Survival and cure trends for European children, adolescents and young adults diagnosed with acute lymphoblastic leukemia from 1982 to 2002

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ABSTRACT

Proportion cured is a potentially more informative cancer outcome measurement than 5-year survival. We present population-based estimates of cure for young patients diagnosed with acute lymphoblastic leukemia in Europe from 1982 to 2002. Thirty-five European cancer registries provided data. Survival was estimated by age, period of diagnosis and European region, and used as input for parametric cure models, which assume cured patients have the same mortality as the general population. For acute lymphoblastic leukemia diagnosed in 1-14 year olds in 2000-2002, over 77% were estimated cured. The proportion cured improved significantly over the study period: an impressive 26-58% in infants (up to 1 year), 70-90% in 1-4 year olds, 63-86% in 5-9 year olds, 52-77% in 10-14 year olds, and 44-50% in 15-24 year olds. Regional variations in proportion cured reduced over time for 1-14 year-olds, but persisted in infants and 15-24 year olds. Five-year survival was always slightly higher than proportion cured. Considerable proportions of young patients were estimated cured of acute lymphoblastic leukemia. Nevertheless, a small excess risk of death persisted beyond five years after diagnosis when patients remained at risk for late treatment effects, late relapses and second primaries.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer in childhood (0-14 years) constituting slightly less than one-third of all childhood cancers diagnosed, while in adolescents and young adults (15-19 years) it constitutes approximately 10% of cancers diagnosed.[1] EUROCARE[2] found that 5-year survival for ALL in European children and young adults improved significantly from 1995 and 2002, although survival was poorer in adolescents and young adults than children.[1-3] The EUROCARE study did not provide a detailed breakdown of survival by age, country or European region.

Five-year survival is the traditional outcome measure for childhood cancers. However, for several of these cancers, including ALL, an excess risk of death persists for five years and over after diagnosis.[4,5] A new indicator of outcomes in children (the estimated proportion of cured cases) was first used by Shah *et al.*[6] in UK children with acute lymphoblastic leukemia. The proportion of cured cases is estimated by cure models.[7]

The aim of the present paper was to estimate the proportion of cured cases over time and by age for European children, adolescents and young adults diagnosed with ALL in various European populations, using the most recent data available from population-based cancer registries participating in EUROCARE-4.[2-8]

Design and Methods

ALL was defined according to the third edition of the International Classification of Childhood Cancer, diagnostic group Ia.[9] Since there was a big difference between the diagnosis periods covered by the participating cancer registries, we restricted the analyses to children diagnosed between 1982 and 2002, and to adolescents and young adults diagnosed between 1988 and 2002. We stratified these periods into 3-year sub-periods. Although 85 cancer registries participated in EUROCARE-4, we only used data from the 21 registries that provided information on ALL in children for at least one year of each 3-year period within the 1982-2002 study period. Similarly, for adolescents and young adults we used data from the 29 cancer registries with information for at least one year in each of the 3-year periods between 1988 and 2002. In all cases, follow up was complete up to 31st December 2003. We excluded 59 cases that were known to registries only by death certificate or that were discovered incidentally at autopsy. Only ALL as first malignancy was included in the analyses.

We analyzed 22,886 cases, of which 21,538 were children and 1348 were adolescents/young adults. The large difference in the number of cases between the two groups is mainly due to the fact that there is extensive registration of childhood cancers in the European registries (with several countries having national coverage) whereas cancer registration for adults (including adolescents and young adults) only covers smaller populations. Furthermore, leukemia is considerably more rare in adolescents/young adults than in children.[1,10] We grouped the

 doi:10.3324/haematol.2012.071597
Manuscript received on June 6, 2012. Manuscript accepted on November 13, 2012.
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cancer registries into five European regions (see *Appendix*). Table 1 presents the childhood and adolescent/young adult cases, respectively, according to cancer registry and European region, together with the main quality indicators. Table 2 presents the cases according to European region, age group and period of diagnosis.

Survival in children was estimated as observed survival calculated by the actuarial method[11] while, for adolescents and young adults, survival was estimated as relative survival (calculated by the Hakulinen method).[12] For both, the cohort approach was used.[12] Relative survival was not calculated in children since deaths due to competing causes are rare, so relative survival is very similar to observed survival.

Because survival is usually dependent on patient age, and because the age distribution of children differs between countries, survival rates were adjusted to the age distribution of all European children diagnosed with cancer in the study period, to ensure comparability.[2] The input data for the cure models were observed survival for children and relative survival for adolescents and young adults.[7] Cure models are parametric survival models that assume patients can be divided into cured cases, with the same mortality as the rest of the population of the same age and sex, and fatal cases, with an excess risk of death compared to the rest of the population. These models require specification of a parametric excess mortality function for fatal cases. For this purpose, we used a Weibull distribution representing the failure time of fatal cases. The models assume both a linear increase in risk and proportionality of risks across the entire study period. Age and period of diagnosis effects were modeled as covariates of the exponent of the cumulative survival function. We applied the cure models (to observed and relative survival data separately) by age class at diagnosis (0-1, 1-4, 5-9, 10-14, 15-19, 20-24 years) and diagnosis period (1982-1984, 1985-1987, 1988-1990, 1991-1993, 1994-1996, 1997-1999, 2000-2002) for females and males together. Patient age was a categorical covariate, period of diagnosis was a continuous covariate and considered according to age class. We applied the cure models to the entire dataset (producing data for Europe as a whole) and separately to each European region as defined above. However, we do not present cure models for Eastern Europe due to insufficient numbers of cases. We carried out separate analyses for adolescents (15-19 years) and young adults (20-24 years) for the whole of Europe, but this was not possible for individual European regions because of marked statistical instability, making the results unreliable. Therefore, for the regional analyses, we considered the single age category 15-24 years. Assuming a proportional survival function, model parameters were also used to estimate 5-year survival and cured proportion for children and adolescents/young adults diagnosed in the most recent periods, for which follow up was less than five years. Cure model parameters were estimated using the NLIN procedure of the SAS statistical package.[13]

Results

Long-term survival

Age-standardized cumulative survival curves for children with ALL are shown in Figure 1A. Survival increased significantly over the study period. Nine-year survival (longest follow up common to most diagnosis periods) increased from 66% (95%CI: 64-67%) in 1982-84 to 81% (95%CI: 79-82%) in 1994-96, and 15-year survival increased from 64% (95%CI: 62-66%) in 1982-84 to 73% (95%CI: 71-75%) in 1988-90. Survival curves tended to flatten out ten years after diagnosis, but nevertheless continued to decrease over the entire follow-up period. This finding indicates that a small excess risk of death still persisted for up to 20 years after diagnosis, at least for children diagnosed in the period 1982-84. Similarly, the survival curves for adolescents and young adults had not completely flattened out 16 years after diagnosis (Figure 1B).

Figure 2 shows the long-term annual survival probabilities for three cohorts of children with ALL defined by period of diagnosis. From the first to the tenth year after diagnosis, annual survival probabilities increased for all cohorts. After ten years, survival probabilities became constant at approximately 99.6% for all cohorts.

For most age classes of children, the risk of dying was greatest in the first year after diagnosis, the only exception being children aged 5-9 years diagnosed between 1985 and 1996, for whom risk of dying was greatest in the second year after diagnosis (*data not shown*). For infants, the risk of death in the first year after diagnosis was 44% (95%CI: 37-50%) in 1982-1984 but reduced markedly to 18% (95%CI: 16-19%) in the period 2000-2002. The corresponding reductions for children 1-9 years old and 10-14 years old were 8-9% to 2-3% and 17% to 8%, respectively (*data not shown*).

Proportion cured according to age and diagnosis period

Estimates of the proportion cured by age class and period of diagnosis are shown in Figure 3. The age trend was similar to that for 5-year survival: poor in infants, best for children 1-4 years old and declining progressively in the 5-9 and 10-14 years age groups. The proportion of adolescents and young adults cured was similar to that for children under one year of age, but did not improve so steeply for more recent diagnosis periods.

The proportion cured improved significantly over the study period (Figure 3). The greatest improvement was in infants: 26% (95%CI: 25-28%) to 58%, (95%CI: 56%-59%). However, marked improvements were also observed for the childhood age groups: 70% (95%CI: 69-71%) to 90% (95%CI: 89-90%) for 1-4 year olds; 63% (95%CI: 61-64%) to 86% (95%CI: 85-86%) for 5-9 year olds; and 52% (95%CI: 51-53%) to 77% (95%CI: 76-78%) for 10-14 year olds. Small but significant increases between 1988-1990 and 2000-2002 were seen for adolescents (15-19 year olds): 47% (95%CI: 46-48%) to 51% (95%CI: 50-52%); and young adults (20-24 year olds): from 38% (95%CI: 35-41%) to 48% (95%CI: 45-51%). The proportion of young adults cured was significantly lower than for adolescents from 1988 to 1999, while from 1999 to 2001, cured proportion estimates for both these ages groups were closer to each other, but remained significantly lower than for infants.

Proportion cured according to European region and age

Regional and over time variations in cured proportion estimates are shown in Figure 4 for each group. For children aged 1-14 years old, cured proportion differences across European regions narrowed over time. For those aged 1-4 years old, the range was 62% (95%CI: 60-65%) to 74% (95%CI: 73-75%) in 1982-84, and 87% (95%CI: 87-88%) to 92% (95%CI: 91-93%) in 2000-02. In this age group, the cured proportion in Central Europe was significantly higher than that in Southern Europe and the UK over the entire period 1982-2002, while the cured propor-

tion in Northern Europe was similar to that for Central Europe. For children aged 5-9 years old, the cured proportion ranged from 57% (95%CI: 54-60%) to 67% (95%CI: 65-68%) in 1982-84 and from 83% (95%CI: 82-84%) to 89% (95%CI: 88-90%) in 2000-02. In this age group, cured proportions were very similar for Central and Northern

Table 1. Cases of childhood acute lymphoblastic leukemia diagnosed in 1982-2002 and cases of acute lymphoblastic leukemia diagnosed in 1988–2002 in adolescents and young adults by European region and cancer registry, with data quality indicators.

Region	Cancer registry	Total malignant cases		Cases with major errors	Cases without major errors excluded from analyses			Cases included in analyses	
		Childhood (1982-2002)	Adolescents/ young adults (1988-2002)		Death certificate only	Only discovered at autopsy	Multiple primaries	Number of cases	Microscopic verification (%)
Northern Europe									
	Finland	847	113	0	1	2	2	955	99.2
	Iceland	40	8	0	0	0	0	48	100.0
	Norway	665	82	0	0	0	3	744	99.8
	Sweden	1270	170	1	0	4	5	1430	99.9
Central Europe									
	Amsterdam	–	53	0	0	0	2	51	100.0
	Austria	906	138	0	21	0	1	1022	98.8
	Basel	36	9	0	0	0	1	44	100.0
	Côte d'Or Hematologic	75	–	0	0	0	0	75	100.0
	Eindhoven	102	18	0	0	0	0	120	98.3
	Geneva	49	11	0	0	0	0	60	100.0
	Germany West	7691	–	8	0	0	17	7666	100.0
	Germany Berlin	287	–	0	0	0	1	286	100.0
	Germany Saarland	–	15	0	1	0	0	14	100.0
	Lorraine	294	–	0	0	0	0	294	100.0
Eastern Europe									
	Cracow	81	11	1	0	0	0	91	100.0
	Slovakia	690	86	0	16	7	4	749	100.0
	Warsaw	–	16	0	0	0	0	16	100.0
	West Bohemia	–	13	0	0	0	0	13	92.3
Southern Europe									
	Firenze	–	28	0	0	0	0	28	50.0
	Genova	–	10	0	0	0	0	10	90.0
	Modena	–	8	0	0	0	0	8	100.0
	Parma	42	11	0	0	0	0	53	100.0
	Piedmont	480	–	0	0	0	0	480	100.0
	Ragusa	45	8	0	1	0	0	52	100.0
	Region of Valencia	314	–	0	0	0	0	314	100.0
	Romagna	–	12	0	1	0	0	11	100.0
	Slovenia	240	52	0	0	0	0	292	100.0
	Torino	–	12	0	0	0	0	12	100.0
	Veneto	–	45	0	0	0	0	45	100.0
United Kingdom									
	England and Wales	6770	–	0	1	0	15	6754	98.9
	East Anglia	–	49	0	0	0	1	48	72.9
	Northern & Yorkshire	–	73	0	0	0	0	73	97.3
	Oxford	–	71	0	0	0	0	71	100.0
	Scotland	699	106	0	0	0	3	802	95.4
	Wales	–	69	0	4	0	4	61	78.7
	West Midlands	–	94	0	0	0	0	94	67.0
Totals		**21623**	**1391**	**10**	**46**	**13**	**59**	**22886**	**99.1**

Europe, and also for the UK and Southern Europe. Cured proportions were significantly lower for the UK and Southern Europe than for Central and Northern Europe for the entire study period (1982-2002). For children 10-14 years old, the proportion of cured ranged from 41% (95%CI: 38-44%) to 58% (95%CI: 56-60%) in 1982-1984 and from 74% (95%CI: 73-76%) to 82% (95%CI: 80-83%) in 2000-02. For this group, Northern and Central Europe had a significantly higher cured proportion than the UK, while the significant cure differences between Northern plus Central Europe and Southern Europe in 1982-1993 had disappeared by 1994-96.

For infants and for adolescents plus young adults, the marked regional variation in cured proportions at the beginning of the 1980s had not decreased by the early years of the new millennium. For infants, regional cured proportions generally increased in parallel over the study period, except for those of Northern Europe which increased more steeply than all the others: from lowest (14%, 95%CI: 10-19%) in 1982-1984 to highest (76%, 95%CI: 73-79%) in 2000-2002. For this last period, infant cured proportion estimated in the Northern Europe was statistically higher than the other regions, for which values equal to 44% (95%CI: 41-47%), 59% (95%CI: 57-61%) and 66% were estimated (95%CI: 61-71%) for the UK, Central Europe and Southern Europe, respectively. In the UK, the cured estimated proportion was significantly lower than for Central and Southern Europe throughout the study period. For adolescents and young adults, cured proportion estimates also increased in parallel between 1988 and 2002: for Northern Europe from 53% (95%CI: 50-55%) to 62% (95%CI: 60-65%); for Central Europe from 35% (95%CI: 31-39%) to 46% (95%CI: 42-50%); and for the UK from 47% (95%CI: 45-50%) to 51% (95%CI: 49-54%), less marked than the other regions. Cured proportions for Southern European adolescents/young adults are not reported due to insufficient numbers of cases. Observed 5-year survival was 53% (95%CI: 43-64%) in 1988-1990, 42% (95%CI: 32-56%) in 1991-1993, 40% (95%CI: 27-59%) in 1994-1996 and 49% (95%CI: 38-63%) in 1997-1999, based on approximately 20 cases for each period.

Table 2. Numbers of infants, children, adolescents and young adults diagnosed with acute lymphoblastic leukemia in 1982–2002 and included in the analyses, by European region, age and diagnosis period (3-year periods).

	1982-84	1985-87	1988-90	1991-93	1994-96	1997-99	2000-02
Northern Europe	**355**	**404**	**437**	**461**	**523**	**504**	**493**
Under 1 year	13	19	11	10	16	10	17
1-4 years	168	200	198	206	247	218	206
5-9 years	118	118	95	105	117	137	108
10-14 years	56	67	66	71	67	62	83
15-19 years	–	–	48	51	51	50	52
20-24 years	–	–	19	18	25	27	27
Central Europe	**1121**	**1201**	**1276**	**1440**	**1543**	**1570**	**1481**
Under 1 year	25	32	43	42	51	33	37
1-4 years	558	617	613	718	760	804	711
5-9 years	303	339	357	426	442	458	431
10-14 years	235	213	204	212	245	228	267
15-19 years	–	–	38	25	25	26	21
20-24 years	–	–	21	17	20	21	14
Eastern Europe	**96**	**110**	**156**	**132**	**143**	**120**	**112**
Under 1 year	4	4	4	3	2	4	2
1-4 years	40	58	67	52	48	51	48
5-9 years	36	36	43	23	42	23	21
10-14 years	16	12	23	29	26	17	18
15-19 years	–	–	14	15	14	18	16
20-24 years	–	–	5	10	11	7	7
Southern Europe	**163**	**167**	**210**	**213**	**202**	**198**	**152**
Under 1 year	6	7	8	2	8	5	4
1-4 years	78	67	78	80	99	76	74
5-9 years	54	55	55	48	37	52	25
10-14 years	25	38	31	31	23	30	24
15-19 years	–	–	27	31	19	24	13
20-24 years	–	–	11	21	16	11	12
United Kingdom	**967**	**963**	**1136**	**1198**	**1181**	**1221**	**1237**
Under 1 year	29	39	40	41	41	32	38
1-4 years	498	497	573	597	576	564	564
5-9 years	246	267	272	302	303	346	320
10-14 years	194	160	159	153	187	197	218
15-19 years	–	–	66	69	47	56	57
20-24 years	–	–	26	36	27	26	40

Discussion

We have provided estimates of survival and cured proportions for European patients aged 0-24 years old diagnosed with ALL from 1982 to 2002. The estimates were derived from a model that makes it possible to extrapolate longer follow up even for cases (particularly those diagnosed in 2000-2002) with limited follow up. The accuracy of these estimates depends on whether its basic assumptions are correct, i.e. that the absolute death risk varies linearly with year of diagnosis in each interval, but the relative risk of death between different follow-up intervals does not depend on the year of diagnosis. For cases in the most recent cohort (2000-2002), accuracy relies on the persistence of a linear trend up to around 2012.

We found that the proportions of young Europeans cured of ALL diagnosed in the early years of the new millennium, were 58%, 90%, 86%, 77%, 51% and 48%, respectively, for age groups under 1, 1-4, 5-9, 10-14, 15-19 and 20-24 years (Figure 3). The corresponding 5-year survival estimates were higher at 59%, 92%, 89%, 81%, 55% and 50% respectively (*data not shown*). Thus, an excess risk of death was still present five years after diagnosis. There are likely to be several reasons for this: disease progression, late recurrence, late effects of therapy, and increased risk of second primaries.[4] Based on SEER data, Armstrong *et al.*[14] estimated that for 5-year survivors of childhood ALL, the 10-year cumulative risk of death from recurrence/progression was 3.5%. In a retrospective cohort of US childhood ALL survivors (mean follow up 9 years, range 2 months to 30 years), the risk of developing a second primary was 5-fold higher than in the general population.[15] Similarly, in a British childhood cancer survivor study with a mean follow up of 25 years, the stan-

dardized incidence ratio of subsequent primary neoplasms was 4.3.[16] Shah *et al.*[6] found that both survival and the proportion of children cured of lymphatic leukemia had increased, but the excess mortality of patients had spread over a longer period of time: from 11 years after diagnosis for children diagnosed in 1971-75, to 16 years for those diagnosed in 1986-1990. It was suggested that secondary malignancy and treatment-related toxicity were the reasons for the persisting excess mortality.

In spite of this, therefore, the assumption of our model that cured patients were those with a risk of death equal to that of the general, age-matched population, we found that the excess risk of death did not disappear completely even over the entire follow-up period. However, this excess risk was small compared to that expected due to ALL, accounting for less than 1% of the cumulative survival proportion. Thus, our model-based estimates of the proportion of ALL cured include a small fraction still at risk of death for disease-related causes, such as late effects of treatment and second tumors.

Considering the proportion of infants cured, we note that estimates overall were low and had only reached 58% by 2000-2002. This is consistent with data indicating that infants who develop ALL are at high risk of treatment failure.[17] An MLL gene translocation is present in approximately 80% of infants with ALL and is associated with poor prognosis. About one-third of these patients relapse, often during the first year. Infants are also at high risk of treatment-related complications; in the large Interfant-99 study, 5% of infants died of toxicity, mainly infections.[17]

With regard to adolescents and young adults, we found only a modest increase in the estimated cured proportion

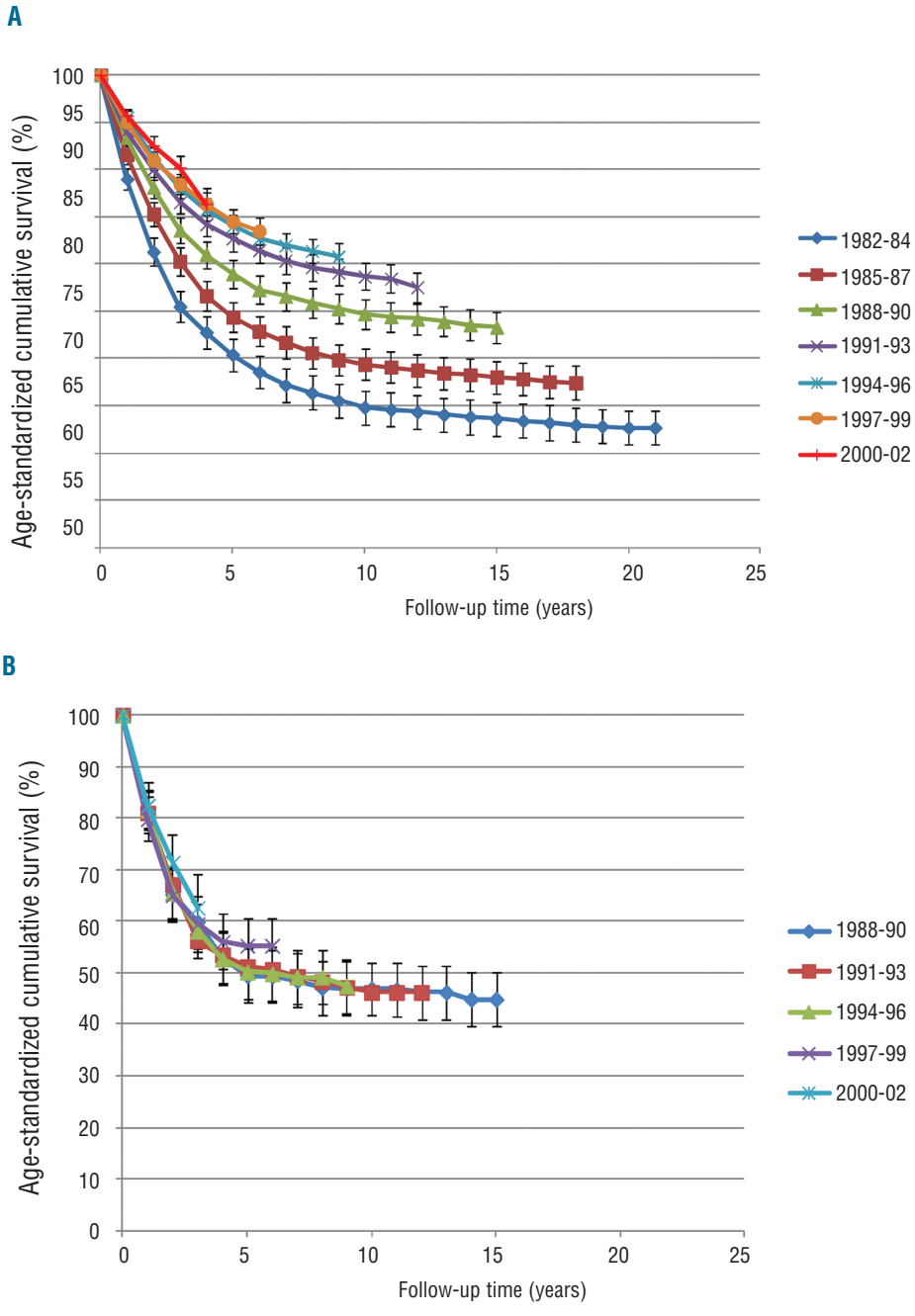

Figure 1. (A) Age-standardized cumulative survival in children (age 0-14 years) of both sexes by diagnosis period (3-year periods from 1982 to 2002). (B) Cumulative relative survival in adolescents and young adults (15-24 years) by 3-year periods from 1988 to 2002. Vertical bars indicate 95% confidence intervals.

over the study period, so that by 2000-2002 it was equal to 51% and 48%, respectively, perhaps because treatment protocols effective in children may be less effective in adolescents and young adults.[3] Several studies indicate that by using intensified pediatric-based regimens without stem cell transplantation, outcomes similar to those in younger children can be achieved.[3] Adolescents and young adults are under-represented in trials of therapies that may improve their outcomes.[18,19] The recently published Children's Oncology Group (COG) study[18] reported that for adolescents with ALL enrolled in COG trials from 1990 to 2005, 5-year survival improved significantly from 66% (1990-1994) to 76% (2000-2005). Both figures are considerably higher than our overall estimate for 2000-2002 (55% for adolescents, 50% for young adults). COG trial outcomes were also superior to population-based SEER survival for US adolescents. Hunger *et al.*[18] emphasized that adolescents/young adults with ALL should be referred to pediatric treatment centers and, wherever appropriate, enrolled in pediatric trials. By contrast, a Finnish study[20] reported similar outcomes for pediatric and adult protocols, and suggested that pediatric and adult protocols were fairly similar. In Finland, adults and children with ALL are treated in one of five academic centers,

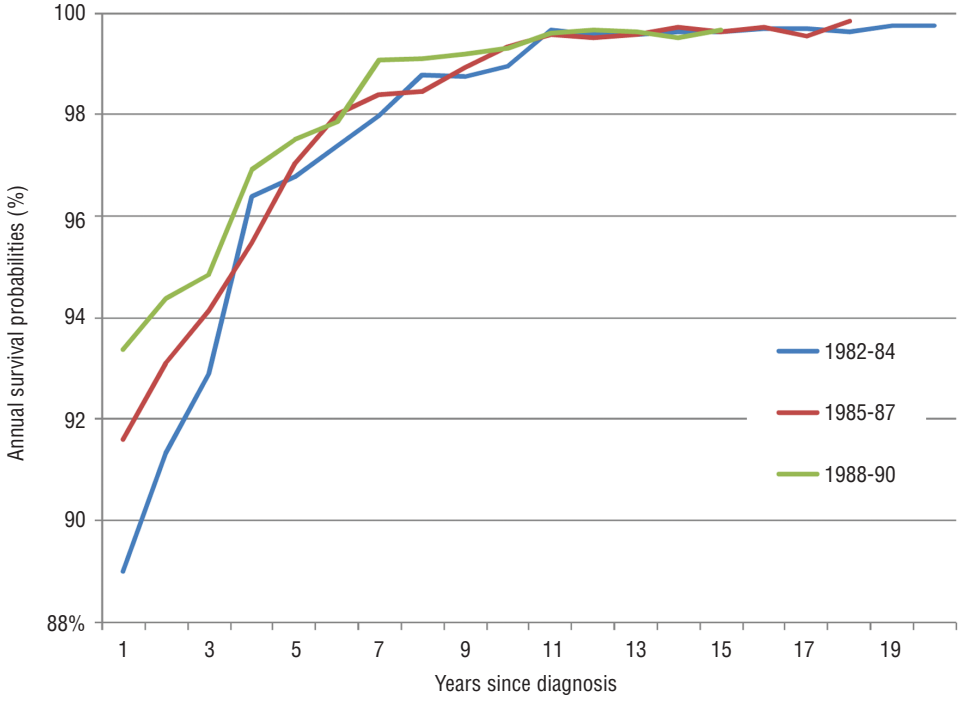

Figure 2. Annual survival probabilities for children (age 0-14 years) diagnosed with acute lymphoblastic leukemia by diagnosis period (3-year periods from 1982 to 1990).

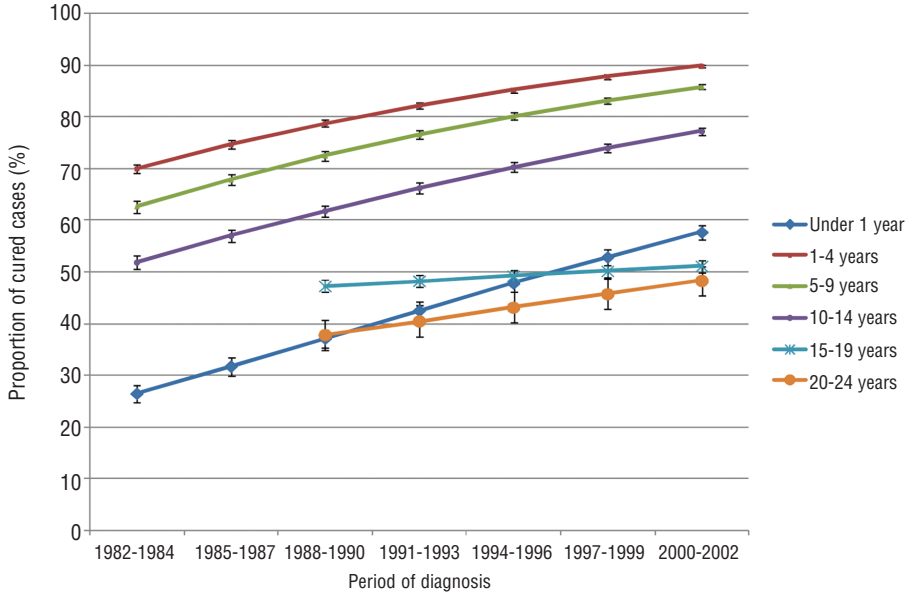

Figure 3. Cure model-based estimates of proportion of infants, children (three age classes), adolescents, and young adults cured of acute lymphoblastic leukemia by diagnosis period (3-year periods from 1982 to 2002) in Europe. Vertical bars indicate 95% confidence intervals.

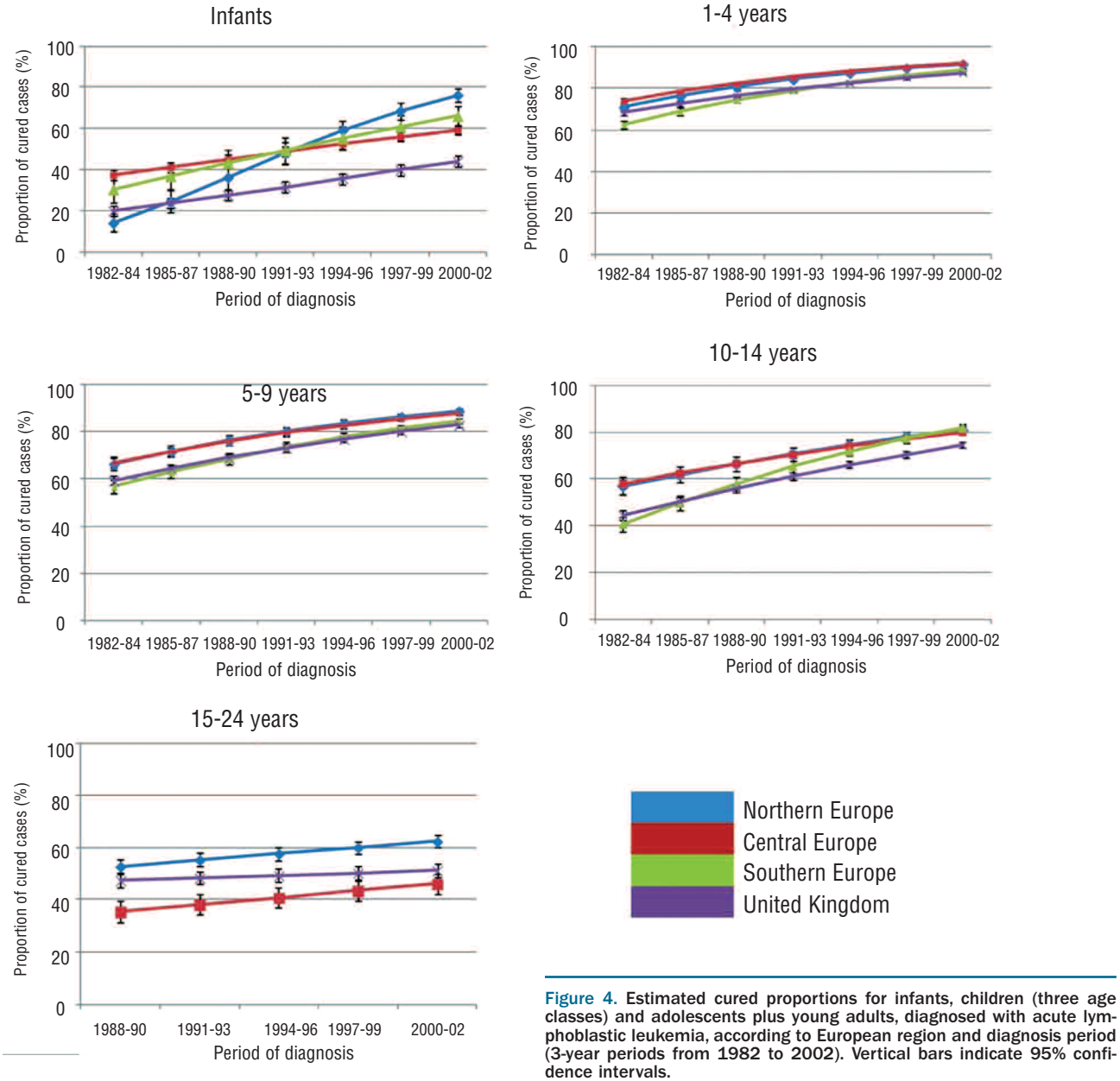

Figure 4. Estimated cured proportions for infants, children (three age classes) and adolescents plus young adults, diagnosed with acute lymphoblastic leukemia, according to European region and diagnosis period (3-year periods from 1982 to 2002). Vertical bars indicate 95% confidence intervals.

and there is high adherence to protocols.[20]

Cancer biology might also contribute to the modest increase in proportion of adolescents/young adults cured over the study period. Compared to children, adolescents/young adults with ALL are more likely to have adverse biological characteristics, such as pro-T cell immunophenotype and the t(9,22) BCR–ABL (Philadelphia chromosome) translocation.[21] The BCR–ABL genotype occurs in less than 3% of children but 3-26% of adolescents and young adults with ALL.[22] Nearly half of all children but only 10% of adolescents have blast cells with a favorable genotype, such as the TEL–AML1 translocation.[21] Cancer registries did not systematically include information on the underlying disease biology and so this could not be analyzed in our study.

Although we found that across-Europe differences in cured proportions narrowed considerably over time for children, this was not the case for infants and adolescents/young adults. An important reason for regional (and over time) disparities in outcome is variation in risk of early death. It has been proposed that much of the decline in early mortality in children with ALL is due to improved support therapy, including prompt recognition and control of infection, hemorrhage and tumor lysis syndrome.[23] It is likely that these improvements were not applied uniformly over all the cancer registry areas involved in this study. It has been urged that children with ALL should always be treated at specialist centers, at least during induction therapy when there is a high risk of early death.[23]

The principal limitation of the study is that for Eastern Europe for all age groups, and for Southern Europe for adolescents and young adults, it was not possible to estimate proportions cured because there were too few cases. Increasing coverage in future EUROCARE studies to new

countries or enlarged coverage of countries with only partial cancer registration is necessary in order to effectively monitor the success of cancer control policies in young people across the whole of Europe. Estimates of cured proportion for malignant diseases are appearing more frequently in the literature to supplement the traditional prognosis measurement of 5-year survival. The findings of the present population-based study on a large number of young European patients with ALL are in agreement with previously published data: we estimated that over 75% of the children aged 1-14 years diagnosed with ALL in 2000-2002 were cured of their disease, while cured proportions for infants and adolescents/young adults were considerably lower. Furthermore, our study revealed clear regional differences in cured proportion, and these were more marked in infants and adolescents/young adults. The European Commission has called for a network of clinical and research excellence in pediatric and adolescent oncology in Europe in order to improve outcomes for these diseases. This call has been taken up by the European Network for Cancer Research in Children and Adolescents (ENCCA)[24] that aims to establish a durable European network of research into childhood and adolescent cancers that will facilitate clinical trials on new targeted drugs and introduce them into clinical practice. A recent European directive on Cross-Border Healthcare may also help improve outcomes for these rare diseases,[25] particularly for those European countries with limited resources that also lack the sophisticated infrastructure necessary for adequately treating these diseases.

Acknowledgments

The authors thank Don Ward for help with language revision.

Funding

The research was supported by the Compagnia di San Paolo, Torino, Italy. The Childhood Cancer Research Group receives funding from the Department of Health, the National Cancer Intelligence Network and the Scottish Government. The views expressed here are those of the authors and not necessarily those of the Department of Health, the National Cancer Intelligence Network or the Scottish Government.

Appendix

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Authorship and Disclosures

Information on authorship, contributions, and financial and other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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