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Molecular Investigation And Clinical Features in Children With Medulloblastoma

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Abstract

Medulloblastoma, is a high-grade paediatric tumour of the brain which is created in the posterior fossa mostly. It includes multiple fields such as risk factors, incidence, pathogenesis, clinical features, diagnostic techniques, therapy, and prognosis. Through a synopsis of ongoing research, the paper will be aimed to promote knowledge and increase the chance of better treatment for children who have this defect. Objective :The goal of this paper is to look into maximum extensively Medulloblastoma, from its molecular mechanism to clinical treatment. that evidenced the existence of such carriers and established their regulating roles in medulloblastoma biology.

*** Material and methods**

Patients with age varying from 3-21 years were divided into two groups: low level of risk and high level of risk. Hierarchy was used based on the extent of metastasis and the degree of resection. Medulloblastomas were molecularly classified into subgroups (WNT , SHH), and subtypes were made based on DNA modifications by methyl sequencing combined with mutation data obtained by next

generation sequencing. The primary endpoints explored were (1) the correlation between tumor-based expression of ERBB2 and progression-free survival (PFS); and (2), the frequency of mutations related to WNT and SHH tumors.

In relation to molecular and clinical risk factors, the features with the highest robustness were modelled and used for the risk classification. Histopathological Examination as in Fig(3,4)were performed on formalin-fixed, paraffin-embedded (FFPE) tumor samples. Hematoxylin and eosin (H&E) staining were used to evaluate tumor morphology .

*** RESULTS**

It was on this population of patients who were diagnosed with medulloblastoma that we had random sampling of 333 cases. Five-year PFS was 83. 2% (95% CI, 78. 4 to 88. In contrast to PI that are managed by a nurse and reduced risk of serious treatment consequences, patients will on the other band stay to the regimen of drugs. 7% (95% CI, 49. 8 to 69.

The department of multidirectional services will offer a group of non-professionals consisting objectors who are suffering from that. In case the study is a broad survey that covers the whole target population, the p-value will be zero. However, the p-value would be equal to zero even if you had a study that was a sampling that uses a known population. 74.

In the end the significance level distribution moves towards the vicinity of the positive tail of the significance interval. 05. CTNNB1 (96%) and DDX3X (37%) are the major known mutations found at epigenetic complexes' cores and they determine this markers phenotypes, while SMARCA4 mutation (24%) is the most and one of the cancer characteristic mutations. That is, the carbon isotope "W" (DNA) was trapped through the photosynthesis process where it constituted 4% of its result., the population shows expected populations by group: Humanize the suggested wording. 4: Alongside, the future will see "modern mammography with advanced computer imaging" as the main detection method. Production is shown here using the profile of the wide/other NT + low/opposite SHH and regular SHH groups. The next two were the controls that is, about as similar to the pattern in this case. Interestingly, high-risk groups have a greater number of five-year survivals than they used to in the past; by now, it is more than 60%.

*** CONCLUSION**

These results establish a new risk stratification for future medulloblastoma trials.

*** Introduction**

Medulloblastoma is a malignant brain tumor predominantly found in children, accounting for approximately 20% of pediatric brain tumors. It is one of the most common primary brain tumors in childhood, with a peak incidence between the ages of 3 and 8 years(1). This introduction will provide an overview of the disease, its incidence, etiology, and impact on affected children and their families. Medulloblastoma arises in the posterior fossa, specifically from the cerebellum, which is responsible for coordinating voluntary movements, balance, and muscle tone. Its location can lead to symptoms related to increased intracranial pressure, such as headaches, vomiting, and ataxia. Due to its aggressive nature and location, it can also cause obstructive hydrocephalus, leading to further neurological deficits if not treated promptly(2).Medulloblastoma affects approximately 0.5 to 0.6 per 100,000 children per year, making it one of the most common malignant brain tumors in the pediatric population. While it can occur at any age, it most commonly presents in children between 3 and 8 years old, with a slight male predominance. However, rare cases have been reported in infants and adults. The exact cause of Medulloblastoma remains elusive, but several factors contribute to its development(3). Genetic predisposition, environmental factors, and molecular abnormalities all play a role. Certain genetic syndromes, such as Gorlin syndrome (nevoid basal cell carcinoma syndrome), Li-Fraumeni syndrome, and Turcot syndrome, have been associated with an increased risk of developing Medulloblastoma.

Additionally, exposure to ionizing radiation has been implicated as a risk factor.Medulloblastoma is a heterogeneous disease with distinct molecular subtypes, each with unique genetic alterations and clinical characteristics(4).

Four main subgroups have been identified: Wingless (WNT), Sonic Hedgehog (SHH), Group 3, and Group 4. These subtypes differ in their underlying genetic mutations, gene expression profiles, and clinical outcomes. For example, the WNT subgroup is associated with better prognosis, while Group 3

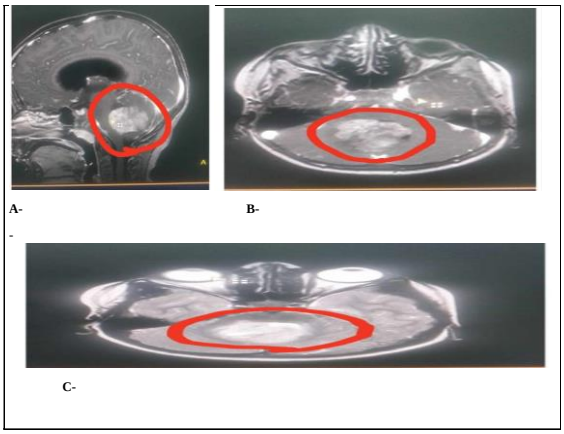
tumors tend to be more aggressive and have poorer outcomes.Medulloblastoma poses significant challenges in diagnosis and treatment due to its aggressive nature and complex molecular landscape. Understanding its epidemiology, etiology, and clinical presentation is essential for early detection and intervention. Advances in molecular profiling have improved risk stratification and personalized treatment approaches, offering hope for improved outcomes for children affected by this devastating disease(5).

*** Etiology and Pathogenesis**

Medulloblastoma is highly heterogeneous malignant brain tumor which predominantly troubles children. Although the exact mechanism by which Medulloblastoma arises is yet to be fully understood, a liaison of both hereditary predisposition, environmental factors, and molecular abnormalities all together works to cause the tumor. Identification of etiology and pathogenesis is an important factor for explaining the mechanisms of Medulloblastoma and assisting in the development of targeted therapies(6).

*** Genetic Factors**

In some cases, genetic predisposition may be also the cause of Medulloblastoma tumor appearances. Different types of genetic disorders have been ever discovered to be rising factor of this form of cancer(7). Likewise, Gorlin syndrome (nevoid basal cell carcinoma syndrome), in which there is a mutation in the PTCH1 gene causing SHH pathway misregulation is the most frequent risk factor of Medulloblastoma due to PTCH1 gene mutation. The mutation, of gene PTCH1, in Sling-Fraumeni syndrome, and gene, APC, mutation in Turcot syndrome (by APC gene) are found to increase the chance of the appearance of Medulloblastoma. as in Fig(1).



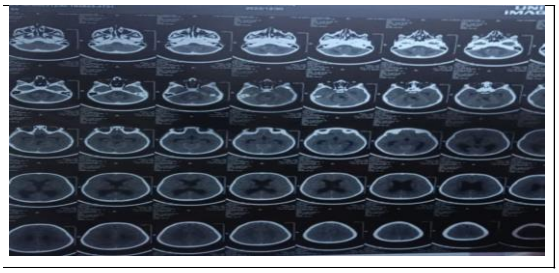
Fig(1): The pictures shows medulloblastoma in the brain.

*** Environmental Factors**

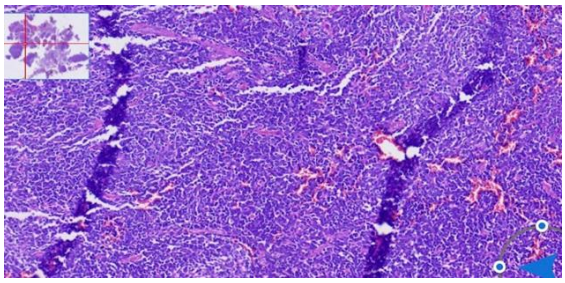
Despite the fact that researchers incline to think that genetic disposition is the major factor to consider, it may be ensured

that the environment too can as well play some role in the growth of tumor (8).

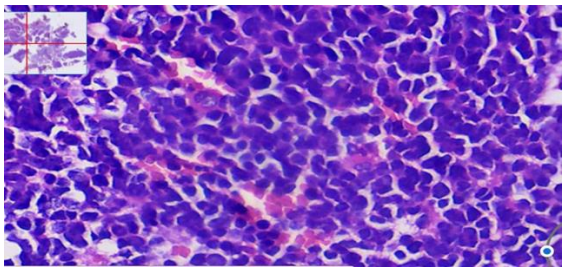
Radiation effects and especially radiations received during childhood were known as a factor that increases the risk of this tumour occurrence. Patients, especially those with previous history of cranial radiation therapy, are known to carry a higher risk of brain tumors due to the underlying radiation phenomenon. Secondly, the influence of prenatal factors and some dietary composition has also been theorized, but future studies are a must in order to ascertain their part.



Fig(2):Pictures shows medulloblastoma in different size.



Fig(3): Histopathological picture of medulloblastoma demonstrate sheets of malignant cells with scanty eosinophilic cytoplasm & hyperchromatic nuclei (H&E stain) x10



Fig(4): High power view of medulloblastoma reveal the high grade cellular morphology with high N:C ratio, scant cytoplasm & hyperchromatic nuclei (H& E) stain, X40

* Molecular Pathways Involved

The phenomenon of medulloblastoma classification is carried out through the identification of molecular subgroups which might have different genetic mutations, but also different clinical presentation. WNT, SHH, and other basic units subgroup are key among necessary group. The patients with the WNT subgroup experience mostly mutations in the WNT signaling way (particularly in the CTNNB1 gene) and these types of patients usually have positive prognosis. SHH pathway is abnormal in SHH subgroup tumors due to their mutations in PTCH1, SMO or the SUFU gene. in regard to the molecular features and clinical manifestations(9).

* TP53 Mutation and Other Genetic Aberrations

Demarcation of medulloblastoma is done by examination of molecular subgroups

that in their turn comprise of different genetic mutations as well as diverse clinical features. WNT, SHH and BMPs, the members of the foundation group, all seem to be important in their own way.

The CTNNB1 gene is mutated specifically in the WNT signalling pathway. The mutant of subtypes is mostly the WNT subtypes. They usually make good recovery. The SHH pathway of the SHH group is disabled because of the PTCH1, SMO and/or SUFU gene mutations. about the molecular variations and patient outcomes(9).(10).

The origin and development of pediatric Medulloblastoma is multifactorial including molecular alterations, genetic predisposition, and some environmental insults. Currently, there are recent advancements in genomic profiling and molecular subgroups which make it possible to properly risk stratify and define the targeted therapies. Meanwhile it is not yet clear how complex the mechanisms that cause Medulloblastoma are and if such novel treatment strategies based on their findings exist. (11).

*** Epidemiology**

Medulloblastoma is the biggest malignant brain tumor of children that takes about 20% of the whole tumor cases in kids. Addressing the ecology of the disease such as its distribution, variance based on gender and age and geographic popularity is an absolute must in healthcare for appropriate management and cost allocation.(12).

*** Incidence and Prevalence**

The pediatric Medulloblastoma annual incidence estimate is approximate 0. 5 to 0. In the world 6 per 100,000 of children. Though comprising a sizeable portion of pediatric brain tumors, it is still a rather rare occasion. Though the impact may be significant yet it is defined by the nature of the disease which may have a possibility of long-term neurological (13).

*** Age Distribution**

While astrocytoma of medulla is significantly seen in children which rarely occurs among adults, and around 7 years old is the average age at which it is insidiously developed. Radically, it may be noted that sporadic cases of infants and children with more than ten years old who after being infected with the disease also carried the disease is a scenario.

This age distribution can show a range of diversities between molecular subtypes, wherein some of these subgroups might even be classified with such wide ranges.

It is something that might lead to worry in particular molecular substitutions (14).

*** Gender Distribution**

Medulloblastoma manifests with a little inclination towards it in males potentially more than in females. And at this stage the gender disparity as a whole is a puzzle in view of which we only guess the genetic, hormonal, or environmental factors as a likely reason. (15).

*** Geographical Variations**

While Medulloblastoma occurs worldwide, there may be geographical variations in its incidence and molecular subtypes. Some studies have suggested differences in incidence rates among populations, possibly related to genetic predisposition, environmental exposures, or diagnostic practices. Additionally, certain molecular subtypes may be more prevalent in specific geographic regions(16).

*** Ethnic and Racial Disparities**

Limited data suggest that there may be ethnic and racial disparities in the incidence and outcomes of Medulloblastoma. Studies have reported differences in tumor biology, treatment response, and survival rates among different ethnic and racial groups. These disparities underscore the importance of equitable access to healthcare and tailored treatment approaches for all patients(17).

*** Prognostic Factors and Survival Rates**

The prognosis of Medulloblastoma varies depending on several factors, including age at diagnosis, extent of resection, presence of metastasis, and molecular subtype. Overall, advancements in treatment modalities, including surgery, radiation therapy, and chemotherapy, have led to improved survival rates over the past few decades. However, challenges remain in managing high-risk and recurrent disease, highlighting the need for continued research and innovative therapeutic strategies.Medulloblastoma is a significant health burden in the pediatric population, with its incidence in early childhood. While rare, its aggressive nature and potential long-term effects necessitate prompt diagnosis and appropriate treatment. Understanding its epidemiology, including age distribution, gender predilection, and geographical variations, is essential for optimizing clinical management and improving outcomes for affected children. Further research is needed to elucidate the underlying factors

contributing to its occurrence and to develop targeted interventions to reduce its impact(18).

*** Methodology**

SJMB03 was a randomized placebo-controlled phase III clinical trial of metastatic medulloblastoma, supratentorial primitive neuroectodermal tumor, or atypical teratoid rhabdoid tumor for 3-21 years of age, newly diagnosed.

We used SJMB96 eligibility criteria which are as follows: They were grouped postoperatively as average risk and high risk groups based on their predicted mortality rates based on the log rank test. Patients with M0 status and intracranial and/or spinal MRI and post-op cytology of CSF plus post-op MRI indicating a GTR or NTR R0 were classified as average risk; M1-3 on MRI of the head/ spine or cytology of the CSF were considered high risk, as was residual tumor > 1 cm. Patients with an area of repeatability of > 5 cm2 on the postoperative MRI (R+) were categorized as high risk. Symptoms of toxic effects were noted and evaluated by the Common Terminology Criteria for Adverse Events version 3. 0. Diagnoses made at surgery were confirmed histologically by an independent pathologist in a central reference laboratory.

Classic medulloblastomas were defined as histologic subtype, while D/N and LC/A were considered molecular subgroups. Immunohistochemistry staining was conducted where the tumor and corresponding blood samples were tested for molecular expression. Immunoblotting of the fresh frozen tumor was used to confirm the expression of ERBB2 protein. Genomic DNA was isolated from FFPE tumor tissue using Maxwell blood DNA FFPE kit (# AS 1450, Promega USA) and from matched fresh/liquid PBMCs or PBXCT using Dneasy blood and tissue kit (# 69581, Qiagen, Germany) after approval of the institutional review board. Total RNA was isolated from snap-frozen medulloblastomas by using STAT-60 reagent and common mRNA expression data were obtained by using Human U133 Plus 2.0. , 0 microarray (Affymetrix, Santa Clara, CA). DNA methylation classification was done as follows using methods which have been earlier reported in literature. Insubtypes prediction we used a random forest classifier with external reference data sets. CNVs were called using the Conumee R package, which utilizes the

normalizing method to compare the ratio of target gene probes to reference gene probes against a database of CNVs across tumour and normal tissues. Germline and tumor DNA exomes were enriched by a SureSelect Human All Exon V5 kit that was obtained from Agilent Technologies, Inc., USA. SJMB03 had received approval from the St Jude IRB and institutional review boards at various centers that participated in the study. Verbal as well as written informed consent was obtained from the patients and parents or guardians where applicable.

*** Histopathological Examination**

Histopathological reviews were performed on formalin-fixed, paraffin-embedded (FFPE) tumor samples. Hematoxylin and eosin (H&E) staining were used to evaluate tumor morphology as in Figures(3,4).

*** Treatment**

Average-risk disease patients were treated with CSI (23.The). 4 Gy) and a boost to the primary tumor (total tumoricidal dose 55. 8 Gy; 1. 8 Gy daily fraction). The high-risk disease patients on CSI included 36 M0-1, 39. 6 [M2-3] Gy) the booster dose of 12 Gy was prescribed for the focal RT of the primary tumor. 8-59. 4 Gy; 1. 8 Gy daily fraction). For the clinical target volume a margin of 1 centimeter was added to the postoperative tumor bed. 30 min., while their counterparts in the high-risk Facebook group had zero cm for both [P = 0.694]. Macroscopic extra-hepatic malignancy > 0. 5 cm – additional irradiation (total dose 50. 4-59. 4 Gy). Twenty-nine patients underwent proton-beam radiotherapy (RT).

Another group of patients received four cycles of high-dose chemotherapy along with vincristine (1. 0 mg/m2 once daily [maximum dose 2.The recommendation does not mean that the new dose is safe for females, it only indicates the dose that has been used in the previous studies before reporting harms to females was 2 mg/m2 once daily. Day −4, 6: 5 mg methylprednisolone; Day −4: 75 mg/m cisplatin; Days −3 and −2: 2 g/m2 dose of cyclophosphamide. Each cycle was accompanied by stem-cell or bone-marrow rescue on the day 0.

Filgrastim was administered at a dose of 5μg/kg once daily per day starting from day + 1 until the ANC ≥ 2000 on two consecutive days. If such approaches were planned, the predicted duration of chemotherapy was 4 weeks per cycle or 16 weeks in total. They included continuation

of treatment until terminations, disease progression, patient refusal, or toxicity. Disease evaluations were carried out at some fixed time points till 72 months from diagnosis.

*** Statistical Analysis**

To address this aim, patients initiating RT were considered for analysis, if they were otherwise eligible for the trial. The main objectives of the coprimary analyses were as follows: The key objectives were to determine the overall PFS between the two groups in (1) ERBB2 protein expression and (2) mutated WNT and SHH tumor types. Power calculations of the desired sample size required to determine if the PFS rate of ERBB2-negative patients was 15% better than patients with ERBB2-positive at 2 years with type I error of 5% and desired power of 80 percent were estimate based on the anticipated difference in the rate of ERBB2 status positivity between the two risk groups. For the purpose of the overall analysis evaluating the outcome according to the subgroup, only the patients with sufficient tissue to perform the methylation analysis were considered. Other targets were to identify/examine the alterations in oncoproteins and tumor suppressor gene/protein products; to analyze the molecular profiles and to address the relationship between these molecular features and ASC subtype, clinical features, and survivals. Censoring was handled using the Kaplan and Meier estimator to estimate the outcome distributions.

Comparisons of outcome were made by Kaplan-Meier survival analysis and log-rank test or stratified log-rank test when applicable. Using hospital Cox proportional hazard models, coefficient estimates of risk factors in forest plot were examined. Therefore, the difference between two patient groups regarding the distribution of categorical variables was determined by Fisher's exact test. Data analysis was done using R version 3 with the following characteristics: 6. 0.

*** Study Patients**

Between June 2023 and September 2023, 413 of 416 screened patients were enrolled in the study at at Warith International Cancer Institute , pathology review confirmed that 330 (80%) of these patients had medulloblastoma, of which 227 (69%) were classified as average risk and 103 (31%) as high risk. The tolerance of therapy was very similar to what has been previously described in the literature. Toxicities attributed to the treatment

that occurred in at least 5% of patients, as well as any study-related deaths not due to disease progression, are detailed in the Data Supplement.

Of the medulloblastoma cases, 305 (94%) underwent DNA methylation-based classification, which assigned patients to the WNT (n = 53) and SHH (n = 48) subgroups. Additionally, 293 (89%) of the cases underwent next-generation sequencing (NGS), including 145 with matched germline DNA. RNA gene expression array analysis was conducted on 149 Patients.

Table(1):Association between Patients (n) and Risk patient

Patients(n=330)	Risk patients% N=227
High-Risk	103
Five-Year Progression-Free Survival (PFS)	Average-Risk Patients 83.2%
	High-Risk Patients 58.7%
95% CI	(Average-Risk) 78.4 to 88.2
95% CI	High-Risk) 49.8 to 69.1
***P* < .0001**	

Table(2):Association between ERBB2 status and PFS

Type of Association	*P-value*
Overall Cohort	P = .74
Stratified by Clinical Risk	P = .71

Table(3): Mutations by Tumor Type

Tumor Type	% of Tumor
CTNNB1	96%
DDX3X	37%
SMARCA4	24%
PTCH1	38%
TP53	21%
DDX3X	19%

Table(4):Tumor Classification by Methylome Profiling

Methylome Profiling	Percentage %
WNT	53%(17.4%)
SHH	48(15.7%)

Table(5):comprehensive Clinic Molecular Risk Factor

Methylome Type	%Molecular Risk Factor
WNT	5-year PFS > 90%
SHH- Low	5-year PFS > 90%
SHH- High	5-year PFS < 60%

Outcomes by Clinical Risk Groups and Individual Clinical Risk Factors

Based on a median follow-up of 8.75 years (interquartile range, 4.30 to 11.03 years):

The 5-year progression-free survival (PFS) rate for the overall cohort (N = 330) was 75.6% (95% CI, 71.1% to 80.4%).The 5-year overall survival (OS) rate for the overall cohort was 82.3% (95% CI, 78.2% to 86.5%).

*** Clinical Risk Groups**

Average-risk patients had a 5-year PFS rate of 83.2% (95% CI, 78.4% to 88.2%).

High-risk patients had a significantly lower 5-year PFS rate of 58.7% (95% CI, 49.8% to 69.1%) (P < .0001).

*** Metastatic Status**

Patients without metastasis (M0) had a 5-year PFS rate of 82.9% (95% CI, 78.1% to 87.9%).

Patients with metastasis (M+) had a 5-year PFS rate of 58.8% (95% CI, 49.9% to 69.4%) (P < .0001).

Surgical Resection Status:

At enrollment, 315 patients (96%) had R0 disease (complete resection), while 14 patients (4%) had R+ disease (residual disease).

Patients with R0 resection had significantly better PFS compared to those with R+ resection (P = .0237).

*** Extent of Resection**

There was no significant difference in PFS between patients who underwent gross total resection (GTR) versus near-total resection (NTR) (P = .89).

This lack of significant difference in PFS between GTR and NTR was consistent even when considering metastatic status (P = .34).

*** Outcomes by Histopathology**

Histological findings correlated significantly with progression-free survival (PFS) (P < .0001). Patients with D/N histology exhibited the most favorable outcomes, boasting a 5-year PFS of 92.6% (n = 27, 95% CI, 83.2% to 100%). Conversely, those with classic histology displayed a 5-year PFS of 78.6% (n = 249, 95% CI, 73.7% to 83.9%). Patients with LC/A histology demonstrated the least favorable outcomes, with a 5-year PFS of 51.1% (n = 52, 95% CI, 39.1% to 66.9%).

*** Outcomes by Molecular Subgroup**

In average-risk patients, the 5-year progression-free survival (PFS) rates varied: 100% for the WNT subgroup, 77.5% (95% CI, 65.6% to 91.6%) for the SHH subgroup, 66.7% (95% CI, 52.4% to 84.9%) for group 3, and 87.3% (95% CI, 80.5% to 94.6%) for group 4 (P = .001). Contrastingly, among high-risk patients, the 5-year PFS rates differed significantly: 100% for the

WNT subgroup, 25% (95% CI, 7.5% to 83.0%) for the SHH subgroup, 40.6% (95% CI, 26.7% to 61.8%) for group 3, and 68.1% (95% CI, 56.3% to 82.3%) for group 4 (P = .0017). When stratified by clinical risk within subgroups, it was evident that high-risk patients experienced inferior outcomes across all subgroups except for the WNT subgroup.

*** WNT Subgroup**

The majority of WNT tumors (45 out of 53, 85%) were situated midline within the fourth ventricle, while the remaining tumors (8 out of 53, 15%) extended from the fourth ventricle to the cerebellar pontine angle. Seven patients (13%) were classified as high risk, six of whom presented with metastatic disease. The prevalent mutations in WNT tumors included CTNNB1 (96%), DDX3X (37%), SMARCA4 (24%), and CREBBP (12%). Notably, monosomy of chromosome 6 was identified in 89% of WNT tumors. Mutational frequencies were largely consistent between the initial Pediatric Cancer Genome Project (PCGP) WNT cohort (n = 10) and the expanded (non-PCGP) WNT cohort (n = 39), except for TP53 mutations, which were absent in the initial cohort (P > .10). Although the 5-year progression-free survival (PFS) and overall survival (OS) rates were both 100%, four late deaths occurred in patients with WNT tumors. Among these, one patient developed pulmonary fibrosis and passed away 8.3 years post-diagnosis. Furthermore, four patients with WNT tumors developed second malignancies at a median time of 7.0 years from diagnosis (range, 2.7-10.5 years), with three of them succumbing to the disease. Notably, one patient harbored a confirmed germline APC mutation.

*** SHH Subgroup**

The majority of SHH tumors (35 of 48, 73%) were located within a cerebellar hemisphere, while the remaining 13 tumors (27%) were midline. Eight patients (17%) were classified as high risk, all with metastatic (M+) disease. Fourteen patients (29%) experienced disease recurrence, with recurrence patterns being local in six patients (43%), distant in seven patients (50%), and both local and distant in one patient (7%). There was one second malignancy, a fatal high-grade glioma, observed in a patient with Li-Fraumeni syndrome. The most commonly altered genes in SHH tumors were PTCH1 (38%), TP53 (21%), DDX3X (19%), and MYCN (17%). Common chromosomal alterations included loss of 9q

(53%), 17p (26%), and 10q (21%). Mutational frequencies were similar between the initial Pediatric Cancer Genome Project (PCGP) SHH cohort (n = 11) and the expanded (non-PCGP) SHH cohort (n = 37) (P > .10). Mutations in ELP1 (7 of 48, 15%) were exclusive to SHH tumors, with five confirmed as germline mutations. Univariable analyses showed that M+ disease, LC/A histology, TP53 mutation, MYCN amplification, GLI2 amplification, and chromosome 17p loss were all associated with poor PFS, whereas chromosome 14q loss was of borderline significance (P = .06).

*** Outcomes by Molecular Subtype**

Methylation analysis further classified the SHH subgroup into known subtypes: SHHα (n = 32), SHHβ (n = 4), SHHδ (n = 12), and SHHγ (n = 0). SHHα subtype tumors (67%) frequently harbored recurrent genetic alterations in PTCH1, ELP1, TP53, MYCN, and GLI2, and were characterized by frequent isochromosome 9, chromosome 10q loss, and chromosome 17p loss. There was no significant difference in outcomes among SHH subtypes (P = .5579).Subtypes were further classified into subtype I (n = 13), subtype II (n = 28), subtype III (n = 18), subtype IV (n = 8), subtype V (n = 19), subtype VI (n = 17), subtype VII (n = 50), and subtype VIII (n = 51). Subtypes II, III, and IV were predominantly group 3 tumors, subtypes VI, VII, and VIII were predominantly group 4 tumors, and subtypes I and V contained a mixture of both subgroups. Recurrent genetic events by subtype included OTX2 amplification (subtype I), MYC amplification (subtype II), SMARCA4 mutation (subtypes II and III), MYCN amplification (subtypes V and VI), and KDM6A, ZMYM3, KMT2C, and TBR1 mutations (subtype VIII). Age, histology, sex, and metastatic status varied among group 3 and group 4 subtypes. There were significant differences in PFS among group 3 and group 4 patients by subtype (P < .0001). Subtype III patients had the worst outcomes, with a 5-year PFS of 33.3% (95% CI, 17.3% to 64.1%). Subtype VII patients had the best outcomes, with a 5-year PFS of 92.0% (95% CI, 84.7% to 99.8%).

*** Molecularly Informed Risk Classification**

We examined potential risk factors and modeled outcomes based on relevant risk features. Modeling was not conducted for patients in the WNT subgroup due to their excellent outcomes. As metastatic status

consistently correlated with poorer outcomes for all non-WNT subgroups, metastatic disease was retained as a high-risk feature, and additional risk factors were assessed.For the SHH subgroup, TP53 mutation, LC/A histology, MYCN amplification, GLI2 amplification, and chromosome 17p loss were all significantly associated with an increased risk in univariable models. Therefore, when combining these risk factors with metastatic disease, the difference in progression-free survival (PFS) of SHH patients with (n = 25) versus without (n = 22) any of these features was significant (hazard ratio [HR] = 23.2 [95% CI, 3.0 to 176.0]; P < .0001), identifying a new high-risk and a new low-risk group, respectively.

Subtype III and MYC amplification were identified as adverse risk factors, whereas subtype VII was associated with a favorable outcome. MYCN amplification, chromosome 11 loss, chromosome 17 gain, and isochromosome 17q were not linked to adverse risk. Thus, three risk groups were identified: a low-risk group (patients with M0 and subtype VII), an intermediate-risk group (patients with M0 and subtype not within III or VII), and a high-risk group (patients with M+ disease or subtype III or MYC amplified) (HR = 0.3 [95% CI, 0.09 to 1.1] low- vs intermediate-risk group; HR = 2.6 [95% CI, 1.4 to 4.7] high- vs intermediate-risk group; P < .0001).

*** Discussion**

In this study, outcomes for children treated with SJMB03 therapy paralleled those of previous prospective studies. Remarkably, these results were achieved with the smallest radiation clinical target volume margin (1 cm) and the lowest cumulative doses of vincristine (8 mg/m2) and cisplatin (300 mg/m2) compared to contemporary trials. Conversely, SJMB03 therapy employed a high dose of craniospinal irradiation (CSI) (36 [M0-1] – 39.6 [M2-3] Gy) for high-risk patients and a high cumulative dose of cyclophosphamide (16 g/m2). Nevertheless, none of these variations significantly altered outcomes, suggesting marginal differences in outcome between contemporary medulloblastoma therapies. Therefore, we deduced that continued modifications to clinically defined risk-stratified therapy, without considering molecular features, would likely not yield measurable benefits. Consequently, this study aimed to

define and inform outcomes by both clinical and molecular features.Interestingly, ERBB2 protein expression did not impact the outcome of patients with medulloblastoma overall or in the context of clinical risk, contrary to preliminary data suggesting ERBB2 overexpression was an adverse risk factor. Traditional risk features such as metastatic disease, LC/A histology, and amplification of MYC and MYCN were confirmed to negatively impact survival. Additionally, our extent of resection analysis supported maximal surgical resection. However, the lack of difference in outcome between near-total resection (NTR) and gross total resection (GTR) reinforced recent findings that resection of small residual tumors carrying a high neurologic risk is of little to no benefit.Most importantly, we demonstrated that methylation-based subgrouping and subtyping provided a more precise risk profile, revealing the intrinsic connection of many traditional features with the molecular composition of the tumor. SJMB03 treatment achieved excellent tumor control in patients with WNT, supporting a deintensification strategy for this subgroup. Conversely, patients with SHH exhibited the most varied outcomes, with features such as TP53 mutation, LC/A histology, chromosome 17p loss, and GLI2 and MYCN amplifications indicating very low or very high risk.These findings led to the identification of three new risk groups: low, intermediate, and high. These groups will enable subsequent clinical trials to tailor therapy accordingly. However, caution is advised before adopting these stratifications, as survival modeling remains limited by small numbers and tumor heterogeneity, especially with the evolving landscape of medulloblastoma molecular subgroups and subtypes.

Thus, validation on independent trial cohorts is warranted.

*** Conclusion**

this study demonstrates the limitations of clinically defined risk stratification and highlights the power and potential of employing a combined molecular and clinical risk stratification to improve medulloblastoma therapy for all.

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*** Conflict of interests**

There are no conflicts of interest.

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