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ORIGINAL ARTICLE

Surgical outcome of children with medulloblastoma: a retrospective study of a 405-patient series from Children's Cancer Hospital Egypt (CCHE-57357)

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Abstract

Purpose To analyze the impact of increasing the extent of resection (EOR) on the survival rates and on the surgical outcome of children with medulloblastoma.

Methods A series of consecutive 405 children operated for medulloblastoma between July 2007 and April 2018 was identified. The details of pre-operative data, surgical interventions, post-operative complications, and survival rates were analyzed.

Results The Kaplan-Meier (KM) analysis showed no advantage of gross total resection (GTR) over near and subtotal resection regarding over all (OS) (p=0.557) and progression free survival (PFS) (p=0.146). In the same time, increasing the EOR was not associated with higher morbidity. Tumor dissemination at onset correlated to worse OS (KM: p=0.003, OR 1.999, 95% CI: 1.242–3.127; p = 0.004) and PFS (KM: p<0.001, Cox: OR 2.171, 95% CI: 1.406–3.353; p<0.001). OS was significantly affected in patients < 3 years old (KM: p=0.011, OR 2.036, 95% CI: 1.229–3.374; p = 0.006), while PFS was worse among patients who had pre-op seizures (KM: p=0.036, Cox: OR 2.852, 95% CI: 1.046–7.773; p=0.041) or post-op pseudomeningocele (KM: p=0.021, Cox: OR 2.311, 95% CI: 1.123–4.754; p=0.023).

Conclusions Although surgical excision of medulloblastoma is the standard of care, there was no significant benefit for GTR over near or subtotal resection on the OS or PFS rates that are mainly influenced by the patient's age and tumor dissemination. However, GTR should be targeted, as it is not associated with increased incidence of mutism or other surgery-related complications.

Keywords Medulloblastoma · Mutism · Pseudomeningocele · Hydrocephalous with posterior fossa tumors

Introduction

Medulloblastoma (MB) is one of the commonest brain tumors in the pediatric age group [4]. MB has four histological subtypes; all of them are World Health Organization (WHO) grade IV malignant tumors [24]. MB cannot be fully cured by surgery alone; however, surgical tumor resection is a fundamental component of the current MB multimodal therapy protocols [33].

The extent of resection (EOR) is either gross total resection (GTR) with no residual tumor in post-operative contrast-enhanced MRI, near-total resection (NTR) with < 1.5 cm^2 residual, subtotal resection (STR) with >1.5 cm^2 residual, or biopsy [12]. The benefit of increasing the EOR is a matter of debate. On the other hand, the current treatment protocols consider patients with subtotal resections as high-risk patients and assign them for more aggressive adjuvant therapy measures [26].

We hereby present our 11-year experience with the surgical management of 405 MB patients in a high-flow pediatric oncology center, and we analyze the surgical outcome and survival rates among those patients. The primary study endpoint is to determine the impact of increasing the EOR on overall

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survival (OS) and progression-free survival (PFS). The secondary study endpoint is to analyze the relation between the EOR and the incidence of various surgery-related complications.

Patients and methods

We retrospectively analyzed our database, and all the available paper and electronic records of the posterior fossa MB patients operated in Children's Cancer Hospital Egypt (CCHE-57357) for tumor excision from July 2007 until April 2018. Patients who underwent any tumor excision or biopsy outside the hospital were excluded, while we freely included all patients who underwent uneventful emergency CSF diversion surgeries in other hospitals prior to admission to our center.

The data analysis included the patients' demographics and clinical presentation, tumor subtype and stage (metastatic or not), cerebrospinal fluid (CSF) diversion surgeries, extent of tumor resection, peri-operative complications, and the 5-year overall and progression-free survival rates. Tumor subtype was defined according to the histopathological analysis: classic, desmoplastic/nodular, anaplastic/large cell variant, or MB with extensive nodularity.

Gadolinium-enhanced MRI of the brain and whole spine were performed in all cases before surgery to evaluate the tumor in the posterior fossa and to detect any brain or spine metastasis. Computed tomography (CT) of the brain is done on the same day of surgery to exclude hydrocephalus (HCP), operative bed hematoma, or epidural hematoma or fractures that may be related to the Mayfield pins. Tumor residue was assessed by post-operative gadolinium-enhanced MRI that was done within 48 h after surgery to evaluate the extent of tumor resection. A 1.5-T MRI machine was used in all cases. The T2-weighted images were examined to detect any non-enhancing tumor residuals that may be missed on the contrast-enhanced T1-weighted images. The extent of tumor resection was classified into either GTR (no residual), NTR (<1.5 cm residual), or STR (>1.5 cm residual).

The legal guardians of all the children included in the study provided written informed consents for using the clinical data and images, and the Standing Medical Advisory Committee (SMAC) ethical approval was obtained. All the procedures mentioned in this study were done in accordance with the 1964 Helsinki Declaration and its later amendments.

Surgical procedures

CSF diversion surgery (ventriculoperitoneal shunt (VP shunt) or endoscopic third ventriculostomy (ETV)) was offered initially to all patients who presented with vision and/or life-threatening manifestations of increased intracranial pressure secondary to hydrocephalus (HCP). In most of the cases, the tumor resection was done within 1 week after the CSF diversion surgery due to overloaded operative schedules.

All patients were operated in the prone position, using the telovelar approach. Maximal tumor resection was attempted in all cases. Tumor parts invading brain stem and peduncles that were not smoothly dissectible were left. Surgeries were performed by the senior author (M. El B.).

The pre-operative data and details of adjuvant therapy are mentioned in Table 1. After the end of the multimodal therapy, all patients were followed up on a regular basis in the outpatient clinic. The follow-up (FU) visits and FU MRI scans were scheduled at a 3-month interval during the first FU year, and then a FU is scheduled every 6 months.

Statistical analysis

The statistical analysis was performed using the statistical package IBM-SPSS, version 20. Fisher's exact test was used to identify the correlation between the extent of tumor resection and the frequency of post-operative complications. The overall survival (OS) is defined as the time from registration to death from any cause, while the progression-free survival (PFS) is defined as the time from registration until the first evidence of tumor progression, or until death from any cause, whichever comes first. The Kaplan-Meier function was used for survival analysis. Univariate and multivariate Cox regression analyses were used to identify predictor variables associated with a significant difference in the OS and PFS. A p value of less than 0.05 is considered significant.

Results

This study included 405 consecutive MB patients, with 49 patients (12%) under the age of 3 years. The mean age at diagnosis was 7.3 years. Overall, 15% of cases presented to our center with disseminated tumors. The clinical presentations and histological subtypes are listed in Table 1. ETV was done before tumor excision in 26 patients (6%), though it failed in 15 of these patients, for whom VP shunts were inserted. VP shunt was done before tumor excision in 317 patients (78%); this number includes 35 patients who were operated in other hospitals before admission to our center.

Sixty-two patients (15%) underwent primary tumor resection (PTR) with no prior CSF diversion. HCP persisted after PTR in 14 patients; this was treated by VP shunts in 11 patients, and by ETV in three patients. Shunt revision was needed in 62 cases, and in 17 of them, infection was the cause of shunt failure. Moreover, 11 patients developed subdural hematomas after shunt surgery.

GTR was done in 81% of cases, NTR in 7%, and STR in 12%. The tumor histological subtype did not influence the EOR (p=0.115) and no second-look surgeries were done. Regarding the primary study endpoint, the Kaplan-Meier (KM) survival

Table 1 Pre-operative patients' characteristics, adjuvant therapy protocols, and follow-up status.

Character	No. (%)
Age category	
<3 years	49 (12.1)
≥ 3 years	356 (87.9)
Gender	
Male	257 (63.5)
Female	148 (36.5)
Tumor dissemination	
Positive	62 (15.3)
Negative	335 (82.7)
N/A	8 (2.0)
Pre-op squint	
Positive	40 (9.9)
Negative	363 (89.6)
N/A	2 (0.5)
Pre-op ataxia	
Positive	163 (40.2)
Negative	240 (59.3)
N/A	2 (0.5)
Pre-op fits	
Positive	8 (2.0)
Negative	395 (97.5)
N/A	2 (0.5)
Pre-op bulbar palsy	
Positive	9 (2.2)
Negative	394 (97.3)
N/A	2 (0.5)
Histological subtypes	
Anaplastic/large cell MB	127 (31.4)
Classic MB	180 (44.4)
Desmoplastic MB	49 (12.1)
MB with extensive nodularity	22 (5.4)
MB NOS	27 (6.7)
Adjuvant therapy details	
HRMB	212 (52.3%)
SRMB	155 (38.27%)
Infantile MB protocol	36 (8.88)
Baby POG protocol	2 (0.49%)
Progression	
Positive	118 (29.1)
Negative	287 (70.9)
Current status (at time of data collection)	
Dead	103 (25.4)
Alive	302 (74.6)

HRMB, high-risk medulloblastoma protocol; *SRMB*, standard risk medulloblastoma protocol; *MB*, medulloblastoma; *NOS*, not otherwise specified

analysis showed no significant difference among the three groups regarding the 5-year OS (p=0.557) and the 5-year PFS (p=0.146) (Tables 2 and 3). The KM survival analysis showed that OS was significantly influenced by the age <3 years (p=0.011), tumor dissemination (p=0.003), and presence of pre-operative fits (p=0.037). The multivariate Cox survival analysis showed that OS was significantly influenced by the age <3 years (OR 2.036, 95% CI: 1.229–3.374; p = 0.006) and tumor dissemination (OR 1.999, 95% CI: 1.242–3.127; p = 0.004), while it was not affected by the presence of pre-operative fits (OR 2.336, 95% CI: 0.836–6.516; p = 0.105) (Table 2 and Fig. 1).

Moreover, KM survival and multivariate Cox analyses showed that PFS was significantly influenced by tumor dissemination (KM: p<0.001, Cox: OR 2.171, 95% CI: 1.406–3.353; p<0.001), presence of pre-operative fits (KM: p=0.036, Cox: OR 2.852, 95% CI: 1.046–7.773; p=0.041) and post-operative pseudomeningocele (KM: p=0.021, Cox: OR 2.311, 95% CI: 1.123–4.754; p=0.023) (Table 3 and Fig. 2). The rest of the analyzed factors (e.g., gender, tumor histopathology) had no significant impact on patients' survival (Tables 2 and 3).

Regarding the secondary study endpoint, increasing the extent of tumor resection did not seem to result in higher operative morbidity (Table 4). Cerebellar mutism (CM) was the commonest post-operative complication (9%), followed by bulbar palsy (6%), limb weakness (4%), and pseudomeningocele (4%). The rate of CM could not be attributed to the extent of resection (p=0.197). Post-operative pseudomeningocele was self-limited in nine cases (50%); one VP shunt insertion/revision was needed in eight cases (44%), while five surgeries were needed (three EVDs and two VP shunts) in one case that was associated with infection.

Discussion

To our knowledge, this is the largest single-center study on the surgical outcome of pediatric MB. Surgery is an independent predictor of survival in children with MB [40]; however, a balance should always be kept between the potential benefits of performing GTR and the potential hazards, especially as GTR has not proven to offer added benefit compared to NTR [36].

The survival analysis in our study yielded no significant difference between GTR, NTR, and STR regarding either the OS (p=0.557) or the PFS (p=0.146). This finding comes in concordance with the results of previously published studies which suggested that the resection margin is not a predictor of either OS or PFS [3, 16, 27, 35, 39, 42]. In the same context, Gajjar et al. reported no PFS advantage for GTR over NTR or STR in their study on 40 children with MB invading the brainstem [10].

Nevertheless, a multicenter retrospective study on 787 patients from a total of 35 centers has shown no significant OS benefit for a greater extent of resection for patients with all MB subtypes (WNT, SHH, group 3, and group 4 tumors), though

Table 2 Kaplan-Meier and Cox multivariate regression analysis for overall survival (OS) among all patients.

Variables	Mean			*p* value	Cox survival				
					B	*p* value	OR	95% CI	
	Estimate	Lower	Upper					Lower	upper
Age category									
<3 years	72.01	56.03	87.99	**0.011**	0.711	**0.006**	2.036	1.229	3.374
≥ 3 years*	90.12	83.58	96.65						
Tumor dissemination at onset									
Positive	64.01	47.14	80.88	**0.003**	0.692	**0.004**	1.999	1.242	3.127
Negative *	92.11	85.63	98.66						
Pre-op fits									
Positive	30.50	13.63	47.37	**0.037**	0.848	0.105	2.336	0.836	6.516
Negative*	88.91	82.73	95.09						
Gender									
Male	88.04	80.36	95.71	0.832					
Female	87.20	77.48	96.92						
Initial CSF diversion									
VP shunt	78.69	73.36	84.01	0.717					
ETV	90.10	69.01	111.19						
PTR	82.41	67.89	96.93						
Shunt infection	46.51	33.95	59.07	0.463					
Pre-op squint	83.65	72.39	94.91	0.128					
Pre-op ataxia	82.67	74.04	91.30	0.481					
Pre-op bulbar palsy	33.53	15.33	51.73	0.109					
Extent of resection									
GTR	87.57	80.91	94.23	0.557					
STR	79.53	63.68	95.38						
NTR	96.33	78.71	113.95						
Post-op bulbar palsy	80.10	61.48	98.71	0.934					
Post-op mutism	66.65	52.14	81.17	0.823					
Post-op fits	75.50	52.80	98.20	0.638					
Post-op limb weakness	64.05	46.12	81.97	0.472					
Post-op C.N. palsy	56.78	30.83	82.74	0.457					
Post-op pseudomeningocele	56.83	33.27	80.38	0.057					
Post-Op CSF Leak	74.28	41.71	106.86	0.505					
Post-Op infection	63.38	34.75	92.00	0.935					
Histological subtypes									
Anaplastic/large cell MB	74.82	66.16	83.48	0.164					
Classic MB	87.05	79.30	94.81						
MB with extensive nodularity	84.68	67.20	102.17						
Desmoplastic MB	70.47	66.65	92.28						
MB NOS	75.16	53.98	96.34						
Post-shunting subdural hemorrhage	46.51	33.95	59.07	0.463					

*Indicator

ETV, endoscopic third ventriculostomy; *PTR*, primary tumor resection; *GTR*, gross total resection; *NTR*, near-total resection; *STR*, subtotal resection; *MB*, medulloblastoma; *NOS*, not otherwise specified

Significant *p* values are in bold

GTR had a significant benefit over STR regarding the PFS only in group 4 tumors, especially in patients with metastatic tumors [36]. Earlier, two reports from the children's cancer group have shown that the extent of residual tumor correlates with PFS only

Table 3 Kaplan-Meier and Cox multivariate regression analysis for progression-free survival (PFS) among the patients.

Variables	Mean			*p* value	Cox survival				
					B	*p* value	OR	95% CI	
	Estimate	Lower	Upper					Lower	Upper
Age category									
<3 years	71.32	55.14	87.50	0.052					
≥ 3 years	84.59	77.88	91.30						
Gender									
Male	82.68	74.78	90.58	0.692					
Female	84.13	74.55	93.71						
Tumor dissemination at onset									
Positive	49.83	36.37	63.29	**<0.001**	0.775	**<0.001**	2.171	1.406	3.353
Negative *	87.95	81.33	94.57						
Initial CSF diversion									
VP shunt	75.09	69.59	80.59	0.367					
ETV	81.40	59.83	102.96						
PTR	74.07	59.08	89.05						
Shunt infection	40.13	27.17	53.08	0.382					
Pre-op squint	80.06	67.19	92.93	0.104					
Pre-op ataxia	77.58	68.60	86.55	0.508					
Pre-op fits									
Positive	31.63	11.52	51.74	**0.036**	1.048	**0.041**	2.852	1.046	7.773
Negative*	83.92	77.59	90.24						
Pre-op bulbar palsy	37.86	20.51	55.20	0.140					
Extent of resection									
GTR	83.86	77.06	90.67	0.146					
STR	70.13	53.74	86.51						
NTR	86.13	66.06	106.20						
Post-op bulbar palsy	81.73	63.73	99.74	0.665					
Post-op mutism	67.85	53.23	82.46	0.832					
Post-op fits	75.50	52.80	98.20	0.461					
Post-op limb weakness	55.67	37.39	73.96	0.196					
Post-op C.N. palsy	55.28	28.18	82.83	0.550					
Post-op pseudomeningocele									
Positive	46.08	22.65	69.51	**0.021**	0.838	**0.023**	2.311	1.123	4.754
Negative*	84.47	78.19	90.95						
Post-op CSF leak	74.28	41.71	106.86	0.687					
Post-op infection	61.21	30.38	92.04	0.923					
Histological subtypes									
Anaplastic/large cell MB	71.64	62.83	80.45	0.214					
Classic MB	79.60	71.42	87.79						
MB with extensive nodularity	82.55	63.69	101.42						
Desmoplastic MB	79.03	65.83	92.24						
MB NOS	68.39	46.27	90.51						
Post-shunting subdural hemorrhage	53.49	36.21	70.7	0.722					

*Indicator

C.N, cranial nerve; *ETV*, endoscopic third ventriculostomy; *PTR*, primary tumor resection; *GTR*, gross total resection; *NTR*, near-total resection; *STR*, subtotal resection; *MB*, medulloblastoma; *NOS*, not otherwise specified

Significant *p* values are in bold

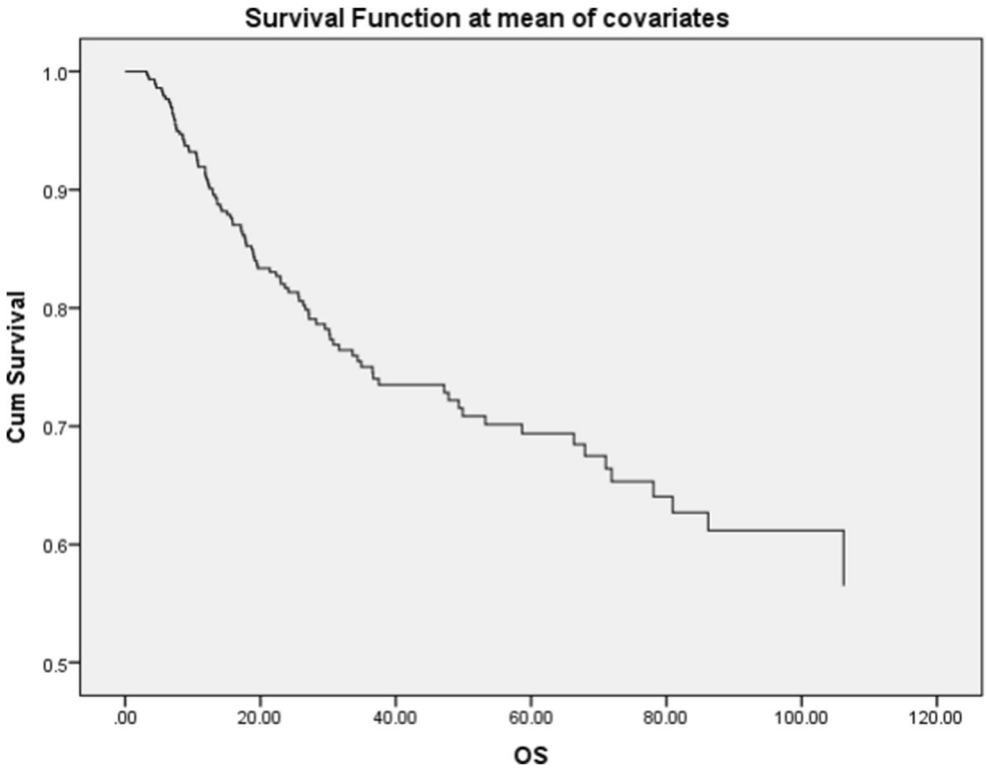

Fig. 1 Cox survival curve for significant covariate of overall survival (OS)

in children older than 3 years of age, with no tumor metastasis [1, 43]. A recent Norwegian study reported better 5-year OS for pediatric MB patients with GTR compared to those with non-GTR (64% versus 22%; p <0.001) [33].

Children younger than 3 years old and those with metastatic tumors at onset are considered high-risk patients, and they tend to have lower survival rates [1, 6, 14, 20, 31, 36]. In our study, tumor dissemination at onset was related to worse OS

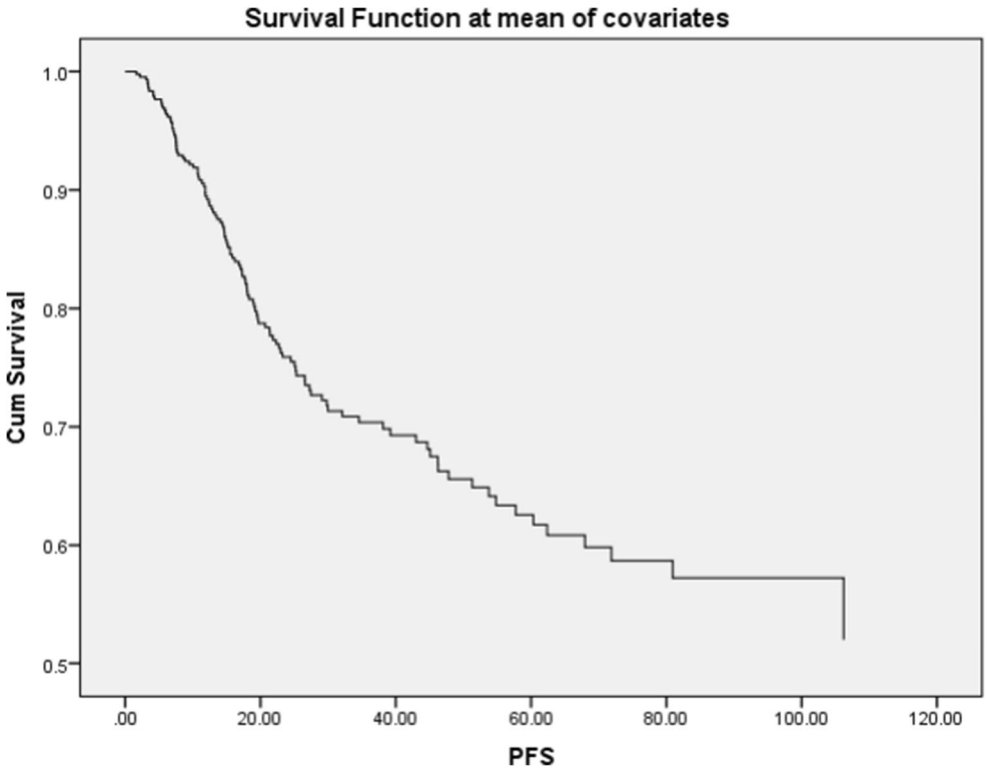

Fig. 2 Cox survival curve for significant covariate of progression-free survival (PFS)

Table 4 EOR and post-operative complications

Operative complications	EOR			*p* value
	GTR (*n*=327), no (%)	NTR (*n*=30), no (%)	STR (*n*=48), no (%)	
Post-operative bulbar palsy				
Positive	24 (7.3)	0 (0.0)	2 (4.1)	0.286
Negative	301 (92)	30 (100.0)	46 (95.9)	
N/A	2 (0.6)	0 (0.0)	0 (0.0)	
Post-operative mutism				
Positive	31 (9.5)	0 (0.0)	5 (10.4)	0.197
Negative	294 (90)	30 (100.0)	43 (89.6)	
N/A	2 (0.6)	0 (0.0)	0 (0.0)	
Post-operative fits				
Positive	8 (2.4)	2 (6.7)	1 (2.1)	0.308
Negative	317 (97)	28 (93.3)	47 (97.9)	
N/A	2 (0.6)	0 (0.0)	0 (0.0)	
Post-operative limb weakness				
Positive	12 (3.6)	1 (3.4)	5 (10.4)	0.107
Negative	313 (95.7)	29 (96.7)	43 (89.6)	
N/A	2 (0.6)	0 (0.0)	0 (0.0)	
Post-operative cranial nerve palsy				
Positive	5 (1.5)	1 (3.4)	3 (6.1)	0.084
Negative	320 (97.8)	29 (96.7)	45 (93.8)	
N/A	2 (0.6)	0 (0.0)	0 (0.0)	
Post-operative pseudomeningocele				
Positive	14 (4.3)	0 (0.0)	4 (8.3)	0.226
Negative	311 (95.1)	30 (100.0)	44 (91.7)	
N/A	2 (0.6)	0 (0.0)	0 (0.0)	
Post-operative CSF leak				
Positive	7 (2.1)	0 (0.0)	1 (2.1)	1.00
Negative	318 (97.2)	30 (100.0)	47 (97.9)	
N/A	2 (0.6)	0 (0.0)	0 (0.0)	
Post-operative wound infection				
Positive	7 (2.1)	0 (0.0)	1 (2.1)	1.00
Negative	318 (97.2)	30 (100.0)	47 (97.9)	
N/A	2 (0.6)	0 (0.0)	0 (0.0)	

and PFS. In addition, OS was significantly affected among patients with age < 3 years, while PFS was worse among patients who had either pre-operative fits or post-operative pseudomeningocele.

Although posterior fossa tumors do not present mainly with seizures, some series had reported its occurrence in the presenting symptoms in 6 to 27% of their cases [11, 15, 25, 38] and 5 to 8% of medulloblastoma cases had pre-operative fits [11, 38]. Although some authors referred to the cortical injury secondary to shunt placement as a predisposing factor [13, 17], others assumed that this typically occurs with the associated cerebral metastasis or the increase of intracranial pressure due to hydrocephalus [8]. Based on our results that OS and PFS rates were significantly affected by the presence of pre-operative fits, we can hypothesize that the most probable cause of these seizures is the presence of tumor dissemination or non-identified seedling that led to a worse outcome rather than secondary to hydrocephalus that was present in almost all cases while 2% only of our MB cases had pre-operative fits.

Pseudomeningocele is a well-reported complication of posterior fossa surgeries [18, 32]. In our series, pseudomeningocele was more frequently encountered in patients who underwent initial ETV before tumor excision, compared to those who were offered PTR or VP shunt (p=0.045) (Fig. 3). The finding that a more worse PFS is correlated to post-operative pseudomeningocele can be explained by the delay and/or interruption of the adjuvant therapy either by waiting for the effect of conservative measures, shunt insertion, or revisions in order to manage such complication.

Cerebellar mutism (CM) occurred after tumor excision in 38 (9%) of our cases and was reversible within 3-month duration in all cases. Cerebellar mutism represents a group of

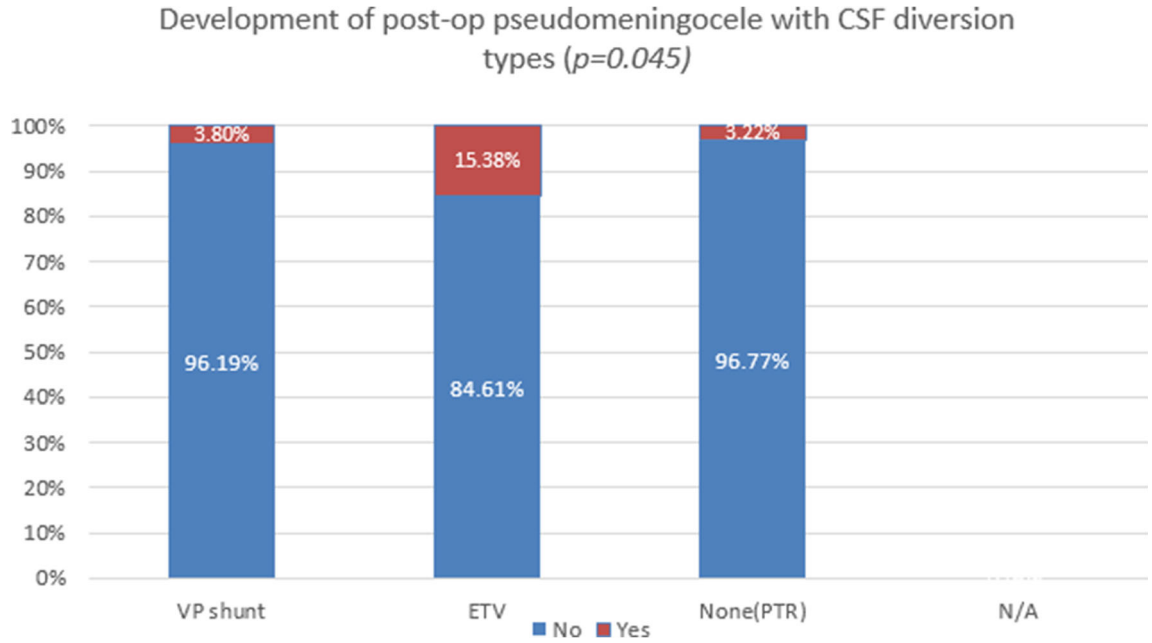

Fig. 3 Development of post-op pseudomeningocele with CSF diversion types

neurological and neurocognitive disorders, including reduced speech, hypotonia, ataxia, and irritability or emotional lability [28]. CM is more common in the pediatric age group and in surgeries involving the midline cerebellar structures [41]. In our study, the incidence of CM could not be linked to the extent of tumor resection (p=0.197). The role of the surgical technique in the development of CM has been a matter of debate [5, 34]; however, iatrogenic injury is usually blamed as the reason beyond CM, especially injury to dentatothalamic-cortical tract [23]. The rate of CM in similar studies ranges from 0 to 30% [28, 37, 41].

The percentage of patients who underwent initial CSF diversion before tumor excision was quite high in our series (VP shunt in 78%, and ETV in 6%), given that HCP is reported in 60–90% of children with posterior fossa tumors preoperatively and in only 18–40% post-operatively [22]. We offered PTR to 15% of the study population; however, HCP persisted in 22.5% of them and needed CSF diversion. Numerous studies noted that 10–40% of patients experience persistent HCP after a PTR [2, 9, 19, 21, 30]. Persistent HCP after PTR is more common in the young age, moderate to severe HCP, trans-ependymal permeation, tumor dissemination, and certain tumor entities (ependymoma and MB) [19]. The high percentage of initial CSF diversion in our study can be partly explained by the late presentation of numerous patients with vision and/or life-threatening HCP which mandated immediate CSF diversion; moreover, among the 317 patients with initial VP shunting, 11% of the shunt surgeries were done in other hospitals before the definitive admission to our center.

In our study, ETV failed in 15 out of 26 patients and it correlated to the development of post-operative pseudomeningocele. In a previous study, we noted the high rate of ETV failure in cases of pediatric MB, compared to other tumor types even with the total tumor resection, and the absence of debris, blood, and adhesions in the tumor bed [7]. The possible causes of the low success rate of ETV in MB cases include swelling of the cerebellum, alteration in CSF reabsorption due to surgery-induced subarachnoid hemorrhage, and development of adhesions at the level of the fourth ventricle outlets and the adjacent cisterns [7, 29].

Limitations of the study

The main limitation of this study is its retrospective nature where data collection was occasionally difficult to accomplish especially for patients operated in the first 2 years of the study period.

Conclusions

Although surgical excision of medulloblastoma is the standard of care, there was no significant benefit for gross total excision over near or subtotal resection on the overall or progression-free survival rates that are mainly influenced by the patient's age and tumor dissemination. However, gross total resection should be targeted in medulloblastoma whenever possible and safe, as it is not associated with an increased incidence of

mutism or other various complications related to posterior fossa surgery. Significant pseudomeningocele interfering with radiotherapy and delaying it should be managed promptly to avoid a worse outcome.

Declarations

Conflict of interest The authors declare that they have no conflict of interest in personal, financial, institutional, or industry affiliations in any of the drugs, materials, or devices described in this article. The authors have no conflicts that may affect ethical adherence.

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