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Relapse Risk and Loss of Lifetime After Modern Combined Modality Treatment of Young Patients With Hodgkin Lymphoma: A Nordic Lymphoma Epidemiology Group Study

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PURPOSE Estimates of short- and long-term survival for young patients with classic Hodgkin lymphoma (cHL) are of considerable interest. We investigated cHL prognosis in the era of contemporary treatment at different milestones during the follow-up.

PATIENTS AND METHODS On the basis of a Nordic cohort of 2,582 patients diagnosed at ages 18 to 49 years between 2000 and 2013, 5-year relapse risks and 5-year restricted losses in expectation of lifetime were estimated for all patients and for patients who achieved event-free survival (EFS) for 12 (EFS12), 24 (EFS24), 36 (EFS36) or 60 (EFS60) months. The median follow-up time was 9 years (range, 2.9 to 16.8 years).

RESULTS The 5-year overall survival was 95% (95% CI, 94% to 96%). The 5-year risk of relapse was 13.4% (95% CI, 12.1% to 14.8%) overall but decreased to 4.2% (95% CI, 3.8% to 4.6%) given that patients reached EFS24. Relapse risk for patients treated with six to eight courses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) was comparable to that of patients treated with six to eight courses of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) despite more adverse risk criteria among patients treated with BEACOPP. Both from diagnosis and if EFS24 was reached, the losses in expectation of lifetime during the following 5 years were small (from diagnosis, 45 days [95% CI, 35 to 54 days] and for patients who reached EFS24, 13 days [95% CI, 7 to 20 days]). In stage-stratified analyses of 5-year restricted loss in expectation of lifetime, patients with stages I to IIA disease had no noteworthy excess risk of death after they reached EFS24, whereas risk remained measurable for patients with stages IIB to IV cHL.

CONCLUSION Real-world data on young patients with cHL from the Nordic countries show excellent outcomes. The outlook is particularly favorable for patients who reach EFS24, which supports limited relapse-oriented clinical follow-up.

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INTRODUCTION

The treatment of classic Hodgkin lymphoma (cHL) is one of the great success stories of modern oncology.¹ The introduction of combined modality treatment of limited-stage disease and effective multiagent chemotherapy regimens for advanced-stage disease were paradigm shifts that led to high cure rates across all disease stages.²⁻⁶ The first peak in the bimodal incidence pattern of Hodgkin lymphoma (HL) appears around the age of 20 to 30 years; cHL differs from many other malignancies in that a large fraction of the patients are young, otherwise healthy, and fit enough to receive full-dose curative-intent treatment.⁷ Favorable short-term outcomes in a young patient group

with long residual life expectancy have led to a focus on reducing short- and long-term toxicity without compromising treatment efficacy.⁸⁻¹⁰ At present, cardiovascular disease, fatigue, infertility and risk of secondary malignancies are some of the major health issues faced by patients with HL.^{2,7,11-15} Replacement of vincristine, nitrogen mustard, procarbazine hydrochloride, and prednisone (MOPP) chemotherapy with the less toxic regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and improved radiotherapy (RT) techniques are anticipated to reduce late toxicities substantially in the coming years.^{16,17} These modified treatment options have led to increases in relative survival for Swedish patients

ASSOCIATED CONTENT

Data Supplement

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

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with HL diagnosed before age 65 years.¹⁸ A recent study of 1,402 patients with cHL diagnosed in British Columbia (including some treated with MOPP combinations) documented increased standardized mortality ratios in cHL, even for patients in ongoing remission for many years.¹⁹ This could indicate that late toxicities still have an impact on residual life expectancy despite efforts to reduce serious long-term toxicities.¹⁹ In this Nordic population-based study of patients with cHL age 18 to 49 years and diagnosed during 2000 to 2013, we compared the survival with that of a healthy background population and explored the evolution of the relapse risk for patients in ongoing remissions at different milestones.

Study Population and Data Sources

Patients were identified using national and regional registers and databases.²⁰⁻²² The Danish cohort was extracted from the nationwide Danish Lymphoma Register (LYFO), which includes clinical and outcome data. In a recent quality assessment, LYFO was shown to have a coverage of 95% of all Danish patients with lymphoma.²³ The Swedish cohort consisted of patients included in the Swedish Cancer Register, which covers nearly 100% of all Swedish patients with cancer, for whom clinical information was retrievable from the Swedish Lymphoma Register (SLR).^{24,25} The Cancer Registry of Norway covers approximately 99% of all cancer occurrences in Norway and was used to identify patients with HL who were covered by the Southern and Eastern Regional Health Authority/Oslo University Hospital.²² For the Norwegian patient cases, clinical data were extracted from the clinical lymphoma database at Oslo University Hospital (CLDOUH), which covers approximately 55% of the Norwegian population, and were supplemented by local review of medical files in cases of missing data. Complete follow-up for all patients was ensured by a merge with the national population registers, which contain accurate information on vital statuses for all citizens of Denmark, Sweden, and Norway.^{23,24} The follow-up end dates were November 16, 2016, October 31, 2015, and December 15, 2016, for Denmark, Sweden, and Norway, respectively. Patients who experience a relapse/progression are reported to LYFO, the SLR, or the CLDOUH. To identify missing relapses, LYFO is merged regularly with the Danish National Pathology Registry, which includes biopsy-confirmed relapses.²⁶ Patients who receive chemotherapy or RT within 9 months post diagnosis are automatically signaled to the treating physician to be reviewed for possible relapse. To identify unreported relapses in the Swedish data, retrospective review of medical records was performed in three of six health care regions, and all performed stem-cell transplantations were identified in the National Patient Register, as previously described.^{21,27} In Norway, treatment of cHL is fully centralized to the regional hospital, and relapses/progressions are prospectively registered in CLDOUH. In this study, stable or progressive disease at

the time of response evaluation after first-line treatment was included in our definition of progression.

Inclusion criteria for this study were as follows: newly diagnosed cHL in 2000 to 2013; treated with chemotherapy alone or combination therapy with involved-field or involved-node RT; and age of 18 to 49 years at diagnosis. Treatment information and clinicopathologic variables were retrieved directly from LYFO, SLR, and CLDOUH (Table 1). Patients with limited-stage disease were preferably treated with two to four courses of ABVD (four courses if one or more of the following risk factors were present: erythrocyte sedimentation rate > 50, bulky disease, involvement of three or more lymph node regions) and 20 to 30 Gy of involved-field/-node RT. Patients with advanced-stage disease were treated with six to eight courses of ABVD, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP-14), or escalated BEACOPP (eBEACOPP); the two BEACOPP treatments were mainly administered to patients with international prognostic scores greater than 2. Consolidative RT to isolated areas may have been used after full chemotherapy and was aimed at extranodal disease sites or residual masses of uncertain significance in the prepositron emission tomography (PET)/computed tomography (CT) era and single residual fluorodeoxyglucose-avid lesions when PET/CT became available. Between 2008 and 2012, a limited number of patients were included in the Response Adapted Therapy in Advanced Hodgkin Lymphoma (RATHL) trial and received PET-guided treatment with two courses of ABVD followed by random assignment to four additional courses of doxorubicin, vinblastine, and dacarbazine or ABVD if they had PET-negative disease and to BEACOPP-14/eBEACOPP if they had PET-positive disease.¹⁰

Statistical Analysis

Overall survival (OS) was defined as time from cHL diagnosis until death as a result of any cause. Event-free survival (EFS) was defined as the time from diagnosis to death, or progression (evaluated at the response evaluation after first-line treatment) or relapse, whichever came first. Because of the structure of the databases, we were unable to determine whether consolidative RT was administered as part of planned combined-modality treatment or to areas of disease with suboptimal response to chemotherapy. Thus, we did not include consolidative RT in our definition of EFS. Patients who did not experience an event were censored at the end of follow-up. Exact dates of the response evaluation after first-line treatment were not available in the Swedish and Norwegian cohorts, and response evaluations were assumed to have happened 243 days after diagnosis, which was the median time from diagnosis to response evaluation after first-line treatment in the Danish cohort. Sensitivity analyses with respect to the imputed time were performed. Survival curves were estimated with the Kaplan-Meier estimator.

TABLE 1. Clinical Characteristics of Danish, Swedish, and Norwegian Patients With Classic Hodgkin Lymphoma Age 18 to 49 Years at Diagnosis

Characteristic	No. (%) of Patients			
	Denmark (n = 863)	Sweden (n = 1,236)	Norway (n = 483)	Combined (N = 2,582)
Age at diagnosis, years				
18-34	505 (58.5)	849 (68.7)	314 (65.0)	1,668 (64.6)
35-49	358 (41.5)	387 (31.3)	169 (35.0)	914 (35.4)
Sex				
Female	394 (45.7)	620 (50.2)	225 (46.6)	1,239 (48.0)
Male	469 (54.3)	616 (49.8)	258 (53.4)	1,343 (52.0)
Calendar period				
2000-2005	344 (39.9)	510 (41.3)	195 (40.4)	1,049 (40.6)
2006-2013	519 (54.3)	726 (58.7)	288 (59.6)	1,533 (59.4)
Ann Arbor stage				
I	128 (14.8)	122 (9.9)	54 (11.2)	304 (11.8)
II	405 (46.9)	678 (54.9)	223 (46.2)	1,306 (50.6)
III	184 (21.3)	217 (17.6)	89 (18.4)	490 (19.0)
IV	139 (16.1)	206 (16.7)	116 (24.0)	461 (17.9)
Missing	7 (0.8)	13 (1.1)	1 (0.2)	21 (0.8)
Limited (IA-IIA)	362 (41.9)	554 (44.8)	191 (39.5)	1,107 (42.9)
Advanced (IIB-IV)	494 (57.2)	669 (54.1)	291 (60.2)	1,454 (56.3)
Bone marrow involvement				
No	816 (94.6)	603 (48.8)	442 (91.5)	1,861 (72.1)
Yes	47 (5.4)	53 (4.3)	31 (6.4)	131 (5.1)
Missing	0 (0.0)	580 (46.9)	10 (2.1)	590 (22.9)
Extranodal disease				
No	678 (78.6)	603 (48.8)	341 (70.6)	1,622 (62.8)
Yes	185 (21.4)	236 (19.1)	131 (27.1)	552 (21.4)
Missing	0 (0.0)	397 (32.1)	11 (2.3)	408 (15.8)
Treatment*				
Chemotherapy 2-4 and RT	290 (33.6)	352 (28.6)	159 (32.9)	801 (31.0)
Chemotherapy 2-4 no RT	21 (2.4)	34 (2.8)	16 (3.3)	71 (2.7)
Chemotherapy 6-8 and RT	176 (20.4)	119 (9.6)	61 (12.6)	356 (13.8)
Chemotherapy 6-8 no RT	277 (32.1)	471 (38.1)	244 (50.5)	992 (38.4)
Missing RT status	1 (0.1)	256 (20.7)	3 (0.6)	260 (10.1)
RT and chemotherapy	98 (11.4)	0 (0)	0 (0.0)	98 (3.8)
Other	0 (0.0)	4 (0.3)	0 (0.0)	4 (0.2)
Chemotherapy†				
ABVD 2-4	309 (35.8)	366 (29.6)	171 (35.4)	846 (32.8)
ABVD 6-8	357 (41.4)	400 (32.4)	190 (39.3)	947 (36.7)
BEACOPP 6-8	88 (10.2)	168 (13.6)	45 (9.3)	301 (11.7)
Unspecified chemotherapy‡	0 (0.0)	245 (19.8)	3 (0.6)	248 (9.6)

(continued on following page)

TABLE 1. Clinical Characteristics of Danish, Swedish, and Norwegian Patients With Classic Hodgkin Lymphoma Age 18 to 49 Years at Diagnosis (continued)

Characteristic	No. (%) of Patients			
	Denmark (n = 863)	Sweden (n = 1,236)	Norway (n = 483)	Combined (N = 2,582)
MOPP/MOPP-ABV 2-4§	2 (0.2)	7 (0.6)	0 (0.0)	9 (0.3)
MOPP/MOPP-ABV 6-8§	8 (0.9)	5 (0.4)	3 (0.6)	16 (0.6)
Other	99 (11.5)	45 (3.6)	71 (14.7)	215 (8.3)

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; MOPP/ABV, mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, and vinblastine; RT, radiotherapy.

*Chemotherapy courses are designated by numeric ranges (eg, two to four courses represented by Chemotherapy 2-4). For RT and chemotherapy group, cycles were unspecified.

†Patients who received one course of chemotherapy were put into the group with two to four courses of treatment (eg, ABVD 2-4), and patients who received five courses were put into the group with six to eight courses (eg, ABVD 6-8 or BEACOPP 6-8).

‡ABVD and BEACOPP regimens were the recommended treatments during the study period, but the exact chemotherapy was not specified in the register data.

§Treatments were two to four courses (MOPP/MOPP-ABV 2-4) or six to eight courses (MOPP/MOPP-ABV 6-8).

||Other includes patients who changed treatment plan according to the results of an interim positron emission tomography scan, mainly patients included in the RATHL (Response Adapted Therapy in Advanced Hodgkin. Lymphoma) trial.

Progression/relapse risk was estimated using the Aalen-Johansen estimator with death as competing risk. The evolution of the 5-year relapse risk from diagnosis and conditional on reaching EFS milestones was also investigated by use of logistic regression models with progression/relapse within 5 years after the studied milestone as outcome. The censoring and competing risk (death without disease progression) were accounted for by relying on pseudo-observations (Data Supplement).²⁸

The 5-year restricted loss in expectation of lifetime (5y-RLEL) was defined as the numeric difference in the number of days a healthy person and a patient are expected to survive within the next 5 years.²⁹ Estimates were obtained for all patients and for patients who reached 12 months (EFS12), 24 months (EFS24), 36 months (EFS36) or 60 months (EFS60) of survival. The analyses were based on pseudo-value methodology (Data Supplement).³⁰

All analyses were performed both in a stratified manner and by use of multivariable models. An analysis of the unrestricted loss in expectation of lifetime is reported in the Data Supplement.

The pseudo-value (pseudo and geepack packages) analyses were done in R (version 3.4.4). In case of missing information, available-case analyses were performed. The study was approved by the Danish Data Protection Agency (internal ID No. 2016-93) and relevant review boards in Stockholm (Sweden) and Oslo (Norway). All data were anonymized for analysis.

RESULTS

Demographic Characteristics and OS

In total, 2,582 patients with cHL were included (Denmark, n = 863; Sweden, n = 1,236; Norway, n = 483; Table 1).

Among those with available data on chemotherapy type, the majority received ABVD treatment (n = 1,793), and a fraction (n = 301) received BEACOPP-14 or eBEACOPP (Table 1). Patients with advanced-stage disease who were treated with BEACOPP were more often male and more often had involvement of bone marrow and/or other extranodal sites (stage IV) compared with those who had advanced-stage disease but were treated with six to eight cycles of ABVD (Data Supplement). More patients were diagnosed with advanced-stage disease in 2006 to 2013 than in the earlier inclusion period (2000 to 2005; Data Supplement). The median follow-up time was 9 years (range, 2.9 to 16.8 years).³¹ The 5-year OS was 95.2% (95% CI, 94.4% to 96.1%), and estimates were similar by country (Fig 1).

Relapse Risk in Clinical Subgroups

The overall 5-year progression/relapse risk was 13.4% (95% CI, 12.1% to 14.8%) from diagnosis, and estimates were similar by country (Data Supplement). For patients who reached the EFS24 and EFS60 milestones, 5-year relapse risks after the milestone and onward were 4.2% (95% CI, 3.8% to 4.6%) and 1.3% (95% CI, 1.0% to 1.6%), respectively (Fig 2). The 5-year relapse risk for patients with advanced-stage disease was twice as high as for patients with limited-stage disease from diagnosis, but the difference decreased substantially among patients who reached later EFS milestones and was minimal after EFS36 (advanced stage, 2.5% [95% CI, 2.1% to 2.9%] v limited stage, 2.0% [95% CI, 1.6% to 2.4%]) and after EFS60 (advanced stage, 1.5% [95% CI, 1.1% to 2.0%] v limited stage, 1.1% [95% CI, 0.7% to 1.6%]). Male patients and patients diagnosed between 2000 and 2005 had a higher 5-year relapse risk than female patients and patients diagnosed between 2006 and 2013, respectively (Fig 2).

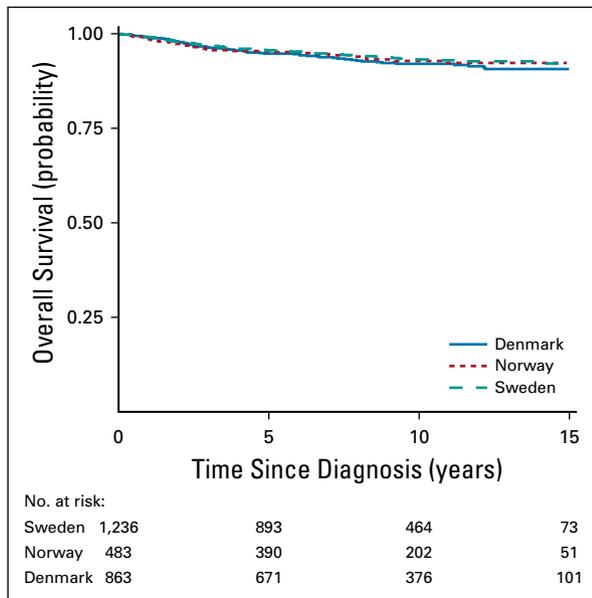


FIG 1. Overall survival curves of patients with classic Hodgkin lymphoma in Denmark, Sweden, and Norway estimated using the Kaplan-Meier method.

Relapse risks were similar for patients with advanced-stage disease who were treated with six to eight cycles of ABVD and those with advanced-stage disease who were treated with six to eight cycles of BEACOPP at all analyzed time points despite the fact that the BEACOPP-treated group displayed more high-risk features (Fig 2; Data Supplement). The 5-year relapse risk was similar for patients who were 18 to 34 or 35 to 49 years old at diagnosis, but, after EFS60, the group of patients age 35 to 49 years had a slightly higher risk of relapse (35 to 49 years, 2.3% [95% CI, 1.6% to 3.1%] v 18 to 34 years, 0.8% [95% CI, 0.1% to 1.2%]). Sensitivity analyses with respect to the imputed response evaluation data led to changes in the estimated relapse risk of less than 1% for the period between diagnosis and EFS12; the changes observed from EFS12 onward were negligible (Data Supplement).

Loss of Expectation of Lifetime

5y-RLEL was computed as an absolute measure of loss of lifetime in a 5-year period. Within the first 5 years post-diagnosis, patients with HL were expected to live 45 days (95% CI, 35 to 54 days) less than the background population (Fig 3). For patients who reached the EFS24 milestone, this difference was 13 days (95% CI, 7 to 20 days). For patients who reached the EFS60 milestone, the subsequent 5y-RLEL was 8 days (95% CI, 2 to 14 days). We observed that the impact of baseline high-risk features on the 5y-RLEL estimates decreased for patients in ongoing remission. As an example, 5y-RLEL estimates from diagnosis were 67 days (95% CI, 52 to 82 days) for patients with advanced-stage disease and 14 days (95% CI, 5 to 22 days) for patients with limited-stage disease, whereas

the corresponding estimates for patients who reached EFS24 were 23 days (95% CI, 13 to 34 days) for advanced-stage disease and 2 days (95% CI, -4 to 7 days) for limited-stage disease. The 5y-RLEL differences when patients were stratified by sex (female, 35 days [95% CI, 23 to 46 days] v male, 54 [95% CI, 39 to 68 days]), by diagnosis year (2000 to 2005, 46 days [95% CI, 31 to 60 days] v 2006 to 2013, 44 days [95% CI, 32 to 56 days]), by age (18 to 34 years, 39 days [95% CI, 29 to 50 days] v 35 to 49 years, 54 days [95% CI, 36 to 72 days]), and by treatment for advanced-stage patients (six to eight courses of ABVD, 45 days [95% CI, 29 to 62 days] v six to eight courses of BEACOPP, 67 days [95% CI, 35 to 99 days]) were less pronounced.

Multivariable models for the 5y-RLEL and relapse risk and an unrestricted loss in expectation of lifetime analysis showed similar results with respect to the effects of the different risk factors and confirmed the favorable disease outlook for patients who reached the EFS24 and EFS60 milestones (Figs 4 and 5; Data Supplement).

DISCUSSION

This study was based on patients with cHL who were treated in a real-world clinical setting and used population-wide registers from the Nordic countries. We focused exclusively on young patients, who are typically healthy and fit enough to receive curative-intent therapy, and found that outcomes were excellent with only a minimal relapse risk and a low restricted loss in expectation of lifetime for patients who reached EFS24. Interestingly, the effect on relapse risk of disease stage, one of the most widely recognized prognostic factors in cHL, disappeared over time and became negligible after EFS36. We believe that conclusions drawn from this study are of major importance to patients with cHL and their families as well as to health care providers who manage the disease and follow-up.

We observed a consistent low risk of relapse for patients with cHL who reached the EFS24 and, in particular, EFS60 milestones. Five-year relapse risks of 5% or lower were observed in nearly all subgroups of patients who reached EFS24, which suggests that those patients can be comforted and reassured that their future relapse risk is low. For patients with limited-stage disease, the loss in life expectancy after EFS24 within the next 5 years was nearly zero, which suggests that this group of cHL survivors are not at increased short-term risk of death compared with people of similar age and sex without cHL. The 5y-RLEL and 5-year relapse risk estimates were lower for patients diagnosed between 2006 and 2013 than for those diagnosed between 2000 and 2005. However, given the potential stage migration (Data Supplement), this effect should be considered in light of the use of more accurate staging methods that have led to more adequate treatment of some patients in addition to other general treatment improvements.³² The

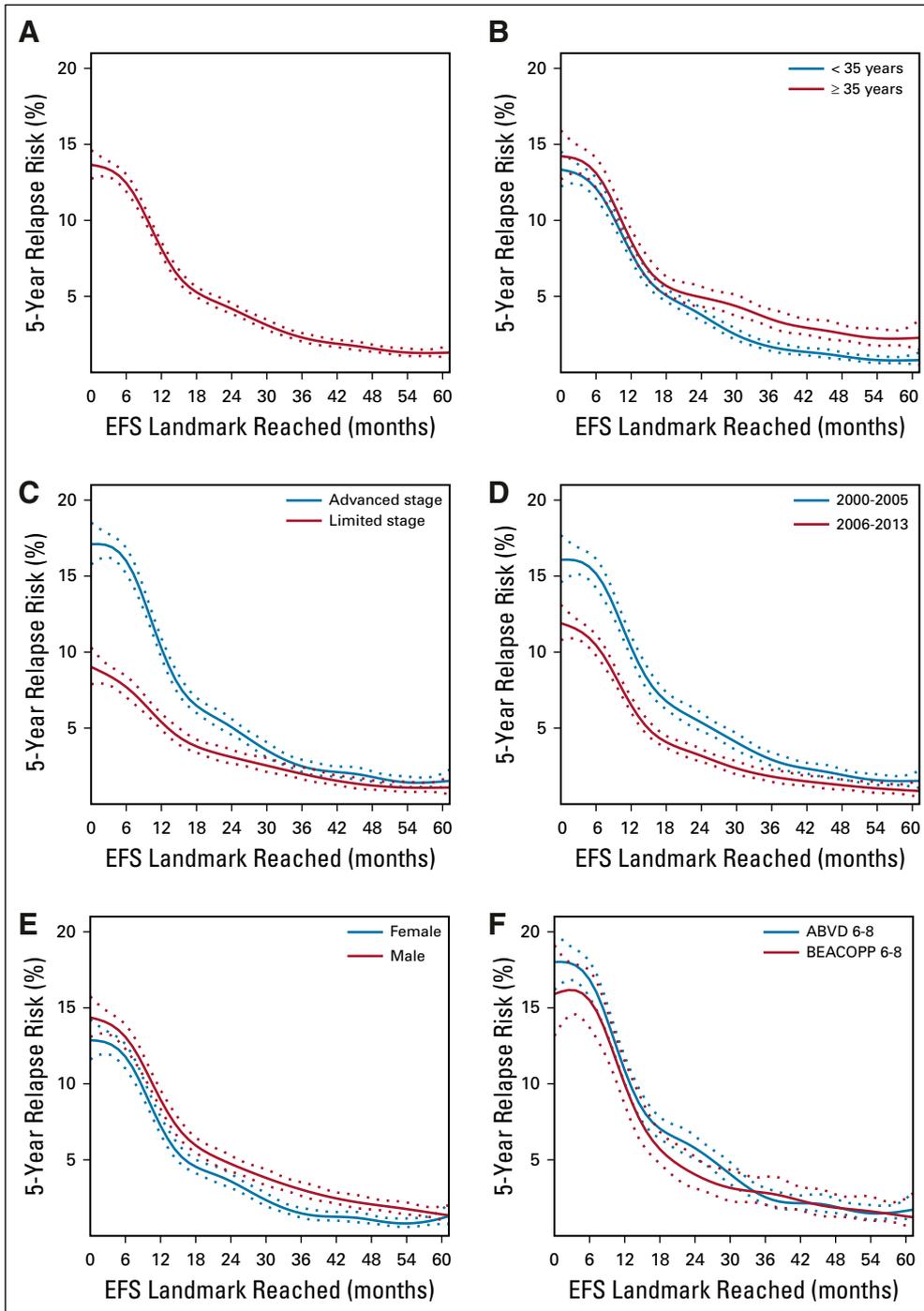


FIG 2. Estimated 5-year relapse risk conditional on reaching event free survival milestones. The x-axis represents the event-free survival (EFS) milestone reached, and the y-axis shows the estimated risk of a relapse in the 5 years from the EFS milestone onward. eg. In all patients, the 5-year relapse probability measured from diagnosis onward was 10%. The 5-year relapse risk of patients who reached 2 years of EFS was 3.6% and decreased to 1.2% for patients who reached 5 years of EFS. (A) The 5-year relapse risk estimates were calculated and stratified by (B) age at diagnosis, (C) stage, (D) calendar period of diagnostic year, and (E) sex, (F) treatment for advanced stage patients (six to eight cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine [ABVD] or bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone [BEACOPP]). Limited-stage was defined as Ann Arbor stage I or IIA; advanced stage, as Ann Arbor stage IIB, III, or IV.

large reduction in relapse risk and loss of expectation of lifetime observed already after EFS24 confirm that events mainly occur in the first 2 years after therapy. This is consistent with results from the study by Hapgood et al¹⁹ that involved a cohort of 1,402 patients with cHL from British Columbia, Canada. In that study, the 5-year relapse risk of 18.1% decreased to 5.6% for patients who reached EFS24. In general, the 5-year relapse risks tended to be lower in our study; most importantly, our 5-year relapse risk from the time of diagnosis was lower than that

reported by Hapgood et al¹⁹ (13.4% in this study v 18.1% in that of Hapgood et al¹⁹). This is likely partially explained by the inclusion in the study by Hapgood et al¹⁹ of elderly patients up to age 69 years at diagnosis, who had a higher relapse risk. Furthermore, Hapgood et al¹⁹ included unplanned treatments in their EFS definition, which we could not do because of limitations of our data. Finally, in this study, a limited number of patients were treated with BEACOPP, a treatment not used in the British Columbia series.¹⁹ A recent meta-analysis of clinical trials

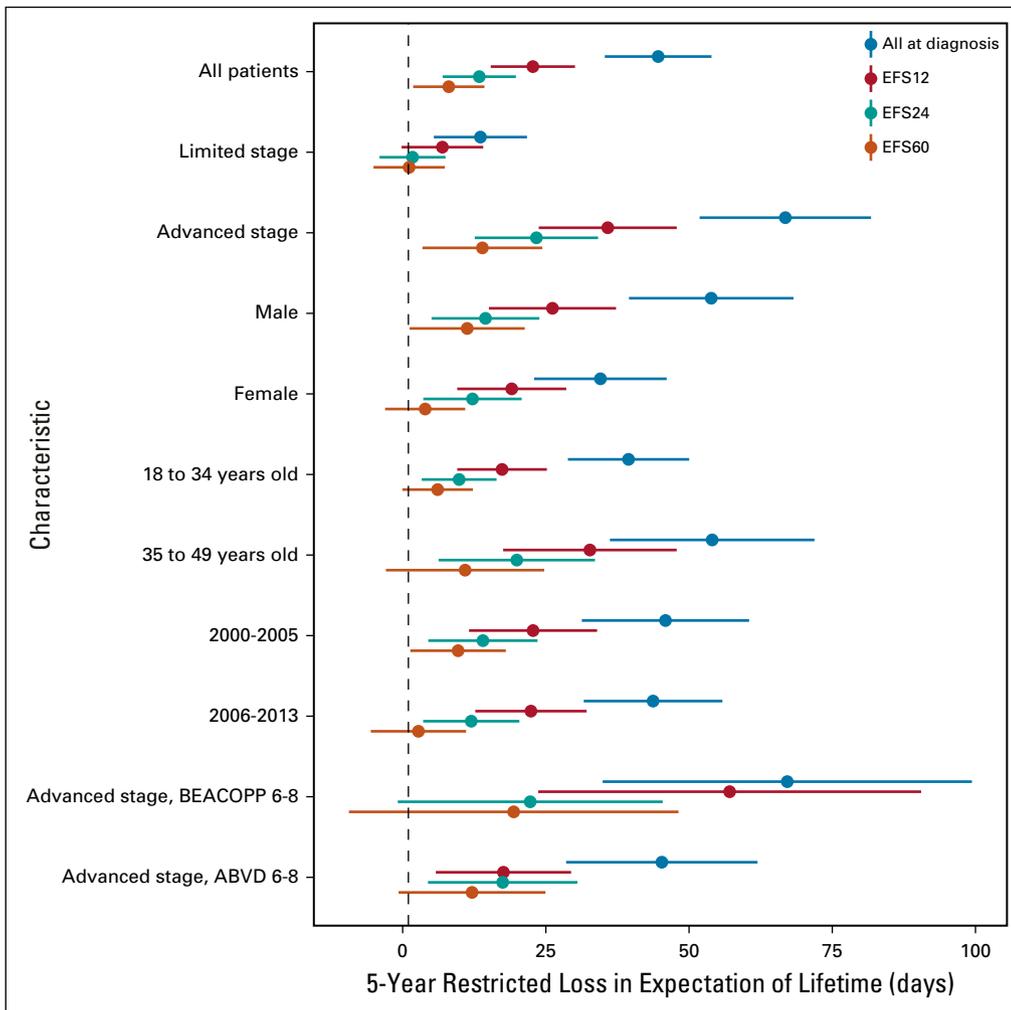


FIG 3. Estimated 5-year restricted loss of expectation of lifetime for all patients and conditional on reaching 12, 24, or 60 months event-free survival (EFS12, EFS24, and EFS60, respectively). The 5-year restricted loss of expectation of lifetime estimates were calculated stratified by stage, sex, age at diagnosis, calendar period of diagnostic year, and treatment for advanced stage patients (six to eight cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine [ABVD] or bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone [BEACOPP]). Limited-stage was defined as Ann Arbor stage I or IIA; advanced stage, as Ann Arbor stage IIB, III, or IV.

suggests a greatly reduced relapse risk as well as improved OS (although with limited follow-up time) for patients with advanced-stage disease who begin treatment with BEACOPP.³³

Of particular interest for patients and relatives is that our results and those of similar population-based studies^{18,19,27} show a very low mortality and relapse risk for young patients with cHL who are treated with contemporary treatments. This information is helpful for patients from a psychological perspective, and it allows them to plan their futures. Our study also included 301 patients treated with BEACOPP, which was established as one of the standard therapies for advanced-stage cHL after the results of the HD9 and HD11 trials.³⁴⁻³⁶ Although patient numbers are limited in this study, the results are in line with previous reports that showed the superior efficacy of BEACOPP on progression-free survival/EFS: relapse risks were similar for patients with advanced-stage disease treated with BEACOPP and ABVD in our series despite more high-risk features in the BEACOPP subgroup.

Results about relapse risk for patients in ongoing remission are relevant not only to patients but also to physicians who

manage cHL. Most patients respond to first-line chemotherapy and achieve complete remission, so there is a clinical need for relevant survivorship care. Many patients are routinely observed for several years in outpatient clinics, where detection of preclinical relapses and late toxicities is the focus. Survivorship programs are focusing more on screening for serious late toxicities in HL, such as secondary breast cancer and lung cancer^{37,38} and cardiovascular disease, as well as the impact on quality of life (eg, the impact of fatigue and sexual dysfunction).^{39,40} Our data support the concept that rational cHL survivorship programs should focus mainly on appropriate management of late toxicities rather than on screening for preclinical relapse in patients in complete remission. In particular, actively screening for relapse after EFS24 does not seem cost effective, because 5-year relapse risk is reduced to less than 5% for nearly all young patients with cHL. This is also supported by data that show that preclinical relapse detection using serial CT scans does not improve outcomes and that the majority of patients who experience relapse typically present with clinical symptoms outside pre-planned visits.⁴¹⁻⁴⁵

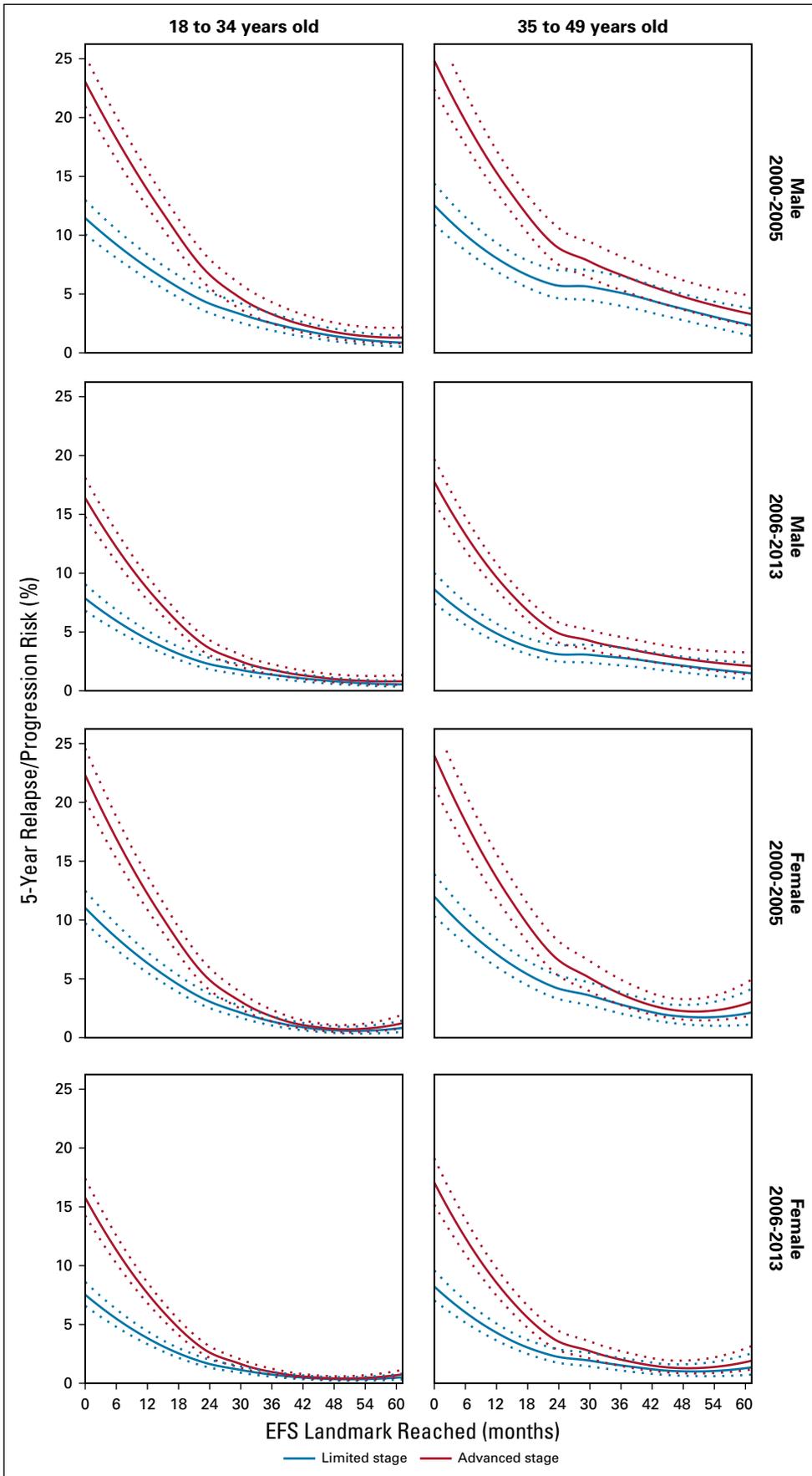


FIG 4. Estimated 5-year relapse risk conditional on reaching event-free survival (EFS) milestones obtained from a multivariable model that included sex, diagnosis year, age, and stage effects. The x-axis represents the EFS milestone reached, and the y-axis shows the estimated risk of a progression or relapse in the 5 years from the EFS milestone onward. Limited-stage was defined as Ann Arbor stage I or IIA; advanced-stage, as Ann Arbor stage IIB, III, or IV.

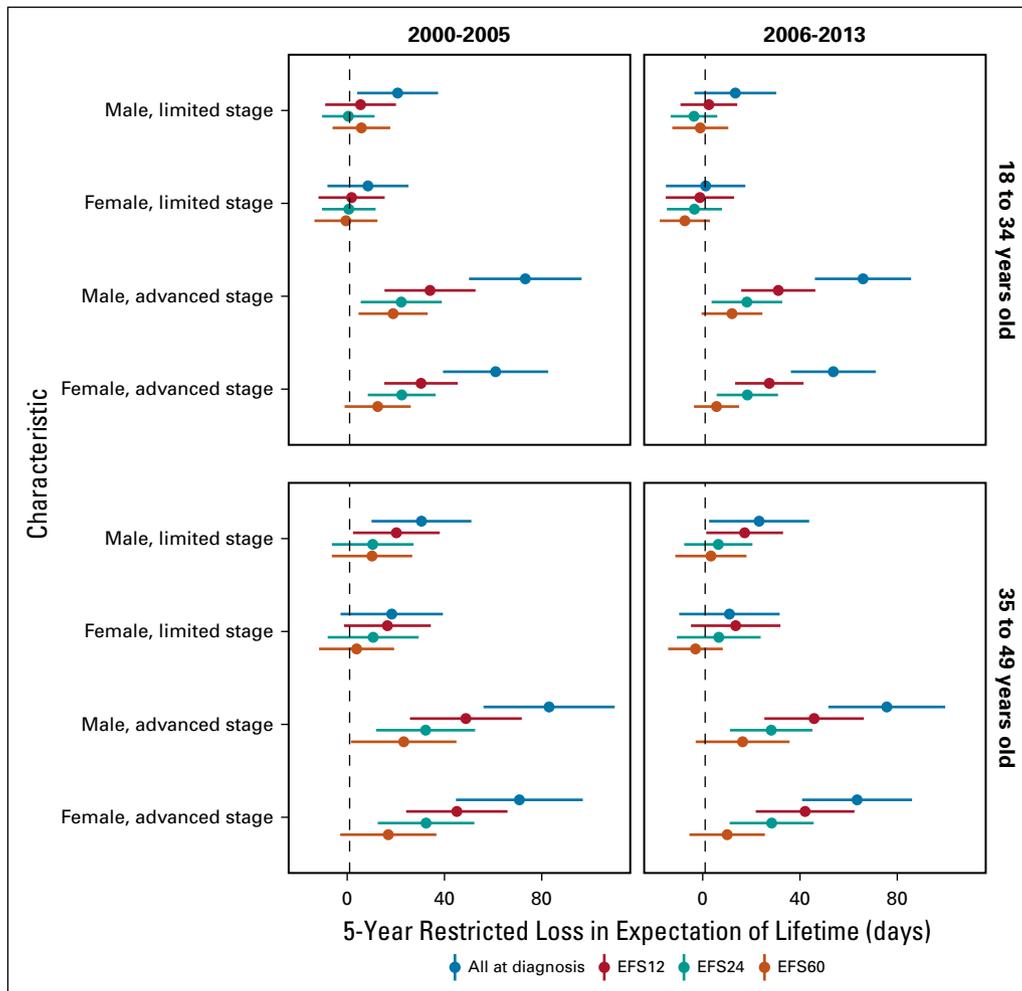


FIG 5. Estimated 5-year restricted loss of expectation of lifetime for all patients, and conditional on reaching 1-, 2-, or 5-year event-free survival (EFS12, EFS24, EFS60, respectively) obtained from a multivariable model that included sex, diagnosis year, calendar period of diagnostic year, age, and stage effects. Limited-stage was defined as Ann Arbor stage I or IIA; advanced stage, Ann Arbor stage IIB, III, or IV.

A strength of this study is the use of data from three population-based registers that implemented measures to safeguard against missing information. However, we cannot exclude that a limited number of relapses were missed, because we did not perform dedicated health record review for this study. By use of register data, some of the usual limitations of clinical trials, such as short follow-up^{4,46} and high levels of patient selection,⁴⁷ were avoided. Given the large number of patients, analyses stratified by different clinical subgroups were possible. By focusing on patients diagnosed after the year 2000, we minimized the influence of outdated treatments, in particular extended-field RT and obsolete chemotherapy regimens. Although we consider the inclusion of patients treated with BEACOPP a strength of this study, the lack of random assignment between ABVD and BEACOPP could result in confounding, so these results should be interpreted with that in mind. Furthermore, the reported analyses only describe the survival and relapse

risk, since we have no information on detrimental effects of cHL on health-related quality of life, such as fatigue or sexual and psychosocial health.⁴⁸ A final caveat of this study is that the median follow-up of 9 years, although long compared with clinical trials, does not enable us to evaluate the very long-term effects of contemporary treatments.

With the use of 5-year relapse risks and loss of life expectancy measures, we provide estimates of the prognosis conditioned on specific clinical characteristics and years in remission for patients with cHL who received contemporary treatments. The results are reassuring and indicate that patients with limited-stage disease who remain event free at 2 years after diagnosis have a future life expectancy close to that of HL-free individuals. In addition, in the majority of risk groups, the 5-year relapse risk was minimal after 2 years of EFS were reached, and this information should be considered when survivorship programs are planned.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

- Hodgkin: On some morbid appearances of the absorbent glands and spleen. *Med Chir Trans* 17:68-114, 1832
- Devita VT, Jr., Serpick AA, Carbone PP: Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann Intern Med* 73:881-895, 1970
- Evens AM, Hutchings M, Diehl V: Treatment of Hodgkin lymphoma: The past, present, and future. *Nat Clin Pract Oncol* 5:543-556, 2008
- Canellos GP, Rosenberg SA, Friedberg JW, et al: Treatment of Hodgkin lymphoma: A 50-year perspective. *J Clin Oncol* 32:163-168, 2014
- Anderson H, Deakin DP, Wagstaff J, et al: A randomised study of adjuvant chemotherapy after mantle radiotherapy in supradiaphragmatic Hodgkin's disease PS IA-IIb: A report from the Manchester lymphoma group. *Br J Cancer* 49:695-702, 1984
- Engert A, Plütschow A, Eich HT, et al: Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med* 363:640-642, 2010
- Aleman BMP, van den Belt-Dusebout AW, Klokmans WJ, et al: Long-term cause-specific mortality of patients treated for Hodgkin's disease. *J Clin Oncol* 21:3431-3439, 2003
- Borchmann P, Goergen H, Kobe C, et al: PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): Final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. *Lancet* 390:2790-2802, 2018
- André MPE, Girinsky T, Federico M, et al: Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: Final results of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol* 35:1786-1794, 2017
- Johnson P, Federico M, Kirkwood A, et al: Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med* 374:2419-2429, 2016
- Brusamolino E, Anselmo A, Klersy C, et al: The risk of acute leukemia in patients treated for Hodgkin's disease is significantly higher after [see binned modality programs than after chemotherapy alone and is correlated with the extent of radiotherapy and type and duration of chemotherapy: a case-co... *Haematologica* 83:812-823, 1998
- Cunningham J, Mauch P, Rosenthal DS, et al: Long-term complications of MOPP chemotherapy in patients with Hodgkin's disease. *Cancer Treat Rep* 66:1015-1022, 1982
- van Nimwegen FA, Ntentas G, Darby SC, et al: Risk of heart failure in survivors of Hodgkin lymphoma: Effects of cardiac exposure to radiation and anthracyclines. *Blood* 129:2257-2265, 2017
- van Leeuwen FE, Ng AK: Late sequelae in Hodgkin lymphoma survivors. *Hematol Oncol* 35:60-66, 2017
- von Tresckow B, Kreissl S, Goergen H, et al: Intensive treatment strategies in advanced-stage Hodgkin's lymphoma (HD9 and HD12): Analysis of long-term survival in two randomised trials. *Lancet Haematol* 5:e462-e473, 2018
- Eloranta S, Lambert PC, Sjöberg J, et al: Temporal trends in mortality from diseases of the circulatory system after treatment for Hodgkin lymphoma: A population-based cohort study in Sweden (1973 to 2006). *J Clin Oncol* 31:1435-1441, 2013
- Maraldo M V., Brodin NP, Aznar MC, et al: Estimated risk of cardiovascular disease and secondary cancers with modern highly conformal radiotherapy for early-stage mediastinal Hodgkin lymphoma. *Ann Oncol* 24:2113-2118, 2013
- Sjöberg J, Halthur C, Kristinsson SY, et al: Progress in Hodgkin lymphoma: A population-based study on patients diagnosed in Sweden from 1973-2009. *Blood* 119:990-996, 2012
- Hapgood G, Zheng Y, Sehn LH, et al: Evaluation of the risk of relapse in classical Hodgkin lymphoma at event-free survival time points and survival comparison with the general population in British Columbia. *J Clin Oncol* 34:2493-2500, 2016
- Arboe B, Josefsson P, Jørgensen J, et al: Danish National Lymphoma Registry. *Clin Epidemiol* 8:577-581, 2016
- Glimelius I, Ekberg S, Linderöth J, et al: Sick leave and disability pension in Hodgkin lymphoma survivors by stage, treatment, and follow-up time: A population-based comparative study. *J Cancer Surviv* 9:599-609, 2015
- Larsen IK, Småstuen M, Johannessen TB, et al: Data quality at the Cancer Registry of Norway: An overview of comparability, completeness, validity and timeliness. *Eur J Cancer* 45:1218-1231, 2009
- Arboe B, El-Galaly TC, Clausen MR, et al: The Danish National Lymphoma Registry: Coverage and data quality. *PLoS One* 11:e0157999, 2016
- Weibull CE, Eloranta S, Smedby KE, et al: Pregnancy and the risk of relapse in patients diagnosed with Hodgkin lymphoma. *J Clin Oncol* 34:337-344, 2016

25. Barlow L, Westergren K, Holmberg L, et al: The completeness of the Swedish Cancer Register: A sample survey for year 1998. *Acta Oncol* 48:27-33, 2009
26. Erichsen R, Lash TL, Hamilton-Dutoit SJ, et al: Existing data sources for clinical epidemiology: The Danish National Pathology Registry and Data Bank. *Clin Epidemiol* 2:51-56, 2010
27. Glimelius I, Ekberg S, Jerkeman M, et al: Long-term survival in young and middle-aged Hodgkin lymphoma patients in Sweden 1992-2009: Trends in cure proportions by clinical characteristics. *Am J Hematol* 90:1128-1134, 2015
28. Andersen PK, Perme MP: Pseudo-observations in survival analysis. *Stat Methods Med Res* 19:71-99, 2010
29. Royston P, Parmar MK: Restricted mean survival time: An alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. *BMC Med Res Methodol* 13:152, 2013
30. Andersen PK, Hansen MG, Klein JP: Regression analysis of restricted mean survival time based on pseudo-observations. *Lifetime Data Anal* 10:335-350, 2004
31. Schemper M, Smith TL: A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 17:343-346, 1996
32. Feinstein AR, Sosin DM, Wells CK: The Will Rogers phenomenon: Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 312:1604-1608, 1985
33. Skoetz N, Will A, Monsef I, et al: Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced-stage Hodgkin lymphoma. *Cochrane Database Syst Rev* 5:CD007941, 2017
34. Eichenauer DA, Aleman BMP, André M, et al: Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 29:iv19-iv29, 2018
35. Diehl V, Franklin J, Pfreundschuh M, et al: Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *N Engl J Med* 348:2386-2395, 2003
36. Eich HT, Diehl V, Görge H, et al: Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: Final analysis of the German Hodgkin Study Group HD11 trial. *J Clin Oncol* 28:4199-4206, 2010
37. Ng AK, Garber JE, Diller LR, et al: Prospective study of the efficacy of breast magnetic resonance imaging and mammographic screening in survivors of Hodgkin lymphoma. *J Clin Oncol* 31:2282-2288, 2013
38. Wattson DA, Hunink MGM, DiPiro PJ, et al: Low-dose chest computed tomography for lung cancer screening among Hodgkin lymphoma survivors: A cost-effectiveness analysis. *Int J Radiat Oncol Biol Phys* 90:344-353, 2014
39. Behringer K, Goergen H, Müller H, et al: Cancer-related fatigue in patients with and survivors of Hodgkin lymphoma: The impact on treatment outcome and social reintegration. *J Clin Oncol* 34:4329-4337, 2016
40. Kiserud CE, Schover LR, Dahl AA, et al: Do male lymphoma survivors have impaired sexual function? *J Clin Oncol* 27:6019-6026, 2009
41. Jakobsen LH, Hutchings M, de Nully Brown P, et al: No survival benefit associated with routine surveillance imaging for Hodgkin lymphoma in first remission: A Danish-Swedish population-based observational study. *Br J Haematol* 173:236-244, 2016
42. Dann EJ, Berkahn L, Mashlach T, et al: Hodgkin lymphoma patients in first remission: Routine positron emission tomography/computerized tomography imaging is not superior to clinical follow-up for patients with no residual mass. *Br J Haematol* 164:694-700, 2014
43. Pingali SR, Jewell SW, Havlat L, et al: Limited utility of routine surveillance imaging for classical Hodgkin lymphoma patients in first complete remission. *Cancer* 120:2122-2129, 2014
44. Bestawos A, Foltz L, Srour N, et al: Patients' and physicians' roles in detecting recurrent Hodgkin lymphoma following complete remission. *Ann Oncol* 24:1359-1363, 2013
45. El-Galaly TC, Mylam KJ, Bøgsted M, et al: Role of routine imaging in detecting recurrent lymphoma: A review of 258 patients with relapsed aggressive non-Hodgkin and Hodgkin lymphoma. *Am J Hematol* 89:575-580, 2014
46. Meyer RM: Limited-stage Hodgkin lymphoma: managing uncertainty. *J Clin Oncol* 32:1180-1182, 2014
47. Terschüren C, Gierer S, Brillant C, et al: Are patients with Hodgkin lymphoma and high-grade non-Hodgkin lymphoma in clinical therapy optimization protocols representative of these groups of patients in Germany? *Ann Oncol* 21:2045-2051, 2010
48. Linendoll N, Saunders T, Burns R, et al: Health-related quality of life in Hodgkin lymphoma: A systematic review. *Health Qual Life Outcomes* 14:114, 2016



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Relapse Risk and Loss of Lifetime After Modern Combined Modality Treatment of Young Patients With Hodgkin Lymphoma: A Nordic Lymphoma Epidemiology Group Study**

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