Original Article

Treatments associated with all-cause mortality among children with primary brain and central nervous system tumors: a retrospective cohort study from the SEER database

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Background: Evidence on treatment modalities and survival in childhood primary brain and central nervous system (CNS) tumors remains contradictory, with previous studies often lacking sufficient patient cohort sizes to assess the differences in histological subtypes. This cohort study based on a large population investigated the effects of various treatments on the mortality of patients with different histological types of primary brain and CNS tumors from the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: Data of demography, primary tumor site, histology, tumor grade and treatments from all pediatric patients with primary brain and CNS tumors were extracted in this retrospective cohort. The outcomes were overall, 1-, 5-, and 10-year all-cause mortality. Multivariate Cox proportional hazards models were to explore the associations of treatment with overall, 1-, 5-, and 10-year all-cause mortality, with hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: Totally 10,994 children were included, with the mean age at diagnosis of 7.3 years, and the median follow-up time of 5.0 years. Of which, 2,003 (18.2%) were diffuse astrocytoma, 3,188 (29.0%) were embryonal tumors, and 3,691 (33.5%) were malignant glioma. Then 4,333 (39.41%) children died during the follow-up. For diffuse astrocytomas and malignant gliomas, patients who received all other treatments were associated with overall, 1-, 5- and 10-year all-cause mortality compared to those only received resection. Embryonal tumors patients receiving resection with radiation only and those receiving resection with both chemotherapy and radiation were associated with lower odds of overall, 1-, 5- and 10-year all-cause mortality compared to patients who only received resection. For ependymal tumors, no surgery/only biopsy with chemotherapy, resection with chemotherapy only, resection with both chemotherapy and radiation, and other treatments had increased risks of overall all-cause mortality compared with resection. The risk of 1-year all-cause mortality increased in ependymal tumors with treatment involving resection and radiation. However, resection with both chemotherapy and radiation was not significantly associated with the 1- nor 5-year all-cause mortality.

Conclusions: Resection may be recommended for children with diffuse astrocytoma, ependymal tumors, and malignant glioma, while resection with radiotherapy or chemoradiation may be recommended for children with embryonal tumors.

Keywords: Brain and central nervous system tumors; children; treatment; Surveillance, Epidemiology, and End Results (SEER)

Submitted Jun 26, 2023. Accepted for publication Aug 21, 2023. Published online Aug 28, 2023.
doi: 10.21037/tp-23-362
View this article at: https://dx.doi.org/10.21037/tp-23-362

Introduction

Cancer is the second most common cause of death in children and adolescents in the United States (US), with brain and central nervous system (CNS) tumors being the most prevalent, accounting for 26% of cancers in childhood and 21% of cancers in adolescents (15–19 years) (1). Malignant solid tumors in children have an insidious onset, lack specific clinical manifestations, and are associated with poor prognosis (2,3). In addition to age at diagnosis, race, gender, tumor grade, tumor histologic subtype, and anatomic site, treatment has been shown to be a key prognostic factor (4-6). Due to limitations associated with conducting clinical research in children, there is currently a paucity of data examining the impact of different treatment methods on the prognosis of brain and CNS tumors in children.

Brain and CNS tumors have a high degree of malignancy and strong invasiveness, and there is currently no good treatment method. Generally, a comprehensive treatment regimen of surgery and/or radiotherapy and/or chemotherapy is used. In germ cell tumors, radiotherapy alone showed better survival outcomes compared with biopsy and resection, however, there was no difference in survival compared with chemotherapy alone (7). Combining resection with radiotherapy or chemotherapy did not improve survival compared with resection alone (7). Lam *et al.* found that gross total resection was associated with improved survival in pediatric glioblastoma patients (8). Mishra *et al.* demonstrated that gamma knife radiosurgery may be an indispensable tool in pediatric CNS tumor management (9). To date, evidence on treatment modalities and survival in children with CNS tumors remains contradictory, with these studies often lacking sufficient patient cohort sizes to assess the differences in histological subtypes.

This investigation intended to explore the effects of different treatments on the mortality of children with primary brain and CNS epithelial tumors, based on data of a large population from the Surveillance, Epidemiology, and End Results (SEER) database. Furthermore, CNS tumors according to histology were to further explore the effects of different treatments on mortality. This article was presented in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-362/rc).

Highlight box

Key findings

- For primary brain and CNS epithelial tumors, children who received chemotherapy had an increased risk of all-cause mortality compared with children who did not receive chemotherapy; and those who underwent resection had a reduced risk of mortality compared to children who did not receive resection. The subgroup results were shown that other treatment modalities were associated with higher overall all-cause mortality in children with diffuse astrocytoma, ependymal tumor, malignant glioma, compared with resection alone.

What is known and what is new?

- Studies have shown that gross total resection is associated with improved survival in pediatric glioblastoma patients.
- For children with primary brain and CNS epithelial tumors, treatment should be comprehensively selected according to histological classification.

What are the implications, and what should change now?

- Resection may be recommended for children with diffuse astrocytoma, ependymal tumors, and malignant glioma, while resection with radiotherapy or chemoradiation may be recommended for children with embryonal tumors.

Methods

Study design and population

The retrospective cohort study enrolled 119,566 participants diagnosed as primary brain and CNS tumors of neuroepithelial tissue between 1975 and 2016, from 18 SEER registries. SEER is a population-based program of the National Cancer Institute. The SEER registry is geographically diverse, covering approximately 27.8% of the US population, with a distribution similar to that of the general US population in terms of gender, race, poverty, and education. Patients were extracted from the SEER database for this study if they satisfied the following criteria: (I) diagnosed with primary brain and CNS tumors; (II) aged <18 years old at diagnosis; (III) total number of *in situ*/malignant tumors was 1; and (IV) information regarding treatment characteristics and survival was available. Patients with primary brain and CNS tumors were identified using the International Classification of Diseases for Oncology, third edition (ICD-O-3): (C70.0-9, C71.0-9, C72.0-9) or (C30.0 and 9522-9523). The exclusion criteria were as follows: (I) age ≥18 years (n=107,577); (II) total number of *in situ*/malignant tumors >1 (n=552); and (III) patients with data collected from autopsy or death certificate or unknown survival data (n=443). Finally, a total of 10,994 patients were

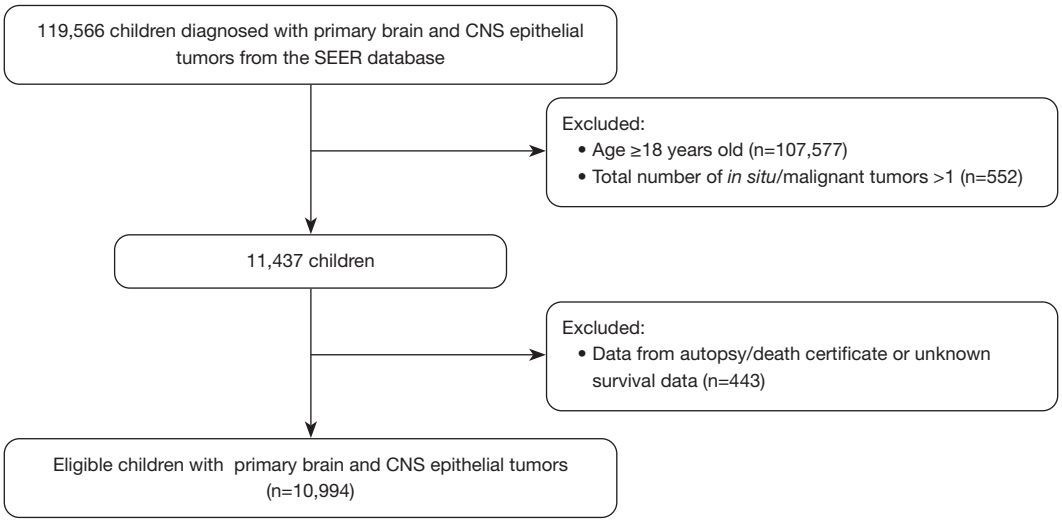

Figure 1 A flow chart showing the study population. CNS, central nervous system; SEER, Surveillance, Epidemiology, and End Results.

included in this analysis. *Figure 1* shows the flow chart of the study population. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Outcome variable

The primary outcome of this study was overall all-cause mortality. The maximum follow-up time was 503 months. The secondary outcomes were 1-, 5-, and 10-year all-cause mortality. Survival time was calculated as months from diagnosis to death in the SEER database.

Treatment

Treatment data collected included surgery performed and the use of radiation therapy and chemotherapy. Surgery performed included excisional biopsy and resection. Radiation therapy included radiation after surgery and other radiation sequences.

Potential covariates

The demographic information of children was collated, including age at diagnosis, gender, and race (Hispanic, non-Hispanic White, non-Hispanic Black, and other). Tumor factors including primary tumor site (cerebellum, cerebrum, frontal lobe of brain, temporal lobe of brain, parietal lobe of brain, occipital lobe of brain, ventricle, brain stem, spinal cord and cauda equina, cranial nerves, and other) (10), histology (diffuse astrocytoma, embryonal tumors, ependymal tumors, malignant glioma, and other), and tumor grade were also collated. Histology was recoded as subgroups reported in a previously published study (10). The tumor grade in the SEER database uses the World Health Organization (WHO) grading system (grades I–IV) (11).

Statistical analysis

The distribution of the overall all-cause mortality and survival was summarized by demographics and clinical variables. Characteristics of dead and alive children were compared using the t-tests for continuous variables and the Chi-square tests for categorical variables. The univariate Cox proportional hazards model was used to explore associations of covariates and treatment with overall all-cause mortality risk. Kaplan-Meier curves were generated to compare the survival rates of different treatment modalities. The multivariate Cox proportional risk model was used to explore the adjusted association between treatment and overall all-cause mortality risk. The adjusted variables were age at diagnosis, gender, race, primary tumor site, histology, and tumor grade. Hazard ratios (HRs) for univariable and multivariable models were reported along with 95% confidence intervals (CIs). The effects of treatment on 1-year all-cause mortality, 5-year all-cause mortality, and 10-year all-cause mortality were investigated using multivariate Cox proportional risk models based on histology. Age at diagnosis, gender, race, primary tumor

site, and tumor grade were adjusted. Two-tailed P values <0.05 were considered statistically significant. All statistical analyses were performed using R v. 3.6.3 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of the study population

Of the 10,994 cases included in this study, there were 6,661 (60.59%) live and 4,333 (39.41%) deceased patients. The median follow-up time was 5.0 years. The mean age at diagnosis was 7.3 years, and 45.0% were female and 55.0% were male. More than half of the patients were non-Hispanic White (60.6%). Malignant glioma accounted for 33.5% of the patients, followed by embryonal tumors (29%), ependymal tumors (10.8%) diffuse astrocytoma (18.2%), and other tumors (8.5%). Other histological types are detailed in Table S1. *Table 1* summarizes the characteristics of children diagnosed with primary malignant brain and CNS tumors. There were significant differences in age at diagnosis (P<0.001), race (P<0.001), primary tumor site (P<0.001), histology (P<0.001), tumor grade (P<0.001), radiation (P<0.001), chemotherapy (P<0.001), and surgery (P<0.001) between the survival and deceased groups (*Table 1*).

Influencing factors for overall all-cause mortality

Figure 2 displays the estimated Kaplan-Meier probability of survival by treatment. Univariable Cox proportional hazards models revealed that age at diagnosis, race, primary tumor site, histology, tumor grade, radiation, chemotherapy, and surgery played significant roles in the mortality risk of brain and CNS tumors (*Table 2*). Consistent with results from the univariable Cox proportional hazards models, all study factors, with the exception of radiation, remained significant in the adjusted multivariable Cox proportional hazards model (*Table 2*).

Association between treatments and overall all-cause mortality according to histology types

The risk of overall mortality associated with treatment modalities, with and without adjustment for confounders, is presented in *Table 3*. For diffuse astrocytoma, patients who received no surgery/only biopsy (HR =3.17, 95% CI: 2.08, 4.84), no surgery/only biopsy with chemotherapy (HR =7.52, 95% CI: 4.93, 11.48), resection with radiation only (HR =4.75, 95% CI: 3.00, 7.51), resection with chemotherapy only (HR =2.65, 95% CI: 1.49, 4.74), resection with both chemotherapy and radiation (HR =6.23, 95% CI: 3.81, 10.18), and other treatments (HR =4.79, 95% CI: 3.32, 6.90) had higher risks of overall all-cause mortality compared with patients who underwent resection alone in the adjusted model.

For embryonal tumors, compared with patients who only had resection, patients who received resection with radiation only and those who received resection with both chemotherapy and radiation were associated with lower risks of overall all-cause mortality (HR =0.50, 95% CI: 0.35, 0.71; and HR =0.47, 95% CI: 0.37, 0.58, respectively, in the adjusted model).

Among patients with ependymal tumors, those who underwent no surgery/only biopsy with chemotherapy (HR =3.93, 95% CI: 1.48, 10.46), resection with chemotherapy only (HR =1.92, 95% CI: 1.26, 2.94), resection with both chemotherapy and radiation (HR =1.59, 95% CI: 1.04, 2.42), and other treatments (HR =4.49, 95% CI: 3.01, 6.69) had increased risks of all-cause mortality compared with patients who underwent resection alone.

For patients with malignant gliomas, no surgery/only biopsy (HR =2.07, 95% CI: 1.55, 2.77), no surgery/only biopsy with chemotherapy (HR =4.81, 95% CI: 3.59, 6.44), resection with radiation only (HR =5.81, 95% CI: 4.08, 8.27), resection with chemotherapy only (HR =2.62, 95% CI: 1.75, 3.91), resection with both chemotherapy and radiation (HR =5.77, 95% CI: 4.32, 7.72), and other treatments (HR =4.41, 95% CI: 3.30, 5.90) had higher risks of all-cause mortality than resection alone (*Table 3*).

Association between treatment and 1-, 5-, and 10-year all-cause mortality according to histology

No significant association was observed between resection with chemotherapy only and 1-year all-cause mortality in patients with diffuse astrocytoma, which was not consistent with the association between treatment and overall all-cause mortality (*Table 4*). For embryonal tumors, the risk of 1-year all-cause mortality in patients who underwent resection with chemotherapy only (HR =0.54, 95% CI: 0.41, 0.72) was higher than those who underwent resection only. However, there were no significant associations between resection with chemotherapy only and the 5- nor 10-year all-cause mortality. The risk of 1-year all-cause mortality increased in patients with ependymal tumors who underwent resection and radiation (HR =0.13, 95% CI: 0.04, 0.41) compared

Table 1 The basic characteristics of children diagnosed with primary malignant brain and CNS tumors

Variables	Total (n=10,994)	Alive (n=6,661)	Deceased (n=4,333)	Statistics	P
Age at diagnosis (years), mean ± SD	7.3±5.1	7.4±5.2	7.1±4.9	3.43	<0.001
Gender, n (%)				0	0.992
Female	4,947 (45.0)	2,997 (45.0)	1,950 (45.0)		
Male	6,047 (55.0)	3,664 (55.0)	2,383 (55.0)		
Race, n (%)				46.06	<0.001
Hispanic	2,220 (20.2)	1,322 (19.8)	898 (20.7)		
Non-Hispanic White	6,662 (60.6)	4,174 (62.7)	2,488 (57.4)		
Non-Hispanic Black	1,257 (11.4)	664 (10.0)	593 (13.7)		
Others	855 (7.8)	501 (7.5)	354 (8.2)		
Primary tumor site, n (%)				917.95	<0.001
Cerebellum	2,486 (22.6)	1,635 (24.5)	851 (19.6)		
Cerebrum	794 (7.2)	409 (6.1)	385 (8.9)		
Frontal lobe of brain	731 (6.6)	470 (7.1)	261 (6.0)		
Temporal lobe of brain	776 (7.1)	577 (8.7)	199 (4.6)		
Parietal lobe of brain	420 (3.8)	267 (4.0)	153 (3.5)		
Occipital lobe of brain	146 (1.3)	111 (1.7)	35 (0.8)		
Ventricle	609 (5.5)	374 (5.6)	235 (5.4)		
Brain stem	2,369 (21.5)	950 (14.3)	1,419 (32.7)		
Spinal cord and cauda equina	454 (4.1)	303 (4.5)	151 (3.5)		
Cranial nerves	687 (6.2)	658 (9.9)	29 (0.7)		
Others	1,522 (13.8)	907 (13.6)	615 (14.2)		
Histology, n (%)				240.28	<0.001
Diffuse astrocytoma	2,003 (18.2)	1,478 (22.2)	525 (12.1)		
Embryonal tumors	3,188 (29.0)	1,880 (28.2)	1,308 (30.2)		
Ependymal tumors	1,188 (10.8)	788 (11.8)	400 (9.2)		
Malignant glioma	3,681 (33.5)	2,027 (30.4)	1,654 (38.2)		
Others	934 (8.5)	488 (7.3)	446 (10.3)		
Tumor grade, n (%)				444.61	<0.001
Grade I	439 (4.0)	363 (5.4)	76 (1.8)		
Grade II	1,054 (9.6)	829 (12.4)	225 (5.2)		
Grade III	392 (3.6)	181 (2.7)	211 (4.9)		
Grade IV	1,849 (16.8)	842 (12.6)	1,007 (23.2)		
Unknown	7,260 (66.0)	4,446 (66.7)	2,814 (64.9)		

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Total (n=10,994)	Alive (n=6,661)	Deceased (n=4,333)	Statistics	P
Radiation, n (%)				49.38	<0.001
No	6,789 (61.8)	4,269 (64.1)	2,520 (58.2)		
Radiation after surgery	3,986 (36.3)	2,290 (34.4)	1,696 (39.1)		
Other radiation sequences	219 (2.0)	102 (1.5)	117 (2.7)		
Chemotherapy, n (%)				367.99	<0.001
No/unknown	5,897 (53.6)	4,063 (61.0)	1,834 (42.3)		
Yes	5,097 (46.4)	2,598 (39.0)	2,499 (57.7)		
Surgery, n (%)				343.27	<0.001
No	2,871 (26.1)	1,635 (24.5)	1,236 (28.5)		
Excisional biopsy	116 (1.1)	53 (0.8)	63 (1.5)		
Resection	6,263 (57.0)	4,207 (63.2)	2,056 (47.4)		
Unknown	1,744 (15.9)	766 (11.5)	978 (22.6)		

CNS, central nervous system; SD, standard deviation.

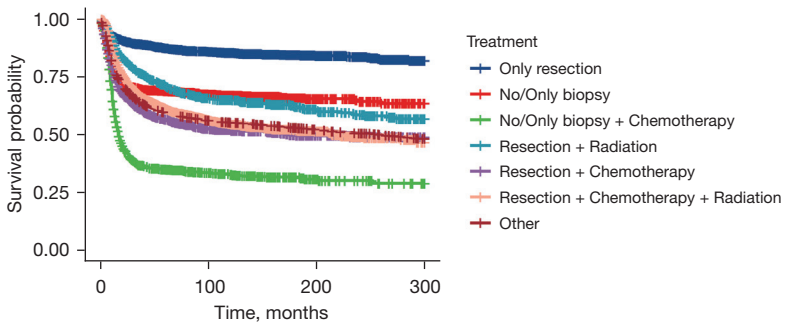

Figure 2 The survival of pediatric brain and CNS tumors patients by treatments. CNS, central nervous system.

with patients with ependymoma who underwent resection alone. In patients with ependymal tumors, the treatment modality involving resection with both chemotherapy and radiation was not significantly associated with the 1- nor 5-year all-cause mortality. Among patients with malignant glioma, the associations between treatment and 1-, 5-, and 10-year all-cause mortality were consistent with the results of treatments and overall all-cause mortality.

Discussion

For primary brain and CNS epithelial tumors, children who received chemotherapy had an increased risk of all-cause mortality compared with children who did not receive chemotherapy; and those who underwent resection had a reduced risk of mortality compared to children who did not receive resection. In addition, other treatment modalities were associated with higher overall all-cause mortality in children with diffuse astrocytoma, ependymal tumor, and malignant glioma, compared with resection alone. Interestingly, for embryonal tumors, resection with radiotherapy or resection with chemoradiation was associated with lower overall all-cause mortality compared with resection alone. The results of this study may have certain guiding significance for the treatment of children with primary brain and CNS epithelial tissue tumors. Treatment should be comprehensively selected according to histological classification and short-, medium-, and long-

Table 2 The influencing factors for overall all-cause mortality using univariate and multivariate Cox proportional hazards analyses

Variables	Univariate Cox model		Multivariate Cox model	
	HR (95% CI)	P	HR (95% CI)	P
Age at diagnosis	0.98 (0.98, 0.99)	<0.001	0.98 (0.98, 0.99)	<0.001
Gender				
Female	Ref		Ref	
Male	0.99 (0.93, 1.05)	0.747	0.98 (0.93, 1.05)	0.622
Race				
Hispanic	Ref		Ref	
Non-Hispanic White	0.79 (0.73, 0.85)	<0.001	0.88 (0.82, 0.96)	0.002
Non-Hispanic Black	1.12 (1.01, 1.24)	0.031	1.10 (0.99, 1.22)	0.078
Others	1.02 (0.90, 1.15)	0.757	1.11 (0.98, 1.26)	0.096
Primary tumor site				
Cerebellum	Ref		Ref	
Cerebrum	1.71 (1.52, 1.93)	<0.001	1.64 (1.43, 1.88)	<0.001
Frontal lobe of brain	1.13 (0.98, 1.29)	0.094	1.24 (1.07, 1.45)	0.004
Temporal lobe of brain	0.72 (0.62, 0.84)	<0.001	0.94 (0.80, 1.12)	0.508
Parietal lobe of brain	1.11 (0.93, 1.31)	0.250	1.21 (1.01, 1.45)	0.038
Occipital lobe of brain	0.68 (0.48, 0.95)	0.023	0.81 (0.57, 1.14)	0.226
Ventricle	1.24 (1.07, 1.43)	0.004	1.35 (1.16, 1.57)	<0.001
Brain stem	2.60 (2.39, 2.84)	<0.001	2.35 (2.12, 2.61)	<0.001
Spinal cord and cauda equina	1.01 (0.85, 1.20)	0.880	1.29 (1.08, 1.54)	0.005
Cranial nerves	0.11 (0.08, 0.16)	<0.001	0.08 (0.05, 0.12)	<0.001
Others	1.24 (1.12, 1.38)	<0.001	1.28 (1.14, 1.43)	<0.001
Histology				
Diffuse astrocytoma	Ref		Ref	
Embryonal tumors	2.07 (1.87, 2.29)	<0.001	1.46 (1.29, 1.66)	<0.001
Ependymal tumors	1.55 (1.36, 1.77)	<0.001	1.15 (1.00, 1.33)	0.053
Malignant glioma	2.51 (2.27, 2.77)	<0.001	2.17 (1.95, 2.43)	<0.001
Others	2.56 (2.25, 2.90)	<0.001	1.54 (1.33, 1.77)	<0.001
Tumor grade				
Grade I	Ref		Ref	
Grade II	1.23 (0.95, 1.60)	0.118	1.17 (0.90, 1.52)	0.238
Grade III	4.27 (3.28, 5.55)	<0.001	3.26 (2.50, 4.25)	<0.001
Grade IV	4.96 (3.93, 6.27)	<0.001	3.48 (2.73, 4.44)	<0.001
Unknown	2.97 (2.37, 3.73)	<0.001	1.99 (1.58, 2.51)	<0.001

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Univariate Cox model		Multivariate Cox model	
	HR (95% CI)	P	HR (95% CI)	P
Radiation				
No	Ref		Ref	
Radiation after surgery	1.09 (1.02, 1.16)	0.007	1.05 (0.97, 1.14)	0.201
Other radiation sequence	1.20 (1.00, 1.44)	0.055	1.20 (0.99, 1.45)	0.069
Chemotherapy				
No/unknown	Ref		Ref	
Yes	1.99 (1.87, 2.11)	<0.001	1.93 (1.79, 2.07)	<0.001
Surgery				
No	Ref		Ref	
Excisional biopsy	1.07 (0.83, 1.37)	0.617	1.18 (0.91, 1.53)	0.206
Resection	0.63 (0.58, 0.67)	<0.001	0.61 (0.55, 0.67)	<0.001
Unknown	0.89 (0.82, 0.97)	0.010	1.40 (1.26, 1.55)	<0.001

HR, hazard ratio; CI, confidence interval; Ref, reference.

term survival.

Diffuse astrocytoma, a tumor composed of astrocytes, is an invasive growth tumor and is the most common neuroepithelial tumor of the nervous system (12). Clinical symptoms such as headaches, vomiting, hemiplegia, disturbance of consciousness, and decreased vision, can damage the CNS (13). Currently, complete surgical resection is the mainstay of treatment for diffuse astrocytoma (14,15). In the present study, resection was found to be associated with a lower risk of overall mortality, as well as 5- and 10-year mortality, compared with no/only biopsy, no/only biopsy with chemotherapy, resection with radiation only, resection with chemotherapy only, and resection with both chemotherapy and radiation. Scarpelli *et al.* (16) found that in children with pleomorphic xanthoastrocytoma, those who received radiotherapy and chemotherapy had poorer survival compared to those treated by resection only. After resection, most diffuse astrocytomas present with good prognosis, but are prone to recurrence, accompanied by cerebral edema, epilepsy, hydrocephalus, and other symptoms. Thus, some patients may receive adjuvant treatments such as chemotherapy or radiation therapy after resection to reduce the risk of recurrence (17).

Embryonic tumors are collections of biologically heterogeneous lesions with a tendency to spread throughout the nervous system via the cerebrospinal fluid (CSF) pathway (18). Resection with radiation only and resection with both chemotherapy and radiation were beneficial for survival compared with resection alone in children with embryonic tumors, and there was no significant difference between other treatment modalities and resection. Deng *et al.* (19) found that older children with pineocytoma who received radiation therapy had better overall survival, and gross total resection also appeared to improve survival, which were consistent with the findings. In other studies, complete or near-complete tumor resection was considered the best option if resection was feasible (20), and radiation therapy was usually started after surgery, with or without concurrent chemotherapy (21). In addition, the resection with chemotherapy only had a protective effect on 1-year all-cause mortality, suggesting that the treatment may be beneficial for early embryonic tumor survival, but there were no significant differences in medium- and long-term survival at 5 or 10 years compared with resection alone.

Ependymomas arise from ependymal cells, a type of radial glial cell in the brain and spinal cord (22). In the treatment of ependymomas, all tumors should be removed as much as possible under the premise of safety (23). Ependymomas are usually located in the posterior cranial

Table 3 The association between treatment and overall all-cause mortality according to histology

Treatment	Death/Total	Crude model		Adjusted model*	
		HR (95% CI)	P	HR (95% CI)	P
Diffuse astrocytoma					
Resection only	35/647	Ref		Ref	
No surgery/only biopsy	65/282	5.16 (3.42, 7.79)	<0.001	3.17 (2.08, 4.84)	<0.001
No surgery/only biopsy with chemotherapy	72/141	14.30 (9.54, 21.45)	<0.001	7.52 (4.93, 11.48)	<0.001
Resection with radiation only	41/110	7.69 (4.90, 12.07)	<0.001	4.75 (3.00, 7.51)	<0.001
Resection with chemotherapy only	18/93	4.36 (2.47, 7.70)	<0.001	2.65 (1.49, 4.74)	0.001
Resection with both chemotherapy and radiation	36/76	13.60 (8.53, 21.67)	<0.001	6.23 (3.81, 10.18)	<0.001
Others	258/654	5.73 (4.01, 8.20)	<0.001	4.79 (3.32, 6.90)	<0.001
Embryonal tumors					
Resection only	96/200	Ref		Ref	
No surgery/only biopsy	30/59	1.09 (0.72, 1.65)	0.673	0.99 (0.65, 1.50)	0.956
No surgery/only biopsy with chemotherapy	66/115	1.27 (0.93, 1.74)	0.131	1.17 (0.85, 1.61)	0.339
Resection with radiation only	49/149	0.46 (0.32, 0.65)	<0.001	0.50 (0.35, 0.71)	<0.001
Resection with chemotherapy only	321/650	1.01 (0.81, 1.27)	0.903	0.91 (0.72, 1.15)	0.414
Resection with both chemotherapy and radiation	477/1,602	0.46 (0.37, 0.58)	<0.001	0.47 (0.37, 0.58)	<0.001
Others	269/413	0.92 (0.73, 1.16)	0.485	1.01 (0.79, 1.29)	0.948
Ependymal tumors					
Resection only	35/197	Ref		Ref	
No surgery/only biopsy	5/27	1.24 (0.49, 3.17)	0.648	1.51 (0.59, 3.91)	0.391
No surgery/only biopsy with chemotherapy	5/10	5.51 (2.16, 14.08)	<0.001	3.93 (1.48, 10.46)	0.006
Resection with radiation only	110/466	1.44 (0.99, 2.11)	0.058	1.17 (0.79, 1.73)	0.423
Resection with chemotherapy only	71/143	3.17 (2.11, 4.75)	<0.001	1.92 (1.26, 2.94)	0.003
Resection with both chemotherapy and radiation	66/200	2.18 (1.44, 3.28)	<0.001	1.59 (1.04, 2.42)	0.031
Others	108/145	5.06 (3.44, 7.44)	<0.001	4.49 (3.01, 6.69)	<0.001
Malignant glioma					
Resection only	61/499	Ref		Ref	
No surgery/only biopsy	417/1,389	3.12 (2.38, 4.08)	<0.001	2.07 (1.55, 2.77)	<0.001
No surgery/only biopsy with chemotherapy	481/756	8.37 (6.41, 10.93)	<0.001	4.81 (3.59, 6.44)	<0.001
Resection with radiation only	68/105	8.08 (5.72, 11.42)	<0.001	5.81 (4.08, 8.27)	<0.001
Resection with chemotherapy only	42/114	3.74 (2.52, 5.54)	<0.001	2.62 (1.75, 3.91)	<0.001
Resection with both chemotherapy and radiation	289/370	9.99 (7.57, 13.18)	<0.001	5.77 (4.32, 7.72)	<0.001
Others	296/448	6.45 (4.89, 8.52)	<0.001	4.41 (3.30, 5.90)	<0.001

*, adjusted for age at diagnosis, gender, race/ethnicity, primary tumor site, and tumor grade. HR, hazard ratio; CI, confidence interval; Ref, reference.

Table 4 The association between treatment and 1-, 5-, and 10-year all-cause mortality according to histology*

Treatment	HR (95% CI)		
	1-year mortality	5-year mortality	10-year mortality
Diffuse astrocytoma			
Resection only	Ref	Ref	Ref
No surgery/only biopsy	3.61 (1.73, 7.55)	3.18 (1.97, 5.12)	3.34 (2.12, 5.25)
No surgery/only biopsy with chemotherapy	6.00 (2.85, 12.66)	6.82 (4.22, 11.03)	7.53 (4.77, 11.88)
Resection with radiation only	4.89 (2.14, 11.17)	3.81 (2.19, 6.62)	3.94 (2.34, 6.66)
Resection with chemotherapy only	2.33 (0.83, 6.50)	2.57 (1.34, 4.92)	2.76 (1.50, 5.09)
Resection with both chemotherapy and radiation	6.81 (3.05, 15.18)	6.57 (3.82, 11.30)	6.99 (4.16, 11.72)
Others	6.20 (3.15, 12.18)	4.77 (3.11, 7.33)	4.92 (3.28, 7.38)
Embryonal tumors			
Resection only	Ref	Ref	Ref
No surgery/only biopsy	0.89 (0.54, 1.46)	1.00 (0.66, 1.54)	0.97 (0.63, 1.48)
No surgery/only biopsy with chemotherapy	0.70 (0.47, 1.04)	1.08 (0.77, 1.50)	1.12 (0.81, 1.55)
Resection with radiation only	0.41 (0.24, 0.71)	0.49 (0.34, 0.72)	0.50 (0.35, 0.72)
Resection with chemotherapy only	0.54 (0.41, 0.72)	0.86 (0.67, 1.10)	0.90 (0.71, 1.14)
Resection with both chemotherapy and radiation	0.22 (0.16, 0.30)	0.41 (0.32, 0.52)	0.45 (0.36, 0.57)
Others	0.60 (0.43, 0.83)	0.95 (0.73, 1.23)	0.99 (0.77, 1.27)
Ependymal tumors			
Resection only	Ref	Ref	Ref
No surgery/only biopsy	0.88 (0.11, 6.96)	1.40 (0.49, 4.01)	1.55 (0.60, 4.02)
No surgery/only biopsy with chemotherapy	0.92 (0.11, 7.93)	3.19 (1.08, 9.43)	4.09 (1.53, 10.91)
Resection with radiation only	0.13 (0.04, 0.41)	1.02 (0.66, 1.57)	1.16 (0.77, 1.72)
Resection with chemotherapy only	1.08 (0.48, 2.46)	1.62 (1.01, 2.60)	1.85 (1.20, 2.87)
Resection with both chemotherapy and radiation	0.48 (0.19, 1.23)	1.29 (0.80, 2.06)	1.46 (0.94, 2.26)
Others	3.52 (1.69, 7.32)	4.60 (2.97, 7.12)	4.53 (3.00, 6.84)
Malignant glioma			
Resection only	Ref	Ref	Ref
No surgery/only biopsy	1.93 (1.29, 2.89)	2.31 (1.67, 3.20)	2.09 (1.54, 2.82)
No surgery/only biopsy with chemotherapy	3.06 (2.04, 4.60)	5.21 (3.76, 7.24)	4.82 (3.56, 6.53)
Resection with radiation only	3.85 (2.35, 6.31)	6.06 (4.10, 8.97)	5.66 (3.92, 8.17)
Resection with chemotherapy only	1.89 (1.07, 3.36)	2.80 (1.80, 4.36)	2.60 (1.72, 3.93)
Resection with both chemotherapy and radiation	3.02 (2.00, 4.56)	6.29 (4.54, 8.69)	5.80 (4.30, 7.83)
Others	3.17 (2.11, 4.76)	4.81 (3.46, 6.67)	4.44 (3.28, 6.01)

*, adjusted for age at diagnosis, gender, race, primary tumor site, and tumor grade. HR, hazard ratio; CI, confidence interval; Ref, reference.

fossa, close to the cranial nerves and brainstem, so the risk of resection is high, and surgery is more difficult if the tumor invades the brainstem (24,25). Adjuvant radiation therapy is given after surgery to treat the remaining tumor cells to reduce the risk of recurrence (23). Chemotherapy is only suitable for the treatment of young children, residual disease in patients with bulky tumors, and relapsed, refractory tumors (26,27). The results suggested that resection combined with chemotherapy increased the risk of mortality compared to resection alone. Evidence supporting the role of chemotherapy in the management of ependymoma is limited (28). In a single-center retrospective cohort study, patients with chemotherapy had worse outcomes compared to patients without chemotherapy (29). Those patients had likely more aggressive tumors to start with and were more likely to die from their tumor and a small number likely died from chemo complications itself. Resection with both chemotherapy and radiation showed no significant difference for early and mid-term survival, but was associated with a higher risk of all-cause mortality for long-term survival.

In this study, children with malignant gliomas were found to have a higher overall, 1-, 5-, and 10-year risk of all-cause mortality with treatments other than resection compared with resection alone. Standard treatment consists of total resection followed by adjuvant radiation therapy plus chemotherapy (30,31). The results suggested that resection is the primary consideration for children with malignant gliomas. The appropriate surgical approach should be selected for resection based on the location and relevant clinical information of the tumor to achieve good outcomes and reduce complications (14).

The advantage of this study was that the SEER database was used to obtain a large sample size with a relatively long follow-up time. Herein, brain and CNS tumor histological types were classified, and the effects of treatment modalities on overall mortality, short-term, and mid- to long-term all-cause mortality were explored in different subgroups. However, some limitations require caution in interpreting of the findings. First, although some covariates were adjusted, there was no available information on genetics, comorbidities, physical status, socioeconomic status, nor lifestyle factors based on the database used, and therefore, it was not possible to control for these confounders. Second, although this work investigated the effects of radiotherapy, chemotherapy, and other treatment modalities on brain and CNS tumor survival, the types and doses of chemotherapy drugs used for treatment, as well as the data related to radiation dose and radiation field, were not examined. Third, data from the SEER database may be heterogeneous, even within tumor pathology, which may reduce the generalizability.

Conclusions

Treatment should be comprehensively selected according to histological classification for children with primary brain and CNS epithelial tumors. Resection may be recommended for children with diffuse astrocytoma, ependymal tumors, and malignant glioma, while resection with radiotherapy or chemoradiation may be recommended for children with embryonal tumors. Future well-designed studies need to further validate the findings.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The author has completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-362/rc

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-362/prf

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form available at available at https://tp.amegroups.com/article/view/10.21037/tp-23-362/coif). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Cite this article as: Zhou H. Treatments associated with all-cause mortality among children with primary brain and central nervous system tumors: a retrospective cohort study from the SEER database. Transl Pediatr 2023;12(8):1504-1516. doi: 10.21037/tp-23-362