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CLINICAL INVESTIGATION **Sarcomas and Pediatric Cancer**

INFANT BRAIN TUMORS: INCIDENCE, SURVIVAL, AND THE ROLE OF RADIATION BASED ON SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) DATA

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Purpose: To evaluate the incidence of infant brain tumors and survival outcomes by disease and treatment variables.

Methods and Materials: The Surveillance, Epidemiology, and End Results (SEER) Program November 2008 submission database provided age-adjusted incidence rates and individual case information for primary brain tumors diagnosed between 1973 and 2006 in infants less than 12 months of age.

Results: Between 1973 and 1986, the incidence of infant brain tumors increased from 16 to 40 cases per million (CPM), and from 1986 to 2006, the annual incidence rate averaged 35 CPM. Leading histologies by annual incidence in CPM were gliomas (13.8), medulloblastoma and primitive neuroectodermal tumors (6.6), and ependymomas (3.6). The annual incidence was higher in whites than in blacks (35.0 vs. 21.3 CPM). Infants with low-grade gliomas had the highest observed survival, and those with atypical teratoid rhabdoid tumors (ATRTs) or primary rhabdoid tumors of the brain had the lowest. Between 1979 and 1993, the annual rate of cases treated with radiation within the first 4 months from diagnosis declined from 20.5 CPM to <2 CPM. For infants with medulloblastoma, desmoplastic histology and treatment with both surgery and upfront radiation were associated with improved survival, but on multivariate regression, only combined surgery and radiation remained associated with improved survival, with a hazard ratio for death of 0.17 compared with surgery alone ($p = 0.005$). For ATRTs, those treated with surgery and upfront radiation had a 12-month survival of 100% compared with 24.4% for those treated with surgery alone ($p = 0.016$). For ependymomas survival was higher in patients treated in more recent decades ($p = 0.001$).

Conclusion: The incidence of infant brain tumors has been stable since 1986. Survival outcomes varied markedly by histology. For infants with medulloblastoma and ATRTs, improved survival was observed in patients treated with both surgery and early radiation compared with those treated with surgery alone.

Pediatric, Brain tumors, SEER, Survival, Radiation.

INTRODUCTION

Pediatric brain tumors are the most common pediatric solid malignancy, second in overall cancer incidence only to leukemias, and represent between 16% and 23% of all pediatric malignancies (1, 2). Among children aged from 0 to 14 years, there is a roughly equal distribution of brain tumors by age (3). Those arising in infants, here defined as children less than 1 year, represent approximately 10% of all pediatric central nervous system tumors (2), with half of those arising in the first 6 months of life (3).

Although the diagnosis and management of pediatric brain tumors in general is challenging, the problem of infant brain tumors is particularly vexing. The onset of symptoms may be delayed by the ability of the expandable infant skull to accommodate increasing intracranial pressure, and when symptoms do arise, they are often nonspecific, contributing to further diagnostic delay (4, 5). Brain tumors arising in the first year of life are more often supratentorial than those diagnosed later in childhood (6), and it is believed that they demonstrate biologically more aggressive behavior (7). Surgical resection can be complicated by small surgical fields and anesthetic difficulties in infants (8), which contribute to higher perioperative mortality, especially in neonates (9). Additionally, justifiable concerns about the late toxicity of radiation lead to delay in radiation, reductions in dose and/or volume, or complete avoidance. All of these and other factors may contribute to the higher mortality seen in infants with brain tumors than in older children with brain tumors (10).

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Although infant brain tumors have been included in randomized trials of brain tumors in very young children (11–15), prospective trials limited to brain tumors diagnosed in those aged less than 1 year have not been undertaken to date, and single institutions can rarely report more than small numbers of infant cases accrued over a long period of time. The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute collects data on cancer incidence and survival from 17 cancer registries covering approximately 26% of the U.S. population (16), which is available for public use. In this report, we used the SEER database to evaluate a larger number of cases to examine the incidence, treatment, and survival outcomes of infant brain tumors.

METHODS AND MATERIALS

SEER*Stat 6.5.2 software (17) was used to interrogate the SEER database. For incidence analysis, the SEER 9 Registries database (18) was accessed, obtaining incidence rates age-adjusted to the 2000 U.S. Standard Population. Incidence rates were calculated by the SEER*Stat software and expressed in cases per million. Overall incidence rates were obtained by year of diagnosis, gender, and race, and major histology subgroups. Joinpoint 3.4.1 software (19) was used to analyze trends in incidence rates using a weighted least squares methodology with random permutations to fit a model of 0–3 joinpoints via a grid search method. The year of diagnosis was plotted against the natural logarithm of the age-adjusted incidence rate for all infant brain tumors to obtain average annual percentage changes in incidence. For incidence analysis of cases treated with or without radiation, a Poisson model was used to accommodate a few years with zero count. Further analysis of trends in incidence rates for different histology groupings was not carried out because multiple years had small or zero counts, which markedly increases the relative standard error.

For survival outcomes analysis, the November 2008 SEER 17 registry database (20) was queried to evaluate all malignant brain tumors (site codes C70.0, C71.0–71.9, C72.2–72.8), diagnosed at age less than 1 year. Additional variables analyzed included tumor histology, gender, race, brain location, tumor grade, presence of distant metastatic disease, use of surgery, extent of surgery, use of radiation, survival time, and vital status. The SEER database captures information on the use of surgery or radiation therapy only in the first 4 months from diagnosis. Patients coded as having atypical teratoid rhabdoid tumors (ATRTs) and those with primary rhabdoid tumors of the brain were considered together given the substantial overlap between the two diagnoses (21). Individual case data was exported to SPSS 17.0.2 software (Chicago, IL) for analysis. Before survival analysis, individual patients who both (a) were not treated with radiation and (b) died with less than 1 month of follow-up time were excluded to eliminate patients diagnosed at autopsy alone and to reduce bias against surgical monotherapy by excluding patients who died in the immediate postoperative period before adjuvant therapy could be administered. Kaplan–Meier survival analysis was performed to estimate the observed and median survival outcomes. Using the log-rank test, univariate analysis was performed by treatment decade, gender, race, location of tumor (supratentorial versus infratentorial), histology subtype and/or grade as appropriate, presence of distant/drop metastasis, extent of surgery (total vs. subtotal resection), and overall treatment group (surgery and radiation, surgery alone, radiation alone, neither surgery nor radiation). For the medulloblastoma patient group, a Cox regression analysis model was fitted by including statistically significant variables on univariate analysis and those with a p value of <0.2.

RESULTS

Between 1973 and 2006, the overall annual incidence rate for malignant brain tumors in children less than 1 year old was 31.2 cases per million. From 1973 to 1986, there was a statistically significant increase in the overall incidence from 16 to 40 cases per million per year ($p = 0.005$). From 1986 through 2006, the incidence rate has been stable, with an average annual incidence of 35 cases per million (Fig. 1). Table 1 breaks down the overall incidence rate by

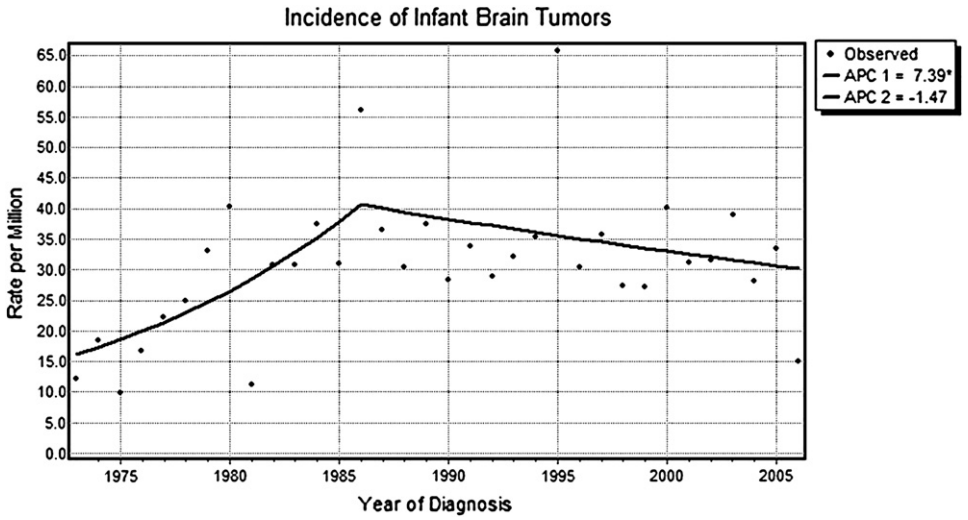

Fig. 1. Incidence trend in infant brain tumors between 1973 and 2006. Between 1973 and 1986, the incidence rose with an annual percent change (APC) of 7.39%, which was statistically significant (denoted by the asterisk). From 1986 through 2006, there was no statistically significant change in the annual incidence rate, with an average of 35 cases per million per year.

Table 1. Incidence rates by histology of primary brain tumors diagnosed between 1973 and 2006

Histology	Total	Gender		Race		
		Male	Female	White	Black	Other*
Gliomas	13.8	13.3	14.4	15.9	7.9	2.5
Medulloblastoma/PNET	6.6	6.0	7.3	7.5	3.7	4.1
Ependymoma	3.6	4.7	2.5	4.3	1.2	1.7
Germ cell tumors	1.6	1.3	1.9	1.6	1.8	0.8
Choroid plexus	1.1	1.5	0.7	1.1	1.2	0.8
ATRT/CNS rhabdoid	1.0	1.0	1.0	1.2	0.6	<0.1
All other histologies	3.4	3.6	3.2	3.4	4.9	1.7

Abbreviations: ATRT = atypical teratoid rhabdoid tumor; CNS = central nervous system; PNET = peripheral neuroectodermal tumor.

All incidence rates reported as average annual cases per million.

* Other includes American Indian, Alaskan Native, Asian, or Pacific Islander.

major histology groups, gender, and race. The leading histologies by incidence were gliomas (13.8 per million), medulloblastoma and primitive neuroectodermal tumors (6.6 per million), and ependymomas (3.6 per million). All patients had pathologically confirmed diagnoses except for 9% of the infants with gliomas who were coded as a radiographic diagnosis. There was no appreciable difference in incidence rate by gender. The incidence was higher in whites (35.0 cases per million) than in blacks (21.3 cases per million) or in those categorized as "other" race, which includes Native American, Alaskan Natives, Asians, and Pacific Islanders (11.6 cases per million).

Examining the incidence of cases treated with and without radiation over time, there was a significant decline in the rate of cases treated with radiation within the first 4 months from diagnosis between 1979 and 1993, from 20.5 cases per million to less than 2 cases per million. This was followed by a nonsignificant trend toward increasing use through 2006 (Fig. 2), with an average annual incidence of 3.6 cases per million per year treated with upfront radiation.

Querying individual case data from the SEER 17 registry yielded a total of 597 patients with brain tumors diagnosed at age less than 1 year. Kaplan–Meier survival curves for each of several major histology groups are shown in Fig. 3. Survival varied markedly by histology. Infants with low-grade gliomas had the highest observed survival, 85.6% at 3 years, whereas those with ATRTs or primary rhabdoid tumors of the brain had the lowest, with a 1-year survival of 39.7%. Median survival estimates and observed survival at 12, 36, and 60 months are reported for each of the major histology groups in Table 2.

Gliomas represented 42.5% (n = 254) of the individual cases in the SEER database. Of those, 104 were low-grade histology, 57 high grade, and 81 had unspecified malignant glial tumors without a documented grade. Ten patients were excluded from survival analysis (1 low grade, 9 high grade). Among the remaining 103 low-grade gliomas, 48 were pilocytic astrocytomas. Radiation therapy was used in the management of 9 patients with low-grade gliomas. The observed survival for all low-grade gliomas at 3 years was 85.6% and was independent of any of the variables tested in univariate analysis. In contrast, for high-grade gliomas (n = 48), 3-year survival was 52.1%, with Grade 3 tumors including anaplastic astrocytomas having a 3-year survival of 66.7% compared with the 40.7% observed in Grade 4 tumors, including glioblastoma (p = 0.024). Radiation therapy was uncommonly employed in upfront management of infants with high-grade gliomas, which was documented in only one case. Survival outcomes for the patients with gliomas of unspecified grade closely mirrored those of infants with low-grade gliomas (Table 2).

There were 97 cases of medulloblastoma, including infants coded as primitive neuroectodermal tumors arising in the posterior fossa, of which 10 were excluded from survival

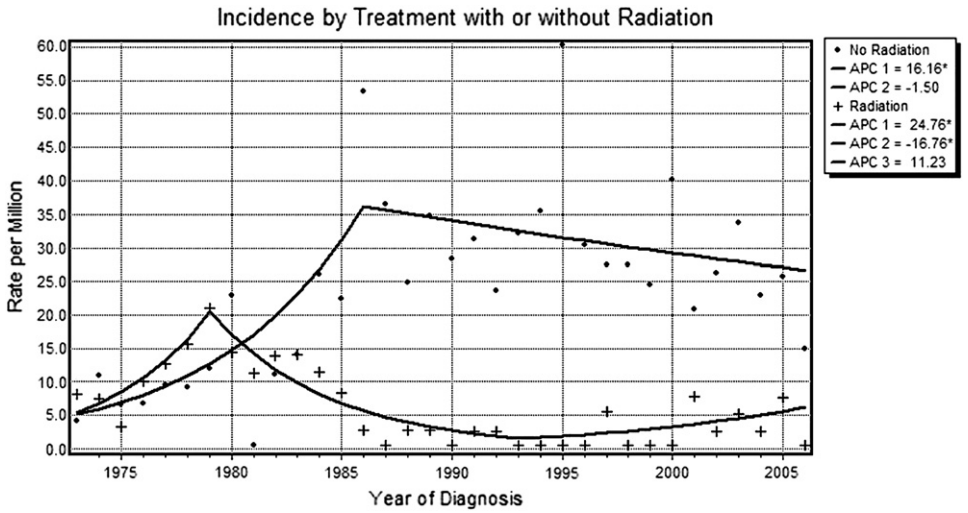

Fig. 2. Incidence trend by treatment with or without early radiation therapy. After an initial increase in the incidence of cases treated with early radiation therapy, between 1979 and 1993, the incidence of cases treated with upfront radiation declined with an annual percent change (APC) of –16.76%, which was statistically significant (denoted by asterisk). The incidence of cases treated without upfront radiation rose between 1973 and 1986, with an APC of 16.16%.

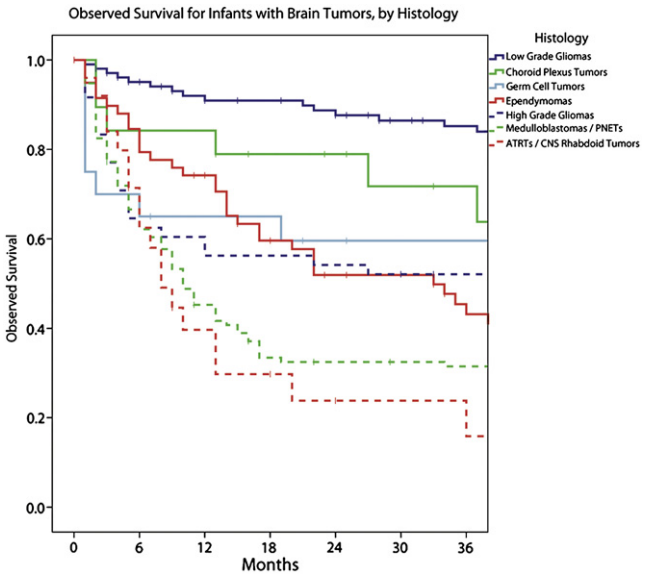

Fig. 3. Observed survival for infants with brain tumors, by histology. ATRTs = atypical teratoid rhabdoid tumors; CNS = central nervous system; PNETs = primitive neuroectodermal tumors.

analysis. For the remaining 87 infants, the observed survival at 12 months was 43.7%. Among the 84 patients with available data on radiation, 19 (22.6%) received radiation. At 3 years, patients treated with both surgery and radiation had an observed survival of 64.7%, compared with 22.1% for those treated with surgery alone ($p = 0.001$, Fig. 4). Patient with desmoplastic histology had an observed survival of 77.8% at 3 years compared with 25.4% for nondesmoplastic histologies ($p = 0.013$). A Cox proportional hazards model incorporating treatment group and histology as well as gender ($p = 0.087$), race ($p = 0.109$), and the presence or absence of drop metastases ($p = 0.099$) found that only combination treatment with surgery and radiation was significant, with a hazard ratio for death of 0.17 when compared with treatment with surgery alone ($p = 0.005$).

There were 63 cases of ependymoma, of which 4 were excluded from survival analysis. In the remaining 59 patients, 3-year observed survival was 43.1% and was higher in patients treated in more recent decades ($p = 0.001$). No other variables were found to be significant on univariate analysis. Radiation use was documented in 28.6% of cases and the proportion of patients treated with radiation did not appear to change between the first and later half of the study period ($p = 0.21$).

Thirty cases of ATRTs, including primary brain rhabdoid tumors, were identified, of which three were excluded from survival analysis. In the remaining 27 infants, the 12-month survival was 39.7%. Those treated with surgery and radiation had a 12-month survival of 100% compared with 24.4% for those treated with surgery alone ($p = 0.016$, Fig. 5). No other variables were significant on univariate analysis.

DISCUSSION

The SEER database demonstrated a statistically significant rise in the incidence of infant brain tumors between 1973 and 1986, with an annual percent change of 7.4%, which has thereafter been stable. A similar increase in incidence between 1973 and 1985 was described in children across all ages in a SEER analysis by Smith *et al.* (22), who noted that the rise was driven by increasing incidence of low-grade gliomas and hypothesized that it was the result of development and increasing availability of neuroimaging including computed tomography and magnetic resonance imaging. In our analysis, restricted to infants less than one year old at the time of diagnosis, attempts to analyze incidence trends by histology were limited because many years had a small or zero case count for a given histology, which results in a high relative standard error. However, with an additional 12 years of data available in SEER since the Smith *et al.* analysis, the overall observed incidence of infant brain tumors in our analysis remained stable since 1986, with an average annual rate of 35 per million.

Epidemiological findings in this SEER analysis are supported by other research. Gliomas, medulloblastomas, and ependymomas were the three histologies with the highest

Table 2. Kaplan–Meier Survival by Major Histology Groupings

		Follow-up (months)		Observed survival (%)			
Histology	No. patients	Median	Range	12 months	36 months	60 months	Median survival (months)
Low-grade glioma	103	55	1–337	90.9	85.2	77.2	Not reached
Gliomas, NOS[†]	81	50	1–329	84.9	77.6	67.4	247
Choroid plexus	20	30	0–230	84.2	71.8	46.5	58
Germ cell tumor	20	21	1–283	65.0	59.6	59.6	Not reached
Ependymoma	59	22	1–223	74.2	43.1	*	33
High-grade glioma	48	32	1–221	56.2	52.1	52.1	100
Supratentorial PNET	28	11	1–231	50.0	34.6	34.6	11
Medulloblastoma	87	10	1–340	43.7	30.5	*	10
ATRT/CNS rhabdoid	27	7	0–73	39.7	*		8
All others	57	30	0–351	67.5	56.0	53.9	Not reached
All histologies	530	27	0–351	68.8	56.8	51.2	73

Abbreviations: ATRT = atypical teratoid rhabdoid tumor; CNS = central nervous system; PNET = peripheral neuroectodermal tumor.
* Number at risk too few (≤20%).
[†] NOS = Not otherwise specified (no tumor grade).

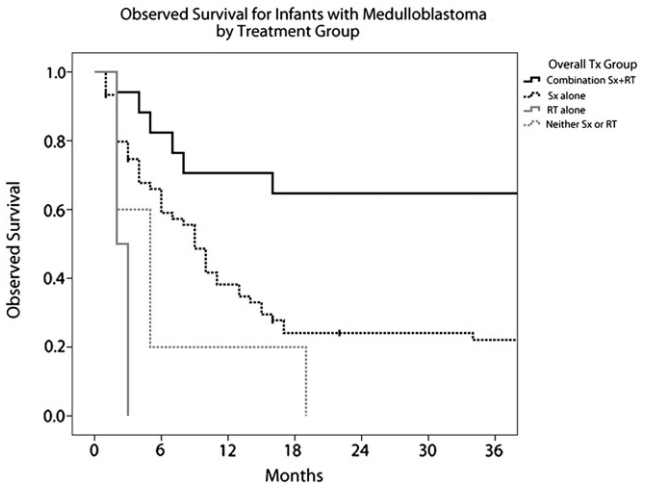

Fig. 4. Observed survival for infants with medulloblastoma, by treatment group. RT = radiation; Sx = surgery; Tx = treatment.

incidence in the SEER database, consistent with the findings by Larouche *et al.* (23) in their comprehensive literature review of 1,289 infants diagnosed with tumors of the central nervous system. Our SEER analysis showed a higher incidence in whites (35.0 cases per million) than in blacks (21.3 cases per million), which is internally consistent with SEER analysis of brain tumors in children and adolescents (1), which found that the incidence of CNS tumors among whites and blacks is nearly equivalent in childhood except in the first 2 to 3 years of life.

The use of radiation therapy in the initial management of infant brain tumors has decreased over time, although the SEER data do not capture the children who received delayed or salvage radiation therapy. Our joinpoint model demonstrated a statistically significant decrease in the use of radiation during the 1980s, nadiring in the early 1990s, and stable since. Given that the increased incidence of childhood brain tumors in the period before 1985 appears to be driven by the detection of more low-grade gliomas (22), which

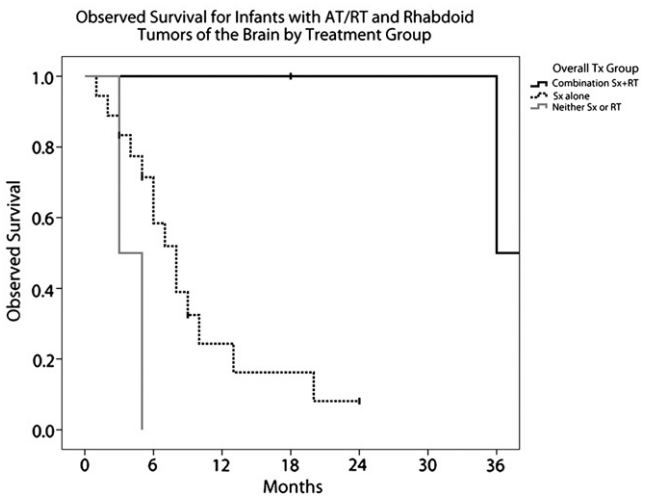

Fig. 5. Observed survival for infants with ATRT and rhabdoid tumors of the brain by treatment group. RT = radiation; Sx = surgery; Tx = treatment.

would presumably have otherwise remained undetected for prolonged periods (24), at least part of the decline in the use of radiation therapy is presumably driven by this change in histology makeup because radiation therapy can typically be delayed or avoided in children with low-grade gliomas without adversely affecting survival (25), as was also found in adults (26).

Another explanation for the observed decline in the incidence of cases treated with radiation undoubtedly reflects a general change in practice toward strategies that seek to delay or avoid radiation therapy by introducing or intensifying chemotherapy (11–15). The motivation for this is to minimize or avoid the well-documented late neurocognitive (27), endocrine (28), and social (29) dysfunction seen in survivors of childhood malignancy who received cranial irradiation. Because the SEER database captures information about radiation use only in the first 4 months following diagnosis, an unknown percentage of patients coded as not receiving radiation may have received delayed radiation after prolonged upfront chemotherapy or at the time of disease relapse. It is therefore not possible to parse out the percentage of patients who may have received delayed radiation or to assess its potential utility in the cohort of patients who were managed without upfront radiation therapy.

Although randomized comparisons between delayed radiation strategies and upfront treatment have not been made, the outcomes of prolonged postoperative chemotherapy regimens have been underwhelming, with a high risk of disease progression at a median time of 12–18 months. For example, in prospective attempts to substitute chemotherapy for craniospinal irradiation in children under 5 with medulloblastoma, the 5-year progression-free survival was 29% for the most favorable subgroup, although their overall survival was 73% after salvage therapy, which included radiation for nearly 60% after a median time to progression of 17 months (15). In the Pediatric Oncology Group Protocol 8633, children <2 years of age with malignant brain tumors were treated with chemotherapy for 2 years before planned local radiation and had a 5-year progression-free survival of 12.7% (30). However, children between 2 and 3 years of age received 1 year of chemotherapy before local radiation, with a 5-year progression-free survival of 54.8%, suggesting that the timing of radiation may affect outcomes, with better results seen when radiation was delayed 1 year compared with those in whom it was delayed for 2 years. The great majority of relapses for childhood brain tumors occur at the primary site, and salvage radiation results in disappointing progression-free survival (31), suggesting that optimizing local control upfront may be important to achieve long-term survival.

Our SEER analysis found that for children with medulloblastoma and ATRTs, including rhabdoid tumors of the brain, those managed with both surgery and upfront radiation have improved survival compared with those who are managed with surgery alone. These data suggest that for these particularly aggressive histologies, outcomes are optimized by the early inclusion of radiation therapy. It should

be noted that ATRTs are a relatively newly recognized pathologic entity (21), and there are presumably a number of unrecognized cases of ATRTs among the infants coded as medulloblastoma in the early years of this experience before the pathologic criteria were established and promulgated in the 1990s. The current Children's Oncology Group trial for medulloblastoma in children aged under 3 years does not include radiation therapy, although if it is given, focal irradiation of the primary tumor site alone is recommended unless metastatic disease is present. For ATRTs, both single institution (32) and registry data (33) suggest a benefit to early radiation therapy, and the current Children's Oncology Group protocol for ATRTs incorporates involved field radiation therapy after surgery and two cycles of chemotherapy. In addition to limiting radiation therapy to the primary tumor site, techniques such as intensity-modulated radiation therapy and proton therapy may further reduce the volume of normal brain irradiated.

The SEER data for infants with high-grade gliomas show relatively favorable survival outcomes compared with expected outcomes in adults, with 52% of these infants alive 5 years after diagnosis. All but 1 of the 48 infants in this data set were managed without upfront radiation therapy. These data are consistent with some institutional (34) and cooperative group (3) experiences with infant high-grade gliomas using delayed radiotherapy, and genetic analysis of pediatric glioblastoma have identified differences in molecular features despite similar histologic features to their more lethal adult counterparts (35).

Although it is presumed that chemotherapy was commonly employed in the management of many of the infants reported here, data on chemotherapy use is unfortunately not collected in the SEER database. Additional limitations of the SEER database include the lack of central pathologic review, incomplete data, underreporting of radiation therapy, lack of radiotherapy details, and, inherent in all nonrandomized data, the possibility of unaccounted selection biases (36). In the SEER data set, unknown selection biases may drive treatment intent, potentially obscuring or enhancing apparent differences in therapeutic effect. In this analysis, we included patients over a long time span, over which many changes in diagnosis and treatment have occurred. By limiting the analysis to children diagnosed in the first year of life, subgroup analysis of all but the most common histologies is limited by small patient numbers, which greatly reduces the statistical power to detect potential differences in outcome by treatment variables. This likely explains why some known prognostic factors did not appear to affect outcome in this analysis. In addition, inconsistencies in the ascertainment of the degree of surgical resection (surgical assessment or postoperative imaging) in the SEER data set may obscure the impact of this variable, which has validated prognostic significance in pediatric brain tumors including medulloblastoma and ependymoma.

CONCLUSION

The incidence of infant brain tumors increased from 1973 to 1986 and was thereafter stable at an average annual rate of 35 cases per million. The incidence of cases treated with early radiation therapy decreased in the 1980s to early 1990s and was then stable through 2006. Gliomas, medulloblastomas, and ependymomas were the three most common histologies in infants. Survival outcomes varied markedly by histology. For infants with medulloblastoma and ATRT, improved survival was observed in patients treated with both surgery and radiation compared with those treated with surgery alone. Although limited by potential selection biases and incomplete data, including lack of information on chemotherapy, results from the SEER database suggest a significant survival benefit for the incorporation of upfront radiation therapy in the management of infants with these aggressive histologies.

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