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Evaluating the Heterogeneity of Hippocampal Avoidant Whole Brain Radiotherapy Treatment Effect: A Secondary Analysis of NRG CC001

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Abstract

Background: Hippocampal avoidant whole brain radiotherapy (HA-WBRT) is the standard of care for patients needing WBRT for brain metastases (BM). This study, using existing data from NRG Oncology CC001 including baseline tumor characteristics and patient-reported MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT) scores, sought to identify subgroups of patients that demonstrate differential neuroprotective treatment response to HA-WBRT.

Methods: An exploratory analysis of NRG CC001, a phase III trial in which 518 patients were randomly assigned to WBRT plus memantine or HA-WBRT plus memantine, was performed. Rates of neurocognitive function failure (NCFF) were estimated between subgroups and stratified by arm. Covariate and subgroup interaction with differential treatment response were calculated.

Results: The benefit of HA-WBRT on decreasing NCFF was seen in patients living \geq 4 months (HR 0.75, 95% CI: 0.58-0.97, P=0.03), whereas patients living < 4 months derived no significant neurocognitive benefit. Significant association between baseline MDASI-BT cognitive factor and treatment response (interaction P=0.03) was identified. Patients with lower MDASI-BT scores (less patient-reported cognitive impairment) derived significantly greater benefit (HR=0.64, 95% CI: 0.48-0.85, P=0.002) compared to those with highest MDASI-BT scores (HR=1.24, 95% CI: 0.76-2.04, P=0.39). Tumor histology also had significant interaction (P=0.01) with treatment response. Primary lung histology patients derived cognitive failure risk reduction (HR=0.58, 95% CI: 0.43-0.77, P=0.0007) from HA-WBRT, in contrast to non-lung primary histology patients (HR=1.15, 95% CI: 0.78-1.50, P=0.48).

Conclusions: Differential neuroprotective response to HA-WBRT was identified in this analysis. Patients surviving \geq 4 months derived benefit from HA-WBRT. There is evidence of heterogeneity of treatment effect for patients with less severe patient-reported cognitive impairment at baseline and those with primary lung histology.

Keywords: Hippocampal avoidance whole brain radiotherapy; brain metastases; heterogeneity of treatment effect; neurocognitive toxicity.

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