Stereotactic Body Radiation Therapy and Stereotactic Radiosurgery (for Kentucky Only)

Policy Number: CS180KY.02
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➲ Instructions for Use

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Related Policies

- Intensity-Modulated Radiation Therapy (for Kentucky Only)
- Proton Beam Radiation Therapy (for Kentucky Only)
- Radiation Therapy: Fractionation, Image-Guidance, and Special Services (for Kentucky Only)

Application

This Medical Policy only applies to the state of Kentucky.

Coverage Rationale

Stereotactic radiation therapy including stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) for the brain, skull, or neck is proven and medically necessary under certain circumstances. For medical necessity clinical coverage criteria, refer to the InterQual® CP: Procedures, Stereotactic Radiosurgery, Brain, or Skull Base.

Click here to view the InterQual® criteria.

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

- 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
- 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 up to 3 metastatic lesions, 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
    - SBRT must be completed in 5 fractions for an entire course of treatment regardless of number of lesions treated
- Glomus jugulare tumors
- Recurrent gliomas
- To treat a previously irradiated field
- Uveal melanoma

Definitions

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 sites are considered to have Oligometastatic Disease. However, progression of a limited number of metastatic sites 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

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

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

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 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

Chordoma and Chondrosarcoma

Kano et al. (2015) conducted a multicentered retrospective evaluation to analyze the outcome of SRS for patients with chondrosarcoma who underwent this treatment as part of a multimodality management. Forty-six patients who underwent SRS for skull-based chondrosarcomas were identified at seven participating centers of the North American Gamma Knife Consortium (NAGKC). Thirty-six patients had previously undergone tumor resections and five had been treated with fractionated radiation therapy. The median tumor volume was 8.0 cm3 (range 0.9-28.2 cm3), and the median margin dose was 15 Gy (range 10.5-20 Gy). At a median follow-up of 75 months after SRS, eight patients 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 patients. 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 patients required salvage resection, and three patients (7%) developed AREs. Cranial nerve deficits improved in 22 (56%) of the 39 patients who deficits before SRS. Clinical improvement after SRS was noted in patients 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 patients. The authors concluded that SRS provided a reasonable benefit-to-risk profile for patients 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 patients who present with diplopia related to abducens nerve palsy.

Hasegawa et al. (2007) conducted a case series analysis to evaluate outcomes of patients 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 patients (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 patients 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 patients 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 patients 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 patients with chordomas and chondrosarcomas. A total of 28 patients 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 patients, 93%). In two patients, SRS was the sole treatment. Twenty-six patients 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 patients.

Noël et al. (2003) conducted a single-center case series analysis to evaluate outcomes of patients 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 patients 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 LC 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 patients died from their tumor and one from a nonrelated condition (pulmonary embolism). The maximum tumor diameter and the GTV were larger in relapsing patients, 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 $\leq$ 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 LC. On multivariate analysis, only age was an independent prognostic factor of LC. The authors concluded that in patients 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 guideline 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, 2023).

Craniopharyngioma

Lee et al. (2014a) conducted a single-center case series analysis to report long-term outcomes of patients with craniopharyngioma and treated with RS, and to define the prognostic factors of craniopharyngioma. Patients with craniopharyngioma were treated by GKS and then, all the patients underwent clinical and endocrinological evaluations at an average of 6-month intervals. Patient 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 patients who underwent 162 sessions of GKS treatments were included in the analysis. The patients' 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 patients who had clinical follow-up, new-onset or worsened pituitary deficiencies were detected in 11 patients (8.0%). Two patients without tumor growth had a worsened visual field, and one patient 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 patients 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 LC rate (for both solid tumor and cyst control) was 91%, 81%, and 68% at one, three, and five years, respectively. No patients with normal pituitary function developed hypopituitarism after SRS. Two patients 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 patients treated with GKS for residual or recurrent craniopharyngiomas after microsurgery, and the effects of dose reduction. A total of 107 patients with craniopharyngiomas were treated with GKS, and 98 patients 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 patients died. Deterioration both in vision and endocrinological functions were documented as side effects in six patients (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 patients with HCC in a hepatitis B virus-endemic area. Eligible patients were aged ≥ 20 years who were diagnosed with unresectable HCC. Patients 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 LC, PFS, and OS rates. A total of 74 patients were enrolled, and 65 eligible patients 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 patients who underwent EGD. The 2-year and 3-year LC 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 patients 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 patients, 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 patients with tumors sized > 2 cm, but no significant difference was observed in patients 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 hepatocellular carcinoma (HCC). A search, using predetermine criteria, was performed using PubMed, Medline, Embase, and Cochrane Library databases. Primary endpoints were OS and LC, and the secondary endpoint was grade ≥ 3 complications. A total of 32 studies, comprising 33 cohorts and consisting of 1,950 patients 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 LC 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 LC rates. In addition, radiation dose showed no difference for OS and a marginal difference for 1-year LC rate. Pooled rates of hepatic and gastrointestinal 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 LC persisting up to three years. They reported that both OS and LC were affected by tumor size, and radiation dose marginally affected LC, 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 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).

National Comprehensive Cancer Network (NCCN)

The NCCN guideline for hepatocellular carcinoma 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, 2023).

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

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 patients 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 patients were enrolled with 31 patients randomized to SABR and 27 patients 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 patients 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%) patients in the SABR group had grade 3 treatment-related adverse events (three patients with chest wall pain, two with dyspnea or cough, and one with fatigue and rib fracture). No patients given SABR had grade four events or treatment-related death. In the surgery group, one (4%) patient died of surgical complications and 12 (44%) patients had grade 3–4 treatment-related adverse events. Grade 3 events occurring in more than one patient in the surgery group were dyspnea (four patients), chest pain (four patients), and lung infections (two patients). 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 patients needing a lobectomy, and that the equipoise suggested by the results justifies efforts for additional randomized clinical trials.

Haasbeek et al. (2010) conducted a single-center case series analysis to evaluate outcomes of stereotactic radiotherapy (SRT) in elderly patients. Patients diagnosed with stage IA/IB NSCLC and aged ≥ 75 years at the time of SRT were included. SRT was delivered using three fractionation schemes: fractions of 20 grays (Gy) (for T1 tumors), five fractions of 12 Gy (for T1 tumors with broad contact with the chest wall and for T2 tumors), or eight fractions of 7.5 Gy (for tumors adjacent to the heart, large blood vessels, hilus, brachial plexus, or mediastinum). Patients 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 patients aged ≥ 75 years were treated using SRT (118 T1 tumors, 85 T2 tumors). The median patient age was 79 years, 80% of patients were considered medically inoperable, and 20% of patients 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 patients. 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 patients), 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 LC rate at three years was 89%. Acute toxicity was rare, and late Radiation Therapy Oncology Group grade ≥ 3 toxicity was observed in < 10% of patients. The authors concluded that SRT achieved high LC rates with minimal toxicity in patients aged ≥ 75 years despite their significant medical comorbidities and that these results indicated that more active diagnostic and therapeutic approaches are justified in elderly patients, 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 patients with early stage but medically inoperable lung cancer. Patients with biopsy-proven peripheral T1-T2, N0, M0 non-small cell tumors less than 5 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 patients accrued, of which 55 were evaluable (44 T1 and 11 T2 tumors) with a median follow-up of 34.4 months (range, 4.8 to 49.9 months). Only 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 patients 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 patients experienced regional failure; the local-regional control rate was 87.2% (95%CI, 71.0%, 94.7%). Eleven patients experienced disseminated recurrence; the 3-year rate of disseminated failure was 22.1% (95% CI, 12.3% to 37.8%). The rates of DFS and OS at 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 patients (12.7%; 95% CI, 9.6% to 15.8%); grade 4 events were reported in two patients (3.6%; 95%CI, 2.7% to 4.5%). No grade 5 adverse events were reported. The authors concluded that patients with inoperable NSCLC who received SBRT had a survival rate of 55.8% at 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 patients with medically inoperable Stage I NSCLC (Timmerman 2003 and McGarry 2005). A total of 70 medically inoperable patients who had clinically staged T1 (34 patients) or T2 (36 patients) (≤ 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 LC at three years was 88.1%. Regional (nodal) and distant recurrence occurred in six (8.6%) and nine (12.9%) patients, 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 patients 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 patients with peripheral vs. central tumors (MS 33.2 vs. 24.4 months, p = 0.697). Grade 3 to 5 toxicity occurred in five of 48 patients with peripheral lung tumors (10.4%) and in six of 22 patients (27.3%) with central tumors (Fisher's exact test, p = 0.088). The authors concluded that use of SBRT results in high rates of LC in medically inoperable patients 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 LC in patients 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 patients with Stage I NSCLC. The authors reported that LC 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 patients (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 patients 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 patients 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 patients (5.4%). Local progression occurred in 36 patients (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 patients 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, LC and survival rates are superior to those of conventional RT, HypoFXSRT should be a standard of care for medically inoperable patients, and additional studies that randomly compare HypoFXSRT and surgery for medically operable patients 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 guideline 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, 2023).

Definitive Treatment of Pancreatic Adenocarcinoma Without Evidence of Distant Metastasis

In a retrospective review, Zhong et al. (2017) compared SBRT with conventionally fractionated radiation therapy (CFRT) in locally advanced pancreatic cancer (LAPC) using the National Cancer Database. Patients 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 CFRT. Overall survival was the primary outcome. The total number of patients included in the review was 8,450, CFRT = 7,819 and SBRT = 631. Receipt of SBRT was associated with superior OS in the multivariate analysis (hazard ratio, 0.84; 95% confidence interval, 0.75–0.93; $p < .001$). With propensity score matching, 988 patients in all were matched, with 494 patients 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 CFRT. The authors concluded SBRT was superior to OS when compared with CRFT, 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 patients 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 patients treated with GEM and a single 25-Gy fraction of SBRT. Patients with locally advanced pancreatic cancer (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, patients 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 Radiation Therapy Oncology Group radiation morbidity scoring criteria. Patients completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) and pancreatic cancer-specific QLQ-PAN26 module before SBRT and at four weeks and four months after SBRT. A total of 49 patients 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 patients 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). Patients reported a significant improvement in pancreatic pain (p = 0.001) 4 weeks after SBRT on the QLQ-PAN26 questionnaire. The median plasma carbohydrate antigen 19-9 (CA 19-9) level was reduced after SBRT [median time after SBRT, 4.2 weeks; 220 U/mL 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 patients (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 locally advanced pancreatic cancer (LAPC). The center's internal database was queried to identify all patients who received at least one dose of induction chemotherapy and SBRT for the treatment of BRPC or LAPC. After staging, medically fit patients underwent chemotherapy for 2–3 months, with regimen at the discretion of the treating medical oncologist. Then, patients 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 patients, 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 patients who completed neoadjuvant therapy was 51% and 96%, respectively. Estimated median OS was 19.2 months for BRPC patients and 15.0 months for LAPC patients (p = 0.402). Median OS was 34.2 months for surgically resected patients versus 14.0 months for unresected patients (p < 0.001). Five of 21 (24%) patients with LAPC received FOLFIRINOX chemotherapy underwent R0 resection. Among patients 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 patients 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 patients 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 patients were considered for resection. The primary endpoints were OS and PFS. A total of 73 patients 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 patients (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 patients 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 patients 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 patients. The 1-year LC in nonsurgical patients 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 patients with BRPC pancreatic cancer while maintaining a high rate of LC in unresectable patients, 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 patients with BRPC and LAPC who underwent surgery after neoadjuvant SBRT. Patients were treated with SBRT followed by resection and chemotherapy was to the discretion of the medical oncologist and preceded SBRT for most patients. A total of 12 patients were included in the analysis. Most (92%) received neoadjuvant chemotherapy, and gemcitabine/capecitabine was most frequently prescribed (n = 7). Most patients 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 patients 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 patients (n = 11/12). In 25% (n = 3/12) of patients, 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 patients 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 patients with locally advanced pancreatic cancer who received a planned strategy of initial chemotherapy with restaging and then, for those patients with no evidence of metastatic progression, treatment with SBRT. Patients received GEM (1,000 mg/m^2 per week for 3 weeks then 1 week off) until tolerance, at least six cycles, or progression. Patients 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 patients were included in the analysis. Of those, 8 (17%) patients were found to have metastatic disease after two cycles of GEM; the remaining 39 patients received SBRT. The median follow-up for survivors was 21 months (range, six to 36 months). The median OS for all patients who received SBRT was 20 months, and the median PFS was 15 months. The LC rate was 85% (33 of 39 patients); and 54% of patients (21 of 39) developed metastases. Late Grade III toxicities such as GI bleeding and obstruction were observed in 9% (3/39) of patients. The authors concluded that for patients 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 patients.

Koong et al. (2004) conducted a phase I dose escalation study to determine the feasibility and toxicity of delivering SRS to patients with LAPC. Patients 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 gastrointestinal toxicity was scored according to the Radiation Therapy Oncology Group criteria. Response to treatment was determined by serial high-resolution computed tomography scanning. A total of 15 patients were treated at the 3 dose levels (three patients received 15 Gy, five patients received 20 Gy, and seven patients received 25 Gy). At those doses, no grade 3 or higher acute gastrointestinal toxicity was observed. This trial was stopped before any dose-limiting toxicity was reached, because the clinical objective of LC was achieved in all six evaluable patients treated at 25 Gy. The authors concluded that it is feasible to deliver SRS to patients with locally advanced pancreatic cancer, and the recommended dose to achieve LC without significant acute gastrointestinal toxicity is 25 Gy.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

The NCCN guideline for pancreatic adenocarcinoma states that as first-line therapy, SBRT may be used in select patients 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 (2023).

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 gastrointestinal (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 patients. Twenty-two studies were clinical trials, of which one was a phase I trial that included 45 patients, four were phase 1/II trials that included 245 patients, 17 were phase II or III trials that included 2,174 patients, and 16 were prospective observational studies, which included 3,652 patients. 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 patients, 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 genitourinary and gastrointestinal 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. Patients 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 patients 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 patients vs. 132 (23%) of 578 patients; 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 patients vs. 13 (2%) of 529 patients; 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 patients 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 external beam radiation therapy (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 guideline for prostate cancer states that SBRT is acceptable in practices with appropriate technology, physics, and clinical expertise (2023).

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 patients 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 patients 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 patients 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 patients with oligorecurrent prostate cancer. All prospective studies including prostate cancer patients 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 patients, 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 prostate cancer oligometastatic patients. 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 Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases (SABR-COMET) trial. The SABR-COMET trial was a multi-center, randomized, phase II, open-label, randomized trial to assess standard of care palliative treatments with or without SABR in patients with a controlled primary tumor and up to five metastatic lesions (Palma 2012). Eligible patients 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. Patients were seen every three months after randomization for the first two years, and every six months thereafter. A total of 99 patients 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 patients 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 patients in the control group and 35 (53%) of 66 patients 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, patients with controlled primary tumors and one to five oligometastases who received SABR demonstrated a 22-month improvement in median OS compared with patients 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 patients 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 patients who received LCT compared to patients 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 patients (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 patients 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 patients 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 International Stereotactic Radiosurgery Society guideline below).

Iyengar et al. (2018) conducted a single-center, phase II, randomized trial to determine if noninvasive stereotactic ablative radiotherapy (SAbR) prior to maintenance chemotherapy in patients with non–progressive limited metastatic NSCLC after induction therapy led to significant improvements in PFS. Patients 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 patients (nine women and 20 men) were enrolled; 14 patients 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 patients 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 patients 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 patients 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 patients 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 International Stereotactic Radiosurgery Society 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 patients with non-resectable colorectal liver metastases. A total of 119 patients with unresectable colorectal liver metastases (< 10 metastases and no extrahepatic disease) participated in the study. Fifty-nine patients were randomized to systemic treatment alone and 60 patients 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%) patients 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 patients died of progressive disease (35 patients in the combined modality arm, 49 patients 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 patients 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 ten (IQR 5 to 24) months. In ten of 11 studies, there was no demonstrable difference in OS. Seven RCTs, published from 1995 to 2016, randomly assigned 3,325 patients 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

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

Iyengar et al. (2023), developed an ASTRO/ESTRO Clinical Practice 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

An ESTRO/ASTRO consensus document defined oligometastatic disease as one to five metastatic lesions, with a controlled primary tumor being optional, but where all metastatic sites must be safely treatable (Lievens et al, 2020).

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 patients with glomus tumors who underwent RS. A total of 134 patient procedures (132 unique patients) were included in the study. Prior resection was performed in 51 patients, and prior fractionated external beam radiotherapy was performed in six patients. The patients' 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 patients at last follow-up; actuarial tumor control was 88% at five years post radiosurgery. 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. Patients demonstrating new or progressive cranial nerve deficits were also likely to demonstrate tumor progression ($p = 0.002$). Pulsatile tinnitus improved in 49% of patients who reported it at presentation. New or progressive cranial nerve deficits were noted in 15% of patients; improvement in preexisting cranial nerve deficits was observed in 11% of patients. None of the patients 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 patients, and overall neurological status and cranial nerve function were preserved or improved in the majority of patients after RS.

Guss et al. (2011) performed a systematic review and meta-analysis regarding management of glomus jugulare with radiosurgery. 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 radiosurgery for glomus jugulare tumors. Nineteen studies with a total of 335 patients were included in the meta-analysis. Data on 335 glomus jugulare patients were extracted, including 278 who had received gamma knife and 57 who had received linear accelerator (LINAC) or CyberKnife. The results across all studies found 97% of patients achieved tumor control, and 95% of patients achieved clinical control. Eight studies reported a mean or median follow-up time of > 36 months. In these studies, 95% of patients 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, radiosurgery should be considered for the primary management of glomus jugulare tumors. The authors recommend future prospective studies with larger patient numbers treated with radiosurgery 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 patients with 16 tumors were included in this analysis. All patients were treated with frame-based LINAC or CKRS, with doses ranging from 1,400 to 2,700 cGy. Patients were assessed for posttreatment side effects, which included hearing loss, tongue weakness, and vocal hoarseness. The patients' 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 patients 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 glomus jugulare tumors and results in low rates of morbidity.

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 progression-free survival, 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 progression-free survival 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 patients who underwent CyberKnife treatment alone, compared to 9.5 months for patients 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 patients with WHO grade III gliomas and patients 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 fractionated stereotactic radiotherapy (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 patients aged 23 to 74 years were re-irradiated with LINAC-based SRS and fSRT. Patients 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%. LC, assessed for 28 tumors, after six months was 57%, while LC after one year was 39%. Three patients 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 LC in the salvage setting.

Sharma et al. (2018) conducted a single-center, retrospective, case series analysis to evaluate the role of SRS in patients with recurrent glioblastoma (GBMs). Patients' 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 patients 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 patients 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. Patients 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 patients 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 patients (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 patients, 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 patients with rGBM and re-irradiated with RS or fractionated stereotactic radiotherapy. A total of 22 patients 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 patients that accepted RS had a cumulative normalized total dose of more than 100 Gy, whereas only a few (44%) of fSRT patients had a cumulative normalized total dose exceeding 100 Gy. Median follow-up from re-irradiation was 54 months. At the time of analysis, all patients 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%) patients that accepted RS developed asymptomatic brain radionecrosis. The cumulative normalized total dose for the three patients 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 recurrent glioblastoma patients, 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.

Uveal Melanoma

In a systematic review and meta-analysis, Parker et al. (2020) evaluated the clinical outcomes of patients 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; 1,010 patients had uveal melanoma and three with intraocular metastasis. The authors found that 840 of 898 patients (0·96, 95% CI 0·94-0·97; I2 = 16%) from 19 studies had LC, and 378 of 478 patients (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 patients 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 (EFS). Secondary endpoints included OS, DFS, distant metastasis-free survival (DMFS), visual acuity (VA), and late treatment toxicity. LC 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 patients (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 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 patients. 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 EFS 73%. There was a significant correlation between tumor size and DFS, SRS/FSRT dose and EFS; 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 patients 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 (TD) (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) LC was achieved in 98% (n = 88). The mean relative tumor reductions were 24%, 27%, and 37% after 12, 24 and 36 months. Three patients (3.3%) developed metastases. Secondary enucleation was performed in seven patients (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 guideline 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, 2023).

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 July 13, 2023)

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Policy History/Revision Information

Date	Summary of Changes
11/01/2024	**Template Update** • Modified font and InterQual® reference link styles; no change to policy content

04/01/2024	**Coverage Rationale**
	• Revised list of proven and medically necessary indications for stereotactic radiation therapy, including stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT):
	  ○ Added:
	  ▪ Craniopharyngioma
	  ▪ Glomus jugulare tumors
	  ○ Removed “acoustic neuroma (vestibular schwannoma)”
	  ○ Revised coverage criteria extracranial Oligometastatic Disease; added criterion requiring “SBRT must be completed in 5 fractions for an entire course of treatment regardless of number of lesions treated”
	Supporting Information
	• Updated *Description of Services, Clinical Evidence*, and *References* sections to reflect the most current information
	• Archived previous policy version CS180KY.01

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state, or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state, or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state, or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state, or contractual requirements for benefit plan coverage. 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.

UnitedHealthcare uses InterQual® for the primary medical/surgical criteria, and the American Society of Addiction Medicine (ASAM) for substance use, in administering health benefits. If InterQual® does not have applicable criteria, UnitedHealthcare may also use UnitedHealthcare Medical Policies, Coverage Determination Guidelines, or Utilization Review Guidelines that have been approved by the Kentucky Department for Medicaid Services. The UnitedHealthcare Medical Policies, Coverage Determination Guidelines, or Utilization Review Guidelines 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.