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Survival of children with malignant germ cell, trophoblastic and other gonadal tumours in Europe

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Abstract

Collaborators of the EUROCARE study had provided records on 1263 cases of germ cell, trophoblastic and other gonadal neoplasms, registered in 34 cancer registries in 16 European countries over the period 1978–1992 and followed-up until the end of 1994. Observed 5-year actuarial survival for 490 cases diagnosed in 1985–1989 was 80% (95% confidence interval (CI) = (76, 83)). The corresponding figures were calculated for the intracranial and intraspinal germ cell tumours (68%, 95% CI = (57, 76)), other non-gonadal germ cell tumours (76%, 95% CI = (68, 82)), gonadal germ-cell tumours (89%, 95% CI = (85, 93)) and gonadal carcinomas (50%, CI = (24, 76)). Relatively large differences in survival were observed between age-sex subgroups, which also differed with histology, with extremely poor survival of young children with intracranial and intraspinal germ cell tumours. Lower survival was observed in the countries with formerly socialist economies. Time trends in survival were examined for the entire study period, including only the cases registered in the large contributing registries. For all germ cell tumours, the risk ratios calculated in the Cox regression analysis were markedly lowered for the years after the reference period of 1978–1981. The improved outcome is attributed to treatment advances.

Keywords: Childhood cancer; Survival; Germ cell tumours; EUROCARE

1. Introduction

Germ cell, trophoblastic and other gonadal neoplasms are a heterogeneous group of rare tumours, which occur at the rate of 3 to 5 cases per million population at risk per year in Europe, representing approximately 2–4% of all paediatric malignancies [1]. Almost all the tumours of this group arise in totipotential germ cells, which have migrated from the extra-embryonic yolk sac endoderm to the gonads or aberrantly to other sites. They may be benign (mature teratoma) or malignant (germinoma, malignant teratoma, embryonal carcinoma, endodermal sinus tumour or choriocarcinoma) or may contain several of these elements [2]. About half of germ cell tumours arise in the gonads and the remainder in intracranial and intraspinal or other non-gonadal sites [3]. Gonadal carcinomas, extremely rare in children, arise in epithelial cells of the gonads and constitute a separate subgroup. Sex and age distribution reflects the heterogeneity of these tumours. In summary, boys reach a peak of occurrence as infants and girls around age 13 years, but the pattern varies widely according to the histology of the subgroup and the site of the tumour.

Because of the dissimilarity of the subgroups, survival has rarely been described for the overall group. For the patients diagnosed during the 1980s, the 5-year population-based survival varied from 56% in Slovakia

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[4] to 85% in the former West Germany [5]. Reports of clinical studies were even more specific to selected groups of patients according to tumour histological type, anatomical site, patient's age, stage and extent of disease.

The multimodality treatment approach was characterised in the 1970s by use of radiation and chemotherapy, in addition to surgical resection while, in the 1980s, intensive chemotherapy and refined surgery for preserving reproductive and hormonal function were developed [6].

EUROCARE [7,8] is the first international study to evaluate systematically the survival of cancer patients on a population basis in Europe. This paper is devoted specifically to survival of children with malignant germ cell, trophoblastic and other gonadal tumours. The wide geographical coverage and long time period allowed information to be collected on over 1000 cases of these rare tumours.

2. Patients and methods

All malignant germ cell, trophoblastic and other gonadal tumours, classified into diagnostic group X of the International Classification of Childhood Cancer (ICCC) [9] were included in this analysis. This group of tumours is divided into five subgroups: intracranial and intraspinal germ cell tumours (Xa), other non-gonadal germ cell tumours (Xb), gonadal germ cell tumours (Xc), gonadal carcinomas (Xd) and other and unspecified gonadal tumours (Xe). Although non-malignant intracranial germ cell tumours also belong to subgroup Xa, they were excluded from the analyses, because of selective registration of these tumours in the contributing registries. There were no cases identified from death certificate only (DCO) in this series.

All eligible cases registered in patients younger than 15 years of age in the 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 [10]. The overall total number of cases included was 1263. The number of cases per country varied considerably, depending on the geographical and temporal coverage of the contributing registries. However, the incidence rates and data quality in the registries included in the analyses were comparable [1].

A standard set of variables was available for each case: sex, age at diagnosis, topography [11], morphology [12] and most valid basis of diagnosis of the tumour. Information on the stage at diagnosis was not available consistently and it was therefore not included in the analyses. No data on treatment were collected.

Overall boy to girl ratio was 0.89, but the sex ratio varied by diagnostic group and the age of patients.

Observed survival probabilities were calculated by the actuarial method [13] for the period of 1985–1989, representing the most recent period available for the largest number of participating registries for the total of 490 cases collected in 17 countries. Survival probabilities for this period were calculated for each country, sex and age-group (0, 1–4, 0–4, 5–9, 10–14 years). European average survival was obtained by simply pooling all available data for the relevant period.

Mantel–Haenszel or Fisher's exact χ^2 test for 2×2 tables was applied to test differences in proportion of survivors at 5 years after the diagnosis.

To compare overall survival between the different countries, age-standardised survival was calculated. The standard population was represented by the pool of all childhood cancer cases in the EUROCARE database, using grouping into the three age groups: 0–4, 5–9 and 10–14 years for the relevant time period [10]. The standardisation allows the overall survival probabilities to be adjusted for differences in the age-structure of individual populations, although it is not possible to calculate the standardised survival for countries with no cases in one of the age and sex groups.

The subset included in the time trend analyses constituted cases registered in countries providing a minimum of 15 cases in each analysed diagnostic subgroup during the entire period of 1978–1992. Cox proportional hazard models [14] were used to describe survival time-trends in terms of risk ratios for the periods 1982–1985, 1986–1989 and 1990–1992 compared with the reference time period of 1978–1981, adjusted for sex, age group and country. In the subgroups Xa and Xc, the model was adjusted for age groups 0–4, 5–9, 10–14 years and in the subgroup Xb for age groups 0, 1–4, 5–9, 10–14 years. 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 data-sets used for evaluation of time trends were also examined for intercountry variations in survival, although the number of countries providing sufficient number of cases for meaningful analyses was small. The differences were expressed as the risk ratio of dying in the individual countries compared with the reference country (UK, England and Wales), which were adjusted for sex, age group and period in a Cox regression model, the categories being the same as described for the time trend models.

More detail is given in the methodology chapter [10].

3. Results

Table 1 shows the number of children included in the analyses. For the 490 children diagnosed in 1985–1989 with all germ cell, trophoblastic and other gonadal

Table 1
Number of germ cell, trophoblastic and other gonadal tumours (group X of the ICCC) in children included in analyses, by diagnostic subgroup, period and country

	Period 1978–1984						Period 1985–1989						Period 1990–1992						Proportion of the total	
	Xa	Xb	Xc	Xd	Xe	Group X	Xa	Xb	Xc	Xd	Xe	Group X	Xa	Xb	Xc	Xd	Xe	Group X	% MV	% Lost[a]
All countries combined	97	124	240	15	9	485	96	142	237	10	5	490	84	70	129	3	2	288	95	2.7
Austria (Tyrol)	–	–	–	–	–	–	1	1	1	0	0	3	0	0	2	0	0	2	100.0	0.0
Denmark	2	3	14	1	0	20	4	3	9	0	0	16	5	1	4	0	0	9	100.0	0.0
Estonia	0	7	0	2	1	10	0	3	6	0	1	10	0	2	2	0	0	4	95.8	0.0
Finland	3	6	10	2	0	21	3	7	8	1	0	19	2	0	14	0	0	16	100.0	0.0
France (Amiens, Calvados, Doubs)	0	1	3	0	0	4	0	1	1	0	0	2	0	0	0	0	1	1	100.0	0.0
Germany (West)	20	36	41	1	0	98	37	62	63	0	1	163	34	42	51	1	0	128	100.0	7.2
Iceland	0	0	0	1	0	1	1	0	1	0	0	2	–	–	–	–	–	–	100.0	50.0
Italy (Florence, Genoa, Latina, Modena, Parma, Piedmont, Ragusa, Varese)	3	4	7	0	0	14	5	5	11	1	0	22	1	1	1	0	0	3	100.0	2.4
Poland (Krakow, Warsaw)	1	0	3	0	0	4	0	1	7	1	1	10	0	0	1	0	0	1	100.0	0.0
Slovakia	1	15	22	1	1	40	0	11	22	0	0	33	1	3	7	0	0	11	100.0	0.0
Slovenia	–	–	–	–	–	–	5	1	3	0	0	9	0	0	2	0	0	2	90.9	0.0
Spain (Basque country, Girona, Mallorca, Navarra, Tarragona)	–	–	1	–	–	1	2	1	6	0	0	9	0	2	0	0	0	2	100.0	8.3
Sweden (South)	1	5	5	0	1	12	0	0	1	0	0	1	–	–	–	–	–	–	100.0	0.0
Switzerland (Geneva)	0	0	0	0	0	0	0	0	0	0	0	0	–	–	–	–	–	–	–	–
The Netherlands (Eindhoven)	0	1	4	0	0	5	0	1	0	0	0	1	–	–	–	–	–	–	100.0	33.3
UK, England and Wales	57	43	122	7	5	234	33	43	88	6	2	172	36	15	38	2	1	92	93.3	0.4
UK, Scotland	9	3	9	0	1	22	5	2	10	1	0	18	4	4	7	0	0	15	94.6	0.0

ICCC, International Classification of Childhood Cancer.

[a] Proportions of microscopically verified (% MV) and lost to follow-up (% Lost) cases indicate the quality of data.

Table 2
Proportion of survivors 1, 3 and 5 years after diagnosis of germ cell, trophoblastic or other gonadal tumour (ICCC group X) by sex and age group among childhood cancer cases included in the EUROCARE database for the period 1985–1989: 95% confidence intervals (CI) for survival proportions are shown

	No. of cases	1-year survival		3-year survival		5-year survival	
Age-group (years)	*n* (%)	Observed	95% CI	Observed	95% CI	Observed	95% CI
All children	490 (100)	89	(86, 91)	82	(79, 85)	80	(76, 83)
0	78 (16)	86	(76, 92)	83	(73, 90)	83	(73, 90)
1–4	176 (36)	90	(84, 93)	81	(75, 86)	80	(73, 85)
5–9	71 (14)	84	(74, 91)	77	(66, 85)	72	(61, 82)
10–14	165 (34)	92	(86, 95)	85	(79, 90)	82	(75, 87)
Boys	225 (100)	93	(89, 95)	88	(83, 91)	84	(78, 88)
0	46 (20)	89	(77, 95)	86	(73, 94)	86	(73, 94)
1–4	106 (47)	96	(91, 99)	91	(85, 95)	89	(82, 94)
5–9	18 (8)	89	(67, 97)	77	(54, 91)	58	(35, 78)
10–14	55 (24)	90	(79, 96)	84	(72, 92)	78	(64, 87)
Girls	265 (100)	86	(81, 90)	78	(72, 82)	77	(71, 82)
0	32 (12)	81	(64, 91)	78	(60, 89)	78	(60, 89)
1–4	70 (26)	80	(69, 88)	66	(54, 76)	66	(54, 76)
5–9	53 (20)	83	(70, 91)	77	(64, 86)	77	(64, 86)
10–14	110 (42)	93	(86, 96)	86	(78, 91)	84	(76, 90)

tumours combined (group X of the ICCC). The proportion of survivors at 1, 3 and 5 years after the diagnosis is shown by sex and age group in Table 2. Boys older and girls younger than 5 years of age tended to have lower survival. Differences in 5-year survival were significant between boys and girls aged 1–4 years, as documented by the non-overlapping 95% confidence intervals in Table 2 ($\chi^2 = 13.6$, $P = < 0.001$). When standardised by age, the overall 5-year survival was 77%, 95% CI = (67, 85).

Comparing age-standardised survival between the countries in Table 3, there appears to be a significant difference in 5-year survival between Germany and England and Wales who have around 85% of survivors and Estonia (43%) and Slovakia (57%). The curves of observed survival are graphically presented in Fig. 1 for all countries providing at least 10 cases for the time period of 1985–1989.

Table 3
Age-standardised 5-year survival of children diagnosed with germ cell, trophoblastic and other gonadal neoplasms between 1985 and 1989 in Europe: only countries with sufficient number of cases are shown

		5-year age standardised survival	
Country	No. of cases		95% confidence interval
Europe	490 (100)	77	(67, 85)
Denmark	16 (3)	61	(36, 81)
Estonia	10 (2)	43	(18, 72)
Finland	19 (4)	79	(53, 93)
Germany	163 (33)	88	(81, 92)
Italy	22 (4)	78	(55, 91)
Poland	10 (2)	72	(32, 93)
Slovakia	33 (7)	57	(40, 73)
Slovenia	9 (2)	52	(17, 85)
Spain	9 (2)	100	(100, 100)
UK, England and Wales	172 (4)	84	(78, 89)

The heterogeneity of the group of germ cell, trophoblastic and other gonadal germ cell tumours is reflected in the survival pattern of children with different tumour types (Table 4). Combined European data showed the most favourable outcome for gonadal germ cell tumours (Xc), 5-year survival being significantly superior to the outcome for intracranial and intraspinal germ cell neoplasms (Xa, $\chi^2 = 24.9$, $P < 0.0001$) or gonadal carcinomas (Xd, $\chi^2 = 21.8$, $P < 0.0001$), extracranial and extragonadal germ cell neoplasms (Xb, $\chi^2 = 11.2$, $P < 0.001$).

3.1. Malignant intracranial and intraspinal germ cell tumours (Xa)

More boys than girls were diagnosed with intracranial and intraspinal germ cell tumours, the sex ratio increasing with age and reaching almost 2.2 in the age group 10–14 years. Over half of intracranial and intraspinal germ cell tumours occurred after the age of 10 years.

Survival varied according to sex and age. Seven of the eight infants (diagnosed before the age of 1 year) have died within 1 year of their diagnosis and one boy survived 3 years with the tumour, 5-year survival thus being zero (Fig. 2). The proportion of survivors clearly increased with age. None of the girls younger than 5 years of age survived 5 years, even if overall survival was slightly higher for girls (72%, 95% CI = (56, 84)) than for boys (64%, 95% CI = (51, 76)).

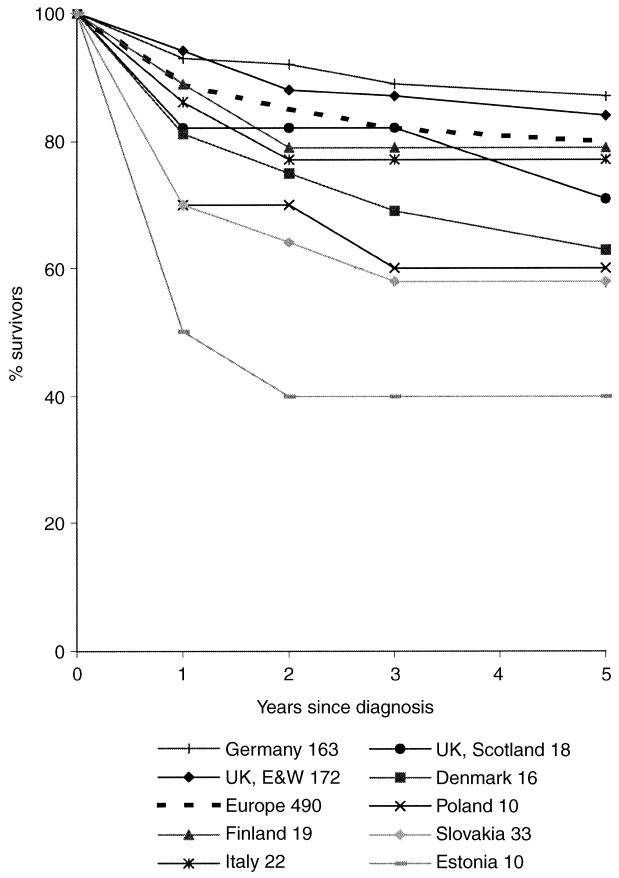

Fig. 1. Curves of observed survival in children with germ cell, trophoblastic and other gonadal tumours in Europe in 1985–1989. The number of cases included for each country is shown.

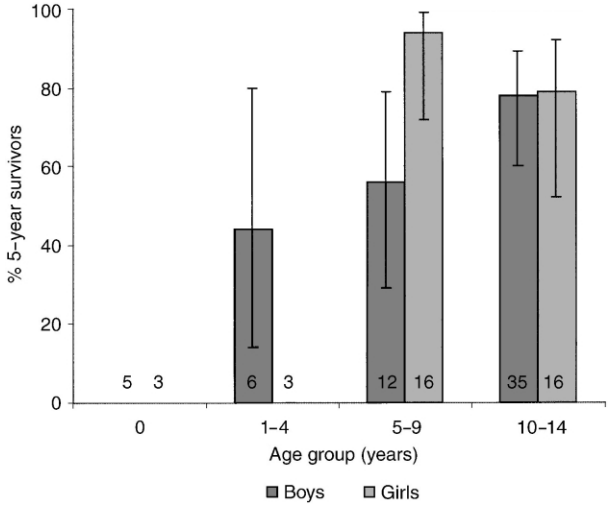

Fig. 2. Proportion of five-year survivors among 96 children diagnosed with intracranial and intraspinal germ cell tumours (Xa) in Europe during the period 1985–1989. The number of children in each sex-age category is shown at the base of corresponding column. The error bars represent 95% confidence intervals of the observed survival proportions.

Only three registries provided the required number of cases for inclusion in the examination of time trends: UK (England and Wales), Germany and Scotland (Table 5). Adjusted for sex, age group and country, and compared with the reference period of 1978–1981, the risk ratio for all three successive periods was non-significantly lower ($\chi^2 = 0.8$, $P = 0.34$).

The same 235 cases diagnosed in 1978–1992 were included in the geographical comparison (Table 6). Although the risk ratio was lower in Germany compared with England and Wales, the difference was non-significant.

3.2. Other non-gonadal germ cell tumours (Xb)

About 85% of the 'other' germ cell tumours, (extracranial, extraspinal and extragonadal) occurred in infants and children before the age of 5 years. Almost three-quarters of tumours in this diagnostic subgroup were diagnosed in girls. The highest 5-year survival was observed for infants of both sexes (90%, 95% CI = (77, 96)). Boys younger than 5 years had a slightly better outcome than the girls, while among the older children more girls than boys survived. For all ages combined, survival in boys (81%, 95% CI = (65, 90)) was non-significantly superior to that in girls (74%, 95% CI = (65, 82): Fig. 3).

270 cases from three countries were included in the Cox regression analysis of time trends; Germany, UK

Table 4
Proportion of survivors 1, 3 and 5 years after diagnosis in children registered in Europe in 1985–1989, by diagnostic subgroup: 95% confidence intervals (CI) for survival proportions are shown

		Number of cases			1-year survival		3-year survival		5-year survival	
		All *n* (%)	Boys *n* (%)	Girls *n* (%)	Observed	95% CI	Observed	95% CI	Observed	95% CI
Xa	Intracranial and intraspinal germ cell tumours	96 (100)	58 (60)	38 (40)	84	(75, 90)	76	(66, 84)	68	(57, 76)
Xb	Non-CNS, non-gonadal germ cell tumours	142 (100)	39 (27)	103 (73)	89	(82, 93)	77	(69, 83)	76	(68, 82)
Xc	Gonadal germ cell tumours	237 (100)	127 (54)	110 (46)	93	(89, 95)	90	(85, 93)	89	(85, 93)
Xd	Gonadal carcinomas[a]	25 (100)	4 (16)	21 (84)	60	(31, 83)	60	(31, 83)	50	(24, 76)

CNS, central nervous system.
[a] Period 1978–1989.

Table 5
Time trends of survival of children registered in Europe with germ cell tumours[a]

	No. of cases included in analyses	Risk ratio	95% confidence interval
Xa: intracranial and intraspinal germ cell tumours			
1978–1981	49	1.00	
1982–1985	54	0.81	(0.45, 1.47)
1986–1989	58	0.59	(0.30, 1.15)
1990–1992	74	0.79	(0.42, 1.47)
Xb: other non-gonadal germ cell tumours			
1978–1981	52	1.00	
1982–1985	67	0.20	(0.11, 0.38)
1986–1989	91	0.17	(0.10, 0.31)
1990–1992	60	0.20	(0.09, 0.44)
Xc: gonadal germ cell tumours			
1978–1981	121	1.00	
1982–1985	140	0.75	(0.42, 1.35)
1986–1989	157	0.39	(0.20, 0.76)
1990–1992	121	0.17	(0.05, 0.56)

[a] Countries contributing at least 15 cases in each diagnostic group over the entire time period 1978–1992 were included in the analysis. Risk ratios (shown with their 95% confidence intervals) are adjusted for sex, age group and country.

Table 6
Geographical analysis of survival of children with germ cell tumours[a]

	No. of cases included in analyses	Risk ratio	95% confidence interval
Xa: intracranial and intraspinal germ cell tumours			
Germany	91	0.71	(0.42, 1.21)
UK, England and Wales	126	1.00	Reference
UK, Scotland	18	0.99	(0.50, 1.95)
Xb: other non-gonadal germ cell tumours			
Germany	140	0.93	(0.55, 1.59)
Slovakia	29	2.24	(1.22, 4.11)
UK, England and Wales	101	1.00	Reference
Xc: gonadal germ cell tumours			
Denmark	27	1.15	(0.45, 2.97)
Finland	32	1.70	(0.66, 4.41)
Germany	155	0.53	(0.24, 1.15)
Slovakia	51	1.55	(0.78, 3.05)
UK, England and Wales	248	1.00	Reference
UK, Scotland	26	0.95	(0.29, 3.11)

[a] Countries contributing at least 15 cases in each diagnostic group over the entire time period 1978–1992 were included in the analysis. Risk ratios are shown with their 95% confidence intervals and are adjusted for sex, age group and period of diagnosis.

(England and Wales) and Slovakia (Table 5). Compared with the period 1978–1981 and adjusted for sex and age group, hazard ratios were significantly lower for all the subsequent periods, which indicates a major improvement in survival since the early 1980s.

Geographical analyses including cases from the same data set showed significantly inferior survival in Slovakia relative to England and Wales (Table 6).

3.3. Gonadal germ cell tumours (Xc)

Approximately equal numbers of germ cell tumours occurred in the gonads of boys and girls, but with a different age distribution. More than 80% of cases in boys occurred before the age of 5 years, with the lowest numbers in the age group 5–9 years. The number of cases in girls increased with age, with about three-quarters of them occurring after the age of 10 years.

Survival proportion varied with sex and age, reaching higher values for the subgroups with more cases: higher survival was observed in younger boys and in older girls (Fig. 4). In the age-group 0–4 years; 5-year survival of the 106 boys (95%, 95% CI = (89, 98)) was significantly higher ($P = 0.01$) than that of the 8 girls (63%, 95% CI = (31, 86)). Other differences between the sex–age groups were not significant. Overall 5-year survival in boys was 93%, 95% CI = (88, 97) and in girls 84%, 95% CI = (76, 90).

Survival time trends were examined on a set of 539 cases from England and Wales, Germany, Slovakia, Finland, Denmark and Scotland (Table 5). In comparison with the reference period of 1978–1981, survival was continuously and significantly improving over time ($\chi^2 = 14.8$, $P < 0.0001$).

Geographical analysis including the same subset of data did not show any significant differences in survival (Table 6).

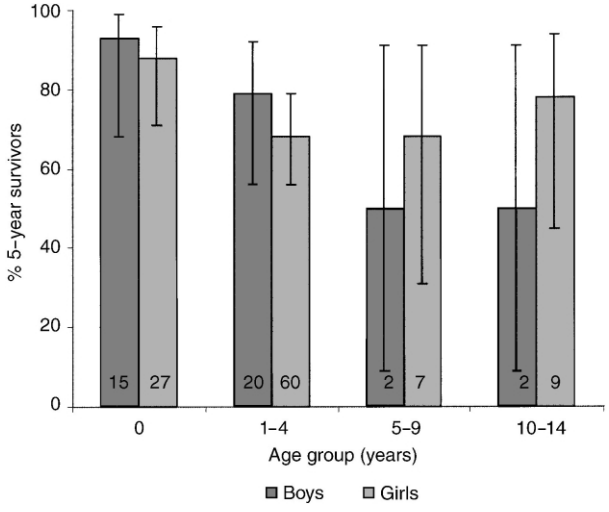

Fig. 3. Proportion of five-year survivors among 142 children diagnosed with other non-gonadal germ cell tumours (Xb) in Europe during the period 1985–1989. The number of children in each sex-age category is shown at the base of corresponding column. The error bars represent 95% confidence intervals of the observed survival proportions.

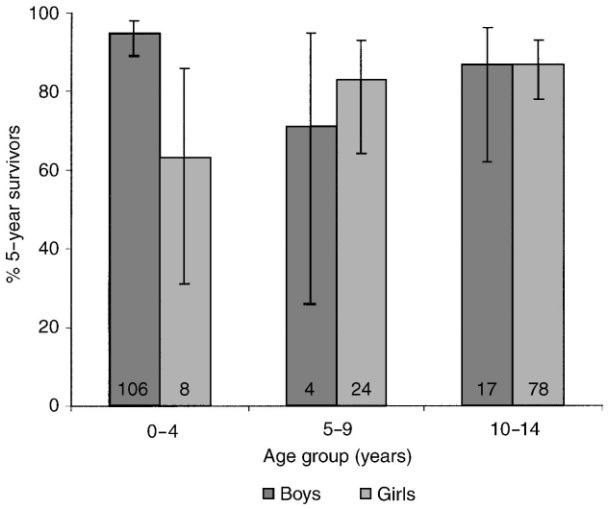

Fig. 4. Proportion of five-year survivors among 237 children diagnosed with gonadal germ cell tumours (Xc) in Europe during the period 1985–1989. The number of children in each sex-age category is shown at the base of corresponding column. The error bars represent 95% confidence intervals of the observed survival proportions.

3.4. Gonadal carcinomas (Xd)

There were only 28 cases of gonadal carcinomas in the EUROCARE database covering the total period 1978–1992. Since no boys were registered during 1985–1989, the results for the longer period 1978–1989 are reported in Table 4, but survival figures are imprecise due to the still relatively small numbers of cases. Time-trend and geographical analyses were not conducted because of the meagre size of the subgroups.

3.5. Other and unspecified (group Xe)

In the period of 1978–1989 there were 14 cases classified in the Xe ICCC subgroup in the contributing registries. This number of eligible cases would give unreliable estimates of survival, it is therefore not reported.

4. Discussion

This first systematic assessment of survival of children with germ cell, trophoblastic and other gonadal neoplasms demonstrates that 80% of patients diagnosed in 1985–1989 in Europe survived at least 5 years after their diagnosis. This is a relatively favourable overall outcome of this population-based survival study. However, large differences in the proportion of survivors were observed among the different subgroups of patients. While, for example, over 90% of all infants with extracranial non-gonadal germ cell tumours survive 5 years, intracranial and intraspinal germ cell tumours in infants are still fatal within 5 years and the prognosis remains extremely poor for children aged 1–4 years. Differences were also observed between the two sexes, the overall survival being slightly inferior in girls.

The quality of data included in this study was relatively high with more than 95% of cases microscopically verified, no DCO cases and less than 3% of cases lost to follow-up. The quality and comparability of incidence data for the relevant time period of most of the registries contributing to this EUROCARE study were examined in detail and certified in the monograph International Incidence of Childhood Cancer [1].

The Surveillance, Epidemiology and End Results (SEER) Programme in the USA [15] reported 82% overall 5-year relative survival for children diagnosed in 1985–1994 with the tumours classified in the ICCC group X, which is similar to the 80% survival in EUROCARE and the results for the diagnostic subgroups did not differ markedly from those in Europe.

The present analysis confirmed results of population-based studies previously published in Europe [3,4,5,16] and provided a possibility of formal testing of the differences, although this was often limited by the small number of cases. Continuing follow-up and update of the EUROCARE database into the future will enable further evaluation of geographical and other differences in the survival of patients with specific tumour types.

The countries with formerly socialist economies represented by Estonia, Poland, Slovakia and Slovenia tended to have lower survival, although the difference was not always possible to quantify because of the small number of cases.

The differences in the outcome between the different subgroups of patients categorised by sex, age-group or country within the same diagnostic group show a potential for improvement on all levels of health care and patient management. In several comparisons, the subgroups with larger numbers of cases tended to have higher survival. This might be partly due to a better management of more frequently encountered tumour types (the effect of centralisation of treatment) [20], but also due to non-similar representation of different histology groups in individual age–sex subgroups of patients. For example, survival of CNS germ cell tumours (Xa) is related to histology, germinomas doing much better than non-germinomas ('secreting tumours') [21]. Germinomas are more often found in older and non-germinomas in younger children; a statistically significant trend of this pattern was confirmed also in the present dataset (data not shown). In contrast, in the group of the extracranial extragonadal germ cell tumours (Xb), almost all tumours in children under 5 years of age were non-germinomatous; this age group being associated with a high survival.

The association between the histology type and survival differed according to sex in the subgroup of gonadal germ cell tumours (Xc). In girls, the majority of gonadal tumours occurred after 10 years, the age group comprising

both germinomas (39%) and non-germinomas (61%) and showing the best point estimate of survival among the three age groups. Survival in boys was very high in the age group 0–4 years, where virtually all tumours were non-germinomatous, represented by classic childhood germ-cell tumours (often yolk-sac tumours). The survival was also relatively high in the age group 10–14 years, where 23% of tumours were germinomas, the adult type of the tumour. The 87% 5-year survival (95% CI = 62, 96) in this age group is in agreement with the 5-year relative survival of 91% for adolescents and young men (aged 15–44 years) with testicular cancer (ICD-9 185) observed in the EUROCARE II study for the period of 1985–1989 [8].

The positive finding of this study was the improvement of survival over time. During more than 20 years of follow-up, survival improved for the three largest subgroups: non-significantly for intracranial and intraspinal germ cell tumours, and significantly for the other germ cell tumour categories (Xb and Xc). The improvement seems to be universal and was reported from Europe [3,4,16], the USA [15] and other countries [17,18].

Although the treatment methods were not examined in this EUROCARE study, the remarkable improvement in the outcome over time is in large part likely to be due to advances made in treatment. In the case of germ cell, trophoblastic and other gonadal neoplasms, childhood patients benefited from the success of therapeutic methods applied to adults with germ cell tumours, notably the intensive platinum-based chemotherapy regimens combined with bleomycin and vinblastine or etoposide [6,19]. The high survival was, however, accompanied with some toxic effects affecting particularly renal, auditory, pulmonary and reproductive functions. In the 1990s, the joint priorities are to save lives and preserve normal organ function where possible [6].

In several European countries, large clinical trials conducted since the early 1980s have led to significant progress. Of special interest are the treatment protocols used in the UK and Germany, these two countries representing the large majority of cases included in the EUROCARE study.

In the UK, the first national protocol for children with malignant extracranial germ cell tumours corresponding to the Xb and Xc subgroups of ICCC ran from 1978 to 1988 (GCI). In the early years of the study, children requiring chemotherapy were given VAC-based treatment (vincristine, actinomycin and cyclophosphamide) but this was replaced by more effective platinum-based regimens in the later years (PVB — cisplatin, vinblastine and bleomycin; then BEP — bleomycin, etoposide and cisplatin) [22]. For 122 evaluable patients studied between 1978 and 1987, 5-year actuarial survival was 83%, but renal toxicity and hearing impairment attributed to the cisplatin were present in some survivors [23]. The second UKCCSG study (GCII) opened in 1989 and aimed to maintain high cure rates, while reducing drug-induced toxicity and surgical morbidity. Carboplatin was used instead of cisplatin with etoposide and bleomycin (JEB) for patients needing chemotherapy and damaging surgery was avoided in favour of biopsy and then chemotherapy for children with extensive tumours. For 184 patients treated between 1989 and 1997, 5-year survival was 93%. While non-fatal haematological toxicity was common, ototoxicity and renal toxicity were rare [24]. In the UK, about 75% of children with extracranial germ cell tumours were entered on the national clinical study GCII in the period 1989–1997.

In Germany, children with malignant extracranial non-testicular tumours have been treated with the Maligne Keimaelltumoren (MAKEI) series of protocols since 1983 with platinum-based chemotherapy protocols. There were some treatment-related deaths and renal impairment, which were reduced in MAKEI 89, using refined chemotherapy regimens [25–27]. Boys with testicular tumours in Germany have been treated with the MAHO protocols 82, 88 and 94. Surgery alone cured about two-thirds of the cases, the remainder requiring PVB chemotherapy, resulting in high survival [27,28]. In Germany, some 95% of germ cell tumours are entered into clinical trials, the proportion being lower for carcinomas (Xd, about 50%) and other and unspecified gonadal neoplasms (Xe, 67%) [29].

In France, patients with extracranial non-seminomatous tumours (requiring chemotherapy) who were treated at the Institut Gustave Roussy between 1978 and 1984, received actinomycin, cyclophosphamide, vincristine, bleomycin, doxorubicin and cisplatin. The first protocol of the French Society of Paediatric Oncology (SFOP TGM 85) ran from 1985 to 1989 [30,31]. The first Italian AEIOP protocol opened in 1991 [32].

Intracranial germ cell tumours are for treatment purposes divided into germinomas and secreting tumours (that is germ cell tumours, mostly non-germinomas, producing alpha-fetoprotein or high levels of human chorionic gonadotrophin). The conventional treatment for intracranial germinoma is craniospinal radiotherapy and this has produced cure rates, for example in the German MAKEI 86 and 89 protocols, approaching 100% [33], albeit with some endocrine and cognitive late effects. The SFOP TC 88 protocol introduced a combination of chemotherapy and local irradiation for non-metastatic cases with similar encouraging results [21].

Non-germinoma/secretory tumours had a very poor prognosis before the use of chemotherapy [34]. The German MAKEI and French TC protocols using chemotherapy, as well as surgery and irradiation showed very good response [21], radiotherapy being craniospinal in Germany, but limited when possible to

local treatment in France. For European patients receiving both radiation and cumulative cisplatin doses of 400 mg/m^2, the survival was better than for treatment with lower doses and there were no survivors among those having no cisplatin-containing chemotherapy [27]. In 1996, an international study under the auspices of International Society for Pediatric Oncology (SIOP) was opened for germinomas and secreting tumours with encouraging preliminary results.

5. Conclusions

The overall survival of childhood cases of germ cell, trophoblastic and other gonadal neoplasms is relatively high, although differences in outcome were observed between subgroups defined by tumour type, age, sex and country of origin of the patients. The existence of such differences indicates a potential for further improvements. A marked improvement of survival was observed over the period 1978–1992 in Europe, which is attributed primarily to advances in treatment.

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