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**The Changing Landscape of Whole-Brain Radiation Therapy**

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The Japanese Radiation Oncology Study Group (JROSG) 99-1 investigators conducted a randomized clinical trial (RCT) of stereotactic radiosurgery (SRS) with or without whole-brain radiation therapy (WBRT) in patients with 1 to 4 brain metastases. When originally published in 2006, the data suggested that the inclusion of WBRT improved rates of 12-month brain tumor recurrence and use of salvage brain treatment but not overall survival. In the secondary post hoc analysis in this issue of *JAMA Oncology*, Aoyama and colleagues conclude that treatment with WBRT plus SRS is significantly associated with improved overall survival compared with SRS alone in the cohort limited to non-small-cell lung cancer (NSCLC) with a favorable prognosis (disease-specific Graded Prognostic Assessment 2.5-4.0). In the current era of personalized medicine, this is an appropriate attempt to renew interest in a subset of patients who may derive a survival benefit from WBRT using prospectively gathered data. However, the landscape of managing multiple brain metastases is complex and rapidly changing. The decision to use WBRT revolves around its impact on 3 interrelated components: (1) overall survival, (2) intracranial control, and (3) neurocognitive sequelae.

With respect to overall survival, there are no appropriately powered RCTs to suggest an improvement with WBRT. There are now 3 RCTs that have confirmed a lack of survival benefit, and this consensus has built considerable inertia. There are now 3 RCTs that have confirmed a lack of survival benefit, and this consensus has built considerable inertia. There are now 3 RCTs that have confirmed a lack of survival benefit, and this consensus has built considerable inertia. There are now 3 RCTs that have confirmed a lack of survival benefit, and this consensus has built considerable inertia.
death from other causes. In the present JROSG 99-1 secondary analysis, the small evaluable cohort limits it to being hypothesis generating for NSCLC but not conclusive.

It is well established that WBRT improves total intracranial control, but this role is being challenged by more effective systemic therapies that have intracranial penetration. For example, brain metastases from melanoma were once notoriously difficult to control with either WBRT or systemic therapy. Recent data suggest that ipilimumab and other checkpoint inhibitors may afford an intracranial response rate that is similar to extracranial responses. For BRAF-mutant melanoma, dabrafenib elicits at least a partial response in 50% of patients or more. In NSCLC, EGFR- and ALK-mutant brain metastases, several systemic options have shown favorable results; gefitinib and erlotinib have demonstrated up to 83% intracranial control in never-smokers. In brain metastases from ALK-rearranged NSCLC, alectinib led to an objective intracranial response in 52% and stability in an additional 38%. There are several agents with central nervous system activity for metastatic breast cancer, including capecitabine and various combinations of cyclophosphamide, fluorouracil, methotrexate, and vincristine.

While WBRT is believed to negatively affect neurocognition, measuring its true impact is not straightforward. Robust reporting of neurocognition is notoriously difficult in patients with brain metastases. Many trials have used the Mini-Mental State Examination (MMSE), which is grossly inadequate. In patients receiving WBRT, cognitive function is often confounded by other negative factors such as surgical intervention, systemic therapy, and disease progression. Recently, the RTOG has concluded 2 RCTs that attempt to mitigate the late neurocognitive sequelae of WBRT. The first, RTOG 0614, randomized patients to receive WBRT with memantine (an N-methyl-D-aspartate receptor agonist) vs placebo. Memantine was associated with improved time to cognitive decline, executive function at 16 weeks, and processing speed and delayed recognition at 24 weeks. The other study, RTOG 0933,9 suggested that selective avoidance of the hippocampal neural stem-cell compartment during WBRT for brain metastases is associated with a less severe decline in delayed recall compared with historical controls.

Our recommendation is to view the choice of WBRT not as a binary decision to achieve intracranial control but rather as 1 of several options in a growing armamentarium. It is often the most appropriate therapy in properly selected patients when the threat of disease progression on survival and neurocognition outweighs the toxic effects of therapy. In cases of wild-type EGFR and ALK NSCLC, there are few effective systemic options, and therefore WBRT may have a more prominent role. When WBRT is used, there is encouraging evidence of strategies to mitigate late neurocognitive toxic effects.

**REFERENCES**