Long-term survival and cure fraction estimates for paediatric central nervous system tumours in 31 European countries (EUROCARE-6): a population-based study

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Summary

Background Clinically relevant survival outcomes, including cure fraction estimates, and long-term survival outcomes of paediatric CNS tumours from large-scale databases have not been reported for Europe. Moreover, various biases hinder direct geographical comparisons, thereby limiting the effective translation of population-based findings into cancer care, surveillance, and research. We aimed to estimate these survival outcomes across Europe through the EUROCARE database.

Methods In this population-based study, we analysed survival data from the EUROCARE-6 database from children younger than 15 years with a CNS tumour across 31 European countries. For the period 2008–13, we estimated observed survival via the actuarial method, and 5-year observed survival was reported at the European level and national level for four major CNS tumour groups. For the period 1998–2013, cure fraction was estimated through a mixture cure model assuming constant long-term mortality from other causes. Additionally, model-based 10-year and 15-year survival were estimated.

Findings For observed survival analyses, 13 782 tumour cases were included. 5-year observed survival was 72% (95% CI 68 to 75) for ependymomas, 92% (91 to 93) for low-grade gliomas, 47% (45 to 49) for high-grade gliomas, 24% (21 to 27) for high-grade gliomas excluding glioma not otherwise specified, and 64% (62 to 67) for medulloblastomas. A total of 30 392 children were included in the cure fraction analysis. During the study period, the largest absolute increase in cure fraction was observed for ependymomas from 65% (57 to 73) in 1998–2001 to 79% (69 to 89) in 2010–13, whereas low-grade gliomas increased from from 89% (85 to 94) to 95% (89 to 100), high-grade gliomas had a 6 percentage point change increase (2 to 10), and medulloblastomas increased from 52% (49 to 55) to 56% (51 to 60). The estimated 10-year and 15-year survival rates were highest for low-grade gliomas at 90·6% (89·4 to 91·7) at 10 years and 88·5% (87·2 to 89·8) at 15 years, whereas the lowest survival rates were observed for high-grade gliomas excluding glioma not otherwise specified at 20·5% (17·0 to 24·1) and 19·0% (15·6 to 22·5).

Interpretation This study is the first to report a comprehensive evaluation of survival parameters for paediatric CNS tumour patients in Europe. These outcomes are important to evaluate advances in care for children with a CNS tumour.

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Introduction

Paediatric CNS tumours are the most common solid tumours and the leading cause of death in children with cancer.[1] This broad group of malignant and non-malignant tumours consists of a wide variety of tumour types and with 5-year survival ranging from 2% for diffuse midline gliomas located at the pons to almost 100% for pilocytic astrocytomas.[2,3] Additionally, survival probabilities vary by age and tumour location.[4,5] Moreover, when comparing survival estimates across countries, different diagnostic and registration practices could introduce bias.[6] All these circumstances need careful consideration when analysing survival outcomes of paediatric CNS tumours.

Population-based studies have shown large variations in survival estimates between European countries.[7] These studies typically rely on the International Classification of Diseases (ICD) for Oncology behaviour codes to define CNS tumours groups. However, this variable does not capture the clinical heterogeneity of paediatric CNS tumours. These limitations make it hard to inform stakeholders (eg, clinicians and policy makers) sufficiently, leaving the potential of population-based studies largely unaddressed.

In this study, we used the comprehensive EUROCARE database to assess the 1-year, 3-year, and 5-year survival for 12 paediatric CNS tumour groups, considering clinical characteristics such as sex, age, CNS WHO

Research in context

Evidence before this study

Assessing population-based cancer survival is one of the crucial measures for evaluating the effectiveness of a country's health-care system in addressing cancer management. Detailed insight into clinical characteristics, cure fraction, long-term survival outcomes, and geographical differences in the survival of paediatric CNS tumours is needed to effectively inform stakeholders, such as clinicians and policy makers. Due to the rarity of paediatric CNS tumours, large-scale population-based studies that use cancer registry data can have an important role in this process. We searched Medline from Jan 1, 2014, to March 14, 2024, with the search string: "child* OR paediatric AND (brain cancer OR brain neoplasm OR central nervous system tumour) AND survival AND registries AND Europe". No studies reported details on the underlying clinical characteristics and reported survival outcomes beyond 10 years. Several studies have evaluated survival differences between European countries, but all studies were limited by the use of the The International Classification of Diseases for Oncology (ICD-O), third edition, behaviour code (ie, the fifth digit in the morphology code). Although the behaviour code allows for stratifying other cancer types by malignancy, its application to CNS tumours results in clinically non-informative groupings that do not encompass the heterogeneity inherent to these neoplasms. These deficiencies have hindered the ability to translate findings into clinical implications and effective policies. Consequently, the potential of population-based studies for paediatric CNS tumours has remained partly unaddressed.

Added value of this study

To address the deficiencies of earlier reports, this study uses EUROCARE data to analyse more than 30 000 cases of paediatric CNS tumours from the period 1998–2013 at a European level, encompassing 80 registries from 31 countries. To the best of our knowledge, this study is the first to report detailed survival outcomes on a European level, informing on survival patterns in underlying patient characteristics and providing a unique insight into the cure fraction and projected long-term survival outcomes for paediatric CNS tumours. In addition, this study includes a survival comparison specific to tumour groups between European countries, accounting for differences in registration procedures and under ascertainment of cases, and providing a more accurate, and clinically relevant, insight into survival outcomes of children with a CNS tumour in Europe.

Implications of all the available evidence

The results of this study provide insights into survival for 12 CNS tumour groups and their underlying heterogeneity in clinical characteristics. Moreover, by estimating cure fraction and long-term survival outcomes the results of this study inform on long-term disease outcomes, potentially affecting the duration of clinical follow-up for children treated for a CNS tumour. Finally, a geographical survival comparison of major tumour groups offers valuable information for policy makers in directing targeted resource allocation and improving cancer registry procedures for paediatric CNS tumours.

grade, and tumour location. The large European cohort and coverage since 1998 make it possible to estimate the proportion of children cured and long-term survival (up to 15 years). Additionally, for selected countries, we aimed to evaluated 5-year survival outcomes for four major tumour groups.

Methods

Study design and data collection

EUROCARE-6 is a European population-based study, encompassing data on cancer cases in European children age 0–14 years and covers around 85% of the European paediatric population. All children with a CNS tumour (ICD for Oncology, third edition [ICD-O-3] topography codes C70–C72·9 and C75·1–C75·3.8) were included from the EUROCARE-6 database, regardless of tumour behaviour code (either 0 for benign, 1 for low malignant potential, or 3 for malignant).[8] We included diagnoses between Jan 1, 1998, and Dec 31, 2013, with follow-up data on vital status until Dec 31, 2014.

Information was sourced from 80 cancer registries across 31 European countries (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, England, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, the Netherlands, Northern Ireland, Norway, Poland, Portugal, Scotland, Slovakia, Slovenia, Spain, Switzerland, and Wales). Details on data collection have been described previously.[8] The complete study period (1998–2013) was used to estimate cure fraction and estimate long-term survival for the diagnostic period Jan 1, 2010, to Dec 31, 2013. Following the period outlined in previous EUROCARE-5 results, all remaining analyses were confined to the period from Jan 1, 2008, to Dec 31, 2013.[7] Data underwent predefined quality checks (RH, HEK-K) based on previously specified indicators balanced to the sample size and specific details of the registry.[9]

We assessed malignant-to-non-malignant ratio, proportions of malignant glioma not otherwise specified (ICD-O-M9380/3), malignant optic nerve tumours, and non-malignant brain stem tumours. We identified cases of brain stem glioma not otherwise specified (ICD-O-M9380/3) and evaluated 5-year observed survival. Additionally, we grouped CNS tumours with a dismal prognosis (ie, considered lethal) and estimated their 5-year observed survival. These indicators collectively reflect case completeness, coding precision, and overall

data quality. Additionally, we examined the data for major errors, misclassification of morphological codes, death certificate or autopsy-only registrations, zero survival time, and the presence of additional tumours. Based on the grouping scheme for glial tumours described by Hoogendijk and colleagues,[9] CNS tumours were classified into 12 tumour groups: ependymomas, low-grade gliomas (LGGs), high-grade gliomas (HGGs), medulloblastomas, atypical teratoid or rhabdoid tumours including primitive neuroectodermal tumours, choroid plexus tumours, meningiomas, neuronal and mixed neuronal-glial tumours, pineal tumours, sellar tumours, germ cell tumours, and unspecified tumours (appendix pp 4–6). Of note, multiple tumours diagnosed in the same patient were included in the analysis, but only the first diagnosed tumour was considered for each single survival estimate.

Ethical approval was provided by the Ethics Committee of the National Cancer Institute of Milan (INT73/16).

Statistical analysis

For this study, the main outcomes of interest were observed survival, age-standardised incidence rates, cure fractions, and model-based long-term survival. Observed survival was defined as the time from the date of diagnosis until death from any cause (ie, event), date of emigration (ie, censored), or Dec 31, 2014 (ie, study endpoint).

The actuarial method (SEER*Stat) was used to calculate observed survival for the period 2008–13. The actuarial method estimates the probability of surviving past a specific time by partitioning the observed period into intervals and calculating conditional survival rates that adjust for censored data and changing risk over time. 1-year, 3-year, and 5-year observed survival, including their 95% CIs, were reported for CNS tumour groups in total and by sex, age, CNS WHO grade, tumour location, and morphology. Additionally, 5-year observed survival was calculated for all CNS tumour groups in total by country. Incidence rates were reported as the annual number of cases per million person-years with the annual mid-year population size of Europe or each country. The revised European standard population was used for age standardisation.[10] The age for both denominators was restricted to children younger than 15 years. Cure fraction, the proportion of patients no longer at risk of dying from progression or relapse, was estimated in 4-year periods between 1998 and 2013, via a mixture cure model with a parametric survival curve function assuming constant long-term mortality from other causes, including other cancers. Finally, model-based up-to-date 10-year and 15-year survival was estimated for the period 2010–13 as described by Botta and colleagues.[8] Additional methodological details on cure fraction analyses and model selection can be found in the appendix (p 32). For complete registries, 5-year observed survival was reported on a national level for ependymomas, LGGs, HGGs, and medulloblastomas. All statistical analyses were done in Stata (version 17) and SEER*Stat software (version 8.4.3).

For the **SEER*Stat software** see seer.cancer.gov/seerstat

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From Jan 1, 2008, to Dec 31, 2013, 14745 CNS tumours were identified; 22 with major errors and 670 with misclassified morphology codes were excluded, leaving 14053 for incidence analyses. For survival analyses, 44 death-certificate-only or autopsy-only cases, 202 cases without survival data, and 25 second tumours were excluded, yielding 13782 cases. For cure fraction analyses (1998–2013), 36320 tumours were recorded; 59 with major errors, 5287 were misclassified, 196 death-certificate-only or autopsy-only cases, 324 zero-survival-time cases, and 62 second tumours were excluded, leaving 30392 children included (figure 1; appendix pp 2–3).

See **Online** for appendix

17 of 31 countries had data quality concerns (appendix pp 2–3). Seven countries provided clarifications: four countries (Bulgaria, Cyprus, Portugal, and Slovenia)

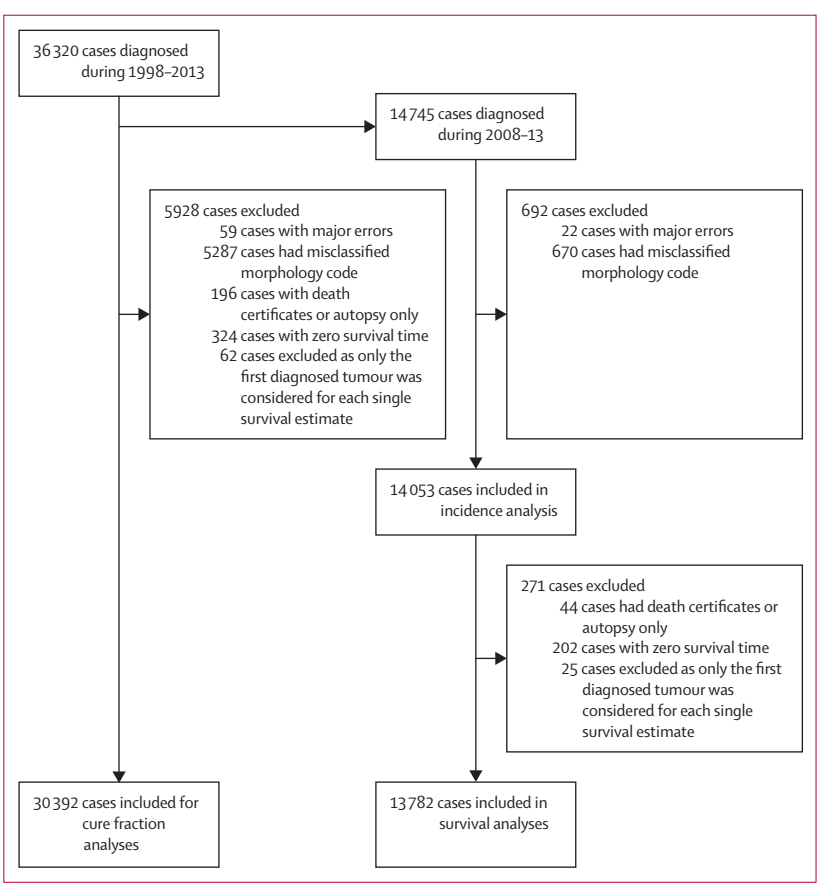

Figure 1: **Flowchart of case inclusion and exclusion for incidence and survival analyses**

reported incomplete registration of non-malignant CNS tumours; three countries (France, Germany, and Switzerland) might have misclassified some low-grade CNS tumours as malignant glioma not otherwise specified (ICD-O-M9380/3). Of the ten countries that did not respond to our queries about data quality, three (Austria, Latvia, and Poland) were previously documented as having incomplete registration and seven (Croatia, Czech Republic, England, Greece, Malta, Norway, and Slovakia) had incomplete non-malignant tumour registration in EUROCARE-6. All 31 countries contributed to pooled European analyses (including the 17 with data quality concerns); only the 14 countries with complete data were used at the country-level analyses (Belgium, Denmark, Estonia, Finland, Hungary, Iceland, Ireland, Italy, Lithuania, the Netherlands, Northern Ireland, Scotland, Spain, Wales). As outcomes for LGGs and HGGs were reported with and without malignant glioma not otherwise specified (ICD-O-M9380/3), France, Germany, and Switzerland were retained in the geographical analyses (17 countries included).

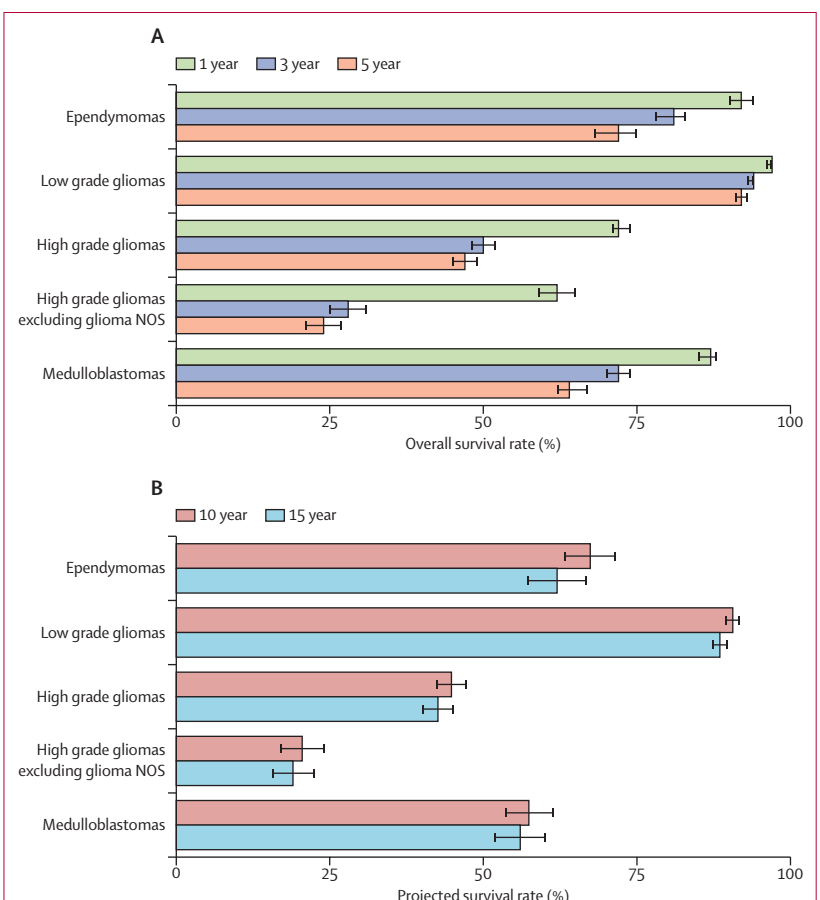

Figure 2: **Survival rates for major paediatric CNS tumour groups**
Observed survival (A) and corresponding projected survival rates (B) with their 95% CIs for major paediatric CNS tumour groups. NOS=not otherwise specified.

5-year observed survival for ependymomas was 72% (95% CI 68–75; figure 2; appendix pp 7–11). 5-year observed survival increased with age at diagnosis, from 64% (95% CI 59–69) for patients diagnosed at age 0–4 years to 84% (78–89) for patients aged 10–14 years. 5-year observed survival for CNS WHO grade I ependymomas was 98% (85–100) and 70% (66–74) for CNS WHO grade II or III. Regarding morphology, anaplastic ependymomas, the most common type (incidence rate 1·5 per million person-years), exhibited the lowest 5-year observed survival of 61% (95% CI 56–66). Subependymomas had a 5-year observed survival of 92% (57–99) and myxopapillary ependymomas a 5-year observed survival of 100% (100–100). Posterior fossa ependymomas showed a 5-year observed survival rate of 66% (60–71) compared with 92% (85–96) for spinal ependymomas and 74% (67–79) for supratentorial ependymomas.

5-year observed survival for LGGs was 92% (95% CI 91–93; appendix pp 7–11). Excluding malignant glioma not otherwise specified (ICD-O-M9380/3) did not affect survival estimates (table 1). All age groups had similar 5-year observed survival of between 91% (95% CI 89–92) and 93% (91–95). Most LGGs were diagnosed as WHO grade I, with a 5-year observed survival of 96% (96–97), compared with 81% (78–84) for WHO grade II tumours. Pilocytic astrocytomas, the most common LGG (incidence rate 6·8 per million person-years), with a 5-year observed survival of 96% (95% CI 95–97), and subependymal giant cell astrocytomas, with a 5-year observed survival of 98% (94–100), had the highest survival probabilities of all LGGs. The lowest 5-year survival was observed for pilomyxoid astrocytomas with 86% (68–94) and diffuse LGGs with 79% (76–82). LGGs located in the brain stem had the poorest 5-year survival of 82% (78–85), in contrast to optic nerve-located tumours with 96% (93–98).

For HGGs, 5-year observed survival was 47% (95% CI 45–49; appendix pp 7–11). 627 (22%) of the HGGs were reported with a tumour located at the optic nerve (C723), with the majority of these classified as malignant glioma not otherwise specified. Excluding malignant gliomas not otherwise specified from the HGGs led to a 23 percentage point decrease in 5-year observed survival for the European pool, resulting in a 5-year observed survival estimate of 24% (21–27; table 1; appendix pp 7–11). Older children had inferior survival outcomes, with a 5-year observed survival of 36% (95% CI 33–40) among those aged 5–9 years and 38% (35–42) among those aged 10–14 years, compared with 67% (64–70) for children aged 0–4 years. 5-year observed survival was 30% (25–34) for CNS WHO grade III and 18% (14–22) for grade IV HGGs. Glioblastoma and variants were the most common specified HGGs (incidence rate 1·4 per million person-years) and had the worst survival, with 5-year observed survival of 18% (95% CI 14–22) and anaplastic astrocytomas were next with 20% (16–26).

	Ependymomas				Low-grade gliomas				Low-grade gliomas excluding malignant glioma not otherwise specified*		High-grade gliomas				High-grade gliomas excluding malignant glioma not otherwise specified*		Medulloblastomas			
	n†	Incidence rate	n‡	5-year observed survival (95% CI)	n†	Incidence rate	n‡	5-year observed survival (95% CI)	n‡	5-year observed survival (95% CI)	n†	Incidence rate	n‡	5-year observed survival (95% CI)	n‡	5-year observed survival (95% CI)	n†	Incidence rate	n‡	5-year observed survival (95% CI)
Belgium	31	2·9	31	71% (44–87)	222	20·0	216	94% (89–97)	201	93% (88–96)	77	6·8	77	28% (17–40)	35	11% (3–24)	67	6·0	67	64% (51–74)
Denmark	8	1·4	8	83% (27–98)	37	6·2	37	97% (82–100)	37	97% (82–100)	19	3·2	19	52% (27–71)	14	40% (15–65)	30	5·2	30	64% (46–77)
Estonia	6	4·9	6	0%	13	10·7	13	92% (57–99)	13	92% (57–99)	2	1·7	2	50% (1–91)	2	50% (1–91)	7	5·7	7	0%
Finland	15	2·9	15	63% (27–85)	101	19·0	101	91% (84–95)	100	91% (83–95)	13	2·4	13	0%	13	0%	32	6·0	32	53% (33–69)
France	201	3·0	199	78% (70–85)	710	10·3	710	93% (91–95)	707	93% (91–95)	643	9·3	642	50% (46–54)	202	17% (12–23)	367	5·3	367	65% (59–70)
Germany	208	3·4	205	73% (64–80)	823	12·5	823	94% (91–96)	823	94% (91–96)	650	10·0	600	49% (44–54)	235	24% (17–31)	325	5·1	325	67% (60–72)
Hungary	21	2·5	21	66% (42–82)	143	16·4	143	91% (84–95)	143	91% (84–95)	65	7·4	65	46% (33–58)	34	42% (25–58)	58	6·8	58	60% (46–71)
Iceland	0	..	0	..	6	14·9	6	100%‡	6	100%	3	7·7	3	0%	0	..	2	4·9	2	0%
Ireland	11	1·9	11	69% (31–89)	61	10·5	61	98% (89–100)	61	98% (89–100)	43	7·4	43	50% (34–64)	20	30% (12–50)	29	4·9	29	50% (32–65)
Italy	65	2·9	65	75% (62–85)	216	9·6	216	91% (86–95)	215	91% (86–95)	116	5·1	116	50% (40–59)	55	35% (22–48)	115	5·0	115	61% (51–70)
Lithuania	7	2·6	7	64% (15–90)	10	3·6	10	77% (35–94)	10	77% (35–94)	8	2·9	8	38% (9–67)	6	17% (1–52)	5	1·8	5	0%
Netherlands	59	3·5	59	66% (49–79)	255	14·8	255	96% (92–98)	255	96% (92–98)	103	5·8	103	22% (15–31)	43	12% (4–24)	100	5·8	100	59% (48–68)
Northern Ireland	8	3·9	8	63% (23–86)	26	12·2	26	92% (54–99)	26	92% (54–99)	9	4·2	9	11% (1–39)	2	0%	14	6·7	14	84% (49–96)
Scotland	13	2·6	13	88% (39–98)	7	1·3	7	100%‡	7	100%	29	5·7	29	38% (21–55)	8	0%	24	4·7	24	58% (37–75)
Spain	59	2·4	59	61% (45–74)	188	7·7	188	91% (85–94)	188	91% (85–94)	117	4·7	116	55% (45–64)	29	0%	107	4·3	107	53% (43–62)
Switzerland	16	2·4	16	87% (57–97)	73	10·2	73	93% (81–97)	73	93% (81–97)	61	8·5	61	39% (26–52)	18	22% (6–45)	31	4·4	31	66% (47–80)
Wales	5	1·6	5	60% (13–88)	25	8·0	25	100%‡	25	100%	20	6·5	20	70% (45–85)	4	0%	13	4·2	13	42% (11–70)
European pool	1086	2·7	1082	72% (68–75)	3997	9·8	3922	92% (91–93)	3971	92% (91–93)	2813	6·9	2747	47% (45–49)	1106	24% (21–27)	2022	5·0	2014	64% (62–67)

*Malignant glioma not otherwise specified (ICD-O-M9380/3) are excluded from these groups due to their possibility to introduce bias in survival estimates. †n for the overall number of patients diagnosed. ‡n for the number of patients with survival data. ‡95% CI sare not provided as no mortality events were available for estimation.

Table 1: **Paediatric CNS tumours cases diagnosed in Europe in 2008–13, age-adjusted incidence rate per million person-years, and 5-year observed survival per country and tumour group**

From the histologically defined entities, anaplastic oligoastrocytic tumours had the highest 5-year observed survival at 48% (39–58). When differentiating by tumour location, brain stem HGGs had a 5-year observed survival rate of 20% (18–23) and a median observed survival of 12·4 months, compared with 98% (96–99) for optic nerve tumours.

Medulloblastomas are the second most common paediatric CNS tumours (incidence rate 5·0 per million person-years; appendix pp 7–11). The 5-year observed survival for these tumours was 64% (95% CI 62–67). Survival increases with age, with 5-year observed survival at 53% (48–57) for children age 0–4, 68% (64–71) for those age 5–9, and 77% (71–81) for those age 10–14 years. Atypical teratoid or rhabdoid tumours had the worst 5-year observed survival at 28% (23–34) within the embryonal tumour group, followed by primitive neuroectodermal tumours at 43% (38–49), which are now generally reclassified into other tumour types such as embryonal tumours with multilayered rosettes or atypical teratoid or rhabdoid tumours, and large cell or anaplastic medulloblastoma at 47% (30–63; appendix pp 7–11). Incidence rates, percentage of microscopic verification, and survival estimates for other CNS tumour groups and stratified according to sex are provided in the appendix (pp 12–18).

Cure fraction, long-term mortality, and estimated long-term survival for selected tumour groups are provided in table 2. Cure fraction for ependymomas increased steadily with an absolute increase of 14 percentage points (95% CI 2 to 26) from 65% (57 to 73) in 1998–2001 to 79% (69 to 89) in 2010–13. However, as a result of the high long-term mortality rate of 16·1 (9·4 to 22·8) per 1000 surviving patients per year, ependymomas had an estimated 10-year survival of 67·4% (63·2 to 71·6) and 15-year survival of 62·0% (57·2 to 66·8; figure 2). For LGGs, the cure fraction also increased over time by 5 percentage points (95% CI –2 to 13), from 89% (85 to 94) in 1998–2001 to 95% (89 to 100) in 2010–13, and 10-year survival was 90·6% (89·4 to 91·7) and 15-year survival was 88·5% (87·2 to 89·8). For HGGs, cure fraction increased by 6 percentage points (2 to 10), from 44% (41 to 47) in 1998–2001 to 50% (47 to 52) in 2010–13. For HGGs excluding glioma not otherwise specified, cure fraction remained similar over time, varying between 27% (21 to 32) in 1998–2001 and 24% (18–30) in 2010–13. For these tumours, projected 10-year survival was 20·5% (17·0 to 24·1) and 15-year survival was 19·0% (15·6 to 22·5). For medulloblastomas, cure fraction increased by 3 percentage points (–2 to 8), from 52% (49 to 55) in 1998–2001 to 56% (51 to 60) in 2010–13, which was similar to the 15-year survival of 56·0% (51·8 to 60·2). 10-year survival for medulloblastomas was 57·4% (53·5 to 61·4). Cure fraction and long-term survival estimates for other tumour groups and subgroups and related model fits are provided in the appendix (pp 23–30).

Country-specific survival estimates for ependymomas, LGGs, HGGs, and medulloblastomas (only for countries with complete registry data), are provided in table 1. For ependymomas, the variation in 5-year observed survival is low across countries. A similar pattern of variation is observed in LGGs, with most countries reporting a 5-year observed survival of 90% or higher. For LGGs excluding malignant glioma not otherwise specified, tumours did not affect survival outcomes by country. In contrast, HGGs had more variable 5-year observed survival between countries but variation is driven by small patient numbers. The 5-year observed survival rates for medulloblastomas exhibited greater variability, ranging from 0% to 84% (95% CI 49–96; table 1). In line with HGGs, this variability is largely influenced by the small number of patients in some countries.

	Model	Long-term mortality per 1000 patients per year (95% CI)	Proportion cured, % (95% CI)				Percentage point difference in proportion cured between first and last period* (95% CI)	Projected 10-year survival, % (95% CI)	Projected 15-year survival, % (95% CI)
			1998–2001	2002–05	2006–09	2010–13			
CNS tumours overall	Log-normal	7·1 (6·1–8·1)	70% (68–72)	71% (70–73)	75% (73–76)	75% (73–77)	5 (3 to 7)	70·0% (68·9–71·0)	67·4% (66·3–68·5)
Ependymomas	Weibull	16·1 (9·4–22·8)	65% (57–73)	68% (61–75)	73% (65–80)	79% (69–89)	14 (2 to 26)	67·4% (63·2–71·6)	62·0% (57·2–66·8)
Low-grade gliomas	Log-normal	4·6 (3·6–5·5)	89% (85–94)	91% (87–96)	93% (88–98)	95% (89–100)	5 (–2 to 13)	90·6% (89·4–91·7)	88·5% (87·2–89·8)
High-grade gliomas	Log-normal	10·2 (8·0–12·5)	44% (41–47)	46% (43–48)	50% (48–53)	50% (47–52)	6 (2 to 10)	44·8% (42·3–47·3)	42·6% (40·0–45·1)
High-grade gliomas excluding glioma not otherwise specified	Log-normal	14·7 (8·0–21·4)	27% (21–32)	25% (20–29)	27% (22–31)	24% (18–30)	3 (–1 to 5)	20·5% (17·0–24·1)	19·0% (15·6–22·5)
Medulloblastomas	Weibull	0·0†	52% (49–55)	53% (50–56)	56% (53–59)	56% (51–60)	3 (–2 to 8)	57·4% (53·5–61·4)	56·0% (51·8–60·2)

Long-term mortality was defined as the number of deaths attributable to causes other than the diagnosed cancer per 1000 patients per year. *Discrepancies are due to rounding. †95% CI are not available as there were no mortality events.

Table 2: **Long-term mortality, cure fraction, and projected 10-year and 15-year survival for selected tumour groups**

Discussion

By using data from the EUROCARE project, we comprehensively analysed paediatric CNS tumour survival in Europe for, to our knowledge, the largest number of patients to date. Survival varied largely between CNS groups, with a 5-year observed survival of less than 30% for HGGs (excluding malignant glioma not otherwise specified) and greater than 90% for LGGs. By stratifying analyses by sex, age, CNS WHO grade, and tumour location, we provide insight into underlying disparities and patterns, showing that (for most tumour groups) age, morphology, and topography were important prognostic factors. To our knowledge, this study is the first time long-term survival and cured fraction for CNS childhood cancers have been estimated.

5-year observed survival for ependymomas was 72%, which is similar to clinical trial outcomes.[11] Ependymomas are currently classified according to their primary anatomical location and molecular profile.[12] Although the EUROCARE database does not include any molecular data, by grouping tumours to their respective anatomical location we provided survival estimates that could serve as a proxy. Previous clinical trial results showed that 5-year observed survival for posterior fossa ependymoma was 70% and for supratentorial ependymoma was 69%, slightly differing from our results of 66% for posterior fossa ependymoma and 74% for supratentorial ependymoma.[11] These differences might reflect low ICD-O tumour location code specificity or selection bias in trials versus a population-based approach.

In the HGG group, a large number of tumours were assigned an optic nerve tumour location (627 cases, 22%), almost solely consisting of malignant glioma not otherwise specified. Malignant optic nerve gliomas are uncommon and typically manifest in older adults, and these tumours should therefore be considered misclassified.[13] This misclassification is supported by the 23 percentage point difference in 5-year observed survival when excluding these tumours. HGG 5-year observed survival has been reported to range between 15% and 35%,[14] which is similar to our estimate of 24% when excluding malignant glioma not otherwise specified. To our knowledge, only one population-based study has reported 5-year observed survival for brain stem HGG.[15] The authors reported a 5-year relative survival of 37%, contrasting our 5-year observed survival of 20%. In addition, median observed survival has been estimated to be 15 months,[16] contrasting with our results with a median survival of 12 months. This difference might be explained by the inclusion of malignant glioma not otherwise specified in the aforementioned studies. Unfortunately, a dedicated ICD-O-3 morphology code for diffuse midline gliomas has only been included in the fourth revised version of the WHO classification, published in 2016, and, therefore, we were unable to report diffuse midline gliomas as a separate entity for the study period. Overall, children with an HGG age 0–4 years had better survival outcomes than older children, which is probably driven by the infant-type hemispheric gliomas that in general have a favourable prognostic profile compared with the diffuse midline gliomas that commonly occur in older children and have very poor outcomes.[4,17]

Survival estimates for the different morphological medulloblastoma tumour types are similar to the EUROCARE-5 study and, as a collective group, align with findings from country-specific population-based studies.[7,18] Although the fifth edition of the WHO classification of tumours provides the opportunity to diagnose medulloblastoma based on histology, the majority of these tumours are currently classified into four molecular subtypes.[12] Although our database does not contain molecular information, some overlap remains. For instance, although not all SHH-activated medulloblastomas are desmoplastic or nodular, nearly all desmoplastic or nodular tumours are SHH-activated, reflected by similar survival rates.[19] Primitive neuroectodermal tumours have previously been found to consist of a very heterogeneous group of tumours ranging from medulloblastomas to atypical teratoid or rhabdoid tumours.[20] These tumours complicate retrospective registry analyses, and grouping them with atypical teratoid or rhabdoid tumours is debatable. However, we analysed primitive neuroectodermal tumours with atypical teratoid or rhabdoid tumours, and not medulloblastomas, due to their prognostic profile and sample size considerations. This decision to classify primitve neuroectodermal tumours with atypical teratoid or rhaboid tumours, and not medulloblastomas, underscores ongoing challenges in evolving CNS tumour classifications, as noted by others.[6]

Our study did not implement the International Classification of Childhood Cancer (ICCC) classification system as its approach to CNS tumours is outdated. Although proposed alternatives better align with current diagnostics, none have been implemented in Europe, limiting robust clinical translation of registry data.[6,21] The use of a novel grouping scheme for paediatric CNS tumours reduces comparability with previous studies but provides more accurate information. Future efforts should modernise the ICCC to align with contemporary diagnostics and rapidly integrate new WHO Blue Book updates.

To our knowledge, this study is the first to report cure fraction estimates for specific paediatric CNS tumour groups. Previous EUROCARE-6 analyses presented a small, but significant increase in the cure fraction over time for all malignant paediatric CNS tumours combined.[8] In this study, we showed that this increase is largely dependent on the CNS tumour subgroup, with ependymomas having the largest increase and HGGs (excluding glioma not otherwise specified) showing no increase. Moreover, paediatric CNS tumours have been reported to have the highest level of long-term mortality

rates across paediatric cancers.[8] In line with findings for the cure fraction, we show large variation in long-term mortality rates across tumour subgroups, with medulloblastomas having a mean long-term mortality rate similar to the general population (0·2 per 1000 people in the general population *vs* 0·0 per 1000 patients with medulloblastomas). It is important to note that our definition of cure (the proportion of patients no longer at risk of dying from their tumour) is a statistical estimation and needs careful consideration before translating these findings to the individual patient. So far, few studies have reported long-term survival for paediatric CNS tumours. Notable differences between 5-year observed survival and estimated 10-year and 15-year observed survival were found for ependymomas overall and related subgroups. These findings suggest that a subset of ependymoma patients remain at an important tumour-related mortality risk even 15 years after diagnosis, underscoring the importance of prolonged surveillance. A previous Surveillance, Epidemiology, and End Results analysis that excluded ependymoma patients dying within 5 years after their diagnosis reported survival rates at 87·0% at 10 years, 77·7% at 20 years, and 57·3% at 30 years.[22] These results, probably higher than the findings in our study due to the exclusion of early deaths, support the conclusion that ependymoma patients have a long-term elevated risk of dying. For LGGs, HGGs, and medulloblastomas, the difference was less marked. However, in LGGs specifically, a subset of patients had poorer long-term survival, probably attributable to radiotherapy-related risks, including subsequent malignancies and vasculopathy.[23]

Previous studies revealed substantial international discrepancies in reporting non-malignant CNS tumours, potentially misleading national-level survival estimates.[7,24,25] Additionally, non-microscopically verified tumours, particularly gliomas, are prone to misclassification without histomolecular data. By excluding incomplete registries and addressing data quality concerns (eg, malignant glioma not otherwise specified misclassification), this study is the first to elucidate pan-European survival differences across four major paediatric CNS tumour groups. For ependymomas, LGGs, HGGs, and medulloblastomas, survival variation was small and probably influenced by small sample sizes. Excluding malignant glioma not otherwise specified from the HGG group decreased 5-year observed survival by 23 percentage points and decreased survival differences, supporting the hypothesis that misclassifying non-microscopically verified low-grade tumours as malignant glioma not otherwise specified biases cross-country comparisons.[25] Excluding these tumours could also create bias by omitting highly aggressive entities such as diffuse midline gliomas that in the past did not commonly have a biopsy sample taken, yielding artificially elevated survival. These factors complicate valid HGG outcomes, underscoring the need for improved data quality to enable more reliable conclusions.

Data quality concerns and variations in registration practices in the context of paediatric CNS tumours in Europe have also been addressed by others.[7,26] This issue remains topical, as molecular diagnostics and pathological capacities vary across Europe, potentially leading to a further discrepancy in registration practices in Europe and affecting the validity of future international comparisons. In this context, it is important to note that the European Network of Cancer Registries revised recommendations in 2023 for coding the basis of diagnosis in cancer registries, and is in the final stages of developing recommendations for CNS tumour coding, promising improved data quality.[27] The absence of specific ICD-O codes for newly defined entities in fifth edition of the WHO classification of tumours has widened the gap between population-based registry research and clinical practice, underscoring the need to maintain relevant data for paediatric CNS tumours. Although ICD-11 offers an alternative coding system, implementation across cancer registries remains challenging.[6] Therefore, the upcoming ICD-O-4, expected in summer 2025, represents the most logical solution, as it will include new CNS morphology codes, enabling more clinically accurate outcome reporting.

One limitation of this study is that data collection extends only to 2014, primarily due to the complexities of data sharing and regulatory constraints, which delays the timely reporting of outcomes. Despite General Data Protection Regulation constraints in Europe, future initiatives should aim to provide more recent data by investigating innovative ways to share cancer registry data in Europe. Another limitation is the absence of molecular data, an inherent challenge of retrospective cancer registry datasets. However, the implemented grouping scheme serves as an effective proxy indicator. Additionally, variations in the distribution of non-malignant tumours across countries have been shown to yield biased survival outcome estimates.[25] The grouping scheme minimises bias due to incomplete data, and stringent quality criteria ensured that only countries with comprehensive registries were included in the geographical comparison. Finally, from a statistical standpoint, it is essential to recognise that the reported 95% CIs for the cure rate and projected long-term survival outcomes are conditional on the survival model fitted to the data. Consequently, potential inaccuracies arising from model specification represent the primary source of uncertainty. For an example, refer to ependymomas in the appendix (p 32).

In conclusion, this large-scale, population-based study reveals novel insights into the survival probabilities of paediatric CNS tumours in Europe. Our findings support clinicians, pathologists, and policy initiatives, such as Europe's Beating Cancer Plan and the WHO Childhood Cancer Act.

Contributors

RH, HEK-K, GG, and RC drafted the protocol. GG, and RC contributed to data acquisition. GG and RC had full access to all the data in the study, accessed and verified all the raw data, prepared the data, and performed quality control. GG and RC performed the analyses. All the authors checked the results. RH drafted the report. All authors contributed to writing the final report, approved the version to be published, and had final responsibility for the decision to submit for publication. All members of the EUROCARE-6 Working Group had access to the results of all steps of data preparation, quality control, and analyses, and contributed to interpretation of the findings.

Declaration of interests

We declare no competing interests.

Data sharing

We analysed pseudonymised data collected from 80 population-based cancer registries. We hold these data in trust from each participating registry for the statistical analyses agreed in the EUROCARE-6 protocol, available at http://www.eurocare.it. We are not permitted to share individual data. Aggregated-level data, in the form of counts, rates, or survival proportions, can only be shared after express permission from the participating registries. These data should be requested by contacting the corresponding author or the EUROCARE Secretariat (eurocare.secretariat@istitutotumori.mi.it).

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