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# Survival of children with bone sarcoma in Europe since 1978: results from the EUROCARE study

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**Abstract**

Malignant bone tumours in children are rare, accounting for approximately 5% of all childhood cancers in European countries. In the EUROCARE childhood cancer study, there were 1785 registrations from 16 countries for bone cancers in patients aged 0–14 years during 1978–1989. Of this total, almost three-quarters were contributed by childhood cancer registries in Germany and the UK. Estimated 5-year survival rates were 52% for osteosarcoma and 50% for Ewing's sarcoma over the entire study period and 60% for both diagnostic groups in 1985–1989. For osteosarcoma, survival rates increased substantially until about 1985, but then showed no further improvement. For Ewing's sarcoma, there was a steady increase throughout the study period. Improvements in survival which had previously been reported from individual countries and in clinical series are confirmed as having taken place throughout much of Europe on a population basis. 

*Keywords:* Population-based survival; Cancer registries; Survival trends; Children; Europe; Osteosarcoma; Ewing's sarcoma; Bone neoplasms

## 1. Introduction

Malignant bone tumours account for 4–6% of all cancers occurring among children aged 0–14 years in most European countries [1]. They are exceedingly uncommon before the age of 5 years and more than half the childhood cases are diagnosed at ages 10–14 years. Incidence reaches a peak at around age 15 years before declining to a minimum in middle age. The two principal histological types are osteosarcoma, accounting for approximately 50% of childhood bone cancer, and Ewing's sarcoma (including primitive neuroectodermal tumour of bone), accounting for 40–45%; the remaining 5–10% are chondrosarcoma, other rare specified tumours, and tumours of unspecified cell type.

In this paper, we describe the pattern of survival from childhood bone cancers diagnosed in European populations during 1978–1989, a period during which there were substantial changes in treatment, particularly regarding the frequency of use of chemotherapy and its intensity. Trends in survival are also assessed in a multivariate analysis of data from a selection of registries for the period 1978–1992.

## 2. Patients and methods

Malignant bone tumours were defined as all diagnoses in Group VIII of the International Classification of Childhood Cancer [2]. In total, 1785 cases diagnosed during 1978–1989 were identified in the EUROCARE childhood cancer database. Table 1 shows the distribution of all cases and the two main diagnostic subgroups between countries and by age and gender. Osteosarcoma accounted for 52% of registrations and Ewing's sarcoma for 42%. The marked excess of osteosarcoma in Finland and the excess of Ewing's sarcoma in Slovakia are consistent with previously published incidence data [1]. Chondrosarcoma, other specified and unspecified tumours each accounted for under 5% of

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Table 1
Numbers of bone cancer cases in the EUROCARE childhood cancer database for 1978–1989[a]

| Country | Total | | Osteosarcoma | Ewing's sarcoma |
|---|---|---|---|---|
| | 1978–1989 *n* (%) | 1985–1989 *n* (%) | *n* (%) | *n* (%) |
| Northern Europe | | | | |
| Denmark | 70 (4) | 25 (3) | 28 (3) | 34 (5) |
| Finland | 67 (4) | 19 (3) | 46 (5) | 13 (2) |
| Iceland | 8 (0.4) | 2 (0.3) | 4 (0.4) | 3 (0.4) |
| Sweden[b] | 22 (1) | 7 (0.9) | 8 (0.9) | 13 (2) |
| UK | | | | |
| England and Wales | 680 (38) | 253 (33) | 348 (38) | 297 (40) |
| Scotland | 69 (4) | 22 (3) | 38 (4) | 26 (3) |
| Western and Central Europe | | | | |
| France[b] | 30 (2) | 12 (2) | 15 (2) | 14 (2) |
| Germany | 557 (31) | 271 (36) | 316 (34) | 220 (30) |
| Switzerland[b] | 6 (0.3) | 1 (0.1) | 1 (0.1) | 5 (0.7) |
| The Netherlands[b] | 18 (1) | 5 (0.6) | 5 (0.5) | 13 (2) |
| Southern Europe | | | | |
| Italy[b] | 123 (7) | 65 (9) | 68 (7) | 45 (6) |
| Spain[b] | 19 (1) | 19 (3) | 9 (1) | 9 (1) |
| Eastern Europe | | | | |
| Estonia | 23 (1) | 13 (2) | 10 (1) | 6 (0.8) |
| Poland[b] | 8 (0.4) | 4 (0.5) | 2 (0.2) | 3 (0.4) |
| Slovakia | 76 (4) | 30 (4) | 20 (2) | 42 (6) |
| Slovenia | 9 (0.5) | 9 (1) | 7 (0.8) | 2 (0.3) |
| Age (years) | | | | |
| 0–4 | 103 (6) | 45 (6) | 22 (2) | 67 (9) |
| 5–9 | 460 (26) | 205 (27) | 193 (21) | 231 (31) |
| 10–14 | 1222 (68) | 507 (67) | 710 (77) | 447 (60) |
| Gender | | | | |
| Boys | 913 (51) | 398 (53) | 453 (49) | 404 (54) |
| Girls | 872 (49) | 359 (47) | 472 (51) | 341 (46) |
| Total | 1785 (100) | 757 (100) | 925 (100) | 745 (100) |

[a] No cases were registered from Austria.
[b] <20% of national population covered.

the total. Table 2 shows indicators of data quality overall and by country. Both tables include cases from some registries which only contributed data for the later 1980s [3]. Some registries also provided data for the period 1990–1992. These included 193 additional cases of osteosarcoma and 142 of Ewing's sarcoma.

Survival rates were calculated by the actuarial method. Except in the graphs of the European pooled results, crude survival rates have been presented in preference to age-standardised. The latter could only be calculated for countries with cases in all age groups. The extreme rarity of bone tumours at ages 0–4 years meant that age-standardised survival could not be estimated even for some countries with quite large numbers of cases. Overall (European) survival was estimated as the weighted average of survival in individual countries, with weights proportional to the total childhood population of each country, assuming that survival of patients included in the study for each country was representative of survival at the national level. Because of the very small numbers of cases contributed by registries from some of the larger countries, the weighted European average survival rates [3] had very wide confidence intervals. We therefore also present unweighted overall survival rates in this paper.

Univariate survival analysis was carried out on two overlapping series of cases. The first contained cases diagnosed throughout 1978–1989, but was restricted to those registries whose contribution to the database included at least the whole of the period 1981–1986. The second consisted of all those diagnosed during 1985–1989.

Two Cox proportional hazards analyses were done for the osteosarcoma and Ewing's sarcoma groups separately. The first was designed to investigate trends in survival during 1978–1989, taking into account the varying distributions of age at diagnosis, gender and country. The total calendar period was divided into

three sub-periods, 1978–1981, 1982–1985 and 1986–1989. This analysis was confined to countries with at least 15 cases and with registrations included in all three 4-year periods. The second analysis covered the period 1978–1992, with 1990–1992 as a fourth sub-period. It was limited to countries with cases from all four sub-periods and with a total of at least 15 cases.

## 3. Results

### 3.1. Univariate analysis

Figs. 1 and 2 show the age-standardised survival from osteosarcoma and Ewing's sarcoma in the weighted European pooled data for 1985–1989. The highest mortality from osteosarcoma occurred between 1 and 2 years after diagnosis. For both diagnostic groups there was still a substantial risk of death between 3 and 5 years postdiagnosis. Table 3 shows 5-year survival rates for the two study periods where there were sufficient cases for analysis. Survival rates from osteosarcoma for 1978–1989 were relatively low in England and Wales and in Scotland, with upper confidence limits below the average for European registries. The survival rate for Germany was relatively high, with a lower confidence limit above the unweighted European average. For 1985–1989, the German survival rate was also high, and the unweighted average for European registries coincided with its lower confidence limit. In this latter period, the average was well within the confidence intervals for all other countries with sufficient cases. For Ewing's sarcoma in 1978–1989, there were again relatively low survival rates in England and Wales and a high rate in Germany with, in the latter country, the lower confidence interval above the unweighted average for the European registries; Denmark also had a low survival

Table 2
Data quality for bone cancer cases in the EUROCARE childhood cancer database for 1978–1989[a]

| Country | Total cases *n* (%) | % VIIIe | % MV | % Lost to follow-up |
|---|---|---|---|---|
| Northern Europe | | | | |
| Denmark | 70 (4) | 6 | 98 | 0 |
| Finland | 67 (4) | 6 | 99 | 0 |
| Iceland | 8 (0.4) | 13 | 100 | 0 |
| Sweden[b] | 22 (1) | 5 | 100 | 0 |
| UK | | | | |
| England and Wales | 680 (38) | 1 | 98 | 1 |
| Scotland | 69 (4) | 3 | 100 | 0 |
| Western and Central Europe | | | | |
| France[b] | 30 (2) | 0 | 97 | 0 |
| Germany | 557 (31) | 1 | 100 | 4 |
| Switzerland[b] | 6 (0.3) | 0 | 100 | 0 |
| The Netherlands[b] | 18 (1) | 0 | 94 | 39 |
| Southern Europe | | | | |
| Italy[b] | 123 (7) | 2 | 96 | 2 |
| Spain[b] | 19 (1) | 0 | 100 | 0 |
| Eastern Europe | | | | |
| Estonia | 23 (1) | 22 | 83 | 0 |
| Poland[b] | 8 (0.4) | 13 | 88 | 0 |
| Slovakia | 76 (4) | 3 | 99 | 0 |
| Slovenia | 9 (0.5) | 0 | 100 | 0 |
| Age (years) | | | | |
| 0–4 | 103 (6) | 9 | 96 | 1 |
| 5–9 | 460 (26) | 2 | 96 | 2 |
| 10–14 | 1222 (68) | 2 | 94 | 2 |
| Gender | | | | |
| Boys | 913 (51) | 2 | 94 | 2 |
| Girls | 872 (49) | 2 | 95 | 2 |
| Total | 1785 (100) | 2 | 95 | 2 |

VIIIe, International Classification of Childhood Cancer, Group VIIIe, unspecified malignant bone tumours; MV, morphologically verified.

[a] No cases were registered from Austria.

[b] <20% of national population covered.

Table 3
5-year % survival rates (95% confidence limits) for childhood bone cancer, 1978–1989 and 1985–1989[a]

| | 1978–1989 | 1985–1989 |
|---|---|---|
| Osteosarcoma | | |
| Denmark | – | 62 (36–82) |
| England and Wales | 43 (37–48) | 55 (46–63) |
| Finland | 52 (38–66) | 77 (50–92) |
| France[b] | – | 68 (36–89) |
| Germany | 65 (59–70) | 69 (60–76) |
| Italy[b] | 56 (43–68) | 56 (40–71) |
| Scotland | 32 (19–47) | – |
| Europe (unweighted) | 52 (48–55) | 60 (55–65) |
| Europe (weighted) | 60 (50–70) | 70 (58–81) |
| Ewing's sarcoma | | |
| Denmark | 32 (19–49) | – |
| England and Wales | 45 (39–50) | 57 (48–66) |
| Germany | 60 (53–67) | 67 (58–75) |
| Italy[b] | 53 (38–69) | 60 (40–78) |
| Scotland | – | 82 (52–95) |
| Slovakia | 43 (29–59) | 42 (20–67) |
| Europe (unweighted) | 50 (46–53) | 60 (55–66) |
| Europe (weighted) | 56 (45–66) | 59 (51–67) |
| Chondrosarcoma | | |
| Europe (unweighted) | 57 (40–72) | 60 (38–78) |
| Europe (weighted) | 59 (36–78) | 63 (30–87) |
| Other specified | | |
| Europe (unweighted) | 51 (35–67) | 66 (43–84) |
| Europe (weighted) | 44 (26–63) | 59 (32–82) |
| Unspecified | | |
| Europe (unweighted) | 38 (24–54) | 57 (33–79) |
| Europe (weighted) | 53 (28–77) | 70 (32–92) |

[a] Results for individual countries only reported where there were at least 30 cases (1978–1989) or at least 10 cases (1985–1989).

[b] <20% of national population covered.

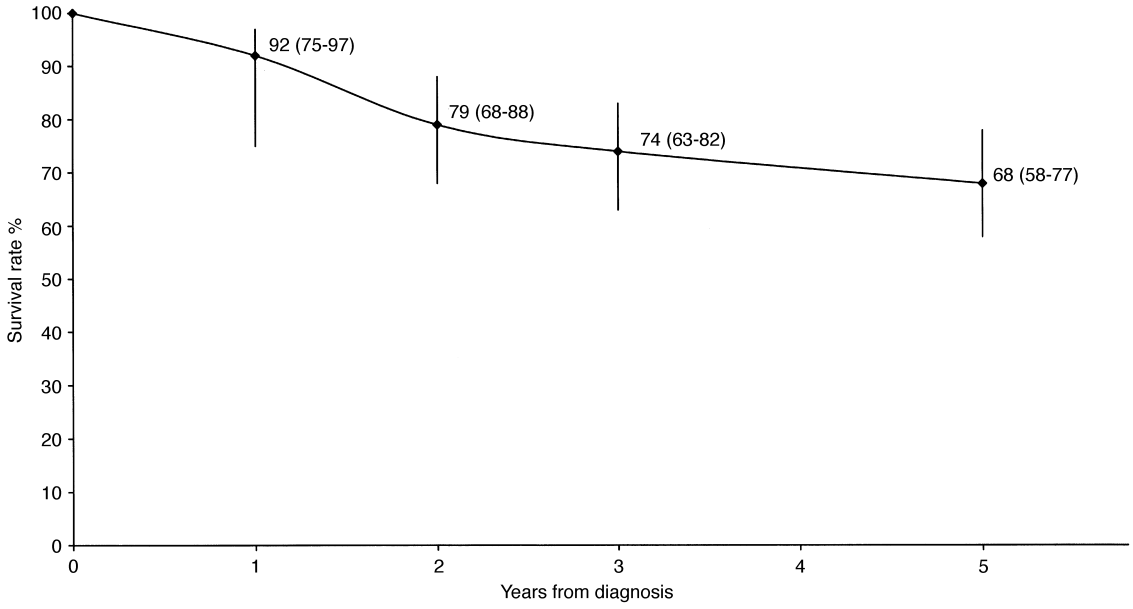


Fig. 1. Age-standardised survival rates for childhood osteosarcoma diagnosed in 1985–1989 (and 95% CI).

rate. In 1985–1989, the unweighted average was within the confidence intervals for all countries with sufficient cases.

### 3.2. Multivariate analysis

Table 4 shows results of the Cox proportional hazards analyses. The results for gender, age and country relating to 1978–1992 were very similar to those for 1978–1989 (data not shown). There was little evidence of a difference in survival between boys and girls. Survival from osteosarcoma was worst at age 0–4 years, whereas for Ewing's sarcoma the prognosis was poorer at ages 10–14 years. Germany had a significantly reduced relative risk (RR) compared with England and Wales for both osteosarcoma ($P = 0.0001$) and Ewing's sarcoma ($P = 0.003$). For osteosarcoma, the survival rate increased very substantially when comparing 1978–1981 and 1982–1985 but there was hardly any further improvement thereafter in the periods 1986–1989 and 1990–1992. For Ewing's sarcoma, survival increased steadily until the end of the 1980s but, in those countries contributing more recent data, survival for 1990–1992 was very similar to 1986–1989.

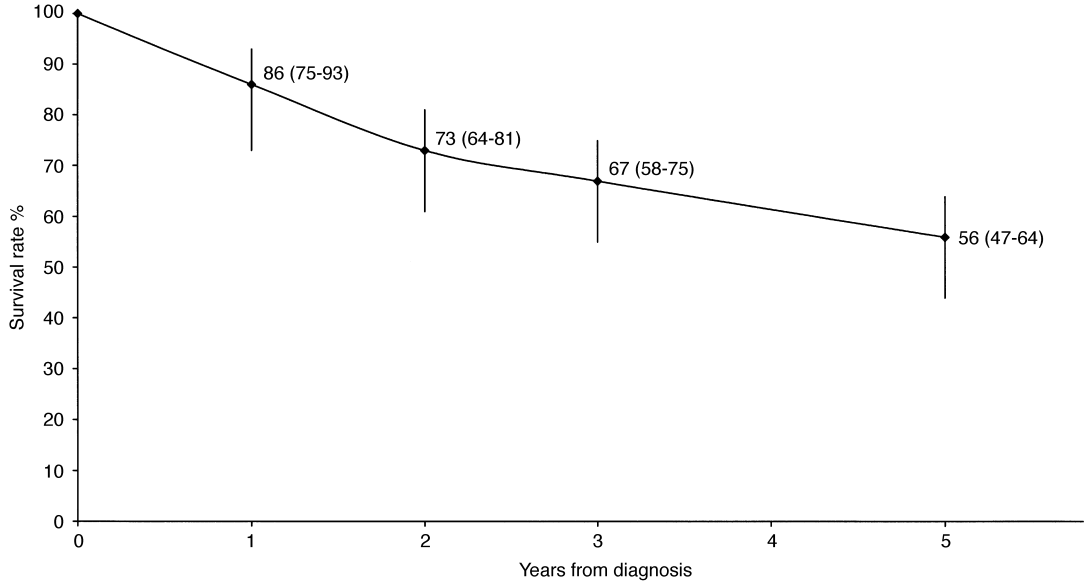


Fig. 2. Age-standardised survival rates for childhood Ewing's sarcoma diagnosed in 1985–1989 (and 95% CI).

Table 4
Results of Cox proportional hazards analyses for osteosarcoma and Ewing's sarcoma

| | Osteosarcoma RR (95% CI) | Ewing's sarcoma RR (95% CI) |
|---|---|---|
| 1978–1989[a] | | |
| Gender | | |
| Boys | 1 (reference) | 1 (reference) |
| Girls | 0.96 (0.80–1.16) | 0.89 (0.72–1.09) |
| Age (years) | | |
| 0–4 | 1.34 (0.71–2.52) | 0.75 (0.50–1.11) |
| 5–9 | 0.82 (0.64–1.05) | 0.76 (0.60–0.96) |
| 10–14 | 1 (reference) | 1 (reference) |
| Period | | |
| 1978–1981 | 1 (reference) | 1 (reference) |
| 1982–1985 | 0.61 (0.49–0.76) | 0.78 (0.62–1.00) |
| 1986–1989 | 0.55 (0.43–0.69) | 0.47 (0.35–0.62) |
| Country | | |
| Denmark | 0.81 (0.47–1.39) | 1.38 (0.90–2.12) |
| Finland | 0.80 (0.53–1.21) | – |
| Germany | 0.55 (0.44–0.69) | 0.67 (0.52–0.87) |
| Italy[c] | 0.70 (0.47–1.04) | 1.01 (0.65–1.57) |
| Slovakia | 1.62 (0.92–2.85) | 1.11 (0.71–1.72) |
| UK (England and Wales) | 1 (reference) | 1 (reference) |
| UK (Scotland) | 1.25 (0.83–1.86) | 1.09 (0.66–1.79) |
| 1978–1992[b] | | |
| Period | | |
| 1978–1981 | 1 (reference) | 1 (reference) |
| 1982–1985 | 0.64 (0.51–0.81) | 0.80 (0.62–1.02) |
| 1986–1989 | 0.55 (0.43–0.71) | 0.46 (0.34–0.60) |
| 1990–1992 | 0.62 (0.47–0.82) | 0.45 (0.32–0.64) |

95% CI, 95% confidence interval; RR, relative risk.

[a] 1978–1989 countries with fewer than 15 cases or not covering at least 1981–1986 are excluded.

[b] 1978–1992 countries with fewer than 15 cases or not covering at least 1981–1990 are excluded. Age, gender and country were also included in the model.

[c] $<20\%$ of national population covered.

## 4. Discussion

Bone sarcomas are among the less common forms of childhood cancer and most countries could only provide rather small numbers of cases. In consequence, confidence intervals for survival rates and hazard ratios were generally wide and interpretation must be correspondingly tentative. The unweighted survival estimates for Europe approximate to averages of the survival rates for England and Wales and for Germany because of the preponderance of cases from these two countries in the database. The weighted estimates, especially for osteosarcoma, tended to be higher than the unweighted. This is because the survival estimates were higher for some large countries that had very incomplete coverage and whose registries could only contribute small numbers of cases. When comparing survival rates between countries, it should be borne in mind that the 1978–1989 results from Germany are almost certainly overestimates as data for 1978–1979, which might be expected to have lower survival rates, were not included.

In the late 1970s, multidrug chemotherapy regimes were instituted for osteosarcoma in addition to surgery. These were based around high dose methotrexate. The T-10 protocol devised by Rosen [4] has for the past 20 years remained the gold standard against which all other regimens are compared. Recently ifosfamide has been introduced as a new agent along with etoposide but there is little evidence of any major improvement in national and international trials over the past 20 years. Patients in the UK and Germany have been treated in large trials, whilst those in many of the other countries represented in the EUROCARE study have been treated according to these international protocols although not necessarily entered into trials [5]. The EUROCARE study confirms the impression from population series in individual countries and from clinical trials that, following the substantial increase in survival rates until the early to mid 1980s [6–9], there has been little further improvement in more recent years [10,11]. Although international comparisons are generally limited by small numbers, the difference in survival between Germany and the UK seems consistent with differences reported from clinical trials in these countries.

In the 1970s and early 1980s, most treatment regimens for Ewing's sarcoma were based around a four drug combination of vincristine, doxorubicin, actinomycin and cyclophosphamide [12,13]. Both the German and the UK groups switched from cyclophosphamide to ifosfamide and have shown a 10–20% improvement in survival [14,15]. Very similar regimens have been followed in most other European countries and the results of the EUROCARE study reflect the general improvement. As with osteosarcoma, few meaningful international comparisons can be made because of small numbers. The higher survival rate in Germany compared with the UK is surprising as clinical trial results in the two countries have been very similar.

The mortality rate for bone cancer in childhood fell between 1980 and 1995 in many European countries [16], most likely reflecting improvements in survival. In particular, mortality halved during this period in Germany and the UK, the two countries contributing by far the largest number of cases to the EUROCARE study, and this is consistent with the halving of the risk of death among children with osteosarcoma and Ewing's sarcoma between 1978–1981 and 1986–1989. Incidence increases with age throughout childhood and many deaths of patients diagnosed in childhood occur at ages 15 years and over. Some of the decline in bone cancer mortality at ages 15–19 years in the European Union must therefore also be attributable to improved survival of patients diagnosed before the age of 15 years.

Table 5
Comparison of EUROCARE results with other series — 5-year actuarial survival rates (%)

| | Osteosarcoma | Ewing's sarcoma |
|---|---|---|
| Europe 1978–1989 | 52 | 50 |
| Europe 1985–1989 | 60 | 60 |
| USA (SEER) 1983–1987 [17] | 53 | 54 |
| Australia (Victoria) 1980–1989 [18] | 48 | 48 |
| Japan (Osaka) 1980–1984 [19] | 51 | – |

Recorded incidence rates for childhood bone cancer vary considerably. Among countries included in this study, the age-standardised rate (ASR) for all malignant bone tumours in *International Incidence of Childhood Cancer*, Volume II [1] ranged from 4.5 to 7.5 per million. For this reason, and because of the fairly long survival time for many ultimately fatal cases, it is not surprising that there should be little sign of correlation between the survival rates of children aged 0–14 years for individual countries in this study and national mortality rates for the same age group.

Table 5 shows population-based survival data from other industrialised countries outside Europe. The results for childhood bone cancers in Europe are broadly similar to those reported from the USA, Australia and Japan.

The most important conclusion of this study is that improvements in survival from these tumours during the 1980s, already reported from individual countries and in clinical series, are confirmed as having taken place throughout much of Europe on a population basis.

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