# Omission of Upfront Craniospinal Irradiation in Patients with Low-Risk WNT-Pathway Medulloblastoma Is Associated with Unacceptably High Risk of Neuraxial Failure

Tejpal Gupta[1], Shizan Pervez[1], Archya Dasgupta[1], Abhishek Chatterjee[1], Sridhar Epari[2], Girish Chinnaswamy[3], and Rakesh Jalali[1]

## ABSTRACT

**Purpose:** Medulloblastoma is a heterogenous disease comprising four molecular subgroups: wingless (WNT), sonic hedgehog (SHH), group 3, and group 4, respectively. Excellent long-term outcomes have prompted deintensification of therapy in WNT-pathway medulloblastoma. We assessed the safety of avoiding upfront craniospinal irradiation (CSI) in children with low-risk WNT-pathway medulloblastoma.

**Patients and Methods:** Children with low-risk WNT-pathway medulloblastoma were treated with postoperative focal conformal radiotherapy, avoiding upfront CSI, followed by six cycles of adjuvant systemic chemotherapy. A group-sequential design (triangular test) with predefined stopping rules if the rate of relapse exceeded 15% at 2 years was incorporated to ensure the safety of study participants.

**Results:** 7 children with low-risk WNT-pathway medulloblastoma were accrued after written informed consent/assent and treated as per protocol. One child died of neutropenic sepsis and multiorgan dysfunction during chemotherapy. Three children were detected with neuraxial failure (supratentorial brain and/or spine) on surveillance neuro-imaging within 2 years from index diagnosis, leading to premature study termination. At relapse, children were treated with salvage CSI plus boost irradiation of metastatic deposits followed by second-line chemotherapy. Two of them continue to be in remission (32 and 26 months after first relapse), while one child developed a second relapse, necessitating further systemic chemotherapy and craniospinal reirradiation, resulting in excellent clinico-radiologic response. At a median follow-up of 42 months, the 2-year Kaplan–Meier estimates of event-free survival, recurrence-free survival, and overall survival were 42.9%, 50%, and 85.7% respectively.

**Conclusions:** Omission of upfront CSI in low-risk WNT-pathway medulloblastoma is associated with an unacceptably high risk of neuraxial failure.

*See related commentary by Remke and Ramaswamy, p. 4161*

## Introduction

Medulloblastoma is the commonest primary malignant tumor of the central nervous system (CNS) in children (1). Novel biological insights gained during the last decade have improved our fundamental understanding of various pediatric barin tumors including medulloblastoma with potential to transform therapy (2, 3). It is now widely accepted that medulloblastoma is a heterogeneous disease (4) comprising four distinct molecular subgroups–wingless (WNT), sonic hedgehog (SHH), group 3, and group 4 respectively with unique developmental origins, distinct molecular genetics, diverse phenotypes, and varying clinical behavior (4, 5) which has also been incorporated in the revised World Health Organization (WHO) classification (6). WNT-pathway medulloblastoma is associated with the best outcomes, while group 3 tumors generally have the worst survival (3, 7).

The contemporary standard-of-care for noninfantile medulloblastoma comprises maximal safe resection followed by risk-stratified postoperative radiotherapy and adjuvant systemic chemotherapy (37). Traditionally, children (≥3 years of age) with good surgical resection (residual tumor <1.5 $cm^2$) and no evidence of leptomeningeal metastases (M0) were classified as average-risk disease (8) with more than 80% long-term survival (9); while younger age (<3 years), large residue (≥1.5 $cm^2$), and presence of leptomeningeal metastases (M+ disease) either alone or in combination were considered high-risk features (8) yielding much worse 5-year survival (30%–60%) despite aggressive multi-modality therapy (10). This traditional risk-stratification has been further refined by incorporating molecular/genetic information in the molecular era (11). Given the high propensity of neuraxial spread via cerebrospinal fluid (CSF) pathways, craniospinal irradiation (CSI) to a dose of 23.4 to 36 Gy plus posterior fossa/tumor-bed boost (18–30.6 Gy) for total primary-site dose of 54 Gy remains the cornerstone of adjuvant radiotherapy in medulloblastoma (8–10). Such treatment however, results in significant dose-dependent long-term toxicity (12), particularly in children, as younger age is associated with higher therapy-related late-effects. Herein, we report early

[1]Department of Radiation Oncology, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, Maharashtra, India. [2]Department of Pathology, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, Maharashtra, India. [3]Pediatric Oncology, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, Maharashtra, India.

Clinical trial registration ID: CTRI/2017/12/010767

Prior presentation: Initial results were presented by T. Gupta at the 6th Biennial SNO Pediatric Neuro-Oncology Research Conference in June 2021 (virtual).

**Corresponding Author:** Tejpal Gupta, Radiation Oncology, ACTREC, Tata Memorial Centre, HBNI, Kharghar, Navi Mumbai, Maharashtra 410210, India. Phone: 9122-2740-5510; Fax: 9122-2740-5061; E-mail: tejpalgupta@rediffmail.com

Clin Cancer Res 2022;28:4180–5

**doi:** 10.1158/1078-0432.CCR-22-0758

## Translational Relevance

Medulloblastoma is a heterogenous disease comprising four molecular subgroups—wingless (WNT), sonic hedgehog (SHH), group 3, and group 4—with distinct molecular genetics and varying prognosis. Excellent long-term outcomes (5-year survival >90%) in WNT-pathway tumors has prompted attempts at treatment deintensification in clinical trials to reduce late treatment-related toxicity without compromising survival. We assessed the safety of avoiding upfront craniospinal irradiation in low-risk WNT-pathway medulloblastoma through a single-arm prospective study with predefined stopping rules. Seven children with low-risk WNT-pathway medulloblastoma were treated with focal conformal radiotherapy (54 Gy/30 fractions) followed by six cycles of standard adjuvant systemic chemotherapy. However, three children were detected with early neuraxial failure on surveillance neuro-imaging within 2 years of index diagnosis, leading to premature termination of the study. Findings from our study should guide researchers and clinicians to plan controlled deintensification of therapy even in low-risk WNT-pathway medulloblastoma in future prospective clinical trials.

results of our prospective study of omission of upfront CSI in WNT-pathway medulloblastoma.

## Patients and Methods

### Patient eligibility

All patients with newly-diagnosed WNT-pathway medulloblastoma registered at a single tertiary-care comprehensive cancer center were screened for eligibility. Children with low-risk WNT-pathway medulloblastoma defined as aged between 3 to 16 years at diagnosis, with residual tumor less than 1.5 $cm^2$ on postoperative MRI, and no evidence of leptomeningeal metastases (M0 status) on rigorous neuraxial staging (spinal MRI and CSF cytology) were included. All imaging was interpreted by dedicated neuro-radiologists and suspicious findings, if any, were discussed in a multi-disciplinary joint clinic for decision-making. Adjuvant radiotherapy was scheduled to start within 6 weeks of surgery. Molecular subgroup assignment was based on a validated assay combining differential expression of 12 protein-coding genes and 9 microRNAs (13). Molecular diagnosis of WNT-pathway medulloblastoma was further confirmed in all 7 included patients through supplementary orthogonal techniques such as *CTNNB1* mutation (Sanger sequencing) and/or monosomy 6 (FISH) as appropriate in accordance with international recommendations (11). The study was approved by Institutional Ethics Committee that functions in accordance with the Declaration of Helsinki and is registered with the Clinical Trials Registry of India (CTRI/2017/12/010767). Written informed consent (from parents) and assent (from children as applicable) was obtained prior to study participation. The sponsors had no role in the study design, conduct, data collection, statistical analysis, interpretation, or reporting of results.

### Treatment protocol

Following surgery, focal radiotherapy was delivered to the tumor-bed only (54 Gy/30 fractions over 6 weeks) using image-guided intensity modulated radiation therapy (IMRT). Resection cavity and residual tumor, if any, was delineated as initial clinical target volume (CTV). An isotropic margin of 15 to 20 mm was applied to initial CTV and edited away from natural anatomic barriers (bone, tentorium) to generate final CTV. An isometric margin of 3 mm was applied to final CTV to create planning target volume (PTV) to account for daily set-up errors. 4 weeks later, patients were started on standard adjuvant systemic chemotherapy comprising six cycles of cisplatin (75 $mg/m^2$ intravenously on day 1 in alternate cycles 2, 4, 6); cyclophosphamide (1,000 $mg/m^2$ intravenously on days 1–2 in cycles 1, 3, 5 and days 2–3 in cycles 2, 4, 6); and vincristine (1.5 $mg/m^2$ i.v. on days 1 and 8 in all six cycles) administered at 4-weekly intervals with requisite dose modifications as appropriate. Following adjuvant therapy, patients were periodically followed up clinico-radiologically. All children underwent neuro-cognitive, endocrine, and audiologic assessments at baseline and periodically on follow-up.

### Statistical considerations

The study was designed according to group-sequential methods specifically the triangular test (14) with an early stopping rule if the rate of relapse exceeded 15% at 2 years to ensure safety of participants. Triangular test is one way of analyzing group-sequential trials and uses straight line stopping boundaries. It involves analyzing the data as they accumulate, with points being plotted relative to a triangular region and stopping when the upper or lower boundary of the region is crossed. By using *S* plus module of sequence trial analysis software we got a total sample size of 60 patients for our study. Sequential analyses were planned after every 15 assessable patients (minimum 12-month follow-up) with decision to stop prematurely if 5 of 15, 6 of 30, 7 of 45, or 8 of 60 assessable patients relapsed. Any documented relapse (local and/or neuraxial) on surveillance neuro-imaging was defined as event for recurrence-free survival (RFS) while death from any cause was considered as event for overall survival (OS). Any recurrence or mortality (whichever occurred earlier) was counted as event for event-free survival (EFS). All time-to-event outcomes were calculated from date of surgery till the defined event of interest (with December 31, 2021 as cut-off date) using Kaplan–Meier methods and reported as survival probabilities at 2 years with 95% confidence intervals (CI). All statistical analyses was done on R$^{TM}$ Version 4.03 (R Corporation).

### Data availability statement

All data generated in this study are available within the article itself; additional individual patient data can be made available on reasonable request without any patient-identifying information.

### Data access, responsibility, and analysis

The principal investigator and corresponding author (T. Gupta) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## Results

Between June 2017 to January 2019, 17 patients with newly-diagnosed WNT-pathway medulloblastoma were screened for eligibility, 10 of whom were deemed screen failures due to older age (>16 years, $n = 1$), large residue (>1.5 $cm^2$, $n = 3$), leptomeningeal metastasis at presentation (M+ disease, $n = 2$), and delay in molecular subgrouping (>6 weeks, $n = 4$). Supplementary genetic testing using orthogonal techniques demonstrated presence of either *CTNNB1* mutation (in 4 of 5 samples tested, uninterpretable in 1) and/or monosomy 6 (in all 6 samples tested) confirming the diagnosis of WNT-pathway medulloblastoma (**Table 1**). 7 children were identified as having low-risk WNT-pathway medulloblastoma and treated with focal IMRT to the tumor-bed (54 Gy/30 fractions) followed by six

**Table 1.** Individual patient, disease, and treatment characteristics (at baseline and relapse), with survival outcomes of low-risk WNT-pathway medulloblastoma treated with focal conformal radiotherapy plus adjuvant systemic chemotherapy without upfront CSI at initial diagnosis.

| Case | Age at diagnosis | Gender | Histologic subtype | Additional genetic testing | Time to RT start | Adjuvant therapy at initial diagnosis | Time to relapse | Patterns of failure | Salvage therapy at relapse | Response to treatment | Status (last follow-up) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 13 years | Female | Classic | *CTNNB1* Mut: ND<br>Monosomy 6: P | 30 days | Focal RT (54 Gy)<br>Chemotherapy (6 cy) | 21 months | Multiple spinal metastases, single metastatic deposit in supratentorial brain | CSI (35 Gy) + boost<br>RT salvage ICE × 6 cy | Complete response | Alive in remission at 32 months after relapse |
| 2 | 10 years | Female | Classic | *CTNNB1* Mut: P<br>Monosomy 6: ND | 37 days | Focal RT (54 Gy)<br>Chemotherapy (6 cy) | 15 months<br>43 months | 1st: multiple spinal deposits; 2nd: tumor-bed relapse + multiple spinal deposits | CSI (40 Gy), no boost<br>RT COMBAT × 8 cy<br>ICE × 4 cy followed by re-CSI (30 Gy) plus boost | Near complete response | Alive in remission at 37 months after 1st relapse and 9 months after 2nd relapse |
| 3 | 11 years | Male | Classic | *CTNNB1* Mut: ND<br>Monosomy 6: P | 27 days | Focal RT (54 Gy)<br>Chemotherapy (1 cy) | N/A | N/A | N/A | N/A | Died of chemotherapy toxicity after 1st cycle |
| 4 | 7 years | Female | Classic | *CTNNB1* Mut: P<br>Monosomy 6: P | 32 days | Focal RT (54 Gy)<br>Chemotherapy (6 cy) | 23 months | Left lateral ventricle, spinal deposit + tumor-bed relapse | CSI (35 Gy) + boost<br>RT COMBAT × 1 cy | Complete response | Alive in remission at 26 months after relapse |
| 5 | 9 years | Male | Classic | *CTNNB1* Mut: P<br>Monosomy 6: P | 39 days | Focal RT (54 Gy)<br>Chemotherapy (6 cy) | No relapse | N/A | N/A | N/A | Alive without relapse at 42 months |
| 6 | 7 years | Female | Classic | *CTNNB1* Mut: UI<br>Monosomy 6: P | 38 days | Focal RT (54 Gy)<br>Chemotherapy (6 cy) | No relapse | N/A | N/A | N/A | Alive without relapse at 35 months |
| 7 | 10 years | Male | Classic | *CTNNB1* Mut: P<br>Monosomy 6: P | 42 days | Focal RT (54 Gy)<br>Chemotherapy (6 cy) | No relapse | N/A | N/A | N/A | Alive without relapse at 35 months |

Abbreviations: COMBAT, combined oral metronomic and bio-differentiating therapy; cy, cycles; ICE, ifosfamide, carboplatin, and etoposide; Mut, mutation; N/A, not applicable; ND, not done; P, present; RT, radiotherapy; UI, uninterpretable.

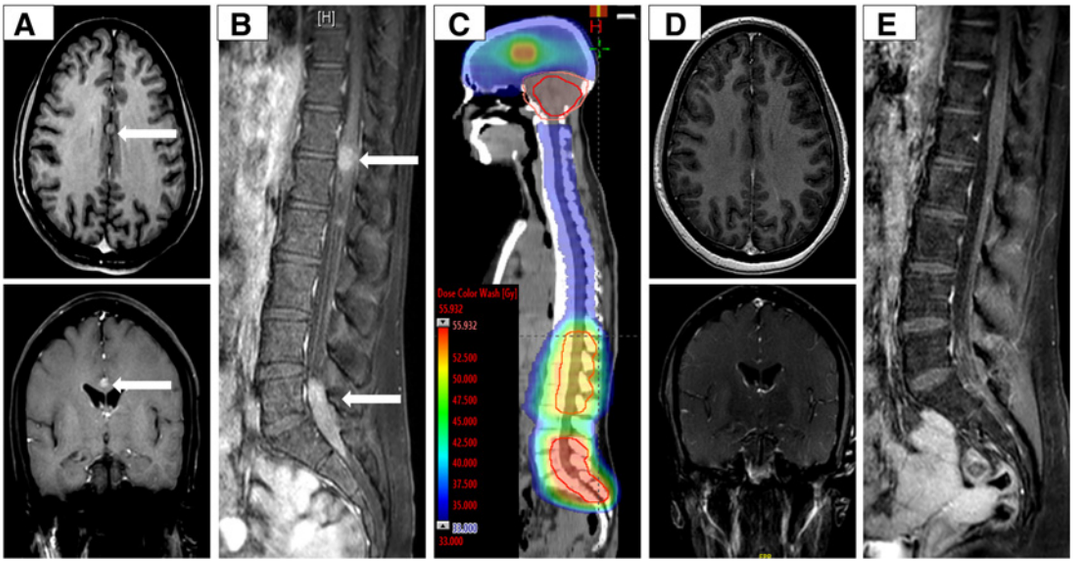


**Figure 1.**

Representative T1-weighted postcontrast MRI demonstrating neuraxial failure (white arrows) in the juxta-ventricular region in brain (**A**) and lumbo-sacral spine (**B**) at 21 months from initial diagnosis after treatment with postoperative focal conformal radiotherapy and adjuvant systemic chemotherapy. At relapse, the child was treated with salvage craniospinal irradiation with conformal avoidance of previously treated tumor-bed plus focal boost irradiation of metastatic sites (**C**), with complete regression of metastatic deposits in the supratentorial brain (**D**) and spinal leptomeninges (**E**) on response imaging. She received another six cycles of salvage systemic chemotherapy and remains alive in sustained remission at 32 months after first relapse.

cycles of standard adjuvant chemotherapy after written informed consent/assent. Median time to initiation of radiotherapy (from surgery) was 37 days (interquartile range 30–39 days). All children completed fractionated IMRT uneventfully and were started on adjuvant chemotherapy. 6 children completed all planned six cycles, while 1 child (case 3) succumbed to neutropenic sepsis and multi-organ dysfunction after first cycle of chemotherapy. Three children (cases 1, 2, 4) were detected with neuraxial failure (supratentorial brain and/or spine) including 1 with synchronous local recurrence on surveillance neuro-imaging at 21, 15, and 23 months from index diagnosis following which the study was terminated prematurely (**Table 1**). At relapse, all 3 children were treated with tomotherpay-based CSI with conformal avoidance of previously-treated tumor-bed (as appropriate) plus boost irradiation of metastatic deposits followed by second-line salvage chemotherapy. 2 children (cases 1, 4) continue to be in remission (32 and 26 months after first relapse) while 1 child (case 2) developed a second relapse (involving tumor-bed and spine) 28 months after first relapse and was further treated with salvage chemotherapy and craniospinal reirradiation resulting in excellent clinico-radiologic response. Representative images of a patient with neuraxial relapse and complete response to salvage therapy is illustrated in **Fig. 1**. Imaging patterns of first relapse of the other 2 patients are also presented in online supplementary file (Supplementary Fig. S1). 3 patients (cases 5, 6, 7) are relapse-free at 42, 35, and 35 months from index diagnosis. Patient, disease, and treatment-related characteristics with survival outcomes for individual patients are summarized in **Table 1**. At a median follow-up of 42 months, 2-year Kaplan–Meier estimates of EFS, RFS, and OS with 95% CI were 42.9% (95% CI, 18.2–100), 50% (95% CI, 22.5–100), and 85.7% (95% CI, 63.3–100) respectively (**Fig. 2**). The current analysis was

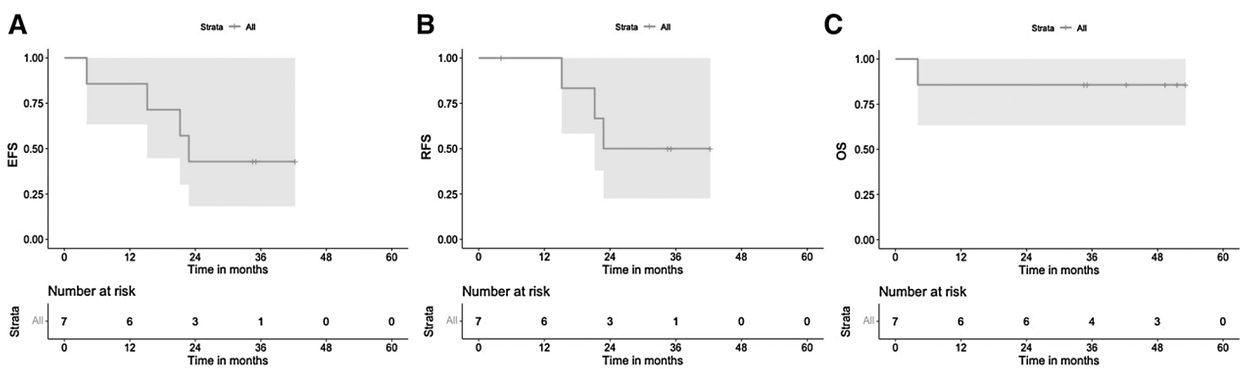


**Figure 2.**

Kaplan–Meier estimates with 95% CIs of EFS (**A**), RFS (**B**), and OS (**C**).

unplanned and not part of the original study design wherein first interim analysis was scheduled to be done after 15 evaluable patients. However, unacceptably high risk of neuraxial failure prompted us to terminate our study prematurely without formal statistical analysis.

## Discussion

Novel biological insights have led to classification of medulloblastoma into four distinct molecular subgroups (4, 5), prompting prospective testing of subgroup-specific treatment paradigms for optimization of adjuvant therapy (15). We hypothesized that focal IMRT to primary-site avoiding upfront CSI would significantly reduce radiotherapy-related late toxicity without compromising survival in low-risk WNT-pathway medulloblastoma. We also postulated that salvage CSI plus boost irradiation of metastatic sites followed by further systemic chemotherapy would provide sustained disease control for any neuraxial relapse. Unfortunately, three children relapsed within 2 years of initial diagnosis necessitating early termination of our study. Limited patient numbers and relatively short follow-up can be considered limitations of our study. Inferences and conclusions of the current analyses are not based on formal early stopping rules as originally planned reducing statistical rigor.

Cohen and colleagues (16) explored a primary chemotherapy only approach eliminating upfront radiotherapy completely following surgery in children with low-risk WNT-pathway medulloblastoma. First 2 patients on their study relapsed (both local and disseminated) at 3 and 6 months after completion of planned adjuvant systemic chemotherapy comprising of Children's Oncology Group (COG) ACNS0331 AAB-AAB-AAB (A = cisplatin/lomustine/vincristine; B = cyclophosphamide/vincristine) backbone following which further accrual was halted on the study. Of the remaining 4 subjects, 2 were in remission after completion of primary chemotherapy while other 2 were in midst of protocol therapy (at time of reporting). Additional therapy in the form of radiotherapy and/or intensification of chemotherapy was recommended for these 4 children to reduce their risk of relapse. An updated analysis (17) reconfirmed that primary chemotherapy approach omitting upfront CSI/radiotherapy is insufficient treatment for WNT-activated medulloblastoma. The first 2 relapsed patients were successfully salvaged with CSI plus focal boost followed by systemic chemotherapy. 2 patients who had completed primary chemotherapy at time of study closure received consolidation CSI plus focal boost and remain in remission 1 year from completion of treatment. Of the remaining two children on treatment, one aborted protocol therapy and transitioned to Head Start type regimen and remains in remission at 10 months. The final subject who recently completed primary chemotherapy developed new areas of restricted diffusion suspicious of early recurrence necessitating salvage CSI plus boost, but experienced further relapse and is receiving salvage chemotherapy. Findings from both these studies should inform and guide neuro-oncology researchers as well as practicing clinicians to tread cautiously and plan for controlled deintensification of therapy in even in good-biology disease. The physical, mental, and emotional suffering endured by patients and care-givers after early relapse due to deintensification of therapy to mitigate toxicity in a disease setting with high cure rates can be devastating thereby mandating strict stopping rules. Despite using stringent criteria for patient selection, both studies had to be terminated prematurely due to unacceptably high risk of neuraxial failures suggesting that radiotherapy, particularly CSI remains an integral component of treatment even in low-risk WNT-pathway medulloblastoma.

Various platforms exist for robust molecular subgrouping of medulloblastoma including IHC panel, gene expression profiling, microRNA profiling, and DNA methylation array (4, 13). DNA methylation is considered gold-standard and method of choice for molecular classification (18); however, there remain issues with its availability, accessibility, and affordability. It is generally recommended to use complementary orthogonal techniques such as nuclear β-catenin staining, *CTNNB1* mutation, or monosomy 6 to molecularly confirm the diagnosis of WNT-pathway medulloblastoma before planning deescalation of therapy (11). Using our assay (13), we have previously accurately classified all 34 medulloblastoma samples from an external dataset (based on NanoString) excepting for one group 4 tumor that was misclassified as group 3 medulloblastoma providing an accuracy rate of 97%. NanoString assay has recently been reported to have 100% concordance with DNA methylation array for WNT-pathway medulloblastoma (18). Heatmap illustration of our assay used to define WNT-pathway medulloblastoma is provided as online supplementary file (Supplementary Fig. S2).

The optimal dose of CSI in WNT medulloblastoma is currently being explored in several prospective clinical trials (15) such as the SJMB-12 (NCT01878617), COG ACNS1422 (NCT02724579), and PNET-5 (NCT02066220). Previous data has shown that deferral of radiotherapy (19) or reduction of CSI dose (20) in younger children (aged between 3 to <8 years) with molecularly unselected medulloblastoma results in inferior survival. We are now recruiting children with low-risk WNT-pathway medulloblastoma in a successor study (NCT04474964) using 18 Gy CSI plus 36 Gy tumor-bed boost for total primary-site dose of 54 Gy followed by six cycles of standard adjuvant chemotherapy. Low-dose CSI (15–18 Gy) as being tested in ongoing clinical trials or current standard-dose CSI (23.4 Gy) as being used in routine clinical practice in the upfront adjuvant setting are likely to be associated with decreased neuro-cognitive toxicity compared with full-dose CSI (35–36 Gy) delivered upfront or in the salvage setting at neuraxial relapse. The potential of using lower doses of CSI in the salvage setting for relapsed medulloblastoma after deintensified therapy remains unexplored. For children with isolated local recurrence in the index tumor-bed, lower doses of CSI (23.4 Gy) might suffice; however, for disseminated disease, full-dose CSI would be warranted for durable disease control.

Over the last two decades, a number of molecular players and associated signaling pathways involved in metastases from medulloblastoma have been described (21). However, given the excellent long-term survival (5-year survival >90%) with very low risk of relapse in adequately treated WNT-pathway medulloblastoma, prognostic factors affecting outcomes, patterns of failure, and drives of metastatic dissemination have not been described well in this subgroup. Recently, Nobre and colleagues (22) have reported on a retrospective multi-institutional clinically annotated cohort of 93 patients with WNT-pathway medulloblastoma using an integrated genomic approach. 15 patients with relapse were identified, 12 in metastatic compartment including 1 with extra-neuraxial metastases, and 3 in the surgical cavity. Interestingly, 8 of 11 neuraxial relapses were in lateral ventricles (6 confined to frontal horns). Maintenance systemic chemotherapy ($P = 0.032$) specifically the cumulative dose of cyclophosphamide/ifosfamide (<12 mg/m$^2$) and male gender (0.033) were associated with significantly increased risk of relapse ($P = 0.033$). Age at diagnosis, extent of resection, metastatic status at presentation, dose of CSI, and additional molecular/genetic alterations did not predict the risk of relapse in WNT-pathway medulloblastoma. All children in our study (excepting 1 who succumbed to chemotherapy-related complications after first cycle) had received 12 mg/m$^2$ of cumulative

cyclophosphamide dose. All three relapses in our cohort occurred in the female gender in contrast to the findings from retrospective multi-institutional analysis (22); remaining 3 children (2 boys and 1 girl) continue to be relapse-free and in sustained remission on follow-up. All 3 children with failure experienced metastatic relapse in the neuraxis including two in and around the lateral ventricles (one each in frontal horn and juxta-ventricular region) reinforcing the view that ependymal lining of lateral ventricles possibly provides unique micro-environment conducive to homing and growth of WNT-medulloblstoma tumor cells (22).

### Conclusion

Treatment of the tumor-bed alone with postoperative focal conformal radiotherapy avoiding upfront CSI in children with low-risk WNT-pathway medulloblastoma followed by six cycles of standard adjuvant systemic chemotherapy is associated with an unacceptably high risk of neuraxial failure and should not be tested any further even in the context of prospective trials.

## Authors' Disclosures

T. Gupta reports grants from Tata Memorial Centre, SOHN Conference Foundation, and Daivesh Doshi - Brain Tumor Foundation (BTF) Endowment Fund during the conduct of the study. A. Dasgupta reports grants from Tata Memorial Centre Intramural Research Grant, SOHN Conference Foundation, and Daivesh Doshi - BTF Endowment Fund during the conduct of the study. No disclosures were reported by the other authors.

## Authors' Contributions

**T. Gupta:** Conceptualization, data curation, formal analysis, supervision, funding acquisition, investigation, methodology, project administration, writing–review and editing. **S. Pervez:** Data curation, formal analysis, writing–original draft. **A. Dasgupta:** Formal analysis, writing–original draft. **A. Chatterjee:** Formal analysis, writing–review and editing. **S. Epari:** Data curation, writing–review and editing. **G. Chinnaswamy:** Data curation, writing–original draft. **R. Jalali:** Conceptualization, writing–review and editing.

## Acknowledgments

Intramural Research Grant-Tata Memorial Centre, SOHN Conference Foundation, and Daivesh Doshi - BTF Endowment Fund. The funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

## Note

Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Received March 10, 2022; revised April 9, 2022; accepted May 26, 2022; published first June 2, 2022.

## References

1. Ostrom QT, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2014–2018. Neuro Oncol 2021;23(12 Suppl 2):iii1–iii105.
2. Gajjar A, Pfister SM, Taylor MD, Gilbertson R. Molecular insights into pediatric brain tumors have the potential to transform therapy. Clin Cancer Res 2014;20:5630–40.
3. Northcott PA, Robinson GW, Kratz CP, Mabbott DJ, Pomeroy SL, Clifford SC, et al. Medulloblastoma. Nat Rev Dis Primers 2019;5:11.
4. Taylor MD, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford SC, et al. Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol 2012;123:465–72.
5. Gomez S, Garrido-Garcia A, Garcia-Gerique L, Lemos I, Sunol M, de Torres C, et al. A novel method for rapid molecular subgrouping of medulloblastoma. Clin Cancer Res 2018;24:1355–63.
6. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol 2021;23:1231–51.
7. Kool M, Korshunov A, Remke M, Jones DT, Schlanstein M, Northcott PA, et al. Molecular subgroups of medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations, and clinical data of WNT, SHH, group 3, and group 4 medulloblastomas. Acta Neuropathol 2012;123:473–84.
8. Zeltzer PM, Boyett JM, Finlay JL, Albright AL, Rorke LB, Milstein JM, et al. Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: conclusions from Children's Cancer Group 921 randomized phase III study. J Clin Oncol 1999;17:832–45.
9. Packer RJ, Gajjar A, Vezina G, Rorke-Adams L, Burger PC, Robertson PL, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol 2006;24:4202–8.
10. Bouffet E. Management of high-risk medulloblastoma. Neurochirurgie 2021;67:61–68.
11. Ramaswamy V, Remke M, Bouffet E, Bailey S, Clifford SC, Doz F, et al. Risk stratification of childhood medulloblastoma in the molecular era: the current consensus. Acta Neuropathol 2016;131:821–31.
12. Fossati P, Ricardi U, Orecchia R. Pediatric medulloblastoma: toxicity of current treatment and potential role of protontherapy. Cancer Treat Rev 2009;35:79–96.
13. Kunder R, Jalali R, Sridhar E, Moiyadi A, Goel N, Goel A, et al. Real-time PCR assay based on the differential expression of microRNAs and protein-coding genes for molecular classification of formalin-fixed paraffin embedded medulloblastomas. Neuro Oncol 2013;15:1644–51.
14. Bellisant E, Benichou J, Chastang C. The group sequential triangular test for phase II cancer clinical trials. Am J Clin Oncol 1996;19:422–30.
15. Thompson EM, Ashley D, Landi D. Current medulloblastoma subgroup specific clinical trials. Transl Pediatr 2020;9:157–62.
16. Cohen K, Bandopadhayay P, Chi S, London W, Rodriguez F, Hawkins C, et al. MEDU-34. Pilot study of a surgery and chemotherapy-only approach in the upfront therapy of children with WNT-positive standard risk medulloblastoma. Neuro Oncol 2019;21(Suppl 2):ii110.
17. Cohen K, Chi S, Hawkins C, Rodriguez F, London W, Castellino RC, et al. MBCL-25. pilot study of a surgery and chemotherapy-only approach in the upfront therapy of children with wnt-positive standard risk medulloblastoma: updated outcomes. Neuro Oncol 2020;22(Suppl 3):iii3934.
18. Korshunov A, Sahm F, Zheludkova O, Golanov A, Stichel D, Schrimpf D, et al. DNA methylation profiling is a method of choice for molecular verification of pediatric WNT-activated medulloblastomas. Neuro Oncol 2019;21:214–21.
19. Kann BH, Park HS, Lester-Coll NH, Yeboa DN, Benitez V, Khan AJ, et al. Postoperative radiotherapy patterns of care and survival implications for medulloblastoma in young children. JAMA Oncol 2016;2:1574–81.
20. Michalski JM, Janss AJ, Vezina LG, Smith KS, Billups CA, Burger PC, et al. Children's oncology group phase III trial of reduced-dose and reduced-volume radiotherapy with chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol 2021;39:2685–97.
21. Li M, Deng Y, Zhang W. Molecular determinants of medulloblastoma metastasis and leptomeningeal dissemination. Mol Cancer Res 2021;19:743–52.
22. Nobre L, Zapotocky M, Khan S, Fukuoka K, Fonseca A, McKeown T, et al. Pattern of relapse and treatment response in WNT-activated medulloblastoma. Cell Rep Med 2020;1:100038.