Original Article

Relative Survival of Childhood and Adult Medulloblastomas and Primitive Neuroectodermal Tumors (PNETs)

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BACKGROUND: Medulloblastomas are 1 of the most common brain tumors in children but can affect individuals of all ages. For this report, the author investigated the impact of medulloblastomas/primitive neuroectodermal tumors (PNETs) on the US population with a focus on age differences. **METHODS:** Data from the Surveillance, Epidemiology, and End Results (SEER) database were used to describe cumulative relative survival (CRS) using crude, period, and longitudinal period approaches for patients diagnosed with all medulloblastoma subtypes and PNETs. CRS estimates were obtained using SEER expected mortality data and the Ederer II method for expected survival estimation. These data were applied to the construction of rational follow-up scheduling protocols. **RESULTS:** The 5-year period CRS for all patients who were followed between 2001 and 2006 was 69%. Adults had a worse overall prognosis, but this difference in excess hazard rates appeared only after 4 years of follow-up. Furthermore, the 5-year and 10-year CRS has improved a minimum of 11% in children, adolescents, and adults over the past 25 years. **CONCLUSIONS:** The survival difference between children, adolescents, and adults with medulloblastomas and PNETs depended on the length of follow-up, which was described in this report as an age-by-follow-up interaction and observed as a "fork" on Kaplan-Meier curves. Differences in survival between children and adults emerged only 4 years after diagnosis, and adults fared worse. There has been significant improvement in survival from medulloblastomas/PNETs since the late 1970s and early 1980s. ***Cancer* 2011;000:000–000.** © *2011 American Cancer Society.*

KEYWORDS: medulloblastoma, primitive neuroectodermal tumor, relative survival, covariate-by-follow-up interaction, regression, follow-up, survival modeling.

INTRODUCTION

A medulloblastoma is a brain tumor primarily of the posterior fossa that has a predilection for affecting children. It is estimated that to medulloblastoma affects 9.6 children per million and 0.54 adults per million.[1,2] In those who survive this disease, the tumor and its treatment continue to cause effects into adulthood: 55% of survivors require endocrine-replacement therapy, and 78% have residual neurologic deficits post-treatment.[3]

Recently reported overall survival rates for both children and adults are in the 60th and 70th percentiles, a significant increase from the 29% 5-year overall survival rate reported in earlier periods.[2,4–10] Studies have demonstrated that medulloblastomas in adults and children are histologically and genetically different diseases.[11–13] Because of obvious differences in expected survival between adults and children in the general population (with adults more likely to die than children), comparing the survival profiles of children and adults with brain tumors requires a particular approach, namely, the use of *relative survival*.

The primary objective of this study was to provide an overview of the impact that medulloblastomas and primitive neuroectodermal tumors (PNETs) have had on the US population over the past 25 years by reviewing the relative survival profile of patients with medulloblastomas/PNETs, with a focus on the differences between adults and children. Furthermore, this study also raises several issues important to all forms of survival analysis: the importance of assessing for covariate-by-follow-up interactions and how to recognize these on Kaplan-Meier or cumulative relative survival (CRS) plots;

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the use of a longitudinal period approach to quantify CRS time trends in population-based studies; and the pertinence of the use of relative survival methods when the patient population has a young age distribution.

MATERIALS AND METHODS

The US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database was used to identify patients with medulloblastomas/PNETs (medulloblastoma not otherwise specified [International Classification of Diseases for Oncology code 9470/3], desmoblastic medulloblastoma [9471/3], medullomyoblastoma [9472/3], large cell medulloblastoma [9474/3], and PNET [9473/3]).[14] The SEER database is a large, nationwide database that currently covers an estimated 25% of the US population. It has a previously reported (when it covered 14% of the US population) 97.7 case ascertainment rate, indicating that only an estimated 2.3% of cancers have been missed, which is impressive for such a large population-based database.[15] Its ascertainment of radiation oncology records is approximately 99%.

Four age groups were used in this analysis: "infants" (from birth to age 1 year) "children" (ages 1-9 years), "adolescents" (ages 10-19 years), and "adults" (aged >19 years). The choice of this age classification was because of the visual observation of incidence rate age distribution and, more specifically, a drop in incidence at age 20 years of in the SEER data as well as in other studies. In addition, the median age at diagnosis was 9 years.[16] It is acknowledged that this age grouping may include patients in the adolescent category who may be considered younger than the adolescent population and does not follow the Adolescent and Young Adult Oncology Progress Review Group's age criteria definitions (adolescents and young adults are defined as ages 15-39 year).[17] However, various age groupings were tested to ensure the stability of these results. Individual patient survival data were obtained from the SEER 17 registries and were matched to SEER expected mortality tables by year of birth, age, sex, and race using the Ederer II technique.

Cumulative Relative Survival, Regression Methods, and Standardized Mortality Ratios

The use of relative survival methods to quantify differences in survival between age groups is crucial because of differences in the underlying expected general population mortality estimates. For example, a Caucasian male aged 5 years has a 0.0171% chance of dying from any cause in the year 2006. Conversely a white man aged 70 years had a 2.5004% chance of dying from any cause in the year 2006.[18] Therefore, to accurately quantify the difference in the survival profiles between 2 different age groups, patients first must be matched with their expected mortality rates, and the crude hazard rates must be adjusted according to these profiles. Adjustment is performed by subtracting the expected hazard rates from the observed hazard rates to obtain an *excess hazard rate* for each period. The portion of the hazard rate that is above that of the general population's mortality rate can be considered caused by the disease and is independent of age or expected mortality. The excess hazard ratio (eHR), as described below, is the ratio between the excess hazard rates in each age group. Also, the standardized mortality ratio is a ratio of the total observed mortality and matched expected general mortality rates. Note that CRS has become the standard method by which cancer registries present cause-specific survival measures and is interpreted in the same manner as Kaplan-Meier survival estimates, although it is adjusted to account for general population mortality estimates.

Three methods of estimating survival estimates were used in the current study. The crude CRS approach simply uses all patients in all time periods to calculate CRS. The period CRS approach involves a method first described by Brenner in 1996 to provide up-to-date estimates of survival by including only patients who are followed within a certain time window (5 years).[19,20] In the current study, Brenner's period CRS approach is used to generate longitudinal CRS rates by estimating 5-year CRS rates every year between 1981 and 2006. For each consecutive year, the steady 5-year follow-up window is used to calculate 5-year period CRS rates, resulting in a longitudinal CRS data set unaffected by the age-cohort-period effect.

Regression of relative survival estimates produces eHRs, which are interpreted similarly to usual hazard ratios obtained by Cox proportional hazards or parametric regression methods, while accounting for general population mortality estimates. This model, which was presented by Dickman et al in 2004, allows the calculation of excess hazard ratios through maximum likelihood estimation methods.[21] Different age categorizations were explored, and the regression models fit best when patients ages birth to 1 year and patients who did not receive radiation or surgery were excluded from the regression modeling.

Table 1. Tumor and Treatment Characteristics of Patients with Medulloblastomas[a]

	Infants		Children		Adolescents		Adults		Total	
Characateristic	No.	%	No.	%	No.	%	No	%	No.	%
Sex										
Male	64	47	879	62	298	62	432	58	1673	60
Female	72	53	535	38	185	38	309	42	1101	40
Year of diagnosis[b]										
1973-1984	16	12	220	16	93	19	87	12	416	15
1985-1995	47	35	356	25	124	26	192	26	719	26
1996-2007	73	54	838	59	266	55	462	62	1639	59
Tumor location										
Supratentorial	17	12	173	12	52	11	87	12	329	12
Infratentorial	89	65	1084	77	371	77	577	78	2121	76
Other[c]	30	22	157	11	60	12	77	10	324	12
Histology										
Medulloblastoma	83	61	1034	73	367	76	553	75	2037	73
PNET	53	39	380	27	116	24	188	25	737	27
Radiation[d]										
None	112	82	361	26	65	13	144	19	682	25
Radiation	24	18	1053	74	418	87	597	81	2092	75
Surgery[d]										
No surgery or unknown	22	16	83	6	49	10	67	9	221	8
Surgery performed	114	84	1331	94	434	90	674	91	2553	92
Total	136	100	1414	100	483	100	741	100	2774	100

Abbreviations: PNET, primitive neuroectodermal tumor
[a] There was no differences in distribution according to sex or histology if the infant category was excluded.
[b] Chi-square *P* values were <.05 comparing adolescents with adults.
[c] Other locations included brain or central nervous system not specified, unknown location, overlapping, and cranial nerves not otherwise specified.
[d] Chi-square *P* values were <.05 comparing children with adolescents and comparing children with adults.

In addition, standardized mortality ratios are used to describe the total observed mortality divided by the expected mortality in a matched general population. This is interpreted as how much more likely individuals with disease were to die than the matched general population.

Significance and Hypothesis Testing

The significance level for likelihood ratio tests of the inclusion of variables into a regression model was $P < .05$. Determination of significance for CRS rates was approached by using nonoverlapping confidence intervals as indicators of significance. A potential trend is defined as a P value $< .10 > .05$. All statistical analyses were performed on using Stata software (version 11.1; Stata Inc., College Station, Tex).

RESULTS

Demographic Variables

From the SEER 17 registries, 2774 patients were identified (53% children) with a total of 15,260 years of patient follow-up. There were 2037 medulloblastomas and 737 PNETs with a total of 12,397 years and 2863.5 years of follow-up, respectively. The median patient age was 9 years (interquartile range, 4-22 years). Ninety percent of all patients who were diagnosed with medulloblastomas/PNETs were aged ≤35 years at diagnosis. Males formed 60% of those diagnosed, and 84% of patients were considered "white."

The only baseline differences observed between age groups were in the receipt of treatment (see Table 1). Specifically, 82% of infants did not receive radiation, whereas 13% to 26% of children, adolescents, and adults did not receive radiation. These differences were taken into account when building the regression model.

Cumulative Relative Survival

The CRS rate for all age groups and histology follow-up was 60%, 52%, and 47% at 5 years, 10 years, and 20 years, respectively (see Table 2). The long-term (15-year) CRS rate in both tumor types differed significantly between children (53%; (95% confidence interval [CI], 50%-57%) and adults (43%; 95% CI, 37%-48%; crude approach) (see Table 2). Plotted Kaplan-Meier curves and

Table 2. Crude Approach to Cumulative Relative Survival Estimation[a]

	Infants (Aged <1 y)		Children (Ages 1-9 y)		Adolescents (Ages 10-19 y)		Adults (Aged >20 y)		Overall	
Year	CRS	95% CI	CRS	95% CI	CRS	95% CI	CRS	95% CI	CRS	95% CI
1	0.45	0.36-0.54	0.85	0.83-0.87	0.92	0.89-0.94	0.85	0.82-0.88	0.85	0.83-0.86
2	0.34	0.25-0.43	0.75	0.72-0.77	0.82	0.78-0.85	0.75	0.71-0.78	0.74	0.72-0.76
5	0.30	0.22-0.39	0.62	0.59-0.65	0.64	0.59-0.69	0.59	0.55-0.63	0.60	0.58-0.62
10	0.26	0.18-0.35	0.57	0.54-0.60	0.54	0.48-0.60	0.46	0.41-0.51	0.52	0.50-0.55
15	0.26	0.18-0.35	0.53	0.50-0.57	0.53	0.47-0.58	0.43	0.37-0.48	0.49	0.47-0.52
20	0.26	0.18-0.35	0.51	0.47-0.54	0.51	0.45-0.57	0.42	0.36-0.48	0.47	0.44-0.50

Abbreviations: CI, confidence interval; CRS, cumulative relative survival.
[a] CRS estimates using the crude oerall survival (OS) rates do not differ significantly from crude CRS rates at 5 years, 10 years, or 15 years (infant OS: 0.29, 0.25, and 0.25, respectively; child OS: 0.62, 0.56, and 0.52, respectively; adolescent OS: 0.63, 0.53, and 0.51, respectively; adults OS:, 0.57, 0.43, and 0.38, respectively).

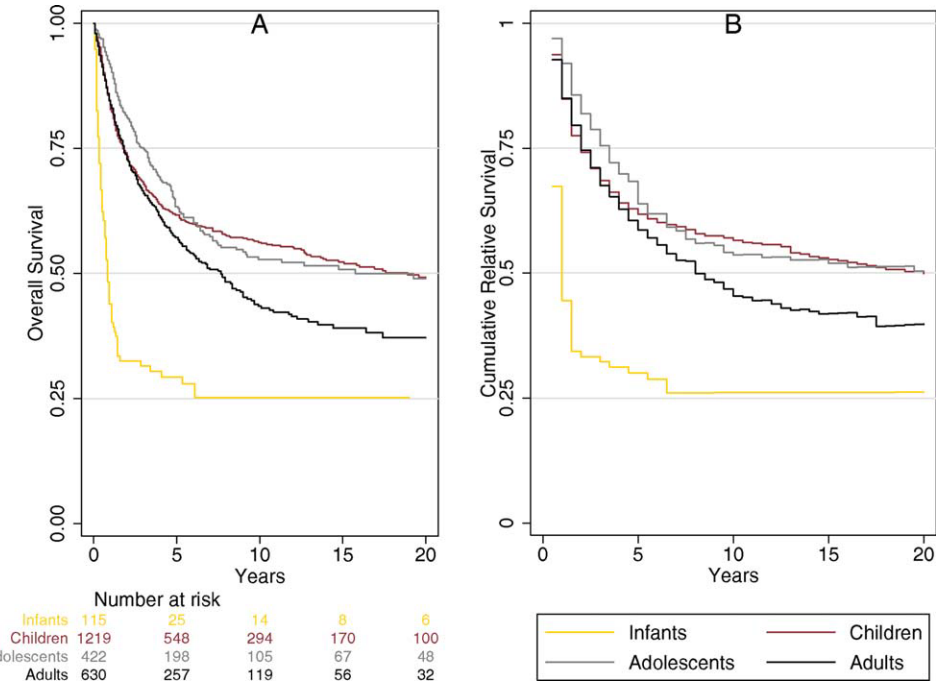

Figure 1. The overall survival of all patients is illustrated using (A) the Kaplan-Meier method and (B) cumulative relative survival (CRS). Because of the age distribution of patients with this disease, the expected mortality is very small; therefore, little difference is observed between A and B. Note the very slight lifting of the CRS curve in B compared with the Kaplan-Meier curve in A, indicating a very slight but present effect of adjusting values for expected mortality particularly in adults.

CRS curves are provided in Figure 1. It appears that there was little difference in the overall survival and relative survival estimates, probably because of the age distributions of patients with medulloblastomas and PNETs.

Because of the differences between each tumor type, CRS estimates are presented separately for each type. The population-based CRS estimates at 5 years for patients with medulloblastoma and PNET are 69% and 53%, respectively (see Tables 3 and 4). The CIs at 2 years and 5 years did not intersect, indicating a significant difference in survival between patients with medulloblastomas and PNETs at 5 years who were diagnosed between 2001 and 2006.

Longitudinal Relative Survival

The temporal 5-year and 10-year CRS trend over the past 25 (23 years for 10-year CRS) is described in Figure 2. In all patients who were diagnosed, the 5-year period CRS in 1981 was 45% (95% CI, 37%-53%), and it rose to 64%

Table 3. Cumulative Relative Survival Rates in Patients Diagnosed With Medulloblastomas Between 2001 and 2006 (n = 2037)

	Infants (Aged <1 y)		Children (Ages 1-9 y)		Adolescents (Ages 10-19 y)		Adults (Aged >20 y)		Overall	
Year	CRS	95% CI	CRS	95% CI	CRS	95% CI	CRS	95% CI	CRS	95% CI
1	0.52	0.30-0.70	0.90	0.86-0.93	0.92	0.85-0.96	0.86	0.79-0.91	0.88	0.85-0.90
2	0.47	0.26-0.65	0.80	0.75-0.85	0.84	0.75-0.90	0.80	0.72-0.85	0.79	0.75-0.82
5	0.42	0.22-0.61	0.72	0.66-0.77	0.69	0.58-0.78	0.67	0.58-0.74	0.69	0.64-0.73

Abbreviations: CI, confidence interval; CRS, cumulative relative survival.

Table 4. Cumulative Relative Survival Rates of Patients Diagnosed With Primitive Neuroectodermal Tumors Between 2001 and 2006 (n = 737)

	Infants (Aged <1 y)		Children (Ages 1-9 y)		Adolescents (Ages 10-19 y)		Adults (Aged >20 y)		Overall	
Year	CRS	95% CI	CRS	95% CI	CRS	95% CI	CRS	95% CI	CRS	95% CI
1	0.31	0.09-0.58	0.88	0.81-0.93	0.94	0.82-0.98	0.74	0.61-0.83	0.83	0.77-0.87
2	0.14	0.02-0.38	0.75	0.66-0.82	0.73	0.59-0.84	0.48	0.35-0.60	0.65	0.58-0.70
5	0.14	0.02-0.39	0.64	0.54-0.72	0.57	0.41-0.70	0.35	0.24-0.47	0.53	0.46-0.59

Abbreviations: CI, confidence interval; CRS, cumulative relative survival.

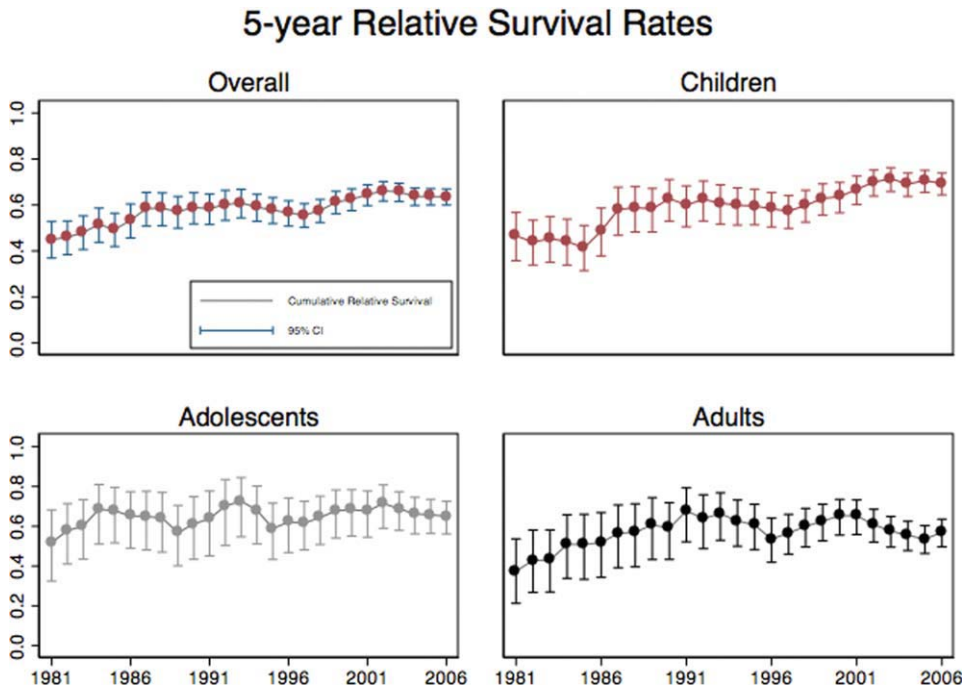

Figure 2. Five-year longitudinal relative survival trends from 1981 to 2006 are illustrated. For this calculation, the period approach was used with a 5-year window for each point estimate. CI indicates confidence interval.

(95% CI, 60%-67%) 25 years later in 2006, indicating a significant 19% improvement in CRS.

These data demonstrate that an improvement in period CRS has occurred since 1981 for 5-year survival (see Fig. 2) and since 1983 for 10-year survival (data not shown). In children, a nonlinear trend was observed in which the 5-year CRS increased by approximately 22% from 47% (95% CI, 36%-57%) in 1981 to 69% (95% CI, 64%-73%) in 2006, and the greatest increase in CRS occurred between 1985 and 1987, when the 5-year period CRS increased by 17%, from 41% to 58%. Similarly, the 10-year CRS increased by 41% between 1983 and 2006

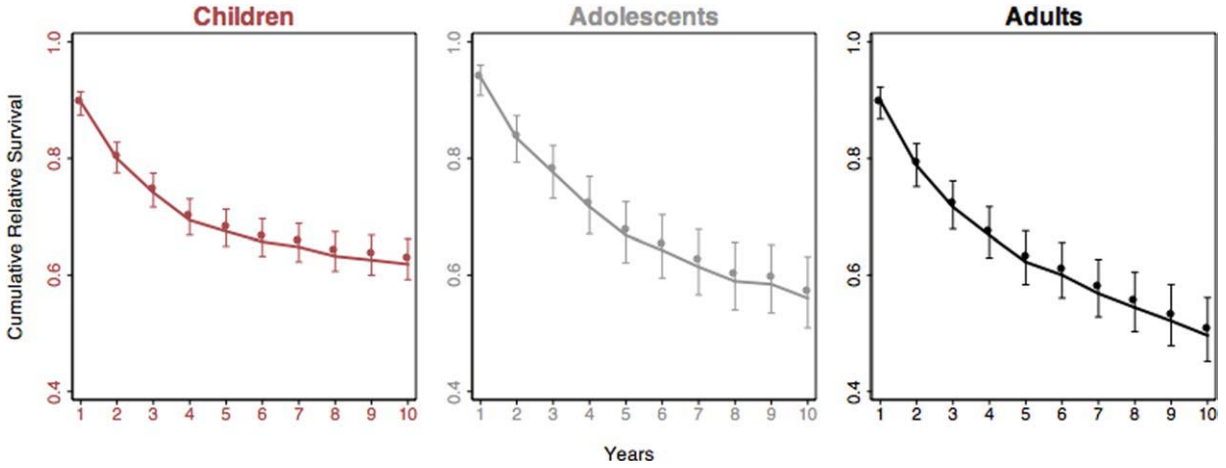

Figure 3. This is a plot of relative survival estimates from a regression model with an age-by-follow-up term (line) and observed values (dots and capped spikes) by age group.

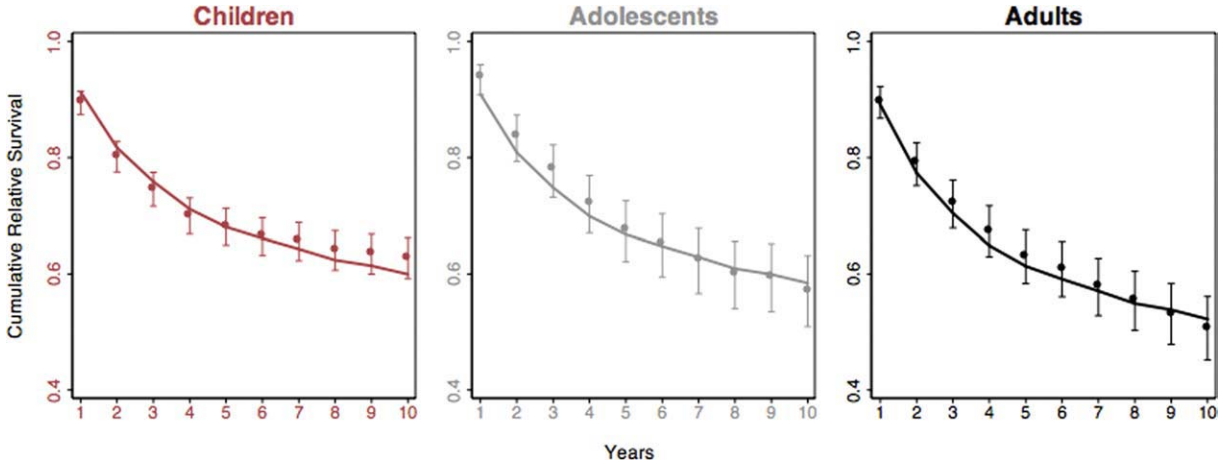

Figure 4. This is a plot of relative survival estimates from a regression model without an interaction term (line) or observed values (dots and capped spikes) by age group. Note the lack of fit at early and late follow-up intervals.

from 23% (95% CI, 8%-44%) to 64% (95% CI, 58%-69%; data not shown).

Adult 5-year period CRS rates increased by 20% from 37% (95% CI, 21%-54%) to 57% (95% CI, 50%-64%), and 10-year rates increased by 10% from 32% (95% CI, 15%-50%) to 42% (95% CI, 34%-50%). Adolescents improved by 13% from 52% (95% CI, 32%-68%) to 65% (95% CI, 56%-73%) in 5-year period CRS rates and had a 16% increase in 10-year CRS rates from 44% (95% CI, 24%-62%) to 60% (95% CI, 50%-68%).

Relative Survival Regression Modeling

Several models were explored with the objective of finding the mathematical model that fit these data most appropriately. The first model assumed that each age category would have proportional hazards, indicating that the hazard rates would differ proportionately throughout follow-up. However, because the proportional hazards model was not estimating the observed relative survival rates accurately, an interaction term was used to improve the fit of the model (for the final accurate model, see Fig. 3; for the inaccurate proportional hazards model, see Fig. 4). An interaction term—in this case, "variable 1" (age category) multiplied by "variable 2" (follow-up year)—resulted in a single variable combination. In this model, the resulting variable is described as an age-by-follow-up interaction variable or term and assumes that the eHRs vary over the categories of the variables. Described differently, an interaction term recognizes that the magnitude of the differences between predictors (in this case, age categories) can

Table 5. Main Excess Hazards Survival Model Describing the Survival Profile of Children, Adolescents, and Adults Who Underwent Surgery and Also Received Radiation[a]

	Medullloblastoma/PNET Years 1 to 5: HR (95% CI)				
Age Group	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Children	1.00 (1.00-1.00)	1.07 (0.79-1.43)	0.70 (0.49-1.00)	0.61 (0.41-0.90)	0.26 90.14-0.46)
Adolescents	0.57 (0.36-0.92)	1.79 (0.96-3.34)	1.68 90.81-3.47)	2.08 (0.98-4.42)	4.45 (1.79-11.06)
Adults	0.98 (0.69-1.38)	1.18 (0.72-1.93)	1.28 (0.72-2.28)	1.08 (0.56-2.10)	2.60 (1.15-5.89)
	Medullloblastoma/PNET Year 6 to 10: HR (95% CI)				
Age Group	**Year 6**	**Year 7**	**Year 8**	**Year 9**	**Year 10**
Children	0.25 (0.13-0.46)	0.13 (0.05-0.32)	0.23 (0.11-0.48)	0.10 (0.03-0.31)	0.10 (0.03-0.35)
Adolescents	2.55 (0.83-7.82)	5.72 (1.56-21.04)	2.88 (0.84-9.92)	1.43 (0.11-18.08)	6.43 (1.27-32.54)
Adults	1.40 (0.50-3.94)	4.03 (1.25-12.97)	1.79 (0.57-5.57)	4.27 (0.93-19.61)	4.43 (0.96-20.42)

Abbreviations: CI, confidence interval; HR, hazard ratio; PNET, primitive neuroectodermal tumor.
[a] The interaction between age group and follow-up year (covariate-by-follow-up interaction) is interpreted by using the excess hazard rate (eHR) of children that year as the base or reference category (1.00). All other categories are referenced to this category. Thus, adults who live to year 5 are 2.6 times as likely to die as children who survived to year 5, and we are 95% confident that this effect size lies between 1.15 and 5.89. Children's eHRs at any year after the first year are interpreted with the first year as the baseline category.

vary over the levels of the other covariates (in this case, follow-up years). The eHRs vary over the follow-up years after diagnosis, as discussed below.

The model was tested for the inclusion of the above described age-by-follow-up interaction term. The likelihood ratio P value for inclusion of this term into the model was $P = .062$ and, thus, did not meet criteria for inclusion. However, when the visual fit of the model was reviewed, the interaction term had markedly improved the fit (see Fig. 3 for the model with the interaction term and Fig. 4 for the model without the interaction term) and was retained in the final model, as discussed above. This indicates that the hazard ratios are not proportional throughout follow-up and that the hazard ratios comparing age categories change during follow-up. Postestimation testing, which is used to validate the performance or fit of the model, demonstrated that the model performed well at predicting the observed values. The final model (see Table 3) predicted every observed death and did not overestimate the number of deaths in each time period.

Overall, differences in the hazards for patients diagnosed with medulloblastoma/PNET depended on the year of follow-up, and differences only emerged in the fifth year. The data in Table 5 indicate that there were no differences between age groups during the first 4 years of follow-up, but significant differences were apparent in the fifth and seventh years, and all other years (except the eighth year) trended toward significance.

In children, the risk of death decreased every year after the second year of follow-up. Adults generally followed the same trend as children until the fifth year after diagnosis, when the hazard rates differed significantly (eHR, 2.60; 95% CI, 1.15-5.89). This significantly different trend also was observed in the seventh year (eHR, 4.03; 95% CI, 1.25-12.97), and all subsequent years trended toward increased hazards.

Adolescents were significantly less likely to die in the first year after diagnosis compared with children and, thus, fared better than both adults and children in the early course of the disease. Adolescents then resumed a survival course similar to that of children until the fifth, seventh, and 10th years, when their excess hazard rate was significantly higher than the rate in children and was similar to the adult rate.

An analysis also was performed on data that did not include PNETs, and 2 alternative age categorizations were used (ages <3 years, 3-15 years, and >15 years and ages <2 years, 3-9 years, 10-19 years, and >19 years) to ensure the stability of these results. The results remained essentially unchanged despite alternate parameterizations.

Standardized Mortality Ratios

The follow-up data set included 1047 deaths. When these patients were compared with the general population (matched by year of birth, age, sex, and race), 20.8 deaths were expected in this patient cohort. Thus, the standardized mortality ratio for patients diagnosed with medulloblastoma or PNET is 50 (95% CI, 47.4-56.3).

DISCUSSION

This study demonstrates that the recent, population-based, 5-year cause-specific survival estimate for patients with medulloblastomas is approximately 69%. Patients who are diagnosed with medulloblastomas or PNETs are 50 times as likely to die from their disease compared with a matched individual from the general population. Furthermore, children, adolescents, and adults have different survival profiles depending on the year of follow-up.

In using traditional Kaplan-Meier life table or overall survival estimation methods to assess the relation of childhood and adult survival after the diagnosis of any tumor type, it is assumed that expected hazard profiles are similar in both children and adults; however, according to the SEER expected mortality tables, they are not. This means that, in overall survival measurements, adults would be expected to have a worse survival profile simply because of the age difference, thus necessitating the use of relative survival estimation.

In population samples with age distributions similar to those in the current study, however, it appears that the use of traditional survival methods (overall survival) may not necessarily bias the estimates significantly. Therefore, relative survival methods may not be required (the low expected mortality count would be 20.8 deaths) (data shown in Fig. 1 and Table 2).

Although several epidemiologic studies have included medulloblastomas and PNETs together as a single entity,[22–26] a landmark study has identified genetic differences that point to a difference in cell origin between these 2 tumor types.[27] The inclusion of both histologic subtypes into the regression model was because PNETs were distributed similarly across age groups (see Table 1); therefore, any survival differences between tumor types would result in differences that were consistent across age categories and would not alter the overall differences between age groups, which was the key issue addressed in the current study. Because the results indicated a difference between survival estimates for each tumor type, and because the 2 entities clearly are separate, the survival estimates are presented separately for each tumor type (see Tables 3 and 4).[28]

The current results indicate that approximately 25% of patients do not receive radiotherapy, which seems greater than would be expected, because radiotherapy is the expected standard of care. Other studies have indicated that, for various reasons, between 5% and 10% of patients did not receive radiotherapy after it was offered.[29,30] The SEER data do not provide information about why radiation was not received. It is important to remember that the SEER database collects information at a population level, as distinct from a controlled clinical environment; therefore, other factors may contribute to the lower uptake of radiotherapy, such as socioeconomic status or performance status.

Because the SEER database is population-based, its size imposes several limitations. First, there is no central pathology review. Second, the SEER database does not routinely collect data on the type of chemotherapy offered to or received by patients, performance status at diagnosis, or socioeconomic status, all of which are important factors. Therefore, although the current study included large numbers of patients and used relative survival techniques, unobserved variables may better explain the survival differences observed here between age groups.

The differences in survival between adults and children that emerged after 4 years may be due to treatment differences between adults and children. In 2000, Greenberg et al noted in a series of 17 adults that adults had higher rates of toxicity from chemotherapy, and 100% of adults required dose reductions during their course of treatment compared with 4.4% of children who were unable to complete treatment.[30,31] Thus, different treatment protocol and other unrecorded variables may be the source of the differences observed in this study.

Recent genetic studies have demonstrated important differences in medulloblastomas.[12,13] A recent study by Parsons and colleagues revealed that children had fewer passenger mutations compared with adults, but they had the same amount of driver mutations (probable cancer-causing mutations).[13] Korshunov and colleagues reported that pediatric tumors had gains of chromosomes 1q, 2, 7, and 17q and loss of 16q, whereas adult tumors more frequently had gains of chromosomes 3q, 4, and 19. In addition, adult tumors exclusively had much more monosomy 17, whereas pediatric tumors had trisomy 17.[12] The driver of differences in survival after the fourth year remains unclear; potentially, it may be that genetic differences produce more aggressive tumors, or perhaps treatment differences begin to show their effects only after 4 years.

Longitudinal Cumulative Relative Survival

The longitudinal period approach to CRS estimation enables us to view changes in survival over time while controlling for the age-period-cohort effect and has enabled a demonstration of significant improvements in the treatment of medulloblastomas/PNETs. It is reasonable to assume that the results from the randomized trials

performed in the 1980s and 1990s, leading to the standardization of treatment (including radiotherapy and chemotherapy), have played a major role in this improvement in survival rates.[4–6,32] However, it should be noted that overlapping error bars during the 1985 and 1987 time period in children indicate that an improvement of this magnitude may be caused by random error and should be interpreted cautiously. Nonetheless, there is an overall improvement in survival noted throughout the entire study period, and it is possible that the greatest strides were made during the late 1980s.

Covariate-by-Follow-Up Interaction

In a recent study, Curran et al also investigated epidemiologic differences in the survival of adults and children using similar SEER data, but those authors observed no differences.[33] In contrast to those results, the current study identified differences in survival when different age categories were compared. The presence of a covariate-by-follow-up interaction can give the appearance of a lack of effect and may cause spurious findings when using regression models that have proportional hazards as an assumption (such as the Cox proportional hazards regression model). The differences in survival between age groups emerge at different times during follow-up. This result was produced using an age-by-follow-up interaction term in the construction of a CRS regression model. The survival curves visually demonstrate the presence of this interaction by progressing identically (in children and adults) until the 4-year mark (see Fig. 1), when they begin to separate or "fork," thus demonstrating visually the covariate-by-follow-up interaction on survival plots.

Applications for Follow-Up

In 1985, Kun and colleagues suggested a follow-up schedule for pediatric medulloblastomas. Although this has been disputed, it was believed that identifying and treating a disease recurrence as early as possible would have an effect on disease progression and survival.[34,35] If an institution has a particular follow-up schedule protocol in place, then the results from the current study suggest that, regardless of the follow-up schedule protocol chosen, its frequency should be consistent for the first 2 years for both children and adults, because the likelihood of mortality remains the same for the first 2 years. For reasons that are unclear, adolescents are significantly less likely to die in the first year after diagnosis compared with adults and children. In the fifth year after diagnosis, the data suggest that the risk of death for children decreases to <70% (her, 0.26; 95% CI, 0.14, 0.46) (see Table 3) of the risk during of the first year after diagnosis. Therefore, changes in follow-up scheduling protocol frequency reasonably could occur at the end of 2 years in all patients and again at the end of the fifth year after diagnosis in children, provided clinical, treatment, and patient-specific indicators do not suggest otherwise. For adults and adolescents, it appears that the risk of death remains higher than for children from ages 5 to 10 years (the risk is unknown after 10 years and only trends toward significance in years 6, 9. and 10). Therefore, the current data do not suggest changing of follow-up schedule protocols, which may occur for children. Note that this study does not recommend a particular follow-up schedule protocol or even its frequency but only makes recommendations on the times when changes in frequency may be appropriate.

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