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Survival of children with Wilms' tumour in Europe

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Abstract

A total 2535 cases of Wilms' tumours registered in children aged 0–14 years by 34 population-based cancer registries in 16 countries of Europe in 1978–1992 and followed-up until the end of 1994 were included in this EUROCARE study. Overall 5-year observed survival of all children diagnosed in 1985–1989 was 83%, 95% confidence interval (CI) 80–85. Relatively large differences were observed between the European countries, with significantly lower survival of patients registered in the formerly socialist countries, Estonia, Poland and Slovakia. Overall European survival was slightly lower in comparison with results reported from the USA and Australia, which demonstrate a potential for improvement. Over the study period, overall survival adjusted for age, sex and country has increased significantly. This favourable trend is attributed primarily to improvements in treatment, particularly to the introduction of new chemotherapeutic agents.

Keywords: Childhood cancer; Survival; Wilms' tumour; Europe; EUROCARE

1. Introduction

A broad spectrum of renal tumours occurs in infants and children ranging from the benign cystic nephroma to the extremely aggressive malignant rhabdoid tumour of the kidney [1]. In European populations, 97% of the malignant neoplasms of the kidney are Wilms' tumours [2]. The remainder are carcinomas, neuroblastoma, lymphomas, sarcomas or unspecified tumours.

The majority of Wilms' tumours (approximately 80%) occur before the age of 5 years; this early onset suggests the role of a genetic element in its aetiology [3]. Wilms' tumour occurs slightly more often in girls than in boys. The standardised incidence rates range within Europe from approximately 6.5 per million in Spain and Slovakia to over 10 per million in Northern European countries [2]. While incidence is relatively stable across Europe, mortality rates for childhood renal cancer have recently decreased considerably in most European countries [4], presumably due to improvements in treatment [5]. The decrease was less marked in some countries of Central and Eastern Europe [4], where the application of the latest advances in treatment may have been delayed.

In the EUROCARE I study [6], 5-year survival of children diagnosed with kidney tumours during 1978–1984 was 75%, 10-year survival 70%. However, that analysis also included a few tumours other than Wilms', because classification was based only on site of occurrence.

In the present study, we report on the survival of children diagnosed with Wilms' tumour in 1978–1992 in Europe, and compare the differences between subgroups of patients, as defined by sex, age group, country and period of diagnosis. The results are compared with outcomes observed in other world regions. Time trends in survival are complemented with a brief account of the evolution of therapy.

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2. Patients and methods

All primary cases of Wilms' tumour registered in patients younger than 15 years of age in 34 participating European population-based cancer registries between 1978 and 1992 and followed-up until the end of December 1994 were retrieved from the EUROCARE database [7]. The eligible cases were those classified to subgroup VIa of the International Classification of Childhood Cancer (ICCC) [8], which includes Wilms' tumour (nephroblastoma) and its histologically distinct variants rhabdoid sarcoma and clear cell sarcoma of kidney [9]. Renal carcinoma (VIb) and unspecified malignant renal tumours (VIc) were not included.

For each case, a standard set of variables recorded in a cancer registry was provided, notably sex and age at diagnosis, topography and morphology of tumour and most valid basis of diagnosis. Clear cell sarcoma and rhabdoid tumour of the kidney were not evaluated separately, because ICD-O-1 (required by the EUROCARE protocol) does not recognise these morphology codes. Information was not available on tumour laterality and treatment, and stage was available for only approximately half of the cancer registries. These variables were therefore not considered in this study.

Overall, 2561 cases were included in the analyses (Table 1). Data from regional registries were pooled to represent one of the 16 countries included in the analyses. The number of cases per country varied considerably, as shown in Table 1, because of the different period and area of coverage of the registries.

Observed survival was calculated by the actuarial method [10] for the period 1985–1989 and presented by sex, age-group and country. Mantel–Haenszel χ^2 test for 2×2 tables was applied to test differences in proportion of survivors at 5 years after the diagnosis. A European average was obtained by pooling all data sets provided by the contributing registries, as described elsewhere [7]. This average was influenced by the considerable predominance of cases from large registries, notably England and Wales and Germany.

Geographical comparison between countries for period 1985–1989 is described using age standardised survival, to adjust for differences in age distribution of children in the contributing countries. However, this technique allows the inclusion only of countries providing at least 1 case in each age–sex group [7].

Cox proportional hazard models [11] were used to evaluate time trends in survival, adjusting for age-group (0–4, 5–9, 10–14 years), sex and country. Three periods, 1982–1985, 1986–1989 and 1990–1992, were compared to the reference period 1978–1981. Only the countries contributing at least 30 cases of Wilms' tumour over the entire time period 1978–1992 were included, while the inclusion of the regional registries was restricted to those covering the entire time period, as described in the methodology paper [7]. The P values reported for the time trends in survival refer to the Wald χ^2 test of regression coefficient for calendar year (fitted as a continuous variable) being zero. The same data set was used to test the geographic differences adjusted for sex, age group (0–4, 5–9, 10–14 years) and period of diagnosis (as a continuous variable), by comparison of risk ratios.

More detail is given in the methodology chapter [7].

3. Results

All 2535 Wilms' tumour cases included in the analyses are tabulated by age group, country and period of registration in Table 1. Over 70% of cases came from the two largest cancer registries, England and Wales, UK and Germany. More than three quarters (77%) were diagnosed before 5 years of age. The boy to girl ratio was 0.99.

Table 1 also shows the indicators of data quality for respective countries. The high proportion of microscopically verified diagnoses in the majority of the countries implies high validity of diagnosis and, consequently, of classification. Overall, there were only 17 cases lost to follow-up, which represents less than one 1% of cases and documents a good follow-up procedure in the contributing registries. A small number of cases registered from death certificate only (DCO cases) classified into VIa subgroup signifies high completeness of registration. Because DCO cases have, by definition, zero survival time, they were excluded from analyses. We also show in Table 1 the number of unspecified renal tumours (ICCC subgroup VIc), its percentage in the entire group VI of renal tumours and the proportion of unspecified cases verified microscopically. In Estonia and Slovakia they constituted around 10% of all renal tumours, with a low proportion of microscopically verified diagnoses. In other countries, the proportion of unspecified renal tumours without microscopic verification was negligible, which reduces to a minimum the probability of misclassification of Wilms' tumour.

Overall 5-year survival for all children registered with Wilms' tumour during 1985–1989 was 83%, with a 95% confidence interval (95% CI) of 80–85 (Table 2). Three-year and 5-year survival in boys tended to reach higher values than in girls, but the differences were non-significant (for 5-year survival $\chi^2=0.66$, $P=0.4$).

Survival improved over time (Table 3). Compared with the period 1978–1981 and adjusted for sex, age group and country, the risk ratio reduced for cases diagnosed after 1985, although further improvement was not observed between the two latest periods 1986–1989 and 1990–1992. The overall improvement was statistically significant ($\chi^2=9.94$, $P=0.002$).

One-year, 3-year and 5-year age-standardised survival is shown for the individual countries with some cases in

Table 1
Number of cases of Wilms' tumour included in the survival analyses for the period 1978–1992: data quality indicators are shown[a]

Country	Wilms' tumours VIa						Unspecified renal tumours (VIc)		
	1978–1984	1985–1989	1990–1992	MV[b]	Lost to follow-up	DCO[c]		Proportion of total VI group	MV[b]
Age group (years)	*n*	*n*	*n*	%	*n*	*n*	*n*		%
Europe	1014	951	570	93.7	46	25	32	1.2	43.8
0–4	765	731	461						
5–9	215	189	97						
10–14	34	31	12						
Austria (Tyrol)		2	2	75.0	0	0	0	0.0	–
0–4	–	2	1						
5–9	–	0	1						
10–14	–	0	0						
Denmark	44	44	16	100.0	0	0	0	8.6	100.0
0–4	23	33	12						
5–9	20	8	4						
10–14	1	3	0						
Estonia	22	11	14	100.0	4	3	6	10.9	16.7
0–4	20	10	10						
5–9	2	1	4						
10–14	0	0	0						
Finland	49	54	25	100.0	0	1	1	0.8	100.0
0–4	38	40	21						
5–9	10	11	4						
10–14	1	3	0						
France (Amiens, Calvados, Doubs)	10	14	3	100.0	1	0	1	2.5	100.0
0–4	8	10	1						
5–9	2	3	2						
10–14	0	1	0						
Germany (West)	307	367	261	100.0	29	0	0	0.0	–
0–4	233	290	211						
5–9	60	70	43						
10–14	14	8	7						
Iceland	3	1	0	100.0	0	0	0	0.0	–
0–4	2	1	0						
5–9	1	0	0						
10–14	0	0	0						
Italy (Florence, Genoa, Latina, Modena, Parma, Piedmont, Ragusa, Varese)	33	38	2	89.9	0	2	1	1.1	–
0–4	22	26	1						
5–9	9	8	1						
10–14	2	4	0						
Poland (Cracow, Warsaw)	5	14	2	100.0	0	1	0	0.0	–
0–4	4	8	2						
5–9	1	4	0						
10–14	0	2	0						
Slovakia	67	31	8	100.0	0	13	12	10.1	8.3
0–4	46	24	7						
5–9	20	6	1						
10–14	1	1	0						
Slovenia		11	3	100.0	1	0	1	6.3	100.0
0–4	–	10	3						
5–9	–	1	0						
10–14	–	0	0						

(continued)

Table 1 (*continued*)

Country	Wilms' tumours VIa						Unspecified renal tumours (VIc)		
	1978–1984	1985–1989	1990–1992	MV[b]	Lost to follow-up	DCO[c]		Proportion of total VI group	MV[b]
Age group (years)	*n*	*n*	*n*	%	*n*	*n*	*n*		%
Spain (Basque country, Girona, Mallorca, Navarra, Tarragona)		12	2	100.0	0	0	0	0.0	
0–4		10	2						
5–9		2	0						
10–14		0	0						
Sweden (South)	17	9	10	100.0	0	0	0	0.0	
0–4	11	7	7						
5–9	5	2	3						
10–14	1	0	0						
Switzerland (Geneva)	2	1	0	100.0	0	0	0	0.0	
0–4	2	0	0						
5–9	0	1	0						
10–14	0	0	0						
The Netherlands (Eindhoven)	6	8	1	80.0	3	0	0	0.0	
0–4	6	7	1	13.3[d]					
5–9	0	1	0						
10–14	0	0	0						
UK, England and Wales	403	301	201	97.8	8	5	0	0.0	
0–4	314	230	168	1.0[d]					
5–9	76	63	29						
10–14	13	8	4						
UK, Scotland	46	33	20	99.0	0	0	0	0.0	
0–4	36	24	14						
5–9	9	8	5						
10–14	1	1	1						

[a] Refer to Ref. [7] for exact periods supplied by each registry.
[b] %MV, percentage of microscopically verified diagnoses.
[c] DCO, cases registered from death certificate only.
[d] Percentage with unknown basis of diagnosis (for all ages).

Table 2
Observed survival of children with Wilms' tumour diagnosed in 1985–1989 and included in the EUROCARE study[a]

		1-year survival		3-year survival		5-year survival	
Age-group (years)	*n* (%)	%	95% CI	%	95% CI	%	95% CI
All children	951 (100)	92	(91, 94)	84	(82, 86)	83	(80, 85)
0	128 (13)	87	(80, 92)	83	(76, 89)	82	(74, 87)
1–4	603 (63)	94	(91, 95)	85	(82, 88)	84	(81, 87)
5–9	189 (20)	93	(88, 96)	82	(76, 87)	81	(74, 86)
10–14	31 (3)	87	(71, 95)	81	(64, 91)	81	(64, 91)
Boys	468 (100)	92	(89, 94)	85	(81, 88)	84	(80, 87)
0	63 (13)	87	(76, 93)	84	(72, 91)	84	(72, 91)
1–4	305 (65)	94	(90, 96)	86	(82, 90)	85	(80, 88)
5–9	89 (19)	92	(85, 96)	82	(73, 89)	82	(73, 89)
10–14	11 (2)	82	(52, 95)	73	(43, 90)	73	(43, 90)
Girls	483 (100)	93	(90, 95)	84	(80, 87)	82	(78, 85)
0	65 (13)	88	(78, 94)	83	(72, 90)	80	(69, 88)
1–4	298 (62)	94	(90, 96)	84	(80, 88)	83	(79, 87)
5–9	100 (21)	93	(86, 97)	82	(73, 88)	79	(70, 86)
10–14	20 (4)	90	(70, 97)	85	(64, 95)	85	(64, 95)

95% CI, 95% confidence intervals of survival proportion.
[a] *n* (%), number and percentage of cases in each age–sex group.

Table 3
Risk ratios for different periods of diagnosis as predicted in Cox hazard model, adjusted for sex, age-group (0–4, 5–9, 10–14) and country (Denmark, Estonia, Finland, Germany, Slovakia, Sweden, UK, England and Wales and Scotland)[a]

Period of diagnosis	*n*	Risk ratio	95% CI
1978–1981	485	1	
1982–1985	632	0.93	(0.73, 1.19)
1986–1989	688	0.65	(0.50, 0.84)
1990–1992	555	0.73	(0.55, 0.96)

[a] 95% confidence intervals (95% CI) of risk ratios are also shown; $n = 2360$.

each age–sex category for the period 1985–1989 in Table 4. Apart from France, with a 100% 1-year survival for the 14 cases, 1-year survival was not substantially different between the countries. Some differences become apparent 3 years after the diagnosis, notably between the UK (England and Wales), Germany and Finland compared with Poland, which has further increased at 5 years after diagnosis and extended also to Scotland–Poland comparison. In Fig. 1, we show 5-year observed survival for the period 1985–1989 with the 95% confidence intervals represented by error bars. Five-year survival observed in Poland was significantly lower compared with the European average ($\chi^2 = 10.37$, $P = 0.0013$). Complementary geographical comparison for each registry with 30 or more cases for the entire study period in Table 5 provides risk ratios, which are adjusted for sex, age and year of diagnosis (continuous). Two countries have significantly elevated hazard ratios: Slovakia (1.96, 95% CI 1.38, 2.79) and Estonia (5.26, 95% CI 3.60, 7.67).

4. Discussion

This is the first systematic international evaluation of survival of children with Wilms' tumour in Europe, based on well over 2000 cases. Since the analyses were

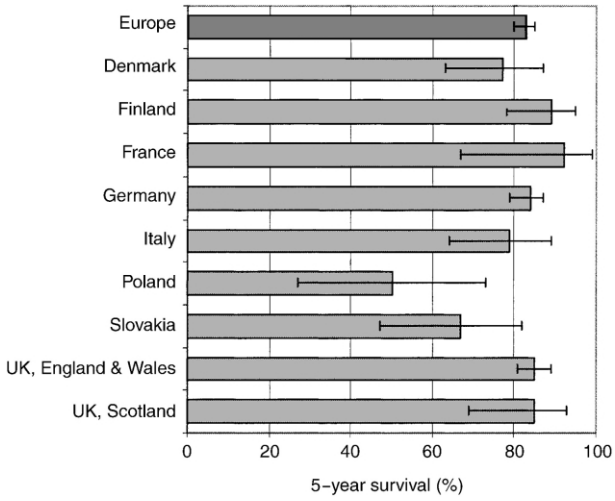

Fig. 1. Five-year observed survival of children with Wilms' tumour registered in 1985–1989 and included in the EUROCARE study, sex and age combined. 95% confidence intervals shown as error bars.

conducted on population-based data, the survival figures represent the average chance of survival of a child with Wilms' tumour in a general population covered by the contributing registries. The presented survival figures therefore reflect the totality of underlying socio-economic and medical conditions of the patients, such as access to medical care, alertness of physicians, early diagnosis, availability and quality of treatment, supportive care and attentive follow-up.

The population-based survival data collected in the framework of the EUROCARE study have to be evaluated in the light of a few factors inherent in the way the data were collected. Firstly, in the population-based registry, the exact data on stage and treatment are not consistently collected, and prognostic factors are therefore limited to the general demographic characteristics, such as sex, age, period of diagnosis and region of residence. Secondly, only some of the included registries covered their countries nationally. In the other countries considered, data were provided from regional registries,

Table 4
Age-standardised survival of children with Wilms' tumour registered in 1985–1989 and included in the EUROCARE study: age and sex combined[a]

		1-year survival		3-year survival		5-year survival	
Country	*n*	%	95% CI[a]%	%	95% CI	%	95% CI
Europe	951	89.6	(80.7, 94.7)	80.1	(72.7, 85.8)	78.2	(70.8, 84.1)
Denmark	44	87.3	(70.4, 95.2)	77.8	(63.3, 87.7)	77.8	(63.3, 87.7)
Finland	54	98.1	(52.9, 100.0)	89.4	(78.2, 95.2)	89.4	(78.2, 95.2)
France	14	100.0	(100.0, 100.0)	96.7	(0.7, 100.0)	96.7	(0.7, 100.0)
Germany	367	94.0	(91.1, 96.1)	84.9	(80.8, 88.3)	83.5	(79.2, 87.0)
Italy	38	82.7	(66.5, 92.1)	77.3	(60.7, 88.3)	77.3	(60.7, 88.3)
Poland	14	85.4	(54.7, 96,6)	51.6	(25.5, 76.9)	42.0	(18.9, 69.3)
Slovakia	31	77.6	(57.4, 89.9)	71.1	(53.0, 84.2)	–	–
UK, England and Wales	301	93.0	(89.5, 95.4)	86.4	(82.0, 89.8)	85.4	(80.9, 88.9)
UK, Scotland	33	93.5	(75.9, 98.5)	87.9	(74.6, 94.7)	84.6	(70.1, 92.9)

[a] 95% CI, 95% confidence intervals of survival proportion.

Table 5
Risk ratios for individual countries for the cases diagnosed in 1978–1992, as predicted in Cox hazard model, adjusted for sex, age-group (0–4, 5–9, 10–14 years) and year of diagnosis (continuous)[a]

Country	*n*	Risk ratio	95% CI
Denmark	104	1.06	(0.69, 1.64)
Estonia	47	5.26	(3.60, 7.67)
Finland	128	0.72	(0.45, 1.16)
Germany	935	0.87	(0.70, 1.08)
Slovakia	106	1.96	(1.38, 2.79)
Sweden	36	0.49	(0.18, 1.32)
UK, England	905	1.00	–
UK, Scotland	99	1.27	(0.84, 1.93)

[a] 95% CI, 95% confidence intervals of risk ratio; $n = 2360$.

which often contributed a small number of cases and consequently less precise estimates of national survival. Thirdly, the nature of data collection in a cancer registry makes data available only with a relatively long delay of 2–3 years, which is further prolonged by their submission and management in an international study. Finally, for a small proportion of patients among those diagnosed during the period 1990–1992, the maximum follow-up was less than 5 years [7].

However, the high quality of registry data included in this study, documented by the large proportion of microscopically-verified diagnoses, low numbers of DCO cases, cases lost to follow-up and unspecified renal tumours in the EUROCARE data set, endorse the obtained results.

The overall 83% 5-year observed survival is relatively high, although the differences between the age and sex subgroups of the patients and between the countries indicate possibilities for further improvement. The increasing survival over time should be monitored and all means should be taken to reinforce this trend, concentrating on all aspects of healthcare from early detection to therapeutic development.

Population-based survival data from cancer registries have been reported previously from several European countries. In Great Britain, the 5-year survival for childhood Wilms' tumour diagnosed in the period 1971–1973 was 58% [12], improving to 84% for the years 1986–1988 [13]. In Sweden, the 5-year survival for kidney cancer (predominantly Wilms' tumour) in childhood and adolescence increased from 36 to 77% during 1960–1984 [14]. The childhood cancer registry in Germany reported an increase from 84 to 90% between the periods 1980–1982 and 1980–1991 [15]. In Denmark, 388 cases of Wilms' tumour were registered between 1943 and 1987 and their 5-year survival increased from below 20% to approximately 80% [16]. In Italy, 5-year survival also improved from 50% for children diagnosed in 1967–1969 in the province of Torino [17], to 78% for those diagnosed in 1986–1989 in nine Italian regions [18]. In Slovakia, the population-based survival improved substantially from 20% among the patients diagnosed between 1968–1972 to around 60% during the 1980s [19]. In other developed countries of the world, the most recently published monograph of the SEER program in the USA (Surveillance, Epidemiology and End Results) [20] reports an increase in 5-year relative survival from 78 to 91% in boys and from 83 to 94% in girls between the time periods 1975–1984 and 1985–1994. Although reported figures show relative survival of patients younger than 20 years, the consequences on the comparison with EUROCARE results are immaterial in practice. The previously published data indicated 60% 5-year survival during the 1970s [21]. The cancer registry of Victoria state in Australia reported a very high 5-year survival of 85% for the entire period 1970–1989 [22]. In Australia as a whole, the 5-year survival was lower, 77% for children diagnosed between 1977 and 1982 [23]. Still lower 5-year survival, 63–68%, was observed in 69 Wilms' tumour patients registered during 1975–1984 in Osaka Cancer Registry in Japan [24].

The observed survival probabilities presented in this study were consistent with the data reported earlier in Europe, but appear slightly lower than in the USA or Australia. However, a comparable outcome was observed in some parts of Europe, namely the UK, Finland and Germany. Naturally, the European average is lower due to less favourable prognosis for children diagnosed in Estonia, Poland and Slovakia.

Assuming that the indisputable increase of the proportion of survivors over time will continue in Europe, the overall results will eventually attain the levels reported from the USA or Australia. Great potential can be especially seen in the improvement of outcome in the group of former socialist countries, where survival tended to be low for the studied period.

Although no data on treatment were available in this analysis, the spectacular improvement in survival of childhood Wilms' tumour patients is undoubtedly due to therapeutic advances. Three-year survival of 335 patients diagnosed in the UK between 1962 and 1966 was only 32% [25]. Most of those patients were subjected to surgery and only approximately 35% received chemotherapy. The chemotherapeutic era began later, with the introduction of dactinomycin, vincristine and doxorubicin. Doxorubicin, ifosfamide, etoposide and carboplatin have recently been used in Wilms' tumours. However, as yet, they have not been demonstrated to improve the prognosis further [26].

The irradiation applied in the early years, with high radiation doses and eccentric field arrangements, was responsible for significant late toxicity [27]. The successful treatment currently offered to patients may still be associated with late effects, for example growth defects after radiotherapy, late cardiac toxicity due to doxorubicin and anthracycline, the risk of the second tumour, although the most important late effect remains the relapse of the disease, in 14–20% of survivors [26].

The most important step in the improvement of treatment outcome was the recognition that a single institution could not collect enough experience to successfully manage this rare condition. Large study groups evolved, such as the multinational Societé Internationale d'Oncologie Pediatrique (SIOP) study group in Europe [28,29], the Nationwide Study in the Federal Republic of Germany [30], the Italian Group (CNR-AIEOP) [31], or the United Kingdom Children's Cancer Study Group (UKCCSG) [26,32]. The first UKCCSG Wilms' tumour trial included 78% of all British children diagnosed with this cancer in the years 1980–1985 [26], and 90% of those diagnosed in the period 1986–1991 were included in the second trial [32].

The past few years showed a breakthrough in understanding of some of the genetic factors involved in Wilms' tumour development and possible chromosomal prognostic factors have been identified: loss of heterozygosity of 16q and 1p markers. Genetic manipulations may therefore play a direct role in treatment of the Wilms' tumour in the future [33].

Before this knowledge is introduced in practice, survival might possibly be improved and adverse late effects of treatment reduced by the early identification of, at least, high-risk patients [34]. In Germany, 11% of the 373 patients included in a nationwide study during 1980–1988 were diagnosed during routine non-specific health examination offered to children under 2 years of age aimed at the detection of developmental problems [30].

5. Conclusions

The main benefit of the EUROCARE study of childhood cancer can be seen in drawing together a large number of records and uniformly analysing the data from different countries. Improvement in survival over the study period was substantial as well as variation between countries. Survival of children diagnosed in the former socialist countries was clearly inferior compared with the rest of Europe. The slightly lower survival in Europe compared with the SEER results in the USA indicates a scope for further improvement of survival for children with Wilms' tumour.

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