Late effects after childhood brain tumor treatment: it's not just about the radiation

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The parents of a child with a brain tumor are inundated with information at diagnosis and follow-up medical visits. Such information overload ranges the gamut of treatment details, medical appointments, as well as the necessary but difficult discussion of treatment late effects. It is presently not possible for oncologists to precisely predict an individual child's risk of late cognitive or psychosocial late effects, leaving parents and families yearning for more details. The work by Willard et al is a small step toward achieving individualized prediction of late toxicities and how they evolve over time, in a diverse cohort of brain tumor patients treated with focal irradiation.¹

In their research, the authors assembled a large cohort of 350 patients with comprehensive follow-up over 5 years. The research team at St Jude Children's Research Hospital is to be congratulated for maintaining very high levels of adherence to serial monitoring—a majority of patients had 5 or more assessments. The use of person-centered analysis is novel to pediatric brain tumor research, but is increasingly common to psychology research.^{2,3} In this type of longitudinal data analysis, a model is created that categorizes a heterogeneous group of subjects into distinct classes, and then describes group-level change over time and factors that distinguish the classes.⁴ This is to be contrasted with variable-centered analyses, where distinct variables (such as age) are correlated using a model (such as regression) to another variable (such as survival). Defining distinct classes, each with its own unique trajectories over time, allows identification of patients who fall into at-risk classes who may benefit from early intervention and allocation of supportive resources in formal education.

Factors that predicted for class membership included age at diagnosis, use of chemotherapy, number of prior surgeries, and presence of a cerebrospinal fluid shunt. The finding that neurocognitive and psychosocial functioning depend not only on the receipt of radiation but also on the combined burden of other anticancer therapies is an important point that is often neglected by patients and oncologists alike. Although part of

an exploratory analysis, this finding adds to a growing body of literature that chemotherapy and surgery (including shunt placement) are not always benign interventions, and can cause long-standing toxicities that are cumulative over time in patients with primary brain tumors^{5–8} as well as those with extracranial malignancies.^{9,10}

The state of pediatric late-effects research needs to move toward a state where the detriment to specific cognitive or psychosocial domains can be quantified on a granular, per-treatment level (Fig. 1). For example, in a patient with an expanding craniopharyngioma cyst, what is the expected late-effects cost of a repeat surgery? of placement of an Ommaya reservoir? How do these interventions compare with fractionated radiotherapy or intracystic therapy? When such knowledge becomes available, then patients and oncologists can make truly informed decisions about the next best course of action when faced with treatment decisions at tumor progression. Such a paradigm to modeling late effects is particularly relevant in children with tumors that have varying treatment options, such as low-grade glioma and craniopharyngioma.

There are other gaps in knowledge that need to be filled. As alluded to by the authors, the optimal balance of minimizing testing burden and comprehensive evaluation of processing speed, attention, working memory, and other executive functions—the domains most sensitive to radiotherapy—has not yet been determined. Moreover, measuring longitudinal change deserves careful consideration of several factors (eg, test reliability, practice effects, test-retest intervals).¹¹ Evaluation of change over time across the lifespan of a child also requires consideration of comparing scores between different tests or different versions of tests, normed on different populations; there is no consensus as to how best to address this issue. The role of ethnic differences and whether the instruments used in such studies are valid in non-Caucasian populations is not clear, and continues to be an area of research in the field of neuropsychology.¹² Notwithstanding these challenges, the finding that a

Fig. 1 Hypothetical profile of longitudinal cognitive performance in 2 subjects with diagnoses at different ages who received brain tumor treatment. The detriment in measured performance over time (red arrows) is broken down into the contributions from chemotherapy, radiation, and surgery.

quadratic model was best suited to some outcomes while linear models were better for others is a useful guide to other late-effects researchers. The implications of a quadratic relationship are particularly important over time, emphasizing the importance of extended longitudinal follow-up. The Childhood Cancer Survivor Study has decades of data but is limited by lack of objective evaluations. In contrast, the St Jude Life study (ClinicalTrials.gov identifier, NCT00760656) has enrolled more than 5000 long-term survivors of childhood cancer as of 2018 with prospective, comprehensive follow-up, including neurocognitive evaluations. With future public availability of the St Jude Life Data Resource comes expanded opportunity for researchers around the world to evaluate and learn more about cognitive and social functioning of cancer survivors over an extended period of time.

As the neuro-oncology community learns more about cognitive and social late effects and how to minimize exposure of children to risk factors, treatments are continually improving with better, non-invasive surgical techniques, targeted systemic therapies, and improved targeting of radiation with proton beam therapy. Much as a patient with unfavorable clinicopathologic characteristics of medulloblastoma may receive intensified radiation and chemotherapy on a study, patients identified as belonging to a category with a trajectory at risk of cognitive or social problems over time—due to the cumulative impact of surgeries, chemotherapy, or radiotherapy—should be the subject of intensified support in school and at home to help them succeed in education and life at large. Our hope is that the combined efforts of improved treatments and targeted, risk-adapted interventions will drive down the cumulative burden of toxicity in childhood brain tumor survivors.

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