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Remote Supratentorial Recurrent Medulloblastoma: Case Study and Literature Review

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Abstract

Medulloblastomas comprise 10% of pediatric brain tumors. Subfrontal recurrence is uncommon and has been associated with prone positioning, inadequate irradiation of the cribriform plate area, and hydrocephalus management. We discuss the case report of an 8-year-old boy with subfrontal medulloblastoma recurrence. The literature was reviewed using terms such as "medulloblastoma," "subfrontal recurrence," and "child." Forty-eight cases of subfrontal medulloblastoma recurrence were identified. The mean age at presentation was 12.3 years. Gross total resection was achieved in 44%, most patients received adjuvant radiation therapy, and approximately 25% received chemotherapy. The mean recurrence interval was 2.6 years. The mean number of recurrences per patient was 1.2 and the mean survival period was 3.3 years. Even in the case of meticulous resection and sufficient irradiation, recurrences may still occur. Our case indicates that resection of the recurrent lesion and repeat irradiation may benefit patients with satisfactory short-term results.

Keywords
- subfrontal
- recurrence
- medulloblastoma
- child
- predisposing factors
- treatment

Key Messages

- We herein present a case of an 8-year-old boy with subfrontal recurrence of medulloblastoma. Our case among others shows that medulloblastomas may recur even after appropriate treatment and in the absence of local relapse. Repeat surgery and radiation therapy might benefit patients with a satisfactory clinical course.
- Another 47 similar cases were identified in the literature. Data regarding socio-demographics, recurrence interval, treatment of the primary and recurrent tumor, and outcomes are presented. Additionally, an analysis of the cases with respect to risk factors for recurrence in the subfrontal area was conducted.
- Further research is needed, especially aiming to quantify the herein presented data. Emphasis should be placed on assessing and/or reporting molecular and immunohistochemical

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data, as they might aid in predicting recurrences and planning targeted treatment.

Introduction

Medulloblastomas are the most common malignant brain tumors in children, comprising 10% of all pediatric brain tumors.[1,2] They are highly malignant and often recur even after appropriate treatment.

Among areas of recurrence, the subfrontal area is relatively rare. Certain factors have been postulated to increase the risk for this type of tumor spread: prone position, inadequate irradiation of the cribriform plate area, management of hydrocephalus, adverse histopathologic, immunohistochemical, and/or molecular profile. We herein present a case of pediatric subfrontal recurrence and analyze similar cases identified in the literature, focusing on the commonly described risk factors for subfrontal recurrence.[3]

Case History

An 8-year-old boy presented with a space-occupying lesion in the subfrontal area. The mass was identified on scheduled follow-up screening and the patient had no symptoms or change in clinical status.

At the age of 4 years, the patient was diagnosed with a medulloblastoma of the fourth ventricle, for which he underwent surgery followed by chemotherapy, radiation therapy, and proton beam therapy. At the time of surgery, a right-sided ventriculoperitoneal shunt was placed and the pressure was set at 7 cm of H_2O. The patient is on levetiracetam following an episode of status epilepticus 5 months before the current presentation.

On physical exam, there is postural and gait instability, a 4/5 left-sided hemiparesis, dysarthria, and psychomotor retardation. More specifically, the patient is able to stand, but walks with support, and he is able to feed himself, but has difficulty drawing and writing. The onset of all neurological deficits can be traced back to the postoperative period.

A right frontal craniotomy was performed and the tumor was resected to macroscopic clear margins (►**Figs. 1**–**2**). The intraoperative blood loss was as little as 70 mL. The course of the operation was uneventful. The patient was then admitted to the pediatric intensive care unit (ICU), where he stayed for 6 days and no adverse events were reported other than delayed awakening. At the time of discharge from the ICU, the patient was alert and able to move all four limbs against gravity. No new neurological deficits or clinical deterioration were noted.

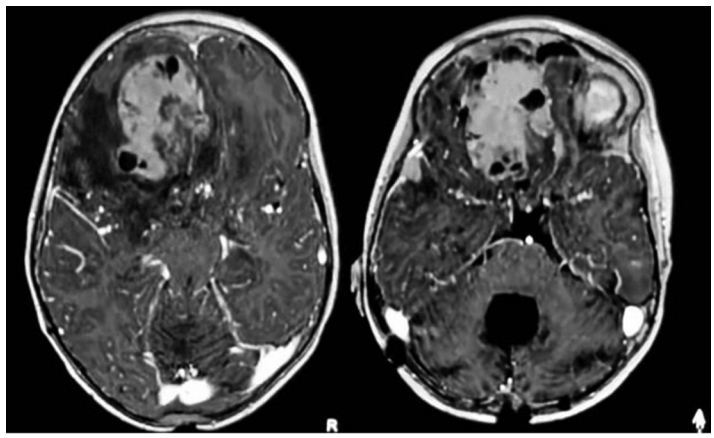

Fig. 1 Preoperative magnetic resonance imaging scans—axial view.

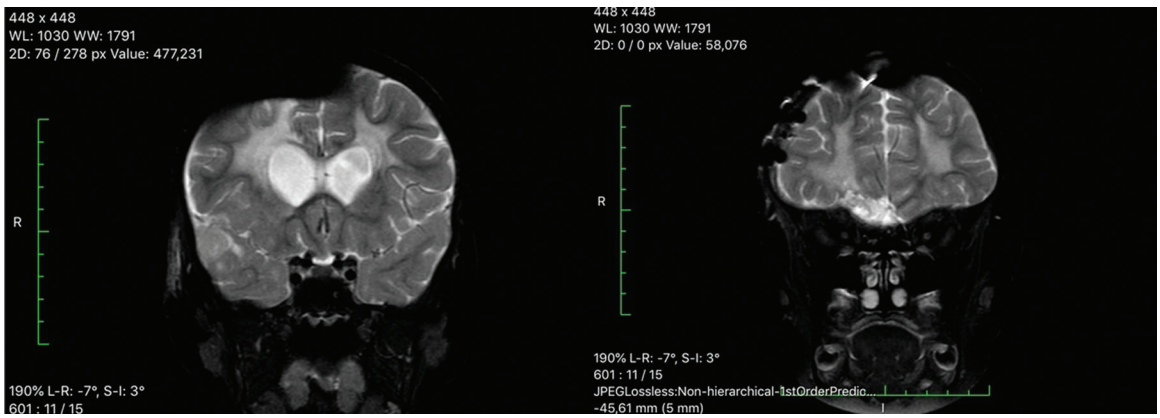

Fig. 2 Preoperative magnetic resonance imaging scans—coronal view.

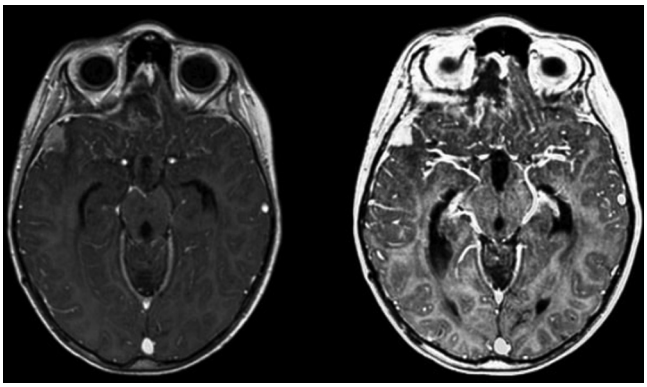

Fig. 3 First postoperative magnetic resonance imaging scans.

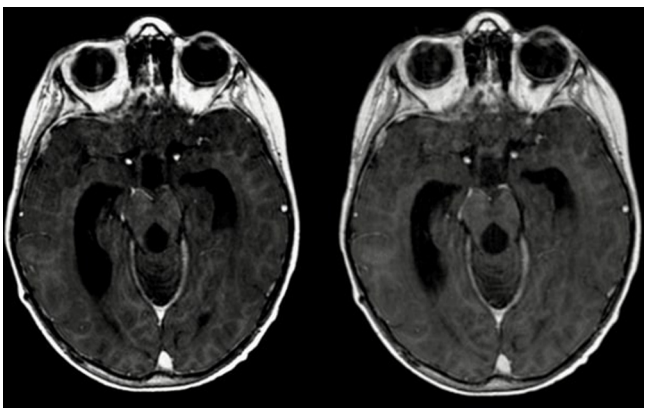

Fig. 4 Postradiation magnetic resonance imaging scans—axial view.

The pathology report confirmed that the tumor was a medulloblastoma and its molecular profile is currently under investigation.

Upon the first postoperative imaging, a small residual lesion was noted on the temporal neocortex and there were no other lesions across the neuraxis (►**Fig. 3**). The patient then received adjuvant radiation therapy in the form of simultaneous boost-volumetric modulated arc therapy. A dose of 39.6 Gy was administered for the tumor bed and 50.6 Gy in the area of the residual tumor. The patient underwent a total of 22 sessions. Post radiation magnetic resonance imaging) showed near-total tumor recess (►**Figs. 4**, **5**).

For the purpose of long-term follow-up, the patient was referred to the Pediatric Oncologic Department of our institution.

Discussion

Literature Review Strategy

A literature search was performed on PubMed, Web-Of-Science, and Ovid, using the search terms "Subfrontal recurrence," "Medulloblastoma," and "Child." The search was last performed on August 10, 2021, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram was used to graphically present the study selection process.[4] The included studies were critically appraised using the Joanna Briggs Institute critical appraisal tools: Checklist for Case Series[5] and Checklist for Case Reports.[6] The Risk-of-bias VISualization tool[7] was then used to generate traffic light plots. The extracted data for individual patients is presented in tabular form. Patient data was additionally analyzed with respect to the most prominent risk factors for medulloblastoma recurrence described in the literature: degree of resection; local relapse; prone position during surgery, and/or radiation therapy; type of radiation therapy received; adequacy of irradiation of the subfrontal area; management of perioperative hydrocephalus; histopathologic characteristics; immunohistochemical profile. The results of our analysis are presented in the form of pie charts.

Summary of Literature Review Results

The initial search returned a total of 10 results, out of which 8 articles referring to data on patients with subfrontal medulloblastoma recurrence were chosen for further analysis. Four additional articles were later identified by handsearching. A detailed flowchart of the study selection process can be seen in ►**Fig. 6**. ►**Fig. 7** graphically presents the results of quality assessment.

Patient data, including demographics, treatment of the primary tumor, recurrence interval, location of recurrence(s),

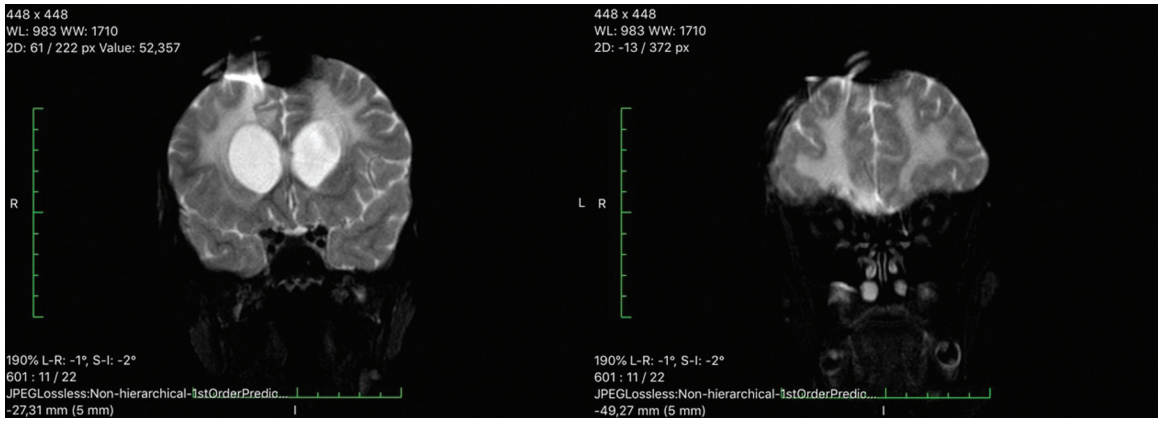

Fig. 5 Postradiation magnetic resonance imaging scans—coronal view.

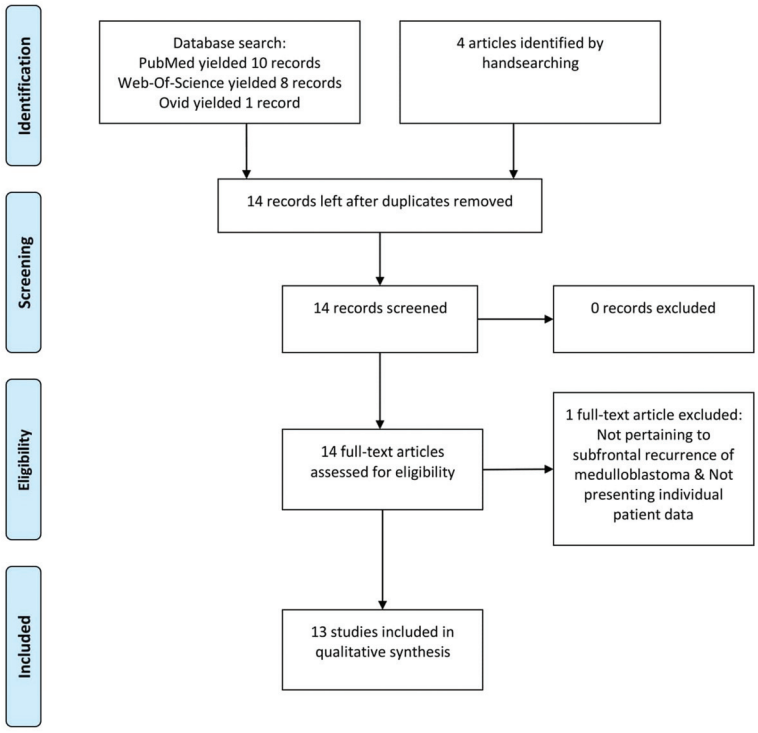

Fig. 6 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

treatment of recurrent lesion(s), and patient outcomes after management of one or more recurrences are presented in ►**Table 1**.[8–19] ►**Table 2**[8–19] summarizes the predisposing factors per patient, namely the presence of a local relapse, prone position during surgery and/or radiation therapy, inadequate irradiation of the cribriform plate area (as reported by the authors of each included article), shunt placement for the management of perioperative hydrocephalus, as well as histopathologic and immunohistochemical characteristics of the tumor.

A total of 48 cases (including the case reported by the authors) were studied. The mean age of the patients is 12.3 years of age and the male:female ratio is 5:2. The resection of the primary tumor was characterized as "gross total resection or GTR" in 21 patients (44%), "near-total resection or NTR" in one patient (2%), "subtotal resection or STR" in one patient (2%), "partial resection or PR" in three patients (6%), "resection - degree not specified or R(DNC)" in 19 patients (40%), and as just "biopsy" in one patient (2%). For two patients (4%), no information on degree of resection was found. Most of the patients then received adjuvant radiation therapy, in the form of craniospinal irradiation or CSI (27 patients or 56%), CSI and irradiation of the posterior fossa (six patients or 13%), radiation therapy for which no specific characteristics were reported (13 patients or 27%), and no relevant information was identified for another two cases or 4%. At least 12 patients (25%) additionally received chemotherapy. The details on the chemotherapeutic agents used in each patient can be seen in ►**Table 1**. The mean recurrence interval was found to be approximately 2.6 years (30.8 months). Forty-one patients (85.4%) had only one recurrence, six patients (12.5%) had two recurrences, and one patient (2.1%) had three recurrences. The mean number of recurrences per patient is 1.2. Most patients had their first recurrence in the cribriform plate/subfrontal area. Additional recurrences were found in the frontal lobe/olfactory plate (six cases), the spine (four cases), both temporal poles (two cases), as well as one of each of the following: bulbar metastases, distant supratentorial metastases, meningeal seeding, the presence of atypical cells in the cerebrospinal fluid. The treatment of the first recurrent lesion consisted of surgery alone in five patients (10.42%), radiation therapy alone in three patients 6.25%), surgery followed by chemotherapy in three patients (6.25%), surgery followed by radiation therapy in one patient (2.08%), chemotherapy and radiation therapy in one patient (2.08%), surgery followed by adjuvant chemotherapy and radiation therapy in seven patients (14.58%), and neoadjuvant chemotherapy and radiation therapy and then surgery followed by adjuvant chemotherapy and radiation therapy in one patient (2.08%). In 27 patients (56.25%), no information regarding treatment of the (first) recurrent lesion was identified. For the management of the second recurrence, one out of the six patients who presented with a second recurrent lesion (16.7%) underwent radiation therapy alone, two patients (33.3%) were treated with a combination of chemotherapy

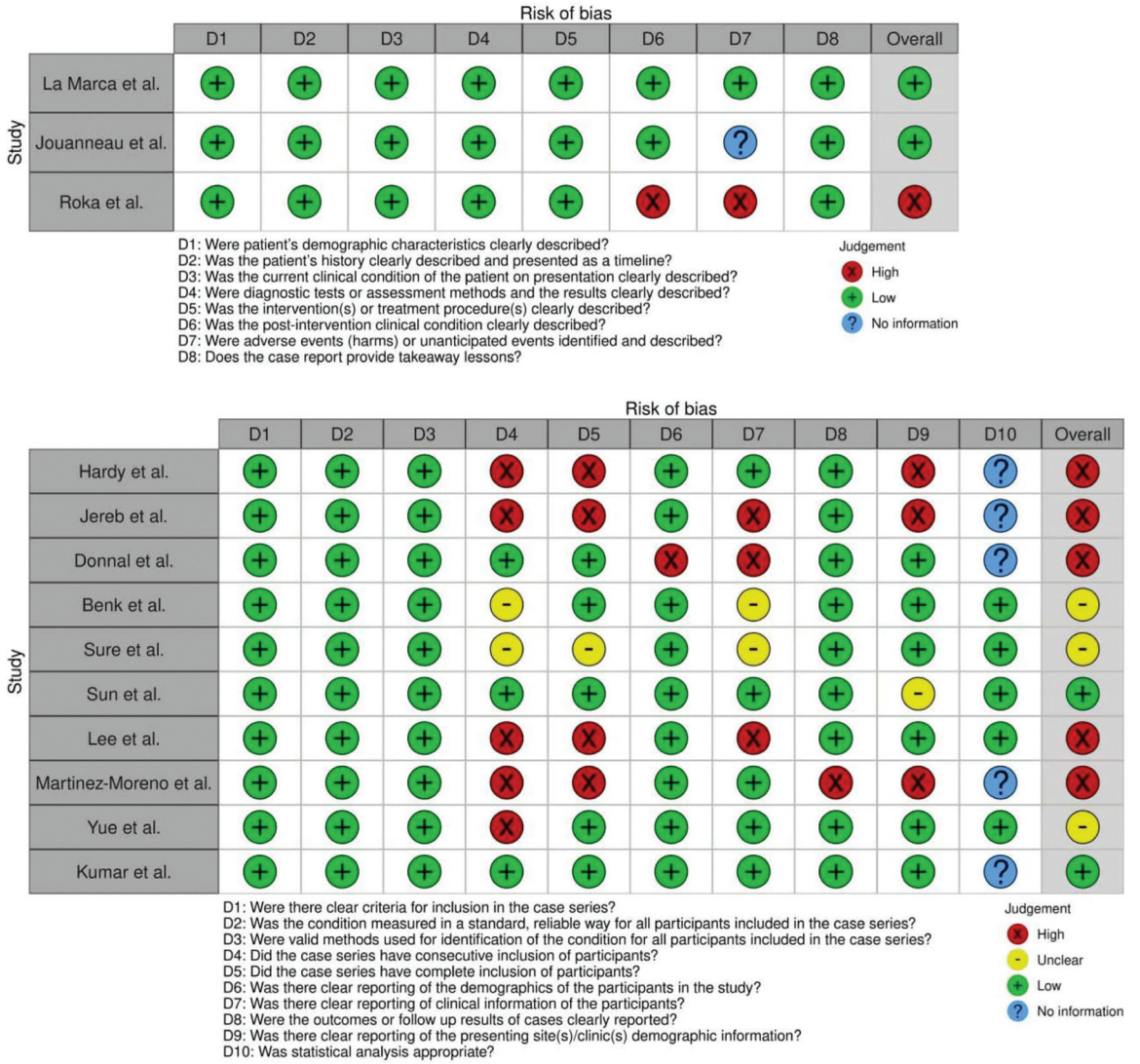

Fig. 7 Quality assessment using the Joanna Briggs Institute critical appraisal tools.

and radiation therapy, and for the remaining three patients (50%) no relevant data was found. The only patient in our analysis who had a third recurrence was managed with surgical resection of the lesion. Nine patients (18.75%) had an uneventful recovery and/or clinical improvement after treatment of the first recurrence. The mean survival period after diagnosis of the primary tumor for the patients whose death was documented in the included articles was calculated to be 39.5 months (3.3 years). For an additional five patients, death was reported in the absence of specific data on the time interval since the initial presentation. Moreover, one patient was noted to have no improvement after receiving surgery and chemotherapy for the recurrent lesion and he refused further treatment. However, it is unclear when (and if) he succumbed to the disease. No data on clinical outcomes was found for 25 patients (52.08%).

Risk Factors for Subfrontal Medulloblastoma Recurrence

According to Jereb et al, medulloblastomas most commonly recur within the posterior fossa, and supratentorial metastases are quite uncommon.[20] Among them, subfrontal recurrences seem to be even rarer, given that no more than 50 such cases have been described in the literature.

Our case describes a patient in whom remote tumor spread occurred in the absence of local relapse. Moreover, some of the many factors postulated to increase the risk of subfrontal recurrence, such as the "face-down" position during posterior fossa surgery, and the presence of a ventriculoperitoneal shunt, seem to apply to our case. Other factors such as adequacy of irradiation of the cribriform plate area cannot be appraised since the primary tumor was treated at another institution in a different country. Following is a brief discussion of our findings with regard to all identified cases.

Degree of Resection

Although meticulous resection of the primary tumor is considered critical in preventing local and remote spread of the tumor, it seems that it is not on itself enough to protect against it. Among the 48 cases of subfrontal recurrence studied in this review, 21 patients (44%) had undergone gross total resection of the primary tumor, and for the rest of the patients varying degrees of resection have been

Table 1 Summary of similar cases described in the literature

Name of study	Number of cases	Patient demographics	Treatment of primary tumor	Recurrence interval	Location of recurrence	Treatment of recurrence	Outcomes
Hardy et al 1978[8]	3	M, 11 yo	PR, CSI	13 mo, 9 mo	Subfrontal region Atypical cells in the CSF and bulbar involvement	GTR, CT (IT methotrexate, IV vincristine)	Uneventful recovery, no new neurological deficits Death 2 months after second recurrence
		M, 12 yo	GTR, CSI	17 mo	Subfrontal region	CT (PO CCNU, IV vincristine), RT (frontal lobes) Followed 5 months later by: GTR, CT (IT methotrexate), RT (cribriform plate)	Clinical improvement and decrease in tumor size After resection: Asymptomatic and in good clinical status
		M, 2 yo	PR, CSI	7 mo	Subfrontal region	RT (subfrontal region)	No residual tumor noted following RT, good clinical status and active
Jereb et al 1981[9]	6	F, 6 yo	PR, CSI, CT (vincristine)	19 mo	Cribriform plate/subfrontal region	RT (cribriform plate)	Clinical improvement
				3 mo	Lumbar spine, ilium, femur	RT (lumbar spine)	Death within 1 y
		M, 6 yo	STR, CSI	49 mo	Cribriform plate/subfrontal region	STR, RT (frontal lobes), CT (BCNU)	Temporary improvement
				15 mo	Frontal lesion and meningeal seeding	RT (spina l cord), CT (methotrexate, vincristine, BCNU)	
				6 mo	Cribriform plate region	TR	Death within 4 mo
		F, 5 yo	GTR, CSI	23 mo, 2 mo	Cribriform plate/subfrontal region Lumbar spine	R(DNC), (cribriform plate) RT (lumbosacral region), CT (vincristine, Me-CCNU, methotrexate)	Death 10 months after the bony metastases were identified
		F, 5 yo	Biopsy, CSI	16 mo	Cribriform plate/subfrontal region	R(DNC)	Good clinical status and no signs of CNS relapse up to 6 months follow-up
		N/A	N/A	N/A	Cribriform plate/ subfrontal region (identified on autopsy)	N/A	N/A
		N/A	N/A	N/A	Cribriform plate/subfrontal region (identified on autopsy)	N/A	N/A

(*Continued*)

Table 1 (*Continued*)

Name of study	Number of cases	Patient demographics	Treatment of primary tumor	Recurrence interval	Location of recurrence	Treatment of recurrence	Outcomes
Donnal et al, 1992[10]	5	N/A	GTR, CSI	N/A	Subfrontal region	N/A	Death (uncontrolled tumor growth)
		N/A	GTR, CSI	N/A	Subfrontal region	N/A	Death (uncontrolled tumor growth)
		N/A	GTR, CSI	N/A	Subfrontal region	N/A	Death (uncontrolled tumor growth)
		N/A	GTR, CSI	N/A	Subfrontal region	N/A	Death (uncontrolled tumor growth)
		N/A	GTR, CSI	N/A	Subfrontal region and spine (synchronous lesion)	N/A	Death (uncontrolled tumor growth)
Benk et al, 1995[11]	5	N/A	R(DNC), RT	10–35 mo	Frontal lobe/olfactory plate	N/A	N/A
		N/A	R(DNC), RT	10–35 mo	Frontal lobe/olfactory plate	N/A	N/A
		N/A	R(DNC), RT	10–35 mo	Frontal lobe/olfactory plate	N/A	N/A
		N/A	R(DNC), RT	10–35 mo	Frontal lobe/olfactory plate	N/A	N/A
		N/A	R(DNC), RT	10–35 mo	Frontal lobe/olfactory plate	N/A	N/A
Sure et al, 1995[12]	6	N/A	GTR, CSI, RT (posterior fossa), CT	At first admission	Subfrontal region	N/A	N/A
		N/A	GTR, CSI, RT (posterior fossa), CT	At first admission	Subfrontal region	N/A	N/A
		N/A	GTR, CSI, RT (posterior fossa), CT	At first admission	Subfrontal region	N/A	N/A
		N/A	GTR, CSI, RT (posterior fossa), CT	At first admission	Subfrontal region	N/A	N/A
		N/A	GTR, CSI, RT (posterior fossa), CT	16 mo	Subfrontal region	N/A	N/A
		N/A	GTR, CSI, RT (posterior fossa), CT	29 mo	Subfrontal region	N/A	N/A

Table 1 (*Continued*)

Name of study	Number of cases	Patient demographics	Treatment of primary tumor	Recurrence interval	Location of recurrence	Treatment of recurrence	Outcomes
La Marca and Tomita, 1997[13]	1	M, 11 yo	GTR, CSI	36 mo	Subfrontal region	R(DNC), GKR (tumor bed), CT	Good health and able to support himself, below average height (GH discontinued)
Kumar et al, 2001[14]	1	M, 9 yo	GTR, CSI	20 mo	Subfrontal region	GTR, CT (vincristine, etoposide, cisplatin)	No improvement, refused further treatment
Sun et al, 2002[15]	7	N/A	R(DNC), RT	N/A	Subfrontal region	N/A	N/A
		N/A	R(DNC), RT	N/A	Subfrontal region	N/A	N/A
		N/A	R(DNC), RT	N/A	Subfrontal region	N/A	N/A
		N/A	R(DNC), RT	N/A	Subfrontal region	N/A	N/A
		N/A	R(DNC), RT	N/A	Subfrontal region	N/A	N/A
		N/A	R(DNC), RT	N/A	Subfrontal region	N/A	N/A
		N/A	R(DNC), RT	N/A	Subfrontal region	N/A	N/A
Jouanneau et al, 2006[16]	1	M, 45 yo	R(DNC), CSI, CT	21 y	Subfrontal region	GTR, (subfrontal region), CT (etoposide, carboplatin)	Good clinical status, able to work
				13 mo	Distant supratentorial metastasis	N/A	
Roka et al, 2009[17]	1	F, 13 yo	GTR, CSI	60 mo	Subfrontal region	GTR	N/A
Lee et al, 2015[18]	5	M, 7 yo	R(DNC), CSI	18.2 mo	Subfrontal region	R(DNC), RT, CT	Death 16 months after recurrence
		F, 5 yo	R(DNC), CSI	17.1 mo	Subfrontal region	RT	Death 1 month after recurrence
		M, 6 yo	R(DNC), CSI	5.7 mo	Subfrontal region	RT, CT	Death 9 months after recurrence
		N/A	R(DNC), CSI	N/A	Subfrontal region	N/A	N/A
		N/A	R(DNC), CSI	N/A	Subfrontal region	N/A	N/A
Martinez-Moreno et al, 2018[19]	2	M, 34 yo	GTR, CSI, CT	48 mo	Simultaneous bilateral recurrence on both temporal poles	GTR (One procedure per tumor)	N/A
		M, 38 yo	R(DNC), CSI, CT	72 mo	Simultaneous bilateral recurrence on both temporal poles	GTR (One procedure per tumor)	N/A
				48 mo	N/A	N/A	

(*Continued*)

Table 1 (*Continued*)

Name of study	Number of cases	Patient demographics	Treatment of primary tumor	Recurrence interval	Location of recurrence	Treatment of recurrence	Outcomes
Yue et al, 2018[3]	4	M, 14 yo	NTR, CSI, CT (temozolomide)	45 mo	Subfrontal region	PR, Local RT, CT (temozolomide)	Death 21 months after resection of recurrent tumor
		M, 4 yo	GTR, CSI	48 mo	Subfrontal region	PR, Local RT, CT (temozolomide, bevacizumab, Vp16, CTX, VDS)	Death 15 months after recurrent tumor resection
				N/A	Spine	N/A	
		F, 7 yo	GTR, CSI	12 mo	Subfrontal region	PR, Local RT, CT (temozolomide)	Death 20 months after resection of recurrent tumor
		M, 13 yo	GTR, CSI	21 mo	Subfrontal region	PR, Local RT, CT (temozolomide)	Death 18 months after resection of recurrent tumor
Present case, 2021	1	M, 8 yo	GTR, CT, proton beam therapy	48 mo	Subfrontal region	GTR, SIB-VMAT	Near-total tumor recess, no symptoms/new neurological deficits

Abbreviation: BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea; CCNU, 1-(2-chloroethyl)-3-cycloethyl-1-nitrosurea; CSI, craniospinal irradiation; CT, chemotherapy; F, female; GKR, Gamma knife radiosurgery; GTR, gross total resection; IT, intrathecal; IV, intravenous; M, male; Me-CCNU, 1-(2-chloroethyl)-3(4-methylcyclohexyl)-1-nitrosourea; mo, month(s); NTR, near-total resection; PO, per os; PR, partial resection; R(DNC), resection (degree not clarified); RT, radiation therapy; SIB-VMAT, simultaneous boost volumetric-modulated arc therapy; STR, subtotal resection; y, years(s); yo, years old.

Table 2 Predisposing factors for subfrontal recurrence of medulloblastoma in cases reported in the literature

Name of study	Local r elapse	Prone position during surgery	Prone position during radiation therapy	Inadequate irradiation of the cribriform plate areaa	Perioperative hydrocephalus management	Histopathologic characteristics	Immunohistochemical markers	Comments
Hardy et al, 1978[8]	N/A	✓	✓	N/A	N/A	Typical medulloblastoma and foci of oligodendroglial cells	N/A	Extracerebral recurrent lesion without oligodendroglial elements
	N/A	✓	✓	N/A	N/A	Typical medulloblastoma, foci of oligodendroglial cells, Microscopic calcifications	N/A	Extracerebral recurrent lesion with oligodendroglial elements
	N/A	✓	✓	N/A	N/A	Typical medulloblastoma	N/A	N/A
Jereb et al, 1981[9]	N/A	–	✓	✓	N/A	Medulloblastoma	N/A	Surgery in the sitting position, prone position during RT Calculated dose of RT to the cribriform plate area: 350 rads
	N/A	–	✓	✓	N/A	Medulloblastoma	N/A	Surgery in the sitting position, prone position during RT Calculated dose to the cribriform plate area: 400 rads
	N/A	–	✓	✓	N/A	Medulloblastoma	N/A	Surgery in the sitting position, prone position during RT Calculated dose to the cribriform plate area: 350 rads
	N/A	–	✓	✓	N/A	Medulloblastoma	N/A	Surgery in the sitting position, prone position during RT Calculated dose to the cribriform plate area: 900 rads
	N/A	N/A	N/A	✓	N/A	Neuronal differentiation	N/A	Recurrent tumor: primitive undifferentiated medulloblastoma
	N/A	N/A	N/A	✓	N/A	Glial differentiation	N/A	Recurrent tumor: primitive undifferentiated medulloblastoma
Donnal et al, 1992[10]	N/A	✓	✓	✓	N/A	Medulloblastoma	N/A	N/A
	N/A	✓	✓	✓	N/A	Medulloblastoma	N/A	
	N/A	✓	✓	✓	N/A	Medulloblastoma	N/A	
	N/A	✓	✓	✓	N/A	Medulloblastoma	N/A	
	N/A	✓	✓	–	N/A	Medulloblastoma	N/A	

(*Continued*)

Table 2 (*Continued*)

Name of study	Local r elapse	Prone position during surgery	Prone position during radiation therapy	Inadequate irradiation of the cribriform plate areaa	Perioperative hydrocephalus management	Histopathologic characteristics	Immunohistochemical markers	Comments
Benk et al, 1995[11]	N/A	N/A	N/A	✓	N/A	Medulloblastoma	N/A	1/5 recurrence in the subfrontal area, 4/5 recurrences in the frontal/cribriform plate area, 3/5 solitary recurrent lesion, 2/5 additional recurrent lesions
	N/A	N/A	N/A	✓	N/A	Medulloblastoma	N/A	
	N/A	N/A	N/A	✓	N/A	Medulloblastoma	N/A	
	N/A	N/A	N/A	✓	N/A	Medulloblastoma	N/A	
	N/A	N/A	N/A	✓	N/A	Medulloblastoma	N/A	
Sure et al, 1995[12]	N/A	–	N/A	N/A	✓ (VA, VP, or EVD)	Medulloblastoma	MIB-1 (+), NSE (+)	Surgery in the sitting position
	N/A	–	N/A	N/A	✓ (VA, VP, or EVD)	Medulloblastoma	MIB-1 (+), NSE (+)	
	N/A	–	N/A	N/A	✓ (VA, VP, or EVD)	Medulloblastoma	MIB-1 (+), NSE (+)	
	N/A	–	N/A	N/A	✓ (VA, VP, or EVD)	Medulloblastoma	MIB-1 (+), NSE (+)	
	N/A	–	N/A	N/A	✓ (VA, VP, or EVD)	Medulloblastoma	MIB-1 (+), NSE (+)	
	N/A	–	N/A	N/A	✓ (VA, VP, or EVD)	Medulloblastoma	MIB-1 (+), NSE (+)	
La Marca and Tomita, 1997[13]	–	✓	✓	✓	N/A	Medulloblastoma—DNA aneuploid tumor	N/A	GH supplementation therapy
Kumar et al, 2001[14]	N/A	✓	✓	N/A	N/A	Medulloblastoma	N/A	Primary tumor in the CPA
Sun et al, 2002[15]	N/A	✓	✓	N/A	N/A	Medulloblastoma	N/A	N/A
	N/A	✓	✓	N/A	N/A	Medulloblastoma	N/A	
	N/A	✓	✓	N/A	N/A	Medulloblastoma	N/A	
	N/A	✓	✓	N/A	N/A	Medulloblastoma	N/A	
	N/A	✓	✓	N/A	N/A	Medulloblastoma	N/A	
	N/A	✓	✓	N/A	N/A	Medulloblastoma	N/A	
	N/A	✓	✓	N/A	N/A	Medulloblastoma	N/A	
Jouanneau et al, 2006[16]	N/A	✓	✓	N/A	✓ (VAS)	Medulloblastoma	N/A	N/A
Roka et al, 2009[17]	N/A	✓	✓	N/A	✓ (VPS)	Medulloblastoma	N/A	N/A

Table 2 (*Continued*)

Name of study	Local r elapse	Prone position during surgery	Prone position during radiation therapy	Inadequate irradiation of the cribriform plate areaa	Perioperative hydrocephalus management	Histopathologic characteristics	Immunohistochemical markers	Comments
Lee et al, 2015[18]	N/A	✓✓	✓✓	✓✓	N/A	Medulloblastoma	N/A	Surgery in prone position, 3/5 patients RT in supine position and 2/5 in prone position
	N/A	✓✓	✓✓	✓✓	N/A	Medulloblastoma	N/A	
	N/A	✓✓	–	✓✓	N/A	Medulloblastoma	N/A	
	N/A	✓✓	–	✓✓	N/A	Medulloblastoma	N/A	
	N/A	✓✓	–	✓✓	N/A	Medulloblastoma	N/A	
Martinez-Moreno et al, 2018[19]	–	✓✓	✓✓	✓✓	–	Classic medulloblastoma	N/A	N/A
	–	✓✓	✓✓	✓✓	✓✓ (Intra-op VPS placement 6 years ago)	Classic medulloblastoma	N/A	
Yue et al, 2018[3]	–	✓✓	✓✓	✓✓	✓✓ (Pre-op VD)	Medulloblastoma	Syn (+), VIM (−), GFAP (−), EMA (−), S-100 (−)	N/A
	–	✓✓	✓✓	✓✓	✓✓ (Pre-op VD)	Medulloblastoma	NeuN (+), Syn (+), CD56 (+), CD99 (+), VIM (+), GFAP (+), PCK (−), EMA (−), CgA (−), NSE (−), S-100 (−), Nestin (−), K_i-67 > 90%	
	–	✓✓	✓✓	✓✓	✓✓ (Pre-op VD)	Medulloblastoma	NeuN (+), Syn (+), VIM (+), GFAP (−), EMA (−), CgA (−), NSE (−), S-100 (−), Nestin (−)	
	–	✓✓	✓✓	✓✓	✓✓ (Pre-op VD)	Medulloblastoma	NeuN (+), Syn (+), CD56 (+), CgA (+), Myogenin (+), CD99 (−), GFAP (−), PCK (−), EMA (−), Desmin (−), MyoD1 (−), Ck8/18 (−), K_i-67 = 40%,	
Present case, 2021	–	✓✓	✓✓	N/A	✓✓ (VPS placed at the time of the initial surgery)	Medulloblastoma	N/A	N/A

Abbreviations: EVD, external ventricular drainage; GH, growth hormone; intra-op, intraoperative; NSE, neuron-specific enolase; pre-op, preoperative; RT, radiation therapy; VAS, ventriculoatrial shunting; VD, ventricle drainage; VPS, ventriculoperitoneal shunting.
[a]As reported by the authors.

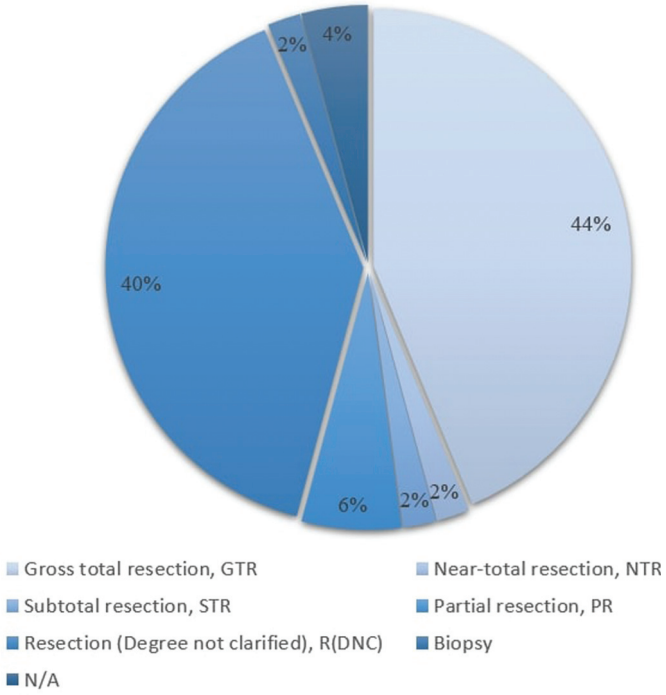

Fig. 8 Degree of resection of the primary tumor.

reported (►**Fig. 8**). These findings highlight the well-known fact that medulloblastomas are very aggressive tumors and additionally indicate the presence of other factors that may affect the potential of this tumor for spread, other than just excision of as much of the tumor bulk as possible.

Presence of Local Relapse

The presence of local tumor relapse is commonly described as one of the predisposing factors for additionally developing remote metastases from medulloblastoma. Remarkably, this factor is absent in our patient. Unfortunately, the data gathered from the included articles does not suffice for even the rough analysis performed for other risk factors.

"Face-Down" Position

The "face-down" or prone position is typically used both in surgery and during radiation therapy sessions for posterior fossa tumors like medulloblastomas. This is also the case in the studies analyzed herein, given that 31 patients (64%) were positioned "face-down" during surgery for the primary tumor, 32 patients (67%) underwent adjuvant radiation therapy in the prone position, and a total of 35 cases (73%) were placed in the same position in at least one of the above treatment modalities (►**Fig. 9**). It is worth noting, however, that some centers have attempted either surgery[9] or radiation therapy[18] in the sitting position, in an attempt to tackle the assumed higher risk of supratentorial spread with the use of the prone position.

Management of Perioperative Hydrocephalus

Shunt placement and external ventricular drainage are another commonly described risk factor for medulloblastoma spread. In this study, 14 patients (29%) had a ventriculoperitoneal shunting (VPS) or ventriculoatrial shunting (VAS) placed or underwent external drainage for the management of perioperative hydrocephalus, and one patient (2%) did not undergo any procedure related to hydrocephalus (►**Fig. 10**). However, for the vast majority of cases, we have not been able to spot relevant patient-specific information.

Adequacy of Irradiation to the Subfrontal Area

Adjuvant radiation therapy is an essential component of medulloblastoma treatment and attention needs to be paid to the proper design and administration of treatment. Inadequate irradiation of the subfrontal area, among others due to shielding of the eyes during radiation therapy, is commonly held responsible for the development of metastases in the cribriform plate area. As defining inadequate irradiation is not easy, we additionally attempted to collect authors' views on the adequacy of subfrontal area irradiation received by their patients. It appears that in more than half (56%) of the included studies, authors thought that the amount of radiation reaching the cribriform plate could be insufficient. However, in a large number of studies (42%) no clear view was expressed (►**Fig. 11**).

Histopathologic Characteristics and Immunohistochemical Profile

Histopathologic characteristics, the presence of certain immunohistochemical markers, as well as the molecular profile of the tumor are considered of paramount importance in classifying tumors and predicting long-term prognosis. Classification according to tumor histology is done

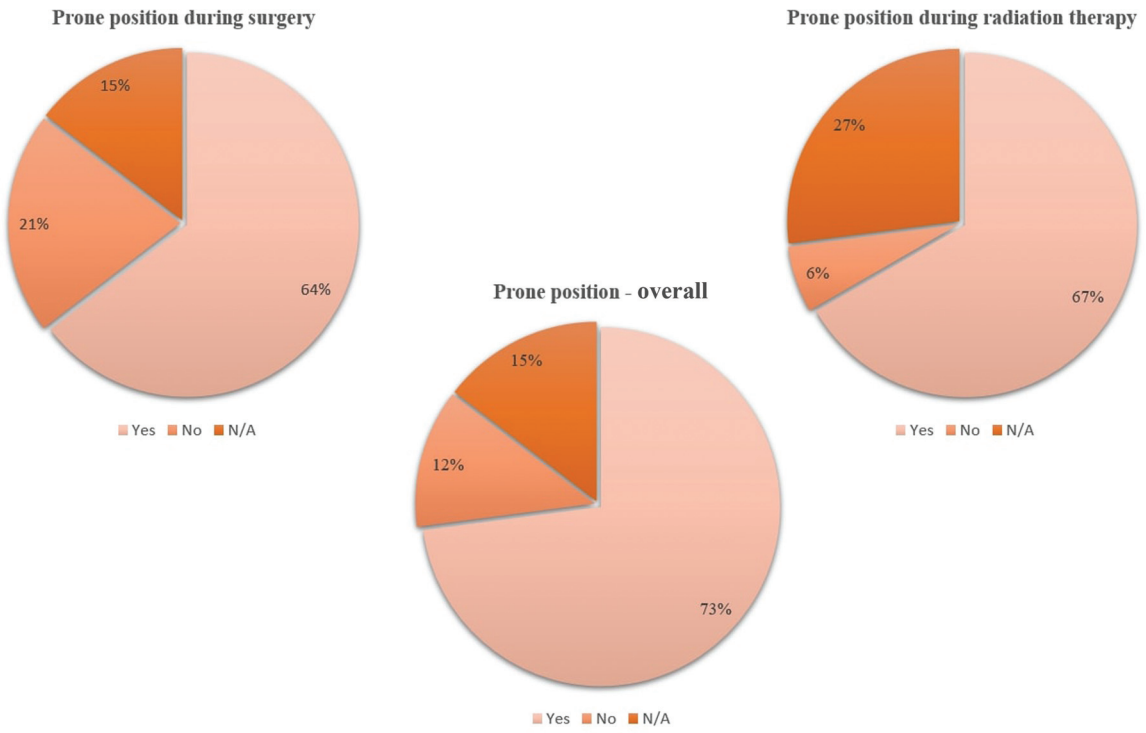

Fig. 9 Prone position during surgery and/or radiation therapy.

based on the WHO classification, which is subject to regular modifications. For the purpose of determining the molecular identity of the tumor, certain biochemical pathways are monitored, such as the Wingless or Wnt/β-catenin pathway or the Sonic hedgehog pathway. Last but not least, several immunohistochemical markers have been found to be positive in the different subtypes of medulloblastoma.[2]

In this review of 48 patients, five primary tumors were characterized as typical or classic medulloblastoma,[8,19] one tumor as medulloblastoma with neuronal differentiation, one tumor as medulloblastoma with glial differentiation,[9] and one tumor was referred to as a DNA-aneuploid type medulloblastoma.[13] For the remaining 40 primary medulloblastomas, we have not been able to retrieve any specific histopathologic information. Regarding immunohistochemical markers, Sure et al[12] and Yue et al[3] have reported relevant findings for a total of 10 patients. Among their findings, certain well-known markers, such as neuron-specific enolase, S-100, glial fibrillary acidic protein, and CD56, have been identified. Again, no information has been found for the rest of the patients included in our analysis.

Although the importance of the above characteristics has been emphasized in the literature, both in terms of recognizing possible recurrence patterns[21] and in designing targeted treatment,[22] it appears that pathology results are usually only briefly discussed, and molecular and immunohistochemical test results may not be reported at all. Dedicating part of the diagnostic and therapeutic efforts into

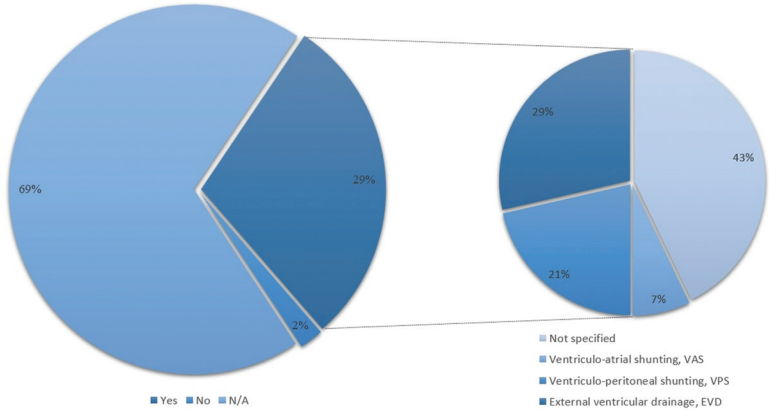

Fig. 10 Management of perioperative hydrocephalus.

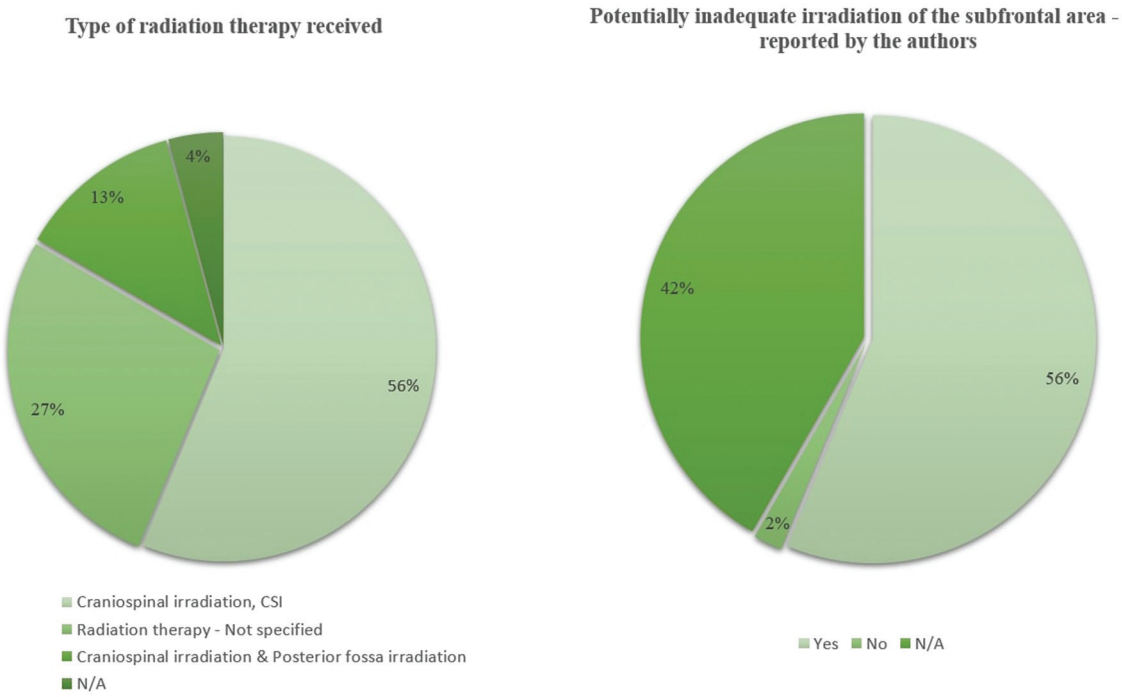

Fig. 11 Radiation therapy received after resection of the primary tumor and adequacy of irradiation of the subfrontal area.

interpreting these findings may lead to improvement in the care of medulloblastoma patients.

Limitations

This study aims to summarize the available data on patients with recurrence of medulloblastoma in the subfrontal area. Since the latter is a rare entity, some relevant cases have likely been reported as part of larger series focusing on supratentorial recurrences as a whole. Cases of subfrontal recurrence embedded in those studies have not been included in our analysis, unless clearly defined as recurrence to the subfrontal/cribriform plate area. As a result, the number of cases presented here is rather an estimation of the total number of cases reported in the literature. Moreover, there seems to be a lack of primary studies investigating the impact of treatment choices, such as the risk:benefit ratio of using excessive eye shielding during radiation therapy, on the risk of developing a subfrontal recurrence. Other than maximizing efforts toward conducting more randomized studies on the topic, future research could greatly benefit from systematic documentation of treatment details and patient outcomes, as the population of interest is quite small.

Conclusions

Medulloblastomas may relapse locally and/or spread distally even after total resection of the primary tumor. Achieving meticulous resection of the primary lesion, restricting the need for VPS placement as much as possible, and ensuring a sufficient dose of radiation to the cribriform plate area might help prevent this type of remote recurrence. Future research should aim to quantitatively assess these data. Last but not least, as demonstrated in our case among others, there may be value in proceeding with repeat resection and adjuvant radiation therapy in patients with acceptable short-term results.

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Conflict of Interest
None.

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