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Clinical Features and Prognostic Indicators for Brainstem Ependymomas : A Population-Based Retrospective Surveillance, Epidemiology, and End Results Database Analysis

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Objective : Ependymomas is a rare brain tumor. Accumulative evidence has revealed that there are differences between pediatric and adult patients. However, the clinical features and survival prognosis of pediatric and adult patients with brainstem ependymomas remain unclear.

Methods : Pediatric and adult patients with brainstem ependymomas diagnosed between 2000 and 2021 were identified from the Surveillance, Epidemiology, and End Results (SEER) database. The clinical characteristics (age, sex, race, tumor size treatment methods, etc.) of the included patients were reviewed, and the survival analysis was estimated via the Kaplan-Meier method.

Results : A total of 701 patients, including 269 pediatric patients and 432 adult patients, were identified. The median age of pediatric patients is 3.0 years old and the adult patients is 46.0 years old. Compared with adult brainstem ependymomas, pediatric patients showed a higher prevalence of anaplastic ependymoma, larger tumor size, and more frequent receipt of gross total resection (GTR), radiation, and chemotherapy (all $p<0.001$). Cox regression analysis identified that black race ($p=0.032$), and chemotherapy ($p=0.048$) are independent risk factors for pediatric brainstem ependymomas, and aging ($p<0.001$), male ($p=0.034$), and black race ($p=0.002$) for adult brainstem ependymomas. Survival analysis showed that GTR combined with radiation had significant overall survival advantage compared with other treatment regimens in both pediatric and adult cohorts ($p=0.045$ and $p=0.034$, respectively).

Conclusion : This study comprehensively investigated the clinical features and survival outcomes of patients with brainstem ependymomas, and identified several independent prognostic variables. The best recommended treatment method was GTR combined with radiation.

Key Words : Brainstem · Ependymomas · Prognosis · Survival analysis · Risk factors.

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INTRODUCTION

The ependymoma is a rare neuroepithelial tumor that accounts for only 6.9% of primary central nervous system (CNS) tumors diagnosed annually[14]. Ependymomas predominantly originate from the ependymal cells of the ventricular system and the central canal of the spinal cord[10]. Ependymomas can grow in the brain's supratentorial region, posterior cranial fossa, or spinal cord[29]. The anatomical distribution of ependymomas demonstrates a distinct age-dependent predilection, with pediatric cases predominantly arising from intracranial locations, while adult cases exhibit a higher incidence within the spinal cord[12,35].

Posterior cranial fossa is located in the lower posterior part of the cranial cavity, and includes important structures such as brainstem, fourth ventricle, and cerebellum. Posterior cranial fossa is the most common location for pediatric ependymomas[12]. Given the anatomical complexity of this region, tumors in this location can exert profound and multifaceted effects on the patient's neurological and systemic functions. According to the World Health Organization (WHO) 2021 classifications of CNS tumors, posterior cranial fossa ependymomas are divided into posterior fossa group A (PFA) and posterior fossa group B (PFB) ependymomas based on the methylation group, and the WHO grading is II/III[16].

Brainstem is the most important structure in the posterior cranial fossa and even in the human body. To date, our current understanding of brainstem ependymomas is still insufficient. There are also differences between children and adults with brainstem ependymomas. The Surveillance, Epidemiology, and End Results (SEER) database contains clinical data on brainstem ependymomas collected over the past two decades. Therefore, we conducted a comprehensive retrospective study utilizing the SEER database to systematically analyze the clinical features and prognostic indicators for pediatric and adult brainstem ependymomas.

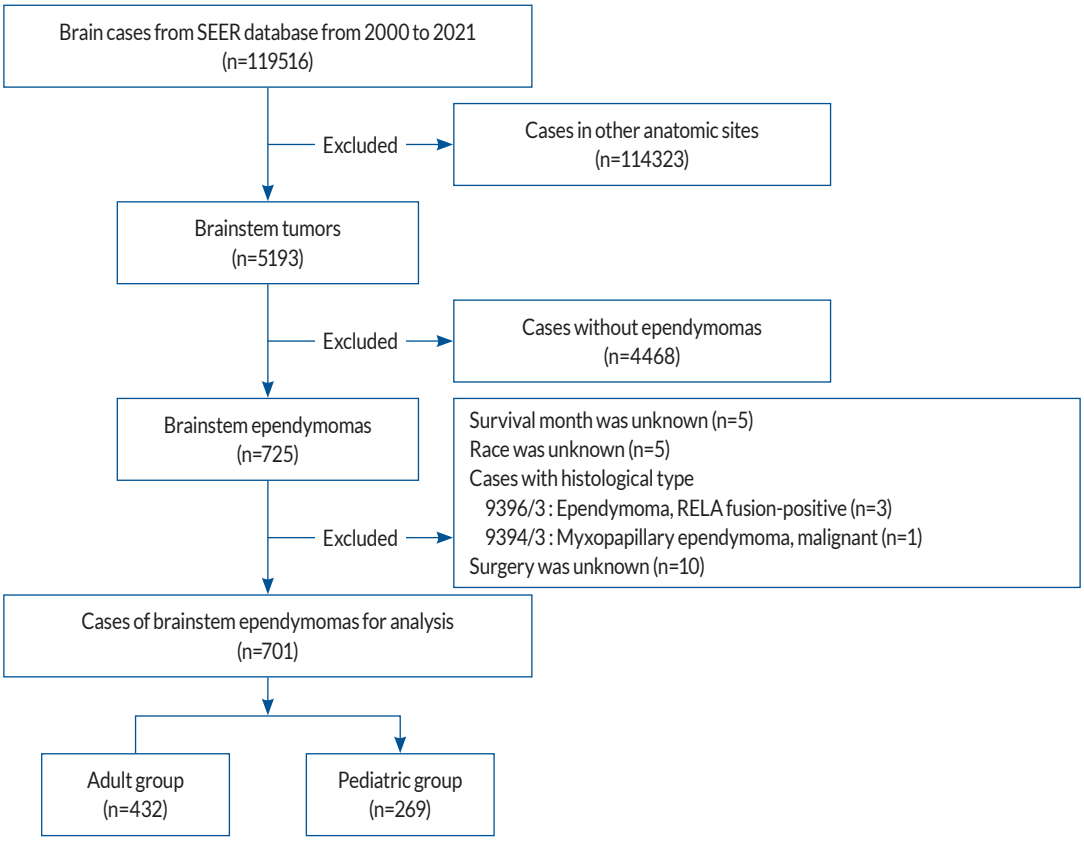

Fig. 1. Flow chart of patient selection. SEER : Surveillance, Epidemiology, and End Results, RELA : V-rel avian reticuloendotheliosis viral oncogene homolog A.

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MATERIALS AND METHODS

This study did not require review by the Ethics Committee of West China Hospital because the SEER database is publicly and freely available.

Study subjects

The SEER (17 registries) database was used for analysis and accessed through SEER*Stat (version 8.3.9; National Cancer Institute, Bethesda, MD, USA). The SEER program, established by the National Cancer Institute, is a population-based cancer registry that covers approximately 28% of the American population. The SEER database contains comprehensive data on pa-

Table 1. Summary of clinical features and treatments of brainstem ependymomas

Variable	Adults (n=432)	Children (n=269)	Total (n=701)	*p*-value
Age (years)	46.0 (18.0, 85.0)	3.0 (0.0, 17.0)	28.0 (0.0, 85.0)	<0.001
Sex				0.481
Male	240 (55.6)	157 (58.4)	397 (56.6)	
Female	192 (44.4)	112 (41.6)	304 (43.4)	
Year of diagnosis				0.722
2000–2007	145 (33.6)	98 (36.4)	243 (34.7)	
2008–2015	158 (36.6)	96 (35.7)	254 (36.2)	
2016–2021	129 (29.9)	75 (27.9)	204 (29.1)	
Race				0.644
White	361 (83.6)	224 (83.3)	585 (83.5)	
Black	41 (9.5)	30 (11.2)	71 (10.1)	
Other	30 (6.9)	15 (5.6)	45 (6.4)	
ICD.O.3 stage				<0.001
Ependymoma, NOS	390 (90.3)	147 (54.6)	537 (76.6)	
Ependymoma, anaplastic	34 (7.9)	120 (44.6)	154 (22.0)	
Papillary ependymoma, NOS	8 (1.9)	2 (0.7)	10 (1.4)	
Tumor size				<0.001
≤30 mm	143 (33.1)	45 (16.7)	188 (26.8)	
>30 mm	168 (38.9)	182 (68.4)	346 (50.2)	
Unknown	121 (28.0)	40 (14.9)	161 (23.0)	
GTR performed				<0.001
No	240 (55.6)	100 (37.2)	340 (48.5)	
Yes	192 (44.4)	169 (62.8)	361 (51.5)	
Radiation				<0.001
No	237 (54.9)	53 (19.7)	290 (41.4)	
Yes	195 (45.1)	216 (80.3)	411 (58.6)	
Chemotherapy				<0.001
No	424 (98.1)	175 (65.1)	599 (85.4)	
Yes	8 (1.9)	94 (34.9)	102 (14.6)	
Status				0.386
Alive	308 (71.3)	200 (74.3)	508 (72.5)	
Dead	124 (28.7)	69 (25.7)	193 (27.5)	

Values are presented as median (min, max) or number (%). ICD.O.3 : Third edition of the International Classification of Diseases for Oncology, NOS : not otherwise specified, GTR : gross total resection

tients with ependymomas, such as demographic information (age, sex, race), tumor characteristics (site, pathology), and treatment details.

Patients with brainstem ependymomas were identified based on the following inclusion criteria : patients diagnosed with brainstem ependymomas between 2000 and 2021. Patients with incomplete clinical features or survival information were excluded. Histological types were identified according to the Third edition of the International Classification of Diseases for Oncology (ICD.O.3) grading criteria. Eventually, we compiled a population-based sample of 269 pediatric patients (age at diagnosis <18 years) and 432 adult patients (age at diagnosis ≥18 years). The specific data screening process was shown in Fig. 1.

Table 2. Summary of clinical features and treatments of children with brainstem ependymomas

Variable	Age <4 years (n=136)	Age ≥4 years (n=133)	Total (n=269)	*p*-value
Age (years)	2.0 (0.0, 3.0)	9.0 (4.0, 17.0)	3.0 (0.0, 17.0)	<0.001
Sex				0.216
Male	74 (54.4)	83 (62.4)	157 (58.4)	
Female	62 (45.6)	50 (37.6)	112 (41.6)	
Year of diagnosis				0.725
2000–2007	52 (38.2)	46 (34.6)	98 (36.4)	
2008–2015	49 (36.0)	47 (35.3)	96 (35.7)	
2016–2021	35 (25.7)	40 (30.1)	75 (27.9)	
Race				0.879
White	114 (83.8)	110 (82.7)	224 (83.3)	
Black	14 (10.3)	16 (12.0)	30 (11.2)	
Other	8 (5.9)	7 (5.3)	15 (5.6)	
ICD.O.3 stage				0.001
Ependymoma, NOS	62 (45.6)	85 (63.9)	147 (54.6)	
Ependymoma, anaplastic	74 (54.4)	46 (34.6)	120 (44.6)	
Papillary ependymoma, NOS	0 (0.0)	2 (1.5)	2 (0.7)	
Tumor size				0.132
≤30 mm	17 (12.5)	28 (21.1)	45 (16.7)	
>30 mm	100 (73.5)	84 (63.2)	184 (68.4)	
Unknown	19 (14.0)	21 (15.8)	40 (14.9)	
GTR performed				0.380
No	47 (34.6)	53 (39.8)	100 (37.2)	
Yes	89 (65.4)	80 (60.2)	169 (62.8)	
Radiation				0.032
No	34 (25.0)	19 (14.3)	53 (19.7)	
Yes	102 (75.0)	114 (85.7)	216 (80.3)	
Chemotherapy				0.005
No	77 (56.6)	98 (73.7)	175 (65.1)	
Yes	59 (43.4)	35 (26.3)	94 (34.9)	
Status				
Alive	100 (73.5)	100 (75.2)	200 (74.3)	0.781
Dead	36 (26.5)	33 (24.8)	69 (25.7)	

Values are presented as median (min, max) or number (%). ICD.O.3 : Third edition of the International Classification of Diseases for Oncology, NOS : not otherwise specified, GTR : gross total resection

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Study variables and survival analyses

Patients were categorized into two groups : pediatric and adult. The following variables were retrieved from the SEER database : 1) demographic information : age, sex, race; 2) tumor characteristics : tumor size, behavior (ependymoma, not otherwise specified [NOS] [9391/3]; papillary ependymoma, NOS [9393/3]; ependymoma, anaplastic [9392/3]); 3) treatment methods : extent of surgical resection, radiation, chemotherapy; 4) survival : overall survival (OS) time (OS was defined as the time interval from tumor diagnosis to death); and 5) year of diagnosis.

The survival prognosis of pediatric and adult patients was evaluated through survival analyses. Firstly, we conducted subgroup analyses to explore the survival prognosis of pediatric

Table 3. Summary of clinical features and treatments of adults with brainstem ependymomas

Variable	Age 18–50 years (n=255)	Age >50 years (n=177)	Total (n=432)	*p*-value
Age (years)	34.0 (18.0, 50.0)	62.0 (51.0, 85.0)	46.0 (18.0, 85.0)	<0.001
Sex				0.008
Male	128 (50.2)	112 (63.3)	240 (55.6)	
Female	127 (49.8)	65 (36.7)	192 (44.4)	
Year of diagnosis				0.442
2000–2007	88 (34.5)	57 (32.2)	145 (33.6)	
2008–2015	87 (34.1)	71 (40.1)	158 (36.6)	
2016–2021	80 (31.4)	49 (27.7)	129 (29.9)	
Race				0.453
White	211 (82.7)	150 (84.7)	361 (83.6)	
Black	23 (9.0)	18 (10.2)	41 (9.5)	
Other	21 (8.2)	9 (5.1)	30 (6.9)	
ICD.O.3 stage				<0.001
Ependymoma, NOS	219 (85.9)	171 (96.6)	390 (90.3)	
Ependymoma, anaplastic	29 (11.4)	5 (2.8)	34 (7.9)	
Papillary ependymoma, NOS	7 (2.7)	1 (0.6)	8 (1.9)	
Tumor size				0.025
≤30 mm	74 (29.0)	69 (39.0)	143 (33.1)	
>30 mm	112 (43.9)	56 (31.6)	168 (38.9)	
Unknown	69 (27.1)	52 (29.4)	121 (28.0)	
GTR performed				0.095
No	133 (52.2)	107 (60.5)	240 (55.6)	
Yes	122 (47.8)	70 (39.5)	192 (44.4)	
Radiation				<0.001
No	122 (47.8)	115 (65.0)	237 (54.9)	
Yes	133 (52.2)	62 (35.0)	195 (45.1)	
Chemotherapy				0.722
No	251 (98.4)	173 (97.7)	424 (98.1)	
Yes	4 (1.6)	4 (2.3)	8 (1.9)	
Status				<0.001
Alive	211 (82.7)	97 (54.8)	308 (71.3)	
Dead	44 (17.3)	80 (45.2)	124 (28.7)	

Values are presented as median (min, max) or number (%). ICD.O.3 : Third edition of the International Classification of Diseases for Oncology, NOS : not otherwise specified, GTR : gross total resection

and adult patients with various demographic and clinical features. Secondly, we evaluated the survival benefits associated with different treatment methods (surgery, radiation, and chemotherapy).

Statistical analysis

Categorical variables, including sex, race, year of diagnosis, ICD.O.3, tumor size, surgery, radiation, and chemotherapy, were compared using the chi-squared test. Continuous variable, including age, is summarized as median (with minimum and maximum values). The Wilcoxon rank sum test was used to compare continuous variables. Survival analyses were performed using the Kaplan-Meier method, and comparisons were made using the log-rank test. Statistical analyses were conducted using R software (version 4.4.3; R Rstudio, Boston, MA, USA), with a significance level set at $p<0.05$. Additionally, we calculated the annual percentage of ependymoma cases diagnosed in pediatric and adult patients to identify trends over the study period.

RESULTS

Clinical characteristics of patients with brainstem ependymomas

In this cohort, 701 patients with brainstem ependymomas were enrolled. The clinical characteristics of patients with brainstem ependymomas were presented in Table 1. Among all patients, the median age of patients was 28.0 years old. The children patient was 3.0 years old and the adult was 46.0 years old. Brainstem ependymomas had a greater impact on males (56.6% vs. 43.4%). The same results were observed in both pediatric and adult patients. White people were the ethnic group with the highest proportion of brainstem ependymomas (83.5%), followed by black people (10.1%). The same results were observed in both pediatric and adult patients. There was no significant difference in the number of cases between different years. The 50.2% of the population had tumors larger than 30 mm in size. Overall, the tumor size in children was larger than that in adult patients. According to the WHO 2016 classification, the most common tumor behavior was ependymoma, NOS (76.6%), followed by ependymoma, anaplastic which was WHO grade III (22.0%). Papillary ependymoma, NOS that was WHO grade II accounted for 1.4%. Overall, high-grade ependymomas were more common in pediatric patients. The 51.5% patients accepted gross total resection (GTR), and 58.6% patients accepted radiation. The proportion of patients receiving chemotherapy was relatively small (14.6%). Children tended to receive more surgery, radiation, and chemotherapy (Table 1).

There was a total of 269 pediatric patients. Among them, 136 children were under 4 years old and 133 children over 4 years old. The median age of all pediatric patients was 3 years old. Male patients accounted for 58.4%, while female patients accounted for 41.6%. The most common patient race was white (83.3%), followed by black (11.2%). There was no significant difference in these demographic characteristics between the two patient populations. The most common pathological type of brainstem ependymomas in children was ependymoma, NOS (54.6%), followed by ependymoma, anaplastic (44.6%), and papillary ependymoma, NOS (0.7%). Overall, younger children patients tended to be ependymoma, anaplastic, and the tumor size is larger. The 62.8% of the patients received GTR, 80.3% re-

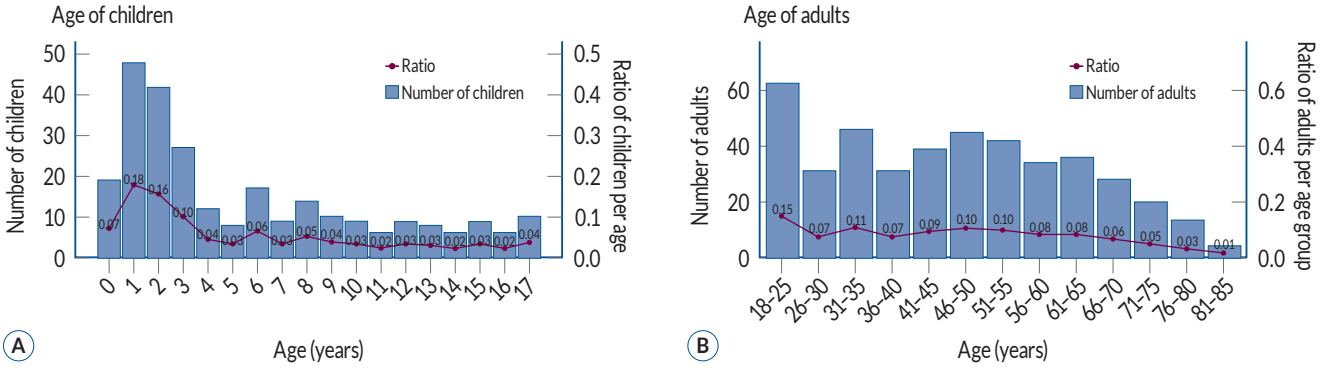

Fig. 2. Proportion and trends in pediatric (A) and adult (B) patients with brainstem ependymomas diagnosed annually from 2000–2021 on the basis of the SEER (Surveillance, Epidemiology, and End Results) database.

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ceived radiation, and 34.9% received chemotherapy. There was no significant difference in GTR treatment between the two groups of pediatric patients. However, older pediatric patients had a higher proportion receiving radiation and a lower proportion receiving chemotherapy (Table 2).

There was a total of 432 adult patients. Among them, 255 adults were from 15–50 years old and 177 adults over 50 years old. The median age of all adult patients was 46 years old. Male patients accounted for 55.6%, while female patients accounted for 44.4%. Brainstem ependymomas tended to be in older male patients. The most common patient race was also white (83.6%), followed by black (9.5%). There was no significant difference in the number of adult patients between different years. The most common pathological type of brainstem ependymomas in adult was ependymoma, NOS (90.63%), followed by ependymoma, anaplastic (7.9%), and papillary ependymoma, NOS (1.9%). Overall, younger adult patients tended to be ependymoma, anaplastic, and the tumor size was larger. The 44.4% of adult patients received GTR, 45.1% received radiation, and only 1.9% received chemotherapy. Younger adult patients had a higher proportion receiving radiation. Older adult patients had a higher proportion of deaths in this study (Table 3).

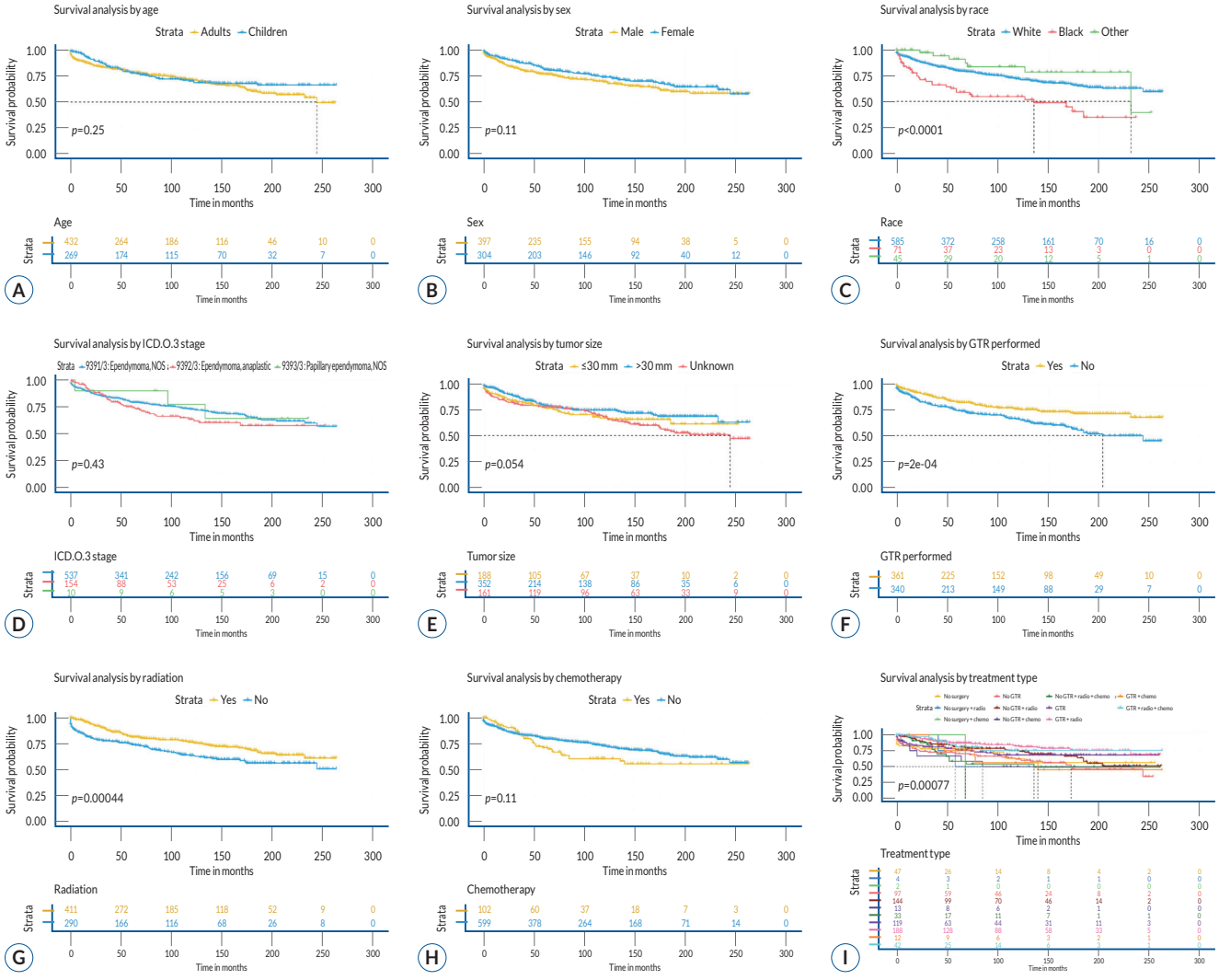

Fig. 3. Survival analyses of brainstem ependymomas. A : Survival analysis between pediatric and adult patients. B : Between different male and female. C : Among white, black, and other race. D : Among ependymoma, ependymoma, anaplastic, and papillary ependymoma, NOS. E : among ≤30 mm, >30 mm, unknown. F : Between GTR and not GTR. G : Between radiation and not radiation. H : Between chemotherapy and not chemotherapy. I : Among different treatment methods. ICD.O.3 : Third edition of the International Classification of Diseases for Oncology, NOS : not otherwise specified, GTR : gross total resection.

Proportion and trends of brainstem ependymomas

In this cohort, 269 pediatric patients and 432 adult patients with brainstem ependymomas were enrolled. We investigated the proportion and trends of pediatric and adult patients per year. According to the SEER database, the younger pediatric patients had higher proportion of brainstem ependymomas, especially in children under 4 years old. Among them, 1-year-old children accounted for the highest proportion with 18%. In adult patients, the older adult patients had fewer proportion of brainstem ependymomas. The proportion of patients in the 18–25 age group is the highest with 15% (Fig. 2).

Survival outcomes of patients with brainstem ependymomas

First, we performed a survival analysis of all patients, and found age and sex had no significant effect on survival prognosis. However, patients with black race had a worse prognosis (p<0.001). No survival differences were found among different pathological types and tumor size. Both surgery and radiotherapy had shown survival benefits (p<0.001). Chemotherapy had no impact on survival. Overall, the best recommended treatment method was GTR combined with radiation (p<0.05) (Fig. 3).

Among all pediatric patients, we found that age, sex, ICD.O.3,

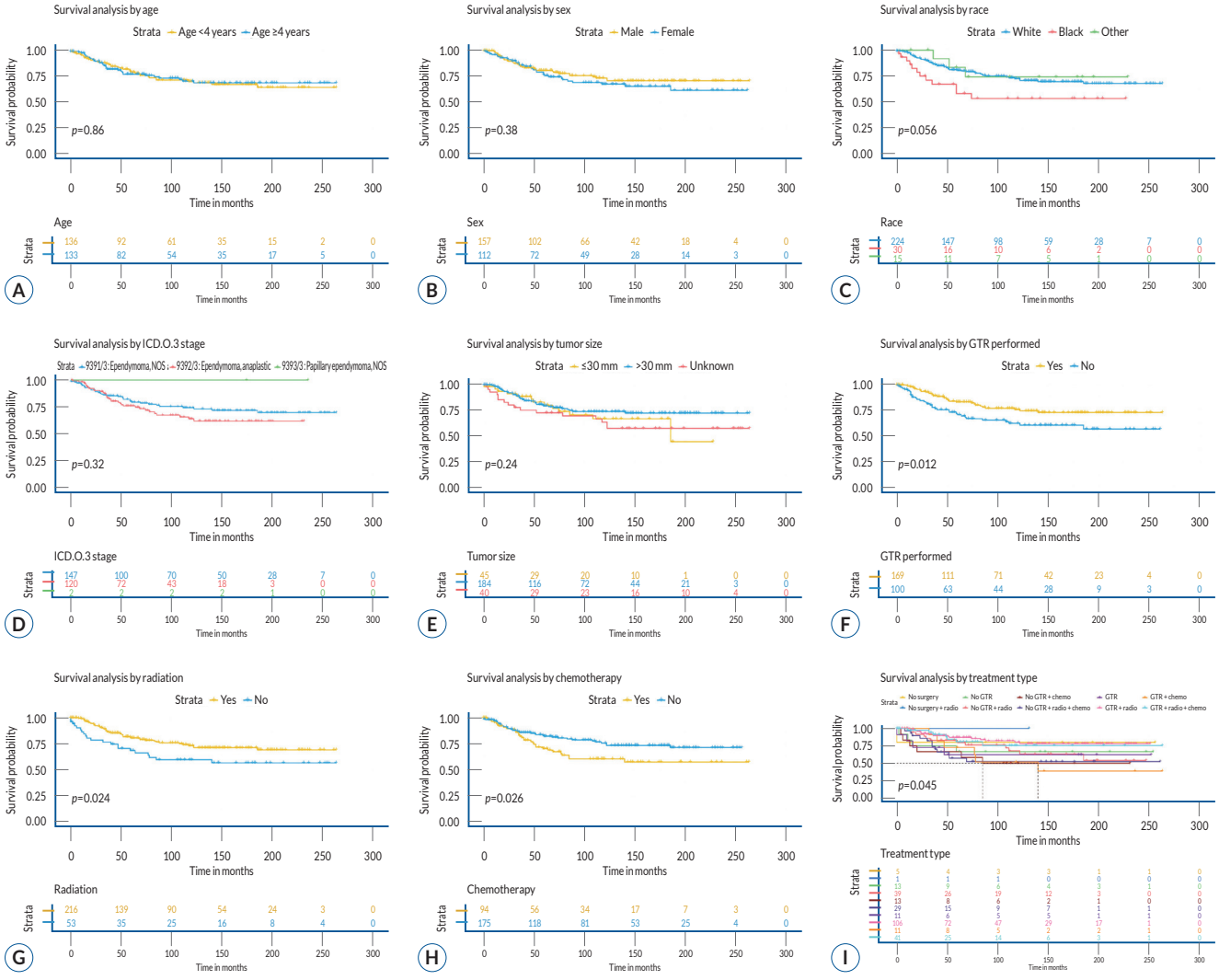

Fig. 4. Survival analyses of pediatric patients with brainstem ependymomas. A : Survival analysis between <4 years old and ≥4 years old. B : Between different male and female. C : Among white, black, and other race. D : Among ependymoma, ependymoma, anaplastic, and papillary ependymoma, NOS. E : Among ≤30 mm, >30 mm, unknown. F : Between GTR and not GTR. G : Between radiation and not radiation. H : Between chemotherapy and not chemotherapy. I : Among different treatment methods. ICD.O.3 : Third edition of the International Classification of Diseases for Oncology, NOS : not otherwise specified, GTR : gross total resection.

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and tumor size had no significant effect on survival prognosis. Regarding the impact of race on survival outcomes, black patients demonstrated significantly poorer prognosis and were subsequently identified as an independent risk factor in the cox regression analysis. Both surgery and radiotherapy had shown survival benefits (p<0.05). However, chemotherapy had a worse impact on survival (p<0.05). The best recommended treatment method was also GTR combined with radiation (p<0.05) (Fig. 4).

Among all adult patients, patients over 50 years old, male patients, and black race had a worse prognosis (p<0.01). ICD.O.3 and tumor size had no significant effect on survival prognosis. Both surgery and radiotherapy had shown survival benefits (p<0.05). Chemotherapy had no impact on survival. The best recommended treatment method was also GTR combined with radiotherapy (p<0.05) (Fig. 5).

Prognostic factors associated with survival

In the pediatric brainstem ependymomas cohort, univariate cox regression analysis revealed a significant difference in OS between subgroups of several variables, including race, GTR, radiation, and chemotherapy. A multivariate cox regression analysis further showed race, and chemotherapy were the inde-

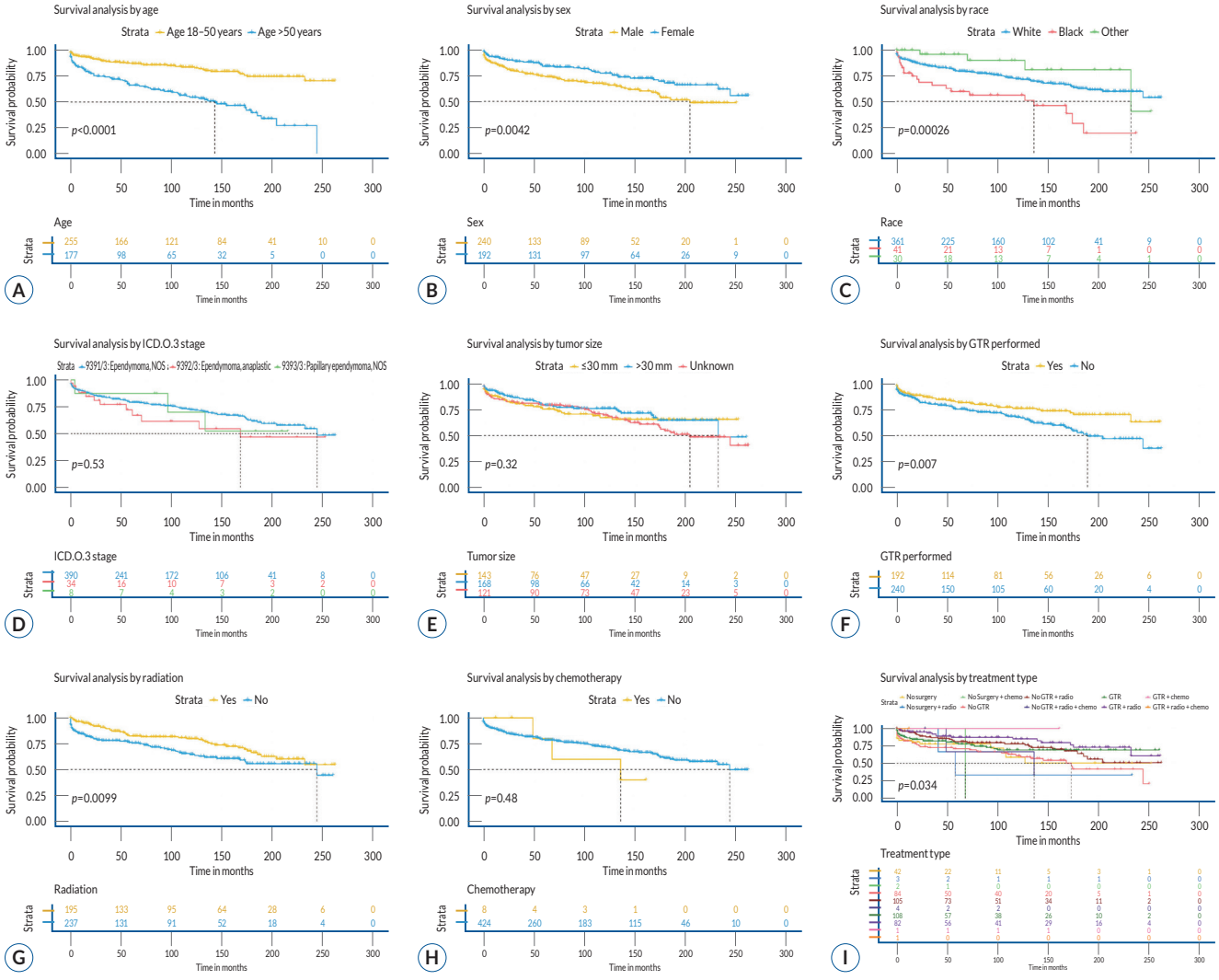

Fig. 5. Survival analyses of adult patients with brainstem ependymomas. A : Survival analysis between 18–50 years old and >50 years old. B : Between different male and female. C : Among white, black, and other race. D : Among ependymoma, ependymoma, anaplastic, and papillary ependymoma, NOS. E : Among ≤30 mm, >30 mm, unknown. F : Between GTR and not GTR. G : Between radiation and not radiation. H : Between chemotherapy and not chemotherapy. I : Among different treatment methods. ICD.O.3 : Third edition of the International Classification of Diseases for Oncology, NOS : not otherwise specified, GTR : gross total resection.

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Table 4. Univariate and multivariate cox regression analysis for brainstem ependymomas

Variable	Pediatric brainstem ependymomas				Adult brainstem ependymomas			
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age								
<4 years/18–50 years	-	-			-	-		
≥4 years/>50 years	0.960 (0.598, 1.540)	0.864			3.386 (2.333, 4.913)	<0.001	2.835 (1.192, 4.162)	<0.001
Sex								
Male	-	-			-	-		
Female	1.234 (0.769, 1.980)	0.384			0.588 (0.407, 0.849)	0.005	0.668 (0.459, 0.971)	0.034
Race								
White	-	-			-	-		
Black	2.058 (1.101, 3.848)	0.024	2.010 (1.062, 3.806]	0.032	2.342 (1.460, 3.758)	<0.001	2.116 (1.317, 3.401)	0.002
Other	0.785 (0.245, 2.510)	0.683	0.795 (0.245, 2.579)	0.702	0.495 (0.182, 1.344)	0.168	0.566 (0.208, 1.540)	0.265
Year of diagnosis								
2000–2007	-	-			-	-		
2008–2015	0.737 (0.440, 1.233)	0.245			1.098 (0.736, 1.636)	0.648		
2016–2021	0.609 (0.276, 1.342)	0.219			0.641 (0.339, 1.212)	0.171		
ICD.O.3 stage								
Ependymoma, NOS	-	-			-	-		
Ependymoma, anaplastic	1.363 (0.848, 2.191)	0.200			1.404 (0.773, 2.552)	0.265		
Papillary ependymoma, NOS	-	-			1.064 (0.338, 3.354)	0.916		
Tumor size								
≤30 mm	-	-			-	-		
>30 mm	1.285 (0.687, 2.404)	0.432			1.225 (0.781, 1.921)	0.377		
Unknown	1.631 (0.912, 2.916)	0.099			1.385 (0.905, 2.118)	0.133		
GTR performed								
Yes	-	-			-	-		
No	1.820 (1.135, 2.919)	0.013	1.619 (0.989, 2.648)	0.055	1.666 (1.146, 2.424)	0.008	1.404 (0.961, 2.052)	0.080
Radiation								
No	-	-			-	-		
Yes	0.559 (0.334, 0.933)	0.026	0.746 (0.430, 1.294)	0.297	0.622 (0.433, 0.893)	0.010	0.720 (0.498, 1.042)	0.081
Chemotherapy								
No	-	-			-	-		
Yes	1.704 (1.059, 2.741)	0.028	1.627 (1.003, 2.639)	0.048	1.499 (0.476, 4.723)	0.489		

HR : hazard ratio, CI : confidence interval, ICD.O.3 : Third edition of the International Classification of Diseases for Oncology, NOS : not otherwise specified, GTR : gross total resection

pendent prognostic factors. In the adult brainstem ependymomas cohort, a significant difference in OS between subgroups of several variables, including age, sex, race, GTR, and radiation, had been found through univariate cox regression analysis. The multivariate cox regression analysis identified that age, sex, and race were independent prognostic factors (Table 4).

DISCUSSION

Ependymomas are rare CNS tumors. There are many differences between pediatric and adult patients, such as tumor location, tumor type, and prognosis[29]. Therefore, it is very important to discuss pediatric and adult ependymomas separately. Recently, a study reported the clinical features of brainstem ependymomas[11]. However, the investigation did not stratify the analysis between pediatric and adult cohorts. To address this limitation, our study analysed the pediatric and adult patients with brainstem ependymoma separately.

In this population-based study, 269 pediatric patients and 432 adult patients with brainstem ependymomas were enrolled. According to previous research reports, posterior cranial fossa was the most common location for pediatric ependymomas[12]. However, more adult patients were recorded in this study. It is unclear whether it is caused by the special part of the brainstem, and further research and exploration are needed. The median age of pediatric patient was 3.0 years old and the adult was 46.0 years old. Previous studies reported that the average age of diagnosis for adults with ependymomas was 45 years, while the average age of diagnosis for children with posterior fossa ependymomas was 5 years[17]. The average age of children with brainstem ependymomas was even younger. Brainstem ependymomas had a greater impact on males which are observed in both pediatric and adult patients. This is consistent with previous research findings[23]. The highest proportion of race was white in both pediatric and adult patients. According to a prior study, childhood ependymomas were less common in African Americans and Native Americans, whereas a greater degree of European genetic ancestry was related to an increased risk of ependymomas[38].

The tumor size in children was larger than that in adult patients. And meanwhile, high-grade ependymomas were more common in pediatric patients. Compared to patients with PFB, those with PFA are younger, and are more likely to experience recurrence, metastasis at recurrence, and death[37]. This indicates that posterior fossa ependymomas in children may have a higher degree of malignancy. In our study, pediatric patients tended to receive more surgery, radiation, and chemotherapy. When dealing with pediatric patients, treatments may be more comprehensive.

Previous study reported that ependymomas had two distributional peaks (0–4 and 55–59 years of age)[13]. We also found that children under the age of 4 accounted for 50% of all pediatric patients. Interestingly, the number of adult cases gradually decreased as age increases. Therefore, we further analyzed the different age groups in pediatric and adult patients separately. Among all pediatric patients, we found that younger children patients tended to be ependymoma, anaplastic, and the tumor size was larger. This suggests that the younger the age, the more malignant the tumor may be. Older pediatric patients had a higher proportion receiving radiation and a lower proportion receiving chemotherapy. For children over 18 months, they are required to receive post-operative radiation[13]. The brain is at risk during radiation because of its toxicity, particularly in younger children[21,28]. Alternative adjuvant therapy such as chemotherapy is recommended for younger pediatric patients[33]. This may be the reason for the above phenomenon. Among adult patients, younger adult patients tended to be ependymoma, anaplastic, and the tumor size was larger. High grade ependymomas may be more common in younger adult patients. There was no significant difference in GTR treatment and chemotherapy between the two groups of adult patients. However, younger adult patients had a higher proportion receiving radiation. Which may be associated with the higher proportion of high-grade tumors in younger adult patients.

Pediatric patients generally have worse prognoses than adults[29]. However, we did not observe the same outcome in our study. We speculate that this may be related to the special area of the brainstem. In terms of demographics, adult patients over 50 years old, male, and black individuals exhibit poorer prognosis ($p<0.01$). However, in pediatric patients, we found that age and gender have no effect on prognosis. Black patients exhibited poorer prognosis, and black race was also identified as an independent risk factor within the pediatric cohort. Aging and cancer have a very important relationship[20]. Among multiple types of cancer, elderly patients exhibit poorer prognosis[6,36]. Accumulating evidence indicate that ependymoma mortality risk may follow a bimodal distribution, peaking in both pediat-

ric and geriatric populations[7,25-27]. Previous studies have reported that ependymoma patients aged ≥60 years face more than fourfold higher mortality risk compared to those aged 18–59 years[2]. However, the exact underlying mechanisms remain unclear. Notably, age-related alterations, including cognitive decline, endocrine changes, and increased comorbidity burden (e.g., diabetes and cardiovascular diseases), may interact with conventional prognostic factors, thereby modifying survival probabilities[2,4]. And meanwhile, the shorter life expectancy in older individuals is also considered. This finding highlights the imperative for future investigations specifically targeting elderly ependymoma patients.

Gender significantly impacts ependymoma patient prognosis. A pooled analysis across all age groups identified male as an independent predictor of poorer outcomes[27]. Age-stratified analyses revealed male as a significant risk factor exclusively in pediatric group, with no prognostic effect observed in adults[7]. Notably, our study further reported an age-dependent sex effect in the prognosis of brainstem ependymomas. While no sex-based survival difference emerged in pediatric cohorts, adult male patients demonstrated significantly worse prognosis. The underlying mechanisms remain unclear. Whether attributable to brainstem-specific pathophysiology or other factors requires further investigation. Race has a significant impact on survival prognosis. Compared to white people, African American patients have poor prognosis[1]. This may be associated with household income, educational attainment, and health care[31]. The pathological type of tumors is an important factor affecting prognosis. Although we did not observe statistical differences in the survival analysis of different pathological types in both pediatric and adult patients, it is evident that the prognosis of ependymoma, anaplastic was worse. Besides, we did not observe the impact of tumor size on survival prognosis in both pediatric and adult patients.

Surgery and radiation are the main treatment options for pediatric and adult ependymomas[15,18,28,39]. GTR has been identified to be associated with better prognosis for ependymomas[19]. In patients with cerebral ependymomas, the advantages of postoperative radiation also have been shown in survival rates[15]. In our study, we found that surgery, especially GTR, and radiation, was beneficial for the survival of both pediatric and adult patients. The role of chemotherapy in the management of ependymomas remains unclear. Multiple retrospective studies analyzing the efficacy of chemotherapy in cohorts of pediatric or adult patients have failed to demonstrate a survival benefit[8,9,22,24]. Overall, the role of chemotherapy is limited in treating ependymomas, particularly in the pediatric patients[29]. In our study, we are the first to report that chemotherapy is a risk factor for pediatric patients with brainstem ependymomas. This may be related to the unique location of brainstem ependymomas. There are genetic differences between supratentorial and infratentorial ependymomas, which may influence their biological behavior[3,30,32]. Previous studies have reported that, compared to supratentorial ependymomas in children, infratentorial ependymomas respond poorly to chemotherapy and may even exhibit disease progression during treatment[34]. However, the exact mechanisms remain unclear and warrant further in-depth research in the future. Through combination therapy analysis, we found that GTR combined with radiation was the best treatment option for both pediatric and adult patients. When GTR proves unattainable, maximal safe tumor debulking followed by adjuvant radiation demonstrates significant therapeutic efficacy.

Our study also has some limitations. Firstly, according to the latest classification by WHO in 2021, posterior fossa ependymomas are divided into PFA group and PFB group, but unfortunately, this information is currently not available in the SEER database. Patients in the PFA group are younger, and the tumors may be more malignant[37]. Secondly, some important information, including tumor specific location, treatment details, is lacking. Tumor location is associated with the survival prognosis, and the tumor in the midbrain indicates a better prognosis[5]. Thirdly, we only used public data for analysis, lacking real-world data for validation. Fourthly, retrospective studies utilizing large databases inevitably face potential selection bias, information bias, and other limitations. Additionally, the limitations in database-derived data collection may preclude comprehensive adjustment for potential confounding variables.

CONCLUSION

In the SEER-based population analysis, this study comprehensively investigated the clinical features and survival outcomes of pediatric and adult brainstem ependymomas. We have identified that black and chemotherapy are independent risk factors for pediatric brainstem ependymomas, and age over 50 years, male, and black for adult brainstem ependymo-

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mas. Overall, there is a significant difference between pediatric patients and adult patients. The best recommended treatment method is surgery combined with radiation.

AUTHORS' DECLARATION

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Informed consent

This type of study does not require informed consent.

Author contributions

Conceptualization : XN; Data curation : RZ, CZ, XN; Formal analysis : RZ, CZ; Funding acquisition : YR, XN; Methodology : RZ, CZ, XN; Project administration : XN; Visualization : RZ, CZ, GJ; Writing - original draft : RZ, CZ, GJ; Writing - review & editing : YR, YZ, XN

Data sharing

None

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