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Preoperative stereotactic radiosurgery in the management of brain metastases and gliomas

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Stereotactic radiosurgery (SRS) is the delivery of a high dose ionizing radiation in a highly conformal manner, which allows for significant sparing of nearby healthy tissues. It is typically delivered in 1–5 sessions and has demonstrated safety and efficacy across multiple intracranial neoplasms and functional disorders. In the setting of brain metastases, postoperative and definitive SRS has demonstrated favorable rates of tumor control and improved cognitive preservation compared to conventional whole brain radiation therapy. However, the risk of local failure and treatment-related complications (e.g. radiation necrosis) markedly increases with larger postoperative treatment volumes. Additionally, the risk of leptomeningeal disease is significantly higher in patients treated with postoperative SRS. In the setting of high grade glioma, preclinical reports have suggested that preoperative SRS may enhance anti-tumor immunity as compared to postoperative radiotherapy. In addition to potentially permitting smaller target volumes, tissue analysis may permit characterization of DNA repair pathways and tumor microenvironment changes in response to SRS, which may be used to further tailor therapy and identify novel therapeutic targets. Building on the work from preoperative SRS for brain metastases and preclinical work for high grade gliomas, further exploration of this treatment paradigm in the latter is warranted. Presently, there are prospective early phase clinical trials underway investigating the role of preoperative SRS in the management of high grade gliomas. In the forthcoming sections, we review the biologic rationale for preoperative SRS, as well as pertinent preclinical and clinical data, including ongoing and planned prospective clinical trials.

KEYWORDS

brain metastases, glioma, stereotactic radiosurgery, neurosurgery, radiation oncology

Introduction

Stereotactic radiosurgery (SRS) was first proposed by Dr. Lars Leksell in 1951 (1). This technique delivers high doses of ionizing radiation in 1–5 sessions in a highly conformal manner that allows for significant sparing of nearby healthy tissues due to the rapid dose gradient outside of the treatment target (1–4). Today, SRS is utilized in a multitude of benign and malignant intracranial indications (5–35).

One of the most common indications for SRS is in the management of brain metastases (13, 16, 19, 36). Multiple randomized trials have demonstrated that SRS is associated with excellent rates of local tumor control and improved rates of cognitive preservation without compromising overall survival (OS) when compared to whole brain radiation therapy (WBRT) (13–15). Historically, patients with a single accessible brain metastasis often underwent surgical resection, which demonstrated improved OS when compared to WBRT alone (37). Additionally, postoperative WBRT has demonstrated improved local and distant brain control, as well as lower rates of neurologic death when compared to surgery alone (38). However, given the cognitive sequelae associated with WBRT, clinicians frequently withheld it in the up-front setting (39). A recent randomized controlled trial comparing adjuvant SRS to observation in the setting of a resected brain metastasis demonstrated a 1 year local control rate of 72% in the SRS arm vs. 43% in the observation arm; however, the findings in the SRS arm were largely dependent on the size of the metastasis, as larger lesions were associated with worse local control (16).

Postoperative SRS is associated with several drawbacks, despite the improvement in local control. First, the use of a clinical target volume (CTV) expansion of 1 mm to 2 mm is commonly utilized to address microscopic, invasive disease. Second, postoperative SRS frequently requires that target volumes that encompass the surgical tract, as well as margin along the bone flap and venous sinuses (40). Taken together, these factors result in an increase in irradiated volume of normal brain, which is associated with an increased risk of treatment-related complications (e.g., radionecrosis) (8, 41–44). Third, the risk of leptomeningeal disease (LMD) is higher in patients undergoing postoperative SRS, likely due to surgical perturbation, compared to WBRT with rates as high as 45% (16, 45–49). Fourth, adherence rates with postoperative SRS are often suboptimal due to variable postoperative clinical courses (49, 50). Fifth, prolonged intervals between surgical resection and postoperative SRS are associated with worse local control (51–53).

Historically, radiation was given following surgery for resected brain metastases, but with the associated drawbacks of postoperative SRS, investigators began to explore incorporation of SRS in the preoperative setting. Preoperative therapy has

become widely adopted in multiple malignancies, such as cancers of the esophagus and rectum (54–57). While most studies exploring the role of preoperative radiosurgery have focused on brain metastases, there has been recent growing interest in applying this treatment paradigm to high grade glioma and glioblastoma (11). While the use of postoperative SRS in the management of glioblastoma yielded disappointing results (58–60); however, its use in the preoperative setting shares many of the potential advantages observed with brain metastases and further might also be used as a strategy to enhance anti-tumor immunity (61, 62). Furthermore, preoperative SRS allows for post-radiotherapy tissue analysis, which can allow for characterization of DNA repair pathways and tumor microenvironment changes in response to SRS.

Brain metastases

Brain metastases are the most common intracranial neoplasm and are diagnosed in approximately 200,000 patients each year in the United States (63–66). These estimates are likely conservative, as brain metastases are commonly diagnosed during the disease course, while national registries (e.g., The National Cancer Database and Surveillance, Epidemiology, and End Results) are largely focused on clinical characteristics present at the time of index cancer diagnosis (67, 68). For many years the standard of care treatment approach in these patients consisted of conventional whole-brain radiation therapy (WBRT) with or without resection and corticosteroids (69). In the absence of surgical resection many patients did not live beyond 3–4 months (37). With advances in systemic therapy (e.g., immune checkpoint inhibitors) the prognosis of patients with brain metastases has markedly improved (5–7, 70–72). Furthermore, greater availability of magnetic resonance imaging has increased detection of subclinical disease. Taken together, the incidence of brain metastases is expected increase, as well as the need for improved intracranial RT delivery.

Surgical management of brain metastases

In 1990, Patchell et al. published a landmark randomized trial, where 48 patients with a single brain metastasis were randomized to surgical resection followed by postoperative WBRT or needle biopsy followed by WBRT (37). Whole brain radiation therapy was delivered to a dose of 36 Gy in 12 fractions. Patients who received surgical resection experienced improved lower rates of local recurrence (20% vs. 52%; $p < 0.02$), as well as improved median OS (40 weeks vs. 15 weeks; $p < 0.01$), and longer period of functional independence (median, 38 weeks vs. 8 weeks; $p < 0.005$).

Postoperative radiotherapy for brain metastases

In 1998, Patchell et al. published the results of a randomized study designed to determine if WBRT improved neurologic outcomes and OS (38). Ninety-five patients with a single brain metastasis who underwent surgical resection were randomized to WBRT to a dose of 50.4 Gy in 28 fractions or observation. Patients in the WBRT arm experienced improved brain control (18% vs. 70%; $p < 0.001$), lower rates of local recurrence (10% vs. 46%; $p < 0.001$), and lower rates of neurologic death (14% vs. 44%; $p = 0.003$). No differences were observed in OS and length of functional independence. The results of the two Patchell studies established the role of postoperative WBRT in the management of a resected brain metastasis.

While WBRT is associated with excellent rates of local and regional brain control, it is also associated with significant rates of cognitive deterioration following treatment (13–15, 73–76). Multiple studies have suggested that there is an association between cognitive functioning and quality of life (77, 78). In 2017, Brown et al. published the results of N107C, which was a phase 3 trial that randomized 194 patients to SRS or WBRT following surgical resection of a brain metastasis (13). Overall cognitive deterioration was 52% vs. 85% ($p = 0.00031$) favoring the SRS arm and 12 month surgical bed control favored the WBRT arm (60.5% vs. 80.6%; $p = 0.00068$). In 2018, Mahajan et al. published the results of a single institution trial that randomized patients following resection of a brain metastasis to postoperative SRS or observation (16). At 12 months, the local control rates were 43% vs. 72% ($p = 0.015$), favoring the SRS arm with no differences in OS observed between the arms. Additionally, the local control rates were highly dependent on tumor diameter. When compared to a tumor diameter of ≤ 2.5 cm, tumors measuring > 2.5 – 3.5 cm [hazard ratio (HR): 6.7; $p = 0.0021$] and > 3.5 cm (HR: 6.6; $p = 0.0032$) had a markedly higher rate of local recurrence. Thus, when managing larger lesions, fractionated radiosurgery is a commonly utilized approach (8, 42, 43) and is being studied in an ongoing prospective randomized trial (79). Taken together, these studies have established the role of postoperative SRS in the setting of a resected brain metastasis.

The development of LMD is a significant concern in patients with brain metastases, particularly following surgical resection. Mahajan et al. observed an approximately 25% LMD rate in the postoperative SRS arm (16). In a 2017 study by Foreman et al., a 35% LMD rate at 1 year following postoperative SRS was observed (47). Additionally, they observed trend towards an increased risk of developing LMD in patients with breast cancer histology (HR: 2.37; $p = 0.07$). A study by Atalar et al. that evaluated 175 brain metastasis resection cavities that were treated with postoperative SRS

observed an 11% cumulative incidence of LMD at 1 year (46). They also noted a 24% LMD rate in breast cancer patients compared to 9% in patients with other histologies ($p = 0.004$). Furthermore, resection and postoperative SRS is associated with a particular subtype of LMD, known as nodular LMD (nLMD) (45, 80). A radiation treatment plan for a patient who underwent resection and postoperative SRS is presented in Figure 1.

Preoperative radiosurgery for brain metastases

Preoperative SRS is a treatment strategy that may mitigate the risk of treatment-related toxicities and local failure (34, 45, 46, 49, 80, 81). This treatment strategy allows for targeting of the intact metastasis, which allows for more precise SRS targeting compared to postoperative treatment. In the postoperative setting, a CTV is generated, which is dependent on resection cavity dynamics (82–84). Additionally, while preoperative SRS volumes may often be smaller than what would be expected in the postoperative setting, relaxation of the resection cavity in the interval between surgery and SRS may lead to smaller SRS volumes. A radiosurgical plan for a

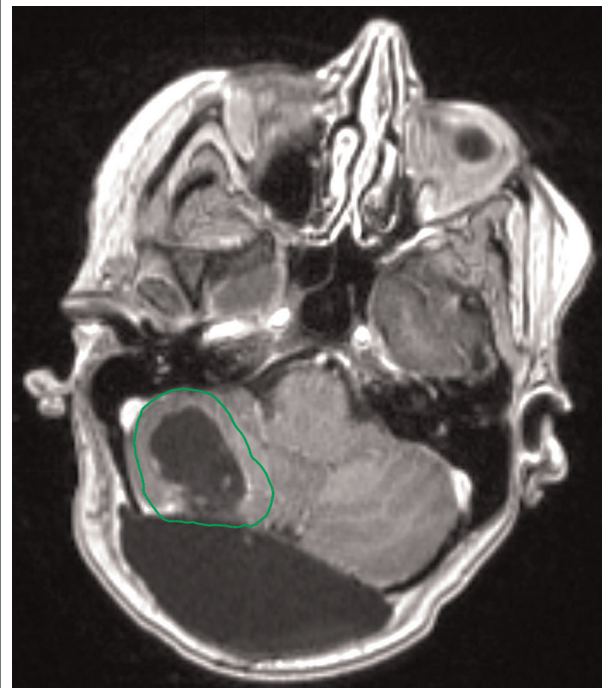


FIGURE 1

Radiation treatment plan of a 65 year old female patient with a history of breast cancer. She underwent a surgical resection followed by postoperative SRS to the resection cavity (outlined in green) to a dose of 27 Gy in 3 fractions.

patient who underwent preoperative SRS is presented in [Figure 2](#).

Local tumor control

As noted in the preceding sections, while postoperative SRS is associated with acceptable rates of local control, with the highest control rates for smaller resection cavities ([8](#), [13](#), [16](#)). In 2016, Patel et al. published a multicenter retrospective study comparing patients who underwent preoperative and postoperative SRS for a brain metastasis ([81](#)). The 1 year cumulative incidence of local recurrence was 15.9% vs. 12.6% in the preoperative and postoperative SRS groups, respectively ($p = 0.33$). A follow-up multicenter study that evaluated 242 patients with 253 index lesions who were treated with preoperative SRS observed 1 and 2 year local recurrence rates of 15% and 17.9%, respectively ([49](#)). Taken together, these findings suggest that preoperative SRS does not compromise local control rates when compared to postoperative SRS.

Radionecrosis

Radionecrosis is a potential complication following SRS that has been observed in 5%–25% of published reports ([41](#), [85–89](#)). The variability in reported incidence is largely due to different definitions in published studies, which incorporate pathologic and/or radiographic characteristics. Approximately 50% of radionecrosis cases are symptomatic and first-line management involves the use of corticosteroids or other systemic agents, such as bevacizumab and pentoxifylline ([90](#)). Patients who are refractory to pharmacologic managements often undergo surgical resection or laser interstitial thermal ablation ([34](#)). The volume of healthy brain irradiated during SRS is correlated with an increased risk of developing radionecrosis ([8](#), [41](#), [42](#)). A commonly used dosimetric parameter for single fraction SRS is to minimize this risk is keeping the volume of brain receiving 12 Gy or more to

$< 10 \text{ cm}^3$ ($V_{12} \text{ Gy} < 10 \text{ cm}^3$). A frequently employed mitigation strategy in the setting of larger lesions, where the brain $V_{12} \text{ Gy}$ would be exceeded with single fraction SRS is fractionated radiosurgery ([42](#)). In 2013, Minniti et al., published a comparative study where 289 patients with brain metastases $> 2 \text{ cm}$ in diameter were treated with single-fraction SRS or fractionated SRS (27 Gy in 3 fractions) ([42](#)). In the fractionated SRS group, the $V_{18} \text{ Gy}$ was found to be the most predictive parameter for radionecrosis with a risk of 5% and 14% for $V_{18} \text{ Gy} \leq 30.2 \text{ cm}^3$ and $> 30.2 \text{ cm}^3$, respectively.

When treating postoperative cavities, it is common to incorporate a 1–2 mm CTV margin. Additionally, coverage of the surgical tract, as well as incorporation of a CTV margin along the dura and venous sinuses are recommended in certain situations ([40](#)). When incorporating a CTV into the SRS treatment volume, the amount of irradiated healthy brain significantly increases, which therefore poses an increased risk of radionecrosis. Patel et al. reported symptomatic radionecrosis rates at 1 year of 14.6% vs. 1.5% for postoperative and preoperative SRS, respectively ($p = 0.01$). Therefore, these findings suggest that rates of symptomatic radionecrosis are lower with preoperative than postoperative SRS.

Leptomeningeal disease

As noted in the preceding sections, LMD is frequently seen following resection and postoperative SRS; additionally, patients with breast cancer carry a higher risk ([45](#), [46](#), [80](#)). Studies have reported that the risk of developing LMD is higher following postoperative SRS than postoperative WBRT ([49](#)). It has been hypothesized that this is due to seeding of the CSF space during surgical resection, which would normally be sterilized with administration of WBRT ([49](#), [80](#), [81](#), [91](#)).

Patel et al. reported LMD rates at 1 year of 3.2% vs. 8.3% and at 2 years of 3.2% vs. 16.6% for pre-operative vs. post-

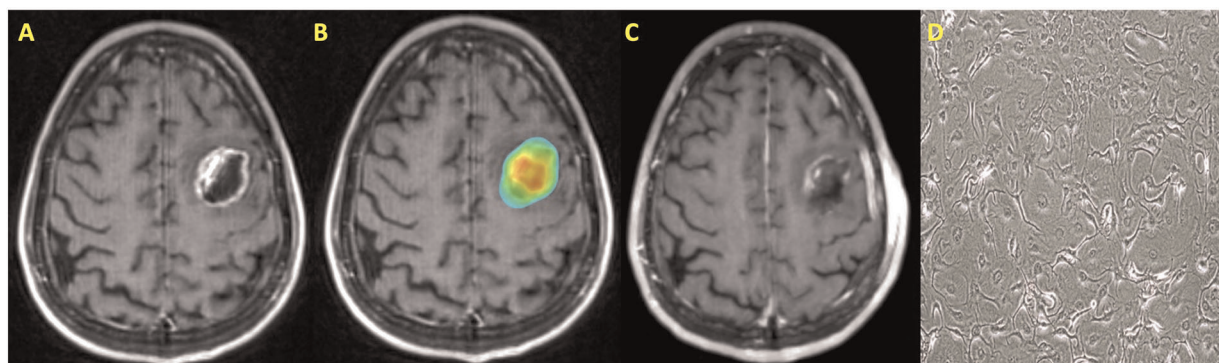


FIGURE 2

Patient with a history of metastatic non-small cell lung cancer who was treated with preoperative SRS. (A) T1 post contrast MRI axial image demonstrating a left frontal metastasis; (B) SRS treatment plan with dose color wash; (C) T1 post contrast MRI axial image following surgical resection; (D) Cell culture microscopy of post-irradiation resected tissue.

operative SRS, respectively ($p = 0.01$) (81). Preoperative SRS may provide field sterilization to reduce the risk of tumor seeding and the subsequent development of LMD, which may occur when postoperative SRS is given postoperatively. Patel et al. conducted an additional study that compared preoperative SRS to postoperative WBRT (92). They observed LMD rates of 3.5% vs. 9.0% for the preoperative SRS and WBRT groups, respectively ($p = 0.66$). Prabhu et al. noted that the median OS following LMD diagnosis was 6.9 months vs. 1.2 months in patients with nLMD and cLMD, respectively ($p = 0.05$) (49). Additionally, the median OS for patients diagnosed with LMD who received salvage treatment was 11.3 months vs. 2.8 months in patients with nLMD and cLMD, respectively ($p = 0.38$). These findings appear to suggest the following: (1) the risk of LMD is significantly lower with preoperative SRS compared to postoperative SRS; (2) rates of LMD with preoperative SRS are not significantly different than those with postoperative WBRT; (3) nLMD is a unique failure pattern observed with postoperative SRS that is associated with better outcomes when compared to cLMD.

Other considerations

Preclinical studies have suggested that ionizing radiation (RT) has the ability to enhance anti-tumor immunity by acting as an in-situ vaccine (93). Additionally, studies have shown that ablative doses of RT (e.g., SRS) lead to increased antigen presentation and CD8⁺ T cell activation (5, 6, 93–97). In recent years, combining SRS with immune checkpoint inhibitors (ICI) has been widely studied. Multiple reports have suggested that SRS and ICI are able to synergize to further enhance anti-tumor immunity, particularly when these therapies are administered within 4-weeks of one another (5–7, 65, 98–101). Preoperative SRS would permit tissue analysis following RT, which can allow for characterization of DNA repair pathways and other changes in the tumor microenvironment in response to SRS. These tissue analyses can aid in our understanding of the role that SRS plays in anti-tumor immunity, as well as identify novel therapeutic targets. Resection cavity dynamics following surgery is an important consideration in the postoperative setting (82, 102–104). This has been shown to be particularly evident in larger irregularly shaped cavities and lesions that were associated with significant amounts of edema preoperatively. Intraoperative radiotherapy (IORT) in the setting of resected metastases and glioblastoma is a novel technique that continues to expand and is associated with less cavity shrinkage compared to SRS following treatment (82–84). Both preoperative SRS and IORT allow for elimination of time to initiation of radiation, minimization of target uncertainty in a resection cavity, and dose escalation (105).

Disadvantages

While preoperative SRS has many advantages, it has disadvantages as well. First, preoperative SRS does not permit for pathologic tissue diagnosis prior to administering treatment. However, patients with brain metastases frequently have pathologic disease confirmation from biopsy of the primary tumor or an extracranial metastatic site prior to SRS. Second, in patients who have significant mass effect and symptoms from a brain metastasis, preoperative SRS is likely not appropriate, as the delay between preoperative SRS and surgical resection could cause an unacceptable risk to the patient. Therefore, these patients should be treated with surgical resection expeditiously.

Ongoing and planned clinical trials

There are multiple phase 3 clinical trials that are underway or planned that are comparing preoperative to postoperative SRS for brain metastases. Trials are underway at both the Mayo Clinic (NCT03750227) and the MD Anderson Cancer Center (NCT03741673). Additionally, NRG Oncology has recently opened the BN012 trial (NCT05438212) (106), which is a phase 3 randomized cooperative group trial comparing preoperative to postoperative SRS.

High grade glioma and glioblastoma

High grade glioma and glioblastoma are primary brain tumors that arise from astrocytes, ependymal cells, and oligodendrocytes. Glioblastoma the most common primary brain tumor, accounting for approximately 50% of all primary brain tumor diagnoses in the United States (107, 108). Glioblastoma is highly resistant to treatment and is associated with a dismal prognosis (109, 110). Despite maximal optimal treatment, the median OS ranges from 15 to 21 months with a 5 year OS of <5% (111–115) for favorable patients who are able to undergo resection. Thus, given the poor prognosis associated with glioblastoma, novel treatments to improve the therapeutic ratio are sorely needed.

Postoperative radiosurgery

Studies have demonstrated that most glioblastoma recurrences occur within 2 cm of the resection cavity, thus there has been interest in radiation dose escalation (59, 60, 116). Radiation Therapy Oncology Group (RTOG) 9305 was a randomized trial of 203 patients with supratentorial glioblastoma who received 60 Gy in 30 fractions and BCNU with or without the addition of an SRS boost (58). The SRS dose was based on the maximum tumor diameter, as recommended in RTOG 9005 (117). With a median follow-up

of 61 months, the median OS was 13.5 months vs. 13.6 months, in the SRS and no SRS groups, respectively. Thus, postoperative SRS is not recommended in the setting of glioblastoma.

Preoperative radiosurgery

Due to patterns of failure on glioblastoma, there has long been an interest in dose intensification; however, studies have yielded disappointing results (11, 110). BN001 is a randomized controlled trial that is comparing standard of care chemoradiotherapy to dose-escalated RT in the management of glioblastoma. Gondi et al. presented preliminary results at the 2020 Annual Meeting of the American Society of Radiation Oncology (118). No meaningful improvements in OS or other patient outcomes were observed. Preoperative SRS is therefore an attractive and novel approach to deliver intensified doses of RT in these patients.

While there is a paucity of clinical data involving the use of preoperative SRS in the management of glioblastoma, much of the theoretical advantages can be extrapolated from what has been observed in the preclinical setting and what has been observed with brain metastases. First, intact glioblastoma may have higher rates of oxygenation when compared to postoperative tissues, which may result in more double-stranded DNA breaks (109). However, this hypothesis needs to be further validated. Second, post-SRS tissue analysis may permit characterization of cellular pathways in response to RT and can aid in the development of novel therapeutic agents.

The risk of LMD in the setting of glioblastoma is approximately 4% and carries a grim prognosis (119, 120). Therefore, while preoperative SRS would be expected to decrease the risk of LMD, the extent at which it does so may be minimal. Preoperative SRS and postoperative RT treatment volumes in a patient with glioblastoma are presented in Figure 3.

Immunogenic effects of preoperative SRS

One of the major potential advantages of utilizing preoperative SRS in glioblastoma and high grade glioma is the ability to enhance anti-tumor immunity. A study by Klein et al., which exposed glioblastoma specimens to increasing doses of RT observed an increase in the expression of major histocompatibility class I antigen expression in response to treatment (62). This suggests that RT may cause enhanced CD8⁺ T cell responses against the tumor. A study by Newcomb et al. assessed the impact of WBRT and vaccination on a murine GL261 glioma model (61). While each of these treatments did not demonstrate a significant impact on OS when administered alone, combining WBRT and vaccination results in a long-term OS increase of 40%–80%. However, GL261 glioma models are suboptimal for studying immunotherapy in gliomas. A study by Zeng et al. in 2012 evaluated the impact of SRS and anti-PD-1 therapy on a murine glioblastoma model (121). While the OS rates were approximately 25 days in each the control, SRS, and anti-PD-1 groups, an OS of 53 days was observed in the combination therapy group. These findings suggest that SRS and anti-PD-1

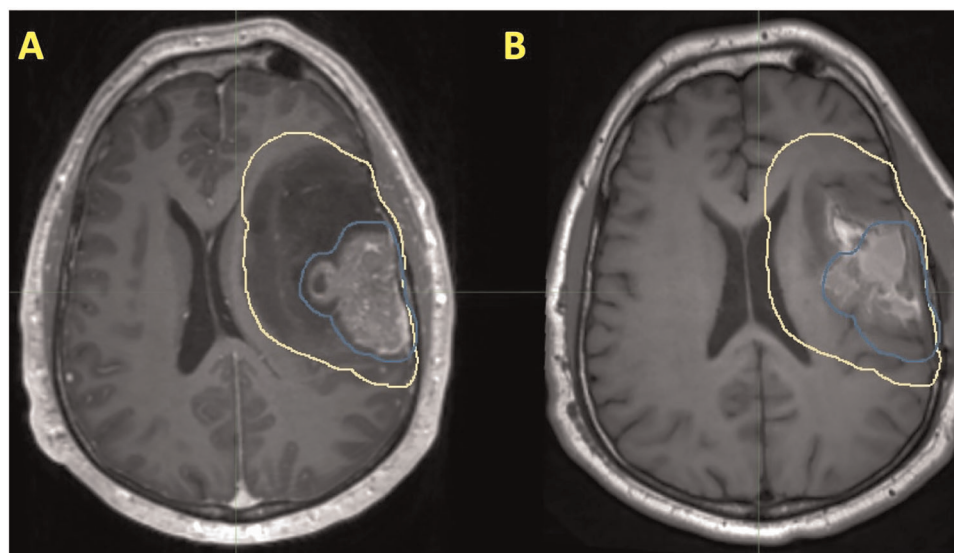


FIGURE 3

Patient with a history of glioblastoma, where the volume encircled in blue represents a preoperative SRS volume and the volume encircled in yellow represents a postoperative radiotherapy volume. Each of these volumes are shown on (A) preoperative T1 post contrast MRI and (B) T1 postoperative T1 post contrast MRI.

therapy may synergistically enhance anti-tumor immunity in glioblastoma.

The timing of surgery following preoperative SRS is also an important consideration from an immunologic standpoint. A study by De La Maza et al. that utilized a murine mesothelioma model demonstrated that performing surgery 7 days after completing RT resulted in lower tumor regrowth rates and enhanced tumor rejection at 90 days following treatment completion (122). These findings were not observed when surgery occurred 1-day following completion of RT. Additionally, these findings were felt to be immunologic in nature, as mice depleted of CD4⁺ T cells had a markedly diminished response. Surgery alone has demonstrated an immunogenic effect on glioblastoma, Khalsa et al. showed that surgery might improve antitumor responses by increasing the presence of activated microglia, SiglecF⁺ macrophages, T cells, while decreasing resident macrophages (123).

Ongoing trials

The NeoGlioma study (NCT05030298) is a prospective clinical trial at the Mayo Clinic that will be investigating the role of preoperative SRS in high grade glioma. Patients will undergo surgical resection within 14 days of SRS (124). Patients in the preoperative SRS arm will undergo stereotactic biopsy prior to radiosurgery. The gross tumor volume (GTV) will be defined as residual contrast-enhancing tumor on thin slice T1-postcontrast MRI; edema will not be included. A 3 mm volumetric expansion will then be generated on the GTV to create a planning tumor volume (PTV). A clinical target volume will not be utilized and an SRS dose of 10 Gy will be prescribed to the PTV. Steroid use is at the discretion of the treating physician. The risks and benefits of steroid administration should be carefully weighed against one another, as they can provide symptom relief but also are immunosuppressive (125–127).

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Conclusion

Preoperative SRS is a treatment paradigm that has multiple significant advantages when compared to postoperative SRS in the management of brain metastases. Multiple retrospective reports have demonstrated excellent rates of local control, as well as lower rates of radionecrosis and LMD. Ongoing and planned phase 3 trials may further validate these findings. Preclinical data has suggested that preoperative SRS in the setting of high grade glioma and glioblastoma may enhance anti-tumor immune responses, which can potentially lead to improved patient outcomes. We eagerly await the results of the NeoGlioma study to better evaluate this hypothesis.

Author contributions

EJL, ROK, and DMT contributed to the conception and design of the article. DMT provided the figures. EJL and ROK wrote the first draft of the manuscript. DMT provided resources and supervision of the project. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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