Neuro Oncol. 2026 Jan 25:noag008. doi: 10.1093/neuonc/noag008. Online ahead of print.

Cognitive Function, Quality of Life, and Survival Outcomes in Patients with Lower Grade Gliomas Treated with Proton Radiation Therapy: A Phase II study

Jason M Slater [1 2], Nora K Horick [3], Lisa B Nachtigall [4 5], Michael W Parsons [5 6], Nicholas A Tritos [4 5], Alexander T Faje [4 5], Jorg Dietrich [5 7], Barbara Fullerton [8], Janet C Sherman [5 6], William T Curry [5 9], Isabel C Arrillaga-Romany [5 7], Daniel P Cahill [5 9], Brian V Nahed [5 9], Irene S Wang [10], Thomas M Botticello [2], Kevin S Oh [2 5], Beow Y Yeap [3 5], Helen A Shih [2 5]

PMID: 41581137 DOI: 10.1093/neuonc/noag008

Abstract

Background: Lower grade gliomas (LGGs) typically affect younger adults and are associated with long-term survival. Treatment-related toxicities, especially neurocognitive and neuroendocrine effects, are a concern. Proton therapy may reduce these risks by minimizing radiation exposure to healthy brain tissue. This study evaluates the safety and efficacy of proton therapy in LGG patients, focusing on neurocognitive, neuroendocrine, and quality-of-life (QOL) outcomes.

Methods: This single-institution, prospective phase 2 trial enrolled 60 patients with WHO grade 1-2 gliomas or IDH-mutant grade 3 gliomas. Proton therapy was delivered at 54 Gy(RBE) or 59.4 Gy(RBE) by tumor grade. The primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival (OS), neurocognitive and neuroendocrine function, and QOL. Neurocognitive testing occurred at baseline and biennially. QOL was assessed using the FACT-Brain questionnaire. Toxicities were graded per CTCAE v4.0.

Results: With a median follow-up of 7.0 years, 5-year PFS and OS were 79.1% and 85.6%, respectively. PFS was highest in IDH-mutant, 1p/19q co-deleted gliomas (100%) and lowest in IDH-wildtype tumors (62.5%). New neurocognitive deficits occurred in 26% of patients at 5 years. Neuroendocrine dysfunction occurred in 5.3%, with only one case attributed to radiation. QOL declined transiently at 6 months, with 15% showing clinically meaningful decline at 5 years. No late grade 3 toxicities were observed; one case of grade 4 radionecrosis occurred.

Conclusions: Proton therapy for LGG can offer effective disease control with modest long-term toxicity. These findings support its use as a standard radiation modality and highlight the need for comparative trials with photon therapy.

Keywords: Cognition; lower grade glioma; neuroendocrine; proton therapy; quality of life.