



# Survival of children with neuroblastoma: time trends and regional differences in Europe, 1978–1992

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## Abstract

Neuroblastoma is one of the most common solid cancers in children. We present the data collected for the EUROCARE II study, describing survival patterns for children diagnosed in Europe 1985–1989 in detail, and exploring time trends from 1978 to 1992. On average, the mean 5-year survival rate was considerably higher in infants (79%) compared with older children (30–33%). The risk of death has dropped by 37% from 1978–1981 to 1990–1992. There is a pronounced difference between countries, with Scotland and England and Wales having two of the lowest survival rates (28% (95% confidence interval (CI) 14–48) and 36% (95% CI 31–41) 5-year survival rates, respectively). The survival rates in France, Germany and Italy (48–66% 5-year survival rate) were among the highest. This pattern corresponds to the incidence rates for these countries. It can be assumed that in neuroblastoma, both incidence and survival are related to the frequency of diagnosing asymptomatic cases with good prognosis among infants. However, one cannot ignore possible intercountry differences in the effectiveness of therapy. © 2001 Elsevier Science Ltd. All rights reserved.

**Keywords:** Neuroblastoma; Survival rates; Time trends in survival; Europe

## 1. Introduction

Neuroblastoma is the most common extracranial solid tumour in children, accounting for approximately 6–10% of all childhood malignancies in European registries [1,2]. It is the most common neoplasm in infants and the leading cause of cancer deaths in children aged 1–4 years [3]. There is evidence for an increase in the incidence of neuroblastoma in the past decades, possibly due to better health care, screening programmes and the increasing availability of ultrasound devices for paediatricians [4,5].

The biology and molecular biology of neuroblastoma are beginning to be well understood. The tumour originates from the cells of the neural crest and can arise from the adrenal gland or any site of the paravertebral

sympathetic chain [6]. The primary site is most frequently found in the abdomen, followed by the thorax and neck.

Very little is known about the external risk factors of neuroblastoma, although this issue has been investigated in a number of studies. The only factor described repeatedly is the maternal use of sex hormones before or during early pregnancy, which seems to increase the risk of developing a neuroblastoma for male children only [7,8].

Survival in neuroblastoma depends on the stage of the disease and the children's age, but also on a number of other variables such as *N-Myc* amplification, chromosomal aberrations, and ploidy. It has been shown that the prognosis of neuroblastoma is much more favourable in infants than in older children, even when the disease presents at a more advanced stage [9,10]. In recent years, it has been suggested that neuroblastoma is really not one, but two or more distinct diseases entities with different clinical behaviour and prognosis and this has been the subject of much debate [11,12].

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Thanks to the concerted effort of 34 population-based cancer registries from 17 countries, the EUROCARE centralised database [13] now provides an opportunity to study the survival from rare cancers like neuroblastoma. In this study, we describe the survival pattern of children with neuroblastoma diagnosed in Europe in 1985–1989, and explore the time trends in survival from 1978 to 1992. In the framework of the EUROCARE I (1978–1985), the survival of neuroblastoma was not analysed [14].

## 2. Patients and methods

### 2.1. Patients

Survival analysis was carried out on 1094 cases of neuroblastoma diagnosed in children aged 0–14 years in 1985–1989 (Tables 1 and 2). Neuroblastoma (ICD-O morphology categories 9490 and 9500) accounted for 7% (1094/16148) of all childhood cancer cases in the EUROCARE database for that period. The nationwide registry in Germany and the registry of England and Wales provided the largest numbers of cases. Finland, Denmark, Scotland, Italy, Spain and Slovakia contributed more than 20 cases each. Some other European countries provided a handful of cases.

Table 1 presents some basic data for 1985–1989. As has been observed before, slightly more than half of the cases were boys. Overall, approximately 37% of all cases were infants. In Scotland and England and Wales, there were more older cases, while in Finland there were more younger ones than on average (countries with small numbers or incomplete registration not mentioned).

The rate of histological verification was generally good. There was hardly any loss to follow-up.

### 2.2. Statistical methods

The 1-, 2-, 3- and 5-year survival rates and their 95% confidence intervals were estimated using the actuarial method. They were computed by age groups and for each country. The age groups analysed were 0 < 1, 1–4, 5–9, 10–14 and all age groups. Additionally, we have calculated a European estimate using pooled data and a European estimate using national data weighted by the national population. Because the size of the registry populations is very unbalanced with Germany and England and Wales together providing 74% of all the cases, the pooled estimate is practically a mean estimate of these two countries. It would be a valid estimate for European survival if Germany and England and Wales together were representative for all of Europe. The weighted estimate would be valid only if the figures

Table 1  
Neuroblastoma cases by age, gender and country, 1985–1989<sup>a</sup>

Registries in	No. of cases (%)	% Male	% infants (age 0–< 1 years)	% HV	% LFU
<b>Northern Europe</b>					
Denmark	37 (3)	62	38	100	0
Finland	43 (4)	63	51	–	0
Iceland	1 (0.09)	100	0	100	0
Sweden <sup>b</sup>	5 (0.5)	40	60	80	0
<b>UK</b>					
England and Wales	373 (34)	53	29	93	0
Scotland	25 (2)	72	24	92	0
<b>Western and Central Europe</b>					
Austria <sup>b</sup>	1 (0.09)	100	0	100	0
France <sup>b</sup>	15 (1)	73	13	100	0
Germany	432 (39)	57	38	100	6
Switzerland <sup>b</sup>	6 (0.5)	67	17	100	0
The Netherlands <sup>b</sup>	6 (0.5)	83	33	83	17
<b>Southern Europe</b>					
Italy <sup>b</sup>	55 (5)	51	38	93	6
Spain <sup>b</sup>	21 (2)	43	29	100	5
<b>Eastern Europe</b>					
Estonia	10 (0.9)	60	20	100	0
Poland <sup>b</sup>	3 (0.3)	100	0	100	0
Slovakia	48 (4)	48	42	100	0
Slovenia	13 (1)	54	62	100	8
<b>Europe</b>	<b>1094 (100)</b>	<b>56</b>	<b>35</b>	<b>93</b>	<b>3</b>

HV, histologically verified; LFU, lost to follow-up.

<sup>a</sup> Source: EUROCARE II data.

<sup>b</sup> Less than 20% of the childhood population covered.

Table 2

Estimated survival probability for neuroblastoma in % (95% CI) by country and age (both genders, diagnosed 1985–1989 (EUROCARE II))<sup>a,b,c</sup>

Country	N (cases)	All ages 1-year survival	All ages 5-year survival	Age 0–<1-year survival	Age 0–<1 5-year survival
Northern Europe					
Denmark	37	76 (60–87)	32 (20–49)	71 (45–88)	64 (39–84)
Finland	43	81 (67–90)	65 (50–78)	77 (57–90)	68 (47–84)
UK					
England and Wales	373	69 (64–73)	35 (31–40)	78 (69–85)	76 (67–83)
Scotland	25	60 (41–77)	28 (14–48)	50 (19–81)	50 (19–81)
Western and Central Europe					
France <sup>d</sup>	15	93 (69–99)	48 (23–74)	100 (34–100)	100 (34–100)
Germany	432	83 (79–87)	58 (54–63)	91 (86–94)	89 (83–93)
Southern Europe					
Italy <sup>d</sup>	55	78 (66–87)	66 (52–77)	76 (55–89)	67 (45–83)
Spain <sup>d</sup>	21	68 (41–79)	52 (32–72)	67 (30–90)	67 (30–90)
Eastern Europe					
Slovakia	48	58 (44–71)	44 (31–58)	60 (39–78)	55 (34–74)
Slovenia	13	77 (50–92)	62 (36–82)	75 (41–93)	75 (41–93)
Europe (pooled)	1094	75 (73–78)	48 (45–51)	82 (78–85)	79 (75–83)
Europe (weighted)		76 (69–82)	51 (44–57)	82 (64–92)	79 (62–90)

<sup>a</sup> Results from countries with 10 cases or less not reported, but included in the pooled and standardised European estimate.<sup>b</sup> Standardised relative survival for all ages was computed for Denmark, England and Wales, Germany, Italy, Spain and Europe standardised, all other survival figures given are raw. Standardised and raw survival rates differ only marginally.<sup>c</sup> Source: EUROCARE II data.<sup>d</sup> Less than 20% of childhood population covered.

from countries with incomplete coverage (<20%) of the national population were representative for their respective countries. As the differences between the two estimates for all of Europe are small, the pooled estimate was presented where a choice had to be made [15].

For geographical survival comparisons, data are presented for countries with more than 10 cases reported between 1985–1989 or 1990–1992; while for time trends in survival, only registries with 30 cases or more between 1978 and 1992 were included. The differences between the time periods were investigated using multiple Cox regression including age at diagnosis, country and gender as potential confounders. The differences between the countries were investigated using a multiple Cox regression investigating age at diagnosis and gender as potential confounders. As the results differ somewhat from those obtained using the crude relative risk of death, confounding seems to be present and the more valid corrected results are presented.

### 3. Results

#### 3.1. Survival rates 1985–1989

Survival rates are presented by age and country. Gender is not a predictor of survival in neuroblastoma.

Fig. 1 shows that the 1-year survival rate (70–84%) did not differ considerably by age at diagnosis, although

it was highest for infants (0–<1 years, 82%) and older children (10–14 years, 84%) and lowest for young children (1–4 years, 70%). In infants (0–<1 years) hardly any deaths were observed after the first year of follow-up, while in the older children (1–14 years) survival dropped dramatically to approximately 30–33% after 5 years. The oldest children (10–14 years) initially con-

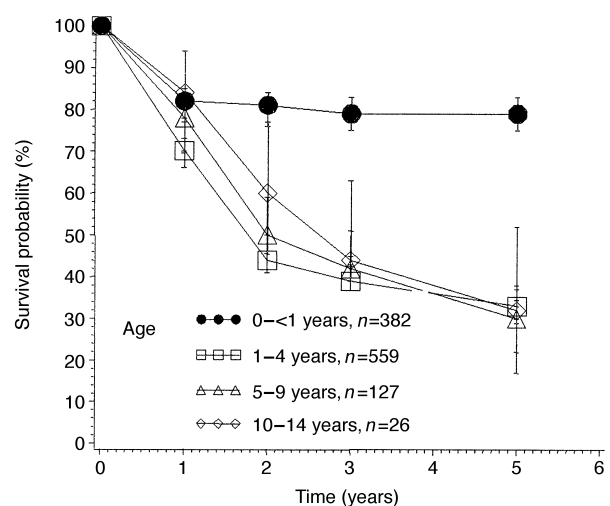


Fig. 1. Estimated survival of children with neuroblastoma by age, Europe pooled, 1985–1989 (EUROCARE II,  $n=1094$ ). No difference between weighted and unweighted summary estimates, so pooled data is presented. At 1, 2, 3 and 5 years, 95% confidence intervals for the point estimates are indicated. Source: EUROCARE II data.

tinued to have a slightly better survival than the 1–9 age group, but 5 years after diagnosis no difference was observed (30–33%) (Fig. 1).

There was no major difference between the European pooled and European standardised (weighted mean) survival estimates. Note that within the countries providing larger numbers of cases, no difference between standardised and non-standardised estimates was seen either (data not shown). For infants, the European survival rate was 82% (95% CI 78–85) at 1 year, and 79% (95% CI 75–83) at 5 years (Table 2). Especially low 1-year rates were observed in Scotland and Slovakia (50% (95% CI 19–81) and 60% (95% CI 39–78), note that the CIs do not include 82%), a high rate was observed in Germany (91% (95% CI 86–94) note again that the CIs do not include 82%). Low 5-year rates were observed in Scotland (50% (95% CI 19–81)) and Slovakia (55% (95% CI 34–74), again the CIs do not include the European rate of 79%). A high rate was observed again in Germany (89% (95% CI 83–93), CIs do not include 79%).

The average 5-year survival rate of all cases was 48% (95% CI 45–51). A much worse 5-year survival was observed in Scotland (28% (95% CI 14–48)), Denmark (32% (95% CI 20–49) and England and Wales (35% (95% CI 31–40), CIs do not include 48%). A much better 5-year survival was observed in Italy (66% (95% CI 52–77), CIs do not include 48%), Finland (65% (95% CI 50–78), CIs do not include 48%), Slovenia (62% (95% CI 36–82)), and Germany (58% (95% CI 53–62), CIs do not include 48%) (Table 2).

Note that, because of the considerable difference between survival for ages 0–<1 and  $\geq 1$ , the proportion of infants among the cases influences the overall survival. See, for example, Scotland and England and Wales, both with low fractions of infants and low survival rate, while Italy and Finland are high in both respects. With the exception of France (15 cases only) all countries, for the most part, fit into this general pattern (Tables 1 and 2).

Table 3  
Trends in survival from neuroblastoma from 1978 to 1992. Europe pooled (EUROCARE II)<sup>a,b</sup> based on 2657 cases

Period	Relative risk of death (95% CI) <sup>c</sup>	P value
1978–1981	1.00	
1982–1985	0.74 (0.63–0.87)	0.0001
1986–1989	0.72 (0.62–0.83)	0.0001
1990–1992	0.63 (0.54–0.74)	0.0001

<sup>a</sup> Countries included: Denmark, England and Wales, Estonia, Finland, Germany, Scotland, and Slovakia ( $\geq 30$  cases each in the investigation period).

<sup>b</sup> Source: EUROCARE II data.

<sup>c</sup> The multiple Cox regression model also included gender, country, and age at diagnosis.

### 3.2. Regression analysis of death rate

Comparing periods, the (age-, gender- and nation-) corrected estimate of the risk of death after diagnosis (hazard rate) dropped by 26% (95% CI: 13–37) from 1978–1981 to 1982–1985. It stayed practically unchanged until 1989 and dropped further in 1990–1992 to 63% (95% CI: 54–74) of the 1978–1981 rate (Table 3).

Country differences were investigated for 1986–1989 as for the period 1990–1992 fewer subjects with a shorter follow-up were available. England and Wales, with its relatively short survival and large registry, was chosen as the reference country. Small databases lead to wide confidence intervals, so these figures should be interpreted with caution. We see that the survival rate in Scotland, Slovenia and Denmark was about as high as in England and Wales. Scotland had the lowest survival of all the countries included. Italy and Germany had significantly better survival than England and Wales. The risk of death in these countries is 40–60% below that in England and Wales (Table 4).

## 4. Discussion

Neuroblastoma is a rare cancer and its reported incidence varies by country. High incidence rates have been observed in the Nordic countries and in the countries of Western Europe and Southern Europe. The rates are lower in Eastern Europe (Table 5) [1].

Reliable population-based data on the survival of children with neuroblastoma is available only for few countries, where a large enough population is covered by a childhood cancer registry or a general cancer regi-

Table 4  
Country differences in survival from neuroblastoma 1986–1989. Europe pooled (EUROCARE II)<sup>a,b</sup>

Country	Relative risk of death 1986–1989 (95% CI) <sup>c</sup> (875 cases)	P value
Scotland	1.11 (0.68–1.83)	0.6686
Slovenia	1.09 (0.48–2.47)	0.8300
Denmark	1.05 (0.66–1.67)	0.8493
England and Wales	1.00	–
Slovakia	0.89 (0.56–1.42)	0.6305
Spain <sup>d</sup>	0.80 (0.42–1.51)	0.4885
Finland	0.76 (0.43–1.33)	0.3335
Germany	0.60 (0.49–0.75)	0.0001
Italy <sup>d</sup>	0.50 (0.30–0.84)	0.0081
France <sup>d</sup>	0.49 (0.18–1.31)	0.1522

<sup>a</sup> Countries included: Denmark, England and Wales, Finland, France, Germany, Italy, Scotland, Slovakia, Slovenia, and Spain ( $\geq 10$  cases each in the investigation period).

<sup>b</sup> Source: EUROCARE II data.

<sup>c</sup> Less than 20% of childhood population covered.

<sup>d</sup> The multiple Cox regression model also included gender and age at diagnosis.

stry (such as England and Wales, Germany, USA SEER (Surveillance, Epidemiology and End Results)) [2,3,16,17]. In these countries, no or only a modest improvement in the survival of neuroblastoma has been observed over the past 20–30 years [3,18].

Our study demonstrated that there was a considerable increase in survival rates in Europe from 1978 to 1985. This then stagnated until some further improvement was seen since 1990. This coincides with the introduction of non-invasive diagnostic techniques and cytotoxic treatments that has occurred from the early to mid-1980s [3].

Results of the present study, based on population-based cancer registries, confirm the well-known fact that age at diagnosis is an important prognostic factor while gender is not related to prognosis in neuroblastoma. The pooled 5-year survival for infants in Europe was 79% (95% CI: 75–83) versus 30% (95% CI: 22–38) to 33% (95% CI: 29–37) for the older age groups.

A recent prospective Children's Cancer Group study showed that the 5-year event-free survival in infants with stage IV-S neuroblastoma was 86% and the overall survival was 92% with minimal therapy [10]. It has been identified that, even in stage IV disease, infants showed a good prognosis [19].

Age greater than 1 year is highlighted as an unfavourable prognostic factor, particularly in disseminated dis-

ease where the outcome remains poor despite the intensification of treatment regimens and even the use of bone marrow transplantation [20,21].

Note that 5-year survival rates, usually chosen to assess cancer treatment in adults, may not be the optimal indicator for treatment success in children, whose life expectancy would normally be far longer [22].

The European Neuroblastoma Study Group surveyed cases from participating institutions in many countries (except Germany) from 1982 to 1992 [23]. The overall survival was slightly below what we see for European pooled values for 1978–1989 (45% (95% CI: 42–48) versus 48% (95% CI: 45–51) (The following international comparisons refer to 5-year survival unless otherwise indicated.), but broken down by age the figures are quite comparable.

In 1998, SENSE (the Study group for the Evaluation of Neuroblastoma Screening in Europe) investigated differences between neuroblastoma incidences in Germany, France, UK and Austria over the time period of 1987–1991. The incidence was lower in the UK compared with the other countries; age at diagnosis was significantly higher as was the proportion of metastatic disease (stage IV). In addition, the incidence of metastatic disease in the UK was significantly higher compared with the other countries (especially after the 1st birthday), while the incidence of stages I–III and IVs was significantly lower (especially in the first year of life). The proportion of symptomatic diagnoses was considerably higher in the UK compared with the other countries. Population-based mortality was also higher in the UK [24].

These observations are in agreement with the lower survival rate in Britain compared with Germany and France described by the EURO CARE II project. The lower overall incidence in connection with the higher incidence of older cases and metastatic cases may partly explain this finding, so that differences in treatment success of diagnosed cases are not necessarily as large as they seem.

Looking beyond Europe to the United States SEER registry, we note that SEER did see an improvement in survival over time since 1975 (Table 6). The survival of infants has not improved in the SEER regions from 1975–1984 to 1985–1994. It was always higher (83%) than in the roughly corresponding periods in Europe (75%, 95% CI: 72–78 to 79%, 95% CI: 62–90). Within Europe, so far only Germany can match this (and actually exceeds it, 89%). The overall survival in the US has improved from 54 to 64% [3,4] (Table 6).

Some data from a population-based registry have also been published from Japan. The survival rate was 37% for 1975–1984 [25]. Note that screening in this region of Japan only started in 1985 (Table 6).

Availability of modern staging procedures, adherence to treatment protocols, and the quality of care for

Table 5  
Incidence per 1 000 000 children in Europe by country<sup>a</sup>

Country	Period covered	Age 0–4 years	Age 0–14 years, crude incidence
Northern Europe			
Denmark	1983–1991	25.3	9.6
Finland	1980–1989	23.8	9.2
Iceland	1960–1989	10.7	5.2
Sweden	1983–1989	18.2	7.7
UK			
England and Wales	1981–1990	20.9	8.1
Scotland	1981–1990	17.9	6.9
Western and Central Europe			
Austria <sup>b</sup>	–	–	–
France <sup>b</sup>	1983–1992	32.7	12.3
Germany	1985–1990	26.1	9.9
Switzerland	1980–1992	31.7	12.0
The Netherlands <sup>b</sup>	1989–1992	17.2	7.1
Southern Europe			
Italy <sup>b</sup>	1980–1991	25.8	8.2
Spain <sup>b</sup>	1980–1991	25.0	8.7
Eastern Europe			
Estonia	1980–1989	11.2	5.3
Poland <sup>b</sup>	1980–1989	10.8	4.9
Slovakia	1980–1989	17.4	7.1
Slovenia	1981–1990	15.3	5.3

<sup>a</sup> Source: IARC No.144 [1].

<sup>b</sup> Incidence data based on less than 20% of the childhood population.

Table 6

Comparison of selected European neuroblastoma survival data with survival data from other countries (5-year survival rate in %)<sup>a</sup>

Data set	Period	All ages (95% CI)	Age 0–<1 years (95% CI)	Age 1–<5 years (95% CI)	Age 5–<10 years (95% CI)
EUROCARE II, Europe, pooled	1978–1989	45 (43–47)	75 (72–78)	31 (28–33)	25 (20–31)
EUROCARE II, Europe, pooled	1985–1989	48 (45–51)	79 (75–83)	33 (29–37)	30 (22–38)
England and Wales <sup>b</sup>	1985–1989	35 (31–41)	76 (67–83)	19 (14–25)	18 (10–30)
Germany <sup>c</sup>	1985–1989	58 (53–62)	89 (83–93)	40 (33–46)	40 (26–56)
SEER, USA	1975–1984	54	83	35	43
SEER, USA	1985–1994	64	83	55	40
Japan	1975–1984	37	57		18

SEER, Surveillance, Epidemiology and End Results.

<sup>a</sup> Source: EUROCARE II data, published SEER data [3] and published data from the Osaka prefecture [25].<sup>b</sup> Second largest European registry.<sup>c</sup> Largest European registry.

children presenting with symptomatic neuroblastoma can differ between the countries. This would partly explain the intercountry differences in survival observed by the EUROCARE II study.

Furthermore, survival differences between European countries revealed by the EUROCARE II study likely reflect differences in health care systems. The lowest overall 5-year survival in for children aged 0–14 years has been observed for Scotland (28%, 95% CI: 14–48), Denmark (32%, 95% CI: 21–51), England (35%, 95% CI: 31–41) and Slovakia (44%, 95% CI: 31–58); based on the recent results of the EUROCARE II analyses for adult patients, these countries also showed relatively low survival rates for the major adult cancers [26]. However, high survival in neuroblastoma was seen for the countries where survival rates were typically above the European average also for adult cancer patients (e.g. Germany 58%).

Spontaneous regression or differentiation into a benign lesion has been observed in neuroblastoma, especially in infants [12,20,27]. Health systems that provide regular, thorough examinations for infants and small children, especially ultrasound examinations or even screening, would lead to a higher number of incidental findings as opposed to symptomatic diagnoses. It is then more likely not only to detect neuroblastomas completely and early, but also to diagnose more of the otherwise spontaneously regressing cases, causing a higher overall incidence [4,24,28]. Such cases have very good prognosis. Inclusion of a large number of these in a survival analysis will consequently improve overall survival without allowing one to draw conclusions about the survival of unfavourable cases (lead time bias, overdiagnosis bias). So far, no reliable markers exist to predict spontaneous regression in individual cases.

Based on eight corresponding countries from the EUROCARE II data set (1978–1989) and the incidences published by the International Agency for Research on Cancer (IARC) in 1998 for similar time periods, crude incidence turns out to be a fairly good predictor of 5-

year survival (Table 5, Fig. 2) [1]. Using crude, standardised or cumulative incidence changes the picture very little. The SENSE paper makes it seem likely that high overall incidence is correlated with a lower age at diagnosis and lower incidence and fraction of metastatic cases (no stage data are available for EUROCARE) [24]. This cautions us against interpreting the survival differences as being entirely due to the differences in the quality of therapy for patients. Regarding the effect of treatment, on the one hand, high survival rates, particularly for children over 1 year, could reflect better care for symptomatic cases. However, it may also partly be due to differences in the general organisation of health care, especially care for children.

For neuroblastoma, an international comparison of population-based mortality would be a more valid basis for decisions than comparison of survival. Unfortunately, European comparisons of childhood cancer mortality are based on the ICD, which does not allow the identification of neuroblastoma [18,29,30].

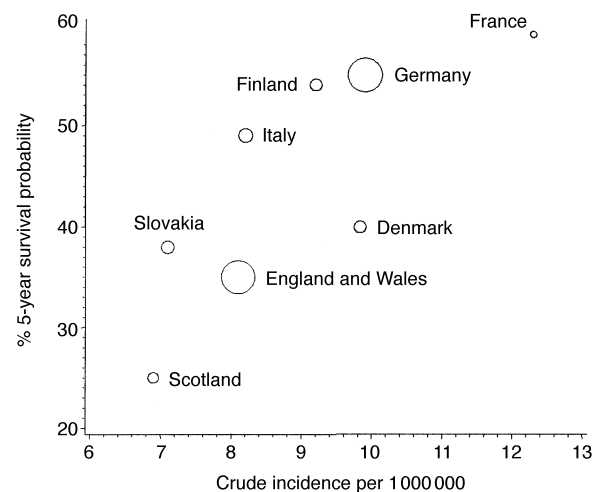


Fig. 2. Comparing neuroblastoma incidence (age 0–14 years) with survival (overall 5-year survival). Survival refers to the time period 1978–1989, for incidence see Table 5. The bubble size is proportional to the number of cases. Source: EUROCARE II data, IARC data [1].

With neuroblastoma, high survival rates and high incidence may both point at optimal health care and a high fraction of possibly 'overdiagnosed' cases. It is, however, very difficult to state where along the line of incidence increases and survival improvement, improvement in health care ends and overtreatment begins.

The issue of whether screening for neuroblastoma is beneficial is currently unresolved. In North America, a screening programme increased incidence and survival through lead-time bias and overdiagnosis bias, while there is evidence for the first time that it does not reduce mortality [25,31]. A consensus exists that screening at age <1 year is not indicated. Conclusions regarding screening at age 1 year will be available from a large German study in 2001 [32].

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