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Childhood central nervous system tumours – incidence and survival in Europe (1978–1997): Report from Automated Childhood Cancer Information System project

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ARTICLE INFO

Keywords:
Childhood cancer
Central nervous system tumours
Incidence
Survival
Population-based cancer registries
Europe
Trends

ABSTRACT

This paper describes the incidence and survival of childhood central nervous system (CNS) tumours in Europe for the period 1978–1997. A total of 19,531 cases, aged 0–14 years, from the ACCIS database were analysed by five regions: the British Isles, East, North, South, and West. Overall age-standardised incidence rate (ASR) of CNS tumours in Europe (1988–1997) was 29.9 per million, with the highest rates in the North. Astrocytoma (ASR = 11.8), primitive neuroectodermal tumours (PNET) (ASR = 6.5) and ependymoma (ASR = 3.4) were the most frequent types. Incidence increased significantly during 1978–1997, on average by 1.7% per year. Diagnostic methods may partially explain incidence rates and trends, although a role of variations in risk factors cannot be excluded. Overall 5-year survival was 64% and varied between 72% in the North and 53% in the East. PNET had the poorest prognosis (49%) and astrocytoma the best (75%). Survival has improved by 29% since late 1970s. The positive trends were seen in all regions, although the interregional differences persisted, as a reflection of the different healthcare systems.

1. Introduction

Neoplasms of the central nervous system (CNS) represent 20% of all childhood cancer (age 0–14 years). They are the second most common group of neoplasms (after leukaemias) and the largest group of solid tumours in children of developed countries. In the 1980s and early 1990s, the incidence rates of CNS tumours ranged between 20 and 40 per million in Europe and North America.[1] Lower rates were observed in developing countries, which might reflect ethnic variations, differences in socio-economic factors,[2,3] but also lower availability of non-invasive diagnostic techniques.[4] CNS tumours are the second cause of death from childhood cancer in Europe[5] and North America.[6] Survival in developed countries im-

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2006.05.009

proved markedly,[6–8] but many survivors of CNS tumours suffer considerable sequelae that may imply lifetime medical surveillance.[9]

CNS tumours are a heterogeneous collection of neoplasms of different histology, behaviour and prognosis. Paediatric CNS tumours differ from adult CNS tumours considerably by histology and anatomical site. Main diagnostic groups in children are astrocytoma (38–50%), ependymoma (8–14%), primitive neuroectodermal tumours (PNET), including medulloblastoma (16–25%), and other gliomas (4–16%).[1] There are large variations among these groups of childhood CNS tumours in terms of prognosis and response to therapies even within diagnostic categories. For example, 'astrocytoma' includes a variety of tumours, ranging from slowly growing pilocytic astrocytoma with a very good prognosis, to extremely malignant glioblastoma multiforme with some 2% 3-year survival.[10] The proportion of various histologies in a group may thus bias the interpretation of survival results. Vulnerability of the brain to therapies, especially in young ages, is a challenge for clinical management.[11]

The aim of this paper is to describe the incidence and survival of childhood CNS tumours in Europe and their geographical and temporal variations using a large European database of the Automated Childhood Cancer Information System (ACCIS).[12]

2. Material and methods

All 19,531 malignant and non-malignant tumours of the central nervous system (CNS), registered between 1978 and 1997 in patients aged less than 15 years and resident in the geographical areas covered by the participating registries at the time of diagnosis were extracted from the ACCIS database. Given a satisfactory evaluation of data comparability by the ACCIS Scientific Committee [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue], 59 cancer registries in 19 European countries participated in this study (Table 1).

The tumours, classified according to the International Classification of Childhood Cancer (ICCC),[13] were all those belonging to the Group III (CNS and miscellaneous intracranial and intraspinal neoplasms). This group (short name 'CNS tumours') includes primary tumours of CNS of any behaviour and excludes the germ cell tumours, neuroblastoma and lymphomas of the CNS. The group is further split into six diagnostic subgroups: IIIa Ependymoma, IIIb Astrocytoma, IIIc PNET, IIId Other gliomas, IIIe Other specified CNS tumours, and IIIf Unspecified CNS tumours. Group IIIb comprises astrocytomas of any grade of malignancy and optic nerve glioma. Group IIId contains other gliomas, principally not otherwise specified, mostly with unspecified histology (NOS), mixed glioma and oligodendroglioma. Most of the tumours in group IIIe are of uncertain or benign behaviour, including meningioma, pinealoma and craniopharyngioma. To account for a possibility of different diagnostic and classification criteria across registries and time periods,[7] the groups IIIa, IIIb and IIId were pooled into a new category, 'Glioma-related tumours'.

Patterns of incidence and survival by sex, age and region were examined using a data-set of cases incident in the 10-year period 1988–1997, covered by almost all contributing registries, thus ensuring a reasonable stability of the estimates. Countries were grouped into five geographical regions: British Isles, East, North, South and West (Table 1). The registries with sufficiently long registration period contributed to the time trend analyses (Table 1). The overall time period 1978–1997 was split in four 5-year periods, as shown in Table 2, which also provides information on the changes in distribution of cases and selected quality indicators over time.

In 27 of the contributing registries, non-malignant tumours were systematically registered (Table 1). Their pooled data, representing 86% of the person-years of the unrestricted data-set, were used to evaluate incidence and survival by the behaviour of CNS tumours and several distinct non-malignant tumour types.

Incidence rates were expressed as the average annual number of cases per million person-years and World standard population was used for age standardisation of the incidence rates (ASR). Differences in incidence rates for geographical areas and trends were evaluated using Poisson regression models, adjusted for age group and sex, using the British Isles as the region of reference. Average annual percent changes (AAPC) were derived from Poisson regression models of incidence rate on calendar year, adjusted for sex, age group and region.

Actuarial life-table method was used for survival analyses. The cases with zero follow-up time were excluded from the analyses (Tables 1 and 2). Differences between survival curves and trends were tested with the log-rank χ^2 tests. Most of the statistical analyses were conducted using the STATA software. Further general details on the database and methods of its exploration are described elsewhere [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue].

3. Results

During 1988–1997, 11,829 cases of a primary CNS tumour were recorded in the participating registries (Table 3). Globally, 88% of cases were microscopically verified, ranging from 78% (British Isles) to 95% (West). In Europe, less than 3% of cases were diagnosed from death certificate only (in the set of registries with access to this source of data) or from an unknown source. Largest inter-regional variations were observed in the unspecified group, followed by the other gliomas group. In these two subgroups, a relatively large proportion of tumours was diagnosed only clinically (58% and 26%, respectively).

Most CNS tumours were malignant (87%), 10% uncertain and 3% benign (Table 3). A similar distribution of tumours by behaviour was seen in the restricted subset of data, constituted of the cancer registries with systematic registration of non-malignant tumours, with 85% of malignant, 11% uncertain and 3% of benign behaviour. The diagnostic groups of astrocytoma and PNET comprised only malignant tumours and there were only a few tumours with uncertain behaviour among other glioma group. The largest proportion of non-malignant tumours was seen in the North, both in the restricted (24%) and the non-restricted (15%) data-set. The widest geographical variation in the proportion of non-malignant tumours was found in the subgroup of unspecified CNS tumours, ranging from 9% in the East to 73% in the British Isles.

Table 1 – Datasets contributed by the European cancer registries for the analyses of central nervous system (CNS) tumours incidence and survival in children (age 0–14 years), with indicators of coverage, data quality and follow-up (Source: ACCIS)

	Region	Registry	Coverage		CNS tumours			Basis of diagnosis			Survival analyses		Follow-up			Notes
			Period	Time trend	Cases	Non-malignant*	NOS	MV	DCO	Unknown			Median	5+ years	Closing date	
					n	%	%	%	%		*n*	%	Years	%		
IR10	British Isles	IRELAND, National	1994–1997		133	6	2	91	0	0	132	99	3.2	0	31.12.1998	
UK2E		UNITED KINGDOM, England & Wales	1978–1995	+	4910	16	6	78	1	6	4744	97	12	99	31.1.2001	P
UKNI		UNITED KINGDOM, Northern Ireland	1993–1996		63	29	52	59	0	0	63	100	1.1	15	31.12.1999	
UKSC		UNITED KINGDOM, Scotland	1978–1997	+	541	–	1	90	0	0	535	99	11.0	84	31.12.1999	
BA10	East	BELARUS, National	1989–1997		653	9	25	80	0	0	635	97	5.9	64	1.9.2000	P
ES10		ESTONIA, National	1978–1997	+	184	–	22	78	0	0	171	93	5.9	57	31.12.1998	
HU30		HUNGARY, National	1978–1997	+	1212	13	4	85	–	0	1190	98	0.5	40	1.1.2000	P
SK10		SLOVAKIA, National	1978–1997	+	725	8	20	80	3	0	588	81	7.7	64	31.12.1997	
GEEA		GERMANY, NCR (only former East)	1978–1989	+	1185	14	10	93	0	0	862	73	5.7	55	31.12.1987	S
DK10	North	DENMARK, National	1978–1997	+	776	26	22	81	<1	1	751	97	8.9	72	31.12.1997	
FI10		FINLAND, National	1978–1997	+	758	8	10	94	0	<1	735	97	9.1	75	31.12.1998	
IC10		ICELAND, National	1978–1997	+	45	11	9	93	0	0	45	100	12.9	81	31.12.2000	
NO10		NORWAY, National	1978–1997	+	595	7	19	89	<1	0	594	100	10.5	80	1.1.2000	
IT31	South	ITALY, Piedmont paediatric	1978–1997	+	448	24	17	81	<1	0	448	100	11.2	89	31.12.1999	P
IT32		ITALY, Marche	1990–1997		41	–	29	73	–	17	41	100	6.0	65	30.9.2000	P
ITFE		ITALY, Ferrara	1991–1995		6	–	50	50	0	0	6	100	3.7	40	31.12.1998	
ITLA		ITALY, Latina	1983–1997	+	29	–	24	72	0	7	29	100	6.3	64	31.12.1998	
ITLI		ITALY, Liguria	1988–1995		13	8	23	38	0	0	13	100	7.6	86	15.4.2000	
ITLO		ITALY, Lombardy	1978–1997	+	85	–	8	84	1	0	84	99	7.3	65	23.9.1999	
ITPA		ITALY, Parma	1978–1995	+	31	13	10	90	0	0	31	100	12.8	100	1.4.1999	
ITRA		ITALY, Ragusa	1983–1997	+	21	–	29	76	0	0	21	100	11.6	86	30.3.2000	
ITSA		ITALY, Sassari	1992–1995		9	–	22	67	0	22	9	100	5.7	100	30.12.1999	
ITTU		ITALY, Tuscany	1988–1997		44	23	18	70	2	0	43	98	5.6	63	31.12.1998	
ITUM		ITALY, Umbria	1994–1996		16	–	31	75	0	0	16	100	3.8	22	31.12.1999	
ITVE		ITALY, Veneto	1990–1996		58	–	10	86	0	0	58	100	4.1	39	31.12.1998	
ML10		MALTA, National	1991–1997		17	29	12	88	0	0	17	100	4.9	43	31.12.1999	

SL10		SLOVENIA, National	1978–1997	+	184	5	13	91	0	0	179	97	9.9	80	31.12.1999	
SP20		SPAIN, National	1990–1995		311	10	10	81	0	2	298	96	6.0	89	31.12.2000	P o1 Z
SPAL		SPAIN, Albacete	1991–1997		10	–	0	80	0	0	10	100	6.5	80	15.9.2000	
SPAS		SPAIN, Asturias	1983–1997	+	65	9	20	85	0	0	61	94	8.4	73	31.12.1997	
SPBC		SPAIN, Basque Country	1988–1994		75	–	25	77	1	0	74	99	9.8	100	31.12.2000	o1
SPCI		SPAIN, Canary Islands	1993–1996		35	–	3	71	3	0	–	–	–	–	–	
SPGI		SPAIN, Girona	1994–1997		11	–	18	82	0	9	11	100	2.7	0	31.12.1997	o1
SPGR		SPAIN, Granada	1988–1997		37	–	8	92	0	5	33	89	6.6	81	31.12.1999	G
SPMA		SPAIN, Mallorca	1988–1995		28	–	18	86	0	0	26	93	7.5	88	31.12.1998	o1
SPNA		SPAIN, Navarra	1978–1996	+	56	–	18	86	0	0	56	100	11.1	81	31.12.1997	o1
SPTA		SPAIN, Tarragona	1983–1997	+	32	–	25	75	0	0	29	91	5.4	53	31.12.1998	o1
SPZA		SPAIN, Zaragoza	1978–1996	+	87	22	16	70	17	3	73	84	8.2	72	31.12.1996	o1
TRIZ		TURKEY, Izmir	1993–1996		50	–	4	86	–	0	–	–	–	–	–	
FR3B	West	FRANCE, Brittany	1991–1997		120	21	3	98	–	2	118	98	4.0	37	1.1.2000	P
FR3L		FRANCE, Lorraine	1983–1997	+	230	13	1	80	–	0	230	100	5.7	57	1.1.1999	P
FR3P		FRANCE, PACA	1984–1996	+	314	13	4	95	–	0	288	92	3.6	49	31.3.1998	P
FR3R		FRANCE, Rhone Alpes	1988–1997		326	13	<1	90	–	0	310	95	3.5	42	1.6.2000	P o2
FRDO		FRANCE, Doubs	1978–1996	+	45	–	11	22	–	4	43	96	2.2	32	1.6.2001	
FRHE		FRANCE, Herault	1988–1997		34	–	9	56	–	0	–	–	–	–	–	
FRIS		FRANCE, Isere	1979–1997	+	135	7	5	90	–	7	–	–	–	–	–	o2
FRMN		FRANCE, Manche	1994–1996		7	–	0	71	–	0	1	14	4.6	0	31.5.2000	S
FRRB		FRANCE, Bas-Rhin	1978–1996	+	81	–	14	85	–	0	81	100	9.0	74	31.12.1997	
FRRH		FRANCE, Haut-Rhin	1988–1997		37	–	0	97	–	0	18	49	7.3	73	31.12.1995	S
FRSO		FRANCE, Somme	1983–1996	+	33	–	6	91	–	0	33	100	2.4	48	15.8.2000	
FRTA		FRANCE, Tarn	1983–1997	+	20	–	5	85	–	0	–	–	–	–	–	
GE10		GERMANY, GCCR (East and West)	1991–1997	+	2333	16	5	98	–	0	1731	74	1.8	28	31.12.1998	P
GEWE		GERMANY, GCCR (only former West)	1983–1990	+	1692	18	8	99	–	0	1578	93	7.6	74	31.12.1998	P
NL10		NETHERLANDS, National	1989–1995		569	–	8	92	–	0	558	98	5.9	66	31.12.1998	S o3
NLEI		NETHERLANDS, Eindhoven	1978–1997	+	93	–	13	86	–	0	93	100	9.8	84	1.7.1999	o3
SZBA		SWITZERLAND, Basel	1983–1997	+	25	–	4	92	–	0	25	100	9.3	80	30.6.2000	
SZGE		SWITZERLAND, Geneva	1978–1997	+	41	–	10	93	0	0	41	100	6.2	67	31.12.1999	
SZGG		SWITZERLAND, Graubunden & Glarus	1989–1997		11	–	27	64	0	18	11	100	0	29	25.5.2000	
SZSG		SWITZERLAND, St. Gallen Appenzell	1983–1997	+	46	11	9	87	0	0	46	100	2.5	38	1.2.2001	
SZVL		SWITZERLAND, Valais	1989–1997		14	–	14	93	0	0	6	43	8.3	100	1.12.1998	S

–: Not applicable; +: Included in time trend analyses; 5+ years: Cases followed-up for 5 or more years, as a percentage of all those not deceased by the closing date; DCO: Registrations from death certificate only; G: General cancer registry, which has only contributed data for age-range 0–14 years; GCCR: National German Childhood Cancer Registry (until 1990 covering only West and since 1991 the reunified Germany); MV: Microscopically verified cases; N: Number of cases; NCR: National Cancer Registry of the former German Democratic Republic. Data for 1978–1987 contributed only to analyses of time trends for Europe as a whole. Data for 1988–1989 were pooled with GCCR and included in West. For explanation, see Steliarova-Foucher, Kaatsch, Lacour and colleagues (this issue); NOS: Cases with unspecified histology, including the ICCC category IIIf; o1-o3: Overlapping registration areas: for the overlapping years, data from the registry with larger coverage are included in each analysis, according to availability; P: Paediatric cancer registry; age range for all registrations is 0–14 years; PACA: Provence, Alps, Côte d'Azur; S: Survival analyses were possible only for a restricted dataset (see Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue); Unknown, Registrations with unknown basis of diagnosis; Z: Covers only selected areas, see Steliarova-Foucher, Kaatsch, Lacour and colleagues (this issue).

* Non-malignant tumours (%) of CNS is only given for the registries with systematic registration of non-malignant tumours.

Table 2 – Numbers of cases and indicators of data quality by region and age group used for time trend analyses of CNS tumours incidence and survival in children (age 0–14 years) in Europe, 1978–1997 (Source: ACCIS)

Region	Period	CNS tumours			Basis of diagnosis			Follow-up	
		Cases *n*	Non-malignant %	NOS %	MV %	DCO %	Unknown %	0 + days %	5 + years %
Europe[a]	1978–82	3100	14	11	82	<1	1	93	96
	1983–87	4592	14	9	86	<1	1	96	77
	1988–92	4854	13	7	87	<1	3	95	79
	1993–97	4511	15	8	90	<1	1	87	32
British Isles	1978-82	1425	14	5	81	<1	2	96	99
	1983–87	1434	14	5	78	1	5	96	99
	1988–92	1493	13	6	76	2	10	98	99
	1993–97	1099	16	6	82	2	5	97	93
East	1978–82	399	8	19	73	2	0	83	74
	1983–87	607	9	11	82	<1	0	92	48
	1988–92	551	12	9	85	<1	0	94	63
	1993–97	564	12	7	88	<1	0	96	21
North	1978–82	502	14	18	88	<1	1	97	100
	1983–87	483	12	16	88	0	0	98	100
	1988–92	573	12	13	88	<1	<1	98	99
	1993–97	616	17	20	87	<1	<1	98	24
South	1978–82	248	25	26	71	6	1	94	99
	1983–87	291	13	16	83	0	0	99	100
	1988–92	258	9	11	88	0	<1	99	97
	1993–97	241	10	11	87	<1	<1	98	38
West	1978–82	102	8	11	74	0	0	99	92
	1983–87	1234	17	8	97	0	<1	96	76
	1988–92	1761	15	6	96	0	<1	90	60
	1993–97	1991	15	5	96	0	<1	73	8

0 + days: Cases followed-up for 1 or more days, as a percentage of all cases in the registries with follow-up; 5 + years: Cases followed-up for 5 or more years, as a percentage of all those not deceased by the closing date; DCO: Cases registered from death certificate only; MV: Microscopically verified diagnosis; *n*: Number of cases; Non-malignant: Includes intracranial and intraspinal non-malignant CNS tumours; NOS: Cases with unspecified histology ICCC (subgroup IIIf).
a Europe includes the data of former German Democratic Republic, not included in any other region.

Considering all CNS tumours in the European pool, the ASR was 29.9 per million children. The most frequent diagnostic group was astrocytoma, accounting for 40% of all CNS tumours (ASR = 11.8), followed by PNET (ASR = 6.5). The highest incidence rate for all CNS tumours combined was in the North (ASR = 43.8) and the lowest in the West (ASR = 27.0) (Table 3). Also, the rates for the glioma-related group and most of the subgroups were significantly higher in the North and lower in the West than those of the reference region (British Isles) (Table 3). The high overall rates of CNS tumours in the North reflected mainly the high incidence of other gliomas and, to a lesser degree, of unspecified and other specified CNS tumours. Few other differences were observed between the regions by diagnostic subgroup (Fig. 1).

In the restricted data-sets comprising the cancer registries with systematic collection of non-malignant tumours the overall age-standardised incidence rate was 30.2 per million. The highest incidence rates were observed in the North (for both malignant and non-malignant tumours) and the lowest in the West (Table 4).

The incidence rates for selected tumour types of the IIIe subgroup (other specified), including those with non-malignant behaviour, were estimated from the restricted data-set (Table 5). Gangliogliomas had significantly higher rates in the North (*n* = 29, IRR = 2.2, 95% confidence interval (CI) 1.3–3.8) and the West (*n* = 98, IRR = 1.7, 95% CI 1.1–2.5). Meningiomas were most frequent in the North (*n* = 22, IRR = 2.3, 95% CI 1.3–3.9) as well as pineal parenchymal tumours (*n* = 25, IRR = 3.8, 95% CI 2.2–6.7). No other geographical differences were observed for these specified tumour types.

All CNS tumours combined and ependymoma showed a slightly higher, statistically significant, frequency among boys than among girls. The highest sex ratio was seen for PNET with about 60% excess of boys (Table 3). Overall, 36% of cases were less than 5 years of age. The CNS tumours were most commonly diagnosed in the age groups 1–4 and 5–9, but the age distribution differed by diagnostic groups (Table 3 and Fig. 2). Age distribution of the malignant and non-malignant tumours is compared in Fig. 3.

A total of 17,057 cases were included in the analyses of incidence time trends for years 1978–1997 (Table 2). Of these, 91 were multiple primary tumours. Overall, microscopically verified diagnosis (%MV) increased over the years in Europe up to 90%, while unknown basis and cases registered from death certificate only (in the registries with access to this source of data) were around 1% or less than this (Table 2).

Table 3 – Incidence of central nervous system (CNS) tumours in European children (age 0–14 years) during 1988–1997 (Source: ACCIS)

	n	Incidence rates per million						Behaviour			IRR		
		Age specific rates				ASR		Be	Un	Ma	IRR	(95% CI)	*P* value
		0	1–4	5–9	10–14	0–14a	M/F	%	%	%			
III.CNS													
EUROPE	11829	28.5	33.9	31.3	24.3	29.9	1.1*	3	10	87			
British Isles	2788	30.9	32.7	32.3	25.5	30.3	1.0	3	11	86	1		
East	1768	27.3	37.3	32.1	26.8	31.8	1.1*	2	8	89	1.0	(0.99, 1.11)	ns
North	1189	46.9	49.5	45.1	35.5	43.8	1.2*	5	9	85	1.4	(1.34, 1.54)	0.000
South	1131	18.3	35.0	30.0	25.5	29.3	1.2*	2	6	92	1.0	(0.90, 1.04)	ns
West	4953	26.5	31.0	28.9	20.9	27.0	1.2*	3	11	87	0.9	(0.85, 0.93)	0.000
IIIa. Ependymoma													
EUROPE	1260	6.1	5.4	2.3	1.7	3.4	1.2*	11	4	85			
British Isles	273	5.5	5.1	1.9	1.7	3.1	1.3*	12	6	82	1		
East	170	3.4	6.3	1.7	1.9	3.3	1.3	6	5	89	1.1	(0.88, 1.30)	ns
North	108	6.8	5.5	3.2	2.7	4.1	1.4	7	5	88	1.3	(1.07, 1.67)	0.011
South	143	6.7	5.8	3.9	1.7	4.0	1.1	6	3	90	1.3	(1.08, 1.62)	0.007
West	566	6.9	5.3	2.2	1.4	3.3	1.1	13	2	84	1.1	(0.91, 1.21)	ns
IIIb. Astrocytoma													
EUROPE	4717	8.2	12.9	12.6	10.7	11.8	1.0	0	0	100			
British Isles	1207	9.4	14.1	14.4	11.5	13.1	0.9	0	0	100	1		
East	679	7.1	13.0	12.2	11.9	12.0	1.0	0	0	100	0.9	(0.84, 1.01)	ns
North	321	7.8	13.7	12.4	10.1	11.8	1.1	0	0	100	0.9	(0.79, 1.01)	ns
South	446	7.1	12.2	10.5	12.1	11.2	1.1	0	0	100	0.9	(0.79, 0.98)	0.017
West	2064	8.1	12.3	12.2	9.6	11.2	1.1	0	0	100	0.9	(0.79, 0.91)	0.000
IIIc. PNET													
EUROPE	2549	5.8	7.9	7.6	4.1	6.5	1.6*	0	0	100			
British Isles	563	6.8	7.2	7.0	4.1	6.2	1.4*	0	0	100	1		
East	377	5.0	8.0	8.7	4.1	6.9	1.5*	0	0	100	1.1	(0.98, 1.27)	ns
North	175	8.9	8.4	6.7	3.8	6.6	1.6*	0	0	100	1.1	(0.89, 1.25)	ns
South	226	0.5	7.9	7.1	4.1	6.0	1.6*	0	0	100	1.0	(0.86, 1.17)	ns
West	1208	6.0	8.1	7.7	4.1	6.6	1.8*	0	0	100	1.1	(0.97, 1.19)	ns
IIId. Other gliomas													
EUROPE	1246	2.1	3.1	3.5	2.9	3.1	0.9	0	3	97			
British Isles	333	2.4	2.9	4.8	3.2	3.6	0.9	0	4	96	1		
East	124	2.2	1.9	2.5	2.1	2.2	1.1	0	2	98	0.6	(0.49, 0.75)	0.000
North	278	5.2	11.6	10.6	9.4	10.2	0.9	0	0.7	99	2.8	(2.40, 3.30)	0.000
South	107	1.8	3.8	2.1	2.7	2.8	1.3	0	0.9	99	0.8	(0.61, 0.94)	0.013
West	404	1.5	2.1	2.5	2.0	2.2	0.8*	0	5	95	0.6	(0.52, 0.70)	0.000
IIIe. Other specified													
EUROPE	1018	1.9	1.8	2.7	3.1	2.5	1.1	13	73	13			
British Isles	228	2.5	1.6	2.4	3.3	2.4	1.2	14	75	11	1		
East	169	0.9	2.1	3.1	3.9	2.8	0.9	18	69	12	1.2	(0.97, 1.45)	ns
North	105	4.7	3.2	3.7	4.3	3.8	1.3	10	68	22	1.5	(1.23, 1.95)	0.000
South	76	0.4	1.1	2.2	2.4	1.8	1.5	16	63	21	0.8	(0.60, 1.01)	ns
West	440	1.8	1.7	2.7	2.7	2.3	1.1	11	78	11	1.0	(0.81, 1.12)	ns
IIIf. Unspecified													
EUROPE	1039	4.4	2.9	2.7	2.0	2.7	0.9	7	33	60			
British Isles	184	4.4	1.8	1.8	1.8	2.0	0.8	9	64	27	1		
East	249	8.7	6.1	3.9	3.0	4.7	1.0	0.4	9	91	2.3	(1.87, 2.73)	0.000
North	202	13.5	7.1	8.5	5.1	7.5	1.2	23	15	62	3.7	(3.03, 4.52)	0.000
South	133	1.8	4.2	4.2	2.4	3.5	1.1	2	13	85	1.8	(1.40, 2.19)	0.000
West	271	2.3	1.6	1.6	1.1	1.5	0.7*	3	58	39	0.7	(0.61, 0.89)	0.002
IIIa + b + d													
EUROPE	7223	16.4	21.4	18.4	15.2	18.2	1.0	2	1	97			
British Isles	1813	17.3	22.1	21.1	16.4	19.7	1.0	2	2	97	1		
East	973	12.7	21.2	16.4	16.0	17.4	1.1	1	1	98	0.9	(0.82, 0.96)	0.002
North	707	19.8	30.8	26.2	22.2	26.0	1.1	1	1	98	1.3	(1.21, 1.43)	0.000
South	696	15.6	21.7	16.5	16.6	18.1	1.1	1	0.9	98	0.9	(0.84, 1.00)	ns
West	3034	16.4	19.7	17.0	13.0	16.6	1.0	3	1	96	0.8	(0.79, 0,89)	0.000

Table 3 – *continued*

Number of cases, age-specific and age standardised incidence rates, and behaviour, by diagnostic group and geographical region; and incidence rate ratios between regions (Poisson regression analysis).

n: Number of cases; ASR: Age-standardised incidence rate; M/F: Ratio of the age-standardised rates for boys and girls; Be: Benign; Un: Uncertain; Ma: Malignant; IRR: Incidence rate ratio; (95% CI): 95% confidence interval; ns: $P \geqslant 0.05$; CNS: All central nervous system tumours combined (Group III. CNS and miscellaneous intracranial and intraspinal neoplasms) (ICCC)[13]; PNET: IIIc. Primitive neuroectodermal tumours; Other specified: IIIe. Other specified intracranial and intraspinal neoplasms; Unspecified: IIIf. Unspecified intracranial and intraspinal neoplasms; IIIa + b + d: Glioma-related (IIIa Ependymoma, IIIb Astrocytoma, IIId Other gliomas).

* Rates are statistically different at 5% level.

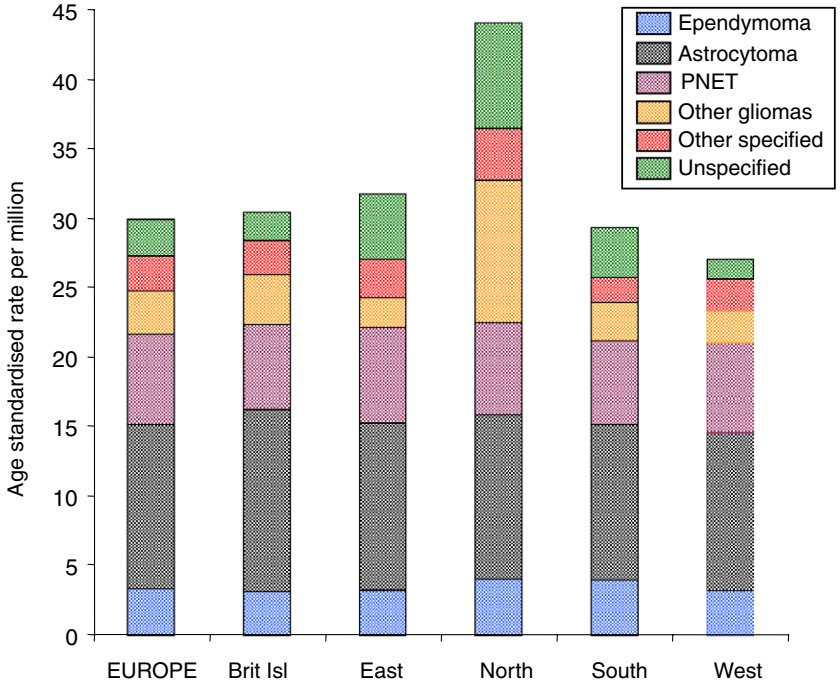


Fig. 1 – Incidence of central nervous system (CNS) tumours in children (0–14 years) in Europe, 1988–1997 by diagnostic group and region (*n* = 11,829). Age-standardised rates (ASR), world standard population. Source: ACCIS.

Rising incidence was recorded for the CNS tumours combined and some subgroups (Fig. 4). The rates of CNS tumours combined increased on average by 1.7% ($P < 0.0001$) per year. Increase was also observed for the rates of astrocytoma ($n = 6561$, AAPC = 2.5%, $P < 0.0001$), PNET ($n = 3592$, 1.3%, $P < 0.0001$), and the combined glioma-related group ($n = 10,495$, AAPC = 1.9, $P < 0.0001$), although the incidence of the other gliomas did not increase ($n = 1976$, AAPC = 0.3%, $P = 0.5$). Other specified CNS tumours increased markedly ($n = 1485$, AAPC = 2.4%, $P < 0.0001$), while incidence of ependymoma did not change ($n = 1958$, 0.8%, $P = 0.07$). Similar pattern was observed in the restricted data-set (Fig. 5), with malignant tumours increasing on average by 1.8% per year ($P < 0.0001$, $n = 13,411$) and non-malignant tumours by 1.7% ($P < 0.0001$; $n = 2360$).

The 10,532 cases diagnosed in 1988–1997 were included in the survival analysis, after excluding 915 cases with a follow-up shorter than 1 day (Table 6). For the pooled European data, 5-year survival was 64%. The North was the area with the highest 5-year survival rate (72%), significantly different ($\chi^2 = 20.53$, $P < 0.0001$) from the other three regions in second rank, British Isles, South and West (pooled estimate of 5-year survival 65% with 95% CI 64–66). The East presented the poorest survival rate (53%). Exclusion of non-malignant tumours from this data-set reduced the 5-year survival by about 2–3 percentage points in Europe and its regions. Based on the total of 9225 malignant tumours, 5-year survival was 61%, with 95% CI 60–62. Similar reduction was seen for the British Isles ($n = 2351$, 59%, 95% CI 57–61), East ($n = 1509$, 52%, 95% CI 49–54), North ($n = 1001$, 69%, 95% CI 66–72), South ($n = 929$, 64%, 95% CI 61–67) and West ($n = 3435$, 63%, 95% CI 61–65). Comparing these results with data in Tables 3 and 6, the reduction in survival after exclusion of non-malignant tumours roughly followed the differences in the proportion of non-malignant tumours in the different geographical areas. The survival figures shown above correspond almost

Table 4 – Incidence and survival of malignant and non-malignant central nervous system (CNS) tumours in Europe, based on the data from the registries with systematic collection of non-malignant tumours (Source: ACCIS)

		Incidence				Survival					
		Malignant		Non-malignant		Malignant			Non-malignant		
		n	ASR	*n*	ASR	*n*	5-year%	(95% CI)	*n*	5-year%	(95% CI)
1988–1997	TOTAL	8786	25.9	1498	4.3	8056	61	(60,62)	1286	84	(81,86)
	MV	89%		18%							
	IIIa. Ependymoma	897	2.8	181	0.6	781	53	(49,57)	162	86	(79,91)
	IIIb. Astrocytoma	4028	11.7	0	–	3603	75	(73,76)	0	–	–
	IIIc. PNET	2189	6.5	0	–	2151	49	(46,51)	0	–	–
	IIId. Other gliomas	1070	3.1	37	0.1	998	55	(52,59)	30	81	(60,92)
	IIIe. Other specified	114	0.3	869	2.4	105	53	(42,63)	765	90	(87,92)
	IIIf. Unspecified	488	1.5	411	1.2	418	72	(37,47)	329	68	(63,73)
	British Isles	2133	26.0	398	4.8	2094	59	(57,61)	369	86	(82,90)
	East	1465	28.1	191	3.5	1403	52	(49,55)	185	68	(60,76)
	North	561	37.6	173	6.2	1001	69	(66,72)	166	87	(80,91)
	South	659	27.4	91	3.6	640	65	(61,69)	91	85	(76,91)
	West	3513	22.8	645	4.1	2749	63	(61,65)	475	84	(80,88)
1978–1982		2380	22.0	425	3.9	2187	51	(49,53)	387	64	(59,68)
1983–1987		3628	23.6	630	4.0	3446	57	(55,59)	587	76	(73,80)
1988–1992		3884	25.3	635	4.1	3458	61	(59,63)	553	84	(80,67)
1993–1997		3519	25.9	670	4.8	3017	61	(62,66)	539	86	(82,89)

n: Number of cases; ASR: Age-standardised incidence rates; (95% CI): confidence interval; TOTAL: Includes data from East Germany, which is not included in any of the regions; MV(%): Microscopically verified cases.

Table 5 – Incidence and survival of the main tumour types in the subgroup IIIe Other specified tumours in Europe, 1988–1997 (Source: ACCIS)

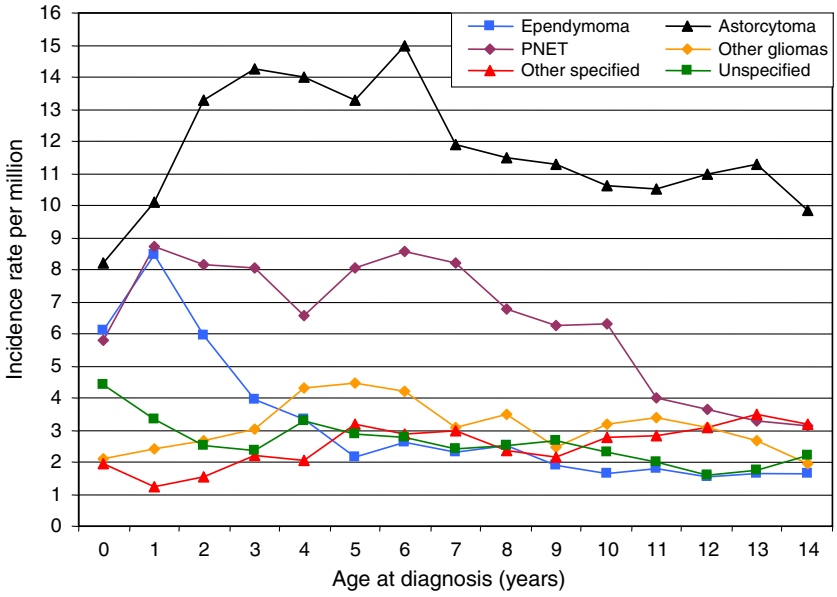
	n	ASR	MV %	Behaviour			Survival		
				Benign %	Uncertain %	Malignant %	*n*	5-year %	(95% CI)
Craniopharyngioma	493	1.4	92	0	100	0	433	90	(86,93)
Ganglioglioma	186	0.5	97	1	97	2	160	91	(84,95)
Meningioma	147	0.4	97	71	5	24	134	85	(77,90)
Pineal parenchymal tumours	127	0.4	91	0	43	57	115	59	(48,67)
Pituitary adenoma	28	0.07	96	93	0	7	27	96	(74,99)

Only the registries with systematic collection of non-malignant tumours are included.
n: Number of cases; ASR: Age-standardised incidence rates; MV(%): Microscopically verified cases; (95% CI): confidence interval.

exactly to those obtained for the malignant tumours in the restricted data-set (Table 4). Survival of patients with non-malignant tumours was markedly more favourable (Tables 4 and 5, and Fig. 6).

Variations were observed among diagnostic groups, with the highest survival in the group of other specified tumours, and lowest in the group of PNET. However, survival within the diagnostic subgroups varied according to the geographical region of residence. To examine the geographical variation in detail, a pooled 5-year survival for those regions where survival did not differ significantly was calculated. For ependymoma survival in the East (48%, 95% CI 40–57) differed from that in the other four regions, where pooled estimate of 5-year survival was 59% (95% CI 56–63). Similar pattern was observed for astrocytoma with the pooled estimate of 5-year survival for the non-East regions of 76% (95% CI 74–77), while in the East was 69% (95% CI 65–73). Children with PNET had lower survival in the British Isles or East (43% (95% CI 39–46)) than in the other three regions (53%, (95% CI 50–56)). For other gliomas three ranks were determined, with highest survival in the North and South (76% (95% CI 71–80)), intermediate in the West and East (52% (95% CI 47–57)) and the lowest in the British Isles. Also for the whole group of 'glioma-related tumours', statistically significant differences were observed among regions, ranking North first, followed by South and West (pooled 5-year survival 70% (95% CI 68–72)) and finally the British Isles and the East (65%, (95% CI 63–67). In the diagnostic subgroup of other specified CNS tumours, survival was higher in the non-East regions than in the East (Table 6). Finally, for the group of unspecified, 5-year survival was 69% (95% CI 64–74) in the North and the British Isles, 46% (95% CI 40–52) in the South and West, and 26% in the East.

In Europe, survival of children with CNS tumours increased with age (test for trend by age group $\chi^2 = 118.69$,



PNET: IIIc. Primitive neuroectodermal tumours; Others pecified: IIIe. Other specified intracranial and intraspinal neoplasms; Unspecified: IIIf. Unspecified intracranial and intraspinal neoplasms.

Fig. 2 – Age-specific incidence rates of central nervous system (CNS) tumours in children (0–14 years) in Europe, 1988–1997, by diagnostic group (*n* = 11,829). Source: ACCIS.

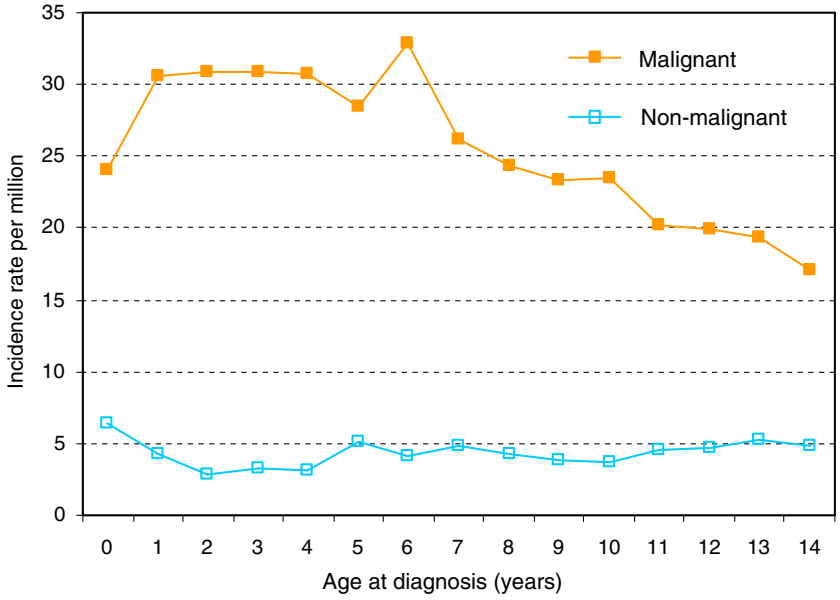
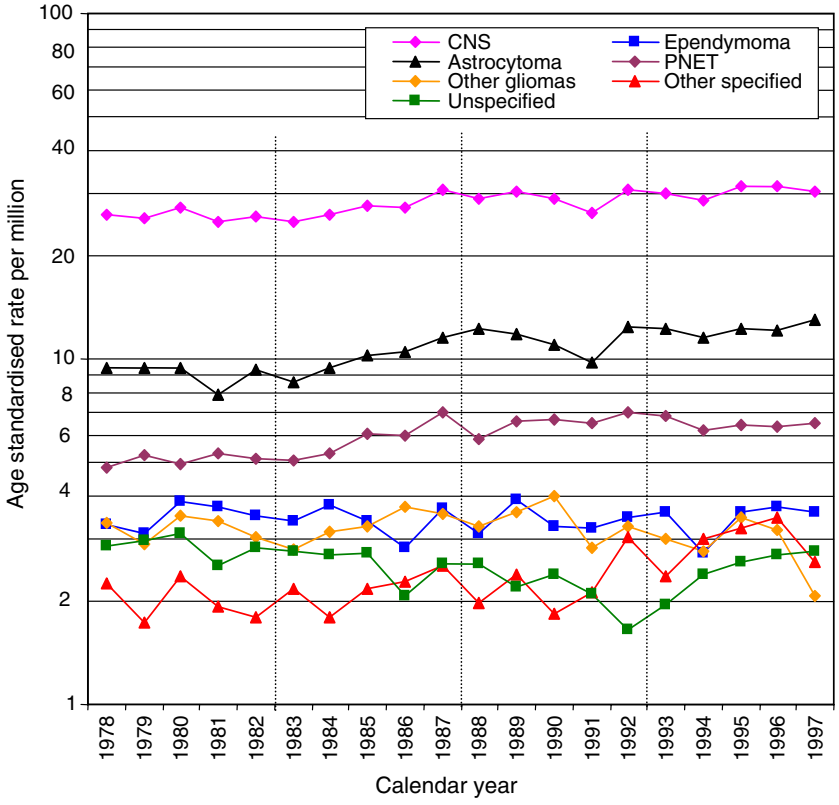


Fig. 3 – Age-specific incidence rates of central nervous system (CNS) tumours in children (0–14 years) in Europe, 1988–1997, by behaviour of tumour. Only the registries with systematic registration of non-malignant tumours are included (*n* = 10,284). Source: ACCIS.

$P < 0.0001$). A similar pattern was observed for the diagnostic subgroups, except for astrocytoma, and other gliomas (Table 6). No differences between East and non-East regions were found for infants. Differences in survival by sex were not observed, except for other gliomas ($P = 0.03$), with better survival in boys (5-year survival 60%, 95% CI 56–64) than in girls (53%, 95% CI 49–57).

After excluding 1269 cases with follow-up shorter than 1 day, 15,415 cases were included in the time trends analyses of survival. For the combined group of CNS tumours, 5-year survival rates increased by 29% in Europe between 1978–1982 and 1993–1997, from 52% to 67%. Survival improved for both malignant and non-malignant tumours (Fig. 6). The 5-year survival increased by 20% for malignant and by 34% for the non-malignant tumours, when comparing the first and the last 5-year periods. Increases were present in each of the regions, although the trend was not statistically significant for the East and the West (Table 7).



CNS: All central nervous system tumours combined (Group III. CNS and miscellaneous intracranial and intraspinal neoplasms) (ICCC)[13]; PNET: IIIc. Primitive neuroectodermal tumours; Other specified: IIIe. Other specified intracranial and intraspinal neoplasms; Unspecified: IIIf. Unspecified intracranial and intraspinal neoplasms.

Fig. 4 – Trends of the incidence of central nervous system (CNS) tumours in children (0–14 years) in Europe, 1978–1997, by diagnostic group (*n* = 17,057). Age-standardised rates (ASR), World standard population. Source: ACCIS.

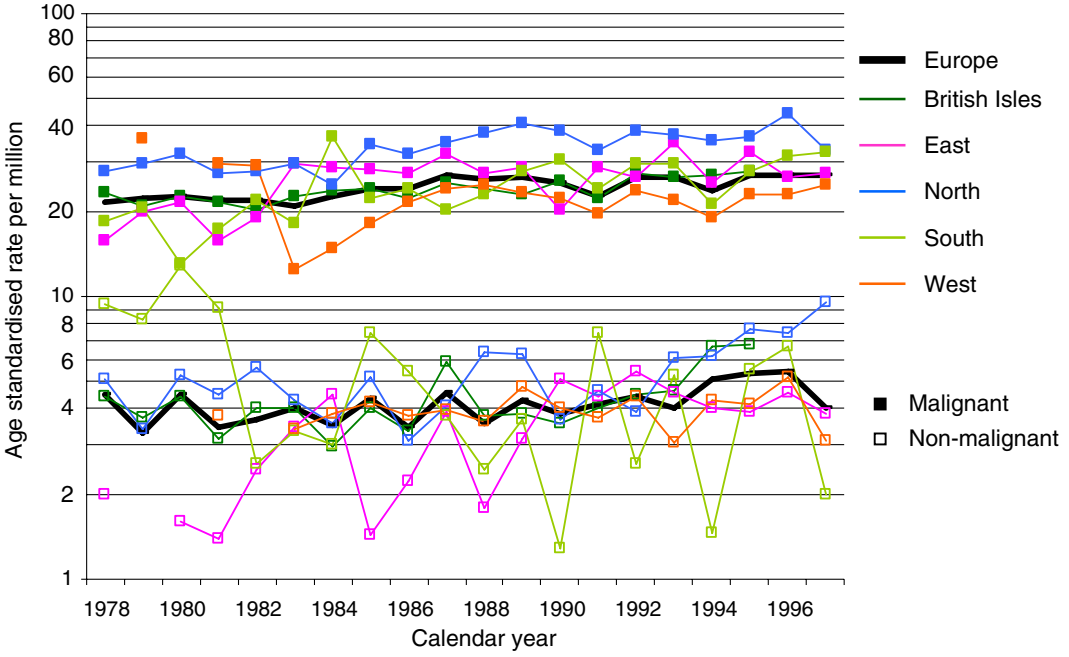
In Europe as a whole, the increase in 5-year survival was observed in all diagnostic subgroups, although its extent was not homogeneous. Survival for ependymoma and PNET increased by more than 40%, for astrocytoma and other specified CNS tumours by around 20%, and for other gliomas by 29%. Survival rates levelled off, or even decreased in some regions, for some diagnostic groups or for all the CNS tumours combined between the last two 5-year periods (Table 7). In the British Isles, the increasing trend of survival was significant for all diagnostic groups, while in the other regions, the results were more heterogeneous (Table 7).

A statistically significant increase in survival was present in all age groups for all CNS tumours combined. However, except for astrocytomas and PNET, lack of improvement was observed in infants for other diagnostic subgroups. The increase in survival was not regular across the whole time period and some combinations of age and diagnostic group showed lower survival rates in the last 5-year period 1993–1997 than in the preceding one, 1988–1992 (data not shown).

4. Discussion

The present study is the largest report on incidence and survival of children with CNS tumours in Europe. The results are based on comparable data from 59 population-based cancer registries with high standards of main indicators of data quality. Despite rigorous data verification and careful evaluation of the comparability of the data-sets, it was not possible to account for all differences in diagnostic, registration and coding practices, specific to CNS tumours, which may have affected the results presented in this paper.

The location of the CNS tumours presents extra difficulty for diagnosis, due to reduced accessibility to the tumour and increased vulnerability of the affected tissues. It is not surprising to find large variations in pathological interpretation and diagnostic practices,[14] often depending on the technical equipment available. Imprecise limits between benign and malignant behaviour in some CNS neoplasms, opens the way for variable determination of diagnosis, which might be not repeatable due to the lack of biopsied specimen. Uncertainty in behaviour classification is also reflected in the changes in recommendations for coding. For example, pilocytic astrocytoma (M-9421), coded malignant in the first edition of the International Classification for Oncology (ICD-O-1)[15] is considered of uncertain behaviour in the ICD-O-3.[16] In the opposite direction, papillary ependymoma (M-9393), coded uncertain in ICD-O-1, receives malignant behaviour code in the ICD-O-3. It is therefore difficult to ensure complete registration of CNS tumours by the registries only collecting malignant cases. Clinical implications, comparable between the



West region, malignant tumours, year 1980 ASR=0; non-malignant, years 1979, 1980 and 1982 ASR=0;
East region, malignant tumours, year 1979 ASR=0.849.

Fig. 5 – Trends of the incidence of central nervous system (CNS) tumours in children (0–14 years) in Europe, 1978–1997, by behaviour and region. Only the registries with systematic registration of non-malignant tumours are included (*n* = 15,771). Age-standardised rates (ASR), World standard population. Source: ACCIS.

malignant and non-malignant CNS tumours, are another valid reason for collecting information on non-malignant CNS tumours, as recommended by the European Network of Cancer Registries (ENCR).[17] Among the registries included in this study, non-malignant CNS tumours were collected systematically in a large proportion of the covered population. This proportion is currently increasing, as more registries start to collect information systematically on non-malignant tumours. While the inclusion of non-malignant tumours may increase the incidence of CNS tumours up to 22% in the USA,[18] in our study this proportion was 15%.

The incidence rates observed in the European pool are similar to those previously described for North America and Europe.[1,6] In the SEER data, the ASR (world standard) for malignant CNS tumours in children was 32.4 per million,[19] which is higher than the European ASR of 26 per million for malignant tumours only. Only the North region had higher rates (ASR = 37.6). Indeed, ASR for CNS were 40% higher in the North than in any other European region and highest observed in the world since the 1970s.[1,2]

Although the rate in the North seemed to be inflated due to the disproportionate relative frequency of the subgroups of other gliomas and unspecified CNS tumours, the distribution of the excess of incidence among the diagnostic groups only reflects the use of outdated classification systems in the Nordic countries until recently. For example, the Finnish cancer registry used the *Manual of Tumor Nomenclature and Coding* (MOTNAC) coding, where all gliomas, except ependymomas, are included in a single group,[20] which does not allow re-classifying of these tumours to ICD-O system retrospectively. All astrocytomas are therefore included among other gliomas. When Finland was excluded from the data-set, the proportion of the individual subgroups became more similar to those in other regions, while the overall rates for the North did not change substantially and continued to be higher than in any other region. The constitution of the compound group 'glioma-related tumours', combining ependymoma, astrocytoma and other gliomas in a single group therefore helped to counteract the differences in classification systems described above.

A high percentage of microscopically verified diagnoses, and the high proportion of non-malignant tumours observed in the North may indicate an increased use of computerised tomography (CT), magnetic resonance imaging (MRI) and stereotactic biopsy,[21,22] but possibly also variations between the North and other regions in the coding practices of tumours without microscopic verification. The high rates of CNS tumours in children in the North of Europe may also result, at least in part, from widespread use of advanced diagnostic technology and the good access to specialised medical care.[22,23] It should be possible to evaluate formally whether variations of incidence could have been caused by the differences in access to diagnostic technology. To do this, information on the use and accessibility of CT and MRI and on the implementation and availability of specialised oncology units for children needs to be collected.

The low rates observed in the West might be explained mainly by the low rates in Germany alone (overall ASR = 26 per million with 95% CI 25–27), since this country represented 69% of person-years in this region in the period 1988–1997.

Table 6 – Number of children (age 0–14 years) with central nervous system (CNS) tumours included in the survival analyses and 5-year survival, Europe, 1988–1997, by diagnostic group, region and age (Source: ACCIS)

	n	Survival				
		Age 0 5-y (95% CI)	Age 1–4 5-y (95% CI)	Age 5–9 5-y (95% CI)	Age 10–14 5-y (95% CI)	All ages 5-y (95% CI)
EUROPE						
III. CNS	10532	48 (44,52)	61 (59,63)	64 (62,65)	70 (68,72)	64 (63,65)
IIIa. Ependymoma	1112	48 (39,56)	49 (44,53)	67 (61,73)	76 (68,81)	58 (55,61)
IIIb. Astrocytoma	4215	61 (53,68)	80 (78,82)	73 (71,76)	72 (70,75)	75 (73,76)
IIIc. PNET	2296	27 (20,35)	41 (37,44)	53 (49,56)	59 (54,63)	49 (47,51)
IIId. Other gliomas	1134	71 (56,82)	61 (55,66)	50 (45,54)	60 (54,65)	57 (54,60)
IIIe. Other Specified	900	57 (40,71)	79 (71,85)	88 (83,91)	87 (83,91)	84 (82,87)
IIIf. Unspecified	875	40 (29,50)	41 (35,47)	48 (42,54)	69 (62,74)	51 (47,54)
IIIa + b + d	6461	57 (52,62)	69 (67,72)	68 (66,70)	70 (68,72)	68 (67,70)
REGIONS						
III. CNS						
British Isles	2720	49 (41,56)	60 (56,63)	62 (59,65)	71 (67,74)	63 (61,65)
East	1696	34 (22,46)	47 (43,52)	54 (49,58)	61 (56,65)	53 (51,56)
North	1167	49 (38,60)	68 (63,73)	74 (69,78)	78 (73,82)	72 (69,74)
South	1022	50 (33,65)	63 (57,68)	65 (60,70)	72 (67,77)	66 (63,69)
West	3927	52 (45,58)	64 (61,67)	66 (63,68)	70 (67,73)	65 (64,67)
Logrank (p)		ns	0.0000	0.0000	0.0000	0.0000
Non-East[a]	8836	50 (46,54)	63 (61,65)	66 (64,67)	72 (70,74)	66 (65,67)
IIIa + b + d						
British Isles	1788	58 (48,66)	67 (63,71)	63 (59,66)	69 (64,72)	65 (63,67)
East	946	42 (22,61)	58 (52,64)	66 (60,71)	68 (62,74)	64 (60,67)
North	698	60 (41,74)	75 (68,80)	74 (68,80)	81 (74,86)	76 (72,79)
South	618	52 (33,68)	75 (68,81)	73 (65,79)	72 (66,78)	72 (68,76)
West	2411	61 (52,68)	72 (69,76)	70 (66,73)	67 (63,71)	69 (67,71)
Logrank, five regions (p)		ns	0.0000	0.0010	0.0297	0.0000
Non-East[a]	5515	59 (53,64)	71 (69,73)	68 (66,70)	71 (68,73)	69 (68,70)
IIIc. PNET						
British Isles	552	27 (14,41)	33 (26,40)	51 (44,58)	55 (45,63)	44 (40,48)
East	371	***36 (13,59)***	35 (25,44)	42 (34,49)	46 (34,57)	40 (35,45)
North	173	***6 (0.4,25)***	43 (30,55)	71 (57,81)	55 (35,71)	52 (43,59)
South	206	#	44 (31,55)	61 (49,71)	61 (47,72)	55 (48,62)
West	994	32 (20,45)	46 (40,52)	55 (49,60)	67 (60,74)	53 (50,56)
Logrank, five regions (p)		ns	0.035	0.0002	ns	0.0001
Non-East[a]	1925	26 (18,35)	42 (38,46)	56 (52,59)	61 (56,66)	50 (48,53)
IIIe. Other Specified						
British Isles	224	***53 (26,74)***	85 (70,93)	88 (78,94)	92 (84,96)	87 (82,91)
East	169	#	60 (36,78)	72 (57,82)	69 (54,80)	68 (59,75)
North	104	#	83 (60,93)	91 (74,97)	85 (68,94)	83 (74,89)
South	74	#	70 (33,89)	84 (62,94)	91 (75,97)	86 (75,92)
West	329	***74 (44,89)***	80 (64,89)	95 (88,98)	92 (84,96)	90 (85,93)
Logrank, five regions (p)		ns	ns	0.0002	0.0004	0.0000
Non-East[a]	731	60 (42,74)	82 (74,88)	91 (86,94)	91 (87,94)	88 (85,90)
IIIf. Unspecified						
British Isles	156	***43 (22,63)***	47 (31,62)	72 (56,83)	95 (83,99)	68 (60,75)
East	210	***23 (7,44)***	20 (11,31)	24 (14,35)	37 (24,50)	26 (20,32)
North	192	***65 (42,81)***	64 (48,76)	68 (56,78)	79 (63,89)	69 (62,76)
South	124	#	39 (23,54)	33 (20,46)	72 (54,84)	46 (37,54)
West	193	***17 (3,43)***	43 (29,56)	44 (31,56)	65 (49,77)	46 (39,54)
Logrank, five regions (p)		ns	0.0000	0.0000	0.0000	0.0000
Non-East[a]	665	45 (32,57)	49 (41,56)	55 (48,61)	78 (71,84)	58 (54,62)

5-y: 5-year survival; *n*: Number of cases; (95%CI): confidence interval; ns: $P \geqslant 0.05$; Italics small bold types: $10 \geqslant n$ cases < 25; #: Number of cases $n < 10$; CNS: CNS: All central nervous system tumours combined. (Group III. CNS and miscellaneous intracranial and intraspinal neoplasms) (ICCC)[13]; IIIa + b + d: Glioma-related (IIIa Ependymoma, IIIb Astrocytoma, IIId Other gliomas); PNET: IIIc. Primitive neuroectodermal tumours; Other specified: IIIe. Other specified intracranial and intraspinal neoplasms; Unspecified: IIIf. Unspecified intracranial and intraspinal neoplasms.

a Non-East = Brit Isl + North + South + West.

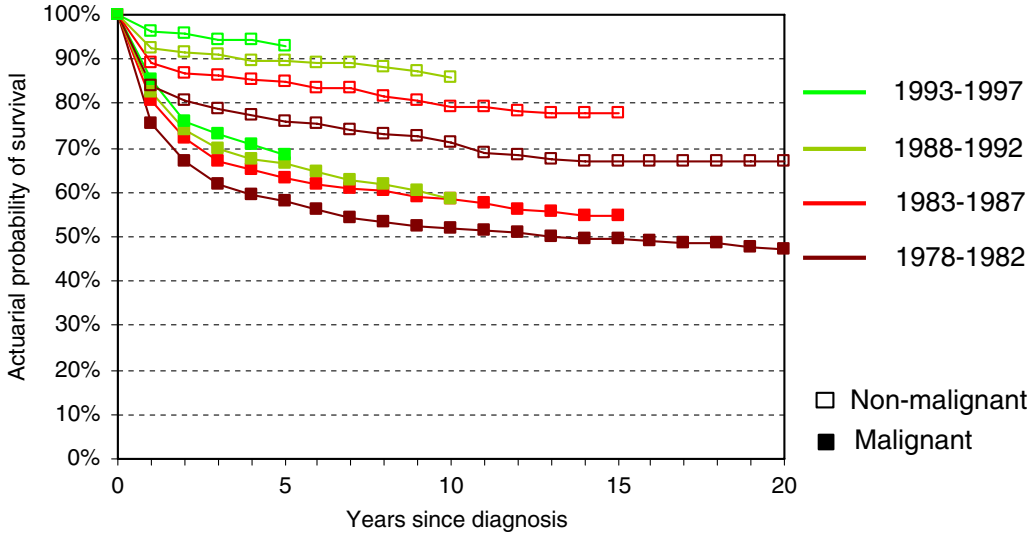


Fig. 6 – Survival curves for children (0–14 years) with central nervous system (CNS) tumours in Europe, by behaviour of tumour and period diagnosis (1978–1997). Only the registries with systematic registration of non-malignant tumours are included (*n* = 14,174). Source: ACCIS.

This low incidence has been explained by under-reporting of CNS tumours in Germany in the 1980s and 1990s.[24] The under-registration concerns probably mainly the subgroups of other gliomas and unspecified CNS tumours, since incidence of astrocytomas was close to the regional average. The German incidence rates of PNET did not differ from those in other countries of the region, since the children with PNET tend to be entered on clinical trials and treated by paediatric oncologists, who are the main contributors to the German Childhood Cancer Registry.[24] With Germany excluded, the overall incidence rate was consistent with European average, 29 per million (95% CI 28–31).

Although it was not significantly different from the reference, the incidence of CNS tumours in the East was the second highest, while overall incidence rates in this region were relatively low [Stiller, Marcos-Gragera, Ardanaz and colleagues, this issue]. It is unlikely that the high incidence of CNS tumours is conditioned by the registration of non-malignant tumours or the extensive use of advanced diagnostic technologies, because the proportion of non-malignant tumours in the East was low. The low survival observed in this region may indicate that the cases present at a later stage, but possibly also lack of access to best practice management of children with CNS tumours.

The time period 1978–1997, used for time trend analyses, was not well balanced with respect to the numbers of cases contributing to each of the 5-year periods, notably the lack of cases in the West at the beginning and in the British Isles at the end of the study period. These were the two numerically largest regions, which weighted the European trends considerably. It is difficult to estimate the direction of possible bias and its extent. However, the time trends of overall incidence rates did not seem to be affected much by the lack of data at the two ends of the study period [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue]. Also within the group of CNS tumours, exclusion of the regions with extreme incidence rates North (high) and West (low) did not alter much the increase in incidence (AAPC = 2.1, $P < 0.0001$). On the whole, therefore, the choice of registries included in time trends analyses did not seem to be the cause of the detected increase. Rising incidence rates of CNS tumours were also reported previously.[23,25–27] Trends observed in North America in the population covered by the SEER Program have been explained as a step increase function ('jump model'), which would correspond mainly to the diffusion of MRI in the mid-1980s. This explanation is supported by the detection of main increases in the tumour types predominantly diagnosed by this technique.[21,25,28] Rising trends of childhood CNS tumours in Sweden have been explained similarly.[23] The secular changes of incidence observed for CNS tumours in Europe in Fig. 4 may resemble those described for the SEER data, although the nature of this step increase could not be mirrored exactly in the European data, since the use of diagnostic technology would probably not be applied in the same way across the heterogeneous healthcare systems in Europe, compared with those in the USA.

Our results show increases in astrocytomas, PNET and other specified CNS tumours, but not in other gliomas or ependymomas. Both astrocytomas and PNET roughly parallel the launch of use of MRI, whereas in other specified CNS tumours rates begun to rise later, during the 1990s. These increases may be explained, at least in part, by diagnostic improvements, which besides incrementing the number of diagnosed cases contributed to the improvement of classification, especially of gliomas and, simultaneously, to a reduction of the unspecified CNS tumours. The change in classification of CNS tumours, which reduced the proportion of low-grade gliomas by classifying them to higher grades in the middle of 1980s,[28] and the gradual introduction of registration of non-malignant tumours along the period studied, may have also contributed to the increase in incidence, particularly in the group of other specified tumours. On the other hand, we have shown that the increases were similar for the malignant and non-malignant CNS tumours. We cannot therefore

Table 7 – Number of children (age 0–14 years) with central nervous system (CNS) tumours included in the survival analyses and 5-year survival time trends, Europe, 1978–1997, by region and diagnostic group (Source: ACCIS)

	n	Survival				Log rank trend *P* value
		1978–82 5-y (95% CI)	1983–87 5-y (95% CI)	1988–92 5-y (95% CI)	1993–97 5-y (95% CI)	
III CNS						
EUROPE	15415	52 (51,54)	59 (58,61)	63 (62,65)	67 (65,69)	0.0000
British Isles	5283	49 (47,52)	57 (54,60)	59 (56,61)	69 (66,72)	0.0000
East	1949	52 (48,56)	52 (49,56)	54 (49,58)	56 (50,61)	ns
North	2125	61 (56,65)	67 (63,71)	73 (69,76)	70 (66,74)	0.0001
South	1011	51 (44,57)	59 (53,65)	69 (63,74)	67 (60,73)	0.0000
West	4189	61 (50,71)	64 (61,66)	67 (64,69)	67 (64,70)	ns
IIIa Ependymoma						
EUROPE	1741	45 (40,50)	52 (47,56)	54 (49,59)	64 (58,69)	0.0000
British Isles	560	35 (28,43)	52 (44,60)	48 (39,55)	72 (63,79)	0.0000
East	249	51 (41,60)	43 (34,51)	41 (28,54)	50 (34,64)	ns
North	200	60 (45,72)	61 (44,74)	64 (48,76)	56 (37,71)	ns
South	132	47 (28,63)	50 (31,66)	59 (41,73)	63 (44,78)	ns
West	460	***50 (18,75)***	58 (49,66)	60 (52,67)	67 (57,76)	ns
IIIb Astrocytoma						
EUROPE	5994	64 (61,67)	71 (69,73)	74 (72,76)	76 (73,78)	0.0000
British Isles	2194	65 (61,69)	71 (67,75)	71 (67,74)	78 (74,81)	0.0000
East	775	61 (55,67)	65 (59,69)	68 (60,74)	69 (60,76)	ns
North	564	69 (60,76)	73 (64,80)	85 (78,89)	71 (63,78)	ns
South	413	60 (49,70)	68 (59,75)	76 (67,83)	72 (62,80)	0.02
West	1671	69 (50,82)	76 (71,80)	76 (72,79)	77 (73,81)	ns
IIIc PNET						
EUROPE	3271	37 (33,41)	44 (40,47)	48 (44,51)	52 (48,56)	0.0000
British Isles	1125	37 (31,42)	44 (39,50)	41 (36,46)	50 (43,57)	0.0016
East	436	30 (22,38)	24 (18,31)	39 (30,48)	46 (35,55)	ns
North	299	36 (24,48)	50 (38,61)	46 (36,56)	57 (43,69)	ns
South	182	52 (36,66)	54 (39,67)	67 (52,78)	52 (34,68)	ns
West	1086	***57 (25,79)***	51 (45,57)	53 (48,58)	55 (48,61)	ns
IIId Other gliomas						
EUROPE	1836	45 (40,50)	53 (48,57)	54 (50,59)	58 (53,63)	0.0000
British Isles	699	30 (24,37)	32 (26,39)	37 (31,44)	46 (36,55)	0.0006
East	181	44 (28,59)	47 (32,61)	46 (28,62)	54 (37,69)	ns
North	523	65 (56,73)	79 (70,85)	77 (69,83)	78 (69,85)	0.031
South	65	#	56 (35,73)	***74 (48,88)***	***67 (34,86)***	ns
West	344	#	61 (51,70)	54 (45,63)	44 (29,59)	ns
IIIe Other Specified						
EUROPE	1349	71 (65,76)	81 (76,84)	88 (84,91)	86 (81,89)	0.0000
British Isles	459	68 (59,75)	76 (67,83)	86 (78,91)	87 (79,92)	0.0000
East	170	69 (55,80)	78 (67,86)	80 (64,90)	68 (45,84)	ns
North	187	78 (63,87)	87 (71,94)	88 (74,94)	81 (67,89)	ns
South	65	#	***95 (72,99)***	***83 (48,96)***	***95 (68,99)***	ns
West	384	#	83 (74,90)	94 (88,97)	90 (80,95)	ns
IIIf Unspecified						
EUROPE	1224	43 (37,49)	47 (41,52)	59 (53,64)	61 (55,67)	0.0000
British Isles	242	37 (25,48)	44 (30,56)	68 (56,78)	73 (58,83)	0.0000
East	138	51 (38,63)	63 (52,72)	32 (15,50)	19 (6,39)	ns
North	352	50 (39,60)	49 (37,59)	69 (57,78)	70 (61,78)	0.0009
South	154	35 (23,47)	33 (20,46)	52 (33,68)	***55 (32,72)***	ns
West	244	***27 (7,54)***	36 (26,47)	53 (40,63)	48 (31,63)	0.0195

5-y: 5-year survival; *n*: Number of cases; (95%CI): confidence interval; ns: $P \geqslant 0.05$; Italics small bold types: $10 \geqslant n$ cases < 25; #: Number of cases $n < 10$; CNS: CNS: All central nervous system tumours combined. (Group III CNS and miscellaneous intracranial and intraspinal neoplasms) (ICCC)[13]; PNET: IIIc. Primitive neuroectodermal tumours; Other specified: IIIe. Other specified intracranial and intraspinal neoplasms; Unspecified: IIIf. Unspecified intracranial and intraspinal neoplasms.

exclude the participation of environmental and other risk factors,[26,27] and further studies are justified.

Survival of children with CNS tumours improved across the period 1978–1997, in all diagnostic subgroups. The least improvement along time was seen in infants and in the East and West regions. Consistent results were reported from different countries[29,30] for the 1980s. In the European studies including the late 1990s, an increase in 5-year survival of children with CNS tumours has been reported, but survival rates levelled off or even decreased towards the end of the study period,[31,32] as seen also in the present study in some tumour subgroups and some regions. This lack of progress in the last part of the study period justifies further attentive monitoring of these trends. The improvement in survival may be attributed mainly to better access to healthcare, resulting in earlier diagnosis, more recruitment to standardised treatment protocols, participation in collaborative groups, better supportive care, establishment of paediatric units, but also to general improvement of socio-economic conditions over the study period.[33–36]

In spite of the increments in survival for childhood CNS tumours reported in this and other studies,[6–8,32,37] inequalities in prognosis persist among geographical areas in Europe.[37] Age at diagnosis, histology, anatomic site, extent of the tumour and type of treatment have been described as the most relevant predictors of survival.[11] While availability of effective therapies is essential, access to medical care, which is generally related to economic and cultural factors,[38] modifies strongly the effectiveness of care. Later diagnosis may be one of the reasons for the markedly lower survival of children with CNS tumours in the East. The factors possibly contributing to the lower overall survival in the East are discussed in detail elsewhere [Pritchard-Jones and Colleagues, this issue].

The significant difference in survival, observed among the other regions, may be explained partly, but not entirely, by the differences in diagnostic and registration practices of CNS tumours. For example, the North region had the highest percentage of non-malignant tumours, but the high survival was observed for both malignant and non-malignant tumours. Beyond the proportion of non-malignant tumours in each data-set, the rules of pathological classification of tumours as malignant or non-malignant may also affect survival rates, without offering a possibility of evaluation of the effect of such differential classification from routine registration data.

Surgery is, in general, the first step in treatment, both to establish the microscopic diagnosis and, if possible, to remove the tumour for a curative purpose. With the extensive use of CT and MRI, the tumours are diagnosed at earlier stage, permitting their complete removal, and better survival.[11] Histology is a well-recognised prognostic factor for CNS tumours[7,11,24,29,30,37] and this is reflected in the differences in survival by diagnostic subgroup. The low survival for PNET and the high survival for astrocytoma is mostly related to the different possibilities of earlier diagnosis and start of treatment.[11] Large variations among the regions were seen in the proportion of microscopically verified tumours. The tumours diagnosed only clinically correspond, at least in part, to unresected tumours, which could have been allocated to a more specific diagnostic subgroup, if histology were available. The variable proportion of these cases in different regions may have biased the comparison of survival for the individual diagnostic subgroups. For the overall CNS group, this concern applies mainly to the British Isles and the West. In the former, the proportion of microscopically diagnosed cases was lower than in other regions, which might have resulted in less specific diagnoses, less well tailored treatment and lower survival. In the West, with high proportion of microscopic verification (probably due to under-ascertainment of the less well defined CNS tumours), the effect would be the opposite.

On the other hand, we do not have enough information to be able to exclude other explanations for geographical variations in survival, such as more or less successful management of CNS tumours in childhood in the relevant areas.

On the whole, this survival study is consistent with EUROCARE-2 results.[7] In the USA, the 5-year survival for the patients diagnosed in 1986–1997 in SEER registration areas was 65%, only including malignant tumours.[6] This is slightly higher than the 5-year survival of 62%, 95% CI 61–63, observed in our restricted data-set for malignant tumours only in the same calendar period. With East excluded, the corresponding figures were 63%, 95% CI 62–64, and for North only they were 69%, 95% CI 66–72.

As in other reports,[30] survival improved with increasing age, and was poorest in infants. More aggressive histological subtypes, higher rates of disease dissemination at diagnosis, lower overall rate of complete tumour resection and problems related to the diagnosis and treatment in young children have been associated with these differences in survival. Delay of diagnosis contributes to the poor survival in infants, as at this age tumours may show only unspecific symptoms, making the diagnosis difficult, until the tumour reaches a large size.[11] This reasoning is supported by the observation of a high proportion of unspecified CNS tumours in infants in this study. This group of patients deserves special attention, since infants present, simultaneously, the highest incidence rate and the lowest survival among the diagnostic subgroups, with up to 50% of cases diagnosed only clinically. Although survival did not differ by the method of diagnosis ($P = 0.5$), this age group comprises perhaps the highest proportion of non-resected tumours, known for their poor prognosis. Due to the special nature of CNS tumours and the serious potential sequelae, principally related to radiotherapy, are usually treated with protocols avoiding or delaying radiotherapy in infants,[11] which might be the reason for the low survival of infants, especially those with PNET or ependymoma.[39–41]

This study showed high incidence rates in the North of Europe, and a general increase in the incidence of CNS tumours in children. These rates and trends could be explained by differences and improvements in diagnosis, ascertainment and practice of cancer registries. However, these artefacts do not account completely for the geographical and temporal differences observed and we cannot therefore exclude a role of variations in risk factors. Survival has improved in Europe, but geographical differences persist. Continuing data collection and improvement of data quality, including retrospectively, are indispensable to monitor future incidence and survival trends and to highlight differences among regions.

Conflict of interest statement

None declared.

Acknowledgements

The ACCIS project was funded by the European Commission from 'Europe Against Cancer' action program (1996–2002)_(contracts SI2.126875, SI2.321970 and SPC.2002303), jointly with the International Agency for Research on Cancer (IARC). Data analyses were partly financed by the French Ligue Nationale Contre le Cancer, Comité du Rhône. In the RNTI-SEOP this study was partially supported by Fundación Científica AECC, ISCIII Network RITSI G03/089, Fundación Villavecchia and Fundación SEOP. In Granada Cancer Registry this study was in the framework ISCIII Network REpIER G03/123 and RCESP C03/09, Spain.

The authors thank Mr Nicolas Mitton for his input in the set-up and management and exploration of the ACCIS database, the members of ACCIS Scientific Committee for steering the study, the Guest Editors for helpful comments on earlier drafts and E. Pardo and A. García of the RNTI-SEOP; M.J Sánchez and E. Sánchez-Cantalejo of the Granada Cancer Registry; and Dr J.M. Cerdá for their help with manuscript preparation.

The following collaborators from the cancer registries contributed actively to this study: S.V. Petrovich, O. Budanov (Belarus); H. Storm, N. Christensen (Denmark); T. Aareleid (Estonia); T Hakulinen, R Sankila, E Pukkala (Finland); E Le Gall, I Tron (Brittany, France), B. Lacour, E. Desandes (Lorraine, France), J.L. Bernard, P. Pillon, J.C. Gentet (PACA and Corsica, France), F. Freycon, C. Berger (Rhone Alps, France), L. Remontet (Francim, France), A. Danzon, M. Mercier (Doubs, France), J.P. Daurès, B. Tretarre (Herault, France), F. Ménégoz (Isère, France), A.V. Guizard (Manche, France), M. Velten (Bas-Rhin, France), A. Buemi (Haut-Rhin, France), N. Raverdy (Somme, France), M. Sauvage, P. Grosclaude (Tarn, France); P. Kaatsch, B. Eisinger, R. Stabenow (Germany); D. Schuler, Z. Jakab, G. Borgulya (Hungary); L. Tryggvadottir, J.G. Jonasson, K. Bjarnadottir (Iceland); H. Comber, F. Dwane (Ireland); C. Magnani, G. Pastore (Piedmont, Italy), F. Pannelli, C. Pascucci (Marche, Italy), S. Ferretti (Ferrara, Italy), E. Conti, V. Ramazzotti, M.C. Cercato (Latina Province, Italy), M. Vercelli, A. Puppo (Liguria, Italy), P. Crosignani, G. Tagliabue, A. Tittarelli (Lombardy, Italy), V. De Lisi, P. Sgargi (Parma, Italy), R. Tumino (Ragusa, Italy), M. Budroni, D. Piras (Sassari, Italy), E. Paci, E. Crocetti (Tuscany, Italy), F. La Rosa, F. Stracci (Umbria, Italy), P. Zambon, S. Guzzinati (Veneto, Italy); M. Dalmas (Malta); J. Paulides, J.W.W. Coebergh, J. van Dijck, A. Wit (Netherlands); F. Langmark, A. Johansen, A. Andersen (Norway); I. Plesko (Slovakia); M. Primic Žakelj, V. Pompe-Kirn (Slovenia); R. Peris-Bonet, B. Giner (Spain), E. Almar Marques, A. Mateos Ramos (Albacete, Spain), J. Ramon Quiros Garcia, A. Cañada Martínez (Asturias, Spain), I. Izarzugaza (Basque, Spain), A. Alemán Herrera (Canary Islands, Spain), P. Viladiu, R. Marcos, A. Izquierdo (Girona, Spain), C. Martínez Garcia (Granada, Spain), A. Obrador, I. Garau (Mallorca, Spain), E. Ardanaz (Navarra, Spain), J. Borràs, J. Galceran (Tarragona, Spain), J. de la Bárcena Guallar, M.C. Martos Jiménez (Zaragoza, Spain); G. Jundt (Basel, Switzerland), C. Bouchardy, M. Usel (Geneva, Switzerland), J. Allemann, H. Frick (Graubünden and Glarus, Switzerland), T. Fisch, S. Ess (St Gallen Appenzell, Switzerland), F. Joris, D. de Weck (Valais, Switzerland); S. Yalcin Eser (Izmir, Turkey); C.A. Stiller, M.G.F. Murphy, G.J. Draper (England and Wales, UK), A. Gavin, C. Fox, W. Hamill, R. Middleton (Northern Ireland, UK), D. Brewster, L. Bhatti, A. McDonald (Scotland, UK). We also acknowledge the collaborators from the other registries participating in ACCIS, whose data were not included in this paper.

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