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Survival and Prognostic Factors of Early Childhood Medulloblastoma: An International Meta-Analysis

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ABSTRACT

Purpose
To assess the prognostic role of clinical parameters and histology in early childhood medulloblastoma.

Patients and Methods
Clinical and histologic data from 270 children younger than age 5 years diagnosed with medulloblastoma between March 1987 and July 2004 and treated within prospective trials of five national study groups were centrally analyzed.

Results
Two hundred sixty children with medulloblastoma and specified histologic subtype were eligible for analysis (median age, 1.89 years; median follow-up, 8.0 years). Rates for 8-year event-free survival (EFS) and overall survival (OS) were 55% and 76%, respectively, in 108 children with desmoplastic/nodular medulloblastoma (DNMB) or medulloblastoma with extensive nodularity (MBEN); 27% and 42%, respectively, in 145 children with classic medulloblastoma (CMB); and 14% and 14%, respectively, in seven children with large-cell/anaplastic (LC/A) medulloblastoma ($P < .001$). Histology (DNMB/MBEN: hazard ratio [HR], 0.44; 95% CI, 0.31 to 0.64; LC/A medulloblastoma: HR, 2.27; 95% CI, 0.95 to 5.54; $P < .001$ compared with CMB), incomplete resection and metastases (M0R1: HR, 1.86; 95% CI, 1.29 to 2.80; M+: HR, 2.28; 95% CI, 1.50 to 3.46; $P < .001$ compared with M0R0), and national group were independent prognostic factors for EFS, and OS. The HRs for OS ranged from 0.14 for localized M0 and DNMB/MBEN to 13.67 for metastatic LC/A medulloblastoma in different national groups.

Conclusion
Our results confirm the high frequency of desmoplastic variants of medulloblastomas in early childhood and histopathology as a strong independent prognostic factor. A controlled de-escalation of treatment may be appropriate for young children with DNMB and MBEN in future clinical trials.

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INTRODUCTION

Medulloblastoma is the most common malignant brain tumor of childhood; 25% to 35% of children with medulloblastoma present at less than 3 years of age.[1] The survival rates of early childhood medulloblastoma ranged from 20% to 50% until the last decade, which have been explained in part by different therapeutic strategies that have been applied and in part by assuming a more aggressive biology of medulloblastoma in younger children.[2,3] Age limitations for the delivery of radiotherapy have been set because of the high susceptibility of the immature brain to radiotherapy-induced neurocognitive deficits,[4-6] which have been shown to increase over time after treatment.[7-9] Hence, strategies for dose reduction of craniospinal irradiation and delay of radiotherapy or avoidance of radiotherapy by postoperative chemotherapy have been investigated, especially in children younger than 3 to 5 years of age.[10-13] More recent strategies to delay or avoid craniospinal radiotherapy have provided evidence for improved survival rates by intensive systemic and intraventricular chemotherapy alone or by intensified systemic chemotherapy and high-dose, marrow-ablative chemotherapy with or without radiotherapy.[14-18] In addition, postoperative residual tumor and metastatic disease have been identified as negative clinical prognostic factors, leading to the concept of stratifying young children with medulloblastoma into the following three different risk groups: localized disease and gross total tumor resection (M0/R0); localized disease and postoperative residual tumor (M0/R+); and metastatic medulloblastoma (M+). In the setting of improved survival rates, treatment-related late effects on the

neurocognitive long-term outcome of young children must be balanced against the potential risk of tumor progression.[19] More recently, it has been suggested that the desmoplastic/nodular variant of medulloblastoma (DNMB), characterized by a nodular architecture and a network of internodular collagen fibers, may be a favorable prognostic factor in early childhood medulloblastoma. Evidence has been presented that DNMB, previously believed to occur predominantly in adolescents and adults, may have a first peak of incidence in early childhood.[14,20-23] Medulloblastoma with extensive nodularity (MBEN) has been described in young children with a good prognosis, is considered to be related to DNMB, and represents the extreme end of neurocytic differentiation.[24] A peculiar pattern of age-related occurrence of different medulloblastoma variants has been shown (ie, MBEN and DNMB *v* classic medulloblastoma [CMB]).[25] Recently, DNMB and MBEN have been defined as distinct medulloblastoma variants in the WHOclassification.[26]

The present cooperative international meta-analysis was undertaken to study the frequencies and the prognostic relevance of clinical and histologic risk factors in a larger patient cohort of this age and to investigate whether children with desmoplasia and extensive nodularity are candidates for a reduction of the intensity of therapy and treatment-induced late effects in future prospective studies.

PATIENTS AND METHODS

Patients

Original data from 270 children (165 males) with medulloblastoma younger than age 5 years at diagnosis, initial craniospinal imaging, and information on extent of resection, who were treated between March 1987 and July 2004 within prospective national study group protocols in France, Germany, Italy, the United States, and the United Kingdom, were collected. Eight children with no information on the histologic subtype and two children with medullomyoblastoma were excluded. The remaining 260 children (60% males) were eligible for these analyses. A national reference histopathology, performed according to the current WHO classification at the time of the respective trials by experienced neuropathologists blinded to clinical outcomes, was available in 239 children (92%).

Treatment

All children were treated according to their respective prospective national trials (Appendix Table A1, online only); 74 children were treated according to the Baby Brain French Society of Pediatric Oncology (BBSFOP) protocol with systemic chemotherapy and received radiotherapy and high-dose chemotherapy with autologous hematopoietic stem-cell transplantation only at relapse, as described.[16,27]

Data from two subsequent prospective trials were collected from 72 children in Germany and Austria. Twenty-nine children from the Therapieprotokoll für Säuglinge und Kleinkinder mit Hirntumoren (HIT-SKK) 87 study received risk-adapted systemic chemotherapy and deferred craniospinal radiotherapy at the age of 3 years or at relapse, as described.[23] Forty-three children treated within the HIT-SKK 92 trial received systemic chemotherapy and intraventricular methotrexate, and radiotherapy was given only if children were not in remission, as described.[14]

Fifty-five children from two Italian Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) trials were included. In AIEOP SNC 9501, children diagnosed between 1995 and 1998 were treated with upfront conventional systemic chemotherapy and delayed or omitted irradiation. From 1998 to 2004, children were treated according to the Italian Infants High Risk Trial by upfront sequential myeloablative chemotherapy and autologous hematopoietic stem-cell transplantation, followed by conformal radiotherapy in case of residual tumor or by craniospinal irradiation in patients with metastases. Thirty-one children from the United States, Argentina, and Australia included in the two Head Start series were treated with systemic chemotherapy and high-dose marrow-ablative chemotherapy with autologous hematopoietic stem-cell transplantation and received radiotherapy in event of residual disease or recurrence, as described.[17,18,28]

Between December 1992 and September 1996, 28 children were treated on the United Kingdom Children's Cancer Study Group (UKCCSG)/International Society of Pediatric Oncology (SIOP) protocol CNS9204, which comprised blocks of alternating myelosuppressive and nonmyelosuppressive drugs repeated at 14-day intervals to produce a high-intensity regimen with modest individual drug dose-intensity.[29] Initially, radiotherapy was delivered only at relapse or tumor progression, but following an interim analysis in January 1997, elective involved-field or craniospinal radiotherapy was advised based on local preference.

Maximal surgical removal of primary tumor, dependent on the anatomic location of the tumor and the condition of the child, was recommended in all studies. Residual tumor was judged by postoperative magnetic resonance imaging as presence of residual tumor more than 1.5 cm^2 (Head Start), by a consensus of neuroradiologic and surgical data as presence of any nodular tumor (BBSFOP), or by presence of any residual tumor (HIT-SKK and AIEOP). In the UKCCSG/SIOP study, a complete resection (R0) was recorded when there was no visible tumor documented by the surgeon at the end of operation; a subtotal resection was recorded when visible tumor remained; and a biopsy was recorded when only sufficient tumor for diagnosis was removed. Initial metastatic stage was classified according to Chang's system[30] with the help of cranial and spinal magnetic resonance imaging (± gadolinium) and lumbar CSF sampling. All studies were approved by the ethics committees of the responsible institutions. Informed consent was obtained from legal representatives of all patients.

Statistical Analyses

Overall survival (OS) and event-free survival (EFS) were calculated using the Kaplan-Meier method, and the log-rank test was used for comparison. EFS was defined as time from the date of diagnosis to the date of first progression, to date of death from any cause, or to date of the last contact, whichever occurred first. OS was defined as time from the date of diagnosis to death from any cause or last contact. SEs are expressed as plus/minus values. All univariable analyses were performed exploratively.

In three of five national groups, the process of central pathology review did not distinguish DNMB from MBEN. At the time, MBEN was not listed as a distinct variant in the WHO classification,[31] but MBENs would have been included among DNMBs because of their abundant nodules and internodular desmoplasia. In the present study, MBENs and DNMBs were consequently evaluated together in univariable and multivariable analyses.

In multivariable analysis, Cox regression models with forward stepwise selection (inclusion criterion: score test, $P \leq .05$; exclusion criterion: likelihood ratio test, $P \geq .10$) were used to analyze the possible impact of the following variables: time from surgery to the date of analysis (continuous), national study group (treatment according the respective protocols from France, Germany, Italy, United Kingdom, and United States), histology (CMB, DNMB/MBEN, or large-cell/anaplastic [LC/A] medulloblastoma), age (continuous), metastatic disease (M0, M1, or M2/3), residual tumor (R0 or R+), sex, localization (midline or hemispheres), and clinical risk group (M0R0, M0R+, or M+). For Cox regression, *P* values of the likelihood ratio test, hazard ratios, and 95% CIs of the independent risk factors are given.

RESULTS

Patient Characteristics

The median age of 260 eligible patients was 1.89 years (range, 0.17 to 4.97 years), and 185 children had localized disease (71% M0 stage). Among these patients, 105 children had gross total tumor resection (40% M0/R0), and 80 children had postoperative residual tumor (31% M0/R+). The remaining 75 children had metastatic disease at diagnosis (29% M+); 20 children had dissemination of tumor cells

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	No. of Patients	CMB (n = 145) No. of Patients	%	DNMB/MBEN (n = 108) No. of Patients	%	LC/A MB (n = 7) No. of Patients	%	P (χ^2)
Study group								
France	74	41	55	33	45	0		
Germany	72	43	60	29*	40	0		
Italy	55	34	62	19†	36	2	4	
United States	31	21	68	10	32	0		
Great Britain	28	6	21	17	61	5	18	
Male		91	63	62	57	3	43	.445
Median age, years		1.93		1.80		2.56		
Central histopathologic reference		125	86	107	99	7	100	.001
Tumor localization								.001
Midline		124	86	69	64	5	71	
Hemispheres		21	14	36	33	2	29	
Unknown		0		3	3	0		
Staging								.001
M0		92	63	90	83	3	43	
M+		53	37	18	17	4	57	
M1		14		6		0		
M2		15		2		1		
M3		24		10		3		
Gross total resection		64	44	70	65	3	43	.004

Abbreviations: CMB, classic medulloblastoma; DNMB, desmoplastic/nodular medulloblastoma; MBEN, medulloblastoma with extensive nodularity; LC/A MB, large-cell/anaplastic medulloblastoma; M0, no metastases; M+, metastatic disease.
* Twelve patients (17%) had MBEN.
† Nine patients (16%) had MBEN.

into the CSF (8% M1), 18 children had macroscopic intracranial metastases (7% M2), and 37 children had macroscopic spinal metastases (14% M3). CMB was diagnosed in 145 children (56%). DNMB/MBEN was diagnosed in 108 patients (41%). In two national groups, 21 MBENs (of 108 DNMBs/MBENs) were described separately. Seven children (3%) had LC/A medulloblastoma. Detailed patient characteristics are listed in Table 1.

Desmoplasia and Localization, M Stage, and Extent of Resection

Tumor localization was midline in 198 children (76%), cerebellar hemispheric in 59 children (23%), and unknown in three children (1%). Compared with CMB (hemispheric, n = 21; midline, n = 124), primary tumors were more frequently located in the hemispheres in DNMB/MBEN (hemispheric, n = 36; midline, n = 69; χ^2 P .001).

Children with DNMB/MBEN had lower M stages (M0, n = 90; M+, n = 18) compared with children with CMB (M0, n = 92; M+, n = 53; χ^2 P = .001). Gross total tumor resection was achieved in 70 of 108 children with DNMB/MBEN and in 64 of 145 children with CMB (χ^2 P = .001, Table 1).

Survival Rates and Univariable Analyses

The median follow-up time of survivors was 8 years (range, 1.24 to 16.25 years). The estimated 8-year EFS and OS rates for all 260 children were 39% ± 3% and 56% ± 3%, respectively. The 8-year EFS and OS rates of 185 patients without metastases were 42% ± 4% and 65% ± 4%, respectively, and among these children, survival differences between groups with complete or incomplete surgical resection were high (8-year EFS: 54% ± 5% in 105 children with M0R0 *v* 27% ± 5% in 80 children with M0R+; $P < .001$; 8-year OS: 77% ± 4% *v* 50% ± 6%, respectively; $P < .001$). Survival rates were lower in 20 children with M1 stage (EFS, 35% ± 11%; OS, 40% ± 11%; Fig 1) and 55 children with M2/M3 stage (EFS, 26% ± 7%, $P = .014$; OS, 27% ± 7%, $P < .001$).

Differences in survival rates according to histologic subtypes were observed. Children with DNMB/MBEN had the most favorable survival rates (8-year EFS, 55% ± 5%; 8-year OS, 76% ± 4%), followed by children with CMB (8-year EFS, 27% ± 4%; 8-year OS, 42% ± 4%) and children with LC/A medulloblastoma (7.5-year EFS, 14% ± 13%; 7.5-year OS, 14% ± 13%; OS/EFS: $P < .001$; Fig 1). Eight-year EFS and OS rates of 21 children who had a diagnosis of MBEN were 86% ± 8% and 95% ± 5%, respectively.

In nonmetastatic disease, survival rates of 90 children with DNMB/MBEN were higher compared with 92 children with CMB (8-year EFS: 54% ± 5% *v* 32% ± 5%, respectively; $P = .001$; 8-year OS: 78% ± 4% *v* 54% ± 5%, respectively; $P < .001$). Difference between histologies remained in the subgroup of children with nonmetastatic disease without postoperative residual tumor. Children with DNMB/MBEN (n = 60) had higher survival rates than children with CMB (n = 44; 8-year EFS: 63% ± 6% *v* 42% ± 8%, respectively; $P = .019$; 8-year OS: 85% ± 5% *v* 67% ± 7%, respectively; $P = .017$). For children with nonmetastatic disease and incomplete tumor resection, 8-year EFS rates were 37% ± 9% in 30 children with DNMB/MBEN and 24% ± 6% in 48 children with CMB ($P = .118$; 8-year OS: 66% ± 9% *v* 42% ± 7%, respectively; $P = .045$). In addition, in children with metastatic disease, outcome rates for children with DNMB/MBEN (n = 18) were higher than in children with CMB (n = 53; 8-year EFS: 56% ± 12% *v* 19% ± 6%, respectively; $P = .003$;

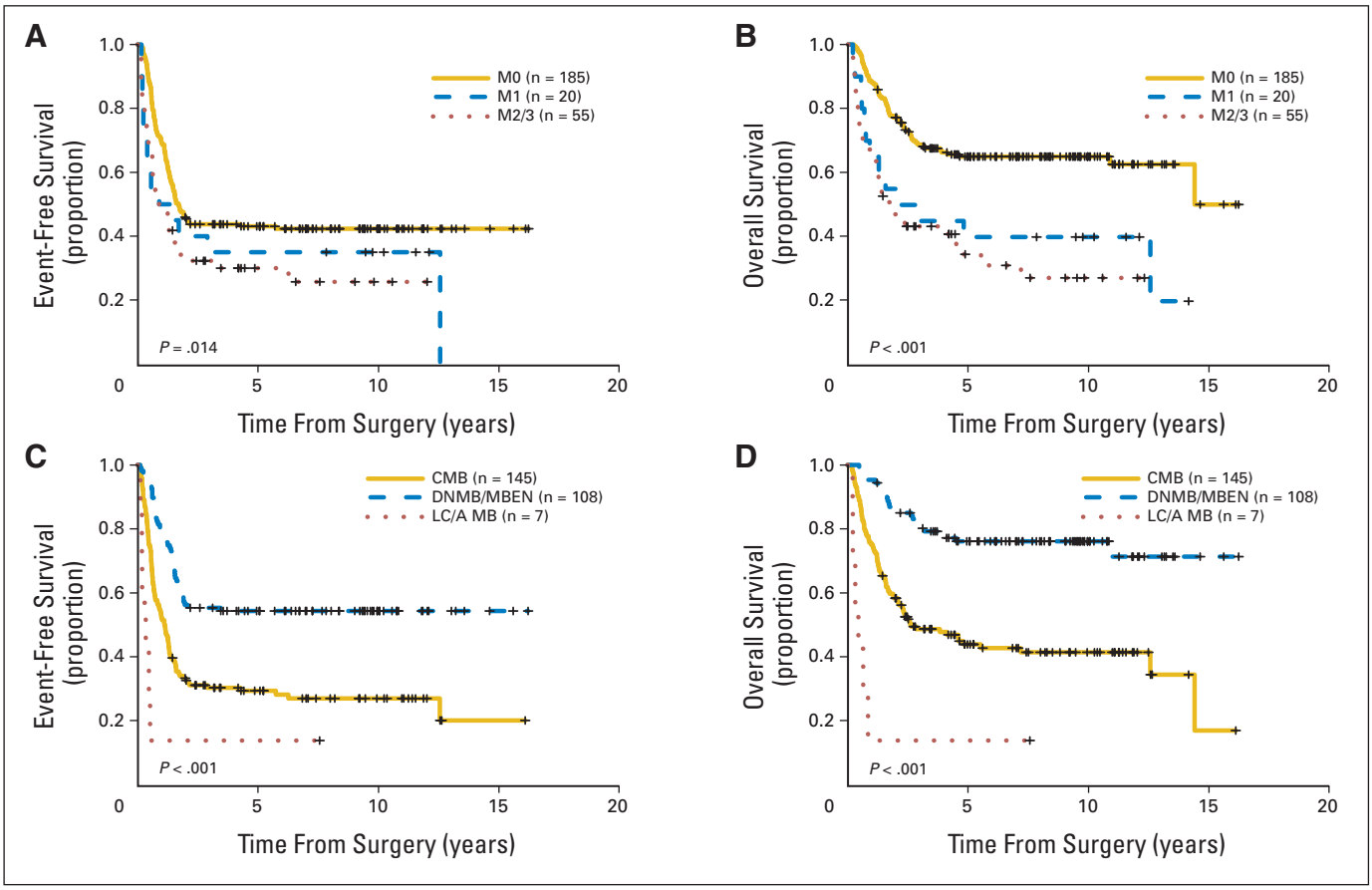

Fig 1. (A) Event-free survival (EFS) and (B) overall survival (OS) according to staging (M0 *v* M1 *v* M2/3). (C) EFS and (D) OS according to histologic subtype (desmoplastic/nodular medulloblastoma [DNMB]/medulloblastoma with extensive nodularity [MBEN] *v* classic medulloblastoma [CMB] *v* large-cell/anaplastic medulloblastoma [LC/A MB]).

8-year OS: 66% ± 12% *v* 19% ± 7%, respectively; $P = .001$; Fig 2). Hemispheric tumor location was related to better outcome than midline location by univariable analysis (8-year EFS: 58% ± 6% *v* 33% ± 3%, respectively; $P = .003$; 8-year OS: 71% ± 6% *v* 51% ± 4%, respectively; $P = .012$). Survival rates of different subgroups are listed in Table 2.

Multivariable Analysis

The respective histologic subtypes (DNMB/MBEN, CMB, and LC/A medulloblastoma), the combination of extent of resection and metastases (M+ *v* M0R1 *v* M0R0), and national study group were identified as independent risk factors for EFS and OS (Table 3). Tumor localization (midline *v* hemispheric) did not reach statistical significance. A summary of adjusted hazard ratios for OS in the different subgroups is given in Table 4.

DISCUSSION

The present meta-analysis represents the largest series of young children with medulloblastoma treated without initial radiotherapy reported so far. Our data demonstrate that distinct histologic entities arise in young children with different clinical behavior implicating important clinical and therapeutic consequences. In our large cohort of 260 young children with substantial follow-up, patients with DNMB variants have a markedly better clinical outcome compared with patients with CMB and LC/A medulloblastoma. Our data confirm previous observations from smaller series where DNMB accounted for more than 40% of all early childhood medulloblastoma.[14,23,25] DNMB and MBEN have also been linked to better survival in a large retrospective series.[21] Here, we have observed high survival rates for DNMB variants of early childhood irrespective of diverse therapeutic strategies that have been applied by the different national groups aiming to avoid or defer craniospinal radiotherapy and irrespective of differences with regard to time of diagnosis, postoperative residual tumor assessment and staging definitions, and histopathologic assessments. Our results indicate that histology is an independent prognostic factor rather than a merely predictive factor that may only be relevant within the context of a specific therapeutic regimen. This further supports a different underlying biology of the medulloblastoma entities. In addition, survival rates of young children with DNMB/MBEN and metastatic disease were as favorable as for children with nonmetastatic DNMB/MBEN in our series (8-year EFS, 56% ± 12% *v* 54% ± 5%, respectively), suggesting that the presence of this histology confers a significantly better outcome irrespective of traditional adverse clinical features such as metastatic status. The histopathologic classification of our series of patients may be compromised by the fact that some medulloblastoma variants may not have been classified according to current standards. Within the DNMB/

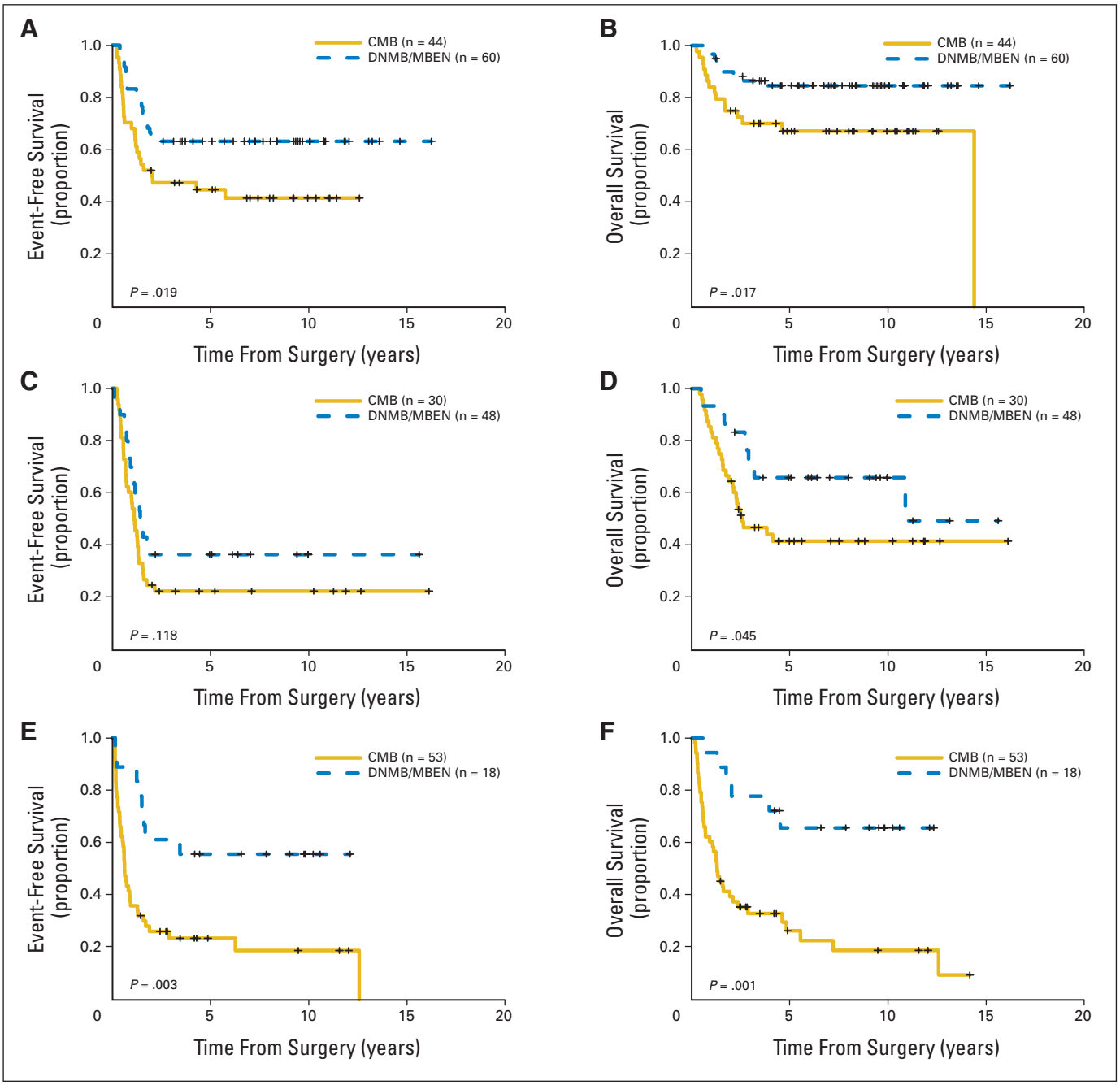

Fig 2. Event-free survival (EFS) and overall survival (OS) of patients with desmoplastic/nodular medulloblastoma (DNMB)/medulloblastoma with extensive nodularity (MBEN) versus classic medulloblastoma (CMB) within the clinical risk groups (A and B) M0R0, (C and D) M0R+, and (E and F) M+.

MBEN group, differentiation between DNMB and MBEN was not performed in all patients, which is reasonable because the MBEN variant was not listed in the WHO classification as a distinct entity at the time of histopathologic review.[31] Furthermore, LC/A medulloblastomas might be included in the CMB subgroup, and it is also possible that a few atypical teratoid/rhabdoid tumors, not recognized at the time of evaluation, are also included in the CMB subgroup. However, these limitations might strengthen the significance of our results even more.

Because MBENs were only specifically diagnosed in two national groups, we could not analyze this subgroup separately. However, within these two groups, outcome for 21 children with MBEN was excellent (8-year EFS and OS, 86% and 95%, respectively), and this subgroup might have an even more favorable prognosis than DNMB. Previous data also indicated a prognostic advantage of MBEN subtype.[24,25,32] This finding awaits prospective evaluation.

The presence of severe anaplasia or large-cell subtype of medulloblastoma has been shown to be predictive of survival in medulloblastoma.[21,33-35] Despite the changing histopathologic definitions over the time during which the patients of our pooled data set were diagnosed, this finding is confirmed by our results. The hazard ratios for OS differed almost 100-fold, ranging from 0.14 for localized

Table 2. EFS and OS According to Histology and Staging: Univariable Analyses in 260 Patients

Histology and Staging Groups	No. of Patients	8-Year EFS			8-Year OS		
		Rate (%)	SE (%)	*P*	Rate (%)	SE (%)	*P*
Metastases							
M0	185	42	4	.014	65	4	< .001
M1	20	35	11		40	11	
M2/M3	55	26	7		27	7	
Histology							
CMB	145	27	4	< .001	42	4	< .001
DNMB	87	47	5		72	5	
MBEN	21	86	8		95	5	
LC/A MB	7	14*	13		14*	13	
M0 and residual tumor							
M0R0	105	54	5	< .001	77	4	< .001
M0R+	80	27	5		50	6	
M0 and histology							
CMB M0	92	32	5	.001	54	5	< .001
DNMB/MBEN M0	90	54	5		78	4	
M0R0 and histology							
CMB M0R0	44	42	8	.019	67	7	.017
DNMB/MBEN M0R0	60	63	6		85	5	
M0R+ and histology							
CMB M0R+	48	24	6	.118†	42	7	.045
DNMB/MBEN M0R+	30	37	9		66	9	
M+ and histology							
CMB M+	53	19	6	.003	19	7	.001
DNMB/MBEN M+	18	56	12		66	12	
Location							
Hemisphere	59	58	6	.003	71	6	.012
Midline	198	33	3		51	4	

Abbreviations: EFS, event-free survival; OS, overall survival; CMB, classic medulloblastoma; DNMB, desmoplastic/nodular medulloblastoma; MBEN, medulloblastoma with extensive nodularity; LC/A MB, large-cell/anaplastic medulloblastoma; R0, no postoperative residual tumor; R+, postoperative residual tumor; M+, presence of metastases.
*EFS and OS rates are 7.5-year rates.
†Not significant.

DNMB in the Head Start series to 13.7 for metastatic LC/A medulloblastoma in the United Kingdom protocol. Our data strongly support the latest WHO classification of tumors of the CNS, where CMB, DNMB, MBEN, and LC/A medulloblastoma have been listed as separate entities.[26]

At the biologic level, the DNMB variants and CMB have been shown to cluster differently in hierarchical analysis of gene expression profiling.[36] The current understanding is that the different medulloblastoma variants originate from different precursor cell populations forming the normal cerebellum, and the cell signaling pathways that

Table 3. Multivariable Analyses of Prognostic Factors (forward stepwise selection; n = 260) for EFS and OS

Parameter	EFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
Histology						
DNMB/MBEN (n = 108) *v* CMB (n = 145)	0.44	0.31 to 0.64	< .001	0.29	0.18 to 0.47	< .001
LC/A MB (n = 7) *v* CMB (n = 145)	2.27	0.95 to 5.45		2.30	0.95 to 5.59	
Metastases/residual tumor						
M0R1 (n = 80) *v* M0R0 (n = 105)	1.86	1.29 to 2.80	< .001	1.92	1.16 to 3.19	< .001
M+ (n = 75) *v* M0R0 (n = 105)	2.28	1.50 to 3.46		3.40	2.05 to 5.65	
Study group						
G (n = 72) *v* F (n = 74)	0.36	0.28 to 0.56	< .001	0.64	0.38 to 1.08	.009
US (n = 31) *v* F (n = 74)	0.31	0.17 to 0.56		0.47	0.23 to 0.97	
I (n = 55) *v* F (n = 74)	0.45	0.29 to 0.72		0.74	0.42 to 1.30	
UK (n = 28) *v* F (n = 74)	0.79	0.46 to 1.36		1.75	0.95 to 3.25	

Abbreviations: EFS, event-free survival; OS, overall survival; HR, hazard ratio; DNMB, desmoplastic/nodular medulloblastoma; MBEN, medulloblastoma with extensive nodularity; CMB, classic medulloblastoma; LC/A MB, large-cell/anaplastic medulloblastoma; G, Germany; F, France; US, United States; I, Italy; UK, United Kingdom.

Table 4. Comparison of HRs

	HR								
	M0								
	R0			R1			M+		
Country	CMB	DNMB/MBEN	LC/A	CMB	DNMB/MBEN	LC/A	CMB	DNMB/MBEN	LC/A
F	1	0.29	2.30	1.92	0.56	4.42	3.40	0.99	7.82
G	0.64	0.19	1.47	1.23	0.36	2.83	2.18	0.63	5.01
US	0.47	0.14	1.08	0.90	0.26	2.08	1.60	0.46	3.68
I	0.74	0.21	1.70	1.42	0.41	3.27	2.52	0.73	5.79
UK	1.75	0.51	4.03	3.36	0.97	7.23	6.00	1.73	13.69

NOTE. HRs are for overall survival. Children with CMB, nonmetastatic disease, and complete tumor resection who were treated in France were defined as the reference patients (HR = 1).

Abbreviations: HR, hazard ratio; CMB, classic medulloblastoma; DNMB, desmoplastic/nodular medulloblastoma; MBEN, medulloblastoma with extensive nodularity; LC/A MB, large-cell/anaplastic medulloblastoma; F, France; G, Germany; US, United States; I, Italy; UK, United Kingdom.

regulate the normal development of the cerebellum are involved in the evolution of the different medulloblastoma variants.[37,38] Desmoplastic medulloblastomas are believed to originate from the external granule layer by pathologic activation of the sonic hedgehog pathway with mutations of its components *PTCH1*, *SMOH*, or *SUFUH*.[38-40] Preclinical murine studies on *PTC*-related tumors have demonstrated antitumoral effects of specific inhibitors of the sonic hedgehog pathway, which may lead to the development of targeted therapies for patients suffering from DNMB/MBEN.[41,42] An appreciation of the molecular phenotype of childhood medulloblastoma and other cancers may be a prerequisite for treatment selection and stratification. By molecular parameters, medulloblastoma can be separated at least into four groups with differences in signaling pathway activation, age, histology, and clinical outcome.[36,43-45] Our data also confirm the prognostic impact of the extent of tumor resection in combination with M stage on OS and EFS. Therefore, maximal safe surgery at diagnosis without putting the patient unnecessarily at an increased risk for postoperative neurologic deficits is justified.

The present analysis was not undertaken to compare the different treatment regimens applied by the involved study groups. Differences in the respective strategies to defer or avoid craniospinal radiotherapy and the resulting survival rates have to be balanced against the acute and long-term toxicities and the neuropsychological outcome of survivors. However, standardized assessment tools to compare late effects between patients from different study groups have not been validated so far. Differences in chosen drugs, drug combinations, doses (eg, conventional doses, high-dose chemotherapy) and dose densities (number and interval of chemotherapy cycles), application routes (eg, systemic, intraventricular), and radiotherapeutic strategies may explain differences in survival rates and late effects between the different study groups and cannot be separated from each other retrospectively. In addition, possible differences in patient referral and selection criteria (eg, different age limits) do not allow reliable conclusions from a comparison of survival rates between the different study groups. Therefore, we have only described the survival differences between the involved national study groups, and the Cox regression analyses were adjusted accordingly. Ideally, comparisons of different therapeutic strategies should be undertaken prospectively. However, our data indicate that controlled de-escalation of treatment strategies without radiotherapy may be appropriate for young children with DNMB. By contrast, given the relatively low survival rates in children with CMB and LC/A medulloblastoma, treatment intensifications with or without reintroduction of local or age-adapted craniospinal radiotherapy may be required in these subgroups.

In conclusion, our study confirms that DNMB variants account for a significant portion of young children with medulloblastoma and that this histology is a strong independent favorable prognostic factor, even for young children with metastatic disease. Our results provide evidence for the first treatment stratification concept in a pediatric brain tumor not only built on clinical risk factors, but also on histopathology. Young children with centrally confirmed DNMB may be candidates for controlled and stepwise de-escalation of treatment regimen and for the use of biology-based therapy within prospective trials. Stratification according to histologic variants is currently investigated prospectively in two ongoing trials for young children with medulloblastoma[46,47] and should be considered in the planning of future treatment strategies for this group of patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

Table A1. Eligibility Criteria and Treatment Overview of Prospective Trials of Analyzed Patients

Study Group	No. of Patients	Age Range (months)	Chemotherapy	High-Dose Chemotherapy With ASCT	Radiotherapy
France[16,27]	74	0-60	Systemic chemotherapy	At relapse only	In case of relapse: 54 Gy PF; in case of metastatic relapse: + CSI 18-24 Gy
Germany, SKK 87[23]	29	0-36	Systemic chemotherapy	No	At 3 years of age: 24-36 Gy CSI, 54 Gy PF
Germany, SKK 92[14]	43	0-36	Systemic and intraventricular chemotherapy	No	In case of residual tumor or metastases after 3 chemotherapy cycles: 24 Gy CSI, 54 Gy PF
Italy	55	0-60	Systemic chemotherapy	Yes, for children diagnosed since 1998	In case of residual tumor or metastases: 23.4 Gy CSI, 54 Gy PF, plus 10- to 15-Gy boost on metastases
Head Start[17,18,28]	31	0-36*	Systemic chemotherapy	Yes	In case of residual tumor at end of induction: 23.4-36 Gy CSI, 54 Gy PF
United Kingdom[29]	28	0-36	Systemic chemotherapy	No	In case of relapse: 25 Gy CSI, 45 Gy tumor bed; since 1996: all children at end of chemotherapy: 45 Gy tumor bed

Abbreviations: ASCT, autologous stem-cell transplantation; PF, posterior fossa; CSI, craniospinal irradiation; SKK, Therapieprotokoll für Säuglinge und Kleinkinder mit Hirntumoren.

*Inclusion into the respective trials was possible up to the age of 72 months (Head Start I, M+) and 120 months (Head Start II, M+), but only patients age 0 to 36 months were reported within this meta-analysis.