PERGAMON

European Journal of Cancer 37 (2001) 711–721

European Journal of Cancer

www.ejconline.com

Variation in survival of children with central nervous system (CNS) malignancies diagnosed in Europe between 1978 and 1992: the EUROCARE study

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Received 27 September 2000; accepted 22 December 2000

Abstract

EUROCARE is a population-based survival study including data from European Cancer Registries. The present paper analyses survival after a malignant neoplasm of the central nervous system (CNS) in childhood (aged 0–14 years at diagnosis). The database includes 6130 cases from 34 population-based registries in 17 countries: 1558 were primitive neuroectodermal tumours (PNET) and 4087 astrocytoma, ependymoma or other gliomas: these morphologies were grouped in the analyses in order to reduce the diagnostic variability among the registries. 87% of cases were microscopically diagnosed (range among registries 71–100%) and losses to follow-up were limited to 2% (range 0–14%). Actuarial analyses indicate that the European (weighted) average of 5 years cumulative survival for cases diagnosed in 1978–1989 was 53% (95% confidence interval (CI) 49–57) for CNS neoplasms, 44% (95% CI 37–50) for PNET and 60% (95% CI 55–65) for the glioma-related types. Analysis of the sub-set of cases diagnosed in 1985–1989 revealed better results: cumulative survival at 5 years was 61% (95% CI: 55–65) for all CNS neoplasms; 48% (95% CI 41–56) for PNET and 68% (95% CI 62–73) for glioma-related types. Compared with older children, infants showed poorer prognosis: in 1978–1989 the 5-year survival rate was 33% (95% CI 23–45) and in 1985–1989 it was 46% (95% CI 34–59). Variability among countries was very large, with 5-year survival for CNS tumours diagnosed in 1985–1989 ranging from 28% in Estonia (95% CI 17–43) to 73% Sweden (95% CI 59–83) and 75% in Iceland (95% CI 35–95) and 73% in Finland (95% CI 66–79). Time trends were studied in a multivariate analysis observing a reduction in the risk of death in periods of diagnosis 1982–1985 (hazard ratio (HR) = 0.85; 95% CI 0.78–0.93) and 1986–1989 (HR = 0.70; 95% CI 0.64–0.77) compared with 1978–1981. The analysis were extended to 1990–1992 for the countries whose registries provided data for that period did not indicate any further progress. Results of this study confirm the large variability in European countries and indicate a positive trend in the survival probability for cases diagnosed in the 1980s.

Keywords: CNS neoplasm; Children; Survival; Europe; Population-based cancer registries

1. Introduction

In developed countries, primary tumours of the central nervous system (CNS) represent the second most frequent neoplasm and the leading cause of cancer-related deaths in childhood. They account for approximately one fifth of incident malignancies and one fourth of cancer deaths in children [1–3]. This group of tumours, however, cannot be considered as a single entity as it is composed of different diagnostic categories, the largest being astrocytoma, ependymoma, primitive neuroectodermal tumours (PNET, including medulloblastoma) and other gliomas [2]. Intracranial tumours account for about 90% of all CNS tumours in children [4]. The anatomical location often precludes the collection of biopsies and therefore in all countries the

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0959-8049/01/$ - see front matter
PII: S0959-8049(01)00046-6

proportion of cases without histological confirmation of diagnosis is larger than for the other childhood neoplasms [2]. Given the limits in diagnosis, the majority of childhood cancer registries accepts also intracranial neoplasms of unknown and benign morphology [5].

The reported incidence rates of childhood CNS tumours in European countries range from 16 per million (Bulgaria) to 41 per million (Sweden, also the highest in the world) [2]. Worldwide variation in incidence is even much larger: the rates lower than 15 per million children-years were reported or estimated by the registries in South America, India, China and Africa [2]. In general, an increasing trend in incidence of CNS tumours among children was seen during last decades, with variable extent and timing among countries [3,6,7]. The trend is often interpreted as the result of diagnostic changes, which are likely to explain also part of the geographical variation as are differences in reporting practices, completeness of ascertainment and classification.

Reliable population-based data on survival of children with CNS neoplasm are available only for few countries or regions, where a large enough population is covered by cancer registration and survival studies [4,8–15]. In general, children with CNS cancer do not share the favourable prognosis of other common childhood cancers, however, during the past 20–30 years some improvement in survival rates has been observed. The prognosis is mainly related to histology, behaviour, size and location of the tumour and to the age of children: the poorest outcome is observed for very young children, especially in PNET and ependymomas [16]. Recent experimental and clinical studies have identified also several molecular genetic markers related to poor outcome in children with CNS cancers [17].

The EUROCARE centralised database — which for children includes data from 34 population-based cancer registries (four specialised childhood cancer registries) from 17 countries [18,19] — now provides an opportunity to study the survival after CNS neoplasm as a whole and, with due allowance of comparability among registries, also for the major morphological types. In the present paper, we aim to describe the survival pattern of children with CNS neoplasm diagnosed in Europe in 1978–1989 (with a focus on the period of 1985–1989, corresponding to the EUROCARE II recruitment), and explore the time trends in survival until 1992. In the framework of the EUROCARE I, the survival of children affected by CNS neoplasm was analysed without consideration of histology-defined categories [20].

2. Patients and methods

2.1. Patients

CNS neoplasms include several morphology categories, grouped according to the International Classification of Childhood Cancer (ICCC) [5] which was adapted for the present study to the ICD-O-I and ICD-IX classifications which are used in most cancer registries and in the EUROCARE protocol.

This study is based on 6130 cases of CNS malignant neoplasms diagnosed in 1978–1989 in children aged 0–14 years and accepted in the EUROCARE database after the quality checks; 2949 cases incident in 1985–1989 were recruited for the EUROCARE II study, while the others had been recruited for EUROCARE I (1978–1984). A further 1769 cases were diagnosed in 1990–1992, but are used only in limited analyses because not all cancer registries contributed data after 1989. The list of registries is presented elsewhere [19].

According to the rules set for the inclusion of cases in the EUROCARE database, cases coded with behaviour code of 0 (benign) were excluded, while cases with code 1 (uncertain behaviour, 3% overall) were included.

CNS neoplasms accounted for 17% of all childhood cancer cases in the EUROCARE database. Thirty-four registries (including four specialised childhood cancer registries: England and Wales, Scotland, Germany and Piedmont Region in Italy) in 17 European countries contributed to the data set, which is one of the largest on childhood cancer survival. The nationwide childhood cancer registries of England and Wales (including data also from the Regional Cancer Registries) and Germany (limited to West Germany in the present study) provided the largest numbers of cases (2615 and 1313, respectively). Case collections over 100 cases were also contributed by Denmark, Finland, Italy, Scotland, Slovakia and Sweden. Cases for which the cause of death is the only available information (DCO) and cases diagnosed at autopsy are not included in the analyses nor in the above mentioned figures. Details on the EUROCARE database and information on the cancer registries are presented in a separate paper [19].

Distribution by descriptive and demographic variables is presented in Table 1 and reflects what is commonly observed in descriptive epidemiology studies on this neoplasm [2]: 55% of the cases of CNS neoplasm were boys (range in registries with at least 30 cases from 41 to 64%); 71% of cases were diagnosed during the first 10 years of age (6% diagnosed in the first year of life). The proportion of cases with microscopic confirmation was 87%, with the lowest figures in Poland (77%) and Estonia (71%): these figures are within the range commonly observed for these neoplasms and reflect the relative difficulty in obtaining biopsy samples. The distribution of cases by ICCC category (Table 2) was relatively homogeneous among countries, except for the Swedish and Finnish registries whose data are not coded using the ICD-O morphological codes and could not be recoded with enough detail. The variation appeared greater across categories related to glioma (i.e. ICCC codes IIIa, IIIb and IIId) which were grouped

Table 1
Distribution of childhood cases of CNS malignant neoplasm diagnosed in 1978–1989 in the EUROCARE database, by country and according to period of diagnosis, selected demographic variables and indicators of the quality of data

Country	No. of cases	Period of diagnosis		Boys	Age at diagnosis (years)				Microscopically confirmed	Lost to follow-up	Unspecified behaviour
		1978–1984	1985–1989		0	1–4	5–9	10–14			
	n (%)	*n* (%)	*n* (%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Northern Europe											
Denmark	365 (6)	208 (7)	157 (5)	51	6	26	36	32	87	0	11
Finland	377 (6)	198 (6)	179 (6)	53	6	33	34	27	96	0	0
Iceland	19 (0.3)	10 (0.3)	9 (0.3)	42	5	26	42	26	95	0	5
Sweden[a]	104 (2)	58 (2)	46 (2)	53	4	26	34	37	96	0	0
UK											
England and Wales	2615 (43)	1551 (49)	1064 (36)	56	6	31	34	30	81	1	4
Scotland	307 (5)	188 (6)	119 (4)	49	6	30	34	30	87	0	3
Western and Central Europe											
Austria[a]	3 (0.05)	0 (0)	3 (0.1)	0	0	0	67	33	100	0	0
France[a]	70 (1)	39 (1)	31 (1)	64	7	27	44	21	79	0	0
Germany	1313 (21)	485 (15)	828 (28)	59	6	35	33	26	98	7	0
Switzerland[a]	14 (0.2)	5 (0.2)	9 (0.3)	50	14	7	36	43	100	14	0
The Netherlands[a]	42 (0.7)	28 (0.9)	14 (0.5)	60	5	12	36	48	81	0	0
Southern Europe											
Italy[a]	330 (5)	172 (5)	158 (5)	53	4	26	39	31	84	1	2
Spain[a]	56 (0.9)	0 (0)	56 (2)	64	4	23	38	36	89	0	2
Eastern Europe											
Estonia	79 (1)	40 (1)	39 (1)	41	4	22	42	33	71	3	0
Poland[a]	35 (0.6)	16 (0.5)	19 (0.6)	49	6	40	23	31	77	3	9
Slovakia	366 (6)	183 (6)	183 (6)	58	5	30	38	28	88	0	1
Slovenia	35 (0.6)	0 (0)	35 (1)	60	0	29	40	31	94	0	0
Total											
n	6130	3181	2949	3396	368	1882	2115	1765	5323	128	166
%	100	52	48	55	6	31	35	29	87	2	3

[a] Countries with coverage lower than 20% of the childhood population.

together for survival analyses. The proportion of cases with unspecified histology wasis in the range 0.3% (Germany) to 29% (Estonia) among countries with at least 10 cases. The ICCC code IIIc (PNET) includes medulloblastoma.

The follow-up was conducted by each registry according to usual procedures, described elsewhere [19,21]. Proportion of cases lost to follow-up was 2%, and most registries had no such cases (Table 1). The higher figures were reported from the German and Swiss registries.

613 cases were located in the hemispheres (ICD-O 191.1–191.4): from those, 13% were ependymomas, 56% astrocytomas, 24% gliomas, and 2% PNET (the remainder were cases with unspecified histology). Among the 2534 cases with neoplasm in undertentorial locations (ICD-O 191.6–191.7), 37% were PNET, 7% ependymomas, 40% astrocytomas and 13% gliomas (as above, the remaining cases had unspecified histology).

2949 cases were diagnosed in 1985–1989, the period of recruitment for the EUROCARE II study: 761 were PNET and 1979 were grouped in the ependymoma, astrocytoma and glioma category; 35 were in the 'other specified' and 173 in the 'unspecified' categories.

2.2. Statistical methods

Cumulative survival was calculated by the actuarial method using the program by Hakulinen [22] and is reported in percentages. Relative survival was not presented as it closely corresponds to the observed data, given the low expected mortality in the relevant age classes. As survival is usually dependent on age, and the age distribution of children may be different among countries, the age-adjusted survival rates were calculated, using the age distribution of cases of the overall study as the standard (three classes: 0–4, 5–9 and 10–14 years). Average (European) survival was calculated as both pooled and weighted average of the age-standardised survival rates of the individual countries; weights were proportional to the childhood population in each country. We assumed that the survival of patients included in the study in countries where cancer registration is not nationwide is representative of the survival at the national level. Actuarial survival in each country was compared with the European average by computing the relative death rate and the corresponding 95% confidence interval (95% CI) [23]. Periods used for actuarial analyses were 1978–1989 and 1985–1989.

Table 2
Distribution of childhood cases of CNS malignant neoplasm diagnosed in 1978–1989 in the EUROCARE database, by country and ICCC diagnostic category

Country	ICCC diagnostic group					
	IIIa — ependymoma (%)	IIIb — astrocytoma (%)	IIIc — PNET (%)	IIId – glioma other and nos (%)	IIIe — other specified (%)	IIIf — unspecified (%)
Northern Europe						
Denmark	10	44	17	7	2	20
Finland	13	0	13	65	0	9
Iceland	0	63	16	11	5	5
Sweden[a]	5	69	22	0	0	5
UK						
England and Wales	11	45	22	17	1	5
Scotland	7	47	27	14	1	4
Western and Central Europe						
Austria[a]	0	0	33	33	0	33
France[a]	11	39	29	9	0	13
Germany	14	39	41	5	2	0.3
Switzerland[a]	7	29	29	29	0	7
The Netherlands[a]	2	60	12	5	2	19
Southern Europe						
Italy[a]	12	49	19	8	1	12
Spain[a]	11	41	27	5	0	16
Eastern Europe						
Estonia	9	42	18	3	0	29
Poland[a]	9	29	29	3	3	29
Slovakia	10	45	26	6	1	13
Slovenia	17	43	26	6	6	3
Total						
No. of cases	673	2524	1558	890	668	416
%	11	41	25	15	1	7

ICCC, International Classification of Childhood Cancer; nos, not otherwise specified; PNET, primitive neuroectodermal tumours; CNS, central nervous system.

[a] Countries with coverage lower than 20% of the childhood population.

Cox proportional hazard models [24] were used to compare hazard ratios (HR) among different periods of diagnosis or countries taking into account the different distribution of covariates. The total calendar period was divided into three sub-periods (1978–1981, 1982–1985, 1986–1989); age at diagnosis was divided in three 5-year groups (0–4, 5–9, 10–14 years). Testing for the proportionality assumption was conducted inspecting survival curves for each variable separately. Multivariate analyses by country were conducted including only the countries with more than 10 cases reported between 1986 and 1989; analyses of time trend included only countries with 30 cases or more between 1978 and 1989 (after the exclusion of the registries that did not provide data in all three sub-periods). Analyses for the period 1990–1992 were conducted separately: these analyses provide less stable results because the follow-up is shorter (average 4.4 years, 23% of cases with follow-up shorter than 3 years and 58% shorter than 5 years) and the number of cases is smaller [19].

All analyses were conducted separately for three diagnostic categories: all CNS malignant neoplasms, PNET and glioma-related neoplasms (astrocytoma, ependymoma, other gliomas).

3. Results

Univariate survival at 1 and 5 years for cases diagnosed in the period 1985–1989 is presented in Table 3 for the entire category of CNS malignant neoplasms and for its two major subgroups. There was little variation between genders. A more favourable prognosis was suggested for older children, but the difference was not statistically significant; children with neoplasms diagnosed in their first year of life showed the worst prognosis: for CNS neoplasms in 1978–1989 their 5-year survival rate was 33% (95% CI 23–45) and in 1985–1989 it was 46% (95% CI 34–59). Data for 1978–1989 are not shown in the table.

Among diagnostic subgroups, PNET always showed the poorer prognosis with the exception of Italy. Data for the entire period 1978–1989 are not reported systematically because of space limitations. Analyses

Table 3
The 1- and 5-year age-standardised cumulative survival rates (CS) and corresponding 95% confidence intervals for children with of CNS malignant neoplasm diagnosed in 1985–1989 in the EUROCARE database, according to country, gender, age group and diagnostic category[a,b,c]

	III — CNS		IIIc — PNET		IIIa, IIIb, IIId — glioma-related	
	1 year	5 years	1 year	5 years	1 year	5 years
	CS (95% CI)	CS (95% CI)	CS (95% CI)	CS (95% CI)	CS (95% CI)	CS (95% CI)
Northern Europe						
Denmark	80 (73–86)	67 (59–74)	58 (42–73)	40 (25–57)	85 (76–91)	72 (63–80)
Finland	86 (81–91)	73 (66–79)	78 (53–91)	52 (33–71)	90 (84–94)	79 (72–85)
Iceland	88 (26–99)	75 (35–95)	–[e]	–	81 (28–98)	81 (28–98)
Sweden[d]	87 (74–94)	73 (59–83)	77 (38–95)	57 (30–81)	93 (61–99)	78 (60–89)
UK						
England and Wales	75 (72–78)	57 (54–60)	74 (68–80)	41 (35–48)	75 (72–78)	60 (57–64)
Scotland	71 (62–78)	57 (48–66)	79 (64–89)	54 (39–69)	69 (58–78)	58 (46–68)
Western and Central Europe						
France[d]	85 (61–96)	40 (21–62)	81 (31–98)	10 (2–41)	89 (52–98)	–
Germany	82 (79–84)	60 (56–63)	82 (77–86)	52 (47–58)	81 (77–85)	66 (61–70)
Switzerland[d]	73 (32–94)	56 (27–81)	–	–	56 (20–86)	–
Southern Europe						
Italy[d]	83 (76–88)	68 (60–74)	94 (21–100)	88 (43–99)	87 (79–92)	73 (65–81)
Eastern Europe						
Estonia	58 (41–73)	28 (17–43)	41 (21–65)	21 (6–53)	64 (43–81)	38 (21–58)
Poland[d]	77 (50–92)	64 (40–83)	–	–	94 (5–100)	77 (34–95)
Slovakia	71 (64–77)	50 (43–57)	72(59–83)	33 (22–46)	78 (69–85)	64 (55–73)
Europe (weighted average)	82 (76–86)	61 (55–65)	78 (69–85)	48 (41–56)	85 (78–90)	68 (62–73)
Gender						
Boys (age-adjusted)	83 (75–89)	60 (53–67)	82 (71–90)	46 (38–55)	84 (75–90)	67 (59–74)
Girls (age-adjusted)	81 (72–87)	61 (54–68)	73 (59–84)	51 (39–62)	86 (75–93)	69 (59–77)
Age at diagnosis (age-specific) (years)						
0	63 (47–77)	46 (34–59)	46 (30–63)	34 (19–53)	66 (49–79)	46 (34–59)
1–4	79 (69–86)	55 (47–63)	65 (49–78)	35 (24–49)	86 (70–95)	64 (55–72)
0–4	78 (70–85)	56 (48–64)	63 (48–77)	35 (24–48)	84 (73–91)	66 (56–75)
5–9	82 (73–89)	60 (52–67)	88 (72–96)	63 (50–74)	82 (72–90)	62 (54–70)
10–14	87 (73–95)	68 (56–77)	84 (68–93)	46 (33–59)	89 (70–96)	76 (62–87)

PNET, primitive neuroectodermal tumours; CNS, central nervous system.
[a] Results are rounded at the nearest unit.
[b] The table shows data only for the countries with enough cases for age standardisation.
[c] All countries are included in the European estimates.
[d] Countries with coverage lower than 20% of the childhood population.
[e] Not enough cases for age standardisation.

including the entire period 1978–1989 consistently showed poorer results than the presented analyses relative to the period 1985–1989. For CNS neoplasms, the weighted European estimate of the cumulative survival at 5 years from the diagnosis was 53% (95% CI 49–57) for cases in the entire period 1978–1989 and 61% (95% CI 55–65) for cases incident in 1985–1989. Corresponding figures for PNET were 44% (95% CI 37–50) in 1978–1989 and 48% (95% CI 41–56) in 1985–1989, while for the glioma-related types the figures were 60% (95% CI 55–65) and 68% (95% CI 62–73).

The range in the 5-year survival rates between countries was wide: for the entire period 1978–1989 from 26% (95% CI 18–36) in Estonia to 73% (95% CI 64–81) in Sweden, and for 1985–1989 from 28% (95% CI 17–43) in Estonia to 75% (95% CI 35–95) in Iceland. Country differences were further explored using multivariate analyses (see later).

Other morphological categories were considered only in analyses at the European level and for the period 1985–1989: 5-year actuarial survival (age-adjusted and weighted) was 75% (95% CI 67–81) for astrocytoma and 55% (95% CI 44–65) for ependymoma.

Table 4 shows the Relative Death Rates with respect to the European average for the period of 1985–1989. For CNS neoplasms, the range of variation in countries with at least 10 cases was between 0.63 (Sweden 95% CI 0.28–0.98 and Finland 95% CI 0.43–0.83) and 2.53 (Estonia 95% CI 1.51–3.55).

Table 5 presents results of the multivariate analyses of age, gender and period of diagnosis, adjusted for country. We observed in more recent periods (compared with

Table 4
Relative death rate and corresponding standard errors of the mean (SEM) computed at 5 years since diagnosis for children with CNS malignant neoplasms diagnosed in 1985–1989 (EUROCARE)[a]

	III — CNS		IIIc — PNET		IIIa, IIIb, IIId — glioma-related	
	Relative death rate	SEM	Relative death rate	SEM	Relative death rate	SEM
Northern Europe						
Denmark	0.80	0.13	1.27	0.32	0.84	0.18
Finland	0.63	0.10	0.90	0.28	0.60	0.13
Iceland	0.57	0.50	–[c]	–	0.53	0.80
Sweden[b]	0.63	0.18	0.76	0.35	0.64	0.26
UK						
England and Wales	1.12	0.11	1.22	0.17	1.30	0.16
Scotland	1.12	0.18	0.85	0.22	1.41	0.30
Western and Central Europe						
France[b]	1.85	0.57	3.23	1.16	–	–
Germany	1.03	0.10	0.89	0.12	1.08	0.15
Switzerland[b]	1.16	0.55	–	–	–	–
Southern Europe						
Italy[b]	0.78	0.13	0.18	0.29	0.79	0.17
Eastern Europe						
Estonia	2.53	0.52	2.17	0.80	2.49	0.48
Poland[b]	0.88	0.38	–	–	0.69	0.66
Slovakia	1.38	0.18	1.54	0.31	1.13	0.22

[a] Reference category: the European average The table shows only the countries with enough cases for age standardisation.
[b] Countries with coverage lower than 20% of the childhood population.
[c] Not enough cases for age standardisation.

Table 5
Results of multivariate analysis of survival of children with CNS malignant tumours by period of diagnosis, age at diagnosis and gender, adjusted by country[a,b].

	III — CNS HR (95% CI)	IIIc — PNET HR (95% CI)	IIIa, IIIb, IIId — glioma related HR (95% CI)
Boys	1	1	1
Girls	0.99 (0.91–1.05)	0.94 (0.82–1.08)	1.02 (0.93–1.13)
Age			
0–4 years	1	1	1
5–9 years	0.79 (0.73–0.86)	0.68 (0.58–0.78)	0.84 (0.75–0.93)
10–14 years	0.69 (0.63–0.76)	0.64 (0.54–0.76)	0.74 (0.66–0.83)
Period			
1978–1981	1	1	1
1982–1985	0.85 (0.78–0.93)	0.82 (0.70–0.98)	0.87 (0.77–0.99)
1986–1989	0.70 (0.64–0.77)	0.71 (0.60–0.84)	0.69 9 (0.620–0.78)
No. of cases and countries in the analysis	$n = 5940$, 12 countries	$n = 1454$, 7 countries	$n = 3930$, 10 countries
	III — CNS HR (95% CI)	IIIc — PNET HR (95% CI)	IIIa, IIIb, IIId — glioma related HR (95% CI)
Period			
1978–1981	1	1	1
1982–1985	0.85 (0.77–0.93)	0.85 (0.72–1.00)	0.87 (0.78–0.98)
1986–1989	0.70 (0.64–0.77)	0.74 (0.63–0.88)	0.71 (0.63–0.80)
1990–1992	0.69 (0.62–0.77)	0.73 (0.61–0.88)	0.72 (0.63–0.83)
No. of cases and countries in the trend analysis	$n = 7293$, 12 countries	$n = 1844$, 6 countries	$n = 4742$, 9 countries

HR, hazard ratio; 95% CI, 95% confidence interval.
[a] Reference categories are: period 1978–1981, boys and age 0–4 years.
[b] The table presents both the analyses of trend for period 1978–1989 and for period 1990–1992 (EUROCARE). See text for details and Appendix for the list of countries included in each analysis.

1978–1981) a statistically significant reduction of the HR for all malignancy types. Results of analyses using period as a continuous variable were very close to those presented here (data not shown). Analysis by age and gender confirmed the results of actuarial analyses as prognosis was similar in the two genders and more favourable for older children. The Appendix lists the countries included in the different analyses; the others are excluded either because the period of registration did not include all three periods or because the number of cases was too low.

Exploratory analyses were conducted for the cases diagnosed during the period 1990–1992, using a multivariate model including also age, gender and country of diagnosis (Table 5). Cases diagnosed in the period 1990–1992 did not show any further advantage in survival compared with cases diagnosed before.

Additional multivariate analyses were conducted to explore intercountry difference in addition to the computation of the Relative Death Rate, using England and Wales as a reference and with adjustment for age and gender. These analyses were conducted separately on cases diagnosed in the most recent quadriennial period of diagnosis (1986–1989) and on cases diagnosed in 1990–1992. Both periods showed large variation among countries: for 1986–1989, analyses included 2382 cases of CNS neoplasms and observed a statistically significant higher risk of death for Estonia (HR = 2.00; 95% CI 1.29–3.10) and lower for Finland (HR 0.52; 95% CI 0.38–0.72) and Italy (HR 0.68; 95% CI 0.49–0.93). Analyses by specific categories of CNS data showed the same pattern, although based on smaller numbers and therefore presenting a greater variability. The analysis of inter country variation in period 1990–1992 showed smaller variation, but the ranking appeared similar with better prognosis for cases from the Nordic countries and poorer results for cases from Eastern Europe (data not shown).

4. Discussion

The reported incidence of primary malignant CNS tumours among children varies greatly in Europe. Incidence rates are systematically elevated in Sweden and other Nordic countries and in some territories of France and Italy; lower rates are reported for Germany, UK and, particularly, for the countries of Eastern Europe. Relative incidence also varies, for instance the percentage of total childhood neoplasms represented by non-PNET neoplasms of the brain ranges from 13% (Germany) to 23% (Finland) [2]. A part of this variation is explained by differences in definitions and registration practices. Since surgery or biopsy is not always feasible, a proportion of CNS tumours are not examined histologically, and decision about their malignant/non-malignant nature or even about diagnosis can be based only on radiological and clinical features. As a consequence, differences in the inclusion of non-malignant tumours can explain differences in incidence among countries as the exclusion of non-malignant neoplasms can seriously underestimate the true burden of CNS tumours [16]. In contrast, low incidence can be also related to incompleteness of case ascertainment or referral from the institutions where children with CNS are diagnosed and treated [25,26]. The effect on measured survival is not always predictable, since the pathological distinction between malignant and non-malignant tumours of the CNS is not always consistent with clinical behaviour and prognosis [4].

In the EUROCARE study on childhood cancer survival, the routinely collected data from the population-based cancer registries have been used. Among the participating countries, the incidence of CNS tumours ranged from 41 per million children-years in Sweden to 20 in Slovenia [2]. Comparability of data among the registries is increased since only malignant tumours and tumours with uncertain or unspecified behaviour were included in the survival analyses in order to reduce the variability in registration criteria and to take into account that general cancer registries often do not include benign tumours. Although differences remain among registries, their extent and causes were investigated and considered whenever possible in the analyses. The results are therefore based on data more homogeneous than usual when comparing published results from independent studies.

The age-standardised 1- and 5-year survival rates varied largely across Europe. In general, the survival rates ranked in the same order as the reported incidence rates, being the highest for Sweden, Finland and Iceland and the lowest for Estonia. The 5-year survival rate for children with all CNS malignancies diagnosed in 1985–1989 was over 60% in Northern Europe, Italy and Poland; rates of 50–60% were observed for the UK, Germany, Switzerland and Slovakia, and rates under 50% were observed for France and Estonia. The difference between the highest and lowest rates was about 3-fold. This pattern is even more extreme than that revealed in the EUROCARE II study on survival of adult patients with malignant brain tumours [27]. The overall survival in children was, however, significantly better than that for adults.

High survival rates in childhood CNS tumours for Nordic countries and low rates for the Eastern European countries have been reported elsewhere [12,15,28]. The multivariate analyses of survival also indicated a significantly elevated risk of death for Estonia and a decreased risk for Finland. A detailed investigation is out of the scope of this paper; however, a discussion of the differences between these two countries can be useful for interpreting differences in Europe. As for other

childhood cancers, there has obviously been a considerable lag in access and quality of care in Estonia compared with Finland: delayed introduction of modern imaging procedures and delayed adherence to effective treatment protocols were likely to contribute to the poor outcome for children with CNS tumours [29]. The first computed tomography (CT) scanner was installed in Helsinki in 1978, and thereafter the number of scanners increased rapidly; the magnetic resonance imager (MRI) became available since the early 1980s and became routine from 1985 [30]. In Estonia, the first CT scanner was only installed in 1983 and MRI scanner in 1992 [29]. It has been assumed that the high incidence has stimulated the good organisation of care in Nordic countries, especially through centralisation of treatment and dissemination of effective protocols [27]. Part of the survival advantage could be attributable to anticipation of diagnosis rather than to more effective treatments, but the present study cannot address this issue.

The heterogeneity among the participating countries in the distribution of cases by histotype, partly attributable also to the heterogeneity in classification, precluded the use of ICCC diagnostic groups in detail. For PNET, the ranking was similar to that for the entire CNS category, although some county-specific rates should be interpreted with caution due to the large random variation.

The basic prognostic factors revealed by this study were similar to those reported by other population-based studies [4] and hospital-based studies [31]. Among the ICCC diagnostic groups, PNET showed the poorest outcome. Gender was not a prognostic factor whereas age was: children under 5 years showed higher HRs and infants always showed the poorest prognosis (infants were considered separately only in the actuarial analyses). A similar age-related pattern of survival was seen for separate diagnostic categories. Small children have a high proportion of malignancies in the cerebellum and brain stem, and their prognosis remains poor despite advances in treatment.

During the last two to three decades, improvements in the treatment strategies for CNS tumours developed slowly. One of the causes of the relative lack of progress compared with Acute Lymphoblastic Leukaemia or Wilms' tumour has been the poor understanding of the biology of these group of tumours. Treatment of childhood CNS tumours, as in adults, consists of surgery, radiotherapy and chemotherapy. The standard primary treatment is surgical resection, and the extent of resection is shown to be a strong independent prognostic factor in clinical series [32]. Chemotherapy in young children may be a valid alternative to radiotherapy and also result in reduced late effects. Applying other therapies — such as radiotherapy and chemotherapy — mainly depends on the tumour's histotype and location. The modern treatment protocols for childhood CNS tumours are complex and intensive, therefore the organisation of care plays a important role in explaining differences in outcome [33]. It has been suggested that the centralisation of management with various aspects of specialisation (caseload, interdisciplinary teams, etc.) can significantly improve the outcome in childhood cancers [34]. Clinical studies have indicated also that the training of a neurosurgeon in paediatric versus adult neurosurgery influenced the extent of resection and patients' survival [35]. Referral rates of CNS tumours to paediatric oncology centres and the proportion of cases included in clinical trials have been lower than for other childhood malignancies [36–38].

PNET are characterised by survival rates in clinical series up to 80% at 5 years from diagnosis [39]. These results are much better than from population-based studies, but are likely also to indicate a high selection of patients. A variety of clinical aspects have been used to allocate patients into risk groups and to tailor treatment strategies. Overall survival seems to have improved for PNET, however, patients in high-risk groups (disseminated or incompletely resected tumour at diagnosis) and children under 3 years of age still fare poorly.

Gliomas comprise a variety of CNS tumours with different anatomical sites and biological behaviour. Better survival is noted in children with ependymoma who have undergone complete resection; the relative effectiveness of radiotherapy over chemotherapy is difficult to prove due to the low incidence of this tumour. The treatment of choice for low-grade astrocytoma is surgery; radiation therapy has been standard therapy for partial resected or progressive tumours and adjuvant chemotherapy could be a second choice when surgery is grossly partial. In addition, severe late effects related to radiotherapy have increased interest in chemotherapy. There has been essentially no progress made in the treatment of children with brain stem gliomas: radiotherapy is still the mainstay of treatment since these gliomas are very resistant to chemotherapy and the role of the surgery is limited by the tumour site [40].

The EUROCARE database did not include information on methods of treatment. In our study, the high proportion of cases without microscopic verification (23–29%), indirectly referring to the proportion of non-resected cases, was found for Estonia and Poland — the countries showing low overall survival rates. Conversely, the countries with the small proportion (2–5%) of these cases corresponded with those with high survival rates, for example, most of the Nordic countries.

In general, during a comparable time period, there was a good accordance between survival rates observed by this study and those reported for the other parts of the world (Table 6). The rates were slightly higher in the USA than in Europe, but differences were limited and more pronounced for PNET. Part of the differences could be explained by the fact that the SEER analyses

Table 6
Comparison of the 5-year survival rates for children with CNS malignant tumours diagnosed in Europe and selected countries and territories of the world

Project or region/country	Period	Five-year survival rate (%)					
		All CNS, by age group			Diagnostic group[a]		
		0–4 years	5–9 years	10–14 years	Ependymoma	Astrocytoma	PNET
EUROCARE/Europe[b]	1985–1989	56	60	68	55	75	48
SEER/USA [4]	1985–1994	56	64	70	56	74	55
Canada [14]	1985–1988	59	63	61	56	71	50
Victoria/Australia [10]	1980–1989	61	63	73	64	80	52

SEER, Surveillance, Epidemiology and End-Results.
[a] The rates presented for the age group 0–14 years for Europe and Australia, and for the age group 0–19 years for the USA and Canada.
[b] Data based on the present study.

included cases diagnosed more recently. The population-based and the hospital-based survival rates for specific diagnostic groups are quite similar. For example, in the USA there has been found a high degree of comparability of survival for malignant brain tumours between the National Cancer Data Base (NCDB) (including all CNS tumours) and the SEER Program (including only malignant CNS tumours) [31]. Based on data of the NCDB, the 5-year survival rate was 74% for childhood astrocytomas and 55% for PNET (45% for age group 0–4 years).

The recent population-based studies have reported a modest or no increase in survival of children with CNS tumours diagnosed during the past few decades [4,15,41]. We observed a continuous improvement of survival rates between 1978 and 1989 in Europe, while no further changes in 1990–1992 (based on a limited dataset only) were seen. In SEER regions (USA), some improvement in survival from 1975 to 1994 was seen, limited to children aged 5 years and more [4]. In a study conducted in Piedmont (Italy), the high survival rate observed for children (age 0–14 years) diagnosed in 1985–1989 was not confirmed for children diagnosed in 1990–1994 [42]. In the USA, the 5-year survival rate remained lower than 60% in 1985–1994 for all histotypes, other than astrocytomas, many of which were low grade malignancies; but also in astrocytoma, the outcome was poorest for infants [4]. During the time period covered by the EUROCARE study, a slight improvement, limited mainly to period from 1984 to 1989, was observed for adult patients with brain cancer in Europe [27]. So, compared with many other cancers, the CNS malignancies do not demonstrate a considerable improvement in prognosis.

In conclusion, the EUROCARE study on childhood cancer survival highlighted a substantial intercountry variation in survival of children with CNS malignancies across Europe in 1978–1989, referring to the differences in access and organisation of care. The estimates are based on a very large dataset (one of the largest available on this issue) and are statistically stable. A positive trend indicating better prognosis was observed, although, compared with the other childhood cancers covered by this special issue, in particular leukaemia, the improvement in survival in CNS tumours was more modest. To understand better the causes of the intercountry differences, a high-resolution study could be useful that will collect data prospectively on the details of diagnosis, classification, grading and treatment in selected countries, and analyse their influence on patients' survival.

5. The EUROCARE Working Group for this study

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Acknowledgements

The EUROCARE study was financed through the BIOMED programme of the European Union. Part of the analyses were conducted thanks to a contribution from AIRC to CPO-Piemonte. The authors are grateful to the registries for collecting data and completing active follow-up and thank Charles Stiller, Oxford, for valuable comments and input.

Appendix. List of the countries included in the multivariate analyses, period 1978–1989

- All CNS malignant tumours: Denmark, Finland, Sweden, England and Wales, Scotland, France, Germany, The Netherlands, Italy, Spain[a], Estonia, Poland, Slovakia, Slovenia[a]
- PNET: Denmark, Finland, England and Wales, Scotland, France[a], Germany, Italy, Spain[a], Slovakia
- Glioma-related category: Denmark, Finland, Sweden, England and Wales, Scotland, France, Germany, Italy, Spain[a], Estonia, Slovakia

[a]Not included in analyses for time trend.

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