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Neuroblastoma incidence and survival in European children (1978–1997): Report from the Automated Childhood Cancer Information System project

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ABSTRACT

The Automated Childhood Cancer Information System (ACCIS) collects and presents data on childhood cancer in Europe. This report describes trends (1978–1997) and geographical differences (1988–1997) in incidence and survival for 6202 children with neuroblastoma from 59 registries in 19 countries, grouped into five regions (British Isles, West, East, North, and South). The age-standardised incidence rate (ASR) of neuroblastoma in Europe in 1988–1997 was 10.9 cases per million children, being highest in infants (52.6). The ASR of neuroblastoma increased in Europe from 8.4 in 1978–1982 to 11.6 in 1993–1997, mostly due to an increase in infants (from 35.4 to 57.8). Overall 5-year survival was 59%, ranging from 47% (East) to 67% (West). It improved markedly from 37% in 1978–1982 to 66% in 1993–1997, especially in infants. A certain amount of overdiagnosis in children under 2 years of age may explain the increased incidence rates and partially the increase in survival. Survival of older children (aged 2–14 years), which is likely to be largely affected by therapy, has also improved from 21% to 45%.

1. Introduction

Neuroblastoma is a typical example of an embryonal tumour of childhood.[1,2] In developed countries it is the most common tumour in infants (children aged less than 1 year), whereafter its occurrence decreases gradually with age; it is rare in school children and almost never seen in adolescents.

Neuroblastoma and related tumours (ganglioneuroblastoma and ganglioneuroma) arise from the neural crest cells that colonise sympathetic ganglia and adrenal medulla in foetal life. These neoplasms are a family of tumours characterised by an array of biological and clinical features ranging from spontaneous regression and the capability of differentiation to benign neoplasm in infants, but potentially aggressively

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disseminating in older children.[1,2] The aetiology of neuroblastoma is largely unknown.[1–4] The raised risks of being diagnosed with neuroblastoma in either early- or late-stage disease support the hypothesis that neuroblastoma consists of at least two distinct disease entities.[2,4]

Prognosis for neuroblastoma is related to extent of disease at diagnosis, infants with localised disease having the best chance of survival. Other prognostic factors are biological features, such as histopathology, tumour ploidy and *MYCN* amplification. These features are used clinically to assign neuroblastoma patients to risk groups with tailored therapeutic strategies.[1,2,5]

This dependence of survival on stage and age, together with the availability of a simple urine test for a tumour marker, made neuroblastoma seem an ideal, and thus-far only, candidate for screening.[1,6–10] Studies of the feasibility or effectiveness of neuroblastoma screening were carried out in England, France, Germany and North America in the 1990s.[9–12] Until recently, screening was mandatory in Japan. The results of the recent major evaluations of neuroblastoma screening led to a non-introduction in Germany and discontinuation of the screening programme in Japan.[13]

This paper presents incidence and survival rates for neuroblastoma among European children, diagnosed during 1978–1997 and made available in the framework of the Automated Childhood Cancer Information System (ACCIS), a collaborative project of 80 population-based cancer registries in 35 European countries.[14] In the interpretation of the observed geographical and temporal patterns of incidence and survival we consider screening activities as they occurred during the study period in the areas covered, as well as the insights into the nature of neuroblastoma gained from these screening studies.

2. Material and methods

Analyses are based on the ACCIS database, which is described in detail elsewhere [Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue]. The ACCIS Scientific Committee evaluated quality and comparability of the registry data-sets, using standard[15] and specific criteria for childhood data-sets. All cases of neuroblastoma (including ganglioneuroblastoma) as defined by diagnostic group IV (a) in the International Classification of Childhood Cancer[16] were included. The analyses are based on a grand total of 6202 neuroblastoma cases from 59 contributing registries in 19 countries. Details of coverage and data quality are presented in Table 1. Countries were grouped into five regions (North, British Isles, West, East, and South), according to geographical location combined with data availability (Table 1). The regional comparisons are based on the most recent 10-year period 1988–1997. Time trends are presented by 5-year periods from 1978 to 1997. Numbers of cases and data quality indicators for the time trend analyses are shown in Table 2. Variation in incidence is reported for age-groups 0, 1–4, 5–9, and 10–14 years. In addition, we also report survival results for the age group 2–14 years, which is outside the target age-range for screening and consists mostly of advanced stage cases.[1,2,6–9,11,12] In the absence of stage-specific information these data can be used as an indicator for changes in survival related to improvements in therapy.

Table 1 – Data-sets contributed by the European cancer registries for the analyses of neuroblastoma incidence and survival in children (age 0–14 years), with indicators of coverage, data quality, and follow-up (Source: ACCIS)

Region	Registry	Period	Time-trend	*n*	Basis of diagnosis			Survival analysis				Notes
					MV	DCO	Unknown	*n*	Closing date	FU > 5 years	Median	
					%	%	%			%	Years	
British Isles	IRELAND, National	1994–1997		18	94	0	0	18	31.12.1998	0	2.7	
	UNITED KINGDOM, England & Wales	1978–1995	+	1327	93	<1	<1	1309	31.1.2001	99	12.0	P Nb
	UNITED KINGDOM, Northern Ireland	1993–1996		9	67	0	0	9	31.12.1999	0	0.6	
	UNITED KINGDOM, Scotland	1978–1997	+	152	94	0	0	152	31.12.1999	85	8.7	
East	BELARUS, National	1989–1997		101	99	0	0	100	1.9.2000	70	6.5	P
	ESTONIA, National	1978–1997	+	45	98	0	0	42	31.12.1998	78	9.3	
	HUNGARY, National	1978–1997	+	428	97	–	0	423	1.1.2000	78	10.5	P
	SLOVAKIA, National	1978–1997	+	206	100	0	0	192	31.12.1997	65	6.7	
	GERMANY, NCR (only former East)	1978–1989	+	320	100	0	0	243	31.12.1987	61	6.3	S
North	DENMARK, National	1978–1997	+	156	97	1	<1	144	31.12.1997	84	11.4	
	FINLAND, National	1978–1997	+	184	100	0	0	178	31.12.1998	72	8.6	

	ICELAND, National	1978–1997	+	7	100	0	0	7	31.12.2000	75	7.2	
	NORWAY, National	1978–1997	+	148	100	0	0	147	1.1.2000	83	11.0	
South	ITALY, Piedmont paediatric	1978–1997	+	132	92	0	0	132	31.12.1999	84	12.2	P
	ITALY, Marche	1990–1997		17	94	–	6	17	30.9.2000	91	8.8	P
	ITALY, Ferrara	1991–1995		4	75	0	0	4	31.12.1998	67	5.1	
	ITALY, Latina	1983–1997	+	7	100	0	0	7	31.12.1998	100	10.3	
	ITALY, Liguria	1988–1995		8	50	0	0	8	15.4.2000	83	8.4	
	ITALY, Lombardy	1978–1997	+	28	93	0	0	28	23.9.1999	47	3.0	
	ITALY, Parma	1978–1995	+	10	100	0	0	10	1.4.1999	100	16.3	
	ITALY, Ragusa	1983–1997	+	3	67	0	0	3	30.3.2000	100	13.2	
	ITALY, Sassari	1992–1995		3	100	0	0	3	30.12.1999	50	5.0	
	ITALY, Tuscany	1988–1997		18	83	6	0	17	31.12.1998	50	4.8	
	ITALY, Umbria	1994–1996		2	100	0	0	2	31.12.1999	0	0.0	
	ITALY, Veneto	1990–1996		17	100	0	0	17	31.12.1998	33	4.0	
	MALTA, National	1991–1997		9	100	0	0	9	31.12.1999	40	3.9	
	SLOVENIA, National	1978–1997	+	57	100	0	0	57	31.12.1999	66	7.0	
	SPAIN, National	1990–1995		110	88	0	<1	107	31.12.2000	89	5.8	P o1 Z
	SPAIN, Albacete	1991–1997		3	100	0	0	3	15.9.2000	67	7.2	
	SPAIN, Asturias	1983–1997	+	19	84	5	0	17	31.12.1997	57	6.9	
	SPAIN, Basque Country	1988–1994		23	100	0	0	23	31.12.2000	100	10.1	o1
	SPAIN, Canary Islands	1993–1996		7	100	0	0	–	–	–	–	
	SPAIN, Girona	1994–1997		5	100	0	0	5	31.12.1997	0	1.8	o1
	SPAIN, Granada	1988–1997		19	100	0	0	19	31.12.1999	82	9.1	G
	SPAIN, Mallorca	1988–1995		13	100	0	0	13	31.12.1998	80	7.9	o1
	SPAIN, Navarra	1978–1996	+	19	100	0	0	19	31.12.1997	62	11.7	o1
	SPAIN, Tarragona	1983–1997	+	18	100	0	0	16	31.12.1998	70	7.8	o1
	SPAIN, Zaragoza	1978–1996	+	30	97	3	0	29	31.12.1996	68	9.6	o1
	TURKEY, Izmir	1993–1996		18	94	–	0	–	–	–	–	
West	FRANCE, Brittany	1991–1997		47	100	–	0	46	1.1.2000	47	4.8	P
	FRANCE, Lorraine	1983–1997	+	70	86	–	0	68	1.1.1999	51	5.0	P
	FRANCE, PACA & Corsica	1984–1996	+	140	98	–	0	129	31.3.1998	66	6.7	P
	FRANCE, Rhone Alpes	1988–1997		132	98	–	0	122	1.6.2000	67	5.8	P o2 Nb
	FRANCE, Doubs	1978–1996	+	19	47	–	5	18	1.6.2001	27	1.3	
	FRANCE, Herault	1988–1997		17	100	–	0	–	–	–	–	
	FRANCE, Isere	1979–1997	+	58	97	–	0	–	–	–	–	o2
	FRANCE, Manche	1994–1996		2	100	–	0	1	31.5.2000	0	4.7	S
	FRANCE, Bas-Rhin	1978–1996	+	56	100	–	0	56	31.12.1997	68	7.5	
	FRANCE, Haut-Rhin	1988–1997		13	100	–	0	7	31.12.1995	100	7.8	S
	FRANCE, Somme	1983–1996	+	8	100	–	0	8	15.8.2000	60	6.9	
	FRANCE, Tarn	1983–1997	+	13	100	–	0	–	–	–	–	
	GERMANY, GCCR (East and West)	1991–1997	+	1013	99	–	0	982	31.12.1998	34	3.8	P Nb
	GERMANY, GCCR (only former West)	1983–1990	+	714	99	–	0	700	31.12.1998	94	10.7	P
	NETHERLANDS, National	1989–1995		135	93	–	0	131	31.12.1998	67	6.3	S o3
	NETHERLANDS, Eindhoven	1978–1997	+	25	96	–	4	25	1.7.1999	38	4.0	o3
	SWITZERLAND, Basel	1983–1997	+	9	100	–	0	9	30.6.2000	100	13.1	

(*continued on next page*)

Table 1 – *continued*

Region	Registry	Period	Time-trend	*n*	Basis of diagnosis				Survival analysis				Notes
					MV	DCO	Unknown		*n*	Closing date	FU > 5 years	Median	
					%	%	%				%	Years	
	SWITZERLAND, Geneva	1978–1997	+	19	100	0	0		18	31.12.1999	56	11.0	
	SWITZERLAND, Graubunden & Glarus	1989–1997		2	50	0	0		2	25.5.2000	0	0.0	
	SWITZERLAND, St. Gallen Appenzell	1983–1997	+	5	100	0	0		4	1.2.2001	0	0.0	
	SWITZERLAND, Valais	1989–1997		5	100	0	0		2	1.12.1998	100	9.0	S

n, number of cases registered in the given period; –; not available; PACA, Provence, Alps, Cote d'Azur; 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)); GCCR, National German Childhood Cancer Registry (until 1990 only West, since 1991 for reunified Germany); +, included in time trends; % MV, percentage of microscopically verified cases; % DCO, percentage of registrations from death certificate only; % unknown, percentage of registrations with unknown basis of diagnosis; %FU > 5 years, percentage of cases followed-up for at least 5 years among those not deceased by closing date; P, paediatric cancer registry, age-range of the patients is 0–14 years; o1–o3: overlapping registration areas: for the overlapping years, data from the registry with larger coverage are included in each analysis, according to availability; S: survival analyses were possible only for a restricted data-set (see Steliarova-Foucher, Kaatsch, Lacour and colleagues, this issue); G: General cancer registry, which has only contributed data for age-range 0–14 years; Nb, organised screening for neuroblastoma (see text); Z, covers only selected areas, see Steliarova-Foucher, Kaatsch, Lacour and colleagues (this issue).

The incidence rates for the age range 0–14 years are standardised (ASR) according to the World standard population.[17] The regional or temporal differences of incidence are evaluated from Poisson regression models with region or year included as the explanatory variables, adjusted for the possible confounders (age, sex, and region, as appropriate).[14] Results of time trends in incidence are reported as average annual percent changes (AAPC). Survival analyses use a non-parametric (actuarial life-table) method, the estimates being presented with approximate 95% confidence intervals (95% CI).[14] In addition to the standard 5-year survival, 10-year survival is presented for cohorts with sufficient follow-up data. Differences in survival of two or more patient groups are evaluated using the log-rank test and changes in survival between periods of diagnosis by log-rank test for trend. The significance level for all statistical tests was 5%.

According to the cancer registries, systematic population-based screening was carried out for neuroblastoma in very young children in a few registration areas included in this study. In the West, children under the age of 1 year were screened in the Rhone-Alps region in France, during 1990–1996.[9,18] In Germany, screening was offered in 1995–2001 to all children between 10 and 18 months of age in 6 of 16 states (Baden-Württemberg, Bremen, Hamburg, Northrhine-Westfalia, Lower Saxony, and Schleswig-Holstein). These were just over 50% of all German children, with participation estimated at 60–65%.[11] In the UK, neuroblastoma screening was conducted among children aged under 1 year in a small area in the North-East of England in 1986–1990 and in the City of Birmingham in 1989–1995.[7,9] Results of these screening programmes are taken into account when interpreting the differences in incidence and survival between different periods and regions.

3. Results

3.1. *Incidence*

Incidence rates by age, sex and geographical region during the last 10 years covered by this data-set (1988–1997), based on 3777 registrations, are shown in Table 3. This represents 7% of the total of 53,717 cancer cases. Neuroblastoma was by far the most common tumour type among 5073 infants [Stiller, Marcos-Gragera, Ardanaz and colleagues, this issue], representing almost 27% among them, with the next most common tumour, retinoblastoma, accounting for 10% [MacCarthy and colleagues, this issue].

The ASR in Europe as a whole was 10.9 cases per million children (Tables 3 and 4). Incidence rates by single year of age for each of the five European regions are shown in Fig. 1. The incidence of neuroblastoma was highest in the first year of life; incidence rates declined considerably thereafter and cases were rare beyond the 10th birthday (Table 3, Fig. 1). In the combined European data the incidence was slightly higher in males of all age groups (Table 3).

The regional variation in ASR was considerable, ranging from 9.1 cases per million children in the British Isles to 12.4 cases per million children in the South. In a model adjusted for age and sex, with the British Isles as the reference region, the West and South each had a significantly

Table 2 – Numbers of cases and indicators of data quality by region for time trend analyses of neuroblastoma incidence and survival in children (age 0–14 years) (Source: ACCIS)

Region	Period	*n*	Basis of diagnosis			Follow-up	
			MV	DCO	Unknown	1+ days	5+ years
			%	%	%	%	%
EUROPE[a]	1978–1982	854	96	<1	<1	96	99
	1983–1987	1470	97	<1	<1	97	91
	1988–1992	1640	97	<1	<1	97	92
	1993–1997	1481	97	<1	<1	98	30
British Isles	1978–1982	346	95	<1	1	99	98
	1983–1987	390	94	<1	<1	99	100
	1988–1992	482	92	<1	<1	99	100
	1993–1997	261	94	<1	<1	100	94
East	1978–1982	158	99	0	0	96	98
	1983–1987	154	98	0	0	95	97
	1988–1992	190	98	0	0	96	96
	1993–1997	177	97	0	0	99	35
North	1978–1982	118	99	<1	0	96	100
	1983–1987	138	99	0	0	98	100
	1988–1992	123	100	0	0	93	100
	1993–1997	116	97	<1	<1	97	28
South	1978–1982	80	88	1	0	99	100
	1983–1987	92	95	1	0	97	98
	1988–1992	71	99	0	0	99	90
	1993–1997	80	99	0	0	100	26
West	1978–1982	30	93	0	3	100	100
	1983–1987	547	98	0	<1	98	93
	1988–1992	725	98	0	0	96	87
	1993–1997	847	98	0	0	97	16

N, number of cases; Neuroblastoma (%), percentage of neuroblastoma (IVa) cases among all tumours of sympathetic nervous system (IV); MV (%), microscopically verified diagnosis.
DCO (%), cases registered from Death certificate only; 1+ 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.
a Europe includes the data of former GDR for 1978–1987.

Table 3 – Incidence rates of Neuroblastoma (ICCC IV(a)) per million in 1988–1997 by age groups, sex, and region (Source: ACCIS)

Region		Incidence by age groups				Incidence for all ages 0–14 years	
		0	1–4	5–9	10–14	Cases	Standardised[a]
Europe	Both sexes	52.6	18.1	2.8	1.0	3777	10.9
	Boys	54.6	19.0	3.1	1.0	2032	11.4
	Girls	50.5	17.2	2.6	0.9	1745	10.3
British Isles	Both sexes	34.4	17.1	3.1	0.6	770	9.1
East	Both sexes	43.2	17.1	2.7	1.8	468	10.0
North	Both sexes	41.2	16.8	2.2	1.5	239	9.6
South	Both sexes	67.5	18.8	3.6	0.6	379	12.4
West	Both sexes	64.0	19.0	2.7	0.9	1921	12.0

a World Standard.

elevated relative risk of 1.3 ($p < 0.0001$). Inter-regional variation in incidence was most marked in the first year of life (Table 3, Fig. 1), with age-specific incidence above 60 per million in the South and West and below 45 per million in the other three regions. Incidence at age 1 year was higher in West than in the other regions (Fig. 1). There was little difference between regions in the incidence rates at age 2–14 years.

Table 4 shows trends in incidence during 1978–1997, based on a grand total of 5445 registrations. In Europe as a whole, the incidence increased significantly ($p < 0.001$) from 1978 to 1997, the average annual percent change (AAPC) was 1.5%. The increase was especially large among infants (age 0), with a significant AAPC of 2.3% ($p < 0.001$) as well as for age group 1–4 years (AAPC 1.6%, $p < 0.001$). Incidence of the relatively rare older cases at age 2–14 years, AAPC 0.6% ($p = 0.100$), age

Table 4 – Incidence rates of Neuroblastoma (ICCC IV(a)) per million in 1978–1997 by age groups, 5-year time periods, and region (Source: ACCIS)

Regions	Time periods	Incidence by age groups				Incidence for all ages 0–14 years	
		0	1–4	5–9	10–14	Cases	Standardised[a]
Europe	1978–1982	35.4	14.4	3.0	0.8	854	8.4
	1983–1987	43.2	17.1	3.4	0.7	1470	10.0
	1988–1992	50.9	18.4	3.0	1.0	1640	10.9
	1993–1997	57.8	19.4	2.6	1.0	1481	11.6
British Isles	1978–1982	32.3	13.9	2.3	0.4	346	7.7
	1983–1987	31.6	15.8	3.0	0.5	390	8.4
	1988–1992	33.6	19.1	3.5	0.8	482	9.8
	1993–1997	34.8	15.4	2.4	0.5	261	8.4
East	1978–1982	32.1	15.5	2.9	0.8	158	8.5
	1983–1987	36.1	13.5	4.8	1.4	154	8.9
	1988–1992	53.4	19.7	3.9	2.1	190	12.1
	1993–1997	64.4	21.4	2.7	1.6	177	12.9
North	1978–1982	44.0	13.1	4.8	1.1	118	9.3
	1983–1987	62.1	17.2	3.9	1.4	138	11.8
	1988–1992	48.9	15.7	3.2	1.5	123	10.1
	1993–1997	33.7	17.8	1.3	1.6	116	9.0
South	1978–1982	40.3	19.2	3.9	1.8	80	10.8
	1983–1987	60.0	19.3	2.8	0.7	92	11.7
	1988–1992	56.4	16.9	2.4	0.3	71	10.4
	1993–1997	82.4	17.7	3.2	0.7	80	13.1
West	1978–1982	30.0	14.1	4.5	2.8	30	8.9
	1983–1987	49.8	19.0	3.4	0.5	547	11.0
	1988–1992	65.4	18.5	2.5	1.0	725	11.9
	1993–1997	70.6	21.4	2.9	0.9	847	13.3

a World Standard.

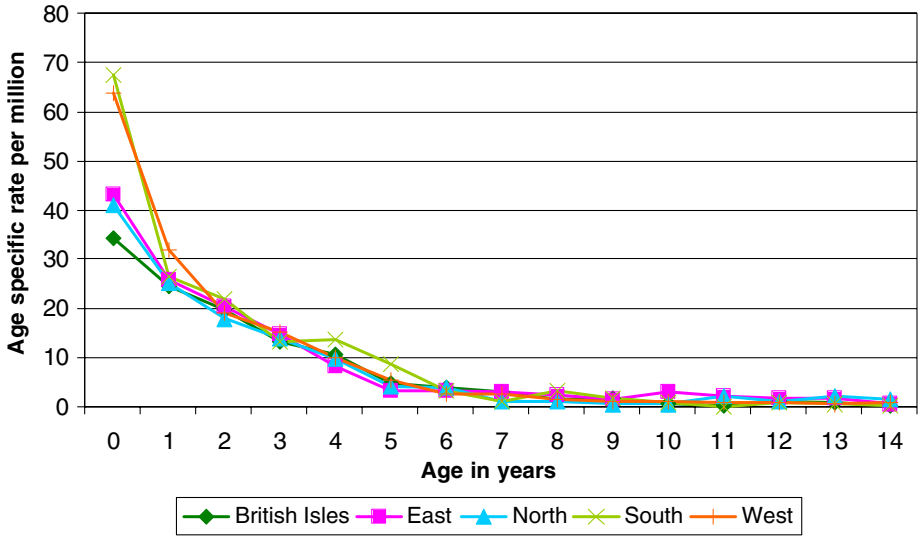

Fig. 1 – Incidence rates of Neuroblastoma (ICCC IV(a)) per million in 1988–1997 by age and region. Source: ACCIS.

5–9 years, AAPC −0.1% ($p = 0.342$) and age 10–14 years, AAPC 0.1% ($p = 0.630$) did not increase.

In the North, no consistent increase was seen (AAPC −0.2%, $p = 0.784$), and there was actually a decrease in incidence among infants in the most recent period. In all other regions, the differences in the average annual percent changes over time were considerable, ranging from a small change in the South (AAPC = 1.1%, $p = 0.256$), not significant due to small absolute numbers of cases, to a 2.8% increase in the East ($p < 0.001$).

3.2. *Survival*

Table 5 shows 5-year survival for the most recent 10-year period included in this data-set (1988–1997), based on 3668 cases. The average 5-year survival in Europe as a whole was 59%.

Table 5 – Five-year survival probabilities of Neuroblastoma (ICGC IV(a)) in 1988–1997 by age groups and region. % survival probability and (95% confidence interval) (Source: ACCIS)

Region	5-year survival per age group				5-year survival for age 2–14 years		5-year survival for all ages 0–14 years	
	0	1–4	5–9	10–14	Cases	2–14	Cases	0–14
Europe	84 (82–86)	47 (44–48)	42 (36–47)	38 (29–47)	1638	38 (36–41)	3668	59 (57–61)
British Isles	80 (74–85)	37 (33–42)	34 (24–44)	26 (10–47)	394	30 (26–35)	770	49 (45–52)
East	78 (69–84)	37 (31–43)	31 (19–44)	29 (14–45)	243	27 (21–33)	468	47 (42–52)
North	81 (71–89)	48 (38–57)	32 (13–53)	36 (11–62)	112	36 (26–46)	239	57 (50–63)
South	85 (80–90)	46 (37–53)	55 (38–70)	38 (9–67)	156	47 (38–55)	354	62 (57–67)
West	87 (84–89)	54 (51–58)	50 (41–58)	51 (35–65)	733	46 (42–50)	1837	67 (64–69)

Survival was highest for infants, 84%, and decreased with age from 47% at age 1–4 years to 38% at age 10–14 years (Table 5). The average survival for the age group 2–14 years was 38% (based on 1638 cases).

There were significant ($p = 0.026$) regional differences in 5-year survival for all ages combined, ranging from 47% in the East and 49% in the British Isles to 62% in the South and 67% in the West, while survival in the North (57%) was similar to the European average. These differences were consistent over the age groups (Table 5).

Table 6 shows trends in survival among children diagnosed during 1978–1997, based on 5325 registrations. Five-year survival in Europe as a whole increased significantly ($p < 0.001$) and steadily from 37% in 1978–1982 to 66% in 1993–1997. The increase was significant in each of the five regions, and was steepest in the West (from 24% to 74%, $p < 0.001$) and the South (from 39% to 67%, $p < 0.001$).

Across regions and time periods, overall survival correlated positively with infant incidence (Tables 4 and 6, Fig. 2).

Table 6 also shows trends in survival in the age groups 2–14 years. A significant ($p < 0.001$) increase in 5-year survival from 21% in the late 1970s to 45% in the mid 1990s was seen in Europe as a whole. The increase was more pronounced in the South (from 21% to 60%, $p = 0.004$) and West (from 12% to

Table 6 – Five- and 10-year survival probabilities of Neuroblastoma (ICGC IV(a)) in 1978–1997 by age groups, 5-year time periods, and region. % survival probability and (95% confidence interval) (Source: ACCIS)

Region	Time period	5-year survival per age group				5-year survival for ages 2–14 years		Survival for all ages 0–14		
		0 year	1–4 years	5–9 years	10–14 years	Cases	2–14 years	Cases	5-year survival	10-year survival
Europe	1978–1982	69 (63–75)	24 (20–28)	19 (12–26)	31 (17–47)	430	21 (17–25)	849	37 (34–40)	36 (32–39)
	1983–1987	79 (75–83)	34 (31–38)	33 (26–40)	29 (16–44)	714	30 (27–34)	1454	48 (45–51)	45 (43–48)
	1988–1992	82 (78–85)	40 (36–43)	37 (30–45)	35 (22–48)	727	34 (30–37)	1564	54 (51–56)	51 (49–54)
	1993–1997	88 (84–90)	56 (52–60)	48 (37–59)	33 (16–51)	603	45 (41–50)	1458	66 (63–69)	–
British Isles	1978–1982	68 (58–76)	21 (16–28)	23 (12–36)	44 (14–72)	167	20 (15–27)	346	37 (31–42)	34 (29–40)
	1983–1987	79 (70–86)	27 (22–33)	20 (11–33)	33 (8–62)	204	24 (18–30)	390	41 (36–46)	38 (33–42)
	1988–1992	80 (72–86)	33 (28–39)	30 (19–42)	31 (10–55)	253	27 (22–33)	482	45 (40–49)	42 (38–47)
	1993–1997	79 (68–86)	46 (37–53)	38 (21–56)	17 (0–52)	128	35 (27–44)	261	54 (48–60)	–
East	1978–1982	69 (52–80)	21 (13–30)	11 (0–28)	–	87	14 (8–22)	158	32 (25–40)	32 (25–40)
	1983–1987	71 (54–83)	36 (25–48)	29 (15–45)	13 (0–42)	87	26 (17–35)	154	42 (34–50)	40 (32–48)
	1988–1992	73 (59–83)	35 (25–45)	21 (8–39)	15 (2–37)	96	23 (15–32)	190	43 (36–50)	41 (33–48)
	1993–1997	85 (73–92)	43 (32–54)	52 (25–74)	38 (10–66)	78	36 (24–47)	177	58 (50–65)	–
North	1978–1982	68 (49–81)	31 (18–44)	29 (13–48)	50 (11–80)	62	32 (21–44)	118	42 (33–51)	40 (31–49)
	1983–1987	76 (62–86)	38 (26–51)	28 (10–49)	57 (17–84)	68	35 (24–47)	138	51 (42–59)	49 (40–57)
	1988–1992	77 (61–87)	39 (26–52)	36 (13–59)	43 (10–73)	56	31 (20–44)	123	53 (44–62)	50 (40–60)
	1993–1997	87 (70–95)	55 (41–68)	24 (1–63)	19 (0–67)	56	42 (25–57)	116	61 (49–70)	–
South	1978–1982	70 (45–85)	33 (20–48)	9 (0–33)	33 (5–68)	43	21 (11–35)	80	39 (29–50)	38 (27–48)
	1983–1987	75 (56–87)	44 (30–58)	70 (33–89)	–	45	51 (35–65)	92	60 (49–69)	53 (42–62)
	1988–1992	85 (66–94)	38 (22–53)	57 (17–84)	–	33	34 (19–51)	71	58 (45–68)	58 (45–68)
	1993–1997	91 (75–97)	36 (18–55)	60 (2–93)	50 (0–91)	27	60 (34–78)	80	67 (54–77)	–
West	1978–1982	–	–	–	25 (1–67)	17	12 (2–31)	25	24 (10–42)	24 (10–42)
	1983–1987	86 (80–91)	39 (33–45)	43 (30–55)	20 (3–47)	243	36 (30–42)	531	55 (51–60)	54 (49–58)
	1988–1992	85 (80–89)	47 (42–52)	51 (37–64)	53 (28–74)	289	44 (38–50)	698	63 (59–67)	60 (56–64)
	1993–1997	90 (86–93)	65 (59–70)	58 (43–70)	43 (14–69)	314	53 (46–60)	824	74 (70–77)	–

–, no estimate available due to small number of cases and/or mostly early censoring.

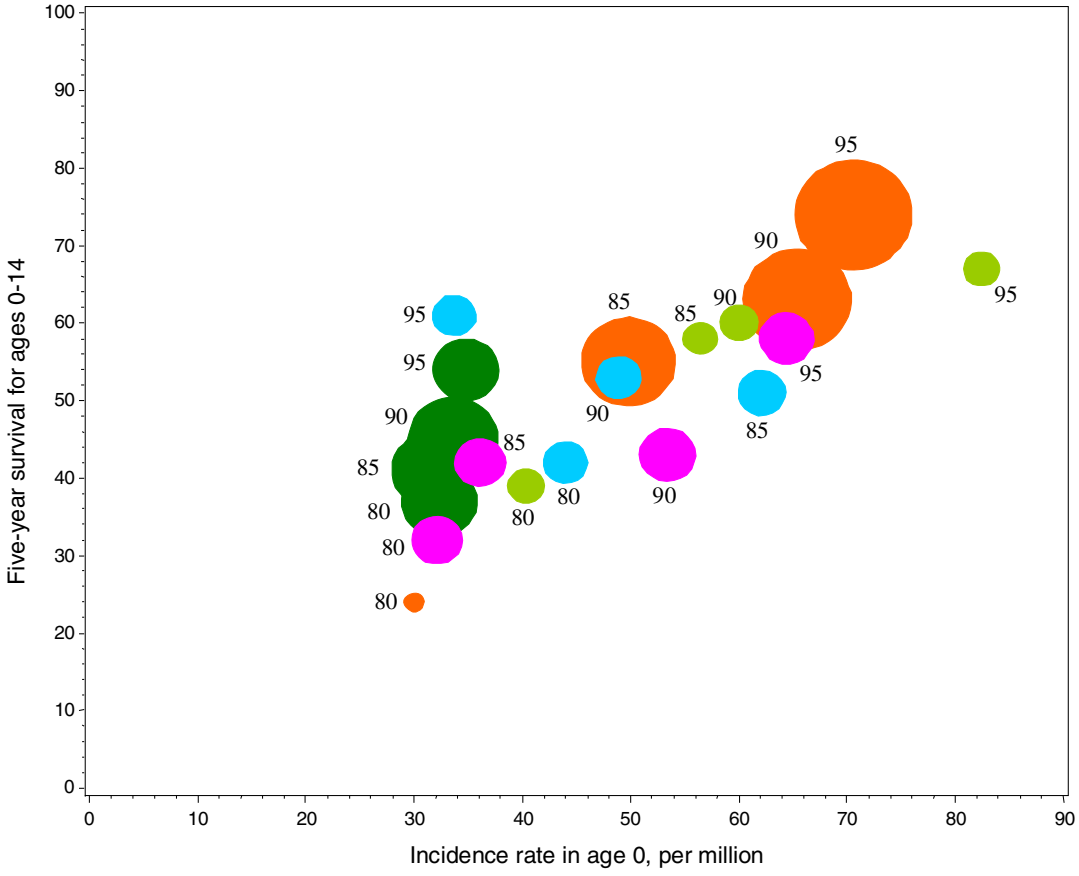

Fig. 2 – Comparison of 5-year survival of children diagnosed with neuroblastoma at age 0–14 years with age-specific incidence rate at age 0 per million person-years per regions and 5-year periods. Bubble sizes represent regions and are proportionate to absolute number of cases included in the survival analyses per region and 5-year period shown in Tables 4 and 6. The numbers are the mid-years of the corresponding 5-year period. British Isles, dark green; East, pink; North, blue; South, light green; West, orange. Source: ACCIS.

53%, $p < 0.001$). Data from the West for 1978–1982 is based on only 17 cases aged 2–14 years, but the increase is still very pronounced in the West when taking into account only data from 1983 onwards (36–53%). The most marked improvement in survival among older cases (age 2–14 years) occurred in the East, where survival was lowest in the first period (14%), but in the latest period it had reached 36%, very similar to the level observed in the British Isles (35%).

4. Discussion

We have confirmed that incidence of neuroblastoma in Europe is highest in infants and decreases thereafter with age. The variations in incidence rates between regions and over time were mostly conditioned by the pattern seen in infants, most of whom present with localised disease with good prognosis.[1,6–8,11] Unfortunately, data on stage were not collected within ACCIS to validate this assumption. Notwithstanding the lack of more detailed information on each cancer case, the data available through ACCIS allowed the assessment of regional differences and trends in incidence and survival on a large scale, including over 6000 cases. The quality of data measured by the 'most valid basis of diagnosis' was consistently good; in almost all regions and time periods well over 90% of all neuroblastoma cases were microscopically verified. Unknown and DCO cases were very rare, also in the registries with access to this source of data. Five-year follow-up was fairly complete, except for the last 5-year period outside the British Isles, due to the early closing date of follow-up (Table 2).

The age-standardised rate of around 11 cases per million children observed in this study lies within the upper end of the range reported previously in white populations (ASR of 7–12 per million).[19] In the USA, white children had an incidence of 11.5 per million compared with 8.5 among Blacks.[20] In some African countries neuroblastoma is registered extremely rarely.[21] The rates in the countries in the southern and eastern Asia, including India (between 3.0 and 3.7 for various registries) and China (3.0) are lower than those in Europe and North America, except in Japan (Osaka 14.0) and Hong Kong (7.3).[19,21] Part of these international variations might result from differences in access to medical care in general and specifically to diagnosis of this tumour. In our data, neuroblastoma represented 7% of all tumours, the lower end of the range of 6–10% seen in other reports for the populations of developed countries.[19,20]

While the ACCIS data give a very good overview of incidence and survival in Europe, background knowledge of the

neuroblastoma histogenesis is necessary to interpret the observed patterns correctly. The screening programmes and their results also contributed to the understanding of the patterns of neuroblastoma occurrence.[8,10–12]

Neuroblastoma screening was first introduced in Japan in the 1970s.[9] The earliest European studies for infants were conducted locally in the United Kingdom (UK) in the late 1980s and early 1990s in the Newcastle area and Birmingham. In the Rhone-Alps region in France another infant study was conducted in 1990–1996. An increase in incidence was observed in these studies.[9] The studies were too small for an evaluation of effect and were labelled as pilot or feasibility studies. In Germany, screening was offered to children aged 10–18 months in six states during 1995–2000, comprising about half of all children. Compliance was about 60–65%, with about 1.5 million participants.[11]

The large size of the studies in Germany[11] and North America[12] permitted an evaluation of the effectiveness of neuroblastoma screening. The considerable increase in incidence at the screening age was not followed by an expected drop in incidence of older cases. Thus, the increase in incidence did not arise from earlier detection of cases that would otherwise have been diagnosed later, but from additional cases, a situation known as overdiagnosis: the screening did not lead to a drop in the incidence of advanced stages or in mortality and the additional cases had localised disease.[11,12] From the observation of single cases of spontaneous regression and the screening feasibility studies, overdiagnosis was a phenomenon expected largely in the first year of life, but not at later ages.[10] Screening in Germany was thus studied at 12 months to determine whether this effect could be avoided. However, considerable overdiagnosis was also observed for these screen-detected cases diagnosed at between 18 to 24 months.[11] As these overdiagnosed cases, which are mostly assumed to undergo spontaneous regression if left untreated,[2] have very good prognosis (almost 100% survival), adding them to the case population increases the survival probability considerably, even in the absence of a decrease in mortality and a real improvement in therapy. Unfortunately it is not generally possible to decide on an individual basis which localised cases require treatment (at least surgery) to prevent progression, and which cases should be subjected to a 'wait and see' policy, waiting to see the tumour regress spontaneously.[2]

The effect of the screening programmes introduced in Europe can be seen only marginally in the ACCIS data, because most of them have been implemented either in small areas, parts of France and northern and central England, or towards the end of the presented study period. The screening in Germany starting in 1995 may explain the higher incidence at age 1 year in the West, and a correspondingly good survival, while the incidence of older cases is not lower in the West than elsewhere (Fig. 1).

We observed a high overall incidence, not only in the West where it may partially be ascribed to the screening programmes, but also in the South, where no screening was organised in the areas and periods covered. The chance of incidental diagnosis (i.e. a chance finding in an asymptomatic case) is especially high when diagnostic ultrasound is used frequently for various reasons, as has been the case at least since the 1990s in Germany ('West')[22] and Italy ('South').[23] Similar mechanisms were probably at work in the other countries included. Insurance policies may encourage the use of ultrasound, which would facilitate the detection of asymptomatic cases of neuroblastoma. Asymptomatic cases were detected especially in very young children, which is reflected in our study: the difference in total incidence of neuroblastoma across regions is mainly the result of variations in incidence in children under 2 years of age, while the incidence at older ages is almost identical all over Europe. There is no reduced incidence in older ages in regions with high infant incidence, neither do we observe a drop in incidence over time in older cases corresponding to the significant increase in infants (Fig. 1, Tables 3 and 4). Without screening, we can therefore assume that a number of relatively benign cases with a tendency to spontaneous regression go undetected. More of them remain undiscovered in children with limited access to paediatricians, while the chance of detection is higher for infants regularly seen by a paediatrician. Screening programmes may therefore also have contributed indirectly to the increased incidence, as a consequence of increased frequency of general medical examinations in early childhood, and an increase in the use of imaging techniques such as ultrasound even for mild and unspecific complaints.

Other patterns seen in the presented data may also be reflections of differences in coding or diagnostic practices, to some extent. With advances in molecular pathology, poorly differentiated neuroblastoma could be distinguished more reliably from other small round cell tumours, such as rhabdomyosarcoma and Ewing's sarcoma.[24] The improvement in classification of peripheral primitive neuroectodermal tumours (pPNET), formerly possibly grouped with neuroblastoma, has been shown in Britain for the age group 10–14 years.[25]

Beside incidence rates, population-based survival was certainly also influenced by provision of care. This may be deduced from the comparison of the 5-year survival of children aged 2–14 years, which is the best indicator for therapy-related survival, since the majority of these cases are diagnosed with metastases.[1,2,5,6] Indeed, we observed somewhat larger inter-regional differences in survival in the age group 2–14 years than in the infants (age 0), while the rank by region was the same for infants and older children. To enable more precise investigations, information on stage at diagnosis and data on neuroblastoma mortality, presently not available, would add value to the ACCIS database in the future.

Over the 20 years described here, a considerable increase in survival was observed in all regions. However, the British Isles and the East stayed consistently below the European average. This result is particularly remarkable in the British Isles, contributing data of high quality and complete follow-up. Similar results were shown for the years 1987–1991, where lower total incidence and localised stage-specific incidence were observed in Britain than in Germany, France, and Austria. This corresponded to higher overall mortality and a higher incidence of older cases with disseminated disease in Britain.[7]

As discussed above, a large proportion of cases with good prognosis in a cohort would lead to improvement in overall

survival. In our data we see a strong positive correlation between infant incidence and overall survival (Fig. 2), which supports the overdiagnosis argument. Similar conclusions were derived in the EUROCARE study.[26]

Survival has also increased in older children, comprising a large proportion of cases diagnosed with advanced stage.[1,6,7] However, the incidence of neuroblastoma beyond the age of 2 years did not increase. Therapeutic success thus has also contributed to the improvement in survival of children with neuroblastoma. The essential element of the therapy protocols in Germany, the UK, or Italy, which led to the survival increases in the last decade, are intense risk-adapted treatment options for high-risk patient groups with very poor prognosis; a large fraction of older cases.[1,2,5,6] Increases in survival reported from therapy study groups in Europe support this.[27–30]

We conclude that the improvements in survival over time as well as the regional differences in survival are due partly to the differences in the incidence of infant cases with very good prognosis and partly to differences in therapy. Despite improved survival, neuroblastoma remains a challenge for paediatric oncologists. Cases with high stage neuroblastoma often suffer from a range of long-term sequelae related to aggressive treatment often given for this cancer diagnosed very early in life.[31]

Conflict of interest statement

None declared.

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