symptoms such as facial numbness) and appears to be effective for the majority of patients, at least initially. TG is a very difficult condition for most patients and SRS is a non-invasive treatment option that does not preclude future options such as surgery.
4	Individuals with chronic pain or other non-neoplastic neurologic disorders other than epilepsy or tremor / movement disorder who receive stereotactic radiosurgery	The background review in Evidence Street from 2017 was reviewed and this author agrees with the prior summary with the following additions below. The purpose of SRS is to use a focused radiotherapy technique to ablate intracranial neuronal foci of chronic pain that have become drug-resistant or when medication adverse events are intolerable as an alternative to other surgical interventions. I could not identify any additional evidence beyond that in the prior 2017 report.
5	Individuals with chronic pain or other non-neoplastic neurologic disorders other than epilepsy or tremor / movement disorder who receive stereotactic radiosurgery	In our practice we do not view these conditions as being indications for radiosurgery
1	Individuals with benign neoplastic intracranial lesion(s) (craniopharyngioma, glomus jugulare tumors) who receive stereotactic radiosurgery	• Gopalan R, Dassoulas K, Rainey J, et al. Evaluation of the role of Gamma Knife surgery in the treatment of craniopharyngiomas. *Neurosurg Focus*. 2008; 24(5): E5. PMID 18447744 • Kano H, Lunsford LD. Stereotactic radiosurgery of intracranial chordomas, chondrosarcomas, and glomus tumors. *Neurosurg Clin N Am*. Oct 2013;24(4):553-560. PMID 24093573
2	Individuals with benign neoplastic intracranial lesion(s) (craniopharyngioma, glomus jugulare tumors) who receive stereotactic radiosurgery	SRS has been shown to yield excellent long term tumor control in most patients with craniopharyngiomas and glomus tumors. In a recent study by Patel et al. (2018; PMID 29652232), they demonstrated 98% 5-year progression free survival of glomus tumor patients treated with SRS. This was with an acceptable toxicity profile which is important given the potential lower cranial nerve dysfunction associated with open surgical treatment of these lesions. In an international multicenter study, tumor control following SRS was achieved in 93% of glomus tumor patients (Sheehan et al., 2012; PMID 22680240). 5 year progression free survival in craniopharyngioma patients was achieved in 91.6% following SRS (PMID 20005637). In another study of 137 craniopharyngioma patients treated with SRS, progression free survival was 70% at 5 years (PMID 25434950). • Sheehan JP, Tanaka S, Link MJ, et al. Gamma Knife surgery for the management of glomus tumors: a multicenter study. *J Neurosurg*. Aug 2012;117(2):246-54. PMID 22680240

No.	Indications	Rationale
		• Niranjan A, Kano H, Mathieu D, et al. Radiosurgery for craniopharyngioma. *Int J Radiat Oncol Biol Phys*. Sep 2010;78(1):64-71. PMID 20005637 • Lee CC, Yang HC, Chen CJ, et al. Gamma Knife surgery for craniopharyngioma: report on a 20-year experience. *J Neurosurg*. Dec 2014;121 Suppl:167-78. PMID 25434950
3	Individuals with benign neoplastic intracranial lesion(s) (craniopharyngioma, glomus jugulare tumors) who receive stereotactic radiosurgery	I have extensive clinical experience treating vestibular schwannomas (VS) and pituitary adenomas with stereotactic radiosurgery (SRS). Most VS can be treated with SRS, which is appropriate when there is evidence of tumor growth and when any brain stem progression is limited (no edema on T2 weighted MRI) and asymptomatic. SRS for pituitary adenoma is appropriate in cases where trans-sphenoidal surgery is contraindicated and/or not expected to effectively remove all growing tumor and where medical management has failed. In both cases, fractionated radiotherapy is usually an option, however the primary advantage of SRS is that it drastically lowers the risk of secondary malignancies, which can be as high as 2% at 10-years for fractionated radiation but is likely far less than 0.1% for SRS. The primary issue with SRS studies for vestibular schwannomas is lack of long -term follow up (i.e. > 10 years), which is necessary. For other benign tumors, such as craniopharyngiomas, the role for SRS is less established. Several retrospective series suggest that treatment can be delivered safely and that it is effective, likely for carefully selected patients and small tumors. In reality, almost all craniopharyngiomas undergo surgery as the primary treatment, usually more than once. Local recurrences in this setting are difficult targets for SRS given unclear the lack of a discrete target and the proximity to sensitive structures such as the optic chiasm. On the other hand, fractionated radiotherapy carries risks, such as secondary malignancies and cognitive toxicities, which are particularly relevant for this patient population. Fractionated SRS of the type referred to in Coombs et al (2007) is fundamentally different than single or limited fraction SRS; it by far the most common radiotherapy used for treating craniopharyngiomas. Although I do not have any experience treating glomus tumors with SRS, there appears to be greater clinical experience with that, including several meta-analyses in addition that cited in the section summary (Shapiro, 2018; Guss, 2011); however there are no prospective studies or comparative studies of this practice that I am aware of. • Shapiro S, Kellermeyer B, Ramadan J, et al. Outcomes of Primary Radiosurgery Treatment of Glomus Jugulare Tumors: Systematic Review With Meta-analysis. *Otol Neurotol*. Oct 2018;39(9):1079-1087. PMID 30124618 • Guss ZD, Batra S, Limb CJ, et al. Radiosurgery of glomus jugulare tumors: a meta-analysis. *Int J Radiat Oncol Biol Phys*. Nov 2011;81(4):e497-502. PMID 21703782
4	Individuals with benign neoplastic intracranial lesion(s) (craniopharyngioma, glomus jugulare tumors) who receive stereotactic radiosurgery	The background review in Evidence Street from 2017 was reviewed and this author agrees with the prior summary with the following additions below. The purpose of SRS is to use a focused radiotherapy technique to treat intracranial and other brain lesions that are relatively inaccessible surgically and which are often located in proximity to eloquent or radio-sensitive areas. Acoustic Neuromas - additional retrospective 5-year follow up study by Chen et. al. on hypo-fractionated SRT showed similar progression outcomes and control rates but with better preservation of hearing. PMID 29556918 Also a review of SRT vs. surgery in NF2, by Chung et. al.,

No.	Indications	Rationale
		vestibular schwannomas may have relevance. Rates of hearing preservation were higher in the surgery cohorts, SRS demonstrated high rates of local control and significantly lower facial nerve complications. This could have implications based on patient selection based on expected adverse outcomes. PMID 28882713. • Chen Z, Takehana K, Mizowaki T, et al. Five-year outcomes following hypofractionated stereotactic radiotherapy delivered in five fractions for acoustic neuromas: the mean cochlear dose may impact hearing preservation. *Int J Clin Oncol*. Aug 2018;23(4):608-614. PMID 29556918 • Chung LK, Nguyen TP, Sheppard JP, et al. A Systematic Review of Radiosurgery Versus Surgery for Neurofibromatosis Type 2 Vestibular Schwannomas. *World Neurosurg*. Jan 2018;109:47-58. PMID 28882713 Pituitary Adenoma - after review, there is no identified additional evidence beyond those included in the prior report and in the summary. No comparative studies found. Craniopharyngioma - additional prospective cohort study by Astradsson et. al., with 16 patients median follow up was 3.3 years, with similarly cited control rate and low complications (1 optic neuropathy) PMID 28084862. No RCTs found. • Astradsson A, Munck A, Rosenschold P, et al. Visual outcome, endocrine function and tumor control after fractionated stereotactic radiation therapy of craniopharyngiomas in adults: findings in a prospective cohort. *Acta Oncol*. Mar 2017;56(3):415-421. PMID 28084862 Glomus Jugulare Tumors - after review, there is no identified additional evidence beyond those included in the prior report and in the summary.
5	Individuals with benign neoplastic intracranial lesion(s) (craniopharyngioma, glomus jugulare tumors) who receive stereotactic radiosurgery	We would consider these indications on a case-by-case basis. In some circumstances radiosurgery might be the best treatment option.
1	Individuals with malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas) who receive stereotactic radiosurgery	• Kano H, Kondziolka D, Lunsford LD, et al. Stereotactic radiosurgery for pilocytic astrocytomas part 1: outcomes in adult patients. *J Neurooncol*. Nov 2009;95(2):211-218. PMID 19468691 • Schwer AL, Damek DM, Kavanagh BD, et al. A phase I dose-escalation study of fractionated stereotactic radiosurgery in combination with gefitinib in patients with recurrent malignant gliomas. *Int J Radiat Oncol Biol Phys*. Mar 2008;70(4): 993-1001. PMID 17967517
2	Individuals with malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas) who receive stereotactic radiosurgery	Radiosurgery has been shown to be of therapeutic value for patients with high and low grade gliomas. In a study by Cuneo et al. (PMID 21489708), concurrent radiosurgery and Avastin resulted in median overall survival of 10 months in recurrent malignant glioma patients. In another study of radiosurgery for glioblastoma patients, 30% of patients had an overall survival of 2 years (PMID 25594327). In a study of SRS for pilocytic astrocytomas (Trifiletti et al., 2017; PMID 28567590), SRS resulted in durable tumor control of 93% of patients treated. • Cuneo KC, Vredenburgh JJ, Sampson JH, et al. Safety and efficacy of stereotactic radiosurgery and adjuvant bevacizumab in patients with recurrent malignant gliomas. *Int*

No.	Indications	Rationale
		J Radiat Oncol Biol Phys. Apr 2012;82(5):2018-24. PMID 21489708 • Niranjan A, Kano H, Kondziolka D, et al. Role of adjuvant or salvage radiosurgery in the management of unresected residual or progressive glioblastoma multiforme in the pre-bevacizumab era. *J Neurosurg*. Apr 2015;122(4):757-65. PMID 25594327 • Trifiletti DM, Peach MS, Xu Z, et al. Evaluation of outcomes after stereotactic radiosurgery for pilocytic astrocytoma. *J Neurooncol*. Sep 2017;134(2):297-302. PMID 28567590
3	Individuals with malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas) who receive stereotactic radiosurgery	I have limited experience treating malignant gliomas with stereotactic radiosurgery (SRS). With regard to grade I gliomas, the primary treatment should be surgery if the lesion is accessible. For tumors that are inaccessible, SRS is likely a reasonable treatment, however there is no high-level evidence to support that management strategy. For grade 2 or higher gliomas, SRS has mainly been used as salvage therapy. Recurrent grade II tumors often recur as a higher grade; glioblastomas (grade IV) universally recur. When these tumors recur in patients who have previously undergone large field conventional radiotherapy, SRS targeting the recurrent lesion within that prior field or outside of if it has been reported in both retrospective and prospective studies, with favorable results, albeit without a comparator arm. Such a strategy is likely beneficial in instances where the recurrence is small, well defined, and where several months have passed since the initial chemoradiotherapy. At least one trial has used SRS for the upfront treatment of glioblastomas (Pollom, 2017), but that strategy should only be employed in the context of a clinical trial. • Pollom EL, Fujimoto D, Wynne J, et al. Phase 1/2 Trial of 5-Fraction Stereotactic Radiosurgery With 5-mm Margins With Concurrent and Adjuvant Temozolomide in Newly Diagnosed Supratentorial Glioblastoma: Health-Related Quality of Life Results. *Int j Radiat Oncol Biol Phys*. May 2017;98(1):123-130. PMID 28586949
4	Individuals with malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas) who receive stereotactic radiosurgery	The background review in Evidence Street from 2017 was reviewed and this author agrees with the prior summary with the following additions below. The purpose of SRS is to use a focused radiotherapy technique to treat certain primary and metastatic intracranial malignant tumors that are relatively inaccessible surgically and which are often located in proximity to eloquent or radiosensitive areas. Primary or Recurrent Gliomas and Astrocytomas - in a recent review by Shah et. al., covers some good ground in this area, " RTOG 9305, the only completed randomized study of SRS in GBM, revealed no difference in survival. Thus, there is no proven role for the SRS boost for newly diagnosed GBM." In recurrent GBM there is no level 1 evidence for SRS. Ongoing trial NCT01120639 PMID 28605463 This information is congruent with the prior summary. • Shah JL, Li G, Shaffer JL, et al. Stereotactic Radiosurgery and Hypofractionated Radiotherapy for Glioblastoma. *Neurosurgery*. Jan 2018;82(1):24-34. PMID 28605463. Brain Metastases - In a recent meta analysis by Qie et. al., identified two RCTs comparing SRS alone vs. SRS+WBRT and showed no difference in OS. This meta analysis included an RCT already mentioned in the prior report but also cites Churilla. PMID: 30113464 This current evidence is in line with the summary of the prior report.

No.	Indications	Rationale
		• Qie S, Li Y, Shi HY, et al. Stereotactic radiosurgery (SRS) alone versus whole brain radiotherapy plus SRS in patients with 1 to 4 brain metastases from non-small cell lung cancer stratified by the graded prognostic assessment: A meta-analysis (PRISMA) of randomized control trials. *Medicine (Baltimore)*. Aug 2018;97(33):e11777. PMID 30113464
5	Individuals with malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas) who receive stereotactic radiosurgery	We use conventional radiation delivery approaches for these patients, rather than radiosurgery. The one exception would be if there was a highly localized recurrence that could be treated with radiosurgery.
1	Individuals with uveal melanoma who receive stereotactic radiosurgery	• Dieckmann K, Georg D, Bogner J, et al. Optimizing LINAC based stereotactic radiotherapy of uveal melanomas: 7 years' clinical experience. Int J Radiat Oncol Biol Phys.2006; 66(4 Suppl): S47-52. https://www.redjournal.org/article/S0360-3016(06)00111-8/fulltext?code=rob-site
2	Individuals with uveal melanoma who receive stereotactic radiosurgery	Stereotactic radiosurgery has been shown to yield a high rate of tumor control and enucleation free survival in patients with uveal melanoma. In a recent study of 181 uveal melanoma patients treated with SRS, 5 year survival was 98% and enucleation free survival was 73% (Yazici et al., 2017; PMID 28586956). Quality of life was found to be superior for most uveal melanoma patients treated with SRS over enucleation (PMID 26573389). • Yazici G, Kirati H, Ozyigit G, et al. Stereotactic Radiosurgery and Fractionated Stereotactic Radiation Therapy for the Treatment of Uveal Melanoma. *Int J Radiat Oncol Biol Phys*. May 2017;98(1):152-158. PMID 28586956 • Klingenstein A, Fürweger C, Mühlhofer AK, et al. Quality of life in the follow-up of uveal melanoma patients after enucleation in comparison to CyberKnife treatment. *Graefes Arch Clin Exp Ophthalmol*. May 2016;254(5):1005-12. PMID 26573389
3	Individuals with uveal melanoma who receive stereotactic radiosurgery	I have no experience treating uveal melanoma with stereotactic radiosurgery (SRS) and a review of the published literature does not reveal any findings that would lead me to a conclusion that is different from that of the evidence summary except to say that, in comparison to brachytherapy, SRS is non-invasive. In comparison to conventionally fractionated radiotherapy, SRS requires far fewer treatment visits. From these perspectives, SRS may provide more value and better quality of life for patients, but that remains untested to date as far as I am aware.
4	Individuals with uveal melanoma who receive stereotactic radiosurgery	This question is outside my scope of practice.
5	Individuals with uveal melanoma who receive stereotactic radiosurgery	I am not an expert in this area.
1	Individuals with primary or metastatic spinal or vertebral body tumors who have received prior radiotherapy who receive stereotactic body radiotherapy	Patients who have previous radiotherapy to the spine will not be able to receive a second course of radiotherapy using conventional technique as the risk of radiation myelopathy will be substantial. Stereotactic body radiation therapy (SBRT) is the only means by which an adequate dose of radiation can be delivered to prevent future neurologic complications from progressive disease. A pooled analysis and a systematic review showed good local control with low toxicities which would not have been possible with any other therapy. Based on the ACR Appropriateness Criteria Expert Panel in Bone Metastasis guideline in recurrent spinal metastasis and spinal cord compression, SBRT with or without surgery is regarded as one of the most appropriate treatments References

No.	Indications	Rationale
		• Hashmi A, Guckenberger M, Kersh R, et al. Re-irradiation stereotactic body radiotherapy for spinal metastases: a multi-institutional outcome analysis. J Neurosurg Spine. Nov 2016;25(5):646-653. PMID 27341054 • Myrehaug S, Sahgal A, Hayashi M, et al. Reirradiation spine stereotactic body radiation therapy for spinal metastases: systematic review. J Neurosurg Spine. Oct 2017;27(4):428-435. PMID 28708043 • Expert Panel on Radiation Oncology-Bone Metastases, Lo SS, Ryu S, Chang EL, et al. ACR Appropriateness Criteria® Metastatic Epidural Spinal Cord Compression and Recurrent Spinal Metastasis. *J Palliat Med*. Jul 2015;18(7):573-84. PMID 25974663
2	Individuals with primary or metastatic spinal or vertebral body tumors who have received prior radiotherapy who receive stereotactic body radiotherapy	Spinal radiosurgery has been shown to be safe and effective for patients with various types of spinal tumors. In a study of 145 consecutive spinal metastasis patients, SRS afforded local control at 1 year in 90.3% of treated spinal metastases. • Tseng CL, Soliman H, Myrehaug S, et al. Imaging-Based Outcomes for 24 Gy in 2 Daily Fractions for Patients with de Novo Spinal Metastases Treated With Spine Stereotactic Body Radiation Therapy (SBRT). *Int J Radiat Oncol Biol Phys.* Nov 2018;102(3):499-507. PMID 30003994 In another systematic review of the literature, spinal radiosurgery was shown to yield significant local control and improvement in pain in patients treated with spinal metastasis from renal cell carcinoma (Smith et al., 2018; PMID 29038086). In that study, pain relief improvements ranged from 41-95%. In addition, radiosurgery in many instances is superior to conventional radiation therapy in that tumors once considered "radioresistant" can be successfully treated with high dose conformal stereotactic xrt with an acceptable side effect profile(PMID 28577828 and 29280455) • Smith BW, Joseph JR, Saadeh YS, et al. Radiosurgery for Treatment of Renal Cell Metastases to Spine: A Systematic Review of the Literature. *World Neurosurg*. Jan 2018;109:e502-e509. PMID 29038086 • Katsoulakis E, Kumar K, Laufer I, et al. Stereotactic Body Radiotherapy in the Treatment of Spinal Metastases. *Seminars in Radiation Oncology*. Mar 2017;27(3):209-217. PMID 28577828 • Katsoulakis E, Jackson A, Cox B, et al. A Detailed Dosimetric Analysis of Spinal Cord Tolerance in High-Dose Spine Radiosurgery. *Int J Radiat Oncol Biol Phys*. Nov 2017;99(3):598-607. PMID 29280455
3	Individuals with primary or metastatic spinal or vertebral body tumors who have received prior radiotherapy who receive stereotactic body radiotherapy	I have extensive experience treating metastatic spinal tumors with stereotactic body radiotherapy (SBRT) and consider SBRT is an extremely important tool for the treatment of patients whose spinal tumors have had prior radiotherapy because of the ability to spare the spinal cord and dose escalate tumor. The key to any type of SBRT, especially with regard to metastatic lesions, is patient selection. Spine tumors that have recurred following prior radiation carry a high risk of spinal cord compression and SBRT can be used to delay or prevent that outcome. Patients who will most benefit from spine SBRT are those with greater than 3 months expected survival. The conclusion of this evidence summary is that most literature addresses metastases that have recurred after prior radiotherapy - this is not accurate. Most retrospective and prospective series have focused on SBRT as first line treatment for spine metastases, where it also has an important role. Two randomized phase III trials are currently ongoing that compare SBRT to conventional radiotherapy for the treatment of metastatic

No.	Indications	Rationale
		spine tumors (RTOG 0631 and CCTG SC.24). A randomized phase II trial evaluating pain response following SBRT compared to conventional radiotherapy was published this year (Sprave, 2018), reporting faster and more robust responses from SBRT. • Sprave T, Verma V, Förster R, et al. Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy. *Radiother Oncol.* Aug 2018;128(2):274-282. PMID 29843899
4	Individuals with primary or metastatic spinal or vertebral body tumors who have received prior radiotherapy who receive stereotactic body radiotherapy	This question is outside my scope of practice.
5	Individuals with primary or metastatic spinal or vertebral body tumors who have received prior radiotherapy who receive stereotactic body radiotherapy	I am not an expert in this area and would have to defer to our radiation oncologist
1	Individuals with non-small-cell lung cancer stage T1 or T2a who are not candidates for surgical resection who receive stereotactic body radiotherapy	Multiple phase II trials and studies in the US, Japan and Europe have showed that SBRT has yielded superior local control and survival with low toxicities compared to conventional radiotherapy for medically inoperable early stage non-small cell lung carcinoma. Most recently, the TROG 09.02 CHISEL, a randomized phase III trial from Australia showed that for patients with early stage lung cancer SBRT was more effective in controlling cancer growth, resulting in longer life expectancy and is just as safe as traditional radiotherapy. ASTRO guideline also establish SBRT as the standard therapy for medically inoperable early stage non-small cell lung cancer. References • Ball DL, Mai T, Vinod SK, et al. A randomized trial of SABR vs conventional radiotherapy for inoperable stage I non-small cell lung cancer: TROG 09.02 (CHISEL). Presented at: International Association for the Study of Lung Cancer 18th World Conference on Lung Cancer; Yokohama, Japan: October 15-18, 2017. Abstract OA 01.01. • Nyman J, Hallqvist A, Lund JA, et al. SPACE - A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. *Radiother Oncol.* Oct 2016;121(1):1-8. PMID 27600155 also supports SBRT as superior to conventional fractionation. • Timmerman RD, Paulus R, Pass HI et al. Stereotactic Body Radiation Therapy for Operable Early-Stage Lung Cancer Findings From the NRG Oncology RTOG 0618 Trial. *JAMA Oncology.* Sep 2018;4(9):1263-1266. PMID 29852037 Current policy is SBRT for patients "who are not candidates for surgical resection" but this study supports its use in operable patients. • Videtic GMM, Donington J, Giuliani M, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. *Pract Radiat Oncol.* Sep-Oct 2017;7(5):295-301. PMID 28596092

No.	Indications	Rationale
		• Woody NM, Stephans KL, Marwaha G, et al. Stereotactic Body Radiation Therapy for Non-Small Cell Lung Cancer Tumors Greater Than 5 cm: Safety and Efficacy. *Int J Radiat Oncol Biol Phys.* Jun 2015;92(2):325-31. PMID 25841625 supports SBRT in lesions >5 cm. Current policy is that SBRT should only be for T2a tumors (<4 cm), but this paper supports its use in T3 (>5 cm) patients
2	Individuals with non-small-cell lung cancer stage T1 or T2a who are not candidates for surgical resection who receive stereotactic body radiotherapy	No response
3	Individuals with non-small-cell lung cancer stage T1 or T2a who are not candidates for surgical resection who receive stereotactic body radiotherapy	I have extensive experience treating non-small cell lung cancer with stereotactic body radiotherapy (SBRT) and consider SBRT is an extremely important tool for the treatment of patients are poor surgical candidates or do not wish to undergo surgery. There is extensive evidence that supports SBRT as resulting in equivalent outcomes to surgery, despite the fact that operable patients are almost always much healthier in general than patients treated with SBRT. Unfortunately, randomized trials have failed to accrue and there is thus no level I evidence of an advantage of one modality over the other.
4	Individuals with non-small-cell lung cancer stage T1 or T2a who are not candidates for surgical resection who receive stereotactic body radiotherapy	This question is outside my scope of practice.
5	Individuals with non-small-cell lung cancer stage T1 or T2a who are not candidates for surgical resection who receive stereotactic body radiotherapy	I am not an expert in this condition
1	Individuals with primary or metastatic tumors of the liver who receive stereotactic body radiotherapy	For metastases: Mahadevan et al. "Stereotactic Body Radiotherapy (SBRT) for liver metastasis - clinical outcomes from the international multi-institutional RSSearch® Patient Registry" PMID 29439707 supports higher dose SBRT as having better outcomes in liver metastases. • Mahadevan A, Blanck O, Lanciano R, et al. Stereotactic Body Radiotherapy (SBRT) for liver metastasis - clinical outcomes from the international multi-institutional RSSearch® Patient Registry. *Radiat Oncol.* Feb 2018;13(1):26. PMID 29439707 For primary HCC: NCCN Hepatobiliary v3.2018 HCC-E 2 of 3 supports the use of SBRT for patients with 1 to 3 primary liver tumors, but also states is can "be considered for larger lesions or more extensive disease if there is sufficient uninvolved liver."
2	Individuals with primary or metastatic tumors of the liver who receive stereotactic body radiotherapy	No response
3	Individuals with primary or metastatic tumors of the liver who receive stereotactic body radiotherapy	I have very limited experience using stereotactic body radiotherapy for the treatment of hepatocellular carcinoma or to oligometastatic lesions. What I do know is the liver SBRT is safe and largely effective as a local therapy. It appears from the studies cited that liver SBRT for localized HCC is associated with very high rates of local control and overall survival appears limited by metastatic disease and comorbid conditions. Liver oligometastases similarly respond well to SBRT with

No.	Indications	Rationale
		excellent rates of local control and low rates of toxicity. Patient selection is key. The implementation of aggressive local therapy in oligometastatic disease is currently being tested in a number of prospective trials that will undoubtedly help to reveal who should be treated and who should not.
4	Individuals with primary or metastatic tumors of the liver who receive stereotactic body radiotherapy	This question is outside my scope of practice.
5	Individuals with primary or metastatic tumors of the liver who receive stereotactic body radiotherapy	I am not an expert in this area.
1	Individuals with primary pancreatic cancer who receive stereotactic body radiotherapy	NCCN Pancreas v2.2018 PANC-F 5 of 9 supports it. Rudra et al. "High dose adaptive MRI guided radiation therapy improves overall survival of inoperable pancreatic cancer" is an abstract that supports SBRT improving overall survival when adapted daily.
2	Individuals with primary pancreatic cancer who receive stereotactic body radiotherapy	No response
3	Individuals with primary pancreatic cancer who receive stereotactic body radiotherapy	I have limited experience using stereotactic body radiotherapy (SBRT) for the treatment of pancreatic cancer. The evidence summary provided is missing a report of a multi-institutional trial phase II trial of gemcitabine and SBRT for unresectable pancreatic cancer. Freedom from local progression at 1-year was 78% and OS was 13.9 months, toxicity was minimal. The evidence summary states that chemoradiotherapy have an established role in the treatment of locally advanced pancreatic cancer, which is inaccurate in my opinion. In fact, many question the role of radiotherapy in comparison to chemotherapy alone based on a recent head-to-head trial that failed to show a benefit for conventional RT (Hammel, 2016). • Hammel P, Huguet F, Van Laethem JL, et al. Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib: The LAP07 Randomized Clinical Trial. *JAMA*. May 2016;315(17):1844-53. PMID 27139057
4	Individuals with primary pancreatic cancer who receive stereotactic body radiotherapy	This question is outside my scope of practice.
5	Individuals with primary pancreatic cancer who receive stereotactic body radiotherapy	I am not an expert in this area.
1	Individuals with primary or metastatic renal cell carcinoma who receive stereotactic body radiotherapy	Patients with primary renal cell carcinoma who are not surgical candidates or with a solitary kidney are left with limited options including partial nephrectomy, probe based therapy, and stereotactic body radiotherapy (SBRT). Recent pooled data from around the globe showed that SBRT for primary renal cell carcinoma was associated with excellent local control and low toxicities. Most recently, the Japanese Ministry of Health approved SBRT for renal cell carcinoma as one of the standard treatments as of April 1, 2018 (personal communication with Professor Hiroshi Onishi from University of Yamanashi). Compared to partial nephrectomy and probe based therapy, SBRT is the most non-

No.	Indications	Rationale
		invasive therapy with equivalent efficacy. References • Siva S, Louie AV, Warner A, et al. Pooled analysis of stereotactic ablative radiotherapy for primary renal cell carcinoma: A report from the International Radiosurgery Oncology Consortium for Kidney (IROCK). *Cancer*. Mar 2018;124(5):934-942. PMID 29266183 • Siva S, Kothari G, Muacevic A, et al. Radiotherapy for renal cell carcinoma: renaissance of an overlooked approach. *Nat Rev Urol*. Sep 2017;14(9):549-563. PMID 28631740 With the advent of systemic targeted therapy/ immunotherapy, the survival of patients with metastatic renal cell carcinoma has dramatically prolonged. In patients with limited metastases (oligometastases) or isolate progression (oligoprogression), SBRT is used to provide local control which can potentially improve survival. When SBRT is used to tackle oligoprogression, it is possible to maintain the patient on the same line of systemic therapy, delaying the need for another line of therapy which is likely to be less effective. References • Meyer E, Pasquier D, Bernadou G, et al. Stereotactic radiation therapy in the strategy of treatment of metastatic renal cell carcinoma: A study of the Getug group. *Eur J Cancer*. Jul 2018;98:38-47. PMID 29864737 • Stenman M, Sinclair G, Paavola P, et al. Overall survival after stereotactic radiotherapy or surgical metastasectomy in oligometastatic renal cell carcinoma patients treated at two Swedish centres 2005-2014. *Radiother Oncol*. Jun 2018;127(3):501-506. PMID 29754859
2	Individuals with primary or metastatic renal cell carcinoma who receive stereotactic body radiotherapy	No response
3	Individuals with primary or metastatic renal cell carcinoma who receive stereotactic body radiotherapy	I have no experience using stereotactic body radiotherapy (SBRT) for the treatment of primary renal cell carcinoma (RCC) and am not an expert in the field. I have extensive experience using SBRT to treat metastases from RCC in the brain and spine. We should not consider these two practices in the same light. The treatment of primary RCC with SBRT is uncommon and is currently most often performed in the context of prospective trials for inoperable patients (Siva_2018). It is experimental in comparison to, for example, the treatment of SBRT for early stage lung cancer. The treatment of oligometastatic lesions with SBRT is a more established practice. RCC in particular is considered a radio-resistant tumor, so SBRT (high dose per fraction) is an important tool for treating oligometastatic patients. Whether from brain metastases, bone metastases (including vertebral bodies), or other less common sites, SBRT can be used when the local control of a particular metastatic tumor is expected to have a significant impact on a patients well-being. That being said, evidence in support of SBRT for metastatic RCC consists of single institution series, some of which were prospective (Ghia, 2016). • Siva S, Louie AV, Warner A, et al. Pooled analysis of stereotactic ablative radiotherapy for primary renal cell carcinoma: A report from the International Radiosurgery Oncology Consortium for Kidney (IROCK). *Cancer*. Mar 2018;124(5):934-942. PMID 29266183

No.	Indications	Rationale
		• Ghia AJ, Chang EL, Bishop AJ, et al. Single-fraction versus multifraction spinal stereotactic radiosurgery for spinal metastases from renal cell carcinoma: secondary analysis of Phase I/II trials. *J Neurosurg Spine.* May 2016;24(5):829-36. PMID 26799117
4	Individuals with primary or metastatic renal cell carcinoma who receive stereotactic body radiotherapy	This question is outside my scope of practice.
5	Individuals with primary or metastatic renal cell carcinoma who receive stereotactic body radiotherapy	I am not an expert in this area.
1	Individuals with metastatic adrenal cancer who receive stereotactic body radiotherapy	Plichta et al. "SBRT to adrenal metastases provides high local control with minimal toxicity" PMID 29204525 is one of the more recent reports that also summarizes other studies showing high local control with SBRT. • Plitchta K, Camden N, Furgan M, et al. SBRT to adrenal metastases provides high local control with minimal toxicity. *Adv Radiat Oncol.* Aug 2017;2(4):581-587. PMID 29204525
2	Individuals with metastatic adrenal cancer who receive stereotactic body radiotherapy	No response
3	Individuals with metastatic adrenal cancer who receive stereotactic body radiotherapy	I have limited experience using stereotactic body radiotherapy (SBRT) for the treatment of adrenal metastases. Although several retrospective case series have been published, there are no series that have included a comparative analysis to other common forms of local therapy such as surgery or radiofrequency ablation (RFA). Undoubtedly, SBRT represents the singular option for some patients with oligometastatic disease that includes one or both adrenal glands in patients who are poor surgical and RFA candidates. The adrenal gland is sometimes a challenging target for RFA or SBRT due to its proximity to small bowel.
4	Individuals with metastatic adrenal cancer who receive stereotactic body radiotherapy	This question is outside my scope of practice.
5	Individuals with metastatic adrenal cancer who receive stereotactic body radiotherapy	I am not an expert in this area.
1	Individuals with primary prostate carcinoma who receive stereotactic body radiotherapy	• Katz AJ, Santoro M, Diblasio F, et al. Stereotactic body radiotherapy for localized prostate cancer: disease control and quality of life at 6 years. *Radiat Oncol.* May 2013; 8(1):118. PMID 23668632 • King CR, Brooks JD, Gill H, et al. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. *Int J Radiat Oncol Biol Phys.* Feb 2012;82(2):877-882. PMID 21300474 • King CR, Collins S, Fuller D, et al. Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: results from a multi-institutional consortium of prospective trials. *Int J Radiat Oncol Biol Phys.* Dec 2013; 87(5):939-945 PMID 24119836

No.	Indications	Rationale
		• Parthan A, Pruttivarasin N, Davies D, et al. Comparative cost-effectiveness of stereotactic body radiation therapy versus intensity-modulated and proton radiation therapy for localized prostate cancer. *Front Oncol*. Aug 2012; 2: 81. PMID 22934286
2	Individuals with primary prostate carcinoma who receive stereotactic body radiotherapy	No response
3	Individuals with primary prostate carcinoma who receive stereotactic body radiotherapy	I have no experience using stereotactic body radiotherapy for the treatment of prostate cancer and am not an expert in the field. Level I evidence with long term follow up will inevitably be required to determine the relative efficacy and safety of SBRT for this indication.
4	Individuals with primary prostate carcinoma who receive stereotactic body radiotherapy	This question is outside my scope of practice.
5	Individuals with primary prostate carcinoma who receive stereotactic body radiotherapy	I am not an expert in this area.
1	Individuals with oligometastases who receive stereotactic body radiotherapy	With the advent of systemic targeted therapy/ immunotherapy, the survival of patients with metastatic carcinoma has dramatically prolonged. In patients with limited metastases (oligometastases) or isolate progression (oligoprogression), SBRT is used to provide local control which can potentially improve survival. When SBRT is used to tackle oligoprogression, it is possible to maintain the patient on the same line of systemic therapy, delaying the need for another line of therapy which is likely to be less effective. References • Gandhidasan S, Ball D, Kron T, et al. Single Fraction Stereotactic Ablative Body Radiotherapy for Oligometastasis: Outcomes from 132 Consecutive Patients. *Clin Oncol (R Coll Radiol)*. Mar 2018;30(3):178-184. PMID 29224900 • Al-Halabi H, Sayegh K, Digamurthy SR, et al. Pattern of Failure Analysis in Metastatic EGFR-Mutant Lung Cancer Treated with Tyrosine Kinase Inhibitors to Identify Candidates for Consolidation Stereotactic Body Radiation Therapy. *J Thorac Oncol*. Nov 2015;10(11):1601-7. PMID 26313684 • Gan GN, Weickhardt AJ, Scheier B, et al. Stereotactic radiation therapy can safely and durably control sites of extra-central nervous system oligoprogressive disease in anaplastic lymphoma kinase-positive lung cancer patients receiving crizotinib. *Int J Radiat Oncol Biol Phys*. Mar 2014;88(4):892-8. PMID 24462383
2	Individuals with oligometastases who receive stereotactic body radiotherapy	No response
3	Individuals with oligometastases who receive stereotactic body radiotherapy	I have extensive experience using stereotactic body radiotherapy (SBRT) to treat oligometastatic disease throughout the body, particularly to the brain, bones, and lung. SBRT is an essential tool for this purpose, however the benefit of ablative therapy in the setting of oligometastatic disease is to date unproven save for specific clinical scenarios, such as lung metastasectomy in sarcoma. Many clinical trials are ongoing that will provide prospective data, including phase II randomized trials comparing SBRT to standard of care treatment (Radwan, 2017; Palma, 2012). I am aware that one of these trials will be

No.	Indications	Rationale
		presented in the fall of 2018 with survival data that supports the use of SBRT, but this is not yet publically available, and in the absence of that, the use of SBRT to treat oligometastatic disease is supported most strongly by phase II single arm studies (Collen, 2014; Sutera 2018) showing promising progression-free and overall survival. In the absence of level I data, patient selection is key: performance status, expected survival, availability of effective systemic treatments, and potential or expected toxicity are all important factors to consider. Ultimately, I support the use of SBRT in instances where I believe durable tumor or pain control will significantly benefit the patient.
4	Individuals with oligometastases who receive stereotactic body radiotherapy	This question is outside my scope of practice.
5	Individuals with oligometastases who receive stereotactic body radiotherapy	I am not an expert in this area.

- Based on the evidence and your clinical experience for each of the clinical indications described below:
  - Respond Yes or No for each clinical indication whether the intervention would be expected to provide a clinically meaningful improvement in net health outcome; AND
  - Rate your level of confidence in your Yes or No response using the 1 to 5 scale outlined below.

No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
1	Individuals with epilepsy who receive stereotactic radiosurgery	Yes			X		
	Individuals with tremor and movements disorders who receive stereotactic radiosurgery	Yes				X	
	Individuals with chronic pain or other non-neoplastic neurologic disorders other than epilepsy or tremor / movement disorder who receive stereotactic radiosurgery	Yes			X		
	Individuals with benign neoplastic intracranial lesion(s) (craniopharyngioma, glomus jugulare tumors) who receive stereotactic radiosurgery	Yes				X	
	Individuals with malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas) who receive stereotactic radiosurgery	Yes				X	
	Individuals with uveal melanoma who receive stereotactic radiosurgery	Yes				X	
	Individuals with primary or metastatic spinal or vertebral body tumors who have received prior radiotherapy who receive stereotactic body radiotherapy	Yes					X
	Individuals with non-small-cell lung cancer stage T1 or T2a who are not candidates for surgical resection who receive stereotactic body radiotherapy	Yes					X
	Individuals with primary or metastatic tumors of the liver who receive stereotactic body radiotherapy	Yes					X

No.	Indications	Yes/No	Low Confidence	Intermediate Confidence	High Confidence
	Individuals with primary pancreatic cancer who receive stereotactic body radiotherapy	Yes			X
	Individuals with primary or metastatic renal cell carcinoma who receive stereotactic body radiotherapy	Yes			X
	Individuals with metastatic adrenal cancer who receive stereotactic body radiotherapy	Yes			X
	Individuals with primary prostate carcinoma who receive stereotactic body radiotherapy	Yes			X
	Individuals with oligometastases who receive stereotactic body radiotherapy	Yes			X
2	Individuals with epilepsy who receive stereotactic radiosurgery	Yes			X
	Individuals with tremor and movements disorders who receive stereotactic radiosurgery	Yes			X
	Individuals with chronic pain or other non-neoplastic neurologic disorders other than epilepsy or tremor / movement disorder who receive stereotactic radiosurgery	Yes			X
	Individuals with benign neoplastic intracranial lesion(s) (craniopharyngioma, glomus jugulare tumors) who receive stereotactic radiosurgery	Yes			X
	Individuals with malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas) who receive stereotactic radiosurgery	Yes			X
	Individuals with uveal melanoma who receive stereotactic radiosurgery	Yes			X
	Individuals with primary or metastatic spinal or vertebral body tumors who have received prior radiotherapy who receive stereotactic body radiotherapy	Yes			X
	Individuals with non-small-cell lung cancer stage T1 or T2a who are not candidates for surgical resection who receive stereotactic body radiotherapy	NR			
	Individuals with primary or metastatic tumors of the liver who receive stereotactic body radiotherapy	NR			
	Individuals with primary pancreatic cancer who receive stereotactic body radiotherapy	NR			
	Individuals with primary or metastatic renal cell carcinoma who receive stereotactic body radiotherapy	NR			
	Individuals with metastatic adrenal cancer who receive stereotactic body radiotherapy	NR			
	Individuals with primary prostate carcinoma who receive stereotactic body radiotherapy	NR			
	Individuals with oligometastases who receive stereotactic body radiotherapy	NR			
3	Individuals with epilepsy who receive stereotactic radiosurgery	Yes		X	
	Individuals with tremor and movements disorders who receive stereotactic radiosurgery	Yes			X
	Individuals with chronic pain or other non-neoplastic neurologic disorders other than	Yes		X	

No.	Indications	Yes/No	Low Confidence	Intermediate Confidence	High Confidence
	epilepsy or tremor / movement disorder who receive stereotactic radiosurgery				
	Individuals with benign neoplastic intracranial lesion(s) (craniopharyngioma, glomus jugulare tumors) who receive stereotactic radiosurgery	Yes		X	
	Individuals with malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas) who receive stereotactic radiosurgery	Yes		X	
	Individuals with uveal melanoma who receive stereotactic radiosurgery	Yes			X
	Individuals with primary or metastatic spinal or vertebral body tumors who have received prior radiotherapy who receive stereotactic body radiotherapy	Yes			X
	Individuals with non-small-cell lung cancer stage T1 or T2a who are not candidates for surgical resection who receive stereotactic body radiotherapy	Yes			X
	Individuals with primary or metastatic tumors of the liver who receive stereotactic body radiotherapy	Yes			X
	Individuals with primary pancreatic cancer who receive stereotactic body radiotherapy	Yes		X	
	Individuals with primary or metastatic renal cell carcinoma who receive stereotactic body radiotherapy	Yes			X
	Individuals with metastatic adrenal cancer who receive stereotactic body radiotherapy	Yes			X
	Individuals with primary prostate carcinoma who receive stereotactic body radiotherapy	Yes		X	
	Individuals with oligometastases who receive stereotactic body radiotherapy	Yes			X
4	Individuals with epilepsy who receive stereotactic radiosurgery	Yes	X		
	Individuals with tremor and movements disorders who receive stereotactic radiosurgery	Yes	X		
	Individuals with chronic pain or other non-neoplastic neurologic disorders other than epilepsy or tremor / movement disorder who receive stereotactic radiosurgery	No			X
	Individuals with benign neoplastic intracranial lesion(s) (craniopharyngioma, glomus jugulare tumors) who receive stereotactic radiosurgery	Yes			X
	Individuals with malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas) who receive stereotactic radiosurgery	Yes		X	
	Individuals with uveal melanoma who receive stereotactic radiosurgery	NR			
	Individuals with primary or metastatic spinal or vertebral body tumors who have received prior radiotherapy who receive stereotactic body radiotherapy	NR			
	Individuals with non-small-cell lung cancer stage T1 or T2a who are not candidates for	NR			

No.	Indications	Yes/No	Low Confidence	Intermediate Confidence	High Confidence
	surgical resection who receive stereotactic body radiotherapy				
	Individuals with primary or metastatic tumors of the liver who receive stereotactic body radiotherapy	NR			
	Individuals with primary pancreatic cancer who receive stereotactic body radiotherapy	NR			
	Individuals with primary or metastatic renal cell carcinoma who receive stereotactic body radiotherapy	NR			
	Individuals with metastatic adrenal cancer who receive stereotactic body radiotherapy	NR			
	Individuals with primary prostate carcinoma who receive stereotactic body radiotherapy	NR			
	Individuals with oligometastases who receive stereotactic body radiotherapy	NR			
5	Individuals with epilepsy who receive stereotactic radiosurgery	No		X	
	Individuals with tremor and movements disorders who receive stereotactic radiosurgery	No		X	
	Individuals with chronic pain or other non-neoplastic neurologic disorders other than epilepsy or tremor / movement disorder who receive stereotactic radiosurgery	No			X
	Individuals with benign neoplastic intracranial lesion(s) (craniopharyngioma, glomus jugulare tumors) who receive stereotactic radiosurgery	Yes		X	
	Individuals with malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas) who receive stereotactic radiosurgery	Yes	X		
	Individuals with uveal melanoma who receive stereotactic radiosurgery	NR			
	Individuals with primary or metastatic spinal or vertebral body tumors who have received prior radiotherapy who receive stereotactic body radiotherapy	NR			
	Individuals with non-small-cell lung cancer stage T1 or T2a who are not candidates for surgical resection who receive stereotactic body radiotherapy	NR			
	Individuals with primary or metastatic tumors of the liver who receive stereotactic body radiotherapy	NR			
	Individuals with primary pancreatic cancer who receive stereotactic body radiotherapy	NR			
	Individuals with primary or metastatic renal cell carcinoma who receive stereotactic body radiotherapy	NR			
	Individuals with metastatic adrenal cancer who receive stereotactic body radiotherapy	NR			
	Individuals with primary prostate carcinoma who receive stereotactic body radiotherapy	NR			
	Individuals with oligometastases who receive stereotactic body radiotherapy	NR			

NR: no response.

- Based on the evidence and your clinical experience for the clinical indications described below:
  - Respond Yes or No whether this intervention is consistent with generally accepted medical practice; AND
  - Rate your level of confidence in your Yes or No response using the 1 to 5 scale outlined below.

No.	Indications	Yes/No	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
1	Individuals with epilepsy who receive stereotactic radiosurgery	No			X		
	Individuals with tremor and movements disorders who receive stereotactic radiosurgery	No			X		
	Individuals with chronic pain or other non-neoplastic neurologic disorders other than epilepsy or tremor / movement disorder who receive stereotactic radiosurgery	No			X		
	Individuals with benign neoplastic intracranial lesion(s) (craniopharyngioma, glomus jugulare tumors) who receive stereotactic radiosurgery	Yes					X
	Individuals with malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas) who receive stereotactic radiosurgery	Yes			X		
	Individuals with uveal melanoma who receive stereotactic radiosurgery	No			X		
	Individuals with primary or metastatic spinal or vertebral body tumors who have received prior radiotherapy who receive stereotactic body radiotherapy	Yes					X
	Individuals with non-small-cell lung cancer stage T1 or T2a who are not candidates for surgical resection who receive stereotactic body radiotherapy	Yes					X
	Individuals with primary or metastatic tumors of the liver who receive stereotactic body radiotherapy	Yes					X
	Individuals with primary pancreatic cancer who receive stereotactic body radiotherapy	Yes					X
	Individuals with primary or metastatic renal cell carcinoma who receive stereotactic body radiotherapy	Yes					X
	Individuals with metastatic adrenal cancer who receive stereotactic body radiotherapy	Yes					X
	Individuals with primary prostate carcinoma who receive stereotactic body radiotherapy	Yes					X
	Individuals with oligometastases who receive stereotactic body radiotherapy	Yes					X
2	Individuals with epilepsy who receive stereotactic radiosurgery	Yes					X
	Individuals with tremor and movements disorders who receive stereotactic radiosurgery	Yes					X
	Individuals with chronic pain or other non-neoplastic neurologic disorders other than epilepsy or tremor / movement disorder who receive stereotactic radiosurgery	Yes					X

No.	Indications	Yes/No	Low Confidence	Intermediate Confidence	High Confidence
	Individuals with benign neoplastic intracranial lesion(s) (craniopharyngioma, glomus jugulare tumors) who receive stereotactic radiosurgery	Yes			X
	Individuals with malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas) who receive stereotactic radiosurgery	Yes			X
	Individuals with uveal melanoma who receive stereotactic radiosurgery	Yes			X
	Individuals with primary or metastatic spinal or vertebral body tumors who have received prior radiotherapy who receive stereotactic body radiotherapy	Yes			X
	Individuals with non-small-cell lung cancer stage T1 or T2a who are not candidates for surgical resection who receive stereotactic body radiotherapy	NR			
	Individuals with primary or metastatic tumors of the liver who receive stereotactic body radiotherapy	NR			
	Individuals with primary pancreatic cancer who receive stereotactic body radiotherapy	NR			
	Individuals with primary or metastatic renal cell carcinoma who receive stereotactic body radiotherapy	NR			
	Individuals with metastatic adrenal cancer who receive stereotactic body radiotherapy	NR			
	Individuals with primary prostate carcinoma who receive stereotactic body radiotherapy	NR			
	Individuals with oligometastases who receive stereotactic body radiotherapy	NR			
3	Individuals with epilepsy who receive stereotactic radiosurgery	Yes			X
	Individuals with tremor and movements disorders who receive stereotactic radiosurgery	Yes			X
	Individuals with chronic pain or other non-neoplastic neurologic disorders other than epilepsy or tremor / movement disorder who receive stereotactic radiosurgery	Yes			X
	Individuals with benign neoplastic intracranial lesion(s) (craniopharyngioma, glomus jugulare tumors) who receive stereotactic radiosurgery	Yes			X
	Individuals with malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas) who receive stereotactic radiosurgery	Yes			X
	Individuals with uveal melanoma who receive stereotactic radiosurgery	Yes			X
	Individuals with primary or metastatic spinal or vertebral body tumors who have received prior radiotherapy who receive stereotactic body radiotherapy	Yes			X
	Individuals with non-small-cell lung cancer stage T1 or T2a who are not candidates for surgical resection who receive stereotactic body radiotherapy	Yes			X

No.	Indications	Yes/No	Low Confidence	Intermediate Confidence	High Confidence
	Individuals with primary or metastatic tumors of the liver who receive stereotactic body radiotherapy	Yes			X
	Individuals with primary pancreatic cancer who receive stereotactic body radiotherapy	Yes		X	
	Individuals with primary or metastatic renal cell carcinoma who receive stereotactic body radiotherapy	Yes			X
	Individuals with metastatic adrenal cancer who receive stereotactic body radiotherapy	Yes			X
	Individuals with primary prostate carcinoma who receive stereotactic body radiotherapy	Yes		X	
	Individuals with oligometastases who receive stereotactic body radiotherapy	Yes			X
4	Individuals with epilepsy who receive stereotactic radiosurgery	Yes		X	
	Individuals with tremor and movements disorders who receive stereotactic radiosurgery	Yes	X		
	Individuals with chronic pain or other non-neoplastic neurologic disorders other than epilepsy or tremor / movement disorder who receive stereotactic radiosurgery	No			X
	Individuals with benign neoplastic intracranial lesion(s) (craniopharyngioma, glomus jugulare tumors) who receive stereotactic radiosurgery	Yes		X	
	Individuals with malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas) who receive stereotactic radiosurgery	Yes		X	
	Individuals with uveal melanoma who receive stereotactic radiosurgery	NR			
	Individuals with primary or metastatic spinal or vertebral body tumors who have received prior radiotherapy who receive stereotactic body radiotherapy	NR			
	Individuals with non-small-cell lung cancer stage T1 or T2a who are not candidates for surgical resection who receive stereotactic body radiotherapy	NR			
	Individuals with primary or metastatic tumors of the liver who receive stereotactic body radiotherapy	NR			
	Individuals with primary pancreatic cancer who receive stereotactic body radiotherapy	NR			
	Individuals with primary or metastatic renal cell carcinoma who receive stereotactic body radiotherapy	NR			
	Individuals with metastatic adrenal cancer who receive stereotactic body radiotherapy	NR			
	Individuals with primary prostate carcinoma who receive stereotactic body radiotherapy	NR			
	Individuals with oligometastases who receive stereotactic body radiotherapy	NR			
5	Individuals with epilepsy who receive stereotactic radiosurgery	No		X	

No.	Indications	Yes/No	Low Confidence	Intermediate Confidence	High Confidence
	Individuals with tremor and movements disorders who receive stereotactic radiosurgery	No		X	
	Individuals with chronic pain or other non-neoplastic neurologic disorders other than epilepsy or tremor / movement disorder who receive stereotactic radiosurgery	No			X
	Individuals with benign neoplastic intracranial lesion(s) (craniopharyngioma, glomus jugulare tumors) who receive stereotactic radiosurgery	Yes		X	
	Individuals with malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas) who receive stereotactic radiosurgery	Yes	X		
	Individuals with uveal melanoma who receive stereotactic radiosurgery	NR			
	Individuals with primary or metastatic spinal or vertebral body tumors who have received prior radiotherapy who receive stereotactic body radiotherapy	NR			
	Individuals with non-small-cell lung cancer stage T1 or T2a who are not candidates for surgical resection who receive stereotactic body radiotherapy	NR			
	Individuals with primary or metastatic tumors of the liver who receive stereotactic body radiotherapy	NR			
	Individuals with primary pancreatic cancer who receive stereotactic body radiotherapy	NR			
	Individuals with primary or metastatic renal cell carcinoma who receive stereotactic body radiotherapy	NR			
	Individuals with metastatic adrenal cancer who receive stereotactic body radiotherapy	NR			
	Individuals with primary prostate carcinoma who receive stereotactic body radiotherapy	NR			
	Individuals with oligometastases who receive stereotactic body radiotherapy	NR			

NR: no response.

- Additional narrative rationale or comments and/or any relevant scientific citations (including the PMID) supporting your clinical input on this topic.

No.	Additional Comments
1	Please see links to ASTRO's SRS and SBRT Model Policies: SRS Model Policy and SBRT Model Policy
2	As noted above, radiosurgery serves as a valuable treatment option for patients with tremor/movement disorder, craniopharyngiomas, glomus tumors, certain types of epilepsy, uveal melanoma, brain and spinal tumors.
3	integrated into my responses above
4	NR
5	I am an academic neurosurgery and direct a large clinical practice and am Chief of the service. The opinions I have rendered in this survey reflect our own institutional practices and my/our group's interpretation of the literature. When I have responded that a certain procedure isn't indicated, what I mean by that is that we think the alternative treatment approaches are better...not that the identified procedure are necessarily ineffective or unsafe.

- Is there any evidence missing from the attached draft review of evidence that demonstrates clinically meaningful improvement in net health outcome?

No.	Yes/No	Citations of Missing Evidence
1	No	
2	Yes	Please see the aforementioned publications summarized above.
3	Yes	Epilepsy • Eekers DBP, Pijnappel EN, Schihns OEMG, et al. Evidence on the efficacy of primary radiosurgery or stereotactic radiotherapy for drug-resistant non-neoplastic focal epilepsy in adults: A systematic review. *Seizure.* Feb 2018;55:83-92. PMID 29414140 • McGonigal A, Sahgal A, De Salles A, et al. Radiosurgery for epilepsy: Systematic review and International Stereotactic Radiosurgery Society (ISRS) practice guideline. *Epilepsy Res.* Nov 2017; 137:123-131. PMID 28939289 • Barbaro NM, Quigg M, Ward MM, et al. Radiosurgery versus open surgery for mesial temporal lobe epilepsy: The randomized, controlled ROSE trial. *Epilepsia.* Jun 2018;59(1):119801207. PMID 29600809 Tremor • Martinez-Moreno NE, Sahgal A, De Salles A, et al. Stereotactic radiosurgery for tremor: systematic review. *J Neurosurg.* Feb 2018:1-12 PMID 29473775 • Niranjan A, Kondziolka D, Baser S, et al. Functional outcomes after gamma knife thalamotomy for essential tremor and MS-related tremor. *Neurology.* Aug 2000;55(3):443-6. PMID 10932286 Glioblastoma • Pollom EL, Fujimoto D, Wynne J, et al. Phase 1/2 Trial of 5-Fraction Stereotactic Radiosurgery With 5-mm Margins With Concurrent and Adjuvant Temozolomide in Newly Diagnosed Supratentorial Glioblastoma: Health-Related Quality of Life Results. *Int j Radiat Oncol Biol Phys.* May 2017;98(1):123-130. PMID 28586949 Spine • Sprave T, Verma V, Förster R, et al. Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy. *Radiother Oncol.* Aug 2018;128(2):274-282. PMID 29843899 Pancreatic • Hammel P, Huguet F, Van Laethem JL, et al. Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib: The LAP07 Randomized Clinical Trial. *JAMA.* May 2016;315(17):1844-53. PMID 27139057 Renal Cell • Siva S, Louie AV, Warner A, et al. Pooled analysis of stereotactic ablative radiotherapy for primary renal cell carcinoma: A report from the International Radiosurgery Oncology Consortium for Kidney (IROCK). *Cancer.* Mar 2018;124(5):934-942. PMID 29266183 • Ghia AJ, Chang EL, Bishop AJ, et al. Single-fraction versus multifraction spinal stereotactic radiosurgery for spinal metastases from renal cell carcinoma: secondary analysis of Phase I/II trials. *J Neurosurg Spine.* May 2016;24(5):829-36. PMID 26799117 Oligometastatic • Radwan N, Phillips R, Ross A, et al. A phase II randomized trial of Observation versus stereotactic ablative Radiation for OLigometastatic prostate CancEr (ORIOLE). *BMC Cancer.* Jun 2017;17(1):453. PMID 28662647 • Palma DA, Haasbeek CJ, Rodrigues GB, et al. Stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors (SABR-COMET): study protocol for a randomized phase II trial. *BMC Cancer.* Jul 2012;12:305. PMID 22823994 • Collen C, Christian N, Schallier D, et al. Phase II study of stereotactic body radiotherapy to primary tumor and metastatic locations in oligometastatic non small-cell lung cancer patients. *Ann Oncol.* Oct 2014;25(10):1954-9. PMID 25114022

No.	Yes/No	Citations of Missing Evidence
		• Sutera P, Clump DA, Kalash R, et al. Initial Results of a Multicenter Phase II Trial of Stereotactic Ablative Radiation Therapy for Oligometastatic Cancer. *Int J Radiol Oncol Biol Phys.* Aug 2018;pii:S0360-3016(18):33573-9. PMID 30149056
4	No	
5	No	

[a] BCBSA had not intended for clinical input responses for this indication to include trigeminal neuralgia because the evidence is sufficient to determine the impact of the technology results in a meaningful improvement in the net health outcome.

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Documentation for Clinical Review

Please provide the following documentation:

- (click here >>>) Radiation Oncology – Prior Authorization fax form
- (click here >>>) Radiation Oncology – Post Service fax form

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	32701	Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (photon or particle beam), entire course of treatment
	61781	Stereotactic computer-assisted (navigational) procedure; cranial, intradural (List separately in addition to code for primary procedure)
	61782	Stereotactic computer-assisted (navigational) procedure; cranial, extradural (List separately in addition to code for primary procedure)
	61783	Stereotactic computer-assisted (navigational) procedure; spinal (List separately in addition to code for primary procedure)
	61796	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 simple cranial lesion
	61797	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, simple (List separately in addition to code for primary procedure)
	61798	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 complex cranial lesion
	61799	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, complex (List separately in addition to code for primary procedure)
	61800	Application of stereotactic headframe for stereotactic radiosurgery (List separately in addition to code for primary procedure)
	63620	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion

Type	Code	Description
	63621	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional spinal lesion (List separately in addition to code for primary procedure)
	77014	Computed tomography guidance for placement of radiation therapy fields
	77261	Therapeutic radiology treatment planning; simple
	77262	Therapeutic radiology treatment planning; intermediate
	77263	Therapeutic radiology treatment planning; complex
	77280	Therapeutic radiology simulation-aided field setting; simple
	77285	Therapeutic radiology simulation-aided field setting; intermediate
	77290	Therapeutic radiology simulation-aided field setting; complex
	77293	Respiratory motion management simulation (List separately in addition to code for primary procedure)
	77295	3-dimensional radiotherapy plan, including dose-volume histograms
	77300	Basic radiation dosimetry calculation, central axis depth dose calculation, TDF, NSD, gap calculation, off axis factor, tissue inhomogeneity factors, calculation of non-ionizing radiation surface and depth dose, as required during course of treatment, only when prescribed by the treating physician
	77301	Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications
	77332	Treatment devices, design and construction; simple (simple block, simple bolus)
	77333	Treatment devices, design and construction; intermediate (multiple blocks, stents, bite blocks, special bolus)
	77334	Treatment devices, design and construction; complex (irregular blocks, special shields, compensators, wedges, molds or casts)
	77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan
	77370	Special medical radiation physics consultation
	77371	Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; multi-source Cobalt 60 based
	77372	Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; linear accelerator based
	77373	Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions
	77387	Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed
	77432	Stereotactic radiation treatment management of cranial lesion(s) (complete course of treatment consisting of 1 session)
	77417	Therapeutic radiology port image(s)
	77470	Special treatment procedure (e.g., total body irradiation, hemibody radiation, per oral or endocavitary irradiation)
	77435	Stereotactic body radiation therapy, treatment management, per treatment course, to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions

Type	Code	Description
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
	G0563	Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance and real-time positron emissions-based delivery adjustments to 1 or more lesions, entire course not to exceed 5 fractions ***(Code effective 1/1/2025)***
	G6001	Ultrasonic guidance for placement of radiation therapy fields
	G6002	Stereoscopic x-ray guidance for localization of target volume for the delivery of radiation therapy
	G6017	Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3D positional tracking, gating, 3D surface tracking), each fraction of treatment

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
01/01/2016	BCBSA Medical Policy Adoption
03/01/2017	Policy revision without position change
05/01/2017	Policy revision with position change
12/01/2017	Policy revision without position change
12/01/2018	Policy revision without position change
04/01/2019	Policy revision with position change
03/01/2020	Annual review. No change to policy statement. Literature review updated.
11/20/2020	No change to policy statement. Policy guidelines updated. Coding update.
04/01/2021	Annual review. No change to policy statement. Literature review updated.
08/01/2021	Annual review. Policy statement and guidelines updated.
12/01/2021	Administrative update. No change to policy statement. Policy guidelines and literature updated.
08/01/2022	Annual review. No change to policy statement.
09/01/2022	Administrative update. Policy statement, guidelines and literature updated.
02/01/2023	Annual review. Policy statement and guidelines updated.
09/01/2023	Administrative update. No change to policy statement. Literature review updated.
03/01/2024	Annual review. No change to policy statement.
10/01/2024	Administrative update.
02/01/2025	Coding update.
04/01/2025	Annual review. Policy statement, guidelines, and literature updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to

treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
Stereotactic Radiosurgery and Stereotactic Body Radiotherapy 6.01.10 **Policy Statement:** I. Stereotactic radiosurgery (SRS) using a gamma-ray or linear accelerator (LINAC) unit may be considered **medically necessary** for **any** of the following indications: A. Acoustic neuromas B. Arteriovenous malformations C. Craniopharyngiomas D. Glomus jugulare tumors E. Malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas) F. Mesial temporal lobe epilepsy refractory to medical management when standard alternative surgery is not an option G. Nonresectable, residual, or recurrent meningiomas H. Pituitary adenomas I. Solitary or multiple brain metastases in individuals having good performance status and no active systemic disease (defined as extracranial disease that is stable or in remission) J. Trigeminal neuralgia refractory to medical management K. Uveal melanoma II. Stereotactic body radiotherapy (SBRT) may be considered **medically necessary** for **any** of the following indications: A. Primary or metastatic spinal or vertebral body tumors in individuals who have received prior spinal radiotherapy B. Spinal or vertebral metastases that are radioresistant (e.g., renal cell carcinoma, melanoma, sarcoma) C. Individuals with stage T1 or T2a non-small-cell lung cancer (not greater than 5 cm) showing no nodal or distant disease and who are not candidates for surgical resection D. Individuals with low or favorable intermediate risk prostate cancer	**Stereotactic Radiosurgery and Stereotactic Body Radiotherapy 6.01.10** **Policy Statement:** I. Stereotactic radiosurgery (SRS) using a gamma-ray or linear accelerator (LINAC) unit may be considered **medically necessary** for **any** of the following indications: A. Acoustic neuromas B. Arteriovenous malformations C. Craniopharyngiomas D. Glomus jugulare tumors E. Malignant neoplastic intracranial lesion(s) (e.g., gliomas, astrocytomas) F. Mesial temporal lobe epilepsy refractory to medical management when standard alternative surgery is not an option G. Nonresectable, residual, or recurrent meningiomas H. Pituitary adenomas I. Solitary or multiple brain metastases in individuals having good performance status and no active systemic disease (defined as extracranial disease that is stable or in remission) J. Trigeminal neuralgia refractory to medical management K. Uveal melanoma II. Stereotactic body radiotherapy (SBRT) may be considered **medically necessary** for **any** of the following indications: A. Primary or metastatic spinal or vertebral body tumors in individuals who have received prior spinal radiotherapy B. Spinal or vertebral metastases that are radioresistant (e.g., renal cell carcinoma, melanoma, sarcoma) C. Individuals with stage T1 or T2a non-small-cell lung cancer (not greater than 5 cm) showing no nodal or distant disease and who are not candidates for surgical resection G. Individuals with low or favorable intermediate risk prostate cancer

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E. Pancreatic carcinoma, in 3 to 5 fractions, with total doses of 30 to 45 Gray (Gy) in individuals with **either** of the following conditions: 1. Unresectable or locally advanced disease 2. Recurrent disease to the pancreatic bed F. Primary or metastatic tumors of the liver as an alternative locoregional treatment for individuals with inoperable primary or metastatic lesions G. Primary renal cell carcinoma in individuals who are not good surgical candidates or who have metastatic renal cell carcinoma H. Oligometastases involving lung, adrenal glands, and bone (other than spine or vertebral body)	H. Pancreatic carcinoma, in 3 to 5 fractions, with total doses of 30 to 45 Gray (Gy) in individuals with **either** of the following conditions: 3. Unresectable or locally advanced disease 4. Recurrent disease to the pancreatic bed I. Primary or metastatic tumors of the liver as an alternative locoregional treatment for individuals with inoperable primary or metastatic lesions D. Primary renal cell carcinoma in individuals who are not good surgical candidates or who have metastatic renal cell carcinoma; E. Oligometastases involving the lung, adrenal glands, and bone (other than spine or vertebral body)
III. When stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT) are performed using fractionation for the medically necessary indications described above, it may be considered **medically necessary**.	III. When stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT) are performed using fractionation for the medically necessary indications described above, it may be considered **medically necessary**.
IV. Stereotactic radiosurgery (SRS) is considered **investigational** for other applications including, but not limited to, the treatment of seizures and functional disorders (other than trigeminal neuralgia), including chronic pain and tremor.	IV. Stereotactic radiosurgery (SRS) is **investigational** for other applications including, but not limited to, the treatment of seizures and functional disorders (other than trigeminal neuralgia), including chronic pain and tremor.
V. Stereotactic body radiotherapy (SBRT) is considered **investigational** for primary and metastatic tumors of the liver, kidney, adrenal glands, prostate and other conditions except as outlined in the policy statements above.	V. Stereotactic body radiotherapy (SBRT) is **investigational** for primary and metastatic tumors of the liver, kidney, adrenal glands, prostate and other conditions except as outlined in the policy statements above.
VI. Stereotactic body radiotherapy (SBRT) is considered **investigational** for **any** of the following for the treatment of pancreatic adenocarcinoma: A. As neoadjuvant therapy in resectable or borderline resectable tumors B. As adjuvant therapy in resected disease (i.e., treatment to the tumor bed)	VII. Stereotactic body radiotherapy (SBRT) is **investigational** for **any** of the following for the treatment of pancreatic adenocarcinoma: A. As neoadjuvant therapy in resectable or borderline resectable tumors B. As adjuvant therapy in resected disease (i.e., treatment to the tumor bed)

POLICY STATEMENT	
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C. For palliative treatment D. If there is direct invasion of the bowel or stomach See Policy Guidelines for allowable codes/number of units. **Image Guided Radiation Therapy (IGRT)** VII. IGRT may be considered **medically necessary** as an approach to delivering radiotherapy when combined with **any** of the following treatments (see Policy Guidelines): A. Intensity-modulated radiotherapy (IMRT) B. Stereotactic body radiation therapy (SBRT) C. Proton delivery VIII. IGRT is considered **investigational** as an approach to delivering radiotherapy when combined with **any** of the following treatments: A. Conventional three-dimensional conformal radiation therapy (3D CRT) (see Policy Guidelines for considerations) B. Stereotactic radiosurgery (SRS) C. Electronic brachytherapy	C. For palliative treatment D. If there is direct invasion of the bowel or stomach See Policy Guidelines for allowable codes/number of units. **Image Guided Radiation Therapy (IGRT)** IX. IGRT may be considered **medically necessary** as an approach to delivering radiotherapy when combined with **any** of the following treatments (see Policy Guidelines): A. Intensity-modulated radiotherapy (IMRT) B. Stereotactic body radiation therapy (SBRT) C. Proton delivery X. IGRT is **investigational** as an approach to delivering radiotherapy when combined with **any** of the following treatments: A. Conventional three-dimensional conformal radiation therapy (3D CRT) (see Policy Guidelines for considerations) B. Stereotactic radiosurgery (SRS) C. Electronic brachytherapy