Editorial

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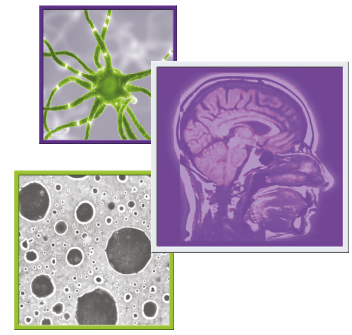

Shifting paradigms: whole brain radiation therapy versus stereotactic radiosurgery for brain metastases

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> "current national guidelines prefer SRS as upfront treatment in patients with 'limited' brain metastases"

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Management of intracranial metastases with radiation has historically been performed with whole brain radiation therapy (WBRT), which encompasses the entire brain, treating both visible and potentially microscopic disease [1]. In 1961, a Swedish neurosurgeon, Lars Leksell introduced the concept of stereotactic radiosurgery (SRS), in which a high dose of radiation could be delivered to a solitary lesion in a single treatment [2]. The concept of SRS, which has since become standard practice at many institutions, is to deliver higher dose per treatment for better disease control with minimal effect on normal brain tissue, leading ultimately to improved cognitive outcomes. This article will evaluate the shift in intracranial radiation from WBRT to SRS.

SRS for intact brain metastases

SRS was initially formally evaluated in the Radiation Therapy Oncology Group (RTOG) 90-05 trial as salvage treatment in patients who previously received WBRT, demonstrating safety of single fraction, high-dose radiation [3]. A subsequent RTOG study showed that the addition of SRS to WBRT in patients with one to three brain metastases, with no lesions over 4 cm in size, improved overall survival (OS) only in patients with a single metastasis [4]. Why a cut-off of three brain metastases was chosen is unclear, but may have been due to evidence of independently worse prognosis in patients with four or more brain metastases [5]. After establishing the safety and efficacy of combination SRS and WBRT, further studies evaluated outcomes when SRS alone was given in the one to three brain metastases population. Two large studies from Europe and Japan comparing SRS alone to SRS and WBRT demonstrated higher rates of intracranial failure rates with SRS alone, without compromising OS outcomes. While WBRT was found to reduce intracranial failure rates, cognitive outcomes were found to be significantly worse, as demonstrated in a randomized study by the MD Anderson group [6–8]. Based on these seminal publications and subsequently others as well, the preferred standard of care for patients with limited intracranial disease, generally considered to be ≤ 3 metastases with the largest lesion smaller than 4 cm, though the definition of 'limited' continues to evolve, has transitioned to SRS instead of WBRT for most histologies [9].

Initial evidence for use of SRS in patients with higher numbers of brain metastases (>3) came from a Japanese multi-institutional prospective study that enrolled patients with one to ten brain metastases in order to evaluate whether SRS to five to ten brain metastases was noninferior to those with two to four metastases [10]. Eligible patients had a cumulative brain metastasis volume of ≤ 15 cubic centimeters (cc) and were stratified depending on if they had one, two to four, or five to ten brain metastases. While patients with a single brain metastasis had improved OS, there was no difference in OS between the two to four and five to ten cohorts, suggesting that the previously studied cut-off of three to five metastases may be arbitrary, and perhaps a volume-based approach may be more appropriate for determining eligibility of SRS. A subsequent study has provided more evidence that

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volume of intracranial tumor is more important to prognosis than the number of lesions [11]. There is currently an ongoing randomized Phase III trial comparing WBRT to SRS in patients with four to ten brain metastases (Clinicaltrials.gov# NCT0235300, [12]). Results from ongoing trials may continue to evolve the definition of 'limited' disease in the brain and the historic answer of three or less may change. Another future trial is comparing WBRT to SRS in patients with five to 15 metastases [13].

Radiation in the postoperative scenario

Surgical resection is frequently done for brain metastases. Common indications include solitary brain metastasis [14], need for pathological diagnosis, excessively large tumors and/or symptomatology due to mass effect from tumor and/or edema without sufficient response to corticosteroids. Historically, postoperative WBRT was proven to improve rates of brain recurrence and neurological death [15]. A Phase III trial showed that replacing WBRT with SRS as postoperative treatment did not affect survival, but reduced declines in cognitive function [16]. A separate Phase III trial randomizing patients to postoperative SRS or observation again showed no differences in OS but did demonstrate improved rates of local progression with postoperative SRS compared with observation [17]. In summary, postoperative SRS offers a lower risk of cognitive decline compared with WBRT, without sacrificing intracranial local control rates. The optimal timing of radiotherapy following surgery continues to be evaluated.

Fractionation schemes for WBRT & SRS

The most standard fractionation scheme for WBRT is 30 Gy in 10 fractions or 37.5 Gy in 15 fractions, although 20 Gy in five fractions can be used for patients with poorer prognosis [9]. For SRS, RTOG 90-05 defined maximum tolerated marginal doses (in patients with previous history of WBRT) of 24, 18 and 15 Gy for tumors <2, 2–3 cm, and >3 cm, respectively [3]. The most concerning dose-limited toxicity from SRS is radiation necrosis (RN). Multiple studies have identified dose limited constraints for normal brain to reduce the risk of RN. For example, the volume of normal brain receiving 10 Gy or 12 Gy in a single fraction of radiation has been predictive of a patient's risk of developing RN [18,19]. In tumors of larger size and volume, patients are at inherently higher risk of developing RN. Given the radiobiological principles of decreased normal tissue toxicity with increasing fractionation, multiple institutional series have demonstrated the feasibility of fractionated SRS, also known as hypofractionated stereotactic radiation therapy (SRT), in an attempt to minimize risks of toxicity. For three-fraction regimens, data have evaluated 7 to 12 Gy per fraction [19,20]. The best evidence for a SRT regimen is generally felt to be 9 Gy × 3, per an Italian retrospective study showing improved rates of toxicity and improved tumor control with 9 Gy × 3 SRT compared with single fraction SRS [21]. In regards to a 5-fraction regimen, studies have shown that a total dose of 30 or 35 Gy is reasonable, 40 Gy leads to excessive toxicity, but 25 Gy may have worse oncologic outcomes [22,23]. As a general principle, post-operative treatment with SRS uses equivalent doses to lesions being treated definitively.

Is whole brain radiation dead?

One of the major concerns with WBRT was the higher incidence of neurocognitive functional deficits. Despite trials showing lower rates of distant intracranial failure with the addition of WBRT to SRS, the corresponding increases in neurocognitive deficits and lack of OS improvement lead most to defer WBRT favoring quality of life. WBRT is still generally indicated in several scenarios including patients with large volume and/or numerous brain metastases. WBRT is also indicated for treatment of brain metastases from small cell lung cancer, both as treatment for visible disease and for prophylactic cranial irradiation. Therefore, interventions to mitigate the risk of neurocognitive deficits were developed and evaluated. Memantine, a N-methyl-D-aspartic acid receptor blocker, was originally used in Alzheimer's dementia patients, but demonstrated neurocognitive protection compared with placebo in patients undergoing WBRT with acceptable toxicity [24]. An additional method developed in the radiation oncology field to mitigate cognitive deterioration with WBRT includes hippocampal sparing or hippocampal avoidance WBRT (HA-WBRT), which, in a Phase II trial, showed better cognitive and equivalent oncologic outcomes compared with historical controls [25]. Most recently, Phase III data comparing WBRT + memantine to HA-WBRT + memantine was presented and showed that HA-WBRT reduced rates of cognitive function failure compared with WBRT, even after both groups of patients received memantine [26]. The authors recommended consideration of HA-WBRT for any patients with WBRT who have an expected survival of 4 months or greater. The authors also made an exploratory statement, that by multiplying the relative benefits of memantine and HA-WBRT compared with WBRT across both trials, rates of neurocognitive decline may be similar to SRS alone. There is one ongoing

trial comparing WBRT (HA-WBRT will be preferred) to SRS in patients with five to 20 brain metastases, the results of which will be critical to determining whether HA-WBRT and SRS will give similar cognitive outcomes (Clinicaltrials.gov # NCT03075072).

In conclusion, current national guidelines prefer SRS as upfront treatment in patients with 'limited' brain metastases, defined as a single digit number of lesions (with variable cut-offs depending on radiation oncologist preferences) or total volume of lesions. While WBRT still plays a role in patients with extensive intracranial disease or poor prognosis or performance status, HA-WBRT with memantine may be the olive branch WBRT requires to continue to play a role in the treatment of brain metastases. In regard to the future role of radiation therapy for brain metastases, the field will need to continue to evolve with improvements in targeted and immunologic therapies. How medical and radiation oncologists will combine their modalities together in the future are currently being studied and further research, in the arena of combining targeted therapies and immunotherapy with radiation (either SRS or WBRT) for patients with brain metastases, is necessary.

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