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Impact of salvage treatment for recurrent medulloblastoma in previously irradiated patients (KROG 23-02): A multi-institutional retrospective study

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ABSTRACT

Background: Despite intensified frontline therapy for medulloblastoma, 20–30% of patients still experience disease failure. Outcomes for recurrent disease remain poor, largely due to the lack of standardized salvage strategies. This study evaluated treatment patterns and outcomes of salvage therapy in recurrent or progressive medulloblastoma.
Methods: Patients aged ≤ 21 years with histologically confirmed medulloblastoma diagnosed between 2000 and 2020 were analyzed. Inclusion criteria required prior surgery or biopsy followed by postoperative radiotherapy and completion of initial therapy. Disease recurrence or progression was confirmed by MRI and clinical assessment. Local control treatment (LCT) was defined as salvage radiotherapy or surgery. Primary endpoints were progression-free survival (PFS) and overall survival (OS) from initial recurrence.
Results: Seventy-six patients from five centers were included. The median time to first failure was 23.9 months (IQR, 14.9–36.2). Salvage treatments included chemotherapy alone (n = 26), LCT alone (n = 11), and combined LCT and chemotherapy (n = 30); 9 patients received best supportive care. The 1- and 3-year PFS rates were 47.4% and 7.2%, while OS rates were 81.1% and 42.8%, respectively. In univariate analysis, MYCN non-amplification, chemotherapy, and LCT were associated with improved PFS. In multivariate analysis, both chemotherapy (HR, 0.39; p = 0.003) and LCT (HR, 0.51; p = 0.013) remained significant prognostic factors for PFS. For OS, focal relapse and chemotherapy were associated with improved survival.
Conclusions: Outcomes for recurrent medulloblastoma remain unfavorable. However, LCT was associated with improved PFS, while chemotherapy was associated with both improved PFS and OS.

Introduction

Medulloblastoma is the most common malignant brain tumor in children, accounting for approximately 20% of all pediatric central nervous system (CNS) neoplasms [1,2]. Over the past several decades, advances in multimodal frontline treatment—including maximal safe resection, craniospinal irradiation (CSI), and risk-adapted chemotherapy—have markedly improved survival outcomes, with 5-year survival now approaching 70–85% depending on risk group [3–5]. The integration of molecular subgrouping has further refined prognostication and has begun to influence treatment decisions in contemporary clinical practice [5].

Despite these advances, 20–30% of patients ultimately experience disease recurrence, and management in the recurrent setting remains

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one of the greatest unmet needs in pediatric neuro-oncology [6–8]. Recurrent medulloblastoma exhibits aggressive biological behavior, often with early dissemination through cerebrospinal fluid pathways [9]. Furthermore, treatment options are often constrained by the cumulative toxicity from prior therapies. Consequently, the prognosis after relapse is dismal, with historical series reporting a median overall survival of only 10–18 months and long-term survival being exceptionally rare [7,8,10,11].

A major hurdle in improving outcomes is the absence of a globally accepted standard salvage strategy. Current practices are highly heterogeneous, ranging from high-dose chemotherapy with autologous stem cell rescue to metronomic regimens, targeted agents, or palliative care [12–14]. Historically, the role of local control treatment (LCT), particularly re-irradiation (re-RT), has been controversial due to fears of severe neurotoxicity, including radionecrosis and neurocognitive decline [15–17]. However, the evolution of modern conformal techniques—such as intensity-modulated radiotherapy (IMRT), proton beam therapy, and stereotactic radiosurgery (SRS)—has prompted a re-evaluation of this paradigm, suggesting that re-irradiation may offer clinically meaningful tumor control with an acceptable safety profile in selected patients [17–20].

Given the diversity of salvage approaches and the scarcity of large-scale data guiding therapeutic decisions, there is a pressing need to define the optimal role of aggressive local therapy in the real-world setting. In this multicenter retrospective study, we aimed to characterize the salvage strategies employed across major institutions and evaluate their impact on survival outcomes. Our primary objective was to assess the efficacy and safety of salvage LCT—including surgery and re-irradiation—and to determine its contribution to survival when combined with systemic therapy. Additionally, we explored clinical prognostic factors and, where data were available, molecular features, to identify subgroups that may derive the greatest benefit from these salvage modalities.

Materials and methods

Study design

This multicenter retrospective study included patients initially diagnosed with medulloblastoma at five centers between January 2000 and December 2020. The inclusion criteria were as follows: (1) age $\leq$ 21 years at the time of initial diagnosis; (2) completion of frontline multimodal treatment, comprising maximal safe resection (or biopsy) followed by standard curative-intent radiotherapy (craniospinal irradiation [CSI] with a focal boost); and (3) documented disease recurrence based on follow-up magnetic resonance imaging (MRI) or clinical assessment. Patients were excluded based on the following criteria: (1) history of prior intracranial radiotherapy before the diagnosis of medulloblastoma; (2) history of other primary brain tumors; (3) receipt of radiotherapy for a secondary intracranial malignancy subsequent to the medulloblastoma diagnosis; or (4) insufficient medical records regarding recurrence or follow-up outcomes.

Treatment outcome

Disease recurrence was determined by the treating oncologist based on radiological evidence (MRI) or clinical findings, such as the presence of malignant cells in cerebrospinal fluid cytology. Local recurrence was defined as tumor recurrence within the primary tumor bed (posterior fossa). Recurrence patterns relative to the initial radiation field were classified as 'in-field' if the recurrent tumor was located within the high-dose volume (boost field) of the initial radiotherapy, and 'out-field' if it occurred outside this volume. A second recurrence was defined as disease progression occurring during or after the completion of salvage treatment. The primary endpoints of this study were progression-free survival (PFS) and overall survival (OS) after the initial recurrence. PFS was calculated from the date of the initial recurrence diagnosis to the date of a second recurrence (progression) or death from any cause, whichever occurred first. OS was defined as the time from the date of initial recurrence to the date of death from any cause.

Clinical and pathological factors

We retrospectively extracted clinical data including age at initial diagnosis, sex, and details of frontline treatment (extent of surgical resection, radiotherapy specifications, and chemotherapy regimens). For pathological assessment, metastatic status was defined according to the Chang staging system. Histological subtypes were classified according to the WHO classification as classic, desmoplastic/nodular, medulloblastoma with extensive nodularity (MBEN), or large cell/anaplastic (LCA). Molecular and genetic profiles were reviewed where medical records were available. These included TP53 mutation status, MYCN amplification, and Ki-67 labeling index. Molecular subgroups were categorized as WNT, SHH, or non-WNT/non-SHH (Group 3 or Group 4) based on the available diagnostic reports. Molecular subgrouping was routinely incorporated into clinical practice at the participating institutions starting around 2013. In this cohort, molecular data were predominantly obtained retrospectively using archived diagnostic tissues from the primary tumor specimens.

Risk stratification at initial diagnosis was determined based on age, extent of resection, and metastatic status. Patients were classified as standard-risk if they were aged $>$ 3 years, underwent gross total resection, and had no evidence of metastasis (M0). Conversely, patients were classified as high-risk if they met any of the following criteria: age $\leq$ 3 years, incomplete resection (subtotal resection or biopsy), or presence of metastatic disease (M +).

To account for the heterogeneity in fractionation schedules among salvage modalities, ranging from standard fractionation to single-fraction SRS, radiation doses were converted to the equivalent dose in 2-Gy fractions (EQD2). Calculations were based on the linear-quadratic model, assuming an alpha/beta ratio of 10 Gy for tumor control and 3 Gy for late normal tissue toxicities.

Salvage treatment

Following the diagnosis of recurrence, treatment patterns were categorized into systemic chemotherapy alone, LCT alone, or a combination of both. LCT was defined as any salvage intervention directed at the tumor site, comprising salvage surgery, re-RT, or combined modality local therapy. In cases of re-RT, detailed planning data were retrieved to evaluate safety and efficacy. To assess the safety of re-RT, treatment-related toxicities were retrospectively reviewed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical analysis

All analyses were conducted using R software (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria). To compare characteristics between subgroups, categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test, as appropriate. Continuous variables were evaluated using Student's *t*-test. Survival outcomes were estimated using the Kaplan-Meier method, and differences between groups were assessed using the log-rank test. To identify independent prognostic factors associated with treatment outcomes or survival, Cox proportional hazards regression models were employed. Variables with a p-value $<$ 0.05 in the univariate analysis were included in the multivariate model; however, variables with insufficient event counts were excluded to ensure model stability.

Ethics statement

This study was approved by the Institutional Review Board (IRB) of each participating institution. The requirement for informed consent was waived due to the retrospective nature of the study.

Results

A total of 76 patients from five medical centers were included in the analysis. Baseline characteristics are summarized in Table 1. The cohort showed a male predominance (67.1%), and 48.7% of patients were younger than 8 years at initial diagnosis (range, 3.6–20.8 years). Notably, subtotal resection or biopsy was performed in 63.2% of cases during the initial management, and metastatic disease (M stage > 0) was observed in 44.7% of patients. According to the risk stratification at initial diagnosis, 20 patients (26.3%) were classified as standard-risk, while 56 patients (73.7%) were identified as high-risk. Among those with available histopathology (n = 54), the classic subtype was most common (48.1%), followed by large cell/anaplastic (LCA) variants (27.8%). Molecular subgroup information was limited (n = 21), with the majority classified as non-WNT/non-SHH (66.7%).

Details of recurrence patterns and salvage treatments are shown in Table 2. The median time from initial diagnosis to recurrence was 23.9 months (IQR, 14.9–36.2). Recurrent disease more frequently involved diffuse dissemination (56.9%), and combined local and distant failure represented the most common recurrence pattern (41.7%). Salvage strategies varied considerably; 26 patients (34.2%) received chemotherapy alone, while 41 patients (53.9%) underwent at least one form of local control treatment (surgery, re-RT, or both). Best supportive care was provided in 9 patients (11.8%).

Median follow-up from the time of initial recurrence was 14.3 months (IQR, 5.7–25.5). A total of 65 PFS events were observed, including 54 documented progressions. The estimated 1-, 3-, and 5-year PFS rates were 47.4%, 7.2%, and 7.2%, respectively. For OS, 36 deaths were recorded, of which 25 occurred after documented progression. The estimated 1-, 3-, and 5-year OS rates were 81.1%, 42.8%, and 28.0%, respectively. Kaplan–Meier curves for PFS and OS for the entire cohort are presented in Supplementary Fig. 1.

In the univariate analysis for PFS, MYCN amplification, absence of chemotherapy, and omission of LCT were associated with inferior outcomes. Because MYCN status was available for a limited number of patients, the multivariate model included only chemotherapy and LCT. Both variables remained significant predictors of improved PFS after multivariate analysis: chemotherapy (HR, 0.39; 95% CI, 0.21–0.72; $p = 0.003$) and LCT (HR, 0.51; 95% CI, 0.30–0.87; $p = 0.013$). For OS, age at recurrence, relapse extent, MYCN amplification and chemotherapy showed significance in the univariate analysis. In the multivariate model, diffuse relapse was associated with a significantly higher mortality risk compared with focal relapse (HR, 3.18; 95% CI, 1.34–7.59; $p = 0.009$), while chemotherapy remained a strong independent predictor of improved OS (HR, 0.19; 95% CI, 0.07–0.47; $p < 0.001$). Table 3 summarizes the univariate and multivariate analyses of prognostic factors in recurrent medulloblastoma.

Table 1
Initial Patient Characteristics for Recurrent Medulloblastoma Patients.

Factors		Patient Number (%)
Age at diagnosis (years)	<8	37 (48.7%)
	≥8	39 (51.3%)
Sex	Male	51 (67.1%)
	Female	25 (32.9%)
M stage	M0	42 (55.3%)
	M+	34 (44.7%)
Histology (n = 54)	Classic	26 (48.1%)
	ND/EN	13 (24.1%)
	LCA	15 (27.8%)
Extent of Resection	GTR	28 (36.8%)
	STR/Bx	48 (63.2%)
Risk Stratification	Standard	20 (26.3%)
	High	56 (73.7%)
Molecular Classification (n = 21)	WNT	2 (9.5%)
	SHH	5 (23.8%)
	Non-WNT/SHH	14 (66.7%)
TP53 Mutation (n = 20)	Wildtype	16 (80.0%)
	Mutant	4 (20.0%)
MYCN Amplification (n = 23)	Yes	4 (17.4%)
	No	19 (82.6%)
Ki-67 level (n = 53)	Low (<30%)	18 (34.0%)
	High (≥30%)	35 (66.0%)

Abbreviations: Bx, biopsy; EN, extensive nodularity; GTR, gross total resection; LCA, large cell anaplastic; M, metastasis; ND, nodular/desmoplastic; SHH, sonic hedgehog; STR, subtotal resection; WNT, wingless.

Table 2
Patient Characteristics at the first recurrence.

Factors			Patient Number (%)
Initial Treatment Response (n = 69)		CR	53 (76.8%)
		PR	13 (18.8%)
		SD/PD	3 (4.3%)
Recurrence time (month)		Median (IQR)	23.9 (14.9–36.2)
Relapse extent (n = 72)		Focal	31 (43.1%)
		Diffuse	41 (56.9%)
Relapse pattern (n = 72)		Local (in-field)	17 (23.6%)
		Local (out-field)	14 (19.4%)
		Distant	11 (15.3%)
		Combined	30 (41.7%)
Salvage modality	Yes	CTx alone	26 (34.2%)
		Surg alone	2 (2.6%)
		Surg + CTx	10 (13.2%)
		Surg + RT	2 (2.6%)
		Surg + RT + CTx	5 (6.6%)
		RT alone	7 (9.2%)
		RT + CTx	15 (19.7%)
	No		9 (11.8%)

Abbreviations: CR, complete remission; CTx, chemotherapy; PD, progressive disease; PR, partial remission; RT, radiotherapy; SD, stable disease; Surg, surgery.

Survival outcomes differed markedly according to the salvage treatment modality (Fig. 1 *and* Supplementary Fig. 2). Chemotherapy was associated with significantly prolonged PFS (p = 0.006) and OS (p = 0.003), with a 3-year OS of 49.3% compared with 14.0% among patients who did not receive chemotherapy. LCT was similarly associated with improved PFS (1-year rate: 63.4% vs. 25.2%; p = 0.033), although its impact on OS did not reach statistical significance (p = 0.27).

Subgroup analyses were performed to identify patients who derived the greatest benefit from salvage LCT and chemotherapy (Fig. 3). The survival benefit of LCT was particularly pronounced in patients aged ≥ 12 years (HR, 0.32; 95% CI, 0.12–0.83; p = 0.019), males, those with M0 disease at diagnosis, and patients with late recurrence (≥24 months). In contrast, chemotherapy demonstrated significant efficacy in patients aged < 12 years (HR, 0.28; 95% CI, 0.12–0.66; p = 0.004), those with metastatic disease, and patients presenting with a diffuse relapse pattern. Notably, patients with a longer time to recurrence (≥24 months) exhibited improved PFS with both LCT and chemotherapy. To evaluate the optimal radiotherapy strategy for disseminated recurrence, a subgroup analysis was conducted among patients with diffuse relapse (n = 41). As illustrated in Fig. 2, patients who received CSI as salvage re-irradiation demonstrated more favorable outcomes compared to those who did not. The addition of CSI was significantly associated with improved PFS (p = 0.0018), though no statistically significant improvement was observed for OS (p = 0.12).

Among the study cohort, 49 patients experienced a second disease recurrence. The median interval between the first and second recurrence was 9.5 months (IQR, 5.5–16.8). Treatment strategies diverged substantially after the second failure. As illustrated in Supplementary Fig. 3, 27 patients transitioned to best supportive care without further tumor-directed therapy, whereas 21 patients underwent a second salvage

Table 3
Univariate and multivariate analysis for factors associated with PFS and OS in recurrent medulloblastoma.

		PFS				OS			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age at recurrence (year)	(≥12 vs < 12)	0.72 (0.44–1.18)	0.196			**0.46 (0.22–0.93)**	**0.031**	0.54 (0.25–1.14)	0.106
Sex	(Male vs Female)	1.26 (0.74–2.15)	0.388			1.06 (0.52–2.17)	0.871		
M stage	(M + vs M0)	1.34 (0.82–2.20)	0.243			1.08 (0.55–2.14)	0.818		
Histology	(Classic vs ND/EN)	**1.00 (0.46–2.19)**	**0.999**			1.12 (0.36–3.47)	0.839		
	(LCA vs ND/EN)	**2.13 (0.92–4.96)**	**0.079**			1.78 (0.52–6.10)	0.360		
Molecular Classification	(SHH vs WNT)	0.78 (0.14–4.33)	0.776			2.18 (0.22–21.44)	0.506		
	(non-WNT/SHH vs WNT)	0.75 (0.16–3.50)	0.718			1.53 (0.19–12.50)	0.691		
Extent of Resection	(STR/Bx vs GTR)	1.47 (0.89–2.45)	0.134			1.24 (0.62–2.47)	0.542		
TP53	(Mutant vs Wildtype)	1.81 (0.57–5.71)	0.314			2.50 (0.64–9.85)	0.189		
MYCN amplification	(Yes vs No)	**90.6 (8.87–12267)** *	**<0.001**			**7.09 (1.10–45.64)**	**0.039**		
Ki-67 level	(High vs Low)	0.65 (0.35–1.20)	0.168			0.85 (0.34–2.09)	0.718		
Recurrent Time (month)	(≥24 vs < 24)	0.79 (0.48–1.30)	0.353			0.74 (0.38–1.44)	0.374		
Relapse Extent	(Diffuse vs Focal)	1.30 (0.79–2.15)	0.304			**2.30 (1.13–4.69)**	**0.022**	**3.18 (1.34–7.59)**	**0.009**
Use of CTx	(Yes vs No)	**0.45 (0.25–0.81)**	**0.008**	**0.39 (0.21–0.72)**	**0.003**	**0.33 (0.15–0.71)**	**0.005**	**0.19 (0.07–0.47)**	**<0.001**
Use of LCT	(Yes vs No)	**0.57 (0.34–0.96)**	**0.034**	**0.51 (0.30–0.87)**	**0.013**	0.68 (0.33–1.37)	0.276		

Abbreviations: Bx, biopsy; CI, confidence interval; CTx, chemotherapy; EN, extensive nodularity; GTR, gross total resection; HR, hazard ratio; LCA, large cell anaplastic; LCT, local control treatment; ND, nodular/desmoplastic; OS, overall survival; PFS, progression-free survival; SHH, sonic hedgehog; STR, subtotal resection; WNT, wingless.
For variables expressed as (A vs B), the latter category (B) serves as the reference group.
* The hazard ratio for MYCN amplification of PFS was estimated using Firth's penalized Cox regression due to the small sample size.

treatment. Treatment information after the second recurrence was unavailable for 1 patient. Among the 21 patients who underwent a second salvage treatment, chemotherapy alone was the most frequently employed modality (42.8%), followed by various re-irradiation–based regimens and limited use of surgery-based approaches. Detailed characteristics of second-recurrence patterns and treatment modalities are summarized in Supplementary Table 1.

Details regarding re-RT parameters and toxicity outcomes are summarized in Supplementary Tables 2 and 3. Among the 36 patients who underwent salvage re-RT, the mean prescribed dose was 23.4 Gy (range, 6.0–54.0). In contrast to the initial setting—which predominantly utilized CSI with a focal boost—the salvage setting most frequently employed focal re-RT (50.0%), followed by CSI alone (33.3%). Toxicity data were evaluable for 23 patients. Overall, re-RT demonstrated a favorable safety profile: 12 patients (52.1%) experienced no treatment-related adverse events. Severe toxicities (CTCAE Grade ≥ 3) were observed in only 4 patients (17.4%), comprising two cases of hematologic toxicity and two cases of Grade 3 or more radiation necrosis. When stratified by re-irradiation parameters, focal re-RT was highly tolerable, with 69.2% of patients experiencing no toxicities, whereas re-CSI yielded a lower toxicity-free rate of 30.0% and accounted for the severe hematologic adverse events. Furthermore, an exploratory analysis evaluating late normal-tissue risk using an EQD_2 with an alpha/beta ratio of 3 Gy did not demonstrate a linear dose-toxicity relationship; paradoxically, a higher proportion of patients in the higher dose group ($EQD_2 \geq 30$ Gy) experienced no toxicities (61.5%) compared to those in the lower dose group ($EQD_2 < 30$ Gy; 40.0%).

To evaluate the impact of evolving clinical practices over the 20-year study period, we conducted an exploratory survival analysis stratified by treatment era, based on the year of relapse (2000–2012 vs. 2013–2023). Kaplan-Meier analysis revealed that patients treated in the more recent era (2013–2023) demonstrated a significantly improved PFS compared to those treated in the earlier era ($p < 0.0001$; Supplementary Fig. 4A). However, this temporal advantage in disease control did not translate into a statistically significant OS benefit ($p = 0.12$; Supplementary Fig. 4B).

Discussion

In this multi-institutional retrospective study, we confirmed that the prognosis for recurrent medulloblastoma remains unfavorable. However, our findings demonstrate that intensified multimodal salvage therapy, incorporating both chemotherapy and LCT, was significantly associated with improved survival outcomes compared to supportive care or monotherapy. Additionally, subgroup analysis demonstrated the potential therapeutic role of CSI in patients with diffuse recurrent medulloblastoma. Lastly, re-RT demonstrated an acceptable safety profile with a Grade ≥ 3 toxicity rate of 17.4%, suggesting that an aggressive combined approach is a feasible and effective therapeutic strategy.

Currently, the reported median survival for recurrent medulloblastoma ranges from 10 to 18 months, highlighting the dismal prognosis associated with this disease [7,8,10,11]. Despite these historically poor outcomes, several large-scale studies have demonstrated the critical value of aggressive local control treatment. Hill et al., in an analysis of 230 recurrent cases, found that the addition of neurosurgical resection or any form of re-irradiation significantly improved survival outcomes [7]. Similarly, Gaab et al. reported a median overall survival of 18.5 months, demonstrating a distinct survival benefit for patients undergoing debulking surgery or radiotherapy compared to those who received only supportive care [8]. While other reports, such as those by Koschmann et al. and Johnston et al., have noted variable statistical significance or persistently low long-term survival rates (5-year OS of 12.4%) [10,11], the collective evidence suggests a potential benefit from active intervention. Consistent with these findings, our study reinforces that intensified multimodal salvage therapy—incorporating both LCT and chemotherapy—could potentially improve survival, offering a viable therapeutic strategy even for previously irradiated patients.

Beyond treatment modalities, clinical characteristics—specifically

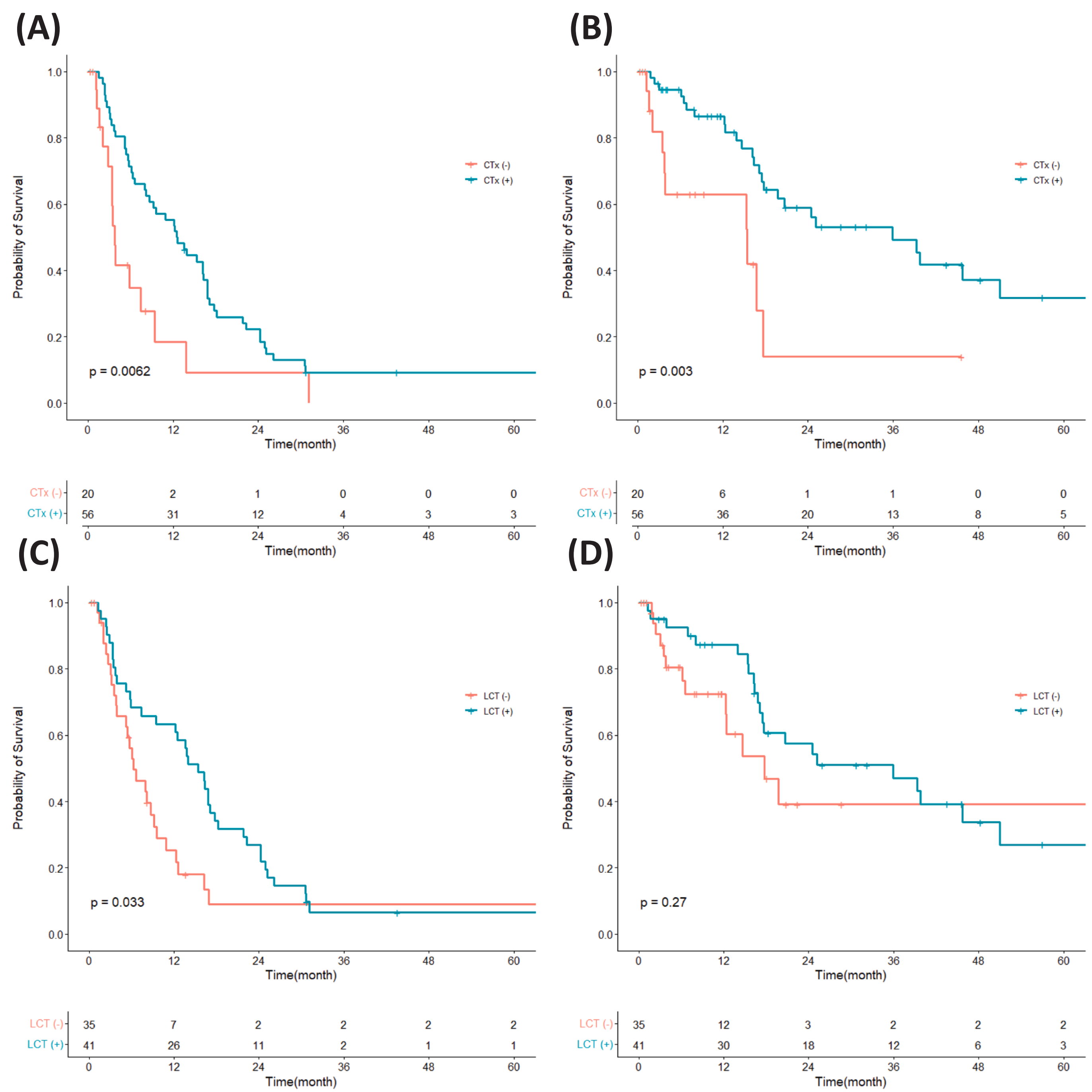

Fig. 1. Kaplan–Meier estimates of progression-free survival (A, C) and overall survival (B, D) among patients with recurrent medulloblastoma. Survival outcomes are shown according to the use of systemic chemotherapy (A, B) and local control treatment (C, D). Abbreviations: CTx, chemotherapy; LCT, local control treatment; OS, overall survival; PFS, progression-free survival.

disease extent and time to recurrence—were critical determinants of survival [6–8]. While our multivariate analysis identified diffuse spread as a potent adverse prognostic factor, subgroup analyses revealed that the addition of LCT or chemotherapy was associated with a significant survival benefit even in this high-risk group. This suggests that intensified multimodal treatment remains a viable strategy to effectively reduce tumor burden [8,17]. Additionally, consistent with previous studies, patients with late recurrence (≥24 months) demonstrated superior outcomes, likely reflecting a more indolent tumor biology compared to the aggressive course observed in early relapses[6–8].

A notable feature of our study cohort was the high prevalence of unfavorable prognostic factors at initial diagnosis, particularly the substantial proportion of patients who underwent incomplete resection. This rate exceeds that observed in general medulloblastoma cohorts [21]. This high rate of incomplete resection likely reflects an inherent referral bias, as complex, high-risk cases—or tumors located in areas precluding safe gross total resection—are frequently referred to our tertiary care centers. The presence of gross residual disease is a well-established predictor of early progression and local failure [21–23]. Nevertheless, most patients in this cohort received standard-dose radiotherapy (mean dose of 54.0 Gy) during initial treatment, which may be suboptimal for achieving durable disease control in the setting of macroscopic residual tumor. To mitigate the risk of early recurrence, more aggressive upfront interventions—such as second-look surgery to

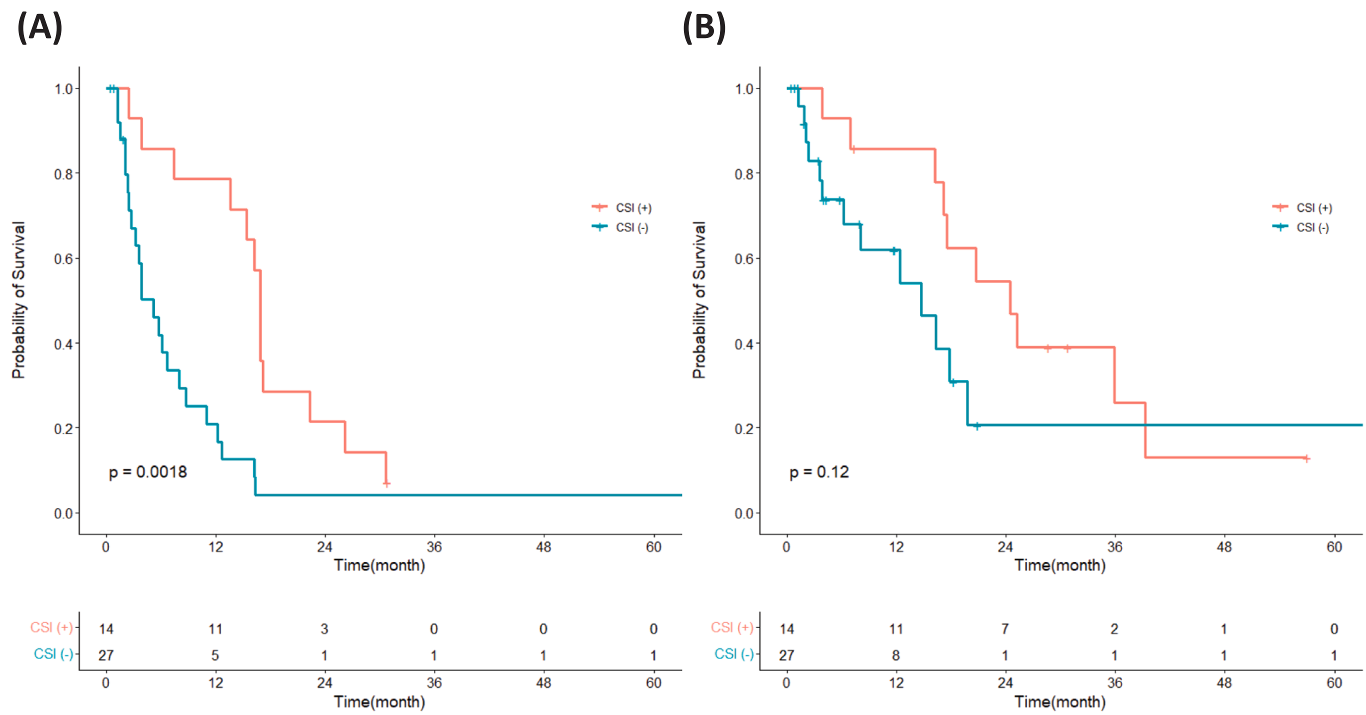

Fig. 2. Kaplan–Meier estimates of progression-free survival (A) and overall survival (B) among patients with diffuse recurrent medulloblastoma. Survival outcomes are stratified by the use of craniospinal irradiation (CSI). Abbreviations: CSI, craniospinal irradiation; OS, overall survival; PFS, progression-free survival; RT, radiotherapy.

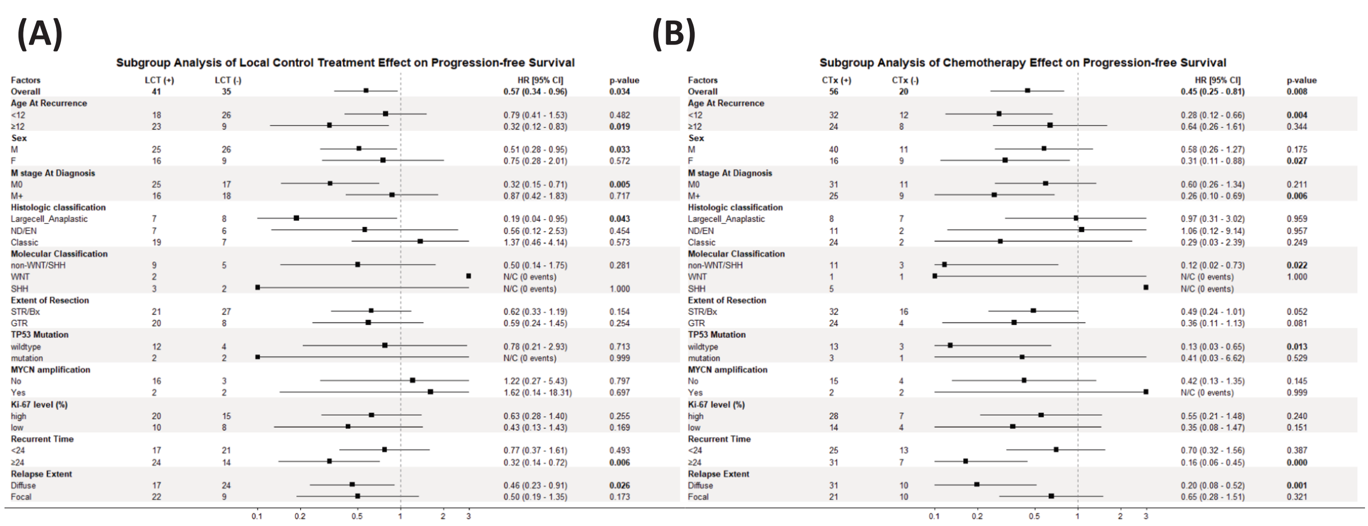

Fig. 3. Forest plot of subgroup analyses evaluating the effect of local control treatment (A) and chemotherapy (B) on progression-free survival. Abbreviations: Bx, biopsy; CI, confidence interval; CTx, chemotherapy; EN, extensive nodularity; GTR, gross total resection; HR, hazard ratio; LCT, local control treatment; ND, nodular/desmoplastic; SHH, sonic hedgehog; STR, subtotal resection; Tx, treatment; WNT, wingless.

maximize cytoreduction or radiotherapy dose escalation to the residual tumor bed—should be considered.

Molecular prognostication remains crucial in the salvage setting. In our univariate analysis, MYCN amplification was associated with a trend toward inferior progression-free survival. This finding aligns with established evidence identifying MYCN amplification as an aggressive disease biology, particularly within Group 3 and SHH medulloblastoma subtypes [24–26]. Tumors harboring this alteration typically exhibit rapid progression and resistance to conventional chemotherapy or radiotherapy. Although MYCN amplification was associated with inferior outcomes in univariate analysis, this finding should be regarded as hypothesis-generating because MYCN status was available in only a small subset of patients and may have been influenced by selection bias in molecular testing and salvage treatment intensity.

Concerns regarding cumulative neurotoxicity and radionecrosis have historically limited the application of re-irradiation in the salvage setting. However, our study suggests that re-irradiation can be delivered with an acceptable safety profile when modern radiotherapy techniques are employed. We observed severe (Grade $\geq$ 3) toxicities in only 17.4% of re-irradiated patients, with no instances of severe gastrointestinal toxicity. This aligns with previous reports, such as those by Celik et al. and Adolph et al., which confirmed minimal severe toxicity following re-irradiation [17,27]. However, it is important to note that these rates may be underestimated due to missing toxicity data in a subset of patients and the relatively short median follow-up after recurrence. Despite this general tolerability, a detailed analysis reveals a critical trade-off: severe adverse events, including radiation necrosis, were mainly confined to the re-CSI subgroup (30% grade 3 toxicity). Our subgroup analysis confirmed that re-CSI was significantly associated with improved PFS compared to focal modalities, suggesting that CSI provides a potential survival advantage for disseminated disease. Nevertheless, this potential benefit and the elevated toxicity risk must be interpreted cautiously. Given the lack of a significant OS benefit and the higher risk of late toxicities, the decision to proceed with re-CSI requires a careful risk–benefit assessment, leveraged by advanced conformal techniques to maximize normal tissue sparing. Further studies are warranted to validate these findings due to the small sample size.

The significant improvement in PFS observed in the recent treatment era (2013–2023) likely reflects the cumulative impact of evolving multidisciplinary management in neuro-oncology. First, advancements in neurosurgical techniques, including enhanced microsurgical approaches and sophisticated neuroimaging navigation, have facilitated safer and more effective local salvage resections. Second, the sophistication of modern radiotherapy—characterized by the transition to highly conformal techniques such as IMRT and SRS—has enabled the delivery of robust ablative doses to the recurrent tumor while strictly sparing adjacent critical structures. Finally, the integration of contemporary systemic therapies, including refined chemotherapeutic regimens and the cautious introduction of targeted agents guided by molecular profiling, has further contributed to prolonged disease control. Collectively, these multidisciplinary advancements effectively delay disease progression; however, as demonstrated by the lack of an overall survival benefit, they remain insufficient to completely overcome the ultimately lethal nature of recurrent medulloblastoma, highlighting the urgent need for novel therapeutic breakthroughs.

This study has several limitations inherent to its retrospective, multi-institutional design. Foremost is the potential for treatment selection bias; because the long study period (2000–2020) precluded the uniform collection of standardized clinical fitness indicators at relapse, the observed benefits of intensified salvage modalities may be confounded by unmeasured variables such as patient performance status or neurologic symptoms. Moreover, multiple modalities such as radiotherapy and surgery are combined as LCT, which represent clinically distinct interventions. Additionally, the relatively small sample size limits the statistical power of our subgroup analyses. Other limitations include the reliance on surgical records rather than centralized magnetic resonance imaging review for residual disease assessment, and the lack of complete molecular profiling, which prevented a contemporary WHO subgroup-based outcome analysis. Finally, the high proportion of high-risk patients and those with subtotal resections in our cohort may limit the generalizability of these findings to the broader, lower-risk recurrent medulloblastoma population.

In conclusion, recurrent medulloblastoma remains challenging, yet multimodal salvage therapy combining chemotherapy and local control treatment significantly improves survival. Given the acceptable toxicity of modern re-irradiation, active local control is a feasible strategy. Future efforts should prioritize molecular profiling to identify high-risk subgroups, such as MYCN-amplified patients, requiring novel targeted interventions.

Data Availability

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Seok-Joo Chun: Writing – original draft, Visualization, Software, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Nalee Kim:** Writing – review & editing, Data curation. **Do Hoon Lim:** Writing – review & editing, Data curation. **Joo-Young Kim:** Writing – review & editing, Data curation. **Chan Woo Wee:** Writing – review & editing, Data curation. **Hong In Yoon:** Writing – review & editing, Data curation. **Seung Hyuck Jeon:** Writing – review & editing, Data curation. **In Ah Kim:** Writing – review & editing, Data curation. **Joo Ho Lee:** Writing – original draft, Validation, Supervision, Resources, Methodology, Data curation, Conceptualization.

Ethics approval

This study was approved by the Institutional Review Board (IRB) of each participating institution. The requirement for informed consent was waived due to the retrospective nature of the study.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Joo Ho Lee reports administrative support, article publishing charges, and statistical analysis were provided by Seoul National University Hospital. Joo Ho Lee reports administrative support, article publishing charges, and statistical analysis were provided by Ministry of Health and Welfare. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2026.101197.

References

[1] Liu X, Ding C, Tan W, Zhang A. Medulloblastoma: Molecular understanding, treatment evolution, and new developments. Pharmacol Ther 2020;210:107516.
[2] Cohen AR. Brain tumors in children. N Engl J Med 2022;386(20):1922–31.
[3] Gajjar A, Robinson GW, Smith KS, Lin T, Merchant TE, Chintagumpala M, et al. Outcomes by clinical and molecular features in children with medulloblastoma treated with risk-adapted therapy: results of an international phase III trial (SJMB03). J Clin Oncol 2021;39(7):822–35.
[4] Michalski JM, Janss AJ, Vezina LG, Smith KS, Billups CA, Burger PC, et al. Children's oncology group phase III trial of reduced-dose and reduced-volume radiotherapy with chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol 2021;39(24):2685–97.
[5] Seidel C, Heider S, Hau P, Glasow A, Dietzsch S, Kortmann R-D. Radiotherapy in medulloblastoma—evolution of treatment, current concepts and future perspectives. Cancers 2021;13(23):5945.
[6] Ramaswamy V, Remke M, Bouffet E, Faria CC, Perreault S, Cho Y-J, et al. Recurrence patterns across medulloblastoma subgroups: an integrated clinical and molecular analysis. Lancet Oncol 2013;14(12):1200–7.
[7] Hill RM, Richardson S, Schwalbe EC, Hicks D, Lindsey JC, Crosier S, et al. Time, pattern, and outcome of medulloblastoma relapse and their association with tumour biology at diagnosis and therapy: a multicentre cohort study. The Lancet Child & Adolescent Health 2020;4(12):865–74.

[8] Gaab C, Adolph JE, Tippelt S, Mikasch R, Obrecht D, Mynarek M, et al. Local and systemic therapy of recurrent medulloblastomas in children and adolescents: results of the P-HIT-REZ 2005 study. Cancers 2022;14(3):471.
[9] Hill RM, Kuijper S, Lindsey JC, Petrie K, Schwalbe EC, Barker K, et al. Combined MYC and P53 defects emerge at medulloblastoma relapse and define rapidly progressive, therapeutically targetable disease. Cancer Cell 2015;27(1):72–84.
[10] Koschmann C, Bloom K, Upadhyaya S, Geyer JR, Leary SE. Survival after relapse of medulloblastoma. J Pediatr Hematol Oncol 2016;38(4):269–73.
[11] Johnston DL, Keene D, Strother D, Taneva M, Lafay-Cousin L, Fryer C, et al. Survival following tumor recurrence in children with medulloblastoma. J Pediatr Hematol Oncol 2018;40(3):e159–63.
[12] Butturini AM, Jacob M, Aguajo J, Vander-Walde NA, Villablanca J, Jubran R, et al. High-dose chemotherapy and autologous hematopoietic progenitor cell rescue in children with recurrent medulloblastoma and supratentorial primitive neuroectodermal tumors: the impact of prior radiotherapy on outcome. Cancer 2009;115(13):2956–63.
[13] Knight TE, Ahn KW, Hebert KM, Atshan R, Wall DA, Chiengthong K, Rotz SJ, Fraint E, Rangarajan HG, Auletta JJ: Effect of autograft CD34+ dose on outcome in pediatric patients undergoing autologous hematopoietic stem cell transplant for central nervous system tumors. *Transplantation and cellular therapy* 2023, 29(6): 380. e381-380. e389.
[14] Peyrl A, Chocholous M, Sabel M, Lassaletta A, Sterba J, Leblond P, et al. Sustained survival benefit in recurrent medulloblastoma by a metronomic antiangiogenic regimen: a nonrandomized controlled trial. JAMA Oncol 2023;9(12):1688–95.
[15] Baroni LV, Freytes C, Fernández Ponce N, Oller A, Pinto N, Gonzalez A, et al. Craniospinal irradiation as part of re-irradiation for children with recurrent medulloblastoma. J Neurooncol 2021;155(1):53–61.
[16] Fredricks N, Price A, Jonzzon S, D'Souza P, Wellons JC, Ramaswamy V, et al. Surgical management of recurrent medulloblastoma: a scoping review. J Neurosurg Pediatr 2025;1(aop):1–7.
[17] İribaş Çelik A, Özkaya Toraman K, Kebudi R, Büyükkapu Bay S, Dizdar Y, Kaytan Sağlam E, et al. Re-irradiation in Children with Recurrent Medulloblastoma. Pediatr Blood Cancer 2025;72(11):e31960.
[18] Ruggi A, Melchionda F, Sardi I, Pavone R, Meneghello L, Kitanovski L, et al. Toxicity and clinical results after proton therapy for pediatric medulloblastoma: a multi-centric retrospective study. Cancers 2022;14(11):2747.
[19] Yoo KH, Marianayagam NJ, Park DJ, Zamarud A, Gu X, Pollom E, et al. The role of cyberknife stereotactic radiosurgery in recurrent cranial medulloblastomas across pediatric and adult populations. J Clin Med 2024;13(12):3592.
[20] Palavani LB, Borges PG, Semione G, Ferreira MY, Ribeiro PVZ, Bocanegra-Becerra JE, et al. Proton versus photon radiation therapy for pediatric medulloblastomas: a systematic review and meta-analysis. Childs Nerv Syst 2025;41(1):1–10.
[21] Keeling C, Davies S, Goddard J, Ramaswamy V, Schwalbe EC, Bailey S, et al. The clinical significance of sub-total surgical resection in childhood medulloblastoma: a multi-cohort analysis of 1100 patients. EClinicalMedicine 2024;69.
[22] Srikantha U, Balasubramaniam A, Santosh V, Somanna S, Bhagavatula ID, Ashwathnarayana CB. Recurrence in medulloblastoma–Influence of clinical, histological and immunohistochemical factors. Br J Neurosurg 2010;24(3):295–303.
[23] Liu Y, Xiao B, Li S, Liu J. Risk factors for survival in patients with medulloblastoma: a systematic review and meta-analysis. Front Oncol 2022;12:827054.
[24] Korshunov A, Remke M, Kool M, Hielscher T, Northcott PA, Williamson D, et al. Biological and clinical heterogeneity of MYCN-amplified medulloblastoma. Acta Neuropathol 2012;123(4):515–27.
[25] Shrestha S, Morcavallo A, Gorrini C, Chesler L. Biological role of MYCN in medulloblastoma: novel therapeutic opportunities and challenges ahead. Front Oncol 2021;11:694320.
[26] Schwalbe EC, Lindsey JC, Danilenko M, Hill RM, Crosier S, Ryan SL, et al. Molecular and clinical heterogeneity within MYC-family amplified medulloblastoma is associated with survival outcomes: a multicenter cohort study. Neuro Oncol 2025;27(1):222–36.
[27] Adolph JE, Fleischhack G, Tschirner S, Rink L, Dittes C, Mikasch R, et al. Radiotherapy for Recurrent Medulloblastoma in Children and Adolescents: Survival after Re-Irradiation and First-Time Irradiation. Cancers 2024;16(11):1955.