editorials

# When Can We Retire 3,600 cGy Craniospinal Irradiation in Medulloblastoma?

Paul Graham Fisher, MD[1]

Nearly 100 years ago, Bailey and Cushing[1] described medulloblastoma as a malignant cancer of the cerebellum, confined largely to childhood. They suggested that the best treatment consists of a suboccipital decompression, followed by persistent roentgen-ray therapy. Just a quarter century later, Paterson and Farr[2] in Manchester, England, did indeed demonstrate that irradiation of the entire neuraxis allowed 11 of 17 patients with medulloblastoma to be alive 3 years later. In the decades thereafter, others confirmed that craniospinal irradiation (CSI) of 3,000 cGy to 5,000 cGy for children with medulloblastoma could result in 5-year survival rates of 53%-73%.[3,4] By the 1970s, SEER data from the Connecticut Brain Tumor Registry (1968-1979) projected that children with medulloblastoma treated at a university center experienced a 5-year overall survival of 74%.[5]

In the late 1980s, Packer et al[6] added chemotherapy for children with poor-risk medulloblastoma, defined by age younger than 5 years, incomplete resection, metastasis, or cellular differentiation. Among 26 children who were treated with 2,400 to 3,600 cGy CSI plus a local tumor boost to 5,400 cGy, followed by eight cycles of lomustine, cisplatin, and vincristine, 2-year survival was 96%. Soon thereafter in low-risk medulloblastoma, defined then by age 3-10 years without metastasis, Packer et al demonstrated 5-year survival to be 79% in 65 children treated after resection with 2,340 cGy of CSI and a boost to the posterior fossa totaling 5,580 cGy; adjuvant vincristine was administered during radiotherapy, and lomustine, vincristine, and cisplatin were administered after radiation.[7] Since that time, our therapeutic paradigm has been largely unchanged: Children with high-risk medulloblastoma, that is, incompletely resected or metastatic at presentation, receive 3,600 cGy CSI plus a boost to the tumor volume, and others receive 2,340 cGy CSI, or rarely less, plus a boost. All children then receive adjuvant chemotherapy. Most recent data from the Central Brain Tumor Registry of the United States (CBTRUS) report that the current 5-year survival for all patients with medulloblastoma diagnosed from age 0 to 19 years is just less than 75%.[8]

How are our children diagnosed with medulloblastoma faring as we near the 100th anniversary of medulloblastoma as an entity? In this issue, Coltin et al[9] have provided a rather sobering progress report from a meticulously conducted, population-based case-control study of all children diagnosed specifically with medulloblastoma in Ontario province between 1987 and 2015 and surviving at least 5 years, compared with five general Ontario population controls without cancer, matched on birth year and month, sex, and geographic area of residence. Of 389 children diagnosed with medulloblastoma during the study period, 230 (60%) met inclusion criteria; 148 had died before 5 years. Two thirds of the survivors were females. Among the medulloblastoma survivors, more than 80% had undergone CSI, and almost a quarter had received cisplatin chemotherapy. By 5 years from diagnosis, 18.7% of survivors were hypertensive. During the follow-up period, 11.3% of the patients experienced cancer-related deaths. At 15 years from diagnosis, 4.8% of survivors had suffered strokes, 24.9% had hearing loss requiring an amplification device, and 44.5% required disability support. Female survivors were 80% significantly less likely to deliver a liveborn child compared with controls. These survivorship outcomes are dismal. From the original 389 children diagnosed with medulloblastoma, about 54% of children were 15-year survivors, and about half of those survivors required disability support or homecare services while 61.3% obtained outpatient mental health services. Put another way, perhaps up to a quarter, and possibly less, of those children originally diagnosed with medulloblastoma were 15-year survivors and not disabled, yet still subject to hypertension, stroke, hearing loss, mental health disorders, or infertility.

The data from Coltin et al indicate that our progress battling medulloblastoma may not be going as well as the oncology community wants to believe. Survival rates are statistically but not overwhelmingly better than a few decades ago. For all children with medulloblastoma combined, we still have a roughly 70+ % 5-year survival from CBTRUS data capturing patients diagnosed from 2001 to 2018.[8] The Coltin study reports children diagnosed from 1987 to 2015, who are closely contemporaneous to those captured by CBTRUS. Moreover, disability support in the study from Coltin et al did not differ by treatment era, and their methods likely underestimated disability, as they acknowledge. It is fair to state today that very few children with medulloblastoma are cured without significant neurodevelopmental and neurologic sequelae. We must recognize that their quality of life is highly compromised forever.

ASSOCIATED CONTENT

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## THE TAKEAWAY

In the article that accompanies this editorial, Coltin et al[9] report devastating long-term outcomes in most children treated for medulloblastoma. Their clinical findings question current therapeutic paradigms and indicate a need to avoid high-dose craniospinal irradiation.

Almost 20 years ago, in *Journal of Clinical Oncology* I wrote with others "we must immediately find a way to accomplish this (biologic risk stratification in medulloblastoma) if we hope to make any further advances toward curing more children of this cancer and reducing its often devastating treatment sequelae. The real time is now."[10] By 2011 in the *Journal*, Cho et al[11] and Northcott et al[12] published landmark articles that led to today's four molecular subgroups of medulloblastoma: Wnt, Shh, group 3, and group 4.[13] Indeed, our biologic understanding has by far surpassed our clinical attempts to advance survival and limit neurotoxicity in this cancer. Over the past 20 years through the Children's Oncology Group clinical trials ACNS0331 and ACNS0332, we have invested considerable resources and children's lives to conclude only that 1,800 cGy is not noninferior to 2,340 cGy CSI in all children age 3 to 7 years with average-risk medulloblastoma[14] and to demonstrate that adjuvant isotretinoin does not increase long-term event-free survival for those with high-risk medulloblastoma.[15]

Prompted by the study from Coltin et al, we should now reexamine why any child with medulloblastoma is receiving high-dose 3,600 cGy CSI. Among their study patients who received CSI, 46.1% received 3,600 to 3,900 cGy and 35.2% low-dose 2,340 Gy.[9] With just a bit of deduction, since two thirds of the study's survivors were female, it is highly likely that a disproportionate percentage of long-term survivors had medulloblastomas that were in the Wnt and Shh molecular subgroups with intermediate to good or sometimes very good prognosis, and some were likely overtreated with 3,600 to 3,900 Gy of CSI. Supplemental data from the study also reveal that high-dose CSI led to significantly higher risks of both hospitalization and disability.[9] Beyond this study, there have been some past attempts to reduce CSI to 1,800 cGy CSI[14,16,17] along with the current Children's Oncology Group trial ACNS1422 limited to nonmetastatic, Wnt-driven medulloblastoma, but have we challenged our CSI paradigms enough in patients with medulloblastoma?

Why does our current treatment paradigm for high-risk remain a backbone of 3,600 cGy CSI? Other than historical tradition dating to the 1950s, what is the evidence that 3,600 cGy results in improved survival compared with 2,340 cGy in high-risk medulloblastoma? Clinicians often say with tautological reasoning that children with high-risk medulloblastoma require 3,600 CSI because they are high risk, endorsing that 3,600 cGy simply seems logically better than 2,340 cGy. Data to support this thinking, which predates the current molecular era for medulloblastoma, are lacking. Furthermore, is residual tumor after resection even a valid marker of high-risk? Probably not.[18] Even if 3,600 cGy CSI does result in overall survival that is a few percentage points higher than 2,340 cGy, is that small gain worth the devastating sequelae? Almost every child treated with 3,600 cGy CSI takes on very striking neurodevelopmental and neurologic sequalae, as Coltin et al have reported. Do parents, who are vulnerable to emotion and fear at diagnosis of their child with medulloblastoma, truly understand the long-term neurodevelopmental and neurologic sequelae of 3,600 cGy CSI should their child survive this cancer? After 30 years of neuro-oncology practice, I do not think so anymore. Is it time to retire 3,600 Gy CSI in medulloblastoma?

As we approach 100 years since the description of medulloblastoma, we are at a crossroads, I think. The pediatric neuro-oncology community is no longer in a position to invest 20 years in another clinical trial. To the point, we must rapidly consider strategies to lower CSI, especially 3,600 cGy. We need to be more clever. Simply put, we need to consider novel study designs and even machine learning simulations that take less time, to develop rapidly new strategies to reduce CSI. We must leverage biologic stratification even more. We need to be bolder right now. Let us retire 3,600 cGy soon for a start. Even 2,340 cGy CSI can have devastating long-term effects, but a lower dose is better than 3,600 cGy. We must stratify risk such that only the smallest number of children are subjected to the higher doses. I am optimistic that the pediatric brain tumor community can do this quickly. Our patients with newly diagnosed medulloblastoma are in our clinics today, and the real time to help them is still now.


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## AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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