Symptomatic radionecrosis after postoperative but not preoperative stereotactic radiosurgery in a single patient: illustrative case

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BACKGROUND Standard of care for brain metastases involves stereotactic radiosurgery (SRS). For cases that also require surgery because of lesion size, edema, or neurological symptoms, whether to provide pre- or postoperative SRS has become a prevalent debate.

OBSERVATIONS Herein, the unique case of a patient with brain metastases of the same pathology and similar size in two different brain locations at two different times is described. The patient underwent surgery with preoperative SRS for the first lesion and surgery with postoperative SRS for the second lesion. Although both treatments resulted in successful local control, the location that received postoperative SRS developed symptomatic and rapidly progressive radiation necrosis (RN) requiring a third craniotomy.

LESSONS Large randomized controlled trials are ongoing to compare pre- versus postoperative SRS for the treatment of symptomatic brain metastases (e.g., study NRG-BN012). Recent interest in preoperative SRS has emerged from its theoretical potential to decrease rates of postoperative RN and leptomeningeal disease. This valuable case in which both therapies were applied in a single patient with a single pathology and similar lesions provides evidence supportive of preoperative SRS.

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KEYWORDS SRS; brain metastases; neurosurgery; neurosurgical oncology; recurrence

When brain metastases cause neurological symptoms, are larger than 3 cm, and/or present with significant edema, resection followed by postoperative stereotactic radiosurgery (SRS) is standard of care to obtain local control.1 However, preoperative SRS has emerged as a potential way to lower rates of symptomatic radiation necrosis (RN) and leptomeningeal disease (LMD). Theoretically, preoperative SRS can reduce RN by minimizing radiation to surrounding normal brain.2 When SRS is performed before surgery, the lesion itself, as opposed to the resection cavity, can be targeted, and a 1- to 2-mm target expansion is not required. Because resections can excise a small margin of normal brain around metastases, targeting postoperative resection cavities can expose more normal brain to radiation than preoperative treatments. Additionally, preoperative SRS can theoretically reduce rates of LMD by pre-treating any tumor cells that may be inadvertently spread into the surrounding meninges or cerebrospinal fluid during surgery. Retrospective studies comparing pre- to postoperative SRS support these hypotheses.3–5 Lowering rates of LMD and RN is extremely important, because the median survival after a classic LMD diagnosis is 2 to 4 months,6 and occurrences of symptomatic RN, as we describe here, can require additional surgery or prolonged medical therapy.

As a unique contribution to the growing literature, herein we describe a rare and important case in which a patient with brain metastases of the same pathology and similar size in two different brain locations received preoperative SRS for one lesion and postoperative SRS for the other. Although both treatments led to successful local control, the location that received postoperative SRS developed symptomatic RN requiring an additional craniotomy, whereas the preoperative SRS site did not.

ABBREVIATIONS LMD = leptomeningeal disease; MRI = magnetic resonance imaging; RN = radiation necrosis; SRS = stereotactic radiosurgery.

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Illustrative Case

A right-handed 36-year-old male with known adenocarcinoma of the colon presented to his oncologist with new-onset left upper-extremity weakness, forgetfulness, and slurred speech. Brain magnetic resonance imaging (MRI) showed an enhancing 1.7 × 1.4 cm nodular mass involving the lateral aspect of the right precentral gyrus just deep to the cortical surface with surrounding edema (Fig. 1). As part of a clinical trial (NCT04545814, PRO00038835), the patient underwent preoperative SRS. Treatment was delivered with five composite shots to deliver 20 Gy to the 52% isodose line. He tolerated the treatment well. One day later, the patient underwent an awake right frontal craniotomy for motor mapping and piecemeal resection of the mass. Pathology revealed the tumor was consistent with his known adenocarcinoma of the colon. At the time of this intracranial recurrence, the patient was not on systemic therapy, because he did not have any evidence of systemic disease. His last dose of systemic therapy was 5 years prior to the discovery of his first intracranial metastasis. Postoperative MRI demonstrated a gross-total resection with expected postoperative linear enhancement at the edges of the resection cavity (Fig. 1).

Follow-up surveillance MRI 8 months later revealed a new 2 × 1.9 × 1.8 cm lesion in the anterior left frontal lobe with surrounding edema, local mass effect, and midline shift. He subsequently underwent a left frontal craniotomy for en bloc resection of the mass, followed by postoperative SRS. Pathology revealed the tumor was again consistent with his known adenocarcinoma of the colon. Post-treatment MRI again showed gross-total resection with expected postoperative findings (Fig. 2). One month later, SRS was delivered with 41 composite shots to deliver 18 Gy to the 48% isodose line. Figure 3 and Table 1 outline the detailed SRS treatment plans for both the right and left frontal lesions.

Routine follow-up MRI 14 months later began to show changes concerning for progression of disease versus RN at the anterior left frontal lobe site (Fig. 4). Increased heterogeneous rim enhancement surrounding the left frontal lobe resection cavity was thought to represent treatment-related changes due to the absence of hyperperfusion on magnetic resonance perfusion imaging. Because of the equivocal nature of the MRI, the patient was scheduled for stereotactic biopsy and laser ablation of the mass to confirm progression versus RN and to treat either pathology. However, it was discovered on a preoperative planning scan that the enhancing lesion had rapidly progressed and developed into a large mass with surrounding edema and midline shift with subfalcine herniation. Upon questioning, we found that the patient had also recently become symptomatic with increased confusion and lethargy. Because of these developments, the plan was changed, and he was taken for a secondary left frontal craniotomy for resection of the lesion (Fig. 4). Pathology confirmed RN. Currently, the patient is without evidence...
FIG. 2. Preoperative (A–C) and postoperative (D–F) MRI of the left frontal metastasis. Axial precontrast T1-weighted (A), postcontrast T1-weighted (B), and FLAIR (C) MRI depicting the left frontal lesion. Axial precontrast T1-weighted (D), postcontrast T1-weighted (E), and FLAIR (F) MRI depicting the resection cavity 24 hours postoperatively. Green arrow - tumor location (B) and corresponding resection cavity (E).

FIG. 3. SRS treatment plans for the right and left frontal lesions. Axial (A), sagittal (B), and coronal (C) postcontrast T1-weighted MRI depicting the preoperative SRS treatment plan for the right frontal lesion. Axial (D), sagittal (E), and coronal (F) postcontrast T1-weighted MRI depicting the postoperative SRS treatment plan for the left frontal resection cavity. Note that despite the similar size of the lesions, the size of the treatment field is larger in the postoperative plan because of planning around a resection cavity rather than a lesion.
of any active disease in the brain and is without neurological symptoms.

**Patient Informed Consent**

The necessary patient informed consent was obtained in this study.

### Discussion

#### Observations

This case represents a scientifically unique occurrence of a single pathology in a single patient who underwent resection at two separate sites and received preoperative SRS at one site and postoperative SRS at another.

#### TABLE 1. SRS treatment plans for the right and left frontal lesions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rt Frontal Lesion</th>
<th>Lt Frontal Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>01/28/2021</td>
<td>10/14/2021</td>
</tr>
<tr>
<td>Pre- or postop SRS</td>
<td>Preop</td>
<td>Postop</td>
</tr>
<tr>
<td>Prescribed dose (Gy/% isodose)</td>
<td>20 Gy/52%</td>
<td>18 Gy/48%</td>
</tr>
<tr>
<td>Conformality index</td>
<td>0.8</td>
<td>0.86</td>
</tr>
<tr>
<td>Vol of brain (skull) receiving</td>
<td>12 Gy: 9.67 mL, from MIM DVH</td>
<td>12 Gy: 29.85 mL, from MIM DVH</td>
</tr>
<tr>
<td>Vol of brain (PTV, CTV, GTV, as it applies) receiving</td>
<td>PTV: 3.358 mL, GTV: 2.518 mL</td>
<td>PTV: 14.736 mL, CTV: 12.196 mL, GTV 7.609 mL</td>
</tr>
</tbody>
</table>

CTV = clinical target volume; DVH = dose-volume histogram; GTV = gross tumor volume; MIM = MIM Software; PTV = planning target volume.

**FIG. 4.** Progressive symptomatic RN of the left frontal lesion site. Axial precontrast T1-weighted (A), postcontrast T1-weighted (B), FLAIR (C), and relative cerebral blood volume (D) MRI sequences depicting initial progression of posttreatment RN. Axial precontrast T2-weighted (E), postcontrast T1-weighted (F), and FLAIR (G) MRI sequences depicting further progression of left frontal RN 25 days later. Axial precontrast T1-weighted (H), postcontrast T1-weighted (I), and FLAIR (J) MRI sequences depicting the postoperative resection cavity 24 hours after secondary left frontal craniotomy for resection of the symptomatic RN.
postoperative SRS at the other. Although local control was achieved at each site, the postoperative SRS site developed symptomatic RN, which required a craniotomy for resection.

The etiology of RN is thought to arise when radiation injures blood vessels, leading to brain parenchymal injury through secondary inflammatory mechanisms.⁷ RN after postoperative SRS is common, and some studies have reported RN rates as high as 25.8%.⁸ Preoperative SRS may be more advantageous than postoperative SRS in that it minimizes exposure of normal brain to unnecessary radiation through lesionol versus resection cavity targeting, respectively.⁹–¹¹ In targeting a lesion, preoperative SRS avoids the necessary surgical cavity delineation and 1- to 2-mm volume expansion¹²,¹³ that postoperative SRS requires, both reducing the risk of anatomical miss and subjecting less normal brain to radiation.²,³,⁵,⁹–¹²,¹⁴–¹⁶ As displayed in Fig. 3 and Table 1, the radiation plan for this case was designed on the basis of the lesion in the preoperative SRS instance, whereas it was designed on the basis of the resection cavity in the postoperative SRS instance (Fig. 3).

The standard of care for resected brain metastases shifted from whole-brain radiation to SRS following publication of the findings of N107C (NCT01372774) given preserved survival with improved cognition with SRS.¹⁸ However, there remains concern that SRS has a higher rate of LMD compared to whole-brain radiation,¹⁷,¹⁸ and questions remain about optimal dose and fractionation for resection cavities of varying sizes.¹⁷ These questions have prompted heightened research efforts aimed at determining how to leverage the advantages of SRS compared to whole-brain radiation, all while managing the incidence of LMD. Early studies demonstrated low rates of LMD after preoperative SRS, sparking large randomized clinical trials (NCT05438212) to further establish the possible benefits of preoperative SRS.²,³,⁵,¹⁶ It has been postulated that preoperative SRS may reduce LMD rates by treating the lesion prior to potential tumor spillage during surgery, thereby making cellular spread into the leptomeninges unviable.²,³,⁵,¹⁴–¹⁶

The main limitation to this study is the sample number of 1, and we caution against drawing broad conclusions about safety or efficacy from this single case. Additionally, even within this individual, subtle differences in size, laterality, location, timing, and systemic therapy remain uncontrolled potential confounders. Despite these limitations, this case provides a unique example of the importance of such ongoing trials investigating these two approaches. Combined with the literature, this unique case supports the notion that preoperative SRS may reduce the incidence of unwanted side effects like symptomatic RN.

Lessons
In this case, although both radiosurgeries resulted in successful local control, the location that received postoperative SRS developed symptomatic and rapidly progressive RN that required an additional craniotomy for resection. Whether preoperative SRS is superior to postoperative SRS is under active investigation. Large randomized clinical trials (NRG-BN012, NCT05438212) are currently accruing and will further clarify the best approach for patients with brain metastases necessitating resection. This case provides a unique demonstration of the importance of such ongoing trials investigating these two approaches.

References

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Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Krucoff, Straza, Mueller, Bovi. Acquisition of data: Krucoff, Laurin, Straza. Analysis and interpretation of data: Krucoff, Laurin, Straza, Mueller. Drafting the article: Krucoff, Laurin, Straza. Critically revising the article: Krucoff, Laurin, Straza, Noid, Mueller. Reviewed submitted version of manuscript: Krucoff, Laurin, Straza, Noid, Connelly, Mueller. Approved the final version of the manuscript on behalf of all authors: Krucoff. Study supervision: Krucoff.

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