

Clinical Investigation: Pediatric

Longitudinal Investigation of Adaptive Functioning Following Conformal Irradiation for Pediatric Craniopharyngioma and Low-Grade Glioma

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Summary

Conformal irradiation for children with craniopharyngioma and low-grade glioma resulted in relative sparing of intellectual and adaptive functioning.

Although clinical and demographic factors such as gender, age at irradiation, and preirradiation chemotherapy affected functional outcomes, highly focused radiation therapy appears to afford some protection against the cognitive effects of treatment in children with brain tumors.

Purpose: Children treated for brain tumors with conformal radiation therapy experience preserved cognitive outcomes. Early evidence suggests that adaptive functions or independent-living skills may be spared. This longitudinal investigation prospectively examined intellectual and adaptive functioning during the first 5 years following irradiation for childhood craniopharyngioma and low-grade glioma (LGG). The effect of visual impairment on adaptive outcomes was investigated.

Methods and Materials: Children with craniopharyngioma (n=62) and LGG (n=77) were treated using conformal or intensity modulated radiation therapy. The median age was 8.05 years (3.21-17.64 years) and 8.09 years (2.20-19.27 years), respectively. Serial cognitive evaluations including measures of intelligence quotient (IQ) and the Vineland Adaptive Behavior Scales (VABS) were conducted at preirradiation baseline, 6 months after treatment, and annually through 5 years. Five hundred eighty-eight evaluations were completed during the follow-up period.

Results: Baseline assessment revealed no deficits in IQ and VABS indices for children with craniopharyngioma, with significant ($P<.05$) longitudinal decline in VABS Communication and Socialization indices. Clinical factors associated with more rapid decline included females and preirradiation chemotherapy (interferon). The only change in VABS Daily Living Skills correlated with IQ change ($r=0.34$; $P=.01$) in children with craniopharyngioma. Children with LGG performed below population norms ($P<.05$) at baseline on VABS Communication, Daily Living Indices, and the Adaptive Behavior Composite, with significant ($P<.05$) longitudinal decline limited to VABS Communication. Older age at irradiation was a protective factor against longitudinal decline. Severe visual impairment did not independently correlate with poorer adaptive outcomes for either tumor group.

Conclusions: There was relative sparing of postirradiation functional outcomes over time in this sample. Baseline differences in functional abilities before the initiation of irradiation suggested that other factors influence functional outcomes above and beyond the effects of irradiation.
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Introduction

The risks of neurocognitive deficits resulting from central nervous system (CNS) tumors and CNS-directed therapies that include radiation therapy are well established in the pediatric oncology literature (1, 2); however, functional outcomes including intelligence, academic achievement, and adaptive functioning (eg, independent activities of daily living) have been investigated less thoroughly. Declines in global skills such as intellect and academic achievement have prompted concerns about the quality of life in long-term childhood cancer survivors. More sophisticated radiation therapy methods such as conformal radiation therapy (CRT), including intensity modulated radiation therapy, shape the prescribed dose to affected brain tissue, while sparing healthy brain tissue. There is early evidence of improved outcomes for intelligence quotient (IQ), verbal learning ability, and adaptive functioning in young patients with posterior fossa tumors treated with CRT (2, 3). Considering the relationship between radiation dose and cognitive outcomes, the observed improvement should not be surprising.

Less is known about the effects of irradiation on children diagnosed with supratentorial tumors including those with craniopharyngioma and low-grade glioma (LGG). Craniopharyngioma accounts for 1% to 4% of all childhood brain tumors (4). Radiation therapy is commonly required because these tumors arise in proximity to critical areas and are considered unresectable (5). Approximately 62% to 84% of children diagnosed with craniopharyngioma present with visual changes at the time of diagnosis (6). Prediagnosis visual impairment serves as a predictor for persistent posttreatment vision loss (5). Despite significant tumor-related and treatment-related complications, survivorship is excellent (7, 8).

Similar clinical features are observed in children with LGG who require radiation therapy. LGG encompasses a number of unique histological diagnoses and accounts for 30% to 50% of childhood brain tumors (4). Progression-free survival rates are approximately 80% with long-term follow-up (9). Similar to children with craniopharyngioma, patients who require irradiation are generally those with tumors arising in the diencephalon or optic pathways for which radical surgery is contraindicated. Visual impairment and hormone deficiencies are also common at diagnosis and following treatment. Unique to LGG, chemotherapy may effectively delay radiation therapy for 3 to 5 years (10); however, most children with centrally located LGGs will eventually require irradiation.

Adaptive functioning, or the ability to perform the tasks of daily living at an age-appropriate level, has only recently been investigated in brain tumor survivors. Adaptive behaviors represent the practical application of cognitive skills, and reduced adaptive skills when combined with intellectual deficits result in a diagnosis of intellectual disability (11). Although deficits in adaptive and intellectual skills frequently occur in tandem, some types of brain dysfunction may result in preserved intellectual function with poor adaptive skills (eg, attention-deficit/hyperactivity disorder) (12). Small to moderate correlations between adaptive and intellectual skills are typically seen in children (13), and adaptive behaviors with a heavier cognitive load (eg, social skills and communication) tend to correlate more strongly with cognitive assessment measures.

One study of adaptive functioning in ependymoma survivors treated with conformal radiation therapy revealed relative sparing of most adaptive skills, with improvement in some domains over time (3). Communication skills showed the greatest decline over time, suggesting ongoing need for the investigation and

development of preventive measures and interventions. The cognitive sparing may be largely attributed to a relatively less vulnerable posterior fossa tumor location. Considering that children diagnosed with craniopharyngioma and LGG are much older than those diagnosed with ependymoma, we anticipated that older age at treatment would offset the relatively more vulnerable supratentorial sites of irradiation and contribute to adaptive skills.

A specific area of concern for the study of children diagnosed with diencephalon or optic pathway tumors is the influence of visual impairment on adaptive behaviors. In children with visual impairment due to etiologies other than brain tumor, adaptive behavior deficits are observed in a number of areas including daily living skills, written communication, and coping skills (14, 15). Protective factors include increased parental education and level of independent mobility (15). The effects of visual impairment in childhood have exhibited a long-term impact on the quality of life and functional abilities well into adulthood. A review of studies suggests that even mild visual acuity loss can negatively affect an individual's perception of daily living skill performance, tendency toward social interaction, and feelings of loneliness (16). The higher risk of visual impairment in patients diagnosed with craniopharyngioma and LGG suggests a need to investigate the association with adaptive functioning in this pediatric brain tumor population.

In this report, we investigate adaptive functioning in children diagnosed with craniopharyngioma and LGG and the effects of a treatment regimen that included conformal radiation therapy on functional outcomes in a pediatric population, with the anticipation that focused irradiation would result in spared functional outcomes. Accordingly, it was hypothesized that intellectual and adaptive functioning scores would remain stable and in the average range for the group as a whole over time, that the variation in intellectual and adaptive functioning scores would be correlated, and children with severe visual impairment would experience more marked decline in daily living and socialization domains.

Methods and Materials

Participants

Between July 1997 and January 2008, children diagnosed with craniopharyngioma (n=62) and LGG (n=77) were enrolled in a phase 2 clinical trial of conformal radiation therapy for pediatric brain tumors ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT00187226). Parental consent and patient assent were obtained for the neurocognitive assessment portion of this institutional review board-approved investigation. The cohort completed a total of 588 neurocognitive evaluations across the 5-year follow-up period. English was required as the primary language. Given the higher rate of visual impairment in the current study, verbal tests alone were administered when participants were unable to complete visually based measures. During the time interval of the study, only 1 patient was unable to participate because of visual impairment. This patient was blind in both eyes as a result of a stroke suffered at the time of the initial surgery. The longitudinal models presented herein include all participants who completed at least 2 neurocognitive assessments (craniopharyngioma, n=54; LGG, n=68). Patients were no longer followed if they completed the protocol or experienced disease progression. Neurocognitive data were used even when obtained during the same follow-up visit when MRI demonstrated asymptomatic tumor progression.

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