ONCOLOGY SCAN

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Stereotactic Radiosurgery for Resected Brain Metastases: New Evidence Supports a Practice Shift, but Questions Remain

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Brain metastases are a common and devastating complication of cancer. Surgical resection of brain metastases remains an important treatment modality, especially for larger lesions with symptomatic mass effect. However, recurrence in the surgical bed occurs in approximately 60% of cases following resection alone (1, 2). For decades, the addition of postoperative adjuvant whole-brain radiation therapy (WBRT) has been the standard of care on the basis of randomized studies demonstrating efficacy in reducing the risk of recurrence in the surgical bed and the incidence of new metastases (1, 2). Alternatively, stereotactic radiosurgery (SRS), which is often the preferred treatment in patients with a limited number of intact brain metastases (3), can deliver focal irradiation to the resection cavity with the aim of maintaining high local control while avoiding the neurocognitive decline associated with WBRT. One-year local control rates from 70% to 90% have been reported in retrospective series of postoperative SRS (4). The efficacy of SRS, administered either preoperatively or postoperatively to the intact lesion or resection cavity, has been evaluated recently in prospective trials. In this Oncology Scan, we review these trials to address how this approach may affect our standard practice.

Mahajan et al. Prospective randomized trial of postoperative SRS versus observation for completely resected brain metastases. *Lancet Oncol* 2017. (5)

Summary: This prospective randomized trial enrolled 132 patients undergoing surgical resection for 1 to 3 brain metastases between 2009 and 2016 at The University of Texas MD Anderson Cancer Center. Study participants were randomized (1:1) to receive either SRS or observation (OBS) only. Patients were stratified by histologic type (melanoma vs nonmelanoma), preoperative diameter of brain metastases (<3 cm vs ≥ 3 cm), and number of brain metastases (1 vs 2 or 3). The SRS target volume was defined as the surgical cavity on the volumetric planning magnetic resonance imaging scan plus a 1-mm circumferential margin. Prescription doses were 16 Gy, 14 Gy, and 12 Gy in 1 fraction for target volumes of ≤ 10 mL, 10.1 to 15 mL, and >15 mL, respectively.

Freedom from local recurrence was the primary endpoint. Secondary endpoints included development of distant brain metastases (DBMs) and overall survival. The final analysis included 128 patients, with 65 in the OBS arm and 63 in the SRS arm, and there were no significant demographic or baseline characteristic differences between groups and stratification factors.

The 12-month freedom-from-local recurrence rates were 43% and 72% in the OBS group and SRS group, respectively, with a hazard ratio (HR) of 0.46 (95% confidence interval [CI], 0.24-0.88; $P = .015$). The median time to local recurrence was 7.6 months in the OBS group and was not reached in the SRS group. Primary tumor histology did not appear to influence local tumor-free recurrence rates. On multivariate analysis, significant predictors of local recurrence were SRS (HR, 0.5; 95% CI, 0.3-1.0; $P = .041$) and a metastasis diameter ≤ 2.5 cm compared with >2.5 to 3.5 cm (HR, 6.7; 95% CI, 2.0-23; $P = .0021$) and >3.5 cm (HR, 6.6; 95% CI, 1.9-23; $P = .0032$). The median survival was similar between groups: 18 months in the OBS group and 17 months in the SRS group, with an HR of 1.29 (95% CI, 0.4-1.9; $P = .24$). Neurologic deaths occurred in 25 of

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39 patients in the OBS group and 22 of 46 in the SRS group ($P=.13$). The probability of being free of DBM at 12 months was 33% in the OBS arm and 42% in the SRS arm (HR, 0.81; 95% CI, 0.51-1.27; $P=.35$).

Comment: SRS of the surgical cavity has been increasingly used over the past several years as a toxicity-sparing alternative to WBRT to improve local control after surgical resection of brain metastases (4). The results of this prospective randomized trial add to the existing evidence on the management of brain metastases by demonstrating that SRS after brain metastasis resection significantly reduces local failure compared with OBS alone. The results also confirm previous evidence that surgical resection alone is insufficient to provide satisfactory local control (1, 2).

Overall survival and development of DBMs were similar between arms. Of note, the incidence of leptomeningeal disease (LMD) was not statistically different between the 2 study arms. At 12 months, the estimated incidence was 16% (95% CI, 4%-26%) in the OBS arm and 28% (95% CI, 12%-40%) in the SRS arm (HR, 1.4; 95% CI, 0.6-3.4; $P=.46$). These findings confirm that the development of leptomeningeal carcinomatosis is a well-recognized complication of surgery; however, the risk is not statistically altered by postoperative SRS.

While this study suggests that patients with 1 to 3 brain metastases benefit from SRS after surgery given decreased local recurrence, many questions remain. First, resection cavity local control was <50% for patients with tumors >2.5 cm in diameter, suggesting that single doses of 12 to 14 Gy delivered to target volumes of >10 to 15 mL are insufficient to control microscopic disease. In contrast, a significant benefit for cavities <2.5 cm was seen, with 100% local control following SRS compared with 77% following OBS. Strategies such as postoperative hypofractionated SRS may be an attractive option to improve local control while minimizing the risk of radiation necrosis (6). A few studies have suggested that SRS given in 3 fractions at a dose to 27 Gy results in high local control for either large resection beds or intact metastases (7, 8). Future research needs to refine SRS techniques, potentially evaluating fractionated SRS for larger cavities, as well as determining the optimal target volume, dose, and need for a margin to the resection cavity. For example, the subsequently described trial (9) prospectively used a 2-mm margin, similar to retrospective data suggesting a benefit (10), compared with 1 mm in the current trial.

Second, it is interesting that the 12-month local control rate of 72% (95% CI, 60%-87%) in the SRS arm is similar to that reported after SRS for intact metastases in recent randomized trials (1, 11, 12). However, the superiority of the postoperative SRS approach over other modalities, including preoperative SRS or SRS to intact metastases, especially for relatively large asymptomatic radiosensitive tumors, remains to be demonstrated. Nevertheless, this study provides class 1 evidence that SRS to the resection cavity provides superior local control compared with surgery alone for patients with 1 to 3 brain metastases.

Brown et al. NCCTG (North Central Cancer Treatment Group) N107C/CEC·3 (Alliance for Clinical Trials in Oncology/Canadian Cancer Trials Group): Phase 3 randomized trial of postoperative SRS compared with WBRT for resected metastatic brain disease. *Lancet Oncol* 2017. (9)

Summary: This multicenter, randomized phase 3 trial enrolled 194 patients aged ≥18 years with Eastern Cooperative Oncology Group performance status 0 to 2 who had 1 resected metastasis with the resection cavity measuring <5.0 cm in maximal extent. Up to 3 unresected metastases (each <3 cm in maximal extent) were allowed. Patients were randomly assigned in a 1:1 ratio to either postoperative SRS (12- to 20-Gy single fraction with dose determined by surgical cavity volume) or WBRT (30-37.5 Gy in 10-15 daily fractions). The surgical cavity was treated with a 2-mm margin. The primary endpoints were overall survival from the time of randomization to death from any cause and cognitive deterioration-free survival. Secondary endpoints included quality of life (QOL), intracranial tumor control, functional independence, long-term cognitive status, toxicity, local surgical bed recurrence, and central nervous system failure patterns (local, distant, and leptomeningeal).

The median cognitive deterioration-free survival was better after SRS to the surgical cavity than after WBRT. At 6 months, for patients undergoing cognitive evaluations, cognitive deterioration was less frequent in the SRS arm (52% vs 85%, $P=.00031$), reaching statistical significance for immediate memory ($P=.00062$), delayed memory ($P=.00054$), processing speed ($P=.023$), and executive function ($P=.015$). Moreover, preservation of QOL and functional independence remained significantly better at 12 months in long-term survivors after SRS as compared with WBRT.

There was no difference in survival between the treatment groups, with a median overall survival of 12.2 months in the SRS arm and 11.6 months in the WBRT arm (HR, 1.07; $P=.70$). Surgical bed control, local control, and distant brain control were all inferior in the SRS arm, but there was no difference in the rate of development of LMD between treatment groups. The 6- and 12-month estimates of surgical bed control were 80% and 61%, respectively, with SRS versus 87% and 81%, respectively, with WBRT ($P=.00068$).

Comment: This trial showed that patients receiving single-fraction SRS to the surgical cavity had better cognitive function and QOL with no difference in survival despite better intracranial control with WBRT. Although intracranial control was better with WBRT, the negative cognitive impact of WBRT persisted over time, consistent with the results of other phase 3 trials that assessed the impact of

WBRT on patients with limited intact brain metastases (9). Thus, SRS should be considered the standard of care for patients with a resected brain metastasis, similar to those presenting with a limited number of brain metastases.

An unexpected finding of the trial was the poor 1-year resection cavity local control rate observed with SRS compared with WBRT. The local control rates were 61% and 81% following SRS and WBRT, respectively, which are inferior to those observed in other studies assessing the use of SRS for either resection cavity or intact metastases (1, 5, 13). These data suggest that doses of 12 to 14 Gy, as used for cavity volumes >20 mL in the current study, may be insufficient to control microscopic disease, especially large resistant metastases, or after incomplete resection. As stated earlier, the optimal SRS dose, margin, and impact of fractionation need to be determined (6, 8).

Overall, data from the NCCTG and MD Anderson trials indicate that SRS to the resection cavity is an effective treatment in reducing local failure as compared with observation, while reducing the risk of cognitive decline and maintaining QOL in patients with brain metastases as compared with WBRT, without decreasing survival. In appropriately selected patients with brain metastases, postoperative SRS to the resection cavity should be the standard of care after surgery, as it provides local control rates comparable to WBRT, better than with surgery alone, and without a negative impact on survival. Future studies need to optimize the SRS regimen, especially for larger tumor cavity volumes that were associated with worse local control. In addition, it will be important to compare this approach with alternative strategies, such as WBRT with hippocampal avoidance (currently studied in NRG CC-001), observation and SRS at relapse, or preoperative SRS, as discussed in the next article.

Patel et al. Comparing preoperative with postoperative stereotactic radiosurgery for resectable brain metastases: A multi-institutional analysis. *Neurosurgery* 2016. (14)

Summary: This retrospective multi-institution study investigated 180 patients with brain metastases treated with either preoperative SRS to the metastasis (66 patients) or postoperative SRS to the surgical cavity (114 patients). Postoperative SRS dose and fractionation were based on the surgical cavity size. Preoperative SRS dose was reduced by approximately 20% as compared with the institutional doses used when no surgical resection was planned. A 2-mm margin was used in post-resection cavity SRS plans with no margin for preoperative SRS. With a median follow-up of 11.1 months, the cumulative incidence of local recurrence at 1 year was not different between the preoperative and postoperative groups (16% and 13%, respectively; $P=.33$). However, the 2-year rate of LMD was significantly lower in the preoperative cohort (3%) compared with the postoperative group (17%, $P=.01$). In addition, radiation necrosis occurred in 5% with preoperative SRS compared with 16% with postoperative SRS ($P=.01$).

Comment: With the use of postoperative SRS likely to increase based on the results of the aforementioned trials, a new, iatrogenic pattern of failure may potentially increase: LMD. As first reported in postoperative cavity SRS, LMD may occur in up to 30% of patients, depending on histology (15). LMD was seen in 7.2% in the NCCTG trial and 28% in the MD Anderson trial. The rationale for preoperative SRS is to treat tumor cells prior to potential iatrogenic dissemination at the time of surgical resection, potentially decreasing the rate of LMD. In addition, contouring an intact tumor for preoperative SRS is much less challenging than for a resection cavity; hence no added margin is needed, irradiating less normal brain, perhaps leading to less radiation necrosis. These retrospective data need to be prospectively evaluated. A prospective cooperative group trial randomizing patients at greatest risk of LMD (eg, posterior fossa location, breast and melanoma histology, pial surface contact) to preoperative SRS versus postoperative, with the primary endpoint of LMD, is under consideration.

Overall, just as our paradigm has shifted from WBRT to SRS for patients with a limited number of intact brain metastases, SRS is replacing WBRT for patients with resectable brain metastases as the standard of care. Despite these recent randomized trials, several questions regarding the optimal SRS timing, target definition, and dose and/or fractionation, particularly in light of the poor local control observed for larger tumor beds, still need to be answered. The role of SRS in the patient with a resected brain metastasis will continue to evolve. New strategies to suppress the development of DBMs, enhance local control, and minimize the risk of LMD are needed, and the impact of different radiosurgical approaches by tumor histology must be defined. Nevertheless, the addition of postoperative SRS to a resected brain metastasis adds yet another tool to the radiotherapeutic armamentarium for what was once a nearly uniformly fatal complication of cancer.

References

1. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: Results of the EORTC 22952-26001 study. *J Clin Oncol* 2011;29:134-141.
2. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: A randomized trial. *JAMA* 1998;280:1485-1489.
3. American Society for Radiation Oncology. ASTRO releases second list of five radiation oncology treatments to question, as part of national Choosing Wisely campaign. Available at: http://www.choosingwisely.org/astro-releases-second-list. 2014. Accessed July 30, 2017.
4. Roberge D, Parney I, Brown PD. Radiosurgery to the postoperative surgical cavity: Who needs evidence? *Int J Radiat Oncol Biol Phys* 2012;83:486-493.

5. Mahajan A, Ahmed S, McAleer MF, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: A single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2017;18:1040-1048.
6. Kirkpatrick JP, Soltys SG, Lo SS, et al. The radiosurgery fractionation quandary: Single fraction or hypofractionation? *Neuro Oncol* 2017; 19(Suppl. 2):ii38-ii49.
7. Minniti G, D'Angelillo RM, Scaringi C, et al. Fractionated stereotactic radiosurgery for patients with brain metastases. *J Neurooncol* 2014; 117:295-301.
8. Minniti G, Scaringi C, Paolini S, et al. Single-fraction versus multifraction (3 x 9 Gy) stereotactic radiosurgery for large (>2 cm) brain metastases: A comparative analysis of local control and risk of radiation-induced brain necrosis. *Int J Radiat Oncol Biol Phys* 2016; 95:1142-1148.
9. Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): A multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2017;8:1049-1060.
10. Choi CY, Chang SD, Gibbs IC, et al. Stereotactic radiosurgery of the postoperative resection cavity for brain metastases: Prospective evaluation of target margin on tumor control. *Int J Radiat Oncol Biol Phys* 2012;84:336-342.
11. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: A randomized controlled trial. *JAMA* 2006;295:2483-2491.
12. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: A randomised controlled trial. *Lancet Oncol* 2009; 10:1037-1044.
13. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: A randomized clinical trial. *JAMA* 2016;316:401-409.
14. Patel KR, Burri SH, Boselli D, et al. Comparing preoperative with postoperative stereotactic radiosurgery for resectable brain metastases: A multi-institutional analysis. *Neurosurgery* 2016;79:279-285.
15. Atalar B, Modlin LA, Choi CY, et al. Risk of leptomeningeal disease in patients treated with stereotactic radiosurgery targeting the postoperative resection cavity for brain metastases. *Int J Radiat Oncol Biol Phys* 2013;87:713-718.