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Clinical characterization of adult medulloblastoma and the effect of first-line therapies on outcome; The MD Anderson Cancer Center experience

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Abstract

Background. Adult medulloblastoma (MB) is rare, and management guidelines are largely based on pediatric clinical trials and retrospective series. Limited data exist with respect to clinical characteristics, prognostic factors, and outcomes based on first-line treatments.

Methods. Two hundred adults with MB seen at a single institution from January 1978 to April 2017 were identified and followed for a median of 8.4 y (7.1, 10.3).

Results. Patient's median age at diagnosis was 29 y (18, 63). One hundred eleven (55.5%) were standard-risk, 59 (29.5%) were high-risk, and 30 (15.0%) were indeterminate. Most received post-operative radiation (RT) (184 [92.0%]), and 105 (52.5%) received first-line chemotherapy. Median overall survival (OS) was 8.8 y (7.2, 12.2) and median progression-free survival (PFS) was 6.6 y (4.9, 11.2). High-risk patients had inferior OS (Hazard ratio [HR] = 2.5 [1.5, 4.2], $P = .0006$) and PFS (HR = 2.3 [1.3, 3.9], $P = .002$) compared to standard-risk patients. Age, sex, and metastatic disease were not associated with survival. After adjusting for risk status, those who received RT plus adjuvant chemotherapy had superior PFS compared to RT plus neoadjuvant chemotherapy [HR = 0.46 (0.22, 0.95), $P = .0357$]. Within a subgroup for whom detailed clinical data were available, those who received RT plus adjuvant chemotherapy had improved PFS compared to RT only [HR = 0.24 (0.074–0.76), $P = .016$]. The substitution of cisplatin for carboplatin and the elimination of vincristine did not negatively affect outcomes.

Conclusion. This is the largest single-institution retrospective study of adult MB to our knowledge and identifies standard-risk status, first-line RT and adjuvant chemotherapy as factors associated with improved outcomes.

Key Points

- Adjuvant and neoadjuvant chemotherapy lead to superior and inferior outcomes in adult MB, respectively.
- Chemotherapy type and number of cycles do not affect outcomes in adult MB.
- We report a population that resembles clinical trial patients to serve as historical controls.

Importance of the Study

In adult medulloblastoma (MB), there is limited evidence regarding the effect of clinical factors and first-line treatments on outcome. Treatment decisions are largely based on pediatric trials. However, adult MB is distinct from pediatric MB and rigorous studies are needed to better understand the clinical and treatment factors associated with survival in adults. The results of prior retrospective analyses have indicated that use of first-line chemotherapy results in improved survival, but no studies have investigated the comparative effect on outcome of the timing of chemotherapy (neoadjuvant, concurrent, and adjuvant) in relation to radiation (RT). Our study represents the largest single institution retrospective study of adult MB. We identified clinical stratification as standard-risk, first-line RT and adjuvant chemotherapy as factors associated with improved survival; neoadjuvant chemotherapy was associated with poor survival. In addition, we demonstrated that chemotherapy regimens that substitute carboplatin for cisplatin and eliminate vincristine do not negatively affect outcomes.

Medulloblastoma (MB) is the most common malignant brain tumor in children. Adult MB is rare accounting for less than 1% of all adult intracranial tumors.[1] An estimated 140 new cases of adult MB are diagnosed in the United States annually in patients aged 15 years and older.[2,3]

The current World Health Organization (WHO) classification categorizes MB based on both molecular characteristics and histopathological features. In order of frequency, the histopathological classification includes classic followed by desmoplastic/nodular, large cell/anaplastic (LCA) and extensive nodularity MB.[4] Transcriptome analyses in the past decade have described at least four distinct molecular subgroups with diverse clinical characteristics, molecular features and DNA methylation status. In adults, these molecular subgroups include Sonic Hedgehog (SHH) (60%), Group 4 (20–25%), Wingless/Integrated (WNT) (15%), and Group 3 (exceedingly rare).[5] These four main subgroups have been further divided into 12 subtypes on the basis of distinct somatic copy-number aberrations, activated pathways and clinical outcomes.[6]

The Chang and Packer staging systems, despite being based mostly on pediatric data, have also been traditionally used to stratify adult MB patients as high-risk or standard-risk. Both are based only on clinical criteria (tumor size and location, age, extent of resection, and presence of tumor spread within and/or outside of the Central Nervous System [CNS]). These clinical risk stratifications are used to determine the intensity of adjuvant treatments and estimate prognosis.[7,8] In general, adult patients with high-risk MB have poorer survival than do patients with standard-risk MB.[9] Metastatic disease at diagnosis is much less frequent in adults than in children (7% vs. 30%).[9,10]

Adopted from pediatric studies,[11,12] maximum safe resection is the goal of surgical resection in adult MB patients. Craniospinal irradiation with a boost to the posterior fossa, tumor bed and when needed, gross metastatic sites (referred to as radiation therapy (RT) in this manuscript), is considered the cornerstone of MB treatment after resection in both standard- and high-risk patients.[13] RT dose and type and the time from surgery to RT are important factors to consider in determining the appropriate treatment course. On the basis of results in the pediatric literature, one of the following doses is delivered in standard-risk adult patients: a reduced dose (23.4 Gy) to the whole brain and spine with a tumor bed boost of 30.6 Gy, along with chemotherapy,[13,14] or a full dose (36 Gy) to the whole brain and spine with a boost of 18 Gy to the tumor bed, with or more commonly without chemotherapy.[15] High-risk patients are treated with 36 Gy to the whole brain and spine with boosts to the tumor bed and to metastatic disease if needed, and commonly chemotherapy. Delays in undergoing RT have been shown to result in a poor outcome in both children and adults.[16,17]

Given the perceived (but insufficiently studied) poor tolerance to multiple-agent cytotoxic chemotherapy in adults after RT, until recently, chemotherapy was generally

reserved for adults with high-risk or recurrent disease, and the benefit of chemotherapy in patients without metastatic disease (M0) who had undergone high-dose RT was uncertain. However, three recent retrospective studies have demonstrated the benefit of first-line chemotherapy in standard-risk adults with MB,[13,14,18] and the feasibility of a first-line regimen of vincristine, cisplatin, and lomustine was demonstrated in a prospective trial.[19] However, there is no consensus regarding the optimal timing of first-line chemotherapy (neoadjuvant. ie, after surgery and before RT; concurrent; adjuvant) and specific chemotherapy regimens. Current practice patterns are derived from the results of three published prospective trials in adults[15,20,21] and are variable across and within institutions. In this retrospective study, we describe the clinical characteristics of 200 adult MB patients who were seen at a single institution and describe the effects of first-line treatment modalities on outcomes.

Methods

Patient Selection

We identified 200 patients with adult MB, defined as those diagnosed at age 18 years or older, who were seen at the adult neuro-oncology, neurosurgery and radiation oncology clinics at the University of Texas MD Anderson Cancer Center (Houston, TX) from January 1978 to April 2017.

Collection of Data

We built a comprehensive data collection instrument in the REDCap database and recorded patient demographics, vital status, and date of death or last follow up, clinical characteristics, and data regarding treatment at diagnosis. The data collection protocol was approved by the MD Anderson Cancer Center Institutional Review Board.

The extent of resection was defined as gross total resection (GTR), no residual disease; near total resection (NTR), < 1.5 cm^2 residual disease; or subtotal resection (STR), more than 1.5 cm^2 residual disease, biopsy, or unknown. The extent of resection was obtained from radiology reports or clinical notes and when the extent of resection was not clear from the report and clinical notes, by reviewing post-operative MRIs, when available. MB was centrally confirmed in almost all patients. Standard-risk was defined as < 1.5 cm^2 of residual disease (ie, GTR or NTR) and no metastasis. All other cases were classified as high-risk. The extent of metastasis was defined as M0, no metastasis; M1, presence of tumor cells in the cerebrospinal fluid; M2, nodular seeding in the cerebellar or cerebral subarachnoid space or in the third or lateral ventricle; M3, metastasis in the spinal subarachnoid space; and M4, metastases outside of the cerebrospinal axis. In most patients, MRI was the modality of choice for CNS imaging; a few had undergone CT scans if MRI was contraindicated or if their treatment pre-dated the wide availability of MRI.

Statistical Analysis

Descriptive statistics (frequency distribution, mean [± s.d.], and median [range]) were used to summarize patients' characteristics. Chi-square test or Fisher exact test was used to test differences in categorical variables, and Wilcoxon rank-sum test was used to detect differences in continuous variables between the two risk groups.[22] Progression-free survival (PFS) was defined as the time from the date of initial surgery to the time of disease progression or death. Overall survival (OS) was defined as the time from the date of initial surgery to death. For events that had not occurred by the time of the last data analysis (April 1, 2018), times were censored at the last contact at which the patient was known to be progression-free for PFS or the last time the patient was known to be alive for OS. The distributions of the time-to-event outcomes were estimated by the Kaplan-Meier method.[23] A log-rank test[24] was performed to test the differences in survival between groups. Regression analyses of survival data based on the Cox proportional hazard model[25] were conducted to evaluate the relationship between various factors and time-to-event endpoints.

Results

Clinical Characteristics

The ratio of male to female patients was 1.6. The median age at diagnosis was 29 years (range, 18–63 y). The median Karnofsky performance score post-surgery was 90 (range, 30 to 100). The most common extent of resection was GTR (110 [55.0%]), followed by STR (55 [27.5%]). Per Packer's clinical staging criteria,[8] 111 (55.5%) had standard-risk and 59 (29.5%) had high-risk disease. Staging was indeterminate in 30 (15.0%) patients because of the lack of information regarding the amount of residual disease after resection and/or appropriate staging. Most patients (126 [63.0%]) had no evidence of dissemination within or outside of the CNS (M0) and only 23 (11.5%) had M+ status. M+ status was indeterminate (ie, specific extent of metastatic disease, M1–M4 was not documented) in 51 (25.5%). The most common original tumor locations were the cerebellar hemispheres (116 [58%]), followed by the vermis (61 [30.5%]) (Table 1). The most common symptom at presentation was headache (147 [73.5%]), followed by nausea (84 [42.0%]), vomiting (76 [38.0%]), and ataxia (69 [34.5%]) (Supplementary Table 1). Histology subtypes were classic (73 [36.9%]), desmoplastic (60 [30.3%]), extensive nodularity (1, [0.5%]), large cell/ anaplastic (8 [4.0%]), and unknown (56 [28.3%]). Molecular subgroups were only known in 10 patients: SHH (9) and group 4 (1).

We identified a subgroup of patients, referred to as the Full data subset, for whom detailed clinical data were available for review ($n = 80$). This subgroup was defined as those who were seen at MD Anderson before any recurrence and had documentation of all of the following: clinical risk category and full staging, including MRI spine and cerebrospinal fluid analyses; RT data (time to start from surgery, dates, and doses) and first-line chemotherapy data (agents

Table 1. Clinical Characteristics of Adult Medulloblastoma Patients

Characteristic	Entire cohort (n = 200) N (%)	Full data subset (n = 80) N (%)
Sex		
Male	122 (61.0%)	51 (63.8%)
Female	78 (39.0%)	29 (36.2%)
Median age, years	29 (18, 63)	28.5 (18, 63)
Extent of resection		
GTR	110 (55.0%)	45 (56.3%)
NTR	19 (9.5%)	11 (13.8%)
STR	55 (22.5%)	21 (26.3%)
Biopsy	5 (2.5%)	3 (3.8%)
N/A	11 (5.5%)	0
M status		
M0	126 (63.0%)	69 (86.3%)
M1	6 (3.0%)	2 (2.5%)
M2	4 (2.0%)	3 (3.8%)
M3	9 (4.5%)	5 (6.3%)
M4	4 (2.0%)	1 (1.3%)
Not specified	51 (25.5%)	0
Risk group		
Standard	111 (55.5%)	57 (71.3%)
High	59 (29.5%)	23 (28.8%)
N/A	30 (15%)	0
Localization		
Vermis	61 (30.5%)	29 (36.3%)
Fourth ventricle	30 (15.0%)	8 (10.0%)
Left cerebellum	56 (28.0%)	24 (30.0%)
Right cerebellum	60 (30.0%)	28 (35.0%)
Other*	21 (10.5%)	9 (11.3%)
Unknown	12 (6.0%)	2 (2.5%)
First-line Treatments		
RT	184 (92.0%)	80 (100%)
Chemotherapy and risk group distribution**		
Neoadjuvant	25 (12.5%)	11 (13.8%)
Standard	8 (32.0%)	3 (27.3%)
High	14 (56.0%)	8 (72.7%)
Concurrent	33 (16.5%)	16 (20.0%)
Standard	24 (72.7%)	11 (68.89%)
High	7 (21.2%)	5 (31.3%)
Adjuvant	78 (39.0%)	30 (37.5%)
Standard	43 (55.1%)	19 (63.3%)
High	26 (33.3%)	11 (36.7%)
Intrathecal	12 (6.0%)	3 (3.8%)
Standard	5 (41.6%)	1 (33.3%)
High	4 (33.3%)	2 (66.7%)
None	114 (57.0%)	47 (58.8%)
N/A	26 (13.0%)	
VP shunt	38 (19.0%)	16 (20.0%)

*Leptomeningeal, brainstem, spine, and third ventricle. More than one location was possible.
**More than one chemotherapy category was possible.

and duration). The Full data subset included patients who received surgery and/or postoperative treatment outside of MD Anderson, but care was driven by MD Anderson faculty recommendations even if they received their care from local providers. This subgroup was selected to resemble the type of patients that are most commonly eligible for or enrolled in clinical trials. Similar clinical characteristics were observed in the Full data subset as in the entire cohort. The male to female ratio of the sub cohort was 1.8. The median age was 28.5 years (range, 18 to 63 y), and the median Karnofsky performance score post-surgery was 90 (range, 40 to 100). The most common extent of resection was GTR (45 [56.3%]), followed by STR (21 [26.3%]). Per Packer's staging criteria,[8] 57 (71.3%) had standard-risk and 23 (28.8%) had high-risk disease. Most patients had no evidence of metastasis in or outside of the CNS (M0, 69 [86.3%]). The most common tumor locations were the cerebellar hemispheres (52 [65%]), followed by the vermis (29 [36.3%]) (Table 1).

Survival Outcome

The median OS was 8.8 y (95% CI = 7.2, 12.2 y), and the median PFS was 6.6 y (95% CI = 4.9, 11.2 y) for our entire cohort (n = 200) after a median follow-up of 8.4 y (95% CI = 7.1, 10.3 y). The 5-year OS rates for all, standard-risk, and high-risk patients were 74% (95% CI = 66%, 80%), 82% (95% CI = 71%, 88%), and 62% (95% CI = 47%, 74%), respectively, and the 5-year PFS rates were 55% (95% CI = 47%, 63%), 71% (95% CI = 60%, 80%), and 39% (95% CI = 25%, 54%) (Supplementary Table 2).

Clinical Characteristics Associated with Survival

On univariate analysis of the entire cohort (n = 200), standard- vs. high-risk status was associated with improved OS and PFS (Table 2). Compared to STR, GTR and NTR were associated with improved OS (HR = 0.60 [95% CI = 0.37, 0.98], P = .039 and .26 [95% CI = 0.08, 0.86], P = .027) and PFS (HR = 0.63 [0.40, 0.99], P =.047 and .26 [95% CI = 0.093, 0.75], P = .012) (Table 2 and Supplementary Figure 1). Age (≤ 29 vs. > 29 y), sex, M status (M0 vs. M+), and the presence of a ventriculoperitoneal shunt were not associated with OS or PFS (Table 2).

In patients with known risk status (n=170), the median OS of standard- and high-risk patients were not reached (NR) (95% CI = 8.4, NR) and 7.0 y (95% CI = 4.4, 11.1 y), respectively (P = .001) (Figure 1A). The median PFS of standard- and high-risk patients were 13.6 years (95% CI = 8.2, NR) and 3.9 years (95% CI = 2.7, 8.4 y), respectively (P = .001) (Figure 1B). To further evaluate the prognostic value of extent of resection, we compared the survival outcomes of the following cohorts: high-risk M+, high-risk M0, and standard-risk M0. Patients with standard-risk M0 status had significantly better OS (P = .009) and PFS (P = .014) than did patients with high-risk M+ and high-risk M0 status who had similar OS and PFS. The median OS for standard-risk M0, high-risk M0, and high-risk M+ were NR (95% CI = 8.4, NR), 8.8 (95% CI = 2.2, 18.3), and 6.5 years (95% CI = 3.3, NR) (P = .009), respectively. The median

Table 2. Association Between Clinical Characteristics and First-line Treatment and Survival

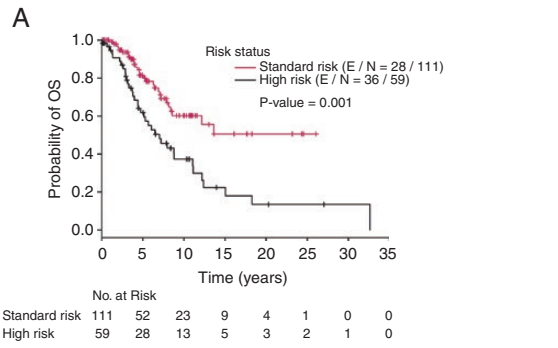
Clinical characteristics	Hazard ratio	95% Hazard ratio confidence limits		*P* value
Overall survival				
Univariate analysis				
Age > 29 vs. ≤ 29 years	0.88	0.57	1.37	0.57
Male vs. female	1.23	0.79	1.92	0.36
Initial surgery (STR)				
GTR	0.60	0.37	0.98	**0.039**
NTR	0.26	0.08	0.86	**0.027**
Risk group (standard)				
Unknown	2.12	1.18	3.81	**0.012**
High	2.30	1.40	3.78	**0.0011**
M+ vs. M0	1.70	0.87	3.33	0.12
VP shunt vs. no VP shunt	0.86	0.48	1.54	0.62
Treatment at diagnosis vs no treatment (for each category)				
RT	0.38	0.15	0.95	**0.038**
Neoadjuvant chemotherapy	2.19	1.18	4.04	**0.013**
Concurrent chemotherapy	0.98	0.47	2.08	0.96
Adjuvant chemotherapy	0.93	0.54	1.59	0.78
Intrathecal chemotherapy	3.61	1.69	7.74	0.001
Multivariate analysis (adjusting for risk status)				
RT vs. no RT	0.28	0.11	0.73	**0.009**
Progression-free survival				
Univariate analysis				
Age > 29 vs. < 29 years	1.04	0.69	1.58	0.85
Male vs. female	1.15	0.74	1.77	0.54
Initial surgery (STR)				
GTR	0.63	0.40	0.99	**0.047**
NTR	0.26	0.09	0.75	**0.012**
Risk group (standard)				
Unknown	2.70	1.59	4.58	**0.0002**
High	2.28	1.40	3.69	**0.0009**
M+ vs. M0	1.61	0.81	3.19	0.18
VP shunt vs. no VP shunt	0.69	0.38	1.24	0.21
Treatment at diagnosis vs. no treatment (for each category)				
RT	0.54	0.20	1.48	0.23
Neoadjuvant chemotherapy	2.13	1.17	3.85	**0.013**
Concurrent chemotherapy	0.88	0.43	1.78	0.72
Adjuvant chemotherapy	0.78	0.46	1.31	0.34
Intrathecal chemotherapy	4.63	2.16	9.90	**< 0.0001**
Multivariate analysis (adjusting for risk status)				
RT vs. no RT	0.44	0.16	1.23	0.12

Bold values indicate statistically significant values.

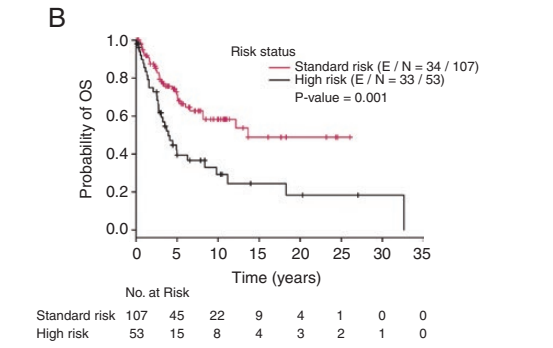
PFS for these categories were 13.6 years (95% CI = 8.2, NR), 2.8 years (95% CI = 1.0, 18.3), and 4.1 years (95% CI = 1.6, NR) (*P* = .014), respectively (Figure 1C,D and Supplementary Table 3).

First-line Treatments

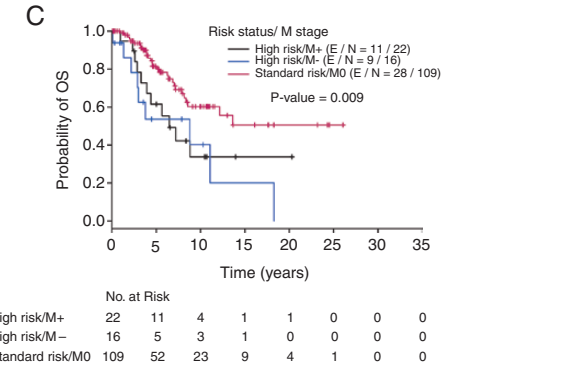
Of our entire cohort of 200 patients, 184 (92.0%) received RT (as defined in Introduction). Twelve patients did not receive craniospinal RT and RT data were missing in four



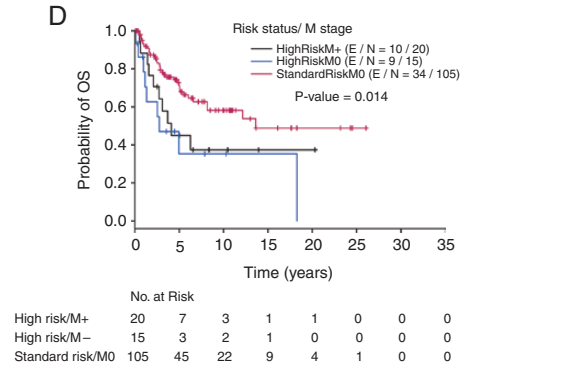
Risk Group	Median FU (year)	Event/Total	Median OS (year)	1-year OS rate	5-year OS rate	10-year OS rate
All	7.9 (5.7, 10)	64/170	11.07 (7.85, 13.64)	0.97 (0.93, 0.99)	0.74 (0.66, 0.81)	0.51 (0.41, 0.6)
SR	6.5 (4.7, 8.5)	28/111	NR (8.38, NR)	0.99 (0.93, 1)	0.82 (0.71, 0.88)	0.6 (0.46, 0.72)
HR	10.5 (7.9, 27)	36/59	7.01 (4.4, 11.07)	0.95 (0.84, 0.98)	0.62 (0.47, 0.74)	0.37 (0.23, 0.52)



Risk group	Event/Total*	Median PFS (year)	1-year PFS rate	5-year PFS rate	10-year PFS rate
All	68/161	8.38 (5.05, 18.27)	0.9 (0.84, 0.94)	0.6 (0.51, 0.68)	0.48 (0.38, 0.57)
SR	34/107	13.64 (8.15, NR**)	0.93 (0.86, 0.97)	0.71 (0.6, 0.8)	0.58 (0.45, 0.69)
HR	33/53	3.92 (2.73, 8.38)	0.86 (0.72, 0.93)	0.39 (0.25, 0.54)	0.29 (0.16, 0.44)



Risk Group / M status	Median FU (year)	Event/Total	Median OS (year)	1-year OS rate	5-year OS rate	10-year OS rate
HR M+	10.5 (5, 14)	11/22	6.48 (3.3, NR)	0.95 (0.68, 0.99)	0.62 (0.36, 0.79)	0.34 (0.12, 0.57)
HR M0	7.9 (1.1, NR)	9/16	8.77 (2.17, 18.27)	0.94 (0.63, 0.99)	0.54 (0.24, 0.76)	0.4 (0.12, 0.67)
SR M0	6.5 (4.7, 8.5)	28/109	NR (8.38, NR)	0.99 (0.93, 1)	0.82 (0.71, 0.88)	0.6 (0.46, 0.72)



Risk Group/ M Status	Event/Total	Median PFS (year)	1-year PFS rate	5-year PFS rate	10-year PFS rate
HR M+	10/20	4.11 (1.58, NR)	0.88 (0.61, 0.97)	0.45 (0.21, 0.67)	0.37(0.15, 0.6)
HR M0	9/15	2.75 (0.98, 18.27)	0.78 (0.47, 0.92)	0.35 (0.1, 0.62)	0.35 (0.1, 0.62)
SR M0	34/105	13.64 (8.15, NR)	0.93 (0.85, 0.96)	0.71 (0.6, 0.8)	0.58 (0.45, 0.69)

Figure 1. Kaplan-Meier curve of OS and PFS by risk status.

patients. One hundred five patients received chemotherapy: neoadjuvant (n = 25 [12.5%]), concurrent (n = 33 [16.5%]), and adjuvant (n = 78 [39%]) (more than one chemotherapy category was possible) (Table 1 and Figure 2). Standard- and high-risk status distributions for neoadjuvant, concurrent, adjuvant among those with known risk status were 32%, 56%; 72.7%, 21.2%; 55.1%, 33.3%; respectively.

Among patients with known risk status (n = 170), 156 (91.8%) had RT. Ten patients either did not have craniospinal RT or were excluded from the analysis (incomplete craniospinal radiation), and data were missing in four patients. Ninety-three (54.7%) received chemotherapy in the form of neoadjuvant chemotherapy (n = 22 [12.9%]), concurrent therapy (n = 31 [18.2%]), and adjuvant therapy (n = 69 [40.6%]) (more than one chemotherapy category was possible).

Outcome based on First-line Treatments

Given the known effect of clinical risk groups on outcome, we evaluated the effects of first-line treatment only in patients with known risk status (n = 170). On univariate analysis, patients who had RT had improved OS, but not PFS, compared to patients who did not have RT (HR for OS = 0.38 [0.15, 0.95], P = .038; HR for PFS = 0.54 [0.2, 0.15], P = .23). On multivariate analysis, patients who had RT had improved OS but not PFS compared to patients who did not have RT after adjusting for risk status (HR for OS = 0.28 [0.11, 0.73], P = .0090 and HR for PFS = 0.44 [95% CI = 0.16, 1.23], P = .12) (Table 2 and Figure 3A,B).

On univariate analysis, patients who had neoadjuvant chemotherapy had inferior OS and PFS compared to patients who had not received neoadjuvant chemotherapy (HR for OS = 2.19 [1.18, 4.04], P = .012; HR for PFS = 2.13 [1.17, 3.85], P = .013). There were no statistically significant differences in OS and PFS in patients who had adjuvant or concurrent chemotherapy compared to those who did not have adjuvant or concurrent chemotherapy (Table 2).

Kaplan-Meier estimates of OS and PFS demonstrated worse survival in patients who had RT plus neoadjuvant chemotherapy compared to patients who had RT only or RT plus adjuvant chemotherapy. The median OS of patients who had RT plus neoadjuvant chemotherapy, RT plus adjuvant chemotherapy, or RT only were 5.7 years (95% CI = 3.8, 11.1), 15.0 years (95% CI = 8.0, NR), and 11.1 years (95% CI = 7.0, 32.6), respectively. The difference in median OS did not reach statistical significance (P = .095). The median PFS of patients who had RT plus neoadjuvant chemotherapy, RT plus adjuvant chemotherapy, or RT only were 3.1 years (95% CI = 2.1,

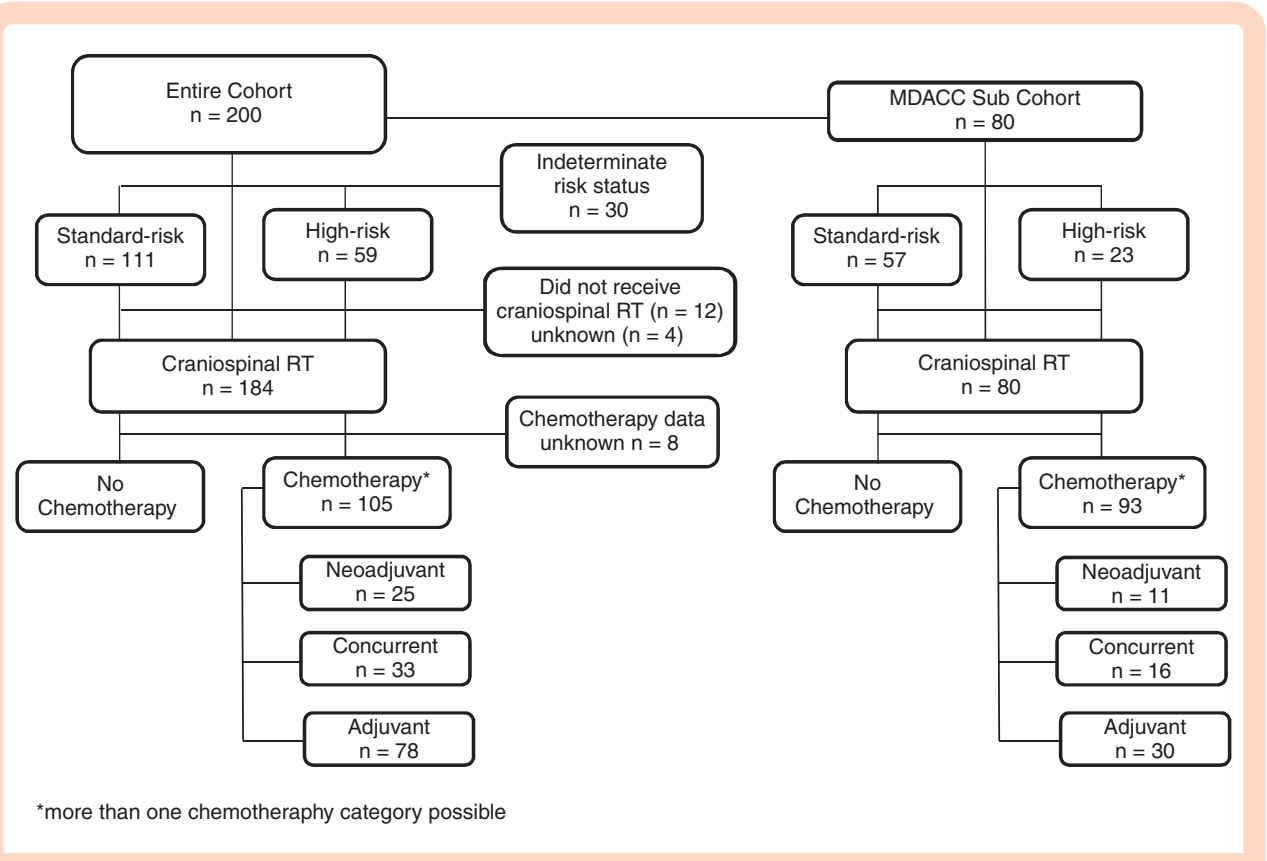


Figure 2. Flow chart of risk stratifications and first-line therapies.

5.0), 11.2 years (95% CI = 8.2, NR), and 8.4 years (95% CI = 4.9, 32.6), respectively. The difference in the median PFS duration reached statistical significance ($P = .023$) (Figure 3C,D).

Given that patients who received neoadjuvant chemotherapy had shorter survival, we excluded them from further analysis of the effects of adding adjuvant or concurrent chemotherapy to RT in particular risk groups. Kaplan-Meier curves of OS and PFS favored patients who had RT plus adjuvant chemotherapy compared to RT only in standard-risk groups; however, this difference was not statistically significant (Supplementary Figure 2A-D).

Effect of Various Chemotherapy Regimens on Outcome

It is common to include a platinum agent (cisplatin or carboplatin), an alkylating agent (lomustine or cyclophosphamide), and vincristine in the chemotherapy regimens in adult MB patients.[26] Some practitioners substitute cisplatin for carboplatin because adults are believed to have a higher tolerance to carboplatin, but the comparative efficacy and safety of carboplatin and cisplatin have not been tested in prospective studies in adults with MB. We found no difference in survival outcomes between patients treated with carboplatin compared to cisplatin regimens (Supplementary Figure 3A,B).

Controversy exists regarding the advantage of vincristine for the treatment of primary brain tumors, as it is a large lipophilic drug with poor blood-brain barrier penetration[27] and its dose-limiting toxicity, neuropathy, limits its use in adults.[19,28] Therefore, we evaluated the effect of vincristine on survival; we found that the use of chemotherapy regimens without vincristine had no negative effect on outcomes (Supplementary Figure 3C,D).

The optimal number of adjuvant chemotherapy cycles is not well defined in adults with MB, and chemotherapy-related toxicity is a common factor that limits the amount of chemotherapy that can be administered.[19] Therefore, we compared the PFS and OS of patients who had undergone < 4 or ≥ 4 adjuvant chemotherapy cycles. The number of adjuvant chemotherapy cycles had no effect on median duration of PFS or OS in our patient population (Supplementary Figure 3E,F).

Effect of RT Dose on Outcome

To understand the optimum RT dose in adults with standard-risk MB, we determined the effect of RT dose on outcome and compared the median duration of OS and PFS of patients who had < 30 Gy RT plus adjuvant chemotherapy ($n = 16$) with those who had ≥ 30 Gy RT ($n = 37$) and did not detect a difference in outcome in these groups (Supplementary Figure 3G,H).

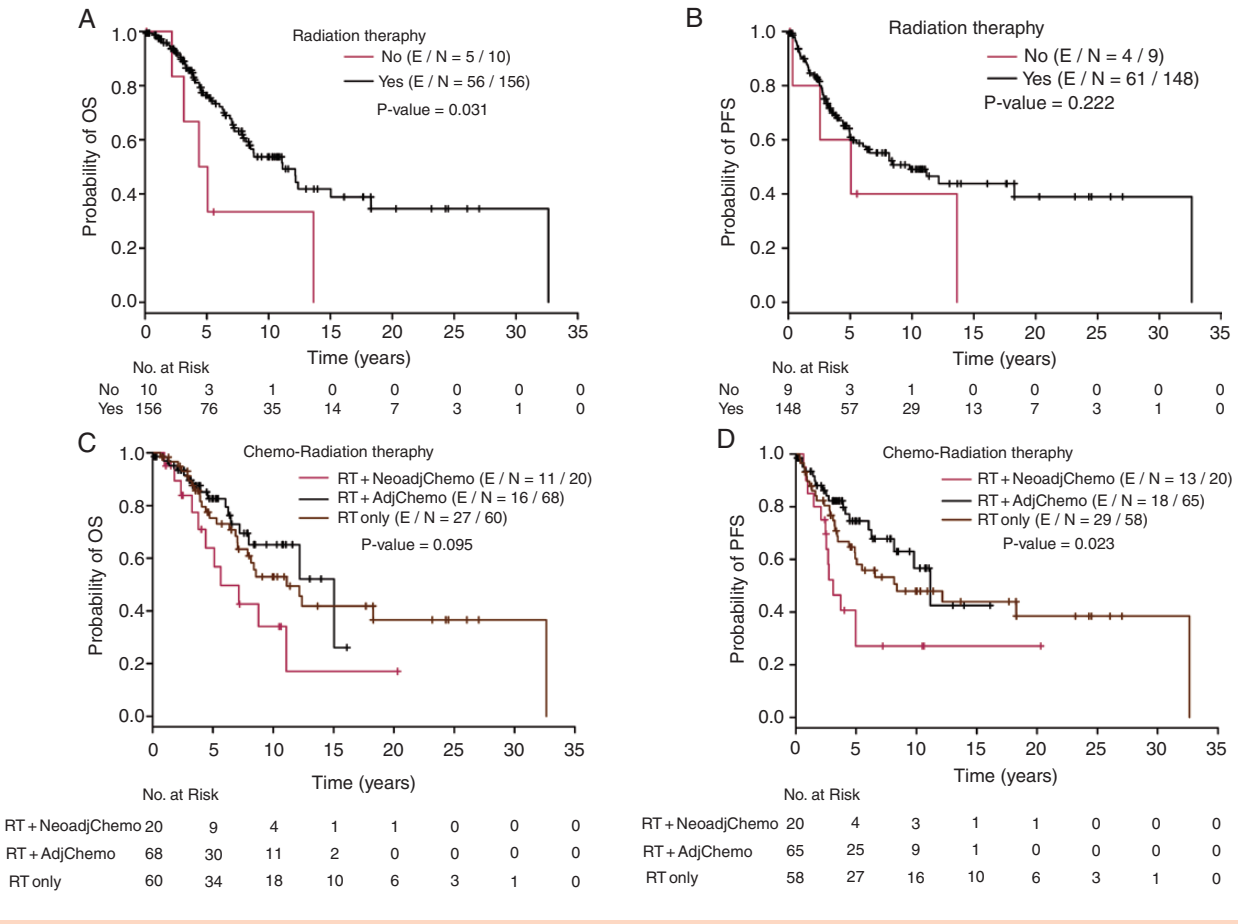


Figure 3. Kaplan-Meier curve of OS and PFS by first-line therapies in patients with known risk status.

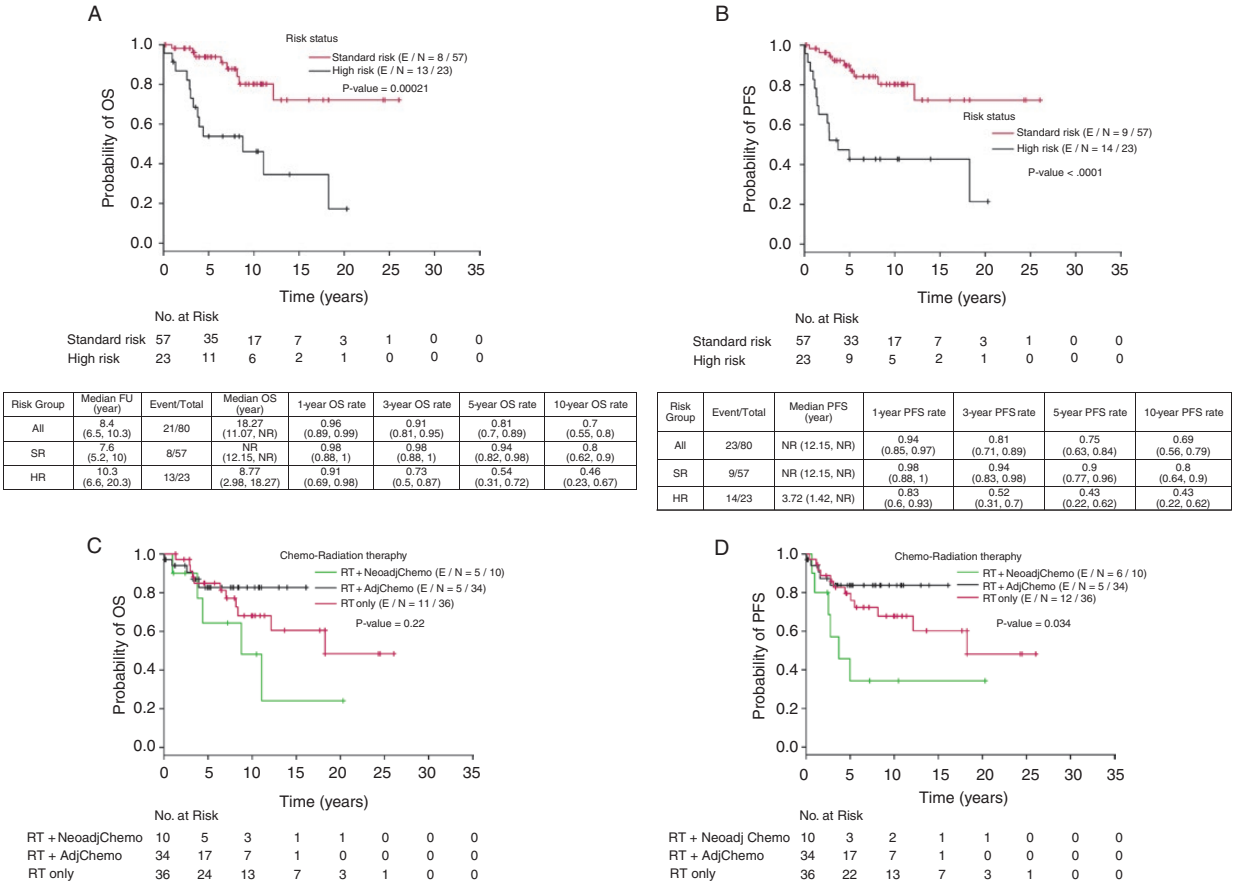
Survival and Effect of First-line Treatment on Outcome in the Full Data Subset

As described above, we identified a subgroup of patients in our cohort called the Full data subset for whom detailed clinical data were available for review (n = 80) (Table 1 and Figure 2). Our objectives when selecting this cohort were to minimize the effect of missing data in a retrospective series. The median OS was 18.3 years (95% CI, 11.1, NR), and the median PFS was NR (12.2, NR) for this subset after a median follow-up of 8.4 years (6.5, 10.3 y). The 3-year survival rates for all, standard-risk, and high-risk patients were 91% (95% CI = 81%, 95%), 98% (95% CI = 88%, 100%), and 73% (95% CI = 50%, 87%), respectively; the 3-year PFS rates were 81% (95% CI = 71%, 89%), 94% (95% CI = 83%, 98%), and 52% (95% CI = 31%, 70%). Standard-risk status was associated with improved median OS and PFS in the sub cohort, similar to the results in our entire cohort of 200 patients (Figure 4A,B).

In the Full data subset, patients who had RT plus adjuvant chemotherapy had improved PFS compared to those who had RT only (HR = 0.24 [0.074–0.76], P = .016) (Supplementary Table 4). The HR for OS in RT plus adjuvant chemotherapy compared to RT alone did not reach statistical significance (HR = 0.32 [0.099, 1.03], P = .057). Neoadjuvant chemotherapy was associated with inferior PFS and OS, similar to the results of our analysis in our entire cohort (Figure 4C,D). Kaplan-Meier estimates of OS and PFS in patients undergoing RT only compared to RT plus adjuvant chemotherapy in high-risk and standard-risk groups were not statistically different, likely because of the low number of cases (Supplementary Figure 4A–D).

Discussion

Treatment decisions, prognosis estimates, and the determination of clinical trial endpoints largely depend on the results of pediatric trials and retrospective studies in adult MB.[29] A large national database analysis and meta-analyses in adult MB patients demonstrated the benefit of chemotherapy in standard-risk patients.[13,14] However, the patient populations included in these analyses were heterogenous in terms of clinical characteristics and patterns of care across many institutions. In addition, a recent single institution retrospective study including 48 patients ≥ 16 years of age demonstrated that adding adjuvant chemotherapy to radiotherapy improves PFS and OS.[18] Our study



Risk Group	Median FU (year)	Event/Total	Median OS (year)	1-year OS rate	3-year OS rate	5-year OS rate	10-year OS rate
All	8.4 (6.5, 10.3)	21/80	18.27 (11.07, NR)	0.96 (0.89, 0.99)	0.91 (0.81, 0.95)	0.81 (0.7, 0.89)	0.7 (0.55, 0.8)
SR	7.6 (5.2, 10)	8/57	NR (12.15, NR)	0.98 (0.88, 1)	0.98 (0.88, 1)	0.94 (0.82, 0.98)	0.8 (0.62, 0.9)
HR	10.3 (6.6, 20.3)	13/23	8.77 (2.98, 18.27)	0.91 (0.69, 0.98)	0.73 (0.5, 0.87)	0.54 (0.31, 0.72)	0.46 (0.23, 0.67)

Risk Group	Event/Total	Median PFS (year)	1-year PFS rate	3-year PFS rate	5-year PFS rate	10-year PFS rate
All	23/80	NR (12.15, NR)	0.94 (0.85, 0.97)	0.81 (0.71, 0.89)	0.75 (0.63, 0.84)	0.69 (0.56, 0.79)
SR	9/57	NR (12.15, NR)	0.98 (0.88, 1)	0.94 (0.83, 0.98)	0.9 (0.77, 0.96)	0.8 (0.64, 0.9)
HR	14/23	3.72 (1.42, NR)	0.83 (0.6, 0.93)	0.52 (0.31, 0.7)	0.43 (0.22, 0.62)	0.43 (0.22, 0.62)

Figure 4. Kaplan-Meier curve of OS and PFS by first-line therapies (the Full data subset).

included 200 adult MB patients ≥ 18 years of age at a single institution from January 1978 to April 2017.

Our cohort's age and sex were similar to those in prior studies and most patients were stratified as standard-risk based on clinical risk factors.[13,14,30,31] We chose an age cut-off of 18 years to reflect patients who were seen in our adult neuro-oncology clinic. Consistent with the results of previously published studies, adult patients with high-risk disease had poorer survival than did patients with standard-risk disease.[9]

Metastatic disease at original diagnosis was only seen in 23 (11.5%) of our entire cohort similar to previously published data in adult MB.[10] M status is a known prognostic indicator in pediatric MB patients,[32] but in our study, M status was not associated with survival; it is possible that this was because of the small number of patients. An alternative explanation is the effect of differences in management (patients with M+ disease typically received chemotherapy as part of their first-line treatment regimen, whereas most M0 patients did not). Unlike in pediatric MB patients, the value of the extent of resection in adults has been controversial. In our study, GTR and NTR were associated with improved OS and PFS in comparison with STR and patients with standard-risk M0 status had significantly improved median PFS and OS compared to patients with high-risk M0 and M+, indicating that residual disease is an independent indicator of poor prognosis in adult MB patients. There was no difference in outcome between those with high-risk M0 vs. high-risk M+, suggesting that M status is not of prognostic value in adults when residual tumor in the posterior fossa is present, unlike in children. The differences between clinical prognostic indicators in adults and children (M status and residual disease) suggest that other factors, such as molecular subtypes or the ability to undergo sufficient first-line treatment, may play important roles in the prognosis of adult MB. We did not have sufficient information on molecular subtypes to perform a meaningful analysis.

The median OS of adult patients with MB varies widely, depending on the type of study and the population included.[13,14,31] We identified a patient subgroup in our dataset called the Full data subset, described above. This subset was defined to minimize the effect of patient heterogeneity and missing data that are typical of retrospective studies and to select a patient population that more closely resembled clinical trial patients. The demographics of this subset were similar to those of our entire cohort; however, their survival was longer than that of our entire cohort. The survival data of this subset can be considered a historical control for the design of future prospective clinical trials.

To better define the impact of first-line treatment on outcome, we evaluated the effect of first-line RT, and chemotherapy on survival. RT is universally used in both standard-risk and high-risk adult MB patients[13,14,31] and has been shown to be associated with improved survival.[33] Compared to patients who did not receive RT, those who did had superior OS on univariate analysis and after adjusting for risk status, which is consistent with prior data supporting the use of RT in adult MB patients. The optimum RT dose in standard-risk patients with MB is unclear, however. Historically, these patients have been treated with high-or low-dose RT and first-line chemotherapy to minimize the risk of cognitive side effects of high-dose RT.[34,35] In this study, we determined the effect of RT dose on outcome in standard-risk patients; we did not detect a difference in patients who received < 30 Gy RT plus adjuvant chemotherapy and those who received ≥ 30 Gy RT alone.

Even though there is consensus regarding the use of first-line chemotherapy in adult MB patients, the timing of chemotherapy (neoadjuvant, concurrent, and adjuvant) and the optimal chemotherapy regimen are unclear. Only three prospective studies of chemotherapy in adult MB patients have been performed to date,[15,19,21,36,37] and they each used different chemotherapy regimens.

In our study, we found an inferior OS and PFS in patients who received neoadjuvant chemotherapy in the univariate analysis. We analyzed the effects of combined treatments on outcome; patients who received neoadjuvant chemotherapy had inferior median PFS and non-statistically significant inferior OS compared with that of patients who received RT alone and RT plus adjuvant chemotherapy. The inferior outcome of patients who received neoadjuvant chemotherapy may have been due to a number of factors such as the delay in starting RT, worse functional status of the patients who were selected for neoadjuvant chemotherapy, or to a preponderance of high-risk patients treated with this modality. Similarly, in the prospective study by Moots et al.,[21] survival outcomes with neoadjuvant chemotherapy were poorer than expected in adults. Overall, the current available data does not demonstrate a survival advantage with the use of neoadjuvant chemotherapy.

Given the poor outcome of patients who received neoadjuvant chemotherapy, we evaluated the PFS and OS of patients who had adjuvant chemotherapy plus RT compared to RT only in the entire cohort of patients with known risk status. We did not observe statistically significant differences in outcomes possibly because of the heterogeneity of the patient population analyzed. We next evaluated the effect of adjuvant chemotherapy in the more unified Full data subset; we observed an improved PFS in patients who received adjuvant chemotherapy plus RT compared to RT alone, after adjusting for risk status. Similar positive effect of adjuvant chemotherapy on PFS was not seen in the entire cohort, likely due to missing data and heterogenous patient population.

The type of first-line chemotherapy used in adult MB patients is very heterogeneous within and across institutions. There are no prospective data that show whether the substitution of cisplatin for carboplatin compromises outcomes and whether vincristine can be safely eliminated, given its poor blood-brain-barrier penetration and neurotoxicity.[26] In our study, we did not observe a statistically significant difference in the PFS and OS of patients who received cisplatin compared to carboplatin or those who received vincristine compared to no vincristine. We do not favor the use of concurrent chemotherapy and RT in adults because of the reported toxicity[19] and our data suggesting that eliminating vincristine does not negatively affect outcomes. Only a prospective randomized clinical trial can provide definite guidelines regarding the optimal timing of chemotherapy; however, such a trial in adult MB patients would involve significant feasibility barriers as a result of the rarity of the disease.

In addition, the number of adjuvant chemotherapy cycles is not well established in adults with MB. We observed no difference in PFS and OS of patients who received < or ≥ four adjuvant chemotherapy cycles. We chose four cycles because 70% of adult MB patients in the Beier et al study were able to tolerate at least this number.[19] The lack of difference in outcome in the various treatment groups in our study (based on chemotherapy type, radiation dose [< 30 Gy vs. ≥ 30 Gy], and number of adjuvant chemotherapy cycles) may be a result of the small number of patients in each category; further studies are needed to confirm these findings.

The major limitations of our study are the retrospective nature of the analyses, the long inclusion period, the lack of molecular subtypes, heterogenous treatments, and the absence of information on treatment side effects. These limitations are common in studies of rare CNS tumors. Future retrospective studies should aim at collecting as much data as possible to debias conclusions regarding the effect of first line therapies on outcome. For example, in our study at least 13 different chemotherapy agents were used and knowledge of specific agents and associated toxicity could alter conclusions drawn regarding the effect of chemotherapy categories on outcomes. Importantly, there is a great need to establish nationwide tumor tissue, peripheral blood, and cerebrospinal fluid banks, along with a data base of comprehensive clinical information in patients with rare diseases,[38] to understand the effects of treatment on particular molecular subgroups, as prognosis is likely largely driven by molecular risk factors. In addition, several ongoing clinical trials include adults with MB (SJMB12, NCT01878617; SJDAWN, NCT03434262) and upcoming clinical trials in newly diagnosed adult MB are planned (PersoMed-I, EORTC-1634-BTG; the alliance trial [AMBUSH trial, Adult and Adolescent MB Using Sonic Hedgehog trial]). All these trials focus on the use of SMO inhibitors for patients with newly diagnosed or recurrent SHH-MB, a targeted therapy of particular importance in adults given that SHH-MB is the most common molecular subtype in adults and that skeletally mature patients are the ideal population to test SMO inhibitors (trials in pediatric patients had to be terminated because of growth plate toxicities).[39] The results of these molecularly risk-directed clinical trials in adult MB are eagerly awaited to improve the outcome of this patient population.

Conclusions

This study represents the largest single-institution retrospective study of adults with MB, to our knowledge. Our study demonstrated the superior survival outcome

of standard-risk compared to high-risk adult MB patients and the benefit of RT. We also found that neoadjuvant chemotherapy has a deleterious effect on outcome and observed improved outcome in standard-risk patients who receive adjuvant chemotherapy plus RT compared to RT alone. In our study, RT dose, chemotherapy type (cisplatin vs. carboplatin and regimens with or without vincristine), and number of chemotherapy cycles did not affect outcomes, indicating that attenuated first-line treatment regimens may still be effective and decrease toxicity. Importantly, our study included a patient population that closely resembled clinical trial participants; this population's survival outcomes can be used as historical controls in future prospective trials in adults. Conducting clinical trials in rare cancers is challenging; well-designed trials that include histopathological and molecular subtypes are needed to improve the outcome of adult MB patients.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Advances* online.

Keywords

adult medulloblastoma | clinical characterization | first-line therapy | chemotherapy | radiation therapy

Disclaimer

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