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REVIEW

Preoperative stereotactic radiosurgery as neoadjuvant therapy for resectable brain tumors

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Abstract

Purpose Stereotactic radiosurgery (SRS) is a method of delivering conformal radiation, which allows minimal radiation damage to surrounding healthy tissues. Adjuvant radiation therapy has been shown to improve local control in a variety of intracranial neoplasms, such as brain metastases, gliomas, and benign tumors (i.e., meningioma, vestibular schwannoma, etc.). For brain metastases, adjuvant SRS specifically has demonstrated positive oncologic outcomes as well as preserving cognitive function when compared to conventional whole brain radiation therapy. However, as compared with neoadjuvant SRS, larger post-operative volumes and greater target volume uncertainty may come with an increased risk of local failure and treatment-related complications, such as radiation necrosis. In addition to its role in brain metastases, neoadjuvant SRS for high grade gliomas may enable dose escalation and increase immunogenic effects and serve a purpose in benign tumors for which one cannot achieve a gross total resection (GTR). Finally, although neoadjuvant SRS has historically been delivered with photon therapy, there are high LET radiation modalities such as carbon-ion therapy which may allow radiation damage to tissue and should be further studied if done in the neoadjuvant setting. In this review we discuss the evolving role of neoadjuvant radiosurgery in the treatment for brain metastases, gliomas, and benign etiologies. We also offer perspective on the evolving role of high LET radiation such as carbon-ion therapy.

Methods PubMed was systemically reviewed using the search terms "neoadjuvant radiosurgery", "brain metastasis", and "glioma". 'Clinicaltrials.gov' was also reviewed to include ongoing phase III trials.

Results This comprehensive review describes the evolving role for neoadjuvant SRS in the treatment for brain metastases, gliomas, and benign etiologies. We also discuss the potential role for high LET radiation in this setting such as carbon-ion radiotherapy.

Conclusion Early clinical data is very promising for neoadjuvant SRS in the setting of brain metastases. There are three ongoing phase III trials that will be more definitive in evaluating the potential benefits. While there is less data available for neoadjuvant SRS for gliomas, there remains a potential role, particularly to enable dose escalation and increase immunogenic effects.

Keywords Radiosurgery · Neoadjuvant · Brain metastases · High LET Radiation · Glioma

Brain metastases

Surgical resection and adjuvant radiation therapy

Brain metastases affect approximately 200,000 patients in the United States each year [1]. Historically, patients with a single accessible brain metastasis often underwent surgical resection; however, resection without adjuvant radiation therapy still results in a local recurrence rate of nearly 50% [2]. WBRT, though effective at reducing recurrence rates, is also associated with significant cognitive side effects. Multiple randomized trials have demonstrated that SRS is

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associated with improved rates of cognitive preservation without compromising overall survival when compared to WBRT [2–6]. For example, in 2017, a phase 3 trial was completed involving 194 patients who underwent surgical resection of a brain metastasis and were randomized to stereotactic radiosurgery (SRS) or WBRT [7]. The study demonstrated a 52% versus 85% overall cognitive deterioration rate in favor of the SRS arm ($p = 0.00031$).

Postoperative SRS, however, has its drawbacks. The irradiated volume of normal brain is increased, which is associated with an increased risk of treatment-related complications, such as radionecrosis [8, 9]. This is because there is typically a 1–2 mm CTV expansion to address microscopic disease and often a requirement for target volumes to cover the surgical tract, with a margin along the bone flap [10]. In addition, the risk of leptomeningeal disease (LMD) is higher in patients undergoing postoperative SRS, likely due to surgical perturbation or seeding of metastatic cells, compared to WBRT with rates as high as 45% [5, 11–14]. Finally, adherence rates with postoperative SRS are often suboptimal due to variable postoperative clinical courses [15]. If there is a prolonged surgical recovery, increased intervals between surgical resection and postoperative SRS are associated with worse local control [7, 16].

Neoadjuvant stereotactic radiosurgery

To address the limitations of postoperative SRS, neoadjuvant radiosurgery has increasingly been adopted in various disease sites to improve local control and decrease toxicity [17–20]. This rationale is now being applied to radiosurgery for brain metastases. Some potential advantages are improving local control by improving target delineation and oxygenation ratio, decreasing leptomeningeal disease by sterilization, decreasing the volume of normal brain irradiated (and resection of irradiated tissue), as well as improving systemic control by decreasing time to systemic therapy.

Radiosurgery in combination with immune checkpoint inhibitors (ICIs)

With the expansion in the number of systemic therapy agents, it is important to consider the potential interaction with radiosurgery. The rationale is that radiation may increase anti-tumor immunity, which has been demonstrated in many studies. MSKCC published a retrospective study evaluating outcomes of patients treated with combined SRS and ipilimumab for melanoma with brain metastases [21]. A survival advantage was reported for patients who received concurrent SRS delivery compared to those who received SRS before and after administration of ipilumumab. A different retrospective study conducted at the University of Virginia demonstrated similar results, with one-year OS improved for SRS prior to or concurrent with ipilumumab [22]. An excellent review by Lehrer et al. summarizes the data combining radiosurgery with ICIs [23]. It remains a question if systemic therapy could be used in conjunction with radiosurgery in the neoadjuvant setting.

Treatment planning

Preoperative SRS simplifies target delineation and reduces uncertainty when contouring an intact brain metastasis. This is because with postoperative SRS, there is a need to recreate a tumor bed and include portions of the surgical tract. Contouring guidelines for post-operative SRS frequently result in larger treatment volumes. In contrast, preoperative SRS targets the intact brain metastasis volume when it is clearly defined—meaning there is no requirement for margin expansion due to uncertainty—and includes less normal brain tissue inside the PTV. Dosimetric studies have illustrated a reduction in the irradiated volume of normal brain tissue in hypothetical neoadjuvant plans compared to postoperative plans [24].

Patient outcomes

While not currently the standard of care, there have been numerous studies supporting the use of neoadjuvant SRS in brain metastases. A case series comprising 117 patients treated between 2005 and 2016 underwent neoadjuvant radiosurgery approximately two days before resection [25]. The 1-year local control rate was 80.1%, and the 1-year distant intracranial control rate was 54.7%. One-year overall survival was 60.6% with a median overall survival of 17.2 months.

When retrospectively compared to those who received adjuvant radiosurgery, there were no significant differences in tumor volume, number of lesions treated, or location between the two groups [26]. There was no compromise in local or distant control, however with improvements in overall survival (17.1 versus 13.5 months), leptomeningeal disease (3.2% versus 8.3%), and radiation necrosis (1.5% versus 14.6%). When compared to adjuvant WBRT, preoperative SRS showed no significant difference in 1-year overall survival and 2-year local control or leptomeningeal disease [27].

Neoadjuvant SRS, adjuvant SRS, and SRS alone have also been compared [28]. Local control was 77.5%, 80.9%, and 63.3%, respectively, with a significant decrease in control for SRS alone. This translated to a difference in overall survival. Importantly, significantly higher rates of radiation necrosis were observed in the adjuvant SRS cohort compared to the neoadjuvant SRS and SRS alone groups (22.6%, 12.3%, 5.0%,). At 2-years, leptomeningeal disease for the

three groups was 16.1% for adjuvant SRS, 5.9% for neoadjuvant SRS and 5.0% for SRS alone.

While the data presented above single fraction SRS, there is a retrospective series of 20 patients looking at 5 fractions prior to surgical resection [29]. No patients got radiation necrosis, one (5%) with leptomeningeal disease, and one (5%) with local failure. This series, among others, demonstrated that fractionated stereotactic radiotherapy (FSRT) may be safe and effective. The thought is spreading the dose over multiple fractions may increase the therapeutic ratio.

Taking into account these promising retrospective data shown in Table 1, there are phase II/III trials underway shown in Table 2. The first Phase III trial is NRG BN012, which will randomize patients to the standard arm of surgical resection followed by adjuvant SRS within 10–30 days, or to the experimental arm with SRS followed by surgical resection within 7 days. The second is MC167C, a Mayo Clinic trial with estimated completion in November 2025, with similar standard and experimental arms albeit different timelines (adjuvant SRS must be delivered within two weeks of surgery; neoadjuvant SRS must be delivered within 4 weeks of surgery). The third is NCT03741673, an MD Anderson trial which will also allow radiosurgery within a month of surgical resection. NCT03741673 is unique in that it will allow up to 5 fractions for treatment, which may provide interesting results, particularly in reducing toxicities. The results of these three trials together will be useful to analyze both fractionation and timing of neoadjuvant SRS.

Delayed systemic therapy

It has been observed that up to 20% of patients may experience some complications within 30 days after resection, which could delay indicated adjuvant therapy, with 20% also unable to undergo planned SRS after resection [14]. In contrast, neoadjuvant SRS presents fewer obstacles for patients to proceed with the resection, as less than 3% of patients requiring hospitalization within 2 weeks after treatment [34, 35]. Postponing adjuvant SRS may lead to even longer delays in starting systemic therapy.

Gliomas

Introduction

High-grade gliomas encompass a group of aggressive and malignant primary brain tumors, with glioblastoma (GBM) being the most prevalent subtype. GBM is known for its aggressive behavior and high resistance to treatment, resulting in a dismal prognosis with a median overall survival (OS) of 15–21 months. The most effective treatment approach for GBM patients typically encompasses a gross total resection, followed by RT with concurrent TMZ, followed by adjuvant TMZ with tumor treating fields [36–40].

Surgery

Maximal tumor resection while preserving neurological function stands as a fundamental aspect of glioblastoma treatment, significantly influencing treatment decisions. Beyond providing tissue for definitive pathological diagnosis, resection allows rapid improvement in neurologic function through tumor debulking and reduction of mass effect. Studies have shown that achieving 98% or more extension of resection (EOR) results in a median OS of 13 months, compared to only 8.8 months in those with less extensive surgery [41–44].

Adjuvant therapy

In 2005, a phase 3 randomized trial by Stupp et al. marked a significant shift in the treatment paradigm. It showed that the addition of concurrent and adjuvant TMZ to RT and

Table 1 Summary of completed series for neoadjuvant SRS

Series	Study type/ status	*N*	Median dose	Fractionation	Timing of RT	Radionecrosis	Leptomeningeal disease	Local control
Prabhu, RS [30]	Retrospective, published	117	15 Gy	1 fraction	Within 2 days	5.1% at one year	4.3% at one year	80.1% at one year
Patel, AR [31]	Retrospective, published	12	16 Gy	1 fraction	Within 1 day	0%	10%	81.6%, 49.1% at 6 months, 12 months
Vetlova E [32]	Retrospective, published	19	18 Gy	1 fraction	Within 2 days	0%	9% (one patient)	91% at 6 months
RAD 1002 [33]	Phase I, completed	20	12–15 Gy	1 fraction	Within 30 days	0%	5% (one patient)	Not published
Shoichi, Deguchi [29]	Retrospective, published	20	30 or 35 Gy	5 fractions	Within 4 days	0%	5% (one patient)	5% (one patient)

Table 2 Summary of currently recruiting trials for neoadjuvant SRS

Study	Phase/type	*N*	Dose	Fractionation	Timing of RT	Outcomes
NCT03368625	II	30, estimated	Not specified	1 fraction	Not specified	Toxicity, local control, LMD, survival
NCT01891318	I/II	36, estimated	< 10 Gy excluded	1 fraction	With 2 weeks of resection	Toxicity, local control, distant brain failure, radiation necrosis
NCT05871307	III—neoadjuvant, intraoperative, adjuvant	90, estimated	Not specified	1 fraction	3 arms: neoadjuvant, intraoperative, post-operative	Local tumor control, tissue analysis
NRG-BN012 (NCT 05438212)	III—adjuvant versus neoadjuvant	TBD	TBD	1 fraction	Within 7 days before surgery	Time to adverse event, overall survival, local control, radiation necrosis, leptomeningeal disease
MC167C, Mayo Clinic	III—neoadjuvant versus adjuvant	TBD	TBD	1 fraction	Within 4 weeks of resection	Time to first CNS event, local control, radiation necrosis, leptomeningeal disease, overall survival
NCT03741673, MDACC	III, recruiting—neoadjuvant versus adjuvant	110, expected	TBD	1–5 fractions (only phase III allowing more than 1 fraction)	Within 30 days of resection	Leptomeningeal disease, local control, distant brain control, overall survival

surgery resulted in a noteworthy improvement in median OS from 12.1 to 14.6 months [37]. Subsequently, this regimen has become the standard of care therapy due to its success and minimal treatment-related toxicity. The optimal RT dose has been a subject of investigation. Dose escalation up to 60 Gy/30 fractions has shown beneficial outcomes, but multiple studies have shown further escalation to 70 Gy does not confer additional advantages [45]. Importantly, these studies were done prior to TMZ being added to the treatment regimen and is being re-visited in the current era. A single-arm phase I study conducted at the University of Michigan demonstrated promising results with safe dose escalation to 75 Gy/30 fx with concurrent/adjuvant TMZ, with a median OS of 20.1 months [46].

Adjuvant SRS

There is growing interest in exploring dose escalation with stereotactic SRS while minimizing treatment-related toxicity [47, 48]. The only level I evidence evaluating the efficacy of stereotactic SRS as boost therapy with EBRT in newly diagnosed GBM comes from the RTOG 9305 randomized trial [49]. This study involved 203 patients with GBM, who were randomized to receive 60 Gy in 30 fractions with BCNU chemotherapy, with or without the addition of postoperative SRS boost. At 61 months follow up, the median OS did not differ between the SRS and non-SRS groups (13.5 vs. 13.6 months). Importantly, however, the generalizability of the findings from this study to contemporary practice are limited by the chemotherapy chosen and the lack of standard molecular characterization and stratification.

Neoadjuvant SRS

Pre-operative SRS offers several advantages over postoperative SRS. First, it enables the use of more compact radiation target volumes, reducing radiation exposure to surrounding healthy tissues. Second, intact tissues have higher oxygen concentrations prior to surgery, potentially leads to more effective induction of double-stranded breaks. Third, it allows for post-irradiation tissue analysis, potentially allowing for personalized treatment strategies [50, 51].

Currently, there are no available published studies on the utilization and clinical outcomes of neoadjuvant SRS in primary glioma. The administration of preoperative SRS can be challenging in certain scenarios, such as when patients with GBM present with significant mass effect requiring urgent surgical intervention and decompression. The large size of GBM tumors can also make precise SRS delivery challenging while maintaining tolerable doses for nearby healthy tissues. Performing SRS without histologic confirmation remains controversial [52, 53]. The NeoGlioma trial (NCT05030298) is currently investigating the role of

preoperative SRS in the management of GBM and high-grade glioma.

There is also promise for preoperative SRS to increase immunogenic effects. Preclinical studies have demonstrated that RT can act as an anti-tumor vaccine by releasing tumor-associated antigens and facilitating adaptive immune responses. Ablation of dividing cells in GBM, could also induce senescence in non-ablated cells. These responses counteract the immunosuppressive tumor microenvironment in GBM, enhancing neo-antigen presentation, promoting dendritic cell maturation, and downregulating Fas ligand expression. In combination with ICIs, this may amplify the anti-tumor immunity [23, 54].

Treatment planning

In the NeoGlioma Study, a gross tumor volume (GTV) was contoured with a recommended planning target volume (PTV) margin of 3 mm. SRS dose of 10 Gy is prescribed to the PTV. A clinical target volume (CTV) margin was not employed. Surgical resection is scheduled within 14 days following SRS.

The PreOperative Brain Irradiation in Glioblastoma (POBIG) phase I clinical trial in Manchester, UK, is aiming to assess the safety and feasibility of single-fraction preoperative RT utilizing VMAT for newly diagnosed glioblastoma patients. Eligible participants will receive a single fraction of radiotherapy (ranging from 6 to 14 Gy) targeted at the highest risk area for postoperative residual disease (hot spot). The remaining part of the tumor (cold spot) will remain unirradiated for diagnostic sampling. POBIG presents a valuable opportunity for translational research by comparing irradiated and unirradiated tissue.

High LET radiation

Linear Energy Transfer (LET), the average energy deposited per length of a radiation track, is the determining factor of the biological potency of a radiation modality. Photon beams, which constitute SRS, exhibit a low LET, characterized by ionization reliant on the indirect effect of oxygen free radical formation to cause DNA lesions. In contrast, High LET radiation induces damage via direct ionization, and has the potential to enlist more potent systemic anti-tumoral immune responses via induction of smaller cleaved DNA fragments with greater disposition for cytosolic leakage.

In this way a neoadjuvant SRS approach may be of the most benefit. This is because it may also allow the high-dose component of the tumor to be resected after carbon ion radiotherapy to analyze the biologic response of the tissue, which could be done on a per-patient basis. The most interesting question is whether patients exposed to carbon ions demonstrate different biomarkers compared to conventional radiotherapy [55]. As it stands currently, there is little genomic data analyzing the response of tissue to carbon ion therapy, however the data available does show differences between radiation modalities (i.e., protons and photons). In vitro studies suggest that carbon ion irradiation reduce angiogenesis and metastasis [56]. While the role of high LET radiation is speculative, with the opening of Mayo Clinic Florida's carbon ion center as the first in North America, we may see this application in the near future.

Benign and low grade intracranial tumors

Historically, the primary role for radiation therapy and SRS for benign tumors (i.e., meningioma, vestibular schwannoma, pituitary adenomas etc.) has been in the inoperable or the adjuvant setting. In tumors where a gross total resection (GTR) is not achieved, tumor recurrence is more likely without adjuvant therapy. For example, a retrospective review from a cohort of 581 Mayo Clinic patients who underwent surgical resection for meningioma, 5- and 10-year PFS was 61% and 39% for incomplete resection, but 88% and 75% with a GTR [57]. There are, however, cases in which a GTR cannot be achieved without significant deficits—for example, low grade glioma involving eloquent cortex or vestibular schwannoma grossly adherent to the facial nerve—in which adjuvant SRS can be anticipated preoperatively. In these specific cases, neoadjuvant SRS to the unresectable component may prove to be beneficial in the future. This would serve to reduce normal tissue dose, reduce rates of progression, and allow for biologic study of the irradiated tissue. It would also deliver radiation when the margin of the target tumor as well as the critical structures around it are well defined. In addition, if the SRS were delivered in a short time frame with respect to the resection to follow, the risk of scar tissue formation at the tumor margins should be minimal thereby allowing the resection to be unimpeded by post-SRS changes at the brain-tumor interface.

Conclusion

In this review, it was first described how preoperative SRS may be superior to adjuvant radiosurgery for brain metastases, particularly to reduce toxicity and improve both local and intracranial control. Three randomized Phase III trials are underway which will help us further understand the ideal timing, dose, and fractionation of neoadjuvant therapy. We also discussed how it may be a potential option for gliomas, which may offer benefits such as precise radiation targeting, higher oxygen concentrations for more effective DNA damage, and potential immunogenic effects. In the setting

of benign tumors, neoadjuvant SRS could potentially be utilized in cases in which a gross total resection is not possible or prudent and a subtotal resection is instead planned. Finally, we discussed how high LET radiation, such as carbon ion therapy, may prove advantageous due to tightly clustered DNA damage, efficacy against cancer stem cells, and potential immunogenicity. Utilizing these high LET radiation modalities in the neoadjuvant setting may also allow the field the move forward by further analysis of the irradiated tissue, which could be done to analyze a patient-specific response.

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Declarations

Competing interests Dr. Trifiletti reports publishing fees from Springer Inc. as he reported on our Title Page.

Conflict of interest Dr. Trifiletti reports clinical trial research support from the Florida Department of Health, Varian Medical Systems, Novocure, and Blue Earth Diagnostics Ltd., publishing fees from Springer Inc., as well as consulting fees from Boston Scientific Corporation. None of the other authors have relevant conflicts of interest.

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