Survival of European patients diagnosed with lymphoid neoplasms in 2000-2002: results of the HAEMACARE project

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ABSTRACT

Background

The European Cancer Registry-based project on hematologic malignancies (HAEMACARE), set up to improve the availability and standardization of data on hematologic malignancies in Europe, used the European Cancer Registry-based project on survival and care of cancer patients (EUROCARE-4) database to produce a new grouping of hematologic neoplasms (defined by the International Classification of Diseases for Oncology, Third Edition and the 2001/2008 World Health Organization classifications) for epidemiological and public health purposes. We analyzed survival for lymphoid neoplasms in Europe by disease group, comparing survival between different European regions by age and sex.

Design and Methods

Incident neoplasms recorded between 1995 to 2002 in 48 population-based cancer registries in 20 countries participating in EUROCARE-4 were analyzed. The period approach was used to estimate 5-year relative survival rates for patients diagnosed in 2000-2002, who did not have 5 years of follow up.

Results

The 5-year relative survival rate was 57% overall but varied markedly between the defined groups. Variation in survival within the groups was relatively limited across European regions and less than in previous years. Survival differences between men and women were small. The relative survival for patients with all lymphoid neoplasms decreased substantially after the age of 50. The proportion of 'not otherwise specified' diagnoses increased with advancing age.

Conclusions

This is the first study to analyze survival of patients with lymphoid neoplasms, divided into groups characterized by similar epidemiological and clinical characteristics, providing a benchmark for more detailed analyses. This Europe-wide study suggests that previously noted differences in survival between regions have tended to decrease. The survival of patients with all neoplasms decreased markedly with age, while the proportion of 'not otherwise specified' diagnoses increased with advancing age. Thus the quality of diagnostic work-up and care decreased with age, suggesting that older patients may not be receiving optimal treatment.

Key words: lymphoid malignancies, survival, outcome.

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The online version of this article has a Supplementary Appendix.

Introduction

Lymphoid neoplasms are a heterogeneous group of hematologic malignancies that include non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL), plasma cell neoplasms and lymphoid leukemias.[1,2] Various classifications of these diseases, based mainly on morphological and clinical criteria,[3-6] were used in the past, but these were superseded by the Revised European-American Lymphoma (REAL) classification of 1994[7] which included immunophenotypic and genotypic, as well as morphological and clinical, criteria. The World Health Organization (WHO) introduced a new classification in 2001. This was based on the REAL classification but gained broader consensus and, together with the revised WHO classification of 2008,[8] is now widely used by clinicians and pathologists.[9,10] The WHO terminology was incorporated into the International Classification of Diseases for Oncology, Third Edition (ICD-O-3)[11] which uses all available criteria to distinguish the various entities of lymphoid neoplasms according to cell lineage and level of differentiation.[1]

Since the ICD-O-3 has been adopted by most European population-based cancer registries it has now become possible, for the first time, to analyze the survival of patients with lymphoid neoplasms in Europe using an internationally recognized disease classification system. Nevertheless major difficulties remain: it is not possible to analyze each disease entity (defined by ICD-O-3 code) separately; there are too many such entities and many of them are rare, so even casting the net across most of Europe would not produce enough cases to enable a robust survival analysis. To address this difficulty, hematologists, pathologists and epidemiologists from several European countries convened under the aegis of a European Cancer Registry-based project on hematologic malignancies (HAEMACARE) to produce a consensus grouping of lymphoid neoplasms (as defined by ICD-O-3 morphology codes and WHO recommendations) into sub-categories based primarily on cell lineage with similar prognosis, of use for clinical and epidemiological studies. The HAEMACARE project made use of data provided by cancer registries participating in EUROCARE-4.[12,13]

The HAEMACARE lymphoid neoplasm grouping system incorporates the changes introduced by the 2001 and 2008 WHO classifications[1,8] and is consistent with the classification of lymphoid neoplasms for epidemiological research proposed by the Pathology Working Group of the International Lymphoma Epidemiology Consortium (InterLymph) in 2007,[14] which was recently updated taking into account the revisions of the WHO classification.[15] The InterLymph and HAEMACARE schemes are comparable except that the InterLymph classification regards the obsolete Working Formulation[3] category of malignant lymphoma, mixed small and large cell, diffuse (code 9675) as not otherwise specified (NOS), whereas in the HAEMACARE grouping strategy this category is grouped as diffuse large B-cell lymphoma.

In the present study we estimated 5-year relative survival rates for patients with lymphoid neoplasms diagnosed in Europe in 2000-2002, according to the groups defined by HAEMACARE, and compared survival across European regions according to age and sex.

Design and Methods

Cancer registries

Data on lymphoid neoplasms from 48 cancer registries operating in 20 countries and participating in EUROCARE-4 were considered for inclusion in the analysis.[16] The registries were grouped into five regions: Northern Europe (Iceland, Norway and Sweden); UK and Ireland (England, Ireland, Northern Ireland, Scotland, and Wales), Central Europe (Austria, France, Germany, Switzerland and The Netherlands); Southern Europe (Italy, Malta, Slovenia, and Spain); and Eastern Europe (Czech Republic, Poland, and Slovakia). Eleven of the cancer registries are national registries, the others cover variable percentages of their respective national populations. The number of cases contributed by each registry is shown in Table 1, together with indicators of data quality.

The cancer registries provided data on lymphoid neoplasms diagnosed in 1995-2002; for most cases follow-up was only available to 2003. We estimated 5-year relative survival for cases diagnosed in 2000-2002. Since most of these cases did not have 5 years of follow-up, we used the period method[17] to estimate survival: with this method, survival over the years for which follow-up data were unavailable was estimated from the survival experience of patients diagnosed in recent time periods.

To obtain a set of cases with adequately specified morphology, we excluded cancer registries in which NOS morphology constituted over 30% of cases. The ICD-O-3 NOS codes are: lymphoma 9590, NHL 9591, and lymphatic leukemia 9820 and 9832. The cancer registries of Sweden, Northern Ireland, Austria, Friuli Venezia-Giulia (Italy), Reggio Emilia (Italy), Umbria (Italy), and Cracow (Poland) were excluded for this reason. The resulting study population, from the remaining 41 cancer registries, consisted of 138,581 cases.

HAEMACARE categories of lymphoid neoplasms

HAEMACARE grouped lymphoid neoplasm morphological entities (defined by ICD-O-3 codes) into six major categories:[18] Hodgkin's lymphoma (HL), mature B-cell neoplasms, mature T-cell and natural killer cell neoplasms (T-NK), precursor cell neoplasms, composite Hodgkin's and non-Hodgkin's lymphoma, and unknown type lymphoid neoplasm (NOS). Each of these categories was further divided into sub-categories of similar cell lineage and prognosis (Table 2). There were very few cases of composite Hodgkin's and non-Hodgkin's lymphoma (29 cases) and B-cell prolymphocytic leukemia (14 cases); for completeness and to comply with WHO indications, we present data for these entities, but do not include them in the survival analyses.

Statistical analysis

Five-year relative survival, by HAEMACARE groups, was estimated overall and for each European region for patients diagnosed in 2000-2002, using the period approach.[17] Survival was also estimated by sex and age. We present relative survival rates in accordance with standard practice for comparative population-based cancer-survival analyses.[19,20] Relative survival was estimated as the ratio of the observed survival of patients with cancer to the expected survival of a group of people of the corresponding sex and age in the general population. Expected survival was based on cancer registry area-specific or country-specific official mortality data, and was estimated according to Hakulinen's method.[21] The analyses were carried out using SEER*Stat software.[22]

Table 1. Lymphoid neoplasms diagnosed in 1995-2002 and recorded in 48 European cancer registries, with data quality indicators

Country/Area	Cancer registry	N. of cases	Lost to follow-up (%)	DCO/ autopsy (%)	Microscopically verified (%)	Poorly specified (NOS) neoplasms (%)
Northern Europe		**29,716**	**0.3**	**1.7**	**98.8**	**32.5**
ICELAND	ICELAND	501	0.0	0.2	99.6	2.4
NORWAY	NORWAY	9,752	0.4	1.5	96.5	18.4
SWEDEN	SWEDEN*	19,463	0.2	1.8	99.9	40.3
UK and Ireland		**66,322**	**0.0**	**2.8**	**87.7**	**24.3**
IRELAND	IRELAND	7,271	0.0	2.1	95.8	24.2
UK England	East Anglia	6,716	0.3	1.7	85.4	24.0
	Northern & Yorkshire	12,715	0.0	0.9	92.5	21.5
	Oxford	6,101	0.0	0.6	100.0	20.2
	West Midlands	11,199	0.0	6.1	84.0	27.3
UK Northern Ireland	NORTHERN IRELAND*	3,545	0.0	1.7	81.9	37.5
UK Scotland	SCOTLAND	11,981	0.0	0.7	94.1	22.2
UK Wales	WALES	6,794	0.0	9.4	58.6	25.8
Central Europe		**33,910**	**0.3**	**5.3**	**93.4**	**19.5**
AUSTRIA	AUSTRIA*	13,775	0.0	11.2	86.8	37.6
France	Cote d'Or Haemat.	1,278	0.0	0.0	100.0	3.4
Germany	Saarland	2,276	0.0	3.7	94.2	5.3
Switzerland	Basel	793	1.5	1.9	98.6	11.7
	Geneva	902	4.0	0.4	97.0	17.9
	St. Gallen	1,044	1.1	1.2	98.5	6.6
	Ticino	791	2.5	3.3	94.4	9.1
The Netherlands	Amsterdam IKN	5,631	0.1	0.5	98.8	4.2
	Eindhoven IKZ	1,524	0.0	0.0	97.3	11.8
	North Netherlands	3,704	0.0	1.8	98.4	7.9
	Twente	2,192	0.6	0.8	98.5	8.1
Southern Europe		**41,222**	**0.8**	**1.2**	**93.0**	**20.2**
Italy	Alto Adige	1,107	0.0	0.2	98.5	11.4
	Biella	681	0.2	1.2	93.1	5.6
	Ferrara	1,252	0.8	1.7	97.0	9.3
	Firenze	3,672	0.1	0.7	74.9	22.1
	Friuli V.G.*	4,049	0.9	1.6	99.4	37.1
	Genova	2,449	0.0	1.0	86.2	8.3
	Modena	2,139	1.8	0.3	99.5	5.4
	Napoli	579	5.0	1.0	86.5	22.1
	Parma	1,513	0.6	0.0	99.7	19.7
	Ragusa	598	0.0	1.2	89.8	13.0
	Reggio Emilia*	1,337	0.1	0.1	95.7	57.4
	Romagna	3,594	0.3	2.2	97.5	10.9
	Salerno	1,823	8.0	1.3	95.6	26.0
	Sassari	1,154	0.0	0.2	95.5	5.9
	Torino	2,373	0.1	1.6	94.1	17.3
	Trento	819	0.4	0.5	97.4	13.1
	Umbria*	2,436	0.9	0.7	79.9	42.9
	Veneto	4,652	0.6	1.5	93.1	23.6
MALTA	MALTA	701	0.0	0.7	95.4	17.3
SLOVENIA	SLOVENIA	3,049	0.1	1.4	99.6	11.8
Spain	Girona	1,245	0.1	2.3	97.3	4.8
Eastern Europe		**12,996**	**0.2**	**6.8**	**91.9**	**20.0**
Czech Republic	West Bohemia	1,571	0.7	7.4	92.9	13.0
Poland	Cracow*	980	1.7	4.1	87.8	41.8
	Kielce	1,748	0.0	0.0	89.8	29.1
	Warsaw	2,195	0.1	1.4	92.0	24.3
SLOVAKIA	SLOVAKIA	6,502	0.0	10.7	92.8	14.5
EUROCARE pool		**184,166**	**0.3**	**3.0**	**92.0**	**23.5**

**Data from cancer registries with more than 30% of NOS cases are not included in the survival analyses. Cancer registries in upper case cover entire national populations.*

Table 2. Total number of lymphoid neoplasms diagnosed in 1995-2002 and archived by 41 European cancer registries, divided by HAEMACARE group, together with mean number of cases used to estimate survival, and period estimates for 2000-2002 of 5-year relative survival.

HAEMACARE grouping	ICD-O-3 morphology Code	ICD-O-3 description	N. of cases 1995-2002	Mean N. of cases[2]	Overall 5-year period survival (95%CI)
Hodgkin's lymphoma, total			**12,405**	**4,730**	**84.5 (83.2-85.7)**
Hodgkin's lymphoma, nodular lymphocyte predominant	9659	Hodgkin's lymphoma, nodular lymphocyte predominant	360	137.5	95.8 (91.4-100.0)
Classical Hodgkin's lymphoma			12,045	4,563.5	84.0 (82.8-85.3)
	9650 9661 9662	Hodgkin's lymphoma, NOS[1] Hodgkin's granuloma [obsolete] Hodgkin's sarcoma [obsolete]	2,025	709.0	73.6 (69.7-77.5)
	9651	Hodgkin's lymphoma, lymphocyte rich	576	204.5	93.1 (88.3-97.8)
	9663 9664 9665 9667	Hodgkin's lymphoma, nodular sclerosis (NOS[1]) Hodgkin's lymphoma, nodular sclerosis cellular phase Hodgkin's lymphoma, nodular sclerosis, grade 1 Hodgkin's lymphoma, nodular sclerosis grade 2	7,054	2,710.0	87.8 (86.3-89.2)
	9652	Hodgkin's lymphoma, mixed cellularity, NOS[1]	2,164	813.5	78.9 (75.5-82.3)
	9653 9654 9655	Hodgkin's lymphoma, lymphocyte depletion, (NOS[1]) Hodgkin's lymphoma, lymphocyte depletion, diffuse fibrosis Hodgkin's lymphoma, lymphocyte depletion, reticular	226	75.0	54.4 (40.5-68.3)
Mature B-cell neoplasms			**89,556**	**33,907**	**53.9 (53.2-54.5)**
Chronic lymphocytic leukemia/small lymphocytic lymphoma	9670 9823	Malignant lymphoma, small B-cell lymphocytic, NOS[1] B-cell chronic lymphocytic leukemia	22,871	8487.5	69.1 (67.7-70.5)
Immunoproliferative diseases	9671 9760 9761 9762	Malignant lymphoma, lymphoplasmacytic Immunoproliferative disease, NOS[1] Waldenström's macroglobulinemia Heavy chain disease	4,128	1531.5	66.2 (63.0-69.4)
Mantle cell lymphoma	9673	Mantle cell lymphoma	2,055	789.0	43.8 (39.7-47.8)
Follicular lymphoma	9690 9691 9695 9698	Follicular lymphoma, NOS[1] Follicular lymphoma, grade 2 Follicular lymphoma, grade 1 Follicular lymphoma, grade 3	9,392	3635.5	72.8 (71.0-74.6)
Diffuse large B-cell lymphoma	9675 9678 9679 9680 9684	Malignant lymphoma, mixed small and large cell, diffuse [obsolete] Primary effusion lymphoma Mediastinal large B-cell lymphoma Malignant lymphoma, large B-cell, diffuse, NOS[1] Malignant lymphoma, B large cell, diffuse, immunoblastic, NOS[1]	18,685	7164.5	49.3 (47.8-50.6)
Burkitt's lymphoma	9687 9826	Burkitt's lymphoma, NOS[1] Burkitt cell leukemia	949	369.5	56.0 (50.7-61.2)
Marginal zone lymphoma	9689 9699 9764	Splenic marginal zone B-cell lymphoma Marginal zone B-cell lymphoma, NOS[1] (MALT lymphoma)[3] Immunoproliferative small intestinal disease (Mediterranean lymphoma)	1,995	797.5	81.4 (77.7-85.2)
B-cell prolymphocytic leukemia	9833	Prolymphocytic leukemia, B-cell type	14	-	-
Hairy cell leukemia	9940	Hairy cell leukemia	1,403	527.5	93.9 (90.1-97.7)
Plasma cell neoplasms			28,064	10299.5	32.6 (31.5-33.7)
	9732 9733 9731, 9734	Multiple myeloma Plasma cell leukemia Plasmacytoma NOS[1], plasmacytoma, extramedullary	25,721 163 2,180		
Mature T-cell and NK-cell neoplasms			**5,149**	**2,051**	**60.1 (57.6-62.7)**
T lymphoma cutaneous	9700 9701 9709 9718 9708	Mycosis fungoides Sézary's syndrome Cutaneous T-cell lymphoma, NOS[1] Primary cutaneous CD30$^+$ T cell-lymphoproliferative disorder Subcutaneous T panniculitis-like T-cell lymphoma	2,620	1,046.5	83.4 (80.0-86.7)

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Other T and NK- cell lymphomas	9702	Mature T-cell lymphoma, NOS[1]			
	9705	Angioimmunoblastic T cell lymphoma			
	9714	Anaplastic large cell lymphoma, T-cell and null cell type	2,529	987.5	38.6 (35.2-41.9)
	9716	Hepatosplenic gamma delta cell lymphoma			
	9717	Intestinal T-cell lymphoma			
	9948	Aggressive NK-cell leukemia			
	9719	NK/T cell lymphoma, nasal and nasal type,			
	9827	Adult T-cell leukemia/lymphoma (HTLV-1 positive)			
	9831	T-cell large granular lymphocytic leukaemia			
	9834	Prolymphocytic leukemia, T-cell type			
Precursor cell neoplasms					
	9728, 9836	Precursor B- cell lymphoblastic lymphoma/leukemia	257		
	9729, 9837	Precursor T-cell lymphoblastic lymphoma/leukemia	118		
	9727, 9835	Precursor cell lymphoblastic lymphoma/leukemia NOS[1]	5,831		
Composite Hodgkin's and non-Hodgkin's lymphoma	**9596**	**Composite Hodgkin's and non-Hodgkin's lymphoma**	**29**	-	
Unknown type lymphoid neoplasm, total			25,236	8,720	48.2 (46.9-49.6)
Lymphoma, NOS[1]	9590	Malignant lymphoma, NOS[1]	9,149	3,097	42.1 (39.9-44.4)
Non-Hodgkin's lymphoma, NOS[1]	9591	Malignant lymphoma, non-Hodgkin's, NOS[1]	15,285	5383	51.8 (50.1-53.5)
Lymphatic leukemia, NOS[1]	9820, 9832	Lymphoid leukaemia, NOS[1], prolymphocytic leukemia, NOS[1]	802	240	39.3 (31.6-47.1)
Lymphoid neoplasms, total			138,581	51,847	56.9 (56.4-57.4)

[1]NOS: not otherwise specified; [2]Mean number of cases contributing to period survival estimates for 2000-2002; [3]Marginal zone B-cell lymphoma, NOS (ICD-O-3 code 9699) includes both MALT lymphoma and nodal marginal zone lymphoma, if site is not known.

Results

Table 1 shows the total number of cases, divided by registry and by European region, with quality indicators. The quality indicators are percentages of cases lost to follow-up, cases determined by death certificate only or notified autopsy (DCO/autopsy), cases microscopically confirmed, and cases with NOS morphology.

Overall, 0.3% of cases were lost to follow-up, with the highest figures in Southern Europe (0.8%; range, 0.0-8.0%). Overall 3.0% of cases were DCO/autopsy, with highest proportions in Central Europe (5.3%; range, 0.0-11.2%) and Eastern Europe (6.8%; range, 0.0-10.7%).

Overall, 92.0% of cases were microscopically verified, although the percentages were lower for UK and Ireland (87.7%) and particularly low for Wales (58.6%), where a large proportion of pathology records was not available to the registry.[12] The proportion of NOS cases was similar across regions (19.5 to 24.3%), but was particularly high in Northern Europe (32.5%; range, 2.4-40.3%). Considering individual cancer registries, the proportion of NOS cases varied more than the other quality indicators, ranging from 2.4% (Iceland) to 57.4% (Reggio Emilia).

Survival of patients according to HAEMACARE group and sex

Table 2 shows, for each ICD-O-3 entity and HAEMACARE group, the total numbers of cases of lymphoid neoplasms diagnosed in 1995-2002, the mean number of cases contributing to the period estimates of 5-year relative survival for 2000-2002, and the period estimate of 5-year relative survival with corresponding 95% confidence intervals for 2000-2002.

The 5-year relative survival rate was 57% overall but varied markedly according to HAEMACARE group. Relative survival was highest for patients with nodular lymphocyte predominant Hodgkin's lymphoma (95.8%), hairy cell leukemia (93.9%), classical Hodgkin's lymphoma (84.0%) and T cutaneous lymphoma (83.4%). This last group consisted mainly of patients with mycosis fungoides. Survival was lowest for patients with mantle cell lymphoma (43.8%), other T/NK-cell lymphomas (38.6%), and plasma cell neoplasms (32.6%).

Figure 1 shows 5-year relative survival by sex and HAEMACARE group. Overall survival was similar in males (57.0%) and females (56.7%). Survival was also similar between the sexes within the individual HAEMACARE groups, although better survival in females than males was found for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

Survival of patients in HAEMACARE groups according to age at diagnosis

Online Supplementary Table S1 shows the distribution of patients in HAEMACARE groups by age category and European region. Approximately 80% of all lymphoid neoplasms occurred in patients over 50 years, and only 3.4% occurred in patients under 14 years. The proportions of the different subtypes of lymphoid neoplasms also varied markedly with age. Thus 5.2% of HL, 24.2% of Burkitt's lymphoma/leukemia (BL) and 52.5% of precursor cell neoplasms occurred in patients under 14 years, whereas 63.8% of HL, 39.1% of BL and 25.7% of precursor cell neoplasms occurred in the age group from 15-49 years old. Follicular lymphoma (FL) (48.5%), hairy cell leukemia (HCL) (46.1%) and mantle cell lymphoma (MCL) (45.6%) were mainly diagnosed in the age group from 50-69 years old. Over half of the patients with CLL/SLL, immunoproliferative diseases, plasma cell neoplasms, and B-cell prolymphocytic leukemia were 70 years or older. The proportion of NOS increased substantially with age, from 1.4% in children under 14 to 47.9%

in people over 70 years old.

Online Supplementary Figure S1 shows trends in 5-year relative survival rates for 2000-2002 according to age at diagnosis. In general survival decreased with advancing age at diagnosis and fell particularly markedly after the age of 50. The survival rate for patients with precursor cell neoplasms fell dramatically from 84.4% in patients under 14 years old, to 8.8% in patients over 70 years old. A similarly marked decline with age was also found for classical HL, BL and NHL NOS.

Patients with diffuse large B-cell lymphoma (DLBCL) and other T/NK-cell lymphomas had the worst survival (74.4% and 72.0%, respectively) in the youngest age category, although for both these entities the number of cases was low, complicating interpretation.

The survival rate of patients with plasma cell neoplasms, mainly represented by multiple myeloma, was significantly higher among patients under 50 years old (59.0%) than among older patients (50-69 years, 39.6%; 70-99 years, 21.9%).

Distribution of HAEMACARE groups by region

HL and precursor cell neoplasms formed high proportions of cases in Eastern Europe (Table 2) (13.2% and 6.1%), while mature B-cell and T/NK-cell neoplasms formed high proportions of all cases in Central Europe (74.6% and 4.7%) and Southern Europe (67.9% and 4.8%) (*Online Supplementary Table S1*). DLBCL formed the highest proportion of cases in Central Europe (20.3%), and the lowest in Eastern Europe (9.6%). Marginal zone lymphomas were uncommon in Eastern Europe (0.5%) and the UK and Ireland (0.5%). MCL accounted for 1.5% of all lymphoid neoplasms in Europe (range, from 1.2 % in UK and Ireland to 1.8% in Southern and Central Europe).

Figure 2 shows 5-year relative survival rates divided by HAEMACARE group and region. For most HAEMACARE entities, survival was similar across regions, although for CLL/SLL and immunoproliferative diseases, survival was significantly lower in Eastern Europe than in other regions.

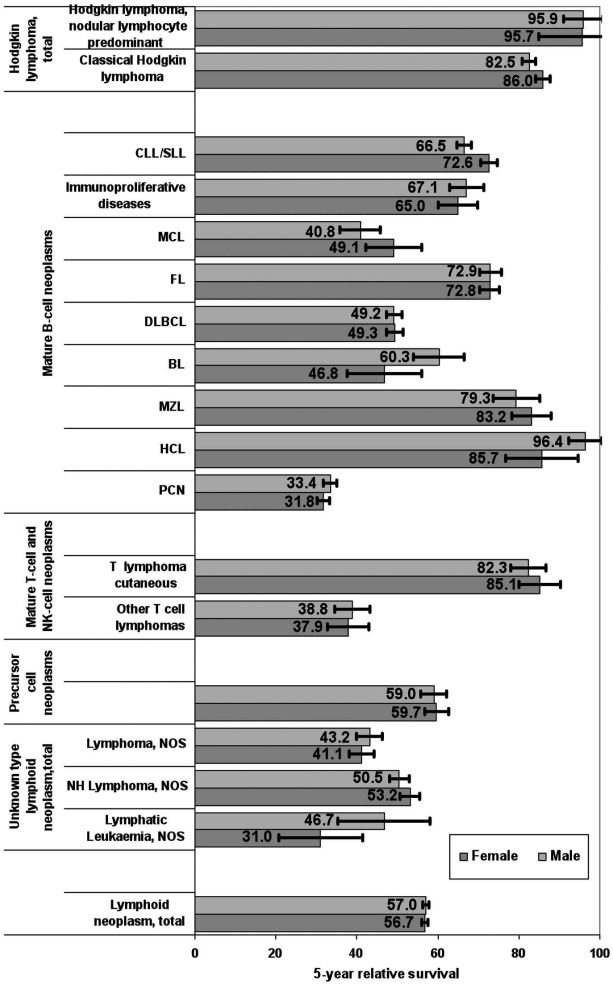

Figure 1. Sex-specific period estimates of 5-year relative survival for patients with lymphoid neoplasms diagnosed in 2000-2002 and grouped according to HAEMACARE.

Discussion

This study provides a comparative analysis of 5-year relative survival rates for patients diagnosed with lymphoid neoplasms in 2000-2002, according to HAEMACARE group, age and sex, across European regions. To our knowledge this is the first population-based study on a large European dataset. It is also novel because it groups individual lymphoid neoplasm entities (defined by ICD-O-3 code) into HAEMACARE categories based primarily on cell lineage and similar prognosis, and is, therefore, useful for clinical and epidemiological studies[18,23] Past population-based studies divided lymphoid neoplasms into broad categories (typically NHL *versus* HL) to investigate incidence and survival.[24] This is unsatisfactory because survival and incidence vary greatly between ICD-O-3 entities, complicating comparisons and in particular making it difficult to interpret regional differences in survival.

A striking finding of the present study is that survival differences between men and women were small. The exception was CLL/SLL, for which the survival of affected women was better than that of men. Previous studies[25,26] had found that, among patients with lymphoid neoplasms, the survival of males was worse than that of females.

With regard to the effect of age on survival, we found that survival decreased with advancing age at diagnosis for most HAEMACARE groups, as has been well documented for most types of cancer.[27] The markedly lower survival in the oldest patients (*Online Supplementary Figure S1*) together with the sharp increase in NOS cases with advancing age (*Online Supplementary Table S1*) point to a decline in the quality of diagnostic workup and of care as the age of the patient increases, suggesting that older patients may not be receiving optimal treatment for their conditions. However 'less insistent' application of potentially effective therapies in the elderly could be due to poor toleration of cytotoxic agents or the frequent presence of comorbidities. In addition elderly patients are under-represented in randomized clinical trials,[28,29] so evidence-based treatment guidelines specifically for the elderly are lacking.

For most lymphoid neoplasms, survival did not vary significantly across the five European regions. This finding suggests a major increase in survival of patients with these diseases in Eastern European countries compared to earlier years.[30,31] The exceptions were for CLL/SLL and immunoproliferative diseases, with survival in Eastern Europe being significantly lower than in other European regions. Incomplete registration of CLL/SLL cases with better sur-

vival may account for the difference: CLL/SLL cases with a better prognosis are generally diagnosed on an outpatient basis, so reporting sources are usually pathology laboratories and doctors' offices.[32] These cases are more likely to be unreported than the poorer prognosis cases treated in (and reported by) hospitals.[33,34] This could be particularly true for Eastern European countries, where the relatively low total national expenditure on health compared to that of other regions[35] may have lowered hospital admissions for patients potentially treatable at home.

We might have expected to see more marked survival differences between regions for DLBCL and FL in relation to a heterogeneous introduction of the use of rituximab. Rituximab is a monoclonal antibody that binds the B-cell transmembrane protein CD20 resulting in lymphoma cell lysis. It started to be used in Europe in 2000, but not simultaneously in all countries[36-38] and significant survival improvements for DLBCL and FL patients treated with rituximab have been described in a population-based study.[39,40]

The treatment of multiple myeloma has also changed over the last decade with the introduction of thalidomide, lenalidomide and proteasome inhibitors (bortezomib), as add-on therapy to conventional cytotoxic and transplantation regimens.[41] We found that the survival of patients with multiple myeloma was poor at 32.4% and unchanged compared to the 35% reported for 1995-1999 by EUROCARE-4.[24] A US study reported a similar survival rate (30%) for the same time period.[25] By contrast, survival of patients with multiple myeloma was significantly better (59%) in European patients under 50 years old, as also observed in the USA.[42] The US study found a significant increase in survival for younger patients from 1990-1992 to 2002-2004, but only a moderate improvement for older patients. Improvements in survival of patients with DLBCL, FL and multiple myeloma may become evident after 2004, in relation to more extensive application of the new treatments. Only longitudinal data from population-based studies can show whether these treatments lead to real survival improvements.

The strengths of our study are its large size (≈140,000 cases), European scope, and use of the period method to estimate 5-year relative survival rates when follow-up was shorter than 5 years. An important limitation regards data quality. Overall, around 16% of the cases we analyzed were NOS and this figure varied considerably with European region (*Online Supplementary Table S1*). Non-specification of the morphology of lymphoid neoplasms results in misclas-

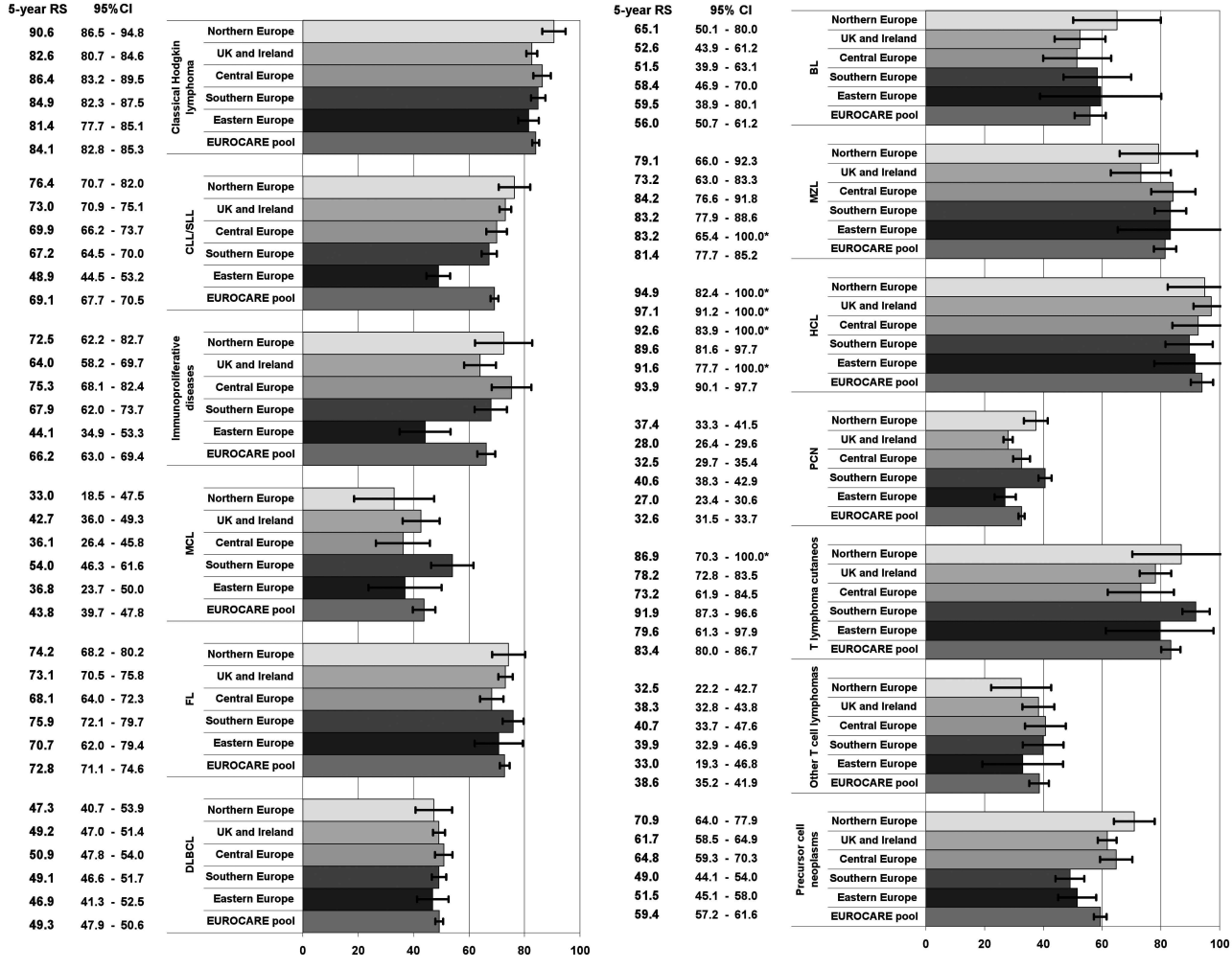

Figure 2. European region-specific period estimates of 5-year relative survival of patients with lymphoid malignancies diagnosed in 2000-2002, and grouped according to HAEMACARE.

sification of subtype-specific distribution, and biases the survival analyses since the majority of NOS cases have poor prognoses. Erroneous automatic conversion of ICD-O codes from previous to recent versions could be responsible for some of the NOS cases.[43,44] In addition, the low proportions, in some regions, of entities first recognized in the 2001 WHO classification (e.g marginal zone lymphomas) suggests that many of these entities were simply classified as NOS. A central pathology review would have reduced the number of NOS cases but this is not feasible in population-based studies involving tens or hundreds of thousands of cases. Nevertheless, the relatively high percentage of NOS cases pinpoints the need to improve the quality of data on hematologic malignancies archived by cancer registries. It is noteworthy that the overall percentage of NOS cases declined from 26% in 1995 to 19.8% in 2002 (*data not presented*) so there was an encouraging improvement over the study period. It is also worth noting that we had a very few cases of composite HL/NHL (n=29). We suspect that this may be an artificially low number, perhaps because of the complexities of the procedures employed by cancer registries for coding multiple malignancies. Furthermore, composite NHL/NHL cases are not recorded by European cancer registries; the coexistence of multiple NHL with the same immunophenotype (particularly the not uncommon occurrence of FL with DLBCL) is not accounted for by cancer registries. This is certainly related to the fact that there is no code in the ICD-O-3 for such cases to be registered.

In conclusion, our findings show that survival for most subtypes of lymphoid neoplasms declined sharply – while the proportion of NOS cases increased steeply – with age at diagnosis, suggesting under-treatment in the elderly, while survival differences between the sexes were small. The comparison of our overall data with those of previous analyses suggests a decline in survival differences across European regions. We emphasize, however, that useful comparisons of survival of patients with lymphoid neoplasms across regions (and over time) require that the individual neoplastic entities be grouped into clinically meaningful categories with similar prognoses; the HAEMACARE groupings used in the present study appear eminently suitable for this purpose. The final message of this paper is that although the quality of cancer registry data on lymphoid neoplasms needs to be improved and the data integrated with detailed information (immunophenotype, genetic abnormalities, molecular data and clinical data) necessary for classifying these diseases according to the latest WHO classification,[8] the information presently available in cancer registries represents a good benchmark for further descriptive and analytical studies.

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