Geographical variability in survival of European children with central nervous system tumours

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Abstract

Survival for childhood central nervous system (CNS) tumours varies across Europe, partly because of the difficulty of distinguishing malignant from non-malignant disease. This study examines bias in CNS tumours survival analysis to obtain the reliable and comparable survival figures.

We analysed survival data for about 15,000 children (age <15) diagnosed with CNS between 2000 and 2007, from 71 population-based cancer registries in 27 countries. We selected high-quality data based on registry-specific data quality indicators and recorded observed 1-year and 5-year survival by countries and CNS entity.

We provided age-adjusted survival and used a Cox model to calculate the hazard ratios (HRs) of death, adjusting by age, site and grading by country.

Recording of non-malignant lesions, use of appropriate morphology codes and completeness of life status follow-up differed among registries. Five-year survival by countries varied less when non-malignant tumours were included, with rates between 79.5% and 42.8%. The HRs of dying, for registries with good data, adjusting by age and grading, were between 0.7 and 1.2; differences were similar when site (supra- and infra-tentorial) was included.

Several sources of bias affect the correct definition of CNS tumours, the completeness of incidence series and the goodness of follow-up. The European Network of Cancer Registries needs to improve childhood cancer registration and stress the need to update the International Classification for Cancer. Since survival differences persisted even when restricting the analysis to registries with satisfactory data, and since diagnosis of CNS tumours is difficult and treatment complex, national plans must aim for the revision of the diagnosis and the coordination of care, with adequate national and international networks.

1. Introduction

The central nervous system (CNS) is the most common site of solid tumours affecting children [1]. Five-year survival of children with malignant CNS tumours in Europe in 2005–2007 was 58%, from 54% in Eastern regions and the UK and Ireland to 65% in the North [2]. There is presumably ample room for improvement in regions with low survival. However, data on CNS tumours collected by European population-based cancer registries (CRs) are not completely comparable. In a previous analysis of European childhood cancer survival, the differences in registration criteria were so extensive that CNS tumours had to be removed from the analysis of all childhood cancers combined for reliable comparison of survival across countries [2].

We analysed the main sources of bias in childhood CNS tumour survival across Europe, considering the completeness of incidence series, standardisation of the definition of disease entities, the collection and completeness of benign and borderline lesions, and the quality of follow-up. The major aim was to produce more reliable survival figures for CNS tumours by country, eliminating as far as possible biases affecting comparisons, to illustrate survival variability between countries.

2. Materials and methods

2.1. Study design and data collection

The EUROCARE-5 database [2] covers about 38,000 CNS tumours, defined as group III in the International Classification of Childhood Cancers, third edition (ICCC-3) [3], diagnosed in European children aged 0–14 years from 1-Jan-1978 to 31-Dec-2007, with vital status updated to 31-Dec-2008. We obtained data from 71 population-based CRs in 27 countries (Table 1). Most countries had national cancer registration. All registries sent data for anonymous central analysis according to a standardised protocol [4].

Table 1. Children with non-malignant or malignant CNS tumours diagnosed in 2000–07 by European country with data quality indicators.

Area	Country	Number of cases excluded for major errors[a]	DCO (%)	Autopsy (%)	Alive with no survival time (%)	Number of cases included in the analysis	MV (%)	Alive 2000–03 censored before 5 years (%)[b]	Non-malignant CNS cases (%)	Unspecified NOS (ICCC IIIf) as a percentage of the cases in the analysis (overall)	Glioma NOS (ICD-O M 9380/3) (%)[c]	Lethal CNS tumours[d] Number of cases	Lethal CNS tumours[d] Five-year survival (%) and (95% CI)
Northern Europe	Denmark	0	0.0	0.0	0.0	264	83.0	0.0	51.9	18.6	n.a	–	n.a
	Finland	0	0.0	0.0	0.0	292	97.3	0.0	23.6	3.8	45.6	5	0
	Norway	0	0.0	0.0	0.0	335	84.2	0.0	48.1	10.4	6.9	12	16.7 (0.2–41)
UK and Ireland	Ireland	1	0.4	0.0	0.0	224	79.5	0.0	37.9	4.0	10.3	8	25.0 (4–56)
	UK–England/Wales	13	0.2	0.2	0.2	2460	79.4	0.9	41.2	4.3	8.7	203	14.2 (10–20)
	UK-Northern Ireland	0	0.0	0.0	0.0	103	71.8	0.0	41.7	27.2	1.0	5	0
	UK–Scotland	1	0.0	0.4	0.0	245	76.3	0.0	44.1	8.2	7.4	14	0
Central Europe	Austria	0	0.0	0.0	0.0	349	95.7	0.0	25.2	4.0	7.7	45	24.1 (13–38)
	Belgium	5	0.0	0.0	1.7	295	94.9	0.0	34.6	2.7	3.4	27	12.2 (2–33)
	France	5	0.0	0.0	0.2	3156	85.6	3.7	43.6	1.5	7.3	219	17.9 (13–24)
	Germany	39	0.0	0.0	1.2	3315	87.5	27.1	40.4	1.3	6.1	398	19.4 (15–24)
	Switzerland	2	0.0	1.3	1.3	84	89.3	10.5	41.7	10.7	1.2	6	0
	The Netherlands	2	0.0	0.2	0.0	869	86.1	0.8	42.1	4.7	7.8	84	20.7 (13–30)
Southern Europe	Croatia	2	0.8	0.0	0.0	260	73.1	0.0	26.2	35.0	4.2	14	40.8 (16–65)
	Italy	1	0.1	0.0	0.0	825	77.2	1.3	37.1	17.3	5.3	53	28.6 (17–42)
	Malta	2	9.5	0.0	0.0	19	84.2	0.0	26.3	0.0	5.3	3	33.3 (1–77)
	Portugal	1	0.0	0.0	0.3	292	88.4	2.0	25.4	4.5	10.3	20	10.0 (2–27)
	Slovenia	0	0.0	0.0	0.0	64	96.9	0.0	34.4	4.7	3.1	10	50.0 (18–75)
	Spain	3	0.0	0.0	0.5	579	75.9	1.6	29.3	8.6	10.2	22	32.7 (13–54)
Eastern Europe	Bulgaria	24	11.6	0.0	0.0	183	82.5	0.0	9.3	17.5	1.6	15	20.0 (5–42)
	Estonia	0	0.0	0.0	0.0	61	77.1	0.0	37.7	21.3	0.0	1	0
	Hungary	0	0.0	0.0	0.0	481	93.8	2.5	34.3	0.4	7.7	21	11.7 (2–30)
	Latvia	12	12.2	2.4	0.0	70	71.4	0.0	1.4	28.6	2.9	8	70.9 (25–92)
	Lithuania	3	3.7	0.0	0.0	79	89.9	30.8	7.6	12.7	2.5	7	0
	Poland	4	0.0	0.0	2.6	149	79.9	6.4	5.4	20.1	4.7	13	26.4 (7–52)
	Slovakia	6	1.7	0.9	0.0	228	88.6	0.0	42.1	9.6	1.8	6	33.3 (5–68)
European pool		126	0.3	0.1	0.4	15,281	87.2	8.4	38.5	5.6	7.5	1219	

MV, microscopic verification; DCO, death certificate only; CNS, central nervous system; CI, confidence interval; ICD-O M, International Classification of Diseases for oncology third edition; n.a., not available; ICCC, International Classification of Diseases for Oncology, third edition.

In **bold type** countries with national coverage; partial coverage for Belgium (56%), Switzerland (29%), Italy (36%), Portugal (70%), Spain (34%), Poland (12%).
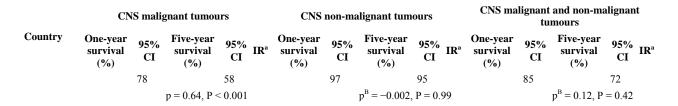
Table 2. CNS childhood tumours diagnosed in 2000–07: incidence rates (IRs) and 1- and 5-year survival with 95% confidence interval (CI) by country and tumour behaviour.

Country	CNS malignant tumours					CNS non-malignant tumours					CNS malignant and non-malignant tumours				
	One-year survival (%)	95% CI	Five-year survival (%)	95% CI	IR[a]	One-year survival (%)	95% CI	Five-year survival (%)	95% CI	IR[a]	One-year survival (%)	95% CI	Five-year survival (%)	95% CI	IR[a]
Denmark	80.3	72–86	60.6	51–69	1.6	93.4	88–97	92.6	87–96	1.7	87.1	83–91	77.1	71–82	3.3
Finland	86.1	81–90	75.3	69–81	3	97.1	89–99	94.5	83–98	0.9	88.7	85–92	79.5	74–84	4
Norway	84.5	78–89	62.5	54–70	2.4	96.9	93–99	94.7	90–97	2.2	90.5	87–93	78.3	73–83	4.6
Ireland	77.0	69–83	59.7	50–68	2	97.7	91–99	89.3	79–95	1.3	84.8	79–90	70.9	64–77	3.3
UK–England & Wales	75.8	74–78	57.1	54–60	2.1	95.3	94–96	92.7	91–94	1.5	83.8	82–85	71.8	70–74	3.6
UK–Northern Ireland	78.3	66–87	55.1	41–67	2.1	95.4	83–99	92.3	78–98	1.5	85.4	77–91	70.5	60–79	3.6
UK–Scotland	72.3	64–79	52.2	43–61	1.9	97.2	92–99	92.8	85–97	1.5	83.3	78–87	69.8	63–76	3.5
Austria	81.6	76–86	63.8	57–70	2.5	100		94.2	85–98	0.8	86.3	82–90	72.1	67–77	3.3
Belgium	76.2	70–82	64.1	57–71	2.4	96.1	90–99	93.1	86–97	1.3	83.1	78–87	74.1	68–79	3.7
France	73.1	71–75	51.8	49–54	2.1	97.9	97–99	95.8	95–97	1.6	83.9	83–85	70.8	69–73	3.8
Germany	79.9	78–82	59.1	57–62	2	98	97–99	96	95–97	1.4	87.2	86–88	73.9	72–76	3.4
Switzerland	73.5	59–84	57.8	42–71	1.7	100		100		1.2	84.4	75–91	75	64–83	2.9
The Netherlands	69.2	65–73	46.4	42–51	2.1	97	95–98	95.7	93–97	1.5	80.9	78–83	67.0	64–70	3.6
Croatia	88.0	83–92	69.6	62–76	3.2	97.1	89–99	93.7	84–98	1.1	90.4	86–93	75.6	69–81	4.4
Italy	80.8	77–84	61.3	57–66	2.4	98	96–99	96	93–98	1.4	87.2	85–89	74.1	71–77	3.8
Malta	78.6	47–93	61.2	29–82	2.4	100		100		0.8	84.2	59–95	71.8	44–87	3.2
Portugal	74.1	68–79	53.4	46–60	2.6	91.9	83–96	84.9	74–91	0.9	78.7	74–83	61.4	55–67	3.5
Slovenia	78.6	63–88	57.2	40–71	1.8	100		100		0.9	85.9	75–92	72.4	59–82	2.7
Spain	81.8	78–85	62.1	57–67	2.6	94.7	90–97	88.5	82–93	1.1	85.8	83–88	70.0	66–74	3.7
Bulgaria	55.4	48–63	38.1	30–46	1.8	94.1	65–99	87.8	60–97	0.2	59.0	52–66	42.8	35–50	2
Estonia	76.3	59–87	61.1	43–75	2.2	91.3	70–98	83.7	56–95	1.3	82.0	70–90	69.9	57–81	3.5
Hungary	75.5	70–80	55.1	49–61	2.5	95.1	91–99	91.9	86–95	1.3	82.2	79–85	67.6	63–72	3.7
Latvia	81.2	70–89	65.6	53–76	2.4	100				0	81.4	70–89	65.8	53–76	2.4
Lithuania	77.6	65–86	49.2	36–61	1.7	100		100		0.1	79.0	67–87	53.1	41–64	1.8
Poland	85.7	79–91	61.7	52–70	2.2	100		70	23–92	0.1	86.4	80–91	62.1	53–70	2.4
Slovakia	74.2	66–81	52.7	43–61	2	97.9	92–99	97.9	92–99	1.4	84.2	79–88	71.9	65–77	3.4
European pool	77.1	76–	57.1	56–	2.2	96.7	96–	94.4	94–	1.4	84.7	84–	71.3	71–	3.5

Country	CNS malignant tumours					CNS non-malignant tumours					CNS malignant and non-malignant tumours				
	One-year survival (%)	95% CI	Five-year survival (%)	95% CI	IR[a]	One-year survival (%)	95% CI	Five-year survival (%)	95% CI	IR[a]	One-year survival (%)	95% CI	Five-year survival (%)	95% CI	IR[a]
	78		58			97		95			85		72		
		p = 0.64, P < 0.001					p[B] = −0.002, P = 0.99					p[B] = 0.12, P = 0.42			

CNS, central nervous system.

p[B] calculated excluding Austria, Finland, Bulgaria, Latvia, Lithuania and Poland because of incomplete collection of non-malignant cases.

a IR are calculated per 100,000 per year.

Tumours were grouped into the six categories defined by ICCC-3, group III [3], [5]. The EUROCARE-5 protocol [4] asked registries to include both malignant tumours (5th digit in the morphology code equal to 3 in the International Classification of Diseases for Oncology third edition, ICD-O M) and tumours with non-malignant behaviour (5th digit in the morphology codes: 0 or 1). However, some registries communicated to have an incomplete collection of non-malignant tumours (Austria, Bulgaria, Finland, Latvia, Lithuania and Poland).

To analyse survival differences between countries, we had to check the quality of data. For CNS tumour, most important indicators of data quality were: the proportions of unspecified intracranial and intraspinal neoplasms—ICCC-3-IIIf; the proportion of glioma NOS (M-9380/2-3, excluding optical nerve); the proportion of non-malignant tumours, which may suggest, if too low, incomplete registration; the 5-year survival of CNS tumours with very bad prognosis—atypical teratoid/rhabdoid tumours (M-9508/3), anaplastic astrocytoma (M-9401/3), anaplastic oligodendroglioma (M-9451/3) and glioblastoma (M-9440/3-9442/3) which, if higher than average, suggests errors in follow-up.

2.2. Data analysis

Observed survival was calculated by the actuarial method. Survival was analysed on a data set containing all childhood cases diagnosed between 1-Jan-2000 and 31-Dec-2007 and followed up until 31-Dec-2008. Survival for 2000–07 was estimated using the complete approach [6]. This is similar to the cohort method but includes recently diagnosed patients (e.g. 2004–2007) with <5 years of follow-up. To ensure comparability between countries, age-standardised country-specific 5-year survivals were also provided. We standardised the estimates to the age distribution of all European children 2000–2007 diagnosed with CNS tumours, defining four classes (<1, 1–4, 5–9 and 10–14 years) [2]. We calculated the crude annual incidence rates (IRs) per 100,000 by country and used Pearson's correlation coefficient (p) to relate these to 5-year survival.

We used a Cox model [7] to calculate the hazard ratios of death (HRs) by country and their 95% confidence intervals (95%CI), according to age, sex, subsite and grading (based on the fourth edition of the WHO classification, which assigned a grade to each ICD-O M, see Table 3) [8]. To adjust for grading, we divided all the tumours as follows: grade I, grade II, grade III–IV, unspecified tumours with non-malignant behaviour, unspecified tumours with malignant behaviour, astrocytoma NOS, glioma NOS (excluding optic nerve). As for the few ICD-O morphological entities not considered in the WHO classification, benign meningioma, pituitary tumour, gliofibroma, choroid glioma, and astroblastoma (even if occasionally it may have an aggressive course), were placed with grade I tumours, and gliomatosi cerebri with grades III–IV.

Table 3. Five-year survival and 95% confidence interval (CI) for children with non-malignant or malignant CNS tumours diagnosed in 2000–07 in Europe by CNS diagnostic group.

Diagnostic group	WHO grade	Number	%	% MV	Five-year survival (%)	95% CI	ICDO3-M[a]
IIIa ependymoma and choroid plexus tumour		1534	10.2	98.9	70	67–72	
Choroid plexus papilloma	I	172	11.2	97.6	97	92–99	9390/0
Subependymoma	I	20	1.3	80	95	65–99	9383/1
Myxopapillary ependymoma	I	75	4.9	100	96	85–99	9394/1
Atypical choroid plexus papilloma	II	35	2.3	100	89	69–97	9390/1
Ependymoma, other and NOS	II	591	38.5	99	70	66–74	9391/3, 9393/3
Choroid plexus carcinoma	III	150	9.8	98	44	36–53	9390/3
Anaplastic ependymoma	III	491	32	100	61	56–66	9392/3
IIIb astrocytomas		6078	40.5	91.5	80	79–81	
Pilocytic astrocytoma	I	3231	53.2	98.9	95	94–96	9421/1
Subependymal giant cell astrocytoma	I	136	2.2	92.7	99	97–99	9384/1
Glioma, optic nerve	I	611	10.1	36.5	99	97–99	9380/3
Pleomorphic xanthoastrocytoma	II	73	1.2	100	85	74–92	9424/3
Fibrillary astrocytoma	II	182	3.0	97.8	75	67–81	9420/3
Protoplasmic astrocytoma	II	19	0.2	100	95	68–99	9410/3
Gemistocytic astrocytoma	II	8	0.1	87.5	41	7–74	9411/3
Anaplastic astrocytoma	III	338	5.6	99.7	21	16–26	9401/3
Glioblastoma and variants	IV	530	8.7	98.7	14	11–18	9440/3, 9441/3, 9442/3
Astrocytomas, NOS	–	948	15.5	92.7	74	71–77	9400/3, 9423/3
Gliofibroma	–	2	0.04	100	100		9442/1
IIIc intracranial and intraspinal embryonal tumour		3097	20.7	99.2	57	55–59	
Medulloblastoma, variants	IV	2006	64.8	99.4	65	62–67	9470/3, 9472/3, 9480/3, 9501/3, 9503/3
Medulloblastoma large cell	IV	52	1.7	100	36	17–56	9474/3
Desmoplastic/nodular medulloblastoma	IV	237	7.6	99.6	72	65–78	9471/3
PNET, variants	IV	544	17.6	98.3	41	36–45	9473/3

Diagnostic group	WHO grade	Number	%	% MV	Five-year survival (%)	95% CI	ICDO3-M[a]
Atypical teratoid/rhabdoid tumour	IV	258	8.3	99.2	23	18–29	9508/3
IIId Other gliomas		1642	10.9	66.1	46	43–49	
Oligodendroglioma	II	212	12.9	98.1	74	67–80	9450/3,9460/3
Oligodendroglioma, anaplastic	III	91	5.6	98.9	30	20–40	9451/3
Glioma, mixed	III	137	8.4	99.3	54	45–62	9382/3
Astroblastoma	–	19	1.2	100	78	53–92	9430/3
Chordoid glioma	–	1	0.1	100			9444/1
Gliomatosi cerebri	–	30	1.8	86.7	32	16–49	9381/3
Glioma NOS (excl.optic nerve)	–	1152	70.2	53	41	38–44	9380/3
IIIe Other specified CNS tumours		1866	12.4	93	93	91–94	
Pinealoma and pineocytoma	I	19	1.0	73.7	89	43–98	9360/1, 9361/1
Desmoplastic infantile astrocytoma	I	59	3.2	98.5	85	73–92	9412/1
Dysembryoplastic neuroepithelial tumour	I	322	17.3	88.5	99	97–100	9413/0
Gangliocytomas, ganglioglioma	I	402	21.6	96.8	96	93–98	9492/1, 9505/1, 9493/1
Meningioma, non-malignant	I	188	10.1	92.5	95	87–96	9530/0, 9530/1, 9531/0-9539/1
Craniopharyngioma	I	608	32.5	93.8	97	96–99	9350/1, 9351/1, 9352/1
Central neurocytoma	II	17	0.9	100	88	61–97	9506/1
Ganglioglioma, anaplastic	III	25	1.3	100	70	48–85	9505/3
Meningioma, malignant	III	29	1.6	100	79	58–90	9530/3,9538/3,9539/3
Pineoblastoma	IV	105	5.6	100	46	35–56	9362/3
Pituitary tumour	–	92	4.9	75	100		8270/0-8281/0, 8300/0
IIIf unspecified CNS		800	5.3	17.9	64	60–67	
Malignant	–	429	53.4	15.2	51	46–56	8000/3-8005/3
Benign	–	371	46.6	21	78	74–82	8000/0,1-8005/0

CNS, central nervous system; MV, microscopically verified.

Includes number of cases, proportion of microscopically verified cases and proportion of cancer cases for each diagnostic group. The column headed 'ICDO3-M' lists all the histological ICD0-3 codes in our Data Base different from 0. In this table, we excluded the cases from Denmark.

aInternational Classification of Diseases for Oncology, third edition.

The conventional two-sided 5% level was chosen as the threshold for statistical significance. The statistical analyses were performed with STATA [9] and SEER*stat software.

3. Results

The data provided, by contributing country, including the basic and specific data quality indicators, are summarised in Table 1. After removing 126 cases known to the registries from death certificate only (DCO) or autopsy, or with no information on follow-up, we finally analysed 15,281 diagnoses of CNS tumours. The proportion of DCO was 0.3% overall, and less than 1% in most countries. High DCO rates in Malta, Bulgaria and Latvia were explained by 2, 24 and 10 cases. In all, 87% of childhood CNS tumours had microscopic verification (MV), ranging from 71 to 72% in Northern Ireland and Latvia to 97% in Finland and Slovenia. The proportion of cases censored before five years of follow-up, among 2000–2003 diagnosed cases still alive, was less than 4% in all countries except Lithuania (31%), Germany (27%), Switzerland (10%) and Poland (6%). DCO and Autoptic cases did not enter in the survival analyses, whereas censored cases contributed with their period of observation and then exited as 'censored'.

There was 39% of non-malignant tumours, but with wide differences from <10% to >40%. Table 1 also includes the proportion of CNS tumours with morphologies not specified: the ICCC IIIf-unspecified intracranial and intraspinal tumours (UNSP, 6% of all CNS tumours) and glioma NOS (ICD-O M 9380/3, optic nerve excluded, 8%). The proportion of UNSP was mostly below 10%, but high proportions (>20%) were registered in Northern Ireland, Latvia, Estonia, Poland and Croatia. The proportions of glioma NOS were mostly <10%, lower for countries with high UNSP, and higher for those without. Finland, however, had a very high proportion of glioma NOS.

As an indicator of completeness of follow-up across countries, we report 5-year survival for highly lethal tumours (anaplastic astrocytoma, glioblastomas, anaplastic oligodendroglioma and atypical teratoid/rhabdoid tumour) which were 8% of all CNS tumours. Too high survival figures suggest difficulties in access to death certificates or administrative sources, so some patients are wrongly considered alive only because the death certificates did not reach the registries or did not match the cases, or the patients become untraceable [10]. Slovenia, Latvia and Croatia had high 5-year survival (≥40%), although with wide 95%CIs. Five-year survival in Europe for this group of tumours was 19% (not in Table). Unfortunately, Denmark coded CNS tumour morphologies in few generic groups (Neoplasm NOS, Ependymoma NOS, Astrocytoma NOS, Glioma malignant NOS, Medulloblastoma NOS and Ganglioglioma NOS), so we could not estimate some quality indicators in Table 1.

Table 2 shows 1- and 5-year survival by country for malignant and non-malignant tumours and for all the tumours combined, with their IRs per 100,000/year. Five-year survival of malignant tumours averaged 57% in Europe, from 75% in Finland to 38% in Bulgaria. Non-malignant tumours had high 5-year survival rates (94% on average), between 100% and 85%, except Estonia, Portugal and Poland. For all CNS tumours, survival reached 71% in Europe and the variability decreased, particularly among non-Eastern European countries. There were no longer any differences in survival within Northern Europe and the UK and Ireland when non-malignant lesions were included. For Central and Southern Europe, differences dropped: 5-year survival was ≥70% in all except Netherlands (67%) and Portugal (61%). For Eastern Europe, Bulgaria, Latvia, Lithuania and Poland, with incomplete registration of non-malignant cases, had low survival (<66%), whereas for Estonia, Slovakia and Hungary, which registered non-malignant cases, survival was 70%, 72% and 68%, respectively. Survival in all regions dropped steeply after the first year from diagnosis, so there were large gaps between 1- and 5-year survival.

The annual IRs (per 100,000/year) of CNS malignant tumours were between 1.6 and 3. The rates for all CNS tumours combined were highest (≥4) in Finland, Croatia and Norway. Rates between 3 and 4 were also reported from all UK and Ireland, and for most of the countries in Southern and Central European countries.

There was a relation between incidence and survival of malignant tumours by country: the higher the incidence, the better the survival (p = 0.6; P < 0.001). A relation between incidence and survival of all CNS cases was not found, when including only registries that had a complete registration of non-malignant tumours (Table 2).

Five-year survival rates by histotype within the six ICCC groups varied widely both between and within the main groups (Table 3). In the category of ependymomas and variant (IIIa), the choroid plexus carcinomas had the lowest survival (44%); non-malignant tumours, 20% of all IIIa cases had survival >89%. Astrocytomas (IIIb) included 14% of anaplastic astrocytomas and glioblastomas, with poor survival 21% and 14%. Pilocytic astrocytoma, 53% of IIIb group, and optic nerve glioma, had both very high outcome (95% and 99%). Sixty-five percent of embryonal tumours (ICCC IIIc) were medulloblastoma with 65% five-year survival. Eighteen percent were other PNET with worse survival (41%). A small proportion of IIIc were atypical teratoid/rhabdoid tumours, with poor survival (23%).

Seventy percent of 'other gliomas' (IIId) were glioma NOS (optic nerve excluded) with 41% 5-year survival. ICCC IIIe 'other specified CNS tumours' consisted mainly of non-malignant tumours with very good prognosis, except pinealoblastoma. The 'unspecified tumours of the CNS' (IIIf) were half non-malignant and half malignant.

Table 4 shows 5-year survival of grades I and III–IV CNS tumours by country. For grade I, survival was >90%, except Bulgaria, Portugal and Poland. Grades III–IV had poor survival (49%), with larger differences across countries, from <40% in Bulgaria, Lithuania and Netherlands to >60% in Finland, Switzerland, Austria, Croatia and Slovenia. Overall, 5-year survival for grade II was 74%, 46% for grade III and 51% for grade IV (not shown).

Table 4. Five-year survival and 95% confidence interval (CI) for children with non-malignant or malignant CNS tumours diagnosed in 2000–07 by country and grade.

Country	WHO grade I tumours[a]			WHO grade III and IV tumours[b]		
	Number	Five-year survival (%)	95% CI	Number	Five-year survival (%)	95% CI
Finland	60	100		49	65.6	50–78
Norway	134	94.4	89–97	96	54.2	43–64
Ireland	96	90.3	81–95	54	52.1	37–65
UK–England/Wales	1017	96	94–97	757	46	42–50
UK–Northern Ireland	29	96.6	78–100	28	49.7	29–68
UK–Scotland	101	94.4	87–98	75	44	31–56
Austria	91	94.4	85–98	147	60.1	51–68
Belgium	119	94.9	89–98	106	50.8	40–60
France	1488	96.4	95–97	1011	46.9	44–50

Country	WHO grade I tumours[a]			WHO grade III and IV tumours[b]		
	Number	Five-year survival (%)	95% CI	Number	Five-year survival (%)	95% CI
Germany	1445	96.9	96–98	1267	53.5	50–57
Switzerland	30	100		33	60.1	41–75
The Netherland	359	95.9	93–98	294	39.8	38–46
Croatia	37	94.4	79–97	75	63.2	51–73
Italy	258	97.1	94–99	243	56	49–62
Malta	5	100		9	41.7	11–71
Portugal	77	86.5	76–93	106	46.5	36–56
Slovenia	21	100		32	60.8	41–76
Spain	161	93.8	88–97	163	50.1	41–59
Bulgaria	17	87.8	60–97	76	36.2	25–48
Estonia	13	92.3	57–99	23	51.4	30–70
Hungary	173	92.6	87–96	180	43.5	35–52
Latvia	1	n.e		13	59.3	28–81
Lithuania	7	100		31	37.3	20–54
Poland	8	70	23–92	65	53.6	39–66
Slovakia	96	97.9	92–100	60	51.4	38–64
European pool	5843	95.9	95–97	4993	49.4	48–51

CNS, central nervous system; n.e, not estimable.

a5843 cases, 39% of all the CNS cases.

b4993 cases, 33% of all the CNS cases.

After excluding registries stated incomplete collection or with a proportion ≤25% of non-malignant cases, or presented possible classification or follow-up problems, we compared age-adjusted 5-year survival figures for 17 countries (Fig. 1).

Comparing to Table 2, including all the countries, variability was lower but still present, with survival between 78% (Norway) and 58% (Portugal).

Table 5 shows the HRs of dying, adjusting by age and grading, both statistically significant in univariate analysis. With England & Wales as reference, Netherlands had a significantly higher and Norway, Italy and Germany lower risk of dying.

Table 5. Hazard ratio (HR) of dying and 95% confidence interval (CI) for children with non-malignant or malignant CNS tumours diagnosed in 2000–07 by country, adjusted by age, grading (model 1), and site (supra- and infra-tentorial; model 2).

Country	Model 1		Model 2	
	HR	95% CI	HR	95% CI
Norway	0.70[a]	0.5–0.9	0.75[a]	0.6–0.99
Belgium	0.92	0.7–1.2	0.95	0.7–1.3
France	1.10	0.99–1.2	1.10	0.98–1.2
Germany	0.85[a]	0.8–0.9	0.88[a]	0.8–0.99
Switzerland[b]	0.76	0.5–1.2	0.85	0.5–1.5
The Netherlands	1.20[a]	1.03–1.4	1.22[a]	1.04–1.4
Italy[b]	0.78[a]	0.6–0.9	0.79[a]	0.6–0.98
Malta	0.87	0.4–2.1	1.31	0.5–3.5
Portugal[b]	1.13	0.9–1.5	1.18	0.9–1.6
Spain[b]	0.86	0.7–1.02	0.76[a]	0.6–0.9
Ireland	0.99	0.8–1.3	0.94	0.7–1.3
England and Wales	REF		REF	
Northern Ireland	0.88	0.6–1.3	0.81	0.5–1.3
Scotland	1.11	0.9–1.4	1.15	0.9–1.5
Slovakia	0.93	0.6–1.5	0.98	0.6–1.7
Estonia	1.04	0.9–1.3	0.99	0.8–1.2
Hungary	1.01	0.8–1.3	0.98	0.7–1.3

CNS, central nervous system; REF, England and Wales was taken as reference group.

aHR statistically significant.

bregistries included: Switzerland: Basel, Geneva, Grisons, St. Gallen, Valais; Italy: Alto Adige, Biella, Catanzaro, Ferrara, Firenze-Prato, Genova, Latina, Mantova, Marche Childhood, Modena, Palermo, Parma, Piemonte Childhood, Ragusa, Romagna, Sassari, Sondrio, Trapani, Veneto; Portugal: Southern Portugal; Spain: Basque country, Cuenca, Girona, Granada, Navarra, Spain Childhood, Valencia Childhood.

Restricting the analysis to supra- and infra-tentorial tumours (72% of all cases) and adjusting the model also for site, divided in two groups, the results remained the same, except Spain with significantly lower risk than England & Wales. The risks by country did not changed excluding CNS unspecified cases (UNSP, glioma NOS and astrocitoma NOS, 17% of all cases) from the multivariate analysis (not in table).

4. Discussion

This EUROCARE analysis illustrates the difficulties in comparing survival of childhood CNS tumours between countries. First, there was incomplete collection of non-malignant tumours. The

proportions of non-malignant cases were 44% in France, 41% in England & Wales and 40% in Germany. We can be confident about the level of completeness of these large childhood CRs, so an acceptable proportion of non-malignant cases should range between about 35% and 50%. Among the countries included in Fig. 1 and Table 5, Malta, Portugal and Spain are outliers with possible under registration.

The correct classification of CNS tumours without microscopic confirmation, 13% in our study, is even more difficult. Nevertheless, the high proportion of microscopically verified CNS tumours does suggest incomplete and selective collection, as we know that part of the lesion can be identified by imaging only. As shown by the national childhood cancer registries, a proportion of microscopically verified cases higher than 90% should be considered suspicious for selective collection of cases. In our study, five countries were over this threshold, some of them with the highest (Finland) and other with low survival figures (Hungary; Table 2).

Another problem is that the definition of malignancy according to the WHO Classification of CNS tumours may vary between and within countries. It is not easy to distinguish malignant from non-malignant or low-grade from high-grade tumours. Even in a trial setting with pathological review, 28% children with glioma were incorrectly diagnosed high grade instead of low grade [11]. Grading is containing a subjective component (Ellison DW *et al.*[14], Journal of Negative Results Biomed 2011; 10:7), actually in entities like ependymoma, there is high variation between grading II and III ependymomas across countries, but no relevant survival difference. Inter-observer variability of the histologic features of anaplasia in CNS tumours illustrates a problem, since histology is so important for diagnostic and therapeutic decisions. Gilles *et al.*[12] suggested four histologic features as indispensable for brain tumour analysis: necrosis, cell density, nuclear pleomorphism and mitoses. It would be interesting to review a population-based sample of pathological reports of childhood CNS tumours, to see how often these characteristics are included in the report. Again, 'benign' (grade I/II) lesions may behave clinically highly malignant if located in an inoperable CNS location (e.g. brain-stem) and vice-versa (grade IV tumours such as medulloblastoma may have very high survival rates based on its biological subgroup). We adjusted by localisation, but we could not take into account biological subgroup, because this is no contemplate in the used classifications [13], [14]. Therefore, classification such as ICCC should be updated, and this could be realised within the ENCR, possibly in agreement with SIOPE.

Another issue can indicate low quality in disease definition: high proportions of UNSP and the use of unspecific codes like glioma NOS. UNSP and glioma NOS (optic nerve excluded) amounted to 13% of all CNS tumours, with 5-year survivals between 64% and 41%. The high proportion of UNSP suggests low-quality disease definition and the erroneous registration of non-malignant tumours or not biopsied tumours among the CNS cases. Survival figures were therefore presumably overestimates for some countries.

An important issue in survival comparisons is the completeness of follow-up, in terms of capturing all the deaths after diagnosis. In some cases, registries are aware that a patient is no longer traceable or require more time for completing follow-up; this is shown in the proportion of early censored cases, which was highest for Germany (27%) and Lithuania (31%). In other cases, no information reaches the registry, so these patients are classified as alive. Dealing with this involves analysing cancers with a very poor prognosis [15]. We studied this by comparing 5-year survival of lethal tumours (Table 1). If the diagnoses were correct, too high survival figures suggest difficulties in access to information from death certificates or administrative sources. Among countries with survival for lethal tumours higher than the European average, Latvia, Slovenia and Croatia had 5-year survival of ≥40%. Again, a certain overestimation must be considered.

The data quality problems and differences in registration practice for CNS tumours should draw the attention of the ENCR to the need to improve the standardisation of registry practices and criteria, taking account of modern diagnostic imaging procedures for tumours where MV is not always possible or convenient. We suggest to update the ENCR recommendation on brain tumour [5] by convene a new working group of expert. We are also aware about the difficulties made by the privacy regulations that limited the access to mortality data and in some cases also to the other source of data for cancer registries. Therefore, even if not specific for CNS cancer, the ENCR should continue to stress the solution of this problem.

Even when restricted to the registries considered to have the most fully comparable data, survival analysis of childhood CNS tumours indicated some variability with, compared with England & Wales, a significant lower risk of dying between 30% and 15% (Norway, Germany, Italy). Since Germany had a high percentage of patients not yet followed for five years at the closing date of this study, we performed an analysis excluding all 2000–2003 diagnosed cases not followed for 5 years; this gave similar results, though no longer significant for Germany (not shown). The high proportion of censured cases in Germany may be partly related to the apparent good survival. Similar survival differences were reported in adult CNS tumours for Europe, same diagnosis period. However, variation between countries was lower than those reported for children, but with the Nordic and some central countries with the highest outcome [16].

The complexity of treating childhood CNS tumours is partly responsible for the observed great variability in histological classification, follow-up and registration practices. To improve this situation, requires much greater collaboration between the treating centres and population-based cancer registries and emphasises the need for quality control of pathological diagnoses for both treatment and registration purposes [17]. This might be best achieved through centralisation of diagnosis and treatment in fewer centres, linked through national networks to permit the continuation of therapies and clinical follow-up close to the child's home.

International networks are also vital, especially since continuing progress in biological stratification of these rare tumours can support risk-adapted therapeutic stratification that will improve outcomes and reduce treatment-related morbidity. Since these cancers require a high level of specialisation and sophisticated infrastructure, close collaboration should be fostered between the Eastern countries and the European regions with better survival for childhood CNS tumours, also taking the advantage of the European Commission's call for twinning programs [18]. The implementation and extension of the European directive on Cross-Border Healthcare [19] is also important for European countries with small populations. Some of these have low-income levels, compared with the rest of Europe, and are unlikely to develop the necessary infrastructure within their borders.

Conflict of interest statement

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Appendix.

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