Stereotactic Body Radiation Therapy and Stereotactic Radiosurgery

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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

Stereotactic radiation therapy including stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) is considered proven and medically necessary for the following indications:

- Acoustic neuroma (vestibular schwannoma)
- 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 ≥ 70% or Eastern Cooperative Oncology Group (ECOG) performance status of 0-2]
    - Absence of leptomeningeal metastases
    - Individual does not have a diagnosis of lymphoma, germ cell tumor, or small cell carcinoma
    - Has up to 10 lesions or cumulative tumor volume of < 15cc
    - All lesions must be treated in a single treatment for SRS, or in 2 to 5 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 ≥ 70% or ECOG performance status of 0-2)
    - Absence of leptomeningeal metastases
    - Stable extra-cranial disease as documented on restaging studies dated within the past two months
    - Life expectancy is > 6 months
    - Total number of brain metastases treated in the past 12 months is ≤ 13
    - All lesions must be treated in a single treatment for SRS, or in 2 to 5 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
    - Non-small cell lung cancer when all the following criteria are met:
        - Stage I or stage IIA with negative mediastinal lymph nodes
        - Tumor size ≤ 5cm
        - Individual is medically inoperable or refuses to have surgery after thoracic surgery evaluation
    - Pancreatic adenocarcinoma without evidence of distant metastasis
    - Prostate cancer without evidence of distant metastases
    - Renal cancer when **all** the following criteria are met:
        - Stage I
        - 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 3 months since original tumor was treated definitively, with no progression at primary site
    - Performance status KPS score ≥ 70% or ECOG performance status of 0-2
    - Life expectancy is at least 6 months
    - Has a total of up to 3 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 3 lesions
    - Each lesion is ≤ 5 cm 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 5 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
- Pineal gland tumors
- Pituitary adenoma
- Recurrent gliomas
- To treat a previously irradiated field
- Trigeminal neuralgia refractory to medical therapy
- Uveal melanoma

Stereotactic body radiation therapy (SBRT) for palliative treatment of bone metastases of the spine is proven and medically necessary when all the following criteria are met:

- Using 2 fractions or less
- Individual has no spinal cord compression or cauda equina compression

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 protocol titled Medical Records Documentation Used for Reviews.

Definitions

Definitive Treatment: Radiation treatments for cancer with a curative intent (Landsteiner et al., 2023).

Oligometastatic Disease: Refers to a stage of disease where the cancer has spread beyond the site of the primary tumor but is not yet widely metastatic (Hellman 1995). Under the current policy, individuals with up to three metastatic lesions are considered to have Oligometastatic Disease. However, progression of a limited number of metastatic lesions in individuals with otherwise controlled widespread disease (Oligoprogression) is not considered Oligometastatic Disease under this policy.

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
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

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

HCPCS Code	Description
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 5 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)

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 vestibular schwannomas (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 (GK) 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. (Boari 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 include lack of randomized controlled trials (RCTs) included in the study, data was reported in a heterogenous manner, and limited study sizes. The authors recommend 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) I. 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 (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 dB at treatment start 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.

Hasegawa et al. (2013) conducted a case series analysis to confirm whether Gamma Knife surgery (GKS) for VS continues to be safe and effective more than 10 years after treatment. A total of 440 individuals with VS (including NF2) were treated with GKS and of these, 347 individuals (79%) underwent GKS as an initial treatment and 93 (21%) had undergone prior resection. Three hundred fifty-eight individuals (81%) had a solid tumor and 82 (19%) had a cystic tumor. The median tumor volume was 2.8 cm^3 and the median marginal dose was 12.8 Gy. The median follow-up period was 12.5 years. The actuarial five- and ≥ 10-year progression-free survival (PFS) was 93% and 92%, respectively. None of the individuals developed treatment failure more than 10 years after treatment. According to multivariate analysis, significant factors related to worse PFS included brainstem compression with a deviation of the fourth ventricle ($p < 0.0001$), marginal dose ≤ 13 Gy ($p = 0.01$), prior treatment ($p = 0.02$), and female sex ($p = 0.02$). Of 287 patients treated at a recent optimum dose of ≤ 13 Gy, three (1%) developed facial palsy, including two with transient palsy and one with persistent palsy after a second GKS, and three (1%) developed facial numbness, including two with transient and one with persistent facial numbness. The actuarial 10-year facial nerve preservation rate was 97% in the high marginal dose group (> 13 Gy) and 100% in the low marginal dose group (≤ 13 Gy). Ten patients (2.3%) developed delayed cyst formation. One patient alone developed malignant transformation, indicating an incidence of 0.3%. The authors concluded that GKS is a safe and effective treatment for the majority of patients followed more than 10 years after treatment. Special attention should be paid to cyst formation and malignant transformation as late adverse radiation effects (AREs), although those appeared to be rare. However, additional long-term follow-up data is needed before making conclusions about the long-term safety and efficacy of GKS, particularly for young individuals with VS.

Clinical Practice Guidelines

Congress of Neurological Surgeons (CNS)

Germano et al. (2018) developed evidence-based guidelines for the CNS regarding the use of radiosurgery (RS) and radiation therapy 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 guideline. 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 VS are enlarging and/or causing hearing loss.
- Patients should be informed that there is minimal risk of malignant transformation of VS after SRS.

Brain Metastasis

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 overall survival (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 whole brain radiation therapy (WBRT) while 120 individuals were treated with postoperative SRS. There was no difference between SRS and WBRT in the risk of local recurrence (RR ¼ 0.92, CI ¼ 0.51–1.66, p ¼ 0.78, I2 ¼ 0%) and leptomeningeal disease (RR ¼ 1.21, CI ¼ 0.49–2.98, p ¼ 0.67, I2 ¼ 18%), neither in the individuals' OS (HR ¼ 1.06, CI ¼ 0.61–1.85, p ¼ 0.83, I2 ¼ 63%). SRS appeared to increase the risk of distant brain failure (RR ¼ 2.03, CI ¼ 0.94–4.40, p ¼ 0.07, I2 ¼ 61%). Neurocognitive function and quality of life (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 include 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 recommend larger scale, prospective studies in the future.

Fogarty et al. (2019) conducted a multi-center, international, phase III, randomized trial (NCT01503827) to compare WBRT with observation (Obs) 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 Obs arm. The mean age was 62 years, 67% males, 61% with single MBM of mean size two centimeters, 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 Obs at baseline, declining to 26 and 35 participants respectively at four months. Within 12 months, 54 (50.5%) participants in the Obs arm had distant intracranial failure compared with 42 (42.0%) participants in the WBRT arm (OR 0.71; 95% confidence interval [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 Obs 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 Obs arm with no systemic therapy however, this difference was not significant (p = 0.228). The Obs arm had greater relative improvement from baseline in HVLT-R at every timepoint. At four months, the Obs 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 brain metastasis 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 brain metastases (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 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 (MSTs) 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 MSTs 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 MSTs 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 small cell lung cancer, 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 radiosurgical 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 JLGK0901 Study (Yamamoto 2014) to confirm the long-term safety of SRS in patients 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 stereotactic RS 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 < 3 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 (hazard ratio [HR] of group A vs. group B, 0.719; 95% CI, 0.437-1.172; p = 0.18; HR of group B vs. 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, 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 vs. group B, 0.850; 95% CI, 0.592 to 1.220; p = 0.38; HR of group B vs. 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; interquartile range, 7.0 to 14.4 months) after WBRT. The authors concluded that neither MMSE score maintenance or 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 vs. 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 vs. SRS plus WBRT. Adult participants(≥ 18 years of age) 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 3-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 vs. −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%] vs. 16/17 [94.1%]; difference, −48.7%; 95% CI, −87.6% to −9.7%; p = 0.007) and at 12 months (6/10 [60%] vs. 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 (small-cell lung cancer excluded) with stable systemic disease or asymptomatic primary tumors and World Health Organization (WHO) performance status (PS) of 0-2 were treated with complete surgery or RS and randomly assigned to adjuvant WBRT (30 Gy in 10 fractions) or OBS. The primary end point was time to WHO PS 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 OBS, 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 PS more than two was 10.0 months (95% CI, 8.1 to 11.7 months) after OBS 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 OBS arms (median, 10.9 vs. 10.7 months, respectively; p = 0.89). WBRT reduced the 2-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 OBS than after WBRT. Intracranial progression caused death in 78 (44%) of 179 participants in the OBS 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.

Aoyama et al. (2006) conducted a multi-center, randomized, controlled trial to determine if WBRT combined with SRS results in improvements in survival, brain tumor control, functional preservation rate, and frequency of neurologic death. Participants with one to four BMs, each less than 3.0 cm in diameter were randomized to receive WBRT plus SRS or SRS alone. The primary end point was OS and secondary end points were brain tumor recurrence, salvage brain treatment, functional preservation, toxic effects of radiation, and cause of death. A total of 132 participants were enrolled (WBRT plus SRS, n = 65; SRS alone, n = 67). The median survival time and the 1-year actuarial survival rate were 7.5 months and 38.5% (95% CI, 26.7 to 50.3%) in the WBRT + SRS group and 8.0 months and 28.4% (95% CI, 17.6 to 39.2%) for SRS alone (p = 0.42). The 12-month brain tumor recurrence rate was 46.8% in the WBRT + SRS group and 76.4% for SRS alone group (p < 0.001). Salvage brain treatment was less frequently required in the WBRT + SRS group (n = 10) than with SRS alone (n = 29) (p < 0.001). Death was attributed to neurologic causes in 22.8% of participants in the WBRT + SRS group and in 19.3% of those treated with SRS alone (p = 0.64). There were no significant differences in systemic and neurologic functional preservation and toxic effects of radiation. The authors concluded that compared with SRS alone, the use of WBRT plus SRS did not improve survival for participants with one to four BMs, but intracranial relapse occurred considerably more frequently in those who did not receive WBRT. Consequently, salvage treatment is frequently required when up-front WBRT is not used.

Andrews et al. (2004) and the Radiation Therapy Oncology Group (RTOG) conducted a multi-center, randomized trial to assess whether SRS provided any therapeutic benefit in participants newly diagnosed with BMs. Participants with one to three newly diagnosed BMs were randomly assigned to either WBRT or WBRT followed by an SRS boost. Participants were stratified by number of metastases and status of extracranial disease. The primary outcome was survival and secondary outcomes were tumor response and local rates, overall intracranial recurrence rates, cause of death, and performance measurements. A total of 333 individuals participated in the study with 167 participants assigned WBRT and SRS and 164 participants assigned to WBRT alone. Univariate analysis showed that there was a survival advantage in the WBRT and SRS group for participants with a single brain metastasis (median survival time 6.5 vs 4.9 months, p = 0.0393). Participants in the SRS group were more likely to have a stable or improved KPS scores at six months of follow-

up than were participants allocated WBRT alone (43% vs. 27%, respectively; p = 0.03). Multivariate analysis showed that survival improved in participants with an RPA class one (p < 0.0001) or a favorable histological status (p = 0.0121). The authors concluded that WBRT and stereotactic boost treatment improved functional autonomy for all patients and survival for patients with a single unresectable brain metastasis and therefore, should be standard treatment for those with a single unresectable brain metastasis and considered for individuals with two or three BMs.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

In a 2022 ASTRO clinical practice guideline entitled Radiation Therapy for Brain Metastases, BMs are addressed. ASTRO strongly recommends SRS for patients with an Eastern Cooperative Oncology Group (ECOG) of 0-2 and up to four intact brain BMs. Single-fraction SRS with a dose of 2000-2400 cGy is strongly recommended for patients with intact BMs measuring < 2 cm in diameter, if multifraction SRS is given, options include 2700 cGy in three fractions or 3000cGy in five fractions. SRS is strongly recommended to improve local control in patients with resected BMs. For patients with resected BMs and limited additional BMs, SRS is strongly recommended over WBRT to preserve neurocognitive function and patient QOL. For patients with a favorable prognosis and BMs receiving WBRT, ASTRO strongly recommends, hippocampal avoidance with the addition of memantine. ASTRO suggests 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).

National Comprehensive Cancer Network (NCCN)

Per NCCN, 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. Common dose-fractionation schedules include 16–20 Gy in one fraction, 24-27 Gy in three fractions, and 30 Gy in five fractions (NCCN, 2024).

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 5 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 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 include 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 a 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 radiation therapy. The median tumor volume was 8.0 cm^3 (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 radiation therapy 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 note 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 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 5- and 10-year survival rates after GKS were 80% and 53%, respectively. The actuarial 5- and 10-year local tumor control (LTC) rates after single or multiple GKS sessions were 76% and 67%, respectively. All individuals with low-grade chondrosarcomas achieved good LTC. A tumor volume of less than 20 ml significantly affected the high rate of LTC ($p = 0.0182$). 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 cm^3. The median dose to the tumor margin was 16 Gy. Transient symptomatic AREs developed in only one patient. 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.

Noël et al. (2003) conducted a single-center case series analysis to evaluate outcomes of individuals with chordomas or chondrosarcomas and treated with fractionated photon and proton radiation. Outcomes included local tumor control, survival, and treatment complications. A total of 67 individuals with a median age of 52 years (range, 14 to 85 years) were treated using the 201-MeV proton beam, 49 for chordoma and 18 for chondrosarcoma. Irradiation combined high-energy photons and protons. Photons represented two thirds of the total dose and protons one third. The median total dose delivered within gross tumor volume (GTV) was 67 Cobalt Gray Equivalents (CGE; range, 60 to 70 CGE). The median follow-up time was 29 months (range, four to 71 months). The 3-year local control rates were 71% and 85% for chordomas and chondrosarcomas, respectively, and the 3-year OS rates 88% and 75%, respectively. Fourteen tumors (21.5%) failed locally (eight within the GTV, four within the clinical target volume [CTV], and two without further assessment). Seven individuals died from their tumor and one from a nonrelated condition (pulmonary embolism). The maximum tumor diameter and the GTV were larger in relapsing individuals, compared with the rest of the population: 56 mm vs. 44 mm ($p = 0.024$) and 50 ml vs. 22 ml ($p = 0.0083$), respectively. In univariate analysis, age ≤ 52 years at the time of radiotherapy ($p = 0.002$), maximum diameter < 45 mm ($p = 0.02$), and GTV < 28 ml ($p = 0.02$) impacted positively on local control. On multivariate analysis, only age was an independent prognostic factor of local control. The authors concluded that in those with chordomas and chondrosarcomas of the skull base and cervical spine, combined photon and proton radiation therapy offers excellent chances of cure, and that their results should be confirmed with longer follow-up.

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 patients) 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: 6-83%), while the improvement in the visual field was 22% (95% CI: 0-51%). Regarding endocrine function, the new-onset hypopituitarism rate was found to be 5% (95% CI: 0-11%). Relative to FSRT effectiveness, the pooled estimate of the complete tumor response rate was 17% (95% CI: 4-30%), and the tumor progression rate was 7% (95% CI: 1-13%). Also, a 3-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 recommend further research to assess the clinical utility and associated risks. Limitations include 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 6-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 were increased to 77.3% and 61.2% at five and 10 years, respectively. The OS rates were 91.5% and 83.9% at the 5- 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 Gamma Knife SRS 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 cm^3 (range, 0.07 to 8.0). The median prescription dose delivered to the tumor margin was 13.0 Gy (range, 9 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 5 years. The 3- and 5-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.

Kobayashi et al. (2005) conducted a single-center case series analysis to evaluate long-term outcomes of individuals treated with GKS for residual or recurrent craniopharyngiomas after microsurgery, and the effects of dose reduction. A total of 107 individuals with craniopharyngiomas were treated with GKS, and 98 individuals were followed up for six to 148 months (mean 65.5 months). The mean tumor diameter and volume were 18.8 mm and 3.5 ml, respectively. The tumors were treated with a maximal dose of 21.8 Gy and a tumor margin dose of 11.5 Gy by using a mean of 4.5 isocenters. Final overall response rates were as follows: complete response 19.4%, partial response 67.4%, tumor control 79.6%, and tumor progression 20.4%. Reducing the tumor margin dose resulted in decreased therapeutic response and increased tumor progression, although the rate of visual and pituitary function loss also decreased. Among the factors examined, age (for adults) and the nature of the tumor (cystic or mixed) were statistically significant favorable and unfavorable prognostic factors, respectively. The actuarial 5- and 10-year survival rates were 94.1 and 91%, respectively. The PFS rates were 60.8 and 53.8%, respectively. Patient outcomes were reportedly excellent in 45 cases, good in 23, fair in four, and poor in three; 16 individuals died. Deterioration both in vision and endocrinological functions were

documented as side effects in six individuals (6.1%). The authors concluded that stereotactic GKS is safe and effective, in the long term, as an adjuvant or boost therapy for residual or recurrent craniopharyngiomas after surgical removal and has minimal side effects.

Definitive Treatment of Hepatocellular Carcinoma (HCC) Without Evidence Regional or Distant Metastasis

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 2-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 patient experienced radiation-induced liver disease with acute grade ≥ 3 toxicity 1 month after SBRT. In addition, one patient 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 2-year and 3-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 is an effective treatment modality.

Wang et al. (2020) conducted a systematic review and meta-analysis aimed at comparing the safety and efficacy of radiofrequency ablation (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 hazard ratios (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 > 2cm. Limitations include the retrospective nature of the studies included in the review, and the population in each study was different which may result in heterogeneity. The authors recommend 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 1-, 2-, and 3-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 1-, 2-, and 3-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 1- and 2-year OS rates and 1-, 2-, and 3-year local control rates. In addition, radiation dose showed no difference for OS and a marginal difference for 1-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 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)

In an ASTRO guideline for primary liver cancers, using external beam radiation therapy (EBRT) as a potential first-line treatment in patients with liver-confined HCC who are not candidates for curative therapy, as consolidative therapy after incomplete response to liver-directed therapies, and as a salvage option for local recurrences is strongly recommended. ASTRO conditionally recommends EBRT for patients with liver-confined multifocal or unresectable HCC, or those with macrovascular invasion, sequenced with systemic or catheter-based therapies. Additionally, the authors recommend future high-quality RCTs to further define the role of EBRT in HCC treatment (Apisarnthanarax et al., 2021).

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 1-9 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 HCC states 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 3-5 fractions and is often used for patients with 1-3 tumors (NCCN, 2024).

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

Ball et al. (2019) performed a phase 3, 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 quality of life. 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 0 or 1, 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 (hazard ratio 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 include a large proportion of patient had previous cancer and small sample size. In 2023, Bucknell et al. conducted an analysis of the TROG 09.02 (CHISEL) phase 3 trial to compare pulmonary function tests and the 6-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 vs. 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 patient 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 patient had regional nodal recurrence and two had distant metastases; in the SABR group, one patient 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%) patient died of surgical complications and 12 (44%) participants had grade 3–4 treatment-related adverse events. Grade 3 events occurring in more than one patient 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 20Gy (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 patient 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 patient's risk for toxicity. SRT was well tolerated, and all but one patient 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 1½-2 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 patient had a primary tumor failure; the estimated 3-year primary tumor control rate was 97.6% (95% CI, 84.3% to 99.7%). Three participants had recurrence within the involved lobe; the 3-year primary tumor and involved lobe (local) control rate was 90.6% (95% CI, 76.0% to 96.5%). Two participants experienced regional failure; the local-regional control rate was 87.2% (95%CI, 71.0%, 94.7%). Eleven participants experienced disseminated recurrence; the 3-year rate of disseminated failure was 22.1% (95% CI, 12.3% to 37.8%). The rates of DFS and OS at 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 3-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 vs. central tumors (MS 33.2 vs. 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 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 (SRT) 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 biological effective dose (BED) was 111 Gy (range, 57 to 180 Gy) based on $\alpha/\beta = 10$. For the comparison to surgery, the 5-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 5-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 states 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, 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 with concurrent chemotherapy (CFRT) 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 ¾ toxicity were the secondary outcomes. For SBRT, the median dose was 30 Gy, and the most common regimen was 30 Gy/5 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 2-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 1-year OS was 53.7% (95% CI, 39.3%-67.9%) for SBRT versus49.3% (95% CI, 39.3%-59.4%) for CFRT, and was not statistically significant. The random effects estimate for acute grade 3/4 toxicity was5.6% (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 ¾ toxicity and not change in one -year OS or late toxicity. Limitations include the phase one or two studies and retrospective nature of the SBRT studies, whereas the CRFT studies were all phase 2 or phase 3. The authors recommend future quality studies to evaluate SBRT for these individuals.

In a retrospective review, Zhong et al. (2017) compared SBRT with conventionally fractionated radiation 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 radiation therapy delivered at ≤ 2 Gy was deemed conventionally fractionated radiation therapy . Overall survival was the primary outcome. The total number of individuals included in the review was 8,450, conventionally fractionated radiation therapy = 7,819 and SBRT = 631. Receipt of SBRT was associated with superior OS in the multivariate analysis (hazard ratio, 0.84; 95% confidence interval, 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 vs 11.6 months) and the 2-year OS rate (21.7% vs 16.5%) were significantly higher with SBRT versus conventionally fractionated radiation therapy . The authors concluded SBRT was superior to OS when compared with conventionally fractionated radiation therapy , and an additional benefit of SBRT was the shorter duration of treatment. Additionally, the authors recommend future randomized trials to evaluate these results. Limitations include 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/m^2) followed by a 1-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 of 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 0 at both follow-ups; p > 0.05 for both). Participants reported a significant improvement in pancreatic pain (p = 0.001) 4 weeks after SBRT on the QLQ-PAN26 questionnaire. The median plasma carbohydrate antigen 19-9 (CA 19-9) level was reduced after SBRT (median time after SBRT, 4.2 weeks; 220 U/mL vs. 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 stereotactic body radiotherapy 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 2–3 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 (5 of 21 vs. 0 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, 1-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, 1-year OS, median PFS, and 1-year PFS for BRPC vs. LAPC individuals was 16.4 months vs. 15 months, 72.2% vs. 68.1%, 9.7 vs. 9.8 months, and 42.8% vs. 41%, respectively (all $p > 0.10$). BRPC individuals who underwent R0 resection had improved median OS (19.3 vs. 12.3 months; $p = 0.03$), 1-year OS (84.2% vs. 58.3%; $p = 0.03$), and 1-year PFS (56.5% vs. 25.0%; $p < 0.0001$), respectively, compared with all nonsurgical individuals. The 1-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 = 7). Most individuals were treated with fractionated SBRT to 36 Gy/3 fractions (n = 7) and the remainder with single fraction to 24 Gy (n = 5). 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 = 3/12) of individuals, a complete pathologic response was achieved, and an additional 16.7% (n = 2/12) demonstrated < 10% viable tumor cells. Kaplan-Meier estimated median progression free survival is 27.4 months. OS was 92%, 64% and 51% at 1-, 2-, and 3-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.

Mahadevan et al. (2011) conducted single-center, retrospective, case series analysis to evaluate outcomes of individuals with LAPC who received a planned strategy of initial chemotherapy with restaging and then, for those individuals with no evidence of metastatic progression, treatment with SBRT. Individuals received GEM (1,000 mg/m^2 per week for 3 weeks then 1 week off) until tolerance, at least six cycles, or progression. Individuals without metastases after two cycles were treated with SBRT (tolerance-based dose of 24–36 Gy in three fractions) between the third and fourth cycles without interrupting the chemotherapy cycles. A total of 47 individuals were included in the analysis. Of those, 8 (17%) individuals were found to have metastatic disease after two cycles of GEM; the remaining 39 individuals received SBRT. The median follow-up for survivors was 21 months (range, six to 36 months). The median OS for all individuals who received SBRT was 20 months, and the median PFS was 15 months. The local control rate was 85% (33 of 39 individuals); and 54% of individuals (21 of 39) developed metastases. Late Grade III toxicities such as GI bleeding and obstruction were observed in 9% (3/39) of individuals. The authors concluded that for those with locally advanced pancreas cancer, their strategy uses local therapy for those who are most likely to benefit from it and spares those patients with early metastatic progression from treatment, and SBRT delivers such local therapy safely with minimal interruption to systemic chemotherapy, thereby potentially improving the outcome in these individuals.

Koong et al. (2004) conducted a phase I dose escalation study to determine the feasibility and toxicity of delivering SRS to participants with LAPC. Participants with ECOG performance status ≤ 2 received a single fraction of RS consisting of either 15 Gy, 20 Gy, or 25 Gy to the primary tumor. Acute GI toxicity was scored according to the RTOG criteria. Response to treatment was determined by serial high-resolution computed tomography scanning. A total of 15 participants were treated at the 3 dose levels (three participants received 15 Gy, five participants received 20 Gy, and seven participants received 25 Gy). At those doses, no grade 3 or higher acute GI toxicity was observed. This trial was stopped before any dose-limiting toxicity was reached, because the clinical objective of local control was achieved in all six evaluable participants treated at 25 Gy. The authors concluded that it is feasible to deliver SRS to those with locally advanced pancreatic cancer, and the recommended dose to achieve local control without significant acute GI toxicity is 25 Gy.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for pancreatic adenocarcinoma states 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 second-line therapy, SBRT may be used if not previously given and if the primary site is the sole site of progression (2024).

Definitive Treatment of Prostate Cancer Without Evidence of Distant Metastasis

Jackson et al. (2019) conducted a systematic review and meta-analysis to evaluated 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 5-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 1/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, 5- and 7-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 0 - 2. 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 5.0 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 vs. 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 1-year follow-up (32 [6%] of 528 participants vs. 13 [2%] of 529 participants; (p = 0.0037). There were observed 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 1-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 support 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 NCCN guidelines for prostate cancer states that SBRT is acceptable in practices with appropriate technology, physics, and clinical expertise (2024).

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 2 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 0-2, 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 10cm, 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. 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 4·6 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 [3%]), 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 a future randomized trials. Study limitations include lack of randomization, small sample size, and lack of control group.

Clinical Practice Guidelines

International Society of Stereotactic Radiosurgery (ISRS)

An ISRS systematic review and guideline for SBRT for primary renal cell carcinoma 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 renal cell carcinoma include 26 Gy in one fraction if the tumor is ≤ 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 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, is recommended. (Strength of recommendation: strong).
- Optimal post-treatment follow-up schedule after SBRT for primary renal cell carcinoma 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).

Clinical Practice Guidelines

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 or 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).

Extracranial Oligometastatic Disease

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 recommend 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 5-year OS rate was 17.7% in the control group (95% CI, 6% to 34%) vs. 42.3% in SABR group (95% CI, 28% to 56%; p = 0.006). The 5-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 8-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 vs. 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] vs. 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 vs. 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).

Iyengar 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, 2-6) and the maintenance chemotherapy-alone arm had a median of two metastases (range, 2-5). 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 vs. 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 PFS in patients 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 radiofrequency ablation (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 radiofrequency ablation ± 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 vs. 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 5 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 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 2 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.

International Stereotactic Radiosurgery Society (ISRS)

Mayinger et al. (2023) developed a ISRS practice guideline related to SBRT for lung oligo-metastases. 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 organs at risk and without broad chest wall contact. (Level of evidence: high; strength of recommendation: strong).

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, 4-268 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 include study heterogeneity and lack of RCTs.

Sheehan et al. (2012) conducted a multi-center case series analysis of 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 external beam radiotherapy 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 GKS 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 linear accelerator 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 recommend future prospective studies with larger participant numbers treated with RS as a primary treatment modality and longer follow-up.

Lim et al. (2001) conducted a single-center, retrospective, case series analysis to report their experience with the application of LINAC or CyberKnife modalities for the treatment of glomus jugulare tumors. A total of 13 individuals with 16 tumors were included in this analysis. All individuals were treated with frame-based LINAC or CKRS, with doses ranging from 1,400 to 2,700 cGy. Individuals were assessed for posttreatment side effects, which included hearing loss, tongue weakness, and vocal hoarseness. The individuals' most recent magnetic resonance (MR) images were also assessed for changes in tumor size. The median follow-up duration was 41 months and the mean follow-up period was 60 months. All tumors remained stable or decreased in size on follow-up MR images. All individuals had stable neurological symptoms, and one experienced transient ipsilateral tongue weakness and hearing loss, both of which subsequently resolved. One patient experienced transient ipsilateral vocal cord paresis; however, that individual had received previous external-beam radiation therapy. The authors concluded that their findings support RS as an effective and safe method of treatment for GJTs and results in low rates of morbidity.

Hemangiomas of the Brain

Lee et al. (2017) conducted a multi-center case series analysis to review 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, adverse radiation effects, 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 patient). 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 patient. 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.

Intracranial Arteriovenous Malformations (AVMS)

Ding et al. (2017) conducted an international multicenter study which analyzed and collected data from patients 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 cm^3 , 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 include the biases of a retrospective study and lack of comparison with other AVM interventions. The authors recommend future prospective trials.

Kano et al. (2012) published a series of studies to evaluate outcomes of individuals with arteriovenous malformations (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 arteriovenous malformations (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 cm^3 (range 0.2–26.3 cm^3) at initial SRS but was reduced to 2.3 cm^3 (range 0.1–18.2 cm^3) 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 0-2 and 2-10 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 cm^3 (range, 0.1 to 20.7 cm^3) 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 patient a delayed cyst developed 56 months after SRS. No patient 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 cm^3 (range, 0.1 to 13.4 cm^3). 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 patient 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 cm^3 (range, 4.0 to 26 cm^3) in the first-stage SRS and 9.5 cm^3 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 2-stage SRS were 7%, 20%, 28%, and 36% at three, four, five, and 10 years, respectively. The 5-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 2-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 patient 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 0 -1, 1 -5, and 5 -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 patient died as a result of an adverse radiation effect. Delayed cyst formation did not occur in any patient 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.

Murray and Brau (2011) conducted a single-center, retrospective, case series analysis to describe a 10-year experience in the use of RS for individuals with AVMs. All individuals were treated by the first author, and demographic, clinical and radiographic data were obtained from retrospective chart review. A total of 83 individuals were treated and 86 RS procedures for AVMs were performed during a 10-year period. Eight individuals were lost to follow-up. The remaining 75 individuals included 36 males and 39 females with a median age of 34.5 years. Hemorrhage was the initial presentation in 40% of individuals. Fifty-seven AVMs (73%) were treated previously with endovascular neurosurgery, without success. The median volume of the malformation was 17.7 ml. Almost 65% of the malformations were considered large (≥ 10 ml) in volume. Forty individuals had AVMs with largest diameter ≥ 3.5 cm^3. The overall obliteration rate was 56.4%, and the median time for obliteration was 29 months. The AVMs ≥ 3.5 cm^3 in diameter had a greater latency period than those < 3.5 cm^3 (31 months vs. 46 months, respectively; p = 0.01). In addition, AVM obliteration was inversely associated with its volume, especially in large lesions (p = 0.037). Individuals achieving obliteration had lower SM scores compared with individuals in whom obliteration was not achieved (p = 0.009). Post RS hemorrhages were seen in nine cases. Eleven individuals underwent surgery after RS. Major neurological deficits developed in nine individuals, whereas 17 had only minor deficits. The occurrence of neurological deficits was significantly associated with lesions with volume ≥ 10 ml. The authors concluded that RS is a reasonable treatment option for AVMs in the majority of cases, in spite of large, difficult-to-treat malformations.

Maruyama et al. (2005) conducted single-center, retrospective, case series analysis to evaluate the risk of hemorrhage after RS for AVMs. Individuals with malformations who were treated with RS with the use of a Gamma Knife were included in the analysis. The rates of hemorrhage were assessed during three periods: before RS, between RS and the angiographic documentation of obliteration of the malformation (latency period), and after angiographic obliteration. A total of 500 individuals were included in the analysis. Forty-two hemorrhages were documented before RS (median follow-up, 0.4 year), 23 during the latency period (median follow-up, 2.0 years), and six after obliteration (median follow-up, 5.4 years). As compared with the period between diagnosis and RS, the risk of hemorrhage decreased by 54 percent during the latency period (HR, 0.46; 95% confidence interval [CI], 0.26 to 0.80; p = 0.006) and by 88 percent after obliteration (HR, 0.12; 95% CI, 0.05 to 0.29; p < 0.001). The risk was significantly reduced during the period after obliteration, as compared with the latency period (HR, 0.26; 95% CI, 0.10 to 0.68; p = 0.006). The reduction was greater among individuals who presented with hemorrhage than among those without hemorrhage at presentation and similar in analyses that considered the delay in confirming obliteration by means of angiography, and analyses that excluded data obtained during the first year after diagnosis. The authors concluded that RS significantly decreases the risk of hemorrhage in individuals with cerebral AVMs, even before there is angiographic evidence of obliteration, and the risk of hemorrhage is further reduced, although not eliminated, after obliteration.

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 note a limitations as small sample size and high risk of bias (Graffeo et al., 2020).

Meningioma

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. 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 cm^3; 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 5- 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 1- and 5-year radiation-related complication rate was 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 cm^3, 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 vs grade I meningiomas ($p < 0.001$), for female vs male individuals ($p < .001$), for sporadic vs multiple meningiomas ($p < .001$), and for skull base vs

convexity tumors (p < 0.001). 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.

Kondziolka et al. (2008) conducted a case series analysis to evaluate clinical and imaging outcomes of individuals with meningiomas stratified by histological tumor grade. A total of 972 individuals with 1,045 intracranial meningiomas managed during an 18-year period were included in the analysis. The series included 70% women, 49% of whom had undergone a previous resection and 5% of whom had received previous fractionated radiation therapy. Tumor locations included middle fossa (n = 351), posterior fossa (n = 307), convexity (n = 126), anterior fossa (n = 88), parasagittal region (n = 113), or other (n = 115). The overall control rate for individuals with benign meningiomas (WHO Grade I) was 93%. In those without previous histological confirmation (n = 482), tumor control was 97%. However, for individuals with WHO Grade II and III tumors, tumor control was 50 and 17%, respectively. Delayed resection after RS was necessary in 51 individuals (5%) at a mean of 35 months. After 10 years, Grade 1 tumors were controlled in 91% (n = 53); in those without histology, 95% (n = 22) were controlled. None of the individuals developed a radiation-induced tumor. The overall morbidity rate was 7.7%. Symptomatic peritumoral imaging changes developed in 4% of the individuals at a mean of eight months. The authors concluded that SRS provided high rates of tumor growth control or regression in individuals with benign meningiomas with low risk, and that their study confirms the role of RS as an effective management choice for individuals with small to medium-sized symptomatic, newly diagnosed, or recurrent meningiomas of the brain. (This study is included in the ISRS systematic review and meta-analysis below).

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-yr local control rate ranged from 71% to 100%. The 10-yr progression-free-survival rate ranged from 55% to 97%. The prescription dose ranged typically between 12 and 15 Gy, delivered in a single fraction. 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 include the retrospective nature of the majority of included studies in the 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, 2024).

Pineal Gland Tumors

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 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 1-, 3- and 5-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.

Hasegawa et al. (2002) conducted retrospective case series analysis of individuals with pineal parenchymal tumors and treated with SRS to clarify the role of SRS in conjunction with other surgical, radiation, and medical approaches. A total of 16 individuals who had undergone RS as the primary or adjuvant treatment for pineal parenchymal tumors were included in the analysis. Ten individuals (62.5%) had pineocytomas, two (12.5%) had mixed pineocytoma and pineoblastoma, and four (25%) had pineoblastomas. The mean marginal dose was 15 Gy, and the mean tumor volume was 5.0 cm^3. The mean follow-up periods from the time of diagnosis or the time of RS were 61 and 52 months, respectively. The overall actuarial 2- and 5-year survival rates after diagnosis were 75.0% and 66.7%, respectively. In 14 individuals who were evaluated with imaging, four (29%) demonstrated complete remission, eight (57%) had partial remission, two (14%) had no change, and no patient had local progression. The local tumor control rate (complete remission, partial remission, or no change) was 100%. Five individuals died during follow-up. One patient with a pineocytoma and three individuals with pineoblastomas died secondary to leptomeningeal or extracranial spread tumor. No cause of death was established for one patient. Two individuals developed AREs after RS. The authors concluded that SRS is a valuable primary management modality for individuals with pineocytomas, and as adjuvant therapy, RS may be used to boost local tumor dose during multimodality management of malignant pineal parenchymal tumors.

Pituitary Adenoma

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: 5–35 Gy) and HSRT in eight studies (median total dose: 21 Gy, range: 12–25 Gy, delivered in 3–5 fractions). The 5-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: 0–7%). 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 note 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).

Starke et al. (2012) conducted a single-center case series analysis of individuals with nonfunctioning pituitary macroadenomas and treated with GKS. A total of 140 individuals (56% were male) with a median age of 51 years (range, 21 to 82 years) were included in the analysis. The mean tumor volume was 5.6 cm^3 (range, 0.6 to 35 cm^3). Thirteen individuals were treated with GKS as primary therapy, and 127 had undergone at least one open resection prior to GKS. Ninety-three individuals had a history of hormone therapy prior to GKS. The mean maximal dose of GKS was 38.6 Gy (range, 10 to 70 Gy), the mean marginal dose was 18 Gy (range, 5 to 25 Gy), and the mean number of isocenters was 9.8 (range, 1 to 26). Follow-up evaluations were performed in all 140 individuals, ranging from 0.5 to 17 years (mean five years, median 4.2 years). Tumor volume remained stable or decreased in 113 (90%) of 125 individuals with available follow-up imaging. Kaplan-Meier analysis demonstrated radiographic progression free survival at two, five, eight, and 10 years to be 98%, 97%, 91%, and 87%, respectively. In multivariate analysis, a tumor volume greater than 5.0 cm^3 (HR, 5.0, 95% CI 1.5 to 17.2; p = 0.023) was the only factor predictive of tumor growth. The median time to tumor progression was 14.5 years. Delayed hypopituitarism occurred in 30.3% of individuals. No factor was predictive of post-GKS hypopituitarism. A new or worsening cranial nerve deficit occurred in 16 (13.7%) of 117 individuals. Visual decline was the most common neurological deficit (12.8%), and all individuals experiencing visual decline had evidence of tumor progression. In multivariate analysis, a tumor volume greater than 5.0 cm^3 (OR, 3.7, 95% CI 1.2 to 11.7; p = 0.025) and pre-GKS hypopituitarism (OR, 7.5, 95% CI 1.1 to 60.8; p = 0.05) were predictive of a new or worsened neurological deficit. The authors concluded that in individuals with nonfunctioning pituitary macroadenomas, GKS confers a high rate of tumor control and a low rate of neurological deficits.

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 patient and consisted of consistent headache. Of the 68 individuals with adrenocorticotropic 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 (GH) 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 the others however, treatment must be tailored to meet the patient's symptoms, tumor location, tumor morphometry, and overall health. The authors also recommend 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 recommend 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 re-irradiated with LINAC-based SRS and FSRT. Individuals were treated to a median dose of 25 Gy in 5 fractions. The median OS after (initial) diagnosis was 39 months with an actuarial 1-, 3-, and 5-year OS rates of 88%, 56%, and 30%, respectively. After treatment with SRS or FSRT, the median OS was nine months with an actuarial 1-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 (GBMs). 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 cm^3 and 3.80 cm^3, 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 ≥ 80 was independently associated with longer OS, while small tumor volume (< 15 cm^3) 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 vs. 3.2 months), while three were identified for OS (median OS of 15.2 vs. 10.5 vs. 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, 1 to 6), and median target volume and prescriptions were 7.0 cm^3 (range, 0.3 to 39.0 cm^3) 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 vs 35% showing purely recurrent tumor. The necrosis/mixed group had lower mean isodose prescription compared with the tumor group (16.2 vs. 17.8 Gy; p = 0.003) and larger mean treatment volume (10.0 vs. 5.4 cm^3; 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.

Maranzano et al. (2011) conducted a single-center case series analysis to evaluated long-term outcomes individuals with rGBM and re-irradiated with RS or fractionated stereotactic radiotherapy. A total of 22 individuals were treated with RS or FSRT for 24 lesions of recurrent glioblastoma. The male/female ratio was 14:8, median age 55 years (range, 27 to 81), and median KPS90 (range, 70 to 100). The majority of the cases (77%) was in recursive partitioning analysis classes III or IV RS or FSRT was chosen according to lesion size and location. Median time between primary radiotherapy and re-irradiation was 9 months. Median doses were 17 Gy and 30 Gy, whereas median cumulative normalized total dose was 141 Gy and 98 Gy for RS and fractionated stereotactic radiotherapy, respectively. All individuals that accepted RS had a cumulative normalized total dose of more than 100 Gy, whereas only a few (44%) of FSRT individuals had a cumulative normalized total dose exceeding 100 Gy. Median follow-up from re-irradiation was 54 months. At the time of analysis, all individuals had died. After re-irradiation, one (4%) lesion was in partial remission, 16 (67%) lesions were stable, and the remaining seven (29%) were in progression. Median duration of response was six months, and median survival from re-irradiation 11 months. Three of 13 (23%) individuals that accepted RS developed asymptomatic brain radionecrosis. The cumulative normalized total dose for the three individuals was 122 Gy, 124 Gy, and 141 Gy, respectively. In one case, the volume of the lesion was large (14 cc), and in the other two the interval between the first and second cycle of radiotherapy was short (five months). The authors concluded that re-irradiation with RS and FSRT is feasible and effective in individuals with recurrent glioblastoma, and apart from the importance of an accurate patient selection, cumulative radiotherapy dose and a correct indication for RS or FSRT must be considered to avoid brain toxicity.

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, 2024).

Trigeminal Neuralgia Refractory to Medical Therapy

Peciu-Florianu et al. (2021) conducted a systematic review and meta-analysis that focused on trigeminal neuralgia treated with SRS for meningiomas and vestibular schwannoma 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 recommend 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 radiosurgery (CKR) 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 CKR (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 CKR. Actuarial initial freedom from pain (FFP) 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 CKR. 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 CKR. 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 CKR. 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 Heath 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

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; I2 = 16%) from 19 studies had local control, and 378 of 478 individuals (0·81, 0·70-0·90; I2 = 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 recommend future research focusing on generating level 1 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 fractionated stereotactic radiation therapy (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 patient age was 54 years (range, 18 to 82 years) and 104 (58%) were male. The median tumor diameter and thickness was 10 mm (range, 2 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, 2 to 79 months). Complete and partial response was observed in eight and 104 eyes, respectively. The rate of 5-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 recommend 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.

Dieckmann et al. (2003) conducted a case series analysis to evaluate local tumor control and radiogenic side effects after fractionated LINAC based -SRS for uveal melanoma. A total of 90 individuals with uveal melanoma and treated at a LINAC with 6 MV were included in the analysis. The head was immobilized with a modified stereotactic frame system (BrainLAB). For stabilization of the eye position a light source was integrated into the mask system in front of the healthy or the diseased eye. A mini-video camera was used for on-line eye movement control. Tumors included in the study were either located unfavorably with respect to macula and optical disc (< 3 mm distance) or presented with a thickness > 7.0 mm. Median tumor volume was 305+/-234 mm^3 (range, 70 to 1,430 mm^3), and mean tumor height was 5.4+/-2.3 mm (range, 2.7 to 15.9 mm). Total doses of 70 (single dose 14 Gy @ 80% isodose) or 60 Gy (single dose 12 Gy @ 80% isodose) were applied in five fractions within 10 days. The first fractionation results in total dose (2 Gy) of 175 Gy for tumor and 238 Gy for normal tissue, corresponding values for the second fractionation schedule are 135 and 180 Gy, respectively. After a median follow-up of 20 months (range, 1 to 48 months) local control was achieved in 98% (n = 88). The mean relative tumor reductions were 24%, 27%, and 37% after 12, 24 and 36 months. Three individuals (3.3%) developed metastases. Secondary enucleation was performed in seven individuals (7.7%). Long term side effects were retinopathy (25.5%), cataract (18.9%), optic neuropathy (20%), and secondary neovascular glaucoma (8.8%). The authors concluded that fractionated LINAC based stereotactic photon beam therapy in conjunction with a dedicated eye movement control system is a highly effective method to treat unfavorably located uveal melanoma, and that total doses of 60 Gy (single dose 12 Gy) are considered to be sufficient to achieve good local tumor control.

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, 2024).

Palliative Treatment of Bone Metastases of the Spine

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). 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 0-2, 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 vs 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. Limitation 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 radiation therapy 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, quality of life, and patient values and goals. Per the guideline:

- 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 1 fraction, 1600 cGy in 2 fractions, 2000 cGy in 5 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 1 fraction (nonspine) and 2400cGY in 2 fractions (spine) are recommended. (Strength of recommendation: strong; quality of evidence: moderate).
- For patients with symptomatic bone metastases with ECOG PS 0-2, 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).

National Comprehensive Cancer Network (NCCN)

Per NCCN guidelines regarding radiation therapy 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 (NCCN, 2024).

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 October 8, 2024)

References

Alcorn S, Cortés ÁA, 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 September 23, 2024.

American Society for Radiation Oncology (ASTRO) website. ASTRO Radiation Oncology Coding Resource 2024. Available at https://www.astro.org/Daily-Practice/Coding/Coding-Resource. September 1, 2024.

American Society for Radiation Oncology (ASTRO) website. ASTRO stereotactic body radiation (SBRT) model policy. June 2022. Available at https://www.astro.org/ASTRO/media/ASTRO/Daily%20Practice/PDFs/ASTROSBRTModelPolicy.pdf. Accessed September 23, 2024.

American Society for Radiation Oncology (ASTRO) website. ASTRO stereotactic radiosurgery (SRS) model policy. June 2022. Available at https://www.astro.org/ASTRO/media/ASTRO/Daily%20Practice/PDFs/ASTRO-SRS_ModelPolicy.pdf. Accessed September 23, 2024.

Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomized trial. Lancet. 2004;363(9422):1665-1672.

Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA. 2006;295(21):2483-2491.

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.

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.

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.

Dieckmann K, Georg D, Zehetmayer M, et al. LINAC based stereotactic radiotherapy of uveal melanoma: 4 years clinical experience. Radiother Oncol. 2003 May;67(2):199-206.

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.

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.

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.

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.

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.

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.

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.

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, Kida Y, Kato T, et al. Long-term safety and efficacy of stereotactic radiosurgery for vestibular schwannomas: evaluation of 440 patients more than 10 years after treatment with Gamma Knife surgery. J Neurosurg. 2013;118(3):557-565.

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

Kobayashi T, Kida Y, Mori Y, et al. Long-term results of gamma knife surgery for the treatment of craniopharyngioma in 98 consecutive cases. J Neurosurg. 2005;103(6 Suppl):482-488.

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.

Koong AC, Le QT, Ho A, et al. Phase I study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2004;58(4):1017-1021.

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.

Lim M, Gibbs IC, Adler JR, Chang SD. Efficacy and safety of stereotactic radiosurgery for glomus jugulare tumors. Neurosurg Focus. 2004;17(2):E11. Published 2004 Aug 15.

Mahadevan A, Miksad R, Goldstein M, et al. Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreas cancer. Int J Radiat Oncol Biol Phys. 2011;81(4):e615-e622.

Maranzano E, Anselmo P, Casale M, et al. Treatment of recurrent glioblastoma with stereotactic radiotherapy: long-term results of a mono-institutional trial. Tumori. 2011;97(1):56-61.

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.

Maruyama K, Kawahara N, Shin M, et al. The risk of hemorrhage after radiosurgery for cerebral arteriovenous malformations. N Engl J Med. 2005;352(2):146-153.

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.

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.

Murray G, Brau RH. A 10-year experience of radiosurgical treatment for cerebral arteriovenous malformations: a perspective from a series with large malformations. Clinical article. J Neurosurg. 2011;115(2):337-346.

Naruke T, Tsuchiua 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 Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Bone cancer. V1.2025.

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

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

V2.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Kidney cancer. V2.2025.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Melanoma: uveal. V1.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. V8.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Pancreatic adenocarcinoma. V3.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Prostate cancer. V4.2024.

National Comprehensive Cancer Network (NCCN) Radiation Therapy Compendium®.

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

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.

Noël G, Habrand JL, Jauffret E, et al. Radiation therapy for chordoma and chondrosarcoma of the skull base and the cervical spine. Prognostic factors and patterns of failure. Strahlenther Onkol. 2003;179(4):241-248.

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.

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.

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):djx015.

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.

Santacroce 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.

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.

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., 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.

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

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

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.

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.

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
05/01/2025	**Template Update** • Created shared policy version to support application to Rocky Mountain Health Plans membership **Supporting Information** • Archived previous policy version 2025T0611H

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.