Hippocampal-Avoidance Whole-Brain Radiation Therapy: A New Standard for Patients With Brain Metastases?

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The use of whole-brain radiation therapy (WBRT) for brain metastases was first described in the 1950s.¹ Since that time, WBRT has long been considered the treatment of choice, given its wide availability, ease of delivery, and effectiveness in providing palliation for many patients. Numerous phase III trials have also validated its benefit in improving neurologic signs and symptoms for many patients, with median survival times ranging from 3 to 6 months.²⁻⁵ Because of the poor outcomes for most patients with brain metastases, some physicians developed a nihilistic view of brain metastases and considered the routine use of WBRT as an obvious approach, given the limited treatment options. As a result, the potential toxicities resulting from WBRT were largely dismissed. However, with the many advances in neurosurgery, imaging, medical oncology, and radiation oncology, the outcomes for some patients have greatly improved, particularly for those with favorable prognostic factors.^{6,7} With this improvement in outcomes and the higher expectations of patients and physicians, the routine use of WBRT has been highly scrutinized, considering its potential impact on neurocognitive function (NCF) and quality of life (QOL). As a result, the optimal management of brain metastases remains one of the most controversial areas of oncology, even among experts.^{8,9}

Given the improved outcomes for some patients with brain metastases, the impact of WBRT on NCF has recently been an active area of investigation. A comprehensive phase III trial (PCI-P-120-9801) of WBRT versus WBRT plus metaxafin gadolinium, a radiation sensitizer, was performed and included a battery of neurocognitive tests.^{10,11} This study of 401 patients demonstrated that the vast majority of patients with brain metastases (90.5%) had some decline in NCF before initiation of treatment. Neurocognitive test scores and global neurocognitive impairment at baseline were correlated with brain tumor volume and also predicted for survival. Further analysis suggested the adverse impact of tumor progression on NCF was greater than the treatment-related effects of WBRT.¹² In addition, recent neurocognitive data from RTOG (Radiation Therapy Oncology Group) 0214, a phase III randomized trial of observation versus prophylactic cranial irradiation (PCI) for patients with non-small-cell lung cancer, have also suggested a negative impact of PCI.¹³

In addition to the neurocognitive effects, the impact of WBRT on QOL and functional independence has also been investigated. Al-

though phase III trials of stereotactic radiosurgery (SRS) and WBRT for patients with a limited number of brain metastases ($\leq$ four) have shown a significant improvement in local and distant brain control with the addition of WBRT to SRS, the decline in Hopkins Verbal Learning Test-Revised (HVLRT-R) scores at 4 months and lack of improvement in the duration of functional independence have further decreased the advocacy for WBRT.^{14,15} In addition, the health-related QOL (HRQOL) data from the phase III European Organisation for Research and Treatment of Cancer trial of SRS or surgery with or without WBRT have also introduced additional concerns.¹⁶ In this trial, the WBRT arm had a statistically significant detriment in mean global QOL scores at 9 months and also had lower cognitive function at 8 weeks and 1 year; however, this trial did not formally assess patients with a battery of neurocognitive tests and had only a 45% compliance rate at 1 year. On the basis of the results of these studies and the concerns regarding the effects of WBRT on NCF, strategies to mitigate the late effects of WBRT have been actively explored.

Omission of WBRT through the use of SRS is emerging as an attractive treatment approach compared with WBRT, given its inherent advantages, including its multidisciplinary approach, single-session outpatient delivery, minimal recovery time, patient convenience, and more rapid initiation of systemic treatments. Technologic advances in treatment delivery and treatment planning have also facilitated the use of SRS alone as the primary treatment for patients with $\geq$ five lesions. Recently, a prospective observational study of SRS alone in 1,194 patients with one to 10 brain metastases suggested no difference in survival or treatment-related adverse events for patients with two to four and five to 10 lesions.¹⁷ To confirm this and other studies, the North American Gamma Knife Consortium will be performing a prospective randomized trial evaluating NCF of SRS versus WBRT for patients with $\geq$ five metastases (ClinicalTrials.gov NCT01731704).

Another approach to minimize the neurocognitive effects of WBRT uses memantine, an N-methyl-D-aspartate receptor antagonist, as a potential neuroprotector, which has been used for patients with mild to moderate dementia in Alzheimer's disease. RTOG 0614 was a double-blind, placebo-controlled phase III trial of WBRT plus memantine versus WBRT plus placebo.¹⁸ This trial randomly assigned 554 patients to WBRT with or without memantine 10 mg initially then

titrated up to 20 mg per day, continued for 24 weeks. The results demonstrated less decline in delayed recall in the memantine arm at 24 weeks ($P = .059$), although the difference was not statistically significant, possibly because there were only 149 analyzable patients at 24 weeks, resulting in only 35% statistical power. Patients treated with memantine had better cognitive function over time; specifically, memantine reduced the rates of decline in memory, executive function and processing speed, and delayed the time to cognitive decline.

In the article that accompanies this editorial, Gondi et al¹⁹ report the results from the phase III RTOG 0933 trial of hippocampal-avoidance WBRT (HA-WBRT) as another approach to possibly mitigate the neurocognitive effects of WBRT. This trial was based on the hypothesis that injury to the neural stem cells of the subgranular zone of the hippocampal dentate gyrus leads to the early cognitive decline resulting from radiation therapy.²⁰ Using modern radiotherapy planning techniques commonly used for other cancers, the mean radiation dose to the neural stem-cell compartment of the hippocampus was reduced by $\geq 80\%$, while providing adequate coverage and dose homogeneity for the remaining whole brain.²¹ The primary end point of the trial was HVLt-R Delayed Recall (DR) at 4 months using a historical control from the PCI-P-120-9801 study.¹⁰ The eligibility criteria were typical for brain metastasis trials, except that the trial required the brain metastases to be > 5 mm outside the hippocampus, patients had to be proficient in English, and volumetric magnetic resonance imaging (MRI) with ≤ 1.5 -mm slice thickness was required for planning. Specific technology requirements for this trial included MRI fusion to planning brain computed tomography scans ≤ 2.5 -mm slice thickness, test case for intensity-modulated radiation therapy delivery, and quality assurance testing. Specific physician requirements included hippocampal contouring and approval of an intensity-modulated radiation therapy plan (dose to hippocampus, D100% ≤ 9 Gy; maximum dose, ≤ 16 Gy) for HA-WBRT from test cases. To ensure planning and contouring guidelines were followed, central rapid review was conducted in real time. Standardized cognitive assessments, HRQOL assessments (measured by Functional Assessment of Cancer Therapy–Brain subscale and Barthel's index of activities of daily living), and brain MRIs were performed at 2, 4, and 6 months. Of the 100 analyzable patients, 42 had a 7% decline in HVLt-R DR from baseline to 4 months, compared with a 30% mean relative HVLt-R DR decline observed in the historic control, which was statistically significant ($P < .001$). Over time, a significant decline was seen in the HVLt-R DR. Age ≥ 60 years, higher hippocampal D100% dose, and presence of ≥ 1 minor neurologic symptom at baseline predicted greater decline in HVLt-R DR over time. QOL scores remained stable. Median survival was 6.8 months, and only 7.3% of patients died as a result of their brain metastases.

Although RTOG 0933 reached its primary end point as measured by HVLt-R DR, and the results compare favorably with those of the MD Anderson phase III trial of SRS with or without WBRT for one to three brain metastases using HVLt-R DR deterioration at 4 months, RTOG 0933 was a single-arm phase II trial that warrants further validation before its approach is offered to patients. The design and results of the study also underscore some important points about brain metastasis trials. Although overall survival is no longer the primary end point for many current brain metastasis trials, overall survival needs to improve to justify the increased cost of HA-WBRT. The limited survival of patients in this trial (6.8 months *v* historic control of 4.9 months) also makes it difficult to determine the true impact of any

therapy on NCF. Because compliance with QOL and neurocognitive testing continues to drop off with time secondary to many factors, enough patients need to be analyzable to demonstrate a possible benefit. Factors like the number of brain metastases, size of brain metastases, extracranial disease status, and graded prognostic assessment scores influence outcomes; therefore, these factors need to be considered in future trials to determine who may benefit from an innovative treatment approach like HA-WBRT. As in many other cancers, the impact of older age was evident, which emphasizes the need for some biomarker or imaging characteristics to help identify those who are most vulnerable to the late effects of WBRT. Because brain metastases represent a heterogeneous group of diseases with a wide range of outcomes, a “no brainer” approach to treatment is highly discouraged, given the deeper understanding that we now have about brain metastases and the potential impact biologic targets may have on outcomes. Finally, comparative-effectiveness and cost-effectiveness data are important for this and future brain metastasis trials.

To corroborate the results of RTOG 0933, two cooperative group trials will test the hypothesis of whether HA decreases the risk for neurocognitive decline in patients undergoing WBRT. The first study, NRG (National Surgical Adjuvant Breast and Bowel Project, Radiation Therapy Oncology Group, and Gynecologic Oncology Group) CC (Cancer Control) 003, is a randomized phase II/III trial of PCI comparing WBRT versus HA-WBRT in patients with extensive and limited-stage small-cell lung cancer who achieve a complete or partial response to chemotherapy. The second study, NRG-CC001, is a randomized phase III trial of HA-WBRT plus memantine versus WBRT plus memantine. Both these important studies will help establish if HA-WBRT is worth the time, resources, cost, and effort in this era of value-based medicine.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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