Impact of Craniospinal Dose, Boost Volume, and Neurologic Complications on Intellectual Outcome in Patients With Medulloblastoma

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Processed as a Rapid Communication manuscript; listen to the podcast by Dr Armstrong at www.jco.org/podcasts

ABSTRACT

Purpose
To examine the impact of radiation (ie, craniospinal irradiation [CSR] dose and boost volume) and complications (ie, hydrocephalus and other neurologic complications, including mutism) on patterns of change in intellectual functioning in medulloblastoma survivors.

Patients and Methods
We conducted a retrospective review of 113 patients treated for medulloblastoma between 1983 and 2011 who were seen for neuropsychological assessment, including longitudinal follow-up of intellectual function. Patients were treated with either standard-dose CSR with a posterior fossa (PF) boost (n = 51), standard-dose CSR plus tumor bed (TB) boost (n = 9), reduced-dose CSR plus PF boost (n = 28), or reduced-dose CSR plus TB boost (n = 23), with or without chemotherapy. A subset of patients developed hydrocephalus that required cerebrospinal fluid (CSF) diversion (n = 54) and/or other neurologic complications (n = 40), more than half of which were postoperative mutism (n = 25). Growth curve analysis was used to determine stability or change in intelligence scores over time.

Results
Patients treated with reduced-dose CSR plus TB boost showed stable intellectual trajectories, whereas patients treated with higher doses and larger boost volumes experienced intellectual declines. Presence of complications was associated with worse intellectual outcome; however, hydrocephalus requiring CSF diversion and mutism differed in their pattern of decline.

Conclusion
These results improve our understanding of factors that impair intellectual outcome in patients treated for medulloblastoma. Lower doses of CSR and smaller boost volumes seem to mitigate intellectual decline. Our findings validate the use of TB boost and suggest PF boost should be reconsidered.

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INTRODUCTION

Medulloblastomas are the most common malignant CNS tumors in childhood, accounting for 50% of all posterior fossa (PF) tumors. Current treatment protocols include surgery, craniospinal irradiation (CSR) with a boost to the tumor site, and chemotherapy—a lifesaving combination that unfortunately contributes to long-term physical, endocrine, and neuropsychological impairments in survivors; > 90% percent of survivors require long-term special education services and have reduced rates of high school graduation and employment. Treatment with CSR after surgical resection of medulloblastoma results in a decline in neuropsychological functioning over time. However, much less is known about the mediating impact of specific radiation doses and boost volumes on changes in intellectual outcome. Neurologic complications can also have deleterious effects on cognitive function. It is crucial to understand the relationship between radiation dose/exposure and complications on the time course of intellectual change after treatment, because this will help to inform current protocol selection as well as the nature and design of future treatment protocols and may identify time windows for the delivery of protective or rehabilitative interventions. To address these critical issues, we examined patterns of change in intellectual...
functioning for patients with medulloblastoma as a function of radiation dose and boost volume and, separately, as a function of neurologic complications. Patients with medulloblastoma are currently stratified into average- or high-risk disease groups. Average-risk disease is defined by a lack of neuraxis dissemination and/or no minimal residual tumor after surgery. Radiation dose de-escalation has been adopted for average-risk patients, because they have more favorable disease outcomes. Typically, these patients are treated with reduced-dose CSR (ie, 23.4 Gy to neuraxis), whereas high-risk patients receive standard-dose CSR (ie, 36 Gy). As new stratification and dose de-escalation strategies are considered in the treatment of medulloblastoma, it is important to establish the effect of different CSR doses and boost volumes on intellectual functioning.

The premise of dose de-escalation is that delivering less radiation to the brain should result in more favorable outcomes. Several cross-sectional studies have suggested treatment with reduced-dose CSR and a PF boost may result in less cognitive impairment than treatment with standard-dose CSR, but this has not always been observed. In fact, impairments were still observed across all studies. Moreover, patients treated with reduced-dose CSR and a PF boost exhibited intellectual declines over time. PF boost volume may be critical in determining outcome. A PF boost delivers substantially more radiation to structures located outside the targeted area, including the cochlea, temporal lobes, and parotid glands, than a boost limited to the tumor bed (TB). To date, one study has suggested preserved intelligence after treatment with reduced-dose CSR and sequential focal concomitant boosts to the PF and TB. However, TB boost is not as yet a part of standard care. A boost to the entire PF is included in at least one treatment arm in most ongoing clinical trials for medulloblastoma, including the ACNS 0331 and SIOP (International Society of Paediatric Oncology)/PNET (Primitive Neuroectodermal Tumor) 4 trials. The SJMB (St Jude Medulloblastoma) trials, where a TB boost has been used exclusively since 1996, are an exception. Of the trials that compare PF with TB boost (eg, ACNS 0331), the focus is on event-free survival rather than cognitive outcome. To our knowledge, our study is the first to directly compare intellectual outcome in patients treated with different clinically relevant CSR dose and boost volume combinations. Our first goal was to examine the rate of change over time in intelligence scores in patients with medulloblastoma as a function of CSR dose and boost volume.

Radiation is not the only insult to the brain with the capacity to affect intellectual functioning. We recently showed that patients with any of the following complications—motor deficits, cranial nerve deficits, mutism, and/or meningitis—had greater impairment in information processing speed than patients without such complications. However, the impact of specific neurologic complications on the evolution of intellectual development remains unknown. Longitudinal studies are ideally suited to monitor this evolution, because they provide information regarding the timing of onset and trajectory of intellectual decline. Although each CNS complication has a unique potential to negatively affect intelligence, hydrocephalus and mutism are potentially the most debilitating and warrant individual attention.

Hydrocephalus is characterized by accumulation of cerebrospinal fluid (CSF) in the CNS ventricular system, resulting in increased intracranial pressure, and has been correlated with lower intellectual functioning and academic skills in survivors of pediatric brain tumors. Most patients present with hydrocephalus, but some require intervention to divert CSF. The impact of hydrocephalus requiring treatment on intelligence has not been studied longitudinally in patients with medulloblastoma. Cerebellar mutism is an acute complication characterized by diminished speech output, linguistic difficulties, and dysarthria, affecting nearly one quarter of all patients with medulloblastoma. Recent research has suggested mutism is associated with poor intellectual outcome. Our second goal was to longitudinally evaluate the impact of hydrocephalus requiring CSF diversion and mutism on intellectual outcome.

To address these goals, we retrospectively evaluated intelligence scores for 14 years for 113 patients diagnosed with medulloblastoma. Information gleaned from this study will improve our understanding of the factors affecting long-term intellectual outcome in patients treated for medulloblastoma.

**Patients**

A total of 113 patients treated for medulloblastoma between August 1983 and January 2011 at the Hospital for Sick Children (Toronto, Ontario, Canada) were seen for neuropsychological assessment. (This represents 53% of all patients with medulloblastoma treated in the same time period; we note our sample represents 79% of all patients treated and available for neuropsychological assessment since systematic monitoring was instituted in 1995. Patients who experienced early relapse and subsequently died (19%) did not undergo follow-up with neuropsychological assessments. Other factors that reduced our evaluation rate included geographic distance and parent refusal of clinical neuropsychology services. Before 1995, resource limitations at our institution did not allow routine assessment of all patients, but there was no systematic bias toward who was or was not referred. Finally, access to neuropsychological evaluation was not related to ability to pay). Patient characteristics, including incidence of hydrocephalus, mutism, and other neurologic complications, are summarized in Table 1. Patients treated with CSR received either standard- (ie, 30.6 to 39.4 Gy) or reduced-dose (ie, 18 to 23.4 Gy) radiation to the entire brain and spine. Because of changes in the treatment protocol used at our institution, patients seen before 2006 received a boost to the entire PF, whereas those seen from 2006 onward were treated on the SJMB 03 protocol and received a focal conformal boost with a margin of 1 cm around the TB; in both cases, total boost volume dose was 45 to 55.4 Gy.

**Materials and Procedures**

There is variability in both the number of times patients in our sample were assessed and the number of years over which they were assessed. All patients were seen after a single course of CSR. (Three patients initially treated without radiation were assessed after recurrence and treatment with CSR.) Assessment details are summarized in Table 1. The Full Scale Intelligence Quotient (FSIQ) is a reliable measure of overall cognitive functioning; the Verbal Comprehension Index (VCI) measures verbal reasoning and conceptualization abilities; the Perceptual Reasoning/Organization Index (PRI) evaluates the ability to interpret and organize visually presented nonverbal information. The Working Memory/Freedom From Distractibility Index (WMI) measures attention abilities, and the Processing Speed Index (PSI) evaluates the speed of graphomotor and mental processing. Research ethics board approval was obtained before data extraction from clinical records.

**Statistical Analyses**

First, analyses were conducted to compare patient and sample cohorts and patients in each treatment arm. Second, mixed-model growth curve analyses were used to determine the stability/change in intelligence scores over time as a function of: one, radiation dose and boost volume while controlling for hydrocephalus requiring CSF diversion and mutism; and two, individual...
Table 1. Patient Characteristics, Medical Variables, and Assessment Details

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<th>Total (N = 113)</th>
<th>Standard-Dose CSR + PF Boost (n = 51)</th>
<th>Standard-Dose CSR + TB Boost (n = 9)</th>
<th>Reduced-Dose CSR + PF Boost (n = 28)</th>
<th>Reduced-Dose CSR + TB Boost (n = 23)</th>
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Hydrocephalus

- Presence at diagnosis
- Requiring CSF diversion
- Third ventriculostomy
- EVD only
- VPS
- ≥ 1 revision
- Mutism§
- Motor deficits¶
- Cranial nerve deficits¶
- Meningitis
- Male sex
- Age at diagnosis, years
  - Mean
  - SD
  - Range
- Time from diagnosis to first assessment, years #
  - Mean
  - SD
  - Range
- Time from diagnosis to last assessment, years
  - Mean
  - SD
  - Range
- No. of assessments
  - Average
  - Range
- Patients seen for a single assessment

**P** values reflect analyses conducted between four radiation treatment groups.

†Chemotherapy protocols and associated agents are as follows: A, Baby POG (cyclophosphamide, vincristine, cisplatin, and etoposide); B, ICE (ifosfamide, carboplatin, and topotecan); C, CCG 9961 (vincristine, lomustine/cyclophosphamide, and cisplatin); D, POG 9631 (etoposide, cisplatin, cyclophosphamide, and vincristine); E, SJMB 03 (vincristine, cisplatin, and cyclophosphamide); F, ACNS 0331 (vincristine, cisplatin, lomustine, and cyclophosphamide); G, 99703 (cisplatin, vincristine, cyclophosphamide, and etoposide); and H, MOPP (mechloroethamine, vincristine, procarbazine, and prednisone). Patients who did not receive chemotherapy were treated before 1999.

‡Data unavailable for one patient.

§Patients classified as having mutism if they had diminished speech output, linguistic difficulties, or dysarthria after surgery.

¶Patients classified as having motor deficits if they had ataxia, dysmetria, or hemiparesis on neurologic examination.

#Seventy-six patients assessed within 12 months from diagnosis.
complications (ie, hydrocephalus, other neurologic complications, and mutism alone). The mixed-model technique can handle unbalanced and missing data, a common phenomenon in clinical samples, and can account for the different times since diagnosis assessments were conducted. Single–time point data were included, because these contribute to overall group means and add stability to the overall modeled function representing change over time; for indices that decline over time, it indicates that the rate of decline from year to year decreases as time increases.) The intercept produced by the model estimates group functioning at the beginning of the modeled time period, which was shortly after tumor resection in our sample. This mixed-model technique was applied using the PROC MIXED procedure in SAS software (version 9.1; SAS Institute, Cary, NC). In mixed-model approaches, single–time point data were included, which was shortly after tumor resection in our sample. This mixed-model technique was applied using the PROC MIXED procedure in SAS software (version 9.1; SAS Institute, Cary, NC). In mixed-model approaches, single–time point data were included, because these contribute to overall group means and add stability to the overall grouped on a single time point, approximately 5 years after diagnosis. For all analyses, results were considered significant if $P < .05$. Finally, a Kaplan-Meier survival plot was generated to display overall survival for patients separated by treatment group. Because our groups did not correspond to specific treatment arms, the plot was not used for statistical analysis.

### RESULTS

**Patient and Sample Cohort Comparisons**

First, we compared patients treated before and after 1995 on factors that might contribute to cognitive risk. The cohorts did not differ in age at diagnosis ($P = .72$), rate of hydrocephalus requiring CSF diversion ($P = .95$), or mutism ($P = .08$). Patients treated before 1995 had a longer average time from diagnosis to first...
assessment (P = .01), and the cohorts differed in CSR treatment received (P = .002).

Second, for patients diagnosed after 1995, we compared the cohort included in our sample with those who were not included. The groups did not differ in age at diagnosis (P = .16) or rate of hydrocephalus requiring CSF diversion (P = .57). Patients not included in our sample had a shorter time from diagnosis to death (P < .001) and more deaths (P < .001). Furthermore, patients not included in our sample had a lower incidence of mutism (P = .01), and more patients received standard-dose CSR plus PF boost (P = .001).

Finally, patients who had their first assessment within 1 year (n = 76) had higher initial FSIQ and greater decline than those who had their first assessment after 1 year post-treatment (n = 37; all P < .02), presumably because patients in the latter group experienced significant declines before their first assessment. Slopes for PRI, PSI, VCI, and WMI did not differ between groups (all P > .05).

**CSR Dose and Boost Volume**

We compared the four radiation treatment groups (summarized in Table 1) while controlling for the most prevalent and potentially debilitating complications: hydrocephalus requiring CSF diversion and mutism. Patients treated with reduced-dose CSR plus TB boost showed stable FSIQ scores (Table 2; Fig 1A). Strikingly, individual patient trajectories in this group indicated that the majority of patients showed stable FSIQ scores (Table 2; Fig 1A). Furthermore, patients not included in our sample had a shorter time from diagnosis to death (P < .001) and more deaths (P < .001). Furthermore, patients not included in our sample had a lower incidence of mutism (P = .01), and more patients received standard-dose CSR plus PF boost (P = .001).

Patients treated with reduced-dose CSR plus TB boost had stable or improved performance over time (Fig 2A), whereas decreases were seen in patients treated with a PF boost (Fig 2B). Patients treated with standard-dose CSR plus PF boost and reduced-dose CSR plus PF boost showed declines of at least 2 FSIQ points per year (all P < .05; Table 2; Fig 1A). Declines were also evident in patients treated with standard-dose CSR plus TB boost, but the small sample size (n = 9) and limited longitudinal data (n = 2) precluded statistical significance (Table 2). The FSIQ slope for patients receiving reduced-dose CSR plus TB boost
differed from those of patients receiving reduced-dose CSR plus PF boost and standard-dose CSR plus PF boost (all \( P < .05 \); Table 2; Fig 1A). Because patients treated with reduced-dose CSR plus TB boost did not show FSIQ declines, whereas all other treatment groups did, and because there were no mean slope differences between patients treated with standard-dose CSR plus PF boost, reduced-dose CSR plus PF boost, and standard-dose CSR plus TB boost, all subsequent analyses compared patients in these three treatment groups considered together (ie, all-other-treatments group) with patients treated with reduced-dose CSR plus TB boost.

Patients treated with reduced-dose CSR plus TB boost showed stable trajectories for all IQ indices (Table 2; Figs 1A to 1E). In contrast, PSI, PRI, WMI, and VCI declined by at least 1.4 points per year over the modeled time period (all \( P < .001 \); Table 2; Fig 1C) for patients in the all-other-treatments group. Finally, the PRI slope differed between the reduced-dose CSR plus TB boost and all-other-treatments groups (\( P = .03 \); Table 2; Figs 1B to 1E).

Furthermore, we examined outcomes between the two groups at the latest time point for which we had maximal intelligence data, approximately 5 years after diagnosis (\( n = 79 \); mean, 5.26 years; standard deviation, 1.82). Patients treated with reduced-dose CSR plus TB boost had higher WMI scores than patients in the all-other-treatments group (\( P = .03 \); Table 2; Figs 1B to 1E).

Neurologic Complications

FSIQ, PSI, PRI, and WMI declined by at least 1.5 points per year regardless of hydrocephalus status (all \( P < .01 \); Table 3). The slope for PRI differed between patients treated for hydrocephalus and those who did not require treatment (\( P = .02 \); Table 3). Furthermore, VCI declined by 4.2 points per year for patients with hydrocephalus requiring treatment (\( P = .001 \)). Patients who were treated for hydrocephalus did not have lower intelligence intercepts than patient not requiring treatment for hydrocephalus but showed lower mean FSIQ, PRI, WMI, and VCI scores across the modeled time period (all \( P < .05 \); Table 3).

Patients who experienced neurologic complications—motor deficits, cranial nerve deficits, meningitis, or mutism—had lower intercepts (all \( P < .005 \)) and lower means (all \( P < .005 \)) on all IQ indices compared with patients without complications. Likewise, when mutism was considered alone, patients with mutism had lower intercepts for FSIQ, PSI, WMI, and VCI (all \( P < .05 \); Table 3) and lower means for all IQ indices (all \( P < .05 \); Table 3) than patients without mutism. Notably, FSIQ, PSI, PRI, and WMI declined by at least 2.2 points per year in patients with and without mutism (all \( P < .005 \)), and mean slope did not differ for any IQ index (Table 3).

Survival Plot

Kaplan-Meier survival plot revealed that patients treated with reduced-dose CSR plus TB boost did not show worse survival than patients in the all-other-treatments group (Fig 3).

**DISCUSSION**

We compared patterns of change in intellectual functioning for patients treated with different clinically relevant CSR dose and boost volume combinations and for patients with neurologic complications. Our findings demonstrate that patients treated with reduced-dose CSR plus TB boost experience stable intelligence trajectories and that both hydrocephalus requiring CSF diversion and mutism are associated with poor intellectual functioning but show distinctive trajectories of decline.
## Table 3. Neurologic Complications

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Abbreviations: FSIQ, Full Scale Intelligence Quotient; PRI, Perceptual Reasoning/Organization Index; PSI, Processing Speed Index; VCI, Verbal Comprehension Index; WMI, Working Memory/Freedom From Distractibility Index.

*Refers to hydrocephalus requiring treatment to divert cerebrospinal fluid.
dysfunctional. The time course of intellectual impairment we observed suggests that hydrocephalus produces a sustained injury. Additionally, shunting procedures cause direct structural damage and increase the risk of postoperative complications. Thus, patients with hydrocephalus may receive several cumulative insults to the brain, rendering them susceptible to continued intellectual impairment. Patients with hydrocephalus may therefore benefit from increased neuropsychological monitoring and rehabilitation strategies designed to help compensate for an ongoing injury.

The underlying cause of mutism is largely unknown, but mutism has been most commonly observed in children with large, aggressive tumors that require radical resection. The time course of intellectual decline and profile of patients who developed mutism in our sample suggest the impairment results from acute effects of the tumor and surgery. Thus, patients with mutism may benefit from vigilant neuropsychological monitoring immediately after treatment and rehabilitation strategies focused on acute injury recovery.

Our findings should be considered in light of some limitations. First, the use of different test versions to assess intelligence over time is not optimal; however, we were limited to the versions available in the patient records, and these changed with time. Furthermore, our sample size was smaller for certain IQ indices because of lack of availability from some measures (eg, WASI). Second, it would have been preferable to include cognitive outcome measures other than IQ. Future studies seeking to characterize the cognitive domains most compromised by treatment and complications would benefit from using specific measures of neuropsychological function. Third, chemotherapy protocols, surgical practice, and supportive care have changed over the time period studied and may have been confounding factors in outcome. Finally, our finding that patients treated with reduced-dose CSR plus TB boost showed stable intelligence after treatment should be interpreted with caution, because their follow-up time was shorter than that for patients treated with a PF boost. Declines may emerge over a longer time period not captured in our investigation.

With biologically based strategies presently well positioned to guide treatment de-escalation in medulloblastoma, our findings are timely. For instance, patients with WNT medulloblastoma have excellent disease prognosis and are ideal candidates for therapy de-escalation. We have demonstrated that lower CSR dose and smaller boost volume lead to stable intellectual trajectories without seeming to worsen survival. As a result, we suggest that PF boost be reconsidered in the treatment of medulloblastoma. We also showed that hydrocephalus requiring CSF diversion and mutism worsen intellectual outcome but show different trajectories. Establishing the impact of specific neurologic complications and delineating the time course of impairment are essential to identifying time windows for the delivery of protective or rehabilitative intervention. Our findings improve our understanding of the factors that impair intellectual outcome in patients with medulloblastoma and stress the importance of longitudinal studies in the development of time-sensitive intervention strategies.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

The author(s) indicated no potential conflicts of interest.

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