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Preoperative Radiosurgical Management of Brain Metastases: Evidence and Challenges

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Abstract: About 30% of all adult patients with solid tumors will develop brain metastases. The prognosis of patients with brain metastasis is poor, with a median overall survival of 4–7 months. Nevertheless, with efficient systemic and local therapies, some specific patient groups may experience longer survival times. Currently, the options for the management of brain metastasis include surgery, systemic chemotherapy, targeted therapies, stereotactic radiosurgery (SRS), post-operative stereotactic radiosurgery, whole-brain radiotherapy (WBRT), and their

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combination variants. Given the severe neurotoxic effects of WBRT, increased risk of radionecrosis, leptomeningeal dissemination after postoperative SRS, and the ineligibility of certain patients for SRS during the postoperative period (usually first 21 days), an active search for alternative treatment strategies for such patients ensued. It has been suggested that novel preoperative stereotactic radiosurgery, which has a lower risk of radionecrosis and leptomeningeal dissemination, would provide at least equivalent local control rates in this regard. The purpose of the current chapter is to outline the justification and available evidence for the novel preoperative stereotactic radiosurgery in the management of brain metastasis while accepting the paucity of related literature.

Keywords: brain metastases; management of brain metastases; postoperative stereotactic radiosurgery; preoperative radiosurgery; survival

INTRODUCTION

The incidence of brain metastasis (BM) varies among patients, with a 10–40% chance of developing BM over the course of the disease, depending on the primary tumor type (1). BMs originating from lung and breast carcinomas, and malignant melanoma account for over 80% of all BMs (1). Patients who present with BM have a poor prognosis, with an anticipated median overall survival (OS) of 4–7 months (2). It has been shown that patients with uncontrolled BM often die from neurological dysfunction rather than extracranial disease progression, underscoring the critical importance of BM control (3). Reducing the neurocognitive effects of BM may improve the quality of life (QoL) of patients, even if effective local therapies do not extend survival due to extracranial disease progression (4).

Whole-brain radiotherapy (WBRT), surgery (where applicable), definitive stereotactic radiosurgery (SRS), postoperative SRS, systemic chemotherapy, targeted treatments, and their different combinations are current choices for the active care of BMs. Nevertheless, concerns about the apparent ineffective blood brain barrier penetration of the majority of the currently available systemic medications, severe neurotoxic side effects of WBRT, increased risk of radionecrosis (RN), and leptomeningeal dissemination (LMD) following postoperative SRS have led to a legitimate need for alternative treatment strategies for these patients. Sadly, due to early disease recurrence, general medical deterioration, large-sized surgical cavities, and loss of follow-up, roughly 20% of surgically managed patients become unable to undergo the desired postoperative SRS (5). In this context, preoperative SRS could overcome the necessity for postoperative logistics coordination. Preoperative SRS has been hypothesized to induce at least equal local control (LC) rates with decreased RN and LMD risk. Given the advances in the recently described preoperative SRS, the intention of this chapter is to systematically detail the reasonable justifications and accessible data for the preoperative SRS in the care of patients with BMs.

CHOICE OF TREATMENT

Choosing the best treatment option and technique for patients who have BM is a difficult task. The historically accepted standard of care for treating BMs has been WBRT, with an OS of 2 to 11 months (6–8). In 1990, Patchel et al. showed that the surgical removal of the BM before WBRT significantly lengthened the OS durations from 15 to 40 weeks ($P < 0.01$) in patients presenting with a single BM (9). The surgery plus WBRT arm was superior to the WBRT alone arm in terms of the significantly lower rates of brain failures and neurological death, even though the follow-up study of the same group was unable to confirm these findings ($P = 0.39$) (10).

The Radiation Therapy Oncology Group (RTOG) researchers conducted a landmark phase III trial (RTOG 95–08) to compare the WBRT alone against the WBRT plus SRS in patients presenting with 1 to 3 BMs (11). The patients with a single BM appeared to have significantly longer median OS durations with SRS boost after WBRT than their WBRT-alone counterparts (6.5 vs. 4.9 months; $P = 0.04$) but this was not significant. Several researchers compared SRS-alone to SRS plus WBRT for up to 3–4 BMs (12–15). The omission of WBRT appeared to have no detrimental effects on the OS outcomes; however, the intracranial and local tumor control rates in the SRS-alone group were relatively lower. The choice of SRS-alone as the initial treatment for patients with up to 4 BMs was made since the deliberate omission of WBRT did not adversely influence the survival outcomes, and SRS-alone achieved nearly a 30% reduction in the neurocognitive decline rates with an accompanying improvement in the QoL outcomes (13–15).

Another feasible treatment option for selected BMs is surgery, either by itself or in combination with WBRT, or postoperative SRS. To our knowledge, there are no large-scale randomized controlled phase 3 trials that directly compared surgery and SRS, even though both treatments are acknowledged to be comparative. The usual indications for surgery include: (i) global medical fitness; (ii) expected survival >3–6 months; (iii) limited number of BMs; (iv) presence of BMs >2 cm; (v) ineloquent tumor location; (vi) the need for decompression of a significant mass effect; (vii) requirement for decompression surgery to alleviate steroid-refractory neurological symptoms or seizures refractory to antiepileptic drugs; and (viii) the need for tissue diagnosis. The mass effect and accompanying edema may be quickly eliminated by prompt surgical resection of large and symptomatic BMs in the bulk of the severely affected patients, resulting in significant symptom relief and refinement in QoL measures. Additionally, incorporating surgery with SRS may significantly boost LC and OS rates compared to SRS alone in carefully selected patient groups with large BMs (16, 17). According to Prabhu and colleagues' findings in 217 patients with BMs, which corroborate these data, gross total resection with SRS was associated with significantly reduced local recurrences (LR) at 1 year (20.5% vs. 36.7%; $P = 0.007$) compared with SRS alone for patients with large BMs (18). Consequently, with a predicted LR rate of 47% to 59% at 1 to 2 years, surgical resection as the sole definitive treatment option for BMs appears insufficient to attain satisfactory LC rates (19). The modest LC rates

must be improved by radiotherapy, either WBRT/postoperative SRS (usually within first 21 days after the surgery) or preoperative SRS (usually within 48 hours before the surgery). In this situation, postoperative or preoperative SRS are viable adjuvant or neoadjuvant radiotherapy options for averting the severe neurocognitive side effects of WBRT.

WBRT has traditionally been considered the adjuvant standard of care for surgically resected BMs, owing to the positive results of Patchell's randomized trial (9). Given the severe neurocognitive toxicity of WBRT, postoperative SRS was proposed as a feasible substitute for adjuvant WBRT with 70% to 100% overall crude 1-year LC rates (5, 19–38). A recent NCCTG randomized, controlled, phase 3 trial (N107C/CEC3) enrolled 194 patients from 48 centers and randomly assigned them to SRS (N=98) or WBRT (N=96) (37). Although there was no significant difference in median OS times between the two groups (12.2 months for SRS vs. 11.6 months for WBRT; P = 0.70), the SRS arm had a longer neurocognitive-deterioration-free survival (3.7 vs. 3.0 months; P < 0.0001) than the WBRT arm. Likewise, the rate of 6-month neurocognitive dysfunction was lower in patients who received SRS than in those who received WBRT (52% vs. 85%; P = 0.00031). Hearing impairment (3% vs. 9%) and cognitive disturbance (3% vs. 5%) were the most common grade 3 or 4 adverse events, with no treatment-related deaths. These results led the authors to suggest that SRS, a less toxic alternative to WBRT for this patient population, be accepted as the standard of care after BM resection (37).

The significant findings of the postoperative cavity SRS studies were: (i) high rates of LRs (≤44%); (ii) radiation necrosis (≤49.4% in 24 months); (iii) LMD (≤31%, mostly in the first year of treatment); (iv) higher neurotoxic events due to the need for planning target volume (PTV) margins; and (v) target volume definition difficulties caused by postoperative cavity dynamics (39–42). When these significant limitations of the postoperative SRS are considered together, they have solidly expanded the enthusiasm for preoperative SRS as a theoretically valid alternative.

PREOPERATIVE SRS CLINICAL DATA

Preoperative SRS, which uses the principles of SRS for intact BMs (Figure 1), has emerged as a novel treatment modality to maximize the LC rates while minimizing the RN and LMD of postoperative SRS and the neurocognitive risks of standard WBRT, mainly due to the previously stated drawbacks of postoperative SRS (43–46).

The North Carolina and Georgia groups have presented the most convincing evidence, despite the fact that the first use of preoperative SRS dates back to Japanese studies conducted in the 1990s (18, 47–50). Following the initial study's publication, which included 47 patients treated with preoperative SRS from the Levine Cancer Institute and Carolinas Medical Center and revealed an 85.6% LC at 1 year (47), the same group later reported an 80.1% LC at 1 year in an updated series of 117 patients treated with a median dose of 15 Gy of preoperative SRS delivered at a median time of 2 days before the surgical resection (50). Compared to the dose used in the RTOG protocol 90–05, the dose used in this study was

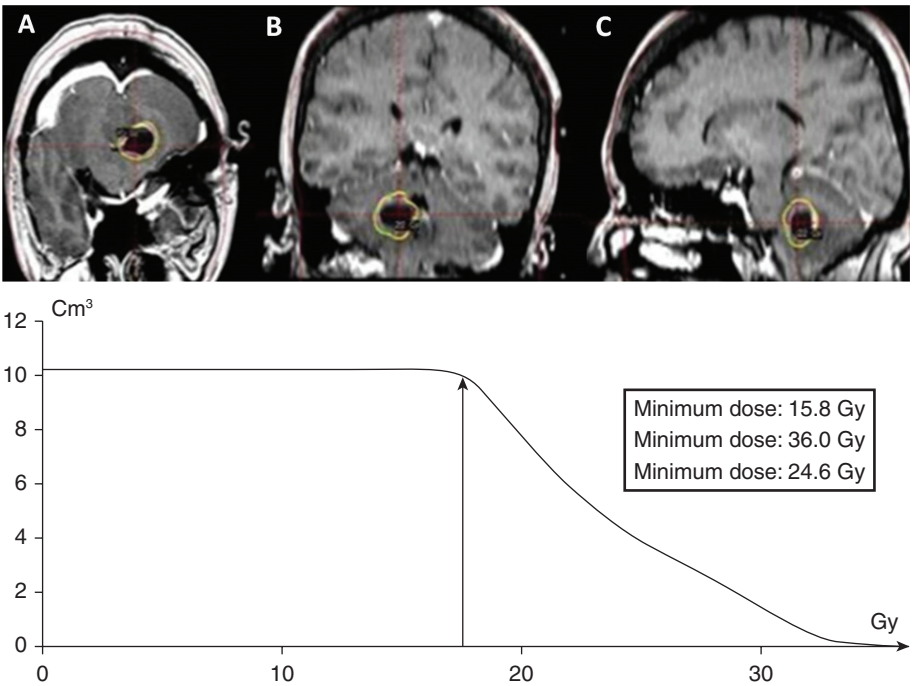

Figure 1. A typical Gamma-Knife stereotactic radiosurgery plan and related dose-volume histogram. A: Axial; **B:** Coronal; **C:** Sagittal view.

about 20% lower (51). The 1-year RN and LMD rates were 5.1% and 4.3%, respectively, with a 2.6% overall grade 3 toxicity rate. In a subsequent multi-institutional study, the same team retrospectively compared postoperative WBRT with preoperative SRS (49). According to the authors, there was no difference between the adjuvant WBRT (25.1%) and preoperative SRS (24.5%) groups in OS or 2-year cavity recurrences (P = 0.81). The authors suggested that preoperative SRS was capable of sterilizing tumor cells that might otherwise be spilled into the cerebrospinal fluid at the time of neurosurgery. At 2 years, there was no difference in the rates of LMD between the two groups (3.5% for preoperative SRS vs. 9.0% for adjuvant WBRT; P = 0.66). Nevertheless, the preoperative SRS performed worse than adjuvant WBRT in terms of overall RN development [9.9% (5.6% symptomatic) vs. 0%; P 0.05]. However, since RN can be effectively managed in the majority of patients, fear of RN should not preclude its use in BM patients. Newman et al. recently investigated the relationship between the extent of resection (EOR) of pathologically confirmed RN and postoperative radiographic and symptomatic outcomes in 46 patients (52). Most patients underwent prior SRS with or without whole-brain irradiation (N = 42, 91%). Twenty-seven (59%) operations resulted in gross-total resection (GTR). T2-FLAIR edema was decreased by a mean of 78% by 6 months postoperatively, which was sustained to the last follow-up (P< 0.05). EOR was related to edema reduction at the last follow-up,

with GTR reducing T2-FLAIR significantly more than subtotal resection ($P < 0.05$). A significant proportion of surviving patients were able to reduce their steroid use: steroid dependence decreased from 54% preoperatively to 15% at 12 months postoperatively ($P = 0.001$). Accordingly, the authors concluded that RN resection provided both long-term T2-FLAIR reduction, which correlated with EOR, and decreased steroid dependency. Hence, even though RN is among the most severe consequences of SRS, it should be kept in mind that surgery can offer significant relief and RN control in the majority of these cases.

Different investigations have also contrasted the preoperative SRS and postoperative SRS. In an abstract presentation from 2011, Yamamoto et al. compared 16 preoperative SRS patients with their 139 postoperative SRS counterparts using the propensity score matching analysis (PSMA) technique (53). The authors found no significant differences between the two groups in terms of LC, distant control, and OS outcomes. However, the authors noted significantly lower rates of LMD in the preoperative SRS cohort (6.2% vs. 43.8%; $P < 0.05$). Prabhu et al. (18) conducted a study in which they compared the outcomes of preoperative SRS ($N = 63$), postoperative SRS ($N = 94$), and SRS alone ($N = 60$). In comparison to the preoperative SRS (77.5%) and postoperative SRS (80.9%) groups, the results showed that the 1-year LC in the definitive SRS alone (without surgery) group (63.3%) was significantly lower ($P< 0.05$). However, the 1-year RN rates in the postoperative SRS group (22.6%) were significantly higher than in the preoperative SRS (12.3%) and definitive SRS alone (5.0%) groups ($P<0.05$). Similarly, the 2-year LMD incidence was higher in the postoperative SRS group (16.1%) than in the preoperative SRS (5.9%) or definitive SRS alone (5.0%) groups ($P = 0.12$). In a large series of 180 patients, Patel et al. compared the outcomes of 66 preoperative SRS patients with 114 patients who received postoperative SRS (48). Despite no differences in LC rates, the preoperative SRS group had significantly lower 2-year rates of LMD (3.2 vs. 16.2%; $P < 0.05$) and symptomatic RN (4.9 vs. 16.4%; $P < 0.05$). Udovicich et al. recently examined the outcomes of 28 patients with 29 BMs who underwent preoperative SRS (54). Hypofractionated preoperative SRS was used in 62.1% of the cases. The average duration of follow-up was 12.8 months. The 12-month LC and LMD rates were respectively 91.3% and 4.0%. The respective 12-month RN, distant intracranial, and OS rates were 5.0%, 51.5%, and 60.1%.

The primary objective of PROPS-BM (Preoperative Radiosurgery for Resected Brain Metastases) was to assess preoperative SRS outcomes and prognostic factors in a large multicenter cohort (55). From 5 institutions, patients with BM from solid cancers who underwent a planned resection and at least 1 lesion treated with preoperative SRS were included. The study included 242 patients with a total of 253 index lesions. Cavity LR rates were 15% and 17.9%, respectively, at 1 and 2 years. Subtotal resection was a potent independent predictor of LR (hazard ratio, 9.1; $P < 0.001$). The findings of this expanded multicenter analysis supported those of previously published preoperative SRS studies, and there was no indication that there was an excessive risk of postoperative surgical complications. Although uncommon, subtotal resection in this study was linked to significantly worse cavity LR, highlighting the significance of GTR in such patients.

Preoperative Stereotactic Radiosurgery for Brain Metastases (STEP) is a national, multicentre, open-label, prospective, non-randomized, phase-II trial to evaluate the efficacy and toxicity of preoperative SRS for patients with BM in France (56). Seven study centers will follow 17 patients for a total of 12 months

during the study period. Patients may enroll if they have more than four distinct BMs, one of which has a surgical indication, as well as an indication for SRS and surgery. The trial's primary goal is to evaluate 6-month LC after preoperative SRS. Secondary goals include evaluating LC, RN, OS, toxicities, LMD, distant control, cognitive function, and QoL. The findings of this first European prospective trial could provide beneficial insights into preoperative SRS, given the study's hypothesis that the LC provided by preoperative SRS will be at least equivalent to that of postoperative SRS, but with a better safety profile.

Preoperative SRS may lower the risk of RN and LMD, whereas fractionated treatments may improve LC by allowing higher biologically effective doses to be delivered. Hypothesizing that pre-operative fractionated stereotactic RT (FSRT) can minimize rates of local failures (LF), RN, and LMD, Palmer et al. conducted a retrospective, multi-institutional analysis and included patients who had pre-operative FSRT for large or symptomatic BMs (57). The study included 53 patients with 55 lesions. FSRT at a dose of 24–25 Gy in 3–5 fractions was prescribed. There were no LFs, three Grade 2–3 RN events, and one LMD occurrence, for a per-patient composite endpoint event rate of 8%. Although prospective confirmatory research is needed, these results suggest that pre-operative FSRT is safe and effective, and may reduce the incidence of adverse outcomes in large BMs.

Neoadjuvant stereotactic radiosurgery for intracerebral metastases of solid tumors (NepoMUC) is a phase I dose escalation trial conducted to find the maximum tolerated dose (MTD) of preoperative SRS for BMs (58). For this trial, a rule-based traditional 3 + 3 design with three dose levels and four different cohorts based on lesion size will be used. The MTD for which no dose-limiting toxicities (DLT) eventuate is the primary endpoint. Secondary endpoints include LC rate, survival, immunological tumor characteristics, QoL, grades of late clinical, neurological, and neurocognitive toxicities. Depending on the occurrence of DLT, up to 72 patients will be enrolled during a 24-month recruitment period. We are eager to see the findings of this study, which will add to the relevant literature in a significant manner.

Takami et al. carried out a phase II prospective trial to determine whether the rate of symptomatic radiation toxicity at 1-year in patients who receive preoperative SRS differs significantly from historical rates for patients treated with postoperative SRS (59). Over a 4-year recruitment period, this multicenter, non-randomized, open phase II clinical trial will enroll 30 patients with a maximum of 10 BMs, at least 1 of which is suitable for surgical resection after preoperative SRS. When available, the findings of this study should shed light on whether symptomatic radiation toxicity caused by preoperative SRS is meaningfully reduced when compared to historical rates associated with postoperative SRS.

Although more research is needed in this arena, available clinical evidence suggests that the preoperative SRS is superior to the postoperative SRS in terms of RN and LMD rates, with at least comparable LC, distant control, and survival rates (Table 1). The results of ongoing trials and future phase 3 randomized trials comparing these two SRS techniques will allow us to make solid concluding remarks on their relative efficacy and safety profiles. Anyway, fitting patients can be offered preoperative SRS or FSRT to improve LC outcomes, which may translate into a survival advantage with the availability of more potent systemic therapies that can easily penetrate the blood brain barrier.

TABLE 1 **Reported major research outcomes in preoperative stereotactic radiosurgery**

Author	Study design	Patients (n)	Interval to surgery	1-year LC (%)	RN (%)	LMD (%)
Yamamoto et al. 2011(60)	Retrospective Preoperative SRS vs. postoperative SRS	32	NR	75.0	NR	6.2
Patel et al. 2016 (48)	Retrospective Preoperative SRS vs. postoperative SRS	180	< 2 days	84.1	1.5	3.2
Patel et al. 2017 (49)	Retrospective Preoperative SRS vs. adjuvant WBRT	102	< 2 days	75.5 (2-year)	9.9	3.5
Prabhu et al. 2017 (18)	Retrospective Preoperative SRSvs. postoperative SRS vs. SRS alone	223	< 2 days	77.5	5.0	5.9
Prabhu et al. 2018 (50)	Retrospective	117	Median 48 hours	80.1	4.3	5.1
Diehl et al. 2019 (58) (Ongoing study)	Prospective, phase 1 dose escalation Three dose levels of preoperative SRS	72	NR	NR	NR	NR
Takami et al. 2020 (59) (Ongoing study)	Prospective, phase 2 Preoperative SRSvs. historic postoperative SRS	30	NR	NR	NR	NR
Prabhu et al. 2021 (55)	Retrospective, multi-institutional	242	1-3	85.0	6.8 (All toxic events)	7.9
Ginzac et al. 2021 (56) (Ongoing study)	Prospective, phase 2 Efficacy and toxicity of preoperative SRS	17	NR	NR	NR	NR
Palmer et al. 2022 (57)	Retrospective,, multi-institutional Efficacyand toxicity of FSRT	53	Last day of FSRT	100.0	5.7	1.9
Udovicich et al. 2022 (54)	Retrospective Efficacy and toxicity of FSRT	28	5.0	91.3	5.0	4.0

FSRT: Fractionated stereotactic radiotherapy; LC: Local control; LMD: Leptomeningeal dissemination; NR: Not reported; RN: Radiation necrosis; WBRT: Whole brain radiation therapy

DISCUSSION

Despite the lack of randomized controlled phase 3 trials comparing the two SRS options in different scenarios, both preoperative SRS and postoperative SRS are credible local treatments for patients suffering from BMs. However, each SRS modality typically has advantages and disadvantages over the alternative modality depending on the patient's health and the resources available to the treating departments. Table 2 lists the preferences and shortcomings of preoperative SRS.

Postoperative SRS is typically reported to have lower LC rates than its preoperative SRS counterpart, especially for large lesions (>3 cm), with a 1-year local failure rate of 44%. (39). Tumor spillage is a common issue faced by up to 50% of patients undergoing BM surgery, despite the fact that en-bloc tumor resection, as opposed to piecemeal tumor resection, may reduce the potential hazard to some extent when feasible (39). Preoperative SRS may sterilize spilled tumor cells in this manner, reducing the risk of recurrences at the tumor's margins or beyond the surgical cavity. Increased likelihood of dose escalation with preoperative SRS in non-eloquent tumors followed by a larger tumor resection may also increase tumor control rates without significantly increasing the risk of severe toxicity. Such an effective strategy may result in significantly lower LMD rates, individual reductions in salvage WBRT needs, and neurologic death rates. Any reduction in WBRT rates will undoubtedly result in improved QoL and social and psychological satisfaction.

RN may be identified as a significant cause of morbidity in up to 49.4% of patients who initially present with BMs >1 cm after two years of follow-up. Sadly, 20% of these RN patients may have intractable symptoms and need additional

TABLE 2 **Advantages and disadvantages of preoperative stereotactic radiosurgery compared to postoperative radiosurgery**

Superiorities	Inferiorities
• Better or equivalent tumor control rates • Lower risk of tumor spillage • Higher likelihood of tumor cell sterilization • Possibility of safer dose escalation • Possible dose reduction with equivalent efficacy • More precise target volume definition • No need for planning target volume margins • Less normal tissue volume in prescribed dose • Chance of lower overall toxicity • Possibility for anti-tumor immunity activation • Lower risk of radiation necrosis • Lower risk of leptomeningeal dissemination • Shorter hospitalization period • Zero potential of treatment cancellation • Prompt systemic treatment initiation	• Lack of pathologic verification • The lack of a targetable driver mutation status information • Risk of irradiating non-tumorous lesions unnecessarily • Unbefitting irradiation technique or dose for primary benign or malignant brain tumors (meningioma, glioma, etc.) • Debatable wound healing issues • Refutable increased risk for wound infection

treatments, such as surgical removal of the symptomatic lesion (60). The RN incidence, which exhibits significant correlations with tumor size and SRS dose, places a limit on the possibility of increasing the usual doses above the advised dose ranges. In this case, preoperative SRS, as opposed to postoperative SRS, may reduce the amount of normal tissue that needs to be removed around the high-dose region (61). Contrariwise, in postoperative SRS, the planning target volume (PTV) typically encircles the surgical cavity with a 2 mm safety margin of hypothetically healthy brain parenchyma in all directions, potentially expanding the risk of RN development (62). As a result, postoperative SRS may pose a higher threat to RN development, which is especially important in tumor locations close to the eloquent regions.

A growing body of research has demonstrated a clear and significant connection between postoperative SRS and LMD occurrence when postoperative SRS is used as the sole strategy of BM treatment. The breast tumors, posterior fossa BM location, piecemeal tumor resection, meningeal tumor contact, large tumor size, and postoperative SRS are now recognized as the most robust factors demonstrating a significant association with LMD risk (56). Accessible data infers that preoperative SRS and WBRT have comparable LMD incidence rates, which are significantly lower than those reported with postoperative SRS (49). For example, Patel et al. recently reported that in a series of 180 patients, the 2-year risk of LMD was significantly higher in the postoperative SRS than in the preoperative SRS (16.6% vs. 3.2%; P = 0.01) (48). As previously stated, this result could be attributed to the lower proliferative capability of irradiated tumor cells that have been spilled. However, more histopathological and radiobiological research is needed to pinpoint the precise mechanism underlying this phenomenon.

A guideline for accurate delineation of the post-surgical BM cavity, as shown in Table 3, was recently published (62). However, because of the uncertainty in target volume definition brought on by unforeseen postoperative changes in the tumor cavity, postoperative tumor cavity contouring continues to be challenging. Sadly, these ambiguities can cause substantial differences in clinical target volume (CTV) definitions among radiation oncologists or radiologists (62, 63). The investigation of this crucial issue by Vellayappan et al. showed that preoperative SRS improved plan conformity and significantly reduced inter-observer variability

TABLE 3 **Guidelines for postoperative stereotactic radiosurgery for resected brain metastasis (62)**

[a]Cavityvolume	[b] Single fraction postoperative stereotactic radiosurgery dose	Fractionated postoperative stereotactic radiosurgery dose	Planning target volume margin
< 10 cc	18 – 20Gy	27 Gy in 3 fractions	2 mm
10–20 cc	15 – 17 Gy	27 Gy in 3 fractions	2 mm
20–30 cc	14 Gy	27 – 30 Gy in 3 – 5 fractions	2 mm
> 30 cc	12 Gy	27 - 30 Gy in 3 – 5 fractions	2 mm

[a]Treatment volume includes adjacent/attached dura, treatment week 3 to 4 after resection.
[b]Dose reduction is carried out in specific locations. (brainstem, proximity to optic pathway, etc.).

compared to postoperative SRS (64). This justification calls for a generous PTV margin of 2 mm to be added to the CTV to lower the risk of geographic misses, which implies that the 2 mm rim of healthy brain parenchyma will receive the prescribed excessive doses like the tumor cavity. Some authors recommend using a 3 mm margin to cover at least 90% of tumor relapses, which complicates the already daunting task (65). Because contouring intact tumor volume is less challenging and no PTV margin is required per guidelines (Table 4), it is reasonable to assume that preoperative SRS is more accurate and safer in terms of target volume definition and severe toxicity risks (47).

Due to a reduction in the oxygen enhancement ratio, basic radiobiological principles dictate that radiotherapy is less efficacious in hypoxic circumstances like postsurgical tumor cavities. Given this well-established concept, it is reasonable to assume that the tumor cells in the post-surgical tumor cavity may be less radiosensitive than the well-oxygenated intact tumors, especially when fractionated SRS is intended. This might be caused primarily by the surgical intervention's diminishing impact on the vascular supply of the target volume. Additionally, the brain's ability to repair itself may be hampered by this reduced vascular supply, which could result in an increased risk of RN genesis. As a result, preoperative SRS may exert roughly equivalent or better tumor control rates with lower SRS doses when compared to postoperative SRS results. Importantly, these comparable or superior tumor control rates can be achieved with significant reductions in the rates of severe toxic events.

Because it is simpler to implement and has a lower workload, preoperative SRS is not only a less resource-intensive procedure than postoperative SRS, but it is also clinically more feasible. The preoperative SRS is typically followed by surgery in the post-procedural 24 to 48 hours since both procedures can be executed during a short-term hospital stay. In contrast, the optimal interval between surgery and postoperative SRS remains controversial (66, 67). It may also be challenging to perform postoperative SRS in a timely manner in cases of delayed wound healing or postoperative complications, particularly if fractionated postoperative SRS is intended. Aside from the logistical issues of the postoperative SRS, severe postoperative complications or a decline in overall medical condition may even necessitate the cancellation of the SRS. In a prospective phase 2 trial of postoperative

TABLE 4 **Guidelines for preoperative stereotactic radiosurgery for brain metastasis (47)**

Lesion size	Single fraction preoperative stereotactic radiosurgery dose	Fractionated preoperative stereotactic radiosurgery dose	Planning target volume margin
0–2 cm	18 – 20 Gy	27 Gy in 3 fractions	Not required
2.1 – 3.0 cm	15 – 18 Gy	27 Gy in 3 fractions	Not required
3.01 – 4.0 cm	15 – 18 Gy	27 – 30 Gy in 3 – 5 fractions	Not required
>4.0 cm	12 – 15 Gy	27 - 30 Gy in 3 – 5 fractions	Not required

Note: Dose-reduction is required for specific locations (brainstem, proximity to optic pathway, etc.).

SRS, 20% of patients were not treated because of early disease recurrence, general medical decline, large surgical cavities, or loss of follow-up (5). As a result, preoperative SRS virtually guarantees that the patient receives both SRS and surgery.

Despite its obvious benefits, the preoperative SRS is not without limitations. The preoperative SRS has drawn harsh criticism for what appears to be a lack of pathological confirmation before the SRS procedure, putting patients at risk of receiving completely unnecessary or objectionable radiotherapy for primary intracranial malignancies or benign lesions. Patchell et al. found that up to 11% of suspected BMs were non-metastatic during biopsy or surgery in 1990 (9). However, it is worth noting that the discriminative power of imaging techniques has evolved significantly since this publication, and the diagnostic accuracy of current imaging tools now far exceeds that of historical ones. In a 2018 study involving 118 patients who underwent preoperative SRS and surgery for BMs, Prabhu et al. provided evidence supporting this claim by showing that the risk of a non-metastatic lesion after preoperative SRS was only 0.8% (50). Hence, the preoperative SRS appears to be safe in terms of pathological concerns, as the risk of inappropriate preoperative SRS use is negligible, if not zero.

As a significant disadvantage, treatment plan modifications may be required during the interval between the preoperative SRS and planned surgery for a variety of reasons, similar to the postoperative SRS. Nevertheless, as demonstrated by Prabhu et al., only 2 (1.7%) of 120 patients were unable to have the planned surgery due to co-existing illnesses (50). In contrast to the typical 6 to 48-hour interval between the preoperative SRS and surgery, frame-based SRS is frequently performed within 2 to 5 weeks of surgery, resulting in a longer time frame provision for the development of postoperative complications, which may defer or cancel the intended postoperative SRS for a variety of reasons.

Recent whole-exome sequencing studies have identified significant genomic alterations associated with BMs that are absent from primary tumors and that have been successfully replicated in xenograft mouse models (68). A study using 86 BMs matched to primary tumors and healthy tissues found potential clinically actionable alterations in 53% of the BMs that weren't present in primary tumors (69). The same patient's multiple BM comparisons show similar actionable changes, which is of utmost importance clinically. The lack of genomic analysis appears to be a significant hindrance to preoperative SRS, emphasizing the increasingly pressing need for the development of minimally invasive biopsy techniques in such patients. Finally, while there is no solidly proven link, preoperative SRS has been unfairly accused of increasing the risk of wound healing problems, infections, and postoperative complications when compared to postoperative SRS. Any unfortunate complications following preoperative SRS ought to be lower than the risk associated with postoperative SRS. This is mainly due to the fact that postoperative SRS applications cover the relatively hypoxic surgical tract with a global 2–3 mm PTV margin of healthy brain parenchyma as opposed to preoperative SRS, which uses prescription doses that are 20% lower and no PTV margin.

CONCLUSION

The standard treatment for BMs originating from different solid tumors has been WBRT. To lessen the unfavorable neurocognitive effects of WBRT, definitive or adjuvant SRS largely replaced it in patients undergoing BM resection. The high rates of RN and LMD in postoperative SRS prompted a search for novel alternative techniques. In this regard, preoperative SRS has been shown to convincingly reduce the excessive rates of symptomatic RN and LMD to more reasonable levels while maintaining or improving tumor control rates. The preoperative SRS is also a more practical treatment option for BMs than its postoperative SRS counterpart, requiring only one short-term hospitalization session and 48 hours or less of total treatment time. In the era of immunotherapy, the avoidance of healthy brain tissue irradiation due to the lack of PTV margins and potential activation of neo-antigen presentation (self-vaccination) with an irradiated intact tumor suggests that preoperative SRS is a safer and superior anti-tumoral immunity-enhancing SRS technique over postoperative SRS. Although preoperative SRS appears to be more practical and secure than postoperative SRS, the published preoperative SRS research findings should be interpreted with caution until the results of phase 3 randomized controlled trials comparing preoperative SRS to postoperative SRS in terms of tumor control efficacy and actual RN and LMD incidences are available.

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