Actual prognosis during follow-up of survivors of B-cell non-Hodgkin lymphoma in the Netherlands

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ABSTRACT

Survival rates determined at diagnosis are often too negative for cancer survivors. Conditional relative survival reflects actual prognosis during follow-up better. Data from all 54,015 patients newly diagnosed in the Netherlands with B-cell non-Hodgkin lymphoma during 1989-2008, aged 15-89 years (Netherlands Cancer Registry), were used. Five-year conditional relative survival was computed for every additional year of survival up to 16 years after diagnosis, according to entity, grade, gender, age, and Ann Arbor stage. The prognosis for survivors of indolent B-cell non-Hodgkin lymphoma improved slightly with each additional year survived up to 91%. For patients with aggressive non-Hodgkin lymphoma conditional relative survival improved strongly during the first year after diagnosis (from 48% to 68%) and gradually thereafter to 93% after 16 years. There were differences between morphological entities. Initial differences in conditional relative survival at diagnosis between groups with different disease stages became smaller with increasing number of years survived. Age remained a prognostic indicator, also after prolonged follow-up. These results help caregivers to plan optimal surveillance and inform patients about their actual prognosis during follow-up. Long-lasting excess mortality among patients with B-cell non-Hodgkin lymphoma indicates the need for additional care long after their diagnosis.

Introduction

Mature B-cell non-Hodgkin lymphoma (NHL) is the most common hematologic malignant neoplasm in adults in most populations worldwide.[1] The incidence of indolent NHL has increased since 1989 in the Netherlands, but that of aggressive neoplasms has remained stable.[2] The incidence of NHL in Europe and the USA has been stable for over 10 years.[3,4] Survival has increased for patients with mature B-cell neoplasms, resulting in decreasing mortality from these conditions since the beginning of this century. The diverging trends in incidence and mortality have resulted in an increased prevalence of NHL in the Netherlands.[2,3]

There is a clear difference in biological behavior between subtypes of B-cell NHL, which affects survival estimates resulting in an initially better survival for patients with indolent subtypes of B-cell NHL. The ongoing mortality of patients with indolent NHL with prolonged follow-up is most likely caused by further disease progression.[5,6]

Survival estimates for cancer patients, traditionally reported from the time of cancer diagnosis, are not generally applicable to patients who have already survived for some time after initial diagnosis and treatment. Especially for aggressive NHL these standard survival curves at diagnosis are rather pessimistic since they are based on all patients, including those who died within the first few years.[2] Conditional relative survival analysis is a method for estimating the survival rate for those who have already survived for a certain period of time.[7-9] Such survival estimates seem useful for cancer survivors, yielding more relevant information about their current prognosis, which can be used for personal health-related planning and by treating physicians for planning optimal cancer surveillance.[8,9] Furthermore, they give information about excess mortality which might be caused by either the underlying NHL, late treatment-related toxicity, and/or co-morbidity.

Most previous studies on conditional survival for patients with NHL did not subdivide between the distinct entities of NHL,[10-12] except one study on diffuse large B-cell lymphoma that displayed conditional survival up to 5 years after diagnosis.[13] It is, however, obvious that better information would be provided by subdividing these entities, each with a different prognosis.

With the marked increase in the number of NHL patients and their improving survival, there is a growing need for a more up-to-date and subgroup-specific analysis of actual survival. In this study we estimated conditional 5-year relative survival rates for B-cell NHL patients, according to morphological entity, grade, gender, age, and stage at each additional year survived up to 16 years after diagnosis.

Methods

Data collection

The population-based data used were from the nationwide Netherlands Cancer Registry.[14] Information on patients' characteristics as well as tumor characteristics such as morphology,[15] and Ann Arbor

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stage,[16] were obtained routinely from the medical records about 9 months after diagnosis.

In addition to passive follow-up via the hospitals, date of death was also retrieved from the Municipal Personal Records Database. Follow-up of vital status was complete until January, 1st, 2010.

For the present study, all patients with mature B-cell NHL newly diagnosed in the period 1989-2008 in the Netherlands were included (n=54,015). Patients with plasma cell neoplasms were excluded. NHL entities were defined according to the World Health Organization classification, 4th edition.[18] The exact codes used for each entity are described in a previous publication.[2] Sufficient patients were available to report the entity-specific conditional relative survival for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL), marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma (LPL), follicular lymphoma (FL), mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL).

We also used two major diagnostic subgroups, based on a combination of entities of more or less similar clinical behavior and comparable response to therapies: indolent and aggressive B-cell neoplasms. The entities included in each subgroup are shown in Table 1. Unspecified cases were excluded from these analyses.

Patients younger than 15 years and older than 89 years were excluded from the analysis, as were cases diagnosed at autopsy. Patients were divided into four age groups (15-44, 45-59, 60-74, and 75-89 years old). Patients aged 15-29 and 30-44 years were merged, because of the small numbers.

Statistical analyses

Relative survival is an approximation of disease-specific survival. It is calculated as the absolute survival among cancer patients divided by the expected survival of a comparable group from the general population (same period, age, and gender). Expected survival was calculated from population life tables from the Netherlands, according to the Ederer II method.[19]

Period analysis[20,21] was used to provide up-to-date survival estimates; all observations included in the analysis are left-truncated at the beginning of the period of interest, in addition to being right-censored at its end. Furthermore, to enable the estimation of even more up-to-date survival, hybrid analysis was used.[22]

Five-year relative survival rates were computed for every additional year of survival up to 15 years after diagnosis, conditional on being alive at the beginning of that year (conditional 5-year relative survival, CRS), unadjusted for other variables. Conditional survival was computed according to disease entity, grade, gender, 15-year age group, and stage of disease. For the analysis according to period of diagnosis (1995-2000 *versus* 2003-2008) conditional 3-year relative survival rates were computed, since follow-up time for patients diagnosed in 2003-2008 was limited. When the CRS persistently reached 95% for a group of patients, they were considered to have minimal excess mortality compared to the general population. For the calculation of CRS estimates, a saturated Poisson regression model for period analysis[23] was used.

Results

Table 1 presents the number of patients per entity of B-cell NHL. For entities for which there were sufficient numbers of patients, the numbers of patients available for survival analysis at diagnosis and after 5 and 10 years are shown, according to gender and age group when possible, in Table 2. This table also presents the last year for which a reliable estimate of the CRS could be given, as well as the CRS at diagnosis and 5 and 10 years after diagnosis.

The prognosis (CRS) for patients with indolent B-cell NHL improved slightly with each additional year survived after diagnosis, especially for those with FL (from 72% at diagnosis to 86% after 10 years) and MZL (from 80% at diagnosis to 93% after 10 years) (Figure 1). However, the CRS of patients with CLL or LPL was stable over time

Table 1. Number of patients per entity of B-cell non-Hodgkin lymphoma in the Netherlands 1989-2008

Group	WHO classification	Number of patients	Entity[a]
Indolent			
	Chronic lymphocytic leukemia/small lymphocytic lymphoma	13,549	CLL
	B-cell prolymphocytic leukemia	153	-
	Splenic marginal zone lymphoma	203	MZL
	Extranodal marginal zone lymphoma	2,196	
	Nodal marginal zone lymphoma	432	
	Hairy cell leukemia	990	-
	Lymphoplasmacytic lymphoma	3,425	LPL
	Follicular lymphoma, grade I-II	6,802	FL
	Primairy cutaneous follicle center lymphoma	310	
Aggressive			
	Follicular lymphoma, grade III	912	
	Mantle cell lymphoma	2,440	MCL
	Diffuse large B-cell lymphoma (DLBCL)	17,010	DLBCL
	Primary DLBCL of the central nervous system	1,011	
	Primary cutaneous DLBCL, leg type	438	
	Primary mediastinal large B-cell lymphoma	106	
	Primary effusion lymphoma	11	-
	Burtkitt lymphoma	616	-
	Other, unclassifiable B-cell neoplasms	3,408	-

[a]*CLL: chronic lymphocytic leukemia/small lymphocytic lymphoma, MZL: marginal zone lymphoma (splenic, extranodal and nodal), LPL: lymphoplasmacytic lymphoma, FL: follicular lymphoma (grade I, II & III, including primary cutaneous follicle center lymphoma), MCL: mantle cell lymphoma, DLBCL: diffuse large B-cell lymphoma (including central nervous system, cutaneous, mediastinal).*

since diagnosis (around 70%). The prognosis of CLL started to improve after 9 years (from 71% to 81% after 14 years). CRS improved greatly for DLBCL survivors during the first year after diagnosis (from 48% at diagnosis to 71% after 1 year). In the additional years after diagnosis the improvement in the prognosis of DLBCL patients leveled off, but became slightly higher (87% after 10 years) than that of patients with the indolent B-cell NHL subtype CLL (74% after 10 years) (Figure 1). MCL survivors had the worst prognosis of patients with all entities, although this prognosis gradually inproved with each additional year survived after diagnosis (from 40% at diagnosis to 68% after 6 years). The patterns of CRS for indolent and aggressive B-cell NHL were similar for males and females (*data not shown*). However, a significantly better CRS was found for female patients with CLL compared to male patients with CLL (Table 2).

Five-year relative survival at diagnosis was better for younger patients than for elderly patients for both indolent and aggressive NHL [at diagnosis: 88% for those 15-

Table 2. Conditional survival for patients with B-cell non-Hodgkin lymphoma in the Netherlands 1989-2008 (n=54,015).

		N. of patients available for estimation of conditional relative survival after 5 years			Reliable estimate up to year[a]	Conditional 5-year relative survival (%)		
		Diagnosis (0)	5	10		At diagnosis (95% CI)	At 5 years (95% CI)	At 10 years (95% CI)
CLL								
	Overall	6362	2366	641	14	71 (70-72)	71 (69-72)	74 (71-78)
	Males	3620	1246	336	12	68 (66-70)[$]	67 (65-70)[$]	73 (68-77)
	Females	2742	1120	305	13	75 (73-77)	75 (72-78)	76 (71-81)
	15-44 years	259	139	-	9	89 (85-93)[$]	82 (76-87)[$]	-
	45-59 years	1539	721	234	12	82 (80-84)	76 (73-79)*	77 (72-81)
	60-74 years	3143	1212	320	12	73 (71-74)	69 (66-71)	71 (66-76)
	75-89 years	1422	295	-	5	59 (56-61)	64 (58-71)	-
MZL								
	Overall	1370	559	165	13	80 (78-83)	90 (87-93)*	93 (87-99)*
	Males	663	275	77	11	79 (76-82)	89 (84-94)*	96 (88-103)*
	Females	708	284	89	10	82 (79-84)	91 (87-95)*	91 (83-99)
	15-44 years	180	99	51	15	95 (92-98)[$]	98 (96-101)[$]	95 (90-101)
	45-59 years	401	186	54	10	89 (86-92)	90 (86-94)	93 (86-101)
	60-74 years	575	233	-	8	79 (75-82)	89 (84-95)*	-
LPL								
	Overall	1609	619	172	10	71 (69-74)	68 (64-71)	70 (64-77)
	Males	919	322	-	7	71 (68-74)	65 (60-70)	-
	Females	690	297	-	6	72 (68-75)	71 (66-76)	-
	45-59 years	374	186	-	7	82 (78-86)[$]	80 (74-85)[$]	-
	60-74 years	726	291	-	6	73 (69-76)	61 (56-66)*	-
FL								
	Overall	3961	1696	614	15	72 (71-73)	79 (77-81)*	86 (83-89)*
	Males	1965	813	287	15	72 (70-74)	78 (75-80)*	87 (82-91)*
	Females	1996	883	327	14	72 (70-74)	80 (77-82)*	84 (81-89)*
	15-44 years	755	448	199	15	85 (82-87)[$]	90 (88-93)*[$]	88 (84-92)
	45-59 years	1577	719	268	15	78 (76-80)	80 (77-82)	88 (84-91)*
	60-74 years	1274	453	-	9	67 (65-69)	72 (68-76)	-
MCL								
	Overall	650	215	80	6	40 (37-42)	61 (55-66)*	-
DLBCL								
	Overall	5621	2706	1066	15	48 (47-49)	85 (84-87)*	87 (84-89)*
	Males	2956	1409	571	15	49 (48-50)	86 (83-88)*	90 (86-93)*
	Females	2665	1297	496	16	48 (46-49)	84 (83-87)*	84 (80-88)*
	15-44 years	1126	716	368	15	69 (67-71)[$]	95 (93-96)*[$]	97 (95-99)*[$]
	45-59 years	1620	884	386	15	61 (59-62)	87 (85-89)*	88 (84-91)*
	60-74 years	2010	885	282	12	47 (45-49)	80 (77-83)*	77 (72-83)*
	75-89 years	865	-	-	4	31 (29-33)	-	-

*[a]Standard error ≤ 5% of survival rate; [B]CLL = chronic lymphocytic leukemia/small lymphocytic lymphoma, MZL = marginal zone lymphoma (splenic, extranodal and nodal), LPL = lymphoplasmacytic lymphoma, FL = follicular lymphoma (grade I, II & III, including primary cutaneous follicle center lymphoma), MCL = mantle cell lymphoma, DLBCL = diffuse large B-cell lymphoma (including central nervous system, cutaneous, mediastinal); *A significant (P<0.05) improvement in CRS since diagnosis; [$]A significant (P<0.05) difference between subgroups within an NHL entity.*

44 years *versus* 59% for those 75-89 years with indolent NHL ($P<0.05$) and 69% for those 15-44 years *versus* 31% for those 75-89 years with aggressive NHL ($P<0.05$)]. This initial difference in relative survival between patients in different age groups remained among patients with both indolent and aggressive NHL [CRS after 5 years: 90% for those 15-44 years *versus* 66% for those 75-89 years with indolent NHL ($P<0.05$) and 94% for those 15-44 years *versus* 75% for those 75-89 years with aggressive NHL ($P<0.05$)]. Similar results were found for all examined entities of NHL (Figure 2A-D). Age does, therefore, remain an important prognostic factor.

As expected, patients with higher stages of FL had a poorer CRS at diagnosis than patients with lower stages of FL [86% (stage I-II) *versus* 66% (stage III-IV, $P<0.05$)]. This initial difference in survival at diagnosis between stage groups for patients with FL decreased somewhat with time survived since diagnosis, but remained statistically significant (CRS after 10 years: 92% *versus* 77%, $P<0.05$) (Figure 3A). For patients with DLBCL a similar difference in CRS at diagnosis was found (64% for stage I *versus* 88% for stage II-IV, $P<0.05$), which largely disappeared after patients had survived for 5-10 years (after 10 years: 88% *versus* 86%) (Figure 3B).

For indolent and aggressive NHL 3-year relative survival at diagnosis was significantly better in 2003-2008 than in 1995-2000 (3-year relative survival at diagnosis was 79%

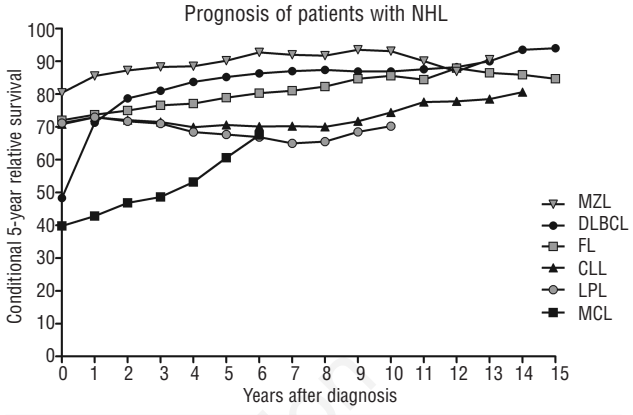

Figure 1. Conditional 5-year relative survival for every additional year survived after initial diagnosis of patients with B-cell non-Hodgkin lymphoma, according to entity.

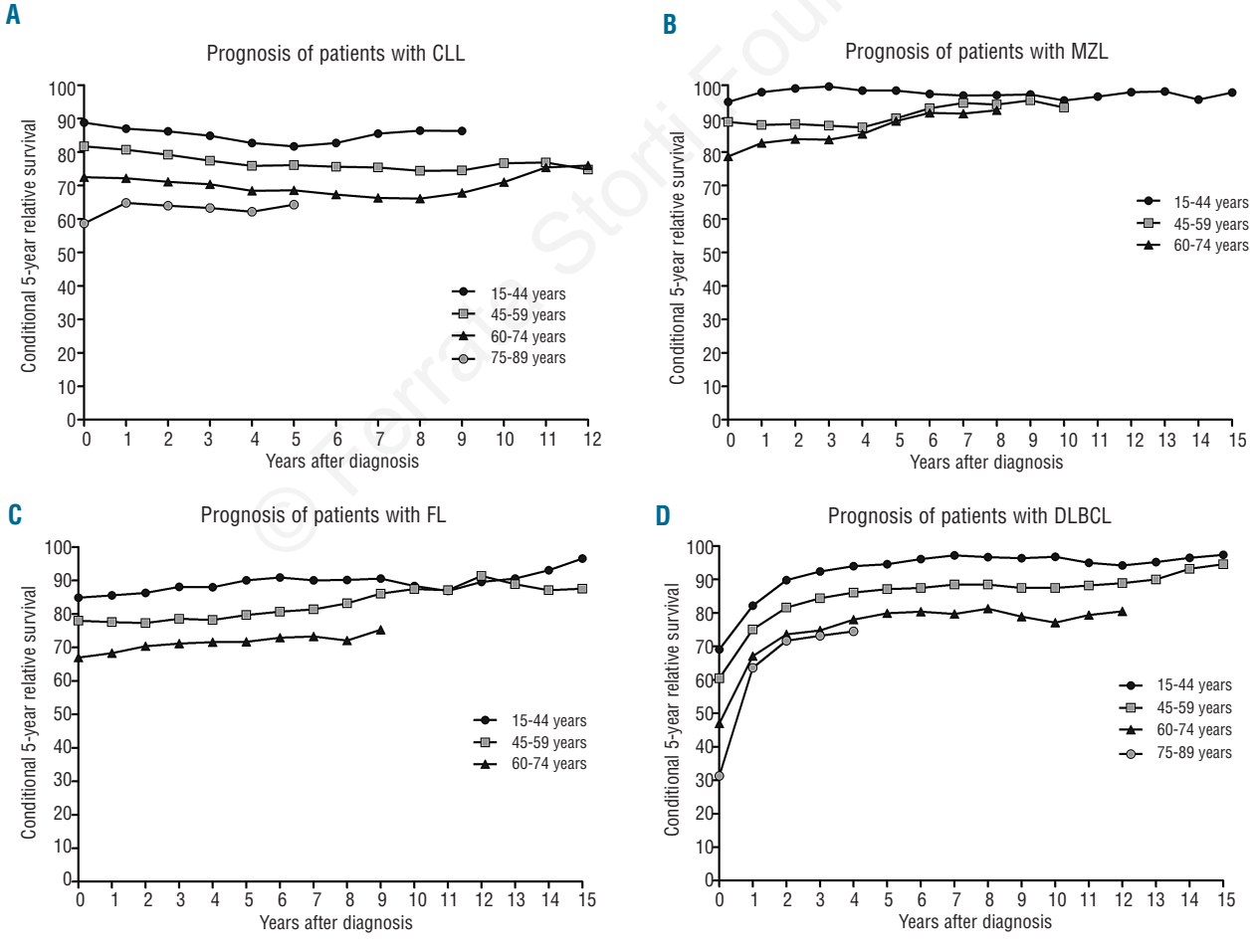

Figure 2. (A) Conditional 5-year relative survival for every additional year survived after initial diagnosis of patients with chronic lymphocytic leukemia, according to age group. (B) Conditional 5-year relative survival for every additional year survived after initial diagnosis of patients with marginal zone lymphoma, according to age group. (C) Conditional 5-year relative survival for every additional year survived after initial diagnosis of patients with follicular lymphoma, according to age group. (D) Conditional 5-year relative survival for every additional year survived after initial diagnosis of patients with diffuse large B-cell lymphoma, according to age group.

versus 85% for indolent NHL and 49% *versus* 60% for aggressive NHL; both $P<0.05$). This difference in survival decreased with years since diagnosis, especially for aggressive NHL (Figure 4).

Minimal excess mortality (CRS >95%) only occurred in younger patients (15-44 years) with MZL from diagnosis, DLBCL from 6 years after diagnosis and FL for those who had already survived for 15 years after diagnosis. For all other groups of NHL patients survival remained lower compared to that in the general population.

Discussion

The prognosis for survivors with any subtype of indolent B-cell NHL improved slightly, up to 80-90%, with each additional year of survival after diagnosis. For patients with DLBCL CRS improved markedly during the first year after diagnosis (from 48% at diagnosis to 71%) and thereafter gradually to 95% after 16 years. Differences in survival by gender were small. Age remained a prognostic indicator, also after prolonged follow-up. Initial differences in CRS at diagnosis between groups with different stages of disease became smaller with increasing number of years survived.

To the best of our knowledge, this is the first study reporting separately on conditional 5-year relative survival for several entities of NHL and for the subgroups of patients with indolent or aggressive mature B-cell NHL alive up to 16 years after diagnosis according to age, gender, and Ann Arbor stage. We were able to compute up-to-date and detailed CSR using high-quality data from the long-standing Netherlands Cancer Registry, and by application of period analysis.[20] The results give insight into excess mortality for each additional year after diagnosis a group of NHL patients has survived.

For indolent lymphoma conditional survival rates improved slightly in the years following diagnosis but remained lower than those in the general population. This probably reflects the natural history of this chronic disease. Patients with indolent lymphomas have mostly been managed by a primary wait-and-see strategy without the achievement of a long-lasting complete remission.[24-26] This strategy is more common in CLL and LPL patients than in MZL and FL patients. This is reflected by the larger improvement in prognosis in patients with the latter entities. In the younger age group of patients with the indolent B-cell NHL entities FL and MZL minimal excess mortality was observed, suggesting cure of their disease at diagnosis for MZL and 15 years after diagnosis for FL. Unfortunately, we could not pin down any association with treatment, because we could not document the exact therapy or therapies of each patient and subgroups would have become too small for analysis.

For patients with DLBCL survival improved greatly during the first years after diagnosis, resulting in a better prognosis 1-4 years after diagnosis, which is in line with the main treatment goal in this disease: achievement of a sustained complete remission. The long-term prognosis of individuals with DLBCL became similar to that of the general population for younger patients who had survived for 6 years. This suggested that many patients can be considered cured. However, after prolonged follow-up relevant cardiovascular and second tumor effects cannot be excluded. A remaining excess mortality among NHL patients aged 45 years or older also appeared in some studies from Europe, as well as Canada and Australia.[10-12] Late recurrences of lymphoma are likely as well as late effects of chemotherapy and radiotherapy (mainly cardiovascular disease and secondary tumors).[27,28] Furthermore, a large proportion of NHL patients reported a high level of fatigue up until 10 years after diagnosis.[29] The gradual improvement in prognosis for patients with MCL could indicate that secondary therapies resulted in cure for some of these individuals.

Survival of patients with B-cell NHL depends on several pretreatment prognostic variables.[5,30-32] In this study the prognostic effect of Ann Arbor stage at diagnosis decreased with time since diagnosis. In other words, conditional survival improved more with time since diagnosis in the groups with more advanced stage disease. This decrease in prognostic value of stage (and probably also

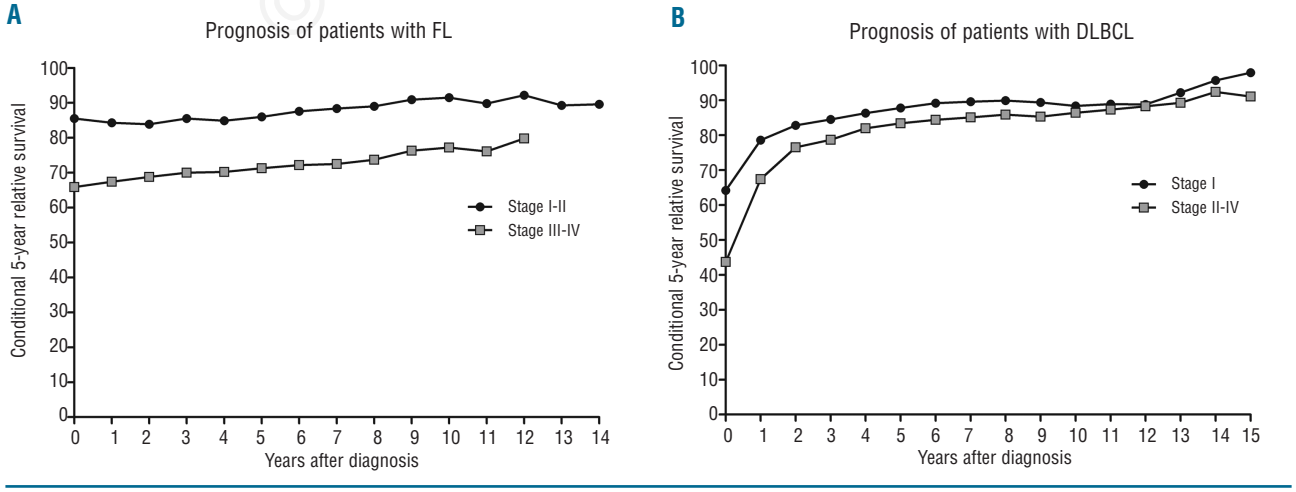

Figure 3. (A) **Conditional 5-year relative survival for every additional year survived after initial diagnosis of patients with follicular lymphoma, according to Ann Arbor stage.** (B) **Conditional 5-year relative survival for every additional year survived after initial diagnosis of patients with diffuse large B-cell lymphoma (including central nervous system, cutaneous, mediastinal), according to Ann Arbor stage.**

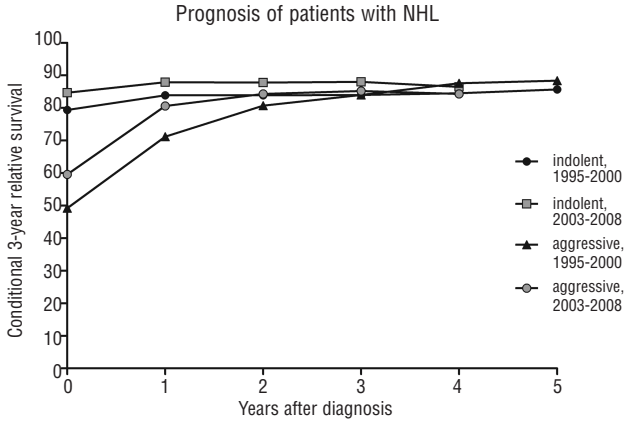

Figure 4. **Conditional 3-year relative survival for every additional year survived after initial diagnosis of patients with NHL according to grade and period of diagnosis.**

other disease-related prognostic factors) during follow-up is in line with the known natural behavior of the disease, especially of aggressive NHL. Initially mortality is largely due to disease progression. For those who survive this period the disease is either in complete remission because of successful therapy or the less aggressive clinical behavior results in a decreased impact of disease-related prognostic factors. This decrease of impact of stage on survival during follow-up confirms the earlier published observation of Moller *et al.* in DLBCL patients.[13]

In contrast, age at diagnosis remained of prognostic value in our study during prolonged follow-up. The negative effect of older age on long-term survival generally reflects the reduced ability of older patients to tolerate intensive salvage therapy, the age-related propensity for late doxorubicin-induced cardiomyopathy, but also increased mortality from co-morbidity.[31,33-37]

The prognosis of B-cell NHL patients has improved in recent decades due to the introduction of more effective drugs for newly diagnosed and relapsed patients (e.g. rituximab),[38,39] to which the large scale HOVON trials may have contributed in the Netherlands. Furthermore, research towards more accurate diagnostics, better prognostication, and better supportive care could have improved the prognosis of patients diagnosed in more recent years. This appears to be reflected in our data. Understandably, the direct effect of these therapies, diagnostics, and prognostication on conditional survival could not be demonstrated in this population-based study.

Long-term follow-up is required to calculate clinically informative measures of conditional survival. The Netherlands Cancer Registry has collected population-based data since 1989, thus long-term follow-up information is available. However, a changing classification system, improvements in disease detection and evolving cancer registration procedures may have contributed to temporal trends in incidences of lymphoma entities.[40] Variation in the incidence of entities of lymphoma over time could have resulted in differences in prognosis per period of diagnosis.

A web-based tool has been constructed to make conditional relative survival estimates available for physicians treating cancer patients. A user-friendly program provides insight into CRS estimates for every additional year after diagnosis survived for several tumor sites, including indolent and aggressive NHL, according to gender and age at diagnosis. This program (*www.dutchcancersurvival.com*) is available for caregivers, for counseling their patients, e.g. concerning the planning of their remaining life. However, they should of course also consider the actual condition of the patient.

In conclusion, with the marked increase in the number of NHL survivors there is a growing need for information of actual prognosis during follow-up, which is provided by conditional survival figures. These figures can help caregivers to plan optimal cancer surveillance and patients to get on with the planning of their remaining life. Long-lasting excess mortality for B-cell NHL patients indicates the need for prolonged care following diagnosis, with a consequent impact on patients and the healthcare system.

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Authorship and Disclosures

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