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Survival difference between brainstem and cerebellum medulloblastoma: the surveillance, epidemiology, and end results-based study

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Abstract

To investigate the prognoses associated with different locations of medulloblastoma (MB) in terms of survival through a case-control study and evaluate the prognostic factors for MB.

The Surveillance, Epidemiology, and End Results database was used to identify MB patients diagnosed from 1975 to 2016. Each brainstem MB (bMB) patient was matched to a cerebellum MB (cMB) patient by propensity score matching based on age, sex, tumor size, extent of metastasis, extent of surgical resection, radiotherapy status and chemotherapy status. Univariate and multivariate analyses were performed to assess the effect of prognostic factors on overall survival. Ethical approval was not necessary as this study is based on a public database.

A total of 172 bMB patients and 1417 cMB patients were included in the study. A total of 144 pairs of patients were matched to constitute the matched cohort. Within the matched cohort, the median survival times were 213 months and 96 months for cMB and bMB, respectively. Within the unmatched cohort, the median survival times were 111 months and 97 months for cMB and bMB, respectively. Brainstem location detrimentally affected the survival time of MB patients in both the matched cohort (hazard ratios =8.14, 95% confidence interval =5.98–11.08) and the unmatched cohort (hazard ratios =1.44, 95% confidence interval =1.20–1.74). Age <5 years and receipt of radiotherapy were favorable prognostic factors, whereas gross total resection, brainstem location and receipt of chemotherapy were unfavorable prognostic factors. Radiotherapy alone was associated with superior outcomes concerning adjuvant chemotherapy or radiotherapy.

This study uncovers a survival advantage for cMB patients versus bMB patients. Additionally, prognostic factors include age, extent of surgical resection, and receipt of radiotherapy or chemotherapy. Radiotherapy after surgery and rational use of chemotherapy drugs are crucial for treatment of MB patients. Further studies of these prognostic factors are required to improve the survival time.

Abbreviations: bMB = brainstem medulloblastoma, CI = confidence interval, cMB = cerebellum medulloblastoma, GTR = gross total resection, HR = hazard ratios, MB = medulloblastoma, OS = overall survival, RT = radiotherapy only, SEER = the surveillance, epidemiology, and end results, STR = subtotal resection.

Keywords: epidemiology, medulloblastoma, population study, prognosis, the surveillance, epidemiology, and end results, survival analysis

1. Introduction

Medulloblastoma (MB) is the most common malignant brain tumor in children, comprising 30% of pediatric central nervous system tumors.[1,2] Early literature reported that MB was a rare disease in adults,[3] but up to 30% of MB patients are adults in our study. MB is generally thought to derive from the cerebellum vermis, and most tumors grow into the cerebellar hemisphere or fourth ventricle. A few studies demonstrated that tumor location was associated with prognosis[4,5]; however, they only compared the outcomes of hemisphere-lateral tumors and midline-vermis tumors in the cerebellum. Little is known concerning the prognosis of brainstem MB (bMB) patients. To improve the understanding of MB and formulate a proper treatment plan for MB patients, it is important to assess the effects of tumor location as well as other potential prognostic factors. Patient age, extent of resection, dissemination, histology subtype, molecular subtype, and receipt of chemotherapy or radiotherapy have been established as prognostic factors of MB, while the effects of the brainstem location versus the cerebellum location have not been reported in a large-scale study due to, in part, the low incidence of bMB.[6–15] Herein, we use the Surveillance,

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The datasets generated during and/or analyzed during the current study are publicly available.

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Epidemiology, and End Results (SEER) database to perform a retrospective study and provide insight into the comparison of prognoses between bMB and cerebellum MB (cMB). In this study, a bMB is defined as a MB that originates from the brainstem or cerebellar vermis when it mainly grows anteriorly into the fourth ventricle and infiltrates the brainstem. A cMB is defined as a MB that originates from the cerebellar vermis or cerebellar hemisphere and that is confined to the cerebellum.

2. Method

2.1. Patients and study groups

Patient data were extracted retrospectively from the SEER*Stat Database: Incidence-SEER 18 Registries Limited Use, November 2018 Submission (1975–2016). We identified patients diagnosed with MB based on the International Classification of Diseases for Oncology, Third Edition, histology code ICD-O3:9470. A total of 2,749 MB patients were identified from the data compiled between 1975 and 2016, among which 2,336 patients (84.98%) had cMB(C71.6) and 210 patients (7.64%) had bMB(C71.7). We excluded patients without information on surgery, primary tumor site, tumor size, and receipt of chemotherapy or radiotherapy. A total of 1,589 MB patients were included in the study. Of these, 172 and 1,417 patients were diagnosed with brainstem MB and cerebellum MB, respectively. A case-control study was employed to eliminate the influence of confounders. Each bMB patient (case) was matched to a cMB patient (control) by propensity score matching. The matching factors included age, sex, tumor size, extent of metastasis, extent of surgery, radiotherapy status, and chemotherapy status, the inclusion criteria of the matched cohort was PS<0.01.

2.2. Variable classification

Demographic variables extracted from the SEER*Stat Database included age, sex and race. Clinical variables included extent of surgical resection, tumor site, tumor size, extent of metastasis, chemotherapy status, radiotherapy status, vital status and survival months. Studies have suggested that age younger than 3 years is a high-risk factor for MB patients. However, age information in the SEER database was displayed as a 5-year interval instead of a specific age. To minimize bias, age was categorized into 2 categories (<5 years old and ≥5 years old). The extent of surgical resection was categorized into gross total resection (GTR) and non-GTR (no surgery, biopsy only, subtotal resection [STR], and surgery not otherwise specified). Chemotherapy and radiotherapy protocols were not available, so chemotherapy status and radiotherapy status were defined as receipt of therapy or no therapy. Other variables included tumor size (by category: ≤3 cm or >3 cm), extent of metastasis (by category: M0 or M1~4), and vital status (dead or alive at the study endpoint).

2.3. Statistical analysis

Demographics of the matched cohort were compared with the chi-square test. A Kaplan-Meier curve was used to display the overall survival (OS) between groups, and a log-rank test was used to compare the difference in survival time. Multivariate analyses for the unmatched cohort, bMB cohort and cMB cohort were performed to investigate the possible prognostic factors of MB using a Cox proportional hazard model. The variables above were all included in the model with the "enter" method. Hazard ratios (HRs), 95% confidence intervals (95% CIs) and p values were reported. A 2-side P-value < .05 was considered statistically significant.

3. Results

3.1. Demographics of and treatment for participants

A total of 2749 MB patients were identified between 1975 and 2016, 1589 of which were included in the study. A total of 172 patients were diagnosed with brainstem MB, and 1417 patients were diagnosed with cerebellum MB (Table 1). Approximately one-quarter of the patients were younger than 5 years old in both groups (P = .350) (Fig. 1). The majority of patients were male, but the percentages were statistically different between the bMB (70.3% male patients) and cMB (62.0% male patients) groups (P = .033). Most patients had tumors 3 cm or larger in diameter in both the bMB (93.0%) and cMB (88.2%) groups (P = .060). The distant metastasis rate and radiation therapy rate were both comparable in the 2 groups (P = .530 and P = .372, respectively). However, the bMB group had a higher rate of receipt of chemotherapy than the cMB group (P < .001). For the extent of resection, there were 5 categories; STR and GTR accounted for a vast majority of cases, and no significant difference was observed between the 2 groups (P = .149). After propensity score matching, 144 pairs of patients were selected to constitute the matched cohort. Within the matched cohort, 7 covariates (age, sex, tumor size, extent of metastasis, extent of surgical resection, chemotherapy status, and radiotherapy status) were all comparable (P values ranging from 0.256 to 1.000).

3.2. cMB patients had a favorable prognosis compared with bMB patients in terms of OS.

Within the unmatched cohort, the median survival times were 111.0 ± 4.0 months and 97 ± 6.0 months for cMB and bMB, respectively. Survival analysis showed that the cMB group had an OS advantage over the bMB group in both the short term (Wilcoxon P = .009) and the long term (log-rank P < .001). Within the matched cohort, the OS advantage of the cMB group was much more significant. The median survival times were 213.0 ± 5.8 months and 96.0 ± 5.8 months for cMB and bMB, respectively. The Kaplan-Meier curve of the matched cohort showed a greater statistical difference in OS than that identified in the unmatched cohort (P < .001) (Fig. 2). The HR of the bMB group assessed by univariate Cox regression were 1.44 (95% confidence interval [CI] = 1.20–1.74) for the unmatched cohort and 8.142 (95% CI=5.98–11.08) for the matched cohort.

3.3. Prognostic factors for MB patients

A multivariate Cox proportional hazards model was built with the unmatched cohort, which revealed that predictors for MB patients included age, GTR, tumor site, radiotherapy status and chemotherapy status (Table 2). Age <5 years (versus age ≥ 5 years, HR = 0.80, 95% CI = 0.68–0.94, P = .006) and receipt of radiotherapy (versus no radiotherapy, HR = 0.80, 95% CI = 0.67–0.95, P = .011) were favorable prognostic factors, whereas GTR (versus no GTR, HR=1.18, 95%

Table 1

Patient demographics and treatment for cerebellar and brainstem medulloblastoma.

	Unmatched cohort			Matched cohort		
	Brainstem (n=172)	Cerebellar (n=1417)	*P*	Brainstem (n=144)	Cerebellar (n=144)	*P*
Age at diagnosis			.350			.684
≤4 yr old	42	302		35	38	
>4 yr old	130	1115		109	106	
Sex			.033			.897
Male	121	879		101	102	
Female	51	538		43	42	
Size			.060			1.000
<3cm	12	167		11	11	
>3cm	160	1250		133	133	
Extent of metastasis			.530			.597
M0	148	1243		124	127	
M1∼4	24	174		20	17	
Extent of resection			.149			.256
No Surgery	1	33		0	0	
Biopsy only	0	2		0	0	
Surgery, NOS	2	54		1	5	
Subtotal	66	469		52	51	
Gross Total	103	859		91	88	
Radiotherapy			.372			.597
No	30	288		17	20	
Yes	142	1129		127	124	
Chemotherapy			.001			1.000
No	25	367		2	2	
Yes	147	1050		142	142	

GTR = Gross Total Resection, NOS = Not Otherwise Specific.

CI=1.04–1.34, *P*=.011), brainstem location (versus cerebellum location, HR=1.39, 95% CI=1.15–1.68, *P*= .001) and receipt of chemotherapy (versus no chemotherapy, HR=1.87, 95% CI=1.60–2.19, *P* < .001) were unfavorable prognostic factors. Presence of metastasis exhibited a trend toward worse outcomes (*P*=.107). Sex and tumor size were not prognostic factors for MB. A separate analysis of cMB cohort showed the same prognostic factors of the unmatched cohort, but separate analysis of bMB showed chemotherapy was the only prognostic factor (Table 3).

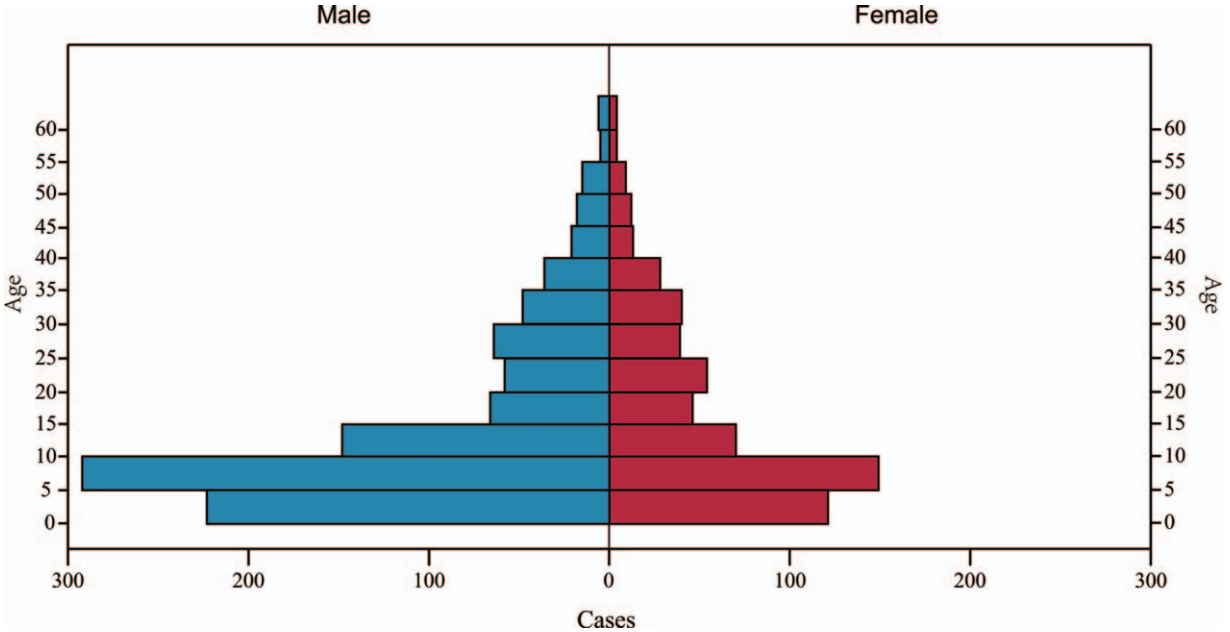

Figure 1. Age-sex plot of 1589 medulloblastoma patients included in this study. The bottom row represents the number of patients aged 0∼4 years old. The second row from the bottom represents the number of patients aged 5∼9 years old, and so forth.

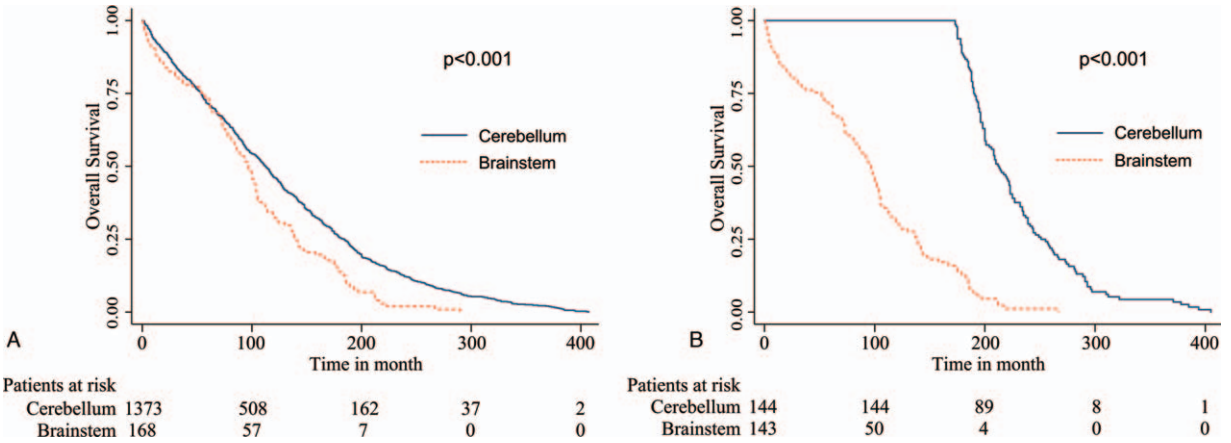

Figure 2. Kaplan-Meier curves of overall survival for patients with cerebellum medulloblastoma or brainstem medulloblastoma in unmatched cohort (A) and matched cohort (B).

Further exploration was carried out for chemotherapy status and radiotherapy status due to their opposite effects on the OS of MB patients. All patients in the unmatched cohort were divided into four groups according to chemotherapy and radiotherapy status (CRS): BLANK (neither chemotherapy nor radiotherapy), chemotherapy only, radiotherapy only (RT) and both chemotherapy and radiotherapy. Survival analysis, without adjustment for confounding factors, indicated that RT could significantly improve prognosis ($P < .001$) compared to BLANK (HR=1.81, 95% CI=1.34–2.45, $P < .001$), chemotherapy only (HR=1.97, 95% CI=1.54–2.51, $P < .001$) and both chemotherapy and radiotherapy (HR=2.07, 95% CI=1.73–2.46, $P < .001$), whereas no difference in OS was observed among these 3 groups (Fig. 3). During 1975 to 2005, the OS difference in 4 treatment groups is similar to that of the whole cohort, characterized by OS superiority of the RT group. However, during 2006 to 2016, 4 treatment groups have no OS difference, which could be interpreted as improvement of the other 3 groups (Fig. 4).

Table 2

Hazard ratios, 95% confidence intervals and *P* values of multivariate survival analysis of unmatched cohort.

Variables	HR	95%CI	Comparison group	*P*
Age				
<5 yr old	0.80	0.68–0.94	≥5 years old	.006
Sex				
male	0.89	0.79–1.01	female	.074
Extent of resection				
GTR	1.18	1.04–1.34	non-GTR	.011
Site				
brainstem	1.39	1.15–1.68	cerebellar	.001
Extent of metastasis				
M1∼4	1.17	0.97–1.43	M0	.107
Size				
≤3 cm	1.07	0.88–1.30	>3 cm	.489
Radiotherapy				
yes	0.80	0.67–0.95	no	.011
Chemotherapy				
yes	1.87	1.60–2.19	no	<.001

CI = confidence interval, HR = hazards ratio.

4. Discussion

Brainstem MB is a rare entity compared with its cerebellum counterpart. Large-scale studies on bMB have not been performed in recent decades. Herein, we report the largest cohort of patients with bMB and cMB represented by data extracted from the SEER database (1975–2016). cMB made up the vast majority of MB cases with an incidence of 84.98%, more than eleven times as high as the proportion of bMB cases (7.64%) (Table 4). This is in accordance with the view that 3-quarters of MBs are derived from the vermis cerebelli.[16] Our study uncovered a disappointing 97.0 ± 6.0 month median survival time for patients with bMB compared to the corresponding 111.0 ± 4.0 month median survival time for patients with cMB. The estimated 5- and 10-year OS for bMB were 72.4 ± 3.7% and 32.1 ± 4.2%, respectively, and the corresponding estimates for cMB were 70.9 ± 1.3% and 45.8 ± 1.6%, respectively. This is comparable to the 5-year OS reported by another similar study,[6] although it focused on comparisons between children and adults. The HR of the bMB group versus the cMB group was 1.44 and 8.14 among the unmatched and matched cohorts, respectively, demonstrating a worse prognosis for bMB than for cMB. The brainstem has numerous critical structures in a small area, which decreases the tolerance to mass effect when a tumor occurs in the brainstem or infiltrates the brainstem. Rutkowski

Table 3

Hazard ratios, 95% confidence intervals and *P* values of multivariate survival analysis of bMB cohort and cMB cohort.

	bMB cohort			cMB cohort		
	P	HR	95%CI	*P*	HR	95%CI
Age (<5 yr old)	.60	.870	0.52–1.45	.01	0.78	0.66–0.93
Sex (male)	.27	.798	0.54–1.19	.15	0.91	0.80–1.03
Extent of resection (GTR)	.98	1.01	0.69–1.46	.01	1.20	1.05–1.38
Extent of metastasis (M1∼4)	.09	1.57	0.94–2.63	.29	1.12	0.91–1.38
Size (≤3cm)	.73	0.86	0.37–1.99	.49	1.07	0.88–1.31
Radiotherapy (yes)	.08	0.54	0.27–1.07	.03	0.81	0.68–0.98
Chemotherapy (yes)	.03	2.05	1.09–3.89	0.00	1.89	1.61–2.23

bMB = brainstem medulloblastoma, CI = confidence interval, cMB = cerebellum medulloblastoma, HR = hazards ratio.

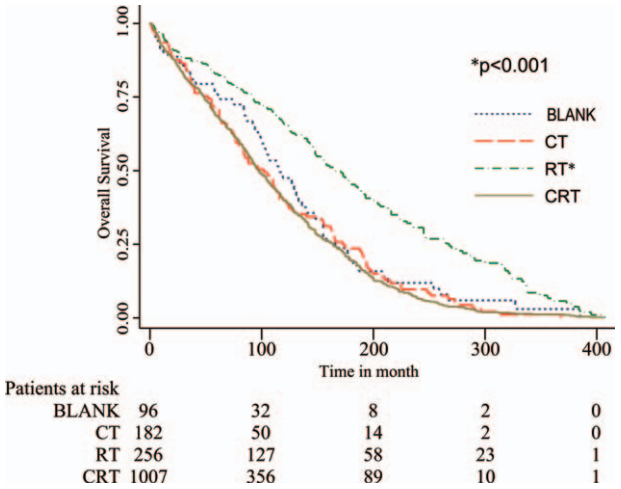

Figure 3. Kaplan-Meier curves of overall survival for patients with different chemotherapy and radiotherapy status. *means $P<.001$ for RT group vs other 3 groups.

Table 4

Frequencies and percentages of medulloblastoma in different locations.

	Frequency	Percentage
Cerebrum	6	0.22
Parietal lobe	1	0.04
Occipital lobe	3	0.11
Ventricle, NOS	77	2.80
Cerebellum, NOS	2336	84.98
Brainstem	210	7.64
Overlapping lesion of brain	11	0.40
Brain, NOS	105	3.82
Total	2749	100.00

et al[14] and Padovani et al[15] reported a better prognosis for cerebellum MBs than midline MBs. Jeswani et al[17] whose hypothesis may also apply to MB, suggested that the proximity to the brainstem could be responsible for the prognosis of cerebellum glioblastoma being worse than that of supratentorial glioblastoma. However, Packer et al[11] reported that brainstem involvement was not associated with the 3-year and 5-year event-free survival of newly diagnosed average-risk MB patients, but longer-term prognosis data were absent. Our study also revealed a similar OS at the point of 5 years; we found that the survival difference started at approximately 10 years between the 2 cohorts.

The impact of age at diagnosis on prognosis remains controversial. Packer's study[11] including patients aged 3 to 21 years found that 5-year progression-free survival (PFS) and OS did not differ between the age groups ($P=.97$). Li et al[6] also reported a similar OS between children (age>3 years) and adults. However, both studies excluded patients aged <3 years, which was considered a negative predictor for MB patients. In contrast, Lai et al[18] reported that children, especially older children, had a better outcome than adults. Our multivariate analysis revealed that age <5 years conferred a better OS, while the univariate analysis for age indicated a comparable outcome in the 2 groups ($P=.39$).

The multivariate analysis revealed that receipt of radiotherapy was a favorable predictor, whereas receipt of chemotherapy was a negative predictor for MB. The benefit of radiotherapy was obvious in patients with MB whose age was >3 years. Li et al[6] reported that receipt of radiotherapy was the only identical, favorable, significant predictor in both children and adults (HR = 0.36 and 0.47, respectively, $P<.05$). Another SEER-based study for the pediatric MB cohort drew a similar conclusion regarding radiotherapy improving survival (HR = 0.37).[13] However, the benefit of chemotherapy remains unclear.[19] A cohort of 66 adults with MB failed to show a benefit from chemotherapy for the cohort as a whole, but there was a trend for improvement in 5-year PFS from 36% to 71% and in 5-year OS from 49% to 100%.[7] Evans et al[20] compared the outcomes of radiotherapy with and without CCNU, vincristine, and prednisone in 233 MB patients and found that the outcome differences were not statistically significant. Furthermore, they reported a high rate of severe infections and hematological toxicity in the group receiving adjuvant chemotherapy, which offset the potential advantages of chemotherapy. This may be a partial reason why receipt of chemotherapy was an adverse factor in our study. The radiotherapy and chemotherapy protocol was not analyzed in this study due to the limited available data. The patients included in our study were monitored for a long time and received different

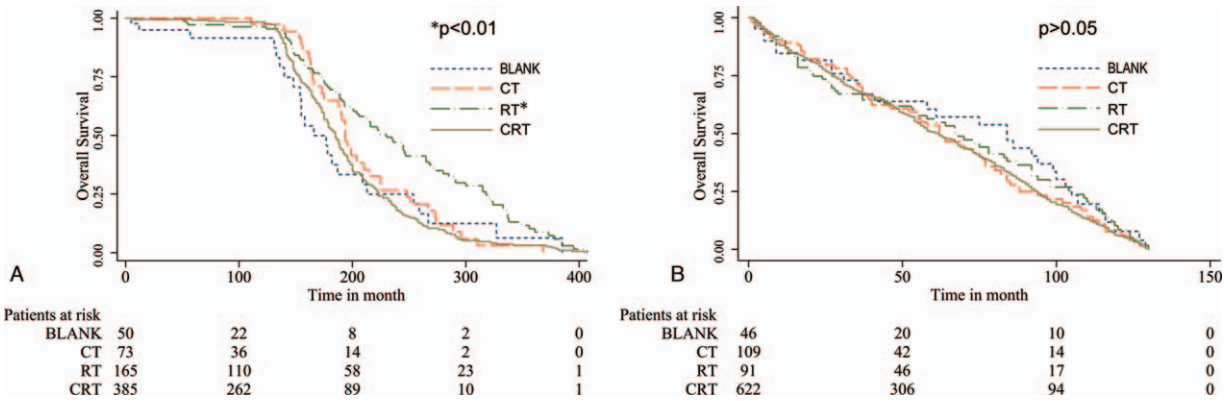

Figure 4. Kaplan-Meier curves of overall survival for patients with different chemotherapy and radiotherapy status during different time periods: (A)1975–2005 (B) 2006–2016. *means $P<.01$ for RT group vs other 3 groups. Pairwise comparsion shows P value >.05 among all groups during 2006 to 2016.

treatment regimens, as chemotherapy drugs have undergone great improvements. The result in Figure 3 was calculated when considering all the patients in different eras as a whole, and it represents the average effect. Then we did survival analysis for 4 treatment groups during different time periods. Changes in survival differences would indicate the effects of chemotherapy have improved a lot. An in vitro study showed that MB can benefit from the combination of low-dose radiotherapy and a DNA-PKcs inhibitor that radiosensitizes human MB cells.[21] Clinical studies have also suggested that chemotherapy can improve radiation sensitivity to reduce irradiation dose.[22,23]

Interestingly, GTR was associated with a higher risk than non-GTR in our multivariate analysis. Li et al[6] found that GTR was a favorable prognostic factor among the adult group, comprising only one-third of the entire cohort, consistent with the age distribution in our study. Call et al[7] reported that GTR was associated with a better 5-year OS (84 months) and 10-year OS (73 months) than STR (57 and 47 months, respectively) in a cohort of 66 adult MB patients ($P = .03$). However, these studies did not define what constituted GTR. Jiang et al[9] defined GTR as residual tumor size $<1.5\,cm^2$ or no visible tumor remaining and reported a 5-year OS of $61.4 \pm 4.8\%$ for GTR versus $16.7 \pm 8.8\%$ for STR, but the extent of surgery was not a prognostic factor in their multivariate survival analysis. Thompson et al[12] subdivided the extent of resection into GTR (no residual tumor), NTR (near-total resection, $<1.5\,cm^2$ tumor remaining), or STR ($\geq 1.5\,cm^2$ tumor remaining) based on postoperative imaging. Thompson et al[12] included 787 MB patients to study the outcome of extent of resection in 4 molecular subtypes and found that OS and PFS between GTR and NTR did not differ in all groups (WNT, SHH, group 3, and group 4). Only in patients with metastatic group 4 MB did GTR confer a benefit to PFS over STR (HR = 2.22, $P = .050$); however, their OS values were not significantly different. Thus, maximum surgical removal of MB is not recommended because there is no definitive benefit to GTR compared with NTR.[12] A reasonable explanation for the high risk of GTR in our study is that performing GTR may be associated with more surgery-related neurological sequelae, or even worse, with high mortality, especially in earlier years, when the resolution of radiology was low and microscopes were not available for neurosurgical techniques.

The presence of metastasis exhibited a trend toward worse outcomes in our multivariate analysis. This is in accordance with the multivariate analysis by Jiang et al,[9] who also reported a trend toward worse outcomes for the presence of metastasis ($P = .054$); however, in the univariate analysis, they found a significant difference in both short-term and long-term OS. Kann et al[10] failed to demonstrate a negative effect of metastasis (M1–3) on mortality by analyzing 751 MB patients from the National Cancer Database. Additionally, they found that patients with M0 disease were less likely to receive chemotherapy, which may be responsible for the similar mortality in M0 and M1–3 patients. In addition, tumor size and sex were not predictors for patients with MB, consistent with the findings of earlier studies.[6,18]

5. Limitation

To our knowledge, there is no standard therapy strategy for MB because the heterogeneous design of clinical trials has limited the evaluation of their impact on prognosis.[24] Heterogeneity still existed in our study. To acquire more details of patients, a portion of patients were excluded from the cohort, which may influence the predictors' impacts on survival time. In addition, we were interested in the survival difference between the brainstem location and the cerebellum location of MB, which together represent 92.62% of cases of MB extracted from the SEER database. Patients with MB in other sites could have a different survival pattern, thus altering the predictors' impacts on survival time despite their rarity within MB as a whole. Some detailed information was not available in the SEER database, such as the chemotherapy and radiotherapy protocols and the molecular subtype, which are known to be essential factors for risk stratification.[25,26]

6. Conclusion

This study uncovers a survival advantage for cMB patients over bMB patients. Additionally, prognostic factors include age, extent of surgical resection, radiotherapy status and chemotherapy status. Radiotherapy after surgery and rational use of chemotherapy drugs are crucial for the treatment of MB patients. Further studies on these prognostic factors are needed to provide a better therapeutic strategy for MB and improve survival time.

Author contributions

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Supervision: Yugang Jiang.
Validation: Dezhi Huang.
Writing – original draft: Qilin Qin, Dezhi Huang.
Writing – review & editing: Qilin Qin, Dezhi Huang, Yugang Jiang.

References

[1] Tarbell NJ, Friedman H, Polkinghorn WR, et al. High-risk medulloblastoma: a pediatric oncology group randomized trial of chemotherapy before or after radiation therapy (POG 9031). J Clin Oncol 2013;31:2936–41.
[2] Spreafico F, Massimino M, Gandola L, et al. Survival of adults treated for medulloblastoma using paediatric protocols. Eur J Cancer 2005;41:1304–10.
[3] Giordana MT, Schiffer P, Lanotte M, et al. Epidemiology of adult medulloblastoma. Int J Cancer 1999;80:689–92.
[4] Zhao F, Li C, Zhou Q, et al. Distinctive localization and MRI features correlate of molecular subgroups in adult medulloblastoma. J Neurooncol 2017;135:353–60.
[5] Teo WY, Shen J, Su JM, et al. Implications of tumor location on subtypes of medulloblastoma. Pediatr Blood Cancer 2013;60:1408–10.
[6] Li Q, Dai Z, Cao Y, et al. Comparing children and adults with medulloblastoma: a SEER based analysis. Oncotarget 2018;9:30189–98.
[7] Call JA, Naik M, Rodriguez FJ, et al. Long-term outcomes and role of chemotherapy in adults with newly diagnosed medulloblastoma. Am J Clin Oncol 2014;37:1–7.
[8] Goschzik T, Schwalbe EC, Hicks D, et al. Prognostic effect of whole chromosomal aberration signatures in standard-risk, non-WNT/non-SHH medulloblastoma: a retrospective, molecular analysis of the HIT-SIOP PNET 4 trial. Lancet Oncol 2018;19:1602–16.
[9] Jiang T, Zhang Y, Wang J, et al. Impact of tumor location and fourth ventricle infiltration in medulloblastoma. Acta Neurochir (Wien) 2016;158:1187–95.
[10] Kann BH, Lester-Coll NH, Park HS, et al. Adjuvant chemotherapy and overall survival in adult medulloblastoma. Neuro Oncol 2017;19:259–69.

[11] Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol 2006;24:4202–8.
[12] Thompson EM, Hielscher T, Bouffet E, et al. Prognostic value of medulloblastoma extent of resection after accounting for molecular subgroup: a retrospective integrated clinical and molecular analysis. Lancet Oncol 2016;17:484–95.
[13] Weil AG, Wang AC, Westwick HJ, et al. Survival in pediatric medulloblastoma: a population-based observational study to improve prognostication. J Neurooncol 2017;132:99–107.
[14] Rutkowski S, von Hoff K, Emser A, et al. Survival and prognostic factors of early childhood medulloblastoma: an international meta-analysis. J Clin Oncol 2010;28:4961–8.
[15] Padovani L, Sunyach MP, Perol D, et al. Common strategy for adult and pediatric medulloblastoma: a multicenter series of 253 adults. Int J Radiat Oncol Biol Phys 2007;68:433–40.
[16] Millard NE, De Braganca KC. Medulloblastoma. J Child Neurol 2016;31:1341–53.
[17] S J, M N, V F, et al. Comparison of survival between cerebellar and supratentorial glioblastoma patients: surveillance, epidemiology, and end results (SEER) analysis. Neurosurgery 2013;73:240–6.
[18] Lai R. Survival of patients with adult medulloblastoma: a population-based study. Cancer 2008;112:1568–74.
[19] Michiels EM, Schouten-Van Meeteren AY, Doz F, et al. Chemotherapy for children with medulloblastoma. Cochrane Database Syst Rev 2015;1: CD006678.
[20] Evans AE, Jenkin RD, Sposto R, et al. The treatment of medulloblastoma. Results of a prospective randomized trial of radiation therapy with and without CCNU, vincristine, and prednisone. J Neurosurg 1990;72:572–82.
[21] Tanori M, Pannicelli A, Pasquali E, et al. Cancer risk from low dose radiation in Ptch1(+)(/)(−) mice with inactive DNA repair systems: therapeutic implications for medulloblastoma. DNA Repair (Amst) 2019;74:70–9.
[22] Packer RJ, Zhou T, Holmes E, et al. Survival and secondary tumors in children with medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology Group trial A9961. Neuro Oncol 2013;15:97–103.
[23] Jakacki RI, Burger PC, Zhou T, et al. Outcome of children with metastatic medulloblastoma treated with carboplatin during craniospinal radiotherapy: a Children's Oncology Group Phase I/II study. J Clin Oncol 2012;30:2648–53.
[24] Bautista F, Fioravantti V, de Rojas T, et al. Medulloblastoma in children and adolescents: a systematic review of contemporary phase I and II clinical trials and biology update. Cancer Med 2017;6:2606–24.
[25] Northcott PA, Korshunov A, Witt H, et al. Medulloblastoma comprises four distinct molecular variants. J Clin Oncol 2011;29:1408–14.
[26] von Bueren AO, Kortmann RD, von Hoff K, et al. Treatment of children and adolescents with metastatic medulloblastoma and prognostic relevance of clinical and biologic parameters. J Clin Oncol 2016;34: 4151–60.