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Commentary

Commentary on effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1-3 brain metastases by Brown *et al*. JAMA 2016;316:401-9

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The team of Brown *et al*. are to be congratulated for the recent publication of a prospective randomized trial that evaluated cognitive function and tumor control in patients with 1–3 brain metastases (primarily lung).[1] This level 1 evidence provided additional confirmatory support regarding the role of stereotactic radiosurgery (SRS) as a primary management option for patients whose cancer has spread to the brain. The confirmation that SRS reduces the early cognitive function decline in cancer patients compared to the use of whole brain radiation therapy (WBRT) provides additional data that has gradually led to the displacement of reflex WBRT as the usual strategy for brain metastatic disease.

This challenge to the existing dogma related to the widespread adoption of fractionated WBRT was brought about by the increasing availability of radiosurgical technologies and the large volume of patients with metastatic brain cancer. In the United States, the estimated number of such patients ranges from 200,000–400,000 patients per year. Prior to SRS, several general philosophic principles guided the use of WBRT administration. First, no other options existed. Second, the average survival of brain metastasis patients was 5–7 months, and hence, the consequence of increasing cognitive impairment related to WBRT had consequences in relatively few patients. Third, WBRT had become a well-taught standard management that had a fixed—some might think enviable—reimbursement, but yet required relatively little work effort to start, provide, and complete.

So what has changed? First, SRS as an alternative strategy designed to selectively inactivate tumors easily recognized by magnetic resonance imaging (MRI) became increasingly available worldwide. Second, physicians and oncologists began to more often request a staging contrast-enhanced MRI as part of the initial screening in patients with newly diagnosed cancer. This led to the early recognition of brain spread even before clinical symptoms emerged, requiring that less toxic brain treatment be developed. Third, increasingly aggressive beneficial systemic cancer therapies—prime examples now being lung cancer, breast cancer, melanoma—have emerged. The recognition of brain spread no longer implied that both the patient and the oncologist could punch the timer of surviving estimated life. This required that quality and quantity of life became twin critical goals.

It is worth noting this important publication randomized 213 patients from 34 institutions and took 11 years to complete and 3 more years to get published in a high impact journal. During this time, the standard management of brain metastasis evolved regardless of the presence of ongoing prospective randomized trials. In

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these 34 institutions, one could imagine that thousands of patients were screened during this interval, but were not entered into the trial. Some surely got WBRT, perhaps many got SRS. We like to rely scientifically on the importance of randomized trials, and of course third party reimbursement insurance entities like to stand behind this methodology, often in order to reduce their medical costs. In the case of brain metastasis, the standard management of brain mets began to evolve more than 20 years ago. We knew it reduced cognitive dysfunction and delayed white matter injury (leukodystrophy). We also knew that application of SRS significantly increased the role of neurosurgeons in the care of this frequent clinical problem. Changing the standard strategy for radiation oncologists proved more difficult, and only recently have revised guidelines been endorsed by their professional organization ASTRO. We are all affected by training bias—radiation oncologists taught that WBRT is the standard, neurosurgeons in training often receiving very little if any meaningful exposure to SRS despite its endorsement as a critical part of neurosurgery training by organized neurosurgery.

As the JAMA editorial takes pain to point out, readers should only take the Brown *et al*. article to indicate that benefit pertains only to patients with 1–3 brain mets,[3] We must stand behind the scientific method! In reality, experienced centers already know that number is unimportant, other factors are.[2] These include age, systemic disease status, primary diagnosis, neurological signs and symptoms graded prognostic assessment (GPA) classification, and most importantly tumor volume, not number. And so the reviewers caution the reader to not take this report beyond the number 3 in the face of ample evidence that these other factors are more important. An ongoing prospective thoroughly scientific clinical trial is evaluating whether more selective WBRT (by reducing dose to the hippocampus) provides adequate control while reducing memory dysfunction. How amazing that the organizers know so little neuroanatomy that they think that dose reduction to the medial temporal lobe will improve cognition while delivering the standard dose to the fornices, the thalamus, and the frontal lobes!

And so the work does and must go on, especially spurred on by major advances in targeted therapies for systemic disease. Do these targeted therapies work for brain spread? At present no one knows but already oncologists are withholding both WBRT and SRS to selected patients as they assess (in phase 1 efforts) whether such agents are potentially effective. Perhaps they will be but for the present we know that SRS is more effective and less toxic than WBRT and should be utilized. If additional disease becomes apparent, SRS can be repeated effectively to achieve local control. The use of WBRT to reduce the need for future SRS cannot be justified. WBRT has a residual indicated role of miliary brain disease and late leptomeningeal spread. If WBRT has already been used, additional WBRT for these indications becomes increasingly toxic.

So based on what we know now, if you or your family member gets metastatic disease in the brain what would you do?

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