Simultaneous integrated boost using stereotactic radiosurgery for resected brain metastases: rationale, dosimetric parameters, and preliminary clinical outcomes

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Background Radiosurgery has been shown to reduce the rates of local recurrence in the postoperative bed after the resection of brain metastases, but the ideal radiation dose has not been well defined.

Objective To present dosimetric parameters and preliminary clinical outcomes for patients undergoing postoperative stereotactic radiosurgery (SRS) with simultaneous integrated boost (SIB) for brain metastases.

Methods and materials 3 patients underwent surgery for a dominant metastatic focus and had residual or recurrent disease in the resection cavity. Our technique delivered a low dose to the resection cavity with an SIB dose to the gross tumor. Clinical target volume (CTV) was the magnetic resonance (MR)-defined resection cavity. Gross tumor volume (GTV) was the MR-defined residual disease. No additional margin was added to either the resection cavity or the residual disease area. Doses ranged from 14-15 Gy for CTV and 17-18 Gy for GTV prescribed to the 71%-78% isodose line. A traditional postoperative radiosurgery plan was constructed for each patient, and dosimetric values were compared using the paired t-test.

Results 3 patients were treated at our institution using SRS with SIB. No patient experienced local recurrence. 2 patients developed distant brain failure (mean, 3.5 months). No grade 3 or greater toxicities were observed. The volume of brain receiving 12 Gy was significantly reduced using SIB compared with traditional postoperative SRS (P = .04). There were no differences in the maximum dose delivered to the tumor (P = .15) and cavity (P = .13). The average mean cavity dose was 16.20 Gy using the SIB plan, compared with 19.71 Gy using the traditional plan (P = .05).

Conclusions In patients with either recurrent or residual disease following surgical resection, SRS using SIB is technically feasible and safe.

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lesions, and emergency decompression. A drawback of surgical resection as a sole modality is the high rate of local failure (range, 46%-59%). In patients who undergo surgical resection of a brain metastasis, Patchell and colleagues have demonstrated that the use of WBRT decreases local failure and rates of neurologic death, and it is considered the standard of care. There is more interest in combining failure and rates of neurologic death, and it is considered have demonstrated that the use of WBRT decreases local disease to the brain.

The use of SRS as an adjuvant treatment is a new approach. To our knowledge, no randomized phase 3 trials have been published to date, despite the 2014 publication of the first prospective phase 2 trial. Many questions exist, and the best way to apply this exciting treatment approach is not yet clear. Most series use regimens from the RTOG 90-05 trial; but it is not clear if this is the ideal regimen when a tumor no longer exists. In addition, in cases in which an incomplete resection has been performed or a tumor has recurred in the resection cavity before SRS, the ideal treatment approach is unknown.

We present preliminary results of a new treatment approach using postoperative SRS for residual or recurrent brain metastases by applying a low dose to the resection bed and simultaneously integrating a boost dose to the gross tumor volume (GTV).

Methods and materials
Since 2010, our institution has offered postoperative radiosurgery as an alternative to WBRT to patients who have undergone surgery for a dominant metastatic focus and had limited synchronous metastatic disease. We reviewed all cases of postoperative SRS delivery and identified 3 cases in which different dose prescriptions were used. These cases were treated during 2011–2014.

Radiosurgery was delivered using the Trilogy Linear Accelerator (Varian Medical Systems, Palo Alto, CA) and the CyberKnife System (Accuray Inc, Sunnyvale, CA). Treatment was frameless, and thermoplastic masks were used for patient immobilization. Optical guidance with an infrared mouthpiece was used with the Trilogy for setup verification. Orthogonal kV X-ray imaging was used with the CyberKnife System. All of the patients underwent gadolinium-enhanced magnetic resonance (MR) imaging of the brain within 48 hours of surgical resection to delineate any residual disease and assess the quality of the resection. Another MR of the brain was done and a computed tomography (CT) simulation was created using a 1.5-mm slice interval. Both MR images were registered and fused with CT data from the simulation using either the Varian Eclipse Treatment Planning System or the Accuray CyberKnife system. Segmentation was performed by our institution's radiation oncologist, neurosurgeon, and neuroradiologist. For each partially resected metastasis, 2 target volumes were delineated. The clinical target volume (CTV) resection cavity is the MR-defined resection cavity with no added margin. The GTV is the MR-defined residual disease based on both the immediate postoperative and treatment planning MR images. No additional margin was added on the CTV or GTV for treatment planning. Prescription doses varied between the 3 treated patients, but ranged from 4-15 Gy for the CTV and 17-18 Gy for the GTV prescribed to the 71%-78% isodose line. For patients who were treated with the CyberKnife, a sum plan was used to combine the dose from both targets. Using the Eclipse Treatment Planning System, it was possible to construct a single plan. Patients were seen in follow-up every 2–3 months with new MR brain imaging.

We constructed a traditional postoperative radiosurgery plan by prescribing the higher definitive dose to the larger CTV target. This new plan was compared with the simultaneous integrated boost (SIB) plan, which was originally delivered. Dosimetric information was collected from the treatment planning systems and included minimum, maximum, and mean doses for the cavity and residual tumor, the volume of brain receiving 12 Gy (V12Gy), and conformity indices. Values were compared using a paired t test.

Results
Clinical courses of patients treated with technique
There were 3 patients treated at our institution using this technique. Patient characteristics and indications for surgical resection are listed in Table 1. The first patient treated with this technique presented with headaches, visual field deficits, and right-sided neglect. Imaging of the brain showed a 3.1-cm rim-enhancing lesion in the left parietal lobe with vasogenic edema and 1 cm of subfalcine herniation. Further workup revealed a likely primary mass in the right kidney. The patient underwent a left parietal craniotomy and resection of the mass, which was found on pathology to be consistent with renal cell carcinoma. A postoperative MRI showed expected postsurgical changes and no residual disease in the resection cavity; however, 1 month after surgical resection, the MR brain image used for SRS planning revealed a small local recurrence at the posterior aspect of the previously resected cavity. A SIB plan was developed with 15 Gy prescribed to the larger postresection cavity and 18 Gy to the gross tumor, both prescribed to the 74% isodose line (Figures 1 and 2). Treatment was delivered without complication, and follow-up imaging confirmed resolution of the contrast-enhancing region of the resection cavity. Subsequent imaging confirmed local response but showed distant brain failure with multiple new lesions. The patient underwent WBRT 4 months after the postoperative SRS with SIB.

The second patient presented to the emergency department with left facial droop. Imaging revealed a 3-cm...
enhancing mass in the right temporal lobe with 4 mm of midline shift secondary to vasogenic edema. The patient was taken for a right frontotemporal craniotomy with image guidance and microdissection, but complete resection was impossible because of the tumor’s proximity to the middle cerebral artery. The patient did well after surgery, and an SRS with SIB plan was constructed. The resection cavity received 15 Gy, and the focal area of residual disease received 18 Gy prescribed to the 78% isodose line. The patient did well, and follow-up imaging confirmed resolution of the contrast enhancement in the resection cavity. Six months after SRS, there was no evidence of disease.

The third patient presented to his primary care physician with a right-sided headache. MR imaging of the brain showed a 1.7-cm enhancing lesion in the right frontal lobe. Steroids did not improve his symptoms, and the patient underwent a craniotomy and gross total resection of the metastasis based on the neurosurgeon’s intraoperative observations and postoperative imaging. Follow-up imaging showed an area of nodular enhancement felt to be consistent with recurrent disease. The postoperative cavity was treated to 15 Gy with a SIB of 17 Gy to the area of residual disease using SRS prescribed to the 71% isodose line. The patient tolerated SRS well with only a slight headache for several days. Follow-up imaging revealed distant brain failure, which was treated 3 months after the original SRS. There was no evidence of intracranial disease 6 months after SRS.

Clinical outcomes
All treated lesions responded to SRS with SIB. No local recurrence has been observed in or adjacent to the postoperative cavity in any of the patients treated with this technique. However, 2 of the 3 patients developed distant brain failure after SRS with SIB (mean, 3.5 months). Of the 2 patients, 1 was salvaged with traditional SRS for a new lesion, and 1 patient was treated with palliative WBRT for multiple new lesions. None of the patients who were treated with this technique developed grade 3 or greater clinical toxicity, and no imaging findings consistent with radionecrosis have been observed.

Dosimetric outcomes
Dosimetric comparisons of SRS with SIB plans and traditional postoperative SRS plans are presented in Table 2 and Figure 3. The V12Gy was significantly reduced using SIB plans compared with traditional postoperative SRS (mean, 15.6 vs 20.0 cm³; \( P = .04 \)). There were no differences in the maximum dose delivered to either the tumor (\( P = .15 \)) or cavity (\( P = .13 \)) using the 2 plans. The average mean tumor dose was 17.86 Gy using the SIB plan, compared with 20.38 Gy using the traditional plan (\( P = \)
metastasis of a similar size and greater than what is needed for control of the postresection cavity. Hartford and colleagues have demonstrated adequate local control of 84% with a median marginal dose of only 10 Gy.15 Although authors state that their typical dose is now higher; it is clear that in postoperative SRS, an inadequate dose is not the primary factor that drives recurrence.

Rogers and colleagues reported on the use of the GliaSite system (IsoRay Medical, Richland, Washington, USA) for treatment of the resection cavity after surgical resection of brain metastases.36 Despite doses of 60 Gy at 1 cm, authors observed local control of 13%-18%. It seems clear that dose escalation is not the answer to improving local recurrence after adjuvant treatment of resected brain metastases.

In the absence of data demonstrating the necessity of higher doses, all efforts should be made to reduce toxicity in patients treated for brain metastases. The rate of observed radionecrosis was 17.5% in a study by Brennan and colleagues.32 It can be difficult to predict which patients will develop radionecrosis after SRS, but it seems to be related to dose and volume.13 The volume of the brain receiving 12 Gy (V12Gy) in a single fraction has been shown to predict the development of radionecrosis.37,38 This V12Gy rapidly increases with even slightly larger target volumes. By using the SIB technique, an adequate dose can be given to the residual disease with a minimum increase in volume of the normal brain at risk for radionecrosis.

### Table 2 Dosimetric factors

<table>
<thead>
<tr>
<th>Patient</th>
<th>V12 (cm³)</th>
<th>GTV Max (Gy)</th>
<th>CTV Max (Gy)</th>
<th>CI</th>
<th>HI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SIB TRD</td>
<td>SIB TRD</td>
<td>SIB TRD</td>
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<tr>
<td>1</td>
<td>20.3 26.6</td>
<td>20.2 20.6</td>
<td>20.2 20.8</td>
<td>1.46 1.42</td>
<td>1.15 1.15</td>
</tr>
<tr>
<td>2</td>
<td>15.8 19.9</td>
<td>20.0 24.0</td>
<td>20.0 24.0</td>
<td>1.08 1.12</td>
<td>1.33 1.33</td>
</tr>
<tr>
<td>3</td>
<td>10.6 13.6</td>
<td>21.1 23.9</td>
<td>21.1 23.9</td>
<td>1.40 1.40</td>
<td>1.41 1.41</td>
</tr>
</tbody>
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CI, Conformity Index; CTV Max, maximum dose to the resection cavity; GTV Max, maximum dose to the gross tumor volume; HI, Homogeneity Index; SIB, simultaneous integrated boost plan; TRD, traditional; V12, volume receiving 12 Gy.

.03). The average mean cavity dose was 16.20 Gy using the SIB plan, compared with 19.71 Gy using the traditional plan (P = .05). No statistically significant differences were observed in the Conformity Index, New Conformity Index, or Homogeneity Index. In both of the patients who were treated with the CyberKnife linear accelerator (where treatment times can be calculated), the treatment times were similar for delivery of the 2 plans (SRS with SIB and SRS alone; 43 vs 30 minutes and 53 vs 55 minutes, respectively).

### Discussion

There has been increasing interest in using SRS after surgery in place of traditional WBRT as an adjuvant to surgery. SRS can offer similar postoperative local control with only a single treatment and reduce acute toxicity for many patients. However, perhaps the most exciting benefit of postoperative SRS is the potential reduction in neurocognitive side effects seen with WBRT. Investigators continue to better define dosing schedules, target delineation techniques, and timing of postoperative SRS.34

Residual or recurrent disease can present a management challenge in postoperative SRS. Brennan and colleagues observed that 3 patients out of 49 had local recurrence in the surgical resection cavity in the interim between surgery and SRS.32 Rates of subtotal resections in a postoperative SRS series vary between 75% and 100%.13-22,24,25,28,30,31 Taken together, the risk of a patient having either residual disease following surgery or recurrent disease that developed in the treatment interval is a significant problem. In our series, 2 patients were treated for recurrent disease, and 1 patient was treated for a subtotal resection. Our treatment approach did not differ for these 2 groups of patients. Both groups likely resulted from residual disease (either clinically recognized or not) with continued progression.

Without the SIB technique, in cases of persistent or recurrent disease, a high dose is traditionally prescribed to the entire cavity either with or without an added margin.13-22,24,25,28,30 This approach results in a compromise of dose, typically less than would be used for an intact metastasis of a similar size and greater than what is needed for control of the postresection cavity. Hartford and colleagues have demonstrated adequate local control of 84% with a median marginal dose of only 10 Gy.15 Although authors state that their typical dose is now higher; it is clear that in postoperative SRS, an inadequate dose is not the primary factor that drives recurrence. Rogers and colleagues reported on the use of the GliaSite system (IsoRay Medical, Richland, Washington, USA) for treatment of the resection cavity after surgical resection of brain metastases.36 Despite doses of 60 Gy at 1 cm, authors observed local control of 13%-18%. It seems clear that dose escalation is not the answer to improving local recurrence after adjuvant treatment of resected brain metastases.

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### Figure 3

Comparison of traditional stereotactic radiosurgery plan (A) and simultaneous integrated boost plan (B).
Conclusion
In patients with recurrent or residual disease following surgical resection, SRS using a SIB is technically feasible and safe. This technique places a smaller volume of normal brain tissue at risk for radionecrosis, which may result in less patient toxicity. More patients and longer follow-up are required to better assess the clinical outcomes following treatment with this new technique.

References

24. Mathieu D, Konzdiolka D, Flickinger JC, et al. Tumor bed radio-


28. Quigley MR, Fuhrer R, Karlovits S, Johnson M. Single session ste-

33. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treat-

35. Steinmann D, Maertens B, Janssen S, et al. Hypofractionated stereotac-

37. Korytko T, Radroevitch T, Colussi V, et al. 12 Gy gamma knife rad-