Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT)

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DESCRIPTION

Stereotactic radiosurgery (SRS) (also referred to as stereotactic ablative surgery) is a form of radiation therapy used to deliver a large dose of ionizing radiation with a high degree of precision and spatial accuracy while sparing surrounding healthy tissue. SRS may be used to treat a variety of benign and malignant disorders involving intracranial structures, as well as select extracranial lesions.

Stereotactic body radiation therapy (SBRT) (also referred to 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 a very high accuracy, substantially higher doses per treatment that those given in conventional fractionation while minimizing radiation exposure to adjacent normal tissue.

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

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

Delivery systems for SRS and SBRT include, but may not be limited to, the following:

- **Cyberknife** is a radiation delivery system that consists of a lightweight linear accelerator device (LINAC) that is mounted to a multi-jointed robotic arm. This device reportedly utilizes a proprietary real-time image-guidance system to deliver stereotactic radiosurgery or radiotherapy. It was designed to enable access hard to reach or complex shaped tumors that may not be accessible by surgery and other radiosurgical technologies.
- **Gamma Knife** (e.g., Perfexion SRS system, Target System, Gamma Knife Icon, Leksell, Akesis Galaxy) is s radiosurgery technology, which by design is restricted to treating brain tumors. The device utilizes ionizing radiation (gamma rays) produced by 201 radioactive colbalt-60 sources to ablate intracranial targets via a fixed stereotactic frame.
- **GammaPod** is a stereotactic radiotherapy system that is designed to deliver SBRT by purportedly using thousands of individual focused beams from 36 rotating radioactive Cobalt-60 sources. It is intended for use in the noninvasive stereotactic delivery of radiation to a portion of the breast in conjunction with breast conserving treatment. The individual will lie prone on a table with the breast immobilized in a vacuum-assisted cup, which supposedly provides increased accuracy in the delivery of the radiation.

Clinical Context and Therapy Purpose

Stereotactic radiosurgery (SRS) (also referred to as stereotactic ablative surgery) is a form of radiation therapy in which three-dimensional (3D) images are utilized to specifically direct focused radiation to obliterate abnormal tissues while sparing surrounding healthy tissue.

Stereotactic body radiation therapy (SBRT) (also referred to as stereotactic ablative radiotherapy [SABR]) a method used to deliver external beam radiation therapy to a well-defined extracranial target in 5 fractions or less. It can deliver, with a very high accuracy, substantially higher doses per treatment that those given in conventional fractionation while minimizing radiation exposure to adjacent normal tissue.

Populations
The relevant population of interest is individuals with neoplastic and non-neoplastic conditions.

Interventions
The therapy being considered is stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT).

Comparators
Alternatives to SRS and SBRT include, but may not be limited to, the following:

- Chemotherapy
- Deep brain stimulation
- Endovascular embolization
- Intensity modulated radiation therapy (IMRT)
- Prescription drug therapy
- Proton beam radiation therapy
- Radiotherapy
- Surgical removal

Outcomes
The outcomes of interest are overall survival (OS), symptom improvement, and treatment-related morbidity.

Clinical Input 2018
In 2018, Clinical input was sought by the BCBSA to help determine whether the use of SRS and SBRT for individuals with various neoplastic/non-neoplastic conditions would provide a clinically meaningful improvement in the net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 5 respondents, including 2 specialty society-level responses, 1 of which included multiple specialty societies, and 3 physician-level responses either identified by specialty societies or an academic medical center, while this policy was under review.

Review of Evidence
The review of evidence regarding stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) includes systematic reviews, randomized controlled trials (RCTs), nonrandomized observational studies (comparative/noncomparative) and case series.

Summary of Evidence
Cardiac radioablation (CRA) is currently being studied as a possible treatment for end-stage ventricular tachycardia (VT). This non-invasive treatment uses SBRT to ablate the diseased myocardium harboring the VT circuit(s) while sparing as much of the surrounding healthy cardiac tissue as possible. The ENCORE study was one of the early studies that evaluated the efficacy of CRA for VT. Despite encouraging results, the

authors concluded that due to limited long-term follow-up, treatment at a single center, and limited number of patients and narrow patient selection, which prohibited generalization to a larger population this technique remains investigational. Further evaluation of the necessity or optimal patient selection for use of this modality will be important necessitating the need of additional randomized controlled trials to demonstrate the safety and efficacy of this treatment approach for VT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

For individuals with tremor and movement disorder, the evidence related to the use of SRS includes a systematic review and nonrandomized observational studies, many of which reported outcomes from the treatment of tremors of varying etiologies. Most studies report improvements in standardized tremor scores, although few studies used a blinded evaluation of tremor score, allowing for bias in assessment. No studies comparing SRS with alternative methods of treatment, or a control group were identified. Limited long-term follow-up is available, making the long-term risk-benefit ratio of an invasive therapy uncertain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with non-neoplastic intracranial conditions (e.g., trigeminal neuralgia refractory to medical management), the evidence includes systematic reviews and case series. Clinical input supports SRS provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice. Based on clinical input and professional society guidelines the evidence is sufficient to determine that the technology results in an improvement in net health outcomes.

For individuals with benign neoplastic intracranial lesions (arteriovenous malformations less than 3cm in size and poor surgical risk or surgically inaccessible, acoustic neuromas, pituitary adenomas, craniopharyngiomas, pineocytomas, schwannoma, glomus jugulare tumors) the published evidence for the use of SRS remains limited to systematic reviews

of nonrandomized observational studies, other nonrandomized observational studies, and case series. These reports would suggest that long-term outcomes of fractionated radiosurgery for these benign neoplasms are associated with good local control and acceptable treatment-related side effects. Clinical input supports SRS provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice. Based on clinical input and professional society guidelines the evidence is sufficient to determine that the technology results in an improvement in net health outcomes.

For individuals with central nervous system (CNS) cancers (i.e., gliomas, meningiomas, adult medulloblastomas, adult intracranial and spinal ependymoma with spine or brain recurrence, metastatic spinal tumors), clinical input supports SRS provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice. Based on clinical input and professional society guidelines the evidence is sufficient to determine that the technology results in an improvement in net health outcomes.

For individuals with malignant neoplastic intracranial conditions (i.e., brain metastases), the evidence includes systematic reviews, randomized controlled trials (RCTs), and nonrandomized observational studies. The existing evidence body indicates that SRS improves outcomes in the treatment of brain metastases. Stereotactic radiosurgery appears to be feasible for treatment of larger numbers (e.g., >10) of brain metastases, and outcomes after SRS treatment do not appear to be worse for patients with larger numbers of metastases, at least for patients with ≤10 metastases. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have uveal melanoma, evidence for use of SRS is limited to a meta-analysis of case series and individual case series. The condition is rare with poor clinical outcomes and treatment options. Clinical input supports SRS provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice. Clinical input reported that the use of SRS to treat uveal melanoma could provide patients with low-risk disease (based on tumor size using the Collaborative Ocular Melanoma Study definition of small and medium) an option to avoid or postpone enucleation with preservation of some visual acuity and functional abilities. Based on clinical input and professional society guidelines the evidence is sufficient to determine that the technology results in an improvement in net health outcomes.

For individuals who have primary and metastatic spinal or vertebral body tumors who have received prior radiotherapy who are treated with SBRT, the evidence includes an RCT that compared SBRT to external beam radiotherapy (EBRT) in patients with painful spinal metastasis and observational literature that primarily addresses metastases that recur after prior radiotherapy. Repeat administration of conventional radiation therapy increases the risk of treatment-related myelopathies. Nonrandomized study results are sufficient to determine that SBRT improves outcomes (reduces pain) in patients with

spinal (vertebral) tumors. Clinical input supports that SBRT provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice. Clinical input reported that SBRT is an important treatment option for patients whose spinal tumors had prior radiotherapy because of the ability to spare the spinal cord and escalate tumor dose. Based on clinical input, literature, and professional society guidelines the evidence is sufficient to determine that the technology results in an improvement in net health outcomes.

For individuals who have T1 and T2A non-small cell lung cancer (NSCLC), there is no direct comparative evidence for the use of SBRT compared to surgical resection in patients with stage T1 and T2A cancer without nodal or distant disease. Although no direct comparative evidence is available, evidence suggests that survival rates may be similar for SBRT and surgical resection for patients with stage T1 and T2A NSCLC tumor (not >5 cm in diameter) who show no nodal or distant disease and who are not candidates for surgical resection because of comorbid conditions. Additionally, SBRT was associated with improved survival and a reduced risk of adverse events as compared to conventional radiotherapy or radiofrequency ablation in inoperable NSCLC. Clinical input supports that this use provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected patients. The following patient selection criteria are based on clinical expert opinion from clinical study populations: patients with NSCLC who are poor surgical candidates or who do not wish to undergo surgery. Based on clinical input, literature, and professional society guidelines the evidence is sufficient to determine that the technology results in an improvement in net health outcomes.

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

For individuals who have primary prostate carcinoma on the use of SBRT the evidence consists of systematic reviews, retrospective comparative studies, and noncomparative studies. Noncomparative observational studies of SBRT have reported increased patient survival compared with historical data. Limited clinical input reported that the use of SBRT to treat primary prostate cancer provides biochemical control of disease (based on prostate-specific antigen surveillance), preserved quality of life (primarily focused on erectile dysfunction) and acceptable short-term urinary tract toxicity posttreatment. This

input did not differentiate candidate patients using guideline-based risk stratification for localized prostate cancer. Based on clinical input, literature, and professional society guidelines the evidence is sufficient to determine that the technology results in an improvement in net health outcomes.

For individuals who have pancreatic adenocarcinoma, the evidence for the use of SBRT consists of systematic reviews, retrospective comparative studies, and noncomparative studies. Limited clinical input reported that the use of SBRT for inoperable pancreatic adenocarcinoma also referred to guideline-based recommendations for use in localized disease. Based on clinical input, literature, and professional society guidelines the evidence is sufficient to determine that the technology results in an improvement in net health outcomes.

For individuals who have renal cell carcinoma (RCC), the evidence consists of systematic reviews of case series and observational studies. Clinical input supports use stereotactic radiotherapy (SBRT) which provides a clinically meaningful improvement in the net health outcome and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected patients. The following patient selection criteria are based on clinical expert opinion from clinical study populations: patients with primary RCC who are not good surgical candidates, or for relapsed or stage IV disease. Based on clinical input, literature, and professional society guidelines the evidence is sufficient to determine that the technology results in an improvement in net health outcomes.

Oligometastases
Oligometastases is described as an intermediate state in the spread of cancer between early-stage localized disease and widespread metastases. Specifically, it is a malignancy that has progressed to a limited number of hematogenous metastatic sites, defined in most studies as 1 to 3 sites. Chemotherapy remains the standard of care for patients with metastatic cancer, however, this is rarely curative. The concept of oligometastases has important implications for cancer treatment because it is believed that patients with limited numbers of metastasis previously thought by some clinicians to be incurable may be cured with local treatments such as radiotherapy.

The data supporting the treatment of extracranial oligometastases is largely limited to single institutions studies, registry studies or limited phase II randomized studies. Some of the retrospective studies have demonstrated improved outcomes compared to historical controls.

In 2019, Palma et. al., published the results of the SABR-COMET (Stereotactic Ablative Radiation Therapy for the Comprehensive Treatment of Oligometastatic Tumors) trial. The randomized phase II trial included patients with controlled primary site and up to 5 sites of hematogenous metastasis. Inclusion criteria required histologically confirmed malignancy (of the primary or metastatic site), Eastern Cooperative Oncology Group (ECOG) status 0-1, at least 3-month interval since definitive treatment of primary without

recurrence, maximum of 3 metastases in any one organ system, not a candidate for surgical resection at all sites, and no concurrent chemotherapy. This trial was designed as a randomized phase II "screening" trial to determine possible evidence of efficacy. Additionally, this trial was designed to allow for more modest patient accrual numbers and to provide an initial, non-definitive comparison between the two arms. Sixty-six patients were randomized to the SABR group, and 33 patients were randomized to the control group. The study was interpreted as positive with median survival in the SABR arm of 41 months compared to 28 months in the control group (p=0.09). Although the results of the SABR-COMET trial added significantly to the knowledge base for this clinical setting, there are several important limitation and observations of the study. Ongoing prospective randomized disease specific trials are needed to define the benefit of SBRT in this population. Considering the limitations of this study, SBRT for the treatment of patients with >3 metastases and less than 1 year disease free interval from time of definitive therapy is not supported at this time.

The selection of an appropriate individual is important when deciding who is eligible to receive SBRT in the oligometastatic setting. One study revealed a 40% progression rate within 3 months of SBRT for 1 to 5 metastases and 80% progression at 2 years, which emphasizes the fact that vast majority of patients have micro-metastatic disease at the time of treatment. Furthermore, disease free survival (DFS) after SBRT is associated with time to recurrence after initial diagnosis. One analysis found 3-year survival after SBRT was 53% for patients with a disease-free interval of more than 12 months versus 19% of patients with a disease-free interval of less than 12 months. Another analysis found a disease-free interval of more than 12 months was also associated with improved outcomes following treatment with SBRT for oligometastatic disease.

There is limited data on the survival benefit of treatment multiple metastases (>3 metastases). Surgical studies have suggested that tumor burden is predictive of overall survival. In the surgical literature, the number and size of metastatic lesions (>3 hepatic metastases $\geq$5 cm, >1 lung metastasis), extrahepatic spread, poorly differentiated disease, positive resection of margins and a short disease-free interval (<36 months) have been independent predictors for poor survival. Studies have reported a longer progression free survival (PFS) in patients with 1-3 metastatic sites versus those with 4-5 metastases receiving escalating SBRT doses to all sites of disease. The toxicity of using SBRT for treatment multiple metastases (>3 metastases) can be potentially significant. the Radiation Therapy Oncology Group (RTOG) is currently conducting a phase I study examining the safety of SBRT for the treatment of multiple metastases. Furthermore, SABR-COMET 10 is an ongoing randomized Phase III trial evaluating SBRT in the treatment of 4-10 metastases.

Based on ongoing studies, the limitation in the number of metastases treated in most reports, and the lack of evidence of a clinically significant benefit for treatment of larger number of metastases in the limited randomized literature, SBRT to > then 3 sites the evidence is insufficient to determine that the technology results in an improvement in net health outcomes. Based on the current studies in regard to the number of metastases

treated the evidence is sufficient to determine that the use of SBRT results in improved net health outcomes for oligometastatic disease in individuals with 1-3 metastatic sites, current studies in the medical literature has primarily only examined metastases to lung, liver and bone.

Practice Guidelines and Position Statements

American Academy of Ophthalmology
In 2015, the American Academy of Ophthalmology updated its evidence-based preferred practice pattern on age-related macular degeneration. For extrafoveal choroidal neovascularization, radiotherapy was not recommended (SIGN grade: III; GRADE assessment: moderate level of evidence, strong recommendation).

In their 2019 Preferred Practice Pattern for age-related macular degeneration, they state that current data is insufficient "to demonstrate clinical efficacy" for extrafoveal choroidal neovascularization or radiotherapy.

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

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

- SRS alone (as opposed to WBRT [whole brain radiotherapy] or combination of WBRT and SRS) should be offered to patients with one to four unresected brain metastases, excluding small-cell carcinoma."
    - "Qualifying Statement: The inclusion criteria of the randomized trials that underly this recommendation were generally tumors of less than 3 or 4 cm in diameter and did not include radioprotectant strategies of memantine or hippocampal avoidance"
- "SRS alone should be offered to patients with one to two resected brain metastases if the surgical cavity can be safely treated and considering the extent of remaining intracranial disease."

- "Qualifying Statement: The randomized trials upon which this recommendation is based were of single-fraction SRS and conventional WBRT (without radioprotectant strategies of memantine or hippocampal avoidance)"

- "SRS, WBRT, and the combination of SRS plus WBRT are all reasonable options for patients with more than four unresected or more than two resected brain metastases and better performance status (e.g., [Karnofsky Performance Status] KPS ≥70). SRS may be preferred for patients with better prognosis or where systemic therapy that is known to be active in the CNS [central nervous system] is available."

American Society for Radiation Oncology (ASTRO)

ASTRO Model Policy for Stereotactic Body Radiation Therapy (SBRT)
The current ASTRO model policy (June 2020) for stereotactic body radiation therapy (SBRT) includes the following indications as medically necessary:

SBRT is indicated for primary malignant tumors of the lung, liver, kidney, adrenal gland, pancreas, bone, and prostate, and primary malignant and benign tumors of the spine and spinal cord. The patient's general medical condition (namely, the performance status) must justify aggressive, curative treatment to a primary, non-metastatic tumor and be specifically documented in the medical record.

SBRT is indicated for treatment of (1) secondary, or metastatic, tumors and (2) recurrent tumors or (3) any tumor arising within or near previously irradiated volumes when at least one of the following criteria is met and specifically documented in the medical record:

1. The patient's general medical condition (namely, the performance status) justifies aggressive local therapy to one or more deposits of metastatic cancer in an effort either to achieve total disease clearance in the setting of oligometastatic disease or to reduce the patient's overall burden of systemic disease for a specifically defined clinical benefit.
2. Recurrent disease requiring palliation, or any tumor cannot be treated as effectively or safely by other radiotherapy methods due to proximity of previously irradiated volumes and a high level of precision and accuracy is needed to minimize the risk of injury to surrounding normal tissues.

Additional Coverage Considerations

Spinal Metastases
SBRT has been demonstrated to achieve durable tumor control when treating lesions in vertebral bodies or the paraspinous region, where extra care must be taken to avoid excess irradiation of the spinal cord when tumor-ablative doses are administered. There is an important clinical distinction between the status of patients described above and a patient with widely metastatic disease for whom palliation is the major objective. In one

setting, a patient with limited metastatic disease and good performance status is treated with the intention of eradicating all known active disease or greatly reducing the total disease burden in a manner that can extend progression-free survival. For such a patient, SBRT can be a reasonable therapeutic intervention. However, for uncomplicated, previously untreated bone metastases in a patient with widespread progressive disease in the spine or elsewhere and where the prognosis is unfavorable, it is generally appropriate to use a less technically complex form of palliative radiation therapy rather than SBRT.

ASTRO Model Policy for Stereotactic Radiosurgery (SRS)
The current ASTRO model policy (June 2022) for stereotactic radiosurgery states the following indications are considered proven and medically necessary:

- Primary Central nervous system malignancies, generally used as a boost or salvage therapy for lesions.
- Primary and secondary tumors involving the brain parenchyma, meninges/dura or an immediately adjacent bony structures such as the cranial vault or skull base.
- Benign brain tumors such as meningiomas, acoustic neuromas, other schwannomas, pituitary adenomas, pineocytomas, craniopharyngeal, glomus tumors or hemangioblastomas.
- Arteriovenous malformation and cavernous malformations.
- Other cranial non-neoplastic conditions such as trigeminal neuralgia and select cases of medically refractory epilepsy, movement disorders such as Parkinson's disease and essential tremor, and hypothalamic hamartomas.
- As a boost treatment for larger cranial or spinal lesions that have been treated initially with external beam radiation therapy or surgery (e.g., sarcomas, chondrosarcomas, chordomas and nasopharyngeal or paranasal sinus malignancies).
- Metastatic brain lesions, independent of the number of lesions, if other positive clinical indications exist, e.g., stable systemic disease, Karnofsky Performance Status 40 or greater (and expected to return to 70 or greater with treatment), and otherwise reasonable survival expectations, or ECOG Performance Status of 3 or less (and expected to return to 2 or less with treatment).
- Relapse in a previously irradiated cranial field where the additional stereotactic precision is required to avoid unacceptable vital tissue radiation.
- Uveal or ocular melanoma.
- Patients treated under the paradigm of Coverage with Evidence Development (CED) provided the patient is enrolled in either an IRB-approved clinical trial or in a multi-institutional patient registry adhering to Medicare requirements for CED. At this time, no indications are deemed inappropriate for CED.

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

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

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

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

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

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

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

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

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

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

International Stereotactic Radiosurgery Society

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

Strength of Evidence	**Strength of Recommendation**
Class I: • High quality randomized trial with statistically significant difference or no statistically significant	Level I: High degree of clinical certainty (Class I evidence or overwhelming Class II evidence)

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

RCT: randomized controlled trial

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

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

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

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

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

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

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

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

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

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

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

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

to the resection cavity is recommended to minimize cognitive toxicity compared with WBRT (recommendation level I)."[222,]

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

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

National Comprehensive Cancer Network (NCCN)

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat, and manage patients with cancer. These guidelines evolve continuously as new treatments and diagnostics emerge and may be utilized by Wellmark BlueCross BlueShield when determining medical necessity and investigational according to this medical policy

NCCN Recommendations for Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SABR)

Cancer Guideline/Cancer Type	Recommendation
Acute Lymphoblastic Leukemia Version 1.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of acute lymphoblastic leukemia.
Acute Myeloid Leukemia Version 2.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of acute myeloid leukemia.

Ampullary Adenocarcinoma Version 1.2022	• Recurrent unresectable disease may include: ▪ Induction chemotherapy followed by chemoradiation or SBRT o There are limited data to support a specific RT dosing for SBRT, therefore, for the recurrent ampullary cancer, it should be used as part of clinical trial or at an experienced, high-volume center. • Palliative ▪ Metastatic disease – metastatic sites causing pain (i.e., osseous) may be palliated with a short course of RT. SBRT may be used in select cases for metastatic sites, including oligometastatic disease. ***Note**: SBRT should be avoided if direct invasion of the bowel or stomach is observed on CT, MRI and/or endoscopy.*
Anal Carcinoma Version 1.2022	The consensus of the panel is that intensity-modulated RT (IMRT) is preferred over 3D conformal RT in the treatment of anal carcinoma. • Image guided RT (IGRT) with kilovoltage (kV) imaging or cone beam CT imaging should be routinely used during the course of treatment with IMRT and stereotactic body RT (SBRT) • Consider SBRT for patients with oligometastatic disease For untreated patients presenting with synchronous local and metastatic disease, a platinum-based regimen is standard practice, and radiation can be considered for local control. The approach to radiation, depends on the patients' performance status and extent of metastatic

	disease. If performance status is good and metastatic disease is limited, treat involved fields, 45-54 Gy to the primary tumor and involved sites in the pelvis, in coordination with plans for a platinum-based regimen. If there is a low volume of liver oligometastasis, an SBRT dosing schema after systemic therapy may be appropriate depending on response. If metastatic disease is extensive and life expectancy is limited, a different schedule and dose of radiation should be considered, again in coordination with plans for 5-FU/cisplatin or a platinum-based regimen. In the setting of pure palliation, doses of 20-25 Gy in 5 fractions to 30 Gy in 10 fractions can be considered. SBRT can also be considered for treatment of primary and nodal recurrence in the setting of low-volume metastatic disease.
Basal Cell Skin Cancer Version 2.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of basal cell skin cancer.
B-cell Lymphomas Version 5.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of B-cell lymphomas.
Bladder Cancer Version 2.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of bladder cancer.
Bone Cancer Version 1.2023	**Principles of Radiation Therapy** • Specialized techniques such as intensity-modulated RT (IMRT); particle beam RT with protons, carbon ions, or other heavy ions; or stereotactic radiosurgery (SRS) should be considered as indicated in order to allow high-dose therapy while maximizing normal tissue sparing. ▪ The RT doses listed for chondrosarcoma and chordoma

	are for conventional fractionated regimens. Alternative total dose and fractionation schemes are necessary for specialized technique such as SRS and stereotactic body RT (SBRT). **General Treatment & Dosing Information – Ewing Sarcoma** • **Treatment of Metastatic Disease** ▪ Consider use of SRS/SBRT especially for oligometastases. **General Treatment and Dosing Information _ Giant Cell Tumor of Bone** • **Treatment of Metastatic Disease** ▪ Consider use of SRS/SBRT, especially for oligometastases.
Breast Cancer Version 4.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of breast cancer.
Central Nervous System Cancers Version 1.2022	• **Meningiomas**: Stereotactic or image-guided therapy is recommended when using tight margins or when close to critical structures. • **Metastatic Spine Tumors**: ▪ Stereotactic radiation approaches (SRS/stereotactic body radiotherapy [SBRT]) for spinal cases may be preferred for patients with oligometastatic disease where tumor ablation is a goal of treatment of tumors considered radioresistant (e.g., renal cell, melanoma, sarcoma, hepatocellular, some colorectal and NSCLC cases)

	▪ Stereotactic radiation approaches may also be preferred in the setting of tumor recurrence or progressive disease after prior radiation as a strategy to limit radiation dose to the spinal cord or other critical structures. Careful adherence to consensus guidelines for radiosurgery planning and delivery recommended. ▪ Recommend SBRT for oligometastases or radioresistant histologies. • **Primary Spinal Cord Tumors** ▪ In some instances, focal SRS/SBRT to spinal tumors like hemangliobastoma may be appropriate, with care to respect normal tissue constraints of spinal code and surrounding structures. **Adult Intracranial and Spinal Ependymoma (Excluding Subependymoma)** • **Spine or brain recurrence** ▪ Resectable → no prior RT → Gross total or subtotal resection; CSF cytology negative → standard RT → treatment for progression or recurrence→ consider stereotactic radiosurgery (SRS) if geometrically favorable. ▪ Unresectable → evidence of metastasis (brain, spine or CSF) → treatment for progression or recurrence → consider stereotactic radiosurgery (SRS) if geometrically favorable. **Adult Medulloblastoma**

	• Treatment for recurrence: chemotherapy and/or additional radiation such as stereotactic radiosurgery (SRS) after resection or high dose chemotherapy with autologous stem cell reinfusion **Reirradiation for Gliomas** • Highly focal techniques like intensity-modulated radiation therapy (IMRT), proton therapy or stereotactic radiosurgery (SRS) may be required in these reirradiation settings in order to improve distribution to critical structures and reduce overlap with prior radiation. **Limited Brain Metastases** • Disseminated systemic disease with poor systemic treatment options → SRS in select patients • Newly diagnosed or stable systemic disease or reasonable systemic treatment options exist → SRS preferred • **Recurrence** ▪ Recurrent disease local site → previous surgery only → Surgery followed by SRS or RT to the surgical bed; or single dose or fractionated stereotactic RT; or WBRT for large volumes; or consider systemic therapy ▪ Recurrent disease local site→ previous WBRT or prior SRS → surgery followed by SRS or RT to the surgical bed; or single dose (category 2B or fractionated stereotactic RT; or consider systemic therapy ▪ Recurrent disease distant brain +/- local recurrence → limited brain metastases → surgery followed by SRS or RT to the

	surgical bed; or single dose or fractionated stereotactic RT; or WBRT for large volumes if not previously administered; or consider systemic therapy • **Relapse** ▪ Stable systemic disease or reasonable systemic treatment options → surgery; or SRS; or WBRT; or laser thermal ablation; or systemic therapy ▪ Systemic disease progression with limited systemic treatment options and poor PS o No prior WBRT → WBRT; or SRS in select patients; or palliative/best supportive care o Prior WBRT → Reirradiation if prior positive response to RT; or SRS in select patients; or palliative/best supportive care **Extensive Brain Metastases** ▪ **Primary treatment:** o WBRT; or SRS; or systemic therapy (SRS can be considered for patients with good performance and low overall tumor volume and/or radioresistant tumors such as melanoma) ▪ **Recurrent disease** o Stable disease or reasonable systemic treatment options ☐ Surgery; or SRS; or WBRT; or systemic therapy

	Leptomeningeal Metastases • Good risk (KPS $\geq$ 60; no major neurologic deficits; minimal systemic disease; reasonable systemic treatment options if needed) SRS or RT (involved-filed and/or whole brain) to bulky disease and neurologically symptomatic (such as cranial neuropathies) or painful sites. Radiation oncologists use several different treatment modalities in patients with primary brain tumors, including fractionated stereotactic RT and stereotactic radiosurgery (SRS). RT for patients with primary brain tumors is administered within a limited field (covering tumor or surgical cavity and small margin of adjacent brain tissue), while whole-brain RT (WBRT) and SRS are used primarily for treatment of brain metastases. SRS offers an excellent minimally invasive ablative treatment option for brain metastases. Patients undergoing SRS avoid the risk of surgery-related morbidity, and SRS is generally preferred over surgery for patients with small, asymptomatic lesions that do not require surgery and for patients with lesions that are not surgically accessible.
Cervical Cancer Version 1.2022	• IMRT is helpful in minimizing the dose to bowel and other critical structures in the post-hysterectomy setting and in the treating of the para-aortic nodes when necessary. These techniques can also be useful when high doses are required to treat gross disease in regional lymph nodes. However, conformal external beam therapies such as IMRT or stereotactic body radiation therapy (SBRT) should not be used as routine alternative to brachytherapy for treatment

	of central disease in patients with an intact cervix. • SBRT is an approach that allows for delivery of high doses of focused EBRT in 1-5 fractions and may be applied to isolated metastatic sites, consideration can be given for limited disease in the re-irradiation setting. • SBRT is not considered an appropriate routine alternative to brachytherapy. **Radiation Treatment Planning** CT-based treatment planning with conformal blocking and dosimetry is considered standard of care for EBRT. Brachytherapy is a critical component of definitive therapy in patients with cervical cancer who are not candidates for surgery (i.e., those with intact cervix); it may also be used as adjuvant therapy. Brachytherapy is typically combined with EBRT in an integrated plan. MRI imaging immediately preceding brachytherapy may be helpful in delineating residual tumor geometry. Stereotactic body radiotherapy (SBRT) allows delivery of very high disease of focused external beam radiation and may be applied to isolated metastatic sites.
Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia Version 3.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of chronic lymphocytic leukemia/small lymphocytic leukemia.
Chronic Myeloid Leukemia Version 3.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of chronic myeloid leukemia.
Colon Cancer Version 1.2022	**Principles of Radiation and Chemoradiation Therapy** **General Principles** • In patients with a limited number of liver or lung metastases, ablative radiotherapy

	to the metastatic site can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3-D conformal radiation therapy, intensity-modulated radiation therapy (IMRT), or stereotactic body radiation therapy (SBRT) **Treatment Information** • Consider SBRT for patients with oligometastatic disease. • Image-guided radiation therapy (IGRT) with kilovoltage (kv) imaging or cone-beam CT imaging should be routinely used during the course of treatment with IMRT or SBRT. **Perioperative Chemoradiation** • If RT is to be used, conformal beam radiation should be the routine choice; intensity-modulated RT (IMRT) which uses computer assisted inverse treatment planning to focus radiation to the tumor site and potentially decrease toxicity to normal tissue, or stereotactic body RT (SBRT; also called stereotactic ablative radiotherapy [SABR] should be considered for unique clinical situations, such as reirradiation of previously treated patients with recurrent disease or anatomical situations where IMRT facilitates the delivery of recommended target volume doses while respective accepted normal issue dose-volume constraints. While colorectal cancer has been shown to be a relatively radioresistant histology, multiple studies have demonstrated effective local control

	with minimal toxicity using SBRT in the treatment of liver and lung metastases. In addition, data on the benefit of using SBRT to treat multiple metastatic lesions are emerging. A recent randomized phase II trial with multiple cancer types, including a small number of CRC origin, and up to five metastatic lesions in different organs demonstrated on improvement in overall survival (OS) with the addition of SBRT to standard-of-care treatment. In patients with liver or lung limited disease that is amendable to complete resection or ablation, SBRT may be considered as local therapy in centers with expertise. SBRT for the treatment of extrahepatic disease can be considered in select cases, or as part of clinical trial.
Dermatofibrosarcoma Protuberans Version 2.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of dermatofibrosarcoma protuberans.
Esophageal and Esophagogastric Junction Cancers Version 3.2021	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of esophageal and esophagogastric junction cancers.
Gastric Cancer Version 2.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of gastric cancer.
Gastrointestinal Stromal Tumors (GIST) Version 1.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of gastrointestinal stromal tumors.
Gestational Trophoblastic Neoplasia Version 1.2022	• High risk GTN confirmed ≥7 prognostic score or stage IV: Consider brain radiotherapy: stereotactic brain radiotherapy +/- intrathecal methotrexate; or whole brain radiation **Management of CNS Metastases** The panel recommends that whole-brain radiation or stereotactic brain radiotherapy

	(SBRT with or without intrathecal methotrexate also be considered for patients with brain metastases. Reported cure rates with brain metastases range from 50% to 80%, depending on the patient's symptoms as well as number, size, and location of brain lesions.
Hairy Cell Leukemia Version 1.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of hairy cell leukemia.
Head and Neck Cancers Version 2.2022	**Principles of Radiation Techniques** **Palliative 3D conformal RT, IMRT and Stereotactic Body (SBRT)** • Palliative radiation should be considered in the advanced cancer setting when curative-intent treatment is not appropriate. • No general consensus exists for appropriate palliative RT regimens in head and neck cancer. For those who are either medically unsuitable for standard RT or who have widely metastatic disease, palliative RT should be considered for relief or prevention of locoregional symptoms if the RT toxicities are acceptable. RT regimens should be tailored individually; severe RT toxicities should be avoided when treatment is for palliation. **Reirradiation with 3D-CRT, SBRT, PBT, or IMRT** • If the area in consideration overlaps with the previously radiated volume, the prior radiotherapy should have been more than 6 months from the appearance of new disease. • When using SBRT techniques for reirradiation, careful selection of patients is advised. The best outcomes are seen in patients with smaller tumors and no skin involvement. Caution should be

	exercised in cases of circumferential carotid artery involvement. • Current SBRT scheduled being used or investigated are in the range of 35-44 Gy using 5 fractions. • Clinical trials should be strongly considered for patients receiving reirradiation. **Stereotactic Body Radiation Therapy** Stereotactic Body RT (SBRT) is an advanced technique of external beam ET (EBRT) that delivers large ablative doses of radiation in a limited number of fractions. Advantages of SBRT include shorter treatment time, promising local control rates, and higher but acceptable toxicity depending on the specific location treated. There is currently insufficient evidence to recommend SBRT for treatment of H&N cancers, but the NCCN Panel acknowledge that it might be beneficial in the settings of re-irradiation, palliation or for older adults. Careful anticipation of toxicity is especially important in planning the delivery of this modality to a patient. SBRT has been delivered in conjunction with systemic therapy, but caution is advised due to the relatively limited experience with combining these modalities.
Hepatobiliary Cancers Version 2.2022	**Principles of Radiation Therapy** • All tumors irrespective of the location may be amendable to radiation therapy (RT) (3D conformal RT (3D-CRT), intensity-modulated RT (IMRT), or stereotactic body RT (SBRT). Image guided RT (IGRT) is strongly recommended when using EBRT, IMRT and SBRT to improve treatment accuracy and reduce treatment-related toxicity. • SBRT is an advanced technique of hypofractionated EBRT with photons that delivers large ablative doses of radiation.

	• There is growing evidence for the usefulness of SBRT in the management of patients with HCC. SBRT can be considered as an alternative to ablation/embolization techniques or when these therapies have failed or are contraindicated. • SBRT (typically 3-5 fractions) is often used for patients with 1 to 3 tumors. SBRT could be considered for larger lesions or more extensive disease, if there is sufficient uninvolved liver and liver radiation tolerance can be respected. There should be no extrahepatic disease, or it should be minimal to address in a comprehensive management plan. **Radiation Therapy** Radiation therapy options for patients with unresectable or inoperable HCC, include EBRT and stereotactic body radiation therapy (SBRT). SBRT is an advanced technique or EBRT that delivers large ablative doses of radiation. There is growing evidence (primarily from non-RCTs) supporting the usefulness of SBRT for patients with unresectable, locally advanced, or recurrent HCC. SBRT is often used for patients for 1 to 3 tumors with minimal or uncertain extrahepatic disease. There is no strict size limit, so SBRT may be used for larger lesions if there is sufficient uninvolved liver and liver radiation dose constraints can be respected. The majority of safety and efficacy data on the use of SBRT are available for patients with HCC and Child-Pugh A liver function; limited safety data are available for the use of SBRT in patients with Child-Pugh B or poorer liver function. The safety of Child-Pugh C cirrhosis has not been established, as there are not likely to be clinical trials available for this group of patients with a very poor prognosis.

Histiocytic Neoplasms Version 1.2022	• Current guideline does not include or indicate the use of SRS or SBRT in treatment histiocytic neoplasm.
Hodgkin Lymphoma Version 2.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of Hodgkin lymphoma.
Kaposi Sarcoma Version 1.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of Kaposi sarcoma.
Kidney Cancer Version 2.2023	• Stereotactic body radiotherapy (SBRT) may be considered for medically inoperable patients with stage I kidney cancer (category 2B), with stage II/III kidney cancer (both category 3) Patients who have undergone a nephrectomy and years later develop an oligometastatic recurrence also have the option of metastastectomy, stereotactic body radiation therapy (SBRT), or ablative techniques, in addition to the first-line therapy options. Supportive care remains a mainstay of therapy for all patients with metastatic RCC. Stereotactic radiotherapy, if available, is an alternative to surgery for limited-volume brain metastasis, and whole brain irradiation is recommended for those patients with multiple brain metastases.
Malignant Pleural Mesothelioma Version 1.2022	**Principles of Radiation Therapy** • Advanced technologies may be used such as image-guided RT (IGRT) for treatment involving IMRT/Stereotactic radiosurgery (SRS)/stereotactic body RT (SBRT), and intensity-modulated proton therapy (IMPT).
Melanoma Cutaneous Version 3.2022	**Principles of Radiation Therapy for Melanoma** **Distant Metastatic Disease**

	• Oligometastatic disease – treatment of metastatic disease stereotactic ablation therapy.
	• **Brain metastases**
	  o Stereotactic radiosurgery (SRS) and fractionated stereotactic RT (SRT) are techniques for delivering a high dose of radiation to a specific target while delivering a minimal dose to surrounding tissues, generally in the brain and spine and in 1 to 5 sessions. IGRT should be used to improve accuracy of radiotherapy delivery, where clinically appropriate.
	  o SRS or SRT as primary treatment
	  o SRS/SRT as adjuvant treatment
	
	Radiation for Brain Metastases
	SRS is gaining importance in the management of CNS metastases from melanoma. With the increasing use of stereotactic radiation, the value of WBRT in patients with melanoma brain metastases is increasingly unclear and controversial. In clinical practice, the use of SRS in patients with a limited number of brain tumors is gaining wider acceptance because studies have demonstrated late adverse effects of WBR on cognitive function. Prospective randomized studies are needed to determine the best approach to radiation for melanoma brain tumors.
	
	Ablative Treatment of Intact Extracranial Metastasis
	• Higher doses utilizing conformal techniques such as stereotactic body RT (SBRT) may offer more durable local control
	• SBRT may be considered for selected patients with oligometastasis

	Higher doses utilizing conformal techniques such as stereotactic body radiation therapy (SBRT) may offer more durable local control and freedom from regional or distant progression. SBRT may be used in selected patients with oligometastasis. The potential benefit must be weighed against potential toxicities, and strict adherence to normal tissue constraints is recommended.
Melanoma Uveal Version 2.2022	**Primary Treatment** • Tumor Size o Largest diameter > 19 mm (any thickness); **or** o Thickness > 10 mm (any diameter); **or** o Thickness > 8 mm with optic nerve involvement (any diameter) ☐ Options ➢ Radiation therapy: Particle beam radiation **or** stereotactic radiosurgery (SRS) ➢ Enucleation **Principles of Radiation Therapy** **Stereotactic Radiosurgery (SRS)** • SRS is the least often used form of definitive radiotherapy for the treatment of primary or recurrent intraocular tumors o Few prospective studies have assessed the efficacy and safety of radiosurgery. o Tumor localization, fiducial marker use, and planning for SRS are generally consistent with particle beam therapy approaches. • For symptom palliation o For ablative therapy of oligometastases, doses of 16-24 Gy/1 fraction or 24-60 Gy/2-8

	fractions should be prescribed to the appropriate target volume using appropriate stereotactic body radiotherapy (SBRT) techniques with image guidance. **NCCN Recommendations for Stereotactic Radiation** Due to the lack of randomized prospective data (compared with other RT techniques), SRS is the least often used form of definitive RT for the treatment of primary or recurrent intraocular tumors. Like particle beam RT, SRS can be used to treat large choroidal melanomas. The choice between these two options generally depends on the radiation oncology facilities available. In rare cases where both particle beam RT and SRS facilities are available, some NCCP Panel members prefer particle beam RT because there are more supporting data for this approach.
Merkel Cell Carcinoma Version 2.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of Merkel cell carcinoma.
Multiple Myeloma Version 5.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of multiple myeloma.
Myelodysplastic Syndromes Version 3.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of myelodysplastic syndromes.
Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes Version 1.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of myeloid/lymphoid neoplasms with eosinophilia with tyrosine kinase fusion genes.
Myeloproliferative Neoplasms Version 1.2021	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of myeloproliferative neoplasms.

Neuroendocrine and Adrenal Tumors Version 1.2022	**Neuroendocrine Tumors of the Gastrointestinal Tract (Well-Differentiated grade 1/2), Lung and Thymus** **Clinical location: Bronchopulmonary** • Localized disease stage I-II: Primary therapy o Lobectomy or other anatomic resection + mediastinal node dissection or sampling; **or** o If surgery contraindicated, thermal ablation or stereotactic body RT (SBRT). **Well-Differentiated, Grade 3 Neuroendocrine Tumors** • Locally advanced/metastatic disease unfavorable biopsy (relatively high Ki-67 (≥55), rapid growth rate, FDG avid tumors, negative SSRT-based on PET imaging. o Treatment: ☐ Clinical trial ☐ Systemic therapy ☐ Consider addition of liver-directed therapy (embolization, selective internal RT, ablation, SBRT); **or** ☐ Palliative RT for symptomatic bone metastases. **Adrenal Gland Tumors** • Locoregional unresectable or metastatic disease o Consider local therapy (i.e., SBRT, thermal ablative therapies, liver-directed therapy. **Principles of Liver-Directed Therapy for Neuroendocrine Tumor Metastases** • Stereotactic body radiation therapy (SBRT)/stereotactic ablation radiotherapy (SABR) (≤5 fractions) and

	hypofractionated RT (6-20 fractions) using stereotactic or intensity-modulated RT/volumetric modulated arc therapy techniques with image- guided RT can be considered of oligometastatic disease at multiple sites, including (but not limited to) liver, adrenal, bone (including spine), lung, mediastinum, head and neck and lymph nodes. An ablative dose is delivered to the tumor while respecting the surrounding organ and adjacent normal tissue constraints. Generally, if this is possible in 5 or fewer fractions, SBRT/SABR techniques are used, while hypofractionated RT is used for larger lesions next to large vessels, large airways, or hollow viscous organs at risk of complications. Motion management and image-guided RT techniques are strongly recommended to maintain RT techniques are strongly recommended to maintain RT precision and reduce the risk of toxicity.
Non-Small Cell Lung Cancer Version 3.2022	• Stage IA (peripheral T1abc, N0) with negative mediastinal nodes → medically inoperable → definitive RT preferably stereotactic ablative therapy (SABR) • Stage IVA, M1b → PS 0-2 Limited metastases confirmed → Brain → stereotactic radiosurgery (SRS) alone; **or** surgical resection if symptomatic **or** warranted for diagnosis, followed by SRS or whole brain RT (WBRT) • Palliative RT for Advanced/Metastatic NSCLC o Single-fraction stereotactic RT produced better control of pain response and local control of non-spine bone metastases compared to standard 30 Gy in 10 fractions **SABR**= stereotactic ablative RT also known as stereotactic body RT (SBRT)

	Overview • For multiple metastases, whole brain RT is recommended; stereotactic radiosurgery (SRS) may be preferred for patients who have good PS and low systemic tumor burden. • Patients with medically inoperable early-stage NSCLC may be candidates for definitive RT, preferably SABR, also known as stereotactic body RT (SBRT). If SABR is considered for patients at high risk, a multidisciplinary evaluation is recommended. **General Treatment Information** • Definitive RT, preferably SABR, is recommended for patients with early-stage NSCLC (i.e., stage I-II, N0) who are medically inoperable or those who refuse surgery. **Stereotactic Ablative Radiotherapy** SABR (also known as SBRT) uses short courses of very high (ablative) highly conformal, and dose-intensive RT precisely delivered to limited-size targets. Studies including prospective multi-institutional trails, have demonstrated the efficacy of SABR for patients with inoperable stage I NSCLC or for those who refuse surgery. SABR can also be used for patients with limited lung metastases or limited metastases to other body sites. SABR is recommended in the NSCLC algorithm for patients with stage I and II (T1-3, N0, M0) NSCLC who are medically inoperable; SABR is a reasonable alternative to surgery for patients with potentially operable disease who are high risk, elderly, or refuse surgery after appropriate consultation. If possible, biopsy should confirm NSCLC before use of SABR. SRS or SABR for limited oligometastases to the brain or other body sites, respectively, is recommended for patients with good PS if their

	thoracic disease can be treated with definitive therapy. SRS or SABR can be considered for select patients with stage M1c disease who have a limited number and volume of metastatic lesions that amendable to treatment with definitive local therapy; limited number is not defined by clinical trials have included up to 3 to 5 small metastases. For patients with disease progression on targeted therapy for ALK rearrangements, ROS1 rearrangements, or the common EGFR mutations, consideration of local therapy (e.g., surgery or SABR [or SRS]) is recommended for limited lesions, depending on the type of progression. Decisions about whether to recommend SABR should be based on multidisciplinary discussion. **Whole Brain RT and Stereotactic Radiosurgery** Many patients with NSCLC have brain metastases (30%-50%) which substantially affect their quality of life. Whole brain RT is associated with measurable declines in neurocognitive function in clinical trials, particularly with increasing dose and advanced age of the patient. However, control of brain metastases confers improved neurocognitive function. For limited metastases, randomized trials have found that the addition of whole brain RT to SRS decreases intracranial recurrence but does not improve survival and may increase the risk of cognitive decline. Thus, SRS alone is recommended for patients with limited volume metastases. Treatment options for limited brain metastases in patients with NSCLC include: 10 SRS alone; and 2) surgical resection for selected patients followed by SRS or whole brain RT. Decisions about whether to recommend SRS alone or brain surgery followed by whole brain RT or SRS for limited brain metastases should be based on multidisciplinary discussion, weighing the potential benefit over the risk for each individual patient. Treatment should be individualized for

	patients with recurrent or progressive brain lesions. Treatment recommendations for limited brain metastases in patients with NSCLC differ from recommendations in NCCN guidelines for Central Nervous System Cancers because patients with NSCLC and brain metastases often have long-term survival; therefore, the potential neurocognitive issues that my occur with whole brain RT are a concern. Clinicians are using whole brain RT less often in patients with NSCLC and limited brain metastases (3-5). For multiple metastases, whole brain RT is recommended; SRS may be preferred for patients who have good PS and low systemic tumor burden (see the NCCN Guideline for Central Nervous System Cancers).
Occult Primary (Cancer of Unknown Primary [CUP]) Version 1.2023	**Localized adenocarcinoma or carcinoma not otherwise specified; Lung nodules** • Management based on workup findings: o If completely resectable consider surgery o Clinical trial preferred o Consider systemic therapy o Symptom control o Stereotactic body radiotherapy (SBRT) **Principles of Radiation Therapy** **General Principles** • **Localized Disease** o Consider definitive radiotherapy for patients with localized disease ☐ Consider stereotactic ablative radiotherapy (SABR) for limited (1-3) metastases and pulmonary metastases Systemic therapy, preferably as part of a clinical trial, or stereotactic body RT (SBRT) can be

	considered for oligometastatic lung nodules with or without resection. **Radiation Therapy** Stereotactic ablative radiotherapy (SABR) may be used for limited (1-3) metastases or pulmonary metastases.
Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer Version 3.202	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of ovarian cancer/fallopian tube cancer/primary peritoneal cancer.
Pancreatic Adenocarcinoma Version 1.2022	**Locally Advanced Disease with good performance status** • First-Line Therapy: Induction chemotherapy (preferably 4-6 months) followed by chemoradiation or stereotactic body RT (SBRT) in selected patients (Locally advanced without systemic metastases); **or** • SBRT in patients who are not candidates for induction chemotherapy. If patients present with poorly controlled pain or local obstructive symptoms, if may be preferrable to start with upfront chemoradiation or SBRT. **Good Performance Status with Disease Progression – Subsequent Therapy** • Clinical trial (preferred); or • Systemic therapy; or • Chemoradation; or • SBRT if not previously given and if primary site is the sole site of progression. **Recurrence after Resection** • Local recurrence to pancreatic operative bed o Clinical trial (preferred); **or**

	○ Systemic therapy +/- chemoradiation; or SBRT (if not previously done); **or** ○ SBRT; **or** ○ Palliative and best supportive care. **Radiation and Chemoradiation Approaches** Stereotactic body RT (SBRT) is another technique aimed at increasing does to the gross tumor while sparing radiation to nearby healthy tissue. SBRT should not be used if direct invasion of the bowel or stomach is observed on imaging, and care should be taken to limit dose to these areas to reduce treatment-related toxicity, particularly in patients with unresectable disease. Since the data regarding appropriateness use of SBRT are evolving, the panel recommends that SBRT should be used preferably in the context of a clinical trial and at an experienced high-volume center. **Upfront Chemoradiation or SBRT in Locally Advanced Disease** Upfront SBRT may be used in patients with locally advanced disease who are not candidates for combination systemic treatment. Chemoradiation or SBRT Following Chemotherapy in Locally Advanced Disease Starting with 2 to 6 cycles of systemic chemotherapy followed by chemoradiation or SBRT is an option for selected patients with locally advanced disease and good performance status who have not developed metastatic disease. This sequence is especially recommended in cases where: 1) it is highly unlikely that the patient will become resectable (i.e., complete encasement of superior mesenteric/celiac arteries); 2) there are suspicious metastases; or 30 the patient may not be able to tolerate chemoradiation.

	Summary Patients with locally advanced disease and good performance status can undergo chemotherapy and chemoradiation or SBRT with second-line therapy if performance status is maintained after progression.
Pediatric Acute Lymphoblastic Leukemia Version 1.2022	• Current guideline does not include or indicate the use SRS or SBRT in the treatment of pediatric acute lymphoblastic leukemia.
Pediatric Central Nervous System Cancers Version 1.2023	**Principles of Radiation Therapy and Management** **Pediatric Diffuse High-Grade Glioma (except diffuse midline glioma and diffuse intrinsic pontine glioma); Reirradiation:** • Stereotactic radiosurgery (SRS) with a median marginal dose of 16 Gy. Discussion under development.
Pediatric Hodgkin Lymphoma Version 1.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of pediatric Hodgkin lymphoma.
Penile Cancer Version 2.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of penile cancer.
Primary Cutaneous Lymphomas Version 2.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of primary cutaneous lymphomas.
Prostate Cancer Version 4.2022	**Systemic Therapy for Castration – Naïve Prostate Cancer** • **M1:** SBRT to metastases can be considered in patients with oligometastatic progression where progression-free survival is a goal

	Principles of Radiation Therapy
	Definitive Radiation Therapy General Principles
	• SBRT is acceptable in practices with appropriate technology, physics, and clinical expertise. SBRT for metastases can be considered in the following circumstances:
	  o In patient with limited metastatic disease to the vertebra or paravertebral region with ablation is the goal (e.g., concern for impending fracture or tumor encroachment on spinal nerves or vertebra)
	  o In a patient with oligometastatic progression where progression free survival is the goal
	  o In a symptomatic patient where the lesion occurs in or immediately adjacent to a previously irradiated treatment field.
	
	Definitive Radiation Therapy by Risk Group
	Unfavorable Intermediate Risk
	• Prophylactic nodal radiation can be considered if additional risk assessments suggest aggressive tumor behavior. ADT should be used unless additional risk assessments suggest less-aggressive tumor behavior or if medically contraindicated. The duration of ADT can be reduced when combined with EBRT and brachytherapy. Brachytherapy combined with ADT (without EBRT), or SBRT combined with ADT can be considered if delivering longer courses of EBRT would present medical or social hardship.

	High and Very High Risk • Prophylactic nodal radiation can be considered. ADT is required unless medically contraindicated. Brachytherapy combined with ADT (without EBRT), or SBRT combined with ADT, can be considered if delivering longer courses of EBRT would present a medical or social hardship. **Stereotactic Body Radiation Therapy** Stereotactic body radiation therapy (SBRT) is a technique that delivers highly conformal, high-dose radiation in five or fewer treatment fractions which are safe to administer only with precise image guided delivery. Single institution series with median follow-up as long as 6 years report excellent biochemical PFS and similar early toxicity (bladder, rectal, and QOL) compared to standard radiation techniques. SBRT/extremely hypofractionated image guided IMRT regimens can be considered as an alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise. Longer follow-up and prospective multi-institutional data are required to evaluate longer-term results, especially because late toxicity theoretically could be worse in hypofractionated regimens compared to conventional fractionation. The Panel believes that SBRT to metastases can be considered in the following circumstances: • In patients with limited metastatic disease to the vertebrae or paravertebral region when ablation is the goal (e.g., concern for impending fracture or tumor encroachment on spinal nerves for vertebrae). • In patients with oligometastatic progression where PFS is the goal.

	• In symptomatic patients where the lesion occurs in or immediately adjacent to a previously irradiated treatment field.
Rectal Cancer Version 1.2022	**Principles of Radiation Therapy** **General Principles** • In patients with limited number of liver or lung metastases, ablative radiotherapy to the metastatic site can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in highly conformal manner. The technique can include 3-D conformal radiation therapy, intensity-modulated radiation therapy (IMRT), or stereotactic body radiation therapy (SBRT) **Technical Aspects of Radiation Therapy** Intensity-modulated RT (IMRT) or stereotactic body RT (SBRT) should only be used in the setting of a clinical trial or in unique clinical situations such as re-irradiation of previously treated recurrent disease, localized oligometastatses, or unique anatomical situations where IMRT/SBRT facilitates the delivery of recommended target volumes while respecting accepted normal tissue dose-volume constraints. **Local Therapies for Metastases** SBRT (also called stereotactic ablative radiotherapy [SABR]) is a reasonable option for patients who cannot be resected or ablated. Many patients, however, are not surgical candidates and/or have disease that cannot be ablated with clear margins or safely treated by SBRT. EBRT to the metastatic site can be considered in highly selected cases in which the patient is symptomatic or in the setting of a clinical trial. It should be delivered in a highly conformal manner and should not be used in the place of surgical resection. The possible techniques include three dimensional conformal RT (CRT), SBRT and IMRT, which uses

	computer-assisted inverse treatment planning to focus radiation to the tumor site and potentially decrease toxicity to healthy tissue.
Small Bowel Adenocarcinoma Version 1.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of small bowel adenocarcinoma.
Small Cell Lung Carcinoma Version 2.2022	**Principles of Radiation Therapy** **General Treatment Information** • Selected patients with stage I or IIA (T1-2, N0, M0) SCLC who are medically inoperable or in whom a decision is made not to pursue surgery may be candidates for stereotactic ablative RT (SABR) to the primary tumor followed by adjuvant systemic therapy. Principles of SABR for SCLC are similar to those of NSCLC. **Brain Metastases** • Brain metastases should typically be treated with ABRT; however, selected patients with a small number of metastases may be appropriately treated with stereotactic radiotherapy (SRT)/radiosurgery (SRS). **SABR** The NCCN SCLC Panel recommends (category 2A) SABR followed by systemic therapy as an option for select patients with clinical stage I to IIA (T1-2, N0, M0) who are medically inoperable or decline surgery. Palliative Radiation Therapy For patients with localized symptomatic sites of disease (i.e., painful bony lesions, spinal cord compression, obstructive atelectasis) or with brain metastases, RT can provide excellent palliation. Because patients with SCLC often have a short life span, surgery is not usually recommended for spinal cord compression.

	IMRT, SABR or stereotactic radiosurgery (SRS) may be appropriate for select patients (e.g., those who tumors are in close proximity to organs at risk).
Soft Tissue Sarcoma Version 2.2022	**Extremity/Body Wall, Head/Neck** **Synchronous Stage IV disease** • Single organ (primarily pulmonary) with limited tumor bulk that is amendable to local therapy → Primary Treatment o Consider the following options for metastases ☐ For lung metastases resection preferred or stereotactic body radiation therapy (SBRT) • Disseminated metastasis o Palliative treatment options ☐ RT/SBRT ***Note:*** *In retrospective studies, various SBRT dosing regimens have been reported to be effective for the treatment of sarcoma metastases. Dose and fractionation should be determined by an experienced radiation oncologist based on normal tissue constraints.* **Recurrent Disease** • Metastatic disease o Single organ and limited tumor bulk that are amendable to local therapy → Treatment ☐ SBRT +/- systemic therapy o Disseminated metastases → palliative options ☐ SBRT/RT o Isolated regional disease or nodes ☐ SBRT **Limited Metastases** Patients with limited metastasis confined to single organ and limited tumor bulk that are amendable to local therapy should receive

	primary tumor management as described for stage II or III tumors. In addition, patients can also receive stereotactic body RT (SBRT) or chemotherapy as an alternate method for control of metastatic lesions. Several recent reviews and case series support the use of SBRT for local control, with potential survival benefits in selected patients. **Disseminated Metastases** For patients presenting with disseminated disease, a subsequent distinction is made between asymptomatic and symptomatic patients. Observation with a watchful waiting strategy is a reasonable management option for asymptomatic patients, especially if patients have only a minimal burden of metastases (e.g., sub-centimeter pulmonary nodules). Symptomatic patients can be treated with palliative RT, surgery or chemotherapy. Palliative RT involved expedient treatment with sufficient dose to halt tumor growth or cause tumor regression. The outcome of this approach depends on the rapidity of growth and the status of systemic disease. In addition, the guidelines have included ablation procedures (e.g., radiofrequency ablation [RFA] or cryotherapy) or SBRT as options for symptomatic patients.
Squamous Cell Skin Cancer Version 2.2022	• Palpable regional lymph node(s) or abnormal lymph nodes identified by imaging studies → FNA or core biopsy positive → Unresectable, inoperable or incompletely resected disease RT +/- systemic therapy (Consider palliative RT/surgery for symptomatic sites. Stereotactic body RT (SBRT) may also be considered in select patients) • Regional recurrence or distant metastases o Consider palliative RT/surgery for symptomatic sites SBRT may also be considered in select patients

	The NCCN recommended and preferred treatment for CSCC with lymph node involvement is excision of the primary tumor and regional lymph node dissection for all surgical candidates. Patients treated with dissection of nodes in the trunk and extremities should consider adjuvant RT of the nodal bed, especially if multiple nodes are involved or if ECE is present. For patients with nodal metastasis to the head and neck, the extent of surgery should depend on the number, location and size of effected nodes. Postoperative adjuvant treatment should depend on the pathologic findings after surgery namely the extent or resection, number of positive nodes, and presence or absence of ECE. Patients with ECE or incompletely excised nodes should receive adjuvant RT and consider concurrent systemic therapy depending on the individual toxicity tolerance. Patients with inoperable nodal disease should be treated with RT of the nodal bed and consider concurrent systemic therapy. Multidisciplinary consultation is recommended for these cases and should consider the systemic therapies to treat head and neck squamous cell carcinomas as indicated in the NCCN guidelines for Head and Neck Cancers. For symptomatic sites, palliative RT or surgery should be considered. Stereotactic body radiation (SBR) may be appropriate in select patients.
Systemic Light Chain Amyloidosis Version 1.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of systemic light chain amyloidosis.
Systemic Mastocytosis Version 1.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of systemic mastocytosis.
T-cell Lymphomas Version 2.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of T-cell lymphomas.
Testicular Cancer Version 2.2022	**Treatment of Brain Metastases**

	Brain metastases from testicular GCTs are relatively rare and occur almost exclusively in patients with nonseminoma histology. The development of brain metastases may be more common in patients with higher burden of systemic disease; lung, liver, and/or bone metastases; high levels of serum beta-hCG (>5000 IU/L); in those with neurologic symptoms; and in those who experience relapse after cisplatin-based chemotherapy. The prognosis of patients with brain metastases from testicular GCTs is poor with greater than 50% of patients dying within 1 year of diagnosis. Patients with additional adverse prognostic factors, especially those with metachronous brain metastases, have even worse outcomes. The optimal management of brain metastases from testicular GCTs is controversial, with a lack of evidence from prospective trials to guide treatment decisions. Therefore, management decisions are usually based on institutional preferences, which may in part explain the large variation in treatment modalities received by these patients. The NCCN Guidelines recommend primary cisplatin-based chemotherapy (chemotherapy for poor-risk disease) for patients with brain metastases. The addition of RT to chemotherapy regimens can also be considered. Surgical resection of metastatic brain lesions should be performed if clinically indicated and feasible. A recent retrospective analysis reported the management of 25 patients with relapsed GCTs and progressive brain metastases who received multimodality therapy, which included high dose chemotherapy with stem cell support alone or combined with surgery and/or stereotactic or whole brain RT. At a median follow-up of 24.5 months, 44% of patients were alive with no evidence of disease, suggesting that this subset

	of patients with historically poor prognosis can potentially be cured with this approach.
Thymomas and Thymic Carcinomas Version 2.2022	**Thymomas** • Stereotactic body radiation therapy (SBRT) may be appropriate for limited focal metastases, whereas conventional fractionation is appropriate for larger metastases.
Thyroid Carcinoma Version 2.2022	**Papillary, Follicular and Hurthle Cell Carcinomas** • **Locoregional recurrence** o Consider preoperative iodine total body scan ☐ For select patients with unresectable, non-radioiodine-avid, and progressive disease consider ➢ EBRT (IMRT/stereotactic body radiation therapy [SBRT]) and/or systemic therapies • **Treatment of locally recurrent, advanced, and/or metastatic disease not amendable to RAI therapy** o Unresctable locoregional recurrent/persistent disease or soft tissue metastases (e.g., lung, liver, muscle) excluding CNS metastases ☐ Consider resection of distant metastases and/or EBRT (SBRT/IMRT)/other local therapies when available to metastatic lesions if

	progressive and/or symptomatic • **Treatment of Metastatic Disease not Amendable RAI Therapy** o Bone metastases: Consider surgical palliation and/or EBRT/SBRT/other local therapies when available if symptomatic, or asymptomatic in weight-bearing sites **Principles of Radiation and Radioactive Iodine Therapy External Beam Radiation Therapy (EBRT)** • Bony or soft tissue metastases o For patients with oligometastatic disease and good performance status consider higher doses (45-60 Gy) in 1.8-2 Gy daily fractions, or SBRT following principles for treatment of oligometastases. **External Beam RT and Surgical Excision of Metastases** Surgical excision, EBRT, stereotactic body radiation therapy (SBRT) or other local therapies can be considered for symptomatic isolated skeletal metastases or those that are symptomatic isolated skeletal metastases or those that are asymptomatic in weight bearing sites. Brain metastases pose a special problem because iodine-131 therapy may induce cerebral edema. Neurosurgical resection can be considered for brain metastases. For solitary brain lesions, either neurosurgical resection or stereotactic radiosurgery (SRS) is preferred over whole brain radiation. Most recurrent tumors respond well to surgery; iodine-131; or EBRT, SBRT, or IMRT. Local therapies such as ethanol ablation, cryoablation, or radiofrequency ablation (RFA) may be considered for select patients with limited burden nodal disease.

	Metastatic Disease not Amendable to RAI Therapy For skeletal metastases, consider surgical palliation for symptomatic or asymptomatic tumors in weight-bearing extremities; other therapeutic options are EBRT, SBRT or other local therapies.
Uterine Neoplasms Version 1.2022	**Endometrial Cancer** • Suspected extrauterine disease → Suitable for primary surgery → distant metastases → Primary treatment o SBRT- consider ablative radiation therapy 1-5 metastatic lesions if hysterectomy is performed (category 2B)
Vulvar Cancers Version 1.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of vulvar cancers.
Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma Version 1.2023	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of Waldenstrom macroglobulinemia/lymphoplasmacytic.
Wilms Tumor (Nephroblastoma) Version 1.2022	• Current guideline does not include or indicate the use of SRS or SBRT in the treatment of Wilms tumor (nephrolastoma)

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

A number of LINAC movable platforms that generate high-energy photons have been cleared for marketing by the FDA through the 510(k) process. Examples include the Novalis Tx® (Novalis); the TrueBeam STx (Varian Medical Systems; approved 2012;

FDA product code IYE); and the CyberKnife® Robotic Radiosurgery System (Accuray; approved 1998; FDA product code MUJ). LINAC-based devices may be used for intracranial and extracranial lesions.

PRIOR APPROVAL

Not applicable.

POLICY

Medically Necessary
Stereotactic radiosurgery (SRS) or Stereotactic Body Radiotherapy (SBRT) (also referred to as stereotactic ablative radiotherapy [SABR]) may be considered **medically necessary** for the following indications:

- Anal carcinoma for individuals with low-volume liver oligometastases after systemic therapy **or** for the treatment of primary and nodal recurrence in the setting of low-volume metastatic disease.
- Base of skull chordomas and chondrosarcomas.
- Benign Brain Lesions
    - Arteriovenous malformations less than 3 cm in size **and** individuals who are a poor surgical risk **or** surgically inaccessible AVM
    - Acoustic neuromas
    - Pituitary adenomas
    - Craniopharyngiomas
    - Pineocytomas
    - Schwannoma
    - Glomus jugulare tumors
- Bronchopulmonary neuroendocrine tumor(s) if surgery is contraindicated.
- Central nervous system (CNS) cancers for the following indications:
    - High-grade gliomas and low- grade gliomas
        - ☐ Initial treatment
        - ☐ Treatment of recurrence
        - ☐ To treat previously irradiated field
    - Meningiomas when using tight margins or close to critical structures
    - Adult medulloblastoma for treatment of recurrence
    - Adult intracranial and spinal ependymoma (excluding subependymoma) with spine or brain recurrence
    - Brain metastases as primary treatment or for recurrent disease
    - Metastatic spinal tumors
- Cervical cancer in isolated metastatic sites only.
- Colorectal cancer

- In individuals with limited number of liver or lung metastases (1-3 metastatic lesions); **or**
- Reirradiation of previously treated patients with recurrent disease.

- Gestational Trophoblastic Neoplasia with brain metastases – High risk GTN confirmed ≥7 prognostic score or Stage IV.
- Head and neck cancers
  - For re-irradiation
  - Palliative radiation should be considered in the advanced cancer setting when curative-intent treatment is not appropriate.
- Hepatocellular Carcinoma (HCC) for the following indications:
  - Unresectable (HCC); **or**
  - Locally advanced (HCC); **or**
  - Recurrent HCC
- Kidney Cancer when **ALL** the following criteria are met:
  - Relapse or Stage IV; **and**
  - Unresectable; **and**
  - Symptomatic metastases
- Non-small cell lung cancer (NSCLC)
  - For Stage I, Stage II or Stage IIIA disease and the individual is medically inoperable or refuses surgery; or
  - Stage IVA, M1b with limited metastases (1-3 lesions) to the brain confirmed
  - Palliative therapy for advanced or metastatic NSCLC.
- Occult Primary (Cancer of Unknown Primary [CUP])
  - Localized adenocarcinoma or carcinoma not otherwise specified with limited (1-3) metastatic lesions and pulmonary metastases.
- Pancreatic Cancer locally advanced without systemic metastasis to include no direct invasion of bowel or stomach observed on imaging.
- Prostate Cancer for the following indications:
  - Low-risk prostate cancer defined as having **ALL** the following:
    - ☐ Stage T1 to T2a; **and**
    - ☐ Gleason score < 6; **and**
    - ☐ Prostate specific antigen (PSA) < 10 ng/mL.
  - Intermediate – risk prostate cancer defined as having **ALL** the following:
    - ☐ Stage T2b or T2c; and
    - ☐ Gleason score 7
    - ☐ Prostate specific antigen (PSA) 10 to 20 ng/mL; **and**
    - ☐ Favorable intermediate risk is defined as having **ALL** the following: 1 intermediate risk factor (IRF), Grade Group 1 or 2, **and** < 50% biopsy cores positive; **OR**
    - ☐ Unfavorable intermediate risk defined as having one or more of the following: 2 to 3 intermediate risk factors (IRF), Grade Group 3, and/or ≥50% biopsy cores positive.
  - High-risk prostate cancer defined as having **ALL** the following:
    - ☐ Stage ≥T3a; and

        - ☐ Gleason score ≥8; and
        - ☐ PSA > 20 ng/mL
    - Metastatic prostate cancer in the following circumstances:
        - ☐ In patients with limited metastatic disease to the vertebra or paravertebral region (concern for impending fracture or tumor encroachment on spinal nerves and vertebra); **or**
        - ☐ In a patient with oligometastatic progression (1-3 metastatic sites on imaging); **or**
        - ☐ In symptomatic individuals where the lesion occurs in or immediately adjacent to previously irradiated treatment field.
- Small cell lung cancer
    - In patients with clinical Stage I or Stage IIA who are medically inoperable or refuse surgery.
- Thymomas for limited metastases (1-3 metastatic lesions).
- Thyroid Carcinoma for the following indications:
    - Locoregional recurrence for patients with unresectable, non-radioiodine – avid and progressive disease; **or**
    - Unresectable locoregional recurrent/persistent disease or soft tissue metastases (e.g., lung, liver, muscle) excluding CNS metastases if metastatic lesion is progressive and/or symptomatic.
- Trigeminal neuralgia refractory to medical management.
- Uveal melanoma

Oligometastases
Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) for the treatment of oligometastases may be considered **medically necessary** meeting any of the following criteria:

- An individual with non-small cell lung cancer who meet **ALL** the following criteria:
    - Had had or will undergo curative treatment of the primary tumor (based on T and N stage); **and**
    - Presents with 1 to 3 metastases.
- An individual with colorectal cancer who meet **ALL** the following criteria:
    - Had had or will undergo curative treatment of the primary tumor; and
    - Presents with 1 to 3 metastases in the lung or liver; and
    - Surgical resection is not possible.
- An individual who meets the following criteria:
    - A clinical presentation of 1 to 3 adrenal gland, lung, liver or bone metastases when **ALL** the following criteria are met:
        - ☐ Histology is non-small cell lung cancer, colorectal, breast, sarcoma, renal cell or melanoma; **and**
        - ☐ Disease free interval of > 1 year from the initial diagnosis; **and**
        - ☐ Primary tumor received curative therapy and is controlled; **and**
        - ☐ No prior evidence of metastatic disease (cranial or extracranial); **and**

- ☐ All metastatic lesion present on imaging will be treated concurrently in a single episode of care.

Investigational
Stereotactic radiosurgery (SRS) and Stereotactic body radiotherapy (SBRT) is considered **investigational** including but not limited to the following indications, because the evidence is insufficient to determine the effects of this technology on net health outcomes:

Non-Neoplastic Conditions
- Behavior health disorders
- Cardiac arrhythmia (including but not limited to ventricular tachycardia)
- Cardiac radio-ablation
- Choroidal neovascularization
- Functional disorders (other than trigeminal neuralgia), including chronic pain and headaches
- Mammographic microcalcification
- Parkinson's disease and other movement disorders
- Treatment of seizures, including epilepsy

Neoplastic Conditions
- Acute lymphoblastic leukemia
- Acute myeloid leukemia
- Ampullary Adenocarcinoma
- Anal carcinoma except as indicated above
- Basal cell skin cancer
- B-cell lymphomas
- Bladder cancer – primary
- Bone cancer – primary
- Breast cancer
- Central nervous system cancers except as indicated above
- Cervical cancer except as indicated above
- Chronic lymphocytic leukemia/small lymphocytic leukemia
- Chronic myeloid leukemia
- Colorectal cancer except as indicated above
- Dermatofibrosarcoma protuberans
- Esophageal and esophagogastric junction cancers
- Gastric cancer
- Gastrointestinal stromal tumors (GIST)
- Gestational trophoblastic neoplasia except as indicated above
- Hairy cell leukemia
- Head and neck cancers except as indicated above
- Hepatobiliary cancers except hepatocellular carcinoma as indicated above
- Histiocytic neoplasms

- Hodgkin lymphoma
- Kaposi sarcoma
- Kidney cancer except as indicated above
- Malignant pleural mesothelioma
- Melanoma cutaneous except for individuals who have oligometastatic extracranial disease indicated above
- Merkel cell carcinoma
- Multiple myeloma
- Myelodysplastic syndromes
- Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes
- Myeloproliferative neoplasms
- Neuroendocrine and adrenal tumors except as indicated above
- Non-small cell lung cancer (NSCLC) except as indicated above
- Oligometastatic disease except as indicated above
- Oligoprogression disease limited number of metastatic sites (1-3) while other metastatic disease sites remain controlled
- Occult primary (cancer of unknown primary [CUP] except as indicated above
- Ovarian cancer/fallopian tube cancer and primary peritoneal cancer
- Pancreatic Cancer when invasion of the bowel or stomach is observed on imaging or endoscopy; or except as indicated above
- Penile cancer
- Primary cutaneous lymphomas
- Prostate cancer except as indicated above
- Small bowel adenocarcinoma
- Small cell lung cancer except as indicated above
- Soft tissue sarcoma except for individuals who have oligometastatic extracranial disease indicated above
- Systemic light chain amyloidosis
- Systemic mastocytosis
- T-cell lymphomas
- Testicular cancer
- Thymomas except as indicated above
- Thymic carcinoma
- Thyroid cancer except as indicated above
- Uterine neoplasms
- Vulvar cancers
- Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma
- Wilms Tumor (Nephroblastoma)

Policy Guidelines

Required Documentation
The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested. The medical records submitted should include **ALL** the following:

- History and physical; **and**
- The medical condition requiring treatment; **and**
- Imaging results; **and**
- The physician's treatment plan.

Fractionation

- SRS is most often single-fraction treatment; however, multiple fractions may be necessary when lesions are near critical structures.
- SBRT is commonly delivered over 3 to 5 fractions.

Definitions

Curative Intent: treatment provided with the main intent being to improve or eliminate symptoms that the individual is experiencing and to extend the patient's overall length of life.

Stereotactic Radiosurgery (SRS): Also referred to as stereotactic ablative surgery is a form of radiation therapy in which three-dimensional (3D) images are utilized to specifically direct focused radiation to obliterate abnormal tissues in the head and neck (facilitated by a rigid head frame), while sparing surrounding healthy tissue.

Stereotactic Body Radiotherapy (SBRT): Also referred to as stereotactic ablative radiotherapy (SABR) is similar in technique to intracranial SRS except the target areas are in the body (utilizing a body frame) and do not include the head or neck (extracranial).

Oligometastases Definitions

- **Oligometastatic**: A malignancy that has progressed to 1 to 3 metastatic sites.
- **Synchronous Oligometastasis:** Oligometastatic diseases found at the time of the diagnosis of the primary tumor.
- **Metachronous Oligometastasis:** Oligometastatic disease found after treatment of the primary tumor.
- **Oligoprogression:** Progression of a limited number of metastatic sites (1-3) while other metastatic disease sites remain controlled.

Very Low Risk Prostate Cancer
Has all of the following:

- T1c **and**;
- Grade Group 1 **and**;
- PSA<10 ng/mL **and**;

- Fewer than 3 prostate biopsy fragments/cores positive, ≤ 50% cancer in each fragment/core **and**;
- PSA density < 0.15 ng/mL/g

INTERNATIONAL SOCIETY OF UROLOGICAL PATHOLOGISTS

RISK GROUP	ISUP GRADE GROUP	GLEASON SCORE
Low	Grade Group 1	Gleason Score ≤ 6
Intermediate Favorable	Grade Group 2	Gleason Score 7 (3+4)
Intermediate Unfavorable	Grade Group 3	Gleason Score 7 (4+3)
High	Grade Group 4	Gleason Score 8
Very High	Grade Group 5	Gleason Score 9-10

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 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)

- 77371 Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; multi-source Cobalt 60 based
- 77372 Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; linear accelerator based
- 77373 Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions
- 77432 Stereotactic radiation treatment management of cranial lesion(s) (complete course of treatment consisting of 1 session)
- 77435 Stereotactic body radiation therapy, treatment management, per treatment course, to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions
- 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 5 sessions per course of treatment

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- National Comprehensive Cancer Network (NCCN0 Basal Cell Skin Cancer Version 2.2022
- National Comprehensive Cancer Network (NCCN). B-cell Lymphomas Version 5.2022
- National Comprehensive Cancer Network (NCCN) Bladder Cancer Version 2.2022
- National Comprehensive Cancer Network (NCCN) Bone Cancer Version 1.2023
- National Comprehensive Cancer Network (NCCN) Breast Cancer Version 4.2022
- National Comprehensive Cancer Network (NCCN). Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia Version 3.2022
- National Comprehensive Cancer Network (NCCN). Chronic Myeloid Leukemia Version 3.2022
- National Comprehensive Cancer Network (NCCN). Dermatofibrosarcoma Protuberans Version 2.2022

- National Comprehensive Cancer Network (NCCN). Esophageal and Esophagogastric Junction Cancers Version 3.2022
- National Comprehensive Cancer Network (NCCN). Gastric Cancer Version 2.2022
- National Comprehensive Cancer Network (NCCN). Gastrointestinal Stromal Tumors (GIST) Version 1.2022
- National Comprehensive Cancer Network (NCCN). Gestational Trophoblastic Neoplasia Version 1.2022
- National Comprehensive Cancer Network (NCCN). Hairy Cell Leukemia Version 1.2022
- National Comprehensive Cancer Network (NCCN). Hepatobiliary Cancers Version 2.2022
- National Comprehensive Cancer Network (NCCN). Histiocytic Neoplasms Version 1.2022
- National Comprehensive Cancer Network (NCCN). Hodgkin Lymphoma Version 2.2022
- National Comprehensive Cancer Network (NCCN). Kaposi Sarcoma Version 1.2022
- National Comprehensive Cancer Network (NCCN). Malignant Pleural Mesothelioma Version 1.2022
- National Comprehensive Cancer Network (NCCN). Melanoma Uveal Version 2.2022
- National Comprehensive Cancer Network (NCCN). Merkel Cell Carcinoma Version 2.2022
- National Comprehensive Cancer Network (NCCN). Multiple Myeloma Version 5.2022
- National Comprehensive Cancer Network (NCCN). Myelodysplastic Syndromes Version 3.2022
- National Comprehensive Cancer Network (NCCN). Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes Version 1.2022
- National Comprehensive Cancer Network (NCCN). Myeloproliferative Neoplasms Version 2.2022
- National Comprehensive Cancer Network (NCCN). Occult Primary (Cancer of Unknown Primary [CUP]) Version 2.2021
- National Comprehensive Cancer Network (NCCN). Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer Version 3.2022
- National Comprehensive Cancer Network (NCCN). Pediatric Acute Lymphoblastic Leukemia Version 1.2022
- National Comprehensive Cancer Network (NCCN). Pediatric Aggressive Matures B-Cell Lymphomas Version 1.2022
- National Comprehensive Cancer Network (NCCN). Pediatric Hodgkin Lymphoma Version 1.2022
- National Comprehenisve Cancer Network (NCCN) Pediatric Central Nervous System Cancers Version 1.2023

- National Comprehensive Cancer Network (NCCN) Penile Cancer Version 2.2022
- National Comprehensive Cancer Network (NCCN) Primary Cutaneous Lymphomas Version 2.2022
- National Comprehensive Cancer Network (NCCN) Small Bowel Adenocarcinoma Version 1.2022
- National Comprehensive Cancer Network (NCCN) Squamous Cell Skin Cancer Version 2.2022
- National Comprehensive Cancer Network (NCCN) Systemic Light Chain Amyloidosis Version 1.2022
- National Comprehensive Cancer Network (NCCN) Systemic Mastocytosis Version 1.2022
- National Comprehensive Cancer Network (NCCN) T-cell Lymphomas Version 2.2022
- National Comprehensive Cancer Network (NCCN) Testicular Cancer Version 2.2022
- National Comprehensive Cancer Network (NCCN) Thyroid Carcinoma Version 2.2022
- National Comprehensive Cancer Network (NCCN) Uterine Neoplasms Version 1.2022
- National Comprehensive Cancer Network (NCCN) Vulvar Cancers Version 1.2022
- National Comprehensive Cancer Network (NCCN) Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma Version 1.2023
- National Comprehensive Cancer Network (NCCN) Wilms Tumor (Nephroblastoma) Version 1.2022
- National Comprehensive Cancer Network (NCCN) Pancreatic Adenocarcinoma. Version 1.2022
- National Comprehensive Cancer Network (NCCN) Kidney Cancer. Version 2.2023
- National Comprehensive Cancer Network (NCCN) Melanoma Cutaneous Version 3.2022
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- National Comprehensive Cancer Network (NCCN) Soft Tissue Sarcoma. Version 2.2022
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- UpToDate. Focal Brainstem Glioma. Matthias A Karajannis M.D., MS, Karen J. Marcus M.D., Topic last updated July 28, 2022
- UpToDate. Management of known or presumed benign (WHO grade 1) menigioma. John K. Park M.D., PhD, Helen A Shih M.D., MS, MPH, Topic last updated March 8, 2022
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- UpToDate. Overview of therapeutic approaches for adult patients with bone metastasis from solid tumors. Michael H. Yu M.D., ScM, Sarah E. Hoffe, M.D., Topic last updated August 27, 2021
- UpToDate. Radiation therapy techniques in cancer treatment. Timur Mitin M.D., PhD, Topic last updated January 14, 2022
- UpToDate. Stereotactic body radiation therapy for lung tumors. Josh H, Heinzerling M.D., Robert D. Timmerman M.D., Topic lst updated January 15, 2021
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- UpToDate. Stereotactic cranial radiosurgery. Clark C Chen M.D., PhD, Paul H. Chapman M.D., Jay S. Loeffler M.D., Topic last updated April 5, 2022

POLICY HISTORY		
Date	**Reason**	**Action**
July 2022	Annual Review	Policy Revised
July 2021	Annual Review	Policy Revised
November 2020	Interim Review	Policy Revised
July 2020	Annual Review	Policy Revised
October 2019	Interim Review	Policy Revised
July 2019	Annual Review	Policy Revised
November 2018	Interim Review	Policy Revised
July 2018	Annual Review	Policy Revised
July 2017	Annual Review	Policy Revised
July 2016		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
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