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Review Article

Neoadjuvant Stereotactic Radiotherapy for Brain Metastases

Kaustav Talapatra[1] Rajesh Balakrishnan[2] Ajinkya Gupte[1]

[1] Department of Radiation Oncology, Nanavati Max Super Speciality Hospital, Mumbai, Maharashtra, India
[2] Department of Radiation Oncology, Christian Medical College, Vellore, Tamil Nadu, India

Address for correspondence Ajinkya Gupte, MD, Department of Radiation Oncology, Nanavati Max Super Speciality Hospital, Mumbai 400056, Maharashtra, India (e-mail: ajgupte93@gmail.com).

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Abstract

Introduction Brain metastases occur in ~10% of cancer patients, with rising incidence due to improved diagnostic imaging and advances in systemic therapies. Managing these metastases remains challenging, as they are associated with significant morbidity and mortality. Standard treatment approaches include surgical resection followed by whole-brain radiation therapy or focused radiation techniques such as stereotactic radiosurgery. While whole-brain radiation therapy offers excellent regional control, it is linked with long-term cognitive decline, leading to a shift toward more localized radiation strategies.

Materials and Methods Delivering radiation before surgery, known as neoadjuvant stereotactic radiosurgery, has emerged as a promising approach with several potential advantages. Administering radiation to intact tumors ensures better oxygenation, enhancing the effectiveness of radiation. This approach may also reduce the risk of cancer cell dissemination during surgery by treating the tumor beforehand, lowering the chances of leptomeningeal spread. Additionally, intact tumors are easier to outline on imaging, improving the accuracy of radiation delivery and minimizing exposure to surrounding healthy brain tissue.

Results Preliminary studies indicate that neoadjuvant stereotactic radiosurgery offers comparable outcomes in terms of local control and survival when compared with postoperative radiation. Some evidence also suggests reduced rates of leptomeningeal disease and radiation-related complications. However, challenges remain, including the lack of histopathological confirmation of malignancy before treatment, raising concerns about misdiagnosis. Further clinical trials are needed to establish the safety, efficacy, and optimal use of this approach.

Conclusion This review explores the evolving role of neoadjuvant stereotactic radiosurgery for brain metastases, discussing its potential benefits, limitations, and future research directions.

Keywords
- neoadjuvant
- preoperative
- stereotactic radiotherapy

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Introduction

Brain metastases occur in ~10% of patients during their illness.[1] Notably, patients with either melanoma or lung cancer have a 25% incidence, while for those patients with either breast cancer or renal cell carcinoma, the incidence rate ranges from 5 to 10%.[2] Enhanced imaging modalities and systemic treatments contribute to the increased incidence in the detection of more brain metastases among patients with cancer.[2] Brain metastases lead to considerable morbidity and shortened life spans. Optimal management strategies balancing efficacy and minimal toxicity are crucial.[3–6]

Surgical resection effectively relieves symptoms due to tumor pressure or edema. For solitary brain metastases or oligometastatic disease ($\leq$ 5 lesions), resection improves survival and functional independence. However, local recurrence rates of up to 50% persist even after surgery alone.[7–9]

In recent decades, studies show that combining neurosurgical resection with whole-brain radiation therapy (WBRT) reduces local and distant recurrence rates compared with surgery alone. However, WBRT has long-term neurotoxicity and cognitive decline risks.[8–10]

Stereotactic radiosurgery (SRS) is gaining favor due to its effective tumor control and improved quality of life over postoperative WBRT.[11–14] Despite challenges like leptomeningeal disease risk and logistical complexities, researchers explore preoperative SRS for brain metastases.[15] While preoperative/neoadjuvant therapy has gained widespread acceptance in various malignancies, including esophageal and rectal cancers, there has been a growing interest in applying this treatment approach to brain metastases.[16,17] This review discusses the rationale, evidence, challenges, and ongoing trials in this novel approach.

Rationale for Preoperative SRS

Radiobiology and Preoperative SRS

Radiotherapy effectiveness diminishes in hypoxic environments due to the oxygen enhancement ratio.[18] While adjuvant SRS targets hypoxic postoperative beds with radiation, preoperative SRS (SRS_{Preop}) directs radiation toward tumors that still have an intact blood supply and oxygenation. In the nonhypoxic microenvironment before surgical resection, tumor cells may exhibit higher radiosensitivity. Consequently, SRS_{Preop} is likely to be more effective in these cases.

Leptomeningeal Disease and Preceding Surgery

Studies done by Nguyen et al suggested that patients who undergo SRS to resect cavities face an elevated risk of developing leptomeningeal disease compared with those with intact lesions. This observation posits that tumor cells might be disseminated during surgery, leading to viable cells capable of persisting outside the radiation treatment volume.[19] Preceding surgery with tumor-targeted radiosurgery could potentially mitigate this risk, as any dispersed tumor cells would have been subjected to irradiation, reducing their potential for replication.

Logistical Challenges and Timely Treatment

Coordinating SRS in the postoperative period can be challenging due to the need to balance patient rehabilitation and recovery following surgery. Prolonged delays in commencing SRS after surgery (>38 days) have been shown to reduce its effectiveness.[20] Surgical morbidity, experienced by ~20% of patients, may also hinder the start of adjuvant SRS.[21] Brennan et al in a phase 2 study showed that 20% of patients did not proceed to scheduled SRS following resection.[22] Delays in patients receiving adjuvant SRS may lead to the withholding of systemic therapy for an extended duration, which could adversely affect survival outcomes. To expedite treatment, patients can undergo SRS within 1 to 2 days prior to surgery, shortening the duration from diagnosis to completion of treatment.

Contouring/Delineation

Delineating intact metastases is generally straightforward using imaging and is more reproducible than delineating the postoperative cavities for adjuvant SRS.[23] However, contouring surgical cavities for adjuvant SRS is more complex due to postoperative alterations, leading to an unclear definition of the target volume. Consensus guidelines aim to improve consistency in defining the clinical target volume for better treatment outcomes, but were still found to have significant discrepancies in interrater agreement.[24]

Radiation Necrosis and Preoperative SRS

SRS_{Preop} offers an opportunity to reduce irradiated brain tissue volume. However, there is a potential risk of toxicity when large portions of normal brain tissue receive moderate radiation doses during radiosurgery. Studies focusing on dosimetry show that theoretical SRS_{Preop} plans result in decreased irradiation of normal brain tissue compared with postoperative SRS plans for equivalent lesions. Contouring guidelines for postoperative cavity SRS recommend including additional tissue (surgical tract and applying a 5–10 mm additional margin along the bone flap if the tumor was in contact with the dura before surgery) in both the gross tumor volume (GTV)[24–26] and clinical target volume (CTV), along with the complete contrast-enhancing cavity.[24–26] For SRS_{Preop}, only the metastasis is considered in the target volume, eliminating the need to incorporate normal tissue.

Evidence for Preoperative SRS

In an early retrospective case-matched study of preoperative SRS, an adjuvant SRS was done by Yamamoto et al using the gamma knife. They had 16 patients in each group. Preoperative SRS achieved 75% overall local control, compared with 93.8% with adjuvant SRS. Distant control rates were 68.8 and 56.3% for preoperative and adjuvant cohorts, respectively. Median overall survival (OR) was 10.5 months (preoperative) and 8.9 months (adjuvant). Subdural dissemination occurred in 6.2% (preoperative) and 43.8% (adjuvant) cases.[27]

Asher et al studied 47 patients with 51 lesions treated using preoperative SRS ($\mathbf{SRS_{Preop}}$). At 6 and 12 months, OR rates were 77.8 and 60.0%, respectively. Local control rates were 97.8,

85.6, and 71.8% at 6, 12, and 24 months. Some failures occurred without radiation necrosis. No perioperative adverse events were reported, and 14.8% received WBRT. Lesion characteristics (lesions >10 cc, >3.4 cm, surface lesions or those close to draining veins or in eloquent areas, and presence of dural attachment) influenced local failure risk.[28]

Vetlova's preliminary results involved 19 patients with 22 lesions, including 8 with multiple brain metastases. Median follow-up was 6.3 months. No neurological deterioration occurred during pre-SRS. Local recurrences happened in two cases (at 5.5, 07.4 months), and radionecrosis was observed once. Local leptomeningeal disease (LMD) occurred 1.5 months after partial resection of a metastatic brain lesion near the dura in one patient.[29]

In a multi-institutional retrospective comparison by Patel and colleagues, 180 patients underwent surgical resection for 189 brain metastases. Of these, 66 (36.7%) received pre-SRS, and 114 (63.3%) received post-SRS. The median imaging follow-up period for surviving patients was 24.6 months. Multivariable analyses showed no significant difference between groups for OR, local recurrence, and distant brain recurrence. However, post-SRS was associated with significantly higher rates of LMD (2 years: 16.6 vs. 3.2%, $p = 0.010$) and symptomatic radiation necrosis (2 years: 16.4 vs. 4.9%, $p = 0.010$).[30]

In an ambispective study conducted by Prabhu et al,[31] 117 patients with 125 lesions underwent single-fraction preoperative SRS followed by planned resection. The majority (70.1%) had a single brain metastasis. At 2 years, event cumulative incidence included cavity local recurrence (LR) at 25.1%, distant brain failure (DBF) at 60.2%, LMD at 4.3%, and symptomatic radiation necrosis (RN) at 4.8%. Median OS was 17.2 months, with a 2-year OS rate of 36.7%. Subtotal resection (STR) significantly increased the risk of cavity LR and worsened OS in multivariable analyses.

Patel and colleagues retrospectively reviewed 12 patients who received preoperative SRS at their institution, with a median follow-up of 13 months. Distant disease control rates at 6 and 12 months were 72.7 and 14.5%, respectively, while OR rates were 83.3 and 74.1%. Two patients developed LMD around 11.3 months. There was a tendency toward increased local failure with larger tumor volumes and diameters.[32]

Udovicich et al performed a retrospective multicenter case series involving consecutive patients slated for SRS followed by resection of intracranial lesions with confirmed primary malignancy. Hypofractionated SRS was administered in 62.1% of cases. The 12-month local control (LC) rate was 91.3%, LMD rate was 4.0%, and the 12-month rates for radiation necrosis (RN), distant control (DC), and OR were 5.0, 51.5, and 60.1%, respectively.[33]

In a retrospective review by Deguchi and colleagues, 20 consecutive patients with brain metastases underwent neoadjuvant fractionated stereotactic radiotherapy (FSRT) followed by piecemeal resection between July 2019 and March 2021. The mean follow-up duration was 7.8 months. Postoperative complications included deterioration of paresis in two patients. LR occurred in one patient (5.0%) who underwent STR at 2 months after craniotomy. Distant recurrence was observed in six patients (30.0%) at a median of 6.9 months. Leptomeningeal disease recurrence was detected in one patient (5.0%) at 3 months. Notably, no cases of radiation necrosis developed.[34]

Kotecha and colleagues presented the first results of in-human evaluation of the immediate biological impacts of SRS/SRT on resected brain metastases. Their study included 22 patients with both irradiated and resected brain metastases, paired with non-irradiated primary tumor samples. The rate of necrosis was significantly higher in irradiated brain metastases compared with non-irradiated primary tumors ($p < 0.001$). The median follow-up period was 12.3 months, reporting a 1-year freedom from local failure rate of 95%.[35]

Li and colleagues conducted a single institutional analysis, retrospectively reviewing patients who underwent neoadjuvant SRS (specifically, Gamma Knife radiosurgery) followed by resection of a brain metastasis. In the single-institution cohort of 24 patients, rates of local disease control were 100% at 6 months, 87.6% at 12 months, and 73.5% at 24 months. Among the four patients who experienced local treatment failure, salvage therapy included repeat resection, laser interstitial thermal therapy, or repeat SRS. Remarkably, none of the patients in the cohort developed leptomeningeal carcinomatosis.[36]

In a retrospective analysis by Palmer et al, 53 patients with 55 lesions underwent pre-operative FSRT for large or symptomatic brain metastases. Notably, there were no local failures, but three cases of Grade 2 to 3 radiation necrosis events and one occurrence of meningeal disease were observed, resulting in an 8% per-patient composite endpoint event rate.[37]

The PROPS-BM (Preoperative Radiosurgery for Brain Metastases) multicenter cohort study, led by Prabhu and colleagues, included 242 patients with 253 index lesions. Cavity LR rates at 1 and 2 years were 15 and 17.9%, respectively. STR was a strong independent predictor of LR. LMD rates at 1 and 2 years were 6.1 and 7.6%, respectively, and any grade adverse radiation effects (ARE) were 4.7 and 6.8%. Median OS duration was 16.9 months, with a 2-year OS rate of 38.4%. Most meningeal disease cases were classified as classical leptomeningeal disease. Ten patients (4.1%) experienced grades $\geq$3 postoperative surgical complications.[38]

Palmisciano and colleagues reviewed literature on neoadjuvant stereotactic radiotherapy for brain metastases, including 7 studies with 460 patients and 483 brain metastases, and 13 ongoing trials. Most patients underwent piecemeal (76.3%) and gross-total (94%) resection, typically within a median of 1 day posttreatment. With a median follow-up of 19.2 months, the rates posttreatment were as follows: 4% symptomatic radiation necrosis, 15% LR, 47% distant recurrence, 6% leptomeningeal metastases, 81% 1-year local tumor control, and 59% 1-year OR.[39]

The PROPS-BM collaboration, an international cohort study, compared outcomes and toxicity between preoperative single-fraction SRS and multifraction SRS (3–5 fractions). It included 404 patients with 416 resected lesions; single-fraction SRS was used in 317 patients (78.5%) at a median dose of 15 Gy, and multifraction SRS in 87 patients (21.5%) at a median dose of 24 Gy across three fractions. Single-fraction SRS showed higher cavity LR at 2 years (16.3

Table 1 Summary of published series of neoadjuvant stereotactic radiotherapy (SRS/FSRT) followed by resection

Sl. no.	Author name	Year	Number of patients	Number of lesions	Surgical details	Median time interval NaSRS to resection	Pre-op SRS dose	Median lesion size (cm)/ median lesion volume (cc)/ PTV	Median follow-up	Local control/local recurrence				Overall survival			Adverse events
										6-mo LC	12-mo LC	24-mo LC	6-mo OS	12-mo OS	24-mo OS	Radiation necrosis	Leptomeningeal disease
1	Asher	2014	47	51	GTR: 46 STR: 1	1 d	14 Gy in 1#	Lesion size = 3.04 cm: GTV = CTV = PTV	12 mo	97.80%	85.60%	71.80%	77.80%	60.00%	26.93%	0	0
2	Vetlova	2017	19	22	GTR: 22 (100%)	1–2 d	18 Gy in 1#	14.31 cc	6.3 mo	2 cases (10.5%) of LF, 1 at 5.5 mo and 2nd at 17.4 mo			NR	NR	NR	1 patient	NR
3	Patel	2016	66	71	GTR: 57 STR: 14	Within 48 h	14.5 Gy in 1#	0.83 cm	24.6 mo	1-y LR: 15.9%			Median OS: 17.1 mo			1 y: 1.5% 2 y: 4.9%	1 y: 3.2% 2 y: 3.2%
4	Prabhu	2018	117	125	GTR: 119 STR: 6	2 d	15 Gy in 1 #	GTV: 8.3 cc	14.9 mo	2-y cavity LR: 25.1% 2-y DBF: 60.2%			Median OS: 17.2 mo		2-y OS: 36.7%	2 y: 4.8%	2 y: 4.3%
5	Patel	2018	12	12	GTR: 12 (100%)	1 d	16 Gy in 1#	Median size: 3.66 cm Median volume: 14.69 cc	13 mo	81.80%	49.10%		83.30%	74.10%		0	2 patients at a mean interval of 11.3 mo
6	Christian Udovicich	2021	28	29	GTR: 25 (86.2%) STR: 3 (10.3%) Unknown: 1 (3.4%)	1 d	24 Gy in 3# 20 Gy in 1#	Median PTV: 4.50 cc	12.8 mo		91.30%			60.10%		12-mo RN rate: 5%	12-mo LMD rate: 4%
7	Shoichi Deguchi	202 1	20	20	GTR: 17 (85%) STR: 3 (15%)	4 d	FSRT: 30 Gy in 5#	Median size: 3.66 cm Median volume: 17.6 cc	7.8 mo	LR: 5%			56%	50%		0	1 patient (5%)
8	Rupesh Kotecha	2022	22	22	GTR: 22 (100%)	67.8 h	18 Gy in 1#	Median size: 3.6 cm Median volume: 14.20 cc	12.3 mo	LR: 3 (1.6%)						NR	NR
9	Derek Li	2022	24	24	NR	2 d	17 Gy in 1#	Median size: 3.0 cm Median tumor: 10.1 cc	16.5 mo	100%	87.60 %	73.50 %	75%	70%	Median OS: 2.2 y	NR	NR
10	Joshua D Palmer	2022	53	55	GTR: 52 (98.1%) NR: 1 (1.9%)	2 d	24 Gy in 3#	Median GTV: 12 cc Median PTV: 19 cc	9 mo	LC: no progression			OS: 12 mo survival probability: 70%			12% Grade 2: 33% Grade 3: 67%	2%
11	Paolo Palmisciano	2022	460	483	GTR: 454 (94%) STR: 29 (6%)	1 d	16.5 Gy, 1#: 90.9% 3#: 4.3% 5#: 4.8%	Median PTV: 9.9 cc	19.2 mo		80%		80%	58%	37.80%	32 (7.3%)	30 (6.8%)

Abbreviations: CTV, clinical target volume; FSRT, fractionated stereotactic radiotherapy; GTR, gross total resection; GTV, gross tumor volume NaSRS, neoadjuvant stereotactic radiosurgery; PTV, planning target volume; STR, subtotal resection.

Note: # denotes "number of fractions" (e.g., 1# = 1 fraction; 3# = 3 fractions; 5# = 5 fractions).

vs. 2.3%, $p = 0.004$) on both univariable and multivariate analyses. The propensity-score-matched analysis of 81 pairs confirmed higher recurrence with single-fraction SRS (2 years: 19.8 vs. 3.3%; $p = 0.003$).[40]

Active Research Trials in Progress

Several ongoing trials are currently investigating the use of preoperative SRS for the treatment of brain metastases, aiming to provide novel insights into its safety and effectiveness. Comprehensive details regarding these trials, including their objectives and study designs, are compiled in ►**Table 2**.

The eligibility criteria for ongoing trials examining preoperative SRS are robust, enrolling individuals aged 18 years or older with a favorable performance status and histological confirmation of primary tumors. These patients should have no MRI contraindications and exhibit 3 to 6 contrast-enhancing brain metastases within specific size parameters, with one lesion suitable for surgical resection. They must also be eligible for SRS or SRT, have an estimated survival of 3 to 12 months, and demonstrate the capacity to undergo neurocognitive assessments and provide informed consent. Conversely, individuals are excluded if they have radiosensitive tumor histology, significant midline brain shift, or previous WBRT or SRS/SRT to the lesion to be resected. Additionally, those with leptomeningeal metastases, prior cytotoxic chemotherapy or anti-VEGFR therapy, or psychological disorders or unstable illnesses are ineligible.[41–50]

In addition to assessing common endpoints like local control, toxicity, and leptomeningeal disease rates, one trial specifically compares high-dose versus low-dose steroid therapy in patients undergoing neoadjuvant SRS.[46] Neurocognitive status and quality of life are also evaluated in multiple trials, while another trial investigates RNA biomarkers and their potential correlation with local control.[42,50–53]

Potential Issues or Pitfalls of Using Preoperative SRS

When considering the preoperative SRS approach for brain metastases, several potential issues and pitfalls should be taken into account. First, there is a lack of histopathological diagnosis before treatment, as preoperative SRS does not allow for tissue confirmation. Historically, some patients with suspected brain metastases were later found not to have metastatic lesions after biopsy or resection.[9,28]

However, patients with brain metastases often already have a confirmed pathological diagnosis from a biopsy of the primary tumor or an extracranial metastatic site prior to undergoing SRS.[15]

Although modern imaging techniques have improved accuracy, a definitive pathological diagnosis remains elusive before SRS.[54]

Second, wound dehiscence poses a challenge. Unlike traditional approaches, preoperative SRS does not allow a grace period for wound maturation after resection. Immediate radiation therapy follows, potentially affecting wound healing and complications.[55]

Third, coordination and feasibility challenges arise. Implementing preoperative SRS requires complex coordination among medical teams. Centers with limited oncological expertise may lack the necessary resources and infrastructure for effective implementation. Additionally, there is a risk of radiation necrosis due to exposure of healthy brain tissue to radiation. Close monitoring and management are crucial to minimizing this risk.[36]

Leptomeningeal disease risk has also been reported after preoperative SRS, emphasizing the need for vigilance in follow-up and early detection.[56]

Lastly, patient selection and eligibility criteria play a critical role. Balancing the benefits (such as expedited treatment) with potential risks requires careful consideration. While promising, long-term data on outcomes and survival are still limited, necessitating ongoing trials and further research to establish the efficacy and safety of this approach.[36]

Recommended Time Interval between Preoperative SRS and Surgical Resection

The ideal timing for preoperative SRS ($\mathbf{SRS_{Preop}}$) in brain metastases remains uncertain in the current literature. Kotecha et al reported on a limited case series of 22 patients, showing that tumor necrosis typically occurs ~24 hours after treatment and persists for several days.[35] Similarly, Steverink et al studied timing and necrosis in spinal metastases treated with stereotactic body radiotherapy in a small group of 10 patients. They found that within 6 hours posttreatment, no biopsy specimens demonstrated necrosis, while 83% of specimens collected at least 21 hours after SBRT showed necrosis.[55] Both studies suggest that optimal tumor necrosis occurs around 24 hours after SBRT, indicating a potential optimal timing for surgical intervention following $\mathbf{SRS_{Preop}}$. Surgeons may consider delaying surgery until at least 24 hours after $\mathbf{SRS_{Preop}}$ to enhance surgical outcomes and potentially reduce complications.

Optimal Dose Fractionation Schedule for Preoperative SRS

Among the studies conducted, various dosing regimens were commonly employed for $\mathbf{SRS_{Preop}}$ in the treatment of brain metastases. Single-fraction doses ranged typically from 14 to 18 Gy, while fractionated treatments included doses of 24 to 27 Gy delivered in three fractions, and 30 to 35 Gy administered in five fractions. These dose ranges reflect the diversity in treatment approaches aimed at achieving effective tumor control while minimizing adverse effects, highlighting the flexibility and adaptation of protocols in clinical practice.

Consensus on the Maximum Size of Brain Metastases and Number of Metastases Treatable with Preoperative SRS

Current ongoing trials investigating $\mathbf{SRS_{Preop}}$ have included patients with brain metastases ranging up to 4 to 6 cm in size, with one trial even enrolling patients with lesions up to 7 cm.

Table 2 Ongoing and planned clinical trials of preoperative/neoadjuvant stereotactic radiotherapy for brain metastases

Sl. no.	Article title	Principal investigator	Conducting institute	Clinical trial number	Estimated enrolment	Intervention (pre-operative SRS f/b tumor resection)	Comparison arm	Primary outcome
1	A pilot study analyzing preoperative stereotactic radiosurgery (SRS) with Gamma Knife (GK) for brain metastases[41]	Michael Straza	Medical College of Wisconsin, Wisconsin, USA	NCT04545814	15	15 Gy/single fraction	None	Number of subjects with no identifiable disease on MRI following resection at 20 mo
2	A phase II study analyzing pre-operative stereotactic radiosurgery followed by resection for patients with 1–4 brain metastases[42]	Namita Agrawal	Indiana University School of Medicine, Indianapolis, USA	NCT03398694	50	15 Gy/single fraction	None	Rate of local control of any new, recurrent, or progressing tumors within the PTV at 6 mo
3	A phase II study of neoadjuvant stereotactic radiosurgery for large brain metastases[43]	David Shultz	University Health Network, Toronto	NCT03368625	30	NR	None	Radiation toxicity (symptomatic, i.e., $\geq$ Grade 2) at 12 mo
4	Neoadjuvant radiosurgery for resectable brain metastases: phase I/II study[44]	Erin Murphy	Cleveland Clinic, Case Comprehensive Cancer Center, Ohio, USA	NCT01891318	36	Phase 1 dose escalation study	None	Phase 1: maximum tolerated dose at day 0 Phase 2: local control at 3 y
5	A phase 1 dose escalation trial of neoadjuvant radiosurgery for the treatment of metastatic brain tumors[45]	Stephen Shiao	Cedars-Sinai Medical Center, LA, California, USA	NCT03163368	25	*Phase 1 dose escalation study	None	Maximum tolerated dose at 1 mo postsurgery
6	Preoperative radiosurgery for brain metastases planned for surgical resection: a two-arm pilot study[46]	Zachary Buchwald	Emory University Hospital/Winship Cancer Institute, USA	NCT04895592	20	Arm 1: Pre-op SRS + low-dose steroids, a tumor resection Arm 2: Pre-op SRS + high-dose steroids, a tumor resection	None	Incidence of adverse events $\geq$ grade 3 at 4 mo posttreatment
7	Phase II study determining the efficacy of pre-operative stereotactic radiosurgery followed by resection for brain metastases[47]	Christopher A Wilke	University of Pittsburgh Medical Center	NCT02514915	24	NR	None	Local control at 6,12, and 24 mo

Table 2 (*Continued*)

Sl. no.	Article title	Principal investigator	Conducting institute	Clinical trial number	Estimated enrolment	Intervention (pre-operative SRS f/b tumor resection)	Comparison arm	Primary outcome
8	Pre-operative hypofractionated stereotactic radiosurgery for resectable brain metastases[48]	Michael Yu	Moffitt Cancer Center, Florida	NCT05267587	60	NR	None	Time to progression (local progression or death) up to 12 mo
9	Phase II study to assess Preoperative Hypofractionated Stereotactic Radiotherapy of Brain Metastases (STEP trial)[49]	Angeline Ginzac Couvé	Centre Jean Perrin Groupement Interrégional de Recherche Clinique et d'Innovation (AURA), France	NCT04503772	70	NR	None	Evaluation of 6-mo local control rate
10	A Phase III trial of pre-operative stereotactic radiosurgery (SRS) versus post-operative SRS for brain metastases[50]	Debra Yeboa	M D Anderson Cancer Center, Houston, Texas, USA	NCT03741673	110	Pre-op SRS f/b tumor resection	Tumor Resection à Post-op SRS	1-y leptomeningeal disease-free rate
11	A randomized controlled trial of pre-operative versus post-operative stereotactic radiosurgery for patients with surgically resectable brain metastases[51]	Muhammad Faruqi	Tom Baker Cancer Centre, Calgary, Alberta, Canada	NCT04474925	88	Pre-op SRS f/b tumor resection	Tumor Resection à Post-op SRS	Local control at 12 mo
12	A multicenter prospective, interventional, randomized trial of preoperative radiosurgery compared with postoperative stereotactic radiotherapy for resectable brain metastases[52]	Susanne Rogers	Kantonsspital Aarau, Switzerland	NCT05124236	200	Preop SRS f/b tumor resection	Tumor Resection à Post-op HFSRT	Incidence of leptomeningeal disease at 12 mo
13	Pre-operative vs. post-operative stereotactic radiosurgery for operative metastatic brain tumors (phase 3)[53]	Elizabeth Yan	Mayo Clinic, Rochester, Minnesota, USA		140	Pre-op SRS f/b tumor resection	Tumor resection à post-op SRS	Central nervous system (CNS) composite endpoint event up to 5 y

Table 3 Trial lesion/size eligibility used in ongoing preoperative SRS trials

Author	Clinical trial number	Number of lesions	Size of lesions
Rogers[52]	NCT05124236	≤3	≤4 cm
Couvé[49]	NCT04503772	≤4	≤5 cm
Straza[41]	NCT04545814	≤4	≤5 cm
Agrawal[42]	NCT03398694	≤4	≤5 cm
Shultz[43]	NCT03368625	≤6	<4 cm
Shiao[45]	NCT03163368	(–)	<4 cm
Wilke[47]	NCT02514915	≤4	≤4 cm
Yu[48]	NCT05267587	X	≤6 cm
Murphy[44]	NCT01891318	<4	≤5 cm
Yan[53]	NCT03750227	≤10	≤5 cm
Yeboa[50]	NCT03741673	X	<4 cm—SRS ≤ 7 cm—SRT

The majority of these trials have enrolled patients with up to 4 lesions, though some studies have extended inclusion criteria to patients with up to 6 metastatic lesions, and one study even includes patients with up to 10 metastatic lesions. See ►**Table 3** for the ongoing clinical trials along with the size of lesions being considered for **SRS_{Preop}**.

Future Directions

Future research should aim to standardize both the optimal dose-fractionation schedules and the timing of surgery following neoadjuvant SRS. Current evidence indicates that single-fraction regimens of 14 to 18 Gy are effective for smaller lesions, whereas hypofractionated approaches such as 24 Gy in three fractions or 30 to 35 Gy in five fractions appear to provide superior local control with lower risks of radionecrosis in larger or eloquent lesions. Thus, tailoring the dose according to tumor size may offer the best balance of efficacy and safety. With respect to surgical timing, biological data and early clinical experience suggest that surgery performed at least 24 hours after SRS allows for optimal tumor necrosis and radiosensitization, while remaining safe within a 24- to 48-hour window. Taken together, the most promising strategy at present involves hypofractionated neoadjuvant SRS for larger lesions and single-fraction SRS for smaller ones, with surgical resection scheduled 24 to 48 hours after treatment. Ongoing randomized trials are expected to provide more definitive guidance, but until then, adopting this approach appears most likely to yield favorable neurological and oncological outcomes.

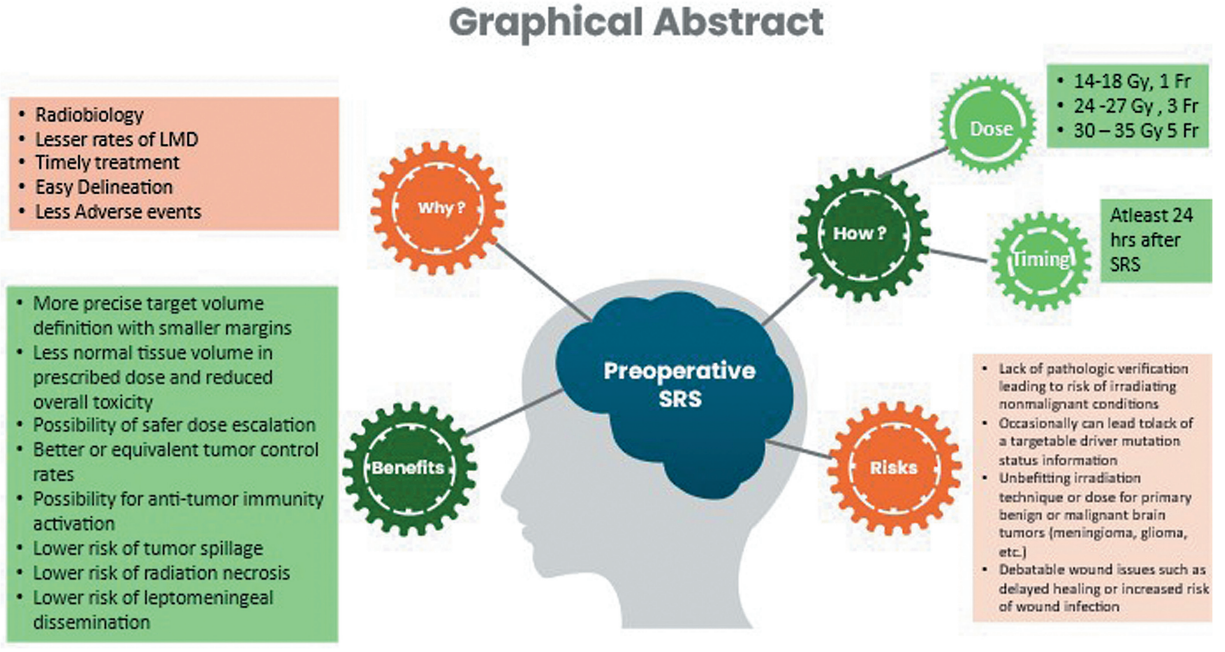

Fig. 1 Graphical abstract.

Conclusion

Emerging evidence suggests that preoperative SRS is a viable and safe option for managing specific brain metastases. Studies indicate that local control and OR rates achieved with **SRS_{Preop}** protocols are comparable to those seen with standard postoperative SRS, although direct comparative research is lacking. The main advantages of **SRS_{Preop}** include lower rates of posttreatment radiation necrosis and leptomeningeal metastases. However, strict criteria and protocols may limit its use in patients with multiple or large brain metastases requiring urgent neurosurgical intervention or those with prior radiotherapy. Ongoing randomized trials aim to evaluate long-term outcomes, particularly local control and neurotoxicity, in larger patient cohorts (►**Fig. 1**).

Patient Consent

No patient consent statement is required, as this is a retrospective analysis of published/available data and does not involve identifiable patient information.

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None.

Conflict of Interest

None declared.

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