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# Point/Counterpoint: Is stereotactic radiosurgery needed following resection of brain metastasis?

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In this article, we will attempt to present and delineate the pros and cons of performing stereotactic radiosurgery (SRS) to the surgical cavity after resection of a single brain metastasis. In this regard, one must consider the relative merits of SRS vis-à-vis whole brain radiotherapy (WBRT) in the context of local control at the resection cavity, distant failure, overall survival, the ability to preserve neurocognition and associated quality of life, treatment toxicity, and ease of integration with systemic therapy.

## Historical Perspective

The role of WBRT, long the mainstay in the management of brain metastases, is evolving. In 1990, the landmark randomized brain metastasis trial published by Patchell and colleagues[1] established surgical resection followed by WBRT as the standard of care for the management of a single brain metastasis, as there was a survival benefit associated with the surgical resection of a single brain metastasis. The Radiation Therapy Oncology Group (RTOG) 95-08 trial established a survival benefit for the addition of SRS to WBRT for single brain metastases.[2] The publication of these 2 trials, and supporting studies, led to worldwide adoption of radiosurgery and surgery in combination with WBRT for the initial management of limited brain metastases over the next 2 decades. Four randomized trials looking at SRS and the value of adding or omitting WBRT[3–6] have now been completed. The results from these 4 trials have questioned the need for routine WBRT following SRS, while favoring SRS alone in the management of 1 to 3 brain metastases. A meta-analysis[7] of the 3 published randomized trials (the Japanese Radiation Oncology Study Group, MD Anderson Cancer Center [MDACC], European Organisation for Research and Treatment of Cancer [EORTC]) has also reported a survival benefit associated with patients randomly assigned to SRS alone who were younger than 50 years of age, further questioning the role of WBRT.

Performing surgery alone for a single brain metastasis is not supported by randomized data. A second randomized trial, published in 1998, by Patchell and colleagues,[8] of resection alone of a brain metastasis compared with resection followed by WBRT, showed a local failure rate at the resection cavity of 46% with surgery alone and 10% with surgery and WBRT ($P < .001$). The EORTC 22952-26001 trial was unique in that it included patients after either surgery or radiosurgery who were randomized to WBRT or observation. This trial confirmed the insufficiency of surgical resection alone for brain metastasis, demonstrating a recurrence rate in the surgical cavity of ~60% without adjuvant radiation. Concerns raised by randomized studies on the neurocognitive sequelae associated with postoperative WBRT, and the infeasibility of omitting all adjuvant radiation, led some institutions to replace postoperative WBRT with postoperative SRS, a practice trend that is increasing.

## Postoperative Stereotactic Radiosurgery: Pros

### *Local Control and Overall Survival*

A review of single institutional retrospective studies supports postoperative radiosurgery to the surgical cavity of resected brain metastasis with local control rates of 85%–100%.[9] The median survival for selected published studies is 14.2 months (range, 10–20.5 mo). Our own published institutional experience at the University of Southern California reported on 82 patients undergoing resection of a brain metastasis and subsequent radiosurgery to the cavity. The actuarial rate of local failure in the cavity was 13% at 12 months. The median overall survival in our series was 20 months.[10] These studies are limited by their retrospective nature, but a recently published phase II trial by Brennan et al[11] investigating SRS boost after surgery demonstrated a local control rate of 78% at 12 months. Importantly, 10 of the 50 patients enrolled did not receive the

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planned boost, due to progression, large cavity size, or other medical reasons, which demonstrates the bias inherent in retrospective analyses.

Overall, the reported local control rates and survival following SRS to the surgical cavity are comparable to those obtained with WBRT, suggesting that postoperative SRS is as effective as WBRT.

### *Neurocognitive Outcomes*

Extrapolation from 2 randomized trials conducted by MDACC and the North Central Cancer Treatment Group (NCCTG) would strongly suggest that replacing postoperative WBRT with SRS would lead to improved neurocognitive outcomes. From the MDACC trial, which enrolled patients with 1–3 intact brain metastases and randomly assigned them to observation or WBRT, one can estimate that for resected brain metastases, postoperative SRS would be estimated to have a similar 25% decline on the Hopkins Verbal Learning Test (HVLT), while postoperative WBRT would be estimated to have a similar 50% decline on the HVLT at 4 months. The NCCTG N0574 (Alliance) trial for patients with 1 to 3 intact brain metastases reported decline in cognitive function at 3 months measured by the HVLT Delayed Recall Test more frequently with the addition of WBRT (51.1%) compared with SRS alone (19.7%). Additional evidence for the deleterious effect of WBRT on cognitive function comes from RTOG 0214,[12] which randomized non-small cell lung cancer patients without evidence of brain disease to prophylactic cranial irradiation or observation. Decrements in HVLT scores were seen persisting up to 1 year post WBRT. As systemic therapies improve, patients with metastatic disease, even within the CNS, will live longer, and the importance of preservation of cognitive function will increase, suggesting that WBRT should be delayed as long as possible. The ongoing NCCTG N107C trial, which randomizes patients to postoperative SRS or postoperative WBRT, has the primary goal and hypothesis of determining if there is less incidence of neurocognitive progression measured at 6 months postradiation in patients randomized to postoperative SRS compared with postoperative WBRT. This should provide much needed neurocognitive outcome data in the context of the postoperative setting. WBRT with hippocampal sparing has been proposed as a means by which the cognitive decline of patients receiving WBRT may be reduced, but prospective clinical data are still forthcoming.[13] SRS cavity boost offers another way to reduce cognitive deficits in patients receiving radiotherapy to the brain.

### *Toxicity of Treatments*

WBRT can cause fatigue, alopecia, skin erythema, dermatitis, folliculitis, otitis media, taste alteration, and appetite changes. SRS is typically not associated with the aforementioned acute toxicities, and the vast majority of SRS patients do not experience any acute toxicity. Rarely, SRS patients may experience headaches, seizures, edema, or hemorrhage.

The most serious and concerning potential late toxicity associated with WBRT is neurocognitive decline. WBRT may also be associated with a risk of leukoencephalopathy, especially when there is a close temporal relationship with chemotherapy. Moreover, patients receiving WBRT can develop dementia when large radiation fractions (>3 Gy) are used.[14] SRS is associated with improved preservation of neurocognitive function over WBRT but may cause long-term treatment-related imaging changes on MRI around the surgical cavity, which may develop into radiation necrosis. The reported rate of pathologically proven radionecrosis in the previously mentioned prospective trial by Brennan et al was 17.5%.[11]

### *Logistics and Coordination of Care*

Postoperative SRS is advantageous to both patient and caregiver, because it can be delivered within a day or 2 following surgery and completed in 1 day. Postoperative WBRT cannot be initiated for at least 10 days to allow for adequate wound healing, and usually requires 2 weeks to complete. If patients are receiving systemic therapy, a break from chemotherapy is necessary during WBRT administration, and up to 1 month following its completion. With postoperative SRS there is minimal to no interruption of systemic agents. As a result, concerns regarding controlling systemic disease and avoiding systemic tumor progression while patients undergo CNS treatment are minimized when postoperative SRS is chosen over WBRT. One of the major difficulties with postoperative SRS is proper delineation of the cavity and addition of an appropriate margin. Early experiences reported that rates of local failure correlated with increasing conformality of the treatment plan and subsequently found that at least a 2-mm margin around the cavity should be treated to avoid excess failure.[15] There is a high degree of variation in size and shape of postoperative cavities, which can make accurate contouring difficult, something that is less than desirable for such a precise treatment. Preoperative SRS is one potential way to mitigate this concern.[16]

### *Quality of Life*

The EORTC study evaluated health-related quality of life (HRQoL) as a secondary endpoint, considering global health status; physical, cognitive, role, and emotional functioning; and fatigue.[17] Patients reported better HRQoL in the observation arm than in the WBRT arm, with differences that were statistically significant at 9 months in global health status, at 8 weeks in physical functioning, at 12 months in cognitive functioning, and at 8 weeks in fatigue. The study did not find observation with serial MRI to be detrimental to HRQoL.

### *Conclusions*

Evidence from 4 randomized radiosurgical trials and multiple institutional retrospective studies strongly support SRS alone for a limited number of newly diagnosed brain metastases based on: local tumor control, overall survival, neurocognitive preservation, and HRQoL, as well as acute and long-term toxicity profiles. Here we have shown that postoperative SRS provides similar control rates to WBRT, with potentially less neurocognitive toxicity. The ongoing N107C trial should provide level I evidence that will further clarify the risk-benefit analysis between administering postoperative WBRT versus SRS. Other means to improve outcomes, such as hippocampal-sparing WBRT and preoperative SRS, are promising and may be evaluated in future trials.

## Postoperative Stereotactic Radiosurgery: Cons

When addressing the cons of SRS to the surgical cavity in single brain metastasis, one must take into account 3 points: the existence of several unsolved technical and clinical problems, the risk of radionecrosis and other neurological complications, and the risk of leptomeningeal relapse.

### *Unsolved Problems*

Despite a growing body of literature,[18–22] SRS to the resection cavity is not superior to WBRT in terms of local or distant control at 1 and 2 years.

Some technical issues are still matters of debate.[11,15,23] The optimal dose and fractionation, especially for large (>3 cm) brain metastases, without or with superficial/dural pial involvement that could be at higher risk for local failure, are unknown. The same holds true for the optimal margin around the resection cavity to be included in the treatment field. From a clinical point of view, to date there is lack of information on HRQoL and neurocognitive functions following SRS to the resection cavity compared with those following the other therapeutic options (surgery or SRS alone, surgery or SRS plus WBRT). Moreover, it is unknown whether postoperative SRS is superior to SRS at the time of tumor progression after initial observation following surgery.

### *Risk of Radionecrosis and Other Neurological Complications*

The risk of radionecrosis following postoperative SRS[11,23,24] is higher (between 5% and 17.5%) than that reported by the EORTC study[5] with WBRT following either surgery or radiosurgery (2.6%) and could increase over time (7% at 1 y and 16% at 2 y).[23] However, the actual incidence of pathologically proven radionecrosis is unknown, as often the values reported in the different series represent a combination of biopsy-proven and MRI-suspected cases of radionecrosis.

There is lack of information on the clinical counterparts of radionecrosis and on the incidence of acute complications of SRS, such as seizures, headache, and hemorrhage.

On the other hand, an increase of T2 signal changes on MRI around the resection cavity (radiation-related edema?) has been reported in 10.8% of patients,[25] and it would be important to know whether these patients concomitantly had neurological symptoms or were asymptomatic.

One of the risks following SRS is the steroid dependency to control chronic edema: so far, neither frequency nor duration of steroid use following postoperative SRS has been recorded.

In case of suspicion of symptomatic radionecrosis, there is often the need for additional neuroimaging techniques (MR spectroscopy, MRI perfusion, PET with 2-fluoro-2-deoxy-D-glucose or amino acids) that often yield conflicting results, and bevacizumab could be clinically useful[26]; however, all these things and possible salvage SRS and other therapies could lead to an increase of financial costs.

### *Risk of Leptomeningeal Relapse*

The incidence of a leptomeningeal relapse following SRS to the resection cavity ranges in the different series from 8% to 13%.[22,24,27–29] A possible explanation could be that the surgical spillage is not treated with postoperative SRS, as it is likely beyond the radiation field, but would be treated with postoperative WBRT.

Patients with breast histology could be at higher risk (at 1 y, 24% vs 9%).[29] It is unknown whether the inclusion of WBRT would decrease this risk of leptomeningeal disease or whether the biology of brain metastases from breast cancer represents an intrinsic risk for this complication. To better characterize this risk, all the future reports on the use of SRS to the resection cavity should include the 3 compartments of failure: local, distant, and leptomeningeal.

### *Conclusions*

The main limitations of available studies on postoperative SRS in single brain metastasis include relatively small sample size, short follow-up, heterogeneous primary histologies, unknown disease stage, and concurrent use of chemotherapy.

With the lack of clear risk-benefit data and the likelihood of increased financial costs to patients and to society, it is imperative that SRS to the surgical cavity be studied in multi-institutional randomized trials before use in routine clinical practice.[30]

The ongoing phase III trial of postoperative SRS versus postoperative WBRT will give a definitive answer. Moreover, hippocampal avoidance and preoperative SRS could represent other future directions of treatment.

## Funding

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