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Critical review

Stereotactic Radiosurgery in the Management of Brain Metastases: A Case-Based Radiosurgery Society Practice Guideline

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Purpose: Brain metastases are common among adult patients with solid malignancies and are increasingly being treated with stereotactic radiosurgery (SRS). As more patients with brain metastases are becoming eligible for SRS, there is a need for practical review of patient selection and treatment considerations.

Methods and Materials: Two patient cases were identified to use as the foundation for a discussion of a wide and representative range of management principles: (A) SRS alone for 5 to 15 lesions and (B) a large single metastasis to be treated with pre- or postoperative SRS. Patient selection, fractionation, prescription dose, treatment technique, and dose constraints are discussed. Literature relevant to these cases is summarized to provide a framework for treatment of similar patients.

Results: Treatment of brain metastases with SRS requires many considerations including optimal patient selection, fractionation selection, and plan optimization.

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Conclusions: Case-based practice guidelines developed by the Radiosurgery Society provide a practical guide to the common scenarios noted above affecting patients with metastatic brain tumors.

Introduction

Brain metastases are common, affecting up to 30% of adult cancer patients.[1] The incidence of brain metastases is increasing as more effective systemic therapies improve extracranial control, leaving the central nervous system (CNS) as a sanctuary site due to the blood-brain barrier preventing ingress of large therapeutic molecules. Although some targeted agents and immunotherapy agents have CNS activities against brain metastases, drug resistance will eventually develop in many patients. Therefore, metastasis-directed focal radiation therapy continues to play a central role in the management of CNS metastases.

Historically, radiation for patients with brain metastases was delivered with whole-brain radiation therapy (WBRT), with the rationale of treating both macroscopic and microscopic disease. Stereotactic radiosurgery (SRS) was introduced as a treatment for brain metastases. Initially, the RTOG 9508 trial demonstrated superior local control with WBRT plus SRS compared with WBRT alone in patients with 1 to 3 brain metastases.[2] Further attempts were then made to omit WBRT due to associated neurotoxicity, with multiple trials demonstrating worse local and "distant" intracranial control with SRS alone in patients with 1 to 3 or 1 to 4 metastases less than 3 to 4 cm in diameter, but with the combined approach being associated with inferior neurocognitive function and quality of life, and equivalent or inferior overall survival (OS).[3-5] Additional trials, including N107C/RTOG 1270, have shown similar results when comparing SRS to WBRT in the postoperative setting.[6] For these reasons, SRS alone became standard in the definitive and postoperative setting for patients with 1 to 4 brain metastases, and it remains a preferred option in modern guidelines for patients with lesions up to 3 to 4 cm in diameter.[7]

SRS is increasingly applied to patients with a larger number of brain metastases and larger tumors. In an effort to preserve cognition, SRS is being increasingly used in the postoperative setting. However, this is associated with a higher risk of nodular meningeal recurrences than WBRT. In an effort to mitigate this concern, preoperative SRS is being explored. Therefore, the purpose of these case-based guidelines, sponsored by the Radiosurgery Society, is to describe in detail the treatment approach used in patients with brain metastases treated with SRS and to provide a practical guide to the nuances of providing SRS to patients with clinical presentations that until recently would have been treated very differently. This work was designed to be consistent with the Radiosurgery Society disease site review criteria.

Case Presentations

Case 1: Patient with 7 brain metastases from non-small cell lung cancer

Case scenario

Patient A is a 69-year-old woman with no significant past medical history who was originally diagnosed 1 year prior with advanced non-small cell lung cancer (NSCLC) following presentation with a persistent cough. CT of the chest revealed a right middle lobe mass and hilar and subcarinal lymphadenopathy. The biopsy was consistent with lung adenocarcinoma. Molecular testing revealed EGFR L858R mutation. Staging positron emission tomography (PET)/CT revealed numerous metastases. Initial staging via brain magnetic resonance imaging (MRI) was negative. She was treated initially with osimertinib, but she developed systemic disease progression. For her next line of therapy, she was considered for a clinical trial. As part of screening, she underwent brain MRI, which revealed 7 enhancing lesions throughout the brain, with the largest lesion measuring 0.5 cm in diameter. Total tumor volume was 5 cc. The MRI imaging of a representative lesion is visualized in Fig. 1A. There was no evidence of leptomeningeal disease. She was referred for consideration of brain SRS.

Treatment and follow-up

Computed tomography simulation with 1.0 mm slices was performed using a thermoplastic facemask for immobilization. T1 postcontrast MRI with thin (1 mm) slices was acquired and registered to the simulation CT using treatment-planning software. Using the contrast enhanced T1 MRI sequence as guidance, the individual gross tumor volumes (GTVs) were contoured, and a 1-mm planning target volume (PTV) margin was applied to each GTV. PTVs are visualized in Fig. 1B. The dose to the PTVs was planned to 20 Gy in 1 fraction, delivered using 2 isocenters and a linear accelerator with cone beam computed tomography (CBCT) image guidance and a flattening filter free (FFF) volumetric modulated arc therapy (VMAT) technique with 5 noncoplanar arcs, administered with surface guidance. The primary dose constraints used were brain − PTV V10 < 12 cc and brain − PTV V12 < 10 cc. Isodose lines and relevant dose metrics are

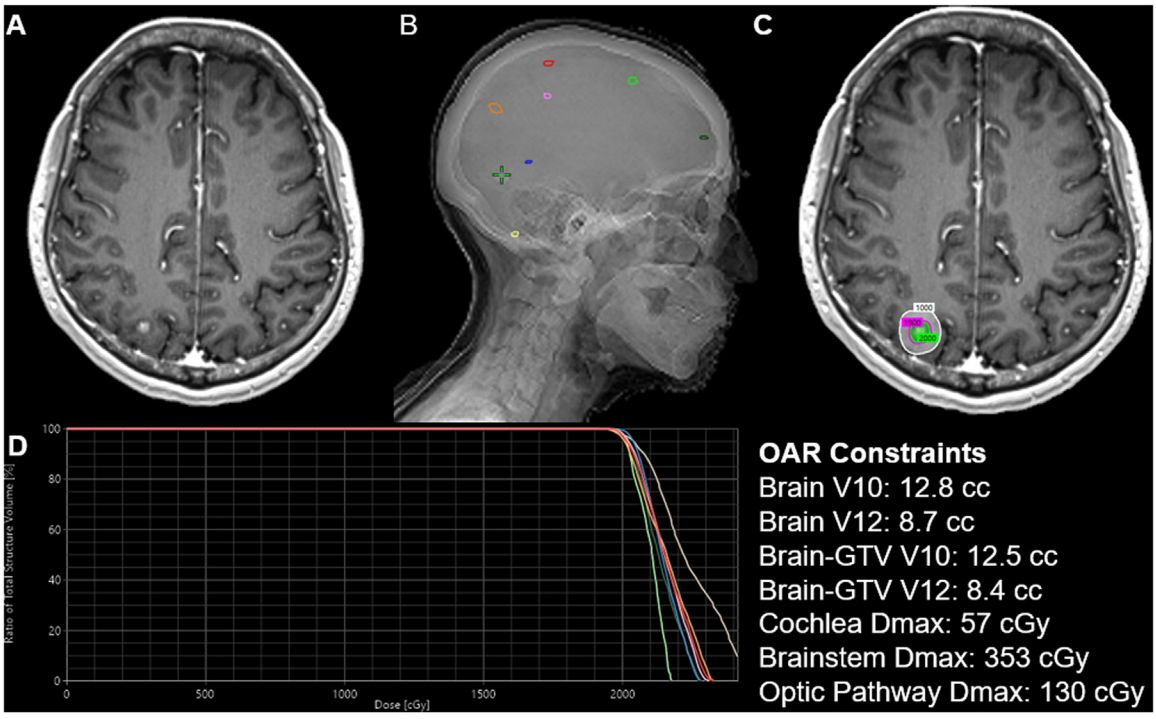

Figure 1 Imaging and treatment volumes for patient A, including (A) pretreatment imaging, (B) treatment volumes, (C) isodose lines, and (D) dose-volume histograms of the PTVs.

shown in Fig. 1C-D. Total treatment time was 38 minutes. The patient tolerated the treatment well, without any significant complications. She is now fifteen months out from completion of treatment with no evidence of progressive intracranial disease or adverse effects. It is important to note, however, that following SRS the median time to adverse event is 7 months, with a range of 1 to 39 months.[8]

Case 1 Discussion

What factors contribute to whether a patient might be a candidate for SRS treatment? Table 1 summarizes selection criteria for SRS. A primary selection criterion for SRS is a quantity cutoff, though there is mounting evidence that total volume of metastases is also critical in determining feasibility of SRS. A 2014 multi-institutional prospective observational study by Yamamoto et al comparing treating 2 to 4 brain lesions versus 5 to 10 lesions (total volume <15 cc) with SRS demonstrated noninferiority with regards to OS and treatment-related adverse events.[9] More recently, a UT—MD Anderson trial comparing SRS to WBRT in patients with 4 to 15 metastases demonstrated improved neurocognitive function, numerically improved OS, comparable local control, and a nonsignificant trend toward inferior overall intracranial control, though it is important to note that this trial was terminated early and has only been published in abstract form.[10] Therefore, prospective evidence supports treatment of up to 15 lesions with SRS, although many centers consistently treat larger numbers of lesions with apparent safety. Current National Cancer Care Network (NCCN) guidelines recommend the use of volume instead of the absolute number of metastases as the limit to determine eligibility for SRS, with potential cutoffs being ≤15 cc.[11]

Another consideration is lesion size, particularly given that prior clinical trials were generally limited to lesions <3 cm in diameter. Single-fraction SRS has proven to be relatively contraindicated for patients with large lesions (>3 cm). In addition, for larger lesions, fractionated regimens produce better control and rates of radionecrosis.[12,13] In Hypofractionated Treatment Effects

Table 1 Suitability for SRS

Suitable	Criteria
Number of lesions	1-15
Metastasis size	Diameter ≤3 cm, volume ≤14 cc
Cautionary	
Number of lesions	>15
Metastasis size	Diameter 3-6 cm, volume >14 cc (operative management preferred)
Specific scenarios	Small cell lung cancer, nodular leptomeningeal disease
Unsuitable	
Metastasis size	>6 cm
Specific scenarios	Classical leptomeningeal disease

in the Clinic (HyTEC) analyses, which combined data from 56 studies, for lesions between 2.1 and 4 cm, single-fraction SRS achieved a 1-year LC of 69% to 75%, while fractionated SRS yielded a 1-year LC of approximately 80%.[12] Further, for single-fraction SRS to brain metastases, V12 (inclusive of the GTV) of 5 cc, 10 cc, or >15 cc were associated with risks of symptomatic radionecrosis of approximately 10%, 15%, and 20%, respectively, meaning that for larger brain metastases it is not possible to attain reasonable risk of radionecrosis with a single-fraction approach.[13]

These conclusions are supported by comparative studies. In a meta-analysis of 24 studies and 1887 brain lesions comparing single-fraction and multi-fraction SRS for large brain metastases (group A: 4-14 cc volume and 2-3 cm diameter vs group B: >14 cc volume and >3 cm diameter), 1-year LC was 77.6% for single-fraction SRS and 92.9% for multifraction SRS in group A (0 = 0.18), while 1-year LC was 77.1% for single-fraction SRS and 79.2% for multifraction SRS in group B ($P = .76$).[14] Radionecrosis rates were 23.1% for group A single-fraction SRS, 7.3% for group A multifraction SRS ($P = .003$), 11.7% for group B single-fraction SRS, and 6.5% for group B multifraction SRS ($P = .29$). Due to limited evidence, SRS is not recommended for patients with lesions >6 cm in diameter.[15] As local control and toxicity are worse in lesions greater than 3 cm in diameter, surgical resection should be considered in these patients, particularly for those with symptoms related to mass effect or those where a pathologic diagnosis is necessary. However, if surgical resection is not a safe option for patients with large lesions, multifraction SRS is an excellent alternative. Selection of treatment (SRS vs multifraction SRS vs surgery plus SRS) can be based on ability to achieve published dosimetric objectives to limit risk of symptomatic radionecrosis. Regardless, risk of necrosis is inherent to brain SRS and the priority should be giving a sufficient dose to control the tumor.

Another relevant factor that correlates with both metastasis quantity and size is total brain volume and associated whole-brain dose. Patients with 2 to 4 lesions have been shown to have improved OS compared with patients with 5+ lesions, and on multivariable analysis (MVA), tumor volume, Karnofsky Performance Status, and histology remained significant for OS, whereas lesion number did not, suggesting that volume may be a more significant prognostic factor than lesion number, specifically volume > 10 cc, and this may influence the decision to deliver SRS versus multifraction SRS, or even WBRT.[16] In a study assessing whole-brain dose in relation to single-fraction SRS, a total of 9 24-36-mm tumors, 177 0-4-mm tumors, or 42 tumors of mixed size were required to yield an 8 Gy whole-brain dose for a single session.[17] This provides a dosimetric estimate of the number and size of lesions, at which point integral brain dose might obviate the benefits of SRS and necessitate consideration of alternative approaches such as WBRT. Another volumetric parameter/goal is reducing V12 Gy, which correlates with reduced probability of symptomatic brain necrosis, and the monitor units generated by the proposed treatment, as scatter from collimation can contribute to whole-brain dose.[13]

Lastly, there are contraindications to SRS, though some of these are beginning to be challenged. In small cell lung cancer (SCLC), brain metastases often portend WBRT as treatment, given that patients with SCLC brain metastases are at high risk for new distant tumors after SRS. Yet, a meta-analysis of 9 studies and 1638 patients demonstrated favorable OS, LC, distant brain failure, and freedom from neurologic death with SRS.[18] Thus, although the role of SRS in SCLC needs to be further clarified in prospective trials, and cannot yet be the default treatment of choice, it is an acceptable option at this point. Similarly, leptomeningeal disease (LMD) is well described in patients with brain metastases, classically serving as an indication for WBRT or possibly craniospinal irradiation (CSI) in rare cases where the disease was exclusively confined to the CNS. The exception is that postoperative cavity SRS might be considered for more focal nodular leptomeningeal disease (nLMD), which is distinct from classical LMD. A recent prospective registry study investigated the utility of SRS for nLMD across 32 brain metastases in 16 patients. Median actuarial OS from SRS for LMD was 10.0 months, and only 6 patients underwent WBRT after SRS for nLMD at a median time of 6 months, suggesting nLMD may be treated with SRS and potentially delay WBRT in some patients.[19] However, this approach for LMD should be used judiciously in carefully selected patients given the limited data in the literature.

What fractionation schemes can be used in SRS?

Based on American Society for Radiation Oncology (ASTRO) guidelines, for patients with metastases <2 cm in diameter, single fraction SRS to a total dose of 20 to 24 Gy in one fraction is recommended, though there are potentially acceptable practice variations outside that range depending on the clinical scenario.[7] Of note, in some cases such as Gamma Knife plans, dose is prescribed to lower isodose lines, which does permit hot spots within tumor greater than the doses cited in ASTRO guidelines. For patients with lesions measuring 2 to 4 cm, 27 Gy in 3 fractions or 30 Gy in 5 fractions is recommended. Based on HyTEC data, when feasible, dose escalation is beneficial for improving LC.[12] Ultimately dose selection is nuanced and can be influenced by a number of factors including lesion size, histology, and total volume of irradiated tumor. An alternative for lesions >2 cm is a staged SRS approach (treatment administered in 2 separate sessions with replanning for each), which has been shown to yield excellent 6-month LC (88%) and adverse event (11%) rates, although data to support this approach is limited and warrants further evaluation.[20] In patients

with lesions >4 cm, surgery is recommended. However, if a patient is unable to undergo surgery, multifraction SRS is recommended over single fraction SRS. Fractionated SRS for larger lesions is driven by increasing concerns about local control and toxicity, particularly as treatment volume increases, and should be strongly considered for larger lesions.[13,21,22] The previously mentioned concerns regarding LMD should also play a role in decision-making, and surgical resection is still the first-line treatment for large brain metastases.

What treatment volumes are used during SRS without surgery? Compared with gliomas, brain metastases are less microscopically invasive, and therefore clinical target volume (CTV) expansions of GTVs are not routinely used. Treatment volumes are simplest in the definitive or preoperative setting. These volumes typically consist of the GTV with a PTV margin ranging from 0 to 2 mm depending on the immobilization applied and delivery platform. The GTV is typically contoured using the contrast-enhanced T1 MRI series. It is critical that treatment volumes be defined based off an MRI that is obtained shortly before initiation of SRS. Otherwise, local control can be compromised, likely due to progression of lesions causing a marginal miss, particularly if little to no PTV margin is used.[23,24] With the advancement in technology, some institutions are using less margin, as margin size directly correlates with the volume of healthy brain being irradiated. Agazaryan et al[25] analyzed 48 plans with V5 Gy, V8 Gy, V10 Gy, and V12 Gy, doubling when margins change from 0 to 1 mm and tripling when changed from 0 to 2 mm. However, without a PTV margin to account for uncertainty with image registration, target delineation, immobilization, and treatment delivery, there is a possibility of inferior local control.[26] Clinicians must weigh these conflicting factors when determining whether to include a margin in the PTV for patients with metastatic tumors. If a PTV margin is used, we recommend using a 1 to 2-mm (1-mm whenever possible) margin based on these perceived uncertainties to minimize exposure of normal brain volume to undue amounts of radiation.

What technique can be used to treat multiple brain metastases using a linear accelerator? Single-isocenter techniques (SITs) are often used to streamline treatment planning and delivery for multiple brain metastases, though this is approach is feasible only with a linear accelerator (LINAC) technique. In a retrospective analysis of multiple-isocenter techniques (MIT) versus SIT for 437 intact brain lesions across 104 patients (2-13 metastases per treatment course), 6-month freedom from recurrence was 96% for SIT and 96% for MIT (P = .81), suggesting that SIT SRS offers efficient and effective control.[27] On MVA, only PTV size was associated with radionecrosis, with both SIT and MIT having similarly high LC rates and low radionecrosis. Therefore, when feasible, SIT plans can facilitate effective and efficient treatment planning and delivery for multiple metastases, allowing for time-efficient clinical feasibility for initial and subsequent SRS courses.

An obstacle to using SRS for patients with numerous metastases is longer treatment times when using a LINAC. SIT SRS allows rapid delivery to multiple targets, and further studies of 1014 metastases in 173 patients treated with SIT SRS in 1 to 5 fractions showed a median beam-on time of 4.1 minutes, suggesting SIT SRS can improve clinical workflows.[28] However, SIT techniques for simultaneous irradiation of multiple targets at one isocenter do require accurate patient positioning, as setup error worsens with increased distance from the isocenter and decreasing tumor size.[29] Therefore, treatment of SIT can be successfully implemented, but should be performed only with high confidence in setup (dependent on distance to the isocenter, which can influence whether a larger PTV margin might be needed), proper patient selection, and careful consideration of treatment margins. LINAC-based MIT SRS is a time-consuming process, relative to non-LINAC—based approaches, so SIT can introduce efficiency with treatment time for LINAC SRS.

What dose constraints are used for SRS? Table 2 contains a detailed list of dose constraints for SRS. Broadly speaking, in patients without prior irradiation there is an abundance of data regarding dose constraints that might be used to limit toxicities, especially radionecrosis, damage to the optic pathway, brain stem injury, and cochlear damage, with the most used constraint being brain minus a target volume. It is worth noting, however, that brain minus target volume constraints may not extrapolate to multitarget plans and might be best assessed by individually treated lesions. Furthermore, these constraints are not strict and might be best used when deciding whether to fractionate. The tumor should not be underdosed to meet these constraints. In previously irradiated fields, there is limited consensus and literature regarding suitable dose constraints, with reasonable goals depending on the specific scenario, though typically a minimum of 5 months should have elapsed before considering such treatment.[30] However, the dose to generally critical structures should be kept as low as reasonably attainable. If the feasibility of reirradiation is being evaluated, maximum doses used in clinical trials may be considered. These include maintaining total brain equivalent dose in 2 Gy fractions (EQD2) to <120 Gy[31] and maximum total summed dose less than 40 Gy[32] and V12 <9 cc[32] if using 1 fraction. Cumulative spinal cord dose should yield an EQD2 of ≤70 Gy, with the reirradiation EQD2 ≤25 Gy and at least 5 months between the initial and subsequent radiation courses.[30]

What motion management approaches can be used during SRS? Radiosurgery is performed either with a frame or mask. Over the last several decades, the masked

Table 2 Common dose constraints used in SRS planning

	Standard treatment		
Organ	**1 fx**	**3 fx**	**5 fx**
Brain	V12 <5-10 cc[13,53] V10 <12 cc[53]	V18 <26 cc[54] V21 <21 cc[54] V24 <16.8 cc[55]	V25 <16 cc[56] V28.8 <7 cc[57] V30 <10.5-30 cc[56]
Brain stem (not medulla)	Dmax <15 Gy[58] V10 <0.5 cc[58]	Dmax <23.1 Gy[58] V15.9 <0.5 cc[58]	Dmax <31 Gy[58] V23 <0.5 cc[58]
Spinal cord and medulla	Dmax <12.4-14 Gy[30,58] V10 <0.35 cc[58]	Dmax <20.3-22.5 Gy[30,58] V15.9 <0.35 cc[58]	Dmax <25.3-28 Gy[30,58] V22 <0.35 cc[58]
Cochlea	Dmax <9 Gy[58]	Dmax <14.4 Gy[58]	Dmax <22 Gy[58]
Optic pathway	Dmax <10 Gy[58,59] V8 <0.2 cc[58]	Dmax <17.4-20 Gy[58,59] V15.3 <0.2 cc[58]	Dmax <25 Gy[58,59] V23 <0.2 cc[58]

method has become increasingly popular as it is completely noninvasive, allows for fractionation if otherwise appropriate, and is better tolerated by patients. If a robotic radiosurgery system is used, the robotic system will track the skull motion in a near real-time fashion while the patient's head is under a mask. Prospective and retrospective studies comparing outcomes between these methods have shown no difference in tumor control and toxicity.[33] Beyond physical immobilization, motion monitoring devices in combination with CBCT are used to detect intrafraction and interfraction movement. Examples of motion monitoring devices include the surface-guided radiation therapy (SGRT) system, infrared marker tracking systems, and a fiducial marker-based system known as high-definition motion management (HDMM). Wang et al[34] compared SGRT and HDMM; these 2 devices detected translational motion with an accuracy of 0.3 mm for displacement up to 1 cm and 0.5 mm for displacement greater than 1 cm. HDMM was found to be more sensitive than SGRT in capturing motion. The sensitivity of both systems was relatively lower in superior-inferior motion.

Can SRS be given concurrently with systemic therapies? There is a concern that concurrent systemic therapy and SRS may increase the risk of radionecrosis, which often leads to delay in systemic therapy until completion of SRS. Notably, there is difficulty in defining concurrent treatment due to differences in half-life among different targeted/immunotherapy agents.[35] In a detailed systematic review by Borius et al, in which the timing of various systemic agents and SRS was evaluated, there was no significant increase in radionecrosis with most treatments.[36] Concurrent erlotinib showed an increased incidence of radionecrosis, though this was in patients who received both WBRT and SRS. V-Raf Murine Sarcoma Viral Oncogene Homolog B (BRAF) inhibitor use concurrently with SRS was associated with a significantly increased rate of intratumoral bleeding, although there were improvements in OS and local control (LC) with this group.[36] Scoccianti et al[37] evaluated the efficacy and toxicity of concurrent immunotherapy (IO) with SRS in patients with NSCLC and found better intracranial local progression-free survival and no significant difference in radionecrosis between SRS + IO versus SRS alone. Currently, it appears most studies support concurrent systemic therapy + SRS with no need for a washout period. Further, in some cases, delaying systemic therapy may be detrimental. Indeed, in one study of 193 patients (37% received myelosuppressive chemotherapy or targeted/IO) with a new primary cancer diagnosis and brain metastasis, those treated with concurrent systemic therapy and SRS had improved survival compared with SRS alone (41.6 months vs 21.5 months; $P < .05$).[38] In another series of 260 patients, concurrent SRS was associated with decreased likelihood of new metastases (odds ratio, 0.337; $P = .045$).[39] Conversely, in select patients, due to intracranial response to certain systemic therapies, treatment of asymptomatic lesions with SRS can be deferred. Per the American Society of Clinical Oncology−Society for Neuro-Oncology−American Society for Radiation Oncology (ASCO-SNO-ASTRO) guidelines, among patients with asymptomatic brain metastases eligible for CNS-active systemic therapy, a multidisciplinary approach with patient-centered decision-making is conditionally recommended regarding deferral of SRS and optimally would be done in the prospective setting.[15] Intracranial progression can still be high (evidenced by greater risk of intracranial than extracranial progression), even with therapies that cross the blood-brain barrier.[40,41]

Case 2: Patient with metastatic colon cancer with single large posterior fossa metastasis

Case scenario

Patient B is a 53-year-old woman with a history of metastatic colon cancer originally diagnosed 4 years

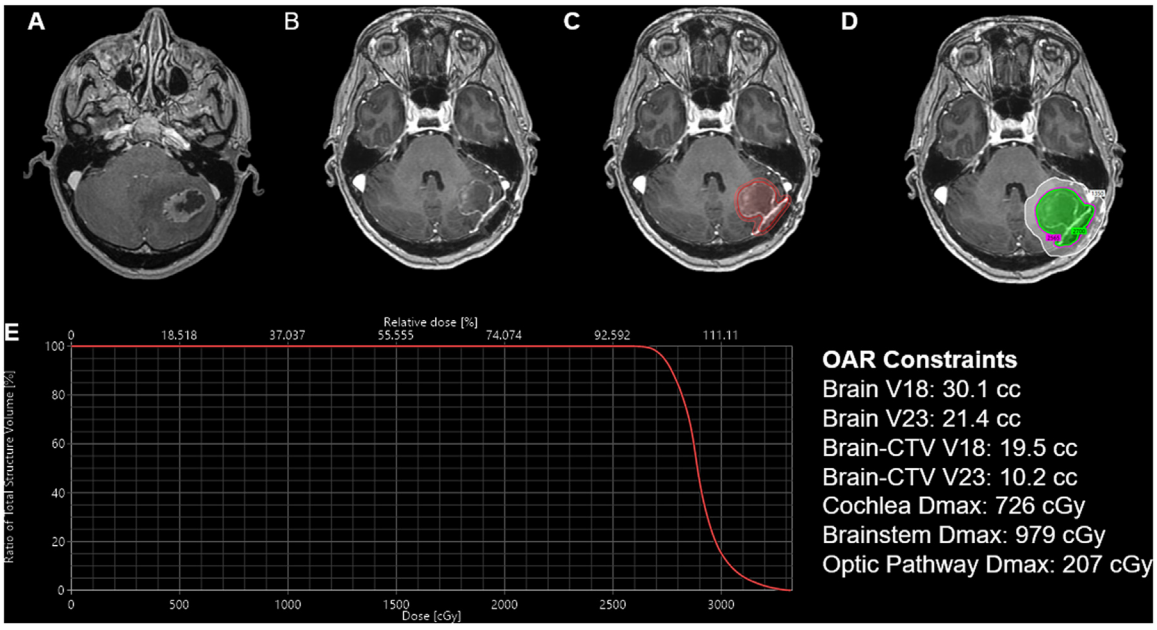

Figure 2 Imaging and treatment volumes for patient A, including (A) preoperative imaging, (B) postoperative imaging, (C) treatment volumes, (D) isodose lines, and (E) dose-volume histograms of the PTV.

prior. She presented to urgent care with new onset of severe headaches and ataxia. MRI of the brain revealed a 3.5-cm mass in the left cerebellum with mass effect on the fourth ventricle and surrounding vasogenic edema. There was no evidence of additional intracranial pathology or leptomeningeal disease. Preoperative imaging is shown in Fig. 2A. The patient underwent a gross total resection, with pathology confirming metastatic colon cancer. Postoperative SRS was to begin 3 weeks later.

Treatment and follow-up

CT simulation (1-mm slices) was performed using a thermoplastic facemask for immobilization. Updated postoperative volumetric MRI (1-mm slices) was obtained on the same day as CT simulation. Postoperative MRI is shown in Fig. 2B. The patient's preoperative and postoperative MRIs were fused to the CT simulation using treatment-planning software. Primarily using the contrast enhanced T1 MRI sequence as guidance, the postoperative bed CTV was contoured, and a 2-mm PTV margin was applied to the CTV. The CTV and PTV are shown in Fig. 2C. The fractionated SRS dose to the PTVs was planned to 27 Gy in 3 fractions given every other day, delivered using a LINAC with CBCT image guidance and a VMAT technique with 3 noncoplanar arcs. Isodose lines and relevant dose metrics are shown in Fig. 2D-E. The patient tolerated the treatment well, without any significant complications. Twelve months after fractionated SRS, she developed multiple new metastases and also developed recurrence in the resection cavity treated with postoperative SRS, as previously described.

Case 2 discussion

What treatment volumes and fractionations are used during postoperative SRS? In the postoperative setting, the target volume is primarily based off the CTV from the postoperative bed.[21,42] The primary recommendation for CTV delineation is the usage of contrast enhancing T1 MRI to delineate the entire postoperative cavity, without the inclusion of vasogenic edema, and a margin up to 5 mm along the meningeal margin/bone flap. For tumors in contact with the dura preoperatively, a margin up to 10 mm along the bone flap beyond the initial region of tumor contact in preoperative MRI may be considered. For tumors in contact with a venous sinus, 1 to 5 mm along the sinus is sufficient for inclusion in the CTV.[42] Including the extent of preoperative tumor in CTV or expanding from the closest meninges (in addition to the resection cavity) provides little benefit.[43] There is no consensus as to whether the surgical tract should be covered. Excluding the surgical tract results in a low failure rate and can decrease the risk of adverse events. Inclusion of the surgical tract should be evaluated on an individual basis, considering risk factors for LMD such as infratentorial location and breast cancer history.[21,42] PTV margin is typically 2 mm, although in select cases it may be reduced to 1 mm, though this is again dependent on confidence in setup, and care must be taken to ensure local control is not compromised.[44-46] When selecting dose fractionation, similar principles to treatment of intact metastases may be applied, though a fractionated approach is often preferred as a means of potentially minimizing risk of toxicity when considering the higher cumulative doses

Table 3 Comparison between potential benefits of preoperative and postoperative SRS

Preoperative SRS	Postoperative SRS
• Improved target delineation • Improved local control • Higher oxygenation • Decreased risk of subsequent leptomeningeal disease • Decreased risk of radionecrosis • Smaller treatment volumes*	• Pathologic confirmation before treatment • Compatible with cases with mass effect • Immediate treatment of neurologic symptoms† • Abundant data including level 1 evidence

* May not apply if surgical cavity shrinks significantly postoperatively, but is related to improved target delineation, not needing to cover elective volumes such as surgical tract, and in some cases allowing smaller treatment margins.
† Can be due to either needing urgent decompression to prevent further neurologic decline/damage, or due to logistical challenges of stabilizing and discharging patients with symptomatic disease to allow for outpatient preoperative treatment.

received by normal tissues, extrapolating principles from SRS outside the reirradiation setting.

When surgical management is indicated, what is the evidence for pre- versus postoperative SRS? Due to high risk of local recurrence following the surgical resection of brain metastasis, randomized data supports the use of postoperative irradiation to reduce the risk of cavity recurrence compared with observation.[47] When clinical factors such as patient stability allow, either pre- or postoperative SRS can be considered. It should be emphasized that preoperative SRS is typically not preferred for symptomatic metastases either due to the patient needing urgent decompression to prevent further neurologic decline/damage or due to the logistical challenges of stabilizing and discharging patients with symptomatic disease to allow for outpatient preoperative treatment. Pre- and postoperative SRS are associated with similar outcomes regarding local control, distant brain failure, OS, and need for salvage WBRT.[48] However, preoperative SRS offers certain advantages.

One difficulty with postoperative SRS stems from target definition. The resection area is prone to change after surgery. Earlier initiation of the treatment may cause irradiation of larger fields, but timing later than 4 weeks after surgery may cause decreased LC. The general consensus is to perform SRS within 4 weeks after surgery, with target planning MRI performed 7 days or fewer before SRS.[21] This difficulty does not apply to preoperative SRS, where treatment volumes are easily seen on MRI. Another concern regarding postoperative SRS is the subsequent development of nodular meningeal disease, which is associated with piecemeal surgical resection, hemorrhagic and cystic lesions, a greater number of brain metastases, posterior fossa location, as well as with breast cancer histology.[21,22] This risk provides a rationale for preoperative SRS, which is hypothesized to decrease the risk of LMD, with initial studies demonstrating meningeal disease rates of 5.8% compared with 16% to 21% in the postoperative setting.[48-50] Other potential benefits of preoperative SRS include improved logistics due to not having to coordinate postoperative treatment, earlier initiation of systemic therapy, and ability to treat to doses that are about 20% to 25% lower.[49,51] A potential disadvantage of preoperative SRS is the risk of irradiation of benign or primary CNS lesions, which has been reported to occur in 2% to 11% of patients.[52] However, proper attention to the patient's history and images should prevent this from being more than a rare event, and especially so for those with benign neoplasms. Table 3 includes a summary of theoretical considerations regarding pre- versus postoperative SRS. Multiple trials are now ongoing to prospectively evaluate preoperative SRS.

Conclusion

As more patients with brain metastases are becoming eligible for SRS, there is a need for practical review of patient selection and treatment considerations. Included as well is an insight into future directions of patient management, including treatment of many lesions, masked SRS, alternative fractionation schedules, and systemic therapies that will serve as an adjunct or alternative to SRS. In the meantime, these guidelines are intended to serve as an accessible and comprehensive guide to brain SRS for patients with metastatic brain tumors.

Disclosures

Grace Gwe-ya Kim reports serveing as a consultant for Varian Medical Systems. Helen A. Shih reports serving as a writer and section editor for UpToDate, serving on the advisory board for Advanced Accelerator Applications, serving on the advisory board and as a consultant for Servier Pharmaceuticals, and having grant funding from AbbVie. Kristin J. Redmond reports research funding from Accuray, Canon, and Elekta; consulting for icotec; honoraria from Accuray; travel support from Elekta, Brainlab, and Accuray; and a radiogenomics patent shared with Canon. He serves on the Data and Safety Monitoring Board for BioMimetix and serves as the Central Nervous System track chair for the American Society

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