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Running head: Trends in aggressive B-cell lymphoma

Key words: incidence, aggressive B-cell lymphoma, NHL, population-based, survival, treatment, trends
Abstract

Only a small number of patients with aggressive B-cell lymphoma participates in clinical trials, particularly elderly patients are underrepresented. Therefore, we studied data of the population-based nationwide Netherlands Cancer Registry to determine trends in incidence, treatment and survival in an unselected patient population.

We included all patients aged 15 years and older with newly diagnosed diffuse large B-cell lymphoma, and Burkitt lymphoma in the period 1989-2010 and mantle cell lymphoma in 2001-2010, with follow-up until February 2013.

We examined incidence, first-line treatment and survival. We calculated annual percentage of change in incidence and carried out relative survival analyses.

Incidence remained stable for diffuse large B-cell lymphoma (n=23,527), while for mantle cell lymphoma (n=1,634) and Burkitt lymphoma (n=724) it increased for men and remained stable for women.

No rise in survival for patients with aggressive B-cell lymphoma was observed during 1989-1993 and 1994-1998 (5-year relative survival 42% [95%CI 39-45%] and 41% [38-44%], respectively), but increased to 46% (43-48%) in 1999-2004 and to 58% (56-61%) in 2005-2010. The rise in survival was most prominent in patients <65 years, while in patients >75 years this was smaller. However, when untreated patients were excluded, in patients >75 years the rise in survival was similar to younger patients.

In the Netherlands, survival for patients with aggressive B-cell lymphoma increased over time, particularly in younger patients, but also in elderly patients when treatment had been initiated. The improvement in survival coincided with the introduction of rituximab therapy and stem cell transplantation into clinical practice.
Introduction
Randomized clinical trials of aggressive non-Hodgkin lymphoma (NHL), including diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL) and Burkitt lymphoma (BL) show considerable improvement in clinical outcome over the last two decades. First, the introduction in 1997 of the monoclonal antibody targeting CD20, rituximab, increased overall survival (OS).1-4 Second, the introduction of more intensive therapy in first-line treatment, including autologous stem cell transplantation (ASCT), improved OS of MCL en BL.5-9 However, only a small selection taken from the entire population typically participates in randomized clinical trials. Particularly patients with comorbidities and age-related organ dysfunction are underrepresented in clinical trials.10 Moreover, patients aged 80 years or older are often excluded from trials.3,11 This situation highlights the importance of population-based registries that provide the opportunity to determine whether new treatment options are implemented and whether this is beneficial in an unselected patient population, including elderly patients or patients with marked comorbidity.

Several existing population-based registries on the clinical outcome in aggressive B-cell lymphoma show an improvement in survival.12-14 However, this is the first large population-based study with separate analyses of specific pathological subtypes of aggressive B-cell lymphoma in different age groups, with regard to incidence and survival over time.

Methods
Study population and data collection
The Netherlands Cancer Registry (NCR) started in 1989 and is based on notification of all newly diagnosed malignancies in the Netherlands by the automated national pathological archive PALGA. Information on patient and tumour characteristics and primary treatment are obtained routinely from medical records.

Information on the date of death (date of last follow-up: February 1st, 2013) was actively obtained from the municipal registries (GBA) and from the database of deceased persons of the Central Bureau for Genealogy. Survival time was calculated as time from date of diagnosis to date of death, date of emigration or to February 1st, 2013.

For the present study, all newly diagnosed patients aged >15 years were selected with DLBCL (ICD-O-3 morphology codes: 9680, 9684, 9675, 9679, 9591, 9590; ICD-O-2: 9593, 9677, 9681, 9682, 9712), BL (ICD-O-3: 9687, 9826) in the period 1989-2010 and MCL (ICD-O-3: 9673) in 2001-2010 (from 2001 MCL was a separate diagnosis).

As the survival pattern (a high number of deaths in the first year after diagnosis) of unspecified NHL was roughly the same as for DLBCL or BL, unspecified NHL (decreasing
from 18% in 1989-1993 to 6% in 2005-2010) was considered as aggressive lymphoma and classified as DLBCL (as 84% of aggressive lymphoma is DLBCL) for the incidence analyses. This was done to minimize the effect of changes in classification on outcome of trends analyses of incidence. For the survival analyses we excluded the unspecified cases. Year of diagnosis was divided into four periods for DLBCL and BL: 1989-1993, 1994-1998, 1999-2004, and 2005-2010, for MCL into two periods: 2001-2004 and 2005-2010.

**Treatment**

Primary treatment was described as percentage of patients who received chemotherapy alone, radiotherapy alone, chemotherapy+radiotherapy, transplantation (+/- radiotherapy/chemotherapy), other therapies, no therapy, and unknown therapy, for subgroup, stage, age group and period. The use of immunotherapy has been completely registered by the NCR since 2007.

**Statistical analyses**

Annual incidence rates according to gender for the period 1989-2010 were calculated per 100,000 person-years, using the annual mid-year population size as obtained from Statistics Netherlands. Rates were age standardized to the European standard population (ASR). Incidence rates were also calculated per age group. Trends in incidence were evaluated by calculating the estimated annual percentage change (EAPC) and the corresponding 95% confidence interval (95%CI).

Relative survival (RS), which can be interpreted as disease-specific survival within a cancer patient population (independent of the cause of death), was estimated as ratio of the observed survival of cancer patients and the expected survival of a comparable age- and sex-matched group of the general population.

For a comparison with results from recent clinical studies we also calculated OS. For each phase 2 or 3 study with a minimum number of cases (DLBCL 140, MCL 60, BL no minimum) published since 2008 (DLBCL, MCL) or 2005 (BL), we selected patients from the NCR with the same age range and same diagnosis as patients in the equivalent trial. OS was calculated for all patients as well as for patients receiving chemotherapy with the same age range and diagnosis for the period 2001-2010.

SAS software (SAS system 9.2; SAS Institute, Cary, NC) was used to perform statistical analyses.

**Results**

**Demographic data**
Table 1 shows the demographic data of patients with newly diagnosed DLBCL, MCL and BL in the Netherlands during 1989-2010. The mean age of patients with Burkitt lymphoma was considerably lower as compared to DLBCL and MCL (49, 66 and 71 years, respectively). There was a strong male predominance for MCL and BL, 74% and 66%, respectively, which was not observed in DLBCL patients (53%). Stage IV disease was more pronounced in MCL and BL (70 and 55% respectively), versus 30% in DLBCL.

**Trends in incidence**

Age-standardized incidence (ASR) per 100,000 person-years remained stable for DLBCL (7.7 in 1989, 7.6 in 2010 for men (EAPC -0.3%, 95% CI -0.4-0.1%), and 5.2 in 1989, 5.0 in 2010 for women (EAPC -0.4%, 95% CI -0.7- -0.1%)) (Figure 1). Little change occurred in age-specific rates (figure 2A).

For patients with MCL, the ASR did not significantly change between 2001 and 2010, in males (ASR 1.3 in 2001 and 1.4 in 2010) nor in females (ASR 0.4 in 2001 and in 2010) (Figure 1). Stratified by age, we found a large increase in MCL patients over 75 years of age (EAPC males +5.4%, 95% CI 1.3-9.6%; females +8.3% 95% CI -2.1-20%). However, the increase was statistically significant in males only (figure 2B).

The ASR of BL increased from 0.2 in 1989 to 0.4 in 2010 for men (EAPC 3.2%, 95% CI 1.6-4.7) and remained stable for women (0.1 in 1989 and 2010 (EAPC 1.4%, 95% CI -1.4-4.2)).

**Trends in first-line treatment**

**DLBCL**

The majority of patients with DLBCL (56%) received “chemotherapy alone”, in particular for stage II, III and IV. The percentage of patients with stage I that received “radiotherapy alone” decreased over time (from 33% to 10%), whereas the percentage of patients that received combination “chemotherapy plus radiotherapy” increased (from 18% to 37%) (figure 3A). A considerable proportion of elderly patients did not receive any treatment (17% in patients 65-74 and 36% in patients ≥75 years, versus only 10% in patients <65 years).

Since 2007, data on treatment with rituximab were available. The percentage of patients receiving immunochemotherapy rose from 83% in 2007 to 97% in 2010, independent of age. Furthermore, patients with DLBCL were generally not treated with a stem cell transplantation in first-line.

**MCL**
The majority of patients with MCL (62%) received “chemotherapy alone”, in particular for stage II, III and IV.
A considerable proportion of elderly patients did not receive any treatment (16% in patients 65-74 and 34% in patients ≥75 years, versus only 10% in patients <65 years).
During 2007-2010, the percentage of patients treated with rituximab (in combination with chemotherapy) rose over time, from 68% in 2007 to 90% in 2010. However, the proportion of patients treated with rituximab in 2010 was considerably higher in patients aged <65 years and 65-74 years, (98% and 94%, respectively) than in patients aged >75 years (78%; chi2-test p=0.004).
Moreover, stem cell transplantation was administered increasingly to patients with MCL aged < 65 years, rising from 18% in 2001-2004 to 50% in 2005-2010 (figure 3B).

BL
The majority of patients with BL (61%) received “chemotherapy alone” without distinction in stage (figure 3C).
The percentage of patients receiving no treatment was considerably higher in patients aged > 65 years than in patients aged 40-64 years and <40 years (38%, 10% and 4%, respectively).
The percentage of patients treated with rituximab (in combination with chemotherapy) rose over time, from 65% in 2007 to 88% in 2010, independent of age.
Furthermore, the percentage of patients with BL aged < 65 years receiving a stem cell transplantation, increased from 5% in 1989-1993 to 18% in 2005-2010.

Trends in survival
In the first ten years of the study period (1989-1998) no increase in survival of aggressive B-cell lymphoma was observed (5-year RS 42% [95% CI 39-45%] and 41% [95% CI 38-44%] in 1989-1993 and 1994-1998, respectively). After 1998, relative survival rose (5-year RS 46% [95% CI 43-48%] in 1999-2004), particularly since 2005 (5-year RS 58%, 95% CI 56-61%).

DLBCL
The 5-year RS for patients with DLBCL aged < 65 years increased remarkably with 28%, from 57% (95% CI 54-59%) in 1989-1993 to 75% (95% CI 73-77%) in 2005-2010. Relative survival for patients aged 65-74 years rose with 22%, from 40% (95% CI 36-43%) in 1989-1993 to 62% (95% CI 59-64%) in 2005-2010. For patients >75 years survival increased with 13%, from 28% (95% CI 24-32%) in 1989-1993 to 41% (95% CI 38-44%) in 2005-2010 (figure 4A). After exclusion of untreated patients, results for patients <75 years were the
same. However, patients >75 years showed a remarkable rise in survival of 20%, from 33% (95% CI 29-38%) in 1989-1993 to 53% (95% CI 49-57%) in 2005-2010 (data not shown). Gender did not significantly affect these results. Furthermore, as expected, with increasing disease stage the outcome deteriorated, with a 5-year RS ranging from 72% for stage I to 42% for stage IV in 2005-2010.

**MCL**

The 5-year RS for patients with MCL aged < 65 years increased remarkably with 20%, from 52% (95% CI 44-60%) in 2001-2004 to 72% (95% CI 66-77%) in 2005-2010. The RS increased with 18% for patients 65-74 years, from 24% (95% CI 19-30%) in 2001-2004 to 42% (95% CI 36-49%) in 2005-2010. For patients >75 years the survival increased with 11%, from 17% (95% CI 11-23%) to 28% (95% CI 22-35%).

The difference in 5-year survival for all patients with MCL aged < 65 years treated with and without a stem cell transplantation was significant, 77% and 48% respectively (p < 0.0001) (data not shown). No difference in survival was observed when untreated patients were excluded. Gender did not significantly affect these results. Furthermore, with increasing disease stage the outcome was inferior, with a 5-year RS ranging from 67% for stage I to 41% for stage IV in 2005-2010.

**BL**

For patients with BL aged <40 years 5-year RS increased with 30%, from 44% (95% CI 28-58%) in 1989-1993 to 74% (95% CI 63-82%) in 2005-2010. The survival for patients 40-64 years rose by 16%, from 32% (95% CI 18-47%) in 1989-1993 to 48% (95% CI 37-58%) in 2005-2010. Relative survival for patients > 65 increased by less than 10%; from 18% (95% CI 6-38%) in 1989-1993 to 28% (95% CI 17-41%) in 2005-2010 (figure 4C). When untreated patients were excluded, the results for patients <65 years were the same, in contrast to patients >65 years who showed a rise in survival of 15%, from 26% (95% CI 8-51%) in 1989-1993 to 41% (95% CI 25-59%) in 2005-2010 (data not shown). However, these data were not statistically significant. Gender did not significantly affect these results.

Table 2 presents a comparison of OS from our study with recent clinical trials, with the same age range and same diagnosis as patients in the equivalent trial. Our study showed inferior survival rates for patients with DLBCL, MCL and BL, even when untreated patients were excluded.

**Discussion**
Our population-based registry showed similar incidence rates to those found in other studies conducted in Europe, in particular the similar increase in incidence of male patients with MCL and BL.\textsuperscript{15-17} The causes for male predominance in MCL and BL are still unknown.\textsuperscript{18-20}

Furthermore, our study showed a pronounced improvement in survival for patients with aggressive B-cell lymphoma, particularly during the last decade. Although the improvement in survival was observed independent of age, the outcome was significantly inferior in the elderly patients, especially in patients over 75 years of age. Compared with previous population-based studies in Europe and the United States, our study showed similar RS for patients with aggressive B-cell lymphoma.\textsuperscript{21-24} For example, the SEER (Surveillance, Epidemiology and End Results) database showed in the period 1973-2003 a RS of 48% for DLBCL, 53% for MCL and 45% for BL.\textsuperscript{23} The European database showed in the period 2000-2002 a RS of 49% for DLBCL, 44% for MCL and 56% for BL.\textsuperscript{21} And the Swedish Lymphoma Registry showed a similar improvement in survival for MCL, a 3-year OS of 47% in 2000-2005 to 62% in the period 2006-2010.\textsuperscript{25} However, compared with clinical trials, our study showed inferior survival rates for patients with DLBCL, MCL and BL, even when the same age range was analysed and when untreated patients were excluded (table 2). The discrepancy in survival in patients <65 years and >65 years was comparable among clinical trials and our study.

As our population based data are not randomized, comparison of DLBCL treated with CHOP with or without rituximab should be interpreted with caution. However, as expected, stratified by age group we found an absolute difference in 5-year survival of approximately 20% in favour of rituximab. Bias in patient selection is likely to have contributed to this large difference.

For the difference in survival between young and elderly patients and the inferior outcome in our study compared with clinical trials, there are several explanations.

First, only a small, selected proportion of the entire population participates in trials. In particular, elderly patients and those with serious comorbidity are underrepresented in clinical trials.\textsuperscript{26,27} Moreover, patients of 80 years or older are often excluded from clinical trials.\textsuperscript{5,28-31} Since age is a strong adverse prognostic factor in aggressive B-cell lymphoma, exclusion of elderly patients results in higher survival rates in trials.\textsuperscript{10,32,33} For example, Advani showed that patients ≥70 years were at increased risk of failure, as compared to patients <70 years, with a 3-year OS of 58% (95% CI: [49, 66]) and 74% (95% CI: [72, 82]), respectively.\textsuperscript{33} Furthermore, comorbidity has been found to be related to age. In the study of Janssen-Heijnen, 79% of patients aged >60 years diagnosed with NHL had serious comorbidity, in contrast to only 48% for patients <60 years.\textsuperscript{34} Besides, in the presence of
comorbidity the percentage of patients receiving chemotherapy declined, especially among elderly patients. This is supported by the significantly higher proportion of elderly patients in our study compared to clinical trials, with a mean age of 66 years in our study versus 61 years in the study of Cunningham. A considerable number of the elderly patients in our study did not receive any treatment and consequently they had a low survival rate. However, even after correcting for non-treatment the survival remains inferior when compared with clinical trials.

Differences in therapy could be a second reason. For example, rituximab came into use in the USA in 1997 and in Europe in 2000, albeit not simultaneously in all countries. This is reflected by the consistently observed higher OS in the rituximab treated patients in the randomized clinical trials as described in Table 2. Besides, in general a delay in the introduction of new agents is observed in the elderly population with comorbidity. For example, the proportion elderly patients with MCL in our study received less treatment with rituximab than younger patients.

A further explanation is that in general elderly patients did not receive intensive chemotherapy combined with an autologous stem cell transplantation, whereas a high percentage of the younger patients did. This is established in our study in particular for the patients with MCL: patients <65 years were treated with a stem cell transplantation in 50% of the cases in contrast to 1% in patients >65 years.

Several studies have reported that elderly patients, aged up to 80 years, are able to tolerate full-dose R-CHOP regimens. Although approximately one third of the cases of NHL occur in patients older than 75 years, few data are available concerning the optimal treatment in this age group. It has been assumed that many older patients are too frail to receive standard therapy. Peyrade showed in very elderly patients aged over 80 years, that addition of rituximab to 50%-reduced CHOP seems to be a good compromise between toxicity and efficacy, with a 2-year OS of 59%. Although precise data on the dose of therapy is lacking, also in our study good results were observed for elderly patients receiving treatment as well, with a 2-year OS of 45% for cases diagnosed 2001-2010.

Several limitations must be considered when interpreting our results. First, the classification of aggressive lymphoma changed considerably over time, with a decrease of the proportion of unspecified cases. These unspecified cases might have been considered as DLBCL, being by far the largest diagnostic group of the aggressive lymphomas, incorrectly. Part of the unspecified cases may actually have been MCL, BL or indolent lymphoma. However, the equivalent survival curves of unspecified and aggressive
lymphoma support our classification strategy, with only 1% difference in survival between both groups and implies that this percentage does not generally affect the analyses.

Second, the classification criteria for BL changed over time, which may have influenced the results for BL. Moreover, during 1989-1992 Burkitt leukaemia could not be included as in that period no separate morphology code was available in ICD-O. Consequently, the observed incidence rate for BL during 1989-1992 is slightly underestimated.

Third, despite the rather clinical nature of the Dutch cancer registries, lack of detailed information regarding exact treatments, comorbidities and dose adherence in our population-based registry limited the possibility to explore and clarify specific reasons for the observed changes in survival.

In conclusion, in the Netherlands, survival for newly diagnosed patients with aggressive B-cell lymphoma has increased over time, particularly in patients aged < 65 years. However, even though survival of elderly patients was inferior in comparison with survival of younger patients, a similar increase in survival occurred when treatment was initiated.

The main contributors for the improvement in survival in our study and clinical trials appear to be rituximab therapy, autologous stem cell transplantation and the use of more intensive chemotherapy.

The therapeutic goal in treating elderly NHL patients must be maintaining a balance between effective therapy and treatment toxicity. As patients over 65 years constitute around two-thirds of all patients with aggressive lymphoma, clinical trials for elderly ‘frail’ patients with no barrier for comorbidity, are needed to determine appropriate therapy for these patients. Comprehensive geriatric assessment (CGA) could be used for additional information.

Since more detailed information regarding exact treatments, dose adherence and comorbidities is important for a better understanding of the treatment and outcome of patients with haematological malignancies, an extensive registry was initiated in the Netherlands, supplementary to the cancer registry. This PHAROS registry (Population-based Haematological Registry for Observational Studies) is expected to supply more detailed data in the near future.
Acknowledgments
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Authorship and disclosures
DEI analysed the data and wrote the paper; SZ and OV designed the research; all other authors contributed to the analyses and to the writing of the data.
This manuscript is not being considered for publication elsewhere and the findings of this manuscript have not been previously published. There is no conflict of interest.
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Table 1. Patient characteristics of aggressive B-cell lymphoma, according to subgroup, in the Netherlands, 1989-2010.

<table>
<thead>
<tr>
<th></th>
<th>DLBCL</th>
<th>MCL</th>
<th>BL</th>
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<tr>
<td>N</td>
<td>23527</td>
<td>1634</td>
<td>724</td>
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<tr>
<td>Mean age (range)(yr)</td>
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<td>71 (28-93)</td>
<td>49 (15-93)</td>
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<tr>
<td>Age (%)</td>
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<td>15-39</td>
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<td>40-64</td>
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<td>65-74</td>
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<td>Male sex (%)</td>
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<td>Unknown</td>
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Table 2. Overview of clinical trials of aggressive B-cell lymphoma; OS compared with outcome in the Netherlands.

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Median age/range</th>
<th>Patient number</th>
<th>OS (%) CI (%)</th>
<th>Study</th>
<th>Regimen</th>
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<th>OS (%) CI (%)</th>
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<tr>
<td><strong>DLBCL</strong></td>
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<tr>
<td>Pfreundschuh et al (2008)</td>
<td>6 CHOP14 8 CHOP14 6 R-CHOP14 8 R-CHOP14</td>
<td>68 (61-80)</td>
<td>1,222</td>
<td>68 (62-74) at 3 yrs 66 (60-72) at 3 yrs 78 (73-83) at 3 yrs 73 (67-78) at 3 yrs</td>
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<td>Feugier et al (2005), Coiffier et al (2010)</td>
<td>R-CHOP21 CHOP21</td>
<td>69 (60-80)</td>
<td>399</td>
<td>58 (51-65) at 5 yrs 45 (39-53) at 5 yrs 44 (36-54) at 10 yrs 28 (21-34) at 10 yrs</td>
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<td>Pfreundschuh et al (2011)</td>
<td>R-CHOP like CHOP like</td>
<td>47 (35-55)</td>
<td>823</td>
<td>90 (86-93) at 6 yrs 80 (75-84) at 6 yrs</td>
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<td>Ohmachi et al (2011)</td>
<td>CHOP14 CHOP21</td>
<td>57 (17-69)</td>
<td>323</td>
<td>55 (47-63) at 8 yrs 56 (47-64) at 8 yrs 44 (36-54) at 10 yrs 28 (21-34) at 10 yrs</td>
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<td>Recher et al (2011)</td>
<td>R-ACVBP R-CHOP</td>
<td>48 (18-59)</td>
<td>379</td>
<td>92 (87-95) at 3 yrs 84 (77-89) at 3 yrs</td>
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<td>Peyrade et al (2011)</td>
<td>6 R-miniCHOP</td>
<td>83 (80-95)</td>
<td>150</td>
<td>59 (49-67) at 2 yrs</td>
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<td>Cunningham et al (2013)</td>
<td>6 R-CHOP14 + 2R 8 R-CHOP21</td>
<td>61 (19-88)</td>
<td>1080</td>
<td>83 (80-86) at 2 yrs 81 (78-84) at 2 yrs</td>
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<td>Delarue et al (2013)</td>
<td>8 R-CHOP 14 8 R-CHOP21</td>
<td>70 (59-80)</td>
<td>602</td>
<td>69 (64-72) at 3 yrs 72 (67-77) at 3 yrs</td>
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<td>R-M-CHOP+ EAR+CBV-ASCT</td>
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<td>79</td>
<td>64 at 5 yrs</td>
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<td>8VAD+C 6(R)VAD+C+ASC T</td>
<td>&gt; 60 (61-75) &lt; 65 (18-64)</td>
<td>35</td>
<td>51 at 3 yrs 67 at 3 yrs</td>
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<td>R-HCVAD-AM Age ≤65 years Age &gt;65 years</td>
<td>61 (41-80)</td>
<td>97</td>
<td>56 at 8 yrs 68 at 8 yrs 33 at 8 yrs</td>
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<td>73 (59-83) at 5 yrs</td>
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<td>R-FC R-CHOP R-CHOP+ MT R R-CHOP+ int RBC</td>
<td>74 (65-83)</td>
<td>60</td>
<td>72 at 4 yrs</td>
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<td>CHOP DHAP +R BEAM-ASCT</td>
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<td>CHOP DHAP +R BEAM-ASCT</td>
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<td>60</td>
<td>75 at 5 yrs</td>
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<td>LMB protocol</td>
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<td>41 (15-64)</td>
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<td>Mead et al (2008)</td>
<td>dm CODOX-M/IVAC</td>
<td>37 (17-76)</td>
<td>45 (17-76)</td>
<td>52 (46-57)</td>
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<td>dm CODOX-M/IVAC</td>
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<td>4 yrs</td>
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<td>BASIC therapy</td>
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<td>52 (46-58)</td>
<td>4 yrs</td>
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OS, overall survival; yrs, years; CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R, rituximab; R-ACVBP, rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; HD Ara-C, high dose cytarabine; BEAM, carmustine, etoposide, Ara-C, melphalan; ASCT, autologous stem cell transplantation; M, methotrexate; EAR, etoposide, cytarabine, rituximab;
CBV, carmustine, etoposide, cyclophosphamide; VAD, vincristine, doxorubicine, dexamethasone; C, chlorambucil; R-HCVAD-AM: rituximab-hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone)-high dose cytarabine, methotrexate; MT, maintenance therapy; int α, interferon alfa; DHAP, dexamethasone, high-dose cytarabine, cisplatin; HD, high dose; CT, chemotherapy; dm CODOX-M/IVAC, dose-modified cyclophosphamide, cytarabine, doxorubicin, leucovorin, methotrexate, vincristine/cytarabine, etoposide, ifosfamide, methotrexate; DA-EPOCH-R; B-NHL, Burkitt Non-Hodgkin lymphoma; B-L, Burkitt leukemia; BASIC, brief, anthracycline-sparing, intensive cyclophosphamide.
Figure 1A. Age-standardized incidence rate (ASR) of DLBCL, according to subgroup and gender, in the Netherlands, 1989-2010

Figure 1B. Age-standardized incidence rate (ASR) of MCL, according to subgroup and gender, in the Netherlands, 2001-2010

Figure 1C. Age-standardized incidence rate (ASR) of BL, according to subgroup and gender, in the Netherlands, 1989-2010
Figure 2A. Age-standardized incidence rate (ASR) of DLBCL, by gender and age, in the Netherlands, 1989-2010

Figure 2B. Age-standardized incidence rate (ASR) of MCL, by gender and age, in the Netherlands, 2001-2010
Figure 3A. Trends in primary treatment for DLBCL, according to period, stage and age, in the Netherlands, 1989-2010.

Figure 3B. Trends in primary treatment for MCL, according to period, stage and age, in the Netherlands, 2001-2010.

Figure 3C. Trends in primary treatment for BL, according to period and age, in the Netherlands, 1989-2010.
Figure 4A. Trends in 5-year relative survival for DLBCL according to age and period, in the Netherlands, 1989-2010

Figure 4B. Trends in 5-year relative survival for MCL according to age and period, in the Netherlands, 2001-2010

Figure 4C. Trends in 5-year relative survival for BL according to age and period, in the Netherlands, 1989-2010
Figure 2A

Figure 2B