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Radiation therapy to the developing brain: advanced technology is ready for robust optimization parameters

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See the article by Tsang et al. in this issue pp. 487–498.

With advancements in therapy, we are in the fortunate position that the majority of pediatric brain tumor patients achieve cure and become long-term survivors of their disease. However, for a significant portion of these survivors, there are long-term cognitive sequelae of therapy that adversely affect school performance, behavior, and the ability to live independently as adults.[1] It is known that radiation therapy significantly affects cognitive performance, especially for young children and for children receiving whole-brain radiation therapy.[2] Strategies to reduce cognitive decline include the omission of craniospinal radiation where appropriate, reduction in craniospinal dosing, and the use of conformal radiation therapy with optimization of dose to reduce radiation to normal structures.

This dose optimization approach is employed with intensity-modulated radiation therapy (IMRT) with photon radiation and with pencil-beam scanning proton therapy. Utilizing inverse planning, very specific constraints of radiation dose can be applied to multiple anatomical structures. In the radiation literature, robust predictors for toxicity exist for structures such as the lung during the treatment of primary lung cancer, where volume of lung receiving 20 Gy (V20) is highly predictive of radiation pneumonitis.[3] However, optimal prioritization of dose reduction to specific brain structures in pediatric brain tumor patients is unknown.

In the article *Intellectual changes after radiation for children with brain tumors: which brain structures are most important?*, Tsang and colleagues retrospectively evaluated associations between cognitive performance and brain structure radiation doses to evaluate radiation dosimetric predictors of cognitive outcome.[4] In their study of 56 pediatric brain tumor patients treated with radiation therapy, right temporal lobe mean dose was strongly associated with decline in full-scale intelligence quotient (FSIQ). Additionally, dose to 50% (D50) of the supratentorial brain was associated with decline in processing speed and working memory while the D50 of the hippocampi was strongly associated with declines in verbal comprehension.

Given the involvement of the hippocampus in neurogenesis, avoidance of the hippocampus during radiation has been proposed as an approach to reduce radiation-induced cognitive decline. In the adult literature, hippocampal avoidance whole-brain radiation therapy (HA-WBRT) has been studied prospectively and demonstrated a significant decrease in cognitive decline compared to historical controls.[5] Whole-brain radiation therapy, as delivered during craniospinal radiation, remains a common treatment for pediatric brain tumors, however, HA-WBRT has never been studied in the setting of curative brain tumors. It is possible that dose sparing in and around the hippocampus could lead to an increased risk of recurrence. If studied in children, a prospective clinical trial would be most appropriate, but there are currently no proposed clinical trials utilizing this approach in children requiring craniospinal irradiation.

In contrast, for tumors treated with conformal radiation, it is very possible to adequately treat the appropriate target volume while limiting radiation to the hippocampi or other pertinent structures through selection of beam angles and plan optimization. The challenge remains in identifying optimal structures for avoidance and dosing constraints. Studies in children have demonstrated strong associations between temporal lobe and hippocampus dose and cognitive decline.[6–8] However, results have been discordant as to the strongest associations (ie, left vs right temporal lobe, left vs right hippocampus). Reasons for such discrepancies include heterogeneous patient populations with different types of exposures, variable neurocognitive follow-up, omission of certain clinical variables, and different measures of neurocognitive testing. Limiting radiation dose can also be achieved in a myriad of ways including modifying mean radiation dose, maximum radiation dose, or through various constraints of volume of structure receiving differing absolute doses of radiation (ie, V40 Gy, V20 Gy). There is an open phase II pediatric low-grade glioma study investigating the feasibility and neurocognitive outcomes of hippocampal avoidance using hippocampal dose constraints of V40 GyRBE <25% and D100 < 5 GyRBE (Clinicaltrials.gov: NCT04065776).

It is important to emphasize that the brain of a child is different from that of an adult. For example, during infancy and childhood, there is progressive advancement of myelination throughout the brain, starting with posterior structures such as the cerebellum and progressing more anteriorly.[9] The last regions to complete myelination are the temporal and frontal lobes. There are also differences within the hippocampus. For example, hippocampal angiogenesis, neuroplasticity, and stem cell pools decline with age.[10] Given that the brain is an evolving dynamic organ, it is important to acquire a deeper biological understanding of the structural changes in the brain and their functional consequences. Although the hippocampus has been identified as an important avoidance structure, there are likely other structures that significantly contribute to learning in a child, such as the corpus callosum and frontal white matter.

We are currently at a place where we have the technology to achieve optimal dosing if only we knew what optimal dosing would look like for a given patient. One challenge lies in developing robust predictive models of cognitive outcome that incorporate important clinical factors such as age, sex, posterior fossa syndrome, hearing loss, and hydrocephalus, among others. Such models may need to be disease-specific in order to homogenize exposures. They should also be designed to provide an aggregated cognitive outcome based on predicted performance in specific domains such as memory, processing speed, attention/inhibition, and executive function. It is important to evaluate a variety of cognitive performance measures because decreasing radiation to the hippocampus through utilization of vertex beams, for example, can lead to increased dose of radiation to the frontal lobes. Another challenge lies in accurately identifying structures critical to cognition in children. Such structures ideally need to be small in order to achieve meaningful dose reduction. Advanced imaging techniques, such as myelin water imaging, may help identify white matter tracts vulnerable to radiation injury.

Despite the challenges ahead, we have made progress in recognizing that the brain is not a homogenous unit. Deeper biological and functional understanding of brain structures and their vulnerability to radiation will allow us to devise treatment plans that will cause the least amount of collateral damage and hopefully mitigate cognitive impairment.

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