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Reply to Letter to the Editor

Short reply to "Proton therapy for newly diagnosed glioblastoma: more room for investigation" by R. Press et al

We appreciate the supportive feedback and shared interpretation of our phase II randomized trial comparing cognitive decline at 6 months following photon therapy vs intensity-modulated radiotherapy (IMRT) in patients with newly diagnosed glioblastoma (GBM).[1] We agree that the impact of insurance reimbursement resulting in major discrepancies in numbers between the intent-to-treat vs treatment-delivered poses a challenge and strategies are needed to account for this additional burden. While ongoing investigations are highly motivated by the potential benefits of proton therapy, randomized trials and future research will need to help identify patients who are most likely to benefit from proton therapy. Although exploration of factors associated with prognosis, including those mentioned by Press et al, may assist in the patient selection for future trials, subset analyses were not pursued due to the limited size of this small signal-seeking phase II trial. However, in our Table 1, all assessed patient demographics, tumor characteristics (eg, tumor location, tumor volume), and baseline cognitive function were balanced between proton therapy vs IMRT arms. We agree in principle and based on extrapolation from whole-brain radiotherapy trials,[2] limiting dose to the hippocampi may reduce radiation-related cognitive decline; however, the high incidence of in-field tumor progression poses a particular challenge of covering the target volume with effective doses of radiation while minimizing normal tissue toxicity.[3] As noted by Press et al, tumor progression may have played a role in the cognitive decline in both arms of the study at 6 months, and suggests that for an aggressive tumor-like GBM, broad deployment of proton therapy for the sake of reducing cognitive toxicity may not be achievable. As mentioned by Press et al, an ongoing trial NRG BN005, (NCT03180502) randomizes patients with isocitrate dehydrogenase (IDH) mutant grade II or III glioma to either IMRT or proton therapy to assess the potential cognitive benefits of proton therapy in this better prognosis population. For GBM, the impact of proton therapy with dose escalation to improve overall survival remains under investigation in NRG BN001 (NCT02179086) and will further explore the effects on cognitive function as a secondary endpoint. For the purpose of minimizing radiation-related toxicity, research to better define the targets of radiation (ie, biologically active gross tumor and microscopic extent) are greatly needed. Better definition of the tumor target will allow better tissue sparing while improving tumor coverage with radiotherapy and potentially enable biologically effective dose escalation. As the feasibility of treatment planning for dosimetric benefits of proton therapy has been demonstrated,[4] thoughtful trial design that will inform patient selection, robust, clinically meaningful quantitative outcomes including cognitive function and biological target definition are required to objectively define evidence-based clinical applications for proton therapy.

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References

1. Brown PD, Chung C, Liu DD, et al. A prospective phase II randomized trial of proton radiotherapy vs intensity-modulated radiotherapy for patients with newly diagnosed glioblastoma. *Neuro Oncol.* 2021;23(8):1337–1347.
2. Brown PD, Gondi V, Pugh S, et al.; for NRG Oncology. Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: phase III Trial NRG Oncology CC001. *J Clin Oncol.* 2020;38(10):1019–1029.
3. Wee CW, Kim KS, Kim CY, Han JH, Kim YJ, Kim IA. Feasibility of hippocampus-sparing VMAT for newly diagnosed glioblastoma treated by chemoradiation: pattern of failure analysis. *Radiat Oncol.* 2020;15(1):98.
4. Harrabi SB, Bougatf N, Mohr A, et al. Dosimetric advantages of proton therapy over conventional radiotherapy with photons in young patients and adults with low-grade glioma. *Strahlenther Onkol.* 2016;192(11):759–769.