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ARTICLE

Epidemiology

Primary therapy and relative survival in classical Hodgkin lymphoma: a nationwide population-based study in the Netherlands, 1989–2017

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Abstract

Population-based studies of classical Hodgkin lymphoma (cHL) in contemporary clinical practice are scarce. The aim of this nationwide population-based study is to assess trends in primary therapy and relative survival (RS) during 1989–2017. We included 9,985 patients with cHL. Radiotherapy alone was virtually not applied as from 2000 among patients aged 18–69 years with stage I/II disease, following the broader application of chemotherapy combined with radiotherapy. Chemotherapy only was the preferred treatment for patients with stage III/IV disease. Throughout the entire study period, around 20% of patients aged ≥70 years across all disease stages received no anti-neoplastic therapy. The most considerable improvements in 5-year RS were confined to patients aged 18–59 years. Five-year RS for patients with stage I/II disease diagnosed during 2010–2017 was 99%, 98%, 100%, 93%, 84%, and 61% for patients aged 18–29, 30–39, 40–49, 50–59, 60–69, and ≥70 years, respectively. The corresponding estimates for stage III/IV disease were 96%, 92%, 90%, 80%, 58%, and 46%. Collectively, the improvements in survival likely relate to advances in cHL management. These achievements, however, do not seem to translate into significant benefits for patients ≥60 years. Therefore, novel therapies are urgently needed to reduce excess mortality in elderly cHL patients.

Supplementary information The online version of this article (https://doi.org/10.1038/s41375-020-0875-0) contains supplementary material, which is available to authorized users.

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Introduction

Hodgkin lymphoma (HL) is a heterogeneous B-cell malignancy with an annual age-standardized incidence rate of 2 to 3 per 100,000 persons in Western countries [1]. The disease can broadly be categorized into two types: classical HL (cHL) and nodular lymphocyte-predominant HL (NLPHL) [2]. This paper focuses on cHL because a comprehensive apprehension of the incidence, treatment, and survival of NLPHL in the Netherlands has been reported recently [3].

The early 1970s marked a critical milestone in the treatment of cHL with the introduction of polychemotherapy with the MOPP (mechlorethamine, vincristine, prednisone, and procarbazine) regimen. This regimen led to a relatively high response rate, with a 5-year overall survival (OS) rate of approximately 65% [4, 5]. Thereafter, significant achievements have been accomplished in the management of cHL, in terms of higher response and OS rates, and less toxicity over the short- and long-term. These achievements include the widespread adoption of the ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) regimen in the early 1990s, the introduction of

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(escalated) BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone) in the late 1990s for patients with advanced-stage disease or unfavorable disease characteristics, and general improvements in supportive care [5–10]. More recently, the PET-CT scan has enabled tailoring of treatment strategies dynamically based on early response evaluation [11–15]. Besides, new salvage treatment options for relapsed or refractory patients were recently introduced [16–19]. At present, depending on age and disease stage, long-term survival rates reported by clinical trials in cHL are around 90% [9, 10, 12, 13]. As a result, the prevalence of cHL survivors is relatively high and continues to increase over time.

Therapeutic advances reported in clinical trials cannot always be readily translated into tangible benefits for patients managed in routine clinical practice. This issue relates to the strict inclusion and exclusion criteria of clinical trials that might hamper the extrapolation of trial results to a broader patient population [20]. In this regard, a population-based cancer registry is a useful instrument to investigate how pivotal findings of clinical trials are implemented in routine clinical practice and affect outcomes among the general patient population. At present, large population-based studies in cHL including patients managed in contemporary clinical practice are scarce and mostly lack comprehensive information on patient characteristics and therapy or report OS rates that do not account for the expected survival from the general population [21–27]. Therefore, it remains mostly unknown how contemporary advances in cHL management have impacted survival at the population-level.

Therefore, we conducted a large, comprehensive, nationwide, population-based study in almost 10,000 adult cHL patients diagnosed in the Netherlands over a 29-year period. This study aimed to assess temporal trends in primary treatment and relative survival among patients with cHL across various subgroups of age and stage.

Patients and methods

The Netherlands Cancer Registry

The Netherlands Cancer Registry (NCR) is maintained and hosted by the Netherlands Comprehensive Cancer Organisation (IKNL) and has a national coverage since 1989 with a completeness of more than 95% of all newly diagnosed malignancies in the Netherlands [28]. The NCR relies on comprehensive case notification through the Nationwide Network of Histopathology and Cytopathology, and the Nationwide Registry of Hospital Discharges (i.e., inpatient and outpatient discharges). Data on dates of birth and diagnosis, sex, disease stage, topography, and morphological subtype, and primary therapy are available in the NCR for individual patients. These data are collected by trained registrars of the IKNL through retrospective medical records review. Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICD-O). Information on vital status (i.e., alive, death, or emigration) is obtained through annually linking the NCR to the Nationwide Population Registries Network that holds these data for all residents in the Netherlands.

Study population

We identified all patients diagnosed with histologically confirmed cHL between January 1, 1989 and December 31, 2017—with follow-up for survival until January 1, 2019—from the NCR using ICD-O morphology codes (details provided in Supplemental Table S1). The ICD-O enabled to classify patients into the following morphological subtypes: nodular sclerosis, mixed cellularity, lymphocyte rich, lymphocyte depleted, and cHL, not otherwise specified (NOS). Patients below age 18 at diagnosis ($n = 969$; 8.8%) and patients diagnosed at autopsy ($n = 35$; 0.3%) were excluded from the analysis of primary therapy and survival. However, these patients were not excluded from the analysis of the overall incidence rate of cHL. This approach allows for a comparison of the overall incidence rates with other international studies.

According to the Central Committee on Research involving Human Subjects (CCMO), this type of observational study does not require approval from an ethics committee in the Netherlands. The use of anonymous data for this study was approved by the Privacy Review Board of the NCR.

The data that support the findings of this study are available via IKNL. These data are not publicly available and restrictions apply to the availability of the data used for the current study. However, these data are available from the authors upon reasonable request and with permission of IKNL.

Primary therapy

Primary therapy was defined as chemotherapy, radiotherapy, chemotherapy with radiotherapy (hereafter referred to as combined modality therapy), no anti-neoplastic therapy, or other/unknown therapy. Data on the exact therapeutic regimens were recorded in the NCR for patients diagnosed as of 2014. These regimens were defined as ABVD, escalated or baseline BEACOPP, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), or other, less common chemotherapeutic regimens.

Primary therapy is presented for three calendar periods (1989–1999, 2000–2009, and 2010–2017) and six age

groups (18–29, 30–39, 40–49, 50–59, 60–69, and ≥70 years), and stratified according to disease stage as per the Ann Arbor classification—that is, stage I/II (limited-stage) and III/IV (advanced-stage). The calendar periods were based on changing treatment practices for cHL in the Netherlands. More specifically, the first calendar period represents the MOPP/ABVD era [4, 5]. The second calendar period marks the era in which ABVD following involved node radiotherapy (INRT) was implemented for limited-stage disease [8]. Also, that era marks the implementation of ABVD or (escalated) BEACOPP for advanced-stage cHL, and high-dose chemotherapy followed by autologous stem-cell transplant for relapsed/refractory cHL [6, 29]. Lastly, the most recent calendar period represents the era in which PET-guided treatment was gradually introduced into daily practice and new targeted therapies have become available for relapsed/refractory cHL [11–13, 30].

Statistical analysis

Patient and treatment characteristics were presented as descriptive statistics overall and according to disease stage (i.e., limited- and advanced-stage disease) across the three calendar periods. Differences among categorical variables were tested with the Pearson chi-square test or Fisher's exact test, whereas differences among continuous variables were tested with the Kruskal–Wallis test.

Overall and sex-specific incidence rates were calculated per 100,000 person-years using the annual mid-year population size as obtained from Statistics Netherlands and age-standardized as per the European standard population. Also, incidence rates were calculated according to the calendar period of diagnosis and stratified by disease stage. Age-specific incidence rates were calculated per 5-year age groupings of 0–4 years to ≥85 years.

Relative survival (RS) was calculated to estimate the disease-specific survival using the cohort methodology [31]. RS is the observed patient survival (i.e., OS) corrected for the expected survival of a comparable group in the general population, matched to the patients by age, sex, and year of diagnosis. Expected survival was estimated as per the Ederer II methodology using Dutch population life tables, stratified by age, sex, and calendar year [32]. The cohort-based methodology was employed since it enables us to assess the current survival outcomes of a well-defined patient cohort according to the calendar period of diagnosis. The main convenience of employing RS to estimate disease-specific survival is that it does not depend on the information on the cause of death. This information is not available in the NCR. Whenever this information is available in cancer registries, one might question whether the cause of death is accurately classified. Collectively, lack of information on the cause of death or its inaccuracy precludes or obscures the computation of mortality attributed to a specific cause (i.e., disease-specific survival). Therefore, RS captures excess mortality—relative to the expected mortality in the general population—associated with a diagnosis of cHL, regardless of whether the excess mortality was directly or indirectly attributed to cHL.

RS was calculated up to ten years after diagnosis according to the calendar period of diagnosis and age at diagnosis and measured from the time of diagnosis to death, emigration, or end of follow-up (January 1, 2019), whichever occurred first. Although we aimed to compare outcomes from both a historical and contemporary perspective, RS was also calculated beyond ten years after diagnosis for patients diagnosed in the first calendar period (1989–1999).

Generalized linear models (GLMs) that assume a Poisson distribution for the observed number of deaths were applied to investigate linear trends in RS over the calendar periods studied [31]. GLMs were also applied to model excess mortality over the calendar periods studied during the first ten years after cHL diagnosis according to disease stage (i.e., limited- and advanced-stage disease), with simultaneous adjustment for sex, age at diagnosis, disease stage, and years of follow-up. Results from these models generate excess mortality rate ratios (EMRRs) with their associated 95% confidence intervals (CIs). The initial two years of follow-up were divided into 1-year time bands. The remaining eight years of follow-up were divided into 2-year time bands. The calendar period 2000–2009 was chosen as the reference as it was clinically relevant to estimate the excess mortality rate in the most recent calendar period (2010–2017).

A P value <0.05 indicates statistical significance. All analyses were performed using STATA/SE 14.2 (StataCorp LP, College Station, Texas, USA).

Results

Patient characteristics

A total of 9,985 adults (≥18 years) were diagnosed with cHL in the Netherlands between 1989 and 2017 and included in the study. The characteristics of these patients according to the calendar period of diagnosis are presented in Table 1. Patient characteristics according to the disease stage are presented in Supplemental Tables S2 and S3. Most patients were diagnosed with limited-stage disease (59%), 39% had advanced-stage disease, and for 2%, the disease stage was unknown. The proportion of patients with advanced-stage disease increased from 31% in the period 1989–1999 to 48% in 2010–2017, primarily owing to an increase in stage IV disease and patients aged ≥50 years.

Table 1 Characteristics of adult patients diagnosed with classical Hodgkin lymphoma in the Netherlands between 1989 and 2017.

Characteristics	Calendar period							
	1989–1999		2000–2009		2010–2017		Total	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Total no. of patients	3527	–	3463	–	2995	–	9985	–
Sex								
Male	2032	(58)	1980	(57)	1676	(56)	5688	(57)
Female	1495	(42)	1483	(43)	1319	(44)	4297	(43)
Age, years								
Median age (range)	37 (18–96)		40 (18–94)		41 (18–98)		39 (18–98)	
18–29	1147	(33)	1041	(30)	889	(30)	3077	(31)
30–39	740	(21)	687	(20)	544	(18)	1971	(20)
40–49	529	(15)	521	(15)	399	(13)	1449	(15)
50–59	343	(10)	446	(13)	372	(12)	1161	(12)
60–69	366	(10)	361	(10)	376	(13)	1103	(11)
≥70	402	(11)	407	(12)	415	(14)	1224	(12)
Ann Arbor stage								
I	722	(20)	509	(15)	304	(10)	1535	(15)
II	1539	(44)	1586	(46)	1249	(42)	4374	(44)
III	694	(20)	805	(23)	675	(23)	2174	(22)
IV	397	(11)	527	(15)	740	(25)	1664	(17)
Unknown	175	(5)	36	(1)	27	(1)	238	(2)
Median age, years (range)								
Stage I/II	35 (18–93)		37 (18–93)		37 (18–98)		36 (18–98)	
Stage III/IV	41 (18–96)		44 (18–94)		46 (18–91)		44 (18–96)	
Morphological subtype								
Nodular sclerosis	2569	(73)	2397	(69)	1500	(50)	6466	(65)
Mixed cellularity	488	(14)	342	(10)	324	(11)	1154	(12)
Lymphocyte rich	69	(2)	104	(3)	137	(5)	310	(3)
Lymphocyte depleted	66	(2)	21	(1)	13	(0)	100	(1)
Not otherwise specified	335	(9)	599	(17)	1 021	(34)	1 955	(20)
B symptoms								
No	1095	(31)	1581	(46)	1664	(56)	4340	(43)
Yes	812	(23)	1153	(33)	1199	(40)	3164	(32)
Unknown	1 620	(46)	729	(21)	132	(4)	2481	(25)

Patients with limited-stage disease were younger compared to those with advanced-stage disease (median age, 36 *versus* 44 years; $P < 0.001$). Overall, nodular sclerosis was the most common morphological subtype across both disease stages. The proportion of patients with this subtype decreased over time, following an increased proportion of patients with unclassified cHL. The other morphological subtypes remained relatively stable over the calendar periods studied. Lastly, B symptoms were more often present in patients with advanced-stage disease compared to those with limited-stage disease (56% *versus* 26% in 2010–2017; $P < 0.001$). Of note, the distribution of B symptoms in earlier periods could not be established adequately since the number of unknown values was high.

Incidence

The incidence rate of cHL remained comparatively steady over time, irrespective of age and sex (Supplemental Table S4). Interestingly, however, there was an overall modest decrease in the incidence of limited-stage disease, following an increase of advanced-stage disease. The overall age-standardized incidence rate (ASR) was 2.44/100,000 in 2010–2017, with corresponding rates of 2.71/100,000 and 2.17/100,000 for males and females, respectively. Before the age of 25, the incidence rate was comparable between both sexes (Fig. 1a). After that age, there was a consistent male predominance. The incidence showed a bimodal age distribution for both sexes with the highest

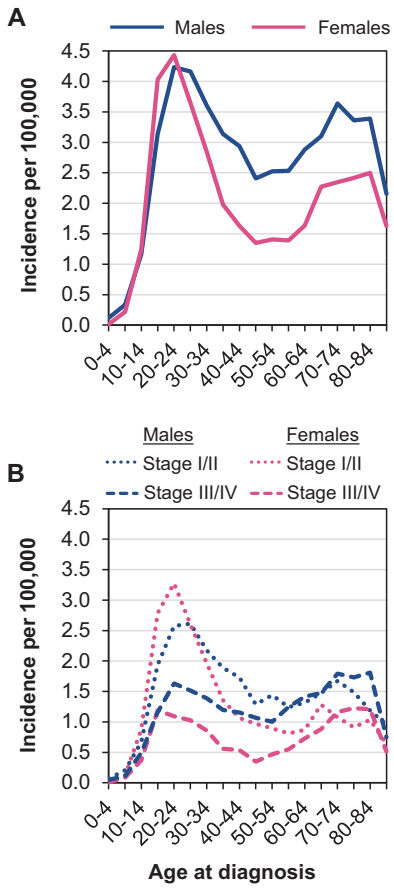


Fig. 1 Age-specific incidence rates of patients with classical Hodgkin lymphoma in the Netherlands according to sex and disease stage, 1989–2017. The age-specific incidence rates are presented per 100,000 person-years. Panel **a** shows the age-specific incidence rates for the overall cohort according to sex, whereas Panel **b** is stratified according to sex and disease stage—that is, limited-stage (I/II) and advanced-stage (III/IV).

peak in the incidence in young adults that was more pronounced for limited-stage disease compared to advanced-stage disease (Fig. 1b).

Primary therapy of limited-stage cHL

The distribution of primary therapy among adult patients with limited- and advanced-stage cHL is presented in Fig. 2a and b, respectively. Noteworthy is the application of radiotherapy alone in the first calendar period across all age groups in patients with limited-stage cHL. Its application, however, decreased dramatically over time, following an increased application of combined modality therapy. Moreover, radiotherapy alone was virtually not applied among patients aged 18–69 years since 2000, whereas 20 and 12% of patients aged ≥70 years diagnosed during 2000–2009 and 2010–2017 still received radiotherapy alone, respectively. The proportion of patients who received chemotherapy alone remained relatively stable over time across all age groups. Overall, the proportion of patients receiving no anti-neoplastic therapy was very low for patients aged 18–69 years compared to patients aged ≥70 years, of whom 16% of the latter group received no anti-neoplastic therapy in the calendar period 2010–2017.

Detailed data on primary therapy among 755 patients with limited-stage cHL, and 748 patients with advanced-stage, diagnosed between 2014 and 2017 is shown in Fig. 3a, b, respectively. For patients with limited-stage cHL, the vast majority of chemotherapy-treated patients were treated with ABVD, of whom most received it in combination with radiotherapy. Only a tiny proportion of patients up to age 60 received (escalated) BEACOPP. In contrast, treatment choices other than ABVD among patients aged ≥60 years included CHOP, a variety of less common chemotherapeutic regimens (Supplemental Table S5), and radiotherapy alone.

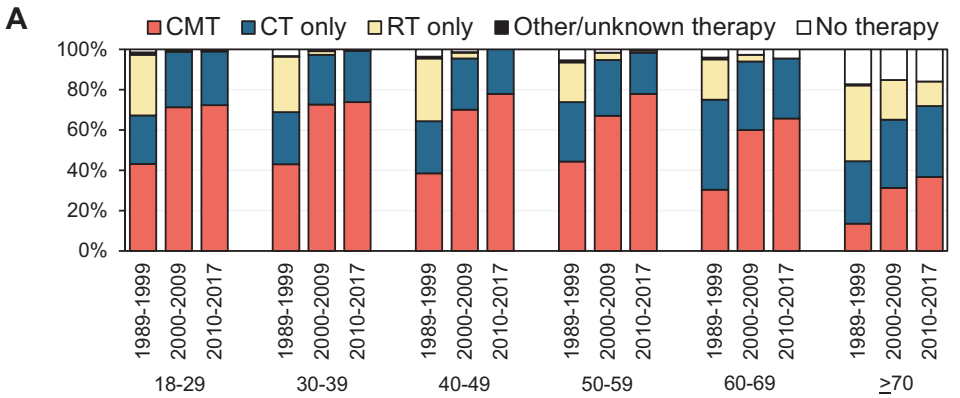
Primary therapy of advanced-stage cHL

The vast majority of patients with advanced-stage cHL received chemotherapy only, of which its application gradually increased over time following the decreased application of combined modality therapy (Fig. 2b). Similar to patients with limited-stage disease, patients aged ≥70 years more often received no anti-neoplastic therapy compared to their younger counterparts.

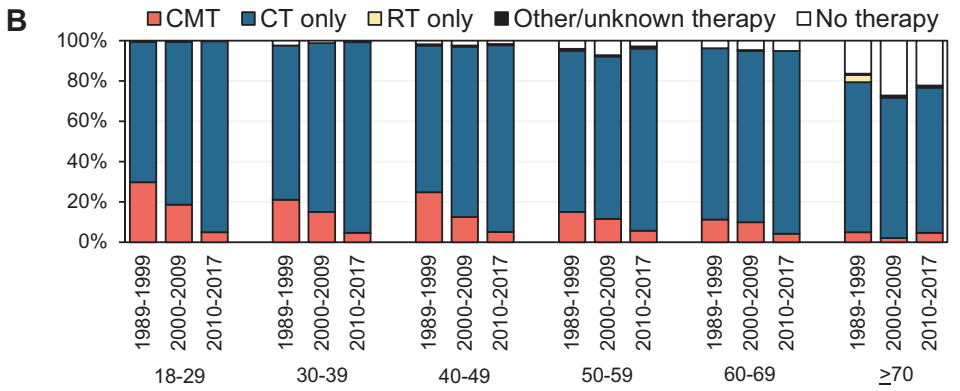
Almost 60% of patients with advanced-stage cHL aged 18–59 years received ABVD—of whom only a few received ABVD in combination with radiotherapy (Fig. 3b). The majority of the remaining patients in that age group were initially treated with (escalated) BEACOPP. As expected, (escalated) BEACOPP was virtually not applied among patients aged ≥60 years. In line with patients aged ≥60 years with limited-stage disease, treatment choices other than ABVD included CHOP and a variety of less common chemotherapeutic regimens (Supplemental Table S5), but not radiotherapy alone.

Relative survival of limited-stage cHL

As shown in Fig. 4, RS rates (RSRs) up to ten years after diagnosis were relatively high over the calendar periods studied for patients up to age 60. However, patients aged ≥30 years diagnosed during the first calendar period (1989–1999), especially those aged ≥50 years, continued to experience considerable excess mortality after ten years since diagnosis (Supplemental Fig. S1). Encouragingly enough, 5-year RSRs improved significantly over the three calendar periods studied (Fig. 4). However, statistically significant improvements were restricted to patients up to age 50. Of note, patients up to age 50 diagnosed during 2010–2017 virtually experienced no excess mortality within



Treatment	Column percentage																	
CMT	43	71	72	43	73	74	39	70	78	44	67	78	30	60	66	14	31	37
CT only	24	28	27	26	25	25	26	25	22	30	28	21	45	34	30	31	34	35
RT only	30	1	0	28	2	0	31	3	0	20	4	1	20	3	0	38	20	12
Other/unknown	1	0	1	0	0	0	1	0	0	1	0	0	1	0	0	1	0	0
No therapy	1	0	0	3	1	0	4	1	0	5	2	1	4	3	5	17	15	16



Treatment	Column percentage																	
CMT	30	19	5	21	15	5	25	12	5	15	11	6	11	10	4	5	2	5
CT only	70	81	95	77	84	94	73	85	93	80	81	90	85	85	91	75	70	72
RT only	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	4	1	0
Other/unknown	0	0	0	0	0	0	1	0	1	0	1	1	0	0	0	1	1	1
No therapy	1	1	0	3	1	0	2	2	2	4	7	3	4	5	5	16	27	22

Fig. 2 Primary therapy of adult patients with classical Hodgkin lymphoma in the Netherlands according to age at diagnosis and calendar period of diagnosis, 1989–2017. Panels **a** and **b** show the results for patients with limited-stage (I/II) and advanced-stage (III/IV) disease, respectively. The absolute number of patients within a specific stage and age group is shown in Supplemental Table S6 for limited-stage disease and Supplemental Table S7 for advanced-stage disease. Abbreviations: CMT combined modality therapy (i.e., chemotherapy with radiotherapy), CT chemotherapy, and RT radiotherapy.

the first five years after diagnosis. Furthermore, RS was substantially lower among patients aged ≥50 years, especially among patients aged ≥60 years, compared to their younger counterparts. As for 10-year RSRs, it improved between the calendar periods 1989–1999 and 2000–2009 for patients up to age 70.

Overall, when adjusted for age, sex, disease stage, and years of follow-up, patients diagnosed in 2010–2017 had 41% lower excess mortality compared to patients diagnosed in 2000–2009 (EMRR, 0.59; 95% CI, 0.45-0.77; $P < 0.001$). Furthermore, there was an independent poor prognostic effect of male sex, older age, and stage II disease compared to stage I disease (Table 2).

Relative survival of advanced-stage cHL

RS was generally lower for patients with advanced-stage disease compared to patients with limited-stage disease (Fig. 4). Nevertheless, 5- and 10-year RS increased over time for patients with advanced-stage disease across all age groups, except for patients aged 60–69 years. Similar to limited-stage disease, RS decreased with older age and was the lowest for the oldest age group. Interestingly, patients up to age 30 diagnosed during 1989–1999 virtually experienced no excess mortality after ten years since diagnosis, indicated by a plateau in RS. In contrast, patients aged ≥30 years, especially those aged ≥40 years, had

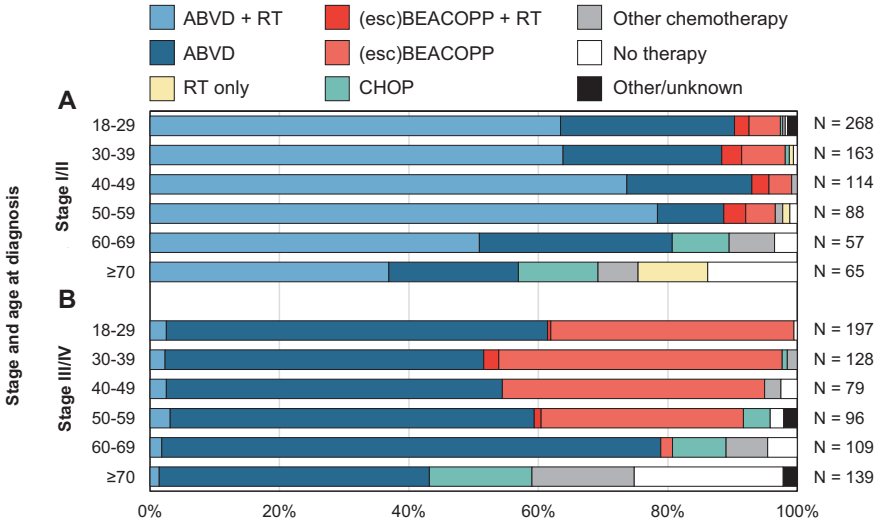


Fig. 3 Primary therapy of adult patients with classical Hodgkin lymphoma in the Netherlands according to disease stage and age at diagnosis, 2014–2017. Panels **a** and **b** show the results for patients with limited-stage (I/II) and advanced-stage (III/IV) disease, respectively. The absolute number of patients within a specific stage and age group is shown in Supplemental Table S8. The group of other or unknown therapy (n=44) includes a variety of modalities and is delineated in Supplemental Table S5. Abbreviations: ABVD adriamycin, bleomycin, vinblastine, and dacarbazine, RT radiotherapy, BEACOPP bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone, and CHOP cyclophosphamide, adriamycin, vincristine, and prednisone.

ongoing excess mortality after ten years since diagnosis (Supplemental Fig. S1).

Patients with advanced-stage disease diagnosed in 2010–2017 had 39% (EMRR, 0.61; 95% CI, 0.52–0.71; $P < 0.001$) lower excess mortality compared to patients diagnosed in 2000–2009. Older age and stage IV disease compared to stage III disease were independent factors associated with inferior outcome. Of note, there was no indication that the EMRR was different between 1989–1999 and 2000–2009 (EMRR, 1.09; 95% CI, 0.94–1.26; $P = 0.253$; Table 2). This finding indicates that there was less, if any, overall improvement in survival among patients with advanced-stage disease between 1989–1999 and 2000–2009.

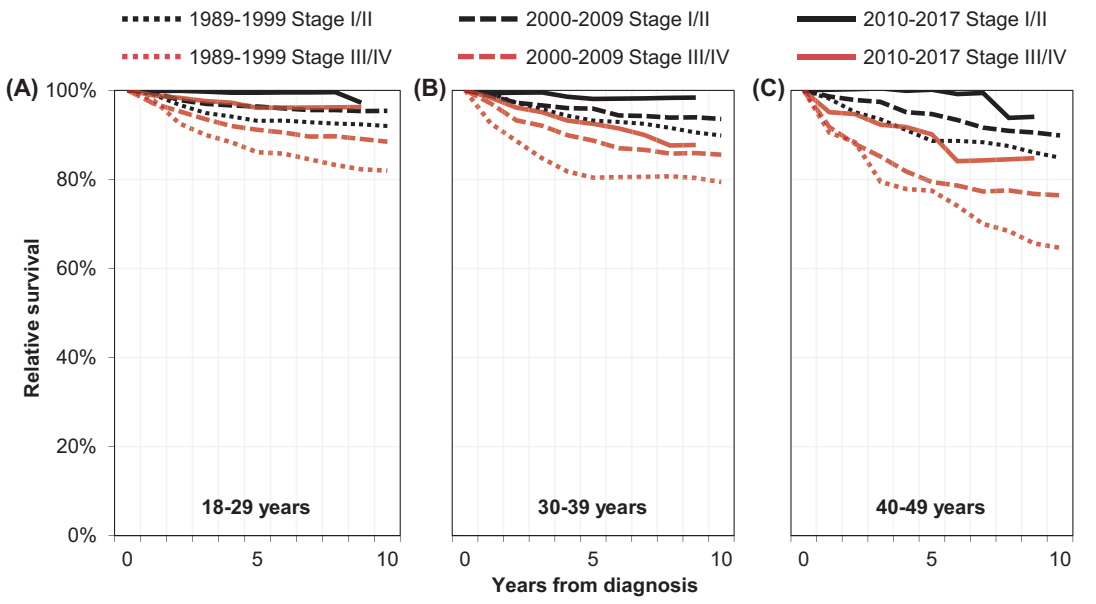
Discussion

In this large, comprehensive, nationwide, population-based study among adult patients with cHL, we show changes in the application of different first-line treatment strategies over time and an improvement in RS for most, but not all, patients. Furthermore, this population-based study complements, but more importantly, extends on prior, relatively outdated population-based series [21–23, 25, 33], because we included patients diagnosed in a contemporary era and had comprehensive information on primary therapy for individual patients.

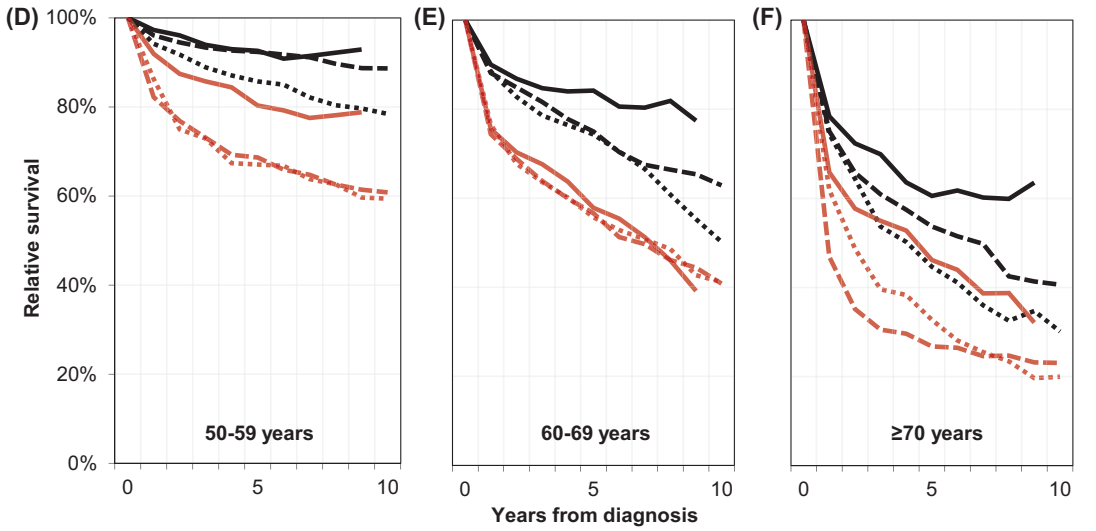
The incidence rates of cHL in the Netherlands are mainly congruent with other epidemiological studies [1, 23, 34, 35]. Interestingly though, we demonstrated that the peak in incidence for young adults was more profound among patients with limited-stage disease. The increase in incidence for advanced-stage, following a modest decrease for limited-stage disease, is probably related to the implementation of the PET-CT scan for staging. PET-CT can more accurately detect small extranodal lesions compared to CT only, which, in turn, may result in stage migration [11].

We observed a substantial decline in the use of radiotherapy only, followed by an increased use of combined modality therapy for patients up to age 70 with limited-stage disease. This finding agrees with the notion that the combination of ABVD and radiotherapy is essential for proper disease control, since several studies have demonstrated that omitting radiotherapy increases the risk of relapse, even in patients with limited-stage disease that have a negative PET-CT scan after two cycles of ABVD [12–14]. For patients with advanced-stage disease, chemotherapy without radiotherapy was the preferred modality. Detailed data for patients diagnosed as from 2014 showed that ABVD was the preferred chemotherapeutic regimen for these patients, followed by (escalated) BEACOPP for patients up to age 60. Nowadays, PET-guided treatment for advanced-stage or early-stage unfavorable disease is becoming the standard treatment strategy. This strategy is likely to provide an advantage for high-risk patients, who can escalate to BEACOPP in case of inadequate response on ABVD [30].

Recent clinical trials that accrued patients with limited-stage disease treated with ABVD and radiotherapy reported



Stage I/II	1989-1999	2000-2009	2010-2017	*P* trend	1989-1999	2000-2009	2010-2017	*P* trend	1989-1999	2000-2009	2010-2017	*P* trend
5-year	93 (91-95)	96 (95-98)	99 (98-100)	<0.001	93 (91-95)	96 (93-97)	98 (95-99)	0.007	89 (85-92)	95 (91-97)	100 (96-101)	<0.001
10-year	92 (90-94)	95 (93-97)		<0.001	90 (87-92)	94 (91-96)		0.001	85 (80-89)	90 (86-93)		<0.001
Stage III/IV												
5-year	86 (82-90)	91 (87-94)	96 (93-98)	<0.001	80 (74-85)	89 (84-92)	92 (87-96)	0.001	77 (70-83)	79 (73-85)	90 (84-94)	0.004
10-year	82 (77-86)	88 (84-92)		<0.001	79 (73-85)	86 (80-90)		0.010	65 (57-72)	76 (70-82)		0.002



Stage I/II	1989-1999	2000-2009	2010-2017	*P* trend	1989-1999	2000-2009	2010-2017	*P* trend	1989-1999	2000-2009	2010-2017	*P* trend
5-year	86 (80-90)	92 (88-96)	93 (87-96)	0.084	74 (67-81)	75 (67-82)	84 (76-90)	0.281	45 (35-54)	54 (44-63)	61 (49-72)	0.155
10-year	78 (71-85)	89 (83-93)		0.023	50 (42-59)	63 (54-71)		0.029	30 (20-42)	41 (30-52)		0.059
Stage III/IV												
5-year	67 (57-75)	69 (61-75)	80 (72-87)	0.006	56 (46-65)	57 (48-64)	58 (50-65)	0.905	33 (24-42)	27 (20-34)	46 (37-55)	<0.001
10-year	59 (49-69)	61 (53-68)		0.004	41 (31-51)	41 (32-49)		0.920	20 (12-30)	23 (15-32)		<0.001

Fig. 4 Relative survival of patients with limited-stage (I/II) and advanced-stage (III/IV) classical Hodgkin lymphoma in the Netherlands according to age at diagnosis and calendar period of diagnosis, 1989–2017. Relative survival is shown for three calendar periods according to the following six age categories: (**a**) 18–29, (**b**) 30–39, (**c**) 40–49, (**d**) 50–59, (**e**) 60–69, and (**f**) ≥70 years. The tables present the projected 5- and 10-year relative survival rates (RSRs) with 95% confidence intervals (CIs) according to the calendar period of diagnosis for the six age categories. Relative survival is the observed patient survival (i.e., overall survival) corrected for the expected survival of a comparable group in the general population, matched to the patients by age, sex, and year of diagnosis. For readers interested in the dynamics of relative survival, we have plotted the relative survival, overall survival, and expected survival for the most recent calendar period (2010–2017) in Supplemental Fig. S2. *P value for likelihood ratio test assessing linear trends between the first and last calendar period.

Table 2 Excess mortality rate ratios (EMRRs), with associated 95% confidence intervals, during the first ten years after Hodgkin lymphoma diagnosis, stratified by limited- (i.e., stage I/II) and advanced-stage (i.e., stage III/IV) disease. EMRRs are presented according to years of follow-up, calendar period of diagnosis, sex, age at diagnosis, and disease stage.

Covariate	Limited-stage disease					Advanced-stage disease				
	EMR[a]	95% CI			P[b]	EMR[a]	95% CI			P[b]
Years from diagnosis										
0–1	1	(ref)				1	(ref)			
1–2	0.66	0.53	–	0.83	<0.001	0.43	0.36	–	0.52	<0.001
2–4	0.49	0.40	–	0.61	<0.001	0.28	0.24	–	0.34	<0.001
4–6	0.35	0.27	–	0.45	<0.001	0.22	0.18	–	0.28	<0.001
6–8	0.34	0.26	–	0.46	<0.001	0.16	0.12	–	0.21	<0.001
8–10	0.30	0.21	–	0.42	<0.001	0.14	0.10	–	0.20	<0.001
Period of diagnosis					<0.001[c]					<0.001[c]
1989–1999	1.49	1.26	–	1.77	<0.001	1.09	0.94	–	1.26	0.253
2000–2009	1	(ref)				1	(ref)			
2010–2017	0.59	0.45	–	0.77	<0.001	0.61	0.52	–	0.71	<0.001
Sex					0.003[c]					0.399[c]
Male	1	(ref)				1	(ref)			
Female	0.79	0.67	–	0.93	0.004	0.95	0.83	–	1.08	0.409
Age at diagnosis, years					<0.001[c]					<0.001[c]
18–29	1	(ref)				1	(ref)			
30–39	1.34	0.99	–	1.81	0.062	1.33	1.00	–	1.77	0.054
40–49	2.02	1.47	–	2.76	<0.001	2.30	1.76	–	3.02	<0.001
50–59	3.16	2.30	–	4.34	<0.001	3.59	2.77	–	4.65	<0.001
60–69	9.37	7.19	–	12.23	<0.001	6.70	5.28	–	8.50	<0.001
≥70	21.74	16.87	–	28.00	<0.001	13.24	10.54	–	16.62	<0.001
Stage					<0.001[c]					<0.001[c]
I	1	(ref)					–	–	–	
II	1.41	1.18	–	1.69	<0.001	–		–		–
III	–		–		–	1	(ref)			
IV	–	–	–			1.56	1.37	–	1.77	<0.001

EMRR excess mortality rate ratio, *CI* confidence interval, *ref* Reference.

[a]All covariates are simultaneously adjusted.

[b]*P* values are compared with the reference category.

[c]*P* values of covariates are derived from the likelihood ratio test that compares the model without the specific covariate with the model containing all covariates.

OS rates exceeding 95% at 5 years [12–14]. In addition, a population-based study in Sweden and Norway also reported that there was no long-term excess mortality for limited-stage, favorable cHL patients diagnosed between 1999 and 2005 [27]. For patients with advanced-stage disease who were treated with ABVD or (escalated) BEACOPP, 5-year OS rates approximate 90% [9, 10]. We could confirm the excellent survival outcomes reported by clinical trials for patients up to age 60 diagnosed during 2010–2017. Significant improvements over time in RSRs were observed for all patients up to age 60, irrespective of stage. Interestingly, a plateau in RS was shortly observed after diagnosis in the most recent calendar period (2010–2017) among patients up to age 60. This finding suggests that these patients eventually do not experience excess mortality compared to the general population. Extended follow-up is, however, needed to evaluate long-term excess mortality (due to late treatment-related sequelae) in contemporary treated patients. Nevertheless, long-term excess mortality is expected to be low for patients with limited-stage disease because of the widespread application of INRT after chemotherapy.

Although cHL is often portrayed as a malignancy that can be successfully treated, this appears to only hold for patients up to age 60. More specifically, patients aged ≥60 years show little, if any, improvement in RS over time and continue to experience considerable excess mortality, especially patients with advanced-stage disease. Elderly patients were often underrepresented in the aforementioned clinical trials, especially in trials for patients with advanced-stage disease. Patients aged ≥60 years are often excluded from clinical trial participation due to concerns related to

treatment-related sequelae associated with more intensive chemotherapeutic regimens, such as (escalated) BEACOPP [9, 10]. Indeed, in line with treatment recommendations [36], (escalated) BEACOPP was rarely applied among patients aged ≥60 years. Collectively, the vast majority of elderly patients did not seem to benefit from the advances in treatment to the same extent as their younger counterparts. Therefore, new effective and less toxic therapies are needed to reduce excess mortality in these patients. Recently, it has been reported that omitting bleomycin from ABVD after a good response on interim PET-CT may reduce toxicity without compromising efficacy [37]. Our study thus serves as a benchmark to assess the impact of a broader application of this strategy on population-level survival.

Approximately 15–30% of patients are primary refractory to first-line treatment or relapse after an initial response [9, 12, 15, 37]. With high-dose chemotherapy and autologous stem-cell transplant, around 40-60% of these patients can be cured [29, 38]. Novel treatment strategies for salvage treatment, such as targeted treatment with brentuximab vedotin or checkpoint inhibitors, could therefore have a significant impact on long-term survival of cHL [16–19]. Besides, these new agents are currently investigated in clinical trials as first-line treatment for elderly patients, to prevent them from toxicity due to chemotherapy [39].

Limitations of this population-based study are that detailed data on the type of chemotherapy regimen were only available from the year of diagnosis 2014 onwards and that there are no data on salvage treatment after relapsed or primary refractory disease. Therefore it is currently not known how advances in salvage treatment have contributed to the RS. Besides, some small improvements in RS were not statistically significant, which could be due to lower numbers of patients in certain subgroups.

The strengths of our study include the use of a nationwide population-based cancer registry with high coverage (i.e., >95%) of all newly diagnosed malignancies in the Netherlands. Therefore, our study represents the general population of cHL. Also, we had information on patient characteristics and primary therapy available for all individual patients. Besides, we used RS as a measure of disease-specific survival and had adequate survival follow-up for all patients.

In summary, in this large, nationwide population-based study, patients up to age 60 who were diagnosed with cHL between 2010 and 2017 have better RS compared to patients diagnosed before 2010, irrespective of stage. The improvements are likely related to advances in therapy across various lines of treatment and improved supportive care. These achievements, however, do not seem to translate into significant benefits for patients aged ≥60 years, as these patients still experience considerable excess mortality in contemporary clinical practice. Therefore, novel treatment strategies are urgently needed to reduce excess mortality in elderly patients.

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Author contributions AGD designed the study; JD analyzed the data; AGD provided statistical support; OV collected the data; JD wrote the manuscript with contributions from all authors, who also interpreted the data, and read, commented on, and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest There is no financial support for this work that could have influenced the outcomes described in the manuscript. However, particular authors report a potential conflict of interest, which is described below. MJK: Millennium/Takeda: Honoraria, Research Funding; Celgene: Honoraria, Research Funding; Roche: Honoraria, Research Funding; Gilead: Honoraria; Kite Pharma: Honoraria; Novartis: Honoraria. PJL: Millennium/Takeda: Consultancy, Research Funding; Servier: Consultancy, Research Funding; Roche: Consultancy; BMS: Consultancy; Sandoz: Consultancy; Genmab: Consultancy. JMZ: Consultant/Advisor: Gilead, Roche, Takeda; Honoraria: Gilead, Roche, Takeda, Janssen. AGD: BMS: Research funding. All remaining authors have declared no competing financial interests.

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