

Stereotactic Body Radiation Therapy and Stereotactic Radiosurgery

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 [Instructions for Use](#)

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Related Commercial/Individual Exchange Policies

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Community Plan Policy

- [Stereotactic Body Radiation Therapy and Stereotactic Radiosurgery](#)

Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans.

Coverage Rationale

Note: This policy applies to individuals 19 years of age and older. Stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) are covered without further review for individuals younger than 19 years of age.

Stereotactic radiation therapy including SRS and SBRT is considered proven and medically necessary for the following indications:

- Acoustic neuroma (vestibular schwannoma)
- Bone metastasis (non-spine) when **all** the following criteria are met:
 - Symptomatic
 - Up to five fractions
- Brain metastasis when **one** of the following criteria is met:
 - Newly diagnosed brain metastasis and **all** the following criteria are met:
 - Individual has a good performance status [Karnofsky Performance Status (KPS) score greater than or equal to 70% or Eastern Cooperative Oncology Group (ECOG) performance status of zero to two]
 - Absence of diffuse brain metastases
 - Absence of diffuse leptomeningeal metastases
 - Individual does not have a diagnosis of lymphoma or germ cell tumor
 - Has up to 10 lesions or cumulative tumor volume of less than 15 cubic centimeters (cc)
 - All lesions must be treated in a single treatment for SRS, or in two to five fractions for SBRT [also known as fractionated stereotactic radiation therapy (FSRT)]
 - Individual is undergoing repeat stereotactic radiation therapy when **all** the following criteria are met:

- Individual has a good performance status (KPS score greater than or equal to 70% or ECOG performance status of zero to two)
 - Absence of diffuse leptomeningeal metastases
 - Extra-cranial disease is well-controlled or there are accessible and effective systemic treatment options available
 - Life expectancy is greater than six months
 - All lesions must be treated in a single treatment for SRS, or in two to five fractions for SBRT (also known as FSRT)
- Retreatment after previous whole brain radiation therapy
- Chordoma and chondrosarcoma
- Craniopharyngioma
- [Definitive Treatment](#) of the following:
 - Hepatocellular carcinoma without evidence of regional or distant metastasis
 - Intrahepatic bile duct cancer (cholangiocarcinoma) for unresectable tumors
 - Non-small cell lung cancer when **all** the following criteria are met:
 - Stage I or stage IIA with negative mediastinal lymph nodes
 - Tumor size is less than or equal to five centimeters
 - Individual is medically inoperable or has made a decision not to pursue surgery after an appropriate consultation
 - Pancreatic adenocarcinoma without evidence of distant metastasis
 - Prostate cancer without evidence of distant metastases (see criteria below for Oligometastatic Disease)
 - Renal cancer when **all** the following criteria are met:
 - Stage I
 - Individual is a non-optimal surgical candidate
 - Small cell lung cancer when **all** the following criteria are met:
 - Stage I or node negative stage IIA
 - Lesion is medically inoperable, or the individual is a non-optimal surgical candidate
- Extracranial [Oligometastatic Disease](#) when **all** the following criteria are met:
 - Primary tumor type is any of the following:
 - Colorectal cancer
 - Melanoma
 - Non-small cell lung cancer
 - Prostate cancer
 - Renal cancer
 - Sarcoma
 - Controlled primary tumor defined as at least three months since original tumor was treated definitively, with no progression at primary site
 - KPS score greater than or equal to 70% or ECOG performance status of zero to two
 - Life expectancy is at least six months
 - Has a total of up to five metastatic lesions
 - Each lesion is less than or equal to five centimeters in size
 - No evidence of malignant pleural effusion, leptomeningeal or peritoneal carcinomatosis
 - All metastatic lesions are to be treated concurrently in a single episode of care
 - SBRT must be completed in five fractions for an entire course of treatment regardless of number of lesions treated
- Glomus jugulare tumors
- Hemangiomas of the brain
- Intracranial arteriovenous malformations (AVMs)
- Meningioma
- Neurologic conditions (epilepsy, Parkinson's disease, essential tremor) that are refractory to medical treatment and/or invasive surgical interventions
- Pineal gland tumors
- Pituitary adenoma
- Recurrent gliomas
- Spinal lesions when **one** of the following criteria are met:
 - Palliative treatment of symptomatic spinal bone metastasis when **all** the following criteria are met (for Oligometastatic Disease, refer to the criteria above):
 - Using five fractions or less
 - Individual has no spinal cord compression or cauda equina compression

- Primary spinal lesions that cannot be treated with surgical resection or 3D conformal techniques
- To treat a previously irradiated field
- Trigeminal neuralgia refractory to medical therapy
- Uveal melanoma

Medical Records Documentation Used for Reviews

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the guidelines titled [Medical Records Documentation Used for Reviews](#).

Definitions

Definitive Treatment: Radiation treatments for cancer with a curative intent (NCCN, 2025; Landsteiner et al., 2023). The National Cancer Institute (NCI) defines curative intent therapy as a treatment designed to eliminate a disease or illness, aiming for a full recovery while maintaining a satisfactory quality of life (QOL). In cancer care, the suitability of a curative approach depends on the specific type and stage of cancer (NCI, 2025).

Oligometastatic Disease (OMD): The Oligometastatic Disease state was first defined by Hellman in 1995 and refers to a stage of disease where cancer has spread beyond the site of origin, but is not yet widely metastatic. In such a state of limited metastatic disease burden, it is hypothesized that eradication of all sites of metastatic disease could result in long-term survival, or even cure, in a subgroup of individuals (Palma et al, 2012).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

CPT Code	Description
32701	Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (photon or particle beam), entire course of treatment
61796	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 simple cranial lesion
61797	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, simple (List separately in addition to code for primary procedure)
61798	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 complex cranial lesion
61799	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, complex (List separately in addition to code for primary procedure)
61800	Application of stereotactic headframe for stereotactic radiosurgery (List separately in addition to code for primary procedure)
63620	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion
63621	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional spinal lesion (List separately in addition to code for primary procedure)
77301	Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications
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

CPT Code	Description
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

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HCPCS Code	Description
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

Description of Services

Stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), is a method used to deliver external beam radiation therapy (EBRT) to a well-defined extracranial target in five fractions or less. It can deliver, with very high accuracy, substantially higher doses per treatment than those given in conventional fractionation while minimizing radiation exposure to adjacent normal tissue (Chao et al., 2020).

Stereotactic radiosurgery (SRS) is a non-surgical radiation therapy that is used to deliver a large dose of radiation with a high degree of precision and spatial accuracy, which can aid in preserving healthy tissue. SRS may be used to treat a variety of benign and malignant disorders involving intracranial structures, as well as select extracranial lesions. Although SRS ordinarily refers to a one-day treatment, physicians may suggest multiple stereotactic delivered treatments for tumors larger than one inch in diameter as the surrounding normal tissue exposed to the single high dose of radiation must be limited, and the volume of normal tissue treated increases proportionally to the tumor size. Safety can be improved, and the normal tissue can be allowed to heal between treatments when delivering the radiation in a few sessions, as opposed to one. Fractionating the treatment allows for high doses to still be delivered within the target, while maintaining an adequate safety profile. This treatment is commonly referred to as fractionated stereotactic radiotherapy (FSRT), and normally refers to the delivery of two to five treatments of focused radiation which are not always given on consecutive days. [American College of Radiology (ACR), 2019].

Clinical Evidence

Acoustic Neuroma (Vestibular Schwannoma)

Hajikarimloo et al. (2024) performed a systematic review and meta-analysis to evaluate the efficacy and outcomes of repeat stereotactic radiosurgery (SRS) in the management of recurrent or progressive vestibular schwannoma (VS) after failing the first SRS treatment. Eleven studies (260 individuals) were included in the review. The median time interval between initial and repeat SRSs ranged from tumor volume ranged from 43 to 62 months. The analysis revealed a pooled tumor control of 91% [95% confidence interval (CI): 86% - 94%]. Regarding the radiological response, the pooled regression rate was 59% (95% CI: 52% - 65%), while the pooled progression rate was 9% (95% CI: 6% - 14%). Regarding the clinical outcomes, the pooled serviceable hearing preservation rate was 36% (95% CI: 22% - 53%), while worsened fifth cranial nerve and seventh cranial nerve rates were 12% (95% CI: 7% - 19%) and 8% (95% CI: 5% - 12%), respectively. In addition, the pooled adverse radiation effect (ARE) rate was 6% (95% CI: 3% - 11%). According to the authors, their findings indicated that performing repeat SRS after the initial SRS fails in VS led to positive outcomes such as effective tumor control, serviceable hearing preservation, and cranial nerve worsening, concurrent with low ARE rates. Limitations included the retrospective nature of all included studies and the presence of other therapeutic interventions before the initial SRS that may influence the outcomes following SRS.

Balossier et al. (2023) conducted a systematic review and meta-analysis that centered on long-term hearing preservation after treatment with SRS. Inclusion criteria consisted of peer-reviewed clinical studies or case series of VS treated with a single dose of SRS that reported hearing outcomes with a median or mean audiometric follow-up of at least five years and were published between January 1990 and October 2020. The primary outcome evaluated was hearing preservation;

secondary outcomes assessed were cranial nerves outcomes, and tumor control. Twenty-three studies were included. Hearing preservation was found in 59.4% of cases (median follow-up 6.7 years, 1409 individuals). Young age, good hearing status, early treatment after diagnosis, small tumor volume, low marginal irradiation dose, and maximal dose to the cochlea were the main favorable prognostic factors. Tumor control was achieved in 96.1%. Facial nerve deficit and trigeminal neuropathy were found in 1.3% and 3.2% of individuals, respectively, both significantly higher in Linear Accelerator (LINAC) series than Gamma Knife series ($p < .05$). The authors concluded hearing preservation can be achieved for at least six years in almost 60% of individuals undergoing SRS for VS. Limitations included small sample size of some included studies and tumor progression and tumor control definitions varied across studies. (Boari et al., 2014, which was previously cited in this policy, is included in this review).

Tosi et al. (2021) performed a systematic review and meta-analysis to assess outcomes of irradiation for large VS. Rate of tumor control, serviceable hearing, need for salvage surgery, trigeminal nerve and facial nerve impairment, presence of vertigo/dizziness, and hydrocephalus requiring shunting were the primary endpoints. Three categories of studies were identified: 1) single-dose SRS (13 studies, 483 individuals), 2) combination of microsurgery and SRS (seven studies, 182 individuals), and 3) fractionated SRS (three studies, 82 individuals). Tumor control was achieved in 89%, 94%, and 91% of individuals, respectively. Odds ratios of post-over pretreatment serviceable hearing were 0.42, 0.47, and 0.60; for facial nerve impairment, these odds ratios were 1.08, 3.45, and 0.87, respectively. The authors note that given the high likelihood of local structure compromise, tendency to continue growing in size, and difficulties associated with both microsurgery and SRS, large VS pose a therapeutic challenge. The authors concluded that SRS, either as a single dose, in conjunction with microsurgery, or fractionated provides good tumor control with acceptable cranial nerve morbidity and is a valid treatment alternative. Limitations included lack of randomized controlled trials (RCTs) included in the study, data were reported in a heterogenous manner, and limited study sizes. The authors recommended further structured studies.

Windisch et al. (2019) conducted a single-center, retrospective, case series analysis to evaluate clinical outcomes of individuals with VS and treated with SRS. Clinical data and imaging follow-up were obtained from the center's database. Outcomes included local tumor control, hearing loss, and adverse events. Tumor response was assessed by magnetic resonance imaging (MRI). Shrinkage and no change in size were scored as a locally controlled disease. Increased size in two consecutive follow-ups was interpreted as a local recurrence. Follow-up assessments were performed after six months, every year for two years, and every two years thereafter. A total of 996 individuals with 1,002 tumors with at least one year of follow-up after SRS and were included for analysis. The median age at SRS was 55.1 years (range, 15.1 to 85.2 years) and the median follow-up was 3.6 years (one to 12.5 years). All tumors were treated in a single fraction, with a median prescription dose of 13 gray (Gy) (range, 11.5 to 15 Gy). The three, five, and 10-year Kaplan-Meier estimated local tumor control was 96.6%, 92.3%, and 90.8%, respectively. The median hearing loss of the affected ear as compared to its healthy counterpart was 17 decibels (dB) at start of treatment and increased to 23 and 29 dB at one and five years. Six individuals (0.6%) developed symptomatic hydrocephalus and underwent the placement of a ventriculoperitoneal shunt. In 30 individuals (3.0%), trigeminal sensory dysfunction developed, five individuals (0.5%) had a mild transient weakness, and nine individuals (0.9%) had a permanent facial weakness (House-Brackmann Grade $> II$) after SRS. The authors concluded that single fraction SRS is highly effective and shows low treatment-related toxicity for VS, and that SRS should be considered a primary treatment option for small and middle-sized VS.

Clinical Practice Guidelines

Congress of Neurological Surgeons

Germano et al. (2018) developed evidence-based guidelines for the Congress of Neurological Surgeons regarding the use of radiosurgery (RS) and RT for individuals with VS. The systematic literature review included 137 articles that met the inclusion criteria that were published from January 1, 1990 to December 31, 2014. Only class III evidence studies were available to develop the guidelines. The following recommendations were made (not all-inclusive):

- As there is no difference in radiographic control using different doses, it is recommended that for single fraction SRS doses, < 13 Gy be used to facilitate hearing preservation and minimize new onset or worsening of preexisting cranial nerve deficits.
- When there has been progression of tumor after SRS, SRS can be safely and effectively performed as a retreatment.
- Radiosurgery is a treatment option for patients with neurofibromatosis type 2 whose VSs are enlarging and/or causing hearing loss.
- Patients should be informed that there is a minimal risk of malignant transformation of VS after SRS.

International Stereotactic Radiosurgery Society (ISRS)

Tuleasca et al. (2025) performed a systematic review and meta-analysis of the literature related to planned subtotal resection for large VSs followed by SRS to the residual tumor to summarize outcomes and provide treatment recommendations. Twelve series met inclusion criteria reporting on treatment outcomes for 677 patients. Overall tumor control was 89.9%, with tumor stability observed in 43.9% and tumor reduction in 39.9% post-SRS. Facial nerve functional

preservation immediately after microsurgery was 88.0%, improving to 94.4% at last follow-up. Cochlear functional preservation immediately after microsurgery was 58.8%, decreasing to 57.4% at last follow-up. The authors concluded that the cranial nerve sparing approach with planned subtotal microsurgical resection and SRS to the residual tumor resulted in a highly satisfactory outcome of facial and cochlear functional preservation and achieved a high rate of tumor control. For management of large VSs with combined microsurgery and SRS, the ISRS recommends:

- Nerve-sparing intracapsular microsurgical resection with facial nerve preservation. Strength of recommendation: strong; level of evidence: III.
- Upfront SRS should be considered as opposed to observation due to the potential to optimize long-term local control and within three to six months following subtotal resection. Strength of recommendation: conditional; level of evidence: III.
- Radiation therapy (RT) alone can be used as upfront treatment in patients with medical comorbidities precluding upfront surgery. Strength of recommendation: strong; level of evidence: III.
- A first post-operative MRI should be performed within three to six months to determine residual disease and an evaluation for post-operative SRS. Strength of recommendation: strong; level of evidence: III.

Bone Metastasis (Non-Spine)

Nguyen et al. (2019) conducted a phase II RCT that compared pain relief from high-dose single-fraction SBRT with conventional multifraction radiotherapy (MFRT) in individuals with mostly non-spine bone metastases. The primary endpoint was pain response. Secondary endpoints were quality of life (QOL) and symptom burden, narcotic use post-treatment, toxic effects, local control of irradiated metastases, and overall survival (OS). Inclusion criteria included those age 18 or older with a diagnosis of cancer and painful bone metastases with more than three months life expectancy. Concurrent treatment of three radiation fields or less was allowed. Prior radiation to the site, untreated spinal cord compression, pathologic fracture at the site, and previous radioactive isotope therapy within 30 days of randomization were the study exclusions. One hundred and sixty participants were randomized to receive either SBRT or MFRT. In this phase II portion of a phase II/III noninferiority trial of 96 men and 64 women, 81 participants received SBRT and 79 received MFRT. Among evaluable participants who received treatment per protocol, the single-fraction group had more pain responders than the MFRT group (complete response + partial response) at two weeks [34 of 55 (62%) versus 19 of 52 (36%)] ($p = .01$), three months [32 of 44 (73%) versus 17 of 35 (49%)] ($p = .04$), and nine months [17 of 22 (77%) versus 12 of 26 (46%)] ($p = .04$). A sub distribution hazard ratio (HR) of 0.71 (95% CI, 0.36 - 1.39) indicated that SBRT had 29% less risk of failure relative to the MFRT after considering death as a competing risk. The upper 95% CI for sub distribution HR was less than the noninferiority margin of 1.5, indicating that SBRT was noninferior to MFRT. No differences were found in treatment-related toxic effects or QOL scores after SBRT versus MFRT. The authors concluded that high-dose, single-fraction SBRT appeared to be an effective option for treating those with painful bone metastases. Among those evaluated, SBRT showed higher rates of pain response (both complete and partial) compared to MFRT and should be considered for individuals with a relatively long expected survival. Limitations comprised the inclusion of metastases from various types of primary cancer and the attrition rate rose with increasing follow-up time due to the nature of having metastatic cancer. The authors recommended larger phase III studies.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

ASTRO's guideline on palliative RT for symptomatic bone metastases (Alcorn et al., 2024) provides recommendations using consensus-building methodology based on a systematic review by AHRQ (Skelly et al., 2023). The authors note that developing the most favorable RT regimen requires an assessment including prognosis, any previous RT doses, normal tissue risks, QOL, and patient values and goals. Per the guidelines:

- For patients with symptomatic spine bone metastases, including those causing compression of the spinal cord or cauda equina, RT is recommended to improve ambulatory status, sphincter function, and reduce pain. Implementation remark: Before initiating RT, evaluation for spine stability and surgery are necessary. Strength of recommendation: strong; quality of evidence: high.
- For patients with symptomatic bone metastases treated with SBRT, 1200 to 1600 centigray (cGy) in one fraction (nonspine) and 2400 cGy in two fractions (spine) are recommended. Implementation remark: Other established SBRT dose and fractionation regimens (e.g., two to five fractions) with similar biological effective doses (BEDs) may be an option based on patient tumor and normal tissue factors, and physician experience. Strength of recommendation: strong; quality of evidence: moderate.
- For patients with symptomatic bone metastases with ECOG PS zero to two, receiving no surgical intervention, and absent neurological symptoms, SBRT is conditionally recommended over conventional palliative RT. Implementation remark: Other factors to consider include life expectancy, tumor radiosensitivity, and metastatic disease burden. Strength of recommendation: conditional; quality of evidence: moderate.

- For patients with symptomatic nonspine bone metastases that would benefit from reirradiation to the same site, single-fraction (800 cGy in one fraction) or multifraction conventional palliative RT (2000 cGy in five fractions or 2400 cGy in six fractions) are recommended. Strength of recommendation: strong; quality of evidence: moderate.

National Comprehensive Cancer Network (NCCN)

Per NCCN guidelines, SRS or SBRT may be considered for metastatic bone disease, especially for oligometastases. (NCCN, 2025).

Brain Metastasis

Gaebel et al. (2023) conducted a systematic review and meta-analysis of controlled trials and cohort studies that compared SRS to whole brain radiation therapy (WBRT) to evaluate survival outcomes and assess treatment outcomes following SRS in those with intracranial metastatic disease (IMD) secondary to small cell lung cancer (SCLC). Inclusion criteria included adults with SCLC and a diagnosis of IMD treated with SRS. Studies were considered eligible if they were published in English and reported on either first-line SRS or salvage SRS and single-arm SRS studies were included retrospectively, but prior to data extraction. Studies not reporting on individuals who received SRS for IMD secondary to SCLC were excluded. Overall survival was the primary endpoint. Thirty-one studies were included in the review and seven were included in the meta-analysis. Overall survival following SRS was longer than following WBRT with or without SRS boost (HR 0.85; 95% CI 0.75 - 0.97; $n =$ seven studies; $n = 18130$ individuals), or WBRT alone (0.77; 0.72 - 0.83; $n =$ seven studies; $n = 16961$ individuals), but not WBRT plus SRS boost (1.17, 0.78 - 1.75; $n =$ four studies; $n = 1167$ individuals). Using single-arm studies, pooled median OS from SRS was 8.99 months (95% CI 7.86 - 10.16; $n = 14$ studies; $n = 1682$ patients). Between-study heterogeneity was considerable when pooled among all comparative studies ($I^2 = 71.9\%$). The authors concluded that survival outcomes are comparable for individuals with SCLC and IMD treated with SRS versus WBRT. Limitations include the retrospective nature of the studies included in the review and most studies did not include those with previous prophylactic cranial irradiation (PCI). The authors recommended further prospective RCTs to evaluate the impact of IMD burden and differences in intracranial control between WBRT and SRS. Rusthoven et al. (2020), summarized below, is included in this study.

Vlachos et al. (2023) conducted a systematic review and meta-analysis to evaluate whether postoperative SRS has comparable results in local and distant recurrence, leptomeningeal disease, and OS compared to individuals with a solitary, previously resected brain metastasis. Two RCTs and two retrospective studies were included in the review. One hundred twenty-eight individuals received postoperative WBRT while 120 individuals were treated with postoperative SRS. There was no difference between SRS and WBRT in the risk of local recurrence [risk ratio (RR) = 0.92, CI = 0.51 - 1.66, $p = 0.78$, $I^2 = 0\%$] and leptomeningeal disease (RR = 1.21, CI = 0.49 - 2.98, $p = 0.67$, $I^2 = 18\%$), neither in the individuals' OS (HR = 1.06, CI = 0.61 - 1.85, $p = 0.83$, $I^2 = 63\%$). SRS appeared to increase the risk of distant brain failure (RR = 2.03, CI = 0.94 - 4.40, $p = 0.07$, $I^2 = 61\%$). Neurocognitive function and QOL in the SRS group were equal or superior to the WBRT group. The authors concluded that SRS may increase the risk of distant brain failure compared to WBRT. However, in terms of local control, risk of leptomeningeal disease, and OS, SRS appears as effective as WBRT and SRS spared the individuals the WBRT-associated cognitive deterioration. Limitations included the various types of primary tumor sites, the type of surgical resection was not reported, and all individuals had a relatively good preoperative performance status. The authors recommended larger scale, prospective studies in the future.

Rusthoven et al. (2020) conducted a cohort study of 710 individuals with SCLC brain metastases (BMs) treated with SRS without prior PCI or WBRT to compare SRS outcomes with those treated with first-line WBRT. Overall survival, time to central nervous system (CNS) progression, and progression-free survival (PFS) after SRS were the primary endpoints. The median OS was 8.5 months, the median time to CNS progression was 8.1 months, and the median CNS PFS was five months. When stratified by the number of BMs treated, the median OS was 11.0 months (95% CI, 8.9 - 13.4) for one lesion, 8.7 months (95% CI, 7.7 - 10.4) for two to four lesions, eight months (95% CI, 6.4 - 9.6) for five to 10 lesions, and 5.5 months (95% CI, 4.3 - 7.6) for 11 or more lesions. Competing risk estimates were 7.0% (95% CI, 4.9% - 9.2%) for local failures at 12 months and 41.6% (95% CI, 37.6% - 45.7%) for distant CNS failures at 12 months. Leptomeningeal progression [46 of 425 patients (10.8%) with available data] and neurological mortality [80 of 647 patients (12.4%) with available data] were uncommon. On propensity score-matched analyses comparing SRS with WBRT, WBRT was associated with improved time to CNS progression (HR, 0.38; 95% CI, 0.26 - 0.55; $p < .001$), without an improvement in OS [median, 6.5 months (95% CI, 5.5 - 8.0) for SRS versus 5.2 months (95% CI, 4.4 - 6.7) for WBRT; $p = .003$] or CNS PFS (median, four months for SRS versus 3.8 months for WBRT; $p = .79$). Multivariable analyses comparing SRS and WBRT, including subset analyses controlling for extracranial metastases and extracranial disease control status, demonstrated similar results. The authors concluded that treatment with SRS for SCLC had encouraging outcomes overall; especially for those with a single BM. This study is included in the Gaebel et al., 2023 systematic review and meta-analysis.

Fogarty et al. (2019) conducted a multi-center, international, phase III, randomized trial (NCT01503827) to compare WBRT with observation after local treatment of one to three melanoma brain metastases (MBMs). The primary endpoint was distant intracranial failure within 12 months of randomization. The a priori neurocognitive function endpoint was Hopkins Verbal Learning Test-Revised (HVLT-R) delayed recall at four months. Secondary endpoints included local failure, OS and global QOL. Analyses were conducted on an intention-to-treat basis with nominal two-sided significance level 5%. Drug therapy was allowed. Effective drugs became available during trial and their impact was analyzed. A total of 215 participants consented to participate in the study and of those, eight withdrew or had no data collected. One hundred participants were randomized to the WBRT arm and 107 participants to the observation arm. The mean age was 62 years, 67% males, 61% with single MBM of mean size two centimeters (cm), and 67% had extracranial disease at randomization. Neurocognitive function was completed by participants who spoke English; 50 participants who were randomized to WBRT and 70 participants to observation at baseline, declining to 26 and 35 participants respectively at four months. Within 12 months, 54 (50.5%) participants in the observation arm had distant intracranial failure compared with 42 (42.0%) participants in the WBRT arm (OR 0.71; 95% CI 0.41 to 1.23; $p = 0.222$). There was no difference in local failure ($p = 0.100$) or OS ($p = 0.861$). At 12 months, 53% of participants in the observation arm and 59% of participants in the WBRT arm were alive. There was no difference in the mean intervention effect on global QOL ($p = 0.083$) between the two arms. Participants who received T-cell checkpoint inhibitors and/or mitogen-activated protein kinase (MAPK) pathway inhibitors and WBRT before or within 12 months of randomization had a distant intracranial failure rate 29% compared with 44% of participants in the observation arm with no systemic therapy however, this difference was not significant ($p = 0.228$). The observation arm had greater relative improvement from baseline in HVLT-R at every timepoint. At four months, the observation arm had a 20.9% improvement from baseline in HVLT-R-delayed recall compared with 2.7% decline in the WBRT arm; the overall adjusted average intervention effect was 23.6% (95% CI 9.0 to 38.2; $p = 0.0018$). There was no difference in time to cognitive failure or in proportions with global cognitive impairment between the arms. The authors concluded that this RCT shows that WBRT does not improve outcomes in MBMs, and that this trial justifies the recent move away from WBRT.

Yamamoto et al. (2019) conducted a retrospective cohort analysis of individuals with BM who underwent multiple SRS procedures to validate whether brain metastasis velocity (BMV), a prognostic grading system, is generally applicable. The BMV score is the cumulative number of new BMs that developed after the first SRS divided by time (years) since the initial SRS. Individuals are categorized into three classes based on their BMV scores (i.e., ≤ 3 , 4 to 13, and ≥ 14). A total of 833 individuals who underwent a second SRS procedure for newly detected BMs were included in the analysis. Of those, 250 underwent a third procedure, and 88 had a fourth SRS procedure. The median survival times after the second SRS were 12.9 months (95% CI, 10.2 to 17.1) for the BMV group with a score of ≤ 3 ; 7.5 months (95% CI, 6.5 to 9.0) for the group scoring four to 13, and 5.1 months (95% CI, 4.0 to 5.6) for the group scoring ≥ 14 ($p = 0.0001$). The corresponding median survival times after the third SRS were 13.2 months (95% CI, 9.1 to 21.6), 8.0 months (95% CI, 6.2 to 11.2), and 5.7 months (95% CI, 4.8 to 7.8; $p = 0.0001$). Respective median survival times after the fourth SRS were 13.2 months (95% CI, 9.1 to 21.6), 8.0 months (95% CI, 6.2 to 11.2), and 5.7 months (95% CI, 4.8 to 7.8; $p < 0.0001$). The mean BMV score of individuals with SCLC, 24.8, was significantly higher than that of individuals with non-small cell lung cancer (NSCLC), 17.7 ($p = 0.032$). The authors concluded that the results of this analysis support the validity of BMV for predicting survival not only after the second SRS but also after the third and fourth SRS.

Farris et al. (2017) conducted a single-center, retrospective, cohort analysis to characterize BMV as a prognostic metric for patient outcomes with BMs, determine the factors that predict for higher BMV, and determine whether BMV is associated with other important clinical outcomes such as OS and likelihood of neurologic death. The BMV score is the cumulative number of new BMs that developed after the first SRS divided by time (years) since the initial SRS. Individuals are categorized into three classes based on their BMV scores (i.e., ≤ 3 , 4 to 13, and ≥ 14). Histology, number of metastases at the time of first SRS, and systemic disease status were assessed for effect on BMV. Following initial SRS treatment, individuals were followed up with MRI of the brain and clinical examination at four to eight weeks after the procedure and thereafter every three months. The number of new metastases on every follow-up MRI scan was recorded to generate the BMV. A new metastasis was determined on follow-up MRI to be completely outside of the prior radio surgical treatment volume as defined by the prescription isodose line. Of 737 individuals treated with upfront SRS without WBRT, 286 (38.8%) had ≥ 1 distant brain failure (DBF) event. The median follow-up was estimated at 66.5 months (95% CI, 50.9 to 85.7 months) and median OS from the time of first SRS for all individuals with BMV data was 16.3 months (95% CI, 14.6 to 18.6 months). A lower BMV predicted for improved OS following initial DBF ($p < 0.0001$). Median OS for the low, intermediate, and high BMV groups was 12.4 months (95% CI, 10.4 to 16.9 months), 8.2 months (95% CI, 5.0 to 9.7 months), and 4.3 months (95% CI, 2.6 to 6.7 months), respectively. Multivariate analysis showed that BMV remained the dominant predictor of OS, with a HR of 2.75 for the high BMV group (95% CI, 1.94 to 3.89; $p < 0.0001$) and a HR of 1.65 for the intermediate BMV group (95% CI, 1.18 to 2.30; $p < 0.004$). A lower BMV was associated with decreased rates of salvage WBRT ($p = 0.02$) and neurologic death ($p = 0.008$). Factors predictive for a higher BMV included ≥ 2 initial BMs ($p = 0.004$) and melanoma histology ($p = 0.008$). The authors concluded that BMV is a novel metric associated with OS, neurologic death, and need for salvage WBRT after initial DBF following upfront SRS alone.

Yamamoto et al. (2017) published a follow-up study to the JLKG0901 Study (Yamamoto 2014) to confirm the long-term safety of SRS in individuals with five to 10 BMs. Yamamoto et al. (2014) was a multi-center, non-randomized observational study to examine whether SRS without WBRT as the initial treatment for individuals with five to 10 BMs is non-inferior to that for individuals with two to four BMs in terms of OS. The study enrolled 1,194 participants and the median OS after SRS was 13.9 months (95% CI, 12.0 to 15.6) in 455 participants with one tumor, 10.8 months (9.4 - 12.4) in 531 participants with two to four tumors, and 10.8 months (9.1 - 12.7) in 208 participants with five to ten tumors. OS did not differ between the participants with two to four tumors and those with five to 10. SRS-induced adverse events occurred in 101 (8%) participants; nine (2%) participants with one tumor had one or more grade 3 - 4 event compared with 13 (2%) participants with two to four tumors and six (3%) participants with five to 10 tumors. The proportion of participants who had one or more treatment-related adverse event of any grade did not differ significantly between the two groups of participants with multiple tumors. Four participants died, mainly of complications related to SRS (two with one tumor and one each in the other two groups). The authors concluded that SRS without WBRT in participants with five to 10 BMs is non-inferior to that in participants with two to four BMs, and that the minimal invasiveness of SRS and fewer side-effects than with WBRT, may make SRS a suitable alternative for participants with up to 10 BMs. The follow-up study (Yamamoto 2017) reappraised, after an additional two years of follow-up, whether GK SRS alone for five to 10 BMs is safe in the long term, as compared with that for two to four BMs, and even that for one BM, as well as reported WBRT results. The focus of this study was Mini-Mental State Examination (MMSE) results and complications. The 1,194 eligible participants were categorized into the following groups: group A, one tumor (n = 455); group B, two to four tumors (n = 531); and group C, five to 10 tumors (n = 208). Cumulative rates of MMSE score maintenance (MMSE score decrease < three from baseline) determined with a competing risk analysis of groups A, B, and C were 93%, 91%, and 92%, respectively, at the 12th month after SRS; 91%, 89%, and 91%, respectively, at the 24th month; 89%, 88%, and 89%, respectively, at the 36th month; and 87%, 86%, and 89%, respectively, at the 48th month (HR of group A versus group B, 0.719; 95% CI, 0.437 - 1.172; p = 0.18; HR of group B versus group C, 1.280; 95% CI, 0.696 - 2.508; p = 0.43). During observations ranging from 0.3 to 67.5 months [median, 12.0 months; interquartile range (IQR), 5.8 - 26.5 months], as of December 2014, 145 participants (12.1%) had SRS-induced complications. The cumulative complication incidences by competing risk analysis for groups A, B, and C were 7%, 8%, and 6%, respectively, at the 12th month after SRS; 10%, 11%, and 11%, respectively, at the 24th month; 11%, 11%, and 12%, respectively, at the 36th month; and 12%, 12%, and 13%, respectively, at the 48th month (HR of group A versus group B, 0.850; 95% CI, 0.592 to 1.220; p = 0.38; HR of group B versus group C, 1.052; 95% CI, 0.666 to 1.662, p = 0.83). Leukoencephalopathy occurred in 12 of the 1,074 participants (1.1%) with follow-up MRI and was detected after salvage WBRT in 11 of these 12 participants. In those 11 participants, leukoencephalopathy was detected by MRI 5.2 to 21.2 months (median, 11.0 months; IQR, 7.0 to 14.4 months) after WBRT. The authors concluded that neither MMSE score maintenance nor post-SRS complication incidence differed among groups A, B, and C and that this longer-term follow-up study further supports the noninferiority of SRS alone for individuals with five to 10 BMs versus two to four BMs.

Brown et al. (2016) conducted a multi-center, randomized trial to determine whether there is less cognitive deterioration at three months after SRS alone versus SRS plus WBRT. Adult participants (18 years of age or more) with one to three BMs, all smaller than 3.0 cm in diameter, were eligible for the trial. Participants who were randomly assigned to SRS alone received 24 Gy in a single fraction if lesions were less than 2.0 cm or 20 Gy if lesions were 2 - 2.9 cm in maximum diameter. Participants who were randomly assigned to SRS plus WBRT received 22 Gy in a single fraction if lesions were less than 2.0 cm or 18 Gy if lesions were 2 - 2.9 cm in maximum diameter. Participants who were randomly assigned to SRS plus WBRT received 30 Gy in 12 fractions of 2.5 Gy WBRT delivered five days a week. Whole brain radiotherapy began within 14 days of SRS. The primary end point was cognitive deterioration [decline > 1 standard deviation (SD) from baseline on at least one cognitive test at three months] in participants who completed the baseline and three-month assessments. Secondary end points included time to intracranial failure, QOL, functional independence, long-term cognitive status, and OS. A total of 213 individuals participated in the study (SRS alone, n = 111; SRS plus WBRT, n = 102) with a mean age of 60.6 years (SD, 10.5 years) and 103 (48%) were women. There was less cognitive deterioration at three months after SRS alone [40/63 participants (63.5%)] than when combined with WBRT [44/48 participants (91.7%); difference, -28.2%; 90% CI, -41.9% to -14.4%; p < 0.001]. Quality of life was higher at three months with SRS alone, including overall QOL (mean change from baseline, -0.1 versus -12.0 points; mean difference, 11.9; 95% CI, 4.8 to 19.0 points; p = 0.001). Time to intracranial failure was significantly shorter for SRS alone compared with SRS plus WBRT (HR, 3.6; 95% CI, 2.2 to 5.9; p < 0.001). There was no significant difference in functional independence at three months between the treatment groups. Median OS was 10.4 months for SRS alone and 7.4 months for SRS plus WBRT (HR, 1.02; 95% CI, 0.75 to 1.38; p = 0.92). For long-term survivors, the incidence of cognitive deterioration was less after SRS alone at three months [5/11 (45.5%) versus 16/17 (94.1%); difference, -48.7%; 95% CI, -87.6% to -9.7%; p = 0.007] and at 12 months [6/10 (60%) versus 17/18 (94.4%); difference, -34.4%; 95% CI, -74.4% to 5.5%; p = 0.04]. The authors concluded that among participants with one to three BMs, the use of SRS alone, compared with SRS combined with WBRT, resulted in less cognitive deterioration at three months, and that in the absence of a difference in OS, these findings suggest that for individuals with one to three BMs amenable to RS, SRS alone may be a preferred strategy.

Minniti et al. (2016) conducted a case series analysis to evaluate the efficacy and toxicity of repeated SRS in individuals with recurrent/progressive BMs. A total of 43 individuals (21 men and 22 women) with 47 lesions received a second course of SRS given in three daily fractions of 7 - 8 Gy. With a follow-up study of 19 months, the one- and two-year survival rates from repeated SRS were 37% and 20%, respectively, and the one- and two-year local control rates were 70% and 60% respectively. Actuarial local control was significantly better for breast and lung metastases as compared with melanoma metastases; one-year local control rates were 38% for melanoma, 78% for breast carcinoma and 73% for NSCLC metastases ($p = 0.01$). The cause of death was progressive systemic disease in 25 individuals and progressive brain disease in 11 individuals. Stable extracranial disease ($p = 0.01$) and KPS ($p = 0.03$) were predictive of longer survival. Radiologic changes suggestive of brain radionecrosis were observed in nine (19%) out of 47 lesions, with an actuarial risk of 34% at 12 months. Neurological deficits (RTOG Grade 2 or 3) associated with brain necrosis occurred in 14% of individuals. The authors concluded that a second course of SRS given in three daily fractions is a feasible treatment for selected individuals with recurrent/progressive BMs, and additional studies that explore the efficacy and safety of different dose-fractionation schedules, especially in individuals with melanoma or large metastases are needed.

Kocher et al. (2011) and the European Organization for Research and Treatment of Cancer conducted a multi-center, randomized trial (EORTC 22952-26001) to assess whether adjuvant WBRT increases the duration of functional independence after surgery or RS of BMs. Participants with one to three BMs of solid tumors (SCLC excluded) with stable systemic disease or asymptomatic primary tumors and World Health Organization (WHO) performance status of zero to two were treated with complete surgery or RS and randomly assigned to adjuvant WBRT (30 Gy in 10 fractions) or observation. The primary end point was time to WHO performance status deterioration to more than two and secondary end points were frequency of intracranial relapse at initially treated and at new sites, PFS, OS, late toxicities, and QOL. Of 359 participants, 199 underwent RS, and 160 underwent surgery. In the RS group, 100 participants were allocated to observation, and 99 were allocated to WBRT. After surgery, 79 participants were allocated to OBS, and 81 were allocated to adjuvant WBRT. The median time to WHO performance status more than two was 10.0 months (95% CI, 8.1 to 11.7 months) after observation and 9.5 months (95% CI, 7.8 to 11.9 months) after WBRT ($p = 0.71$). Overall survival was similar in the WBRT and observation arms (median, 10.9 versus 10.7 months, respectively; $p = 0.89$). WBRT reduced the two-year relapse rate both at initial sites (surgery: 59% to 27%, $p < 0.001$; RS: 31% to 19%, $p = 0.040$) and at new sites (surgery: 42% to 23%, $p = 0.008$; RS: 48% to 33%, $p = 0.023$). Salvage therapies were used more frequently after observation than after WBRT. Intracranial progression caused death in 78 (44%) of 179 participants in the observation arm and in 50 (28%) of 180 participants in the WBRT arm. The authors concluded that after RS or surgery for a limited number of BMs, adjuvant WBRT reduces intracranial relapses and neurologic deaths but fails to improve the duration of functional independence and OS.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

The 2022 ASTRO clinical practice guidelines provided evidence-based recommendations for treatment of BMs. The ASTRO recommendations are as follows (not all inclusive):

- Indications for SRS alone for intact BMs:
 - SRS is recommended for patients with an Eastern Cooperative Oncology Group (ECOG) of zero to two and up to four intact brain BMs. Strength of recommendation: strong; quality of evidence: high.
 - SRS is conditionally recommended for patients with an ECOG performance standard of zero to two and five to 10 intact brain metastases. Strength of recommendation: conditional; quality of evidence: low.
 - Single-fraction SRS with a dose of 2000-2400 cGy is recommended for patients with intact BMs measuring < 2 cm in diameter, if multifraction SRS is given, options include 2700 cGy in three fractions or 3000 cGy in five fractions. Strength of recommendation: strong; quality of evidence: moderate.
- Indications for observation, postoperative SRS, WBRT, or preoperative SRS:
 - RT with SRS or WBRT is recommended to improve intracranial disease control for those with resected BMs. Strength of recommendation: strong; quality of evidence: high.
 - SRS is recommended over WBRT to preserve neurocognitive function and patient-reported QOL for those with resected BMs and limited additional BMs. Strength of recommendation: strong; quality of evidence: moderate.

ASTRO suggested there is an ongoing need for inclusive clinical trials that assess different modalities and have endpoints such as survival, cognitive outcomes, and QOL (Gondi et al., 2022).

American Society of Clinical Oncology (ASCO)

ASCO determined that the recommendations from the ASTRO Radiation Therapy for Brain Metastases Clinical Practice Guidelines are clear, thorough, and based upon the most relevant scientific evidence. ASCO endorsed the guidelines above (Schiff et al., 2022).

Congress of Neurological Surgeons

Graber, Cobbs, and Olson (2019) developed an evidence-based guideline for the Congress of Neurological Surgeons to address the management of adults with new or recurrent BMs from solid tumors. Part four of nine of the guideline provides recommendations for the use of SRS in this patient-population. The guideline recommends (not all-inclusive):

- For newly diagnosed metastatic brain tumors, SRS is preferred over surgery for single BMs when surgery risks neurological harm and radiation can be safely delivered.
- After open surgical resection of a solitary BM, SRS should be delivered to decrease local recurrence rates.
- SRS should be given to reduce tumor growth in patients with one BM, or in those with two to four small tumors [total volume under 7 milliliter (ml)], instead of whole brain radiation.
- SRS alone is recommended to improve median OS for individuals with more than four metastases having a cumulative volume < 7 ml.

National Comprehensive Cancer Network (NCCN)

Per the NCCN guidelines for CNS cancers, SRS is generally preferred over WBRT for limited BMs. When compared to postoperative WBRT, SRS to the surgical cavity improves local control over observation, offers similar OS, and superior overall cognitive preservation. For larger cavities, multi-fractions SRS may be preferred. In the context of reirradiating BMs, SRS alone is generally preferred when there is evidence of tumor progression following prior WBRT. New metastatic lesions that have not previously been treated with SRS can typically be managed safely in future SRS courses. For lesions that have already undergone SRS, repeat SRS may be considered as a treatment option. However, this carries a heightened risk of radiation-induced effects. When recurrence is too diffuse or widespread to be effectively addressed with focal therapies like SRS, WBRT may be reconsidered as a broader treatment strategy. Common dose-fractionation schedules include 16 - 20 Gy in one fraction, 24 - 27 Gy in three fractions, and 30 Gy in five fractions (NCCN, 2025).

The NCCN guidelines for SCLC state that individuals with a small number of BMs may be treated with SRS and for those who develop BMs after PCI, SRS is preferred, if feasible (NCCN, 2025).

Chordoma and Chondrosarcoma

In a systematic review and meta-analysis, Maroufi et al. (2024) aimed to evaluate the safety and effectiveness of SRS in the management of skull based chordomas. Inclusion criteria included primary or recurrent skull based chordomas, treated with SRS as primary, adjunctive, or salvage treatment, and outcomes/complications associated with SRS were reports. Exclusion criteria were other lesions or locations, radiotherapy approaches other than SRS, lack of reported complications or outcomes, non-English studies, studies with less than five cases or not mentioning SRS timing, and non-original studies and case reports. Thirty-three retrospective cohorts and series (n = 714 individuals) published from 1991 to 2023 were included in the review. Individuals, predominantly male (57.37%) with a mean age of 46.54 years, exhibited a conventional chordoma subtype (74.77%) and primary lesions (77.91%), mainly in the clivus (98.04%). The mean lesion volume was 13.49 cubic centimeter (cm³), and 96.68% of individuals had undergone prior surgical attempts. Gamma Knife radiosurgery (GKRS) (88.76%) was the predominant SRS method. Radiologically, 27.19% of individuals experienced tumor regression, while 55.02% showed no signs of disease progression at the latest follow-up. Progression occurred after a mean of 48.02 months. Symptom improvement was noted in 27.98% of individuals. Radiosurgery was associated with a relatively low overall adverse event rate (11.94%), mainly cranial nerve deficits (8.72%). Meta-regression revealed that age and primary lesion type influenced symptom improvement, while factors like extent of resection, radiotherapy, and SRS type affected adverse event rates. The authors concluded that the majority of individuals treated with SRS achieved local tumor control and the safety and efficacy of SRS in the treatment of skull base chordomas is supported. Limitations included many included studies were retrospective in nature and limited long-term data.

Kano et al. (2015) conducted a multicentered retrospective evaluation to analyze the outcome of SRS for individuals with chondrosarcoma who underwent this treatment as part of multimodality management. Forty-six individuals who underwent SRS for skull-based chondrosarcomas were identified at seven participating centers of the North American Gamma Knife Consortium (NAGKC). Thirty-six individuals had previously undergone tumor resections and five had been treated with fractionated RT. The median tumor volume was 8.0 cm³ (range 0.9 - 28.2 cm³), and the median margin dose was 15 Gy (range 10.5 - 20 Gy). At a median follow-up of 75 months after SRS, eight individuals were deceased. The actuarial OS after SRS was 89% at three years, 86% at five years, and 76% at 10 years. Local tumor progression occurred in 10 individuals. The rate of PFS after SRS was 88% at three years, 85% at five years, and 70% at 10 years. Prior RT was significantly associated with shorter PFS. Eight individuals required salvage resection, and three individuals (7%) developed AREs. Cranial nerve deficits improved in 22 (56%) of the 39 individuals who deficits before SRS. Clinical improvement after SRS was noted in individuals with abducens nerve paralysis (61%), oculomotor nerve paralysis (50%), lower cranial nerve dysfunction (50%), optic neuropathy (43%), facial neuropathy (38%), trochlear nerve paralysis (33%), trigeminal neuropathy (12%), and hearing loss (10%). Limitations include the retrospective nature of the study and length

of follow up of less than 12 months for some individuals. The authors concluded that SRS provided a reasonable benefit-to-risk profile for those with residual or newly diagnosed small skull base chondrosarcomas and maximal safe resection should be the primary initial management. The authors additionally noted SRS as a potent treatment option for small to medium-sized chondrosarcomas that is associated with improvement of cranial nerve function in selected cases, especially for individuals who present with diplopia related to abducens nerve palsy.

Hasegawa et al. (2007) conducted a case series analysis to evaluate outcomes of individuals with skull base chordomas and chondrosarcomas and treated with SRS, and to determine which tumors are appropriate for SRS as adjuvant therapy following maximum tumor resection. A total of 37 individuals (48 lesions) were treated using Gamma Knife surgery (GKS); 27 had chordomas, seven had chondrosarcomas, and three had radiologically diagnosed chordomas. The mean tumor volume was 20 ml, and the mean maximum and marginal doses were 28 and 14 Gy, respectively. The mean follow-up period was 97 months from diagnosis and 59 months from GKS. The actuarial five- and 10-year survival rates after GKS were 80% and 53%, respectively. The actuarial five- and 10-year local tumor control rates after single or multiple GKS sessions were 76% and 67%, respectively. All individuals with low-grade chondrosarcomas achieved good local tumor control. A tumor volume of less than 20 ml significantly affected the high rate of local tumor control ($p = 0.0182$). None of the individuals had AREs, other than one in whom facial numbness worsened despite successful tumor control. The authors concluded that as an adjuvant treatment after resection, GKS is a reasonable option for selected individuals harboring skull base chordomas or chondrosarcomas with a residual tumor volume of less than 20 ml. They also concluded that dose planning with a generous treatment volume to avoid marginal treatment failure should be made at a marginal dose of at least 15 Gy to achieve long-term tumor control.

Martin et al. (2007) conducted a case series analysis to evaluate the effect of SRS on local tumor control and survival in individuals with chordomas and chondrosarcomas. A total of 28 individuals with histologically confirmed chordomas ($n = 18$) or chondrosarcomas ($n = 10$) underwent GKRS either as primary or adjuvant treatment. Their ages ranged from 17 to 72 years (median 44 years). The most common presenting symptom was diplopia (26 individuals, 93%). In two individuals, SRS was the sole treatment. Twenty-six individuals underwent between one and five additional surgical procedures. Two underwent an initial transsphenoidal biopsy. The average tumor volume was 9.8 cm³. The median dose to the tumor margin was 16 Gy. Transient symptomatic AREs developed in only one individual. The actuarial local tumor control for chondrosarcomas at five years was 80 +/- 10.1%. For chordomas both the actuarial tumor control and survival was 62.9 +/- 10.4%. The authors concluded that SRS is an important option for skull base chordomas and chondrosarcomas either as primary or adjunctive treatment, and that multimodal management appears crucial to improve tumor control in most individuals.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines regarding chordoma states specialized techniques such as SRS should be considered as clinically indicated in order to deliver high radiation doses while maximizing normal tissue sparing. Additionally, SRS has been evaluated for adjuvant treatment for chondrosarcoma of the skull base (NCCN, 2025).

Craniopharyngioma

Palavani et al. (2024) conducted a systematic review and meta-analysis to evaluate the efficacy and safety of fractionated stereotactic radiotherapy (FSRT) for individuals with craniopharyngioma. Ten studies ($n = 256$ individuals) met the inclusion criteria which consisted of a sample size greater than four, effects of FSRT reported, and at least one the outcomes of interest reported (improvement in visual acuity or field, new-onset hypopituitarism, effectiveness, and tumor progression). The improvement in visual acuity was estimated at 45% (95% CI: six - 83%), while the improvement in the visual field was 22% (95% CI: zero - 51%). Regarding endocrine function, the new-onset hypopituitarism rate was found to be 5% (95% CI: zero - 11%). Relative to FSRT effectiveness, the pooled estimate of the complete tumor response rate was 17% (95% CI: four - 30%), and the tumor progression rate was 7% (95% CI: one - 13%). Also, a three-year PFS rate of 98% (95% CI: 95 - 100%) was obtained. The authors concluded that FSRT may be a viable treatment option with notable benefits for tumor control and visual functions. The authors recommended further research to assess the clinical utility and associated risks. Limitations included the retrospective nature of many included studies and limited long-term data.

Lee et al. (2014a) conducted a single-center case series analysis to report long-term outcomes of individuals with craniopharyngioma and treated with RS, and to define the prognostic factors of craniopharyngioma. Individuals with craniopharyngioma were treated by GKS and then, all the individuals underwent clinical and endocrinological evaluations at an average of six-month intervals. Individual demographics and clinical data including outcome of resection, adjuvant radiosurgical parameters, and imaging results were retrospectively reviewed from the center's database. Outcomes included tumor control, PFS, OS, complications, and prognostic factors. A total of 137 consecutive individuals who

underwent 162 sessions of GKS treatments were included in the analysis. The individuals' median age was 30.1 years (range, 1.5 to 84.9 years), and the median tumor volume was 5.5 ml (range, 0.2 to 28.4 ml). There were 23 solid (16.8%), 23 cystic (16.8%), and 91 mixed solid and cystic (66.4%) craniopharyngiomas. GKS was indicated for residual or recurrent craniopharyngiomas. 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 GKS, the rates of tumor control were 72.7%, 73.9%, and 66.3% for the solid, cystic, and mixed tumors, respectively. The actuarial PFS rates plotted by the Kaplan-Meier method were 70.0% and 43.8% at five and 10 years after RS, respectively. After repeated GKS, the actuarial PFS rates increased to 77.3% and 61.2% at five and 10 years, respectively. The OS rates were 91.5% and 83.9% at the five- and 10-year follow-ups, respectively. Successful GKS treatment can be predicted by tumor volume ($p = 0.011$). Among the 137 individuals who had clinical follow-up, new-onset or worsened pituitary deficiencies were detected in 11 individuals (8.0%). Two individuals without tumor growth had a worsened visual field, and one individual had a new onset of third cranial nerve palsy. The authors concluded that their study results suggest that GKS is a relatively safe modality for the treatment of recurrent or residual craniopharyngiomas, and GKS is associated with improved tumor control and reduced in-field recurrence rates.

Niranjan et al. (2010) conducted a single-center case series analysis to evaluate outcomes of GKRS for residual or recurrent craniopharyngiomas and evaluate the factors that optimized the tumor control rates. A total of 46 individuals with craniopharyngiomas underwent 51 SRS procedures. The series included 22 males and 24 females, with a median age of 23.5 years (range, four to 77). The median tumor volume was 1.0 cm³ (range, 0.07 to 8.0). The median prescription dose delivered to the tumor margin was 13.0 Gy (range, nine to 20). The median maximal dose was 26.0 Gy (range, 20 to 50). The mean follow-up time was 62.2 months (range, 12 to 232). The OS rate after SRS was 97.1% at five years. The three- and five-year PFS rates (solid tumor control) were both 91.6%. The overall local control rate (for both solid tumor and cyst control) was 91%, 81%, and 68% at one, three, and five years, respectively. No individuals with normal pituitary function developed hypopituitarism after SRS. Two individuals developed homonymous hemianopsia owing to tumor progression after SRS. Among the factors examined, complete radiosurgical coverage was a significant favorable prognostic factor. The authors concluded that SRS is a safe and effective minimally invasive option for the management of residual or recurrent craniopharyngiomas, and that complete radiosurgical coverage of the tumor was associated with better tumor control.

Definitive Treatment of Hepatocellular Carcinoma (HCC) Without Evidence of Regional or Distant Metastasis/Intrahepatic Bile Duct Cancer

In a randomized, open-label, controlled trial, Xi et al. (2025) evaluated the safety and efficacy of radiofrequency ablation (RFA) compared to SBRT in the treatment of recurrent HCC with small solitary nodules (≤ 5 cm). The inclusion criteria consisted of individuals (age 18 - 75) with recurrent small HCC without extrahepatic metastasis or vascular invasion at recurrence, KPS score of 90 or more, and liver function of Child-Ough class A. Concomitant severe dysfunction of other systems and contraindications for SBRT or RFA were the primary exclusion criteria. Local progression-free survival (LPFS) was the main endpoint. Secondary endpoints were PFS, OS, local control rate, and safety. Eighty-three participants were assigned to the SBRT group and 83 were assigned to the RFA group. After a median follow-up time of 42.8 and 42.9 months in the SBRT and RFA groups, respectively, SBRT demonstrated a significantly better LPFS than that of RFA [HR, 0.45 (95% CI, 0.24 to 0.87); $p = 5.014$]. The two-year LPFS rates were 92.7% (95% CI, 87.3 to 98.5) with SBRT and 75.8% (95% CI, 67.2 to 85.7) with RFA. The median PFS time of the SBRT and RFA groups was 37.6 (95% CI, 26.0 to 49.2) and 27.6 (95% CI, 20.3 to 34.8) months, respectively [HR, 0.76 (95% CI, 0.50 to 1.15); $p = 5.190$]. Nine participants in the SBRT group and 10 in the RFA group died during the follow-up. The two-year OS rates were 97.6% (95% CI, 94.3 to 100.0) in the SBRT group and 93.9% (95% CI, 88.9 to 99.2) in the RFA group [HR, 0.91 (95% CI, 0.37 to 2.22); $p = 5.830$]. The incidences of both acute and late adverse events were comparable between the groups ($p = 5.436$ and $p = 5.715$, respectively). The authors concluded that in individuals with small, single recurrent HCC, SBRT provided better LPFS than RFA, especially in HCC ≤ 2 cm. Additionally, PFS, OS, and safety were similar between the two treatments. Limitations included the single-center nature of the study and small sample size.

Bisello et al. (2021) conducted a systematic review to evaluate the efficacy and safety of SBRT as treatment for individuals with intrahepatic cholangiocarcinoma. Inclusion criteria consisted of studies in English that had at least 10 participants with inoperable, non-metastatic, primary, or recurrent intrahepatic cholangiocarcinoma. Studies regarding SBRT were included even if preceded or followed by systemic treatments or other local therapies. Studies on adjuvant SBRT after radical surgery were excluded. Overall survival was the primary endpoint, and local control, PFS, and treatment related toxicity were the secondary endpoints. Six studies ($n = 145$ individuals) met inclusion criteria. SBRT was frequently used as a salvage treatment, since 28.6 - 66.7% of individuals received previous systemic or local treatments. The median SBRT dose was 45 Gy delivered in three to five fractions. The median follow-up was 16 months, and median OS time was 14 months. In one of the included studies, SBRT was significantly superior in terms of OS compared with both chemoradiation and transarterial radio embolization (TARE). The one-year local control rate was 85% in one study,

and one-year PFS rates were 50 and 68% in two studies, respectively. Toxicity was generally not reported in detail or was reported including other sites of biliary cancers. The meta-analysis was not conducted. The authors concluded that SBRT yields comparable outcomes to other treatments, with the added benefit of a brief and non-invasive therapy and should be considered for selected individuals with intrahepatic cholangiocarcinoma. Limitations included that there was limited evidence available regarding the effectiveness of SBRT in intrahepatic cholangiocarcinoma, small sample sizes, and the retrospective design of most of the studies.

Jang et al. (2020) conducted a multi-center, phase II, single-arm, open-label trial to evaluate the safety and efficacy of SBRT for individuals with HCC in a hepatitis B virus-endemic area. Eligible participants were aged ≥ 20 years who were diagnosed with unresectable HCC. Participants received SBRT with 45 to 60 Gy in three fractions. To evaluate gastroduodenal toxicity, esophagogastroduodenoscopy (EGD) was performed before and two months after SBRT. The primary endpoint was treatment-related severe toxicity at one year after SBRT. The secondary endpoints were the two-year local control, PFS, and OS rates. A total of 74 participants were enrolled, and 65 eligible participants were analyzed. The median follow-up was 41 months (range, four to 69 months). One participant experienced radiation-induced liver disease with acute grade ≥ 3 toxicity one month after SBRT. In addition, one participant had a grade 3 esophageal ulcer with stenosis five months after SBRT. The actuarial rate of treatment-related severe toxicity at one year was 3%. The pre-SBRT and post-SBRT EGD findings were not significantly different among the 57 evaluable participants who underwent EGD. The two-year and three-year local control rates were 97% and 95%, respectively. The progression-free and OS rates were 48% and 84% at two years, respectively, and 36% and 76% at three years, respectively. The authors concluded that SBRT for individuals with HCC is well tolerated and was an effective treatment modality.

Wang et al. (2020) conducted a systematic review and meta-analysis aimed at comparing the safety and efficacy of RFA with SBRT for HCC. Seven studies were identified from January 1990 to May 2020, for a total of 7,928 individuals, and included in the review. The results showed that SBRT was not inferior to RFA based on the pooled HRs for OS; however, the pooled HR for the local control rate showed the superiority of SBRT. Subgroup analysis showed that the pooled HR for the local control rate favored SBRT in individuals with tumors sized > 2 cm, but no significant difference was observed in individuals with tumors sized ≤ 2 cm. In addition, no significant differences in the incidence of late severe complications were observed between the SBRT and RFA groups. The authors concluded that SBRT had an OS equal to that with RFA, was well tolerated, and may be used as an alternative to RFA. Additionally, SBRT was superior to RFA in terms of local control of HCC, especially in those with tumors > 2 cm. Limitations included the retrospective nature of the studies in the review, and the population in each study was different which may result in heterogeneity. The authors recommended future prospective randomized trials. (Wahl et al. 2016, previously cited in this policy, is included in this review).

Rim et al. (2019) conducted a systematic review and meta-analysis to evaluate the clinical feasibility and efficacy of SBRT for HCC. A search, using predetermine criteria, was performed using PubMed, Medline, Embase, and Cochrane Library databases. Primary endpoints were OS and local control, and the secondary endpoint was grade ≥ 3 complications. A total of 32 studies, comprising 33 cohorts and consisting of 1,950 individuals, were included in the meta-analysis. The majority (85%) of the studies used a retrospective design. Pooled one-, two-, and three-year OS rates were 72.6% (95% CI, 65.7 to 78.6), 57.8% (50.9 to 64.4), and 48.3% (40.3 to 56.5), respectively. Pooled one-, two-, and three-year local control rates were 85.7% (95% CI, 80.1 to 90.0), 83.6% (77.4 to 88.3), and 83.9% (77.6 to 88.6), respectively. The overall median tumor size was 3.3 cm (range, 1.6 to 8.6). Median radiation doses, calculated in equivalent dose in 2 Gy per fraction, ranged from 48 to 114.8 Gy (median 83.3 Gy). A subgroup comparison of tumor size showed significant differences for one- and two-year OS rates and one-, two-, and three-year local control rates. In addition, radiation dose showed no difference for OS and a marginal difference for one-year local control rate. Pooled rates of hepatic and gastrointestinal (GI) grade ≥ 3 complications were 4.7% (95% CI, 3.4 to 6.5) and 3.9% (2.6 to 5.6), respectively. Child-Pugh class was significantly correlated with hepatic complication of grade ≥ 3 ($p = 0.013$). The authors concluded that SBRT for HCC is a feasible option with excellent local control persisting for up to three years. They reported that both OS and local control were affected by tumor size, and radiation dose marginally affected local control, and while severe complications were rare, liver function should be considered to prevent serious hepatic toxicity.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

The ASTRO guideline for primary liver cancers provided evidence-based recommendations for treatment of HCC and IHC with EBRT. The recommendations are as follows (not all-inclusive):

- Use of EBRT as a potential first-line treatment in those with liver-confined HCC who are not candidates for curative therapy and catheter-based therapies are being considered, EBRT is a potential first-line single therapy option. Strength of recommendation- strong; quality of evidence- moderate.

- For those with liver-confined HCC and incomplete response to thermal ablation or catheter-based therapies, EBRT is recommended as a consolidative treatment option. Strength of recommendation: strong; quality of evidence: moderate.
- EBRT is recommended as a salvage treatment option for those with locally recurrent HCC after surgery, thermal ablation, or catheter-based therapies. Strength of recommendation: strong; quality of evidence: low.
- For those with liver-confined HCC, for whom EBRT is recommended, dose-escalated ultra- or moderately hypofractionated EBRT is recommended, with choice of regimen based on tumor location, underlying liver function, and available technology. Strength of recommendation: strong; quality of evidence: moderate.
- For patients with unresectable IHC, induction chemotherapy followed by consolidation with EBRT, alone or in combination with chemotherapy, is recommended. Implementation remark: For patients who are not candidates for induction chemotherapy, EBRT alone or in combination with chemotherapy should be considered. Strength of recommendation: strong; quality of evidence: moderate.

Additionally, the authors recommended future high-quality RCTs to further define the role of EBRT in HCC and IHC treatment (Apisarnthanarax et al., 2022).

International Stereotactic Radiosurgery Society (ISRS)

Bae et al. (2024) developed a guideline for the ISRS based on a systematic review and meta-analysis for liver-confined HCC to address appropriate patient management. The review included 17 observational studies between 2003 and 2019, a total of 1889 individuals, who underwent treatment for HCC with ≤ 9 SBRT fractions. The recommendations are as follows (not all-inclusive):

- Patients with HCC < 3 cm can be considered for SBRT with favorable local control and survival outcomes. SBRT to HCC ≥ 3 cm can be performed with the expectation of durable long-term local control.
- SBRT with one to nine fractions, is recommended for patients with liver-confined HCC. No specific recommendation for the optimal dose fractionation can be made.
- Classic radiation-induced liver disease is a rare event after SBRT to HCC with proper patient selection.

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for biliary tract cancers (intrahepatic cholangiocarcinoma) state that SBRT is preferred for unresectable tumors if dose constraints can be met. Image-guided RT is recommended when SBRT is used to improve accuracy and reduce toxicity (NCCN, 2025).

The NCCN guidelines for HCC state that SBRT can be considered as an alternative to ablation/embolization techniques or when these therapies have failed or are contraindicated. SBRT is typically given in three to five fractions and is often used for those with one to three tumors. The treatment of intrahepatic tumors with hypofractionation using photons or protons is a viable option. However, it is recommended to undergo this treatment at centers with specialized experience (NCCN, 2025).

Definitive Treatment of Non-Small Cell Lung Cancer (NSCLC)

Zhang et al. (2022) conducted a systematic review and meta-analysis of individuals with inoperable early-stage NSCLC to compare local control, OS, and toxicities between SBRT and RFA. Articles published in English in peer-reviewed journals, individuals with stage I NSCLC who were not a candidate for surgery, and the studies that reported on clinical outcomes were eligible for the review. Case reports, comments, editorials, reviews, studies with less than 15 individuals treated with SBRT or less than five individuals treated with RFA, SBRT studies with fraction number > 8 and fraction dose ≤ 8 Gy, and studies involving other treatments were excluded. Eighty-seven SBRT studies (12,811 patients) and 18 RFA studies (1,535 patients) met the eligibility criteria. For SBRT, the local control rates (with 95% CI) at one, two, three, and five years were 98% (97 - 98%), 95% (95 - 96%), 92% (91 - 93%), and 92% (91 - 93%), respectively, which were significantly higher than those for RFA [75% (69 - 82%), 31% (22 - 39%), 67% (58 - 76%), and 41% (30 - 52%), respectively] ($p < 0.01$). There were no significant differences in short-term OS between SBRT and RFA [one-year OS rate: 87% (86 - 88%) versus 89% (88 - 91%), $p = 0.07$; two-year OS rate: 71% (69 - 72%) versus 69% (64 - 74%), $p = 0.42$]. Regarding long-term OS, the three- and five-year OS rates for SBRT were 58% (56 - 59%) and 39% (37 - 40%), respectively, which were significantly ($p < 0.01$) superior to those for RFA [48% (45 - 51%) and 21% (19 - 23%), respectively]. The most common complication of SBRT was radiation pneumonitis (grade ≥ 2), making up 9.1% of patients treated with SBRT, while pneumothorax was the most common complication of RFA, making up 27.2% of patients treated with RFA. The authors concluded that SBRT demonstrates superior local control and long-term OS rates compared to RFA, while short-term OS rates remain similar. The authors suggested large-scale RCTs are needed to further compare the efficacy of SBRT and RFA. Limitations included the heterogeneity of the studies, and the included studies were published between 2000 to 2020 and SBRT and RFA may have evolved during that timeframe.

Ball et al. (2019) performed a phase III, open-label RCT (TROG 09.02 CHISEL) comparing stereotactic ablative body radiotherapy (SABR) and standard fractionated radiotherapy in participants with stage I NSCLC in participants who were either inoperable or who had refused surgery to evaluate local control, OS, toxicity, and QOL. Participants (n = 101) from 11 hospitals in Australia and three in New Zealand were randomly assigned to receive standard radiotherapy (n = 35) or SABR (n = 66). Inclusion criteria consisted of those 18 years or older with an ECOG score of zero or one, and a peripherally located tumor. Exclusion criteria included previous chemotherapy or radiotherapy and multiple primary tumors requiring radiotherapy. Five (7.6%) participants in the SABR group and two (6.5%) in the standard radiotherapy group did not receive treatment, and a further four in each group withdrew before study end. As of data cutoff (July 31, 2017), median follow-up for local treatment failure was 2.1 years (IQR 1.2 - 3.6) for participants randomly assigned to standard radiotherapy and 2.6 years (IQR 1.6 - 3.6) for participants assigned to SABR. 20 (20%) of 101 participants had progressed locally: nine (14%) of 66 participants in the SABR group and 11 (31%) of 35 participants in the standard radiotherapy group, and freedom from local treatment failure was improved in the SABR group compared with the standard radiotherapy group (HR 0.32, 95% CI 0.13 - 0.77, p = 0.0077). Median time to local treatment failure was not reached in either group. In participants treated with SABR, there was one grade 4 adverse event (dyspnea) and seven grade 3 adverse events (two cough, one hypoxia, one lung infection, one weight loss, one dyspnea, and one fatigue) related to treatment compared with two grade 3 events (chest pain) in the standard treatment group. The authors concluded that compared to standard radiotherapy, SABR had superior local control without an increase in major toxicity in those with inoperable peripherally located stage I NSCLC. Limitations included a large proportion of participants who had previous cancer and small sample size. In 2023, Bucknell et al. conducted an analysis of the TROG 09.02 (CHISEL) phase III trial to compare pulmonary function tests and the six-minute walk test after SBRT compared to conventional 3D-CRT at three and 12 months after treatment. The authors concluded that there was no difference in reduced respiratory function between the two groups despite the higher biologically effective doses delivered to the tumor in SBRT.

Chang et al. (2015) conducted a pooled analysis of two clinical trials (STARS and ROSEL) that were halted due to slow recruitment. The STARS (NCT00840749) and ROSEL (NCT00687986) trials were open label, randomized, phase III trials comparing SABR with surgery for individuals with stage I NSCLC. The primary outcome for this pooled analysis was OS according to treatment group (SABR versus surgery) and secondary outcomes included recurrence-free survival, and grade 3 or worse acute or chronic toxicity. A total of 58 participants were enrolled with 31 participants randomized to SABR and 27 participants to surgery. Median follow-up was 40.2 months (IQR 23.0 to 47.3) for the SABR group and 35.4 months (18.9 to 40.7) for the surgery group. Six participants in the surgery group died compared with one participant in the SABR group. Estimated OS at three years was 95% (95% CI 85 to 100) in the SABR group compared with 79% (64–97) in the surgery group (HR, 0.14; 95% CI 0.017 to 1.190, log-rank p = 0.037). Recurrence-free survival at three years was 86% (95% CI 74 to 100) in the SABR group and 80% (65 to 97) in the surgery group (HR, 0.69; 95% CI 0.21 to 2.29, log-rank p = 0.54). In the surgery group, one participant had regional nodal recurrence and two had distant metastases; in the SABR group, one participant had local recurrence, four had regional nodal recurrence, and one had distant metastases. Three (10%) participants in the SABR group had grade 3 treatment-related adverse events (three participants with chest wall pain, two with dyspnea or cough, and one with fatigue and rib fracture). No participants given SABR had grade 4 events or treatment-related death. In the surgery group, one (4%) participant died of surgical complications and 12 (44%) participants had grade 3 - 4 treatment-related adverse events. Grade 3 events occurring in more than one participant in the surgery group were dyspnea (four participants), chest pain (four participants), and lung infections (two participants). The authors concluded that the results of this pooled analysis of STARS and ROSEL data suggest that SABR can be considered a treatment option in operable individuals needing a lobectomy, and that the equipoise suggested by the results justifies efforts for additional RCTs.

Haasbeek et al. (2010) conducted a single-center case series analysis to evaluate outcomes of stereotactic radiotherapy (SRT) in elderly individuals. Individuals diagnosed with stage IA/IB NSCLC and aged ≥ 75 years at the time of SRT were included. SRT was delivered using three fractionation schemes: fractions of 20 Gy (for T1 tumors), five fractions of 12 Gy (for T1 tumors with broad contact with the chest wall and for T2 tumors), or eight fractions of 7.5 Gy (for tumors adjacent to the heart, large blood vessels, hilus, brachial plexus, or mediastinum). Individuals were followed routinely at three months, six months, one year, and annually thereafter. Outcomes included overall and disease-free survival, and actuarial local, regional, and distant failure rates. A total of 193 individuals aged ≥ 75 years were treated using SRT (118 T1 tumors, 85 T2 tumors). The median age was 79 years, 80% of individuals were considered medically inoperable, and 20% of individuals declined surgery. The median Charlson comorbidity score was four, and severe chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease Class III or greater) was present in 25% of individuals. Risk-adapted SRT schemes were used with the same total dose of 60 Gy in three fractions (33%), five fractions (50%), or eight fractions (17% of individuals), depending on the individual's risk for toxicity. SRT was well tolerated, and all but one individual completed treatment. Survival rates at one year and three years were 86% and 45%, respectively. Survival was correlated with performance score (p = 0.001) and pre-SRT lung function (p = 0.04). The actuarial local control rate at three years was 89%. Acute toxicity was rare, and late RTOG grade ≥ 3 toxicity was observed in < 10% of individuals. The authors concluded that SRT achieved high local control rates with minimal toxicity

in individuals aged ≥ 75 years despite their significant medical comorbidities and that these results indicated that more active diagnostic and therapeutic approaches are justified in elderly individuals, and that SRT should be considered and discussed as a curative treatment alternative.

Timmerman et al. (2010) conducted a multi-center, phase II, single arm trial (RTOG 0236) to evaluate toxicity and efficacy of SBRT in a high-risk population of participants with early stage but medically inoperable lung cancer. Participants with biopsy-proven peripheral T1-T2, N0, M0 non-small cell tumors less than 5.0 cm in diameter and medical conditions precluding surgical treatment were included in the analysis. The prescription dose was 18 Gy per fraction in three fractions (54 Gy total) delivered in one and a half to two weeks. The primary endpoint was primary tumor control with OS, disease-free survival (DFS), adverse events, involved lobe, regional, and disseminated recurrence as secondary endpoints. The study aimed to improve the two-year primary tumor control rate from 60% to 80%. A rate of 60% was chosen as the lowest acceptable primary tumor control rate after taking into consideration a $> 80\%$ primary tumor control rate seen in a previously published study (Timmerman 2006). A total of 59 participants 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 one participant had a primary tumor failure; the estimated three-year primary tumor control rate was 97.6% (95% CI, 84.3% to 99.7%). Three participants had recurrence within the involved lobe; the three-year primary tumor and involved lobe (local) control rate was 90.6% (95% CI, 76.0% to 96.5%). Two participants experienced regional failure; the local-regional control rate was 87.2% (95% CI, 71.0% to 94.7%). Eleven participants experienced disseminated recurrence; the three-year rate of disseminated failure was 22.1% (95% CI, 12.3% to 37.8%). The rates of DFS and OS at three years were 48.3% (95% CI, 34.4% - 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). Protocol specified treatment-related grade 3 adverse events were reported in seven participants (12.7%; 95% CI, 9.6% to 15.8%); grade 4 events were reported in two participants (3.6%; 95% CI, 2.7% to 4.5%). No grade 5 adverse events were reported. The authors concluded that individuals with inoperable NSCLC who received SBRT had a survival rate of 55.8% at three years and high rates of local tumor control compared to historical data.

Fakiris et al. (2009) conducted a single-center, phase II, single arm trial to report 50-month follow-up results from a phase I dose escalation trial in individuals with medically inoperable Stage I NSCLC (Timmerman 2003 and McGarry 2005). A total of 70 medically inoperable individuals who had clinically staged T1 (34 participants) or T2 (36 participants) (≤ 7 cm), N0, M0, biopsy-confirmed NSCLC received SBRT at a treatment dose of 60-66 Gy prescribed to the 80% isodose volume in three fractions. Median follow-up was 50.2 months (range, 1.4 to 64.8 months). Kaplan-Meier local control at three years was 88.1%. Regional (nodal) and distant recurrence occurred in six (8.6%) and nine (12.9%) participants, respectively. Median survival (MS) was 32.4 months, and three-year OS was 42.7% (95% CI, 31.1 to 54.3%). Cancer-specific survival at three years was 81.7% (95% CI, 70.0 to 93.4%). For participants with T1 tumors, MS was 38.7 months (95% CI, 25.3 to 50.2) and for T2 tumors MS was 24.5 months (95% CI, 18.5 to 37.4) ($p = 0.194$). Tumor volume (≤ 5 cc, 5 - 10 cc, 10 - 20 cc, > 20 cc) did not significantly impact survival: MS was 36.9 months (95% CI, 18.1 to 42.9), 34.0 (95% CI, 16.9 to 57.1), 32.8 (95% CI, 21.3 to 57.8), and 21.4 months (95% CI, 17.8 to 41.6), respectively ($p = 0.712$). There was no significant difference in survival between participants with peripheral versus central tumors (MS 33.2 versus 24.4 months, $p = 0.697$). Grade 3-5 toxicity occurred in five of 48 participants with peripheral lung tumors (10.4%) and in six of 22 participants (27.3%) with central tumors (Fisher's exact test, $p = 0.088$). The authors concluded that the use of SBRT results in high rates of local control in medically inoperable individuals with stage I NSCLC.

Onishi et al. (2007) reported updated results of a multi-center case series analysis conducted to determine the optimal small-volume stereotactic RT dose that would limit toxicity and obtain local control in individuals with stage I NSCLC, whether the single-institution results were reproducible, and whether single high-dose stereotactic irradiation (STI) results were comparable to those of surgery. In the original study (Onishi, 2004), the authors concluded that hypofractionated high-dose STI with BED < 150 Gy represents a feasible and beneficial method for obtaining curative treatment of individuals with Stage I NSCLC. The authors reported that local control and survival rates were better for BED ≥ 100 Gy than for BED < 100 Gy for all treatment methods and schedules. In addition, survival rates for STI in selected individuals (medically operable and BED ≥ 100 Gy) were excellent and reproducible among institutions, irrespective of specific treatment methods, and were potentially equivalent to those of surgery. In the updated report, Onishi (2007) compared previously reported results for surgery and conventional RT with those for hypofractionated high-dose stereotactic RT (HypoFXSRT). In this retrospective study, 257 individuals with stage I NSCLC (median age, 74 years: 164 T1N0M0, 93 T2N0M0) were treated with HypoFXSRT alone at 14 institutions. Stereotactic three-dimensional treatment was performed using noncoplanar dynamic arcs or multiple static ports. A total dose of 18 to 75 Gy at the isocenter was administered in one to 22 fractions. The median calculated BED was 111 Gy (range, 57 to 180 Gy) based on $\alpha/\beta = 10$. For the comparison to surgery, the five-year OS rates for individuals with stage IA and IB NSCLC and treated with surgery ranged from 61% to 72% and 40% to 50%, respectively (Mountain 2000, Naruke 2001, and Shirakusa 2002). During follow-up (median, 38 months), pulmonary complications of above grade 2 occurred in 14 individuals (5.4%). Local progression occurred in 36 individuals (14.0%), and the local recurrence rate was 8.4% for a BED of 100 Gy or more compared with 42.9% for less than 100 Gy ($p < 0.001$). The five-year OS rate of medically operable individuals was 70.8% among those

treated with a BED of 100 Gy or more compared with 30.2% among those treated with less than 100 Gy ($p < 0.05$). The authors concluded that when compared with conventional RT and surgery, HypoFXSRT is a safe and promising treatment modality, local control and survival rates are superior to those of conventional RT, HypoFXSRT should be a standard of care for medically inoperable individuals, and additional studies that randomly compare HypoFXSRT and surgery for medically operable individuals are needed.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

ASTRO's 2018 guideline, Stereotactic Body Radiotherapy for Early-Stage Non-Small Cell Lung Cancer, recommends that patients with stage I NSCLC should be evaluated by a thoracic surgeon, preferably within a multidisciplinary cancer care team, to determine operability. For patients with standard operative risk (i.e., with anticipated operative mortality of $< 1.5\%$) and stage I NSCLC, SBRT is not recommended as an alternative to surgery outside of a clinical trial setting. For patients with high operative risk (i.e., those who cannot tolerate lobectomy, but are candidates for sublobar resection) and stage I NSCLC, discussions about SBRT as a potential alternative to surgery are encouraged and patients should be informed that SBRT may have decreased risks from treatment in the short term. However, outcomes longer than three years are not well-established (Schneider 2018).

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for NSCLC state that for stage I and selected node-negative stage IIA, SBRT has achieved good primary tumor control rates and OS that are higher than conventionally fractionated radiotherapy. NCCN recommends definitive SBRT for patients with stage I and II NSCLC who are medically inoperable, and SBRT may be a reasonable alternative to surgery for patients with potentially operable disease who are high risk, elderly, or refuse surgery after appropriate consultation (NCCN, 2025).

National Institute for Health and Care Excellence

NICE developed a guideline for the diagnosis and management of lung cancer that states for those with stage I - IIA (T1a -T2b, N0, M0) NSCLC in whom lobectomy is contraindicated or declined, radical radiotherapy may be offered with SABR or sublobar resection (NICE, 2019; updated 2024).

Definitive Treatment of Pancreatic Adenocarcinoma Without Evidence of Distant Metastasis

A systematic review and meta-analysis by Tchelebi et al. (2020) aimed to compare the efficacy and safety of SBRT to conventionally fractionated radiation therapy (CFRT) with concurrent chemotherapy for treatment of locally advanced pancreatic cancer. Twenty-one studies were included in the analysis, including 11 CFRT and nine SBRT studies for a total of 1147 individuals. The primary outcome was efficacy defined as a two-year OS. One-year OS and incidence of acute or late grade 3/4 toxicity were the secondary outcomes. For SBRT, the median dose was 30 Gy, and the most common regimen was 30 Gy/five fractions. For CFRT, doses ranged from 45 to 54 Gy in 1.8- to 2.0 Gy fractions, with the majority of studies delivering 50.4 Gy in 28 fractions with concurrent Gemcitabine. The random effects estimate for two-year OS was 26.9% (95% CI, 20.6% - 33.6%) for SBRT versus 13.7% (95% CI, 8.9% - 19.3%) for CFRT and was statistically significant in favor of SBRT. The random effects estimate for one-year OS was 53.7% (95% CI, 39.3% - 67.9%) for SBRT versus 49.3% (95% CI, 39.3% - 59.4%) for CFRT, and was not statistically significant. The random effects estimate for acute grade 3/4 toxicity was 5.6% (95% CI, 0.0% - 20.0%) for SBRT versus 37.7% (95% CI, 24.0% - 52.5%) for CFRT and was statistically significant in favor of SBRT. The random effects estimate for late grade 3/4 toxicity was 9.0% for SBRT (95% CI, 3.3% - 17.1%) versus 10.1% (95% CI, 1.8% - 23.8%) for CFRT, which was not statistically significant. The authors concluded that for individuals with locally advanced pancreatic cancer, SBRT may provide a modest improvement in two-year OS with reduced rates of acute grade 3/4 toxicity and no change in one-year OS or late toxicity. Limitations included the phase one or two studies and retrospective nature of the SBRT studies, whereas the CFRT studies were all phase II or phase III. The authors recommended future quality studies to evaluate SBRT for these individuals.

In a retrospective review, Zhong et al. (2017) compared SBRT with CFRT therapy in locally advanced pancreatic cancer (LAPC) using the National Cancer Database. Individuals with cT2-4/N0-1/M0 adenocarcinoma of the pancreas diagnosed from 2004 to 2013 were included in the review. Radiation therapy delivered at ≥ 4 Gy per fraction was considered SBRT, and RT delivered at ≤ 2 Gy was deemed CFRT. Overall survival was the primary outcome. The total number of individuals included in the review was 8,450, CFRT = 7,819 and SBRT = 631. Receipt of SBRT was associated with superior OS in the multivariate analysis (HR, 0.84; 95% CI, 0.75 - 0.93; $p < .001$). With propensity score matching, 988 individuals in all were matched, with 494 individuals in each cohort. Within the propensity-matched cohorts, the median OS (13.9 versus 11.6 months) and the two-year OS rate (21.7% versus 16.5%) were significantly higher with SBRT versus CFRT. The authors concluded SBRT was superior to OS when compared with CFRT, and an additional benefit of SBRT was the

shorter duration of treatment. Additionally, the authors recommended future randomized trials to evaluate these results. Limitations included the retrospective nature of the study and lack of control for the specific type of chemotherapy in propensity matching.

Herman et al. (2015) conducted a multi-center, phase II, single arm study to determine whether individual treated with gemcitabine (GEM) administered with fractionated SBRT (in five fractions of 6.6 Gy, to a total 33.0 Gy) would achieve reduced late grade 2-4 GI toxicity compared with a historical cohort of individuals treated with GEM and a single 25-Gy fraction of SBRT. Participants with LAPC received up to three doses of GEM (1000 mg/m²) followed by a one-week break and SBRT (33.0 Gy in five fractions). After SBRT, participants continued to receive GEM until disease progression or toxicity. Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events [version 4.0] and the RTOG radiation morbidity scoring criteria. Participants completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) and pancreatic cancer-specific QLQ-PAN26 module before SBRT and at four weeks and four months after SBRT. A total of 49 participants participated in the study with a median follow-up of 13.9 months (range, 3.9 to 45.2 months). The median age of the participants was 67 years and 84% had tumors of the pancreatic head. Rates of acute and late (primary endpoint) grade ≥ 2 gastritis, fistula, enteritis, or ulcer toxicities were 2% and 11%, respectively. The historical cohort rates for grade 2 acute and late toxicities were 19% and 47%, respectively (Schellenberg 2008). QLQ-C30 global QOL scores remained stable from baseline to after SBRT (67 at baseline, median change of zero at both follow-ups; $p > 0.05$ for both). Participants reported a significant improvement in pancreatic pain ($p = 0.001$) four weeks after SBRT on the QLQ-PAN26 questionnaire. The median plasma carbohydrate antigen 19-9 (CA 19-9) level was reduced after SBRT [median time after SBRT, 4.2 weeks; 220 U/mL versus 62 U/mL ($p < 0.001$)]. The median OS was 13.9 months (95% CI, 10.2 to 16.7 months). Freedom from local disease progression at one year was 78%. Four participants (8%) underwent margin-negative and lymph node-negative surgical resections. The authors concluded that fractionated SBRT with gemcitabine achieves favorable toxicity, QOL, and preliminary efficacy compared with historical data.

Mellon et al. (2015) conducted a single-center case series analysis to evaluate outcomes and toxicity of induction chemotherapy and SBRT for borderline resectable pancreatic cancer (BRPC) and LAPC. The center's internal database was queried to identify all individuals who received at least one dose of induction chemotherapy and SBRT for the treatment of BRPC or LAPC. After staging, medically fit individuals underwent chemotherapy for two to three months, with regimen at the discretion of the treating medical oncologist. Then, individuals received SBRT delivered in five consecutive daily fractions with median total radiation doses of 30 Gy to tumor and 40 Gy dose painted to tumor-vessel interfaces. That was followed by restaging imaging for possible resection. Outcomes included OS, event free survival (EFS), and locoregional control (LRC) rates. A total of 159 individuals, 110 with BRPC and 49 with LAPC, with median follow-up of 14.0 months, were included in the analysis. The resection and margin negative (R0) rate for BRPC individuals who completed neoadjuvant therapy was 51% and 96%, respectively. Estimated median OS was 19.2 months for BRPC individuals and 15.0 months for LAPC individuals ($p = 0.402$). Median OS was 34.2 months for surgically resected individuals versus 14.0 months for unresected individuals ($p < 0.001$). Five of 21 (24%) individuals with LAPC received FOLFIRINOX chemotherapy underwent R0 resection. Among individuals with LAPC, FOLFIRINOX recipients underwent R0 resection more often than other chemotherapy recipients (five of 21 versus zero of 28, $p = 0.011$). There was a trend for improved survival in individuals with LAPC who underwent resection ($p = 0.09$). For those not undergoing resection, one-year LRC was 78%. Any grade ≥ 3 potentially radiation-related toxicity rate was 7%. The authors concluded that their results underscore the feasibility, safety, and effectiveness of neoadjuvant SBRT and chemotherapy for BRPC and LAPC.

Chuong et al. (2013) conducted a single-center, retrospective, case series analysis to evaluate outcomes of individuals with nonmetastatic pancreatic cancer and treated with induction chemotherapy followed by SBRT. SBRT was delivered over five consecutive fractions using a dose painting technique including 7 - 10 Gy/fraction to the region of vessel abutment or encasement and 5 - 6 Gy/fraction to the remainder of the tumor. Restaging scans were performed at four weeks, and resectable individuals were considered for resection. The primary endpoints were OS and PFS. A total of 73 individuals were evaluated, with a median follow-up of 10.5 months. Median doses of 35 Gy and 25 Gy were delivered to the region of vessel involvement and the remainder of the tumor, respectively. Thirty-two BRPC individuals (56.1%) underwent surgery, with 31 undergoing an R0 resection (96.9%). The median OS, one-year OS, median PFS, and one-year PFS for BRPC versus LAPC individuals was 16.4 months versus 15 months, 72.2% versus 68.1%, 9.7 versus 9.8 months, and 42.8% versus 41%, respectively (all $p > 0.10$). BRPC individuals who underwent R0 resection had improved median OS (19.3 versus 12.3 months; $p = 0.03$), one-year OS (84.2% versus 58.3%; $p = 0.03$), and one-year PFS (56.5% versus 25.0%; $p < 0.0001$), respectively, compared with all nonsurgical individuals. The one-year local control in nonsurgical individuals was 81%. There was no acute grade ≥ 3 toxicity, and late grade ≥ 3 toxicity was minimal (5.3%). The authors concluded that SBRT safely facilitates margin-negative resection in individuals with BRPC pancreatic cancer while maintaining a high rate of local control in unresectable individuals, and these data support the expanded implementation of SBRT for pancreatic cancer.

Rajagopalan et al. (2013) conducted a single-center case series analysis to report outcomes of individuals with BRPC and LAPC who underwent surgery after neoadjuvant SBRT. Individuals were treated with SBRT followed by resection and chemotherapy was to the discretion of the medical oncologist and preceded SBRT for most individuals. A total of 12 individuals were included in the analysis. Most (92%) received neoadjuvant chemotherapy, and gemcitabine/capecitabine was most frequently prescribed (n = seven). Most individuals were treated with fractionated SBRT to 36 Gy/3 fractions (n = seven) and the remainder with single fraction to 24 Gy (n = five). No grade 3+ acute toxicities attributable to SBRT were found. Two individuals developed post-surgical vascular complications, and one died secondary to this. The mean time to surgery after SBRT was 3.3 months. An R0 resection was performed in 92% of individuals (n = 11/12). In 25% (n = three of 12) of individuals, a complete pathologic response was achieved, and an additional 16.7% (n = two of 12) demonstrated < 10% viable tumor cells. Kaplan-Meier estimated median progression free survival is 27.4 months. OS was 92%, 64% and 51% at one-, two-, and three-years. The authors concluded that in individuals with BRPC and LAPC, treatment with neoadjuvant chemotherapy and SBRT followed by resection is safe and tolerated well, and a promising area for further exploration in this disease site.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

The ASTRO guideline developed by Palta et al. (2019) for pancreatic cancer recommends (not all-inclusive):

- Following surgical resection of pancreatic cancer, adjuvant SBRT is only recommended on a clinical trial or multi-institutional registry. Strength of recommendation: strong; quality of evidence: 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. Strength of recommendation: conditional; quality of evidence: 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 conventionally fractionated RT with chemotherapy, dose-escalated chemoradiation, or multifraction SBRT without chemotherapy is conditionally recommended. Strength of recommendation: conditional; quality of evidence: low.

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for pancreatic adenocarcinoma state that as first-line therapy, SBRT may be used in select individuals with locally advanced disease without systematic metastases or those who are not candidates for combination therapy. As subsequent therapy, SBRT may be used if not previously given and if the primary site is the sole site of progression (NCCN, 2025).

Definitive Treatment of Prostate Cancer Without Evidence of Distant Metastasis

In 2024, ECRI released a revised analysis of SBRT for localized prostate cancer that included evidence from two systematic reviews, three RCTs and two nonrandomized comparison studies. The analysis gave a favorable rating regarding the safety and efficacy of SBRT compared to other treatments for localized prostate cancer. All studies consistently found minimal differences between treatments, except that prostatectomy patients experienced significantly higher rates of erectile dysfunction compared to SBRT patients.

A phase III RCT (PACE-B) conducted by van AS (2024) assessed non-inferiority of five-fraction SBRT compared to conventionally or moderately hypofractionated radiotherapy for biochemical or clinical failure. Participants (n = 874) were randomized into two groups (CRT = 441, SBRT = 433) in 38 centers. Inclusion criteria included those 18 years or older, with prostate adenocarcinoma, WHO performance status of zero to two, with a life expectancy of five or more years. Participants had T1 or T2 disease low or intermediate risk. Those with Gleason grade four or higher disease, history of previous pelvic radiotherapy or treatment for prostate cancer, bilateral hip prostheses, or any NCCN high risk factors were excluded. Androgen deprivation therapy was not permitted. Median age was 69.8 years, median PSA 8.0 ng/mL, NCCN risk group was 9.3% low, 90.7% intermediate. After 74.0 months median follow-up, five-year biochemical/clinical failure free rate (95% CI) was CRT: 94.6% (91.9%, 96.4%) versus SBRT: 95.8% (93.3%, 97.4%). SBRT was non-inferior to CRT with an unadjusted HR 0.73 (90% CI: 0.48, 1.12; p-value for non-inferiority 0.004). To five years, cumulative rate of late RTOG grade two or worse genitourinary toxicity was CRT: 18.3% (95% CI 14.8, 22.5%) versus SBRT: 26.9% (95% CI 22.8, 31.5%) (p < 0.001) and for gastrointestinal toxicity was CRT: 10.2% (95% CI 7.7, 13.5%) versus SBRT: 10.7% (95% CI 8.1, 14.2%) (p = 0.94). The authors concluded that for those with low/intermediate risk localized prostate cancer, SBRT (five-fraction) is non-inferior to CRT for biochemical/clinical failure and is an effective treatment option which offered similar efficacy with greater convenience for individuals.

Jackson et al. (2019) conducted a systematic review and meta-analysis to evaluate physician- and patient-reported outcomes after prostate SBRT. A search was conducted using Medline and EMBASE for original articles published

between January 1990 and January 2018. The primary endpoints included five-year overall biochemical recurrence-free survival (bRFS), physician-reported acute and late grade ≥ 3 toxicity for both genitourinary (GU) and GI domains, and patient-reported QOL using the Expanded Prostate Cancer Index Composite (EPIC). Secondary analyses included a meta-regression of the impact of covariables on bRFS and late toxicity. A total of 38 studies were included in the analysis, comprising 6,116 individuals. Twenty-two studies were clinical trials, of which one was a phase I trial that included 45 individuals, four were phase I/II trials that included 245 individuals, 17 were phase II or III trials that included 2,174 individuals and 16 were prospective observational studies, which included 3,652 individuals. The median follow-up period was 39 months (range, 12 to 115 months). Ninety-two percent, 78%, and 38% of studies included low, intermediate, and high-risk individuals, respectively. Overall, five- and seven-year bRFS rates were 95.3% (95% CI, 91.3% to 97.5%) and 93.7% (95% CI, 91.4% to 95.5%), respectively. Estimated late grade ≥ 3 GU and GI toxicity rates were 2.0% (95% CI, 1.4% to 2.8%) and 1.1% (95% CI, 0.6% to 2.0%), respectively. By two years post-SBRT, EPIC urinary and bowel domain scores returned to baseline. Increasing dose of SBRT was associated with improved biochemical control ($p = 0.018$) but worse late grade ≥ 3 GU toxicity ($p = 0.014$). The authors concluded that prostate SBRT has substantial prospective evidence supporting its use as a standard treatment option, with favorable tumor control, patient-reported QOL, and levels of toxicity.

Widmark et al. (2019) conducted a multi-center, phase III, randomized, open-label non-inferiority trial to show that ultra-hypofractionation is non-inferior to conventional fractionation regarding failure-free survival without any significant differences in late normal tissue complications. Participants were men up to 75 years of age with histologically verified intermediate-to-high-risk prostate cancer and WHO performance status between zero to two. Participants were randomly assigned to ultra-hypofractionation (42.7 Gy in seven fractions, three days per week for 2.5 weeks) or conventional fractionated radiotherapy (78.0 Gy in 39 fractions, five days per week for eight weeks). No androgen deprivation therapy was allowed. The primary endpoint was time to biochemical or clinical failure. The prespecified non-inferiority margin was 4% at five years, corresponding to a critical HR limit of 1.338. Physician-recorded toxicity was measured according to the RTOG morbidity scale and patient-reported outcome measurements with the Prostate Cancer Symptom Scale (PCSS) questionnaire. A total of 1,200 participants were randomly assigned to conventional fractionation ($n = 602$) or ultra-hypofractionation ($n = 598$), of whom 1,180 (591 conventional fractionation and 589 ultra-hypofractionation) constituted the per-protocol population. Eighty-nine percent ($n = 1,054$) of participants were intermediate risk and 11% ($n = 126$) were high risk. Median follow-up time was five years (IQR 3.1 to 7.0). The estimated failure-free survival at five years was 84% (95% CI 80 to 87) in both treatment groups, with an adjusted HR of 1.002 (95% CI 0.758 to 1.325; $p = 0.99$). There was weak evidence of an increased frequency of physician-reported acute RTOG grade 2 or worse urinary toxicity in the ultra-hypofractionation group at end of radiotherapy [158 (28%) of 569 participants versus 132 (23%) of 578 participants; $p = 0.057$]. There were no significant differences in grade 2 or worse urinary or bowel late toxicity between the two treatment groups at any point after radiotherapy, except for an increase in urinary toxicity in the ultra-hypofractionation group compared to the conventional fractionation group at one-year follow-up [32 (6%) of 528 participants versus 13 (2%) of 529 participants; ($p = 0.0037$)]. There were no differences between groups in frequencies at 5 years of RTOG grade 2 or worse urinary toxicity and bowel toxicity. Patient-reported outcomes revealed significantly higher levels of acute urinary and bowel symptoms in the ultra-hypofractionation group compared with the conventional fractionation group but no significant increases in late symptoms were found, except for increased urinary symptoms at one-year follow-up, consistent with the physician-evaluated toxicity. The authors concluded that ultra-hypofractionated radiotherapy is non-inferior to conventionally fractionated radiotherapy for intermediate-to-high risk prostate cancer as it relates to failure-free survival and therefore, their results supported the use of ultra-hypofractionation for radiotherapy of prostate cancer.

Clinical Practice Guidelines

American Urological Association (AUA)/American Society for Radiation Oncology (ASTRO)

The 2022 AUA/ASTRO guideline for localized prostate cancer strongly recommends utilization of dose escalation when EBRT is the primary treatment for individuals with prostate cancer. Additionally, clinicians should utilize available target localization, normal tissue avoidance, simulation, advanced treatment planning/delivery, and image-guidance procedures to optimize the therapeutic ratio of EBRT delivered for prostate cancer. This guideline was also endorsed by the Society of Urologic Oncology (Eastham et al., 2022).

National Comprehensive Cancer Network (NCCN)

The 2025 NCCN guidelines for prostate cancer states that 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, physics, and clinical expertise. Metastasis-direct therapy with SBRT is recommended for the following:

- For limited metastatic disease (e.g., oligometastatic) when ablation is the goal.
- 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.

Definitive Treatment of Renal Cancer

Siva et al. (2024) conducted the FASTRACK II international, non-randomized clinical trial to evaluate the efficacy of SABR as a treatment alternative for individuals with primary renal cell cancer who are not suitable for surgery and have limited curative options. The phase II study took place in seven centers in Australia and one center in the Netherlands. Seventy participants 18 years of age or older with primary renal cell cancer (single lesion) confirmed by biopsy and an ECOG performance status of zero to two, who declined surgery or were medically inoperable, or at high risk of complications from surgery were included in the study. A multidisciplinary decision that treatment was warranted was also required. Exclusion criteria included tumors larger than 10 cm, tumors abutting the bowel, previous high dose RT to an overlapping area, previous systemic treatment for renal cell cancer, and an estimated glomerular filtration rate (eGFR) of less than 30 mL/min per 1.73 m². The primary endpoint was local control. Before enrollment, 49 (70%) of 70 participants had documented serial growth on initial surveillance imaging. Forty-nine (70%) of 70 participants were male and 21 (30%) were female. Median tumor size was four to six cm (IQR 3.7 – 5.5). All participants enrolled had T1–T2a and N0–N1 disease. Twenty-three participants received single-fraction SABR of 26 Gy and 47 received 42 Gy in three fractions. Median follow-up was 43 months (IQR 38 – 60). Local control at twelve months from treatment commencement was 100% ($p < 0.0001$). Seven (10%) participants had grade 3 treatment-related adverse events, with no grade 4 adverse events observed. Grade 3 treatment-related adverse events were nausea and vomiting [three (4%) participants], abdominal, flank, or tumor pain [four (6%)], colonic obstruction [two (93%)], and diarrhea [one (1%)]. No treatment-related or cancer-related deaths occurred. The authors concluded SABR can be considered a proven modality for inoperable participants with larger renal cell cancer tumors or in a location not amenable to thermal ablation. The authors recommend future randomized trials. Study limitations include lack of randomization, small sample size, and lack of control group.

Suleja et al. (2024) conducted a systematic review and meta-analysis to evaluate the current evidence for treatment of individuals with localized renal cell carcinoma (RCC) using SBRT. Studies that assessed safety and clinical effectiveness in those with localized RCC using SBRT in single-arm trials or compared with other standard-of care therapies and reported on local control, renal function preservation, PFS, OS and rates of grade ≥ 3 adverse events were included in the review. A total of 13 prospective single-arm studies (308 individuals, 312 renal lesions) published between 2015 and 2024 were included in the meta-analysis. The most common clinical stages observed were T1a and T1b. The median diameter of the irradiated tumors ranged between 1.9 and 5.5 cm in individual studies. Grade ≥ 3 adverse effects were reported in 15 patients, and their estimated rate was 0.03 (95% CI: 0.01 - 0.11; $n = 291$). One- and two-year local control rates were 0.98 (95% CI: 0.95 - 0.99; $n = 293$) and 0.97 (95% CI: 0.93 - 0.99; $n = 253$), while one- and two-year OS rates were 0.95 (95% CI: 0.88 - 0.98; $n = 294$) and 0.86 (95% CI: 0.77 - 0.91; $n = 224$). There was no statistically significant heterogeneity, and the estimations were consistent after excluding studies at a high risk of bias in a sensitivity analysis. The authors concluded that the short-term outcomes indicate that SBRT has a low rate of high-grade adverse effects, excellent local control, and is an effective treatment option for certain individuals with localized RCC who are inoperable or those who decline surgery. The authors noted that long-term data from RCTs is needed, and surgical treatment remains the standard of care in operable individuals. Limitations included short-term follow-ups and a lack of RCTs. Siva et al. 2024 is included in this systematic review and meta-analysis.

Clinical Practice Guidelines

International Society of Stereotactic Radiosurgery (ISRS)

An ISRS systematic review and guideline for SBRT for primary RCC developed by Siva et al. (2024) states surgery is the standard of care but SBRT can be an alternative for individuals who are medically inoperable, decline surgery, or are high risk. The summary of recommendations are as follows:

- Optimal dose regimens for SBRT in patients with primary RCC include 26 Gy in one fraction if the tumor is $\leq 4 - 5$ cm and 42 - 48 Gy in three fractions if the tumor is $> 4 - 5$ cm, or potentially 40 Gy in five fractions if the dose constraints for organs at risk (OAR) cannot be met for three fractions. Strength of recommendation- moderate.
- A routine post-SBRT biopsy should not be performed to evaluate response and is only recommended in patients with imaging findings concerning for disease progression. Strength of recommendation: strong.
- For patients with a solitary kidney, SBRT is an approach associated with both excellent local control and acceptable renal function preservation (except in patients with stages 4 and 5 chronic kidney disease); technical approaches to reduce the volume of irradiated kidney, particularly in the intermediate dose-wash region, are recommended. Strength of recommendation: strong.
- Optimal post-treatment follow-up schedule after SBRT for primary RCC includes cross-axial imaging of the abdomen, including both kidneys and adrenals every six months and surveillance scans including chest imaging at a minimum. Strength of recommendation: moderate.

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for kidney cancer state SBRT should be considered as the primary radiation modality unless precluded by anatomic site, proximity to OARs, or previous treatment. For non-surgical candidates, definitive radiation using SBRT may be considered for individuals with T1 tumors (< 7 cm in diameter). Tumors abutting the bowel should be considered not amenable to SBRT and current data is insufficient to consider SBRT in tumors larger than 7mm (NCCN, 2025).

Definitive Treatment of Small Cell Lung Cancer (SCLC)

Safavi et al. (2021) conducted a systematic review and meta-analysis to evaluate and summarize oncologic and toxicity outcomes for those with inoperable T1-2N0M0 SCLC. Inclusion criteria consisted of peer-reviewed journal articles that assessed less than or equal to eight fractions of SABR for T1-2N0M0 SCLC. Excluded from the analysis were reviews, editorials, commentaries, guidelines, prefaces, case series with fewer than five patients, and studies published in languages other than English. Eleven retrospective studies were included in the review and seven were included in the meta-analysis. Inoperability was noted as the indication for SABR in 94% (75 - 100%) of individuals. Median follow-up and tumor size were 19.5 months (11.9 - 32) and 24 mm (19 - 29), respectively. Chemotherapy and PCI use rates were 44.1% (95% CI, 27.0 - 61.9%) and 13.8% (95% CI, 0.4 - 41.2%), respectively. Local control was 97.3% (95% CI, 92.3 - 99.8%) at one year and 95.7% (95% CI, 74.2 - 100.0%) at two years. Overall survival was 86.3% (95% CI, 74.4 - 94.9%) at one year and 63.7% (95% CI, 45.7 - 79.9%) at two years. Nodal and distant recurrence rates were 17.8% (95% CI, 7.5 - 31.2%) and 26.9% (95% CI, 7.4 - 53.0%), respectively. The rates of grade 1, grade 2, and grade 3 toxicity (CTCAE) were 12.6% (95% CI, 6.7 - 19.9%), 6.7% (95% CI, 3.3 - 11.2%), and 1.4% (95% CI, 0.0 - 5.3%), respectively. No grade 4 or 5 events were observed across the studies. The authors concluded that for inoperable early-stage, node-negative SCLC, SABR is locally effective with limited toxicity. Limitations included the retrospective nature of the included studies and small sample sizes. The authors suggested conducting future prospective studies to assess the use of SABR for individuals with higher risks of toxicity with surgery or combined chemoradiation.

In 2018, Verma et al. compared SBRT to conventionally fractionated RT for individuals (n = 2,107) with inoperable stage I SCLC. The National Cancer Database was searched (2004 to 2014) for histologically confirmed T1-2N0M0 SCLC. Inclusion criteria included those with newly diagnosed, T1-2N0M0 SCLC that received chemotherapy. Those who had surgery, were not receiving EBRT, and/or lacked survival/follow-up information, or received chemotherapy starting less than three months before or less than two months after RT were excluded. Of 2,107 patients, 7.1% underwent SABR/chemotherapy, and 92.9% received CFRT/chemotherapy. The median (interquartile range) dose of SABR was 50 (48 - 54) Gy in four (three to five) fractions, and 55.8 (45 - 60) Gy in 30 (30 - 33) fractions for CFRT. Patients receiving SABR/chemotherapy were more often older, had T1 disease, treated at academic/integrated network facilities, and managed in more recent years (p < 0.05 for all). Respective median survival figures were 29.2 versus 31.2 months (p = 0.77), which persisted following propensity matching (25.4 versus 34.3 months, p = 0.85). On multivariable analysis, radiotherapeutic technique was not associated with OS (p = 0.95). According to the authors, for those with stage I SCLC, SABR combined with chemotherapy provided statistically similar outcomes to CFRT combined with chemotherapy. The authors noted that RCTs for this relatively rare scenario would likely have inadequate accrual, and these retrospective data should be strongly considered when advocating for SABR/chemotherapy as the preferred treatment option for this patient group.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

Simone II et al. (2020) developed an ASTRO guideline for RT of SCLC which strongly recommends definitive thoracic RT early in the course of treatment for limited stage SCLC. Furthermore, SBRT or conventional fractionation received a strong recommendation (quality of evidence: moderate) for those with stage I or II node negative disease who are medically inoperable with chemotherapy delivery before or after SBRT.

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for SCLC indicate that the principals of SBRT for SCLC are similar to those for NSCLC. For individuals with stage I-IIA (T1-2, N0, M0) who are medically inoperable, or not surgical candidates may be considered for SBRT to the primary tumor followed by adjuvant systemic therapy. NCCN states that for those SCLC and a small number of BMs, SRS may be appropriate; and SRS is preferred for individuals who develop BMs after PCI (NCCN, 2025).

Extracranial Oligometastatic Disease

Gooijer et al. (2025) published a systematic review that evaluated efficacy following pulmonary metastasectomy and SBRT in those with oligometastatic colorectal lung metastases. Clinical trials and observational studies published between 2000 and 2023 that assessed outcomes (OS, PFS, or local recurrence rate) after metastasectomy or SBRT were included

in the review. Overall survival, PFS, and local recurrence rate were assessed and compared between both groups. A total of 141 studies on metastasectomy (n = 29932) and 16 studies on SBRT (n = 1381) were included in the final analysis. The pooled five-year OS was 52.2 % (CI: 49.8–54.5) and 45.0 % (CI: 31.2 - 58.9) following metastasectomy and SBRT, respectively (p = 0.213). The pooled five-year PFS was 35.1 % (CI: 32.2 - 38.1) following metastasectomy and 11.7 % (CI: 0 - 38.2) following SBRT (p < 0.001). The pooled LRR was 10.5 % (CI: 5.5 - 15.5) following metastasectomy and 28.1 % (CI: 20.8 - 35.4) following SBRT (p < 0.001). The average Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) score of the included studies was low. According to the authors, those with oligometastatic colorectal lung metastases may achieve comparable OS whether treated with surgical metastasectomy or SBRT. However, PFS and local recurrence rates tend to favor surgical resection. A meta-analysis was not done because the outcome measures were too similar across studies, and the known prognostic factors were not evenly balanced between the two groups. Limitations include the non-randomized comparison of the two local treatment strategies. The authors recommend future RCTs comparing surgery and SBRT in this patient population.

Persson et al. (2024) conducted a systematic review and meta-analysis of RCTs to evaluate the efficacy and safety of SBRT as metastasis-directed therapy (MDT) for individuals with oligometastatic prostate cancer (OMPC) compared to those with no MDT. Primary outcomes were OS and grade 3 or greater toxicity. Systemic therapy-free survival, QOL, grade 5 toxicity, LC and PFS were secondary outcomes. Seven phase II RCTs with 559 participants were included in the review. Four trials included multiple types of primary cancer. Outcome definitions were heterogeneous except for OS and toxicity. For OS, only one study reported events in both arms. Meta-analysis of the grade ≥ 3 toxicity results from two trials showed no difference (pooled RR 0.78, 95% CI 0.37 - 1.65, p = 0.52). Four trials reported significantly longer PFS, with a pooled HR of 0.31 (95% CI 0.21 - 0.45, p < 0.00001). Risk of bias was of some concerns or high. The quality of evidence was low or moderate. The authors concluded that phase II trials have demonstrated promising enhancements in PFS for various OMPC states without significant toxicity; however, OS comparisons remain inconclusive. Limitations of the study included small sample sizes and varying patient groups and treatment approaches. The authors suggested that future phase III trials are needed and should include larger sample sizes, blinding, and improved adherence to assigned interventions.

Harrow et al. (2022) states the Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases (SABR-COMET) trial was amended in 2016 to extend follow-up to 10 years; this report contains oncologic outcomes beyond five years. Ninety-nine participants with primary tumor sites in the lung (n = 18), breast (n = 18), colon (n = 18), prostate (n = 16), and other (n = 29), were randomized into two arms, palliative standard-of-care treatment versus SABR to all metastases plus standard-of-care. The primary endpoint was OS and secondary endpoints were PFS, toxicity, QOL and time to new metastases. Eight-year OS was 27.2% in the SABR arm versus 13.6% in the control arm. Eight-year PFS estimates were 21.3% versus 0.0%, respectively. Rates of grade ≥ 2 acute or late toxic effects were 30.3% versus 9.1%, with no new grade 3 to 5 toxic effects. FACT-G QOL scores declined over time in both arms, but there were no differences in QOL scores between arms. The use of systemic therapy overall was similar between arms, but participants in the SABR arm were less likely to require cytotoxic chemotherapy. The authors concluded SABR had significant improvements in OS and PFS. Additionally, there were no new safety signals detected with extended follow-up. Limitations include several participants who were either lost to follow-up or died before the last report, and the trial included multiple histologies which limits conclusions that can be made about specific histologies. The authors recommended future larger studies.

Marvaso et al. (2021) conducted a systemic review and meta-analysis to better define the role of SBRT in individuals with oligorecurrent prostate cancer. All prospective studies including prostate cancer individuals with nodal and/or bone oligometastases and one to five lesions were considered eligible. Six studies published between 2013 and 2020 were included in the review. Data from 445 individuals, of which 396 received SBRT (67 in randomized studies and 329 in observational studies) were incorporated. Five studies considered local PFS and reported values close to 100%, one study reported a value of 80% in the observational arm. Benefit in terms of biochemical PFS brought by SBRT was apparent in all studies. The difference in cumulative probabilities between the comparator arm and the interventional arm was maintained after 24 months from baseline. All studies but one considered toxicity among the endpoints of interest. Most events were classified as either G1 or G2, and the only G ≥ 3 adverse event was reported in one trial. The authors concluded that SBRT is safe and has an almost nonexistent toxicity risk that makes it the perfect candidate for the optimal management of individuals with oligometastatic prostate cancer. A limitation of the study noted by the authors is the absence of a control group comparing SBRT with an active treatment. (Ost et al., 2018, which was previously cited in this policy, was included in this systematic review and meta-analysis).

Palma et al. (2020) reported extended outcomes (greater than 40 months after completion of accrual) from the SABR-COMET trial. The SABR-COMET trial was a multi-center, randomized, phase II, open-label, trial to assess standard of care palliative treatments with or without SABR in participants with a controlled primary tumor and up to five metastatic lesions (Palma 2012). Eligible participants were randomized to either standard of care palliative treatments (control group)

or standard of care plus SABR to all sites of metastatic disease (SABR group). The control group received radiotherapy that was delivered according to the standard principles of palliative radiation. The recommended treatment fractionations depended upon the tumor location and indication, and prescribed doses ranged from 8 Gy in one fraction to 30 Gy in ten fractions. The SABR group received stereotactic radiation to all sites of metastatic disease, with the goal of achieving disease control while minimizing potential toxicities. The allowable doses ranged from 30-60 Gy in three to eight fractions, depending upon target size and location. Participants were seen every three months after randomization for the first two years, and every six months thereafter. A total of 99 participants were enrolled at ten centers; 33 were randomly assigned to the control group and 66 to the SABR group. The primary tumor types were breast (n = 18), lung (n = 18), colorectal (n = 18), prostate (n = 16), and other (n = 29). Ninety-three percent (92/99) of the participants had one to three metastases. In the initial report (Palma 2019), the use of SABR demonstrated a 13-month improvement in median OS after a median follow-up of 28 months. In the subsequent report of extended outcomes, the median follow-up period was 51 months (95% CI, 46 to 58 months). The primary outcome event, death (all cause), occurred in 24 (73%) of 33 participants in the control group and 35 (53%) of 66 participants in the SABR group. The median OS was 28 months (95% CI, 19 to 33) in the control group versus 41 months (26–not reached) in the SABR group (HR, 0.57, 95% CI, 0.30 to 1.10; p = 0.090). The five-year OS rate was 17.7% in the control group (95% CI, 6% to 34%) versus 42.3% in SABR group (95% CI, 28% to 56%; p = 0.006). The five-year PFS rate was not reached in the control group (3.2%; 95% CI, 0% to 14% at 4 years with last patient censored) and 17.3% in the SABR group (95% CI, 8% to 30%; p = 0.001). There were no new grade 2-5 adverse events and no differences in QOL between arms. The authors concluded that with extended follow-up, participants with controlled primary tumors and one to five oligometastases who received SABR demonstrated a 22-month improvement in median OS compared with participants who received a standard-of-care approach alone, corresponding to an absolute survival benefit of 25% at five years. Furthermore, they reported that there were no new safety concerns detected during the extended follow-up period.

In 2019, Gomez et al., reported extended outcomes from a previously published multi-center, phase II, RCT. The original study (Gomez 2016) evaluated PFS after aggressive local consolidative therapy (LCT) versus maintenance therapy or observation (MT/O) for individuals with stage IV NSCLC with ≤ 3 metastases remaining after front line systemic therapy. That trial was closed early after it demonstrated an eight-month benefit in PFS for participants who received LCT compared to participants who received MT/O; the median PFS was 11.9 months in the LCT arm (90% CI, 5.72 to 20.90 months) versus 3.9 months in the MT/O arm (p = 0.005). The extended outcomes included PFS, OS, toxicity, and the appearance of new lesions. A total of 49 participants (LCT arm, n = 25; No LCT arm, n = 24) were included in this analysis. The median follow-up time was 38.8 months (range, 28.3 to 61.4 months), the PFS benefit was durable [median, 14.2 months (95% CI, 7.4 to 23.1 months) with LCT versus 4.4 months (95% CI, 2.2 to 8.3 months) with MT/O; p = 0.022]. There was an OS benefit in the LCT arm (median, 41.2 months [95% CI, 18.9 months to not reached] versus 17.0 months [95% CI, 10.1 to 39.8 months] with MT/O; p = 0.017). No additional grade 3 or greater toxicities were observed. Survival after progression was longer in the LCT arm (37.6 months with LCT versus 9.4 months with MT/O; p = 0.034). Of the 20 participants who experienced progression in the MT/O arm, nine received LCT to all lesions after progression, and the median OS was 17 months (95% CI, 7.8 months to not reached). The authors concluded that in individuals with oligometastatic NSCLC that did not progress after front-line systemic therapy, LCT prolonged PFS and OS compared to MT/O. (This study is included in the ISRS guideline below).

Sutera et al. (2019) conducted a phase II multicenter trial to assess outcomes, toxicity, and QOL of individuals with oligometastatic cancer who were prospectively treated with SABR. Participants were 18 years of age or older, with oligometastatic (one to five metastases in three or fewer organs) or recurrent cancer, with a Zubrod PS of zero to one, and adequate laboratory parameters. Those with lymphoma, leukemia, multiple myeloma, and central nervous primaries were ineligible. Additionally, any individual with another primary cancer within the last three years, diffuse metastatic spread confined to one organ, pregnancy, sites not treatable with SABR, or severe active co-morbidities were excluded. Participants (n = 147) were seen in follow-up six weeks post SABR, then every three months for three years, and at six-month intervals thereafter. Feasibility of SABR in participants with oligometastatic disease was the primary endpoint. Secondary endpoints were five-year OS, five-year local PFS, QOL, and toxicity. The most common primary tumors included lung (21.8%, non-small cell: n = 29, small cell: n = three), colorectal adenocarcinoma (21.1%), and head and neck (10.9%, squamous cell carcinoma: n = 11). In a median follow-up of 41.3 months (interquartile range: 14.6 - 59.0), the median OS was 42.3 months (95% CI: 27.4 - ∞) with a five-year OS of 43%. Five-year local PFS and distant PFS were 74% and 17%, respectively. Acute grade 2+ and 3+ toxicity were 7.5% and 2.0%, respectively, and late grade 2+ and 3+ toxicity were both 1.4%. There was no significant change in QOL at completion and six weeks, three months, and nine months after treatment. At six months and 12 months, participants were found to have statistically significant improvement in patient-reported QOL. The authors concluded that SABR was a feasible and tolerable treatment with minimal acute and late grade 3 toxicity for those with oligometastatic cancer. Limitations included lack of randomization and a heterogeneous participant population. The authors recommended future RCTs to support their results.

lyengar et al. (2018) conducted a single-center, phase II, randomized trial to determine if noninvasive SABR prior to maintenance chemotherapy in individuals with non–progressive limited metastatic NSCLC after induction therapy led to significant improvements in PFS. Participants were eligible if they were 18 years or older, had a KPS score of 70 or better, had biopsy-proven metastatic NSCLC (primary plus up to five metastatic sites with no more than three sites in the liver or lung) and the tumors did not possess EGFR-targetable or ALK-targetable mutations but did achieve a partial response or stable disease after induction chemotherapy. The primary end point was PFS; secondary end points included toxic effects, local and distant tumor control, patterns of failure, and OS. A total of 29 participants (nine women and 20 men) were enrolled; 14 participants with a median age of 63.5 years (range, 51.0 - 78.0 years) were allocated to the SABR-plus-maintenance chemotherapy arm, and 15 participants with a median age of 70.0 (range, 51.0 - 79.0 years) were allocated to the maintenance chemotherapy-alone arm. The SABR-plus-maintenance chemotherapy arm had a median of three metastases (range, two to six) and the maintenance chemotherapy-alone arm had a median of two metastases (range, two to five). The trial was stopped early after an interim analysis found a significant improvement in PFS in the SABR-plus-maintenance chemotherapy arm of 9.7 months versus 3.5 months in the maintenance chemotherapy-alone arm ($p = 0.01$). Toxic effects were similar in both arms. There were no in-field failures with fewer overall recurrences in the SABR arm while those participants receiving maintenance therapy alone had progression at existing sites of disease and distantly. The authors concluded that consolidative SABR prior to maintenance chemotherapy appeared beneficial, nearly tripling PFS in those with limited metastatic NSCLC compared with maintenance chemotherapy alone, with no difference in toxic effects. The irradiation prevented local failures in original disease, the most likely sites of first recurrence. In addition, PFS for individuals with limited metastatic disease appears similar to PFS in those with a greater metastatic burden, further supporting the potential benefits of local therapy in limited metastatic settings. (This study is included in the ISRS guideline below).

In 2017, Ruers et al., published updated outcomes from a previously conducted a multi-center phase II randomized trial. The original study investigated the possible benefits of RFA in individuals with non-resectable colorectal liver metastases. A total of 119 participants with unresectable colorectal liver metastases (< 10 metastases and no extrahepatic disease) participated in the study. Fifty-nine participants were randomized to systemic treatment alone and 60 participants were randomized to systemic treatment plus aggressive local treatment by RFA \pm resection. The authors reported that the primary end point (30-month OS $> 38\%$) was met (Ruers 2012). In this updated report, the authors report long-term OS results. At a median follow up of 9.7 years, 92 of 119 (77.3%) participants had died: 39 of 60 (65.0%) in the combined modality arm and 53 of 59 (89.8%) in the systemic treatment arm. Almost all participants died of progressive disease (35 participants in the combined modality arm, 49 participants in the systemic treatment arm). There was a statistically significant difference in OS in favor of the combined modality arm (HR, 0.58, 95% CI, 0.38 to 0.88, $p = 0.01$). Three-, five-, and eight-year OS were 56.9% (95% CI, 43.3% to 68.5%), 43.1% (95% CI, 30.3% to 55.3%), 35.9% (95% CI, 23.8% to 48.2%), respectively, in the combined modality arm and 55.2% (95% CI, 41.6% to 66.9%), 30.3% (95% CI, 19.0% to 42.4%), 8.9% (95% CI, 3.3% to 18.1%), respectively, in the systemic treatment arm. Median OS was 45.6 months (95% CI, 30.3 to 67.8 months) in the combined modality arm versus 40.5 months (95% CI, 27.5 to 47.7 months) in the systemic treatment arm. The authors concluded that this randomized study demonstrated that aggressive local treatment could prolong OS in individuals with unresectable colorectal liver metastases.

Mokhles et al. (2016) conducted a systematic review and meta-analysis to evaluate evidence on the clinical effectiveness of intensive follow-up after curative surgery for primary colorectal cancer. The primary outcome was the OS difference between the existing monitoring strategy compared with a more intensive monitoring strategy (i.e., measurement of carcinoembryonic antigen and/or CT to detect asymptomatic metastatic disease earlier). Searches were conducted using MEDLINE (Ovid), Embase, the Cochrane Library and Web of Science, Scopus, CINAHL (EBSCO), PubMed publisher, Google Scholar, LILACS, SciELO and ProQuest for randomized comparisons of increased intensity monitoring compared with a contemporary standard policy after resection of primary colorectal cancer. Among 7,081 publications, there were 22 relevant articles, with 16 randomized comparisons and 11 that included survival data. More intensive monitoring advanced the diagnosis of recurrence by a median of 10 (IQR five to 24) months. In 10 of 11 studies, there was no demonstrable difference in OS. Seven RCTs, published from 1995 to 2016, randomly assigned 3,325 individuals to a monitoring protocol made more intensive by introducing new methods or increasing the frequency of existing follow-up protocols versus less invasive monitoring. No detectable difference in OS was associated with more intensive monitoring protocols (HR, 0.98, 95% CI 0.87 to 1.11). The authors concluded that based on pooled data from randomized trials, the anticipated survival benefit from surgical treatment resulting from earlier detection of metastases has not been achieved.

Clinical Practice Guidelines

American Radium Society (ARS)

Amini et al. (2022) developed an ARS Appropriate Use Criteria to evaluate the role of consolidative local therapy for the management of oligometastatic or oligoprogressive NSCLC and provide evidence-based recommendations. The recommendations are as follows (not all-inclusive):

- The panel strongly recommends that consolidative radiotherapy is appropriate for patients with oligometastatic disease (three sites or less, counted after up-front systemic therapy) who have not progressed after two to three months, or two to three cycles, of chemotherapy, provided that all sites are amenable to radiation.
- The panel strongly recommends that consolidative RT is usually appropriate for patients with oligometastatic disease (three sites or less, counted after up-front systemic therapy) who received two to three months of PD-1/PD-L1-based immunotherapy or chemoimmunotherapy with no progression on repeat imaging where the sites are amenable to radiation.
- The panel recommends that consolidative RT in patients with four to five sites of oligometastatic disease (counted after up-front systemic therapy) be considered on a case-by-case basis, owing to the under-representation of these cases in published clinical trials.
- The panel does not currently recommend consolidative RT in patients with six or more sites of metastatic disease outside a clinical trial, rather endorsing systemic therapy alone.
- The panel recommends that RT be considered on a case-by-case basis for oligoprogressive patients harboring limited sites of disease progression while on systemic therapy, provided that other sites of metastatic disease remain controlled.
- In general, if available, the panel strongly recommends enrollment on a clinical trial in the setting of oligometastatic or oligoprogressive disease.

American Society for Radiation Oncology (ASTRO)/European Society for Radiotherapy and Oncology (ESTRO)

Iyengar et al. (2023) developed an ASTRO/ESTRO guideline that provides recommendations based on a systematic review of the literature regarding local therapy for the treatment and management of extracranial oligometastatic NSCLC. A summary of the guideline recommendations are as follows:

- For oligometastatic NSCLC, definitive local therapy is recommended only for patients having up to five distant metastases, diagnosed with appropriate imaging. Implementation remark: Despite some prospective trials including patients with up to five extracranial metastases, most patients enrolled had one to two treated oligometastatic lesions, which should be factored into decision-making. Strength of recommendation: strong; quality of evidence: moderate.
- For patients with oligometastatic NSCLC, highly conformal RT approaches and minimally invasive techniques for surgery are recommended to minimize morbidity. Strength of recommendation: strong; quality of evidence: moderate.
- For patients with oligometastatic NSCLC, a risk adapted approach using stereotactic RT (preferred), hypofractionated RT, or alternatively definitive chemoradiation based on the location and burden of disease is recommended. Strength of recommendation: strong; quality of evidence: high.
- For patients with oligometastatic NSCLC, definitive local RT should use doses and fractionations which achieve durable local control. Strength of recommendation: strong; quality of evidence: high.
- Implementation remarks:
 - Durable local control defined as minimum 85% local control at two years.
 - Higher BED10 (typically > 75 Gy) with SBRT alone is associated with optimal local control.
 - Lower BED10 (50-75 Gy range) is associated with acceptable local control, typically in the setting of combination systemic therapy and SBRT.

Lievens et al. (2020) developed a consensus statement for ESTRO-ASTRO to define oligometastatic disease from the perspective of a radiation oncologist. The authors concluded that based on the current literature, oligometastatic disease could be defined as one to five metastatic lesions, a controlled primary tumor being optional, and where all metastatic sites must be safely treatable. The authors recommended future prospective studies.

International Stereotactic Radiosurgery Society (ISRS)

Mayinger et al. (2023) developed an ISRS practice guideline related to SBRT for lung oligometastases. Thirty-five studies (27 retrospective, five prospective, and three randomized trials) were included in the review that reported on treatment of > 3600 patients and > 4650 metastases. The authors concluded that SBRT is an effective local treatment modality with high local control rates and low risk of radiation-induced toxicities. A total of 21 practice recommendations covering the areas of staging & patient selection, SBRT treatment, and follow-up were developed and summarized below:

- For patients diagnosed with pulmonary oligometastatic disease and an indication for definitive local therapy after discussion in a multidisciplinary tumor board, SBRT and pulmonary metastasectomy are recommended as evidence-based local treatment modalities based on prospective randomized evidence. Level of evidence: high; strength of recommendation: strong.
- For patients diagnosed with pulmonary oligometastatic disease and an indication for definitive local therapy after discussion in a multidisciplinary tumor board, the optimal patient-individual local treatment modality SBRT versus

pulmonary metastasectomy should be discussed in a multidisciplinary setting and should consider the patients' preference. Level of evidence: moderate; strength of recommendation: strong.

- For patients diagnosed with pulmonary oligometastatic disease and an indication for definitive local therapy, SBRT of a single pulmonary metastasis of peripheral location and maximum diameter of 5 cm is recommended as one of the standard of care treatment options based on a favorable safety and efficacy profile. Level of evidence: moderate; strength of recommendation: strong.
- For patients diagnosed with two to five pulmonary oligometastases and an indication for definitive local therapy, simultaneous SBRT can be considered if normal tissue constraints can be met. Level of evidence: moderate; strength of recommendation: strong.
- For patients diagnosed with pulmonary oligometastatic disease and an indication for definitive local therapy, SBRT of pulmonary metastasis with ultracentral location is potentially associated with an increased risk of severe toxicity and the choice of SBRT as definitive local therapy should be carefully evaluated. Level of evidence: moderate; strength of recommendation: strong.
- For patients diagnosed with oligometastatic disease and an indication for definitive local therapy of pulmonary metastases, SBRT in a single fraction can be considered if pulmonary metastases are small, peripherally located, distant to critical serial OAR and without broad chest wall contact. Level of evidence: high; strength of recommendation: strong.

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for kidney cancer recommend considering SBRT for ablative treatment for intact extracranial metastases in individuals with oligometastases unless metastasectomy is planned or SBRT delivery is hindered by factors such as the anatomic location, proximity to OARs, or previous treatments. NCCN states that for prostate cancer, SBRT is recommended for those with limited metastatic disease (e.g., oligometastatic) when ablation is the goal (NCCN, 2025).

Glomus Jugulare Tumors

Ong et al. (2022) performed a systematic review and meta-analysis to evaluate SRS as a treatment for glomus jugulare tumors (GJTs). An online search for articles was executed in March 2019 and the final analysis included 23 studies with a total of 460 patients. Average rates of tinnitus, hearing loss, and lower cranial nerve deficit as presenting symptoms were 56%, 56%, and 42%, respectively. Overall clinical status improvement rate after treatment was 47%. Rates of tinnitus, hearing loss, and lower cranial nerve improvement after treatment were 54%, 28%, and 22%, respectively. The mean follow-up time across studies was 47 months (range, four to 268 months). The aggregate tumor control rate at the time of follow-up was 95%. The authors concluded that the tumor control rate of 95% and 47% symptomatic improvement suggests that SRS may be a viable alternative to resection and a suitable treatment for GJTs. The authors recommend future studies to further evaluate the role of SRS in the management of GJTs. Limitations included study heterogeneity and lack of RCTs.

Sheehan et al. (2012) conducted a multi-center case series analysis to examine the outcomes of individuals with glomus tumors who underwent RS. A total of 134 patient procedures (132 unique individuals) were included in the study. Prior resection was performed in 51 individuals, and prior fractionated EBRT was performed in six individuals. The individuals' median age at the time of RS was 59 years. Forty percent had pulsatile tinnitus at the time of RS. The median dose to the tumor margin was 15 Gy. The median duration of follow-up was 50.5 months (range, five to 220 months). Overall tumor control was achieved in 93% of individuals at last follow-up; actuarial tumor control was 88% at five years post RS. Absence of trigeminal nerve dysfunction at the time of RS ($p = 0.001$) and higher number of isocenters ($p = 0.005$) were statistically associated with tumor progression-free tumor survival. Individuals demonstrating new or progressive cranial nerve deficits were also likely to demonstrate tumor progression ($p = 0.002$). Pulsatile tinnitus improved in 49% of individuals who reported it at presentation. New or progressive cranial nerve deficits were noted in 15% of individuals; improvement in preexisting cranial nerve deficits was observed in 11% of individuals. None of the individuals died as a result of tumor progression. The authors concluded that GKRS was a well-tolerated management strategy that provided a high rate of long-term glomus tumor control, symptomatic tinnitus improved in almost one-half of the individuals, and overall neurological status and cranial nerve function were preserved or improved in the majority of individuals after RS.

Guss et al. (2011) performed a systematic review and meta-analysis regarding management of glomus jugulare with RS. No limits were set on the date of publication or the duration of follow-up. The studies were determined eligible for inclusion if they were original research studies that reported the results of RS for glomus jugulare tumors. Nineteen studies with a total of 335 individuals were included in the meta-analysis. Data on 335 glomus jugulare individuals were extracted, including 278 who had received Gamma Knife and 57 who had received LINAC or CyberKnife. The results across all studies found 97% of individuals achieved tumor control, and 95% of individuals achieved clinical control. Eight studies reported a mean or median follow-up time of > 36 months. In these studies, 95% of individuals achieved clinical control and 96% achieved tumor control. The Gamma Knife, LINAC, and CyberKnife technologies all exhibited high rates of

tumor and clinical control. Limitations noted include small sample size of the studies and the various treatments received (Gamma Knife, LINAC, or CyberKnife). The authors concluded that because of its high effectiveness, RS should be considered for the primary management of GJTs. The authors recommended future prospective studies with larger participant numbers treated with RS as a primary treatment modality and longer follow-up.

Hemangiomas of the Brain

Lee et al. (2017) conducted a multi-center case series analysis to review the outcome of individuals with cavernous sinus hemangiomas (CSH) and treated with SRS. A total of 31 individuals were included in the analysis. Eleven individuals had initial microsurgery before SRS, and the other 20 individuals (64.5%) underwent GKRS as the primary management for their CSH. Median age at the time of RS was 47 years, and 77.4% of individuals had cranial nerve dysfunction before SRS. Individuals received a median tumor margin dose of 12.6 Gy (range, 12 to 19 Gy) at a median isodose of 55%. Tumor regression was confirmed by imaging in all 31 individuals, and all individuals had greater than 50% reduction in tumor volume at six months post-SRS. None of the individuals had delayed tumor growth, new cranial neuropathy, visual function deterioration, AREs, or hypopituitarism after SRS. Twenty-four individuals had presented with cranial nerve disorders before SRS, and six (25%) of them had gradual improvement. Four (66.7%) of the six individuals with orbital symptoms had symptomatic relief at the last follow-up. The authors concluded that SRS was effective in reducing the volume of CSH and attaining long-term tumor control in all individuals at a median of 40 months. The authors also concluded that their experience suggests that SRS is a reasonable primary and adjuvant treatment modality for individuals diagnosed with CSH.

Khan et al. (2009) conducted a single-center case series analysis to evaluate outcomes of individuals diagnosed with cavernous sinus or orbital hemangiomas and treated with SRS. Eight symptomatic individuals with hemangiomas who underwent SRS were included in the analysis. The presenting symptoms included headache, orbital pain, diplopia, ptosis, proptosis, and impaired visual acuity. The hemangiomas were located in either the cavernous sinus (seven individuals) or the orbit (one individual). Four individuals underwent SRS as primary treatment modality based on clinical and imaging criteria. Four individuals had previous microsurgical partial excision or biopsy. The median target volume was 6.8 mL (range, 2.5 to 18 mL). The median prescription dose delivered to the margin was 14.5 Gy (range, 12.5 to 19 Gy). The dose to the optic nerve in all individuals was less than 9 Gy (range, 4.5 to 9 Gy). The median follow-up period after SRS was 80 months (range, 40 to 127 months). Six individuals had symptomatic improvement; two individuals reported persistent diplopia. Follow-up imaging revealed tumor regression in seven individuals and no change in tumor volume in one individual. All the individuals improved after SRS. The authors concluded that their experience confirms that SRS is an effective management strategy for symptomatic intracavernous and intraorbital hemangiomas, and that their study is the first to report long-term safety and efficacy of SRS in this population.

Clinical Practice Guidelines

International Stereotactic Radiosurgery Society (ISRS)

Tos et al. (2024) developed guidelines based on a systematic review and meta-analysis regarding SRS for intracranial cavernous malformations (ICMs). The meta-analysis included 32 studies (n = 2672 individuals) and concluded that SRS was effective for ICM treatment by significantly reducing rates of hemorrhage and improving seizure outcomes. The guideline recommendations are as follows (not all-inclusive):

- For patients with a surgically inaccessible or eloquently situated ICM with previous symptomatic hemorrhage, SRS is recommended with the intent of reducing the risk of subsequent hemorrhage. Low quality of evidence: conditional.
- For patients with ICM causing epilepsy with poor medication control, SRS is recommended with the intent of improving seizure control. Low quality of evidence: conditional.
- SRS is not typically recommended for asymptomatic ICM. Low quality of evidence: moderate.

Intracranial Arteriovenous Malformations (AVMS)

Maroufi et al. (2024) conducted a systematic review and meta-analysis of the available literature to assess the safety and efficacy of repeat SRS for AVMs. Sixteen retrospective cohort studies were included in the review and included 1,168 individuals who received repeat SRS from 1976 to 2022 due to incomplete obliteration. Inclusion criteria consisted of studies of individuals with recurrent or residual AVM following SRS (single session), undergoing repeat SRS, and had the obliteration rate reported after repeat SRS. The meta-analysis, with a mean follow-up of 45.57 months, reveals repeat SRS as a viable option for AVMs, achieving a 60.82% obliteration rate with a mean time to obliteration of 33.18 months. Meta-regression identifies AVM volume and Spetzler-Martin (SM) grade as factors influencing obliteration, with smaller volume and lower SM grades associated with higher rates. Complications include 10.33% radiation-induced changes, 5.26% post-radiosurgery hemorrhage, 2.56% neurologic deficits, and 0.67% cyst formation. Heterogeneity in complications is primarily attributed to male proportion and SM grade, while factors influencing post-radiosurgery hemorrhage remain unclear. The type of RS, whether GKRS or LINAC, does not significantly impact outcomes. The

authors concluded that for AVMs that failed initial SRS, repeat SRS, when used in appropriate patient subgroups, is a safe and effective treatment and has an acceptable risk-to-benefit profile. Limitations included the retrospective nature of the studies in the review.

Ding et al. (2017) conducted an international multicenter study which analyzed and collected data from individuals with Spetzler-Martin (SM) Grade III AVMs treated with SRS at eight institutions. Cohort inclusion criteria comprised individuals with SM Grade III AVMs and a minimum follow-up length of 12 months. AVM obliteration, no post-SRS hemorrhage, and no permanently symptomatic radiation-induced changes were defined as an optimal outcome. The SM Grade III AVM cohort comprised 891 individuals with a mean age of 34 years at the time of SRS. The mean nidus volume, radiosurgical margin dose, and follow-up length were 4.5 cm³, 20 Gy, and 89 months, respectively. The actuarial obliteration rates at five and 10 years were 63% and 78%, respectively. The annual post RS hemorrhage rate was 1.2%. Symptomatic and permanent radiation-induced changes were observed in 11% and 4% of the individuals, respectively. Optimal outcome was achieved in 56% of the individuals and was significantly more frequent in cases of unruptured AVMs (OR 2.3, $p < 0.001$). The lack of a previous hemorrhage ($p = 0.037$), absence of previous AVM embolization ($p = 0.002$), smaller nidus volume ($p = 0.014$), absence of AVM-associated arterial aneurysms ($p = 0.023$), and higher margin dose ($p < 0.001$) were statistically significant independent predictors of optimal outcome in a multivariate analysis. The authors found SRS had an acceptable risk-to-benefit profile and noted better outcomes in small, unruptured SM Grade III AVMs than for large or ruptured SM Grade III nidi. Limitations included the biases of a retrospective study and lack of comparison with other AVM interventions. The authors recommended future prospective trials.

Kano et al. (2012) published a series of studies to evaluate the outcomes of individuals with AVMs and treated with SRS. The authors performed GKS on a total of 996 individuals with AVMs and conducted subgroup analyses based on AVM classification, anatomical location, and clinical scenario. Those subgroups included individuals with 1) SM Grade I and II AVMs; 2) repeat RS for AVMs; 3) basal ganglia and thalamus AVMs, 4) brainstem (medulla, pons, and midbrain) AVMs; and 5) multistaged volumetric management of large AVMs. To describe the outcomes and risks of repeat SRS for incompletely obliterated cerebral AVMs, a subgroup of 105 individuals was analyzed. In this subgroup, the median time after initial SRS was 40.9 months (range, 27.5 to 139 months). The median AVM target volume was 6.4 cm³ (range 0.2–26.3 cm³) at initial SRS but was reduced to 2.3 cm³ (range 0.1–18.2 cm³) at the time of the second procedure. The median margin dose at both initial SRS and repeat SRS was 18 Gy. The actuarial rate of total obliteration by angiography or MR imaging after repeat SRS was 35%, 68%, 77%, and 80% at three, four, five, and 10 years, respectively. The median time to complete angiographic or MR imaging obliteration after repeat SRS was 39 months. Factors associated with a higher rate of AVM obliteration were smaller residual AVM target volume ($p = 0.038$) and a volume reduction of 50% or more after the initial procedure ($p = 0.014$). Seven individuals (7%) had a hemorrhage in the interval between initial SRS and repeat SRS. A total of 17 individuals (16%) had hemorrhage after repeat SRS and six individuals died. The cumulative actuarial rates of new AVM hemorrhage after repeat SRS were 1.9%, 8.1%, 10.1%, 10.1%, and 22.4% at one, two, three, five, and 10 years, respectively, which translate to annual hemorrhage rates of 4.05% and 1.79% of individuals developing new post-repeat-SRS hemorrhages per year for years zero to two and two to 10 following repeat SRS. Factors associated with a higher risk of hemorrhage after repeat SRS were a greater number of prior hemorrhages ($p = 0.008$), larger AVM target volume at initial SRS ($p = 0.010$), larger target volume at repeat SRS ($p = 0.002$), initial AVM volume reduction less than 50% ($p = 0.019$), and a higher Pollock-Flickinger score ($p = 0.010$). Symptomatic AREs developed in five individuals (4.8%) after initial SRS and in 10 individuals (9.5%) after repeat SRS. Prior embolization ($p = 0.022$) and a higher SM grade ($p = 0.004$) were significantly associated with higher rates of AREs after repeat SRS. Delayed cyst formation occurred in five individuals (4.8%) at a median of 108 months after repeat SRS (range 47 to 184 months). The authors concluded that repeat SRS for incompletely obliterated AVMs increases the eventual obliteration rate. They also concluded that the best results for individuals with incompletely obliterated AVMs were seen in individuals with a smaller residual nidus volume and no prior hemorrhages.

To describe the long-term outcomes and risks of SRS for AVMs of the basal ganglia and thalamus, a subgroup of 56 individuals with basal ganglia and 77 with thalamus AVMs was analyzed. In this series, 113 (85%) of 133 individuals had a prior hemorrhage. The median target volume was 2.7 cm³ (range, 0.1 to 20.7 cm³) and the median margin dose was 20 Gy (range, 15 to 25 Gy). Obliteration of the AVM eventually was documented on MR imaging in 78 individuals and on angiography in 63 individuals in a median follow-up period of 61 months (range, two to 265 months). The actuarial rates documenting total obliteration after RS were 57%, 70%, 72%, and 72% at three, four, five, and 10 years, respectively. Factors associated with a higher rate of AVM obliteration included AVMs located in the basal ganglia, a smaller target volume, a smaller maximum diameter, and a higher margin dose. Fifteen (11%) of 133 individuals suffered a hemorrhage during the latency period and seven individuals died. The rate of post-SRS AVM hemorrhage was 4.5%, 6.2%, 9.0%, 11.2%, and 15.4% at one, two, three, five, and 10 years, respectively. The overall annual hemorrhage rate was 4.7%. When five individuals with seven hemorrhages occurring earlier than six months after SRS were removed from this analysis, the annual hemorrhage rate decreased to 2.7%. Larger volume AVMs had a higher risk of hemorrhage after SRS. Permanent neurological deficits due to AREs developed in six individuals (4.5%), and in one individual a delayed

cyst developed 56 months after SRS. No individual died of AREs. Factors associated with a higher risk of symptomatic AREs were larger target volume, larger maximum diameter, lower margin dose, and a higher Pollock-Flickinger score. The authors concluded that SRS is a gradually effective and relatively safe management option for deep-seated AVMs in the basal ganglia and thalamus and that individuals remain at risk during the latency interval between SRS and obliteration. In addition, they concluded that the best candidates for SRS are individuals with smaller volume AVMs located in the basal ganglia.

To describe the long-term outcomes and risks of SRS for AVMs of the medulla, pons, and midbrain, a subgroup of 56 individuals was analyzed. In this series, 51 individuals (76%) had a prior hemorrhage. The median target volume was 1.4 cm³ (range, 0.1 to 13.4 cm³). The median margin dose was 20 Gy (range, 14 to 25.6 Gy). Obliteration of the AVMs was documented in 35 individuals at a median follow-up of 73 months (range, six to 269 months). The actuarial rates of documentation of total obliteration were 41%, 70%, 70%, and 76% at three, four, five, and 10 years, respectively. Higher rates of AVM obliteration were associated only with a higher margin dose. Four individuals (6%) suffered a hemorrhage during the latency period, and two individuals died. The rate of AVM hemorrhage after SRS was 3.0%, 3.0%, and 5.8% at one, five, and 10 years, respectively. The overall annual hemorrhage rate was 1.9%. Permanent neurological deficits due to AREs developed in seven individuals (10%) after SRS, and a delayed cyst developed in two individuals (3%). One individual died with symptoms of AREs and unrecognized hydrocephalus. Higher 12-Gy volumes and higher SM grades were associated with a higher risk of symptomatic AREs. Ten of 22 individuals who had ocular dysfunction before SRS had improvement, nine were unchanged, and three were worse due to AREs. Eight of 14 individuals who had hemiparesis before SRS improved, five were unchanged, and one was worse. The authors concluded that although hemorrhage after obliteration did not occur in their series, individuals remained at risk during the latency interval until obliteration occurred, and that 38% of the individuals who had neurological deficits due to prior hemorrhage improved. In addition, they concluded that higher dose delivery in association with conformal and highly selective SRS is required for safe and effective RS.

To describe the long-term outcomes and risks of AVM management using two or more stages of SRS for symptomatic large-volume lesions unsuitable for surgery, a subgroup of 47 individuals was analyzed. In this series, 18 individuals (38%) had a prior hemorrhage, and 21 individuals (45%) underwent prior embolization. The median interval between the first-stage SRS and the second-stage SRS was 4.9 months (range, 2.8 to 13.8 months). The median target volume was 11.5 cm³ (range, 4.0 to 26 cm³) in the first-stage SRS and 9.5 cm³ in the second-stage SRS. The median margin dose was 16 Gy (range, 13 to 18 Gy) for both stages. In 17 individuals, AVM obliteration was confirmed after two to four SRS procedures at a median follow-up of 87 months (range, 0.4 to 209 months). Five individuals had near-total obliteration (volume reduction > 75% but residual AVM). The actuarial rates of total obliteration after two-stage SRS were 7%, 20%, 28%, and 36% at three, four, five, and 10 years, respectively. The five-year total obliteration rate after the initial staged volumetric SRS with a margin dose of 17 Gy or more was 62% ($p = 0.001$). Sixteen individuals underwent additional SRS at a median interval of 61 months (range, 33 to 113 months) after the initial two-stage SRS. The overall rates of total obliteration after staged and repeat SRS were 18%, 45%, and 56% at five, seven, and 10 years, respectively. Ten individuals sustained hemorrhage after staged SRS, and five of these individuals died. Three of 16 individuals who underwent repeat SRS sustained hemorrhage after the procedure and died. Based on Kaplan-Meier analysis (excluding the second hemorrhage in the individual who had two hemorrhages), the cumulative rates of AVM hemorrhage after SRS were 4.3%, 8.6%, 13.5%, and 36.0% at one, two, five, and 10 years, respectively. This corresponded to annual hemorrhage risks of 4.3%, 2.3%, and 5.6% for years zero to one, one to five, and five to 10 after SRS. Multiple hemorrhages before SRS correlated with a significantly higher risk of hemorrhage after SRS. Symptomatic AREs were detected in 13% of individuals, but no individual died as a result of an ARE. Delayed cyst formation did not occur in any individual after SRS. The authors concluded that prospective volume-staged SRS for individuals with large AVMs and unsuitable for surgery has potential benefit but often requires more than two procedures to complete the obliteration process. The authors also concluded that to have a reasonable chance of benefit, the minimum margin dose should be 17 Gy or greater, depending on the AVM location, and that 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.

Clinical Practice Guidelines

International Stereotactic Radiosurgery Society (ISRS)

In a 2020 ISRS systematic review and meta-analysis, Graffeo et al. aimed to establish SRS practice guidelines for grade I-II AVMs. Inclusion criteria included publications reporting post-SRS outcomes in ≥ 10 grade I-II AVMs with a follow-up of ≥ 24 months. Obliteration and hemorrhage were primary endpoints; secondary outcomes were SM parameters, dosimetric variables and “excellent” outcomes which were defined as total obliteration without new post-SRS deficit. Eight studies were chosen for inclusion representing 1102 AVMs, of which 836 (76%) were grade II. Obliteration was achieved in 884 (80%) at a median of 37 mo.; 66 hemorrhages (6%) occurred during a median follow-up of 68 mo. Total obliteration

without hemorrhage was achieved in 78%. Of 836 grade II AVMs, SM parameters were reported in 680: 377 were eloquent brain and 178 had deep venous drainage, totaling 555/680 (82%) high-risk SRS-treated grade II AVMs. The authors concluded that SRS appears to be a safe, effective treatment for grade I-II AVM and may be considered front-line treatment, especially for lesions in deep or eloquent locations. The authors noted limitations as small sample size and high risk of bias.

Meningioma

Habibi et al. (2025) performed a systematic review and meta-analysis to evaluate the use of GKRS in the management of individuals with NF2-associated meningiomas. Four studies (n = 101 individuals) met the inclusion criteria which consisted of individuals with NF2-associated meningiomas with clinical outcomes after SRS, English publications with human subjects, and original research articles. Overall survival rates remained high (100%) up to three years post-treatment, with slight declines at five years of 98% (95% CI: 0.95 - 1.01) and ten years of 68% (95% CI: 0.48 - 0.87). Progression-free survival rates were similarly favorable, with 95% (95% CI: 89 - 101%) at three years, 93% (95% CI: 86 - 99%) at five years, and 81% (95% CI: 51 - 111%) at ten years. The pooled radiation necrosis rate was 5% (95% CI: 3 - 7%), while the overall radiation toxicity rate was 16% (95% CI: 11 - 21%). Local tumor control rates were high at six months, and at 12 months, they were 100% (95% CI: 1.00 - 1.00). The authors concluded that GKRS is a highly effective treatment option with a favorable safety profile. The authors recommended larger future studies focusing on long-term effects. Limitations included the lack of RCTs and small study sizes.

Sheehan et al. (2014) conducted a multi-center case series analysis to evaluate outcomes of individuals with meningiomas and treated with GKRS. At 10 centers, all individuals with sellar and/or parasellar meningiomas treated with GKRS were included in the analysis. Individuals were required to have a minimum of six months of imaging and clinical follow-up after GKRS. Factors predictive of new neurological deficits following GKRS were assessed via univariate and multivariate analyses. Kaplan-Meier analysis and Cox multivariate regression analysis were used to assess factors predictive of tumor progression. A total of 763 individuals were assessed clinically and with neuroimaging at routine intervals following GKRS. There were 567 females (74.3%) and 196 males (25.7%) with a median age of 56 years (range, eight to 90 years). Three hundred fifty-five individuals (50.7%) had undergone at least one resection before GKRS, and 3.8% had undergone prior radiation therapy. The median follow-up after GKRS was 66.7 months (range, six to 216 months). At the last follow-up, tumor volumes remained stable or decreased in 90.2% of individuals. Actuarial PFS rates at three, five, eight, and 10 years were 98%, 95%, 88%, and 82%, respectively. More than one prior surgery, prior radiation therapy, or a tumor margin dose < 13 Gy significantly increased the likelihood of tumor progression after GKRS. At the last clinical follow-up, 86.2% of individuals demonstrated no change or improvement in their neurological condition, whereas 13.8% of individuals experienced symptom progression. New or worsening cranial nerve deficits were seen in 9.6% of individuals, with cranial nerve (CN) V being the most adversely affected nerve. Functional improvements in CNs, especially in CNs V and VI, were observed in 34% of individuals with preexisting deficits. New or worsened endocrinopathies were demonstrated in 1.6% of individuals; hypothyroidism was the most frequent deficiency. An unfavorable outcome with tumor growth and accompanying neurological decline was statistically more likely in individuals with larger tumor volumes (p = 0.022) and more than one prior surgery (p = 0.021). The authors concluded that GKRS provides a high rate of tumor control for individuals with parasellar or sellar meningiomas, and tumor control is accompanied by neurological preservation or improvement in most individuals. (This study is included in the ISRS systematic review and meta-analysis below).

Pollock et al. (2012) conducted a retrospective case series analysis to evaluate individuals who had single-fraction SRS for benign intracranial meningiomas to determine factors associated with tumor control and neurologic complications. A total of 416 individuals (304 women/112 men) who had single-fraction SRS for imaging defined (n = 252) or confirmed WHO grade I (n = 164) meningiomas were included in the analysis. Excluded were individuals with radiation-induced tumors, multiple meningiomas, NF2, and previous or concurrent radiotherapy. The majority of the tumors (n = 337; 81%) involved the cranial base or tentorium. The median tumor volume was 7.3 cm³; the median tumor margin dose was 16 Gy. The median follow-up was 60 months. The disease-specific survival rate was 97% at five years and 94% at 10 years. The five- and 10-year local tumor control rate was 96% and 89%, respectively. Male sex (HR, 2.5, p = 0.03), previous surgery (HR, 6.9, p = 0.002) and individuals with tumors located in the parasagittal/falx/convexity regions (HR, 2.8, p = 0.02) were negative risk factors for local tumor control. In 45 individuals (11%) permanent radiation-related complications developed at a median of nine months after SRS. The one- and five-year radiation-related complication rates were 6% and 11%, respectively. Risk factors for permanent radiation-related complication rate were increasing tumor volume (HR, 1.05, p = 0.008) and individuals with tumors of the parasagittal/falx/convexity regions (HR, 3.0, p = 0.005). The authors concluded that single-fraction SRS at the studied dose range provided a high rate of tumor control for individuals with benign intracranial meningiomas, and individuals with small volume, non-operated cranial base or tentorial meningiomas had the best outcomes after single-fraction SRS. (This study is included in the ISRS systematic review and meta-analysis below).

Santacroce et al. (2012) conducted a multi-center, retrospective, case series analysis to evaluate long-term efficacy and safety of RS for meningiomas. A total of 4,565 consecutive individuals with 5,300 benign meningiomas were included in the analysis. All were treated with GKRS at least five years before assessment for this study. Clinical and imaging data were retrieved from each center and uniformly entered into a database. Median tumor volume was 4.8 cm³, and median dose to tumor margin was 14 Gy. All tumors with imaging follow-up < 24 months were excluded. Detailed results from 3,768 meningiomas (71%) were analyzed. Median imaging follow-up was 63 months. The volume of treated tumors decreased in 2,187 lesions (58%), remained unchanged in 1,300 lesions (34.5%), and increased in 281 lesions (7.5%), giving a control rate of 92.5%. Only 84 (2.2%) enlarging tumors required further treatment. Five- and 10-year PFS rates were 95.2% and 88.6%, respectively. Tumor control was higher for imaging defined tumors versus grade I meningiomas ($p < 0.001$), for female versus male individuals ($p < .001$), for sporadic versus multiple meningiomas ($p < .001$), and for skull base versus convexity tumors ($p < 0.001$). The permanent morbidity rate was 6.6% at the last follow-up. The authors concluded that RS is a safe and effective method for treating benign meningiomas even in the medium- to long-term.

Clinical Practice Guidelines

International Stereotactic Radiosurgery Society (ISRS)

Marchetti et al. (2022) conducted a systematic review and meta-analysis on SBRT and intracranial noncavernous sinus benign meningiomas and developed an evidence-based guideline on behalf of the ISRS. Studies from January 1964 to April 2018 were evaluated, with a total of 27 studies included in the review. All but one were retrospective studies. The primary outcomes examined were rates of local control, PFS, and OS. Prognostic factors and analyses of symptoms-control, radiation-induced toxicity were the secondary objectives. The 10-year local control rate ranged from 71% to 100%. The 10-year PFS rate ranged from 55% to 97%. The prescription dose ranged typically between 12 and 15 Gy, delivered in a single fraction. The toxicity rate was generally low. The authors concluded SRS can be considered a primary treatment in many cases of intracranial noncavernous sinus benign meningiomas based on the strong consensus of class III evidence with favorable outcomes (recommendation level II). The authors recommend future larger, multi-institutional studies with longer observation periods. Limitations included the retrospective nature of the majority of studies in the review. Kondziolka et al. (2008,) previously cited in this policy, was included in this review.

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines state studies show that SRS is associated with excellent tumor control and good survival outcomes in the treatment of meningiomas, especially in grade 1 tumors. For those with grade 2 meningiomas, such as with recurrent disease, SRS may also be considered (NCCN, 2025).

Neurologic Conditions (Epilepsy, Parkinson's Disease, Essential Tremor)

Dong et al. (2025) performed a systematic review and meta-analysis comparing five surgical methods, open and minimally invasive, used for treatment of individuals with drug-resistant epilepsy. Inclusion criteria consisted of those diagnosed with drug-resistant epilepsy, who were treated with anterior temporal lobectomy (ATL), selective amygdalohippocampectomy (SAH), laser interstitial thermal therapy (LITT), radiofrequency thermocoagulation (RFT), or GKRS and had availability of mean, SD, 95% CI, or median IQR for seizure-free. Studies were excluded if the individual was under 18 years of age, had follow-up of less than one year, lacked qualitative data, had fewer than 10 people, or were case reports, technical notes, repetitive literature, unrelated topics, or articles without full text. A total of 62 studies met inclusion criteria for a total of 5958 individuals. The analysis results indicate that ATL and SAH are the best choice for treating drug-resistant mesial temporal lobe epilepsy in adults. During the overall follow-up period, the seizure free rates for ATL, SAH, LITT, RFT, and GKRS were 62%, 70%, 58%, 47%, and 57%, respectively. Only three studies addressed GKRS, therefore a subgroup analysis based on follow-up time was not performed. The authors concluded that among the surgical treatments included in this review, ATL and SAH were the best in both overall and long-term follow-up. However, the authors note that when choosing a specific treatment, specific situations such as type and location of epileptic seizures should be considered, and a treatment plan developed to maximize effectiveness and reduce risks. Limitations included the limited number of RCTs and lack of unified outcome measures across different studies reduced the ability to analyze adverse effect data, QOL, and cognitive function. The authors recommended future high-quality long-term follow-up studies.

Bilski et al. (2024) conducted a systematic review to evaluate four treatment modalities received by individuals with essential tremors that did not achieve a treatment response to medical management. The methods compared were deep brain stimulation (DBS), SRS, radiofrequency thalamotomy (RF), and focused ultrasound thalamotomy (FUS). Inclusion criteria consisted of prospective and retrospective clinical trials with published results in the English language. Twenty-two studies were included in the review. The results confirm the high efficacy and safety of the SRS procedure in treating drug-resistant intention tremors. The study results present a high response rate reaching 80% and achievement of manual task improvement, lessening of the tremor and increase in the QOL of the majority of the operated individuals. After SRS, a considerable number of individuals showed improvements in activities such as tremor, writing, drawing, and drinking.

The authors concluded that SRS is safe and effective for the treatment of ET. Limitations included the small sample sizes of the included studies.

A systematic review and single-arm meta-analysis conducted by Goncalves et al. (2024) aimed to evaluate the efficacy, safety, and long-term impact of SRS, including GKRS, in ET, focusing on tremor control and related adverse effects. Inclusion criteria consisted of randomized and non-randomized studies of four or more participants who had ET and underwent GKRS. Reviews, case reports, letters, comments, and studies not performed only on those with ET were excluded. The main outcomes assessed included the proportion of successful treatments, instances of technical failure, and the frequency of postoperative complications. Treatment was deemed successful if the individual experienced either complete or near-complete resolution of tremors, or demonstrated a positive response or noticeable improvement. As secondary outcomes, the study evaluated the mean difference (MD) scores in specific components of the Fahn-Tolosa-Marin (FTM) clinical rating scale for tremor; specifically, those related to tremor severity, handwriting, drawing, and drinking tasks. Twelve studies with a total of 414 individuals were included in the review. The treatment success rate with SRS was 86.6%. Conversely, the overall failure rate was 13.4%. Post-procedure complications were observed in 9.7% of patients. A meta-analysis of five studies revealed a statistically significant reduction of tremor from the FTM scale after treatment with GKRS (MD -2.1; 95% CI -2.5 to -1.6; $p < 0.01$; $I^2 = 81\%$). A meta-analysis of eight studies revealed a statistically significant reduction in writing tremor from the FTM scale after treatment with GKRS (MD -1.7; 95% CI -2.3 to -1.2; $p < 0.01$; $I^2 = 93\%$). A meta-analysis of six studies revealed a statistically significant reduction in drawing tremor from the FTM scale after treatment with GKRS (MD -1.9; 95% CI -2.5 to -1.4; $p < 0.01$; $I^2 = 80\%$). Finally, a meta-analysis of three studies revealed a statistically significant reduction in drinking tremor from the FTM scale after treatment with GKRS (MD -1.6; 95% CI -1.9 to -1.3; $p < 0.01$; $I^2 = 11\%$). The authors concluded that GKRS for ET had a high overall success rate and low failure rate and was a safe and effective treatment for managing this patient-population. Limitations included the nature of the retrospective studies included in the review, small sample sizes, and lack of tremor data after six and 12 months.

Barbaro et al (2018) conducted a RCT that compared SRS to ATL for the treatment of individuals with pharmacoresistant unilateral MTLE. Adults 18 years or more who were eligible for open surgery had at least three focal-onset seizures in three months with impairment of consciousness occurring during anticonvulsant administration and no neurological or visual deficits were the inclusion criteria. Pregnancy, supratentorial MRI abnormalities, diabetes mellitus, use of vigabatrin, psychiatric diagnoses that could hinder accurate seizure assessment, significant comorbidities, poor compliance, or current drug abuse were the exclusion criteria. The primary outcomes assessed were seizure remission, verbal memory (VM), and QOL at 36-month follow-up. A total of 58 participants (31 in SRS, 27 in ATL) were treated. Sixteen (52%) SRS and 21 (78%) ATL participants achieved seizure remission. Mean VM changes from baseline for 21 English-speaking, dominant-hemisphere participants did not differ between groups; consistent worsening occurred in 36% of SRS and 57% of ATL participants. Quality of life improved with seizure remission. Adverse events were anticipated cerebral edema and related symptoms for some SRS participants, and cerebritis, subdural hematoma, and others for ATL participants. The authors concluded that ATL offered an advantage over SRS in terms of the proportion of individuals who achieved seizure remission. Both SRS and ATL demonstrated effectiveness and safety as treatment options for MTLE. SRS serves as a viable alternative for participants who have contraindications or are reluctant to undergo open surgery. Limitations included small sample sizes.

Eekers et al. (2018) performed a systematic review to determine the efficacy and treatment-related side effects of SRS for individuals with drug-resistant focal epilepsy. Sixteen studies ($n = 170$ individuals) were included in the review. Twelve of the 16 studies described a positive effect of radiotherapy on seizure frequency reduction, with 98 of the patients (on average 58%, range 25% - 95%) reporting no or rare seizures (defined as radiotherapy-adapted Engel class [RAEC] I and II). In total, 20% (34 individuals) of the individuals needed subsequent surgery due to radionecrosis, cysts formation, edema, and intracranial hypertension or remaining seizures. A dose-effect model was fitted to the available response data in an attempt to derive a relationship between prescribed dose and RAEC frequency. The authors concluded that for those with drug-resistant focal non-neoplastic epilepsy, radiotherapy is a possible treatment option with a favorable effect on seizure outcome. Limitations included a low level of evidence with the absence of control groups.

McGonigal et al. (2017) conducted a systematic review to establish an ISRS guideline for the use of SRS in treating individuals with epilepsy. Fifty-five articles were included in the review; no Level 1 evidence was available. The review consisted of two Level 2 prospective trials specific to mesial temporal lobe epilepsy and two prospective trials with criteria relating to epilepsy associated with hypothalamic hamartoma. For remaining indications including corpus callosotomy as palliative treatment, epilepsy related to cavernous malformation and extra-temporal epilepsy, only Level 4 data was available (case report, prospective observational study, or retrospective case series). The authors concluded that SRS was an effective treatment for controlling seizures in mesial temporal lobe epilepsy that may lead to better neuropsychological outcomes and improved QOL for specific individuals compared to traditional microsurgery. Additionally, SRS offers a more favorable risk-benefit ratio for treating small hypothalamic hamartomas than surgical

methods. Limitations included the retrospective nature of the majority of articles included in the review. A formal ISRS guideline was unable to be developed due to lack of non-randomized prospective trials.

Clinical Practice Guidelines

International Stereotactic Radiosurgery Society (ISRS)

Martínez-Moreno et al. (2018) published a systematic review to summarize the current literature and provide consensus guidelines for the ISRS. A total of 34 studies, three prospective, one retrospective comparative and thirty retrospective, were included in the review. The one retrospective comparative study evaluating DBS, RFT, and SRS reported similar tremor control rates, more permanent complications after DBS and RFT, more recurrence after RFT, and a longer latency period to clinical response with SRS. Similar tremor reduction rates in most of the reports were observed with SRS thalamotomy (mean 88%). Clinical complications were rare and usually not permanent (range 0% - 100%, mean 17%, median 2%). Follow-up in general was too short to confirm long-term results. No meta-analysis was performed. The authors concluded that SRS for tremor is well-tolerated and effective for the treatment of medically refractory tremor. Limitations included small sample sizes and the retrospective nature of most of the studies. The recommendations for management of tremor are as follows (all are level IV evidence):

- SRS is recommended for patients with tremor for whom medical therapy has failed & who are not candidates for invasive surgery.
- SRS should be considered even for patients with tremor for whom medical therapy has failed even if they are candidates for invasive surgery since SRS appears to have a lower level of complications.
- GKRS has been performed with a single 4-mm collimator, single-fraction maximum dose of 130 - 150 Gy and the lesion made in the ventral intermediate nucleus located using advanced imaging modalities and stereotactic atlases.

Pineal Gland Tumors

Gagliardi et al. (2023) performed a systematic review to assess the efficacy and safety of individuals who underwent GKRS for pineal region tumors. Fourteen studies were considered eligible for inclusion. A total of 76 individuals reached the final analysis; 56.5% (n = 43) received a histological diagnosis. Confirmed lesions included pineocytoma WHO grade I (60.5%), pineocytoma WHO grade II (14%), pineoblastoma WHO IV (7%), pineal tumor with intermediate differentiation WHO II/III (4.7%), papillary tumor of pineal region WHO II/III (4.7%), germ cell tumor (2.3%), neurocytoma WHO I (2.3%), astrocytoma WHO II (2.3%) and WHO III (2.3%). Presumptive diagnoses were achieved in the remaining 43.5% (n = 33) of cases and comprised of pineocytoma (9%), germ cell tumor (6%), low-grade glioma (6%), high-grade glioma (3%), meningioma (3%) and undefined in 73%. The mean age at the time of GKRS was 38.7 years and the mean lesional volume was 4.2 ±4 cc. All individuals received GKRS with a mean marginal dose of 14.7 ±2.1 Gy (50% isodose). At a median 36-month follow-up, local control was achieved in 80.3% of cases. Thirteen patients showed progression after a median time of 14 months. Overall mortality was 13.2%. The median OS was not reached for all included lesions, except high-grade gliomas (eight months). The three-year OS was 100% for low-grade glioma and pineal tumors with intermediate differentiation, 91% for low-grade pineal lesions, 66% for high-grade pineal lesions, 60% for germ cell tumors, 50% for high-grade glioma, and 82% for undetermined tumors. The three-year progression-free survival (PFS) was 100% for low-grade glioma and pineal intermediate tumors, 86% for low-grade pineal, 66% for high-grade pineal, 33.3% for germ cell tumors, and 0% for high-grade glioma. Median PFS was five months for high-grade glioma and 34 months for germ cell tumors. The radionecrosis rate was 6%, and cystic degeneration was observed in 2%. Ataxia as a presenting symptom strongly predicted mortality [odds ratio (OR) 104, p = .02], while germ cell tumors and high-grade glioma histology well predicted disease progression (OR: 13, p = .04). The authors concluded that for individuals with pineal tumors, primary treatment with GKRS is safe and effective. The authors suggested that future studies are needed to validate results. Limitations included the retrospective design, lack of control group, and small number of lesions included in the study due to the rarity of the disease. Hasegawa et al. (2002), previously cited in this policy, is included in this review.

Iorio-Morin et al. (2017) conducted a multi-center case series analysis of individuals with SRS-treated pineal region tumors to provide reliable histology stratified outcomes. For individuals with at least six months follow-up, baseline data recorded at the time of the first GK procedure were collected including the indication and treatment parameters. Follow-up data were obtained from the medical records. Local control was assessed on the last available MRI before any subsequent treatment of failure and defined as tumor disappearance, tumor regression (volume reduction $m > 10\%$), tumor stability (change in volume, $< 10\%$), or tumor progression (volume increase, $> 10\%$). A total of 70 individuals were treated with a median follow-up of 47 months. Diagnoses were pineocytoma (37%), pineoblastoma (19%), pineal parenchymal tumor of intermediate differentiation (10%), papillary tumor of the pineal region (9%), germinoma (7%), teratoma (3%), embryonal carcinoma (1%), and unknown (14%). Median prescription dose was 15 Gy at the 50% isodose line. Actuarial local control and survival rates were 81% and 76% at 20 years for pineocytoma, 50% and 56% at five years for pineal parenchymal tumor of intermediate differentiation, 27% and 48% at five years for pineoblastoma, 33% and 100% at five years for papillary tumor of the pineal region, 80% and 80% at 20 years for germinoma, and 61% and 67% at

five years for tumors of unknown histology. New focal neurological deficit, Parinaud syndrome, and hydrocephalus occurred in 9%, 7%, and 3% of cases, respectively. The authors concluded that SRS is a safe modality for the management of pineal region tumors. Its specific role is highly dependent on tumor histology and as such, all efforts should be made to obtain a reliable histologic diagnosis.

Kano et al. (2009) conducted a single-center case series analysis of individuals with pineal parenchymal tumors and underwent RS. The analysis included a total of 20 individuals; 13 individuals had pineocytoma, five individuals had pineoblastoma and two individuals had mixed pineal parenchymal tumors. The median RS prescription dose to the tumor margin was 15.0 (range, 12 to 20) Gy. At an average of 54.1 (range, 7.7 to 149.2) months, six individuals died, and 14 individuals were living. The OS after RS was 95.0%, 68.6%, and 51.4% at one, five and 10 years, respectively. Individuals with pineocytomas had one-, three- and five-year OS of 100%, 92.3% and 92.3%, respectively. In 19 individuals who were evaluated with imaging, five (26%) demonstrated complete regression, nine (47%) had partial regression, two (11%) had stable tumors and two (11%) showed local in-field progression. The PFS after SRS for all types of pineal parenchymal tumors was 100%, 89.2% and 89.2% at one, three, five years after RS, respectively. The authors concluded that SRS is an effective and safe alternative to the surgical resection of pineocytomas as well as part of multimodal therapy for more aggressive pineal parenchymal tumors.

Pituitary Adenoma

De Nigris Vasconcellos et al. (2024) conducted a single-arm systematic review and meta-analysis in order to evaluate the safety and efficacy in tumor control for recurrent/residual nonfunctioning pituitary adenomas (NFPAs) following treatment with SRS. Studies published up to February 2024, both retrospective and prospective, were deemed eligible if they assessed the use of SRS for recurrent or residual NFPA and provided data on procedural outcomes and complications. Exclusion criteria included case reports, studies without abstracts or full texts, those not published in English, and studies that grouped NFPAs with other pituitary adenomas without specific patient counts or treatment timeline. Twenty-four studies, for a total of 3,781 individuals were included; all those in the analysis had at least one prior surgical resection prior to SRS. The mean follow-up duration was 60 months. Tumor control was achieved in approximately 92.3% of patients. The risk of developing hypopituitarism post-SRS was 13.62%, while the risk for panhypopituitarism was 2.55%. New visual field deficits occurred in 3.94% of patients. Cranial nerve deficits were rare, with event rates below 1% for CN III, CN V, and CN VI. The authors concluded that SRS demonstrates high efficacy in the management of recurrent or residual NFPAs. However, there is a significant risk of hypopituitarism post-treatment that will need periodic monitoring, as well as possible visual field deficits. Limitations included the retrospective nature of all included studies, and lack of a direct comparison group. Starke et al. (2012), which was previously cited in this policy, was included in this systematic review and meta-analysis

Kotecha et al. (2020) performed a systematic review and meta-analysis on outcomes and toxicities following SRS for individuals (n = 2671) with non-functioning pituitary adenomas (NFAs). Thirty-five retrospective studies of ≥ 10 individuals with NFAs, treated between 1971 and 2017 with either single fraction SRS or hypofractionated stereotactic radiotherapy (HSRT) were included. SRS was used in 27 studies (median dose: 15 Gy, range: five to 35 Gy) and HSRT in eight studies (median total dose: 21 Gy, range: 12 - 25 Gy, delivered in three to five fractions). The five-year random effects local control estimate after SRS was 94% (95% CI: 93.0 - 96.0%) and 97.0% (95% CI: 93.0 - 98.0%) after HSRT. The 10-year local control random effects estimate after SRS was 83.0% (95% CI: 77.0 - 88.0%). Hypopituitarism was the most common treatment-related toxicity observed post-SRS, with a random effect estimate of 21.0% (95% CI: 15.0 - 27.0%), while visual dysfunction or other cranial nerve injuries were uncommon (range: zero - 7%). The authors determined SRS is a safe and effective treatment for individuals with NFAs and single fraction SRS is associated with long-term (10-year) disease control. The authors noted that HRST can be used in select individuals with NFAs with encouraging short-term results reported; however, mature outcomes are needed before definitive recommendations can be made. (Lee et al., 2014b, and Sheehan et al., 2013, which were previously cited in this policy, were included in this systematic review and meta-analysis).

Wan et al. (2009) conducted a single-center case series analysis to evaluate outcomes of individuals with secretory pituitary adenomas and treated with GKRS. A total of 347 individuals with at least 60 months of follow-up data were included in the analysis. In 47 of those individuals, some form of prior treatment such as transsphenoidal resection, or craniotomy and resection had been conducted. The others were deemed ineligible for microsurgery because of body health or private choice, and GKRS served as the primary treatment modality. Endocrinological, ophthalmological, and neuroradiological responses were evaluated. The mean follow-up period was 67.3 months (range, 60 to 90 months). Late radioreaction was noted in one individual and consisted of consistent headaches. Of the 68 individuals with adrenocorticotrophic hormone-secreting (ACTH) adenomas, 89.7% showed tumor volume decrease or remain unchanged and 27.9% experienced normalization of hormone level. Of the 176 individuals with prolactinomas, 23.3% had normalization of hormone level and 90.3% showed tumor volume decrease or remain unchanged. Of the 103 individuals with growth hormone-secreting adenomas, 95.1% experienced tumor volume decrease or remain unchanged and 36.9%

showed normalization of hormone level. The authors concluded that GKRS is safe and effective in treating secretory pituitary adenomas and may serve as a primary treatment method in some or as a salvage treatment in others; however, treatment must be tailored to meet the individual's symptoms, tumor location, tumor morphometry, and overall health. The authors also recommended that longer follow-up is required for a more complete assessment of late radioreaction and treatment efficacy.

Recurrent Gliomas

De Maria et al. (2021) performed a systematic review and meta-analysis to establish safety and efficacy of CyberKnife treatment for recurrent WHO grade III and IV, malignant gliomas of the brain. Thirteen studies (n = 398) from 2000 to 2021 were included. The primary outcomes were median OS, median PFS and median time to progression. Complications, local response, and recurrence were secondary outcomes. Overall survival from initial diagnosis and CyberKnife treatment was 22.6 months and 8.6 months. Median time to progression and median PFS were 6.7 months and 7.1 months. Median OS from CyberKnife treatment was 8.4 months for WHO grade IV gliomas, compared to 11 months for WHO grade III gliomas. Median OS from CyberKnife treatment was 4.4 months for individuals who underwent CyberKnife treatment alone, compared to 9.5 months for individuals who underwent CyberKnife treatment plus chemotherapy. No correlation was observed between median time to recurrence and median OS from CyberKnife. Rates of acute neurological and acute non-neurological side effects were 3.6% and 13%. Rates of corticosteroid dependency and radiation necrosis were 18.8% and 4.3%. The authors determined that using the CyberKnife system for reirradiation of recurrent malignant gliomas provided encouraging survival rates. For individuals with WHO grade III gliomas and individuals who undergo combined treatment with CyberKnife plus chemotherapy, there is a better survival trend. Complication rates were low. The authors recommended further research with larger prospective studies.

Gigliotti et al. (2018) conducted a case series analysis to evaluate the efficacy of SRS and FSRT as salvage therapy for recurrent high-grade glioma, and to examine the overall efficacy of treatment with LINAC-based RS and fractionated radiotherapy. A total of 25 individuals aged 23 to 74 years were reirradiated with LINAC-based SRS and FSRT. Individuals were treated to a median dose of 25 Gy in five fractions. The median OS after (initial) diagnosis was 39 months with actuarial one-, three- and five-year OS rates of 88%, 56%, and 30%, respectively. After treatment with SRS or FSRT, the median OS was nine months with an actuarial one-year OS rate of 29%. Local control, assessed for 28 tumors, after six months was 57%, while local control after one year was 39%. Three individuals experienced LF. There was no evidence of toxicity noted after SRS or FSRT throughout the follow-up period. The authors concluded that SRS and FSRT remain a safe, reasonable, effective treatment option for re-irradiation following recurrent glioblastoma, and treatment volume may predict local control in the salvage setting.

Sharma et al. (2018) conducted a single-center, retrospective, case series analysis to evaluate the role of SRS in individuals with recurrent glioblastoma (rGBMs). Individuals' electronic medical records were retrospectively reviewed to obtain demographic, imaging, and clinical data. OS and PFS from the date of salvage SRS were the primary and secondary endpoints, respectively. A total of 53 individuals with rGBM underwent salvage SRS targeting 75 lesions. The median tumor diameter and volume were 2.55 cm³ and 3.80 cm³, respectively. The median prescription dose was 18 Gy (range, 12 to 24 Gy) and the homogeneity index was 1.90 (range, 1.11 to 2.02). The median OS after salvage SRS was estimated to be 11.0 months (95% CI 7.1 to 12.2) and the median PFS after salvage SRS was 4.4 months (95% CI 3.7 to 5.0). A KPS score \geq 80 was independently associated with longer OS, while small tumor volume (< 15 cm³) and less homogeneous treatment plans (homogeneity index > 1.75) were both independently associated with longer OS (p = 0.007 and 0.03) and PFS (p = 0.01 and 0.002, respectively). Based on these factors, two prognostic groups were identified for PFS (5.4 versus 3.2 months), while three were identified for OS (median OS of 15.2 versus 10.5 versus 5.2 months). The authors concluded that good performance, smaller tumor volumes, and treatment at higher homogeneity indices were associated with longer OS and/or PFS despite multiple prior treatments for rGBM, and that for individuals with rGBM and those clinical characteristics, SRS is a reasonable salvage treatment option.

Imber et al. (2017) conducted a single-center, retrospective, case series analysis to identify proper indications, efficacy, and anticipated complications of SRS for rGBM. Individuals with pathologically confirmed glioblastoma/gliosarcoma who received comprehensive or radiosurgical care at the center were included in the analysis. The partitioning deletion/substitution/addition algorithm to identify potential predictor covariate cut points and Kaplan-Meier and proportional hazards modeling to identify factors associated with post-SRS and postdiagnosis survival. A total of 174 individuals with glioblastoma (median age, 54.1 years) underwent SRS a median of 8.7 months after initial diagnosis. Seventy-five percent had one treatment target (range, one to six), and median target volume and prescriptions were seven cm³ (range, 0.3 to 39.0 cm³) and 16.0 Gy (range, 10 to 22 Gy), respectively. Median OS was 10.6 months after SRS and 19.1 months after diagnosis. Kaplan-Meier and multivariable modeling revealed that younger age at SRS, higher prescription dose, and longer interval between original surgery and SRS are significantly associated with improved post-SRS survival. Forty-six individuals (26%) underwent salvage craniotomy after SRS, with 63% showing radionecrosis or mixed tumor/necrosis versus 35% showing purely recurrent tumor. The necrosis/mixed group had lower mean isodose

prescription compared with the tumor group (16.2 versus 17.8 Gy; $p = 0.003$) and larger mean treatment volume (10.0 versus 5.4 cm³; $p = 0.009$). The authors concluded that GKRS may benefit a subset of focally recurrent individuals, particularly those who are younger with smaller recurrences. The authors also stated that higher prescriptions are associated with improved post-SRS survival and do not seem to have greater risk of symptomatic treatment effect.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines state that recurrence of glioma can be managed with reirradiation and should be performed with highly focused techniques such as SRS for lower volume disease (NCCN, 2025).

Spinal Lesions (Primary and Metastatic)

The aim of the multicenter, randomized, phase III trial by Guckenberger et al. (2024) was to evaluate whether SBRT for painful vertebral metastases leads to higher rates of pain improvement compared to cEBRT (control) six months post-treatment. Inclusion criteria consisted of those 18 years or older with a diagnosis of a solid tumor, maximum of two painful vertebral metastases, KPS of $\geq 60\%$, and life expectancy of greater than one year. Exclusion criteria included those with spinal instability, involvement of more than three cervical spine or four thoracic, lumbar, or sacral spine contiguous vertebra, more than two treatment sites, neurologic symptoms, previous RT at the site, or surgery of affected vertebra. Patient-reported pain improvement was the primary end point. Acute and late adverse events, OS, and QOL were secondary end points. Sixty-three participants were randomized to receive SBRT ($n = 33$ with 36 metastases) or cEBRT (30 participants with 31 metastases). In the intention-to-treat analysis, the six-month proportion of participants who had metastases with pain reduction by two or more points was significantly higher in the SBRT group versus the control group (69.4% versus 41.9%, respectively; two-sided $p = .02$). Changes in opioid medication intake relative to baseline were nonsignificant between the groups. No differences were observed in vertebral compression fracture or adverse event rates between the groups. The authors concluded that the dose-intensified SBRT was more effective at improving the pain score than cEBRT at six months without increasing toxicity. Limitations included the small sample size and low compliance of the number of participants in reporting QOL.

Guninski et al. (2024) conducted a systematic review and meta-analysis in preparation for an ESTRO guideline for the treatment of spinal metastases with SBRT. Sixty-nine studies, 7236 metastases in 5736 individuals, were included in the review. SBRT for spine metastases showed high efficacy, with a pooled overall pain response rate of 83 % (95 % CI 68 % - 94 %), pooled complete pain response of 36 % (95 % CI: 20 % - 53 %), and one-year local control rate of 94 % (95 % CI: 86 % - 99 %), although with high levels of heterogeneity among studies ($I^2 = 93\%$, $I^2 = 86\%$, and 86 %, respectively). Furthermore, SBRT was safe, with a pooled vertebral fracture rate of 9 % (95 % CI: 4 % - 16 %), pooled radiation induced myelopathy rate of 0 % (95 % CI 0 - 2 %), and pooled pain flare rate of 6 % (95 % CI: 3 % - 17 %), although with mixed levels of heterogeneity among the studies ($I^2 = 92\%$, $I^2 = 0\%$, and 95 %, respectively). Only 1.7 % of vertebral fractures required surgical stabilization. The authors concluded SBRT for the spine is characterized by its effective and safe treatment outcomes, offering long-lasting relief from pain and control over disease progression which is especially beneficial for patients with oligometastatic conditions. Ryu et al. 2023, and Sprave et al. 2018, are included in this review.

In a phase III RCT, Ryu et al. (2023) investigated whether SRS enhanced patient-reported pain relief compared to cEBRT for individuals with one to three vertebral metastases. (According to the authors, the results from the phase II study, Ryu et al. 2014, demonstrated that SRS was both feasible and safe for treating vertebral metastases within a multi-institutional cooperative group setting.) A total of 339 participants, 114 in the SRS group and 70 in the cEBRT group, were included in this study. Those eligible for inclusion were at least 18 years old, with a Zubrod score of zero to two, and had one to three treatment-naïve vertebral metastases. Tumors with vertebral compression fractures with more than 50% height loss and/or bony retropulsion were excluded. Patient-reported pain response defined as a three-point or more improvement on the Numerical Rating Pain Scale (NRPS) without the use of pain medication or worsening pain at the secondary site was the primary endpoint. Treatment-related toxic effects, QOL, and long-term effects on vertebral bone and spinal cord were the secondary endpoints. The baseline mean (SD) pain score at the index vertebra was 6.06 (2.61) in the SRS group and 5.88 (2.41) in the cEBRT group. The primary end point of pain response at three months favored cEBRT (41.3% for SRS versus 60.5% for cEBRT; difference, -19 percentage points; 95% CI, -32.9 to -5.5; one-sided $p = .99$; two-sided $p = .01$). Zubrod score was the significant factor influencing pain response. There were no differences in the proportion of acute or late adverse effects. Vertebral compression fracture at 24 months was 19.5% with SRS and 21.6% with cEBRT ($p = .59$). No spinal cord complications were reported at 24 months. The authors concluded that the study did not demonstrate the superiority of SRS in terms of patient-reported pain response at three months. No clinical or radiographic spinal cord toxic effects were observed two years after SRS, which the authors highlight as a valuable prospective report on long-term spinal cord tolerance following SRS. Additionally, these findings prospectively show that one-year and two-year survival rates of individuals with spine metastases treated with SRS are promising, emphasizing the importance of continuing to

identify the optimal SRS radiation dose and fractionation for those with vertebral metastases. The authors suggested that further research is warranted to explore the use of SRS for oligometastases, where long-term cancer control is crucial. Limitations included lack of blinding and low patient compliance regarding pain reporting.

Conti et al. (2022) performed a systematic review and meta-analysis of RS for individuals with benign spinal hemangiomas. Peer-reviewed studies or case series of individuals with spinal vertebral hemangiomas treated with RS or SBRT were included. Twenty-three individuals with 24 spinal vertebral hemangiomas assessed in three studies. The follow-up time was 7.3 - 84 months. The vast majority of lesions were located at dorsal level ($n = 18$; 75%). In 20 (83.3%) patients, pain was the initial clinical presentation. Complete, partial, and stable responses after radiation were reported in 45.7% ($p < 0.001$), 23.6% ($p = 0.02$), and 37.2% ($p = 0.7$) of cases. The overall response was reported in 94.1% ($p = 0.7$). No progressive disease was reported. Pain relief was achieved in 87.5% of patients ($p = 0.2$). Damage to surrounding tissue caused by irradiation was reported in 22.3% ($p = 0.02$) cases in one study, in which higher doses of radiation were delivered. According to the authors, RS was safe and effective for spinal hemangiomas. Limitations included the small sample size.

In an open-label, multicenter, randomized controlled phase 2/3 trial conducted by Sahgal et al. (2021), the efficacy of SBRT versus conventional external beam radiotherapy (cEBRT) in individuals with painful spinal metastasis was compared. Participants ($n = 229$) were randomized to receive either SBRT (24 Gy in two daily fractions) or cEBRT (20 Gy in five daily fractions). The primary outcome was complete response rate for pain at the treated site three months after radiotherapy. Inclusion criteria included individuals aged 18 and older with MRI-confirmed painful spinal metastasis (pain score ≥ 2 on the Brief Pain Inventory), involving no more than three consecutive vertebral segments, an ECOG performance status of zero to two, and a Spinal Instability Neoplasia Score of less than 12. Those with neurologically symptomatic spinal cord or cauda equina compression were excluded. At three months, 40 (35%) of 114 participants in the SBRT group, and 16 (14%) of 115 participants in the cEBRT group had a complete response for pain ($p = 0.0002$). This significant difference was maintained in multivariable-adjusted analyses ($p = 0.0003$). The most common grade 3–4 adverse event was grade 3 pain [five (4%) of 115 participants in the cEBRT group versus five (5%) of 110 participants in the SBRT group]. No treatment-related deaths were observed. The authors concluded that SBRT at a dose of 24 Gy in two fractions is superior to cEBRT at a dose of 20 Gy in five fractions in improving complete pain relief in those with painful spinal metastases and may be a more effective palliative treatment option. Limitations include that the open-label design could introduce bias, small sample size, and short follow-up duration.

The single institution, non-blinded, randomized phase II trial by Sprave et al. (2018) compared the effectiveness of palliative SBRT and 3D-CRT for managing pain for individuals with previously untreated spinal bone metastasis. The primary objective was to evaluate pain relief in participants ($n = 55$) with histologically or radiologically confirmed painful spinal metastases following treatment with either SBRT or 3DCRT. Pain relief was measured using the visual analog scale (VAS) at three- and six-months post-treatment. Participants were randomly assigned to receive either single-fraction SBRT (24 Gy) or 3D-CRT (30 Gy in 10 fractions). At three months both groups showed pain reduction, but the SBRT group experienced a faster decrease in pain scores ($p = 0.01$). However, there was no significant difference in VAS scores between the groups at three months ($p = 0.13$). At six months, the SBRT group reported significantly lower pain scores compared to the 3D-CRT group ($p = 0.002$). Pain response at three months showed a trend towards better pain response in the SBRT group ($p = 0.057$). At six months, the pain response in the SBRT group was significantly better ($p = 0.003$). There were no significant differences in opioid usage observed between the groups at three months ($p = 0.761$) and six months ($p = 0.174$). No participants in the SBRT group had severe (grade ≥ 3) toxicities. The authors concluded that SBRT provided faster, and more lasting pain relief compared to 3D-CRT for individuals with spinal metastases and may be a more effective option for managing pain in these individuals. Limitations include small study size, trial was non-blinded and conducted at a single institution, and short follow-up period.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

ASTRO's guideline on palliative RT for symptomatic bone metastases (Alcorn et al., 2024) provides recommendations using consensus-building methodology based on a systematic review by AHRQ (Skelly et al., 2023). The authors note that developing the most favorable RT regimen requires an assessment including prognosis, any previous RT doses, normal tissue risks, QOL, and patient values and goals. Per the guidelines:

- For patients with symptomatic spine bone metastases, including those causing compression of the spinal cord or cauda equina, RT is recommended to improve ambulatory status, sphincter function, and reduce pain. Implementation remark: Before initiating RT, evaluation for spine stability and surgery are necessary. Strength of recommendation: strong; quality of evidence: high.
- In patients with spine bone metastases causing compression of the spinal cord or cauda equina who are not eligible for initial surgical decompression and are treated with conventional palliative RT, 800 cGy in one fraction, 1600 cGy in

two fractions, 2000 cGy in five fractions, or 3000 cGy in 10 fractions are recommended. Strength of recommendation: strong; quality of evidence: high.

- For patients with symptomatic bone metastases treated with SBRT, 1200 to 1600 cGy in one fraction (nonspine) and 2400 cGy in two fractions (spine) are recommended. Implementation remark: Other established SBRT dose and fractionation regimens (e.g., three to five fractions) with similar BEDs may be an option based on patient tumor and normal tissue factors, and physician experience. Strength of recommendation: strong; quality of evidence: moderate.
- For patients with symptomatic bone metastases with ECOG PS zero to two, receiving no surgical intervention, and absent neurological symptoms, SBRT is conditionally recommended over conventional palliative RT. Implementation remark: Other factors to consider include life expectancy, tumor radiosensitivity, and metastatic disease burden. Strength of recommendation: conditional; quality of evidence: moderate.
- For patients with spine bone metastases that would benefit from reirradiation to the same site, treatment with SBRT is conditionally recommended. Strength of recommendation: conditional; quality of evidence: expert opinion.

National Comprehensive Cancer Network (NCCN)

Per NCCN guidelines regarding RT for metastatic spinal tumors, stereotactic approaches such as SRS and SBRT may be preferred for those where ablation of the tumor is a goal of treatment, life expectancy is three months or more, the tumors are radioresistant (e.g., renal cell, melanoma, sarcoma, hepatocellular, some colorectal, and NSCLC cases), and in certain individuals for optimal pain relief. In certain cases, SRS/SBRT may be suitable for treating primary spinal cord tumors such as hemangioblastoma, with care to respect normal tissue constraints of the spinal cord and surrounding structures. (NCCN, 2025).

National Institute for Health and Care Excellence (NICE)

NICE developed a guideline for spinal metastases that states to consider SBRT for those who have painful spinal metastases and no metastatic spinal cord compression with a good overall prognosis or oligometastases (up to three discrete metastases) with spinal involvement (NICE, 2023).

Trigeminal Neuralgia Refractory to Medical Therapy

Hajikarimloo et al. (2025) performed a systematic review and meta-analysis aimed to assess the safety and efficacy of SRS in individuals with tumor-related trigeminal neuralgia (TRTN). Inclusion criteria consisted of studies where outcomes and adverse events of SRS in TRTN were reported, publications that reported complete pain-free, adequate pain relief, and AREs, and clinical trials, cohort studies, case reports, or retrospective studies with at least five patients. Nineteen studies met inclusion criteria for a total of 454 individuals. Meningioma (67.7%, 304/449) was the most common tumor, followed by VS (18.3%, 82/449) and trigeminal schwannoma (8.2%, 37/449). The meta-analysis demonstrated that SRS is associated with a pooled complete pain-free rate of 38% (95% CI: 27 - 50%), an adequate pain relief rate of 73% (95% CI: 63-83%), and an AREs rate of 14% (95% CI: 7 - 22%). In those where the underlying etiology was petroclival meningiomas, SRS resulted in a pooled complete pain-free rate of 30% (95%CI: 5 - 64%), an adequate complete pain relief rate of 64% (95% CI: 33 - 90%), and an AREs rate of 13% (95% CI: 0 - 48%). The authors concluded that for individuals with TRTN, SRS provides beneficial pain-related outcomes with low AREs and both tumor-only and dual-targeted approaches produce comparable results. Limitations included the retrospective nature of most studies and the differences in follow-up durations.

Peciu-Florianu et al. (2021) conducted a systematic review and meta-analysis that focused on trigeminal neuralgia treated with SRS for meningiomas and VS which investigated rates of improvement of trigeminal neuralgia symptoms. Articles published between January 1990 and December 2019 (n = 330) were screened and assessed for eligibility. Ultimately, 20 studies were included in the qualitative synthesis and 13 were included in the quantitative synthesis. Pain relief after SRS was reported as Barrow Neurological Institute (BNI) pain intensity scores of BNI I in 50.5% (range 36 - 65.1%) of individuals and BNI I–IIIb in 83.8% (range 77.8 - 89.8%). There was no significant difference in series discussing outcomes for tumor targeting versus tumor and nerve targeting. Recurrences were described in 34.7% (range 21.7 - 47.6; tumor targeting). Maintenance of BNI I was reported in 36.4% (range 20.1 - 52.7) and BNI I–IIIb in 41.2% (range 29.8 - 52.7; tumor targeting series). When both the nerve and the tumor were targeted, only one series reported 86.7% with BNI I–IIIb at last follow-up. Complications were encountered in 12.6% (range 6.3 - 18.8; tumor targeting series) of individuals; however, they were much higher, as high as 26.7%, in the only study reporting them after targeting both the nerve and the tumor. Facial numbness was the most common complication. The authors concluded that SRS for trigeminal neuralgia secondary to benign tumors is associated with a favorable clinical course, but less favorable than idiopathic trigeminal neuralgia. Among reports and targeted approaches, there was heterogeneity. Targeting both the tumor and the nerve seemed to achieve better long-term results, however, the rate of complications was much higher, and the number of individuals treated was limited. The authors recommended future clinical studies that focus on standard reporting of clinical outcomes and randomization of targeting methods.

Tuleasca et al. (2018) conducted a systematic review to provide an objective summary of the published literature specific to the treatment of classical trigeminal neuralgia with RS and to develop consensus guideline recommendations for the use of RS, as endorsed by the ISRS. A search was conducted using Embase, PubMed, and Medline databases for articles published between 1951 to 2015 and identified a total of 585 studies. A total of 65 studies were included in the review and those included 45 GKS studies (5687 individuals), 11 LINAC RS studies (511 individuals), and nine CyberKnife RS studies (263 individuals). All but one of the studies were retrospective. The mean maximal doses were 71.1 to 90.1 Gy (prescribed at the 100% isodose line) for GKS, 83.3 Gy for LINAC, and 64.3 to 80.5 Gy for CyberKnife RS (the latter two prescribed at the 80% or 90% isodose lines, respectively). The ranges of maximal doses were as follows: 60 to 97 Gy for GKS, 50 to 90 Gy for LINAC, and 66 to 90 Gy for CyberKnife RS. Actuarial initial freedom from pain without medication ranged from 28.6% to 100% (mean 53.1%, median 52.1%) for GKS, from 17.3% to 76% (mean 49.3%, median 43.2%) for LINAC, and from 40% to 72% (mean 56.3%, median 58%) for CyberKnife RS. Specific to hypesthesia, the crude rates (all Barrow Neurological Institute Pain Intensity Scale scores included) ranged from 0% to 68.8% (mean 21.7%, median 19%) for GKS, from 11.4% to 49.7% (mean 27.6%, median 28.5%) for LINAC, and from 11.8% to 51.2% (mean 29.1%, median 18.7%) for CyberKnife RS. Other complications included dysesthesias, paresthesias, dry eye, deafferentation pain, and keratitis. Hypesthesia and paresthesia occurred as complications only when the anterior retrogasserian portion of the trigeminal nerve was targeted, whereas the other listed complications occurred when the root entry zone was targeted. Recurrence rates ranged from 0% to 52.2% (mean 24.6%, median 23%) for GKS, from 19% to 63% (mean 32.2%, median 29%) for LINAC, and from 15.8% to 33% (mean 25.8%, median 27.2%) for CyberKnife RS. Two GKS series reported 30% and 45.3% of individuals who were pain free without medication at 10 years. The authors concluded that although the literature is limited in its level of evidence, at present, one can conclude that RS is a safe and effective therapy for drug-resistant trigeminal neuralgia and based on this information consensus statements have been made.

Clinical Practice Guidelines

National Institute for Health and Care Excellence (NICE)

A NICE guideline (2022) on SRS and trigeminal neuralgia states that safety and efficacy is adequate to support using this procedure provided that standard arrangements are in place for clinical governance, consent, and audit. A multidisciplinary team experienced in the management of trigeminal neuralgia should be utilized for patient selection, and the procedure should only be performed in specialized centers.

Uveal Melanoma

Du and Luo (2025) conducted a systematic review to evaluate the effectiveness of CyberKnife radiotherapy for local tumor control, complications, selectivity, secondary enucleations, and OS in individuals with uveal melanoma. Inclusion criteria consisted of single-arm studies, RCT, case or cohort studies of adults with uveal melanoma treated with CyberKnife radiotherapy, and at least one perioperative measure. Ten studies met the inclusion criteria for a total of 2370 individuals (2372 uveal melanomas). Meta-analysis showed 811 of 912 patients (0.89, 95% CI: 0.86, 0.92) maintained local control for three years, and 1448 of 1724 individuals (0.84, 95% CI: 0.81, 0.88) preserved the eye in three years. During follow-up, 91% (0.91, 95% CI: 0.85, 0.97) individuals survived and 351 of 1720 individuals (0.23, 95% CI: 0.09, 0.37) involving 1722 eyes had tumor recurrence. In addition, 1376 individuals (0.79, 95% CI: 0.77, 0.82) preserved the eyeball in five years. Following treatment, approximately 20% of individuals had radiation retinopathy (95% CI: 0.13, 0.28), 19% developed glaucoma (95% CI: 0.11, 0.28), and 22% experienced retinal detachment (95% CI: 0.07, 0.36). The authors concluded that CyberKnife radiotherapy was an effective, noninvasive method for enhancing tumor control and preserving the eye in medium and large UMs. Limitations included the retrospective nature of the studies and most of the studies were single arm with no parallel comparisons.

In a systematic review and meta-analysis, Parker et al. (2020) evaluated the clinical outcomes of individuals with uveal melanomas or intraocular metastases treated with GKS. The primary outcomes analyzed were local tumor control and tumor regression. Fifty-two studies were eligible for systematic review, 1010 individuals had uveal melanoma and three with intraocular metastasis. The authors found that 840 of 898 individuals (0.96, 95% CI 0.94 - 0.97; $I^2 = 16\%$) from 19 studies had local control, and 378 of 478 individuals (0.81, 0.70 - 0.90; $I^2 = 83\%$) from 16 studies experienced tumor regression. The authors concluded GKRS is an effective primary method of treating uveal melanomas and intraocular metastases, with reliable tumor control rates and a similar efficacy and survival profile to outcomes for plaque brachytherapy and charged particle therapy. The authors recommended future research focusing on generating level one evidence RCTs of the efficacy of GKRS in treating ocular tumors, measuring overall complication rates of GKRS, providing consistent reporting of visual acuity measurements after GKRS, and evaluating low-dose regimens to reduce radiation-induced side-effects and subsequent vision loss. (Fakiris et al., 2007) previously cited in this policy is included in this review).

Yazici et al. (2017) conducted a multi-center, retrospective, case series analysis to evaluate treatment outcomes of individuals with uveal melanoma and treated with SRS or FSRT. Treatment was administered with CyberKnife. Primary endpoints were local recurrence-free survival (LRFS) and enucleation-free survival. Secondary endpoints included OS, DFS, distant metastasis-free survival (DMFS), visual acuity, and late treatment toxicity. Local control was defined as the lack of tumor progression (i.e., an increase in tumor volume). Complete response was defined as the disappearance of the tumor, and partial response as a > 50% decrease in the tumor volume. A total of 181 individuals (182 uveal melanomas) who underwent SRS/FSRT were included in the analysis. The median age was 54 years (range, 18 to 82 years) and 104 (58%) were male. The median tumor diameter and thickness was 10 mm (range, two to 12 mm) and 8.0 mm (range, 1.5 to 18 mm), respectively. According to Collaborative Ocular Melanoma Study criteria, tumor size was small in 1%, medium in 49.5%, and large in 49.5% of the individuals. Seventy-one tumors received < 45 Gy, and 111 received ≥ 45 Gy. Median follow-up time was 24 months (range, two to 79 months). Complete and partial response was observed in eight and 104 eyes, respectively. The rate of five-year OS was 98%, DFS 57%, LRFS 73%, DMFS 69%, and enucleation-free survival 73%. There was a significant correlation between tumor size and DFS, SRS/FSRT dose and enucleation-free survival; and both were prognostic for LRFS. Enucleation was performed in 41 eyes owing to progression in 26 and complications in 11. The authors concluded that using SRS/FSRT, better control of large tumors was achieved with ≥ 45 Gy in three fractions. They also recommended increasing the radiation dose, as well as limiting the maximum eye and lens dose to 50 Gy and 15 Gy, respectively, to increase the eye retention rate, and that additional studies with longer follow-up should be conducted.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for uveal melanoma states SRS is the least often used form of definitive radiotherapy of primary or recurrent intraocular tumors. SRS planning, fiducial marker use, and tumor localization are generally consistent with particle beam therapy approaches (NCCN, 2025).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

The FDA has approved a number of devices for use in SBRT and SRS. Refer to the following website for more information (use product codes MUJ and IYE): <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>. (Accessed May 21, 2025)

References

- Alcorn S, Cortés AA, Bradfield L, et al. External beam radiation therapy for palliation of symptomatic bone metastases: an ASTRO clinical practice guideline. *Pract Radiat Oncol*. 2024 May 22:S1879-8500(24)00099-7.
- American College of Radiology (ACR) website. Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT). Reviewed May 1, 2023. Available at: <https://www.radiologyinfo.org/en/info/stereotactic>. Accessed August 12, 2025.
- American Society for Radiation Oncology (ASTRO) website. ASTRO Radiation Oncology Coding Resource 2024. Available at <https://www.astro.org/Daily-Practice/Coding/Coding-Resource>. August 12, 2025.
- American Society for Radiation Oncology (ASTRO) website. ASTRO stereotactic body radiation (SBRT) model policy. June 2020. Available at <https://www.astro.org/ASTRO/media/ASTRO/Daily%20Practice/PDFs/ASTROSBRTModelPolicy.pdf>. Accessed August 12, 2025.
- American Society for Radiation Oncology (ASTRO) website. ASTRO stereotactic radiosurgery (SRS) model policy. June 2020. Available at https://www.astro.org/ASTRO/media/ASTRO/Daily%20Practice/PDFs/ASTRO-SRS_ModelPolicy.pdf. Accessed August 12, 2025.
- Amini A, Verma V, Simone CB 2nd, et al. American Radium Society Appropriate Use Criteria for radiation therapy in oligometastatic or oligoprogressive non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2022;112(2):361-375.
- Apisarnthanarax S, Barry A, Cao M, et al. External beam radiation therapy for primary liver cancers: an ASTRO clinical practice guideline. *Pract Radiat Oncol*. 2022 Jan-Feb;12(1):28-51.
- Bae SH, Chun SJ, Chung JH, et al. Stereotactic body radiation therapy for hepatocellular carcinoma: meta-analysis and International Stereotactic Radiosurgery Society practice guidelines. *Int J Radiat Oncol Biol Phys*. 2024 Feb 1;118(2):337-351.

Ball D, Mai GT, Vinod S, et al; TROG 09.02 CHISEL investigators. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. *Lancet Oncol*. 2019 Apr;20(4):494-503.

Balossier A, Tuleasca C, Delsanti C, et al. Long-term hearing outcome after radiosurgery for vestibular schwannoma: a systematic review and meta-analysis. *Neurosurgery*. 2023 Jun 1;92(6):1130-1141.

Barbaro NM, Quigg M, Ward MM, et al. Radiosurgery versus open surgery for mesial temporal lobe epilepsy: the randomized, controlled ROSE trial. *Epilepsia*. 2018 Jun;59(6):1198-1207.

Bilski M, Szklener K, Szklener S, et al. Stereotactic radiosurgery in the treatment of essential tremor - a systematic review. *Front Neurol*. 2024 Apr 3;15:1370091.

Bisello S, Camilletti AC, Bertini F, et al. Stereotactic radiotherapy in intrahepatic cholangiocarcinoma: a systematic review. *Mol Clin Oncol*. 2021 Aug;15(2):152.

Boari N, Bailo M, Gagliardi F, et al. Gamma Knife radiosurgery for vestibular schwannoma: clinical results at long-term follow-up in a series of 379 patients. *J Neurosurg*. 2014;121 Suppl:123-142.

Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial [published correction appears in *JAMA*. 2018 Aug 7;320(5):510]. *JAMA*. 2016;316(4):401-409.

Bucknell NW, Kron T, Herschtal A, et al; CHISEL coauthors. Comparison of changes in pulmonary function after stereotactic body radiation therapy versus conventional 3-dimensional conformal radiation therapy for stage I and IIa non-small cell lung cancer: an analysis of the TROG 09.02 (CHISEL) phase 3 trial. *Int J Radiat Oncol Biol Phys*. 2023 Oct 1;117(2):378-386.

Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomized trials [published correction appears in *Lancet Oncol*. 2015 Sep;16(9):e427]. *Lancet Oncol*. 2015;16(6):630-637.

Chao ST, Dad LK, Dawson LA, et al. ACR-ASTRO practice parameter for the performance of stereotactic body radiation therapy. *Am J Clin Oncol*. 2020 Aug;43(8):545-552.

Chuong MD, Springett GM, Freilich JM, et al. Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. *Int J Radiat Oncol Biol Phys*. 2013; 86: 516–522.

Conti A, Starnoni D, Barges-Coll J, et al. Radiosurgery for benign vertebral body hemangiomas of the spine: a systematic review and meta-analysis. *World Neurosurg*. 2022 Aug;164:97-105.

De Maria L, Terzi di Bergamo L, Conti A, et al. CyberKnife for recurrent malignant gliomas: a systematic review and meta-analysis. *Front Oncol*. 2021 Mar 29;11:652646.

De Nigris Vasconcellos F, Vilela MAD, Garcia Torrico F, et al. Stereotactic radiosurgery for recurrent/residual nonfunctioning pituitary adenoma: a single-arm systematic review and meta-analysis. *Acta Neurochir (Wien)*. 2024 Oct 2;166(1):392.

Ding D, Starke RM, Kano H, et al. Stereotactic radiosurgery for Spetzler-Martin grade III arteriovenous malformations: an international multicenter study. *J Neurosurg*. 2017 Mar;126(3):859-871.

Dong H, Shi J, Wei P, et al. Comparative efficacy of surgical strategies for drug-resistant epilepsy: a systematic review and meta-analysis. *World Neurosurg*. 2025 Mar;195:123729.

Du K, Luo W. Efficacy and safety of robotic Cyberknife radiotherapy in uveal melanoma: a systematic review and meta-analysis. *Eye (Lond)*. 2025 Feb;39(3):548-555.

Eastham JA, Auffenberg GB, Barocas DA, et al. Clinically localized prostate cancer: AUA/ASTRO Guideline. Part III: principles of radiation and future directions. *J Urol*. 2022 Jul;208(1):26-33.

ECRI. Stereotactic body radiation therapy for localized prostate cancer. Plymouth meeting (PA): ECRI; 2024 Dec. (Evidence Analysis).

Eekers DBP, Pijnappel EN, Schijns 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*. 2018 Feb;55:83-92.

Fakiris AJ, Lo SS, Henderson MA, et al. Gamma Knife-based stereotactic radiosurgery for uveal melanoma. *Stereotact Funct Neurosurg*. 2007;85(2-3):106-12.

Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. *Int J Radiat Oncol Biol Phys*. 2009;75(3):677-682.

Farris M, McTyre ER, Cramer CK, et al. Brain metastasis velocity: a novel prognostic metric predictive of overall survival and freedom from whole-brain radiation therapy after distant brain failure following upfront radiosurgery alone. *Int J Radiat Oncol Biol Phys.* 2017;98(1):131-141.

Fogarty G, Dolven-Jacobsen K, Morton RL, et al. Phase 3 international trial of adjuvant whole brain radiotherapy (WBRT) or observation (Obs) following local treatment of 1-3 melanoma brain metastases (MBMs). *J Clin Oncol* 37, no. 15 suppl (May 20, 2019) 9500-9500.

Gaebe K, Li AY, Park A, et al. Stereotactic radiosurgery versus whole brain radiotherapy in patients with intracranial metastatic disease and small-cell lung cancer: a systematic review and meta-analysis. *Lancet Oncol.* 2022 Jul;23(7):931-939.

Gagliardi F, De Domenico P, Garbin E, et al. Primary Gamma Knife radiosurgery for pineal region tumors: a systematic review and pooled analysis of available literature with histological stratification. *J Pineal Res.* 2023 Dec;75(4):e12910.

Germano IM, Sheehan J, Parish J, et al. Congress of Neurological Surgeons systematic review and evidence-based guidelines on the role of radiosurgery and radiation therapy in the management of patients with vestibular schwannomas. *Neurosurgery.* 2018 Feb 1;82(2):E49-E51.

Gigliotti MJ, Hasan S, Karlovits SM, et al. Re-Irradiation with stereotactic radiosurgery/radiotherapy for recurrent high-grade gliomas: improved survival in the modern era. *Stereotact Funct Neurosurg.* 2018;96(5):289-295.

Gomez DR, Blumenschein GR Jr, Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicenter, randomized, controlled, phase 2 study. *Lancet Oncol.* 2016;17(12):1672-1682.

Gomez DR, Tang C, Zhang J, et al. Local consolidative therapy vs. maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer: long-term results of a multi-institutional, phase II, randomized study. *J Clin Oncol.* 2019;37(18):1558-1565.

Gonçalves OR, Lima HF, Borges CES, et al. Efficacy and safety of stereotactic radiosurgery with Gamma Knife machine in patients with essential tremor: a systematic review and single-arm meta-analysis. *Neurosurg Rev.* 2024 Nov 20;47(1):862.

Gondi V, Bauman G, Bradfield L, et al. Radiation therapy for brain metastases: an ASTRO clinical practice guideline. *Pract Radiat Oncol.* 2022 Jul-Aug;12(4):265-282.

Gooijer SA, Gazendam ASM, Torensma B, et al. Metastasectomy versus stereotactic body radiotherapy for patients with oligometastatic colorectal lung metastases: a systematic review. *Eur J Surg Oncol.* 2025 Apr 17;51(8):110056.

Graber JJ, Cobbs CS, Olson JJ. Congress of Neurological Surgeons systematic review and evidence-based guidelines on the use of stereotactic radiosurgery in the treatment of adults with metastatic brain tumors. *Neurosurgery.* 2019 Mar 1;84(3):E168-E170.

Graffeo CS, Sahgal A, De Salles A, et al. Stereotactic radiosurgery for Spetzler-Martin grade I and II arteriovenous malformations: International Society of Stereotactic Radiosurgery (ISRS) practice guideline. *Neurosurgery.* 2020 Sep 1;87(3):442-452.

Guckenberger M, Billiet C, Schnell D, et al. Dose-intensified stereotactic body radiotherapy for painful vertebral metastases: a randomized phase 3 trial. *Cancer.* 2024 Aug 1;130(15):2713-2722.

Guninski RS, Cuccia F, Alongi F, et al. Efficacy and safety of SBRT for spine metastases: a systematic review and meta-analysis for preparation of an ESTRO practice guideline. *Radiother Oncol.* 2024 Jan;190:109969.

Guss ZD, Batra S, Limb CJ, et al. Radiosurgery of glomus jugulare tumors: a meta-analysis. *Int J Radiat Oncol Biol Phys.* 2011 Nov 15;81(4):e497-502.

Haasbeek CJ, Lagerwaard FJ, Antonisse ME, et al. Stage I nonsmall cell lung cancer in patients aged > or = 75 years: outcomes after stereotactic radiotherapy. *Cancer.* 2010;116(2):406-414.

Habibi MA, Mirjani MS, Ahmadvand MH, et al. Gamma Knife stereotactic radiosurgery for neurofibromatosis 2 (NF2)-associated meningiomas; a systematic review and meta-analysis. *Acta Neurochir (Wien).* 2025 Feb 5;167(1):35.

Hajikarimloo B, Habibi MA, Sabbagh Alvani M, et al. Repeat stereotactic radiosurgery in vestibular schwannoma patients: a systematic review and meta-analysis. *J Clin Neurosci.* 2024 Dec;130:110905.

Hajikarimloo B, Mohammadzadeh I, Tos SM, et al. Stereotactic radiosurgery for tumor-related trigeminal neuralgia: a systematic review and meta-analysis. *BMC Neurol.* 2025 May 3;25(1):195.

Harrow S, Palma DA, Olson R, et al. Stereotactic radiation for the comprehensive treatment of oligometastases (SABR-COMET): extended long-term outcomes. *Int J Radiat Oncol Biol Phys.* 2022 Nov 15;114(4):611-616.

Hasegawa T, Ishii D, Kida Y, et al. Gamma Knife surgery for skull base chordomas and chondrosarcomas. *J Neurosurg.* 2007 Oct;107(4):752-7.

Hasegawa T, Kondziolka D, Hadjipanayis CG, Flickinger JC, Lunsford LD. The role of radiosurgery for the treatment of pineal parenchymal tumors. *Neurosurgery.* 2002;51(4):880-889.

Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol.* 1995;13(1):8-10.

Herman JM, Chang DT, Goodman KA, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. *Cancer.* 2015; 121: 1128–1137.

Imber BS, Kanungo I, Braunstein S, et al. indications and efficacy of Gamma Knife stereotactic radiosurgery for recurrent glioblastoma: 2 decades of institutional experience. *Neurosurgery.* 2017;80(1):129-139.

Iorio-Morin C, Kano H, Huang M, et al. Histology-stratified tumor control and patient survival after stereotactic radiosurgery for pineal region tumors: a report from the international Gamma Knife research foundation. *World Neurosurg.* 2017;107:974-982.

Iyengar P, All S, Berry MF, et al. Treatment of oligometastatic non-small cell lung cancer: an ASTRO/ESTRO clinical practice guideline. *Pract Radiat Oncol.* 2023 Apr 25:S1879-8500(23)00111-X.

Iyengar P, Wardak Z, Gerber DE, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. *JAMA Oncol.* 2018;4(1):e173501.

Jackson WC, Silva J, Hartman HE, et al. Stereotactic body radiation therapy for localized prostate cancer: a systematic review and meta-analysis of over 6,000 patients treated on prospective studies. *Int J Radiat Oncol Biol Phys.* 2019;104(4):778–789.

Jang WI, Bae SH, Kim MS, et al. A phase 2 multicenter study of stereotactic body radiotherapy for hepatocellular carcinoma: safety and efficacy. *Cancer.* 2020;126(2):363-372.

Kano H, Kondziolka D, Flickinger JC, et al. Stereotactic radiosurgery for arteriovenous malformations, part 3: outcome predictors and risks after repeat radiosurgery. *J Neurosurg.* 2012;116(1):21-32.

Kano H, Kondziolka D, Flickinger JC, et al. Stereotactic radiosurgery for arteriovenous malformations, part 4: management of basal ganglia and thalamus arteriovenous malformations. *J Neurosurg.* 2012;116(1):33-43.

Kano H, Kondziolka D, Flickinger JC, et al. Stereotactic radiosurgery for arteriovenous malformations, part 5: management of brainstem arteriovenous malformations. *J Neurosurg.* 2012;116(1):44-53.

Kano H, Kondziolka D, Flickinger JC, et al. Stereotactic radiosurgery for arteriovenous malformations, part 6: multistaged volumetric management of large arteriovenous malformations. *J Neurosurg.* 2012;116(1):54-65.

Kano H, Lunsford LD, Flickinger JC, et al. Stereotactic radiosurgery for arteriovenous malformations, part 1: management of Spetzler-Martin Grade I and II arteriovenous malformations. *J Neurosurg.* 2012;116(1):11-20.

Kano H, Niranjana A, Kondziolka D, Flickinger JC, Lunsford D. Role of stereotactic radiosurgery in the management of pineal parenchymal tumors. *Prog Neurol Surg.* 2009;23:44-58.

Kano H, Sheehan J, Sneed PK, et al. Skull base chondrosarcoma radiosurgery: report of the North American Gamma Knife Consortium. *J Neurosurg.* 2015 Nov;123(5):1268-75.

Khan AA, Niranjana A, Kano H, et al. Stereotactic radiosurgery for cavernous sinus or orbital hemangiomas. *Neurosurgery.* 2009;65(5):914-918.

Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol.* 2011;29(2):134-141.

Kondziolka D, Mathieu D, Lunsford LD, et al. Radiosurgery as definitive management of intracranial meningiomas. *Neurosurgery.* 2008;62(1):53-60.

Kotecha R, Sahgal A, Rubens M, et al. Stereotactic radiosurgery for non-functioning pituitary adenomas: meta-analysis and International Stereotactic Radiosurgery Society practice opinion. *Neuro Oncol.* 2020 Mar 5;22(3):318-332.

Landsteiner A, Sowerby C, Ullman K, et al. Hypofractionation radiation therapy for definitive treatment of selected cancers: a systematic review. Washington (DC): Department of Veterans Affairs (US); 2023 May. PMID: 37769054.

Lee CC, Kano H, Yang HC, et al. Initial Gamma Knife radiosurgery for nonfunctioning pituitary adenomas. *J Neurosurg.* 2014b;120(3):647-654.

Lee CC, Sheehan JP, Kano H, et al. Gamma Knife radiosurgery for hemangioma of the cavernous sinus. *J Neurosurg.* 2017;126(5):1498-1505.

Lee CC, Yang HC, Chen CJ, et al. Gamma Knife surgery for craniopharyngioma: report on a 20-year experience. *J Neurosurg.* 2014a;121 Suppl:167-178.

Lievens Y, Guckenberger M, Gomez D, et al. Defining oligometastatic disease from a radiation oncology perspective: an ESTRO-ASTRO consensus document. *Radiother Oncol.* 2020 Jul;148:157-166.

Marchetti M, Sahgal A, De Salles AAF, et al. Stereotactic radiosurgery for intracranial noncavernous sinus benign meningioma: International Stereotactic Radiosurgery Society systematic review, meta-analysis and practice guideline. *Neurosurgery.* 2020 Oct 15;87(5):879-890.

Maroufi SF, Fallahi MS, Sabahi M, et al. Stereotactic radiosurgery in the management of skull base chordomas: a comprehensive systematic review and meta-analysis. *Neurosurg Focus.* 2024 May;56(5):E10.

Martin JJ, Niranjan A, Kondziolka D, et al. Radiosurgery for chordomas and chondrosarcomas of the skull base. *J Neurosurg.* 2007;107(4):758-764.

Martínez-Moreno NE, Sahgal A, De Salles A, et al. Stereotactic radiosurgery for tremor: systematic review. *J Neurosurg.* 2018 Feb 23;130(2):589-600.

Marvaso G, Volpe S, Pepa M, et al. Oligorecurrent prostate cancer and stereotactic body radiotherapy: where are we now? a systematic review and meta-analysis of prospective studies. *Eur Urol Open Sci.* 2021 Mar 16;27:19-28.

Mayinger M, Kotecha R, Sahgal A, et al. Stereotactic body radiotherapy for lung oligo-metastases: systematic review and International Stereotactic Radiosurgery Society practice guidelines. *Lung Cancer.* 2023 Jun 25;182:107284.

McGarry R.C., Papiez L., Williams M., et. al. Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: phase I study. *Int J Radiat Oncol Biol Phys* 2005; 63: pp. 1010-1015.

McGonigal A, Sahgal A, De Salles A, et al. Radiosurgery for epilepsy: systematic review and International Stereotactic Radiosurgery Society (ISRS) practice guideline. *Epilepsy Res.* 2017 Nov;137:123-131.

Mellon EA, Hoffe SE, Springett GM, et al. Long-term out- comes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma. *Acta Oncol.* 2015; 54: 979–985.

Minniti G, Scaringi C, Paolini S, et al. Repeated stereotactic radiosurgery for patients with progressive brain metastases. *J Neurooncol.* 2016;126(1):91-97.

Mokhles S, Macbeth F, Farewell V, et al. Meta-analysis of colorectal cancer follow-up after potentially curative resection. *Br J Surg.* 2016;103(10):1259-1268. Mountain CF. The international system for staging lung cancer. *Semin Surg Oncol* 2000;18:106–115.24.

Naruke T, Tsuchiura R, Kondo H, et al. Prognosis and survival after resection for bronchogenic carcinoma based on the 1997 TNM-staging classification: the Japanese experience. *Ann Thorac Surg* 2001;71:1759–1764.

National Cancer Institute. NCI Dictionary of Cancer Terms, U.S. Department of Health and Human Services, Available at www.cancer.gov/publications/dictionaries/cancer-terms/def/curative-therapy. Accessed August 4, 2025.

National Comprehensive Cancer Network (NCCN) Radiation Therapy Compendium.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Biliary tract cancer. V2.2025. July 2, 2025.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Bone cancer. V1.2025. February 28, 2025.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Central nervous system cancers. V2.2024. March 18, 2025.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Hepatocellular carcinoma.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Kidney cancer. V3.2025. January 9, 2025.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Melanoma: uveal. V1.2025. February 11, 2025.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. V3.2025. January 14, 2025.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Pancreatic adenocarcinoma. V2.2025. February 3, 2025.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Prostate cancer. V2.2025. April 16, 2025.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Small cell lung cancer. V4.2025. January 13, 2025.

National Comprehensive Cancer Network (NCCN). Guidelines for Patients. Early and Locally Advanced Non-Small Cell Lung Cancer. 2025.

National Institute for Health and Care Excellence (NICE). IPG715. Stereotactic radiosurgery for trigeminal neuralgia. February 2022.

National Institute for Health and Care Excellence (NICE). NG122. Lung cancer: diagnosis and management. March 2019. Updated March 2024.

Nguyen QN, Chun SG, Chow E, et al. Single-fraction stereotactic vs conventional multifraction radiotherapy for pain relief in patients with predominantly nonspine bone metastases: a randomized phase 2 trial. *JAMA Oncol.* 2019 Jun 1;5(6):872-878.

Niranjan A, Kano H, Mathieu D, Kondziolka D, Flickinger JC, Lunsford LD. Radiosurgery for craniopharyngioma. *Int J Radiat Oncol Biol Phys.* 2010;78(1):64-71.

Ong V, Bourcier AJ, Florence TJ, et al. Stereotactic radiosurgery for glomus jugulare tumors: systematic review and meta-analysis. *World Neurosurg.* 2022 Jun;162:e49-e57.

Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer.* 2004;101(7):1623-1631.

Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol.* 2007;2(7 Suppl 3):S94-S100.

Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase ii trial. *J Clin Oncol.* 2018;36(5):446-453.

Palavani LB, Silva GM, Borges PGLB, et al. Fractionated stereotactic radiotherapy in craniopharyngiomas: a systematic review and single arm meta-analysis. *J Neurooncol.* 2024 May;167(3):373-385.

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* 12:305, 2012.

Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. *J Clin Oncol.* 2020 Sep 1;38(25):2830-2838.

Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomized, phase 2, open-label trial. *Lancet.* 2019;393(10185):2051-2058.

Palta M, Godfrey D, Goodman KA, et al. Radiation therapy for pancreatic cancer: executive summary of an ASTRO Clinical Practice Guideline. *Pract Radiat Oncol.* 2019 Sep-Oct;9(5):322-332.

Parker T, Rigney G, Kallos J, et al. Gamma Knife radiosurgery for uveal melanomas and metastases: a systematic review and meta-analysis. *Lancet Oncol.* 2020 Nov;21(11):1526-1536.

Peciu-Florianu I, Régis J, Levivier M, et al. Trigeminal neuralgia secondary to meningiomas and vestibular schwannoma Is improved after stereotactic radiosurgery: a systematic review and meta-analysis. *Stereotact Funct Neurosurg.* 2021;99(1):6-16.

Persson AE, Hallqvist A, Bjørn Larsen L, et al. Stereotactic body radiotherapy as metastasis-directed therapy in oligometastatic prostate cancer: a systematic review and meta-analysis of randomized controlled trials. *Radiat Oncol.* 2024 Dec 17;19(1):173.

Pollock BE, Stafford SL, Link MJ, et al. Single-fraction radiosurgery of benign intracranial meningiomas. *Neurosurgery.* 2012;71(3):604-613.

Rajagopalan MS, Heron DE, Wegner RE, et al. Pathologic response with neoadjuvant chemotherapy and stereotactic body radiotherapy for borderline resectable and locally-advanced pancreatic cancer. *Radiat Oncol.* 2013;8:254. Published 2013 Oct 31.

Rim CH, Kim HJ, Seong J. Clinical feasibility and efficacy of stereotactic body radiotherapy for hepatocellular carcinoma: a systematic review and meta-analysis of observational studies. *Radiother Oncol.* 2019 Feb;131:135-144.

Ruers T, Punt C, Van Coevorden F, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). *Ann Oncol*. 2012;23(10):2619-2626.

Ruers T, Van Coevorden F, Punt CJ, et al. Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. *J Natl Cancer Inst*. 2017;109(9):dix015.

Rusthoven CG, Yamamoto M, Bernhardt D, et al. Evaluation of first-line radiosurgery vs whole-brain radiotherapy for small cell lung cancer brain metastases: the FIRE-SCLC cohort study. *JAMA Oncol*. 2020 Jul 1;6(7):1028-1037.

Ryu S, Deshmukh S, Timmerman RD, et al. Stereotactic radiosurgery vs conventional radiotherapy for localized vertebral metastases of the spine: phase 3 results of NRG oncology/ROG 0631 randomized clinical trial. *JAMA Oncol*. 2023 Jun 1;9(6):800-807.

Ryu S, Pugh SL, Gerszten PC, et al. RTOG 0631 phase 2/3 study of image guided stereotactic radiosurgery for localized (1-3) spine metastases: phase 2 results. *Pract Radiat Oncol*. 2014 Mar-Apr;4(2):76-81.

Safavi AH, Mak DY, Boldt RG, et al. Stereotactic ablative radiotherapy in T1-2N0M0 small cell lung cancer: a systematic review and meta-analysis. *Lung Cancer*. 2021 Oct;160:179-186.

Sahgal A, Myrehaug SD, Siva S, et al; trial investigators. Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: an open-label, multicentre, randomised, controlled, phase 2/3 trial. *Lancet Oncol*. 2021 Jul;22(7):1023-1033.

Santacrose A, Walier M, Régis J, et al. Long-term tumor control of benign intracranial meningiomas after radiosurgery in a series of 4565 patients. *Neurosurgery*. 2012;70(1):32-39.

Schellenberg D, Goodman KA, Lee F, et al. Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2008;72: 678-686.

Schiff D, Messersmith H, Brastianos PK, et al. Radiation therapy for brain metastases: ASCO guideline endorsement of ASTRO guideline. *J Clin Oncol*. 2022 Jul 10;40(20):2271-2276.

Schneider BJ, Daly ME, Kennedy EB, et al. Stereotactic body radiotherapy for early-stage non-small-cell lung cancer: American Society of Clinical Oncology endorsement of the American Society for Radiation Oncology evidence-based guideline. *J Clin Oncol*. 2018;36(7):710-719.

Sharma M, Schroeder JL, Elson P, et al. Outcomes and prognostic stratification of patients with recurrent glioblastoma treated with salvage stereotactic radiosurgery. *J Neurosurg*. 2018;131(2):489-499.

Sheehan JP, Starke RM, Kano H, et al. Gamma Knife radiosurgery for sellar and parasellar meningiomas: a multicenter study. *J Neurosurg*. 2014;120(6):1268-1277.

Sheehan JP, Starke RM, Mathieu D, et al. Gamma Knife radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study. *J Neurosurg*. 2013;119(2):446-456.

Sheehan JP, Tanaka S, Link MJ, et al. Gamma Knife surgery for the management of glomus tumors: a multicenter study. *J Neurosurg*. 2012;117(2):246-254.

Shirakusa T, Kobayashi K. Lung cancer in Japan: analysis of lung cancer registry for resected cases in 1994. *Jpn J Lung Cancer* 2002;42:555 - 562.

Simone CB 2nd, Bogart JA, Cabrera AR, et al. Radiation therapy for small cell lung cancer: an ASTRO Clinical Practice Guideline. *Pract Radiat Oncol*. 2020 May-Jun;10(3):158-173.

Siva S, Bressel M, Sidhom M, et al.; FASTRACK II investigator group. Stereotactic ablative body radiotherapy for primary kidney cancer (TROG 15.03 FASTRACK II): a non-randomised phase 2 trial. *Lancet Oncol*. 2024 Mar;25(3):308-316.

Siva S, Louie AV, Kotecha R, et al. Stereotactic body radiotherapy for primary renal cell carcinoma: a systematic review and practice guideline from the International Society of Stereotactic Radiosurgery (ISRS). *Lancet Oncol*. 2024 Jan;25(1):e18-e28.

Skelly AC, Chang E, Bordley J, et al. Radiation therapy for metastatic bone disease: effectiveness and harms [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2023 Aug. Report no.: 23-EHC026. PMID: 37851844.

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*. 2018 Aug;128(2):274-282.

Starke RM, Williams BJ, Jane JA Jr, et al. Gamma Knife surgery for patients with nonfunctioning pituitary macroadenomas: predictors of tumor control, neurological deficits, and hypopituitarism. *J Neurosurg*. 2012;117(1):129-135.

Suleja A, Bilski M, Laukhtina E, et al. Stereotactic body radiotherapy (SBRT) for the treatment of primary localized renal cell carcinoma: a systematic review and meta-analysis. *Cancers (Basel)*. 2024 Sep 26;16(19):3276.

Sutera P, Clump DA, Kalash R, et al. Initial results of a multicenter phase 2 trial of stereotactic ablative radiation therapy for oligometastatic cancer. *Int J Radiat Oncol Biol Phys*. 2019 Jan 1;103(1):116-122.

Tchelebi LT, Lehrer EJ, Trifiletti DM, et al. Conventionally fractionated radiation therapy versus stereotactic body radiation therapy for locally advanced pancreatic cancer (CRISP): an international systematic review and meta-analysis. *Cancer*. 2020 May 15;126(10):2120-2131.

Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol*. 2006 Oct 20;24(30):4833–4839.

Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early-stage lung cancer. *JAMA*. 2010;303(11):1070-1076.

Timmerman R., Papiez L., McGarry R., et. al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. *Chest* 2003; 124: pp. 1946-1955.

Tos SM, Shaaban A, Mantziaris G, et al. Stereotactic radiosurgery for intracranial cavernous malformations: International Stereotactic Radiosurgery Society, systematic review, meta-analysis, and practice guidelines. *World Neurosurg*. 2024 Dec;192:e366-e401.

Tosi U, Lavieri MET, An A, et al. Outcomes of stereotactic radiosurgery for large vestibular schwannomas: a systematic review and meta-analysis. *Neurooncol Pract*. 2021 Feb 18;8(4):405-416.

Tuleasca C, Kotecha R, Sahgal A, et al. Large vestibular schwannoma treated using a cranial nerve sparing approach with planned subtotal microsurgical resection and stereotactic radiosurgery: meta-analysis and International Stereotactic Radiosurgery Society (ISRS) practice guidelines. *J Neurooncol*. 2025 Jun;173(2):245-262.

Tuleasca C, Régis J, Sahgal A, et al. Stereotactic radiosurgery for trigeminal neuralgia: a systematic review. *J Neurosurg*. 2018 Apr 27;130(3):733-757.

V2.2024. March 20, 2025.

van As N, Griffin C, Tree A, et al. Phase 3 trial of Stereotactic Body Radiotherapy in localized prostate cancer. *n Engl J Med*. 2024 Oct 17;391(15):1413-1425.

Verma V, Hasan S, Wegner RE, Abel S, Colonias A. Stereotactic ablative radiation therapy versus conventionally fractionated radiation therapy for stage I small cell lung cancer. *Radiother Oncol*. 2019 Feb;131:145-149.

Vlachos N, Lampros MG, Filis P, et al. Stereotactic radiosurgery versus whole-brain radiotherapy after resection of solitary brain metastasis: a systematic review and meta-analysis. *World Neurosurg X*. 2023 Feb 1;18:100170.

Wahl DR, Stenmark MH, Tao Y, et al. Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. *J Clin Oncol*. 2016;34(5):452-459.

Wan H, Chihiro O, Yuan S. MASEP Gamma Knife radiosurgery for secretory pituitary adenomas: experience in 347 consecutive cases. *J Exp Clin Cancer Res*. 2009;28(1):36. Published 2009 Mar 11.

Wang L, Ke Q, Huang Q, et al. Stereotactic body radiotherapy versus radiofrequency ablation for hepatocellular carcinoma: a systematic review and meta-analysis. *Int J Hyperthermia*. 2020;37(1):1313-1321.

Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomized, non-inferiority, phase 3 trial. *Lancet*. 2019;394(10196):385-395.

Windisch PY, Tann JC, Fürweger C, et al. Clinical results after single-fraction radiosurgery for 1,002 vestibular schwannomas. *Cureus*. 2019;11(12):e6390. Published 2019 Dec 16.

Xi M, Yang Z, Hu L, et al. Radiofrequency ablation versus stereotactic body radiotherapy for recurrent small hepatocellular carcinoma: a randomized, open-label, controlled trial. *J Clin Oncol*. 2025 Mar 20;43(9):1073-1082.

Yamamoto M, Aiyama H, Koiso T, et al. Validity of a recently proposed prognostic grading index, brain metastasis velocity, for patients with brain metastasis undergoing multiple radiosurgical procedures. *Int J Radiat Oncol Biol Phys*. 2019;103(3):631-637.

Yamamoto M, Serizawa T, Higuchi Y, et al. A Multi-institutional prospective observational study of stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901 Study Update): irradiation-related complications and long-term maintenance of mini-mental state examination scores. *Int J Radiat Oncol Biol Phys*. 2017;99(1):31-40.

Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol.* 2014;15(4):387-395.

Yazici G, Kiratli H, Ozyigit G, et al. Stereotactic radiosurgery and fractionated stereotactic radiation therapy for the treatment of uveal melanoma. *Int J Radiat Oncol Biol Phys.* 2017 May 1;98(1):152-158.

Zhang R, Kang J, Ren Set al. Comparison of stereotactic body radiotherapy and radiofrequency ablation for early-stage non-small cell lung cancer: a systematic review and meta-analysis. *Ann Transl Med.* 2022 Jan;10(2):104.

Zhong J, Patel K, Switchenko J, et al. Outcomes for patients with locally advanced pancreatic adenocarcinoma treated with stereotactic body radiation therapy versus conventionally fractionated radiation. *Cancer.* 2017 Sep 15;123(18):3486-3493.

Policy History/Revision Information

Date	Summary of Changes
12/01/2025	<p>Coverage Rationale</p> <ul style="list-style-type: none"> Added language to indicate this policy applies to individuals 19 years of age and older; stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) are covered without further review for individuals younger than 19 years of age Revised list of proven and medically necessary indications for stereotactic radiation therapy, including SRS and SBRT: <ul style="list-style-type: none"> Added: <ul style="list-style-type: none"> Bone metastasis (non-spine) when all the following criteria are met: <ul style="list-style-type: none"> Symptomatic Up to five fractions Neurologic conditions (epilepsy, Parkinson's disease, essential tremor) that are refractory to medical treatment and/or invasive surgical interventions Spinal lesions when one of the following criteria are met: <ul style="list-style-type: none"> Palliative treatment of symptomatic spinal bone metastasis when all the following criteria are met: <ul style="list-style-type: none"> Using five fractions or less Individual has no spinal cord compression or cauda equina compression Primary spinal lesions that cannot be treated with surgical resection or 3D conformal techniques Revised coverage criteria for: <p>Newly Diagnosed Brain Metastasis</p> <ul style="list-style-type: none"> Added criterion requiring "absence of diffuse brain metastases" Replaced criterion requiring: <ul style="list-style-type: none"> "Absence of leptomeningeal metastases" with "absence of <i>diffuse</i> leptomeningeal metastases" "Individual does not have a diagnosis of lymphoma, germ cell tumor, or <i>small cell carcinoma</i>" with "individual does not have a diagnosis of lymphoma or germ cell tumor" <p>Individual Undergoing Repeat Stereotactic Radiation Therapy for Brain Metastasis</p> <ul style="list-style-type: none"> Replaced criterion requiring: <ul style="list-style-type: none"> "Absence of leptomeningeal metastases" with "absence of <i>diffuse</i> leptomeningeal metastases" "<i>Stable</i> extra-cranial disease as documented on restaging studies dated within the past two months" with "extra-cranial disease is <i>well-controlled</i> or there are accessible and effective systemic treatment options available" Removed criterion requiring "total number of brain metastases treated in the past 12 months is ≤ 13" <p>Definitive Treatment</p> <ul style="list-style-type: none"> Added criterion requiring: <ul style="list-style-type: none"> Intrahepatic bile duct cancer (cholangiocarcinoma) for unresectable tumors Small cell lung cancer when all the following criteria are met: <ul style="list-style-type: none"> Stage I or node negative stage IIA Lesion is medically inoperable, or the individual is a non-optimal surgical candidate Replaced criterion requiring:

Date	Summary of Changes
	<ul style="list-style-type: none"> ▪ “Non-small cell lung cancer when the individual is medically inoperable or <i>refuses to have surgery after thoracic surgery evaluation</i>” with “non-small cell lung cancer when the individual is medically inoperable or <i>has made a decision not to pursue surgery after an appropriate consultation</i>” ▪ “Prostate cancer without evidence of distant metastases” with “prostate cancer without evidence of distant metastases; <i>for Oligometastatic Disease, refer to the criteria [listed in the policy]</i>” <p>Extracranial Oligometastatic Disease</p> <ul style="list-style-type: none"> ○ Replaced criterion requiring: <ul style="list-style-type: none"> ▪ “<i>Performance status KPS score ≥ 70% or ECOG performance status of 0-2</i>” with “KPS score greater than or equal to 70% or ECOG performance status of zero to two” ▪ “<i>Individual has a total of up to three metastatic lesions since diagnosis, and if the individual has previously received local therapy (e.g., SBRT, surgery, or radiofrequency ablation) for metastatic disease, the treated lesion(s) from that therapy are included in the total count of three lesions</i>” with “individual has a total of up to five metastatic lesions” ● Removed language indicating SBRT for palliative treatment of bone metastases of the spine is proven and medically necessary when all the following criteria are met: <ul style="list-style-type: none"> ○ Using 2 fractions or less ○ Individual has no spinal cord compression or cauda equina compression <p>Medical Records Documentation Used for Reviews</p> <ul style="list-style-type: none"> ● Updated list of Medical Records Documentation Used for Reviews: <ul style="list-style-type: none"> ○ Added “life expectancy” ○ Replaced “proposed treatment plan” with “proposed treatment plan <i>including number of fractions</i>” <p>Definitions</p> <ul style="list-style-type: none"> ● Updated definition of: <ul style="list-style-type: none"> ○ Definitive Treatment ○ Oligometastatic Disease (OMD) <p>Supporting Information</p> <ul style="list-style-type: none"> ● Updated <i>Clinical Evidence</i> and <i>References</i> sections to reflect the most current information ● Archived previous policy version 2025T0611I

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence ([Medicare IOM Pub. No. 100-16, Ch. 4, §90.5](#)).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.