Editorial

Radiotherapy for brain metastases: quo vadis?

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The brain is precious real estate. Metastases can wreak havoc by lodging in eloquent areas or by raising intracranial pressure. Fortunately, radiotherapy effectively treats these lesions. Yet the optimal radiotherapy technique has been fiercely debated. In the July 2016 issue of the *Journal of the American Medical Association* (*JAMA*), Brown and colleagues reported a randomized trial that adds clarity to the controversy (1).

At the center of this issue are two different radiotherapy techniques: whole-brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS). WBRT irradiates the entire brain, simultaneously treating both visible metastases and potential unseen microscopic disease. In contrast, SRS targets only the known lesions. Neither approach is thought to be superior for overall survival; instead, the controversy involves balancing intracranial control and side effects (2-4). WBRT decreases the risk of new brain metastases and thus achieves better intracranial control (5-7). However, by exposing a large amount of brain to irradiation, WBRT can cause declines in cognition and quality of life (7-9). SRS minimizes the volume of treated brain, potentially limiting the risk of radiation-induced cognitive toxicity. Yet SRS leaves patients more vulnerable to additional metastases—and these new lesions can impair cognition and quality of life (10-12). So, which is more important: minimizing the amount of irradiated brain or maximizing intracranial control (13)?

Brown and colleagues designed the N0574 trial to help answer this question (1). They randomized 213 patients across 34 North American centers to SRS alone or SRS + WBRT between 2002 and 2013. Eligible patients had 1–3 lesions—each less than 3 cm in diameter—and Eastern Cooperative Oncology Group (ECOG) performance status ≤2. Investigators tested cognition and quality of life before radiotherapy and at 10 time points afterward using a battery of validated instruments. The primary endpoint was cognitive deterioration at 3 months, defined as a decline in any cognitive test ≥1 standard deviation from baseline.

With a median follow-up of 7.2 months, there was no difference in overall survival between the two groups (P=0.92). Intracranial control was better in patients treated with SRS + WBRT compared to SRS alone (3 months: 94% *vs.* 75%, 6 months: 88% *vs.* 65%, 12 months: 85% *vs.* 51%; P<0.001). However, patients receiving WBRT had significantly higher rates of cognitive decline at 3 months (92% *vs.* 64%, P<0.001). Similarly, patients receiving WBRT had significantly worse overall quality of life at 3 months (P=0.001). Functional independence in activities of daily living was not significantly different between the groups (P=0.26).

In summary, the results suggest that SRS alone better preserves cognition and quality of life despite new lesions being more common. This study builds upon and extends previous work. In particular, two smaller randomized trials reported either worsened cognition (7) or quality of life (9) with WBRT. Brown and colleagues now confirm these results, linking declines in cognition to declines in overall quality of life in a single, large trial using established instruments.

Yet the study is not without limitations. For example, the primary endpoint was tested at 3 months. This early time point is relevant given the often limited survival of patients with brain metastases. However, cognitive effects of WBRT are at their worst around this period and may recover somewhat over time (14,15). The study only reported cognitive results at other time points in a small subset of 30 long-term survivors. Additional limitations include lack of blinding to treatment arm and a dropout rate

approaching 25% before the 3-month primary endpoint. Finally, the trial does not guide practice for patients with poor performance status (ECOG >2) (16).

There are also practical questions raised by the study. Many oncologists may not be familiar with intricacies of the Grooved Pegboard Test, the Trail Making Test, and the Hopkins Verbal Learning Test-Revised. What does a 1-standard deviation decline on these instruments look like in the real world? How should physicians explain this concretely to patients? Furthermore, how will a cost-conscious healthcare system (17) view a 12-point quality of life benefit on a 200-point scale—particularly considering the need for more screening and salvage treatment (18)? Indeed, patients on the SRS alone arm required significantly higher rates of salvage radiotherapy or surgery compared to patients treated with WBRT initially (32% *vs.* 8%, P<0.001) (1).

Where do we go from here? The pendulum has been swinging toward SRS alone (19,20), and we expect the N0574 trial will further entrench this approach as a preferred option for many patients with limited metastases. We also anticipate more enthusiasm for SRS in cases with ≥4 metastases; emerging data suggest similar survival and intracranial control for 2–10 lesions (21), and clinicians will likely extrapolate the conclusions of N0574 to these cases.

Yet WBRT will remain a useful tool in the radiation oncologist's arsenal. Patients with many metastases or leptomeningeal disease are well served by WBRT. Following surgical resection of lesions, there is also higher-level evidence supporting adjuvant WBRT (6,22) compared to SRS (23,24)—for now (25). Finally, the cognitive effects of WBRT may be somewhat mitigated by memantine (26) and emerging hippocampal-sparing advanced radiotherapy techniques (27).

For the moment, Brown and colleagues have generated important randomized data that will help guide oncologists and patients. In some situations, the choice of SRS or WBRT is now clearer. For others, it will remain a complex conversation, relying on both the science—and art—of medicine (28).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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