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Variation in survival of European children with acute lymphoblastic leukaemia, diagnosed in 1978–1992: the EUROCARE study

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Abstract

The aim of this study was to provide a comparative description of geographical variations and time trends in the population-based survival of European children with acute lymphoblastic leukaemia (ALL). Data on 13 344 newly diagnosed children (0–14 years) with ALL were included in the EUROCARE study and were collectedwere collected by 34 population-based cancer registries (four comprising only childhood malignancies), operating in 17 countries (four in Scandinavia, two in Southern Europe, three in Eastern Europe, six in Continental Europe and two in the UK). Age-specific crude survival rates were estimated for boys and girls according to country for the period 1985–1989 and in adjusted form to attain comparability. Overall pooled and weighted rates were estimated as European standards. Children dead at diagnosis or diagnosed only through a death certificate were excluded. Geographical variation was also estimated by calculating the relative death rate with respect to the pooled overall European rate. After adjustment for age, gender and country, a Cox regression analysis was used to estimate time trends in survival. Survival was compared with that in the USA, Japan, Canada and Australia. During 1985–1989, the 1-year survival rate varied from 99 to 79%, the 5-year survival rate from over 80 to 56% (with the exception of Estonia; 34%; 95% confidence interval (CI) 20–52) among the various countries; the European weighted means were 90 (95% CI 87–93) and 72% (95% CI 69–75), respectively. Survival was particularly favourable in (south) Sweden, Finland, Germany and The Netherlands and rather unfavourable in Estonia and (surprisingly) France, where only 4% of its population was covered by the participating registries. Compared with the period 1978–1981, the hazard ratio for the period 1986–1989 decreased to 0.59 (95% CI 0.54–0.64) and — in a smaller set of registries — to 0.49 (0.45–0.55) for 1990–1992, an annual decrease in this rate of approximately 3.5%. During 1985–1989, the 5-year survival rates for European children were largely similar to those found in the USA, Canada and Australia, but markedly better than those in Japan. Higher survival rates were found for countries with 'good' access to centrally organised diagnostic and treatment facilities which stimulated 'agggressive' treatments according to a protocol. However, a subdivision according to risk profiles, e.g. according to the initial white blood cell count at diagnosis, could not be made and this might have explained partially the geographical differences in survival, because a positive association appeared between incidence at age 1–4 years and 5-year survival in most countries.

Keywords: Population-based survival; Cancer registries; Survival trends; Children; Acute lymphoblastic leukaemia; Europe

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1. Introduction

In industrialised countries, acute lymphoblastic leukaemia (ALL) usually comprises approximately 80% of all leukaemias in children and is also the most frequent malignancy in children below the age of 5 years [1]. During the 1980s, world standardised incidence rates for ALL varied from 21 to 47 per million person-years for boys and from 16 to 41 for girls in Europe, the boys/girls ratio being about 1.2 in industrialised countries. Incidence rates were positively associated with the Gross National Product per capita. About 1500 children are newly diagnosed with ALL each year in Europe. After the introduction of 'total therapy' and refined diagnosis at the end of the 1960s [2] the 5-year survival rate improved markedly in the early 1970s from less than 10% to about 60% [3]. A distinction developed between 'standard-risk' and 'high-risk' patients, based on clinical features which correlated with the likelihood of a child proving resistant to treatment [4]. In the early 1980s, overall cure rates for ALL had reached 70% or even higher among children with the common-ALL immunophenotype and with an initial low white blood cell count [5–7]. In addition to the influence of leukaemic cell biology and antineoplastic treatment including supportive care, clinical experience and institutional and referral organisation also affect outcome. Furthermore, regional or national willingness to save terminally ill children may vary between cultures. Because chemotherapy and radiotherapy have unwanted short- and long-term effects and such treatments and supportive care appear to be amenable to optimisation, new protocols are continuously being developed, usually with superior outcomes for children enrolled in trials and those in larger institutions [8]. Institutional and geographical differences in survival rates, which can therefore be expected within well-defined groups of patients, can be can be measured by means of population-based cancer registries. The differences are not likely to be large, because access to paediatric oncological care is usually adequate and the various paediatric societies have invested heavily in the diffusion of know-how through the collaborative development of protocols including referral policies [9]. Provision of complex (and costly) care requires intensive staffing and generally leads to centres for paediatric oncology serving up to 1 million children (originating from approximately 4–6 million people), sometimes with trusted satellite centres.

Since 1990, the EUROCARE group has been studying cancer survival in Europe as a concerted effort within the Biomed programme of the European Union. It now includes all (unselected) patients, newly diagnosed since 1978, initially in 11 [10] and since 1985 in 17 countries [11]. These countries are covered, often only partially, covered by 45 population-based registries, 30 of which include childhood cancer and are now supplemented with specific childhood cancer registries [12].

In this paper, the age, gender and geographical variations in survival will be presented for European children with ALL diagnosed in the period 1985–1989 and will be compared with similar data from major industrialised countries in the world. Trends in survival will also be assessed by multiple regression analysis of data collected in the periods 1978–1989 and, for a subset of registries or countries, in the period of 1978–1992.

2. Patients and methods

The study comprised all children diagnosed with ALL (ICCC Ia) [13], for whom more or less complete follow-up data were available (minimum duration of 5 years, albeit less in the period 1990–1992 because the last date of follow-up was in 1994). Data had been recorded and supplied by 34 population-based cancer registries in 17 European countries; four of these registries were specialised in childhood cancer: one in England and Wales which was also fed by the various cancer registries in the UK, a unique clinical registry that possibly became population-based during the 1980s in West Germany, one in the Piedmont region of Italy and one in The Netherlands run by the Dutch Childhood Leukaemia Study Group. Only first primary malignant tumours were considered. Cases had to be microscopically (= histologically or cytologically) verified. Five, possibly erroneously coded, cases of chronic lymphocytic leukaemia diagnosed in three countries were not included. Cases known to registries by death certificate only (DCO) or discovered incidentally at autopsy were not included in the analyses. Descriptions of the cancer registries, their data collection methods, and the standardised procedures for ensuring data comparability were published in the first EUROCARE monograph [10] and in the methods paper in this issue [12]. Descriptions of the coverage and procedures of the specialised childhood cancer registries in England and Wales, West Germany, The Netherlands (leukaemia only) and the Piedmont region showed satisfactory completeness and accuracy for leukaemia [1], whereby completeness is more likely to be attained when regional cancer registries are also present.

Demographic and diagnostic features of the 4663 children with ALL registered during the 1985-1989 period according to country are presented in Table 1. The registries of Finland, Denmark, Iceland, England and Wales, Scotland, The Netherlands, West Germany, Estonia, Slovakia and Slovenia covered entire populations, whereas other countries are represented by one or more regional registries which cover less than 22%.

The proportion of boys ranged from 53 to 58%, approximately 51% of cases aged between 1 and 4 years;the proportion of microscopically verified cases

Table 1
Number of patients with childhood ALL, gender and age distribution and quality of data, according to country, 1985–1989[a]

Country (coverage (%))	No. of cases *n* (%)	% Boys	% 1–4 years of total	% MV	% of lost to FU	% Unspecified type of all childhood leukaemias	ALL as a % of all childhood leukaemias
Finland (100)	185 (4)	53	54	100		1.1	85
(South) Sweden (18)[b]	45 (1)	56	40	100	–	–	80
Denmark (100)	171 (4)	56	54	100	–	0.6	81
Iceland (100)	10 (0.2)	50	40	100	–	20	71
Scotland (100)	161 (3)	54	56	100	–	0.5	82
England and Wales (100)	1452 (31)	56	53	99	1	1.0	80
The Netherlands (100)	378 (8)	55	49	100	0.8	4.8	79
France (4)[b]	54 (1)	54	52	100	-	3.7	72
Austria (8)[b]	8 (0.2)	63	63	100	–	–	100
Switzerland (6)[b]	9 (0.2)	56	56	100	22	–	82
(West) Germany (100)	1603 (34)	56	50	100	1.2	1.4	81
Italy (15)[b]	203 (4)	56	44	87	3.9	3.9	75
Spain (11)[b]	79 (2)	57	49	100	–	6.3	75
Estonia (100)	35 (1)	57	46	100	2.9	20	67
Slovenia (100)	52 (1)	52	60	100	1.9	1.9	76
Slovakia (100)	181 (4)	58	49	99	–	1.7	77
Poland (6)[b]	37 (1)	57	59	92	5.4	–	80
Europe	4663 (100)	55	51	95	1.1	1.8	80

FU, follow-up; MV, microscopy verified.
[a] Source: EUROCARE.
[b] <20% of the national population covered.

was mostly 100%, but was only 87% in Italy and 92% in Poland. The proportion of cases lost to follow-up was 1.1%, ranging from 0.8 to 5.4% (with Switzerland having 92%). The proportion of unspecified leukaemias as a proportion of all childhood leukaemias, being an indicator of the diagnostic process in the country, ranged from 0.5 to 20%; due to varying definitions, at least 3% would probably still reflect provision of adequate care. ALL comprised about 80% of all leukaemias in most countries.

Trends in survival were analysed using approximately 10 500 cases diagnosed during the period 1978–1989 divided into three 4-year periods from the following 11 countries (at least 30 cases each and with at least 8 cases in each period): Denmark, Estonia, France, The Netherlands, England and Wales, Finland, West Germany (since 1980), Italy, Scotland, Slovakia and Sweden. In these countries, another 2944 cases could be studied that were diagnosed in the period 1990–1992 and were available in a subset of registries.

Crude survival rates were calculated by the actuarial method [14] using the computer program of Hakulinen [15]. Overall (European) survival was calculated as an overall pooled rate and as the weighted average of the survival measured in each of the countries, proportional to the childhood population in that country. We thereby assumed that in cases of partial coverage the national survival rate for patients will be similar to that at the regional level. This is uncertain in cases of limited regional coverage in registries of large countries such as France (4%), Poland (5%), Spain (11%), Sweden (18%) and Italy (22%) [12].

Because survival is expected to differ according to age and the age distribution between countries varied, also over time, intercountry variation could only be estimated after direct age-standardisation to a uniform European population; these standardised survival rates were calculated from age- and gender-specific rates for age groups 0–4, 5–9 and 10–14 years [12]. For comparative purposes, the relative death rate was computed as the ratio of the logarithm for survival in each country [16] compared with the pooled European rate as a reference. The standard error was also computed.

Cox proportional hazard models [17] were used to compare hazard rates for different periods of diagnosis (1978–1981, 1982–1985 and 1986–1989) while adjusting for age, gender and country; a separate, but similar analysis was conducted with data from a smaller number of countries for the period of 1978–1992.

The international comparison was based on data from the SEER (Surveillance Epidemiology and End Results) program from the USA [18], and published data from Japan [19], the state of Victoria (Australia) [20] and Canada [21].

3. Results

At 1, 2, 3 and 5 years after diagnosis, weighted overall survival of ALL for European children was clearly bet-

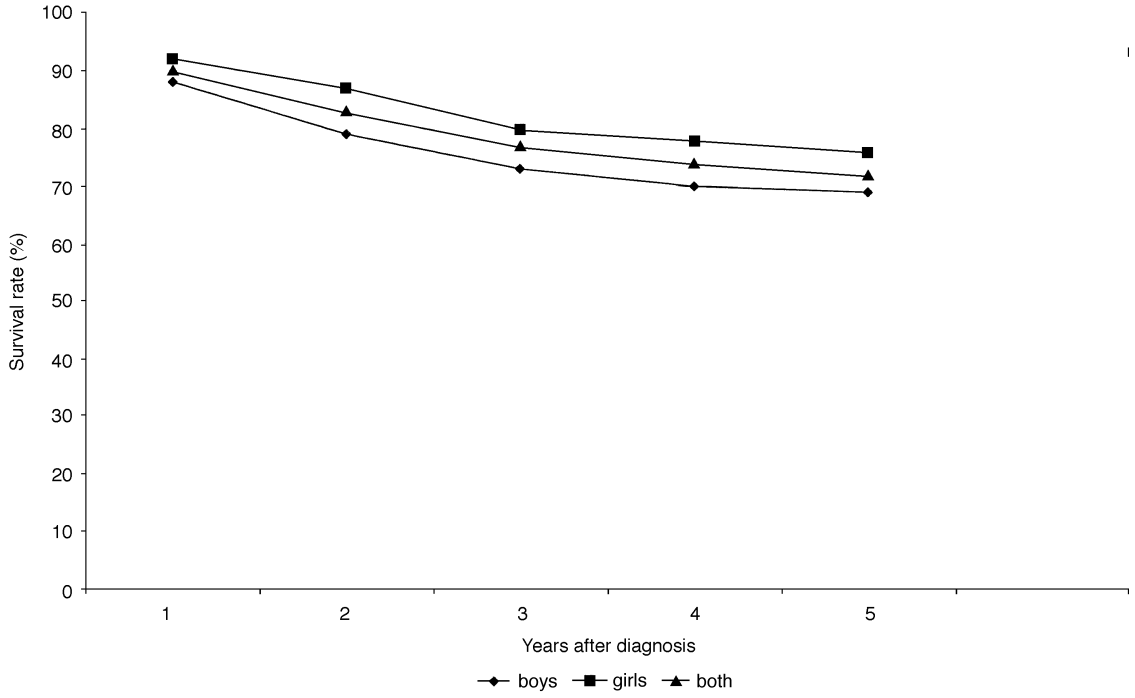

Fig. 1. Survival of European children with acute lymphoblastic leukaemia, diagnosed 1985–1989, according to gender.

ter for girls than for boys (Fig. 1). In the multivariate analysis, the hazard ratio for girls was 0.76 (95% confidence interval (CI) 0.71 — 0.82) compared with boys. Five-year survival forat ages 1–4 years was good (82%, 95% CI 80–83), whereas it was clearly inferior for infants (33%; 95% CI 26–41) and 10–14 year-olds (64%; 95% CI 60–67) (Table 2).

Age- and gender-adjusted survival clearly differed according to country from 99 to 79% at 1 year and from 95 to 34% at 5 years (Table 3). Estimation of the relative death rate yielded a favourable outcome for South Sweden, Finland, Germany and The Netherlands and the worst outcome for Estonia, and to a lesser extent the (small) areas covered by the French and Polish registries, as well as in Slovakia and Slovenia.

According to the Cox regression analysis, the crude 5-year survival rates improved significantly from 1978 to 1989, the hazard ratio becoming 0.59 (95% CI 0.54–0.64) in 1986–1989 relative to the period 1978–1981, which equals an annual improvement of approximately

Table 2
Crude 5-year survival of ALL (95% CI) for European children according to age and gender, during 1985–1989[a]

	0 year	1–4 years	5–9 years	10–14 years	0–14 years
Crude					
Boys	32 (21–44)	80 (77–82)	72 (69–75)	59 (55–64)	73 (71–74)
(*n*)	(61)	(1289)	(785)	(451)	(2586)
Girls	34 (25–44)	84 (82–86)	79 (75–82)	70 (65–75)	78 (76–80)
(*n*)	(96)	(1092)	(569)	(320)	(2077)
Both	33 (26–41)	82 (80–83)	75 (73–77)	64 (60–67)	75 (74–76)
(*n*)	(157)	(2381)	(1354)	(771)	(4663)
Weighted[b]	30 (19–43)	79 (74–83)	71 (64–77)	62 (53–69)	72 (69–75)

[a] Source: EUROCARE study.
[b] From the European pool.

Table 3
The variation in the 1- and 5-year age-standardised survival rates (%) for childhood ALL (95% CI) and relative death rate (standard error of the mean (SEM)) during 1985–1989, according to country[a]

Country	Survival at		At 5 years Relative[b] death rate (SEM)
	1 year	5 years	
Finland	93 (88–96)	81 (75–86)	0.73 (0.13)
(South) Sweden[c]	99 (90–100)	95 (46–100)	0.18 (0.67)
Denmark	92 (88–96)	74 (67–80)	1.05 (0.17)
Scotland	92 (87–95)	75 (68–81)	1.0 (0.17)
England and Wales	91 (90–92)	73 (71–75)	1.09 (0.09)
The Netherlands	93 (90–95)	82 (78–86)	0.69 (0.1)
France[c]	88 (71–96)	56 (42–69)	2.0 (0.45)
Germany	95 (94–96)	78 (76–80)	0.86 (0.07)
Switzerland[c]	81 (35–97)	75 (36–95)	1.0 (0.85)
Italy[c]	91 (86–94)	76 (70–82)	0.95 (0.15)
Spain[c]	88 (79–93)	71 (60–80)	1.19 (0.26)
Estonia	79 (63–89)	34 (20–52)	3.8 (0.87)
Slovenia	92 (80–97)	70 (56–81)	1.24 (0.33)
Slovakia	84 (78–89)	64 (56–71)	1.55 (0.23)
Poland[c]	82 (65–92)	66 (50–79)	1.44 (0.41)
Europe			
Weighted	90 (87–93)	72 (69–75)	
Pooled	92 (91–93)	75 (74–76)	1[b]

[a] Source: EUROCARE study.
[b] Relative to the pooled European rate [16].
[c] < 20% of the national population covered.

Table 4
Cox proportional regression analysis of time trends in ALL within Europe, diagnosed from 1978 to 1992 (models include gender and age)[a]

Number of cases	Period of diagnosis	Study period 1978–1989 Hazard ratio (95% CI)	Study period 1978–1992[b] Hazard ratio (95% CI)
3044	1978–1981	1	1
3663	1982–1985	0.72 (0.67–0.78)	0.74 (0.68–0.80)
3764	1986–1989	0.59 (0.54–0.64)	0.61 (0.56–0.67)
2944	1990–1992	–	0.49 (0.45–0.55)
	Continuous	0.76 (0.73–0.79)	0.79 (0.76–0.81)

[a] Source: EUROCARE study.
[b] Fewer participating registries, but more patients compared with 1978–1989.

3.5% (Table 4). In a different subset of registries, the hazard ratio decreased further to 0.49 (95% CI 0.45–0.55) during the period 1990–1992. In a separate analysis, the difference in hazard ratio between England and Wales (reference group) and The Netherlands and West Germany became smaller in the last period (data not shown).

The comparison of European 5-year survival rates with those found for the USA, Canada and Australia in the same period did not reveal large differences, although inferior results were observed for Japanese children (Table 5).

4. Discussion

This study showed that in all the participating European countries participating in this study, except Estonia, 5-year overall survival rates for childhood ALL increased to over 50% during the 1980s, varying in western Europe from 56% for small regions; i.e. the 4% coverage of France (Doubs, Somme, Cote d'Or and Calvados) to over 80% in Finland and The Netherlands and even over 90% in southern Sweden. Survival rates for Eastern Europe (except Estonia) were not very different from the European average as was the case for survival data in the UK, Denmark and the small areas covered in Spain and Italy. Although the differences in survival could hardly be explained by variations in the proportion of patients aged 1–4 years (Table 1), considered to be an indicator of the presence of favourable prognostic features, the positive correlation between 5-year survival and the incidence rate for that age group for the period of 1983–1992, suggests that biological features play a role [1] (Fig. 2).

Survival was clearly better for girls and children aged 1–9 years, which is generally attributed to biological features [22]. Compared with the period of 1978–1981, the age and gender adjusted hazard ratios for the period 1986–1989 decreased steadily decreased by approximately 40%. The favourable trend in hazard ratios continued in these countries levelled off in the subsequent period of 1990–1992 in The Netherlands, Germany and Sweden, all with previously favourable hazard ratios. What else other than changes in treatment protocols might explain this?

The poor outcome in France for the period 1985–1989, being based on small numbers derived from a coverage of only 4% of the country and might not reflect the national situation. None the less, the nationwide Fralle group, consisting of paediatric oncologists in a large, but declining number (from 59 to 35) of centres [23] , reported a 10–15% lower event-free rate than the national BFM (Berlin–Frankfurt–Münster) group in Germany [24]. The 19 authors, four from the large centres in Paris, explained this difference by the less aggressive approach of these treatment protocols. This was changed in the 1990s and may yield similar results in the future.

With respect to ALL, the desirable coverage for paediatric oncological centres would be at least 0.3 million children (derived from 1.2–2.0 million people overall, largely depending on previous birth rates) which would generate about one child with ALL per month. In contrast, the very favourable (South) Swedish survival rates found for the period 1985–1989 (which was also based

Table 5
Comparison of crude 5-year survival of childhood ALL between Europe, North America, Australia and Japan[a]

	Europe 1985–1989 (%) (95% CI)	USA 1985–1994 (all races) (%)	Victoria, Australia 1980–1989 (%)	Canada 1985–1988 (%)	Osaka, Japan 1980–1984 (%)
1 year	92 (91–93)	92	NP[b] –	92	NP –
5 years	75 (74–76)	77	73	74	44

[a] Sources: EUROCARE study (this study), SEER Program [18], Victorian Cancer Registry [20], Canada [21], Osaka, Japan [19].
[b] NP, not presented.

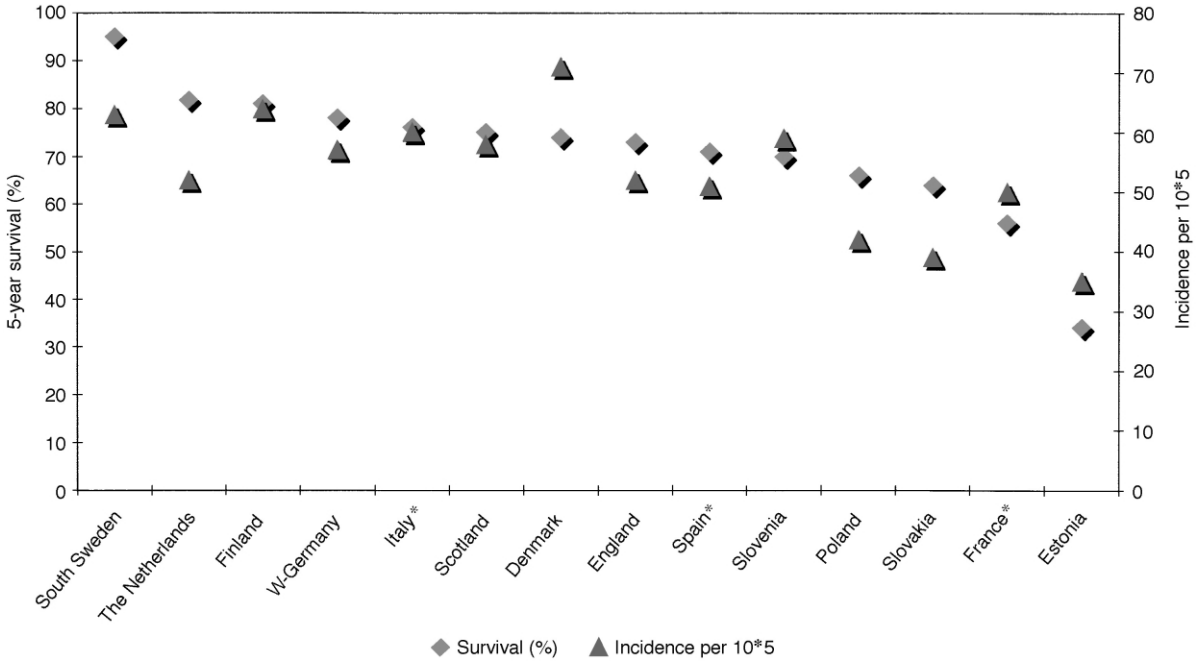

Fig. 2. The association between 5-year survival rates for childhood ALL for 1985–1989 and the incidence per million children aged 1–4 during 1983–1992, according to country.

on small numbers) was higher alsothan those within Scandinavia: 95% versus 80% [25]. Aggressive therapy was apparently also administered in relatively small centres, dictated by a low population density and large distances. Exploration of regional differences within Scandinavia could shed more light on this. The favourable survival rate found for The Netherlands is likely to have resulted from the combination of national protocols, their wide application in the seven centres (with a few satellites) and their (measured) close protocol adherence and surveillance [26]. The slight decrease in survival in the early 1990s, indicated by a stable or even declining hazard ratio (data not shown), had already been demonstrated by other population-based analyses; it seems to be related to — in retrospect — unfortunate changes in the protocol [27].

To what extent should the differences in survival within Europe be explained by underlying variations in the distribution of relevant biological prognostic features which are if not being adjusted for by age and gender? We could not distinguish 'standard risk' from 'high risk' patients, whose 5-year survival rates could have varied from more than 80% to less than 60% in the 1980s. Differences may have existed in the proportions of patients with favourable prognostic factors such as the common-ALL immunophenotype, a low initial white blood cell count, absence of mediastinal widening and cytogenetic features [28]. Even if such differences existed, an adequate structure of (supportive) care for the application of efficacious and aggressive combinations of cytotoxic drugs must be considered overriding. In addition, a systematic and centralised approach to diagnostic procedures leads to more precise classification based on immunology and cytogenetics in addition to morphology, and thus to better survival even if only due to better subgrouping of patients for specific treatments. The results of this analysis may thus underscore the relevance of the organisation of treatment, including systematic (review of) diagnosis according to protocol. There is clear evidence in support of this view in Britain [8,29] where the proportion of children treated in centres, included in trials or treated by protocols increased markedly during the 1980s, and also in The Netherlands [26,27], in Scandinavia [25], Germany [24] and Italy [30]. Nevertheless, comparisons between the results attained in clinical trials and the population-based data of the EUROCARE study remain unequivocal due to selection and subgrouping in the former. It is not clear whether socio-economic and racial factors play an independent role as indicated by American [31] and also recent British [32] data: blacks and Asians fare worse. In contrast, little evidence of a socio-economic gradient in survival was found in a large study in the UK for the period 1970–1990 [33]. However, organisation may have affected outcome, as was also shown by data from The Netherlands for the 1970s [34]: survival of children with 'standard risk' ALL with parents of low educational status initially lagged behind, but soon approached that of children with parents of higher educational background. The proportion of African or Asian patients was however small.

Although assessed independently, the trends in mortality due to childhood leukaemia (probably 60–70% due to ALL) [35] were largely in agreement with the

results of this study: the decreases in mortality occurred earlier and were steeper in the Scandinavian countries and The Netherlands than in France and Southern Europe and even contrasted with those in Eastern Europe. All improvement in survival for children with acute non-lymphoblastic leukaemia (ANLL) generally did not occur until the 1980s; it seemed to be more marked in countries with favourable trends in survival for ALL [36].

A 'good' comparative, in other words population-based, study of childhood ALL on a European scale seems desirable, if it could take the relevant and recordable prognostic factors and indicators into account [28] and also include socio-economic or parental educational status, which can also be related to the country of birth. For this purpose, the EUROCARE study group has developed the concept of 'high resolution' studies of patterns of care and survival. The pattern of care would then also need to be classified according to the degree of appropriateness with respect to staging, classification, therapy and follow-up.

5. Conclusion

This population-based study of survival of childhood ALL, based on one of the largest datasets analysed thus far, showed impressive improvements during the 1980s, but also substantial variations among the European countries. There seems to be considerable room for improvement, especially in Eastern Europe, although the differences could have diminished already for today's children. None the less, an all-out effort to assess the best organisational approach for the near future in Europe would be warranted, for which ALL could be a good sentinel condition.

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References

1. Parkin DM, Kramarova E, Draper GJ, *et al*., eds. *International Incidence of Childhood Cancer,* vol. II. IARC Scientific Publications No. 144. Lyon, IARC, 1998.
2. Pinkel D. Five year follow-up of 'total therapy' of childhood lymphocytic leukaemia. *JAMA* 1971, **216**, 648–652.
3. Steinhorn S. Improved survival among children with accute leukemia diagnosed in the 1970s. *Cancer Treatment Reports* 1984, **68**, 953–958.
4. Mauer A, Simone J. The current status of the treatment of childhood lymphoblastic leukemia. *Cancer Treatment Rev* 1976, **3**, 17–41.

5. Lilleymanm JS. Acute lymphoblastic leukaemia. *Eur J Cancer* 1997, **33**, 85–90.
6. Working Party on Leukaemia in Children. Improvement in treatment for children with acute lymphoblastic leukaemia; Medical Research Council. UK ALL trials. *Lancet* 1986, **i**, 408–411.
7. German Childhood Cancer Registry. *Annual Report 1998*. Mainz, Institut fur Medizinische Statistik und Dokumentation, 1999.
8. Stiller CA, Draper GJ. Treatment centre size, entry to trials and survival in acute lymphoblastic leukaemia. *Arch Dis Child* 1989, **64**, 657–661.
9. Sanders J, Glader B, Cairo M, *et al*. Guidelines for the pediatric cancer centre and role of such centres in diagnosis and treatment. American Academy of Pediatrics Section Statement on Hematology/Oncology. *Pediatrics* 1997, **99**, 139–141.
10. Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T, Esteve J. *Survival of Cancer Patients in Europe: The Eurocare II study*. IARC Scientific Publications No. 132. Lyon, IARC, 1995.
11. Berrino F, Capocaccia R, Estève J, *et al*. *Survival of Cancer Patients in Europe: The EUROCARE II Study*. IARC Scientific Publications No. 132. Lyon, IARC, 1999.
12. Magnani C, Gatta G, Corazziari I, *et al*. Childhood malignancies in the EUROCARE study: the database and the methods of survival analysis. *Eur J Cancer* 2001, **37**, 678–686.
13. Kramarova E, Stiller CA. The international classification of childhood cancer. *Int J Cancer* 1996, **68**, 759–765.
14. Berkson J, Gage RP. Calculations of survival rates for cancer. *Proc Staff Meet Mayo Clin* 1950, **5**, 270–286.
15. Hakulinen T, Abeywickrama K. A computer program package for relative survival analysis. *Comp Prog Biomed* 1987, **9**, 197–207.
16. Esteve J, de Angelis G, Verdecchia A. Trends in cancer survival probability over the period 1978–1989. In *Survival of Cancer Patients in Europe: The EUROCARE II Study*. IARC Publications No. 151. Lyon, IARC, 1999, 543–549 (Chapter 6).
17. Cox D. Regression models and life tables. *J R Stat Soc B* 1972, **34**, 187–220.
18. Miller RW, Young JL, Novakovic B. Childhood cancer. *Cancer* 1995, **75**, S395–S405.
19. Ajiki W, Hanai A, Tsukuma H, Hiyama T, Fujimoto I. Survival rates of childhood cancer patients in Osaka, Japan, 1975–1984. *Japan J Cancer Res* 1995, **86**, 13–20.
20. Giles G, Waters K, Thursfield V, Farrugia H. Childhood cancer in Victoria, Australia, 1970–1989. *Int J Cancer* 1995, **63**, 794–797.
21. Villeneuve PJ, Sankaranarayanan R, Leclerc JM, Huchcroft S, Dryer D, Morrison H. Survival rates among Canadian children and teenagers with cancer diagnosed between 1985 and 1988. *Cancer, Prevention & Control* 1998, **2**, 15–22.
22. Pui CH, Boyett JM, Relling MV, *et al*. Sex differences in prognosis for children with acute lymphoblastic leukemia. *J Clin Oncol* 1999, **17**, 818–824.
23. Donadieu J, Auclerc MF, Baruchel A, *et al*. Critical study of prognostic factors in childhood acute lymphoblastic leukaemia: differences in outcome are poorly explained by the most significant prognostic variables. *Br J Haematol* 1998, **102**, 729–739.
24. Reiter A, Schrappe M, Ludwig W-D, *et al*. Chemotherapy in 998 unselected childhood acute lymphoblastic leukemia patients. Results and conclusions of the multicenter trial ALL-BFM-86. *Blood* 1994, **84**, 3122–3133.
25. Gustaffson G, Kreuger A, Clausen A, *et al*. on behalf of the Nordic society of Paediatric Haematology (NOPHO). Intensified treatment of acute childhood lymphoblastic leukaemia has improved prognosis, especially in high risk patients: the Nordic experience of 2648 patients diagnosed between 1981 and 1996. *Acta Paediatrica* 1998, **87**, 1151–1161
26. Van der Does-van den Berg A, Veerman AP, van Wering ER, *et al*. Childhood acute lymphocytic leukemia in the Netherlands: randomized studies and nationwide treatment results from 1972–1995. *Int J Ped Hem Onc* 1998, **5**, 125–139.
27. Kamps WA, Veerman AJ, van Wering ER, van Weerden JF, Slater R, van der Does-van den Berg A. Long term follow-up of Dutch Childhood Leukemia Study Group protocols for children with acute lymphoblastic leukemia, 1984–1991. *Leukemia* 2001, in press.
28. Smith M, Arthur D, Camitta B, *et al*. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. *J Clin Oncol* 1996, **14**, 18–24.
29. Stiller CA, Eatock EM. Patterns of care and survival for children with acute lymphoblastic leukaemia diagnosed between 1980 and 1994. *Arch Dis Child* 1999, **81**, 202–208.
30. ALL Steering Committee of the Associatione Italiana Ematologia Oncologia Pediatrica (AIEOP). Treating childhood acute lymphoblastic leukaemia (ALL). Summary of ten year's experience in Italy. *Med Pediatr Oncol* 1989, **17**, 83–91.
31. Gloeckler Ries LA, Smith MA, Gurney JG, *et al*., eds. *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program, 1975–1995*. National Cancer Institute, SEER Program NIH Publication No. 99-4649. Bethesda, MD, 1999.
32. Stiller CA, Bunch KJ, Lewis IJ. Ethnic group and survival from childhood cancer: a report from the UK Children's Cancer Study Group. *Br J Cancer* 2000, **82**, 1339–1343.
33. Schillinger JA, Grosclaude PC, Honjo S, Quinn MJ, Sloggett A, Coleman MP. Survival after acute lymphocytic leukaemia: effects of socioeconomic status and geographic region. *Arch Dis Child* 1999, **80**, 311–317.
34. Coebergh JWW, van der Does-van de Berg A, Hop WCJ, *et al*. Small influence of parental educational level on the survival of children with leukaemia in The Netherlands between 1973 and 1979. *Eur J Cancer* 1996, **32A**, 286–289.
35. Levi F, La Vecchia C, Negri E, Lucchini F. Childhood cancer mortality in Europe, 1955–1995. *Eur J Cancer* 2001, **37**, 785–809.
36. Gatta G, Luksch R, Coleman MP, Corazziari I and the EUROCARE Study Group. Survival from acute non-lymphocytic (ANLL) and chronic myeloid leukaemia (CML) in European children since 1978: a population-based study. *Eur J Cancer* 2001, **37**, 695–702.