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Clinical and Biological Predictors of Survival Following Relapse in Pediatric Medulloblastoma

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ABSTRACT

Children with recurrent medulloblastoma face a dismal prognosis, prompting this study to investigate factors that may predict survival after relapse. We retrospectively examined clinical and biological data collected at initial diagnosis, along with key characteristics observed at relapse, for pediatric patients diagnosed with medulloblastoma between 2007 and 2017 at Gustave Roussy and Necker Hospital. Among 155 patients, 48 (31%) experienced a relapse over a median follow-up of 6.6 years (range, 0.4–12.3 years). The interval from diagnosis to relapse ranged from 1.2 to 87.2 months, with a median of 14.3 months. Relapse patterns included local recurrence in 9 patients, metastatic spread in 22, and combined local and metastatic disease in 17. Second-line interventions involved chemotherapy in 31 cases, radiotherapy in 9, SHH inhibitors in 4, while 4 patients received no further treatment. The overall survival rate at one year post-relapse was 44.8% (95% CI, 31.5–59.0%). Survival outcomes were closely linked to molecular subgroup at initial diagnosis, and additional factors such as radiotherapy during relapse and a longer interval before the first relapse (>12 months) may also influence post-relapse survival.

Keywords: Salvage radiotherapy, Recurrent medulloblastoma, Molecular subgrouping, Time to relapse, Outcome after relapse, Pediatric

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Introduction

Over the past thirty years, the management of medulloblastoma (MB) has advanced considerably due to prospective, multicenter clinical trials. The integration of multimodal therapies—including surgical resection, radiotherapy (RT), and chemotherapy (CT)—has improved outcomes, with approximately two-thirds of patients achieving long-term survival [1]. Prognosis is closely linked to patient age and several established or emerging clinicopathological factors, such as metastatic status, histological subtype, postoperative residual tumor size (< or ≥1.5 cm²), MYC amplification, and, more recently, molecular characteristics [2–5]. For standard-risk patients—typically those older than 3 years at diagnosis, non-metastatic, and with gross total tumor resection—five-year overall survival (OS) ranges from 70% to 85% [6–9]. Conversely, children younger than 3 years, those with subtotal resections (>1.5 cm² residual disease), or metastatic disease at diagnosis are classified as high-risk, often exhibiting five-year OS below 70% [10, 11].

Recent molecular studies have revealed that MB consists of at least four transcriptionally and genetically distinct subgroups: Wingless (WNT), Sonic Hedgehog (SHH), Group 3, and Group 4, each associated with differing clinical outcomes. WNT-subgroup tumors have an excellent prognosis, while Group 3 MB is linked to the poorest outcomes [3–5]. These molecular classifications are increasingly being used to guide therapy; for example, international trials such as SJMB12 (NCT01878617) and PNET5 (NCT02066220) have implemented treatment de-escalation for favorable-risk groups like WNT MB and intensified therapy for high-risk subgroups.

Despite these therapeutic advances, relapse in MB remains a significant challenge in pediatric neuro-oncology. Post-relapse survival is generally poor, with five-year survival rates below 10%, except in cases where patients

did not receive RT at initial diagnosis [12–15]. Notably, Ramaswamy *et al*. [16] reported that relapsed MB tumors generally retain their original molecular profiles, with relapse patterns varying according to subgroup.
While prognostic factors for OS at initial diagnosis are well established, limited data exist regarding predictors of survival following relapse. This study aims to perform a detailed assessment of clinico-biological characteristics at diagnosis and therapeutic management at relapse to identify factors most strongly associated with post-relapse survival, potentially informing treatment strategies and clinical trial design for relapsed MB patients.

Results and Discussion

Patient characteristics at diagnosis

Table 1 summarizes the baseline characteristics of the study cohort. A total of 155 patients (83 males, 72 females) were included in this retrospective analysis, with a median follow-up duration of 6.6 years (range, 0.4–12.3 years). The median age at diagnosis was 6.6 years (range, 0.1–18.4 years). Disease was localized (M0) in 92 children (59%), whereas 63 patients (41%) presented with metastatic involvement (M1–M3) at the time of diagnosis.

Table 1. Clinical characteristics at diagnosis and relapse.

Characteristic	Patients at Diagnosis (n = 155)	Patients with Relapse (n = 48)	Patients without Relapse (n = 107)	p-Value *
Age at diagnosis				
<5 years	58 (37%)	25 (52%)	33 (31%)	**0.0115**
≥5 years	97 (63%)	23 (48%)	74 (69%)	
Sex				
Male	83 (54%)	27 (56%)	56 (52%)	**0.6515**
Female	72 (46%)	21 (44%)	51 (48%)	
Histology at diagnosis				
Desmoplastic/nodular	28 (18%)	9 (19%)	19 (18%)	
Classic	105 (68%)	29 (60%)	76 (71%)	**0.2783**
LCA	13 (8%)	7 (15%)	6 (6%)	
NOS	9 (6%)	3 (6%)	6 (6%)	
DNA methylation subgroups at diagnosis				
WNT	15 (11%)	2 (5%)	13 (14%)	
SHH	33 (24%)	9 (21%)	24 (25%)	**0.0475**
Group 3	38 (28%)	18 (43%)	20 (21%)	
Group 4	51 (37%)	13 (31%)	38 (40%)	
Missing data	18	6	12	
M-stage at diagnosis				
M0	92 (59%)	24 (50%)	68 (64%)	
M1	4 (3%)	1 (2%)	3 (3%)	**0.3296**
M2	18 (12%)	6 (13%)	12 (11%)	
M3	41 (26%)	17 (35%)	24 (22%)	
MYC/MYCN amplification				
No	136 (89%)	39 (81%)	97 (93%)	**0.0248**
Yes	16 (11%)	9 (19%)	7 (7%)	
Missing	3	0	3	
Treatment at diagnosis				**0.2380**

CT-based only	33 (21%)	13 (27%)	20 (19%)	
RT-based	122 (79%)	35 (73%)	87 (81%)	
Treatment regimens at diagnosis				
CT alone	24 (15%)	10 (21%)	14 (13%)	**0.0215**
CT-HDCT	9 (6%)	3 (6%)	6 (6%)	
RT alone	38 (25%)	4 (8%)	34 (32%)	
RT – CT	13 (8%)	3 (6%)	10 (9%)	
CT-HDCT-RT	71 (46%)	28 (58%)	43 (40%)	

Abbreviations: LCA: Large cell/Anaplastic; NOS: Not Otherwise Specified; WNT: Wingless; SHH: Sonic Hedgehog; CT: chemotherapy; RT: radiotherapy; HDCT: High dose chemotherapy. *: Chi2 or exact Fisher's test for comparison of patients' characteristics between patients with and without relapse.

Central histopathological assessment classified 105 cases (68%) as classic medulloblastoma (MB), 28 (18%) as desmoplastic/nodular, 13 (8%) as large cell/anaplastic (LCA), and 9 (6%) as not otherwise specified (NOS); no tumors displayed extensive nodularity. DNA methylation-based subgroup assignment was available for 137 patients (88%), showing that Group 4 was the most frequent (37%), followed by Group 3 (28%) and SHH tumors (24%), with WNT tumors representing the smallest group (11%). Strong correlations were observed between histopathology and molecular subgroups: nearly all WNT tumors (13/15) exhibited classic histology, except one LCA and one NOS case, while all desmoplastic/nodular tumors (n = 28) belonged to the SHH subgroup. In Group 3 MB (n = 38), 26 were classic, 8 were LCA, and 4 were NOS. Among 51 Group 4 MB cases, 48 were classic, 2 LCA, and 1 NOS. Metastases at diagnosis were most common in Group 3 (66%, 25/38), followed by Group 4 (41%, 21/51), less frequent in SHH tumors (18%, 6/33), and absent in WNT MB. MYC amplification was identified in 16 out of 152 patients (11%): three MYCN in SHH, five in Group 4 (one without subgroup data), five MYC in Group 3, and two MYC in Group 4.

Regarding initial treatment, 122 patients (79%) received radiotherapy (RT), either as monotherapy (n = 38; 25%) or combined with chemotherapy (n = 84; 54%). Of these, 10 patients underwent focal RT, while 103 received craniospinal irradiation (CSI), with a median total CSI dose of 36 Gy (range 18–36 Gy) and a median posterior fossa/tumor bed dose of 54 Gy (range 32–68 Gy). Nine patients experienced disease progression before RT could be administered.

In the overall cohort, five-year overall survival (OS) was 77.2% (95% CI, 69.6–83.4%; 41 deaths), and five-year event-free survival (EFS) was 67.4% (95% CI, 59.4–74.6%; 54 events) **(Figure 1)**.

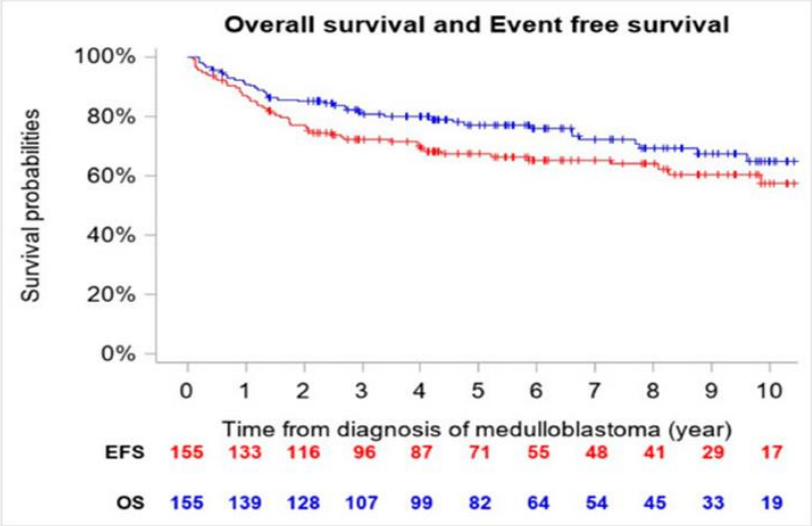
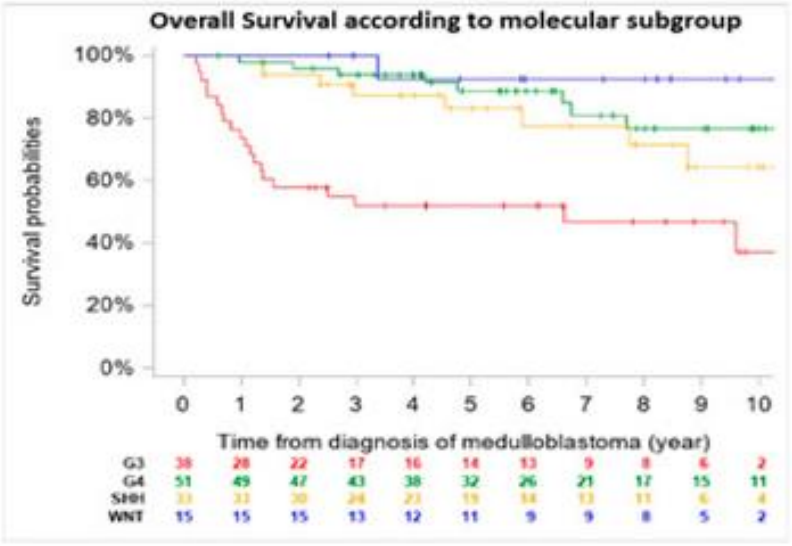


Figure 1. Overall survival (OS) and event-free survival (EFS) for the full cohort (n = 155).

Analysis by molecular subgroup revealed that patients with WNT tumors experienced the highest 5-year OS and EFS, followed in descending order by Group 4, SHH, and Group 3 MB. It should be noted that these survival

estimates were not corrected for variations in initial therapy, such as radiotherapy-based regimens versus chemotherapy alone **(Figure 2)**.



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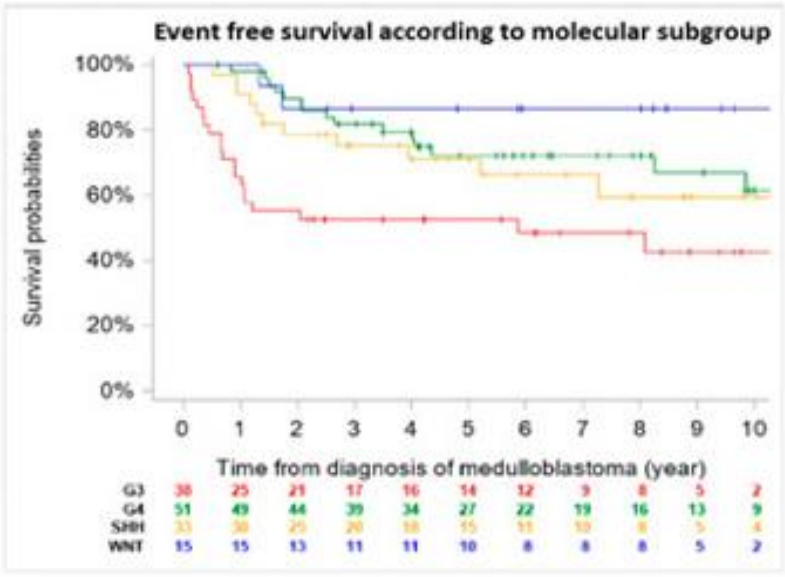


b)

Figure 2. Survival outcomes by molecular subgroup in 137 patients (18 were excluded due to missing DNA methylation data at diagnosis). The 5-year overall survival (OS) was highest for WNT tumors at 92.3% (95% CI, 66.7–98.6%), followed by Group 4 at 88.6% (95% CI, 75.7–95.0%), SHH at 83% (95% CI, 65.6–92.6%), and lowest in Group 3 at 51.8% (95% CI, 36.3–67.0%). Five-year event-free survival (EFS) followed a similar trend: 86.7% (95% CI, 62.1–96.3%) for WNT, 72.2% (95% CI, 57.9–83.1%) for Group 4, 71.3% (95% CI, 53.6–84.2%) for SHH, and 52.6% (95% CI, 37.3–67.5%) for Group 3 MB.

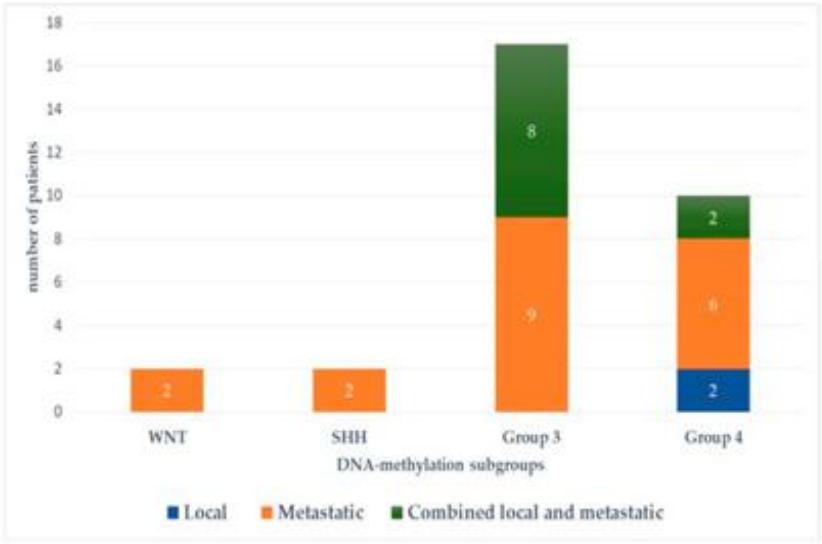
Relapsed medulloblastoma

At the final follow-up, relapse or disease progression was observed in 48 patients (31%), occurring a median of 14.3 months (range 1.2–87.2 months) after initial diagnosis. Surgical intervention or biopsy was performed in focal relapses, particularly in the context of molecular profiling for precision pediatric oncology or when diagnosis was uncertain. The baseline features of relapsed patients are summarized in **Table 1**. Compared with those who

did not relapse, these patients were more often under 5 years of age (p = 0.0115), had Group 3 tumors (p = 0.0475), and carried MYC or MYCN amplifications (p = 0.0248).

Relapses were categorized as local (n = 9), metastatic (n = 22), or combined local and metastatic (n = 17). Although all Group 3 MB patients experienced metastatic relapse, no significant correlation was observed between initial molecular subgroup and relapse pattern when examined individually (p = 0.0769, Fisher's exact test). However, grouping metastatic-only and combined relapses together revealed a statistically significant association between subgroup and relapse type (p = 0.0348).

The type of initial therapy also influenced relapse patterns (p = 0.007, Fisher's exact test). Patients treated with chemotherapy alone were more likely to experience local recurrence, especially in SHH and Group 4 tumors, whereas relapses following upfront radiotherapy were predominantly metastatic across subgroups **(Figure 3)**.



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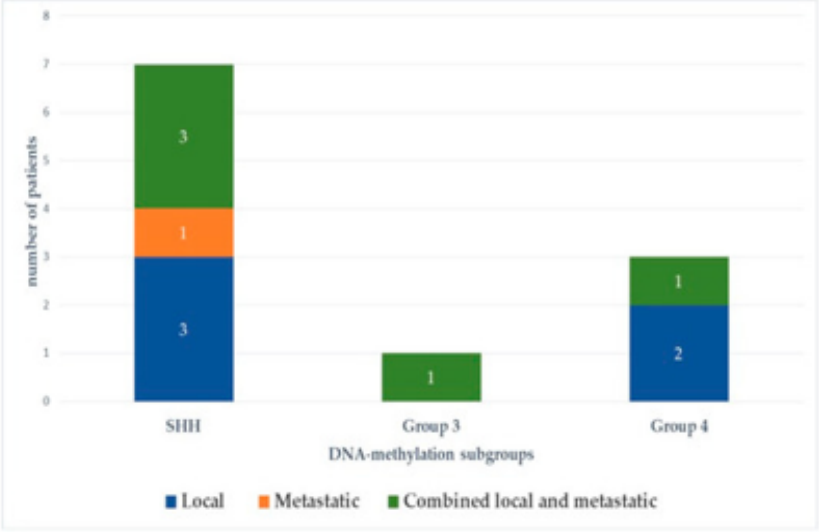


b)

Figure 3. Patterns of relapse stratified by DNA methylation subgroups in patients with medulloblastoma who experienced recurrence after initial therapy, comparing those treated with a radiotherapy-containing regimen (a) versus chemotherapy alone (b).

Time to relapse differed significantly across molecular subgroups (p < 0.0001, Kruskal-Wallis test). The median interval from diagnosis to relapse was shortest for Group 3 MB at 0.66 years (range, 0.1–2.0 years). In comparison, SHH tumors relapsed at a median of 1.29 years (range, 0.51–7.27 years), WNT tumors at 1.53 years (range, 1.33–

1.73 years), and Group 4 MB at 2.08 years (range, 0.84–4.35 years). Considering treatment modality at diagnosis, 20 of the 48 relapses occurred within the first year: 5 of 13 (38%) in the chemotherapy-only group and 15 of 35 (43%) in patients who had received upfront radiotherapy.

Salvage therapies were tailored based on prior treatment and individual patient circumstances. Tumor resection or biopsy was performed in 15 patients, involving nine local recurrences and six metastatic sites. Among the 35 patients who initially received radiotherapy, three underwent re-irradiation (one combined with chemotherapy, two without), two received an SHH-pathway inhibitor (notably, patient #43 was initially classified as SHH MB by IHC but later reclassified as Group 3 by DNA methylation), 26 were treated with chemotherapy alone, and four received no additional therapy. Of the 13 patients whose first-line therapy was chemotherapy alone, three received an SHH inhibitor, four received salvage chemotherapy, and six underwent radiotherapy (three with concurrent chemotherapy, three without).

Figure 4 provides a flowchart illustrating the composition and treatment pathways of the full study cohort.

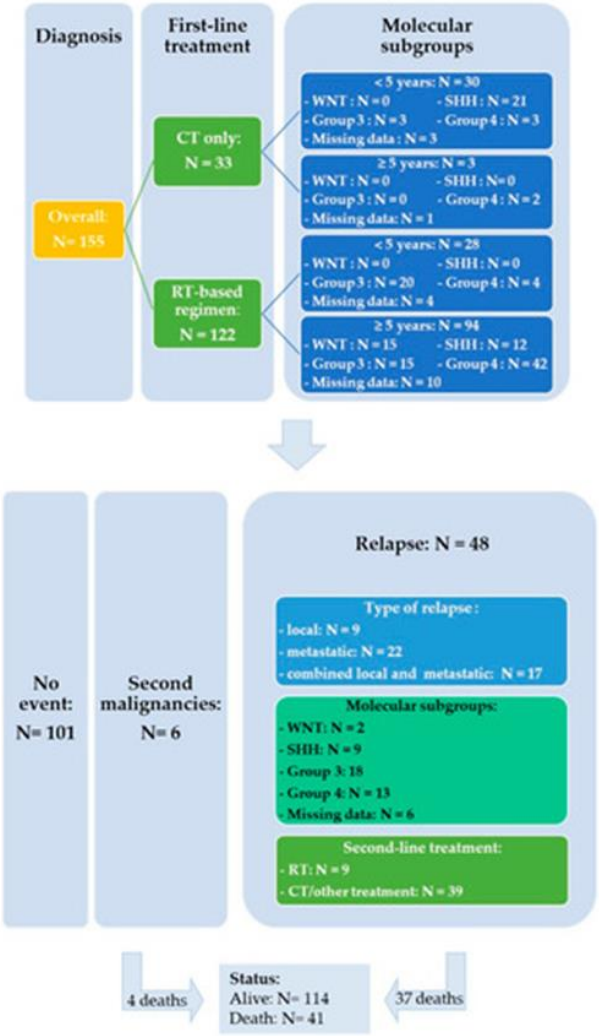


Figure 4. Flowchart of the entire study cohort.

Figure 5 illustrates the initial (upfront) treatment administered to patients with relapsed medulloblastoma, categorized by DNA methylation subgroups. **Figure 6** depicts the therapies delivered at relapse, stratified by molecular subgroup, for patients who had previously received either a radiotherapy-containing regimen or chemotherapy alone.

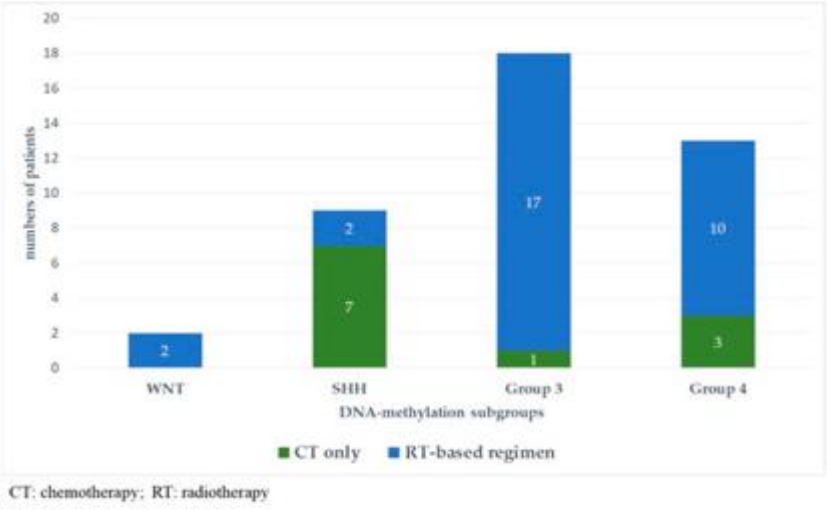
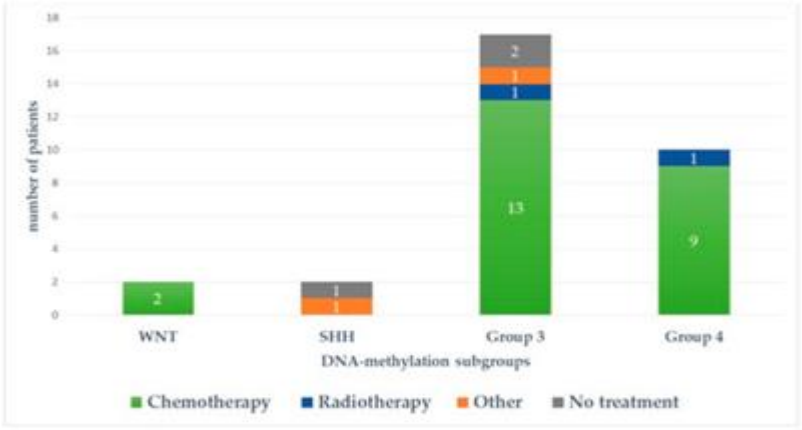


Figure 5. Initial treatment strategies based on DNA-methylation subgroups in patients experiencing relapsed medulloblastoma.



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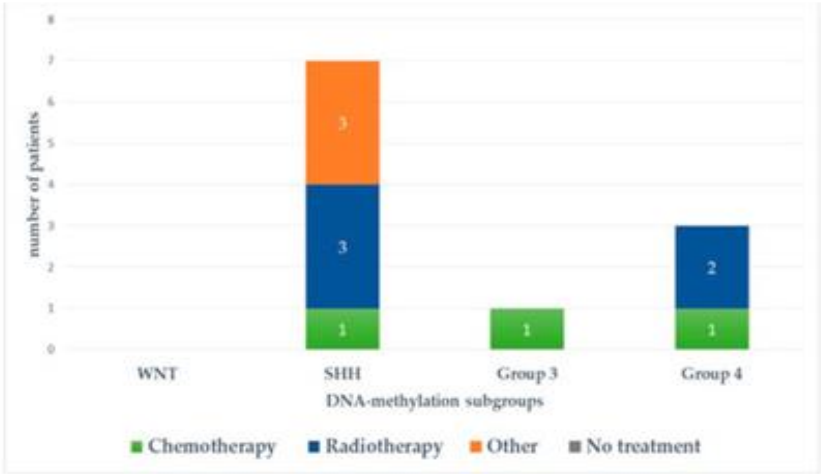

b)

Figure 6. Relapse-phase treatment categorized by DNA-methylation subgroups in patients with medulloblastoma who had previously undergone either radiotherapy-inclusive upfront therapy (a) or chemotherapy-only regimens (b).

Among patients who experienced relapse or disease progression, the median duration of follow-up was 5.6 years (ranging from 0.5 to 10.0 years). From the time of first relapse/progression, the median overall survival was 0.91 years (95% CI: 0.31–1.49; 37 deaths), with estimated overall survival rates at 1, 2, and 5 years of 44.8% (95% CI: 31.5–59.0%), 32.5% (95% CI: 20.5–47.3%), and 19.3% (95% CI: 9.9–34.0%), respectively **(Figure 7)**.

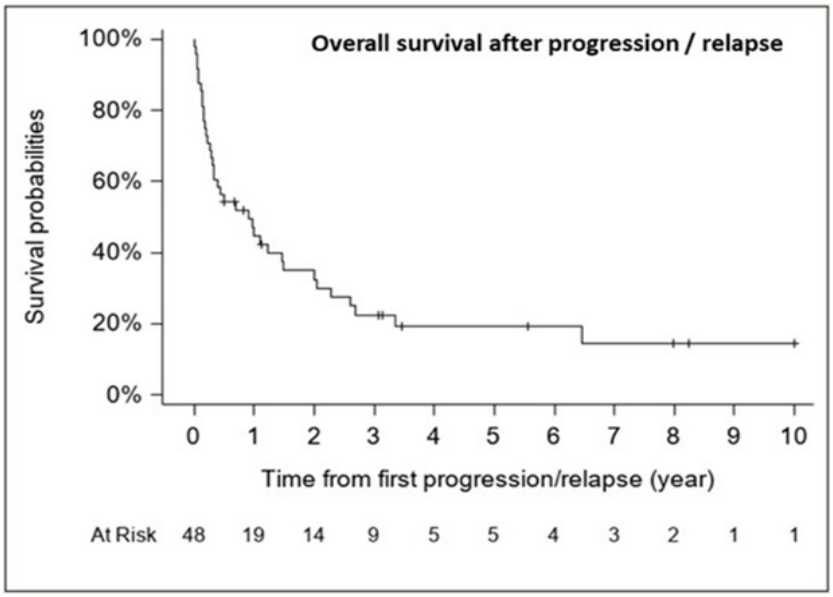

Figure 7. Survival outcomes following relapse or disease progression (n = 48; 37 deaths).

At the latest follow-up, 11 of the 48 relapsed patients were still alive, with a median follow-up of 3.13 years (range: 0.5–10 years). In this subset, relapse or progression occurred at a median of 2.02 years after diagnosis (range: 0.51–3.95 years). Only one patient (#4) experienced recurrence during first-line therapy. Biopsy-confirmed relapse was documented in six cases. The recurrence patterns included local-only in three patients (27%), metastatic in six (54%), and combined local plus metastatic in two (18%).

Of these 11 patients, five had initially received chemotherapy alone; at relapse, four were treated with a combination of therapies including radiotherapy (median 36/54 Gy; range 25.4–36/50.4–54 Gy), and one received SHH-inhibitor therapy. The remaining six patients, who had radiotherapy at diagnosis, were managed at relapse with Temozolomide-based chemotherapy in five cases and SHH-inhibitor therapy in one.

Second malignant neoplasms (SMN)

Six secondary cancers were identified in the cohort: one case of acute leukemia, four posterior fossa high-grade gliomas, and one liver tumor. All were referred for genetic counseling and germline testing, which revealed a TP53 mutation in only a single patient.

Factors influencing post-relapse survival

Table 2 details findings from the penalized multivariable Cox core model and its extensions. The core model incorporated initial treatment, DNA methylation subgroup, age, disease stage (M-stage), and treatment at relapse. DNA methylation subgrouping emerged as the only statistically significant factor for overall survival after relapse ($p = 0.0021$), with Group 3 patients experiencing the highest mortality risk (adjusted HR 13.009; 95% CI: 1.437–117.757), as all 18 Group 3 cases died. Groups 4 and SHH had roughly 1.5-fold increased risk compared to WNT patients.

Although not reaching conventional significance ($p = 0.0910$), radiotherapy at relapse showed a trend toward improved survival (adjusted HR 0.350; 95% CI: 0.104–1.182). Including MYC status produced similar findings. When time to first recurrence was added to the model, DNA methylation subgroup remained significantly associated with post-relapse survival ($p = 0.0190$), and radiotherapy at first relapse became significantly linked to better outcomes (adjusted HR 0.203; 95% CI: 0.055–0.752; $p = 0.0170$).

Table 2. Penalized (Firth's approach) full Cox regression analysis for overall survival post recurrence (n = 48, 37 deaths) (origin time is the date of first progression/relapse) †,*.

Characteristics	# Deaths/ # Patients	Descriptive Core Model		Descriptive Core Model + MYC Status		Descriptive Core Model + Time between Diagnosis and 1st Relapse		Descriptive Core Model + MYC Status + Time between Diagnosis and 1st Relapse	
		HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Treatment at diagnosis CT-based only RT-based	8/13 29/35	1 0.826 [0.233–2.932]	0.7676	1 0.752 [0.199–2.836]	0.6735	1 0.875 [0.242–3.164]	0.8387	1 0.841 [0.221–3.192]	0.7988
DNA methylation at diagnosis WNT SHH Group 3 Group 4	1/2 6/9 18/18 8/13	1 1.437 [0.154–13.391] 13.009 [1.437–117.757] 1.749 [0.246–12.446]	0.0021	1 1.528 [0.158–14.742] 14.682 [1.560–138.158] 1.655 [0.229–11.974]	0.0022	1 1.746 [0.178–17.180] 12.673 [1.349–119.017] 2.514 [0.348–18.147]	0.0190	1 1.782 [0.178–17.872] 13.293 [1.362–129.711] 2.462 [0.335–18.081]	0.0228
Age at diagnosis <5 year ≥5 year	21/25 16/23	1 1.009 [0.361–2.820]	0.9866	1 1.133 [0.381–3.375]	0.8221	1 1.410 [0.482–4.128]	0.5304	1 1.464 [0.481–4.460]	0.5023
M-stage at diagnosis M0 M+	17/24 20/24	1 1.074 [0.423–2.728]	0.8810	1 0.902 [0.319–2.553]	0.8464	1 0.731 [0.280–1.909]	0.5228	1 0.693 [0.246–1.947]	0.4863
Radiotherapy at 1st relapse No Yes	32/39 5/9	1 0.350 [0.104–1.182]	0.0910	1 0.327 [0.095–1.130]	0.0774	1 0.203 [0.055–0.752]	0.0170	1 0.198 [0.052–0.756]	0.0178
MYC/MYCN amplification at diagnosis No Yes	29/39 8/9			1 1.575 [0.574–4.325]	0.3778			1 1.208 [0.441–3.311]	0.7135
Time between diagnosis and 1st relapse *	19/20 18/28					1	0.0235	1 0.295	0.0291

≤1 year	0.289 [0.098–	[0.099–
>1 year	0.846]	0.883]

Abbreviations: CT: chemotherapy; RT: radiotherapy; HR: Hazard Ratio, CI: confidence interval, *: the functional form of the time between diagnosis and 1st relapse was assessed by using a residual-based approach in a univariate analysis, †: Data analysis was based on 42 patients as 6 patients were excluded because of missing data on DNA methylation.

To investigate whether the interval between initial diagnosis and first relapse influences post-relapse survival, we first examined its functional relationship. The assumption of log-linearity was not met (p = 0.0370, univariate analysis). Using quartile-based analysis, we determined a cut-off at the median value of 12 months, revealing a lower risk of death for patients relapsing after this point (HR 0.289; 95% CI: 0.098–0.846, p = 0.0235). Comparable results were observed when MYC status was added to the model along with the other variables (last column of **(Table 2)**).

Given the limited sample size and potential instability of these results, we assessed their robustness using a bootstrap approach. This method involved repeating the analyses on 5,000 randomly resampled datasets (with replacement) drawn from the original cohort and calculating the proportion of times each variable reached statistical significance at the 5% level. Following the threshold suggested by Sauerbrei [17] (60%), the analysis confirmed that DNA methylation-based molecular subgrouping remained a significant prognostic factor for post-relapse overall survival, with a selection frequency exceeding 67%. In contrast, salvage radiotherapy at first relapse showed a selection frequency between 39% and 59%, while the time interval from diagnosis to first relapse was selected in less than 56% of samples. Consequently, no definitive conclusions could be drawn regarding the prognostic impact of these latter two variables on survival after relapse **(Table 3)**.

Table 3. Robustness analyses based on bootstrap resampling.

Characteristics	Descriptive Core Model	Descriptive Core Model + MYC Status	Descriptive Core Model + Time between Diagnosis and 1st Relapse	Descriptive Core Model + MYC Status + Time between Diagnosis and 1st Relapse
Treatment at diagnosis	8.84	9.92	7.62	8.66
DNA methylation at diagnosis	90.24	90.84	67.7	67.32
Age at diagnosis	5.66	5.4	11.66	12.52
M-stage at diagnosis	4.96	9.2	10.88	15.16
Radiotherapy at 1st relapse	39.42	42.42	59.82	59.74
MYC/MYCN amplification at diagnosis		14.7		11.14
Time between diagnosis and 1st relapse			55.38	52.68

There is limited evidence on outcomes after relapse in childhood medulloblastoma (MB) and how clinico-biological features at diagnosis or relapse influence survival post-relapse. In this large retrospective cohort, we investigated factors potentially associated with post-relapse survival, highlighting the prognostic importance of molecular subgrouping at initial diagnosis. Compared with the WNT subgroup, Group 3 MBs carried the highest mortality risk after relapse, followed by Group 4 and SHH tumors. The poor prognosis observed in Group 3 is likely due to the concurrence of several high-risk features at diagnosis, including young age, LCA histology, metastatic disease, and MYC amplification [3–5, 18]. Consistent with earlier studies [16], survival remains low in Group 3 MBs even after relapse.

The timing of relapse is recognized as an important prognostic factor in pediatric cancers, yet its impact in MB is not well defined [19–22]. Our analysis indicated a trend toward improved post-relapse outcomes when relapse occurred beyond 12 months from initial diagnosis. This raises the question of whether specific clinico-biological features at diagnosis could predict early relapse, defined as occurring within the first year. In our cohort, Group 3 MBs relapsed most rapidly, followed by SHH, WNT, and Group 4, with the majority of Group 3 cases relapsing within one year despite most patients receiving upfront radiotherapy. Ramaswamy *et al*. [16] similarly observed subgroup-dependent differences in relapse timing, noting that Group 4 MBs relapse later and tend to survive longer post-relapse, regardless of initial therapy. These findings emphasize the critical need to further characterize

tumor biology at both diagnosis and relapse. Notably, recent studies showed even shorter relapse intervals in previously irradiated Group 3 MB, especially subtype III, when reclassified using second-generation molecular subtypes [18].

Treatment of relapse remains complex and heterogeneous, encompassing options such as re-resection, re-irradiation, conventional chemotherapy, high-dose chemotherapy with autologous stem cell transplantation (HDCT-ASCT), and emerging targeted therapies [23–29]. While upfront radiation combined with chemotherapy has improved survival in children older than 3–5 years with average- or high-risk MB, the benefit of radiotherapy at relapse remains uncertain. Prior reports suggest potential salvage benefits, particularly in young children initially spared radiotherapy, although this approach carries substantial risks of neurocognitive and other long-term toxicities [18, 25, 30]. Despite limited statistical power in our cohort, salvage radiotherapy appeared to influence outcomes positively. Among nine patients who received radiotherapy at relapse, four—initially treated with chemotherapy alone—were alive at the last follow-up.

Contrary to expectations, age, MYC amplification, initial treatment regimen, and metastatic stage at diagnosis were not significantly linked to post-relapse survival in our cohort. The small sample size may have limited the detection of prognostic effects, particularly for MYC status. Previous studies have also found that metastatic dissemination does not necessarily predict post-relapse survival [14, 15].

Interestingly, the relapse pattern did not correlate with the molecular subgroup in our study. Ramaswamy *et al*. [16] reported that subgroup identity rather than initial therapy drives relapse location, with SHH tumors exhibiting more local recurrence and Groups 3 and 4 more often presenting with metastatic relapse. In our cohort, six of nine relapsed SHH patients experienced either metastatic or combined local and metastatic recurrence. Similarly, recent studies confirm a predominance of distant relapses in SHH MB [18]. Although rare in WNT MB, two patients in our cohort developed metastatic relapse despite receiving upfront radiotherapy.

This study has several limitations. Its retrospective design may introduce bias. The small number of relapsed patients restricted analysis of additional potential prognostic factors and limited the ability to draw firm conclusions on the effects of salvage radiotherapy or relapse timing. Additionally, TP53 mutation status was unavailable for SHH MB at diagnosis. Finally, heterogeneity in salvage chemotherapy regimens precludes conclusions regarding the relative effectiveness of different therapeutic approaches.

Materials and Methods

Patient cohort

We retrospectively reviewed the medical records of 155 consecutive patients with medulloblastoma (MB) aged 18 years or younger, diagnosed at Gustave Roussy and Necker University Hospital between 2007 and 2017. Metastatic status was evaluated according to the Chang *et al*. staging system [31]. Written informed consent for the retrospective use of clinical data was obtained from parents or guardians in compliance with Institutional Review Board (IRB) regulations and prior to enrollment in ongoing protocols.

Molecular subgroup classification

Two neuropathologists examined all accessible tumor specimens following the 2016 WHO classification guidelines [32]. DNA was extracted from freshly frozen tumor tissue using the Qiagen DNeasy Blood & Tissue kit (Cat. No./ID 69504) according to the manufacturer's protocol. For methylation profiling, 500 ng of DNA per sample were sent to the Genotyping Core Facility at the German Cancer Research Center (Heidelberg, Germany). Analyses were performed using Illumina Infinium Methylation EPIC or HumanMethylation450 BeadChip arrays following the manufacturer's instructions. Subgroup assignment of MB tumors was obtained through a DNA methylation-based CNS tumor classification platform (www.molecularneuropathology.org, version 11b4). While TP53 mutations are known to correlate with poorer prognosis in SHH MB, this information was not assessed in the current study.

Treatment protocols

Following diagnosis, patients underwent therapy according to different clinical trial protocols, which evolved over time and were tailored based on risk factors, including histology, metastatic involvement, residual disease after surgery, and MYC status at diagnosis. Children under 5 years generally received radiation-sparing protocols [33–38], whereas those older than 5 years were treated with standard multimodal therapy, including craniospinal

irradiation (CSI) [8, 9, 39]. For analytical purposes, patients were categorized into two groups: those receiving chemotherapy (CT) only, and those receiving treatment regimens that included radiotherapy (RT).

Relapse assessment

Disease relapse or progression was confirmed by central review of MRI scans, with biopsy performed in cases where imaging findings were inconclusive.

Statistical analysis

The date of the initial surgery was considered the starting point for diagnosis. Median follow-up duration was calculated following Schemper's approach [40]. Overall survival (OS) was defined from diagnosis to death from any cause or last follow-up, while post-relapse OS was measured from the date of first progression or recurrence to death or last contact. Event-free survival (EFS) encompassed the interval from diagnosis to the first occurrence of relapse, disease progression, second malignancy, or death from any cause. Kaplan–Meier methods were used to estimate OS, post-relapse OS, and EFS. Relapse was defined as the reappearance of local or metastatic disease after an initial treatment response, whereas tumor progression was considered when the lesion grew or new lesions emerged. The time to relapse was calculated from enrollment to the first instance of relapse or progression. Differences in baseline characteristics between patients who experienced relapse/progression and those who did not were evaluated using Chi-Square or Fisher's exact tests.

To explore predictors of survival following relapse, a full Cox proportional hazards model was applied without variable selection, as automated selection techniques in small samples can yield unstable results [41, 42]. A core descriptive model was constructed, including: initial treatment type (chemotherapy alone versus regimens including radiotherapy), DNA methylation subgroup (WNT, SHH, Group 3, Group 4), age at diagnosis (<5 vs. ≥5 years), metastatic stage (M0 vs. M+), and receipt of radiotherapy at first relapse. These variables were chosen because treatment at diagnosis influences OS, other factors are known prognostic markers, and radiotherapy at relapse may serve as salvage therapy. Given the small number of relapsed patients, MYC amplification status and the interval from diagnosis to relapse were added separately and together to examine their effects on post-relapse survival. Histology was excluded from the model due to its strong correlation with DNA methylation patterns. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated using a multivariable Cox model with Firth's penalized maximum likelihood method, which mitigates bias in small datasets [43].

The association between relapse timing and survival was examined using residual-based methods [44]. The proportional hazards assumption was checked using the Grambsch–Therneau test, with no violations detected (data not shown) [45]. Stability of the observed associations was confirmed through bootstrap resampling [17, 46]. P-values were two-sided, with ≤0.05 considered statistically significant. Data were updated as of April 3, 2020, and analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Conclusion

Although survival for newly diagnosed childhood MB has improved over the past decades, outcomes remain poor for patients with recurrent disease. Our study highlights the significant influence of molecular subgroup on survival after relapse and suggests that salvage radiotherapy and a relapse-free interval exceeding 12 months may improve outcomes. These observations could help refine prognostic assessments and support the design of clinical trials targeting relapsed MB.

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