VIEWPOINT

Hippocampal-Sparing Radiotherapy for Patients With Glioblastoma and Grade II-III Gliomas

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Brain irradiation is associated with several adverse events. One that is becoming more recognized in recent years is neurocognitive dysfunction (NCD), which has primarily been studied in the context of whole-brain radiotherapy (WBRT) for brain metastases. Thought to be caused by radiation-induced destruction of hippocampal neural stem cell components, NCD can involve a constellation of symptoms related to memory, speech, executive function, and processing speed.

Historically, NCD following WBRT was not well studied because it was thought to be a later-occurring adverse event in a population that generally experienced limited survival. However, contemporary research illustrates that NCD can start manifesting as early as 8 weeks from WBRT completion.[1] Moreover, patients with metastatic cancers now remain alive for considerably longer than those from historical studies, in part owing to better systemic therapies (eg, immunotherapy and other targeted agents), so late adverse events from radiotherapy have become a greater concern. As a result, sparing the hippocampus from radiation is a major area of active investigation in the treatment of patients with brain metastases. After encouraging phase 2 data, the NRG Oncology CC001 phase 3 trial[2] was launched, which compared conventional WBRT with hippocampal-sparing WBRT for brain metastases. The study revealed significantly attenuated NCD at 4 and 6 months in the hippocampal-sparing WBRT arm, along with superior results on patient-reported domains such as memory, speech, cognition, and symptom interference.

Similar to the prognosis of patients with brain metastases, glioblastoma has historically been associated with poor outcomes. However, the most contemporary treatment paradigms have resulted in impressive survival rates.[3] Moreover, molecular stratification of glioblastomas has identified patient subsets who survive considerably longer. Owing to the substantially higher chance of longer-term survival with current treatment paradigms, reducing radiation-induced late adverse effects such as NCD should be a prime concern in efforts to preserve quality of life. By extension, preserving neurocognition may be even more important for patients with grade II-III gliomas, as they tend to survive longer than patients with glioblastoma.

Although theoretically intriguing, a couple of issues must be addressed regarding the consideration of hippocampal-sparing radiotherapy in these patients. Gliomas differ from brain metastases; the likelihood of the target volumes abutting or involving hippocampal or parahippocampal areas is higher, so sparing the hippocampus may be difficult without compromising radiation target dose coverage. There are also limited data[4] on the use of hippocampal-sparing radiotherapy in patients with gliomas, largely owing to the lack of a historical precedent. Both of these limitations are reflected in a glioblastoma clinical practice guideline by the American Society for Radiation Oncology, which states that "given the absence of data for hippocampal sparing in [glioblastoma] patients, the Panel does not recommend compromising target coverage for hippocampus protection."[5(p223)]

Although these remarks may seemingly discourage hippocampal-sparing radiotherapy for patients with gliomas outside the context of a clinical trial, we interpret and address the aforementioned statement in the following ways. First, radiation target dose coverage should take priority. However, more judicious target volumes may better allow for hippocampal sparing; for instance, target delineation per European guidelines and using smaller target expansions allow for smaller overall treatment volumes than the Radiation Therapy Oncology Group definitions.[3] Second, even though target dose coverage should be maintained, hippocampal dose reduction is still feasible in most cases (especially with modern techniques) by simply applying dose constraints during treatment planning. Abutment of the radiation target volumes to the bilateral hippocampus is relatively uncommon, and therefore it is technically possible to spare the contralateral hippocampus even if the ipsilateral structure is grossly involved. Third, one must recognize that "the absence of data" is not synonymous with the absence of a clinical benefit; the combination of a strong rationale, growing clinical interest, and limited data renders this an important topic for scientific inquiry. Moreover, data are not entirely absent, since a small prospective study did suggest an association between hippocampal dosimetry and NCD, although it comprised heterogeneous patients with multiple types of primary brain tumors.[6] Given the emerging randomized evidence supporting hippocampal avoidance in the setting of brain metastases, further study into hippocampal avoidance in the treatment of patients with primary brain tumors represents a critical area for future research.

Additional criticisms of this proposed approach can also be addressed logically. First, some evidence suggests that dosimetric sparing of the hippocampus may be offset by increased dose exposure to other areas of the uninvolved brain. For instance, the increased dose received by certain areas of the normal brain (eg, white matter) during hippocampal-sparing brain irradiation has been implicated in imaging-detected leukoencephalopathy,[7] which could contribute to cognitive dysfunction,[8] although further investigation is necessary into the relative contributions of regional white matter changes to clinical NCD after radiotherapy. Second, the theoretical benefit of hippocampal sparing may be balanced by the

theoretical risk of sparing cancer stem cells. However, smaller retrospective investigations evaluating the prognostic effect of radiation dose to cancer stem cell niches have produced conflicting results.[9]

Regardless of these criticisms, the adoption of hippocampal-sparing radiotherapy for gliomas (even in an exploratory manner) could have substantial benefits for clinical trial design. The only currently active NRG Oncology trial in patients with glioblastoma (NRG BN001; ClinicalTrials.gov Identifier: NCT02179086) does not mandate or suggest hippocampal dose constraints, similar to the CATNON (ClinicalTrials.gov Identifier: NCT00626990) and CODEL (ClinicalTrials.gov Identifier: NCT00887146) studies for grade II-III gliomas. Despite this fact, neurocognitive function is a prominent secondary end point in each of those trials. We posit that nonmandatory amendments to suggest constraining hippocampal doses in such studies could lead to important exploratory analyses that may in turn set the stage for dedicated clinical trials in these patients.

Further study can also shed light on the clinical ramifications of hippocampal dose exposure in the glioma setting. For instance, it is currently unclear whether sparing of the contralateral hippocampus alone (and if so, to what degree) would provide clinically meaningful benefits if the ipsilateral hippocampus were located within the target volume. It also remains largely unknown whether particular types of dose constraints (eg, mean doses, maximum doses, volumetric doses, or a combination thereof) correlate more strongly with NCD in patients with gliomas.[6] The question should arise whether sparing small volumes of the hippocampus from high mean radiation doses is more clinically beneficial than sparing larger volumes from low mean doses. Furthermore, although the hippocampus is directly addressed in this commentary, its relative contribution to neurocognition as compared with other interconnected brain structures (eg, the subventricular zones, white matter, and specific cortical regions) is unknown. The radiosensitivity of many other cortical and subcortical areas remains undercharacterized in the existing literature; further prospective assessment could eventually facilitate evidence-based dose constraints and prioritization during radiation treatment planning.[8,10] Finally, memantine could theoretically provide neuroprotective advantages for patients with gliomas, but this idea is based on extrapolation from the WBRT setting[1] owing to the lack of studies in these patients. Overall, research efforts addressing these unresolved questions are encouraged and may call attention to the use of hippocampal-sparing radiotherapy for patients with gliomas, who continue to experience longer-term survival with therapeutic advances and whose quality of life would benefit from the mitigation of treatment-related adverse events.

ARTICLE INFORMATION

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