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Improved survival for adolescents and young adults with Hodgkin lymphoma and continued high survival for children in the Netherlands: a population-based study during 1990–2015

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Summary

Population-based studies that assess long-term patterns of incidence, major aspects of treatment and survival are virtually lacking for Hodgkin lymphoma (HL) at a younger age. This study assessed the progress made for young patients with HL (<25 years at diagnosis) in the Netherlands during 1990–2015. Patient and tumour characteristics were extracted from the population-based Netherlands Cancer Registry. Time trends in incidence and mortality rates were evaluated with average annual percentage change (AAPC) analyses. Stage at diagnosis, initial treatments and site of treatment were studied in relation to observed overall survival (OS). A total of 2619 patients with HL were diagnosed between 1990 and 2015. Incidence rates increased for 18–24-year-old patients (AAPC + 1%, $P = 0.01$) only. Treatment regimens changed into less radiotherapy and more 'chemotherapy only', different for age group and stage. Patients aged 15–17 years were increasingly treated at a paediatric oncology centre. The 5-year OS for children was already high in the early 1990s (93%). For patients aged 15–17 and 18–24 years the 5-year OS improved from 84% and 90% in 1990–1994 to 96% and 97% in 2010–2015, respectively. Survival for patients aged 15–17 years was not affected by site of treatment. Our present data demonstrate that significant progress in HL treatment has been made in the Netherlands since 1990.

Keywords: adolescent and young adult, cancer registry, Hodgkin lymphoma, paediatric oncology, population-based.

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In Western countries Hodgkin lymphoma (HL) is the most common type of cancer in late childhood and early adulthood. Among patients with cancer aged 15–19 years, 15% are diagnosed with HL compared to 4% of the patients aged <15 years (Aben *et al.*, 2012; Ward *et al.*, 2014). In patients with cancer aged 20–24 years, 13% are diagnosed with HL (Aben *et al.*, 2012).

Since the end of the 1970s, patients with HL of all ages were treated with combined modality treatment approaches of chemotherapy and radiotherapy (RT), resulting in improved prognosis. The 5-year overall survival (OS) was excellent compared to other cancers in these age groups; 90% for children and 84% for adolescents and young adults (aged 15–44 years) in Europe during the late 1980s (Carli *et al.*, 1998; Pastore *et al.*, 2001). The other side of the coin was long-term adverse effects of therapy among survivors of HL treated before the 1990s, including second primary malignancies, cardiac toxicity, and impaired fertility (Bhatia *et al.*, 1996; van Leeuwen *et al.*, 2000). Since the late 1990s, clinical trials for HL have focussed on a stepwise reduction of RT, while maintaining high OS rates and minimising the risk of long-term toxicity (Schellong *et al.*, 1992; Aleman *et al.*, 2003; Ferme *et al.*, 2007; Mauz-Korholz *et al.*, 2015b). Today, the outcome of these clinical trials has resulted in risk-stratified and response-adapted strategies, in which the number of cycles of chemotherapy and the use of RT depends on initial staging and several anatomical and metabolic response criteria (Engert *et al.*, 2010; Mauz-Korholz *et al.*, 2015b). RT remains an essential component of treatment for patients who do not respond sufficiently to initial chemotherapy (20 Gy in paediatrics and 36 Gy in adults), for patients with bulky disease, and for adult patients with early-stage disease (20–30 Gy involved node RT) (Engert *et al.*, 2010). Furthermore, the diagnostic strategies have changed as well. The availability of computed tomography (CT) dramatically changed diagnostics in the 1990s and made staging splenectomy obsolete. Pathological analysis using immunohistochemistry was implemented in the mid-1990s. The positron emission tomography (PET)-CT scan gradually became a diagnostic method from 2000 onwards.

Besides changes in diagnostics and treatment regimens over time, the upper age limit for a referral to a paediatric oncology centre for HL shifted from 14 to 17 years in the Netherlands since 2004. Moreover, treatment regimens differ between paediatric and adult oncology centres. In Dutch paediatric oncology centres, national treatment protocols were implemented by the Dutch Childhood Oncology Group (DCOG) from 2007 onwards (Kollen *et al.*, 2016); first in collaboration with the Children's Oncology Group (COG) in some centres, and, since

2011, in collaboration with the European Network for Paediatric Hodgkin Lymphoma (EuroNet-PHL) consortium in all paediatric oncology centres. (Körholz *et al.*, 2012) In the (young) adult setting, clinical trials within the European Organisation for Research and Treatment of Cancer (EORTC) consortium started in the 1960s, with an inclusion rate of 30% for patients aged 15–49 years diagnosed between 1986 and 2004 (Liu *et al.*, 2016). Patients who did not participate in clinical trials also benefitted: HL treatment in the non-trial population followed the same trend as in trials, as did survival, just with some lag time (Liu *et al.*, 2016). Where and how to treat adolescent (or even young adult) patients with HL is a difficult question. Two American studies demonstrated better outcomes when treated according to a paediatric treatment protocol (Howell *et al.*, 2007; Henderson *et al.*, 2018).

Population-based epidemiological studies for HL in children, adolescents, and young adults are limited in the literature and hitherto lacking for the Netherlands. The main aim of the present study was to evaluate the progress made for young HL patients (<25 years) diagnosed between 1990 and 2015, by describing trends in incidence, survival and mortality using data from the Netherlands Cancer Registry (NCR). Changes in treatment regimens over time and the shift of treatment for adolescents towards a paediatric oncology centre were also studied in relation to these trends, using young adults (18–24 years) as a comparative group. This group represents the youngest patients treated in adult oncology centres.

Patients and methods

Data sources

Data on incidence, treatment and survival of HL were derived from the NCR, which is maintained and hosted by the Netherlands Comprehensive Cancer Organisation (IKNL) since 1989. The NCR comprises nationwide population-based data on newly diagnosed malignancies (van der Sanden *et al.*, 1995), and currently covers 17 million inhabitants, of whom 28% are aged <25 years. (CBS.nl, 2018) The NCR is notified by the Nationwide Network and Registry of Histopathology and Cytopathology, and the National Registry of Hospital Discharge Diagnoses (i.e. inpatient and outpatient discharges). Retrospectively, data are extracted on patient, tumour and primary treatment characteristics. Tumour characteristics also include data on Ann Arbor stage (Lister *et al.*, 1989) (hereafter referred to as stage) and B symptoms (i.e., >10% weight loss over a period of 6 months, drenching night sweats, and unexplained fever). B symptoms were standardly registered in the

NCR as from 2005. Primary treatment modalities are registered in broad categories (i.e., surgery, RT and systemic chemotherapy). Information on vital status (i.e., alive, dead or emigration) was obtained by annual linkage of the NCR with the Nationwide Population Registries Network that holds vital statistics on all residents in the Netherlands. The most recent linkage was performed on 1 February 2018.

Mortality data on HL [International Classification of Diseases (ICD)-9 code 201, ICD-10 code C81] for the period 1980–2016 were obtained from Statistics Netherlands (CBS.nl, 2019). Mortality data were presented in 5-year age groups, in which age represented age at death.

Patient and data selection

All patients aged <25 years and diagnosed with HL between 1 January 1990 and 31 December 2015 were extracted from the NCR using the definition of subgroup IIa of the International Classification of Childhood Cancer (ICCC), third edition (Steliarova-Foucher *et al.*, 2005), which is based on the ICD for Oncology third edition (ICD-O-3) morphology codes (referred to as ICD-O-3M). (Percy *et al.*, 2000) Within this subgroup IIa, two diagnostic groups can be distinguished: (a) classical HL (cHL) and (b) nodular lymphocyte-predominant HL (NLPHL). NLPHL (ICD-O-3M-9659) has been a distinct entity since ICD-O-2, which was used by the NCR from 1993 onwards. The cHL cases are further classified in five histological categories: (i) nodular sclerosis (ICD-O-3M-9663-9667), (ii) mixed cellularity (ICD-O-3M-9652), (iii) lymphocyte rich (ICD-O-3M-9651, ICD-O-3M-9657, ICD-O-3M-9658), (iv) lymphocyte depleted (ICD-O-3M-9653), and (v) HL, not otherwise specified (ICD-O-3M-9650).

During this study period eight university medical centres (UMCs) were situated in the Netherlands and all had a paediatric oncology centre. Non-academic hospitals may also have treated patients with HL. For the period 2004–2015, it was possible to specify the site of treatment: treatment in a paediatric oncology centre (within a UMC), treatment at an adult UMC oncology centre or in a non-academic hospital. These data obtained via a linkage between the NCR and the registry of the Dutch Childhood Oncology Group were used from previously published work by Reedijk *et al.* (2017), with data update for the diagnostic years 2014 and 2015.

For patients with cHL, treatment was defined as 'chemotherapy only', 'chemotherapy plus RT', and 'RT only'. Patients without treatment ($n = 22$; 1%) or unknown treatment ($n = 7$; 0.3%), as well as patients who received surgery (\pm RT) ($n = 5$; 0.2%) were excluded from treatment analysis, due to probable under-registration of therapy.

Statistical analyses

Characteristics of the two histological entities, cHL and NLPHL, were described by age groups as percentages and

tested with chi-squared tests. Incidence and survival analyses were performed for the age groups <15, 15–17, and 18–24 years, and by histological subtype and according to cHL stage. The study period was divided into five periods, namely 1990–1994, 1995–1999, 2000–2004, 2005–2009, and 2010–2015. However, for NLPHL, the first two periods were merged into 1993–1999. Different age and period groupings were used for mortality analyses, namely age groups <15, 15–19, and 20–24 years and periods 1980–1984, 1985–1989, 1990–1994, 1995–1999, 2000–2004, 2005–2009, and 2010–2016.

Incidence and mortality rates were calculated as the average annual number of cases/deaths per million person-years, using the annual mid-year population size as obtained from Statistics Netherlands. Rates were age-standardised using the age structure of the World standard population for the age group <15 years (Boyle & Parkin, 1991). Changes over time were evaluated by calculating the average annual percentage change (AAPC) for the whole study period (i.e., 1990–2015 for incidence and 1980–2016 for mortality). AAPC was derived from linear regression modelling, including the calendar year as a continuous variable (Boyle & Parkin, 1991).

Changes in therapy modalities over time were tested by age group and stage with logistic regression with period as a continuous variable. The difference in the proportion of chemotherapy by stage between the age groups for the last period was tested with the chi-squared test.

Survival time was calculated as the time elapsed between the date of diagnosis and the date of death due to any cause (event) or date at last follow-up (i.e., alive or censored). Traditional actuarial survival analysis was used to calculate OS at 5 and 10 years after diagnosis. Changes in 5-year OS for the different age groups and stages were evaluated by using parametric survival models (streg) (Cleves *et al.*, 2010). These models were used to estimate the risk of dying for the five periods of diagnosis and were adjusted for follow-up time (years). The variables gender, stage, treatment modality and site of treatment were entered in the model to evaluate the effect on the period of diagnosis.

An overview of the analyses performed and the selected patient cohorts are provided in Figure S1. A $P < 0.05$ was considered statistically significant. All statistical analyses were performed with STATA/SE 14.2 (StataCorp LP, College Station, TX, USA).

Ethical consideration

According to the Central Committee on Research involving Human Subjects (CCMO), this observational study does not require approval from an ethics committee in the Netherlands. Use of the anonymous data for this study was approved by the Privacy Review Board of the NCR, following the principles of the Code of Good conduct of the Federa (<https://www.federa.org/codes-conduct>).

Results

Patient and tumour characteristics

During 1990–2015, data from 436 children (aged <15 years), 490 adolescents (15–17 years), and 1693 young adults (18–24 years) with HL were registered in the NCR; 2619 patients in total. Of all HL cases, 94% were diagnosed with cHL and 6% with NLPHL. Children were significantly more often diagnosed with NLPHL compared to young adults (12% vs. 4%; $P < 0.01$).

Patient and tumour characteristics are presented by histological group, cHL ($n = 2470$) and NLPHL ($n = 149$), in Table I. The median age at diagnosis was 19 (range 2–24) years for patients with cHL. Slightly more girls/females were diagnosed with cHL than boys/males, except in children aged <15 years. The most common histological subgroup was nodular sclerosis (79%). Two-thirds of the patients with cHL had early-stage HL (i.e., Stage I or II), followed by 20% with Stage III, and 12% Stage IV. B symptoms in cHL increased with age from 25% in the youngest age group to 38% at 18–24 years. The median age at diagnosis was 18 (range 4–24) years for across all studied age groups, 77% being a boy/male. Only 11 patients with NLPHL (7%) were classified with Stage III or Stage IV.

Trends in incidence

On average, for all age groups combined, 100 patients (range 83–129) were annually diagnosed with HL (94 with cHL and six with NLPHL). The overall age-standardised incidence rate of HL (WSR 0–24) significantly increased over time (AAPC + 0.8%, $P = 0.01$), as did the age-specific incidence rate for patients aged 18–24 years (AAPC + 1.0%, $P < 0.01$; Table SI).

Age-specific incidence rates for cHL and NLPHL remained virtually unchanged over time, except for a significant increase in cHL in young adults (AAPC + 0.9%, $P = 0.01$; Fig 1A). Stage-specific incidence rates decreased for Stage I cHL (AAPC –5.2%, $P < 0.01$) and increased for Stage IV over time (AAPC + 5.1%, $P < 0.01$) (Fig 1B). Incidence rates and AAPCs by age, histological group, gender and stage are provided in Table SI. There were no other significant incidence changes over time.

Trends in treatment for patients with cHL

The proportion of patients treated in a UMC (either paediatric or adult oncology centre) significantly increased over time for all age groups as presented in Fig 2. Since 2004, virtually all patients aged <15 years (168/170) were treated in a UMC, of whom 99% in a paediatric oncology centre. The proportion of patients aged 15–17 years who were treated in a UMC was <50% before 1998 and increased to 62% in

2003, followed by a steep rise to 85% in 2007 and remained stable after that. However, these adolescent patients were often not treated in a paediatric oncology centre (27% in 2004), but this proportion increased to 81% in 2015 (Fig 2). The proportion of patients aged 18–24 years who were treated in a UMC was <40% before 1996 and remained between 40% and 50% after 1996 (Fig 2).

Trends in initial treatment modalities are shown in Fig 3. The percentage of patients receiving ‘chemotherapy only’ increased over time for early stage patients aged <15 years, from 55% in 1990–1994 to 68% in 2010–2015 ($P = 0.05$). The percentage increased also for patients aged 15–17 years with Stage II, from 44% in 1990–1994 to 60% in 2010–2015 ($P = 0.01$), and 80% of the patients with Stage III received ‘chemotherapy only’ in 2010–2015 ($P = 0.03$). The percentage of ‘chemotherapy only’ increased for patients aged 18–24 years with Stage III from 63% in 1995–1999 to 92% in 2010–2015, and for Stage IV from 60% in 1995–1999 to 96% in 2010–2015 (both $P < 0.01$). The proportion of patients receiving ‘chemotherapy only’ was higher for patients aged <15 years with Stage I/II cHL compared to patients aged 15–17 years and patients aged 18–24 years with the same stage in the most recent period, 2010–2015 (68% for <15 years, 55% for 15–17 years and 25% for 18–24 years; $P < 0.01$). The opposite was true for Stage III and IV cHL, here the proportion of patients receiving ‘chemotherapy only’ was higher for patients aged 18–24 years compared to those aged 15–17 years ($P < 0.01$) (Fig 3). Treatment modality ‘RT only’ disappeared for all age groups after 2004.

Patients aged 15–17 years with cHL treated outside a paediatric oncology centre more often received a combined treatment modality ‘chemotherapy + RT’ than patients treated in a paediatric oncology centre (56% vs. 35%, $P < 0.01$), who received ‘chemotherapy only’ more often. This was mainly observed for patients with Stage II (67% vs. 35%, $P < 0.01$) (Table SII).

Trends in survival for patients with cHL

The median (range) follow-up was 12.7 (0–28) years. For patients with cHL aged <15 years, the 5-year OS was already high in 1990–1994 with 93% (SE 3%) and improved further to 98% (SE 2%) in 2010–2015 (although not statistical significant, $P = 0.38$) (Fig 4A). For the age groups 15–17 and 18–24 years, the 5-year OS significantly increased from 84% (SE 4%) and 90% (SE 2%) in 1990–1994 to 96% (SE 2%) and 98% (SE 1%) in 2010–2015, respectively (both $P < 0.01$). The 10-year OS for patients aged 15–17 years showed the most remarkable improvement over time, namely an increase from 80% (SE 4%) in 1990–1994 to 95% (SE 2%) in 2005–2009 ($P < 0.01$) (Fig 4B). Also, for patients aged 18–24 years, the 10-year OS increased from 88% (SE 2%) to 94% (SE 1%) between 1990 and 1994 and 2005–2009 ($P = 0.02$).

Table I. Characteristics of patients aged <25 years and diagnosed with Hodgkin lymphoma (HL) in the Netherlands between 1990 and 2015 by age group and histological subtype of HL.

Characteristic	Age groups (at HL diagnosis)			Total n (%)	P, χ^2
	<15 years n (%)	15–17 years n (%)	18–24 years n (%)		
<i>cHL type</i>	383	477	1610	2470	
Gender					
Male	206 (54)	209 (44)	786 (49)	1201 (49)	0.01
Female	177 (46)	268 (56)	824 (51)	1269 (51)	
Time period of diagnosis					
1990–1994	70 (18)	83 (17)	315 (20)	468 (19)	0.70
1995–1999	74 (19)	90 (19)	284 (18)	446 (18)	
2000–2004	83 (22)	102 (21)	301 (19)	486 (20)	
2005–2009	69 (18)	83 (17)	314 (20)	464 (19)	
2010–2015*	87 (23)	119 (25)	396 (25)	595 (24)	
Histologic category					
Nodular sclerosis	278 (73)	376 (79)	1290 (80)	1944 (79)	0.01
Mixed cellularity	38 (10)	22 (5)	103 (6)	163 (7)	
Lymphocyte rich	11 (3)	13 (3)	25 (2)	49 (2)	
Lymphocyte depleted	0 (0)	4 (1)	8 (0)	12 (0)	
Hodgkin, not otherwise specified	56 (15)	62 (13)	184 (11)	302 (12)	
Ann Arbor stage					
I	50 (13)	45 (10)	177 (11)	272 (11)	0.22
II	192 (51)	275 (59)	911 (57)	1378 (56)	
III	89 (23)	89 (19)	317 (20)	495 (20)	
IV	49 (13)	61 (13)	188 (12)	298 (12)	
Unknown (1% of total)	3	7	17	27	
B symptoms†					
Absent	115 (75)	133 (68)	438 (63)	686 (65)	<0.01
Present, at least 1	38 (25)	63 (32)	262 (37)	363 (35)	
Unknown (1% of total)	3	5	10	18	
<i>NLPHL type</i>	53	13	83	149	
Gender					
Male	41 (77)	11 (85)	65 (78)	117 (79)	0.85
Female	12 (23)	2 (15)	18 (22)	32 (21)	
Time period of diagnosis					
1993–1999‡	7 (13)	2 (15)	18 (22)	27 (18)	0.92
2000–2004	15 (28)	3 (23)	25 (30)	43 (29)	
2005–2009	16 (30)	4 (31)	17 (20)	37 (25)	
2010–2015*	15 (28)	4 (31)	23 (28)	42 (28)	
Ann Arbor stage					
I	32 (60)	6 (46)	50 (63)	88 (61)	0.15
II	20 (38)	7 (54)	20 (25)	47 (32)	
III	1 (2)	0 (0)	5 (6)	6 (4)	
IV	0 (0)	0 (0)	4 (5)	4 (3)	
Unknown (4% of total)	0	0	4	4	
B symptoms†					
Absent	27 (96)	7 (88)	33 (89)	67 (92)	0.52
Present, at least 1	1 (4)	1 (13)	4 (11)	6 (8)	
Unknown (4% of total)	3	0	3	6	

Note that the analyses are performed by classical Hodgkin lymphoma (cHL) and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) separately. In case of missing data for specific characteristics, percentages were calculated without 'unknown'. Percentages may not add to 100% due to rounding.

Bold values indicate statistical significance.

*Six-year period.

†B symptoms: weight loss (more than 10% within 6 months), fever without (other) cause or night sweat. B symptoms were registered from 2005 onwards.

‡NLPHL has a distinct morphology code which was used by the Netherlands Cancer Registry from 1993 onwards.

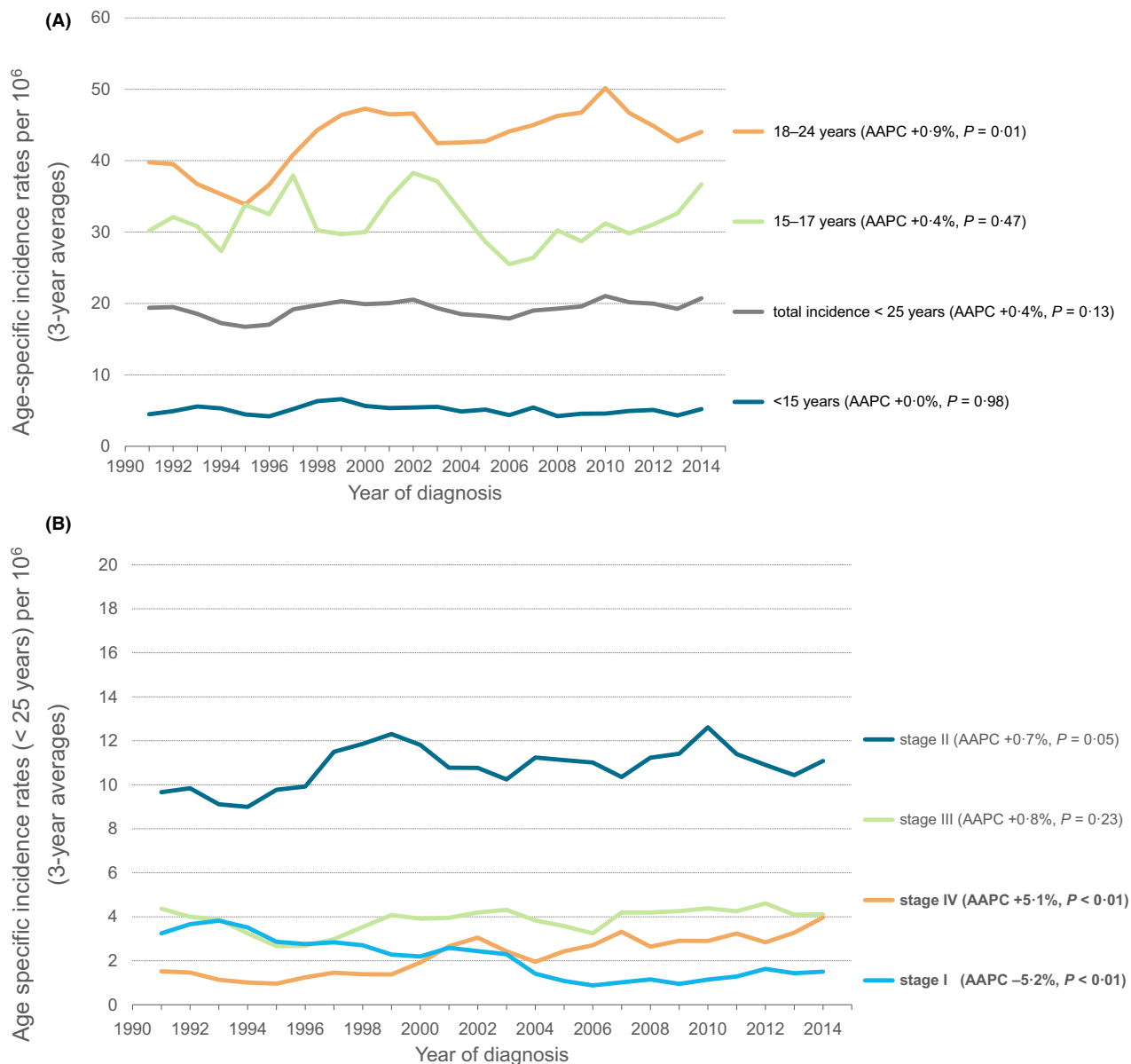


Fig 1. Age-specific incidence rates of patients aged <25 years and diagnosed with classical Hodgkin lymphoma in the Netherlands between 1990 and 2015. (A) Incidence rates by age group. (B) Incidence rates by stage. The 3-year moving averages are shown. The average annual percentage change (AAPC) was calculated for each year of diagnosis with linear regression analyses. [Colour figure can be viewed at wileyonlinelibrary.com]

For patients with Stage II cHL, the 5-year OS significantly increased from 91% (SE 2%) in 1990–1994 to 99% (SE 1%) in the period 2010–2015 ($P < 0.01$) (Fig 4C). Also, for Stage III and IV the 5-year OS improved, 90% (SE 3%) and 79% (SE 7%) in 1990–1994 to 96% (SE 2%) and 95% (SE 3%) in the period 2010–2015 ($P = 0.04$ and $P = 0.01$, respectively). The 10-year OS significantly improved over time for patients with Stage I and Stage II (10-year OS for Stage I 100% (SE 0%) and for Stage II 95% (SE 1%) in the period 2005–2009 (both $P = 0.01$) (Fig 4D). The 5- and 10-year OS rates for cHL over time and by age, gender, histological category, stage and treatment modalities are summarised in Table SIII.

The multivariable survival models by age showed that the survival improvement over time remained significant for patients aged 15–17 and 18–24 years after adjusting for follow-up time, gender, stage, treatment modalities and site of treatment (UMC, yes/no) (Table II). For patients aged 15–17 years and diagnosed between 2004 and 2015, site of treatment did not influence the 5-year OS ($P = 0.16$) (Fig 5). In a multivariable survival model for this subgroup, the site of treatment did not have an effect on the 5-year OS after adjusting for follow-up time, gender, stage and treatment modalities (results not shown).

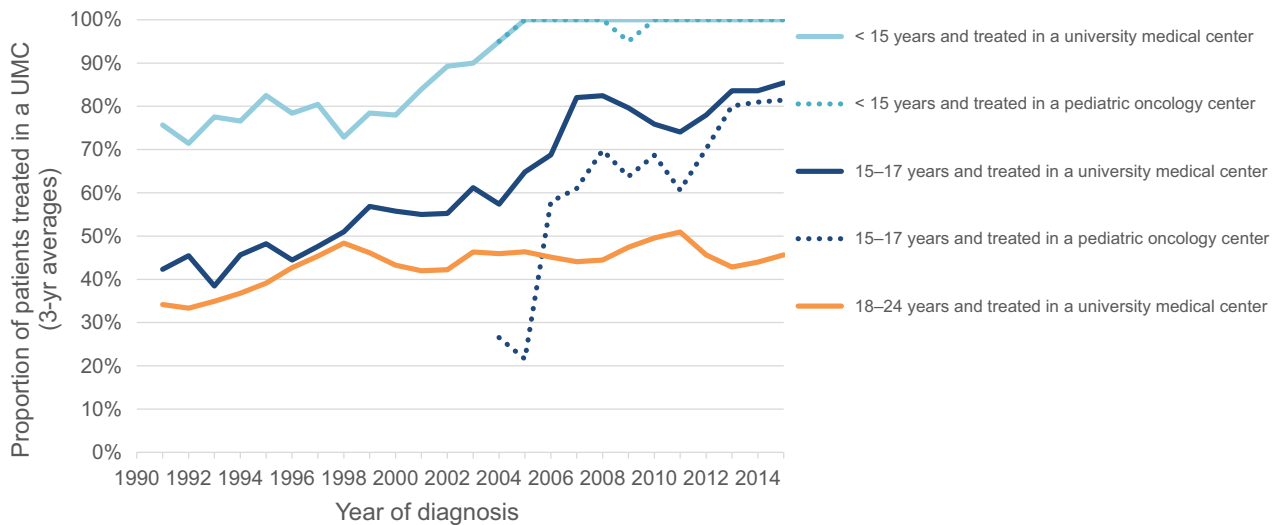


Fig 2. Patients aged <25 years and diagnosed with Hodgkin lymphoma in the Netherlands between 1990 and 2015 and site of treatment. The proportion of patients treated in a University Medical Centre (UMC) by age group is depicted by solid lines. From 2004 onwards, a distinction between UMC and Paediatric Oncology Centre was possible for patients aged <18 years and this is depicted by dashed lines. [Colour figure can be viewed at wileyonlinelibrary.com]

Trends in treatment and survival for patients with NLPHL

For the 149 patients with NLPHL, it was not possible to describe trends in initial treatment modalities in detail due to low numbers per period. A notable change was observed for patients treated in the paediatric oncology setting; watchful waiting was increasingly used for those patients who received a complete resection with or after a diagnostic biopsy. The 10-year OS for patients with NLPHL appeared to be excellent (100%, data not shown).

Trends in mortality

In the early 1980s, approximately nine patients aged <25 years died from HL annually, while during 2010–2015, about two patients died from HL per year. Mortality rates for HL significantly decreased for the age groups 15–19 and 20–24 years during 1980–2016 as presented in Fig 6 (15–19 years AAPC – 6.3%, $P < 0.01$; 20–24 years AAPC – 3.0%, $P < 0.01$).

Discussion

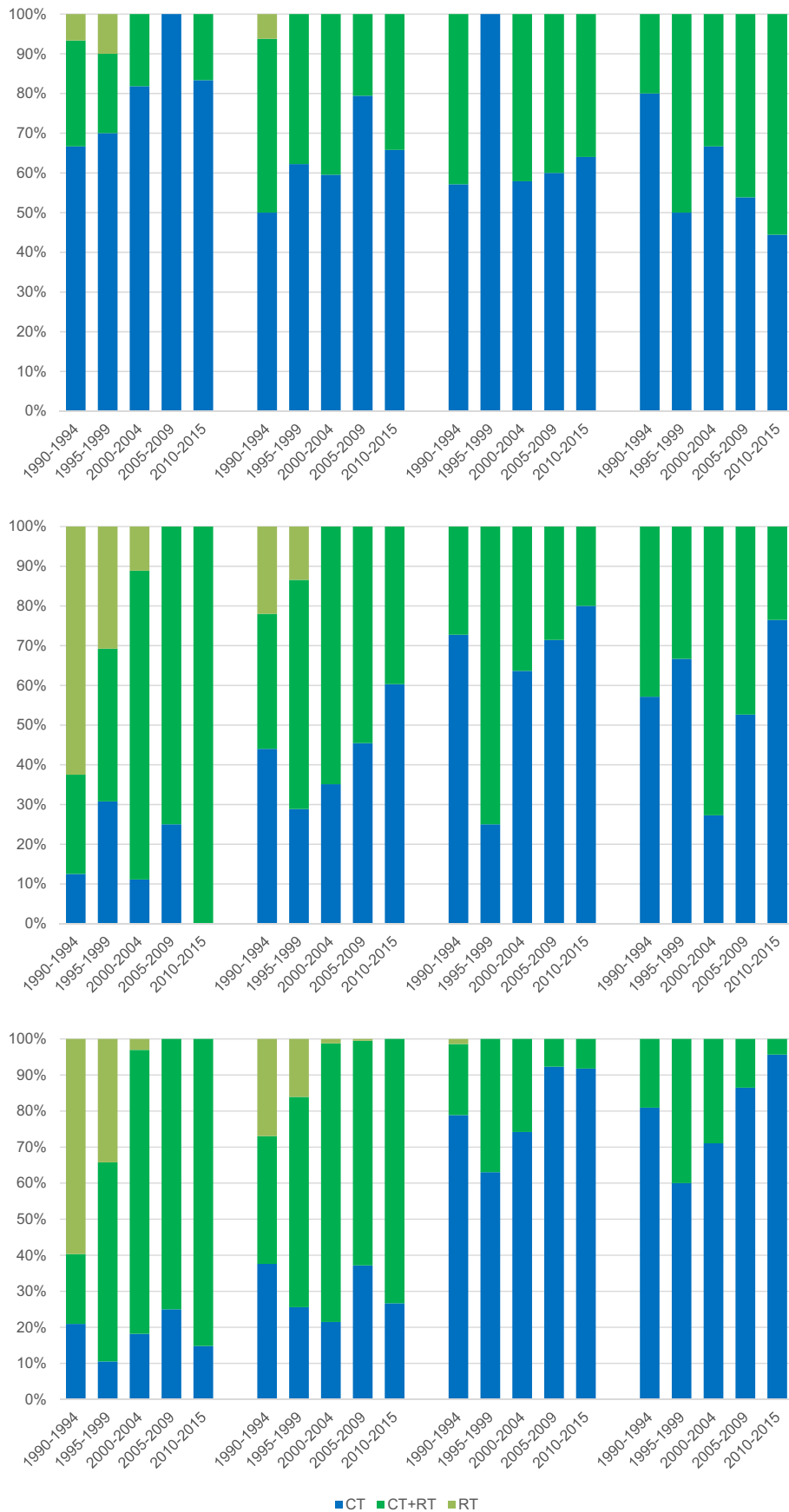
This is the first comprehensive population-based study on trends in incidence, treatment, survival and mortality among children (<15 years), adolescents (15–17 years) and young adults (18–24 years) with HL in the Netherlands. For children, incidence and survival trends remained stable, for adolescents incidence remained stable while survival increased and both incidence and survival increased for young adults. Treatment regimens changed into less RT and more ‘chemotherapy only’. Children with Stage I and II cHL received more ‘chemotherapy only’ over time. The older age

groups received more ‘chemotherapy only’ for Stage II (15–17 years) and III (15–17 years and 18–24 years), and for Stage IV (18–24 years). RT as a sole treatment modality was abandoned.

The increased incidence rates for patients aged 18–24 years, was also observed in other studies, showing an increase in incidence in patients aged 15–19 and/or 20–24 years (Dreifaldt *et al.*, 2004; Clavel *et al.*, 2006; Roder *et al.*, 2018). We have no reason to assume that improved diagnostic procedures, such as the introduction of CT in the early 1990s and PET-CT in the early 2000s or an increase in Epstein-Barr virus and human immunodeficiency virus infection in the Dutch population have primarily driven the increase in HL incidence (Ward *et al.*, 2014). The increased incidence rate is in line with the overall increase of cancer in general, but the reason(s) remains unclear.

While the overall incidence rates of HL remained stable during the entire study period, a significant decline in Stage I disease was seen and a significant increase in Stage IV disease was observed since the diagnostic year 2000. This phenomenon is known as stage migration and is probably caused by improved imaging techniques. For example, improved imaging led to previously Stage II tumours to be classified as Stage III or IV, which, in turn, artificially increased survival in both groups (i.e., the Will Rogers phenomenon) (Feinstein *et al.*, 1985). Stage migration in our present study could, in part, explain the improved survival by stage.

Treatment regimens changed into less RT and more ‘chemotherapy only’, but differed by age group, stage and site of treatment. Patients aged 15–17 years were increasingly treated at a paediatric oncology centre, rising to 81% in 2015. Because of the awareness of long-term adverse effects (e.g., second tumours and cardiotoxicities) (Bhatia *et al.*,



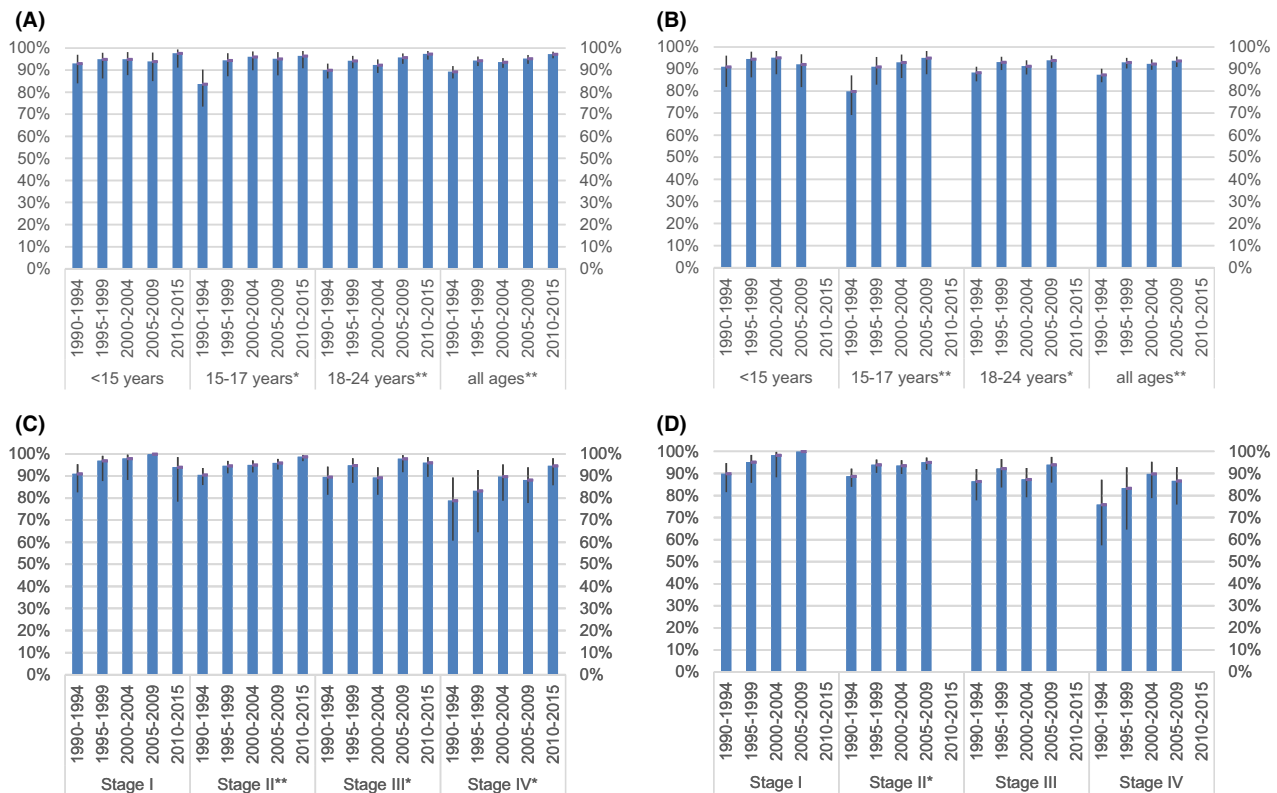


Fig 4. The 5- and 10-year overall survival (OS) for patients aged <25 years and diagnosed with classical Hodgkin lymphoma in the Netherlands by period of diagnosis. (A) 5-year OS by age group. (B) 10-year OS by age group. (C) 5-year OS by stage. (D) 10-year OS by stage. The *P* for trend was tested with streg and corrected for follow-up time. The 10-year OS for the period 2010–2015 is not applicable. **P* < 0.05; ***P* < 0.01. [Colour figure can be viewed at wileyonlinelibrary.com]

1996; van Leeuwen *et al.*, 2000; van der Pal *et al.*, 2012; van Nimwegen *et al.*, 2016), RT has changed over time from high-dose extended field RT via involved field RT (Engert *et al.*, 2003) to involved node RT with lower doses (Girinsky *et al.*, 2006), which substantially reduce cardiovascular disease risks for patients (van Leeuwen & Ng, 2017). Chemotherapy regimens also changed over time, both combinations of anti-cancer drugs and dose reductions; however, anthracyclines (like doxorubicine) and cyclophosphamide, which are also related to long-term adverse effects, are currently still being used (Teepen *et al.*, 2017; Feijen *et al.*, 2019). Furthermore, patients aged 15–17 years with early stage HL more often received a combined treatment modality when treated outside a paediatric oncology centre. Protocolised treatment of HL is very common in both the paediatric and adult setting and is constantly focussing on decreasing the burden of late adverse effects and increasing quality of life. However, monitoring long-term adverse effects

of RT and chemotherapy and quality of life remains needed in the future.

Hodgkin lymphoma is one of the few malignancies with a comparatively favourable prognosis. NPLHL survival is excellent (100%) and currently, reduction of treatment is implemented for the patients treated in the paediatric oncology setting (Mauz-Korholz *et al.*, 2007; Mauz-Korholz *et al.*, 2015a). The 5-year OS for patients with cHL has exceeded 95% across all age groups (<25 years) during the most recent period, 2010–2015. These results were congruent with other industrialised countries. Most recent population-based studies from the USA, Australia, and Europe showed survival rates of approximately 95% for both children and young adults (Smith *et al.*, 2010; Baade *et al.*, 2010; Ward *et al.*, 2014; Stark *et al.*, 2015; Karim-Kos *et al.*, 2016). We investigated whether the observed changes in stage at diagnosis, site of treatment and treatment modalities contributed to improved survival. However, after adjustment for these changes over time, ‘period of diagnosis’ remained as an independent

Fig 3. Trends in initial treatment modalities for patients aged <25 years and diagnosed with classical Hodgkin lymphoma in the Netherlands over time, 1990–2015, by age group and Ann Arbor Stage. CT, chemotherapy only; CT + RT, chemotherapy plus radiotherapy. [Colour figure can be viewed at wileyonlinelibrary.com]

Table II. The adjusted risk of mortality within 5 years after diagnosis of classical Hodgkin lymphoma according to age group.

	<15 years			15–17 years			18–24 years		
	N at risk	HR (95% CI)	P	N at risk	HR (95% CI)	P	N at risk	HR (95% CI)	P
Gender									
Male	200	Ref.		202	Ref.		770	Ref.	
Female	176	2.0 (0.7–5.1)	0.17	258	0.8 (0.4–1.8)	0.63	803	0.8 (0.5–1.3)	0.36
Period of diagnosis									
1990–1994	66	Ref.		76	Ref.		298	Ref.	
1995–1999	74	0.6 (0.1–2.2)	0.44	87	0.4 (0.1–1.0)	0.06	272	0.6 (0.3–1.2)	0.17
2000–2004	81	0.5 (0.1–2.0)	0.36	99	0.2 (0.0–0.6)	0.01	296	0.7 (0.4–1.3)	0.30
2005–2009	68	0.5 (0.1–2.1)	0.37	81	0.2 (0.0–0.6)	0.01	313	0.4 (0.2–0.8)	0.01
2010–2015	87	0.2 (0.0–1.3)	0.11	117	0.1 (0.0–0.5)	<0.01	394	0.2 (0.1–0.4)	<0.01
Stage									
I	48	Ref.		41	Ref.		172	Ref.	
II	191	2.7 (0.3–21)	0.38	271	0.8 (0.2–3.8)	0.79	899	0.8 (0.4–1.8)	0.64
III	88	2.3 (0.3–20)	0.46	88	0.4 (0.1–2.9)	0.40	317	1.2 (0.5–2.8)	0.65
IV	49	4.0 (0.4–36)	0.27	60	2.6 (0.5–14)	0.27	185	1.9 (0.8–4.6)	0.16
UMC									
No	48	Ref.		165	Ref.		910	Ref.	
Yes	328	1.6 (0.3–7.3)	0.58	295	0.7 (0.3–1.5)	0.33	663	0.8 (0.5–1.2)	0.25
Initial therapy									
CT only	244	Ref.		217	Ref.		707	Ref.	
CT + RT	128	0.8 (0.3–2.2)	0.65	218	0.4 (0.2–1.0)	0.04	746	0.8 (0.5–1.4)	0.47
RT only	4	ND		29	0.2 (0.0–1.6)	0.12	120	0.4 (0.1–1.2)	0.12

Bold values indicate statistical significance. CI, confidence interval; CT, chemotherapy; CT + RT, chemotherapy and radiotherapy; HR hazard ratio; ND, not determined; RT, radiotherapy; UMC, university medical centre.

Multivariable analyses were stratified by age. All HRs were adjusted for follow-up time, period of diagnosis, gender, stage, UMC and initial therapy.

The risk of mortality within 5 years after diagnosis was significantly lower over time in patients aged 15–17 and 18–24 years. This finding was independent of gender, stage, site of treatment, and initial therapy. Chemotherapy combined with RT resulted in a significantly lower risk of mortality in patients aged 15–17 years only.

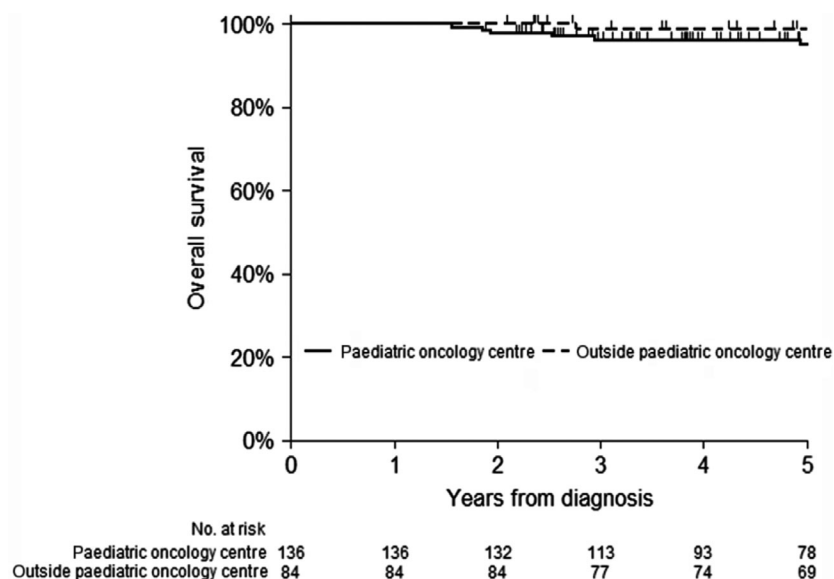


Fig 5. The 5-year overall survival of classical Hodgkin lymphoma patients aged 15–17 years at diagnosis according to site of treatment. The 5-year overall survival (OS) for treatment in a paediatric oncology centre was 95% (95% CI 89–98%). The 5-year OS for treatment outside a paediatric oncology centre was 99% (95% CI 92–100%). P, log rank was 0.16.

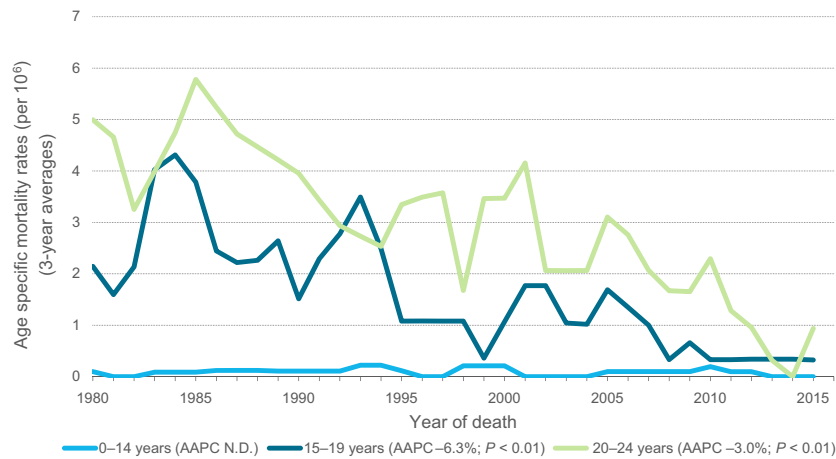


Fig 6. Age-specific mortality rates for deceased Hodgkin lymphoma patients aged <25 years at death and cause of death, in the Netherlands between 1980 and 2016. The 3-year moving averages are shown for three age groups, <15 years at death, 15–19 years at death and 20–24 years at death. The average annual percentage change (AAPC) was calculated for each year of diagnosis with linear regression analyses. AAPC analysis for the age group <15 years was not possible due to many years with zero deaths. [Colour figure can be viewed at wileyonlinelibrary.com]

predictor for improved survival in the older age groups. The impact on survival might be the result of a combination of improved diagnostics (stage migration), improved use of combinations of classic chemotherapeutic agents, response-adapted use of RT and lastly, improved protocolised treatment.

Survival for patients aged 15–17 years was not influenced by the site of treatment. On the contrary, two American studies showed a better 5-year survival outcome for patients with HL when treated at a Children's Oncology Group centre for patients aged 15–19 years (Henderson *et al.*, 2018) or treated according to a paediatric trial (17–21 years) (Howell *et al.*, 2007). Several explanations are worth mentioning as to why we could not confirm this benefit. Our population is more homogenous than the Northern American populations. Moreover, in the Netherlands health insurance is free and obligatory for all residents aged <18 years, resulting in equal access to care. Furthermore, in both the paediatric and adult setting there are multidisciplinary teams with representatives of all relevant care givers and protocolised treatments for HL treatment.

In agreement with several European studies, the mortality rates amongst patients aged 15–19 and 20–24 years declined over time (Levi *et al.*, 2003; Geraci *et al.*, 2007). We could not report on the incidence and survival in the 1980s, because this was before initiation of the NCR. During the 1980s and before, the focus of HL treatment was mainly on improving survival, while by the late 1980s the focus changed to decreasing treatment toxicity (van Spronsen *et al.*, 1997; Hakvoort-Cammel *et al.*, 2004; Eghbali *et al.*, 2005).

Some limitations of the present study require consideration. Detailed information on treatment schemes (initial as well as relapse treatment) and trial inclusion are lacking in the NCR for individual patients. Moreover, analyses according to risk group or response status and late effects of treatment were not possible. Nevertheless, cancer registries remain the 'gold standard' for ascertaining trends in

incidence, treatment and survival in the general patient population (Dinmohamed *et al.*, 2016). There was no central review of pathological specimens, we used the morphology code and defined the cHL subtype by how it was entered in the NCR database according to the then existing classification rules. We noticed a decrease in nodular sclerosis and an increase in unclassified HL. The increase in unclassified HL is in line with the review of pathology reports performed by Glaser *et al.* (2015). They provided evidence that both changing surgical practices, with prevalent use of needle biopsies instead of excisional biopsies of a lymph node, lead to insufficient biopsy specimens for complete histological diagnosis, as well as the lack of prognostic significance for the different cHL subtypes contribute to an increase in unclassified HL. Mortality data included patients who died from HL up to age of 24 years at the time of death. Patients who died after this age were not included. A strength of the present study is the inclusion of the different age groups <15, 15–17 and 18–24 years, which raises awareness regarding differences in HL types, differences in treatment and site of treatment over time, especially for patients aged 15–17 years.

By combining the three epidemiological outcomes (i.e., incidence, mortality and survival) with year of diagnosis, Ann Arbor Stage and initial treatment modalities, we achieved a comprehensive assessment of HL treatment results in the present population-based study. Despite the increase in incidence for the age group 18–24 years, the survival for adolescents and young adults with HL improved and mortality decreased for these age groups. Survival for children aged <15 years was already >90% in the early 1990s. Currently, treatment protocols are more aware of improving quality of life and on decreasing the early and late effects of treatment. The differences in treatment between the paediatric and adult setting, as observed in the present study, could be studied in future treatment protocols, including long-term adverse effects.

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Conflict of interest statement

None.

Authors' contribution

Design of the study: A. Reedijk, E. Zijtregtop, J.W. Coebergh, H. Karim-Kos, L.C. Kremer, R. Pieters and A. Beishuizen. Providing (patient) data: All authors. Collecting the data: A. Reedijk. Analyzing the data: A. Reedijk and H. Karim-Kos.

Interpretation of results: All authors. Writing of the paper: A. Reedijk, H. Karim-Kos and A. Beishuizen. All authors

reviewed the manuscript critically. All authors approved the final version of the manuscript.

Data availability statement

The datasets generated during and/or analysed for the present study are not publicly available due to the potential identifiable nature of the data. However, fully de-identified data be made available from the corresponding author on reasonable request.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Inclusion of patients with Hodgkin lymphoma for the different analyses performed.

Table S1. Incidence for children, adolescents and young adults, aged <25 years and diagnosed with Hodgkin lymphoma in the Netherlands between 1990 and 2015.

Table S2. Site of treatment according to stage for patients aged 15–17 years and diagnosed with classical Hodgkin lymphoma in the Netherlands between 2004 and 2015.

Table S3. Age-specific 5- and 10-year overall survival for classical Hodgkin lymphoma patients over time and by age groups.

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