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Treatment for Brain Metastases With Stereotactic Radiation vs Hippocampal-Avoidance Whole Brain Radiation: A Randomized Clinical Trial

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Abstract

Importance: Brain metastases are common in patients with cancer, and radiation is often used for management. Among patients with more than 4 brain metastases, the effects of stereotactic radiation targeting only individual tumors, compared with whole brain radiation with hippocampal avoidance, which radiates both tumors and normal brain, remain unknown.

Objective: To determine whether stereotactic radiation improves symptom severity and interference with daily functioning, compared with whole brain radiation with hippocampal avoidance.

Design, setting, and participants: Phase 3, open-label, randomized clinical trial conducted at 4 United States-based centers. Eligible patients had 5 to 20 brain metastases and no prior brain-directed radiation. Enrollment occurred between April 11, 2017, and May 17, 2024 (final follow-up, March 18, 2025).

Intervention: Stereotactic radiation, compared with whole brain radiation with hippocampal avoidance.

Main outcomes and measures: Mean weighted patient-reported symptom severity and interference score change over 6 months postbaseline relative to baseline using the MD Anderson Symptom Inventory-Brain Tumor instrument (scale, 0-10; score change range, -10 to 10; -10 = best). A clinically meaningful Δ was defined as 0.98.

Results: Of 196 randomized patients (mean age, 61 years; 129 [66%] female; 176 [90%] White; median number of brain metastases, 14 [IQR, 11-18]; 49 [25%] with prior neurosurgical resection), 83 (42%) completed the 6-month assessment. For the primary outcome, between baseline and postbaseline assessments through the 6-month follow-up, stereotactic radiation changed the weighted composite MD Anderson Symptom Inventory-Brain Tumor score from 2.69 to 2.37 (mean change, -0.32) and hippocampal-avoidance whole brain radiation changed the score from 2.29 to 3.03 (mean change, 0.74) (mean difference, -1.06 [95% CI, -1.54 to -0.58]; P < .001). Related grade 3-5 adverse events

occurred in 12 patients (12%) in the stereotactic radiation group and 13 patients (13%) in the hippocampal-avoidance whole brain radiation group; grade 1-3 fatigue was most frequent (27 [28%] vs 43 [44%], respectively).

Conclusions and relevance: In patients with 5 to 20 brain metastases, these findings support stereotactic radiation over hippocampal-avoidance whole brain radiation to improve symptoms and interference with daily functioning, key components of quality of life.

Trial registration: ClinicalTrials.gov Identifier: NCT03075072.

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