Survival of Patients With Adult Medulloblastoma

A Population-based Study

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BACKGROUND. Adult medulloblastoma accounts for less than 1% of adult intracranial tumors. Previous survival studies have been inconclusive because of small sample sizes and patient ascertainment bias.

METHODS. The Surveillance, Epidemiology, and End Results (SEER) 17 registries database, released April 2007, was used to assess survival rates and prognostic factors in this disease. SEER*Stat was used to calculate observed and relative 2-, 5-, 10-, 15-, and 20-year survival and Cox Proportion Hazard Regression modeling was used to evaluate prognostic variables.

RESULTS. Four hundred fifty-four patients with adult medulloblastoma were diagnosed from 1973–2004 in the 17 regions covered by SEER. The 2-, 5-, and 10-year relative survival rates were 79.9, 64.9, and 52.1%, respectively. The overall median survival was 127 months (10.6 years). The survival of this disease has improved in the last 3 decades. The median survival of those diagnosed $\leq$1980 and from 1981–1990 were 39 (3.3 years) and 127 months (10.6 years), respectively, and has not been reached for those diagnosed from 1991–2000 and after 2000. In multivariable regression modeling, diagnoses after the 1980s, age of diagnosis before 20, gross total resection, and radiation were favorable prognostic factors, whereas large cell histology was associated with poor survival.

CONCLUSIONS. This is the largest and most representative survival study to date, but further assessments are needed to evaluate the potential of using molecular genetic markers, together with clinical and histopathologic variables, in predicting survival. This may have to take place in the context of a large consortium.
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Medulloblastoma accounts for approximately 20% to 30% of all intracranial neoplasms in children, but in adults it is a rare tumor in adults, with an incidence rate of about 0.5 per million.[1] Many studies that reported survival rates and prognostic factors of this rare cancer were often based on single-institution, retrospective series of less than 50 patients, and thus the results were inconclusive and might not have been representative.[2–10] The only prospective study in adult medulloblastoma recruited 36 patients in a 12-year period and found the overall median survival was 8.15 years.[11] In the largest multicenter study that evaluated 253 adults retrospectively over 30 years in France, extension of tumor into the brainstem, floor of fourth ventricle involvement, and radiation dose to the posterior fossa were significant negative prognostic factors.[12]

To date, there has not been a population-based study to assess survival rate and to evaluate prognostic factors in adult medulloblastoma. Such a study is advantageous in a disease that has a low incidence, as a larger sample size and more representative patient

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characteristics will improve the estimate of survival parameters and the power of assessing prognostic factors.

One such large population database is the cancer registry Surveillance, Epidemiology, and End Results (SEER), which is an authoritative source of information on cancer incidence and survival in the US. Its case ascertainment is about 98% and is the standard for quality among cancer registries around the world. Although SEER does not provide detail information on treatment regimens, the patient characteristics are representative of the US.[13] With more than 30 years of data collection, a series of adult medulloblastoma based on SEER will allow an accurate appraisal of survival parameters. Therefore, in this study the most updated SEER database was used to estimate the 2-, 5-, 10-, 15-, and 20-year survival rates of adult medulloblastoma. The relatively large sample size helped to determine, with greater confidence, those factors important for survival in this rare disease.

MATERIALS AND METHODS

Patient Population

This study the used SEER Program (www.seer.cancer.gov) and SEER*Stat Database: Incidence-SEER 17 Registries Limited Use, November 2006 Submission (1973–2004), National Cancer Institute, Division of Cancer Control and Population Sciences (DCCPS), Surveillance Research Program, Cancer Statistics Branch, released April 2007, based on the November 2006 submission. The SEER 17 registries database contains data from Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, Alaska Native Tumor Registry, Greater California, Kentucky, Louisiana, and New Jersey. Individuals with cancer in this database were diagnosed from 1973–2004. All registries collect individual patient information on demographics, treatment, and clinical information at the time of diagnosis; patients were followed annually for survival status. SEER*Stat (v. 6.3.5, produced by DCCPS and Information Management Service) was used to retrieve adult medulloblastoma cases from SEER 17 registries using the following parameters: age > 18, International Classification of Disease in Oncology 3rd edition (ICD-O3) code 9470–9472, primary site in the cerebellum and other clinically relevant variables (see Prognostic Factors for Survival, below).

Estimates of observed and relative survival

SEER*Stat was used to calculate observed and relative survival in 2-, 5-, 10-, 15-, and 20-year intervals. Relative survival excludes causes of death other than the cancer of interest. Only adult medulloblastoma with microscopic confirmation was used in the calculation; those diagnosed at autopsy or presented as second or later cancer were excluded. The Kaplan-Meier method was used to graphically represent survival function.

Prognostic factors for survival

The following clinical variables retrieved from SEER were included as potential prognostic factors: age at diagnosis, year of diagnosis, SEER registry, race, sex, sex, histologic subtypes, extent of disease, size of tumor, degree of surgical resection, radiation, socioeconomic status as reflected by the annual family income (county level), education level represented by at least having a bachelor degree (county level), and marital status. Extent of disease and size of tumors were only available in cases diagnosed after 1988. Prognostic factors such as Karnofsky performance scores, extent of radiation (craniospinal vs more limited field), radiation dose, and chemotherapeutic treatments were not available.

Cox proportional hazard regression modeling

Prognostic variables were first assessed using univariate analyses. Survival for all analyses was defined as the time from diagnosis until death. Those variables that achieved a $P \leq .1$ were included in a multivariable Cox proportional hazard model. Covariates that were deemed to be important prognostic factors from previous studies were included as well, regardless of their results in the univariate analyses. The multivariate Cox model began with all potential covariates and backward elimination was used to remove covariates with $P > .05$. This process continued until covariates kept in the model were all significant. A preliminary main effect model was obtained after this stage. Subsequently, those variables that were not initially selected for model building (P values of univariate analyses $>.1$) were added back into the preliminary main effect model. This process would identify those covariates that were not significantly related to survival by themselves but could make an important contribution in the presence of other variables. To assess for the possibility that nonlinear logit of continuous variables might improve model fit, fractional polynomials were used to explore whether different power terms might significantly change the likelihood ratio test of the model. Meaningful interaction terms, based on prior knowledge of brain tumors, were introduced 1-by-1 into the preliminary main effect model, and each was kept if $P < .05$. They were defined a priori

TABLE 1
Observed and Relative Survivals of Adult Medulloblastoma, Based on SEER 1973–2004, Released April 2007, November 2006 Submission

Year interval	Observed survival rate (% SE)	Relative survival rate (% SE)
2	79.5 (1.9)	79.9 (1.9)
5	64.0 (2.4)	64.9 (2.5)
10	50.4 (2.9)	52.1 (3.0)
15	44.9 (3.2)	47.4 (3.4)
20	42.7 (3.4)	45.8 (3.7)

SE indicates standard error of the mean.

as interactions between age and radiation, age and surgery, year interval and radiation, year interval and surgery, histologic subtype and radiation. After the derivation of the full model (main effect model plus interaction terms), proportional hazard assumptions were tested by plotting Schoenfeld residuals against time for each covariate; afterward a global proportion hazard assumption test based on the technique of Grambsch and Therneau was conducted.[14] All statistical tests were 2-sided and α was set at 0.05. STATA (v. 9.2, College Station, Tex) was used for regression analyses.

RESULTS

There were 454 cases retrieved from SEER 17 registries database between 1973 and 2004. Table 1 presents the observed and relative survival of adult medulloblastoma diagnosed in the US during the past 31 years. The 5-year observed and relative survival was 64% and 64.9%, and the 10-year observed and relative survival was 50.4% and 52.1%, respectively. Figure 1a shows the Kaplan-Meier survival function of this cohort; the median overall survival was 127 months (10.6 years). Figure 1b shows that survival of this disease has improved in the last 3 decades. In this graph, data for patients diagnosed from 2001–2004 was grouped together with those from 1991–2000 because there was inadequate follow-up time for those diagnosed in the current decade (data censored in November 2006). The median survival for those diagnosed before or during 1980, 1981–1990 were 39 months (3.3 years) and 127 months (10.6 years), respectively; the median survival for those diagnosed from 1991–2000 and after 2000 has not been reached. For those who were diagnosed at 18–20 years of age the median survival has not been reached. In contrast, those between 21–40 and older than 40 year of age had worse prognosis, with median survival at 116 months (9.7 years) and 92 months (7.7 years), respectively (Fig. 1c).

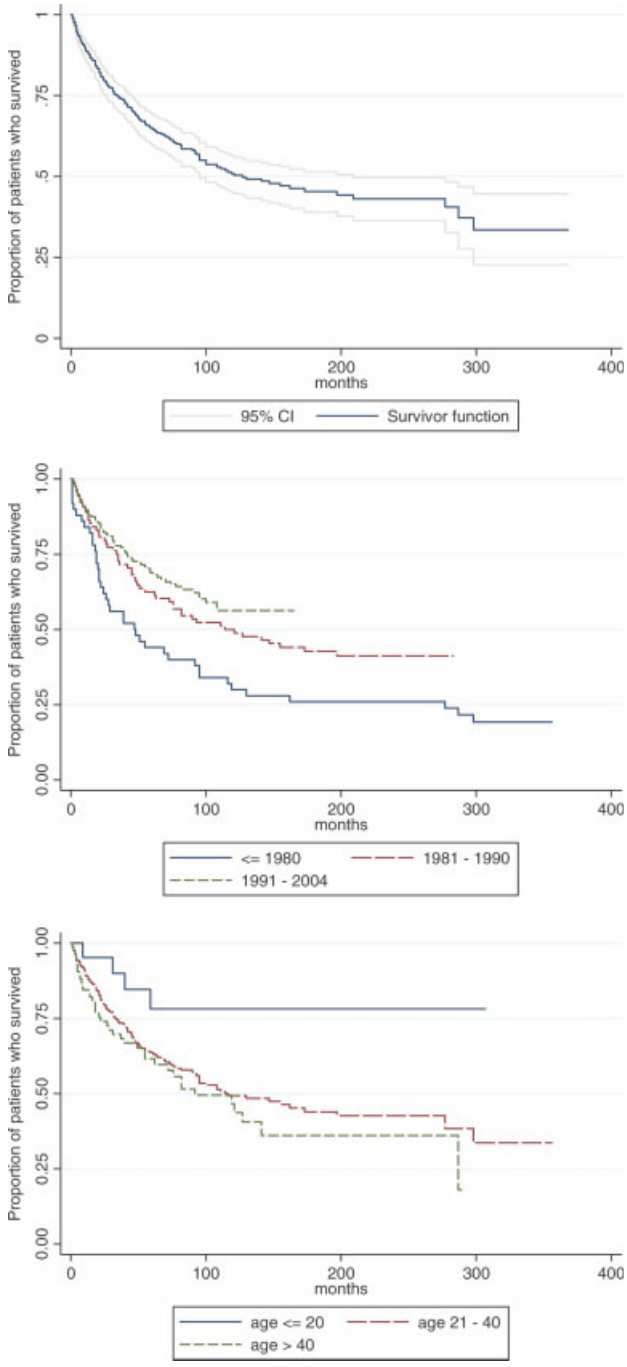

FIGURE 1. (*Top*) Kaplan-Meier survival estimate of adult medulloblastoma based on SEER. (*Middle*) Kaplan-Meier survival estimate of adult medulloblastoma, stratified by the year interval of diagnosis. (*Bottom*) Kaplan-Meier survival estimate of adult medulloblastoma, stratified by age.

The clinical features of the SEER population and the result of univariate analyses are presented in Table 2. The average age of this cohort was 33 (standard deviation [SD] = 11.21). The 1990s contributed the most cases to this cohort, with 198 of 454

TABLE 2
Characteristics of SEER Population and Results of Univariate Analyses

Clinical characteristics	No. of patients (%) N = 454	Univariate analyses hazard ratios (95% CI)	*P*
Age at diagnosis, y			
≤20	22 (4.85)	Reference	
21–40	341 (75.11)	2.99 (1.10–8.08)	.03
>40	91 (20.04)	3.65 (1.31–10.23)	.01
Year of diagnosis			
<1975	18 (3.96)	Reference	
1975–1979	44 (9.69)	1.06 (0.56–1.99)	.86
1980–1984	47 (10.35)	0.55 (0.28–1.09)	.085
1985–1989	49 (10.79)	0.54 (0.27–1.07)	.075
1990–1994	86 (18.94)	0.41 (0.22–0.79)	.007
1995–1999	112 (24.67)	0.36 (0.18–0.70)	.003
≥2000	98 (21.59)	0.92 (0.45–1.88)	.82
Race			
White	399 (87.89)	Reference	
Black	28 (6.17)	1.54 (0.91–2.62)	.11
Others	27 (5.95)	1.03 (0.55–1.97)	.91
Sex			
Women	185 (40.75)	Reference	
Men	269 (59.25)	1.18 (0.87–1.60)	.29
Percentage with bachelor degree (%SD)	28.43 (9.40)	0.99 (0.98–1.01)	.80
Median annual family income, (median US dollars*)	56,820 (19,410)	0.99 (0.99–1.00)	.90
Marital status			
Single/divorced/widowed	199 (43.83)	Reference	
Married	227 (50.00)	0.94 (0.69–1.27)	.66
Marital status unknown	28 (6.17)	0.99 (0.57–1.72)	.96
SEER sites			
Atlanta	25 (5.51)	Reference	
California (excluding SF/SJM/LA†)	31 (6.83)	1.12 (0.62–4.89)	.17
Connecticut	39 (8.59)	1.04 (0.50–2.18)	.91
Detroit (metropolitan)	57 (12.56)	0.95 (0.47–1.94)	.90
Hawaii	7 (1.54)	1.04 (0.33–3.26)	.95
Iowa	43 (9.47)	1.16 (0.57–2.37)	.69
Kentucky	5 (1.10)	0.69 (0.088–5.34)	.72
Los Angeles	63 (13.88)	0.42 (0.18–0.98)	.046
Louisiana	3 (0.66)	1.64 (0.21–12.79)	.64
New Jersey	12 (2.64)	0.43 (0.056–3.37)	.42
New Mexico	29 (6.39)	1.26 (0.58–2.75)	.56
San Francisco-Oakland	55 (12.11)	0.98 (0.48–1.98)	.95
San Jose–Monterey	14 (3.08)	0.50 (0.14–1.78)	.28
Seattle (Puget Sound)	44 (9.69)	0.73 (0.34–1.56)	.42
Utah	27 (5.95)	0.59 (0.24–1.48)	.26
Surgical resection			
Biopsy	16 (3.52)	Reference	
Subtotal resection	91 (20.04)	0.48 (0.20–1.16)	.10
Gross total resection	218 (48.02)	0.35 (0.15–0.82)	.012
Surgery NOS‡	110 (24.23)	0.56 (0.24–1.29)	.17
Unknown	19 (4.19)	0.98 (0.35–2.71)	.97
Histology			
Medulloblastoma	397 (87.44)	Reference	
Demoplastic nodular	52 (11.45)	0.96 (0.49–1.89)	.90
Medullomyoblastoma	2 (0.44)	0.79 (0.29–2.17)	.65
Large cell medulloblastoma	3 (0.66)	1.09 (0.57–2.08)	.25
Extent of disease at diagnoses			
Diseases confined to the brain	271 (59.69)	Reference	
Distal metastases (CSF, spinal cord or extraneural)	81 (17.84)	1.70 (1.02–2.84)	.04
Unknown (diagnosed before 1988)	102 (22.47)	1.49 (0.99–2.01)	.06

(*continued*)

TABLE 2
(*continued*)

Clinical characteristics	No. of patients (%) N = 454	Univariate analyses hazard ratios (95% CI)	*P*
Tumor size			
≤40 mm	128 (28.19)	Reference	
>40 mm	86 (18.94)	0.82 (0.50–1.35)	.44
Unknown	240 (52.86)	1.07 (0.75–1.52)	.72
Radiation			
No radiation	67 (14.76)	Reference	
Radiation given	377 (83.04)	0.52 (0.34–0.80)	.003
Unknown	10 (2.20)	0.34 (0.079–1.44)	.14

* Interquartile range.
† SF/SJM/LA: San Francisco/San Jose–Monterey/Los Angeles.
‡ Surgery not specified.

patients (43.6%) diagnosed during this period. The majority of patients were white (87.9%), and almost 60% of them were men. There were more cases from Los Angeles than any other SEER site; this may reflect the size of the registry area or variation in reporting practice. About 12.8% of histopathology was the desmoplastic nodular type, and less than 1% had the large cell variant. Almost one-half of patients had gross total resection, but precise information on the degree of resection was missing for approximately 24% of them. About 18% of patients had spinal cord, cerebrospinal fluid (CSF), or extraneural metastases at the time of diagnosis, but information on the extent of disease was missing in 22% of patients. Over 80% of patients had cranial radiation.

As shown in Table 2, age at diagnosis, year of diagnosis, SEER site at Los Angeles, extent of disease at diagnosis, surgical resection, and cranial radiation were significant variables in the univariate analyses. Histology is traditionally a strong prognostic factor; therefore, it was also introduced into the Cox model although it was not significant in the univariate analysis. Age was analyzed as a continuous covariate but is shown in Tables 2 and 3 as a categorical variable for easier presentation.

In the preliminary main effect model, diagnosis after 1985, age at diagnosis ≤20, gross total resection, and cranial radiation were associated with better survival, whereas large cell histology was associated with worse prognosis. The generic category *surgery NOS* was also highly significant as a good prognostic factor. SEER site and extent of disease were not significant risk factors in the presence of other covariates. The addition of nonsignificant variables from univariate analyses did not change the preliminary main effect model, and the use of a fractional polynomial (for the variable age at diagnosis) did not improve the fit of the model. Moreover, none of the prespecified interaction terms were significant. Therefore, the final model included only those that were already present in the preliminary model (Table 3). Tests of proportional hazard assumption using both graphic techniques and the global test revealed no violation of assumptions (chi-square = 9.19, $df = 12$, $P = .28$).

DISCUSSION

To date, this is the largest study on survival in adult medulloblastoma. This study population is likely representative of adult medulloblastoma cases in this country, as the demographics of patients captured by SEER is known to be representative of those in the US. The observed 5-year survival rate of 64% is lower than the 72% reported in the French multicenter cohort of 253 patients.[12] The median survival of 10.6 years is also worse than their estimate of 13 years. These differences may reflect uniformly intensive treatment regimens offered at tertiary care centers in the French cohort. In contrast, patients in the SEER population were treated at both metropolitan and community hospitals.

Survival of this disease has improved since the 1980s. This trend most likely reflects better imaging technologies, improved surgical and radiation techniques, and more frequent use of chemotherapy. Computed tomography (CT) scan was introduced in the 1980s and magnetic resonance imaging (MRI) in the early 1990s. Craniospinal radiation along with posterior fossa boost is now used frequently even in disease limited to the cerebellum. Chemotherapies are prescribed more often than 2 decades ago; at first, the regimens were borrowed from those used to treat childhood medulloblastoma, but recently temozolo-

TABLE 3
Final Multivariate Model of Survival Predictors in Adult Medulloblastoma

Survival factors	Hazard ratios (HR)	*P*
Year of diagnosis		
<1975	Reference	
1975–1979	1.03 (0.54–1.95)	.94
1980–1984	0.56 (0.28–1.11)	.097
1985–1989	0.32 (0.12–0.87)	.026
1990–1994	0.15 (0.04–0.48)	.001
1995–1999	0.12 (0.04–0.42)	.001
≥2000	0.31 (0.09–1.03)	.055
Age at diagnosis, y		
≤20	Reference	
21–40	2.98 (1.08–8.22)	.035
>40	4.07 (1.42–11.67)	.009
Histology		
Medulloblastoma	Reference	
Demoplastic nodular	1.16 (0.74–1.81)	.51
Medullomyoblastoma	1.03 (0.13–7.96)	.98
Large cell medulloblastoma	5.37 (1.22–23.65)	.026
Surgical resection		
Biopsy	Reference	
Subtotal resection	0.49 (0.20–1.20)	.12
Gross total resection	0.33 (0.14–0.78)	.012
Surgery NOS	0.14 (0.04–0.52)	.003
Unknown	0.25 (0.06–0.98)	.046
Radiation		
No radiation	Reference	
Radiation given	0.52 (0.33–0.82)	.005
Unknown	0.50 (0.11–2.18)	.35

mide has begun to substitute older chemotherapeutic combinations with some efficacy and decreased adverse effects.[15,16] Thus, a combination of these factors could have improved the survival of this rare disease through the years. Most previously published survival analyses were not able to establish younger age (<20) at diagnosis as a favorable prognostic factor, but this study was able to show the effect of age on survival because of improved power. One may extrapolate that the relative survival of children with medulloblastoma, especially in those older than 3 years of age, may be better than that in adults, but another study that includes children as part of the cohort is necessary to examine this possibility.

Similar to young age at diagnosis, a gross total resection was associated with good prognosis in the US population, but no previous study was large enough to demonstrate a conclusive benefit for complete resection. In fact, 1 study suggested that complete resection only resulted in severely reduced postoperative performance scores, without any survival benefit.[17] However, the benefit of a subtotal resection was not yet clear, as some of those patients in the category *surgery NOS* might have had partial resection, and this category was highly significant. The finding of large-cell medulloblastoma carried the worst prognosis among all histologic subtypes, consistent with data from childhood medulloblastoma; in 1 recent multicenter, prospective study in children, the 5-year event-free survival for the classic histology was 84%, desmoplastic tumors 77%, and large cell variant at 57%.[18] In contrast to smaller series, this study did not find the desmoplastic subtype had any predictive value in survival.[5,9]

Although radiation was a significant factor in both univariate and multivariate analyses, the lack of information on radiation dosage and field limited the utility of this variable. In the French multicenter study, posterior fossa radiation dose less than 50 Gy was a poor prognostic factor.[12] Likewise, tumor staging was not available for the majority of patients, but the variable extent of disease suggested that CSF, spinal cord, or extraneural metastases were of poor prognoses in univariate analysis. Nevertheless, it failed to reach statistical significance in the multivariate model, and it is not clear whether this is because of inadequate power or is because of the influence of more powerful prognostic factors. It is of note that tumor size, an element of the Chang staging system, was not found to be a prognostic factor.[19]

The lack of detailed treatment information in SEER is a major drawback of using this database for prognostic purposes. However, this disadvantage is traded-off by improved power of the study and decreased patient ascertainment bias. As a result, survival parameters derived from this cancer registry are more accurate than previous studies. The SEER-Medicare linkage database provides more information on treatment regimens, but it is of limited use in this setting because only 10 of 454 patients were age 65 or older.

The optimal prognostic model will be 1 that incorporates not only clinical and histopathologic data but also molecular genetic markers. However, because of the rarity of this disease it will be difficult for any center to acquire enough cases to definitively examine any genetic markers. An international consortium may be necessary to achieve such a goal. In childhood medulloblastoma, 1 study found a combination of clinical characteristics and ERBB2 expression provided a highly accurate means of prognosis,[20] but another that combined gene expression profiles and clinical parameters suggested that only gene expression profiles predicted outcome.[21] The value of molecular genetic markers in adult medulloblastoma awaits further studies.

Although there are many challenges in organizing a consortium, this disease will benefit from such

an effort. It will facilitate not only the study of prognostic factors but also clinical trials in chemotherapeutic regimens. This study based on SEER helps to establish some basic survival parameters and prognostic factors, but it is only the beginning for more comprehensive studies to come.

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