Long-term cardiac morbidity in adolescent and young adult survivors of classical Hodgkin lymphoma: the British Columbia experience

Kristin C. Marr,[1] Terry Tang,[2] Jonathan Simkin,[2] Jewon Kim,[3] Andrea C. Lo,[4] Diego Villa,[5] Alina S. Gerrie,[5] Greg Hapgood,[5°] David W. Scott,[5] Laurie H. Sehn,[5] Ryan R Woods[2,6] and Kerry J. Savage[5]

[1]Division of Pediatric Hematology/Oncology, BC Children's Hospital, University of British Columbia, Vancouver, British Columbia; [2]Department of Population Health Sciences, BC Cancer Research Centre, Data and Analytics, BC Cancer, Vancouver, British Columbia; [3]Department of Population Health Sciences, BC Cancer Research Centre, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario; [4]Division of Radiation Oncology, BC Cancer, University of British Columbia, Vancouver, British Columbia; [5]BC Cancer's Centre for Lymphoid Cancer and Department of Medicine, University of British Columbia, Vancouver, British Columbia and [6]Department of Population Health Sciences, BC Cancer Research Centre, School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada

°Current address: Department of Haematology, Princess Alexandra Hospital and School of Medicine, University of Queensland, Brisbane, Queensland, Australia

Correspondence: K.C. Marr
Kristin.marr@cw.bc.ca

K.J. Savage
ksavage@bccancer.bc.ca

Received: May 21, 2025.
Accepted: October 1, 2025.
Early view: October 9, 2025.

https://doi.org/10.3324/haematol.2025.288058

©2026 Ferrata Storti Foundation
Published under a CC BY-NC license

Abstract

Adolescents and young adults (AYA) with classical Hodgkin lymphoma (cHL) have excellent survival outcomes. However, the late effects of treatment, including cardiovascular disease (CVD), can impact long-term disease-free morbidity and mortality. Using population-level administrative data, we evaluated rates of CVD in 2-year AYA survivors of cHL, aged 16-39 years, treated with ABVD or equivalent chemotherapy, with or without radiotherapy (RT). With a median follow up of 17 years (range 2.3-29 years), risk of CVD was 2.9-fold higher relative to controls, with a 5.2-fold risk of heart failure (HF) and 2.4-fold risk of ischemic heart disease (IHD). Risk of HF was associated with anthracycline-containing chemotherapy regimens alone or with combined modality therapy; whereas higher IHD risk was identified only in those treated with RT. At 20 years after the most recent cHL diagnosis or relapse, the cumulative incidence of HF was 4.3% in cases *versus* 0.8% in controls, and for IHD was 8.3% in cases *versus* 2.8% in controls. Treatment after 2005 using a PET scan guided approach reduced the overall use of RT (56.0% before 2005 *vs*. 14.9% 2005 and after), and was associated with a lower 15-year cumulative incidence of IHD (before 2005: 3.4% [95%CI: 1.8-5.1%]; 2005 and after: 0.7% [95%CI: 0-1.7%]) with the latter era comparable to controls; (1.6% [95%CI: 1.3-1.9%]). cHL survivors had increased 20-year cumulative mortality above that of age-matched controls (5.0% *vs*. 2.0%). These results can inform surveillance strategies, screening guidelines, and recommendations for risk factor modification for AYA cHL survivors.

Introduction

Classical Hodgkin lymphoma (cHL) is one of the most commonly diagnosed malignancies in adolescents and young adults (AYA) with a peak incidence between the age of 15 and 34 years.[1,2] ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) was first introduced 50 years ago[3] and has been a standard therapy since that time. With 5-year overall survival over 90%,[4,5] there is a significant population of long-term survivors. The late effects of chemotherapy and radiation therapy (RT) used in cHL are well documented in children and adolescents with

significant burden of chronic health disease compared to healthy peers.[6]

The incidence of late morbidity secondary to treatment rises rapidly ten years after diagnosis; by 20 years after diagnosis, the mortality due to secondary causes surpasses that due to relapse of cHL.[6] In all ages, cardiovascular disease (CVD) has been reported as the third leading cause of mortality in cHL survivors,[7,8] with a 19-fold increased risk of CVD-related mortality in AYA relative to controls.[9] Development of CVD secondary to exposure to anthracycline chemotherapy or mediastinal RT is one of the better characterized late effects in pediatric cohorts, with reports of 16-fold increased risk of heart failure (HF),[10] 5-fold increased risk of ischemic heart disease (IHD) in those exposed to 15 Gy of cardiac radiation or more,[11] and a 5-fold increase in cardiac-related mortality[12] compared to age-and sex-matched controls. In recognition of these risks, life-long surveillance for cardiac disease is recommended in survivors of childhood cancer, with risk-based guidelines to guide modality and frequency of screening.[13]

The risk of CVD late effects for young adults is less well characterized. Existing studies support the view that young adults treated for cHL in earlier eras between 1965 and 1995 have an excess risk of CVD[14] and a higher mortality,[9] similar to pediatric patients, including a 25-year cumulative risk of congestive HF as high as 33%.[14] The latent onset of late effects makes it challenging to extrapolate the impact of historic treatments to modern clinical practice. Given the excellent survival outcomes in cHL, treatment protocols have evolved in the more modern era to reduce treatment intensity, and particularly RT field and dose, without compromising outcomes.[15-18] However, how this has impacted overall CVD risk in this age group remains unknown.

In British Columbia (BC), treatment guideline modifications across the province have included reduced exposure to RT through use of smaller volumes using involved-field RT (IFRT) as of 1997, and use of involved-nodal RT (INRT) less than or equal to 5cm as of 2001.[19] In 2005, PET-guided elimination of RT was introduced for advanced stage cHL patients in a complete metabolic response on PET scan following 6 cycles of ABVD chemotherapy, including those with bulky disease,[20] and similarly, for limited stage disease, RT is only given in those with a positive scan after 2 cycles.[21] We are only now reaching the early time points at which we can measure the impact of reduced-intensity strategies. Of concern, studies of other late effects, such as secondary cancers, over sequential treatment eras in young adult survivors of HL suggest that these risks may not have decreased as anticipated.[22]

Using population-based administrative data, we evaluated the incidence of CVD (HF and IHD) in a cohort of AYA cHL survivors with a focus on young adults, treated using ABVD or equivalent chemotherapy with or without RT in BC.

Methods

Adolescents and young adult patients with cHL newly diagnosed between 1992-2013 to ensure sufficient follow-up for late effects and treated with curative intent with ABVD or equivalent therapy (e.g., COPP (or MOPP)/ABV) in BC, Canada, were identified in the BC Cancer Lymphoid Cancer Database. AYA was defined as ages 16-39 years aligning with the National Cancer Institute definition[23] and commonly used standards from publications in cancer survivors.[24,25] Cases must have survived to an index date defined as two years from the most recent cHL event (primary diagnosis or, if applicable, most recent relapse) and have had a minimum follow-up of one year beyond their index date. Index date of two years from the most recent cHL event was selected based on our prior study describing a very low rate of recurrence in those patients who were event-free at two years.[5] Limited stage disease was defined as stage IA, IB (included as of January 1, 2000, and later) or IIA, non-bulky disease (bulk being defined as any mass size ≥10cm); all others had advanced stage disease. Standard treatment guidelines for this era in BC have been published previously with ABVD or equivalent chemotherapy used during this time period.[5] A PET-adapted approach was introduced in 2005 for limited stage[21] and advanced stage[20] to limit use of RT. Cases were linked to the provincial BC Cancer Radiation Therapy database to identify the types and doses of radiation treatments received.

A control population was derived from the BC Ministry of Health (MOH) Chronic Disease Registry (CDR). The CDR is a population-based registry that captures the chronic disease status of every individual in BC annually. The CDR uses the following administrative health databases to identify chronic conditions (e.g., HF): physician claims through Medical Services Plan (MSP) Payment Information; medical drug claims submitted to Pharmacare; and hospital admission records through Discharge Abstract Database. Chronic diseases are identified based on validated case algorithms adapted from the Canadian Chronic Disease Surveillance System[26] (*Online Supplementary Table S1*). The date of the first event that contributed to the case definition captured in the CDR was used as date of onset of the chronic disease outcome. A 10:1 individually-matched control population was identified from the CDR based on age, sex, and health authority region on the index date of the matched case. Controls were excluded if they had a pre-existing invasive malignancy or *in situ* bladder malignancy (as determined by the BC Cancer Registry), HF, or IHD prior to the study window.

Both the cHL and control cohorts were further linked to the CDR to determine the cumulative incidence CVD over the study follow-up period. Individual outcomes were collected from the index date of the matched case until December 31, 2018, or until an individual was censored due to loss to follow-up or death. Individuals no longer registered with

MSP for a period of two years or more during the study period, or with a gap of less than two years during the study period but who had less than two years of follow-up time after regaining MSP registration, were censored as lost to follow-up due to the potential for misidentification of an outcome event.

Descriptive statistics were used to characterize the study population. The cumulative incidence approach and Gray's test were used to derive and compare estimates of CVD outcomes at 15 and 20 years of follow-up. A competing risk regression analysis was used to evaluate relative risk (RR) of primary outcomes in survivors relative to age-, sex- and region-matched controls. A multivariable analysis of RR was performed adjusting for patient factors (stage and age at diagnosis, and era of treatment before 2005, or 2005 or later), treatment-related factors (anthracycline cumulative dose, mediastinal RT), and the presence of pre-existing cardiovascular risk conditions captured in the CDR (limited to hypertension [HTN], diabetes mellitus [DM], or chronic obstructive pulmonary disease [COPD] as a surrogate for smoking). To capture only pre-existing CV risk conditions, the date of onset of the CV risk condition must have been prior to that of the primary outcome in the CDR for both cases and controls. A sensitivity analysis was performed, including only patients who had received front-line treatment and their matched controls. In all analyses, $P<0.05$ was considered statistically significant. This study was approved through the University of British Columbia/BC Cancer Research Ethics Board.

Results

With a median follow-up time of 16.9 years (range 2.3-29) from the date of diagnosis of cHL or most recent relapse, 806 AYA 2-year survivors were eligible for analysis and compared against age-, sex- and region-matched controls (N=8,058). A total of 602 (75%) patients were 2-year survivors from the initial diagnosis and 204 (25%) were 2-year survivors from relapse, 47% of whom received autologous stem cell transplantation. The proportion of limited and advanced stage disease at diagnosis was 34% and 66%, respectively, and 51% were male (Table 1). At the end of the study period, the age of survivors ranged from 22 to 67 years (median 44 years). In total, 487 patients (39.6%) received mediastinal RT. Fifty-two percent received a cumulative anthracycline dose ≥300 mg/m^2. Of patients with limited stage disease, the median dose of anthracyclines was 100 mg/m^2 and 53.3% received mediastinal RT. For those with advanced stage disease, the median dose was 300 mg/m^2 and 32.7% received mediastinal RT.

At 20 years after the most recent cHL event, survivors had an increased risk of CVD with a cumulative incidence of 10.1% (95%CI: 7.2-12.9%) compared to 3.2% (95%CI: 2.7-3.7%) among controls (Figure 1). Survivors had an increased incidence of all-cause mortality, with 20-year cumulative mortality of 5.0% (95%CI: 3.2-7.0%) relative to 2.0% (95%CI: 1.7-2.4%) in controls (Figure 1B).

The cumulative incidence of both HF and IHD was significantly higher at 20 years after the most recent cHL event in all cases relative to controls (HF: 4.3% in cases *vs*. 0.8% in controls; IHD: 8.3% in cases *vs*. 2.8% in controls) (Figure 2, *Online Supplementary Table S2*). Compared to chemotherapy alone, combined modality treatment had a numerically higher incidence of HF (20-year incidence 3.3% chemotherapy alone *vs*. 5.4% combined modality; $P=0.28$) and a trend was observed for incidence of IHD (20-year incidence 6.0% chemotherapy alone *vs*. 10.7% combined modality; $P=0.08$) at 20 years. The incidence of IHD was not significantly increased at 20 years in those treated with chemotherapy alone without RT, relative to controls. The incidence of HF among those with limited stage disease (2.0%) and advanced disease (5.2%) were both higher than among controls (0.8%). IHD incidence was similarly higher among those with limited (6.7%) and advanced (9.2%) disease compared to the control group (2.8%). Notably, in comparison to controls, a higher incidence of CVD was also seen in those diagnosed at age 30 years or older (18.5%, 95%CI: 12.1-24.8%) compared to those aged under 30 years (5.5%, 95%CI: 2.9-8.0%) and controls (3.2%, 95%CI: 2.7-3.7%) which was most notable for IHD (20 year incidence ≥ 30 years 15.3% [95%CI: 9.3-21.4%]; < 30 years 4.4% [95%CI: 2.1-6.7%]) (Figure 3E) but also elevated for HF (7.4%, 95%CI: 3.1-11.6%) (Figure 3A). The incidence of HF was increased in both males and females, relative to controls (5.9%, 95%CI: 2.7-9.2%; 2.5%, 95%CI: 0.6-4.5%; and 0.8%, 95%CI: 0.5-1.0%; respectively) (Figure 3B). However, only males had a statistically significant increase in incidence of IHD relative to both females and controls (13.1%, 95%CI: 8.6-17.6%; 2.9%, 95%CI: 0.5-5.3%; and 2.8%, 95%CI: 2.4-3.3%; respectively) (Figure 3E).

The incidence of IHD has decreased with a more modern therapy approach, a management era in which RT use was significantly reduced (56.0% before 2005 and 14.9% in 2005 or after). At a shorter time-point of available follow-up, the 15-year cumulative incidence of IHD was 0.7% (95%CI: 0-1.7%) for those treated after 2005, and 3.4% (95%CI: 1.8-5.1%) for those treated prior to 2005, compared with 1.6% (95%CI: 1.3-1.9%) in controls (Figure 3F). However, the 15-year cumulative incidence of HF was the same before and after 2005 (1.7% for both), but was higher overall than the 0.4% in controls (Figure 3C).

Overall, cHL survivors had a 2.9-fold increased risk of CVD relative to controls (Table 2). The relative risk was greatest for onset of HF (RR=5.18, 95%CI: 3.09-8.66) compared with the RR estimated for IHD (RR=2.38, 95%CI: 1.73, 3.29) (Table 2). Independent co-variates that were associated with increased risk of HF included age >30 years at diagnosis and the presence of cardiac comorbidities. Treatment with chemotherapy alone or with combined therapy with RT was significantly associated with risk of HF compared to

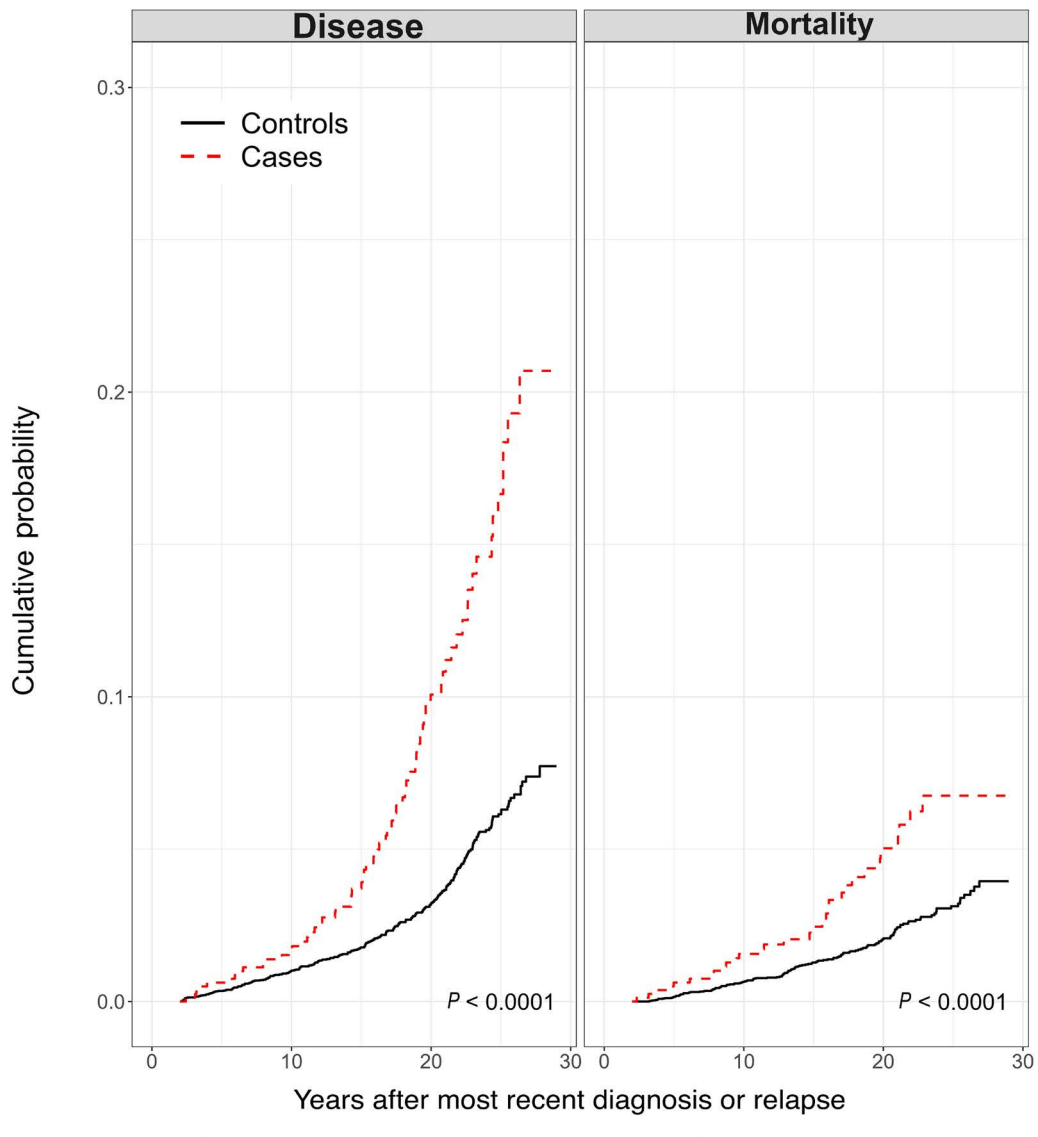
Table 1. Classical Hodgkin lymphoma case cohort characteristics at diagnosis and treatment history.

	N	%
Total	806	100
Period of diagnosis		
Prior to July 1, 2005	484	60.0
After July 1, 2005	322	40.0
Sex		
Male	408	50.6
Female	398	49.4
Age at diagnosis of HL		
16-29 years	527	65.4
≥ 30 years	279	34.6
Diagnosis		
Nodular sclerosing	675	83.7
Mixed cellularity	55	6.8
Lymphocyte rich	9	1.1
Lymphocyte deficient	4	0.5
Not Otherwise Specified	63	7.8
Ann Arbor stage		
I	54	6.7
II	496	61.5
III	156	19.4
IV	99	12.3
Not available	1	0.1
B symptoms		
Yes	330	40.9
No	476	59.1
Bulk ≥10 cm		
Yes	244	30.3
No	555	68.9
Not available	7	0.9
Stage group		
Limited	272	33.7
Advanced	532	66.0
Not available	1	0.1
IPS score group (advanced stage group only)		
Low (0-3)	371	89.0
High (4-7)	46	11.0
Cumulative anthracycline dose (front-line therapy)		
1-299 mg/m^2	366	45.4
300 mg/m^2	361	44.8
>300 mg/m^2	63	7.8
Mediastinal RT		
No	487	60.4
Yes	319	39.6
RT dose		
0 Gy	487	60.4
≤ 35 Gy	273	33.9
> 35 Gy	46	5.7
Mediastinal radiotherapy		
Limited stage		
No	127	46.7
Yes	145	53.3
Advanced stage		
No	358	67.3
Yes	174	32.7
Mediastinal RT by period of diagnosis		
Prior to July 1, 2005		
No	213	44.0
Yes	271	56.0
As of July 1, 2005		
No	274	85.1
Yes	48	14.9
Relapse		
Yes	204	25.3
No	602	74.7
Mediastinal RT in patients treated for recurrence		
No	117	57.4
Yes	87	42.6
Autologous stem cell transplantation		
Yes	95	11.8
No	711	74.7
Diagnosis of cardiac comorbidity after cHL treatment		
Diabetes mellitus	69	8.4
Hypertension	103	12.7
COPD	19	2.2

cHL: classical Hodgkin lymphoma; COPD: chronic obstructive pulmonary disease; IPS: International Prognostic Score; RT: radiotherapy.

controls (Table 3). Of treatment-related factors, significantly increased risk of IHD was identified only in patients who had mediastinal RT compared to patients treated with chemotherapy alone, with RR 3.6 (95%CI: 2.44-5.31) *versus* 1.42 (95%CI: 0.84-2.40), respectively. In multi-regression analysis, the era of treatment was no longer a significant risk factor when adjusted for RT exposure (Table 3). Cumulative dose of anthracycline did not significantly impact RR of IHD (Table 3). Other risk factors for IHD included male sex, age over 30 years at diagnosis, and diagnosis with diabetes and hypertension (Table 3).

In this population of patients that had survived more than two years from their most recent treatment, 204 had undergone treatment for relapsed disease and received additional therapy, including 47% that received autologous stem cell transplantation. However, the frequency of mediastinal RT was only slightly higher for those treated for relapsed disease (42.6%) relative to the frequency in those who received it only as part of their primary therapy (38.5%). Furthermore, the exposure to anthracycline was unchanged. A sensitivity analysis was performed for survivors who had received front-line treatment only (Table 2,



Numbers at risk by years since most recent diagnosis or relapse of cHL

Years	0	7	12	15	17	20
Cases	806	777	589	452	376	252
Controls	8,058	7,836	5,985	4,670	4,010	2,875

Figure 1. Cumulative incidence of combined cardiovascular disease and cumulative mortality in 2-year survivors of classical Hodgkin lymphoma relative to age-, sex-, and region-matched controls. cHL: classical Hodgkin lymphoma.

Online Supplementary Table S3). The results demonstrate a similar pattern of associated CV risks to that observed in the full cohort of patients, with a small reduction in the strength of the association. The relative risk remained greatest for onset of HF (RR=4.09, 95%CI: 2.14-7.84) compared with the RR estimated for IHD (RR=1.80, 95%CI: 1.16-2.78). Similar to findings from the full cohort analysis, factors of male sex, age over 30 years at diagnosis, and diagnosis with diabetes and hypertension were all associated with an increased CV risk.

Discussion

Adolescents and young adults with cHL have excellent disease-specific long-term survival outcomes but their therapy may be associated with late treatment-related morbidity and mortality. Given the young population at risk, the impact of treatment decades later remains a significant concern. Using population-level administrative data, we demonstrate that AYA survivors of cHL have an excess risk of late onset cardiac disease, with 5.2-fold increased risk of HF and 2.4-fold increased risk of IHD relative to matched population controls, contributing to the increase in overall mortality in long-term survivors of cHL.

Cardiotoxicity is a well-recognized late effect of therapy for pediatric cancer.[13,27,28] Extensive data from pediatric cohorts demonstrate an excess risk of dose-dependent anthracycline-related cardiomyopathy, with a synergistic impact of combined modality therapy.[13] Mediastinal RT confers additional risk of IHD and valvular disease. The Childhood Cancer Survivor Study, a large multi-institutional study of self-reported outcomes between 5-year survivors and siblings, reported that the rate of grade 3-5 CVD in pediatric HL survivors at 30 years is 11.1%,[6] with a hazard ratio of 6.8 for HF and 12.2 for myocardial infarction, relative to siblings.[11] The pediatric DAL-HD trial consortium reported a 25-year incidence of 14% for all cardiac disease and reported a dose-dependent relationship between the dose of RT used and rates of CVD.[29] Female sex and younger age at treatment are commonly reported independent risk factors for HF in the pediatric age cohort,[13,30] whereas male sex is reported as a risk factor for IHD, as also observed in our study.[30]

Compared to the pediatric age group, there are far less data regarding the risk of CVD in AYA survivors with a history of cHL, especially those treated as young adults. We demonstrate that age 30 years or over at diagnosis is associated with higher risk of CV disease, highlighting that age-specific outcomes are essential to ensure appropriate guidelines are in place. Van Nimwegen *et al*. previously reported outcomes of 2,524 AYA 5-year survivors aged 50 years or over treated during 1965-1995.[31] In this cohort, 81% had received mediastinal RT, and of those, 30% had also received anthracycline-based chemotherapy. They found a 6.8-fold increased standardized incidence ratio (SIR) of HF and 3.2-fold increased SIR of coronary heart disease. Both mediastinal radiation and exposure to anthracyclines

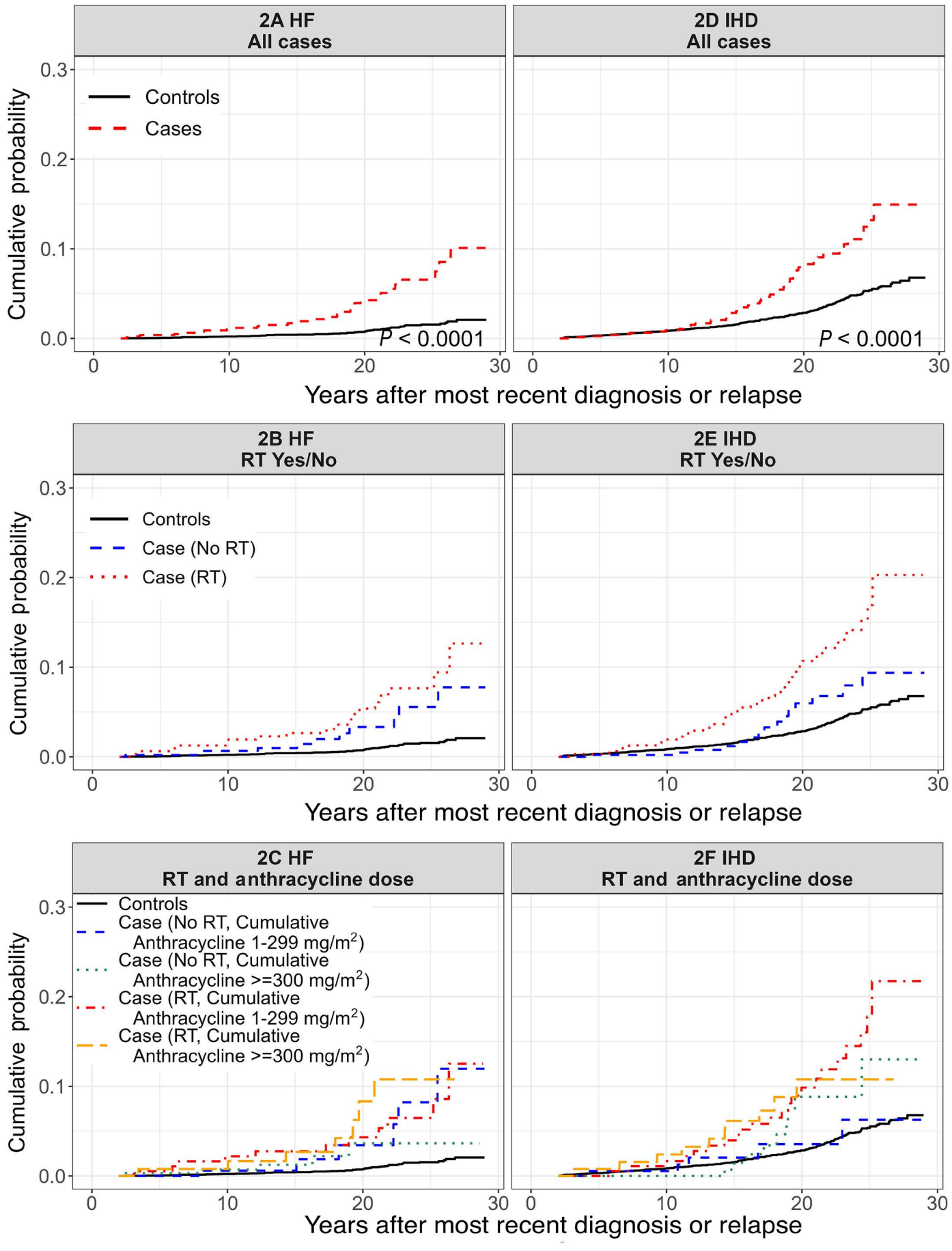


Figure 2. Cumulative incidence of heart failure and ischemic heart disease in all cases and by treatment exposure in 2-year survivors of classical Hodgkin lymphoma relative to age-, sex-, and region-matched controls. HF: heart failure; IHD: ischemic heart disease; RT: radiotherapy.

were associated with an increased risk of CVD,[31] with a dose-response and synergistic impact demonstrated for risk of HF; both mean left ventricle dose of RT, and escalating dose of anthracyclines.[32] At 40 years after cHL, the cumulative incidence of CVD was 49.5%, and in those treated with mediastinal RT, the 40-year incidence was 54.6% compared to 24.7% in those treated with chemotherapy alone.[31] The 25-year cumulative incidence of HF in those treated with anthracyclines and RT >21 Gy was 32.9%, and was 13.3% for those treated with RT alone.[32] Interestingly, they identified a significant increase in SIR for those treated at a younger age, in contrast to our results. Maraldo *et al.*

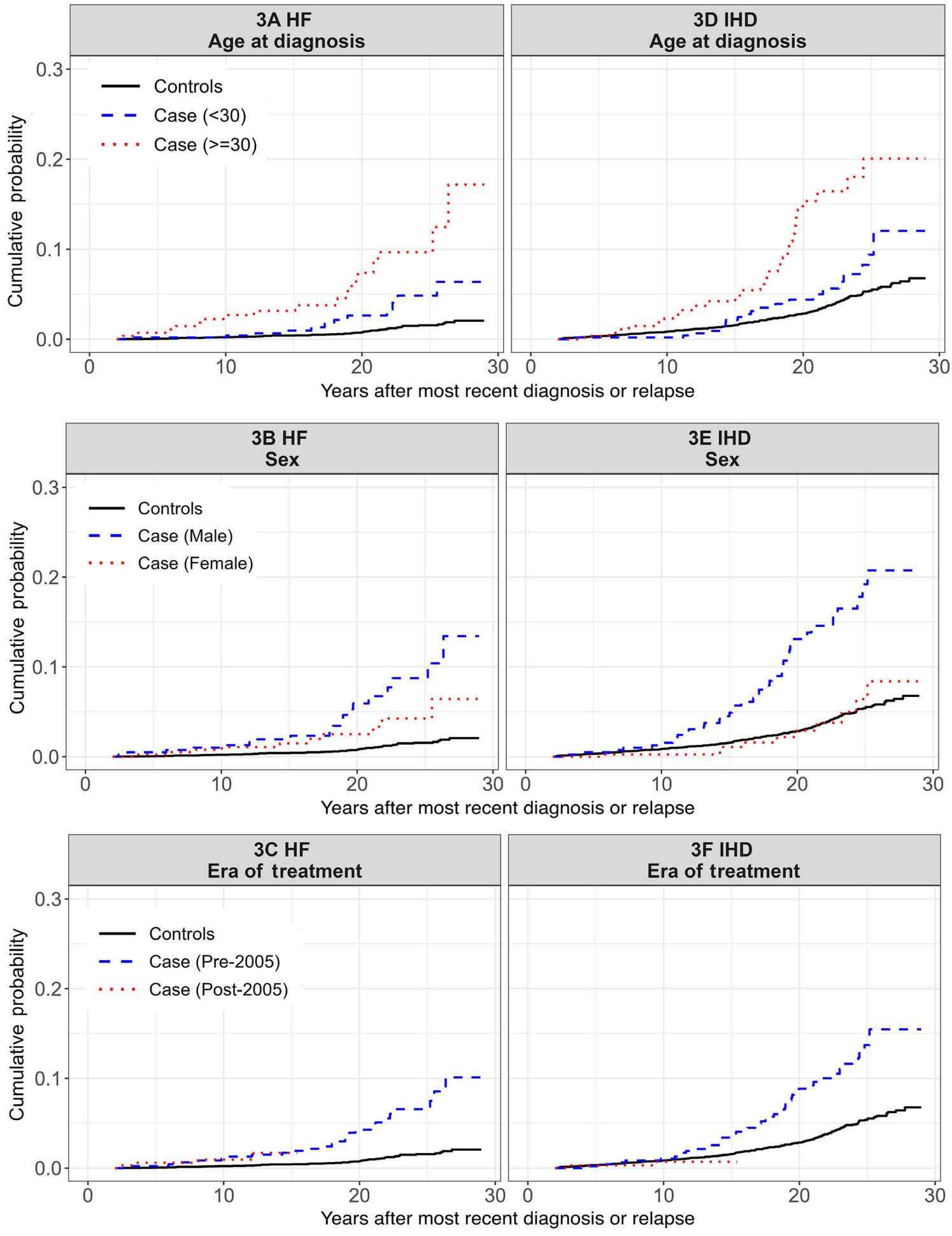


Figure 3. Cumulative incidence of heart failure and ischemic heart disease by sub-group in 2-year survivors of classical Hodgkin lymphoma relative to age-, sex-, and region-matched controls. HF: heart failure; IHD: ischemic heart disease.

Table 2. Relative risk of cardiovascular disease in adolescent and young adult survivors with classical Hodgkin lymphoma *versus* age-, sex- and region-matched population controls.

	All cases			Patients treated with front-line therapy only		
	RR	95%CI	*P*	RR	95%CI	*P*
cHL survivors	2.88	2.19-3.78	<0.001	2.26	1.57-3.23	<0.001
Male	1.65	1.30-2.08	<0.001	2.01	1.51-2.69	<0.001
Advanced stage	0.98	0.78-1.24	0.884	0.91	0.69-1.19	0.492
Era of treatment after 2005	1.00	0.70-1.44	0.981	0.96	0.62-1.48	0.840
Age >30 years at diagnosis	2.27	1.79-2.86	<0.001	2.25	1.70-2.98	<0.001
Diabetes	2.33	1.63-3.34	<0.001	3.07	2.04-4.62	<0.001
Hypertension	2.82	2.11-3.78	<0.001	2.51	1.74-3.61	<0.001
COPD	1.87	1.04-3.36	0.037	1.70	0.81-3.57	0.164

cHL: classical Hodgkin lymphoma; CI: Confidence Interval; COPD: chronic obstructive pulmonary disease; RR: relative risk.

Table 3. Multi-regression analysis of relative risk of heart failure and ischemic heart disease in adolescent and young adult survivors with classical Hodgkin lymphoma *versus* age-, sex- and region-matched population controls.

	HF			IHD		
	RR	95%CI	*P*	RR	95%CI	*P*
Radiation and anthracycline <300 mg/m^2	5.77	2.49-13.40	<0.001	4.00	2.54-6.32	<0.001
Radiation and anthracycline >300 mg/m^2	6.40	2.29-17.92	<0.001	2.84	1.39-5.80	0.004
No radiation and anthracycline <300 mg/m^2	5.46	2.28-13.08	<0.001	1.23	0.53-2.87	0.624
No radiation and anthracycline >300 mg/m^2	3.79	1.48-9.70	0.005	1.57	0.82-3.01	0.176
Male	1.11	0.70-1.78	0.649	1.91	1.46-2.50	<0.001
Advanced stage	1.19	0.70-2.02	0.514	1.01	0.77-1.33	0.916
Era of treatment after January 1, 2005	1.00	0.48-2.07	0.996	1.13	0.75-1.70	0.544
Age >30 years at diagnosis	2.40	1.47-3.90	<0.001	2.31	1.77-3.00	<0.001
Diabetes	3.21	1.69-6.12	<0.001	2.07	1.35-3.16	<0.001
Hypertension	3.06	1.77-5.32	<0.001	2.87	2.05-4.03	<0.001
COPD	5.87	2.69-12.79	<0.001	0.80	0.29-2.22	0.663

CI: Confidence Interval; COPD: chronic obstructive pulmonary disease; HF: heart failure; IHD: ischemic heart disease; RR: relative risk.

evaluated cardiac outcomes in 6,039 patients treated on sequential LYSA HL clinical trials (all ages, median age 29 years), treated between 1964 and 2009.[33] Only mean heart dose of RT and cumulative dose of anthracyclines had a statistically significant effect on risk of CVD. The 25-year cumulative incidence of IHD and HF were 6.0% and 7.1%, respectively. Aleman *et al.*[7] reported on survivors of HL, 95% of whom were treated with RT. The 25-year cumulative incidence of HF was 6.8% for those treated with RT alone, and 7.9% if treated with combined modality with anthracycline-based chemotherapy. The 30-year cumulative incidence of myocardial infarction was 12.9% for those treated with mediastinal RT.

These prior studies primarily reflect treatment eras when there was a high rate of RT use and wider RT fields such as mantle and extended-field RT. Given the evolution of treatment, our study provides important data on the impact of modern therapy approaches on the rate of CVD with the use

of reduced volumes and dose of RT, as well as a PET-guided approach to reduce RT that has been used since July 2005. The rate of mediastinal RT use in our cohort was only 40% overall, considerably lower than the range of 80-95% reported in other studies of CV outcomes in HL survivors.[7,31,34] Furthermore, from 2005 onwards, RT use dropped from 56% to 15% following a treatment policy change recommending integration of a PET scan to guide RT in both advanced and limited stage cHL.[20,21] For patients treated with a risk-adapted approach after 2005, we found a reduced incidence of IHD, which was similar to the incidence in population controls. In multi-regression analysis, the era of treatment was no longer a significant risk factor when adjusted for RT exposure, suggesting that the change in radiation use was an important factor in reducing the risk of IHD. Although longer follow-up is needed, these data suggest that reduction of RT in the management of HL has impacted CVD risk. Similar trends have been documented in pediatric populations, with a trend of reduced rates of both IHD and HF in more recent clinical trials with decreased radiation exposure and with the use of cardio-protectants such as dexrazoxane.[30] Evaluation of late effects of therapy is challenged by the long latency, and because patients are discharged from follow-up well before the onset of late effects. The use of population-level administrative data enabled us to capture clinically significant CVD in a cHL survivor cohort that had been discharged from oncologic follow-up, and for whom the association with previous cancer therapy might not have been recognized. However, our study was limited to the data available in the chronic disease registry and dependent on surrogate standardized case definitions derived for disease surveillance purposes to identify endpoints rather than clinical diagnostic measures. Data regarding other forms of cardiac disease such as valvular disease, and additional cardiac risk factors, such as family history, obesity and dyslipidemia, were not available, and COPD was used as a surrogate for smoking. Furthermore, given the young age of survivors of cHL, young patients are often very mobile, moving out of the province for personal, educational, or occupational opportunities. Our analysis can only follow patients using provincial health data for the duration of their follow-up within their time living in BC and those that emigrate from the region are thus lost to follow-up.

Despite these limitations, similar to prior studies, we found an increased risk of CVD starting ten years after completion of treatment, long after patients have typically been discharged from follow-up care. The risk was particularly striking in males and those aged 30 years or over. Our data support the view that there is a need for informed risk counseling at the time of discharge from oncological care and clear communication to primary care practitioners regarding the potential long-term risks. Patients require counseling regarding their risk of late effects, including written treatment summaries and detailed guides for surveillance and for secondary prevention strategies through management of modifiable risk factors.[35] For risk of CVD, this would include lifestyle counseling and monitoring for hypertension, diabetes and smoking, which we confirmed are independent risk factors for onset of cardiac disease in survivors of cHL. Given that follow-up is transferred to primary care providers, it is essential that this is communicated to both patient and practitioner. A recent comparison of US survivorship guidelines in lymphoma suggests a wide variation in screening approaches when comparing pediatric and adult recommendations, as well as across guidelines.[35] Pediatric guidelines recommend lifelong surveillance with 2-D echocardiogram for early identification of asymptomatic heart disease to prevent or delay disease progression, with screening every 2-5 years based on risk stratification by anthracycline dose and/or mediastinal RT exposure.[13] No guidelines have been published for AYA and adult survivors, with only expert opinion advocating for surveillance.[36] Our data would also support the extension of echocardiogram surveillance beyond the pediatric age group. Trials are underway in pediatric cancer survivors to evaluate if cardiac remodeling with agents such as carvedilol may reverse or delay progression and symptomatic disease.[37]

The landscape of treatment of cHL is rapidly changing with the integration of novel therapies into upfront treatment. Brentuximab vedotin (BV)-AVD demonstrated improved PFS and OS compared to ABVD in stage 3/4 cHL[38] and, more recently, nivolumab with AVD demonstrated superior progression-free survival compared to BV-AVD.[39] These therapies have improved the cure rates of front-line therapy, reducing the need for RT in subsequent salvage therapy, which likely will further impact CV risk. However, anthracycline exposure will remain, and patients with advanced stage disease will continue to receive at least a cumulative doxorubicin dose of 300 mg/m^2. Furthermore, immune checkpoint inhibitors have recently been associated with an increased risk of CVD by worsening atherosclerosis, further highlighting the need for long-term data on CVD with newer therapies.[40] Regardless of this, our data further support the need for refined surveillance strategies, screening guidelines, recommendations for risk factor modification, and counseling for AYA cHL survivors.

Disclosures

LS reports consultancy/honoraria from Abbvie, Acerta, Amgen, Apbiologix, AstraZeneca, Celgene, Chugai, Gilead, Incyte, Janssen, Kite, Karyopharm, Lundbeck, Merck, Morphosys, Roche/Genentech, Sandoz, Seattle Genetics, Servier, Takeda, Teva, TG Therapeutics, and Verastem, and research funding from Roche/Genentech and Teva. DWS reports consultancy from Abbvie, AstraZeneca, GenMab, Roche, and Veracyte, research funding from Roche/Genentech, and is an inventor on patents describing the use of gene expression profiling for subtyping aggressive B-cell lymphomas. DV reports honoraria and advisory board from Abbvie, Janssen, Kite/Gilead, AstraZeneca, Roche, BeiGene, BMS/Celgene, Merck, Zetagen, Eli Lilly and Kyowa Kirin, and research funding to the insti-

tution from Roche and Astra Zeneca. ASG reports honoraria from Abbvie, AstraZeneca, Janssen, Beigene, and Lilly, and research funding to the institution from Abbvie, AstraZeneca, Janssen, Lilly, and Beigene. ACL reports consultancy for Need. KJS reports consultancy/honoraria from BMS, Seagen/Pfizer, and Roche, Data Monitoring Committee for Regeneron, and Steering Committee for Corvus. All of the other authors have no conflicts of interest to disclose.

Contributions

KCM, RRW, ACL and KJS planned the study; RRW, DV, ASG, DWS, JH, LHS, ACL and KJS provided data; KCM, RRW, JS, KJS, ACL and TT performed the research; KCM, RRW, JS, KJS, JK and TT performed data analysis; KCM, RRW and KJS wrote the manuscript; RRW, DV, ASG, DWS, JH, LHS and ACL reviewed the manuscript.

Data-sharing statement

The data that support the findings of this study are available on request from the corresponding authors (KCM, KJS). The data are not publicly available due to restrictions, including data that could compromise the privacy of research participants. Access to data provided by the Data Stewards is subject to approval but can be requested for research projects through the Data Stewards or their designated service providers. The following data sets were used in this study: BC Chronic Disease Registry, BC Cancer Registry, BC Cancer Radiotherapy database. All inferences, opinions, and conclusions drawn in this publication are those of the author(s), and do not reflect the opinions or policies of the Data Steward(s). This Data was provisioned under Information Sharing Plan (ISP) 16-118.

References

1. Bazzeh F, Rihani R, Howard S, Sultan I. Comparing adult and pediatric Hodgkin lymphoma in the Surveillance, Epidemiology and End Results Program, 1988-2005: an analysis of 21,734 cases. Leuk Lymphoma. 2010;51(12):2198-2207.
2. Gatta G, Zigon G, Capocaccia R, et al. Survival of European children and young adults with cancer diagnosed 1995-2002. Eur J Cancer. 2009;45(6):992-1005.
3. Bonadonna G, Zucali R, Monfardini S, de Lena M, Uslenghi C. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. Cancer. 1975;36(1):252-259.
4. Marr KC, Connors JM, Savage KJ, Goddard KJ, Deyell RJ. ABVD chemotherapy with reduced radiation therapy rates in children, adolescents and young adults with all stages of Hodgkin lymphoma. Ann Oncol. 2017;28(4):849-854.
5. 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. 2016;34(21):2493-2500.
6. Castellino SM, Geiger AM, Mertens AC, et al. Morbidity and mortality in long-term survivors of Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study. Blood. 2011;117(6):1806-1816.
7. Aleman BMP, Van Den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood. 2007;109(5):1878-1886.
8. Matasar MJ, Ford JS, Riedel ER, Salz T, Oeffinger KC, Straus DJ. Late morbidity and mortality in patients with Hodgkin's lymphoma treated during adulthood. J Natl Cancer Inst. 2015;107(4):djv018.
9. Bhuller KS, Zhang Y, Li D, et al. Late mortality, secondary malignancy and hospitalisation in teenage and young adult survivors of Hodgkin lymphoma: report of the Childhood/Adolescent/Young Adult Cancer Survivors Research Program and the BC Cancer Agency Centre for Lymphoid Cancer. Br J Haematol. 2016;172(5):757-768.
10. Armstrong GT, Oeffinger KC, Chen Y, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. J Clin Oncol. 2013;31(29):3673-3680.
11. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the childhood cancer survivor study cohort. BMJ. 2009;339:b4606.
12. Tukenova M, Guibout C, Oberlin O, et al. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. J Clin Oncol. 2010;28(8):1308-1315.
13. Ehrhardt MJ, Leerink JM, Mulder RL, et al. Systematic review and updated recommendations for cardiomyopathy surveillance for survivors of childhood, adolescent, and young adult cancer from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. 2023;24(3):e108-e120.
14. 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. 2017;129(16):2257-2265.
15. Johnson PWM, Radford JA, Cullen MH, et al. Comparison of ABVD and alternating or hybrid multidrug regimens for the treatment of advanced Hodgkin's lymphoma: results of the United Kingdom Lymphoma Group LY09 trial (ISRCTN97144519). J Clin Oncol. 2005;23(36):9208-9218.
16. Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med. 2015;372(17):1598-1607.
17. Meyer RM, Gospodarowicz MK, Connors JM, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. J Clin Oncol. 2005;23(21):4634-4642.
18. Hoskin PJ, Lowry L, Horwich A, et al. Randomized comparison of the Stanford V regimen and ABVD in the treatment of advanced Hodgkin's lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. J Clin Oncol. 2009;27(32):5390-5396.
19. Campbell BA, Voss N, Pickles T, et al. Involved-nodal radiation therapy as a component of combination therapy for limited-stage Hodgkin's lymphoma: a question of field size. J Clin Oncol. 2008;26(32):5170-5174.
20. Kim JL, Villa D, Tonseth RP, et al. Long-term follow-up of bulky

classic Hodgkin lymphoma managed with ABVD and PET-guided RT demonstrates excellent outcomes in PET-negative cases. Br J Haematol. 2025;206(1):167-171.
21. Villa D, Sehn LH, Aquino-Parsons C, et al. Interim PET-directed therapy in limited-stage Hodgkin lymphoma initially treated with ABVD. Haematologica. 2018;103(12):e590-e593.
22. Schaapveld M, Aleman BMP, van Eggermond AM, et al. Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. N Engl J of Med. 2015;373(26):2499-2511.
23. National Cancer Institute. SEER Cancer Stat Facts: cancer among adolescents and young adults (AYAs). https://seer.cancer.gov/statfacts/html/aya.html Accessed June 1, 2024.
24. Chao C, Xu L, Bhatia S, et al. Cardiovascular disease risk profiles in survivors of adolescent and young adult (AYA) cancer: the Kaiser Permanente AYA Cancer Survivors Study. J Clin Oncol. 2016;34(14):1626-1633.
25. Bright CJ, Reulen RC, Winter DL, et al. Risk of subsequent primary neoplasms in survivors of adolescent and young adult cancer (Teenage and Young Adult Cancer Survivor Study): a population-based, cohort study. Lancet Oncol. 2019;20(4):531-545.
26. Lix LM, Ayles J, Bartholomew S, et al. The Canadian Chronic Disease Surveillance System: a model for collaborative surveillance. Int J Popul Data Sci. 2018;3(3):433.
27. Lipshultz SE, Adams MJ, Colan SD, et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions: a scientific statement from the American Heart Association. Circulation. 2013;128(17):1927-1955.
28. Armenian SH, Armstrong GT, Aune G, et al. Cardiovascular disease in survivors of childhood cancer: insights into epidemiology, pathophysiology, and prevention. J Clin Oncol. 2018;36(21):2135-2144.
29. Schellong G, Riepenhausen M, Bruch C, et al. Late valvular and other cardiac diseases after different doses of mediastinal radiotherapy for Hodgkin disease in children and adolescents: report from the longitudinal GPOH follow-up project of the German-Austrian DAL-HD studies. Pediatr Blood Cancer. 2010;55(6):1145-1152.
30. Lo AC, Liu A, Liu Q, et al. Late cardiac toxic effects associated with treatment protocols for Hodgkin lymphoma in children. JAMA Netw Open. 2024;7(1):e2351062.
31. Van Nimwegen FA, Schaapveld M, Janus CPM, et al. Cardiovascular disease after Hodgkin lymphoma treatment 40-year disease risk. JAMA Intern Med. 2015;175(6):1007-1017.
32. 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. 2017;129(16):2257-2265.
33. Maraldo MV, Giusti F, Vogelius IR, et al. Cardiovascular disease after treatment for Hodgkin's lymphoma: an analysis of nine collaborative EORTC-LYSA trials. Lancet Haematol. 2015;2(11):e492-e502.
34. Myrehaug S, Pintilie M, Tsang R, et al. Cardiac morbidity following modern treatment for Hodgkin lymphoma: supra-additive cardiotoxicity of doxorubicin and radiation therapy. Leuk Lymphoma. 2008;49(8):1486-1493.
35. Valcarcel B, Savage KJ, Link BK, et al. Comparison of survivorship care guidelines for patients with lymphoma: recommendations for harmonization and future research agenda. JCO Oncol Pract. 2025;21(6):801-812.
36. Ng AK. Current survivorship recommendations for patients with Hodgkin lymphoma: focus on late effects. Hematology. 2014;2014(1):488-494.
37. Armenian SH, Hudson MM, Chen MH, et al. Rationale and design of the Children's Oncology Group (COG) study ALTE1621: a randomized, placebo-controlled trial to determine if low-dose carvedilol can prevent anthracycline-related left ventricular remodeling in childhood cancer survivors at high risk for developing heart failure. BMC Cardiovasc Disord. 2016;16(1):187.
38. Ansell SM, Radford J, Connors JM, et al. Overall survival with brentuximab vedotin in stage III or IV Hodgkin's lymphoma. N Engl J Med. 2022;387(4):310-320.
39. Herrera AF, LeBlanc ML, Castellino SM, et al. SWOG S1826, a randomized study of nivolumab(N)-AVD versus brentuximab vedotin(BV)-AVD in advanced stage (AS) classic Hodgkin lymphoma (HL). J Clin Oncol. 2023;41(17_suppl):LBA4.
40. Barcia Durán JG, Das D, Gildea M, et al. Immune checkpoint landscape of human atherosclerosis and influence of cardiometabolic factors. Nat Cardiovasc Res. 2024;3(12):1482-1502.