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Survival for retinoblastoma in Europe

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Abstract

The survival of 954 cases of retinoblastoma, diagnosed between 1978 and 1989 in 28 populations belonging to 17 European countries and covered by cancer registration, is analysed in this study. Data were collected in the framework of the EUROCARE study following a common protocol and data-check procedures and were analysed centrally by the Kaplan–Meier method and by the Cox regression model. Overall 5-year survival in the European pool was 93% (95% confidence interval (CI): 91–95%), for both sexes. Five-, 10- and 18-year survival for a subset of 235 patients diagnosed in 1978–1981 was 91, 89 and 86%, respectively. Children diagnosed in their first year of age had a slightly higher survival (94%) than those diagnosed subsequently (92%). Survival rates lower than the European average were found in the Eastern European countries, Italy, England and Wales, Scotland, Spain and Denmark. Higher survival was found in the other Nordic countries and in Central European countries. However, none of these differences was statistically significant. There was statistically significant effect related to the period of diagnosis, with a 50% reduction in the relative risk (RR) for children diagnosed in 1986–1989 compared with those diagnosed in 1978–1981.

1. Introduction

Retinoblastoma is a rare malignant eye tumour of childhood, characterised by one of the youngest age at onset of all childhood malignancies. It is a potentially curable and preventable tumour, but the outcome can be seriously impaired by the occurrence of multiple malignancies, chromosomal abnormalities, mental retardation and by the iatrogenic effects of therapy.

The genetic model proposed at the beginning of the 1970s to explain the occurrence of retinoblastoma has become paradigmatic in oncology [1]. Two main types can be identified: hereditary (bilateral and familial unilateral cases), at earlier onset, which are generally diagnosed within the first year of age, and non-hereditary (unilateral). Approximately 40% of retinoblastoma cases have been estimated to be hereditary [2].

The incidence of retinoblastoma is greatest in the first year of life, it declines after this and becomes extremely uncommon in children aged 10 years and over. Prognosis is good compared with other tumours, but this is strictly related to an early diagnosis, the extension of the tumour and the possibility of treatment [3].

Surgical enucleation of the eye is still often performed, but during the last decades efforts have been made towards conservative therapy. Chemotherapy, lasertherapy and local radiotherapy are increasingly employed to reduce the extent of surgery, prolong survival and preserve sight [3]. The therapeutic approach is therefore complex and requires a strict collaboration of oncologists, ophthalmologists and geneticists.

The annual incidence of retinoblastoma varies between 7 per million in African populations, where it represents 10–15% of childhood neoplasms, to 3–6 per million in Europe and the US, where retinoblastoma accounts for 2–4% of childhood cancers, and rates lower than 3 per million in Asian populations [5].

Given the very low incidence of retinoblastoma, a sufficiently high number of cases to study patterns of survival reliably, can be recruited only by large multicentric studies such as the EUROCARE study. This study presents survival by age at diagnosis, sex and geographical areas within Europe, and analyses time trends of survival in the time period of 1978–1989.

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2. Patients and methods

Nine hundred and fifty-four cases from 28 European population-based cancer registries in 17 countries were included in the study. All cases were recruited within the framework of EUROCARE, a population-based study on survival and care of cancer patients in Europe, including cases diagnosed from 1978 to 1989. Cases were collected following a common study protocol, and data checks and basic analyses were performed centrally. Survival rates were computed by the Kaplan–Meier method [6]. Multivariate survival analysis by the Cox regression model [7] was performed in order to estimate the prognostic value of different factors simultaneously. Statistical analyses were performed by the Statistical Package for the Social Sciences (SPSS).

Descriptive and univariate survival analysis were carried out on the total number of cases. In the multivariate analysis, considering the period of diagnosis as a prognostic factor, only those registries providing the complete 1978–1989 study period, were included. In this last analysis, countries with a relatively low number of cases were grouped as follows: Finland, Sweden and Iceland (Nordic countries); Estonia and Slovakia (former Eastern European block); The Netherlands, France and Switzerland (Continental Europe).

3. Results

Table 1 shows for each country the total number of cases, the study years and the distribution of age, sex and microscopic confirmation. For most countries, the study covered the entire period from 1978 to 1989, however, not all the registries belonging to one country provided data covering the same years.

In nine out of 17 countries, 11 cases or less were included in the study. 37% of the cases were diagnosed within their first year of life, 60% of cases were aged less than 2 years and 90% of the cases occurred in children younger than 4 years, and all cases were aged less than 12 years (data not shown).

Cases were equally distributed by sex. The overall percentage of microscopic confirmation was 89%. Excluding the 7 cases from the Dutch registry of Eindhoven (57%), it ranged from 75 to 100%. A part of this variability is simply due to the low number of cases in some registries. Denmark, the UK, Italy and Slovenia had less cases of microscopy confirmed than the overall European average.

The number of new cases observed in the areas of the participating cancer registries has increased during the 1980s. Fig. 1 shows the number of new cases collected by the cancer registries over the period of 1980–1989. Years 1978 and 1979 were excluded due to the lack of complete data from the German cancer registry. Incidence increased from approximately 5–100 new cases diagnosed per year, in the considered study population. Over the same time period, the mean age at diagnosis remained constant at approximately 20 months suggesting that there was no substantial changes in diagnostic techniques or practices. Table 2 shows the 5-year observed overall survival and for each age group for each country. Children diagnosed in their first year of age had a slightly higher survival than those diagnosed at older ages. Survival was lower for the youngest children only in Estonia, Finland, Italy and Scotland. Overall, 5-year survival in the European pool was 93%

Table 1
Retinoblastoma: cases diagnosed in 1978–1989 in the EUROCARE study. Total number of cases and the percentages of patients aged 0–12 months, % of males and % of microscopically confirmed tumours, by country

	Total number of cases *n* (%)	Study period	% Patients aged 0–12 months	% Males	% Microscopically confirmed	Number of cases lost to follow-up
Austria	3 (0.3)	1989		100	100	0
Denmark	38 (4)	1078–1989	29	61	88	0
The Netherlands	7 (0.7)	1978–1989	43	29	57	6
England and Wales	360 (38)	1978–1989	43	54	78	5
Estonia	11 (1)	1978–1989	27	46	100	1
Finland	45 (5)	1978–1989	27	56	100	0
France	11 (1)	1978–1989	46	64	91	1
Germany	296 (31)	1980–1989	35	51	100	13
Iceland	3 (0.3)	1978–1989	67	68	100	0
Italy	30 (3)	1978–1989	30	53	87	0
Poland	1 (0.1)	1989		100	100	0
Scotland	51 (5)	1978–1989	41	53	88	0
Slovakia	63 (7)	1978–1989	22	48	100	0
Slovenia	8 (0.8)	1985–1989	13	50	75	0
Spain	10 (1)	1986–1989	30	20	100	0
Sweden	14 (1)	1978–1989	36	36	100	0
Switzerland	3 (0.3)	1978–1989			100	0
European pooled data	954 (100)	1978–1989	37	52	89	26

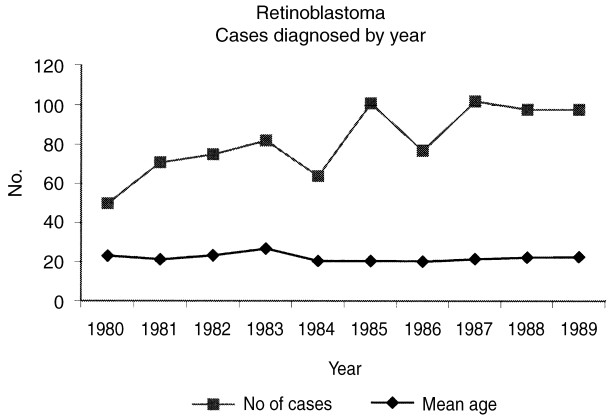

Fig. 1. Time trends of incidence and mean age at diagnosis (in months) in the European pool.

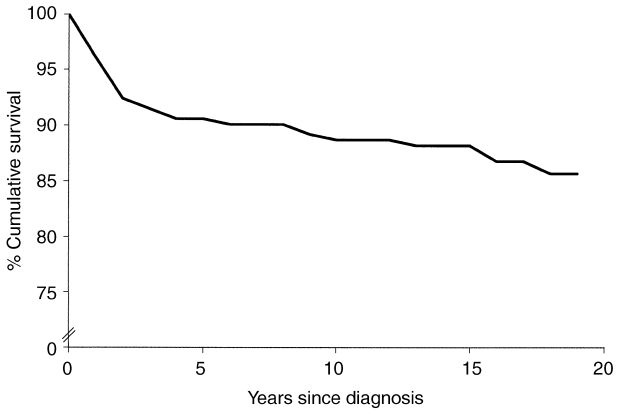

Fig. 2. Long term observed survival of retinoblastoma in the European pool.

for both sexes. Figures lower than this average were found in Denmark, England and Wales, Estonia, Slovakia, Italy, Scotland, Spain and Switzerland. None of these differences was statistically significant, and in Switzerland there were only 3 cases, of whom 1 (girl, aged 1.5 years) died in the second year after diagnosis. Long-term survival rates were estimated for the 235 patients diagnosed in the years 1978–1981, who were followed-up at least until December 1995 (Fig. 2). In this group of patients, survival was 96, 92, 91, 89 and 86% at 1, 3, 5, 10 and 18 years, respectively. Available data did not allow survival estimates for a longer period of follow-up.

Table 3 shows the results of the multivariate survival analysis carried out in order to investigate geographical differences in survival taking into account also the effect of age at diagnosis, sex and period of diagnosis. In this analysis, only the registries with cases from the entire study period from 1978 to 1989 were included, for a total of 922 patients. Countries with a relatively high number of cases were considered individually, the remaining were grouped into Nordic countries, Eastern European countries and Continental Europe. Countries grouped in these areas had a similar survival (with the exception of Switzerland), Italy was considered individually due to the low figures which emerged in the univariate analysis. England was the reference category. Age at diagnosis was treated as a continuous, independent variable. Period of diagnosis was divided into four 4-yearly intervals, 1978–1981 being the reference category.

Table 2
Retinoblastoma. Cases diagnosed in 1978–1989 in the EUROCARE study[a,b]

	Total number of cases	5-year observed survival by age group			All ages (95% CI)
		0 (95% CI)	1–4 (95% CI)	5+ (95% CI)	
Austria	3	*100* (44–100)	*100*	–	*100 (55–100)*
Denmark	38	100 (74–100)	85 (66–94)	*100*	89 (76–96)
Netherlands	7	*100* (44–100)	*100* (44–100)	–	*100 (65–100)*
England and Wales	360	94 (88–96)	92 (87–95)	91 (71–97)	92 (89–95)
Estonia	11	33 (6–79)	100 (65–100)	*100* (21–100)	80 (49–94)
Finland	45	92 (65–99)	97 (83–99)	*100* (51–100)	96 (85–99)
France	11	*100* (51–100)	*100* (51–100)	–	100 (68–100)
Germany	296	100 (96–100)	93 (88–96)	90 (57–98)	95 (92–97)
Iceland	3	*100* (34–100)	*100* (21–100)	–	*100* (45–100)
Italy	30	75 (41–93)	86 (60–96)	*100* (34–100)	83 (63–93)
Poland	1	–	*100* (21–100)		100
Scotland	51	90 (71–97)	90 (74–96)	*100* (21–100)	90 (79–96)
Slovakia	63	93 (69–99)	89 (77–95)	*100* (44–100)	90 (81–96)
Slovenia	8	*100* (21–100)	100 (65–100)		100 (68–100)
Spain	10	100 (44–100)	*82* (44–97)	*100* (21–100)	90 (60–95)
Sweden	14	100 (57–100)	100 (65–100)	*100* (34–100)	100 (78–100)
Switzerland	3	–	*67* (21–94)	–	67 (21–95)
European pooled data	954	94 (91–96)	92 (89–94)	92 (79–97)	93 (91–95)

[a] Five-year observed survival by age and overall, for each country.
[b] Five-year survival figures based on less than 5 cases are in italics.
–, no cases in the age group.

Table 3
Retinoblastoma: cases diagnosed in 1978–1989[a]

Factor (*n* of cases in parentheses)	RR[b]	95% CI
Country/area		
England and Wales[c] (360)	1	
Denmark (38)	1.12	0.39–3.24
The Netherlands, France, Switzerland (18)	0.65	0.08–4.95
Estonia, Slovakia (74)	1.54	0.75–3.19
Finland, Sweden, Iceland (62)	0.45	0.14–1.52
Germany (296)	0.85	0.46–1.57
Italy (23)	1.73	0.59–5.04
Scotland (51)	1.19	0.49–2.88
Age at diagnosis (922)	1.07	0.94–1.22
Sex		
Boys[c] (482)	1	
Girls (440)	0.91	0.58–1.44
Period		
1978–1981[c] (235)	1	
1982–1985 (312)	0.99	0.57–1.67
1986–1989 (375)	0.50*	0.26–0.93

*$P < 0.05$.
[a] Multivariate survival analysis (Cox regression model). Only registries with cases from the complete study period were included.
[b] RR, relative risk of death compared to the reference category.
[c] Reference category.

A lower relative risk of death (RR) compared with England and Wales was found in the Nordic countries, Continental Europe and Germany. The RR was higher than the reference in Estonia and Slovakia and in Italy. None of these differences reached statistical significance. There was approximately 1% increase of the RR by each increasing year of age. Females had an approximately 10% lower RR than males. There was a statistically significant effect related to the period of diagnosis, with a 50% reduction in the RR for children diagnosed in 1986–1989 with respect to those diagnosed in 1978–1981.

4. Discussion

Only multicentric collaborative studies can collect a sufficient number of cases to carry out reliable analyses on very rare tumours such as retinoblastoma. This is one of the largest population-based studies published worldwide.

Many of the published studies report microscopically confirmed cases only [8] or a majority of such cases [2]. In this population-based study, the proportion of tumours confirmed microscopically varied around an average value of 89%. The pathology records are one of the most reliable sources of data for cancer registries, and an underreporting was not evidenced for childhood cancer in the EUROCARE study [9]. Therefore, the variable proportion of microscopic verification suggests some actual variability in the care and diagnostic procedures for retinoblastoma in Europe. For instance, the proportion of microscopic confirmation depends on the type of therapy, which can be surgical (enucleation), or eye saving (radiotherapy or lasertherapy). In a large study carried out in Britain on cases diagnosed from 1962 to 1980, 92% cases were histologically confirmed, the proportion corresponding to that of patients treated surgically. A conservative treatment was used more frequently in the bilateral forms than in the unilateral ones (15% versus 5%), with the aim of preserving sight.

As reported also by other authors, the two sexes were equally represented. In addition, the age distribution was similar to that reported in literature, with more than half the cases occurring before 3 years, cancers occurring before 2 years of age [8,10,12].

Overall survival exceeded 90% in most countries, in agreement with data from most authors in the different countries [8,10,12]. However, there was some inter-country variability within Europe, even though it was lower than that observed for other tumours. A part of this variability is due to the low number of cases; the low survival rate of Switzerland, for instance, was based on 3 cases only. When countries were grouped according to their survival levels and geographical regions in the multivariate analysis, approximately the same levels as those found in adults [13] were seen. Nordic and Continental Europe and Germany fared better than the other European areas, the Eastern European countries had a low survival.

A noticeable result of this study was the poor prognosis in Italy, with an overall survival of 83% (95% confidence interval (CI) 63–93), similar to that in Estonia (80% (95% CI 49–94)). Although there was a low number of cases observed in Italy, this figure requires further investigation, as it may be an indicator of a lack of a centralised management. A specific study may be advisable, carrying out confidential surveys aimed at investigating the prognostic factors and the reasons for the poor outcome. In addition, it is possible that the improving trend in survival that emerged from this study will decrease the differences in survival between countries for patients diagnosed after 1989.

Survival was reported to be higher in the non-hereditary forms than in the familial cases [2,11], and in the unilateral than in the bilateral forms [10]. The poorer prognosis of the hereditary tumours can be explained by the more frequent bilaterality, by multiple tumours associated with familial retinoblastoma, and by the long-term effects of the therapies. A part of the differences in survival between countries can be explained by the different proportion of hereditary and non-hereditary forms in the different populations.

The hereditary bilateral forms are likely to occur during the first year of life. In the present study, we were not able to distinguish between hereditary and non-hereditary forms, but the youngest group, in which the

hereditary forms should be more frequent than in older patients, had a slightly higher survival than the older patients. This is contrary to the above mentioned hypothesis. The better prognosis of younger patients could be due to an anticipation of diagnosis of retinoblastoma in patients belonging to affected families.

We found a better prognosis for patients diagnosed in the last study period compared with those diagnosed in 1978–1981. An increase in survival has also been reported by other authors, both in Europe [2,12] and in the US [11]. The analysis of time trends of mortality, which would help interpret incidence and survival trends, is more difficult, because in the mortality statistics all tumours of the eye are grouped together. However, the analysis of time trends of mortality indicates a slight decrease in the period 1950–1989 [14], which is particularly evident between the 1970s and 1980s. This is similar to what has been observed for other childhood cancers [15]. This is probably related to the implementation of chemotherapy and radiotherapy as adjuvant treatments. In the present study we found a reduction of the relative risk of death over the study years that was particularly evident for patients diagnosed in 1986–1989, who had 50% reduction of their death risk compared with patients diagnosed in the first study period (1978–1981). This risk reduction was not uniformly distributed across countries, but was particularly evident in the Nordic countries and in Germany (data not shown). Although studies on patterns of care for retinoblastoma are scarcely available, the increase of survival and the slight decrease in mortality, suggest an increased efficacy of therapies.

Incidence has been, in general, fairly stable over the last decades, and the observed small increases have been attributed to register artifacts [2], or are negligible [10,11,16]. In England, an increase of bilateral sporadic cases only was reported, but the overall incidence has remained stable over the period of 1960–1989 [17]. In this study, we found a slight increase in the total number of cases, which could be attributed to a more complete ascertainment over time. However, age at diagnosis remained constant over the study period, suggesting that this increase of cases was not related to earlier diagnoses.

In most cases, the prognosis *quoad vitam* is good, and the long-term survival figures are among the highest for any tumour. As reported in other studies analysing long-term survival [10], the risk of death was highest in the 3–4 years following diagnosis; after this survival decreases less steeply. However, the quality of life of these patients is impaired, since therapy is often surgical, and consists in the ablation of the retina or in enucleation. Conservative surgery is not always possible, and depends on the stage of the disease. In addition, these patients are at risk of developing a second tumour, which is a source of anxiety. The addition of chemotherapy or radiotherapy with surgery also increases the risk of a second tumour. Some of these problems are common to many childhood tumours, for which remarkable improvements in survival have been reached in the last two decades. For retinoblastoma, the fact that the mutations causing the disease can be transmitted to children is a further cause of anxiety and may influence the decision of having children [3]. Long-term surveillance is mandatory for patients cured of retinoblastoma to monitor for unwanted late effects of treatment, including second tumours, and visual outcome [4]. In the 30–40% of cases that are hereditary, molecular studies and genetic counselling are indicated.

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