

Children's Oncology Group L991 final study report: Establishing an important benchmark for assessing late effects of trimodality care of pediatric patients treated for high grade gliomas

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As advances are made in children's cancer care, there will be growing numbers of adult survivors of pediatric cancer. In the United States, the number of adult survivors of pediatric cancers is approaching 300,000 (1). According to the National Cancer Institute's Surveillance Epidemiology and End Result's Cancer Statistics Review 1975-2008, the 5 year overall survival rate for children with brain tumors has risen from 58.8 % in 1975-1977 to 75% from 2001-2007 (2). With improved survivorship from childhood cancers, researchers have generated an abundance of literature pertaining to quality of life. A PubMed literature search with the terms "childhood cancer survivors quality of life" yields 420 citations. Studies focus on late effects in nearly every organ system, secondary malignancies, fertility, productivity, socioeconomic impact, and numerous other effects.

In survivors of pediatric brain malignancies, a critical quality of life domain is neurocognitive function. Chemotherapy, surgery and radiation, all of which play a role in treating brain tumors, independently produce long term effects on intellectual functioning. The use of combination therapy increases these effects compared to surgery alone, as has been shown in the matched outcomes of posterior fossa medulloblastoma survivors versus posterior fossa low grade glioma patients (3).

Much of the literature regarding neurocognitive effects of radiation therapy is derived from leukemia and medulloblastoma survivors. Studies have shown that the magnitude of effect correlates with dose, young age, tumor location, and volume of irradiated tissue (4,5). Further,

Armstrong, *et al.* showed that the risk of low grade glioma survivors having an intelligence quotient less than 85 was significantly higher in those receiving chemotherapy in addition to surgery, and there was a trend toward a higher risk in patients who had received radiation (6). Other indirect effects on neurocognitive function have also shown to be important, including interrupted schooling, impact on vision, and neuroendocrine effects (7).

The literature with respect to high grade glioma survivors is less developed, due in part to the poorer long-term prognosis. To this end, the Children's Oncology Group L991 study reported by Sands, *et al.* (8) makes a tremendous contribution to the cognitive expectations of survivors treated for high grade gliomas. CCG-945 compared chemotherapy regimens following surgery in patients who also received radiation therapy. It is the first such study to report long term neuropsychologic, behavioral and quality of life parameters in these patients. Remarkably, it accrued 54 of 79 survivors with a median follow up of greater than 15 years. In addition, the breadth of assessment across various domains of neuropsychology is impressive.

This study's findings are also important. The mean intellectual function of patients who received trimodality therapy was in the low-average range, although half of patients scored as normal or above normal. Not surprisingly, patients treated at an older age or to tumors originating in the spinal cord did better. Visual learning and memory, and psychomotor processing speed were more significantly affected than executive function and verbal learning and memory. Most striking, quality of life with respect to

physical and psychosocial domains was within normal limits for 75% of survivors without significantly discordant findings from siblings and parents. Consistent with data from leukemia survivors, female sex was an independent risk factor for poorer neurocognitive outcomes. Of note, physical quality of life scores were lower in female patients, and female patients were more likely than male patients to have perceived problems with depression by family members. Whether this can be attributed to lower overall neurocognitive function or increased difficulty with social assimilation for female patients is unclear.

There are some important limitations of the study. First, as the authors point out, this was a study of patients who were treated for high grade gliomas, rather than had high grade gliomas. Forty-four percent of survivors from this study were ultimately found to have discordant diagnoses, with the majority having a more favorable histology than high grade glioma. Therefore, the late effects described in this study are as specific brain tumor patients in general as they are to high grade glioma patients in particular. In addition, as the authors point out, the original CCG-945 study did not have a baseline neurocognitive assessment to compare to these late effects results. Without such baseline assessment, one cannot determine whether the impacts of disease are attributable to the disease or the treatments, let alone appropriate effects between treatments.

It is also important to recognize that treatment has continued to evolve in all three domains. Neurosurgery techniques have improved to reduce morbidity, chemotherapy regimens have changed (neither arm of the study would be considered standard therapy now) and radiation techniques have progressed with advancing technology.

The final report of the original study described radiation therapy as follows: "The planned radiation dose was 54 Gy delivered in 30 fractions of 1.8 Gy each over 6 weeks. Allowable energies ranged from Cobalt 60 to 10 mV. Treatments were given with parallel opposed fields, and the dose was calculated at the midplane of the central axis. The prescribed treatment volume was the tumor volume, including edema, as observed on the preoperative imaging study plus a 2-cm margin of apparently normal brain parenchyma (9)."

Radiation treatment planning and delivery has dramatically changed since the time of CCG-945. Prescription doses for high grade gliomas are often closer to 60 Gray rather than 54 Gray. Three dimensional conformal radiotherapy, intensity modulated radiation therapy and proton therapy have sequentially developed since the time of this protocol.

Each is thought to provide equally efficacious cancer treatment with less short term and long term morbidity (10-13). Proton radiotherapy provides a particularly desirable dose profile with virtually no exit dose beyond the target, resulting in much less dose to normal structures. Treatment planning modeling suggests many pediatric patients treated with proton radiation therapy are likely to have lower long term morbidity, including less neurocognitive effects (14). Tumors are now routinely imaged with magnetic resonance imaging that is incorporated into treatment planning to better define the targets as well as protect critical structures such as the hippocampus.

In this paper, Sands *et al.* clearly demonstrate the deleterious neurocognitive effects of multimodality therapy following treatment of high grade gliomas. Their work provides a much needed framework by which health care providers can assess the need for early cognitive rehabilitation as well as more accurately counsel and set expectations of patients and the families of patients undergoing such treatment. Although there is certainly long term morbidity from contemporary therapies, there is ample reason to be hopeful that a similar study of survivors treated today would show less neurocognitive impact of treatment due to advances on in all three modalities. Currently, neurocognitive testing is a component of many national trials of children with brain tumors and we anticipate having this data in the future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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