PERSPECTIVE

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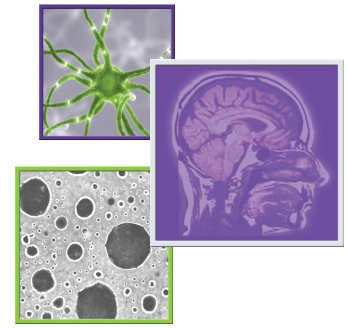

Clinical trials in pediatric neuro-oncology: what is missing and how we can improve

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Practice points

- As a whole, treatment for pediatric brain tumors has greatly improved survival; however, patients can suffer from a myriad of treatment-related morbidities.
- In particular, pediatric patients with low-grade tumors frequently go on to survive their tumor, but carry substantial burden related to prior treatments.
- Quality of life (QoL), decreased neurocognitive ability and neurofunctional impairments are notable concerns for long-term survivors of pediatric brain tumors and these domains should be assessed when determining treatment strategies.
- Historically, clinical trials have not adequately assessed QoL, neurocognition and neurofunctioning. These parameters deserve more attention and should be included as primary or secondary end points of clinical trials.
- The Pediatric Quality of Life scales have been validated in the pediatric population and can effectively assess QoL in pediatric brain tumor patients.
- Validated neurocognitive assessments such as CogState and the NIH Toolbox can play an important role in the evaluation of neurocognition in pediatric brain tumor patients.
- Long-term motor, vision and hearing impairments may occur as a result of tumor and treatment in pediatric brain tumor patients and should be included in pediatric brain tumor clinical trial outcomes.

Brain tumors are the most common solid tumor in childhood, yet outcomes vary dramatically. High-grade gliomas have dismal outcomes with poor survival. By contrast, low-grade gliomas, have high survival rates, but children suffer from morbidity of tumor burden and therapy-associated side effects. In this article, we discuss how current trial designs often miss the opportunity to include end points beyond tumor response and thus fail to offer complete assessments of therapeutic approaches. Quality of life, neurocognitive function and neurofunctional deficits need to be considered when assessing overall success of a therapy. Herein, we identify specific end points that should be included in the interpretation of clinical trial results and accordingly, offer a more comprehensive approach to treatment decision-making.

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Background

In the USA, the number of adult survivors of pediatric brain tumors has been steadily increasing over recent years. The average 5-year survival rate for all-comers of pediatric brain cancers has risen to approximately 73% [1]. However, there is a broad range of survivorship depending on tumor type. Pure germinomas and pilocytic astrocytomas have 5-year survival rates greater than 90%; however, for diffuse intrinsic pontine glioma and other high-grade gliomas, outcomes remain extremely poor [2–5]. The main clinical trial objective for brain tumors with poor prognoses is to improve survival; however, quality of life (QoL) remains an important aspect for these children – especially if median survival is relatively short. Though, the current article is not focusing on explicit recommendations for highly aggressive tumors, QoL measures should still be addressed in trials for this group given the conceivably higher importance of QoL in diseases where one has particularly limited time. Meanwhile, clinical trials designed for tumors with good prognoses are often aimed at prolonging event-free survival or improving cure rates. Effects of therapy though can include both acute and chronic conditions, persisting and/or worsening over the lifetime of the patient [6]. These trials, thus, need to recognize both short- and long-term sequelae of therapies and should include standardized assessments of QoL, neurocognition and neurofunctioning as end points. Broader inclusion of such end points will allow providers and patients to perform more accurate risk-benefit analyses when deciding therapeutic options.

Health-related QoL measures

Health-related quality of life (HRQoL) is a construct based on the impact of health and illness on an individual's QoL, as assessed by dimensions of physical, psychological and social health [7]. Several studies have shown that compared with healthy controls or other cancer survivors, survivors of pediatric brain tumors have the lowest HRQoL [8–10]. Historically, HRQoL measures have rarely been included as clinical trial end points [11–14]; however, this trend is slowly changing. An array of ongoing clinical trials involving tumor types ranging from plexiform neurofibromas (NCT02096471) to medulloblastoma (NCT00085735) to primitive neuroectodermal tumors (PNET4 European Trial) now include HRQoL assessments and neurocognitive outcome measures as end points **(Table 1)**. The PNET4 European Trial is particularly notable in that it is the first international trial to assess QoL in a pediatric brain tumor population and illustrates such evaluations are feasible [15].

The chronicity of a subset of pediatric low-grade gliomas makes them an important example of the need for HRQoL assessments, even during the acute therapy phase. For symptomatic, partially resected or unresectable tumors, the first line approach is traditional chemotherapy. One goal being a delay of potential neurocognitive and vasculopathic effects of radiotherapy, especially in younger children. However, the 5-year progression-free survival for such chemotherapy regimens is less than 50% [17–20]. This leads to many patients being treated on a variety of chemotherapies for years and often at ages where there is high vulnerability to side effects from these therapies [21–24]. For example, children with brain tumors under active therapy are frequently viewed as socially isolated and/or often absent from school by their peers [25]. Cosmetic effects of radiation or chemotherapy treatment (e.g., permanent or temporary alopecia) often occur [26], adding to social burdens and contributing to social isolation. The above scenarios illustrate a likely negative impact on QoL. Unfortunately, vigorous assessments of QoL are largely missing in the literature. Such parameters deserve to be formally investigated when evaluating novel therapeutic approaches and used to assess the effectiveness of an individual treatment strategy.

Several criteria are considered when evaluating the utility of an HRQoL assessment tool. These include: reliability and validity of the measure in the population for which it is used, the option for use of proxy report, development and age appropriate versions, the inclusion of both a generic core (i.e., questions relevant in assessing the HRQoL of any sick child) and disease-specific modules (i.e., questions specific to brain tumor patients), costs of the study and language availability [7,27]. An important note regarding HRQoL measures is that, though the option for parent or proxy reporting is typically necessary, self-report is preferred as parents may view the impact of the disease differently than the child [28]. Additionally, HRQoL measures should not be too generic. For this reason, HRQoL measures should include disease-specific modules to avoid missing clinically significant changes that are disease dependent [12]. This approach might be particularly important

Table 1. Selected list of recent and current clinical trials for pediatric brain tumors that have incorporated nonsurvival-based end points.

Reference or identifier	Tumor type	Intervention	Nonsurvival end points†	Assessment tool
Hummel *et al.* [16]	High-grade glioma and diffuse intrinsic pontine glioma	Bevacizumab	QoL	PedsQL
NCT00085735 (ACNS0331)	Standard-risk medulloblastoma	Radiation and chemotherapy	Neurocognition QoL	ALTE07C1 PedsQL
NCT01096368 (ACNS0831)	Ependymoma	Maintenance chemotherapy following induction chemotherapy and radiation therapy	Neurocognition	ALTE07C1
NCT01602666 (ACNS1123)	Localized primary CNS germinoma	Chemotherapy followed by radiation	Neurocognition	ALTE07C1
NCT02096471	Plexiform neurofibroma	MEK inhibitor PD-0325901	QoL	PedsQL-NF1 Module

†Nonsurvival end points: Quality of life (QoL), neurocognitive or neurological functioning.
QoL: Quality of life.

in clinical trials where detecting even small changes related to an individual disease or treatment is necessary [29]. This type of analysis can be employed as ancillary evidence to support or refute one intervention over another.

There are several cancer-centric assessment tools that satisfy the above criteria [30–37]. The Pediatric Functional Assessment for patients with Brain Cancer (Peds-FACT-Br) is specific to children with brain tumors and English versions are free of charge, making this an attractive assessment tool for HRQoL. Unfortunately, there have been limited studies assessing its validity among different age groups [36]. An alternative is the pediatric QoL (PedsQL) questionnaire. This assessment has the benefits of: a pediatric version; a disease-specific module for brain tumors; the option for proxy reporting; and validation studies supporting its use among different age groups and in patients from countries outside the USA using languages other than English [38]. The PedsQL can be used in children ranging from 2 to 18 years of age and can be administered quickly. In fact, Bhat and others reported administration of the PedsQL took less than 20 min during pediatric neuro-oncology clinic visits, making this assessment a valuable option in the clinical setting [39].

Though many of the HRQoL tools generally assess the same dimensions, there can be variability in the number of items, length of the assessment, availability of proxies and presence of disease-specific modules. Nonetheless, we advocate that clinical trials for pediatric brain tumor therapies employ a universal assessment tool, as the variability of different tools makes it difficult to compare across studies.

Neurocognitive outcomes

Improving survival rates for childhood pediatric brain tumors has also spurred interest in the neurocognitive function of survivors. Long-term neurocognitive sequelae in pediatric brain tumor survivors have been associated with decreased success in education, employment and marital status [40,41]. Neurocognitive outcomes are largely dependent on specific therapy exposures and have been traditionally assessed using measurements of intelligent quotient (IQ) [42]. For example, one meta-analysis including 22 studies found an average decrease in IQ of 12–14 points when comparing patients exposed to radiation therapy to those that were not [42,43]. Beyond IQ, deficits in specific cognitive domains such as attention, working memory and processing speed have been demonstrated in pediatric brain tumor survivors. Risk factors for more severe deficits in attention and working memory include treatment at a younger age, increased time from treatment and higher doses of radiotherapy and chemotherapy [44]. In the pediatric brain tumor population, deficits seen with chemotherapy treatments are less than those seen with radiation. Nonetheless, specific chemotherapies such as methotrexate have previously demonstrated deleterious effects on neurocognition and chemotherapy, as a whole, has been linked to deficits in executive functioning, attention, visual-motor functioning, visual processing and overall IQ in children treated for leukemia [45,46,47]. Interestingly, a study done by Meyers and Hess, found that decreases in cognition preceded tumor progression on imaging in adult patients with brain tumors [48]. This leads to the question of whether similar findings might be present

in pediatric brain tumor patients, and whether these patients are suffering from neurocognitive decline even before we detect clinical tumor changes and modify treatment regimens [49].

Previously, clinical trials have not committed themselves to end points that help us understand neurocognitive changes throughout therapy. Additionally, barriers to neurocognitive assessment, such as lengthy assessment batteries or use of batteries that were not commonly used by psychologists, have resulted in less than 30% compliance with neurocognitive testing [50]. The Children's Oncology Group took a huge step forward in their commitment to the assessment of neurocognition with the development of their nontherapeutic study, "Neuropsychological, social, emotional and behavioral outcomes in children with cancer" (ALTE07C1). As part of ALTE07C1 enrollment, patients complete a neurocognitive evaluation battery at three time points following diagnosis. This evaluation tool takes approximately 1 h to administer and is overseen by a psychologist. To date, several pediatric brain tumor trials including ACNS0331, ACNS0831 and ACNS1123 have incorporated ALTE07C1 as either a primary or secondary outcome [51]. The most notable barrier to ALTE07C1 compliance is the requirement of a psychologist for test administration. Computerized assessment tools, such as CogState or the NIH toolbox, can eliminate this barrier [52,53]. CogState, specifically, has been used in several pediatric populations and is currently being used in The Children's Oncology Group study investigating the role of modafenil in improving neurocognition in children with brain tumors (ACCL0922) [52,54–55]. These tools can be administered by any level of research staff, and though they should not replace formal assessments by psychologists, they undoubtedly make it more feasible to integrate neurocognitive assessments into clinical trial design.

The ALTE07C1 testing battery along with the development of computerized assessment tools are significant steps to bolstering the quantity and quality of data that clinical trials can collect. Providers can then include this data, along with survival and progression outcomes, to make comprehensive treatment decisions.

Neurological impairments

Patients with brain tumors are at risk for acute neurological consequences, both from direct effect of their tumor and as a consequence of therapy. Still, clinical trials often do not include neurological function as a trial end point. Therapeutics contribute to neurological impairments across a variety of domains, including neurosensory hearing loss, motor disturbances, vision impairment and peripheral neuropathies [56]. In a study of 1607 pediatric brain tumor survivors who were compared with sibling controls, 4.6% of cases had one or more persistent motor problems following treatment, but with the greatest deficits occurring during treatment [57]. Motor deficits contribute to decreased physical activity among patients and survivors and as such should be considered when making therapy choices [58,59]. Specifically, platinum-based chemotherapeutic agents and vinca alkaloids are associated with peripheral neuropathy that can persist for years after treatment [60]. Platinum-based agents can also lead to ototoxicity and hearing loss, putting children at risk for reduced learning, speech delay and decreased socioeconomic potential [61]. Compared with sibling controls, survivors of cancer have also shown increased risk for cataracts, glaucoma, legal blindness, double vision and dry eyes [62].

Significant neuroendocrine complications represent another facet of complications reported in childhood brain tumor survivors. One study reported a 43% prevalence of neuroendocrine dysfunction among survivors, with growth hormone deficiency and hypothyroidism being most common [63]. Failure to address neuroendocrine adverse effects can result in poor skeletal growth, problems with weight control and poor neurocognition. Although these adverse effects may occur as a result of the tumor itself, therapy choices can add to this complication risk.

The prevalent neurological impairments seen in survivors of pediatric brain tumors point to the need for earlier and regular monitoring of neurological functioning. Other than motor or sensory dysfunction, ototoxicity, neurocognitive problems and ophthalmological complications are frequently seen in survivors of pediatric brain tumors, but are rarely assessed in a comprehensive manner. Evaluation of neurological functioning, especially vision and motor function, has yet to be regularly included as an end point in clinical trials for pediatric brain tumor patients in a systematic manner. This monitoring should start during treatment with formal evaluations and not be delayed until treatment end, as such information will add another dimension to the evaluation of a specific treatment paradigm.

Conclusion & future perspective

The improved rates of survival among pediatric brain tumors are encouraging but we cannot ignore the serious, life-long morbidities associated with these life-prolonging therapies. We should have concrete data on the ability of survivors to function in their day-to-day lives and within society during and after therapy. To meet these needs, clinical trials should include end points that assess HRQoL, neurocognition and neurological function in a more vigorous and standardized fashion. HRQoL measures should be validated, allow proxy reporting, have age- and development-appropriate versions and offer modules specific for the brain tumor patient population. The Pediatric Quality of Life Inventory (PedsQL) satisfies these criteria. Meanwhile, computerized neurocognitive assessments such as CogState and the NIH toolbox are likely to increase compliance and ability to complete neurocognitive evaluations in any clinical or research setting. Last, formal neurofunctional testing such as vision and motor function testing should start at the beginning of therapy and continue far beyond treatment end. Identifying deficits in these areas will allow providers to better meet the needs of their patients and potentially decrease gaps between them and their peers.

We envision that a more comprehensive picture of the treatment-related effects pediatric brain tumor survivors experience will allow us to develop a composite score system and better standardize therapy comparisons. Composite scoring, though, should be based not only on tumor response and survival, but also HRQoL, neurocognitive sequelae and neurological function. Such a scoring system could better delineate the most effective and least negatively impacting therapy choice for individual patients. The overall goal is the opportunity for patients and clinicians to complete a comprehensive risk-benefit analysis when deciding between therapies. Furthermore, a composite score could extend beyond management and into research, serving as a foundation for improving and designing future therapies.

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