Incidence, Trends, and Survival of Children With Embryonal Tumors

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abstract

BACKGROUND: Central nervous system (CNS) and non-CNS embryonal tumors occur principally in children and are rarely seen in adults. The incidence rates for rare entities such as atypical teratoid/rhabdoid tumors (AT/RT) or primitive neuroectodermal tumors in the CNS are rarely published. Incidence rates for certain subgroups, such as hepatoblastomas, have been increasing in some countries.

METHODS: Data of 8337 embryonal tumors, registered in children (0–14 years) between 1991 and 2012 (for AT/RT 2000–2012) in the population-based German Childhood Cancer Registry with complete national coverage were analyzed for incidence rates, time trends, and survival.

RESULTS: For most entities, the incidence rates were the highest for children <1 year. An important exception was medulloblastomas, which occurred mainly in 1- to 9-year-olds. Neuroblastomas and ganglioneuroblastomas as well as Wilms tumors (nephroblastomas) had the highest age standardized incidence rates (13.7 and 9.4 per million, respectively). A statistically significant increasing trend for hepatoblastomas (annual average percent change 4.6%) was detected. The survival probabilities varied between the diagnostic groups: primitive neuroectodermal tumors and AT/RT had the lowest and retinoblastomas the highest. The survival was dependent on the age at diagnosis, the most extreme examples being neuroblastomas, for which the survival probability declined steeply for children ≥1 year and medulloblastomas, for which the highest survival was seen for 10- to 14-year-olds.

CONCLUSIONS: This study presents a comprehensive overview of pediatric embryonal tumors from a well-established, complete nationwide cancer registry. Significant increasing trend for hepatoblastomas was detected for the first time in Europe.

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WHAT'S KNOWN ON THIS SUBJECT: Embryonal tumors occur almost exclusively in children. The group is heterogeneous and includes relatively common pediatric tumors as well as rare tumors. The incidence rate for hepatoblastoma has been increasing in some countries.

WHAT THIS STUDY ADDS: This population-based study is the first comprehensive study on embryonal tumors in German children. Incidence rates, trends, and survival for 1991 through 2012 are presented. A statistically significant increasing trend for hepatoblastoma was detected for the first time in Europe.

Embryonal tumors are composed of undifferentiated cells similar to the ones in a developing embryo and are almost exclusively encountered in children. However, no established definition exists for embryonal tumors. We have adopted a selection of principal non–central nervous system (CNS) embryonal tumors as described by Willis[1] and used in an earlier study[2]: neuroblastoma and ganglioneuroblastoma, nephroblastoma, retinoblastoma, hepatoblastoma, pulmonary blastoma, and pleuropulmonary blastoma. In addition, we have included the CNS embryonal tumor group III(c) of the *International Classification of Childhood Cancer, Third Edition* (*ICCC*-3)[3]: "Intracranial and intraspinal embryonal tumors," which corresponds to the embryonal tumor group of the World Health Organization brain tumor classification[4] (medulloblastoma, primitive neuroectodermal tumors [PNETs], medulloepithelioma, and atypical teratoid/rhabdoid tumors [AT/RTs]). Renal and extrarenal rhabdoid tumors or some others are not included, although they may share characteristics with the selected embryonal tumors.

Approximately 20% of childhood CNS tumors are embryonal tumors.[5] Neuroblastomas and ganglioneuroblastomas are types of sympathetic nervous system tumors and are the most common cancer among infants.[6,7] They are known to regress spontaneously or mature in some cases. The most common renal tumor in children is nephroblastoma (Wilms tumor). Treatment advances of Wilms tumors have made it one of the success stories among childhood cancer with >90% survival rates currently.[8] Retinoblastomas are the most common childhood eye cancer. Heritable and nonheritable forms are known, the former being caused by germline mutations of the *RB1* gene.[9] Liver malignancies are rare during childhood, and >80% of them are hepatoblastomas. The incidence rate for hepatoblastoma has been shown to have increased in the United States by 4.3% per year between 1992 and 2004 for children and adolescents 0 to 19 years old.[10]

We have analyzed the embryonal tumors registered in the German Childhood Cancer Registry (GCCR) from 1991 to 2012 for incidence rates, trends, and survival probabilities. This is the first comprehensive study on pediatric embryonal tumors in Germany.

METHODS

Embryonal tumor cases (n = 8337) registered in the nationwide, population-based GCCR for children <15 years old who were resident in Germany were included. The following diagnostic groups of the *ICCC-3*[3] were included: III(c) intracranial and intraspinal embryonal tumors, IV(a) neuroblastoma and ganglioneuroblastoma, V retinoblastoma, VI(a)1 nephroblastoma, VII(a) hepatoblastoma, XII(a)2 pancreatoblastoma, and XII(a)3 pulmonary blastoma and pleuropulmonary blastoma. All records were converted in 2005 from the previous version of the *International Classification of Diseases for Oncology* to the current, third edition[11] coding of the tumors. The diagnoses were confirmed histologically, mainly by a central reference pathologist. The time period 1991 to 2012 was selected to achieve maximally complete registration for the majority of the diagnostic groups involved. However, AT/RT was defined first in 1996 as a distinct tumor entity and included in 2000 in the *International Classification of Diseases for Oncology* as a separate entity. Because AT/RT was not systematically registered before 2000, for incidence rates and trends, the time period 2000–2012 was analyzed. Before 2000, AT/RT cases in Germany were classified mainly as medulloblastomas or PNETs.

For all survival analyses, the cases diagnosed between 1991 and 2010 (for AT/RT, 2000–2010) with follow-up information (until December 31, 2010) were included (N = 7307). For ~4% of the cases, no follow-up information was available. Median follow-up times per time period are presented in Table 4 later in the article. Unlike for the other tumor entities, for AT/RT, no 20-year survival probability was calculated due to shorter registration time. Because of extreme rarity of medulloepithelioma, pancreatoblastoma, and pulmonary blastoma/pleuropulmonary blastoma, incidence rates and survival probabilities were not calculated for these. The data in the GCCR are regularly validated and supplemented through therapy optimization studies (TOS) of the German Society for Pediatric Oncology. In Germany during the past decade, 94% of all patients participated in the TOS.[5] Follow-up data are provided by the TOS until the end of clinical follow-up, which usually lasts 5 years after the first clinical treatment phase. After that the GCCR organizes an active open-end follow-up collecting data from various sources, such as hospitals, municipal registration offices, state cancer registries, and patients.

Statistical Analysis

Age- and gender-specific incidence rates were calculated and adjusted, where indicated, to the Segi world standard population under 15 years of age[12] and expressed as per million person years (age-standardized incidence rate, ASR). For incidence rate trends, the age-group adjusted average annual percent change (AAPC) was estimated from a Poisson-model and presented with a 95% confidence interval (CI). The AAPC was considered statistically significant if the 95% CI did not include 0; however, the CIs basically reflect the strength of the trend and

the number of cases. These "tests" are of a descriptive nature and are not to be confused with hypothesis testing. Survival probabilities were estimated by applying an extended life table method.[13]

RESULTS

Incidence Rates, Median Age, and Time Trends

Altogether, 8337 embryonal tumors were registered at the GCCR during 1991–2012, corresponding to ~380 cases annually or ~20% of all cancer cases.

The largest group of tumors, 35.9%, were neuroblastomas and ganglioneuroblastomas (ASR 13.7 per million; Table 1) of which 4.9% (145 cases) were ganglioneuroblastomas. The second most frequent embryonal tumor were Wilms tumors (25.9% of the cases, ASR 9.4), followed by medulloblastomas (17.0%, ASR 5.4).

The highest incidence rates for almost all tumors except medulloblastomas and ganglioneuroblastomas were seen during the first year of life. Medulloblastomas occurred mainly in 1- to 9-year-olds (median age 6 years, 9 months), and ganglioneuroblastomas in 1- to 4-year-olds (median age 4 years). Of note is that among intracranial and intraspinal embryonal tumors, AT/RTs occurred more frequently than medulloblastomas or PNETs in children aged <1 year. The incidence rates per gender and year of age are shown in Fig 1.

Differences in the median age at diagnosis were detected between the genders. A difference of >1 year was detected for PNETs (boys were 15 months older; Table 1) and for medulloepitheliomas (girls were 4.5 years older). However, the medulloepitheliomas included only 17 patients, making chance findings more likely.

Medulloblastomas and hepatoblastomas occurred far more frequently in boys (gender ratios male/female 1.8 and 1.6, respectively); this was also true for PNET and AT/RT (gender ratios 1.4 and 1.3, respectively). In contrast, girls outnumbered boys only in ganglioneuroblastomas and Wilms tumors (gender ratios 0.7 and 0.9, respectively).

For most entities, no trends in the incidence rates over time were seen. Statistically significant increasing trends were detected for AT/RTs and hepatoblastomas (AAPC 6.1% and 4.6%, respectively), where the increase tended to be steeper for girls (AAPC 8.2% and 6.6%, respectively) than for boys (4.6% and 3.5%, respectively). In contrast, PNETs showed a significantly decreasing trend (AAPC –4.3%), which led to a significantly decreasing trend for intracranial and intraspinal embryonal tumors (–1.1%).

Survival Probability

Survival probabilities could be determined only for cases diagnosed until 2010 and having maximum follow-up until 2010. This corresponds to 7629 cases diagnosed until 2010 and for 7307 patients follow-up data were available.

The CNS tumors showed the poorest survival probabilities: 5-year survival for medulloblastomas was 69%, 38% for PNETs, and 32% for AT/RTs (Table 2). The highest survival probabilities, also long term, were seen for retinoblastomas and Wilms tumors (20-year survival; 95% and 90%, respectively). For ganglioneuroblastomas, the survival probability was considerably better than for neuroblastomas (5 year: 94% vs 74%). Late deaths >5 years after diagnosis were relatively rare for most entities. However, for medulloblastomas, the survival probability declined from 69% after 5 years to 51% after 20 years.

Girls tended to have better survival for medulloblastomas and for PNETs (20-year survival for medulloblastomas: boys 47% and girls 57%; for PNETs: boys 28% and girls 38%). For AT/RTs and hepatoblastomas, the survival probabilities tended to be better for boys (5-year survival AT/RT: boys 40% and girls 19%, for hepatoblastomas: boys 77% and girls 67%).

The survival varied between age groups. The children 5 to 14 years old were analyzed as 1 group to have enough cases for the analysis of rare diagnostic subgroups as well. Children <5 years with medulloblastoma had a significantly inferior 5-year survival probability (50% for <1-year-olds; 54% for 1- to 4-year-olds; Table 3) than the 5- to 14-year-olds (77%). This also applied to PNETs (33% for <1-year-olds; 31% for 1- to 4-year-olds; 48% for 5- to 14-year-olds). In contrast, neuroblastoma patients <1-year-old had the best survival probability (92% vs 62% for 1- to 4-year-olds and 54% for 5- to 14-year-olds). For Wilms tumors, a difference in outcome between <5-year-olds and 5- to 14-year-olds (91% for <1-year-old, 94% for 1- to 4-year-olds, 88% for 5- to 14-year-olds) was seen in favor of the younger children.

For medulloblastomas, a notable increase in 5-year survival took place between 1995–1998 and 1999–2002 (from 64% to 80%; Table 4). A minor decrease was seen between 2003–2006 and 2007–2010 (from 77% to 73%). For PNETs, the survival improved from 2003–2006 to 2007–2010 (from 44% to 61%). For neuroblastomas, the 5-year survival probability improved markedly from 1991–1994 to 1995–1998 (from 61% to 79%), and no further improvement was detected later. For hepatoblastomas, the survival improved from 2003–2006 to 2007–2010 (from 71% to 82%).

DISCUSSION

The embryonal tumors altogether accounted for roughly every fifth

TABLE 1 Absolute number (*N*), percentage (%), incidence rate (per million), Gender ratio, median age, and age-corrected AAPC (95% CI) by *ICCC-3* subgroup for children Aged 0 to 14 Years Diagnosed With an Embryonal Tumor During 1991–2012 in Germany (*N* = 8337)

ICCC-3[3] Diagnostic Subgroup	*N*	%	Incidence rates					Gender Ratio Male/Female	Median Age (y, mo)	AAPC % (95% CI)
			Age Specific				ASR[12]			
			0	1–4	5–9	10–14	0–14			
III(c), Intracranial and intraspinal embryonal tumors	1930	23.1	10.9	9.6	8.2	3.8	7.5	1.6	5, 10	−1.1 (−1.8 to −0.3)[a]
Boys	1200		11.2	11.8	10.3	4.4	9.1		5, 11	−0.8 (−1.7 to −0.1)[a]
Girls	730		10.6	7.2	5.9	3.1	5.9		5, 9	−1.5 (−2.7 to −0.3)[a]
III(c)1, Medulloblastomas	1420	17.0	3.7	6.2	7.0	3.2	5.4	1.8	6, 9	−0.3 (−1.2 to 0.5)
Boys	909		4.1	7.9	8.8	3.9	6.7		6, 7	−0.2 (−1.3 to 0.8)
Girls	511		3.4	4.3	5.1	2.6	4.0		6, 11	−0.6 (−1.9 to 0.8)
III(c)2, PNET	315	3.8	2.6	2.2	0.9	0.5	1.3	1.4	3, 7	−4.3 (−6.0 to −2.6)
Boys	182		2.0	2.5	1.2	0.4	1.4		4, 2	−3.7 (−6.0 to −1.4)
Girls	133		3.2	1.9	0.5	0.5	1.1		2, 11	−5.1 (−7.8 to −2.4)
III(c)3, Medulloepithelioma	17	0.2	—	—	—	—	—	—	1, 11	—
Boys	7		—	—	—	—	—		1, 6	—
Girls	10		—	—	—	—	—		6, 0	—
III(c)4, AT/RT[b]	178	2.1	7.9	2.0	0.5	0.1	1.4	1.3	1, 4	6.1 (2.0 to 10.4)
Boys	102		8.6	2.3	0.5	0.1	1.6		1, 4	4.6 (−0.7 to 10.1)
Girls	76		7.2	1.7	0.5	0.1	1.3		1, 4	8.2 (1.8 to 15.0)
IV(a), Neuroblastoma and ganglioneuroblastoma	2989	35.9	77.3	20.5	2.8	0.8	13.7	1.2	1, 3	0.2 (−0.4 to 0.8)
Boys	1621		82.6	21.7	2.8	0.8	14.5		1, 3	0.5 (−0.3 to 1.2)
Girls	1368		71.7	19.3	2.7	0.8	12.8		1, 3	−0.1 (−0.9 to 0.7)
Neuroblastoma	2844	34.1	76.8	19.3	2.3	0.7	13.1	1.2	1, 2	0.2 (−0.4 to 0.7)
Boys	1561		82.0	20.7	2.6	0.6	14.0		1, 3	0.5 (−0.2 to 1.3)
Girls	1283		71.3	17.8	2.1	0.7	12.1		1, 2	−0.3 (−1.2 to 0.6)
Ganglioneuroblastoma	145	1.7	0.5	1.2	0.4	0.2	0.6	0.7	4, 0	1.0 (−1.6 to 3.6)
Boys	60		0.6	1.0	0.2	0.2	0.5		4, 0	−1.9 (−5.7 to 2.2)
Girls	85		0.4	1.4	0.6	0.2	0.7		3, 10	3.0 (−0.4 to 6.6)
V, Retinoblastoma	879	10.5	23.6	6.6	0.4	0.1	4.1	1.1	1, 2	0.5 (−0.5 to 1.6)
Boys	455		24.0	6.6	0.3	0.1	4.1		1, 2	1.4 (0 to 2.9)
Girls	424		23.2	6.5	0.5	0.0	4.0		1, 2	−0.4 (−1.9 to 1.1)
VI(a)1, Nephroblastoma (Wilms tumor)	2160	25.9	20.7	18.9	5.2	0.7	9.4	0.9	3, 2	0.5 (−0.1 to 1.2)
Boys	1026		23.0	17.3	4.3	0.6	8.7		2, 10	0.2 (−0.8 to 1.1)
Girls	1134		18.4	20.6	6.1	0.8	10.0		3, 6	0.8 (−0.1 to 1.8)
VII(a), Hepatoblastoma	351	4.2	8.0	2.9	0.2	0.1	1.6	1.6	1, 4	4.6 (2.9 to 6.4)
Boys	217		9.6	3.5	0.2	0.2	1.9		1, 4	3.5 (1.3 to 5.7)
Girls	134		6.3	2.3	0.2	0.0	1.3		1, 3	6.6 (3.7 to 9.5)
XII(a)2, Pancreatoblastoma	7	0.1	—	—	—	—	—	—	5, 0	—
Boys	2		—	—	—	—	—		—	—
Girls	5		—	—	—	—	—		—	—
XII(a)3, Pulmonary blastoma and pleuropulmonaryblastoma	21	0.3	—	—	—	—	—	—	3, 0	—
Boys	13		—	—	—	—	—		3, 0	—
Girls	8		—	—	—	—	—		3, 0	—
All embryonal tumors	8337	100.0	140.6	58.7	16.8	5.5	36.4	1.2	3, 2	0.3 (−0.1 to 0.6)
Boys	4534		150.5	61.2	18.0	6.1	38.5		3, 2	0.3 (−0.1 to 0.8)
Girls	3803		130.2	56.1	15.5	4.8	34.2		3, 2	0.1 (−0.4 to 0.7)

Dash indicates insufficient data.

[a] Without AT/RT, which has been recognized a distinct disease entity only since 1996.

[b] Data from 2000 to 2012.

cancer in children <15 years in Germany during the time period 1991–2012. Male gender has been identified as a risk factor for medulloblastomas, PNETs, AT/RTs, neuroblastomas, and hepatoblastomas in this and other studies.[14–18] The exceptions to the male predominance were Wilms tumors, as shown by others as well,[19] and ganglioneuroblastomas. A strongly diverging median age at diagnosis between the genders was detected for PNET and medulloepitheliomas, which may reflect greater biological differences between the genders for these tumors than for the others.

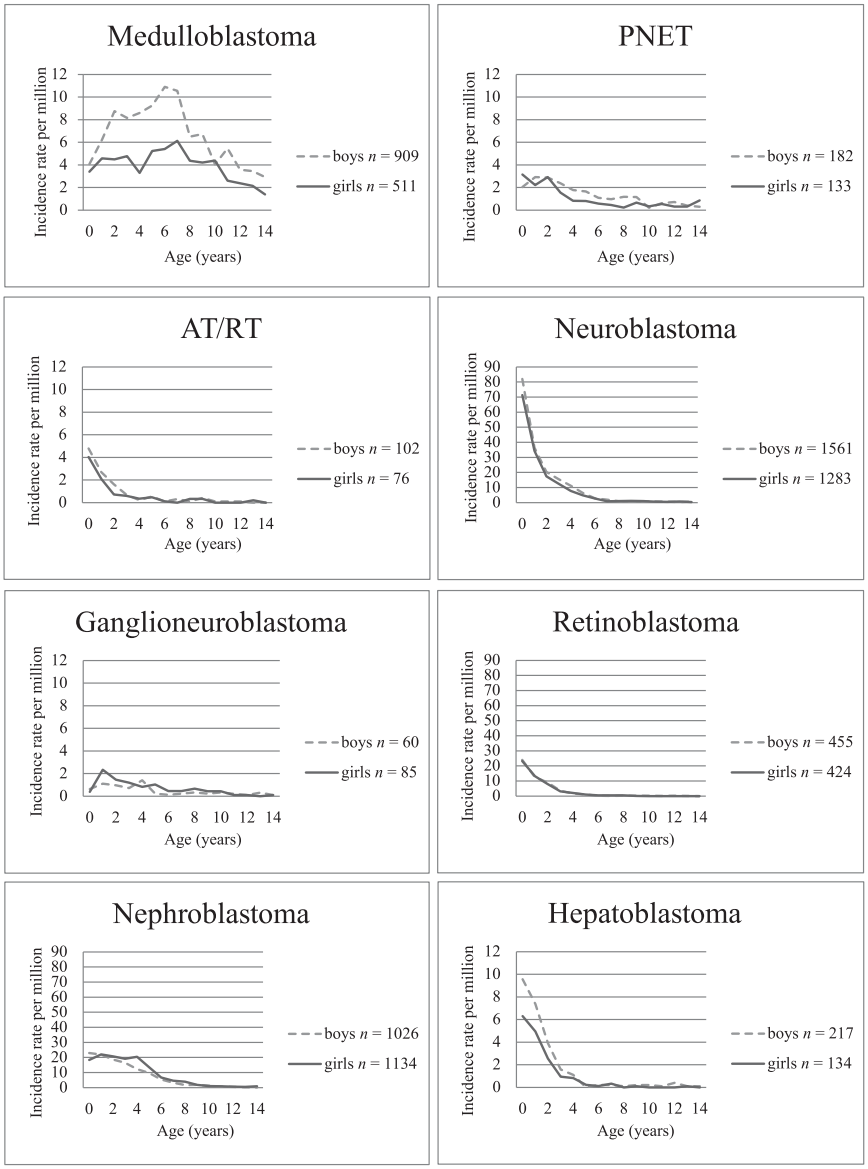

FIGURE 1

Incidence rates per year of age and per diagnostic subgroup for children 0 to 14 years old diagnosed with an embryonal tumor between 1991 and 2012 in Germany (for AT/RT 2000–2012).

The medulloblastoma incidence rate in Germany through 1991 to 2012 remained stable and similar to that reported in France for 2000–2008,[20] in the northwest United Kingdom for 1954–1997,[21] and in Europe for 1978–1997.[22] For AT/RTs, a rate below 1 per million has been reported in the United States for 2001–2010[23] and 1.1 in France 2000–2008.[20] An incidence rate of 1.4 per million, same as in Germany for 2000–2010, was published for Austria for 1996–2006.[24] We detected a quickly increasing incidence rate for AT/RT. However, AT/RT have only been recognized as a distinct pathologic entity since 1996,[25] and therefore the increasing trend is more likely indicative of a higher diagnostic awareness than a real increase. The incidence rate increase did not stabilize in our data set until 2012. A simultaneous decreasing trend for PNET was detected, which may partially derive from the diagnostic differentiation between PNET, AT/RT, and other brain tumors. Before 1996, AT/RT had typically been diagnosed as PNET or medulloblastoma. A weak decreasing trend for medulloblastomas may similarly result in part from the same fact. An increasing use of molecular diagnostic tools in tumors that were formerly classified only by morphologic and immunohistochemical parameters may have contributed to these changes.

The neuroblastoma and ganglioneuroblastoma incidence rate in Germany was similar to the French rate for 2000–2004[26] but was higher than that in the United Kingdom for 1991–2000[27] or for European children in 1978–1987 (Automated Childhood Cancer Information System data),[28] but stable. The median age at diagnosis for ganglioneuroblastoma was considerably higher than for neuroblastoma, which is thought to reflect the time needed for differentiation. Germany had a neuroblastoma screening program in some of the federal states during 1995–2000.[29] The program led to increased incidence rates in the screened age group (1 year) for stages 1 through 3, but not for stage 4. In an earlier trend analysis, a correction for the screening effect was needed for the data from western Germany.[30] However, during the time period analyzed here, a trend was no longer visible.

The retinoblastoma incidence rate was similar to a 1978–1997 rate for European children[31] and to recent (2000–2009) Argentinian[32] and French (2000–2004) rates.[26] The rate remained stable in Germany in 1991–2012, as in the Nordic countries from the mid-1970s to 1998.[33]

The Wilms tumor incidence rate in our study was slightly higher than in Sweden for 1973–2009[34] and the 1978–1997 rate for all malignant renal tumors in European children,[35] but similar to the French rate for

TABLE 2 Five-, 10-, and 20-Year Survival Probabilities (and 95% CI) for Children Aged 0 to 14 Years Diagnosed With an Embryonal Tumor in Germany 1991–2010 (n =7307)

ICCC-3[3] Diagnostic Subgroup	*N*[a]	Survival 1991–2010		
		5 y	10 y	20 y
		% (95% CI)	% (95% CI)	% (95% CI)
III(c)1, Medulloblastoma	1254	69 (67 to 72)	61 (58 to 64)	51 (41 to 60)
Boys	793	67 (64 to 71)	59 (55 to 62)	47 (33 to 61)
Girls	461	72 (68 to 77)	65 (60 to 69)	57 (50 to 64)
III(c)2, PNET	284	38 (32 to 44)	34 (28 to 40)	32 (26 to 38)
Boys	167	35 (28 to 43)	32 (24 to 39)	28 (20 to 36)
Girls	117	43 (34 to 53)	38 (28 to 47)	38 (28 to 47)
III(c)4, AT/RT[b]	137	32 (23 to 41)	26 (13 to 39)	—
Boys	82	40 (28 to 52)	30 (11 to 49)	—
Girls	55	19 (5 to 32)	19 (5 to 32)	—
IV(a), Neuroblastoma and ganglioneuroblastoma	2737	75 (73 to 76)	72 (70 to 74)	71 (69 to 73)
Boys	1476	74 (72 to 76)	71 (69 to 73)	70 (67 to 72)
Girls	1261	76 (73 to 78)	74 (71 to 76)	72 (69 to 75)
Neuroblastoma	2616	74 (72 to 76)	71 (69 to 73)	70 (68 to 72)
Boys	1426	73 (71 to 76)	70 (68 to 73)	69 (66 to 72)
Girls	1190	74 (72 to 77)	72 (70 to 75)	71 (68 to 74)
Ganglioneuroblastoma	121	94 (89 to 98)	90 (84 to 96)	90 (84 to 96)
Boys	50	92 (84 to 99)	86 (76 to 97)	86 (76 to 97)
Girls	71	95 (90 to 100)	93 (86 to 100)	93 (86 to 100)
V, Retinoblastoma	745	98 (97 to 99)	97 (96 to 99)	95 (90 to 100)
Boys	392	98 (96 to 99)	97 (95 to 99)	97 (95 to 99)
Girls	353	98 (97 to 100)	98 (96 to 99)	93 (84 to 100)
VI(a)1, Nephroblastoma (Wilms tumor)	1879	92 (90 to 93)	91 (90 to 92)	90 (88 to 92)
Boys	898	92 (90 to 94)	91 (89 to 93)	91 (89 to 93)
Girls	981	92 (90 to 94)	91 (89 to 93)	89 (85 to 93)
VII(a), Hepatoblastoma	271	73 (68 to 79)	72 (67 to 78)	72 (67 to 78)
Boys	172	77 (71 to 84)	76 (69 to 82)	76 (69 to 82)
Girls	99	67 (57 to 76)	67 (57 to 76)	67 (57 to 76)
All	7307			

Estimated as in Brenner and Spix 2003.[13] Follow-up until December 31, 2010. Dash indicates insufficient data.

[a] Cases with follow-up.

[b] For AT/RT, 2000–2010.

2000–2004.[26] Unlike the 1978–1997 European study,[35] no significant increasing trend for Wilms tumor was seen. The median age for girls was 8 months older than for boys at diagnosis, which seems to result from a sudden increment of incidence for girls at ~4 years of age. In another study, roughly half a year difference in the mean age between boys and girls was seen.[19,36] The reason for the shift of the incidence curve to the right for girls ~4 years old is unknown.

The incidence rate for hepatoblastomas in Germany was similar to the rate in the Nordic countries for 1985–2006,[37] in the United States for 1973–2009,[38] and in France for 2000–2004.[26] For the first time in Europe, a statistically significant increasing trend for hepatoblastomas was noted from 1991 to 2012, which was in the same range as reported in the United States for 1992–2004.[10] The increase did not stabilize during the study period. A nonsignificant increase of ~1% annually was detected in an earlier European study.[15] In Australia, an increase of all pediatric liver tumors was observed for 1983–2006.[39] Under the assumption that the majority of liver tumors in children in developed countries with low hepatitis B prevalence are hepatoblastomas, the Australian data also show an increased incidence. In the United States, the increasing trend of hepatoblastomas was accompanied by a decrease of liver carcinomas, which was attributed to better differentiation diagnostics.[40] In our data set, the incidence rate for hepatic carcinomas also tended to increase, although not statistically significantly (AAPC 2%; data not shown), indicating that better diagnostic differentiation does not explain the trend in Germany. Thus, this increase is likely to be real.

Nongenetic factors are likely to play the most important role in the etiology of hepatoblastomas, although certain congenital syndromes are associated as well. Low or very low birth weight is the strongest known nongenetic risk factor.[41,42] Thus, in the German Pediatric Liver Tumor Registry, 31% of the hepatoblastoma patients registered in 2011–2014 had premature birth (<38 gestational weeks; unpublished data), which is clearly above the World Health Organization rate of 9.2% for Germany. In addition, an increased risk of hepatoblastoma has been detected in children born after assisted conception or presumed use of infertility treatment.[42,43] However, for these children as well, the risk seems to be associated with low birth weight and not with assisted conception.[43,44] The premature birth rates increase worldwide including the majority of industrial countries such as Germany.[45] It has been suggested that the improved survival of preterm babies might explain the increasing trend of hepatoblastomas and that some factors in neonatal intensive care could contribute to it.[46] Unfortunately, the GCCR has no information on birth weight, gestational age, admittance to neonatal intensive care, or usage of assisted conception. The mechanism by which low birth weight could increase hepatoblastoma risk still needs to be investigated. The rareness of the disease, however, complicates such a study.

Medulloblastoma 5- and 10-year survival probabilities in our data were intermediate between the UK

TABLE 3 Five-Year Survival Probabilities (and 95% CI) by *ICCC-3* and Age Group for Children Aged 0 to 14 Years Diagnosed With an Embryonal Tumor in Germany, 1991–2010

ICCC-3[3] Diagnostic Subgroup	5-Year Survival 1991–2010 by Age Group					
	<1 y		1–4 y		5–14 y	
	N[a]	% (95% CI)	N[a]	% (95% CI)	N[a]	% (95% CI)
III(c), Medulloblastoma	53	50 (37 to 64)	374	54 (49 to 59)	827	77 (74 to 80)
III(c)2, PNET	35	33 (18 to 51)	132	31 (23 to 39)	117	48 (38 to 57)
III(c)4, AT/RT[b]	56	23 (10 to 35)	59	37 (22 to 51)	22	41 (16 to 65)
IV(a), Neuroblastoma and ganglioneuroblastoma	1150	92 (90 to 93)	1284	64 (61 to 67)	303	59 (53 to 65)
Neuroblastoma	1143	92 (90 to 93)	1212	62 (59 to 65)	261	54 (47 to 60)
Ganglioneuroblastoma	—	—	72	96 (91 to 100)	42	92 (83 to 100)
V, Retinoblastoma	320	98 (97 to 100)	387	97 (96 to 99)	38	100 (100 to 100)
VI(a)1, Nephroblastoma (Wilms tumor)	303	91 (87 to 94)	1110	94 (92 to 95)	466	88 (85 to 91)
VII(a), Hepatoblastoma	103	78 (70 to 86)	148	70 (63 to 78)	20	70 (48 to 93)

Estimated as in Brenner and Spix 2003.[13] Follow-up until December 31, 2010. Dash indicates insufficient data.

[a] Cases with follow-up.

[b] For AT/RT, 2000–2010.

and US probabilities for 1996–2005.[47] We detected a gender effect tendency in survival for both medulloblastomas and PNET in favor of girls. This has been seen for medulloblastomas in other studies as well.[48,49] In 1 study, the effect was seen only for girls >3 years old.[49] In our data set, the effect was seen for girls ≥1 year (data not shown). The reason for the girls' better survival is unclear but might stem from biological or hormonal differences or a varying response to treatment. For AT/RT, the opposite was noted—namely, the boys seemed to fare better than the girls.

Generally, the lowest survival of all embryonal tumors was observed for AT/RTs, especially for girls. In the United States, a slightly lower 5-year survival probability was observed for children and adolescents 0 to 19 years of age[23] and in France for children 0-14 years of age.[20] In an Austrian study, a 5-year survival rate of 39.5%[24] was reported. However, the study included only a small numbers of patients (N = 19). The poor survival for this highly aggressive disease entity is well known. In addition, AT/RT typically occurs in particularly young children who in general have a considerably inferior prognosis for CNS tumors than older children.

Neuroblastoma and ganglioneuroblastoma 5-year survival probability was similar to that reported for European children during 2000–2007[50] and in France during 2000–2008.[51] The survival was strongly dependent on the age at diagnosis. The children <1 year had the best survival. It has been noticed that for prognostic risk stratification the age of roughly 15 months might be superior to 1 year.[52] However, in our analysis, full years were used, because other diagnostic subgroups were also analyzed with the same stratification. The survival by age groups was similar to the French probabilities in 2000–2008[51] and comparable to the US probabilities in 2003–2009.[53]

Throughout the study period, favorable survival probabilities were observed for Wilms tumors. Due to the treatment success, the aim in TOS has recently been on reducing

TABLE 4 Five-year Survival Probabilities (and 95% CI) by 4-Year Time Period of Diagnosis for Children Aged 0 to 14 Years Diagnosed With an Embryonal Tumor in Germany, 1991–2010

ICCC-3[3] Diagnostic Subgroup	5-Year Survival Probability									
	1991–1994		1995–1998		1999–2002		2003–2006		2007–2010	
	N[a]	% (95% CI)	N[a]	% (95% CI)	N[a]	% (95% CI)	N[a]	% (95% CI)	N[a]	% (95% CI)
Median follow-up time until December 31, 2010		~17 y		~14 y		~10 y		~6 y		~2.5 y
III(c), Medulloblastoma	274	63 (57 to 68)	273	64 (58 to 70)	289	80 (74 to 85)	247	77 (72 to 83)	171	73 (67 to 79)
III(c)2, PNET	79	33 (23 to 44)	67	35 (23 to 46)	69	35 (23 to 47)	49	44 (30 to 58)	20	61 (44 to 78)
III(c)4, AT/RT[b]	—	—	—	—	34	21 (7 to 34)	42	28 (15 to 42)	61	42 (28 to 57)
IV(a), Neuroblastoma and ganglioneuroblastoma	531	63 (58 to 67)	637	79 (76 to 82)	589	76 (72 to 79)	507	77 (74 to 81)	473	80 (76 to 83)
Neuroblastoma	498	61 (57 to 65)	615	79 (76 to 82)	563	75 (71 to 78)	482	76 (72 to 80)	458	79 (75 to 83)
Ganglioneuroblastoma	33	85 (73 to 97)	22	91 (79 to 100)	26	100 (100 to 100)	25	100 (100 to 100)	15	100 (100 to 100)
V, Retinoblastoma	161	98 (96 to 100)	162	98 (96 to 100)	171	98 (95 to 100)	151	100 (100 to 100)	100	97 (94 to 100)
VI(a)1, Nephroblastoma (Wilms tumor)	425	89 (86 to 92)	405	92 (89 to 94)	406	94 (91 to 96)	360	93 (90 to 96)	283	94 (91 to 97)
VII (a), Hepatoblastoma	53	72 (60 to 84)	51	71 (58 to 83)	51	76 (65 to 88)	76	71 (61 to 81)	40	82 (72 to 91)

Estimated as in Brenner and Spix 2003.[13] Follow-up until December 31, 2010. Dash indicates insufficient data.

[a] Cases with follow-up.

[b] For AT/RT, 2000–2010.

toxicity, other side effects, and late effects of the treatment without compromising the cure rates.[54]

The 5-year survival probability for hepatoblastoma patients in Germany (<15 years) was lower than that for French children in 2000–2008[51] but markedly better than in the United States for patients aged <20 years in 1973–2009.[38] The survival also exceeded the probabilities reported for European children in 1978–1997.[15] However, the 1988–1997 probabilities in northern Europe were superior to the German ones, but the patient numbers were much lower, possibly enabling chance findings.

More accurate diagnosis and improvements in treatment regimens applied for the respective tumor types, and even within subgroups of these, are likely the main reason for improved survival probabilities over time. Especially in the past decade, treatments with reduced intensity have been applied in favorable risk patients, aiming to reduce treatment-related late effects while preserving survival rates. The decreased 5-year survival probability in the most recent 4-year time period of diagnosis (2007–2010) in some tumors types may be due to reporting bias.

The major strength of our study is the large data set of >8000 cases derived from the national childhood cancer registry with complete population coverage in Germany. The diagnoses were confirmed histologically, mainly by a central reference pathologist. Limitations of this study are that for rare disease entities, random fluctuations may wrongly appear as time trends, and there was a lack of follow-up data for 4% of the patients. However, patients without follow-up had no or little impact on the survival analyses.

CONCLUSIONS

Embryonal tumors were the most frequent in <1-year-olds, with medulloblastomas and ganglioneuroblastomas being the only exceptions. Boys constituted the majority in almost all diagnostic subgroups. The incidence rate of hepatoblastomas increased during the study period, likely indicating a true increase. The survival probabilities varied greatly between the diagnostic subgroups, with retinoblastomas showing the best survival and AT/RTs the worst. The survival probability was dependent on the age of the child for the majority of embryonal tumors and improved for almost all diagnostic subgroups during the study period.

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ABBREVIATIONS

AAPC: average annual percent change
ASR: age-standardized incidence rate
AT/RT: atypical teratoid/rhabdoid tumor
CI: confidence interval
CNS: central nervous system
GCCR: German Childhood Cancer Registry
ICCC-3: *International Classification of Childhood Cancer, Third Edition*
PNET: primitive neuroectodermal tumor
TOS: therapy optimization studies

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