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Article

Long-term outcomes by clinical and molecular risk stratification in patients with medulloblastoma receiving risk-adapted therapy

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Highlights

- Integrated genetic and clinical features effectively discriminate MB prognoses
- Gr.3-MB harboring *MYC-amp* requires 36.0 Gy CSI for a survival benefit, even at M0 stage
- *CDK6* activation indicates the prognostic significance of patients with Gr.4-MB

Context and significance

The integration of conventional clinical and subgroup-specific key genetic events into medulloblastoma (MB) risk stratification has been adopted worldwide. By analyzing long-term follow-up data in the global cohort, this study reflects that the molecular risk strata enable effective discrimination of patients' OS and PFS. Notably, radiation dose-response effects are highly context dependent within defined molecular risk stratification. In several high-risk molecular subgroups, no significant differences in OS or PFS were observed between patients receiving CSI doses of 30.6 and 36.0 Gy. However, for certain very high-risk subtypes, such as *MYC*-amplified group_3 MB with exceptional aggressiveness, escalated CSI doses may confer a survival benefit even in the absence of dissemination. These findings underscore the potential for molecularly informed strategies to guide risk-adapted treatment customization in MB clinical practice.

Summary

Background

Risk stratification and radiotherapy optimization for medulloblastoma (MB) increasingly rely on molecular classification, yet large-scale, cross-regional, real-world evidence remains limited.

Methods

We assembled a global MB database (Chinese cohort: $N = 729$; international: $N = 494$). Overall survival (OS)/progression-free survival (PFS) and risk stratification were analyzed by integrating clinicopathological data with molecular subgroup-specific genetic events using Kaplan-Meier and Cox regression models.

Findings

While conventional clinical risk stratification effectively separated outcomes, metastatic stage alone, although a crucial factor, failed to adequately stratify survival across molecular subgroups. The average-risk group showed superior 5-year cumulative OS (84.4%) and PFS (77.5%), compared to the high-risk group (77.2% and 68.2%). Key genetic events, including *TP53* mutation/17p loss (Sonic Hedgehog, SHH), *MYC* amplification (group_3), and *CDK6* activation (group_4), were strongly associated with survival. Integrating genetic events with clinical features significantly facilitated prognostic discrimination. Importantly, radiotherapy dose-response effects were highly context dependent within defined molecular subgroups. No significant differences in OS or PFS were observed between craniospinal irradiation (CSI) doses of 30.6 and 36.0 Gy in high-risk patients with SHH, group_3, and group_4 receiving chemotherapy. In particular, 36.0 Gy CSI was warranted for aggressive *MYC*-amplified group_3 MB, even without dissemination.

Conclusions

Integrating subgroup-specific genetic events with clinical features facilitates MB risk stratification, informs context-dependent radiotherapy consideration, and provides actionable candidates for prospective validation.

Funding

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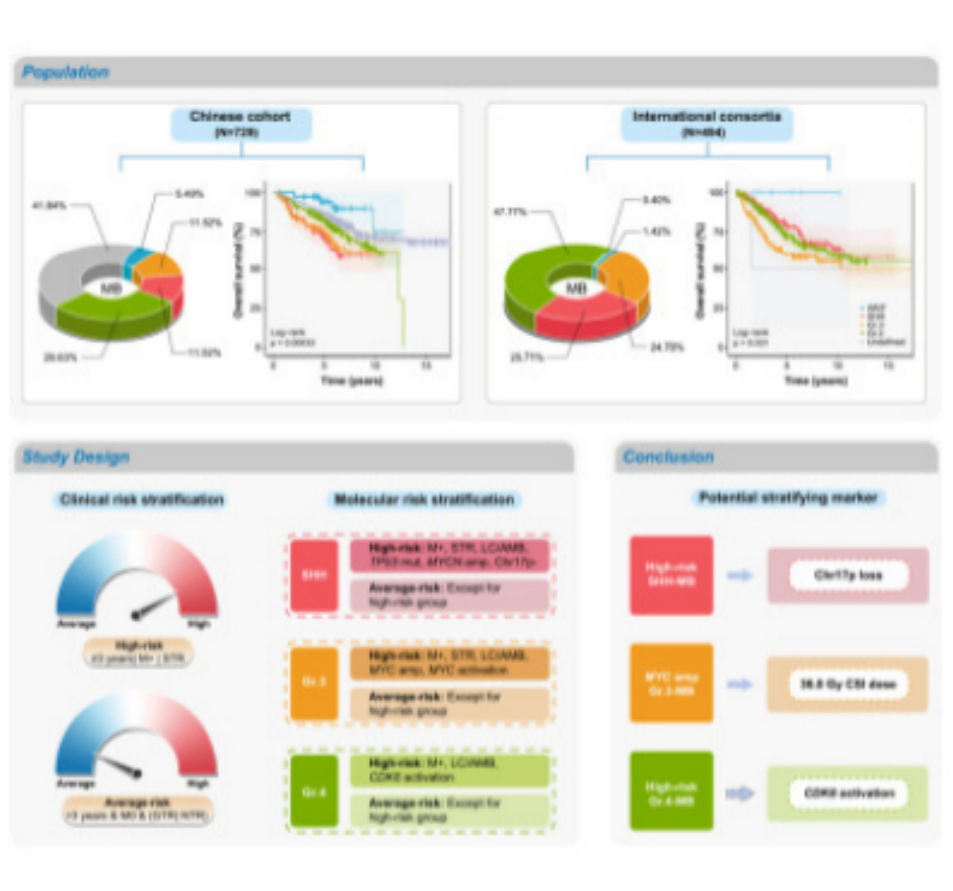
Graphical abstract


Population
Chinese cohort (N=729)
International consortia (N=494)
Study Design
Clinical risk stratification
Molecular risk stratification
Conclusion
Potential stratifying marker
Chr17p loss
36.0 Gy CSI dose
CDK6 activation

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Introduction

Medulloblastoma (MB) is the most common malignant brain tumor in childhood.[1] Current multidisciplinary therapeutic strategies combining maximal surgical resection, craniospinal irradiation (CSI) with posterior fossa tumor bed (PFTB) boost, and chemotherapy have significantly improved the 5-year overall survival (OS) to approximately 75% and the 10-year OS to around 65%.[2] However, long-term follow-up indicates that intensive treatments significantly impacted pediatric patients' quality of life.[3,4] According to National Comprehensive Cancer Network (NCCN) guidelines, risk stratification for pediatric MB should integrate molecular features with clinical factors. Specifically, metastatic status, subtotal resection (STR), and *MYC* amplification are primary indicators for high-risk classification regardless of subgroup, while other variables require more nuanced consideration.[5] The latest version of the NCCN guideline further highlights that the molecular classification and associated risk stratification of pediatric MB may significantly influence clinical management.[5] Effectively identifying risk stratification is crucial to avoid overtreatment of low-risk groups and to meet the requirements of high-risk patients, which remains a pressing issue to be urgently resolved.

Traditionally, since the implementation of the Chang staging system,[6] clinical risk stratification has been based on age, tumor resection extent, and metastasis (M) stage.[7,8] Compared to average-risk patients, high-risk patients receive intensified CSI doses, additional radiation to PFTB, and metastatic sites, as well as consecutive frequent cycles of chemotherapy.[9] Although this stratification has served as the standard of care for over half a century, pathological characteristics have not yet been considered. Moreover, high-dose CSI has actually caused significant long-term sequelae, severely impacting the quality of life for pediatric survivors.[10] In response to these limitations, the NCCN guideline advocates for risk-adapted dose modifications when supported by clinical evidence.[5] Recently, Smith et al. integrated clinical and molecular data from the three largest North American MB trials to propose a refined risk stratification algorithm with standardized treatment protocols, representing a significant advancement in contemporary MB management.[11]

Molecular classification of MB into WNT, SHH, group_3 (Gr.3), and group_4 (Gr.4) has been widely accepted, with each group having distinct genomic characteristics.[12] Actually, these pathological parameters significantly determine MB prognosis.[13] For instance, patients with Gr.3-MB with *MYC* amplification rapidly disseminate, resulting in worse outcomes.[14] Similarly, patients with SHH-MB with *TP53* mutations are generally classified as very high risk.[8] TP53 mutations occur in approximately 16% of pediatric patients with MB and represent a critical adverse prognostic marker strongly linked to treatment resistance. Indeed, *TP53* mutation confers a particularly dismal prognosis, with the 5-year survival rate often approaching 0%, compared to 74% ± 8% for wild-type cases.[15] Additionally, evidence suggests that clinical surveillance for germline *TP53* mutation carriers facilitates earlier tumor detection and improves long-term survival.[16] The NCCN guideline has begun incorporating specific molecular markers into the risk stratification framework.[17] Incorporating molecular risk into treatment protocols can maximize cure rates while minimizing the incidence of long-term, treatment-related morbidities.[18] Notably, Sharma et al.[19] integrated genetic events with clinical and histological factors to propose a risk stratification across eight subtypes of Gr.3/4-MB. While such granular subtyping is insightful and tailoring treatment intensity accordingly has shown survival benefits,[20] the four molecular subgrouping systems remain the most widely applied in real-world practice.

In this work, we presented long-term follow-up results from a multicenter MB cohort by integrating multi-omics profiling, including histological and molecular subgroups, genetic events, treatment modalities, etc., to investigate survival benefits, evaluate risk factors, and verify the risk stratification model under four molecular subgrouping systems, which contributed to planning the risk-adapted radiotherapy. Furthermore, multivariate analyses provided specific molecular guidance regarding the clinical contexts under which different CSI dosing strategies were appropriate, offering preliminary, hypothesis-generating findings that warrant clinical trial validation. We also incorporated additional molecular risk factors, particularly within Gr.4-MB, referring to the NCCN guideline[17] and the model suggested by Gajjar et al.[21]

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Section snippets

Demographics and clinicopathological characteristics

Clinicopathological and molecular characteristics of 729 patients aged ≥3 years with newly diagnosed MB are summarized in Tables 1 and S1. All patients underwent surgical resection followed by postoperative radiotherapy or adjuvant chemoradiotherapy, excluding those who received only biopsy or did not undergo radiotherapy (Figure S1). The median age at diagnosis was 8 years (interquartile range [IQR], 6–11). A total of 110 (15.09%) patients were metastatic (M+) based on the presence of …

Discussion

We analyzed 729 patients with MB in our Chinese cohort and 494 in the international consortia to assess the prognostic impact of clinical and molecular risk categories. By utilizing real-world data, we captured treatment patterns as they occur in routine practice while conducting rigorous quality control and study design in alignment with the framework of a hypothetical randomized controlled trial (RCT).[25] The limitation of conventional clinical risk stratification actually lies in its failure …

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Xiaoguang Qiu (qiuxiaoguang@bjtth.org). …

Materials availability

This study did not generate new unique reagents. …

Data and code availability

The whole-genome bisulfate sequencing (WGBS) dataset has been deposited in the China National Genomics Bank (CNGB) with the accession code CNGB: CNP0006196. The NGS data have been deposited in the CNGB with the accession code CNGB: CNP0006197. The total bulk RNA sequencing data have been deposited …

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Author contributions

H.L., Yu Tian, and X. Qiu designed the study and supervised the overall work. H.L., Yu Tian, and Y. Su had unrestricted access to all data. Y. Su, Jiao Zhang, X.C., K.D., D.H., X.W., and C.D. performed the statistical analyses. L.C., J.F., Jing Zhang, Y.Z., Y. Shi, Z.F., F.L., D.W., M.W., Junping Zhang, X. Qi, J.G., W.L., Yongji Tian, and X. Qiu were responsible for patient enrollment and clinical management. H.L. and Y. Su prepared the first draft of the manuscript. H.L., Yu Tian, Jiao …

Declaration of interests

The authors declare no competing interests. …

Key resources table

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Critical commercial assays		
EZ DNA Methylation-Gold Kit	Zymo Research	Cat# D5005
Accel-NGS Methyl-Seq Kit	Swift Biosciences	Cat# 30024
Deposited data		
Prognoses study of medulloblastoma (WGBS)	This study	CNGB: CNP0006196
Prognoses study of medulloblastoma (NGS)	This study	CNGB: CNP0006197
Prognoses study of medulloblastoma (RNA)	This study	CNGB: CNP0006198
Software and algorithms		
R v4.4.0	N/A	https://www.r-project.org/ ; RRID: SCR_001905
ABySS	BC Cancer/ BCGSC	//github.com/bcgsc/abyss
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Long-term outcomes and late toxicity of adult medulloblastoma treated with combined modality therapy: A contemporary single-institution experience
Neuro Oncol. (2022)

R. Salloum *et al.*
Late Morbidity and Mortality Among Medulloblastoma Survivors Diagnosed Across Three Decades: A Report From the Childhood Cancer Survivor Study
J. Clin. Oncol. (2019)

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