Chemotherapy increases long-term survival in patients with adult medulloblastoma—a literature-based meta-analysis

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Background. Adult medulloblastoma is a potentially curable malignant entity with an incidence of 0.5–1 per million. Valid data on prognosis, treatment, and demographics are lacking, as most current knowledge stems from retrospective studies. Surgical resection followed by radiotherapy are accepted parts of treatment regimes; however, established prognostic factors and data clarifying the role of chemotherapy are missing.

Methods. We investigated 227 publications from 1969–2013, with 907 identifiable, individual patients being available for meta-analysis. Demographic data, risk stratification, and treatment of these patients were similar to previous cohorts.

Results. The median overall survival (mOS) was 65 months (95% CI: 54.6–75.3), the 5-year overall survival was 50.9% with 16% of the patients dying more than 5 years after diagnosis. Incomplete resection, clinical and radiological signs for brainstem infiltration, and abstinence from radiotherapy were predictive of worse outcome. Metastatic disease at tumor recurrence was identified as a new prognostic factor, while neither metastasis at initial diagnosis nor desmoplastic/classic histology was correlated with survival. Patients receiving chemotherapy first-line survived significantly longer (mOS: 108 mo, 95% CI: 68.6–148.4) than patients treated with radiation alone (mOS: 57 mo, 95% CI: 39.6–74.4) or patients who received chemotherapy at tumor recurrence. This effect was not biased by tumor stage or decade of treatment. Importantly, (neo)adjuvant chemotherapy also significantly increased the chance for long-term survival (>5 y) compared with radiotherapy alone or chemotherapy at tumor recurrence.

Conclusions. This meta-analysis clarifies relevant prognostic factors and suggests that chemotherapy as part of first-line therapy improves overall survival and increases the proportion of patients with long-term survival.

Keywords: adult medulloblastoma, chemotherapy, meta-analysis, long-term survival, radiotherapy.

Medulloblastoma is a malignant cerebellar tumor with an estimated incidence of 0.5–1 per million in adults.¹ The World Health Organization classification further differentiates among classic, desmoplastic, and anaplastic/large cell medulloblastoma and describes several additional rare subtypes.² Beyond this histological differentiation, the genetic landscape of both childhood and adult medulloblastoma is becoming clearer and comprises 4 different molecular subgroups with characteristic mutations and activation of signaling cascades.³ In adults, medulloblastomas with alteration in the sonic hedgehog (SHH) signaling pathway are common and have a strong association with desmoplastic medulloblastoma. However, alterations of the SHH signaling pathway are also present in the group of classical medulloblastoma, which also includes tumors with activated Wnt

(wingless) signaling and less well characterized “Group 4” tumors with a higher rate of metastasis.⁴ Preclinical and early clinical data suggest that the frequent SHH activation may allow a successful targeted therapy (ie, Smoothed inhibition) of especially desmoplastic medulloblastoma.⁵

Despite these advances in our understanding of adult medulloblastoma, the entire clinical knowledge on demographics, prognostic factors, and therapy of patients with adult medulloblastoma derives from monocentric studies or retrospective analyses, and there is consensus neither on optimal treatment nor on risk stratification of patients.

While the survival of children has dramatically increased, the outcome of patients with adult medulloblastoma remains poor,⁶ with a 5-year survival of 75% of adult patients treated

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in clinical trials⁷ and of 64.9% reported in epidemiological studies.⁶ In contrast to children, adults commonly have late tumor recurrences (>5 y, ~20%).^{8–10} Few characteristics and prognostic factors of adult medulloblastoma appear undoubted: higher percentage of lateral, desmoplastic medulloblastoma, slight male predominance, worse prognosis of anaplastic medulloblastoma, lack of prognostic relevance of gender. There are oppositional reports on other putative prognostic factors,¹¹ like age and histology, with several reports on a favorable association of younger age^{6,12,13} and desmoplastic differentiation^{12,14,15} (though doubted by others¹⁶). Further, it is unknown whether metastases predict worse outcome in adults and therefore justify a more aggressive treatment.¹⁷ The only prospective clinical trial has confirmed this correlation,¹⁸ while a large patient cohort did not.¹⁶ In children, the local disease extent influences the stratification via the postoperative residual tumor size indirectly.¹⁹ In adults, brainstem involvement, postoperative resection status,²⁰ and postoperative performance status¹⁹ may influence prognosis^{7,12,16,21} but are not widely accepted risk factors. Thus, neurosurgeons remove as much of the tumors as feasible without causing new relevant neurological deficits. Whether a more aggressive resection may be beneficial is unknown.¹¹

With respect to treatment, there is broad consensus that radiotherapy is the most effective modality and that improvements of radiotherapy techniques in the last 25 years have been beneficial for patients. In contrast, the role of chemotherapy in first-line treatment of adult medulloblastoma is controversial. Chemotherapy, as part of first-line and as x-line treatment (at tumor recurrence), has become more common since the 1990s and was the subject of one prospective clinical^{7,18} and several observational trials.^{10–14,20–26} This results in a paradoxical situation that chemotherapy undoubtedly has a place in current treatment protocols of adult medulloblastoma but its role is unproven. Adults are usually treated according to pediatric protocols which are more toxic to adults and of unproven efficacy, and it is unknown whether these patients are under- or overtreated.^{16,21,26} A placebo-controlled clinical trial (comparing treatment with and without chemotherapy) to obtain class I/II evidence appears for all practical purposes impossible because of the low incidence.

The idea of this literature-based meta-analysis was therefore to distill information from all identifiable cases published. We aimed at addressing the open questions by analyzing this information to get the best achievable evidence for this rare disease.

Materials and Methods

Database Search

The meta-analysis was performed as proposed by the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).²⁷ The study strategy was established before gathering and analyzing the data but without a written protocol. Predefined endpoint of the study was overall survival (OS) of all identifiable patients having received chemotherapy as part of the initial therapy (adjuvant or neo-adjuvant) compared with OS of all identifiable patients who received radiotherapy only. In addition, all other available clinical data were gathered for post-hoc analysis (depending on the availability

of data) to control for potential biases within the patient population, to confirm the representativeness of the dataset, and to establish new hypotheses.

A PubMed search was performed until July 1, 2013 to identify publications on adult medulloblastoma by using the keywords “medulloblastoma AND adult,” resulting in 1996 hits. One hundred twelve additional publications were later identified based on the analysis of cited references.

Basic research papers and reviews were excluded. Only publications in English, French, and German were evaluated.

Identified publications

Six hundred seventy-one publications met the inclusion/exclusion criteria—30 were not available, resulting in a total of 641 analyzable papers available for screening for non-ambiguous data on single patients (Supplementary Fig. S1). Two hundred twenty-seven publications included data on single patients (all analyzed studies are listed in Supplementary Table S1) and were systematically analyzed.

Inclusion and exclusion criteria for patients

There is a lack of consensus in the literature on when a patient with medulloblastoma is considered to be “adult” (range: 14–21 y). Therefore, this study included all patients diagnosed with medulloblastoma, who were considered by the authors of the analyzed report to be “adult,” though with a minimum age of 15 years.

Excluded were pediatric patients <15 years, patients with uncertain histological diagnoses, and combined groups of primitive neuroectodermal tumor or other brain tumors with medulloblastoma from which the patients with medulloblastomas could not be separated.

Processing Data and Statistical Analysis

Based on the exclusion/inclusion criteria, 907 patients were identified. All clinical information (47 different variables) was documented as descriptive raw data in an Excel file. Data were not sought to be confirmed by the investigators. After initial collection of uncategorized descriptive data, the data were categorized to allow statistical analysis (Supplementary Table S2). Sensitivity analyses for post-hoc analyses were not performed. Unavailable information was marked as a blank field. All patients not being explicitly reported to be alive were considered to be “dead/lost to follow-up,” and the longest time-period reported was used for survival time. Conversely, only patients who were reported to be alive at the time of publication were censored for Kaplan–Meier analyses. (The statistical tests used and the number of patients available for analyses are given in the legends to the Figures). The data were collected via Microsoft Excel 2007 and analyzed using SPSS 20.0.

Quality Control of the Patient Population

The heterogeneity of the patient population and publication bias may be major problems of literature-based meta-analyses. We therefore compared the basal demographic characteristics with

Table 1. Comparison of the patient population with epidemiological data

Characteristic	Meta-analysis, n = 907	Padovani et al, ¹⁶ n = 253	Lai et al, ⁶ n = 454
Male:female ratio	1.6:1	1.8:1	1.5:1
Mean/median age, y	29.1 (mean)	29 (median)	33 (mean)
Location			
Central	40.5%	58.3%	
Lateral	53.4%	41.7%	
Lateral and central	6.1%		
Extent of disease at diagnosis			
Localized	78.7%	87.9%	77%
Metastatic	21.3%	12.1%	23%
Histologic type			
Desmoplastic	39%	30%	n.a.
Classic	49%	66%	
Anaplastic	3%	n.a.	
Other	9%	3%	
Extent of surgical resection			
Gross total	55.1%	62.8%	67.1%
Subtotal	39.5%	37.2%	28%
Biopsy	5.3%		4.9%
Radiotherapy			
Yes	94%	97.5%	83%
No	6%	2.5%	15%
Chemotherapy			
Yes	71%	58%	
No	29%	42%	

the data from the largest patient series published so far¹⁶ and a register-based epidemiological study.⁶ The patients of the meta-analysis included a higher proportion of desmoplastic medulloblastoma and more lateral tumors compared with the other studies (Table 1). All other characteristics analyzed were in concord with previous studies, suggesting that the patients included in this meta-analysis were representative.

Results

Database Search and Patients' Demographics

An overview of the database search is given in Supplementary Fig. S1. The PubMed search as of July 1, 2013 identified 1996 publications; 112 additional publications were identified based on the analysis of cited references. Thus, 2108 publications were screened; 671 met the inclusion criteria; and 30 publications were not amenable. Two hundred twenty-seven publications allowed the analysis of 907 individual patients with "adult medulloblastoma." The patient population had a non-symmetric age distribution, with an average age of 29.1 years (range: 15–88; Fig. 1A). The estimated median overall survival (mOS) of all patients reported was 65 months (range: 0–432; Table 2). The average survival reported was 50 months (5-year OS 50.9%; Supplementary Fig. S2A) and has substantially increased in the last 4 decades (Fig. 1B). An overview of the demographic data of all patients and those <18 years is given in Table 2.

Prognostic Significance of Clinical Symptoms and Brainstem Invasion

The available data for 194 patients allowed characterization of clinical symptoms at first diagnosis. The median time from start of symptoms to diagnosis was 3 months (range: 0–48; Table 2). Signs of increased intracranial pressure and cerebellar dysfunction were the most common complaints, reported by the majority of patients. However, the spectrum of reported symptoms varied significantly (Supplementary Fig. S2B). Thirty-one percent of patients (79/253) had additional symptoms like double vision and pyramidal tract lesions, indicating more widespread disease affecting the brainstem and other parts of the CNS (for classification of symptoms, see Supplementary Table S2). Clinical symptoms at initial diagnosis correlated with the patients' outcomes: signs of increased intracranial pressure were associated with better prognosis (mOS: 57 mo; 95% CI: 44–69; Supplementary Fig. S3A), while symptoms indicating tumor manifestation in the brainstem or other parts of the CNS were associated with poorer survival^{12,16} (mOS: 42 mo; 95% CI: 24.5–59.4; Supplementary Fig. S3B). Cerebellar symptoms were without prognostic significance.

Prognostic Significance of Metastasis at Initial Diagnosis and Tumor Recurrence

Metastatic disease at initial diagnosis is an established prognostic factor in children but of unproven relevance in adults. In this meta-analysis, Kaplan–Meier analysis of patients with available Chang-M stage at initial diagnosis ($n = 96$) did not reveal a trend toward a prognostic relevance of metastases (Fig. 1C, Supplementary Fig. S3C). Importantly, the presence of metastases at initial diagnosis did not prompt a different treatment in the patients analyzed (percentage of patients receiving (neo)adjuvant chemotherapy: Chang-M0 51.3% vs Chang-M1–3 66.6%; $P = .16$, χ^2 test).

There is even less information on the relevance of metastasis at tumor progression. Of 245 patients with information on extent and pattern at tumor recurrence, 21% had a local recurrence, the remainder showed signs of metastases (among others, 33% extra-CNS metastases; Supplementary Fig. S3D). The analysis of survival after diagnosis of tumor progression ($n = 238$) showed that the Chang-M stage at tumor recurrence correlated with survival (Fig. 1D).

Prognostic Significance of Histological Subtype

There is consensus that^{28,29} anaplastic medulloblastoma is associated with worse outcome. In contrast, there are contradictory data on the prognostic relevance of the desmoplastic and classic subtypes.^{6,14} In this meta-analysis, there was no significant difference between patients with desmoplastic and classic medulloblastoma (Fig. 2A). However, differences in therapy may have biased this result because patients with the classic subtype more often received chemotherapy and radiotherapy than patients with desmoplastic medulloblastoma (radiotherapy: 94% vs 78%, $P = .0008$, χ^2 test; chemotherapy: 57% vs 40%, $P = .03$, χ^2 test). There was no correlation of the histological subtype with the Chang stage at diagnosis, the incidence of metastases, or the prognosis (data not shown).

Fig. 1. Demographic characteristics and the prognostic role of metastases. (A) Age at first diagnosis ($n = 813$). (B) Changes in the average survival between 1970 and 2013 (median $\pm$ SD, $n = 569$). (C) Kaplan–Meier analysis of survival depending on the Chang-M0 stage at initial diagnosis ($n = 96$). (D) Kaplan–Meier analysis of survival after diagnosis of tumor progression depending on the degree of metastasis at tumor recurrence ($n = 238$).

A detailed screening for additional prognosis factors could not identify new, yet unknown prognostic factors at initial diagnosis. Importantly, there was no correlation between age at diagnosis and outcome (Fig. 2B).

Patterns of Care

Most patients received a gross total (55%) or subtotal (40%) resection and radiotherapy (82%; Table 2) as part of the accepted standard of care. Importantly, the radiation field comprised

fossa posterior and the spine in 84% of all patients with available data (Table 2). In contrast, chemotherapy was not routinely given (Tables 1 and 2). Of the 554 patients with available data, 29% did not receive chemotherapy; 59% received (neo)adjuvant chemotherapy, and 41% received chemotherapy at tumor recurrence (Table 2). Chemotherapy has been increasingly used since 1980 but was initially part of the treatment of recurrent tumors. From the late 1980s, patients with first-line (neo)adjuvant chemotherapy were more frequently reported and their proportion increased to about 40% of all patients (Fig. 2C).

Table 2. Patients' characteristics

Characteristic	Estimated Median/Mean $\pm$ SD/Percent of Total	
	All Patients <i>n</i> = 907 ^a	Patients ≥ 15 and ≤ 18 y <i>n</i> = 101
Age at presentation/ diagnosis/surgery, y	Median: 27 mean: 29.1 $\pm$ 11.1 (range: 15–88) <i>n</i> = 813	Median: 17 mean: 16.8 (range: 15–18) <i>n</i> = 101
Gender	<i>n</i> = 712	<i>n</i> = 82
Male	61%	59%
Female	39%	41%
Histology type	<i>n</i> = 403	<i>n</i> = 45
Classic	48%	47%
Desmoplastic	38%	24%
Anaplastic	2%	20%
Other	12%	9%
Time from first symptoms to diagnosis (mo)	Median: 3 mean: 5.3 $\pm$ 6.7 (range 0.5–48) <i>n</i> = 140	Median: 3 mean: 4.4 $\pm$ 3.6 (range: 1–12) <i>n</i> = 16
Race	<i>n</i> = 80	<i>n</i> = 8
Arabic	2.5%	0%
Asiatic	5%	0%
Black	2.5%	33%
Caucasian/White	90%	67%
Symptoms at presentation	<i>n</i> = 273	<i>n</i> = 27
Intracranial pressure	82%	96%
Cerebellar symptoms	59%	37%
Other symptoms	30%	18.5%
Treatment ^b	<i>n</i> = 798	<i>n</i> = 83
Surgery	91%	97%
Radiotherapy	82%	
Chemotherapy	50%	
Extent of resection ^c	<i>n</i> = 432	<i>n</i> = 46
Biopsy	5%	7%
Total/complete	55%	54%
Subtotal/incomplete	40%	39%
Radiotherapy ^c	<i>n</i> = 286	<i>n</i> = 23
Whole CNS	47%	39%
Whole brain	5%	0%
Fossa posterior only	11%	17%
Fossa posterior and spinal cord	37%	44%
Chemotherapy ^c	<i>n</i> = 555	<i>n</i> = 71
Any chemotherapy	71%	83%
• as first-line treatment	59%	45%
• at tumor recurrence	41%	38%
No chemotherapy	29%	17%
OS, mo	Median: 65 mean: 50 $\pm$ 50 (range: 0–432) <i>n</i> = 467	Median: 58 mean: 40 $\pm$ 32 (range: 0.2–156) <i>n</i> = 59

^aTo determine the number of patients with unavailable/unknown data on specific characteristics, the number of patients has to be subtracted from 907.

^bBased on the treatment described in the publication.

^cPatients with specific information on therapy.

Prognostic Relevance of Resection and Radiotherapy

Gross total resection correlated with better survival compared with subtotal resection or biopsy (mOS: 84 vs 48 vs 36 mo, 95% CI: 68.5–99.5 vs 31.8–64.2 vs 0–85.2 mo, $P = .004$, log-rank-test; Fig. 2D). However, the tumor stage of patients treated with gross total resection and patients treated with subtotal differed significantly. Subtotal resection was associated with disseminated disease (Chang-M stage >0 in patients with subtotal vs gross total resection: 58.3% vs 25%, $P = .01$, χ^2 test) and a higher Chang-T stage (>3 in patients with subtotal vs gross total resection: 67.6% vs 35.1%, $P = .006$, χ^2 test). There were no significant differences in treatment between patients with gross total and subtotal resection.

Survival of patients not receiving radiotherapy (Fig. 3A) was also poor (4.8 mo, 95% CI: 2.3–7.2 mo vs mOS: 62 mo, 95% CI: 50.6–73.3 mo). However, the other treatment modalities of these patients also differed substantially (gross total resection: 2.3%, chemotherapy: 11.4%; Supplementary Table S3), suggesting that these patients suffered from relevant comorbidities interfering with radiotherapy and contributing to their worse outcomes.

Prognostic Relevance of Chemotherapy

Confirming previous reports, OS substantially increased from 1965 to 2013 (Fig. 1B), which was paralleled by an increase in the proportion of patients reported after 1990 surviving longer than 5 years (Fig. 3B) and the proportion of patients receiving chemotherapy (Fig. 2C). Five hundred fifty-four patients had available information on treatment with chemotherapy. An analysis of different chemotherapeutic protocols was not feasible, and patients were therefore assigned to 3 groups only: no chemotherapy, (neo)adjuvant chemotherapy (receiving chemotherapy of any kind as part of the initial therapy), and first chemotherapy of any kind at tumor recurrence. The 3 groups did not significantly differ with respect to grade of resection, radiotherapy, and Chang T/M stage (Supplementary Table S3). Patients who received (neo)adjuvant chemotherapy performed significantly better (mOS: 108 mo, 95% CI: 68.6–148.4, $P > .001$, log-rank-test) than patients receiving chemotherapy for the first time when the tumor recurred (Fig. 3C). Conversely, there was no difference between patients receiving only radiotherapy (mOS: 57 mo, 95% CI: 39.6–74.4) and patients receiving chemotherapy at tumor recurrence (mOS: 45 mo, 95% CI: 30.9–59.1). This effect was not biased by the decade of treatment (Supplementary Fig. S4A–D) and was also seen in cases published after the year 2000. Importantly, only the survival of patients treated with (neo)adjuvant chemotherapy but not the survival of patients treated with radiotherapy ($\pm$ chemotherapy at recurrence) plateaued (Fig. 3C), suggesting that (neo)adjuvant chemotherapy may improve long-term survival.

Late Tumor Recurrences and Long-Term Survival

Late recurrences impairing long-term survival are an important clinical problem in the treatment of adult medulloblastoma.⁹ Sixteen percent of all patients died 5 years after initial diagnosis (Fig. 3D), likely due to late tumor recurrences

Fig. 2. Prognostic factors. (A) The histological subtypes were categorized as classic, desmoplastic, anaplastic, or “others.” Large-cell medulloblastoma was classified as anaplastic. Kaplan–Meier analysis of OS depending on histological subtype is given ($n = 295$). (B) Kaplan–Meier analysis of survival depending on the age at initial diagnosis is given ($n = 548$). (C) Use of chemotherapy as part of initial therapy or at tumor recurrence since 1970s ($n = 339$). (D) Prognostic relevance of total resection, subtotal resection, or biopsy of the tumor ($n = 324$). Only tumors with mentioned gross total resection were classified as such. A tumor resection was classified as subtotal if a residual tumor of any size was mentioned, and if the procedure was not explicitly described as “biopsy.”

(>5 y after initial diagnosis) developing in 15.2% of all patients (Supplementary Fig. S5A). To confirm the association of (neo) adjuvant chemotherapy with long-term survival, we compared all patients who were alive more than 5 years after diagnosis (long-term survivors) with all patients who died within 5 years (short-term survivors). The comparison showed the expected association of “decade of diagnosis” and “radiotherapy” with long-term survival. (Neo)adjuvant chemotherapy increased the chance for long-term survival by 180% (Table 3), corresponding to a higher proportion of patients having received chemotherapy at initial therapy among long-term survivors (Supplementary Fig. S5B). In this analysis, (neo)adjuvant chemotherapy was the most important factor significantly associated with long-term survival.

Discussion

This meta-analysis analyzed all available studies on adult medulloblastoma, resulting in the largest cohort so far. The major methodological flaw of this study is evident: it analyzed a heterogeneous group of patients derived from many different retrospective studies who were treated during a period of time in which many improvements in diagnosis, classification, and treatment were made. Especially the heterogeneous way of reporting data impaired the investigation of many interesting problems, like impact of improvements of radiotherapy and optimal chemotherapeutic schedule.

Despite these methodological problems, the patients of this meta-analysis were very similar to patients reported in the

Fig. 3. Prognostic relevance of radiotherapy and chemotherapy and long-term survival. (A) Kaplan-Meier analysis on the prognostic relevance of radiotherapy ($n = 511$). (B) Proportion of patients surviving more than 5 years after first diagnosis compared with all patients reported ($n = 569$). (C) Kaplan-Meier analysis on the prognostic relevance of chemotherapy. The survival of patients receiving chemotherapy as part of the initial therapy (neo-/adjuvant), the survival of patients receiving chemotherapy at tumor recurrence, and the survival of patients who never received chemotherapy are given ($n = 372$). (D) The survival time of all patients who died (or were lost to follow-up) is given, visualizing that proportion of patients dying 5 years after diagnosis or later ($n = 294$).

largest observational cohort reported so far¹⁶ and to epidemiological data,⁶ indicating that the cohort of this meta-analysis is representative (Table 1). Especially, there was no obvious bias with regard to age, disease stage at initial diagnosis, or treatment. One likely explanation for this similarity may be that centers reported all available patients to obtain a relevant patient number for publication. Importantly, this meta-analysis also allowed the confirmation of many previously reported correlations (eg, relevance of brainstem infiltration and anaplastic subtype^{12,16}) and several expected findings (eg, the worse prognosis of patients receiving only biopsy, patients treated without radiotherapy). A selection bias due to studies reporting only successful treatment appears unlikely because the

average survival of the patients in the meta-analysis was lower compared with other studies.^{6-8,10,12,14,16,24,26,30} This may in part also reflect the fact that our study analyzed all patients reported so far, including (a few) patients being treated before the CT era. In summary, we concluded that the meta-analysis is representative and similar to previous studies and not affected by a relevant bias. Thus, the analysis of the cohort was meaningful.

With respect to prognostic factors, the meta-analysis confirmed surgery and radiation as established parts of today's treatment of medulloblastoma, along with other prognostic factors like brainstem invasion (and associated symptoms). The lack of a prognostic significance between desmoplastic

Table 3. Factors associated with long-term survival

	Patients' Survival		Odds Ratio for Long-Term Survival ^a	χ^2 P
	Died within 5 y	Alive >5 y		
Decade of treatment				
1970s	33 86.8%	5 13.2%	0.34	.017
1980s	50 83.3%	10 16.7%	0.45	.016
1990s	61 64.9%	33 35.1%	1.20	.389
2000s	92 61.3%	58 38.7%	1.40	.042
Gender				
M	130 73%	48 27%	0.94	.721
W	74 69.8%	32 30.2%	1.10	.644
Chang M0				
Yes	8 57.1%	6 42.9%	0.88	.805
No	20 62.9%	18 47.4%	1.05	.881
Grade of resection				
R0	61 62.9%	36 37.0%	1.35	.151
R1	65 78.3%	18 21.7%	0.63	.084
Biopsy	9 64.3%	5 35.7%	1.27	.666
Histology				
Anaplastic	5 100%	0 0%	n.a.	.114
Classic	62 70.5%	26 29.5%	0.84	.451
Desmoplastic	45 62.5%	27 37.5%	1.20	.453
Other	6 50%	6 50%	2.00	.221
Chemotherapy				
None	61 72.6%	23 27.4%	0.77	.296
With recurrence	41 83.7%	8 16.3%	0.40	.014
(Neo)adjuvant	48 53.3%	42 46.7%	1.80	.005

^aOdds ratio = ((Patients in category who survived >5 y) / (Patients in category who died <5y)) / ((All patients surviving >5 y) / (All patients died <5 y)).

and classic medulloblastoma (Fig. 2A) is in line with data from the large patient series^{6,16} but is in contrast to a report by Carrie et al.¹⁴ Different treatments of both subtypes may have biased this result and possibly reflect different evaluations of the tumor's putative aggressiveness by the treating physicians.¹⁹

Still, the lack of a statistically significant difference between desmoplastic and classic medulloblastoma in 3 large patient populations (including this study) indicates a lack of a clinically important difference.

In line with other reports, 20% of the patients showed signs of metastases at initial diagnosis, which was not prognostic for OS. This confirms data by, for instance, Padovani et al and Giordana et al^{16,31} but contradicts other reports.^{11,24} In contrast but not surprisingly, Chang-M stage at tumor recurrence had prognostic significance. A closer look at the survival curves showed that this difference was mainly due to the favorable survival of patients with local recurrence at the time-point of recurrence. This difference was not seen with patients at primary diagnosis. Possible explanations for this divergence are either that some of the "local recurrences" were not due to tumor growth but were caused by, eg. pseudoprogression/radionecrosis³² or that the therapy against metastases with tumor recurrence was not as effective as first-line treatment. Although an answer to this question is pending, advanced imaging with, for instance, PET may be warranted with isolated local tumor recurrences.

The predefined endpoint of this study was the effect of chemotherapy. This meta-analysis could show that chemotherapy given as first-line treatment significantly improved survival (Fig. 3C) and, even more important, substantially improved the chance for long-term survival. The increased chance for long-term survival is in line with observations from the only prospective clinical trial so far, where the low-risk group receiving less aggressive therapy had a higher proportion of late relapses.¹¹ This may also correspond to the clinical experience with children, among whom late recurrences are rare, possibly because almost all children receive chemotherapy together with radiotherapy at initial diagnosis. Unfortunately, the patient cohort did not allow any conclusions on the optimal chemotherapy regime.

In line with other reports, prognosis has improved since 1970,^{6,8} with doubling of OS and tripling of the number of long-term survivors after 2000. The improvement of patients' survival paralleled the increasing use of (neo)adjuvant chemotherapy but also the dramatic improvements of imaging and radiotherapy techniques. The difference in survival between patients treated with or without neo-adjuvant chemotherapy was thought consistently present in all decades (Supplementary Fig. S4A–D), suggesting that the differences between both treatment groups were not substantially flawed by other factors.

In addition, risk stages usually drive treatment choices and may thereby influence survival. Indeed, the Chang-M stage differed between patients receiving (neo)adjuvant chemotherapy and patients receiving radiotherapy, but did not reach statistical significance ($P = .16$). The high-risk patients more often received (neo)adjuvant chemotherapy. This difference may have influenced the prognostic relevance of the Chang-M stage at initial diagnosis (Fig. 1C), but this possible bias was not responsible for the better outcome of the patients treated with chemotherapy as part of the initial therapy. Actually, the effects seen may be even more pronounced without differential treatment. Thus, (neo)adjuvant chemotherapy clearly improved OS and increased the chance of long-term survival. However, the actual extent of improvement remains uncertain.

In summary, this meta-analysis clarified prognostic factors in adults with medulloblastoma and provided the best achievable evidence in support of the use of first-line chemotherapy for adult medulloblastoma.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Journal* online (<http://neuro-oncology.oxfordjournals.org/>).

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