original reports

Limited, But Not Eliminated, Excess Long-Term Morbidity in Stage I-IIA Hodgkin Lymphoma Treated With Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine and Limited-Field Radiotherapy

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abstract

PURPOSE Balancing disease control and toxicity from chemotherapy and radiotherapy (RT) when treating early-stage classical Hodgkin lymphoma (cHL) is important. Available data on long-term toxicity after RT for cHL mostly refer to RT techniques no longer in use. We aimed to describe long-term toxicity from modern limited-field (LF)-RT after two or four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD).

PATIENTS AND METHODS This study included all patients with cHL treated with two or four cycles of ABVD and 30 Gy LF-RT during 1999-2005 in Sweden. Patients (n = 215) and comparators (n = 860), matched for age, gender, and region of residence, were cross-checked against national health registries for malignancies, diseases of the circulatory system (DCS), and diseases of the respiratory system (DRS) from the day of diagnosis of cHL.

RESULTS The risk of a malignancy was higher for patients than comparators, hazard ratio (HR) 1.5 (95% CI, 1.0 to 2.4), as was the risk for DCS 1.5 (95% CI, 1.1 to 2.0) and for DRS 2.6 (95% CI, 1.6 to 4.3). The median follow-up was 16 years (range, 12-19 years). Of individual diagnoses in DCS, only venous thromboembolism was statistically significantly elevated. If the first 6 months (ie, time of active treatment for cHL) were excluded and censoring at relapse of cHL or diagnosis of any malignancy, the increased HR for venous thromboembolism diminished. Most of the excess risk for DRS consisted of asthma, HR 3.5 (95% CI, 1.8 to 6.8). Patients diagnosed with DRS were significantly younger than comparators.

CONCLUSION Compared with toxicity from earlier RT techniques, excess morbidity was not eliminated, but lower than previously reported. The elevated risk of DRS was driven by diagnosis of asthma, which could in part be explained by misdiagnosis of persisting pulmonary toxicity.

J Clin Oncol 40:1487-1496. © 2022 by American Society of Clinical Oncology

INTRODUCTION

Treatment for early-stage classical Hodgkin lymphoma (cHL) achieves a high degree of disease control, with more than 90% of patients expected to remain disease-free 5 years after end of treatment.[1] During the past few decades, clinical trials have aimed at reducing toxicity while retaining high cure rates.[1-5] Treatments before 2000[6-8] resulted in a high degree of disease control, but also in long-term toxicity with increased risks for diseases of the circulatory system (DCS),[9-12] secondary cancers,[13-16] and diseases of the respiratory system (DRS).[17-19] To reduce toxicity from combined modality treatment (CMT), radiotherapy (RT) doses have been reduced from 30-40 Gy to 20-30 Gy, with doses depending on clinical risk factors, and target volumes have been reduced, from extended field, to involved field (IF) and then subsequently involved site or even involved node.[6,8,20-23] Chemotherapy has been changed to combinations with less toxicity, and the number of cycles has been reduced to two or four, again depending on clinical risk factors.[1,2] Some clinical trials have omitted RT for selected patients, guided by initial treatment response. These trials were designed to allow some loss of disease control but with expected less long-term morbidity and mortality.[3-5,24,25] The loss of disease control has, in most reported trials, exceeded what was considered acceptable in the design.[3,4] An exception was the HD17 trial in which initial chemotherapy was more intensive, which enabled two-thirds of the patients to avoid RT without relevant loss of disease control.[20]

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on December 22, 2021 and published at ascopubs.org/journal/jco on January 25, 2022: DOI https://doi.org/10.1200/JCO.21.02407

CONTEXT

Key Objective

Long-term disease control in early-stage classical Hodgkin lymphoma (cHL) is expected in more than 90% of patients. As the median age for patients with cHL is slightly more than 30 years, balancing efficacy and toxicity is important, especially when considering the known risks of radiotherapy given during earlier periods. This study is, to our knowledge, the first analysis of long-term excess morbidity in a population-based cohort of patients with cHL uniformly treated with chemotherapy followed by radiotherapy with smaller fields than involved field.

Knowledge Generated

Excess morbidity in the form of secondary cancers, diseases of the circulatory system, and diseases of the respiratory system is reduced, but not eliminated, compared with earlier cohorts.

Relevance (*J.W. Friedberg*)

As upfront therapy for patients with early-stage Hodgkin lymphoma is refined, treatment-related morbidity has decreased, but not disappeared. These results should serve as a benchmark for future studies with long-term end points.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.

There have been few publications describing long-term toxicity with contemporary RT using limited fields and reduced doses.[26-29] Models for normal tissue complication probabilities can be helpful,[30-32] but clinical data with long-term follow-up are needed. We aimed to describe long-term excess morbidity in a population-based cohort of patients with cHL treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in combination with RT during 1999-2005.

PATIENTS AND METHODS

Patients

During 1999-2005, all patients in Sweden with early-stage cHL, Ann Arbor stage I-IIA, were reported at diagnosis and during follow-up to a Nordic registry. As this study was conducted through several registries and databases with data anonymized to all researchers, there was no informed consent from the individuals. Extraction of data from the registry, recruitment of comparators, and cross-checking against health registries were approved by the Regional Ethics Committee in Uppsala, Sweden, and were conducted in accordance with the Declaration of Helsinki. All Swedish patients with planned treatment of two or four cycles of ABVD followed by 30Gy limited-field radiotherapy (LF-RT) in the Nordic registry formed the cohort (Fig 1). The guidelines recommended four cycles of ABVD in the presence of at least one of the clinical risk factors (erythrocyte sedimentation rate $>$ 50 mm, bulky disease, or involvement of more than two lymph node regions), adopted from the HD10 study.[1] Computed tomography, chest x-ray, and abdominal ultrasound were mandatory for staging. The risk factor bulky disease was modified to include any lymph node mass measuring $>$ 10 cm on CT. LF-RT was delivered according to a modification of IF-RT. There was no intention to treat the whole Ann Arbor lymph node region as for standard IF-RT, but a 3-cm craniocaudal margin to macroscopically involved sites, as determined before chemotherapy, was recommended for the clinical target volume. More details on the LF-RT definition are provided in the Data Supplement (online only). The Nordic registry has been reported.[26]

Comparators

Four comparators from the Total Population Register were added for each patient. The comparators were matched for gender, age, and region of residence at the time of diagnosis of cHL for the corresponding patient (Fig 1 and Table 1).

Morbidity and Mortality

The cohort and the comparators were cross-checked against the National Patient Register (NPR), the Swedish Cancer Register and the Cause of Death Register by the National Board of Health and Welfare (SoS). The NPR includes all diagnoses from in-patient care in Sweden since 1987. After 2001, the register also covers specialist outpatient visits. The search in the NPR was limited to DCS and DRS. The definition of any cancer excluded nonmelanoma skin cancer (reported separately). Databases were searched for events until December 31, 2017, the cutoff date for complete reporting to the registries of SoS at the time.

Statistical Analyses

To compare the association between cHL and diagnosis of any malignancy, DCS, and DRS, the Pearson chi-square test was applied. To examine differences in age at diagnosis of malignancies, DCS, and DRS, two-sample *t*-tests were used. In the calculations of cumulative incidence functions of malignancies, DCS, and DRS, including asthma and venous thromboembolism (VTE), time for follow-up was defined as the time from diagnosis of cHL until the first event, death, or last observation (December 31, 2017). For the comparators, time for follow-up started the same date as for the corresponding patient. Crude cumulative incidence

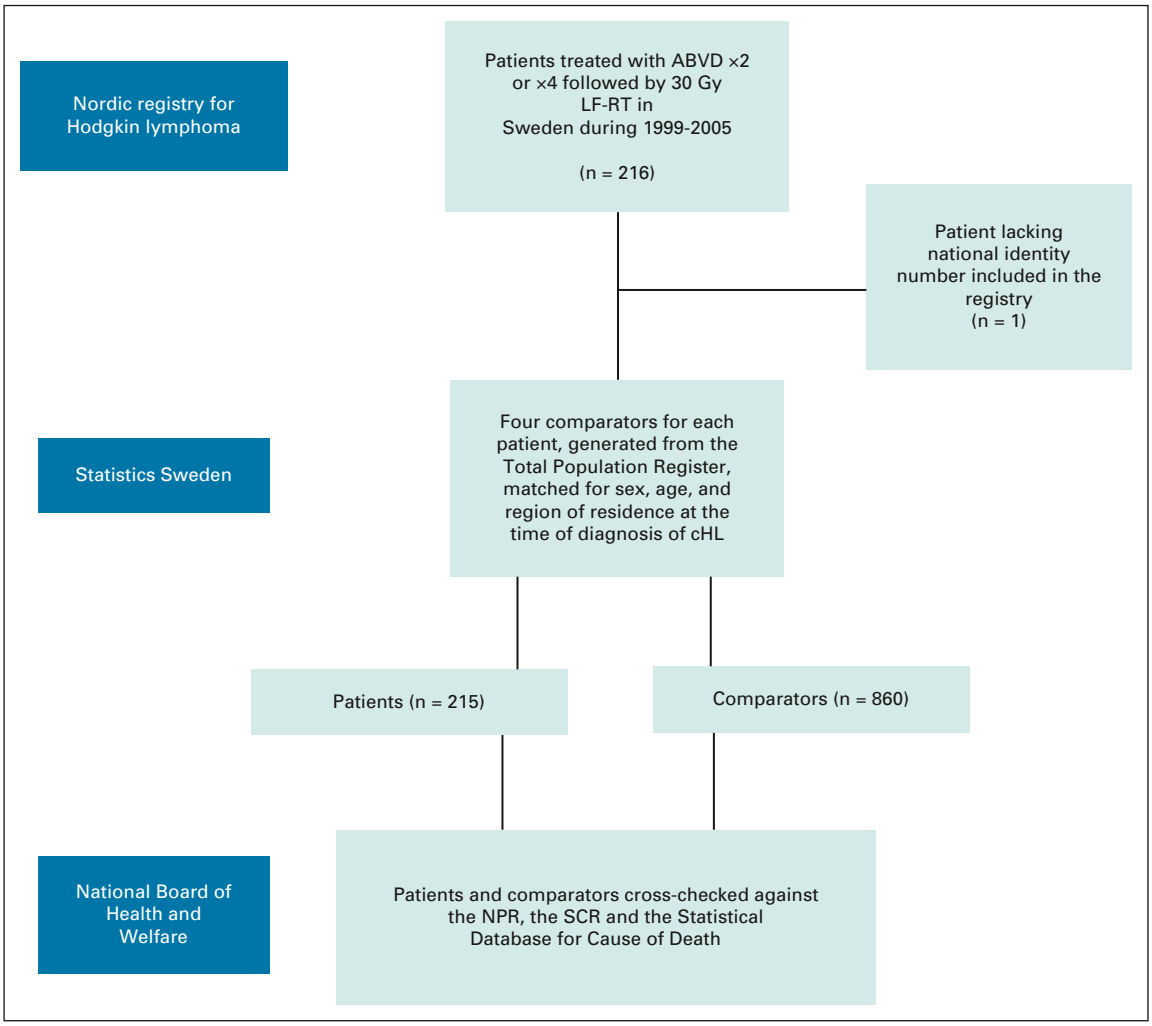

FIG 1. CONSORT diagram for the study population. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; cHL, classical Hodgkin lymphoma; LF-RT, limited-field radiotherapy.

rates were examined.[33] This indicated failure probabilities for a particular type of event, in the presence of other events, which may impede the event of interest to occur. In the analyses of DCS, DRS, VTE, and asthma, death due to any cause was considered as a competing event. In the analysis of malignancies, both death and recurrence of cHL were accounted as competing events. Subhazard ratios (SHRs) and the 95% CIs were estimated on the basis of Fine and Gray's proportional subhazards model. For each analysis, cause-specific HRs on the basis of a Cox regression model were also calculated, censoring for cases corresponding to the competing events above. The SHRs and HRs were similar in these analyses, and since HRs are more straight forward to interpret than SHRs, the HRs are mainly reported with SHRs shown in the Data Supplement. Overall survival analyses were performed using the Kaplan-Meier method, censoring at loss to follow-up or at the date of last observation, December 31, 2017. HR and 95% CI were estimated using the Cox's proportional hazards model. A *P* value of .05 was considered statistically significant.

The statistical analyses were performed using STATA/SE 13.1.[34] The Venn diagrams were produced in R (R Core Team, 2020)[35] using the package eulerr.[36]

RESULTS

Patients and Comparators

The cohort consisted of 215 patients (female, n = 107) with cHL treated in Sweden, during 1999-2005, with two or four cycles of ABVD followed by 30 Gy LF-RT (Table 2) and 860 matched comparators. Patients and comparators were similar regarding matching factors, and no statistically significant difference in history of malignancies, DCS, or DRS were seen between patients and comparators (Table 1). The median age was 34 years (range, 18-77 years) at time of diagnosis. Sixty-one (28%) had stage I disease, of whom 10 (16%) were allocated to four cycles of ABVD, seven of these had bulky disease. One hundred and fifty-four (72%) had stage II disease, of whom 112 (72%) were allocated to four cycles of ABVD and 39 had bulky

TABLE 1. Baseline Characteristics for Patients Treated With Two or Four Cycles of Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine Followed by 30 Gy Limited-Field-Radiotherapy for cHL in Sweden During 1999-2005, and the Comparators Matched for Sex, Age, and Region of Residence at the Time of Diagnosis of cHL in the Corresponding Patient

	Baseline Characteristics of Patients and Comparators (N = 1,075)		
Characteristics	**Patients, n = 215 (% of all patients)**	**Comparators, n = 860 (% of all comparators)**	***P*[a]**
Age at inclusion, years[b]			
18-39	127 (59)	508 (59)	1.00
40-59	57 (27)	228 (27)	
≥ 60	31 (14)	124 (14)	
Gender			
Female	107 (50)	428 (50)	1.00
Male	108 (50)	432 (50)	
Morbidity, individuals diagnosed before inclusion			
Previous malignancy[c]	13 (6)	33 (4)	.15
DCS[d]	13 (6)	60 (7)	.63
DRS[e]	6 (3)	25 (3)	.93

Abbreviations: cHL, classical Hodgkin lymphoma; DCS, diseases of the circulatory system; DRS, diseases of the respiratory system.
[a]*P* values calculated using chi-square test.
[b]No comparator differed more than age 1 year compared with the corresponding patient.
[c]Any malignancy except for nonmelanoma skin cancer.
[d]International Classification of Disease, Chapter IX, except for I83-I86, I88-I86.
[e]International Classification of Disease, Chapter X.

disease. Mediastinal disease was present in 130 patients, and in 29 of these patients, at least one axilla was also involved. Five patients without any risk factor received four cycles of ABVD while three patients with at least one risk factor received two cycles. Thus, 96% of patients received treatment according to risk factors. Two patients received a dose of RT that significantly deviated from the guidelines (21 Gy) with no reasons reported. All patients were analyzed according to intention-to-treat (ie, according to initial report at diagnosis of cHL).

Survival and Disease Control

Survival and disease control for these patients did not differ from results reported earlier in detail in a cohort from the Nordic registry that also included all corresponding patients from Norway.[26] Survival for patients was equal to the expected survival in the general population during almost 20 years (median 17 years) of follow-up for survival. The proportion of patients who remained disease-free was 93% at 5 and 10 years. The median follow-up for malignancies, DCS, and DRS was 16 years (range, 12-19 years). One patient who received four cycles of ABVD in the absence of any risk factor relapsed, and one patient who received two cycles of ABVD in the presence of at least one risk factor relapsed and died with active lymphoma. No other events concerning disease control or survival were recorded among patients with treatment that deviated from guidelines.

Malignancies

The cumulative incidences of second cancers among patients and comparators are visualized in Figure 2A, and the difference was not statistically significant, HR 1.5 (95% CI, 1.0 to 2.4). Thirty (14%) patients, with a median age of 50 years (range, 19-73 years) at the time of diagnosis of cHL, were diagnosed with a total of 33 second cancers at a median age of 60 years (range, 26-83 years) at the time of the first second cancer (Table 3). Of these patients, 10 (4.7% of all patients) were younger than 30 years at diagnosis of cHL. No patient had more than two second cancers. Among comparators, 77 (9%) individuals were diagnosed with a total of 92 cancers. They had a median age of 56 years (range, 19-73 years) at inclusion as comparators and 62 years (range, 26-84 years) at diagnosis of the cancer. Of these, 16 (1.9% of all comparators) were younger than 30 years at inclusion. The difference in age at inclusion was not statistically significant ($P = .30$; Data Supplement). Survival among patients with a second cancer did not differ from survival among comparators diagnosed with a cancer (Data Supplement). There was statistically significantly more nonmelanoma skin cancer among patients (2.3%) than among comparators (0.2%) during follow-up, $P = .001$.

DCS

A larger proportion of patients, n = 65 (30%), than comparators, n = 190 (22%), were diagnosed with at least one DCS during follow-up (Table 4 and Fig 2B), HR 1.5 (95% CI, 1.1 to 2.2). Patients were slightly younger at the time of DCS diagnosis (median age 60 years; range, 18-89 years), compared with comparators (median age 65 years; range, 23-87 years). The difference was not statistically

TABLE 2. Characteristics for Patients Treated With Two or Four Cycles of ABVD Followed by 30 Gy Limited-Field Radiotherapy in Sweden During 1999-2005, n = 215 (Female, n = 107)

Patient and Disease Characteristics	Treatment		
	Two Cycles of ABVD	Four Cycles of ABVD	Mediastinal Radiotherapy[a]
Age at diagnosis, years, median 34 years (range, 18-77 years)			
18-39, n = 127	38	89	95
40-59, n = 57	31	26	25
≥ 60, n = 31	24	7	10
Extent of disease			
Bulky[b]	0	46[c]	37
Mediastinum	30	100	130
Mediastinum and axilla	5	24	29

Abbreviation: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine.

[a]Limited-field radiotherapy, guidelines for target fields available in the Data Supplement.

[b]≥ 0.33 of internal thoracic diameter at Th5-6 level on a posterior anterior chest x-ray or mass/conglomerate > 10 cm in largest diameter on computed tomography.

[c]Of these, 21 patients had mediastinal bulk.

significant, $P = .08$ (Data Supplement). HR for DCS was significantly increased among patients (Fig 2B), 1.5 (95% CI, 1.1 to 2.0). When follow-up was divided into time periods, HR was statistically significantly elevated only during the first 5 years (Data Supplement), 2.3 (95% CI, 1.5 to 3.5). In analyzed individual diagnoses (hypertension, coronary heart disease, heart failure, ischaemic cerebrovascular disease, and VTE), only VTE was significantly increased among patients (Fig 2C), HR 3.7 (95% CI, 1.9 to 7.2). If events from the first 6 months after diagnosis of cHL were excluded and patients and comparators were censored at the time of malignancy or relapse of cHL, the HR for VTE was not statistically significant, 2.2 (95% CI, 0.9 to 5.5). Mortality among patients with DCS did not differ from mortality among comparators with DCS (Data Supplement).

DRS

Twenty-five patients (12%) and 40 comparators (5%) diagnosed with a DRS (Table 4). The median age for these patients and comparators at diagnosis of cHL/inclusion was 35 years (range, 18-73 years) and 62 years (range, 21-74 years), respectively, while at diagnosis of first DRS it was 46 years (range, 22-85 years) and 65 years (range, 22-90 years), respectively. There were significantly more individuals with DRS among patients (Fig 2D), HR 2.6 (95% CI, 1.6 to 4.3), and they were significantly younger at diagnosis ($P = .03$). Significantly more DRS among patients were seen during the first 5 years and after 10 years, HR 3.0 (95% CI, 1.3 to 7.2) and 3.4 (95% CI, 1.5 to 7.7), respectively, but not in between (Data Supplement). In analyses of individual diagnoses (chronic obstructive pulmonary disease, asthma, radiation, and bleomycin induced pneumonitis), only risk for asthma was significantly increased (Fig 2E), HR 3.5 (95% CI 1.8 to 6.8). Only one diagnosis of pneumonitis (bleomycin induced) was recorded. Mortality among patients with DRS did not differ from mortality among comparators with DRS (Data Supplement).

Coexistence of Malignancies, DCS, and DRS

Analyzing coexistence of cancers, DCS, and DRS during follow-up, 6% (n = 13) of patients were diagnosed with a second cancer and DCS, < 1% (n = 1) with a second cancer and DRS, 3% (n = 6) with DCS and DRS, and 2% (n = 4) with a malignancy, DCS, and DRS (Fig 3A). Among comparators, the corresponding groups consisted of 4% (n = 34), < 1% (n = 5), 2% (n = 14), and < 1% (n = 6) of all comparators (Fig 3B). The differences in risk for coexistence of diagnoses between patients and comparators did not reach statistical significance, although second cancer plus DCS and DCS plus DRS were borderline ($P = .06$ for both).

DISCUSSION

In this cohort, patients with early-stage cHL were treated with smaller irradiated volumes and reduced doses, compared with earlier cohorts, without compromised survival.[26] Excess morbidity is seen, but to a lesser extent than repeatedly reported in patient materials during the past several decades.

The increased risk for second cancers, HR 1.5 (95% CI, 1.0 to 2.4), means that of patients diagnosed with at least one malignancy, 11 of 30 might be attributed to treatment toxicity. This is lower than what has been reported previously.[14,15,37] The lack of statistical significance should not be interpreted as no elevated risk for malignancies after treatment for cHL but rather as a lack of power in a cohort with few events. Schaapveld et al[15] found a standardized incidence ratio (SIR) of 4.6 (95% CI, 4.3 to 4.9) with only minor variations of that level during the first 20 years of follow-up and no significant reduction according to the treatment period (1965-2000). Andersson et al[14] found the SIR for malignancies to be 2.62 (95% CI, 2.32 to 2.96) for all patients with cHL diagnosed during 1965-1995. Both these publications include patients with cHL of all stages, and a proportion of the patients were treated without RT. In the report by Schaapveld et al,[15] the risk of a malignancy

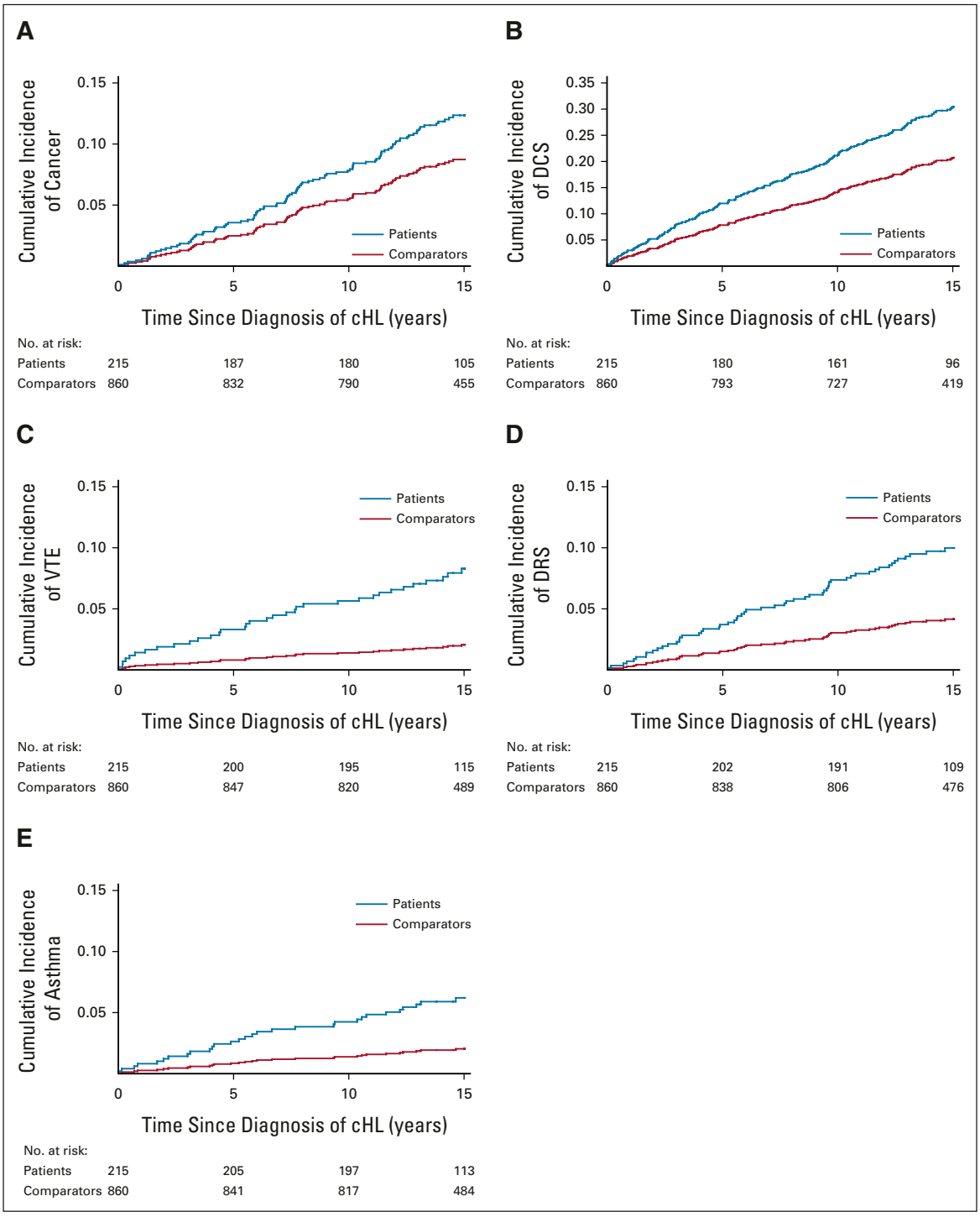

FIG 2. (A) Incidence of any secondary cancer among patients treated, with ABVD ×2 or ×4 followed by 30 Gy LF-RT, for cHL stage IA-IIA in Sweden during 1999-2005, compared with incidence of any cancer among matched comparators from the population. (B) Incidence of DCS among patients treated, with ABVD ×2 or ×4 followed by 30 Gy LF-RT, for cHL stage IA-IIA in Sweden during 1999-2005, compared with matched comparators from the population. (C) Incidence of VTE among patients treated, with ABVD ×2 or ×4 followed by 30 Gy LF-RT, for cHL stage IA-IIA in Sweden during 1999-2005, compared with matched comparators from the population. (D) Incidence of DRS among patients treated, with ABVD ×2 or ×4 followed by 30 Gy LF-RT, for cHL stage IA-IIA in Sweden during 1999-2005, compared with matched comparators from the population. (E) Incidence of Asthma among patients treated, with ABVD ×2 or ×4 followed by 30 Gy LF-RT, for cHL stage IA-IIA in Sweden during 1999-2005, compared with matched comparators from the population. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; cHL, classical Hodgkin lymphoma; DCS, diseases of the circulatory system; DRS, diseases of the respiratory system; LF-RT, limited-field radiotherapy; NPR, National Patient Register; SCR, Swedish Cancer Register; VTE, venous thromboembolism.

TABLE 3. Incidence and HR of Any Malignancy During Follow-Up of Patients Treated for Early-Stage Classical Hodgkin Lymphoma With Two or Four Cycles of Doxorubicin, Bleomycin, Vinblastine and Dacarbazine Followed by 30 Gy Limited-Field Radiotherapy, and Matched Comparators From the General Population in Sweden During 1999-2005

Cancer Diagnosed	No. of Individuals Diagnosed Among Patients, n = 215 (% of all patients)	No. of Individuals Diagnosed Among Comparators, n = 860 (% of all comparators)
Any cancer (excluding skin, nonmelanoma)	30 (14) HR 1.5 (95% CI, 1.0 to 2.4)	77 (9.0)
Lip, oral cavity, and pharynx	4 (1.9)	2 (0.2)
Digestive organs	7 (3.3)	12 (1.4)
Respiratory and intrathoracic organs	< 3	7 (0.8)
Melanoma	< 3	8 (0.9)
Breast	3 (1.4)	21 (2.4)
Female genital organs		
All	4 (1.9)	15 (1.7)
Cervix (HSIL CIN)	4 (1.9)	14 (1.6)
Male genital organs		
All	5 (2.3)	12 (1.4)
Prostate	5 (2.3)	11 (1.3)
Urinary tract	< 3	4 (0.5)
Eye, brain, and other parts of CNS	2 (0.9)	1 (0.1)
Thyroid and other endocrine glands	< 3	2 (0.2)
Lymphoid, haematopoietic, and related tissue	3 (1.4)	5 (0.6)
Unknown primary and categories with < 3 patients diagnosed	5 (2.3)	4 (0.5)
Skin, nonmelanoma	5 (2.3)	2 (0.2)

Abbreviations: CIN, cervical intraepithelial neoplasia; HR, hazard ratio; HSIL, high grade squamous intraepithelial lesion.

was 61% less in patients not irradiated compared with those receiving a mantle field and 39% less than those having less supradiaphragmatic irradiation than a mantle field. In a large British cohort diagnosed during 1963-2001, a subgroup treated with ABVD, and RT had an SIR of 5.0 (95% CI, 2.4 to 9.2) for any malignancy with the highest rate reached 15 years after diagnosis.[37]

As all patients received RT, the risk for nonmelanoma skin cancer is high. This malignancy was analyzed separately as the clinical impact, in terms of survival, quality of life, and treatment given, is much smaller.

The increased risk for DCS, HR 1.5 (95% CI, 1.1 to 2.0), means that of patients diagnosed with at least one DCS, 22 of 65 might be attributed to treatment toxicity: again, lower than previously reported and with a different distribution of diagnoses.[11,38] In a British cohort diagnosed during 1976-2000, analyzed for mortality caused by myocardial infarction, a standardized mortality rate of 2.5 (95% CI, 2.1 to 2.9) was found with the highest rate after ABVD and RT.[38] Van Nimwegen et al[11] reported SIRs for coronary heart disease and heart failure of 3.2 (95% CI, 3.0 to 3.5) and 6.8 (95% CI, 5.9 to 7.6), respectively, for patients with cHL treated during 1965-1995 in the Netherlands, with the highest SIRs 10-24 years after diagnosis. No reduction in risk was seen in later treatment periods. In this more recent cohort, there is no significant excess risk for either. When comparing with the study by van Nimwegen et al, 24% of patients in the Swedish cohort were older than 50 years while no patients older than 50 years were included in the Dutch cohort. The treatment that correlated with the highest risk for cardiovascular disease in the Dutch cohort was CMT including anthracyclines and mediastinal RT, which was used for 22% of patients in the Dutch cohort and for 60% in the Swedish cohort.

Of separate diagnoses, only HR for VTE was statistically significantly increased. Once known risks for VTE from treatment of cHL and second cancers[39] were compensated for, the findings were diminished. The excess risk for VTE can thus be correlated with the risk for VTE during treatment of cHL and as a secondary risk from treatment toxicity.

The excess risk for DRS, HR 2.6 (95% CI, 1.6 to 4.3), is almost entirely made up of excess risk for asthma, HR 3.5 (95% CI, 1.8 to 6.8). Asthma was also increased in another retrospective Swedish cohort of patients with cHL treated with CMT or chemotherapy only.[29] One possible explanation for the excess risk is misdiagnosis of persisting pulmonary toxicity as asthma. In a retrospective study of a Hungarian cohort of patients with cHL, a statistically significant reduction of forced expiratory volume in 1 second

TABLE 4. Incidence and HR of DCS and DRS, According to ICD 10, During Follow-Up of Patients Treated for Early-Stage Classical Hodgkin Lymphoma With Two or Four Cycles of Doxorubicin, Bleomycin, Vinblastine and Dacarbazine Followed by 30 Gy Limited-Field Radiotherapy, and Matched Comparators From the General Population in Sweden During 1999-2005

Chapter and Individual Diagnosis According to ICD	No. of Individuals Diagnosed Among Patients, n = 215 (% of all patients)	No. of Individuals Diagnosed Among Comparators, n = 860 (% of all comparators)
DCS, Chapter IX		
DCS, Chapter IX[a]	65(30) HR 1.5 (95% CI, 1.1 to 2.0)	190 (22)
Hypertension, I10-I15	35 (16)	121 (14)
Coronary heart disease, I20-I25	14 (7)	53 (6)
Heart failure, I42-43, I50, I51.7	10 (5)	27 (3)
Ischaemic cerebrovascular disease, I63-I66, I69.3	6 (3)	27 (3)
VTE, I26, I80-I82	17 (8) HR 3.7 (95% CI, 1.9 to 7.2)	19 (2)
Pulmonary embolism, I26	5 (2)	8 (1)
DRS, Chapter X		
DRS, Chapter X	25 (12) HR 2.6 (95% CI, 1.6 to 4.3)	40 (5)
Chronic obstructive pulmonary disease, J41-44	5 (2)	14 (2)
Asthma, J45	16 (7) HR 3.5 (95% CI, 1.8 to 6.8)	19 (2)

Abbreviations: DCS, diseases of the circulatory system; DRS, diseases of the respiratory system; HR, hazard ratio; ICD, International Classification of Diseases; VTE, venous thromboembolism.

[a]Except for I83-I86 and I88-I86.

and elevated score of the St George Respiratory Questionnaire correlated with a cumulative dose of bleomycin but not to mediastinal RT.[40,41] In prospective studies of pulmonary function in patients treated with bleomycin with or without mediastinal RT, there were patients with persisting pulmonary toxicity, but follow-up is only 1-3 years.[18,42,43]

Another possible explanation is that diagnosis and treatment of asthma in Sweden is, in contrast to malignancies and cardiovascular disease, primarily performed by general practitioners and thus in large part not visible in the NPR. Among comparators, only 2% have a diagnosis of asthma in the NPR, while the prevalence of asthma in Sweden is about 8% in all age groups.[44] Hence, at least part of the HR for asthma among patients may be the result of surveillance for toxicity, in specialist care, making asthma among cHL survivors more visible in the NPR.

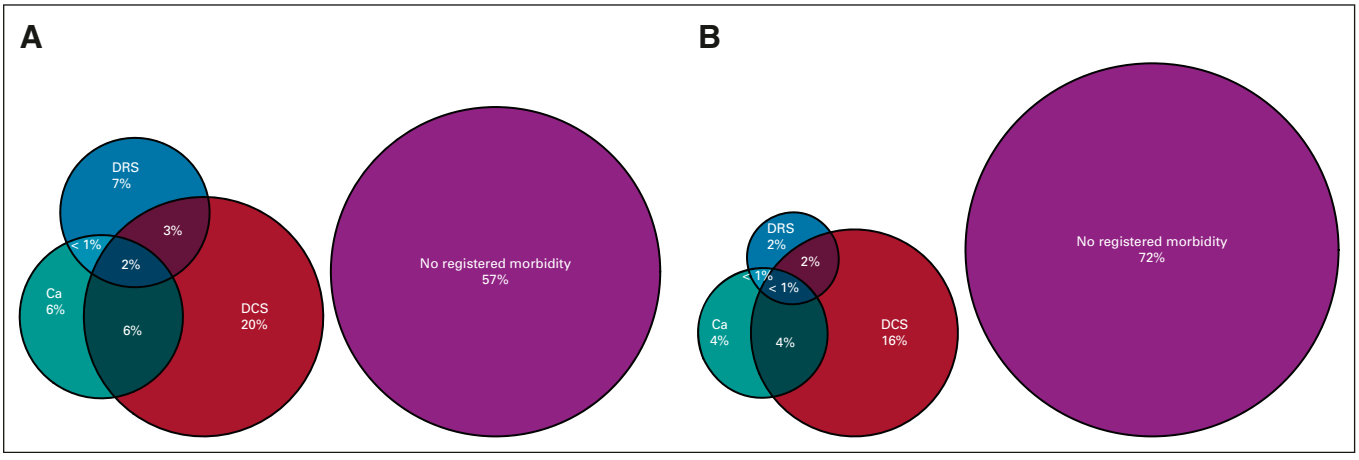

FIG 3. (A) Proportions of patients treated, with ABVD ×2 or ×4 followed by 30 Gy limited-field radiotherapy, for classical Hodgkin lymphoma stage IA-IIA in Sweden during 1999-2005, with any secondary Ca, DCS, DRS, and comorbidities. (B) Proportions of comparators with any Ca, DCS, DRS, and comorbidities. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; Ca, cancer; DCS, diseases of the circulatory system; DRS, diseases of the respiratory system.

Median age at diagnosis of DRS is significantly lower among patients, 46 years compared with 65 years among comparators ($P = .03$), making the impact greater than indicated by the HR alone.

The single diagnosis of pneumonitis may indicate that this complication was underdiagnosed compared with earlier reports.[45] Indeed, bleomycin is removed from treatment on mere suspicion without diagnostic criteria being fulfilled. Clinicians might thus use diagnostic codes for symptoms instead.

Bleomycin has been reduced and removed in trials for first-line treatment of cHL.[42,46,47] Thus, persisting pulmonary toxicity will hopefully not be a large problem for patients treated in the future.

The strength of this study is a population-based cohort with precisely defined extent of disease, and uniformly risk-adapted treatment, with long-term follow-up and comprehensive coverage for cumulative morbidity.

The weakness is a relative lack of power and the fact that almost two decades of follow-up might still not be enough to catch the relevant trends of excess morbidity. Repeated follow-up for survival, late relapses, and excess morbidity with an interval of 3-5 years is thus planned.

In conclusion, we describe toxicity in early-stage cHL, treated with two or four cycles of ABVD followed by 30 Gy LF-RT, with smaller target volumes than IF. The toxicity is reduced, but not eliminated, both regarding second cancers and DCS, compared with earlier cohorts. Persisting pulmonary toxicity may be misdiagnosed as asthma. As excess morbidity is not eliminated, the goal of omitting RT in early-stage cHL, when possible without compromising disease control, remains important.

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SUPPORT

Supported by Stiftelsen Onkologiska Klinikens i Uppsala Forskningsfond and the Swedish Cancer Society.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.02407.

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ACKNOWLEDGMENT

The authors wish to thank the Swedish Hodgkin Lymphoma Group, Regional Cancer Center South-East Sweden, and all persons who have contributed to the Nordic Hodgkin Registry.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Limited, But Not Eliminated, Excess Long-Term Morbidity in Stage I-IIA Hodgkin Lymphoma Treated With Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine and Limited-Field Radiotherapy

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

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Consulting or Advisory Role: Gilead Sciences (Inst)

Bengt Glimelius
Consulting or Advisory Role: PledPharma
Research Funding: Amgen

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Research Funding: Beigene (Inst), Takeda (Inst)

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No other potential conflicts of interest were reported.