Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

# A Long-Term Survival and Prognostic Determinants in Pediatric Medulloblastoma: National Cohort from Kazakhstan with Implications for Central Asia

**Nussupova Raigul**
Non-Joint Stock Company Astana Medical University
**Mussazhanova Zhanna**
Nagasaki University
**Hirokazu Kurohama**
kurohama-h@nagasaki-u.ac.jp

Nagasaki University
**Pak A. Laura**
National Research Oncology Center
**Kenta Masui**
Nagasaki University
**Ibraimov A. Bakytkali**
Corporate Fund University Medical Center
**Muldakhmetov S. Miram**
Non-Joint Stock Company Astana Medical University
**Masahiro Nakashima**
Nagasaki University

**Research Article**

**Keywords:** pediatric medulloblastoma, long-term survival, prognostic factors, histopathology, resource-limited settings

**Posted Date:** July 9th, 2026

**DOI:** https://doi.org/10.21203/rs.3.rs-9746831/v1

**License:** This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

**Additional Declarations:** No competing interests reported.

## Abstract

# Background

Medulloblastoma is the most common malignant pediatric brain tumor. Molecular risk stratification has improved outcomes in high-income countries, but access to molecular diagnostics remains limited in many low- and middle-income settings. This study aimed to evaluate long-term clinical outcomes and prognostic factors in a national pediatric medulloblastoma cohort from Kazakhstan, using histology-oriented diagnostic strategies under resource-constrained conditions.

# Methods

We conducted a retrospective cohort study of children and adolescents (0–18 years) with histologically confirmed medulloblastoma treated between 2015 and 2023 at the Corporate Fund University Medical Center, Astana. Centralized review followed the 2021 WHO classification. In the absence of routine molecular profiling, enhanced histopathology (including reticulin staining) was used to identify nodular variants. Overall survival (OS) and event-free survival (EFS) were estimated by Kaplan–Meier analysis and prognostic factors were evaluated using multivariable Cox models.

# Results

Sixty-eight patients were included, with a median follow-up of 173 months; 68.8% were alive at last follow-up. Combined chemoradiotherapy yielded the most favorable survival (76.6%). Age ≥ 4 years independently predicted improved OS and EFS, whereas metastatic disease at diagnosis, particularly M3 stage, was the strongest adverse factor for OS. Near-total or total surgical resection independently predicted improved EFS. Histological subtype alone was not an independent prognostic factor.

# Conclusion

Standard multimodal therapy achieved long-term survival comparable to the lower range of international reports, despite limited molecular diagnostics. Age and metastatic stage were key prognostic determinants. Resource-adapted histopathologic approaches, including reticulin staining, can improve diagnostic accuracy and support risk-adapted management in settings without routine molecular profiling.

## Introduction

Medulloblastoma (MB) is the most common malignant pediatric brain tumor, representing approximately 20% of all childhood central nervous system (CNS) neoplasms worldwide [1]. Modern management relies on maximal safe resection, craniospinal irradiation (CSI), multi-agent chemotherapy, and

increasingly on molecular subgrouping. This molecular classification has enabled MB classification from a histologically defined tumor into a biologically heterogeneous disease requiring risk-adapted therapy [2]. In high-income settings, survival for standard-risk MB ranges from 70–85%, driven by early diagnosis, specialized neurosurgical care, and integration of molecular diagnostics [3].

In contrast, low- and middle-income countries (LMICs), including Kazakhstan and other countries in Central Asia, face substantial challenges such as limited access to specialized pediatric neuro-oncology centers, diagnostic delays related to geographic disparities, lack of routine molecular diagnostics, and constraints in radiotherapy infrastructure [3,4]. As a result, outcomes in LMICs remain considerably poorer, with reported 5-year survival rates often ranging from 40% to 60% [5,6]. Furthermore, systematic national data from Kazakhstan and Central Asia are largely lacking, hindering regional cancer control strategies, protocol harmonization, and integration into international collaborative trials.

Histopathology remains the cornerstone of MB diagnosis in resource-limited settings. However, relying solely on hematoxylin-eosin (H&E) staining may lead to misclassification of nodular variants, including desmoplastic/nodular (D/N) MB and MB with extensive nodularity (MBEN), resulting in important prognostic implications [7]. Although molecular subgrouping is the diagnostic standard, its routine implementation in LMICs remains limited. Therefore, refined histopathological techniques and surrogate immunohistochemical markers remain essential for risk stratification.

With a population of nearly 20 million spread across the world’s ninth-largest country, pediatric neuro-oncology care in Kazakhstan is concentrated in only two national centers: the Corporate Fund University Medical Center in Astana and the Joint-Stock Company National Scientific Center for Children's Surgery in Almaty. No national MB registry exists, and molecular diagnostics are not routinely performed, leaving a critical gap in understanding disease patterns and outcomes in Central Asia.

To our knowledge, this study represents the first systematic investigation of a national cohort of pediatric patients with MB from Kazakhstan and the Central Asian region. The study aims to characterize the clinical presentation, histopathological features (including the implementation of silver staining for subtype refinement) and treatment approaches in this population, providing a foundation for improved understanding of the disease landscape in a previously underrepresented region.

Beyond describing national outcomes, this study aims to identify the most relevant prognostic factors under real-world LMIC conditions. By examining clinical presentation, treatment heterogeneity, and long-term survival, we sought to highlight diagnostic and therapeutic gaps that currently shape MB care in Central Asia.

## Material and methods

# Patient Cohort

We retrospectively analyzed consecutive pediatric patients (0–18 years) with confirmed MB treated at the Corporate Fund University Medical Center (Astana, Kazakhstan) between 2015 and 2023. Patients with formalin-fixed paraffin-embedded tumor tissue and clinical follow-up were included, while those without histological verification or with secondary CNS tumors were excluded. No additional selection criteria were applied. Cases underwent histopathologic review at Nagasaki University according to the 2021 WHO classification of CNS tumors. Clinicopathologic characteristics are shown in Table 1. This study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee of Non-Joint Stock Company Astana Medical University (approval No. 6). Informed consent was obtained from all patients. In addition, the study protocol was approved by the ethics committees at Nagasaki University, Japan.

Table 1
Clinical and treatment characteristics of pediatric patients with medulloblastoma (N = 68)

| Variables | Categories | N (%) |
|---|---|---|
| Age group | < 4 | 12 (17.6) |
| Sex | Male | 44 (64.7) |
| OS event | Death | 24 (35.3) |
| Relapse event | No relapse/Progression/Death | 40 (58.8) |
| | Relapse/Progression/Death | 28 (41.2) |
| Therapy outcome | Death | 4 (5.9) |
| | Partial response | 10 (14.7) |
| | Process stabilization | 14 (20.6) |
| | Progression | 6 (8.8) |
| | Relapse | 9 (13.2) |
| CSF cytology | Yes | 1 (1.5) |
| Metastatic stage | M0 | 52 (76.5) |
| | M1 | 2 (2.9) |
| | M2 | 3 (4.4) |
| | M3 | 11 (16.2) |
| Tumor stage | T1 | 9 (13.2) |
| | T2 | 24 (35.3) |
| | T3a | 11 (16.2) |
| | T3b | 21 (30.9) |
| | T4 | 3 (4.4) |
| Residual tumor status | R1 | 28 (41.2) |
| | R2 | 21 (30.9) |
| | R3 | 17 (25) |
| | R4 | 2 (2.9) |
| Surgical resection grade | S1 | 27 (39.7) |
| | S2 | 25 (36.8) |
| Due to missing data, the denominators varied across the analyses. | | |

| Variables | Categories | N (%) |
|---|---|---|
| | S3 | 13 (19.1) |
| | S4 | 3 (4.4) |
| Therapy mode | Chemotherapy + Radiotherapy | 47 (69.1) |
| | Chemotherapy + Radiotherapy + Autologous HSCT | 7 (10.3) |
| | Chemotherapy only | 12 (17.6) |
| | Radiotherapy only | 2 (2.9) |
| Metastasis status | Metastatic | 16 (23.5) |
| Histology | Classic | 32 (47.1) |
| | D/N | 28 (41.2) |
| | MBEN | 7 (10.3) |
| | LC/A | 1 (1.5) |
| Due to missing data, the denominators varied across the analyses. | | |

## Histopathological Evaluation and Silver (Reticulin) Staining

Tumors were classified according to the 2021 WHO classification of CNS tumors. Given the limited access to molecular diagnostics during the study period, detailed morphological assessment was emphasized. Silver (reticulin) staining was selectively performed in cases with equivocal H&E morphology to refine histological subtyping, based on diagnostic expertise from Nagasaki University. Manual in-house ammoniacal silver impregnation was used, enabling visualization of reticulin meshwork and nodular architecture critical for distinguishing D/N MB and MBEN from classic subtypes [2]. This histopathology-driven approach aligns with Asian Oceanian Society of Neuropathology–Adapting Diagnostic Approaches for Practical Taxonomy in Resource-Restrained Regions (AOSNP-ADAPTR) principles and provides a practical strategy for diagnostic refinement in resource-limited settings.

## Treatment

Treatment was delivered according to the nationally-approved clinical protocol for pediatric MB in Kazakhstan, based on HIT 2000 and HIT-REZ 2005 regimens [8]. All patients received multimodal therapy including surgery, radiotherapy, and chemotherapy, with risk-adapted intensity. Maximal safe resection was the surgical goal; extent of resection and residual disease were assessed by early postoperative magnetic resonance imaging (MRI) (24–48 h) and incorporated into the risk stratification. Postoperative treatment allocation was determined by age, histological subtype, metastatic status (Chang M-stage), and residual tumor burden (Chang R-stage). Patients aged ≥ 4 years received craniospinal irradiation

(23.4 Gy for standard-risk or 36 Gy for high-risk disease) with a focal boost to 54 Gy, while radiotherapy was deferred or modified in younger patients. Adjuvant chemotherapy followed risk- and age-adapted HIT-based regimens. Disease status and treatment-related toxicity were monitored using serial neuroimaging and clinical assessments per national protocol [8]. Routine molecular classification was not available.

# Statistical Analysis

Baseline demographic, clinical, and pathological characteristics are summarized using descriptive statistics. Categorical variables are reported as frequencies and percentages, and continuous variables as means (SD) or medians (IQR). The primary endpoints were overall survival (OS) and event-free survival (EFS). Survival was estimated using the Kaplan–Meier method and compared using the log-rank test. Prognostic factors were evaluated using Cox proportional hazards models, with hazard ratios (HRs) and 95% confidence intervals (CIs). Variables with p-values < 0.1 in the univariate analyses were considered for multivariable modeling, and final models were derived using backward likelihood ratio selection. Statistical significance was set at $p < 0.05$. Analyses were performed using SPSS (version 25; IBM Corp., Armonk, NY). Due to the retrospective study design and incomplete data, analyses were conducted on available cases, resulting in minor sample size variation without data imputation.

## Results

# Clinical and Treatment Characteristics

Table 1 summarizes the baseline clinical, pathological, and treatment characteristics of the patients with MB included in the study (n = 68). While the majority of patients were aged ≥ 4 years (82.4%), 17.6% were < 4 years at the time of diagnosis. The cohort demonstrated a male predominance (64.7%), consistent with the global trends for MB. At the last follow-up, 44 (64.7%) patients were alive, and 24 (35.3%) had died. Relapse, progression, or death (EFS events) occurred in 28 patients (41.2%), whereas 40 patients (58.8%) remained event-free.

## Extent of Disease and Surgical Status

Cerebrospinal fluid (CSF) dissemination (positive fluid cytology) was documented in only one case (1.5%). Most patients were classified as M0 at presentation (76.5%), followed by M3 (16.2%), M2 (4.4%), and M1 (2.9%), indicating that distant metastases are relatively uncommon in this population (Table 1). Tumor staging revealed the following distributions: T1 (13.2%), T2 (35.3%), T3a (16.2%), T3b (30.9%), and T4 (4.4%). Residual tumor assessment showed R1 resection (≤ 1.5 $cm^2$) in 41.2% of patients, followed by R2 (30.9%), R3 (25%), and R4 (2.9%). The surgical resection grades were S1 (39.7%), S2 (36.8%), S3 (19.1%), and S4 (4.4%).

## Treatment Response and Modalities

Regarding treatment outcomes, 5.9% of patients died during therapy, 14.7% achieved partial response, 20.6% had stable disease, 8.8% experienced disease progression, and 13.2% developed relapse. Multimodal therapy combining chemotherapy and radiotherapy was used in most cases (69.1%), whereas 10.3% of patients received additional autologous hematopoietic stem cell transplantation (HSCT), 17.6% received chemotherapy alone, and only 2.9% underwent radiotherapy alone (Table 1).

# Histopathological Features

MBs were predominantly located along the midline, most commonly in the cerebellum, with frequent extensions into adjacent structures. Histopathological classification showed that the classic subtype was the most frequent, observed in 32 patients (47.1%). D/N MB was identified in 28 patients (41.2%), whereas MBEN was diagnosed in 7 patients (10.3%). Only one tumor (1.5%) exhibited large cell/anaplastic (LCA) morphology (Table 1). Thus, while the classic variant predominated, the proportion of nodular subtypes (DN and MBEN combined) was relatively high compared to that in many Western cohorts.

# Treatment Modalities and Therapy Outcomes

Table 2 presents the distribution of OS events and treatment outcomes among pediatric patients with MB, stratified by treatment modality. Chemotherapy combined with radiotherapy was the predominant treatment approach, followed by chemotherapy alone, chemotherapy and radiotherapy with autologous HSCT support, and radiotherapy alone. At the time of analysis, survival was highest in the chemoradiotherapy group, with 76.6% of patients alive (36/47), compared to 41.7% (5/12) in the chemotherapy-only group and 28.6% (2/7) in patients receiving HSCT-supported treatment. In the radiotherapy-only group (n = 2), one patient survived (50%). Mortality was highest in the HSCT-supported group (71.4%) and in the chemotherapy-only group (58.3%), although interpretation is limited by small sample sizes.

Table 2
Treatment modalities and outcomes in pediatric patients with medulloblastoma (N = 64)

| | | Therapy mode | | | Total | |
|---|---|---|---|---|---|---|
| Variables | Events | Chemotherapy only | Chemotherapy + Radiotherapy | Chemotherapy + Radiotherapy + Autologous HSCT | Radiotherapy only | |
| OS event | Alive | 5 (41.7) | 36 (76.6) | 2 (28.6) | 1 (50) | 44 (64.7) |
| | Death | 7 (58.3) | 11 (23.4) | 5 (71.4) | 1 (50) | 24 (35.3) |
| Therapy outcome | Total response | 2 (16.7) | 22 (46.8) | 0 (0) | 1 (50) | 25 (36.8) |
| | Partial response | 0 (0) | 8 (17) | 1 (14.3) | 1 (50) | 10 (14.7) |
| | Process stabilization | 3 (25) | 9 (19.1) | 2 (28.6) | 0 (0) | 14 (20.6) |
| | Progression | 3 (25) | 2 (4.3) | 1 (14.3) | 0 (0) | 6 (8.8) |
| | Relapse | 2 (16.7) | 5 (10.6) | 2 (28.6) | 0 (0) | 9 (13.2) |
| | Death | 2 (16.7) | 1 (2.1) | 1 (14.3) | 0 (0) | 4 (5.9) |

Due to missing data, the denominators varied across analyses.

Response stabilization: stable disease without progression. Relapse was defined as a radiologically or cytologically confirmed recurrence.

With respect to therapeutic response, the chemoradiotherapy group demonstrated the most favorable outcomes, with 46.8% of patients achieving total response, in addition to partial response (17%) and disease stabilization (19.1%). In contrast, the chemotherapy-only group showed limited efficacy, with total response observed in 16.7% of patients, no partial responses recorded, and stabilization in 25%. In the HSCT-supported group, no total responses were observed, while partial response and stabilization were achieved in 14.3% and 28.6% of patients, respectively.

Disease progression occurred in 8.8% of the total cohort and was more frequent in the chemotherapy-only (25%) and HSCT-supported (14.3%) groups compared to the chemoradiotherapy group (4.3%). Relapse was observed in 13.2% of patients overall, most commonly in the HSCT-supported group (28.6%) and in the chemoradiotherapy group (10.6%), whereas no relapse was recorded in the radiotherapy-only subgroup.

# OS and EFS Outcomes

Among 64 evaluable pediatric patients with medulloblastoma (MB), 44 (68.8%) were alive at last follow-up, with a median follow-up duration of 173.0 months (95% CI: 141.6–204.4), reflecting extended long-term observation. Overall, 20 patients (31.2%) died and 24 (37.5%) experienced an event, defined as relapse, progression, or death. Median overall survival (OS) and event-free survival (EFS) were not reached, as more than half of the cohort remained alive and event-free at the time of analysis (Supplementary Table 1).

# Prognostic Factors for OS: Univariate Analysis

Univariate Cox regression analysis revealed that treatment response had the strongest association with OS ($p < 0.001$) (Table 3). Compared with patients achieving complete response, stabilization, progression, and relapse were associated with significantly increased mortality. Metastatic stage (M1–M3 vs. M0) was a significant predictor of worse OS, with clear separation of survival curves (log-rank $p < 0.001$) and retained prognostic value in multivariable analysis (Supplementary Fig. 1).

Table 3
Univariate regression analysis of overall survival outcomes with HR and 95% CI

| | | Overall survival | | | |
|---|---|---|---|---|---|
| Variables | Categories | HR | LCL | UCL | P value |
| Sex | F | | | | 0.123 |
| | M | 0.422 | 0.141 | 1.262 | |
| Age group | < 4 | 1 | | | 0.063 |
| | ≥ 4 | 0.382 | 0.138 | 1.055 | |
| Therapy outcome | Total response | 1 | | | 0.000 |
| | Death | 1.460 | 0.132 | 16.100 | 0.757 |
| | Partial response | 4.497 | 0.823 | 24.573 | 0.083 |
| | Process stabilization | 23.125 | 4.143 | 129.078 | 0.000 |
| | Progression | 9.058 | 1.750 | 46.875 | 0.009 |
| | Relapse | 51.261 | 8.288 | 317.032 | 0.000 |
| Histology | MBEN | 1 | | | 0.262 |
| | Classic | 1.199 | 0.268 | 5.363 | 0.812 |
| | LC/A | 3.898 | 0.348 | 43.715 | 0.270 |
| | D/N | 0.547 | 0.106 | 2.826 | 0.471 |
| Fluid cytology | No | 8.523 | 1.048 | 69.284 | 0.045 |
| | Yes | 1 | | | |
| Metastatic stage | M0 | 1 | | | 0.031 |
| | M1 | 4.850 | 1.067 | 22.056 | 0.041 |
| | M2 | 4.885 | 1.068 | 22.352 | 0.041 |
| | M3 | 2.959 | 1.026 | 8.535 | 0.045 |
| Tumor stage | T1 | 1 | | | 0.416 |
| | T2 | 2.770 | 0.341 | 22.523 | 0.341 |
| | T3a | 3.157 | 0.328 | 30.373 | 0.320 |

HR, hazard ratio; CI, confidence interval; OS, overall survival; HSCT, hematopoietic stem cell transplantation; MBEN, medulloblastoma with extensive nodularity; D/N, desmoplastic/nodular; LC/A, large cell/anaplastic; T, tumor stage; M, metastatic stage; S, surgical resection grade; R, residual tumor status; CSF, cerebrospinal fluid; LCL, lower confidence limit; UCL, upper confidence limit. * tumor stage T1 vs. T2–T3; ** tumor stage T1 vs. T1 vs T3–T4.

| | | | | | |
|---|---|---|---|---|---|
| | T3b | 3.768 | 0.463 | 30.647 | 0.215 |
| | T4 | 9.458 | 0.849 | 105.419 | 0.068 |
| Residual tumor status | R1 | 1 | | | 0.172 |
| | R2 | 1.950 | 0.595 | 6.392 | 0.270 |
| | R3 | 3.410 | 1.112 | 10.456 | 0.032 |
| | R4 | 3.852 | 0.448 | 33.091 | 0.219 |
| Surgical resection grade | S1 | 1 | | | 0.043 |
| | S2 | 1.495 | 0.456 | 4.899 | 0.507 |
| | S3 | 4.231 | 1.335 | 13.409 | 0.014 |
| | S4 | 4.878 | 0.939 | 25.330 | 0.059 |
| Tumor stage* | T1 | 1.748 | 0.714 | 4.281 | 0.221 |
| | T2–T4 | 1 | | | 0.361 |
| Tumor stage** | T1 | 2.766 | 0.340 | 22.493 | 0.341 |
| | T2 | 3.963 | 0.515 | 30.508 | 0.186 |
| | T3–T4 | 1 | | | |
| Therapy mode | Chemotherapy + Radiotherapy | 1 | | | 0.016 |
| | Chemotherapy + Radiotherapy + Autologous HSCT | 0.232 | 0.086 | 0.626 | 0.004 |
| | Chemotherapy only | 1.002 | 0.259 | 3.878 | 0.998 |
| | Radiotherapy only | 0.891 | 0.109 | 7.259 | 0.915 |
| Metastasis status | Non-metastatic | 1 | | | 0.005 |
| | Metastatic | 3.577 | 1.476 | 8.671 | |

HR, hazard ratio; CI, confidence interval; OS, overall survival; HSCT, hematopoietic stem cell transplantation; MBEN, medulloblastoma with extensive nodularity; D/N, desmoplastic/nodular; LC/A, large cell/anaplastic; T, tumor stage; M, metastatic stage; S, surgical resection grade; R, residual tumor status; CSF, cerebrospinal fluid; LCL, lower confidence limit; UCL, upper confidence limit. * tumor stage T1 vs. T2–T3; ** tumor stage T1 vs. T1 vs T3–T4.

Higher residual tumor burden (R3–R4) and subtotal resection (S3) were associated with poorer OS, although residual tumor status showed limited robustness in Cox modeling despite visible curve separation (Supplementary Fig. 2). Treatment modality also influenced OS, with chemotherapy combined

with radiotherapy and autologous HSCT associated with reduced mortality compared with chemotherapy and radiotherapy alone.

Dichotomized metastatic status (metastatic vs. non-metastatic) was associated with inferior OS and relapse outcomes (Supplementary Fig. 1A, B) but was less prognostically informative than M-stage classification. Relapse-free survival showed a similar trend for M2–M3 disease, with weaker separation and lack of significance in Cox analysis (Supplementary Fig. 3). Age, sex, and histological subtype were not significantly associated with OS.

# Prognostic Factors for EFS: Univariate Analysis

Univariate Cox regression analysis revealed that treatment response had the strongest association with EFS ($p < 0.001$), with stabilization, progression, and relapse conferring markedly higher event risk compared with complete response (Table 4). Metastatic stage at diagnosis (M1–M3 vs. M0) was a significant predictor of inferior EFS, as were positive CSF cytology, higher residual tumor burden (R3), and subtotal resection (S3). Treatment modality influenced EFS, with chemotherapy combined with radiotherapy and autologous HSCT associated with reduced event risk compared with chemotherapy and radiotherapy alone. CSF involvement showed a trend toward worse relapse-free survival without reaching statistical significance (Supplementary Fig. 4). Age, sex, and histological subtype were not significantly associated with EFS.

Table 4
Univariate regression analysis of event-free survival outcomes with HR and 95% CI

| | | Relapse/Progression-free survival | | | |
|---|---|---|---|---|---|
| Variables | Categories | HR | LCL | UCL | P value |
| Sex | F | | | | 0.098 |
| | M | 0.435 | 0.162 | 1.167 | |
| Age group | < 4 | 1 | | | 0.085 |
| | ≥ 4 | 0.413 | 0.151 | 1.128 | |
| Therapy outcome | Total response | 1 | | | 0.000 |
| | Dead | 1.456 | 0.132 | 16.061 | 0.759 |
| | Partial response | 4.822 | 0.882 | 26.377 | 0.070 |
| | Process stabilization | 36.905 | 6.924 | 196.701 | 0.000 |
| | Progression | 16.609 | 3.501 | 78.793 | 0.000 |
| | Relapse | 75.070 | 11.845 | 475.772 | 0.000 |
| Histology | MBEN | 1 | | | 0.192 |
| | Classic | 1.424 | 0.325 | 6.239 | 0.639 |
| | LC/A | 4.504 | 0.400 | 50.751 | 0.223 |
| | D/N | 0.625 | 0.126 | 3.103 | 0.565 |
| Fluid cytology | No | 8.523 | 1.048 | 69.284 | 0.045 |
| | Yes | 1 | | | |
| Metastatic stage | M0 | 1 | | | 0.025 |
| | M1 | 4.784 | 1.061 | 21.568 | 0.042 |
| | M2 | 4.604 | 1.020 | 20.781 | 0.047 |
| | M3 | 2.881 | 1.104 | 7.519 | 0.031 |
| Tumor stage | T1 | 1 | | | 0.396 |
| | T2 | 4.406 | 0.563 | 34.506 | 0.158 |
| | T3a | 3.657 | 0.378 | 35.341 | 0.263 |

HR, hazard ratio; CI, confidence interval; EFS, event-free survival; HSCT, hematopoietic stem cell transplantation; MBEN, medulloblastoma with extensive nodularity; D/N, desmoplastic/nodular; LC/A, large cell/anaplastic; T, tumor stage; M, metastatic stage; S, surgical resection grade; R, residual tumor status; LCL, Lower Confidence Limit; UCL, Upper Confidence Limit; *, tumor stage T1 vs. T2–T3; **, tumor stage T1 vs. T1 vs. T3–T4.

| | | | | | |
|---|---|---|---|---|---|
| | T3b | 4.583 | 0.572 | 36.687 | 0.151 |
| | T4 | 11.434 | 1.019 | 128.238 | 0.048 |
| Residual tumor status | R1 | 1 | | | 0.073 |
| | R2 | 1.526 | 0.510 | 4.569 | 0.450 |
| | R3 | 3.468 | 1.307 | 9.203 | 0.013 |
| | R4 | 3.412 | 0.413 | 28.192 | 0.255 |
| Surgical resection grade | S1 | 1 | | | 0.025 |
| | S2 | 1.384 | 0.482 | 3.971 | 0.546 |
| | S3 | 4.119 | 1.467 | 11.569 | 0.007 |
| | S4 | 4.516 | 0.912 | 22.366 | 0.065 |
| Tumor stage* | T1 | 1.406 | 0.629 | 3.142 | 0.406 |
| | T2–T4 | 1 | | | 0.326 |
| Tumor stage** | T1 | 4.392 | 0.561 | 34.399 | 0.159 |
| | T2 | 4.727 | 0.617 | 36.218 | 0.135 |
| | T3–T4 | 1 | | | |
| Therapy mode | Chemotherapy + Radiotherapy | 1 | | | 0.005 |
| | Chemotherapy + Radiotherapy + Autologous HSCT | 0.228 | 0.091 | 0.572 | 0.002 |
| | Chemotherapy only | 1.069 | 0.320 | 3.570 | 0.913 |
| | Radiotherapy only | 0.595 | 0.073 | 4.851 | 0.628 |
| Metastasis status | Non-metastatic | 1 | | | 0.003 |
| | Metastatic | 3.390 | 1.494 | 7.691 | |

HR, hazard ratio; CI, confidence interval; EFS, event-free survival; HSCT, hematopoietic stem cell transplantation; MBEN, medulloblastoma with extensive nodularity; D/N, desmoplastic/nodular; LC/A, large cell/anaplastic; T, tumor stage; M, metastatic stage; S, surgical resection grade; R, residual tumor status; LCL, Lower Confidence Limit; UCL, Upper Confidence Limit; *, tumor stage T1 vs. T2–T3; **, tumor stage T1 vs. T1 vs. T3–T4.

# Association of Histological Subtype with Clinicopathological Characteristics, Treatment Response, and Survival

Histological subtype (MBEN, classic, LC/A, D/N) was not significantly associated with tumor stage, metastatic status, extent of resection, or residual tumor (Supplementary Table 2). Although metastatic disease was numerically more frequent in the classic and D/N subtypes and absent in LC/A, these differences were not statistically significant. Complete remission occurred more often in MBEN and classic tumors, whereas D/N tumors more frequently showed partial response or disease stabilization; progression was rare across all subtypes. However, no significant association was observed between histological subtype and treatment response. Survival status also did not differ significantly by histological subtype, with broadly comparable proportions of survivors across groups despite numerical variation. Overall, histological subtype was not significantly correlated with clinicopathological features, treatment response, or survival outcomes in this cohort.

# Multivariate Analysis of OS and EFS

Multivariate Cox regression analysis revealed that only two variables demonstrated a statistically significant association with OS (Table 5). Age group (≥ 4 years vs. <4 years) was identified as an independent protective factor ($p = 0.031$), with children aged ≥ 4 years showing a significantly lower risk of mortality (HR = 0.219, 95% CI: 0.055–0.868). In contrast, metastatic stage M3 was associated with a substantially increased mortality risk ($p = 0.020$), with an HR of 7.747 (95% CI: 1.386–43.298) compared with the reference group (M0). Other variables, including fluid cytology status, surgical resection grade (S1–S4), and therapy modality (chemotherapy only, chemoradiotherapy, or chemoradiotherapy with HSCT), did not reach statistical significance (all $p > 0.05$). However, higher HR values were observed.

Table 5
Multivariate analysis of overall survival

| Variable | Category | P | HR | 95.0% CI for HR | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| Age group | < 4 vs. ≥4 | 0.031 | 0.219 | 0.055 | 0.868 |
| CSF cytology | No vs. Yes | 0.153 | 18.95 | 0.335 | 1071.072 |
| Metastatic stage | M0 | 0.110 | | | |
| | M1 | 0.206 | 3.819 | 0.480 | 30.411 |
| | M2 | 0.939 | 0.912 | 0.086 | 9.650 |
| | M3 | 0.020 | 7.747 | 1.386 | 43.298 |
| Surgical resection grade | S0 | 0.229 | | | |
| | S1 | 0.207 | 0.330 | 0.059 | 1.850 |
| | S2 | 0.501 | 1.874 | 0.301 | 11.689 |
| | S3 | 0.992 | 1.017 | 0.044 | 23.701 |
| Therapy mode | Chemotherapy + Radiotherapy | 0.143 | | | |
| | Chemotherapy + Radiotherapy + Autologous HSCT | 0.235 | 0.370 | 0.072 | 1.910 |
| | Chemotherapy only | 0.411 | 0.400 | 0.045 | 3.558 |
| | Radiotherapy only | 0.210 | 5.301 | 0.390 | 72.086 |

CI, confidence interval; HR, hazard ratio; M, metastatic stage; S, surgical resection grade; R, residual tumor status; HSCT, hematopoietic stem cell transplantation; CSF, cerebrospinal fluid.

Multivariate Cox regression analysis revealed that age group and surgical resection grade were significantly associated with EFS (Table 6). Age ≥ 4 years was strongly associated with better EFS ($p = 0.004$; HR = 0.086, 95% CI: 0.016–0.455). Surgical resection grade S1 (more complete tumor removal) was associated with improved EFS ($p = 0.039$; HR = 0.143, 95% CI: 0.023–0.903). Metastatic stage M3 showed a borderline association ($p = 0.069$) with poorer EFS (HR = 4.844, 95% CI: 0.883–26.569). No statistically significant associations were observed with sex, CSF cytology positivity, or therapy modality (all $p > 0.05$).

Table 6
Multivariate analysis of event-free survival

| Variables | | P | HR | 95.0% CI for HR | |
|---|---|---|---|---|---|
| | Category | | | Lower | Upper |
| CSF cytology | No vs. Yes | 0.246 | 8.923 | 0.220 | 361.070 |
| Metastatic stage | M0 | 0.341 | | | |
| | M1 | 0.498 | 2.294 | 0.207 | 25.361 |
| | M2 | 0.939 | 0.911 | 0.083 | 10.058 |
| | M3 | 0.069 | 4.844 | 0.883 | 26.569 |
| Surgical resection grade | S0 | 0.075 | | | |
| | S1 | 0.039 | 0.143 | 0.023 | 0.903 |
| | S2 | 0.724 | 1.408 | 0.210 | 9.422 |
| | S3 | 0.779 | 0.610 | 0.019 | 19.262 |
| Therapy mode | Chemotherapy + Radiotherapy | 0.610 | | | |
| | Chemotherapy + Radiotherapy + Autologous HSCT | 0.557 | 0.551 | 0.075 | 4.030 |
| | Chemotherapy only | 0.933 | 1.092 | 0.140 | 8.519 |
| | Radiotherapy only | 0.525 | 2.442 | 0.155 | 38.401 |
| Sex | F vs. M | 0.641 | 1.345 | 0.387 | 4.672 |
| Age group | < 4 vs. ≥4 | 0.004 | 0.086 | 0.016 | 0.455 |

CI, confidence interval; HR, hazard ratio; M, metastatic stage; S, surgical resection grade; HSCT, hematopoietic stem cell transplantation; CSF, cerebrospinal fluid; F, female; M, male.

# Discussion

Pediatric MB remains a global challenge, with distinct clinical realities in middle-income countries such as Kazakhstan. This study provides the first long-term, systematically analyzed national dataset of pediatric MB, reflecting real-world outcomes in a resource-limited setting. With a median follow-up of 173 months and nationwide case coverage from two specialized centers, our cohort highlights both existing gaps and achievable important observations in current practice, including delayed diagnosis related to geographic and regional disparities.

Metastatic dissemination at diagnosis emerged as the strongest adverse prognostic factor in this cohort. Although only 23.5% of patients presented with M1–M3 disease, metastatic stage demonstrated

the clearest separation of survival curves for both OS and EFS and retained independent significance in the multivariate analysis, particularly for M3 disease. This finding aligns with extensive evidence showing that neuraxis dissemination markedly worsens prognosis in pediatric MB [9–11]. While many studies use broader descriptors such as leptomeningeal or drop metastases, survival disadvantage in disseminated disease is consistently reported. CSF positivity was uncommon but, consistent with prior reports, was associated with inferior outcomes [9]. Variability in CSF involvement across studies likely reflects inconsistent staging practices, underscoring the need for standardized metastatic assessment in Kazakhstan.

Age ≥ 4 years was independently protective for OS and EFS, consistent with international data demonstrating improved outcomes in children able to receive full-dose craniospinal irradiation and achieve more complete resections [12–14]. Although some molecularly stratified cohorts report attenuation of age effects [15], our findings reflect treatment constraints in middle-income settings, where younger children often cannot access risk-adapted radiotherapy.

Surgical quality remained clinically relevant. Maximal safe resection (S1) was independently associated with improved EFS, supporting the continued prognostic importance of surgical extent in settings without routine molecular classification. While large molecularly annotated studies suggest reduced prognostic weight of resection extent [15,16], our results indicate that surgical quality remains a key modifiable factor where biological stratification is limited.

Other variables, including CSF status and treatment modality, did not retain significance in multivariate models, consistent with prior evidence showing diminishing prognostic impact once metastatic status and tumor biology are considered [15–17]. The absence of molecular profiling likely reduced discriminative power, reinforcing the need for biologically informed risk stratification in the future.

Combined chemoradiotherapy provided the most favorable outcomes in our cohort, achieving a long-term survival rate of 68.8%, comparable to the lower range of international reports. These findings align with evidence from high-resource and LMIC settings, including studies by Gajjar et al. [18], Diaz-Coronado et al. [6], and a meta-analysis by Zhang et al. [19], confirming that multimodal chemoradiotherapy remains the cornerstone of MB treatment. Despite limited access to HSCT and molecularly adapted protocols, conventional chemoradiotherapy proved feasible and effective in Kazakhstan.

Following the introduction of silver (reticulin) staining, we observed a higher proportion of nodular subtypes (D/N and MBEN) than typically reported in Western cohorts [20–21]. This likely reflects both younger age distribution and improved morphological detection in the absence of molecular profiling. Although histological subtype was not prognostic in our cohort—consistent with evidence that morphology alone has limited prognostic value [22]—accurate histological classification remains essential for surrogate risk assessment in resource-limited settings.

The main findings of this study include long-term follow-up, nationwide coverage, multivariate modeling, and the first systematic implementation of silver staining for MB in Kazakhstan. Limitations include small subgroup sizes and lack of comprehensive molecular classification. Future priorities include development of a Central Asian MB registry, selective DNA methylation profiling, and phased adoption of molecular risk-adapted protocols.

This study has several notable findings. It represents one of the first systematic analyses of pediatric medulloblastoma (MB) in Kazakhstan and the broader Central Asian region, providing nationwide data from a population that has been underrepresented in the neuro-oncology literature. The extended duration of follow-up enables meaningful evaluation of long-term outcomes. In addition, the use of multivariate survival modeling enhances the analytical framework by identifying independent prognostic factors, while the implementation of silver staining supports refinement of histopathological subtype assessment in the absence of advanced molecular diagnostics.

Several limitations should also be acknowledged. The retrospective design may introduce potential bias related to variability in clinical documentation, staging procedures, and treatment approaches over time. The relatively small sample size, particularly within specific subgroups, limits statistical power for detailed analyses. Furthermore, comprehensive molecular classification was not available for most cases, reflecting limited access to modern molecular diagnostics during the study period.

Future priorities include the development of a regional medulloblastoma registry in Central Asia, the gradual integration of DNA methylation profiling into diagnostic workflows, and the phased adoption of molecularly informed risk-adapted treatment strategies.

## Conclusions

This study demonstrates that, despite significant diagnostic and therapeutic constraints, pediatric MB outcomes in Kazakhstan approach a lower spectrum of international benchmarks when conventional chemoradiotherapy is consistently applied. Metastatic dissemination, particularly M3 disease, remains the dominant prognostic determinant, while age ≥ 4 years and high-quality surgical resection continue to confer survival benefit in the absence of molecular profiling. Histological subtypes showed limited prognostic utility without advanced molecular testing; however, the introduction of silver staining substantially improved diagnostic accuracy and represented a feasible enhancement for other resource-limited regions. Therefore, our findings support the continued use of conventional chemoradiotherapy yields survival outcomes comparable to international lower-range benchmarks, supporting its continued use in resource-limited environments, with enhanced histopathological techniques and surrogate biological approaches offering practical pathways to improve diagnostic accuracy and risk stratification until molecular diagnostics become routinely available. Future priorities include expanding surrogate immunohistochemistry-based molecular stratification, incorporating DNA methylation profiling to enable WHO-aligned risk stratification, and establishing a Central Asian MB registry to improve treatment harmonization, guide policy decisions, and foster collaborative research across regions.

# Abbreviations

WHO
World Health Organization
OS
overall survival
EFS
event-free survival
M
metastatic
CNS
central nervous system
CSI
craniospinal irradiation
MB
medulloblastoma
LMICs
low- and middle-income countries
H&E
hematoxylin-eosin
D/N
desmoplastic/nodular
MBEN
medulloblastoma with extensive nodularity
AOSNP-ADAPTR
Asian Oceanian Society of Neuropathology–Adapting Diagnostic Approaches for Practical Taxonomy in Resource-Restrained Regions
HIT 2000
Health Information Technology 2000 course/program
HIT-REZ 2005
HIT Relapsed/Recurrent Study Protocol 2005
MRI
magnetic resonance imaging,R,residual
HRs
hazard ratios,CIs,confidence intervals
IQR
medians
HSCT
hematopoietic stem cell transplantation
CSF

cerebrospinal fluid
DNA
deoxyribonucleic acid.

## Declarations

**Ethical approval and consent to participate:** studies involving human participants were reviewed and approved by the Non-Joint Stock Company Astana Medical University (Astana, Republic of Kazakhstan) and the Nagasaki University Ethics Committee and were conducted in accordance with the Declaration of Helsinki. Written informed consent to participate in this study was obtained from all participants (legal guardians).

**Consent to publication:** not applicable.

**Availability of data and materials:** the dataset used in this study may be made available upon request from Dr. Hirokazu Kurohama (kurohama-h@nagasaki-u.ac.jp), subject to approval from the Non-Joint Stock Company Astana Medical University (Astana, Republic of Kazakhstan) and the Nagasaki University Ethics Committee.

**Competing of interest:** the authors declare no conflict of interest.

**Funding:** this work was funded by theAtomic Bomb Disease Institute, Nagasaki University and the Grant-in-Aid for Scientific Research from the Japanese Ministry of Education, Science, Sports and Culture grant numbers (20K07424, 21K15402, 22K06982).

**Authors' contributions:** RN, ZM, LP, HK, and MN conceived and designed the study. RN, ZM, HK, LP, BI, ZD, MM, KM, and MN, collected and formalized clinicopathological information. RN, ZM, and HK performed the experiments, analyzed and formalized raw data. RN, ZM, and HK and performed statistical analyses. RN and ZM wrote the manuscript. MM, KM, HK, and MN contributed comments to the paper. All authors read and approved the final manuscript.

**Acknowledgments:** the authors would like to thank all the participants in this study for their collaboration.

**Clinical trial number:** Not applicable.

## References

1. 1. Kameda-Smith MM, Lannon M, Almojuela A, et al: National multicentered retrospective review of salvage therapy for pediatric medulloblastoma: a Canadian experience. Childs Nerv Syst 41:391, 2025. https://doi.org/10.1007/s00381-025-07100-z
2. 2. Smith TW: Pathology of medulloblastoma: morphologic features and molecular classification, in IntechOpen eBooks, 2025

3. 3. Mehta M, Somasundaram DB, Munshi A, et al: Challenges and opportunities for treatment of medulloblastoma. Adv Cancer Res 168:221–268, 2025. doi: 10.1016/bs.acr.2025.06.006.
4. 4. Chokoev AL: Epidemiology of brain tumor among children in Kyrgyzstan. Int J Med Res Prof 3:219–222, 2017
5. 5. Mammadinova I, Seitbekov S, Surdin D, et al: Clinicopathological analysis of pediatric posterior fossa tumors: Insights from a national neurosurgical center. J Clin Med Kaz 21:73–79, 2024
6. 6. Diaz-Coronado RY, Alcasabas APA, Baticulon RE, et al: Outcomes of pediatric medulloblastoma in low- and middle-income countries: A retrospective analysis of 335 cases from 8 countries. Neurooncol Adv 7:vdaf086, 2025. doi: 10.1093/noajnl/vdaf086
7. 7. Prados MD: Current strategies for management of medulloblastoma. Diagnostics (Basel) 13:2622, 2023
8. 8. Ministry of Healthcare of the Republic of Kazakhstan: Clinical protocol for diagnosis and treatment: Medulloblastoma (Protocol No. 6). https://diseases.medelement.com/disease/медуллобластома/14822, 2016
9. 9. Allen JC, Epstein F: Medulloblastoma and other primary malignant neuroectodermal tumors of the CNS. J Neurosurg 57:446–451, 1982. doi: 10.3171/jns.1982.57.4.0446.
10. 10. Jin Y, Lu T, Liu B, et al: Epidemiology and survival of primary intracranial malignant tumor patients with drop metastasis: A population-based analysis. Acta Neurochir 166:413, 2024. doi: 10.1007/s00701-024-06309-2.
11. 11. Hukin J, Siffert J, Cohen H, et al: Leptomeningeal dissemination at diagnosis of pediatric low-gradeneuroepithelial tumors. Neuro-oncol 5:188–196, 2003. doi: 10.1215/S1152851702000297.
12. 12. Zeltzer PM, Boyett JM, Finlay JL, et al: Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: Conclusions from the Children's Cancer Group 921 randomized Phase III study. J Clin Oncol 17:832, 1999. doi: 10.1200/JCO.1999.17.3.832.
13. 13. Johnston DL, Keene D, Bartels U, et al: Medulloblastoma in children under the age of three years: A retrospective Canadian review. J Neurooncol 94:51–56, 2009. doi: 10.1007/s11060-009-9799-2.
14. 14. Rutkowski S, Gerber NU, Von Hoff K, et al: Treatment of early childhood medulloblastoma by postoperative chemotherapy and deferred radiotherapy. Neuro-oncol 11:201–210, 2009. doi: 10.1215/15228517-2008-084.
15. 15. Keeling C, Davies S, Goddard J, et al: The clinical significance of sub-total surgical resection in childhood medulloblastoma: A multi-cohort analysis of 1100 patients. EClinicalMedicine 69:102469, 2024. doi: 10.1016/j.eclinm.2024.102469.
16. 16. Thompson EM, Hielscher T, Bouffet E, et al: Prognostic value of medulloblastoma extent of resection after accounting for molecular subgroup: A retrospective integrated clinical and molecular analysis. Lancet Oncol 17:484–495, 2016. doi: 10.1016/S1470-2045(15)00581-1.
17. 17. Albright AL, Wisoff JH, Zeltzer PM, et al: Effects of medulloblastoma resections on outcome in children: A report from the Children's Cancer Group. Neurosurgery 38:265–271, 1996. doi: 10.1097/00006123-199602000-00007.

18. 18. Gajjar A, Chintagumpala M, Ashley D, et al: Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): Long-term results from a prospective, multicentre trial. Lancet Oncol 7:813–820, 2006. doi: 10.1016/S1470-2045(06)70867-1.
19. 19. Zhang M, Liu C, Xue X, et al: Meta of classical chemotherapy compared with high-dose chemotherapy combined with autologous stem cell transplantation in newly diagnosed medulloblastoma patients after radiotherapy. Ann Oncol 30:v152, 2019 (suppl 5; abstr 026). doi: 10.1097/MD.0000000000029372.
20. 20. Choi JY: Medulloblastoma: Current perspectives and recent advances. Brain Tumor Res Treat 11:28, 2023. doi: 10.14791/btrt.2022.0046.
21. 21. Kuzan-Fischer CM, Juraschka K, Taylor MD: Medulloblastoma in the molecular era. J Korean Neurosurg Soc 61:292–301, 2018. doi: 10.3340/jkns.2018.0028.
22. 22. Sursal T, Ronecker JS, Dicpinigaitis AJ, et al: Molecular stratification of medulloblastoma: clinical outcomes and therapeutic interventions. Anticancer Res 42:2225–2239, 2022. doi: 10.21873/anticanres.15703.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTablefigures.docx