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The descriptive epidemiology of atypical teratoid/rhabdoid tumors in the United States, 2001–2010

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Background. Atypical teratoid/rhabdoid tumor is a rare malignant CNS tumor that most often affects children ≤3 years old. The Central Brain Tumor Registry of the United States contains the largest aggregation of population-based incidence data for primary CNS tumors in the US. Its data were used to describe the incidence, associated trends, and relative survival after diagnosis of atypical teratoid/rhabdoid tumor.

Methods. Using data from 50 cancer registries between 2001 and 2010, age-adjusted incidence rates per 100 000 and 95% CIs were calculated by sex, race, Hispanic ethnicity, age at diagnosis, and location of tumor in the CNS for children aged 0 to 19 years. Relative survival rates and 95% CIs were also calculated.

Results. The average annual age-adjusted incidence rate was 0.07 (95% CI: 0.07, 0.08). Incidence rates did not significantly vary by sex, race, or ethnicity. Age had a strong effect on incidence rate, with highest incidence among children <1 year, and decreasing incidence with increasing age. The 6-month, 1-year, and 5-year relative survival rates for all ages were 65.0%, 46.8%, and 28.3%, respectively. Atypical teratoid/rhabdoid tumor can occur anywhere in the CNS, but supratentorial tumors were more common with increasing age.

Conclusion. We confirm differences in survival by age at diagnosis, treatment pattern, and location of tumor in the brain. This contributes to our understanding of these tumors and may stimulate research leading to improved treatment of this devastating childhood disease.

Keywords: atypical teratoid/rhabdoid tumors, brain tumors, incidence, pediatric brain tumors, survival.

Atypical teratoid/rhabdoid tumor (ATRT) is a rare and aggressive type of embryonal tumor of the central nervous system (CNS) occurring in childhood. The incidence of all embryonal tumors in the United States is 0.66 per 100 000 in children 0–19 years old.[1] ATRT commonly affects infants and young children, especially children ≤3 years old, and prognosis is generally poor.[2] There is no consensus concerning a standard treatment regimen for these tumors. Complete surgical resection can often be challenging due to young age at diagnosis and tumor location in the brain. In addition, most physicians avoid radiation in very young children due to severe neurocognitive late effects. Intensive chemotherapy regimens are currently under study, but no standard chemotherapy regimen exists for these patients.

ATRT was first described as a distinct type of CNS rhabdoid tumor in 1987 and was further described in 1996.[3,4] The updated World Health Organization (WHO) classification of CNS tumors in 2000 included ATRT for the first time.[5] As a result of the relatively new use of this diagnosis, studies involving the epidemiology of ATRT are still developing. Furthermore, due to their rarity, most studies looking at these tumor types have been hospital-based

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(see Athale et al[6] for an overview and meta-analysis of many of these reports) or registry-based case series studies that—though they may be population based—analyze a smaller population of patients than is presented here.[2,7–12] The objective of this report is to describe the epidemiology (incidence and relative survival) of ATRT in the US using population-based data representing ~98% of the US population from 2001 to 2010.

Materials and Methods

Data Collection

This study utilized population-based registry data from the Central Brain Tumor Registry of the United States (CBTRUS) for newly diagnosed ATRT—defined as cases identified with *International Classification of Diseases for Oncology*, 3rd edition (ICD-O-3) morphology code 9508/3—between 2001 and 2010. No other histologic or immunohistochemical information was available in this dataset. CBTRUS obtains these data through a partnership with the National Program of Central Registries (NPCR) of the Centers for Disease Control and Prevention, whereby data collected by NPCR are directly received by CBTRUS under a special agreement. These data are collected via cancer registrar review of hospital records, which are then transmitted to central (state-based) registries and then further transmitted to NPCR before being available to CBTRUS. The NPCR data are combined with data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute and are refined using an edit program created in collaboration with neuropathologists to create the final CBTRUS dataset. The CBTRUS analytic dataset for 2001–2010 contains incidence data obtained from 50 central cancer registries (45 NPCR and 5 SEER) and captures brain tumor incidence for over 98% of the US population during this time period.[1] A system of data quality checks ensures that data are reported as accurately and completely as possible.[1] Incidence calculations are generated using the US 2000 standard population.

Analyses were conducted using 2001–2010 data only. Though ATRT has been recognized as a histologic type since 1997, it was not until after the 2000 revision of the WHO guidelines that it was assigned an ICD-O code, which allowed it to be registered as a specific diagnosis in the US starting in 2001.[5] Diagnostic techniques for this tumor type changed over the time period, and thus cases were analyzed separately for those diagnosed between 2001 and 2004 versus those diagnosed between 2005 and 2010. Cases were included for persons aged 0 to 19 years, categorized into age groups of <1, 1, 2–3, 4–5, and 6–19 years (n = 586). Data provided to CBTRUS from NPCR do not include survival data, which were obtained for ATRT from 18 SEER registries for the years 2001 to 2010.[13] These cases represent a subset of the overall dataset analyzed, as they are incident cases included in the overall incidence calculations (n = 177). SEER registries cover ~26% of the US population, whereas CBTRUS registries cover 98% of the US population. Hence the SEER dataset is not a perfect demographic subsample of the overall dataset.

Statistical Analysis

SEER*Stat 8.1.2 statistical software (http://seer.cancer.gov/seerstat/) was used to calculate frequencies and age-adjusted incidence rates per 100 000 population with 95% confidence intervals (CIs) overall, by sex, race, Hispanic ethnicity, selected age groups, location of tumor in the brain, and year of diagnosis using the US standard 2000 population from the US Census Bureau for comparator groups for all calculations.[14,15] For comparisons based on racial characteristics, categories included whites, blacks, Asian/Pacific Islanders, and other/unknown; the other category included all other racial groups due to small numbers of cases in these groups. For comparisons based on location of tumor in the brain, categories included supratentorial (ICD-O-3 codes C71.0–C71.5), infratentorial (ICD-O-3 codes C71.6–C71.7), other brain (ICD-O-3 codes C71.8–C71.9), spine and cauda equina (ICD-O-3 codes C71.0–C71.1), and other CNS (ICD-O-3 codes C72.2–C72.9). The Joinpoint Regression Program (http://surveillance.cancer.gov/joinpoint/) was used to identify trends in incidence of ATRT in comparison with other embryonal tumor types by calculating an annual percentage change (APC) and 95% CIs.[16] SEER*Stat 8.0.4 was used to calculate relative survival and 95% CIs overall, as well as by age, sex, year of diagnosis, location of tumor in the brain, and treatment pattern. This method takes into account expected survival based on age, sex, and race for the population at large and adjusts observed survival in order to estimate relative survival rates. Rates and counts were excluded when they were based on populations smaller than 16 persons in order to prevent individual identification and due to the instability of these calculations.[1]

Results

Five hundred eighty-six cases of ATRT in children aged 0 to 19 years at diagnosis were identified in the CBTRUS dataset between 2001 and 2010, representing 1.6% of all brain and CNS tumors diagnosed in persons 19 years and younger during this time period. ATRT represented 10.1% of all primary brain and CNS tumor cases in the CBTRUS database for persons under 1 year during the time period. Males accounted for 54.2% of cases; 79.5% of cases occurred in whites; and 79.3% of cases occurred in non-Hispanics (Table 1). Median age at diagnosis was 1 year, and 65.7% of all cases occurred in children <2 years of age. Overall, 35.8% of tumors occurred exclusively supratentorially, 28.3% exclusively infratentorially, 27.8% in other brain (including diagnosis coded as other brain or overlapping regions of brain), 4.6% in the spinal cord and cauda equina, and 3.4% in other CNS (Table 1). This varied by age, with 21.8% and 69.0% of tumors occurring supratentorially for ages 0–1 and 6–18 years, respectively. Percentage of tumors occurring in the nonbrain CNS (including pituitary and spine) remained stable over all age groups.

Average Annual Incidence Rates

The overall age-adjusted incidence was 0.07 per 100 000. The average annual age-, sex-, and race-specific incidence rates are shown in Table 1. Incidence of ATRT was highest in children under 1 year of age and in children 1 year of age, with incidence rates of 0.54 (95% CI: 0.47, 0.62) and 0.41 (95% CI: 0.35, 0.48), respectively. Incidence rates declined with increasing age. Overall, there was no significant difference in incidence by sex, race, or Hispanic ethnicity (Table 1).

There was a statistically significant difference in average annual age-adjusted incidence rates depending on year of diagnosis. For the years 2001 to 2004, incidence was 0.05 per

Table 1. Counts and average annual incidence adjusted by age, y[a]

	0–14			0–19			<1			1			2–3			4–5			6–19		
	n	Rate	95% CI	*n*	Rate	95% CI	*n*	Rate	95% CI	*n*	Rate	95% CI	*n*	Rate	95% CI	*n*	Rate	95% CI	*n*	Rate	95% CI
Sex																					
Male	315	0.10	(0.09, 0.11)	318	0.08	(0.07, 0.09)	109	0.54	(0.44, 0.65)	92	0.46	(0.37, 0.56)	59	0.15	(0.11, 0.19)	26	0.07	(0.04, 0.10)	32	0.01	(0.01, 0.02)
Female	262	0.09	(0.08, 0.10)	268	0.07	(0.06, 0.08)	106	0.55	(0.45, 0.66)	70	0.37	(0.28, 0.46)	49	0.13	(0.10, 0.17)	20	0.05	(0.03, 0.08)	23	0.01	(0.01, 0.01)
Race																					
White	459	0.10	(0.09, 0.11)	466	0.07	(0.07, 0.08)	172	0.57	(0.49, 0.66)	132	0.44	(0.37, 0.52)	87	0.15	(0.12, 0.18)	32	0.05	(0.04, 0.08)	43	0.01	(0.01, 0.01)
Black	76	0.08	(0.06, 0.10)	76	0.06	(0.04, 0.07)	29	0.45	(0.30, 0.64)	–	–	–	16	0.13	(0.07, 0.20)	–	–	–	–	–	–
Asian or Pacific Islander	34	0.11	(0.07, 0.15)	35	0.08	(0.06, 0.11)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Other/ unknown	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Hispanic ethnicity																					
Non-Hispanic	456	0.10	(0.09, 0.11)	465	0.07	(0.07, 0.08)	167	0.56	(0.48, 0.65)	133	0.45	(0.37, 0.53)	85	0.14	(0.11, 0.18)	34	0.06	(0.04, 0.08)	46	0.01	(0.01, 0.01)
Hispanic	121	0.08	(0.07, 0.10)	121	0.06	(0.05, 0.08)	48	0.49	(0.36, 0.65)	29	0.31	(0.21, 0.44)	23	0.13	(0.08, 0.19)	–	–	–	–	–	–
Anatomic site of tumor																					
Supratentorial	205	0.03	(0.03, 0.04)	210	0.03	(0.02, 0.03)	47	0.12	(0.09, 0.16)	58	0.15	(0.11, 0.19)	53	0.07	(0.05, 0.09)	23	0.03	(0.02, 0.04)	29	0.01	(0.00, 0.01)
Infratentorial	164	0.03	(0.02, 0.03)	166	0.02	(0.02, 0.02)	79	0.20	(0.16, 0.25)	53	0.14	(0.10, 0.18)	19	0.02	(0.01, 0.04)	–	–	–	–	–	–
Other brain	163	0.03	(0.02, 0.03)	163	0.02	(0.02, 0.02)	73	0.18	(0.14, 0.23)	40	0.10	(0.07, 0.14)	29	0.04	(0.02, 0.05)	–	–	–	–	–	–
Spinal cord and cauda equina	26	0.00	(0.00, 0.01)	27	0.00	(0.00, 0.00)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Other CNS	19	0.00	(0.00, 0.00)	20	0.00	(0.00, 0.00)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Years																					
2001–2004	180	0.07	(0.06, 0.09)	184	0.06	(0.05, 0.07)	62	0.40	(0.30, 0.51)	46	0.30	(0.22, 0.40)	42	0.14	(0.10, 0.19)	–	–	–	19	0.01	(0.01, 0.01)
2005–2010	397	0.11	(0.10, 0.12)	402	0.08	(0.07, 0.09)	153	0.64	(0.54, 0.75)	116	0.47	(0.39, 0.56)	66	0.14	(0.11, 0.18)	31	0.07	(0.04, 0.09)	36	0.01	(0.01, 0.01)
Total	577	0.09	(0.09, 0.10)	586	0.07	(0.07, 0.08)	215	0.54	(0.47, 0.62)	162	0.41	(0.35, 0.48)	108	0.14	(0.11, 0.17)	46	0.06	(0.04, 0.08)	55	0.01	(0.01, 0.01)

[a]Rates are per 100 000 and are age adjusted to the 2000 US standard population.

Rates for children diagnosed with ATRT by age, sex, race, Hispanic ethnicity (Hispanic ethnicity is not mutually exclusive of race; classified using the North American Association of Central Cancer Registries Hispanic Identification Algorithm, version 2), site, and region of the US (ages 0–19 y, CBTRUS 2001–2010; $n = 586$).

- Counts and rates are not presented when <16 cases were reported for the specific histology category. The suppressed cases are included in the counts and rates for totals.

100 000 (95% CI: 0.04, 0.06) for ages 0 to 19 years, as opposed to 2005–2010, where the incidence rate was 0.08 per 100 000 (95% CI: 0.07, 0.09) (Table 1). When age-specific incidence rates were stratified by these time periods, there was a significant increase in incidence for children younger than 1 year in the latter time period—0.36 per 100 000 (95% CI: 0.26, 0.48) compared with 0.62 per 100 000 (95% CI: 0.53, 0.72)—but no significant difference in incidence rates for older children.

Prior to its identification as an independent histology, tumors that are now classified as ATRT would have been diagnosed as other types of brain tumors. Analyses have shown that they had most commonly been misdiagnosed as other embryonal subtypes, particularly medulloblastoma and primitive neuroectodermal tumors (PNETs).[11] Annual age-adjusted incidence rates of ATRT over time (2001 to 2010) were compared with rates of embryonal tumors overall, as well as with these specific subtypes using Joinpoint (Fig. 1). There was a significant increase in embryonal tumor incidence between 2001 and 2008 (APC, 1.9; 95% CI: 0.1, 3.7), though there was no significant change between 2008 and 2010. Specifically, there was a significant increase in ATRT incidence between 2001 and 2010 (APC, 6.2; 95% CI: 1.4, 11.1) and a significant decrease in PNET incidence during the same time period (APC, −4.6; 95% CI: −6.2, −3.0).

Survival Rates

Relative survival estimates were calculated for a total of 177 cases (30.2% of cohort) from survival information on ATRT reported to the 18 SEER registries between 2001 and 2010 for death from any cause (Table 2). Though there are some differences between this dataset and the larger dataset, these differences are small. Compared with the overall dataset, there were slightly fewer persons younger than 1 year (36.7% of CBTRUS dataset vs 33.9% of SEER 18 dataset) and slightly more persons aged 1–3 years (46.1% of CBTRUS vs 48.6% of SEER 18). The SEER 18 dataset included slightly more males (54.3% of CBTRUS vs 56.5% of SEER 18). Compared with the overall dataset, there was an overrepresentation of cases occurring after 2005 (68.6% of CBTRUS vs 72.3% of SEER 18). There were also differences in tumor site: the subset had a greater proportion of supratentorial tumors (35.8% of CBTRUS vs 40.7% of SEER 18) and a smaller proportion of tumors located in "other brain" (27.8% of CBTRUS vs 22.6% of SEER 18) (Tables 1 and 2).

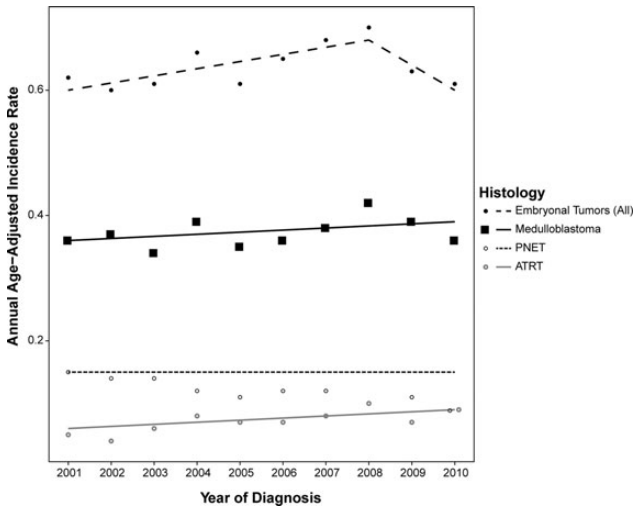

Fig. 1. Annual age-adjusted incidence rate and trends over time for all embryonal tumors and selected embryonal subtypes: medulloblastoma, PNET, and ATRT (ages 0–19 y; CBTRUS 2001–2010).

ATRT cases were divided into age groups of <1 year, 1–3 years, and 4–19 years for incidence reporting. The dataset used for survival analysis consisted of a smaller number of patients, and thus the age groups used in the incidence calculations were merged. These groups were chosen due to differences in treatment protocols between children less than 3 years old and those under 3 years old.[17] Overall, relative survival was 65.0%, 46.8%, and 28.3% at 6 months, 1 year, and 5 years postdiagnosis, respectively. Survival improved with age, though these differences were not statistically significant. Improved 6-month and 1-year survivals were noted for tumors occurring infratentorially as opposed to supratentorially or in other parts of the brain. Poorer survival was noted for persons diagnosed between 2001 and 2004 as opposed to between 2005 and 2010, but these differences were not statistically significant (Table 2). Only 32.8% of cases included in this analysis received both surgery and radiotherapy. Treatment patterns varied significantly with age: 67.7% of those ≥4 years received radiation following surgery compared with 26.7% of those ≤3 years. Treatment had a strong effect on survival rates: children who received surgery and radiation had a 92.9% 6-month survival rate, while those who received only surgery had a 52.5% 6-month survival rate. This survival difference was also evident in 5-year survival, where the 2 groups had survivals of 57.6% and 13.5%, respectively.

Discussion

Recent reports conclude that ATRT contributes to ~6%–7% of all CNS neoplasms in patients under the age of 7.[8,11,18] In the CBTRUS data, ATRT represented 4.4% of all CNS tumors diagnosed in children aged 0–5 years between 2001 and 2010, with an overall annual incidence rate of 0.07 per 100 000 population, reinforcing the rarity of ATRT.

In a study from the population-based nationwide Austrian Brain Tumor Registry, Woehrer and colleagues[11] found 19 cases of ATRT, with an age-adjusted incidence rate of 0.14 per 100 000 population and a median age at diagnosis of 1.44 years for ATRT cases diagnosed between 1996 and 2006. These tumors represented 6.1% of all CNS neoplasms in patients under the age of 7 years. In this analysis, the incidence of ATRT was higher in children younger than 3 years, comprising 68.4% of all ATRT patients, and highest in those 1 year old at diagnosis. Other studies have found the median age at diagnosis to be between 1 and 3 years.[19–21] In our analysis, children under 1 year of age at diagnosis had the highest incidence: 0.54 per 100 000 population compared with all other age groups. Combined, these studies corroborate that ATRT is more common in children aged 0 to 2 years old than in other age groups.

Following the diagnosis of ATRT, life expectancy is short. This tumor is highly malignant and usually progresses quickly. Survival in the study population was similar to that observed in other populations. In other analyses, median survival varied between 6 and 18 months.[2,6–8,12,20,22] In the current study, overall median survival was 11 months (95% CI: 8, 13 mo). An analysis of data

Table 2. Six-month and 1-, 2-, 3-, and 5-y relative survival rates[a,b] for ATRT, by age and sex (ages 0–19 y, SEER 2001–2010[c]; $n = 177$)

	n	6 mo		1 y		2 y		3 y		5 y	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Age, y											
<1	60	60.2	(46.3, 71.6)	39.7	(26.83, 52.3)	22.3	(12.0, 35.0)	–	–	–	–
1–3	86	64.0	(52.7–73.3	46.9	(35.6–57.4)	36.9	(26.1–47.6)	35.1	(24.5–46.0)	35.1	(24.5–46.0)
4–19	31	77.1	(57.9–88.4)	60.5	(39.5–76.2)	50.1	(28.9–68.1)	–	–	–	–
Sex											
Male	100	64.4	(53.8, 73.1)	49.5	(38.7, 59.5)	34.3	(24.1, 44.7)	29.0	(19.1, 39.6)	29.0	(19.1, 39.6)
Female	77	65.9	(54.6, 75.7)	44.6	(32.1, 54.5)	34.3	(23.4, 45.4)	30.3	(19.6, 41.6)	27.5	(16.9, 39.2)
Location											
Supratentorial	72	65.3	(52.7, 75.2)	43.4	(30.9, 55.3)	35.9	(23.9, 48.0)	31.5	(19.9, 43.8)	31.5	(19.9, 43.8)
Infratentorial	50	72.8	(57.7, 83.3)	56.5	(40.8, 69.5)	33.8	(19.5, 48.8)	–	–	–	–
Other brain	40	54.7	(38, 68.6)	43.4	(27.5, 58.3)	–	–	–	–	–	–
Spinal cord and cauda equina	–	–	–	–	–	–	–	–	–	–	–
Other CNS	–	–	–	–	–	–	–	–	–	–	–
Years											
2001–2004	49	55.2	(40.3, 67.8)	40.4	(26.6, 53.8)	34	(21.1, 47.4)	–	–	–	–
2005–2010	128	69.0	(59.9, 76.4)	49.3	(39.8, 58.2)	33.8	(24.7, 43.1)	30.7	(21.7, 40.3)	30.7	(21.7, 40.3)
Treatment											
Surgery + radiation	58	92.9	(82.1, 97.3)	78.5	(64.4, 87.6)	69.3	(53.9, 80.4)	57.6	(41.2, 71.1)	57.6	(41.2, 71.1)
Surgery and no radiation	101	52.5	(42.1, 61.9)	31.2	(22.0, 40.8)	15.3	(8.4, 24.2)	15.3	(8.4, 24.2)	13.5	(6.9, 22.3)
Other/unknown	–	–	–	–	–	–	–	–	–	–	–
Total	177	65.0	(57.4, 71.7)	46.8	(38.9, 54.3)	34.2	(26.7, 41.9)	29.6	(22.2, 37.3)	28.3	(20.9, 36.2)

[a]The cohort analysis of survival rates was utilized for calculating the survival estimates presented in this table. Long-term cohort-based survival estimates reflect the survival experience of individuals diagnosed over the time period, and they may not necessarily reflect the long-term survival outlook of newly diagnosed cases.
[b]Rates are an estimate of the percentage of patients alive at 1, 2, 5, and 10 y. Rates were not presented for categories with ≤27 cases and were suppressed for rates where <16 cases were surviving within a category.
[c]Estimated by CBTRUS using the SEER*Stat Database: incidence – SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2011 Sub (1973–2009 varying) – Linked to County Attributes – Total US, 1969–2010 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2012, based on the November 2011 submission.

collected via the Canadian Paediatric Brain Tumour Consortium found a 2-year overall survival rate of 36.4%.[20]

Overall survival improved with increasing age in all other analyses. A clinical series from St. Jude's Children's Research Hospital found a 2-year overall survival of 89% for children aged ≥3 years compared with 17% for those <3 years treated with radiation and alkylating chemotherapy.[10] The 6-month survival was comparable between patients aged 1–3 years (64.0%; 95% CI: 52.7%, 73.3%) and those under 1 year (60.2%; 95% CI: 46.3%, 71.6%; Table 2). However, the overall 2-year survival rate for patients aged 1–3 years was 36.9% (95% CI: 26.1%, 47.6%), while the 2-year survival rate for patients under 1 year was only 22.3% (95% CI: 12.0%, 35.0%; Table 2). Those aged 4 years or older at diagnosis had improved relative survival compared with both younger groups. These results confirm that survival is poor in ATRT patients and improves with increasing age at diagnosis. This analysis also found that survival for ATRT improves with later year of diagnosis and that survival improved with adjuvant treatment after surgery, a pattern that is also seen in other analyses.[9,10,21,22]

Incidence rates by sex did not differ significantly in the CBTRUS population, although 54.1% of cases were male. Heck and colleagues[23] utilized the California Cancer Registry to study the incidence of ATRT and other rhabdoid sarcoma in children who were <6 years old between 1988 and 2007 and found only 44 cases, 56.8% male and 43.2% female. An analysis of data collected by the Canadian Paediatric Brain Tumour Consortium found that 62% of cases were male.[20]

Our analysis found no significant difference in incidence based on race or Hispanic ethnicity. However, an analysis of SEER data from 1973–2006 by Bishop and colleagues[24] found that the incidence rate for white infants <1 year old was twice that for black infants: 0.12 per 100 000 population for whites and 0.06 per 100 000 population for blacks.

Heck and colleagues[23] also found that children with ATRT in the California Cancer Registry were more frequently born to white non-Hispanic parents: 45.5% of ATRT cases originated from a white non-Hispanic mother and 52.3% originated from a white non-Hispanic father, compared with 36.4% and 34.6%, respectively, statewide. In this analysis, 20.6% of children were of Hispanic ethnicity. This is comparable to the proportion of persons of Hispanic ethnicity in the US overall. Hispanic and non-Hispanic children did not have a statistically significant difference in incidence in the CBTRUS dataset (Table 1).

The CBTRUS analysis found patterns in tumor location that have not been previously reported. Supratentorial tumor location

becomes more common with increasing age, whereas the vast majority of tumors in children younger than 1 year occurred infratentorially and in overlapping locations of the brain or were not given a specific location code (Table 1). This pattern was also present in the subset of patients used for survival analysis. Infratentorial location of tumor was associated with increased relative survival, although this was not statistically significant (Table 2). Unfortunately, sample size was too low to look at the relationships among age, tumor location, and survival.

There was a significant increase in incidence for 2005 to 2010 compared with 2001 to 2004, and this appears to be driven primarily by incidence in children under 1 year old. There was also an increase in relative survival rates over time, but these differences were not statistically significant. It is impossible to determine the causes of this increase using existing registry data.

Our analysis found that there was significant increase in incidence of embryonal tumors overall and in ATRT in particular over the time period of the study. There was also a significant decrease in PNET. This may suggest that the true incidence of ATRT is rising over time or that misclassification of ATRT continues to slowly diminish as this entity becomes increasingly recognized. This may be due to increasing familiarity with this diagnosis among pathologists, as well as increased elucidation of the diagnostic criteria. Mutation of SWitch/Sucrose nonfermentable-related, matrix-associated, actin-dependent regulator of chromatin, subfamily b, member 1 (*INI-1*) is an important biomarker in distinguishing these tumors and has greatly improved accuracy of diagnosis.[25] This may partially explain the upward trend in incidence, but longer-term follow-up is necessary to assess whether this trend will continue. Beginning in 2004, clinical trials began to be available for children diagnosed with ATRT and may have contributed to the improvements in survival between these time periods.

Strengths and Limitations

Cancer registration is decentralized in the United States, more so than in other countries conducting studies of ATRT. Registration of individual cases is conducted by cancer registrars at the institution where diagnosis occurs and transmitted to the central registry, which further transmits this information to NPCR or SEER. Central cancer registries (both NPCR and SEER) only report cases to the Centers for Disease Control and Prevention and the National Cancer Institute for persons who are residents of that particular state, so duplicate records should not occur for persons who may have traveled across state lines for treatment. No mechanism exists for central pathology review of cases, and registration is based on histology information contained in the patient's medical record. Additionally, the diagnostic criteria for ATRT have changed over time. *INI-1* mutation is a hallmark of ATRT and is important in distinguishing the tumor from other rare tumor types. An immunohistochemistry (IHC) stain for this was first developed in 2004 and commercialized shortly thereafter and has become standard for ATRT diagnosis.[26,27] Prior to this, specimens could be tested for the mutation using polymerase chain reaction, although this required the use of frozen tissue and analysis at specific facilities.[28] Depending on location and time when individual tumors were diagnosed, pathologists would have varying access to these resources, leading to potential misdiagnosis. This could also result in both false negative and false positive diagnoses. The Austrian Brain Tumor Registry found that 52.6% of ATRTs diagnosed between 1996 and 2006 were inaccurately diagnosed as another tumor type, most commonly medulloblastoma.[11] Two retrospective case series studies by the British Columbia' Children's Hospital (1986–2006) and the Institute of Neurology in Vienna, Austria (1964–2005) also found numerous ATRT cases upon IHC analysis that had been misdiagnosed as other embryonal tumor types prior to widespread use of the *INI-1* stain.[29,30] As the structure of population-based data collection does not allow for central pathology review, it is only possible to assess tumors based on the diagnosis listed in the pathology report. By assessing cases separately before and after the commercialization of the *INI-1* IHC stain, we hoped to select a subgroup of cases that represents a more uniform pathology. Though there was a significant increase in ATRT incidence over this time period, the rates of embryonal tumor incidence were relatively stable overall, but there was a corresponding decrease in PNET. Any "real" changes in rates of ATRT incidence over the time period are difficult to measure without central pathology review and with shifting patterns of diagnosis.

Due to the nature of cancer registration in the United States, there are multiple relevant variables that were not available and thus were not taken into account in this analysis. Cancer registries record only initial diagnosis of primary tumors. Furthermore, these datasets do not contain any information on the metastatic status of patient. Metastatic status of ATRT has been shown to be an indicator of poorer survival,[31] although not all studies have found this.[20] Since it is a factor that may have significant effect on survival, it should be examined. Similarly, the cancer registry dataset includes no information about physician treatment intent. There is no way to determine whether radiation given was palliative or therapeutic, or why treatments were or were not administered. Reliable information about tumor site is also not always available from tumor registry data. These data are collected by trained cancer registrars (most commonly from pathology reports) and are based solely on the data recorded by physicians within each patient record. The large proportion of cases noted to be "other brain" or "other CNS" may potentially represent missing data, extensively disseminated disease, unknown site of origin, or error.

This is the first population-based description of ATRT in the United States and includes one of the largest populations of ATRT cases analyzed thus far. The population used for the incidence analyses represents 98% of the US population for the time period of study (2001–2010) and includes nearly all children diagnosed with ATRT in the United States since the adoption of the WHO ATRT histology definition in 2000.[1] Data quality in this large registry is ensured by multiple quality control checks and individual quality ratings for each central registry.[1] ATRT is a rare diagnosis, making it difficult to draw statistically significant conclusions about incidence and survival. The SEER 18 population dataset used for the survival analyses is a subset of the larger CBTRUS dataset and covers only ~26% of the US population compared with the 98% population coverage of the larger dataset.[32] Survival estimates obtained from this dataset may be less reliable as representations of "real" ATRT relative survival rates for the US than if they were based on data from a larger portion of the population.

In addition, current clinical trials and therapeutic advances may have altered survival outcomes during the period of this

study. However, this study represents the most complete report of ATRT survival data in the US during this period and does provide an essential benchmark for comparisons with ongoing single arm studies (eg, ACNS0333). Differences were found in incidence and survival in the CBTRUS data for 2001–2010 by age at diagnosis, sex, race, and Hispanic ethnicity. Even though many of these differences did not reach statistical significance, they contribute to quantifying this rare histology in the US population.

Conclusions

ATRT is a rare malignant brain tumor with very short median survival after diagnosis; it is most commonly found in the youngest of children in the United States (<1 y old at diagnosis). The incidence of this tumor has been increasing over time since its inclusion in the *WHO Classification of Tumours of the Central Nervous System* in 2000. Age at diagnosis is associated with tumor location in the brain, as well as relative survival after diagnosis with ATRT. The epidemiological data on incidence and survival found in this report contribute to our understanding of these tumors by quantifying their impact on the US population and may, hopefully, stimulate research leading to improved treatment of these devastating childhood tumors. Though this report is not able to take into account several clinical factors that have been shown to be relevant to prognosis after diagnosis with ATRT, the data presented in this report provide an important population-based comparison group for future research. These limitations demonstrate the importance of specific and accurate cancer registry data in order to conduct clinically relevant population-based analyses.

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