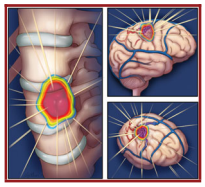

Preoperative vs Postoperative Radiosurgery For Resected Brain Metastases: A Review

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Patients who undergo surgical resection of brain metastases are at significant risk of cavity local recurrence without additional radiation therapy. Postoperative stereotactic radiosurgery (SRS) is a method of focal treatment to the cavity to maximize local control while minimizing the risk of neurocognitive detriment associated with whole brain radiation therapy. Recently published randomized trials have demonstrated the benefit of postoperative SRS in terms of cavity tumor control and preserving neurocognition. However, there are several potential drawbacks with postoperative SRS including a possible increase in symptomatic radiation necrosis because of the need for cavity margin expansion due to target delineation uncertainty, the variable postoperative clinical course and potential delay in administering postoperative SRS, and the theoretical risk of tumor spillage into cerebrospinal fluid at the time of surgery. Preoperative SRS is an alternative paradigm wherein SRS is delivered prior to surgical resection, which may effectively address some of these potential drawbacks. The goal of this review is to examine the rationale, technique, outcomes, evidence, and future directions for the use of SRS as an adjunct to surgical resection. This can be delivered as either preoperative or postoperative SRS with potential advantages and disadvantages to both approaches that will be discussed.

KEY WORDS: Tumor, Radiosurgery, Neurosurgery, Metastases, Radiotherapy, Radiation therapy

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Metastatic brain tumors are a significant source of morbidity and mortality in adult patients with cancer. The incidence rate of secondary brain metastases in adult patients diagnosed with a variety of common solid cancers varies between approximately 8% and 11%, with rates up to 30% for patients with nonsmall cell lung cancer (NSCLC).[1,2] NSCLC, breast cancer, and melanoma account for 67% to 80% of all brain metastatic cases.[1] The incidence of brain metastases is actually thought to be increasing due to more effective systemic therapies which have higher rates of systemic response and improved overall survival (OS), but many of which have limited penetration into the central nervous system (CNS).[3]

The historical standard for the treatment of brain metastases was whole brain radiotherapy (WBRT), which was the subject of the initial Radiation Therapy Oncology Group (RTOG) randomized trials.[4] Outcomes after WBRT for patients with brain metastases were poor, with median OS of only 3 to 4 mo for all patients.[5] Several historical prognostic models that included factors such as age, extent of metastatic disease, performance status, and number of brain metastases found ranges of expected OS after WBRT of approximately 2 mo for the worst prognostic group and up to 7 to 11 mo for the most favorable prognostic group.[5,6]

In an effort to improve these outcomes, Patchell et al[7] published a landmark randomized trial in 1990 investigating the role of surgical resection in addition to WBRT for patients with a single brain metastasis. This study demonstrated a significant improvement in OS with the addition of surgery prior to WBRT compared

ABBREVIATIONS: CDFS, cognitive deterioration-free survival; **CI,** conformality index; **CNS,** central nervous system; **CSF,** cerebrospinal fluid; **GTV,** ; **HR,** hazard ratio; **LF,** local failure; **LMD,** leptomeningeal disease; **LR,** local recurrence; **MRI,** magnetic resonance imaging; **NSCLC,** nonsmall cell lung cancer; **OS,** overall survival; **RT,** radiation therapy; **PTV,** planning target volume; **QOL,** quality of life; **RTOG,** Radiation Therapy Oncology Group; **SRS,** stereotactic radiosurgery; **WBRT,** whole brain radiotherapy

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to WBRT alone (median OS 40 vs 15 wk, respectively, $P < .01$). The follow-up study randomized the same patient population with a single brain metastasis to surgical resection alone vs resection followed by WBRT.[8] There was no difference in OS between the randomized arms (median OS 43 vs 48 weeks, respectively, $P = .39$). However, there were significantly lower rates of local cavity recurrence, distant brain failure, total intracranial failure, and neurological death in the surgery and WBRT arm.

Another major advancement in the treatment of brain metastases was the advent and propagation of stereotactic radiosurgery (SRS). The addition of SRS to WBRT compared with WBRT alone for patients with 1 to 3 brain metastases was found to have a significant improvement in local control and stabilization/improvement of performance status at 6 mo in the phase III RTOG 95-08 trial.[9] The study was negative for the primary endpoint of OS in all patients, but patients with a single brain metastasis were found to have significantly improved OS with SRS boost after WBRT (median OS 6.5 vs 4.9 mo, $P = .04$). Due to the increasing awareness of the potential negative neurocognitive effects of WBRT and the lack of OS benefit with the addition of WBRT to surgery, several trials investigated SRS alone vs SRS and WBRT for patients with a limited number of brain metastases (defined as up to 3-4, depending on the trial).[10-13] In terms of tumor control, all trials showed significantly worse local control, distant brain control, and total intracranial control with SRS alone, but with no detriment in OS with the omission of WBRT. Additionally, the proportion of patients experiencing neurocognitive decline was found to be significantly lower in the SRS alone arms at 3 to 4 mo post-treatment by approximately 25 to 30 absolute percentage points in the 2 trials that used a modern battery of neurocognitive assessments.[11,12] There were also detrimental impacts on patient quality of life (QOL) associated with receipt of WBRT using validated QOL measures.[11,14] For these reasons, SRS alone has become the preferred initial cranial radiation therapy (RT) treatment for patients with a limited number of brain metastases and good performance status.[15]

ROLE OF SURGICAL RESECTION

There has never been an adequately powered randomized trial conducted of surgical resection vs SRS alone for brain metastases. The current role for surgical resection based on consensus guidelines is the consideration of surgical resection for patients with a limited number of brain metastases and good performance status where: (1) a tissue diagnosis is needed, (2) a large brain metastases (>2 cm) is present, (3) significant mass effect that would benefit from decompression is present, and/or (4) the patient has neurological symptoms refractory to steroid management that would benefit from decompression.[16] These recommendations are supported by 2 recent retrospective studies which demonstrated significantly improved local control and OS with the combination of surgery and SRS vs SRS alone for larger brain metastases.[17,18]

Surgical resection alone has an expected 1 to 2-yr local recurrence (LR) rate of 47% to 59%, hence adjuvant RT is generally recommended after surgical resection to minimize risk of cavity LR.[8,13,19] The standard of care for adjuvant RT has been WBRT based on the Patchell et al[8] trial, but there has been increasing use of SRS in the pre- or postoperative setting in order to maximize local control while minimizing risk of neurocognitive detriment. Much of the initial foundation for postoperative SRS was based on single-institutional retrospective studies,[20] but prospective randomized data have recently been published supporting the use of postoperative SRS from both a cavity local control and neurocognitive preservation standpoint.[19,21]

Other potential methods of reducing postoperative cavity LR include partial brain RT, intracavitary I-125 based brachytherapy (Gliasite, Isoray Inc, Richland, Washington),[22] laser thermal ablation,[23] and tumor treating fields (Optune, Novocure Inc, Jersey Isle, United Kingdom; NCT02831959). None of these treatments are currently considered as a first line option for treatment of metastatic brain tumors,[16] and are either used primarily in the post-SRS LR setting or are under investigation as adjuvant therapy for brain metastases treated with SRS.

The goal of this review is to examine the rationale, technique, outcomes, evidence, and future directions for the use of SRS as an adjunct to surgical resection. This can be delivered as either preoperative or postoperative SRS with potential advantages and disadvantages to both approaches that will be discussed. No institutional review board approval or patient consent was required for this review.

POSTOPERATIVE SRS

The initial rationale for postoperative SRS was based on the known substantial risk of cavity LR after surgical resection alone, but wanting to avoid the detrimental effects of WBRT, including neurocognitive deterioration. There was an assumption that the neurocognitive benefits of SRS alone demonstrated in the intact brain metastases setting would also be applicable in the postoperative setting.

Postoperative SRS Technique

The technique for postoperative SRS has evolved over time. An early retrospective study from Stanford included 72 patients treated with postoperative SRS between 1998 and 2006.[24] Most patients were treated to the contoured resection cavity without additional margin. An important finding was that cavity local control was significantly higher in patients with less conformal SRS plans. Conformality index (CI) is a measure of the compactness of the high-dose radiation given during SRS relative to the target volume and is calculated as the ratio: [volume of the prescription isodose line/volume of the target].[25] In order for the target to be completely encompassed by the prescription isodose line, CI necessarily must be ≥ 1. The larger the CI, the more volume is being radiated to the prescription dose relative to the volume of the target. The conclusion from this finding

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was that there was increased risk of marginal miss of the resection cavity in the postoperative SRS setting with more conformal SRS plans compared with less conformal plans as measured by the CI (likely due to difficulty contouring the postoperative cavity), and hence a 2-mm margin expansion on the cavity should be used. The Stanford group started systematically using a 2-mm margin and published a follow-up study comparing outcomes from a prospective group of patients treated with the 2-mm expansion compared with the historical control of patients treated without a margin.[26] The use of a margin was found to have significantly improved local control without an increase of toxicity. The 1-yr cumulative incidence of cavity LR with and without the margin were 3% and 16%, respectively ($P = .04$), while the 1-yr toxicity rates with and without the margin were 3% and 8%, respectively ($P = .27$). These findings led to the adoption of an expansion (generally 1-2 mm) to the cavity as part of standard practice at most institutions in the postoperative SRS setting. The use of these margins does inherently and intentionally increase the volume of normal brain irradiated in order to overcome cavity delineation uncertainty. An example of a postoperative SRS treatment plan using a 2-mm cavity expansion is illustrated in Figure 1.

Resection Cavity Volume Dynamics

There have been several studies looking at the relationship between preresection tumor size and postoperative cavity size on the delayed SRS treatment planning magnetic resonance imaging (MRI). A retrospective study from Stanford demonstrated that the median preresection tumor volume was 14.5 cm^3 compared with a median cavity volume of 10.1 cm^3, representing a median 29% reduction in volume.[27] The cavity was smaller than the preresection volume in 72% of cases, but was larger in 26% of cases. However, the addition of the 2-mm margin expansion increased the target volume from a median of 10.1 cm^3 to a median of 15.6 cm^3, essentially negating the cavity volume reduction from surgical resection. The median time from surgery to postop SRS is generally in the 4- to 5-week range.[26,28,29] This time delay adds an extra layer of complexity in terms of cavity volume changes that occur between the immediate postoperative imaging and the SRS planning imaging. The Stanford group did not find significant cavity volume changes between the immediate postoperative MRI and the SRS planning MRI in 31 patients who had both scans available.[27] In contrast, a study from Dartmouth reported that about half of cavities (46.5%) were stable in size, defined as a change in volume of <2 cm^3, but about a quarter (23.3%) shrunk by >2 cm^3, and about the same proportion (30.2%) enlarged by >2 cm^3.[30] A study from MD Anderson demonstrated a significant association between the amount of T2 edema measured on the immediate postoperative MRI and the probability of significant cavity volume reduction (defined as $\geq$10%) on the SRS planning MRI as a method of potentially predicting cavity volume change in this time interval.[31]

Leptomeningeal Disease Recurrence

There has been increasing evidence that patients treated with postoperative SRS have increased rates of leptomeningeal disease (LMD) recurrence than what was observed when postoperative WBRT was used as the standard. Several retrospective studies have demonstrated 1- to 2-yr LMD rates of approximately 11% to 17% in the postoperative SRS setting.[32-35] Breast cancer histology has been identified in almost all these studies as a significant risk factor for LMD development in this setting, with event rates up to 24%.[32-34,36] Other identified risk factors include infratentorial location,[34] multiple brain metastases,[35,36] and distant brain failure events.[36] When compared to SRS for intact brain metastases in a retrospective study, postop SRS was found to have significantly higher risk of LMD with 1-yr rates of 5.2% vs 16.9%, respectively ($P < .01$).[33] Postoperative SRS has also been retrospectively compared to postoperative WBRT, where reported LMD rates at 18 mo (using the Kaplan–Meier method) were 31% vs 13%, respectively ($P = .045$), indicating that postoperative SRS has a significantly higher risk of LMD recurrence compared with postoperative WBRT.[37] The proposed mechanism of this increased risk is iatrogenic tumor dissemination into the cerebrospinal fluid (CSF) at the time of surgical resection, which was not as apparent when the entire intracranial CSF space was treated with routine postoperative WBRT, but has become more apparent with increasing use of postoperative SRS only. It is important to note that a standardized definition of radiographic LMD does not exist and ascertainment bias as to what constitutes radiographic LMD (vs local or distant meningeal failure as an example) is an unresolved issue.

Tumor Control Outcomes

The 1-yr local control rate from single-arm retrospective studies of postoperative SRS range from 74% to 100%, albeit with wide variability in number of patients included, treatment doses, margin expansions used, median follow-up and imaging periods, and statistical methods, specifically use of cumulative incidence with competing risk of death methodology, which has less bias for estimated event rates in this setting compared with the Kaplan–Meier method.[20]

There had long been a dearth of prospective data supporting the use of postoperative SRS. However, several prospective trials have recently been published concerning this subject and provide the bulk of the high-level evidence in support of this treatment paradigm (Table 1).[19,21,28,38] A prospective single-arm phase II trial of single-fraction postoperative SRS was published in 2014.[28] This trial enrolled 49 patients, but 10 patients (20%) did not receive SRS due to early CNS progression (n = 4, 3 with local failure and 1 with regional failure), large cavity size (n = 2), general medical decline (n = 3), and failure to follow-up (n = 1). In the intention-to-treat analysis, the overall 1-yr cumulative local failure (LF) rate was 22%, with a 1-yr LF rate of 15% for the 40 irradiated cavities compared to 50% for the 10 unirradiated

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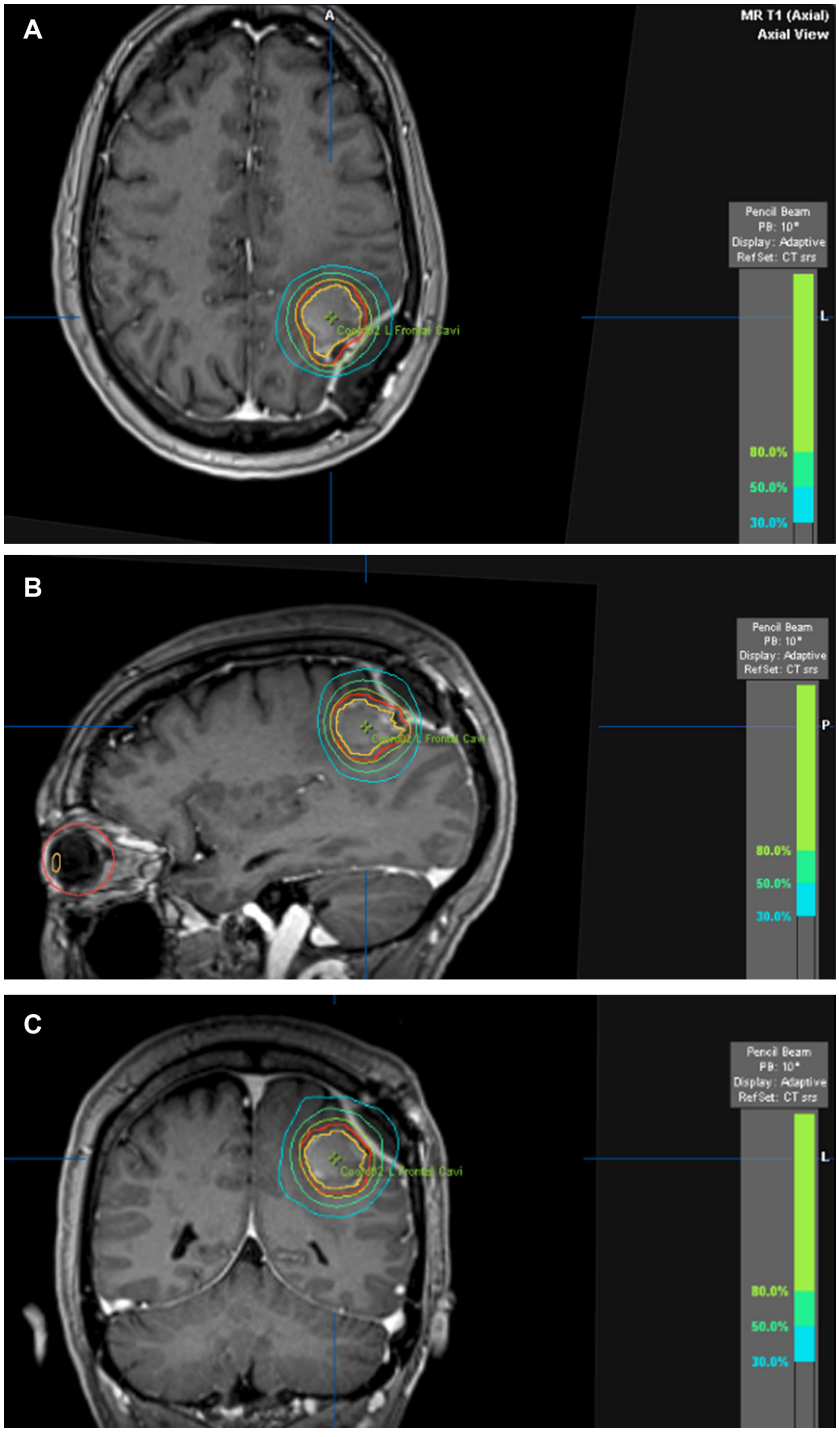

FIGURE 1. *Example of postoperative SRS. Yellow = contoured cavity volume. Red = PTV with 2-mm expansion. 80%, 50%, and 30% prescription isodose lines are shown.* **A**, *Axial;* **B**, *sagittal; and* **C**, *coronal views. Treatment was 15 Gy in a single fraction to the 80% isodose line.*

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TABLE 1. Prospective Trials for Postoperative SRS

Trial	Phase	Interventions	Outcomes	Notes
Brennan et al[28]	II	Postop SRS 2-8 weeks after surgery PTV = cavity + 2 mm	1-yr cavity LF 22% LF 15% for radiated cavities (n = 40) LF 50% for unirradiated cavities (n = 10) 17.5% pathologically proven radiation necrosis	49 patients with 50 cavities enrolled 39 patients with 40 cavities received postop SRS
Soltys et al[38]	I/II	Postop 3-fraction hypofractionated SRS dose escalation trial PTV volume 4.2-14.1 cm^3 (arm 1) and 14.2-33.5 cm^3 (arm 2) PTV = cavity + 2 mm Starting dose level 24 Gy in 3 fractions Highest dose level 33 Gy in 3 fractions	Both arms were escalated to 33 Gy in 3 fractions 22% radiographic radiation necrosis rate 10% asymptomatic 12% symptomatic Grade ≥ 2 events n = 2 at 24 Gy n = 1 at 30 Gy n = 3 at 33 Gy	50 patients Authors recommend 27-30 Gy in 3 fractions for postop hypofractionated SRS
Mahajan et al[19]	III	Patients status post gross total resection randomized to observation or postop SRS Arm 1 cavity observation Arm 2 Postop cavity SRS Primary endpoint cavity LR Postop SRS within 30 days of surgery PTV = cavity + 1 mm Dosing based on PTV 16 Gy ≤ 10 cm^3 14 Gy 10.1-15 cm^3 12 Gy > 15 cm^3	1-yr cavity LR Observation 57% Postop SRS 28% ($P = .015$) 1-yr LMD Observation 16% Postop SRS 28% ($P = .46$) No difference in OS, neurologic death, distant brain failure, or LMD between arms	128 patients included Significantly improved cavity LR with postop SRS No radiation necrosis events in postop SRS arm Median SRS dose 16 Gy Median cavity volume 8.9 cm^3
Brown et al[21]	III	Patients randomized to postop WBRT vs postop SRS to the cavity Arm 1 postop cavity SRS Arm 2 postop WBRT Primary endpoint OS and cognitive deterioration free survival (CDFS) PTV = cavity + 2 mm Dosing based on cavity volume Range from 20 Gy for cavity < 4.2 cm^3 to 12 Gy for volume ≥ 30 cm^3	Median CDFS Postop WBRT 3 mo Postop SRS 3.7 mo ($P < .0001$) 6-mo cognitive deterioration for patients alive with testing Postop WBRT 85% Postop SRS 52% ($P = .0003$) Median OS Postop WBRT 11.6 mo Postop SRS 12.2 mo ($P = .7$) 1-yr cavity local control Postop WBRT 81% Postop SRS 61% ($P = .0007$)	194 patients included Significantly improved median CDFS and 6-mo neurocognition for patients who received postop SRS No difference in OS between arms

Postop = postoperative, SRS = stereotactic radiosurgery, PTV = planning target volume, LF = local failure, LMD = leptomeningeal disease, OS = overall survival, WBRT = whole brain radiotherapy, CDFS = cognitive deterioration free survival

cavities. Of the 40 cavities treated with SRS, 7 (17.5%) demonstrated pathologically proven radionecrosis.

A single-institution phase III trial from MD Anderson randomized patients after gross total resection to observation of the cavity vs postoperative SRS.[19] Eligible patients had up to 3 brain metastases and the largest cavity dimension allowed was 4 cm. Unresected metastases were treated with definitive SRS alone. A 1-mm margin was added to the cavity and dose varied according

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to cavity volume: 16 Gy for ≤10 cm^3, 14 Gy for 10.1 to 15 cm^3, 12 Gy for >15 cm^3. The primary endpoint was cavity LR and 128 patients were randomized. Postoperative SRS was associated with significant reduced risk of cavity LR compared with observation with 1-yr rates of 28% vs 57%, respectively ($P = .015$). There was no difference in OS, other intracranial disease control rates, rate of neurologic death, or use of subsequent WBRT. The incidence of LMD recurrence was 28% and 16% for the postoperative SRS and observation arms, respectively ($P = .46$). This trial confirmed the efficacy of postoperative SRS in reducing the risk of cavity LR after metastasis gross total resection.

A multi-institutional randomized phase III trial compared postoperative WBRT with postoperative SRS to the cavity in 194 patients with 1 to 4 brain metastases.[21] The resection cavity was required to be <5 cm in diameter and up to 3 unresected metastases <3 cm in diameter each were allowed. The unresected brain metastases were treated with SRS in both arms (either definitively or as a boost prior to WBRT). A 2-mm margin was added to the cavity and SRS dose varied with cavity volume, ranging from 12 Gy in a single fraction for volume ≥30 cm^3 to 20 Gy for volume <4.2 cm^3. The coprimary endpoints were OS and cognitive deterioration-free survival (CDFS) at 6 mo, an event for which was defined as >1 standard deviation drop from baseline for any of the 6 cognitive tests, death prior to 6 mo since randomization, or alive ≥6 mo after randomization, but did not complete all of the cognitive tests. Median CDFS was significantly longer at 3.7 mo for postoperative SRS vs 3 mo for WBRT (hazard ratio [HR] 0.47, $P < .001$). The proportion of patients with cognitive deterioration at 6 mo in those alive who underwent neurocognitive testing was significantly lower with postoperative SRS compared with WBRT (52% vs 85%, $P < .001$). There was no difference in median OS between arms. Postoperative SRS was associated with significantly worse cavity local control as 1-yr compared with WBRT (61% vs 81%, $P < .001$). Distant brain and total intracranial tumor control rates also significantly favored the WBRT arm. There was no difference in LMD rates, with 1-yr LMD rates of 7% for postoperative SRS vs 5% for postoperative WBRT. However, these rates do come with the caveat that brain control was not centrally reviewed, and the LMD incidence may have been consequently under-reported and/or misclassified as distant (or local) brain failure (P. Brown, personal communication, August 18, 2017). This trial demonstrated that postoperative SRS is associated with significantly improved neurocognition compared with WBRT, which had only been shown in the intact brain metastases setting prior to this trial.

PREOPERATIVE SRS

Preoperative SRS Rationale and Technique

Due to the perceived drawbacks of postoperative SRS, namely the need for cavity margin expansion due to target delineation uncertainty, the variable postoperative clinical course and potential delay in administering postoperative SRS, and the theoretical risk of tumor spillage into CSF at the time of surgery, investigators began to study the use of preoperative SRS as an alternative paradigm to maximize local control of the resection cavity and minimize neurocognitive detriment associated with WBRT.

Preoperative SRS has several potential advantages compared to postoperative SRS in relation to the perceived drawbacks enumerated above which formed the rationale for its use. Preoperative SRS treats the preoperative intact brain metastasis volume, which is well defined, readily identifiable on imaging, and does not require any margin expansion for target delineation uncertainty. In the case of preoperative SRS, the planning target volume (PTV) is the same as the gross tumor volume (GTV), with no added margin. This is contrasted to postoperative SRS where the PTV is the cavity with a 1- to 2-mm margin. The postoperative cavity does tend to be smaller than the preoperative tumor, but this is offset by the margin expansion where the postoperative PTV is generally similar in size or larger than the preoperative tumor volume. However, even if the total PTV volumes are similar, the postoperative PTV will always include a larger volume of normal brain tissue since the target includes a 1- to 2-mm expansion of the cavity into normal brain, whereas the preoperative target is the intact metastasis only without expansion into normal brain. Increasing volume of normal brain tissue receiving moderate doses of radiation during SRS (ie, 10 or 12 Gy) has been associated with increasing risk of radiation necrosis across a number of studies.[39-41] An example of a preoperative SRS radiation treatment plan is illustrated in Figure 2.

Preoperative SRS is given prior to surgery, with the potential advantage of increased compliance given the variable postoperative clinical course for patients, the variable timing of postoperative SRS due to the need for healing and surgical recovery, and the requirement of a dedicated repeat MRI for postoperative SRS planning to account for cavity volume dynamics. For example, the previously mentioned prospective phase II trial of postoperative SRS reported that 20% of enrolled patients did not receive SRS due to early CNS progression (n = 4), large cavity size (n = 2), general medical decline (n = 3), or failure to follow-up (n = 1).[28]

Preoperative SRS is delivered to an intact tumor with intact blood supply and oxygenation, while postoperative SRS is delivered to a more hypoxic postoperative bed. It is a described phenomenon in radiation oncology that lower doses of RT are required for tumor control when that tumor has an intact blood supply and is oxygenated. This is due to a mechanism of RT-induced DNA damage that ionizes oxygen molecules and generates oxygen-based free radicals that then damage nearby DNA which results in tumor kill. This effect can be quantified as the oxygen enhancement ratio, which is defined as the ratio of radiation doses during lack of oxygen compared to no lack of oxygen for the same biological effect.[42] Extrapolating this to the brain metastases setting, it is plausible that lower RT doses are needed to control residual microscopic disease if the SRS is given in the preoperative setting compared with the postoperative setting. Based on this rationale, a 20% dose reduction compared

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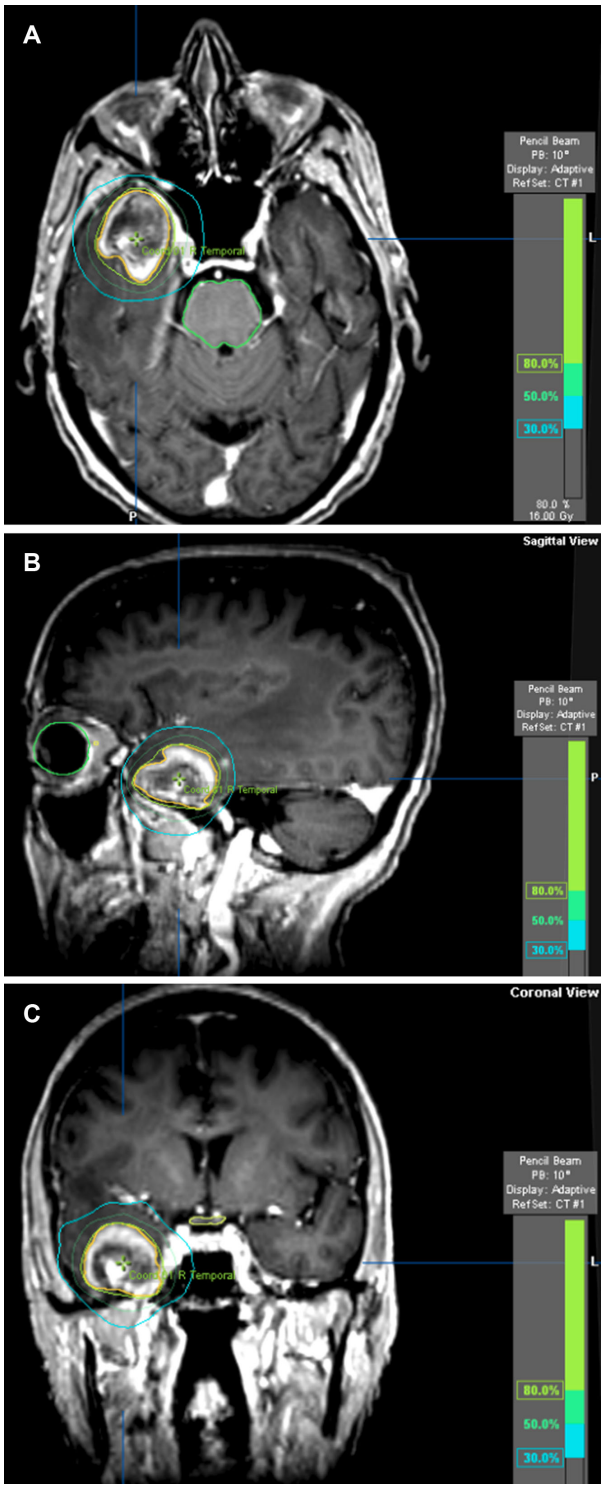

FIGURE 2. *Example of preoperative SRS. Yellow = contoured brain metastasis GTV. No PTV expansion is used. 80%, 50%, and 30% prescription isodose lines are shown.* **A**, *Axial;* **B**, *sagittal; and* **C**, *coronal views. Treatment was 16 Gy in a single fraction to the 80% isodose line.*

to standard maximum lesion diameter based SRS dosing derived from RTOG 90-05 was used in the preoperative SRS studies.[43]

Tumor Control Outcomes

The initial published study for preoperative SRS included 47 patients, of which 24 were enrolled on a prospective trial and 23 were included from a retrospective database.[44] Eligibility criteria included patients with 1 to 3 brain metastases, with at least 1 being dominant and eligible for resection. Patients who were neurologically unstable or who required immediate emergent surgical decompression were not eligible. Treatment consisted of single-fraction linear accelerator based frameless SRS to the lesion without additional margin (GTV = PTV). The dosing used was a reduction of approximately 20% from standard SRS dosing.[43] Resection was planned to occur within 48 h after SRS. The Kaplan–Meier cavity local control rate was 97.8%, 85.6%, and 71.8% at 6, 12, and 24 mo, respectively. Of the 8 patients who had increasing cavity contrast enhancement, 5 underwent surgery and all were proved to be pathologically recurrent tumor with no radiation necrosis in any of the surgical specimens. Based on this, all 8 cases of increasing cavity contrast enhancement were scored as local failures for the purposes of the analysis. No LMD recurrences were seen after a median follow-up period of 12 mo. Also of note, no higher than expected rates of perioperative wound complications, including wound infection or healing difficulties, were observed and there were no cases of perioperative mortality in this study.

A follow-up multi-institutional study from the same group compared preoperative SRS with postoperative WBRT.[45] There was no difference in OS or cumulative incidence of cavity LR between groups (preop SRS vs postop WBRT, 2-yr cavity LR: 24.5% vs 25.1%, $P = .81$). Importantly, there was also no difference in LMD rates between groups, with 2-yr LMD recurrence of 3.5% vs 9%, respectively ($P = .66$). This finding suggests that preoperative SRS is capable of sterilizing tumor cells that could be spilled at the time of surgery and does not confer a higher risk of LMD than WBRT, which treats the entire intracranial CSF space. No patient treated with postoperative WBRT developed radiation necrosis (0%). Of the 71 lesions treated with preoperative SRS, 7 (9.9%) developed radiation necrosis, of which 4 (5.6%) were symptomatic. Neurocognitive and QOL data were not collected or reported as part of this study. A summary of the published literature for preoperative SRS is included in Table 2.

One of the potential issues with preoperative SRS is the possibility of subtotal resection after SRS. The published studies of preoperative SRS (which included patients treated through 2014 at a single institution) did not have any instances of subtotal resection and the gross total resection rate was 100%. The current consensus of practice from that institution in the case of subtotal resection would be to observe the residual disease given that it has been treated with a definitive though modestly reduced dose of SRS, reserving salvage local therapy for cases of progression

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TABLE 2. Published Retrospective Studies of SRS

Study	Type	Interventions	Outcomes	Notes
Asher et al[44]	Combined phase II and retrospective study of preop SRS	Preop SRS generally within 48 h of surgery GTV = PTV 20% dose reduction compared to standard dosing	12-mo Kaplan-Meier cavity local control rate of 85.6% Radiation necrosis rate not reported No LMD events noted	n = 47 total 24 patients on prospective trial 23 patients from retrospective database
Patel et al[35]	Bi-institutional retrospective study comparing preop SRS with postop SRS	Preop SRS generally within 48 h of surgery GTV = PTV (no margin expansion) 20% dose reduction compared to standard dosing Postop single-fraction SRS PTV = cavity + 1 – 2 mm margin	1-yr cavity LR Preop SRS 15.9% Postop SRS 12.6% ($P = .33$) 2-yr LMD Preop SRS 3.2% Postop SRS 16.6% ($P = .01$) 2-yr symptomatic radiation necrosis Preop SRS 4.9% Postop SRS 16.4% ($P = .01$) No difference in OS or distant brain failure between groups	n = 180 patients with 189 brain metastases n = 66 with 71 brain metastases treated with preop SRS n = 114 with 118 cavities treated with postop SRS
Patel et al[45]	Bi-institutional retrospective study comparing preop SRS with postop WBRT	Preop SRS generally within 48 h of surgery GTV = PTV (no margin expansion) 20% dose reduction compared to standard dosing Postop WBRT 30-37.5 Gy over 10-15 fractions	2-yr cavity LR Preop SRS 24.5% Postop WBRT 25% ($P = .81$) 2-yr LMD Preop SRS 3.5% Postop WBRT 9% ($P = .66$) Crude symptomatic radiation necrosis Preop SRS 5.6% Postop WBRT 0% ($P = .29$) No difference in OS between arms	102 patients with 113 brain metastases overall n = 66 with 71 brain metastases treated with preop SRS n = 36 with 42 cavities treated with postop WBRT

Preop = pre-operative, SRS = stereotactic radiosurgery, GTV = gross tumor volume, PTV = planning target volume, LMD = leptomeningeal disease, postop = postoperative, LR = local recurrence, OS = overall survival, WBRT = whole brain radiotherapy

(S. Burri, personal communication, October 27, 2017). This will also be the approach in the cooperative group randomized phase II trial currently in development (NRG-BN1605).

Another potential issue with preoperative SRS is the lack of pathologic confirmation of CNS disease prior to administering SRS, which is not the case in the postoperative setting. The risk of nonmetastatic disease in patients with suspected single brain metastases from trials conducted in the 1980s and 1990s ranged from 2% to 11%. A randomized trial between WBRT only and surgery followed by WBRT with CT based head imaging showed 1 of 41 patients (2%) in the surgery group to have nonmetastatic pathology.[46] A similar trial that also used CT-based head imaging reported a false positive rate of 3% (1 of 32 patients).[47] The Patchell et al trial[7] of WBRT vs surgery followed by WBRT used MRI and 6 of 54 patients (11%) had nonmetastatic pathology.[7] There are not robust available data for the risk of nonmetastatic disease in patients with multiple brain lesions and/or in the modern era due to the fact that the vast majority of patients are treated with SRS alone without CNS pathologic confirmation. The rate of false-positive imaging results is recognized as comfortably low given the lack of CNS biopsy requirements on all recent SRS clinical trials and the adoption of SRS alone as the preferred treatment method for patients with a limited number of brain metastases.[15] There has only been 1 case of nonmetastatic disease found at pathology in the published preoperative SRS series or in an additional 50 patients treated with preoperative SRS subsequent to that (data not published).

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There are currently 4 ongoing prospective phase I or phase II trials for preoperative SRS for brain metastases based on US national clinical trial registration. NCT03163368 and NCT01252797 are both single-institution phase I maximum tolerated dose findings trials. NCT01891318 is a single-institution phase I/II trial and NCT02514915 is a single-institution phase II trial.

PREOPERATIVE SRS VS POSTOPERATIVE SRS

To the best of our knowledge, there has only been 1 published study comparing clinical outcomes for preoperative SRS vs postoperative SRS.[35] This was a retrospective bi-institutional study of 180 patients, of which 66 (36.7%) underwent preop SRS and 114 (63.3%) underwent postop SRS. Patient characteristics were well balanced between groups except for higher rates of performance status score of 0 (62.1% vs 28.9%, $P < .001$) and primary breast cancer (27.2% vs 10.5%, $P = .01$) for preop SRS. The preop SRS cohort also had lower median PTV margin (0 vs 2 mm, $P < .001$) and prescribed dose (14.5 vs 18 Gy, $P < .001$) due to the 20% dose reduction, but similar GTV volume (8.3 vs 9.2 mL, $P = .85$). The median imaging follow-up period was 24.6 mo for alive patients. There was no difference between groups for OS, cavity LR, or distant brain failure in the adjusted analysis. The univariate 1-yr cumulative incidence of cavity LR was 15.9% vs 12.6% ($P = .33$) for preop vs postop SRS.

However, preop SRS had a significantly lower cumulative incidence of LMD recurrence ($P = .01$) compared with postop SRS, with 1-yr rates of 3.2% vs 8.3% and 2-yr rates of 3.2% vs 16.6%, respectively. Postop SRS retained a significantly higher risk of LMD compared to preop in the adjusted analysis (HR: 4.03, 95% confidence interval: 1.2-13.6, $P = .02$). Similar results were found for radiation necrosis and symptomatic radiation necrosis, with 1- and 2-yr cumulative incidence of symptomatic radiation necrosis of 14.6% vs 1.5% and 16.4% vs 4.9%, respectively ($P = .01$). Postop SRS retained a significantly higher risk of symptomatic radiation necrosis in the adjusted analysis (HR: 8.14, 95% confidence interval: 2.16-30.74, $P = .002$). A composite outcome of cavity LR, symptomatic radiation necrosis, and LMD relapse as an indicator of overall toxicity and tumor control was also assessed. Preop SRS had significantly lower rates of the composite endpoint compared with postop SRS, with 1-yr rates of 15.8% vs 31.8% and 2-yr rates of 27.9% vs 39.3%, respectively ($P = .02$). Postop SRS retained a significantly higher risk of the composite endpoint in the adjusted analysis (HR: 1.99, 95% confidence interval: 1.16-3.42, $P = .01$).

In the era of immunotherapy, it has been demonstrated preclinically that high dose per fraction RT is associated with increased surface tumor antigen expression and presentation of usually sequestered tumor antigens that could promote more robust responses in patients treated with immune checkpoint inhibitors.[48] Additionally, there is also increasing evidence that patients treated with RT and immune checkpoint inhibitors may have improved outcomes compared with treatment with immune checkpoint inhibitors alone, as illustrated by a recent secondary analysis of a prospective trial of patients who did or did not receive RT prior to pembrolizumab treatment for advanced nonsmall cell lung cancer.[49] Immunotherapy is also increasingly being shown to have effect across the blood brain barrier for brain metastases. Two recent trials reported in abstract form (CheckMate 204 and ABC) demonstrated intracranial objective response rates of 56% and 44%, respectively, for patients with melanoma brain metastases treated with ipilimumab and nivolumab.[50,51]

In this context, SRS in conjunction with immunotherapy has been associated with improved radiographic brain metastases response,[52] improved OS,[53] and reduced incidence of distant brain failure in retrospective studies.[54] Preoperative SRS has the potential to induce changes in tumor antigen presentation and boost response to immunotherapy since the radiated tumor is still in place until surgical resection occurs. Studies are currently planned to investigate patterns of surface tumor antigen presentation after preoperative SRS compared with a matched cohort who underwent upfront resection and determine if there is an ideal time point for surgical resection after preop SRS to maximize any benefit of surface antigen changes.

FUTURE DIRECTIONS

The increasing use of postoperative SRS has only recently been justified with high-quality randomized trials demonstrating benefit in terms of local control and neurocognitive preservation.[19,21] Prospective randomized evidence is needed to determine if preoperative SRS truly has less risk of radiation necrosis and LMD compared to postoperative SRS, as suggested by retrospective studies. To this end, a cooperative group (NRG) multi-institutional phase II randomized trial is currently in development to address these questions (NRG-BN1605). Patients with 1 to 4 brain metastases, of which 1 requires resection, would be randomized to preoperative vs postoperative single-fraction SRS. This study is designed as a superiority trial with the primary endpoint of LMD relapse, with the hypothesis of significantly less risk of LMD with preoperative SRS. Secondary endpoints include OS, cavity LR, distant brain failure, radiation necrosis, and a prespecified composite endpoint of cavity LR, symptomatic radiation necrosis, and LMD. Additional work is also being done to determine patterns of LMD recurrence after surgery and SRS (ie, focal vs diffuse and relation/distance from the cavity), quantify patterns of salvage for postsurgical LMD (ie, focal RT or WBRT), and determine survival and tumor control outcomes after LMD recurrence in this setting.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Determined by a poll conducted by *Physics World* in 2004 to be the "most beautiful theorem in mathematics," Euler's Identity does make anyone with a concept of numbers pause in curious awe. $e^{i\pi} + 1 = 0$ —how do the 3 best-known special numbers in math relate in such a perfect way? π is the irrational number 3.14159265…, the exact ratio of a circle's circumference to its diameter. i represents the imaginary number $\sqrt{-1}$ (negative numbers have no "real" square root, so i is used to make math possible when such an operation is required). Finally, e is another irrational number, equal to 2.71828183… e was discovered by Euler's family friend, Jacob Bernoulli (of *the* Bernoulli family of famous scientists and mathematicians), when experimenting with compound interest equations. He found he could not get 1 unit of currency compounded at 100% interest over 1 year to ever increase to more than 2.71828183… units of currency, no matter how frequently the interest was compounded. Leonard Euler completed the mathematical gymnastics to get from $e = 2.718\ldots$, to $e^{ix} = sinx + icosx$, to $e^{i\pi} + 1 = 0$. For more information, see https://www.youtube.com/watch?v=sKtloBAuP74, and https://physicsworld.com/a/beauty-is-in-the-eye-of-the-mathematician/. Euler portrait, By Ldelapisa001 - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=67581765.

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