Cause-Specific Mortality in a Cohort of 1,435 Patients With Hodgkin Lymphoma Treated Between 1985 and 2014: A Nationwide Chilean Cohort Study

Maria Elena Cabrera, MD, PhD[1]; Monica Civallero, PhD[2]; Yana Stepanishyna, MD[3]; Lea Derio, BSN[4]; Tetiana Skrypets, MD, PhD[5]; Vivianne Lois, MD[6]; Valeska Vega, MD[7]; Susana Calderon, MD[8]; Hernán Rojas, MD[9]; Alvaro Pizarro, MD[10]; M. Gabriela Mendoza, MD[11]; Monica Romero, MD[12]; Christine Rojas, MD[13]; Jacqueline Oliva, MD[14]; Marvila Intriago, MD[15]; Bernardita Rojas, MD[16]; Luana Conte, PhD[17]; Luigi Marcheselli, BSc[18]; and Massimo Federico, MD, PhD[2]

DOI https://doi.org/10.1200/GO-24-00344

ABSTRACT

PURPOSE Hodgkin lymphoma (HL) is classified as the first malignancy to be cured by a combination of chemotherapy and radiotherapy. However, the life expectancy of HL survivors is hampered by the occurrence of late adverse events, including second malignant neoplasms (SMNs) and cardiovascular diseases (CVDs).

PATIENTS AND METHODS We investigated the causes of death in a cohort of 1,435 patients over age 15 years treated at 18 different public cancer centers in Chile.

RESULTS After a median follow-up of 19 years (0-37), the 5-year overall survival improved from 64% in the cohort 1985-1994 to 81% in the cohort 2009-2014 (P < .001). HL was the main cause of death in the first 10 years after treatment, whereas SMN and CVD risk peaked 10-15 years and remained raised for 30 years or longer. Cumulative incidence of deaths (CIDs) due to SMNs resulted significantly higher in patients treated with cyclophosphamide, vincristine, procarbazine, prednisone (MOPP)/MOPP-like regimens over doxorubicin, bleomycin, vinblastine, dacarbazine. CIDs due to CVDs increased from 0.4 to 4.1 at 5 and 20 years, respectively.

CONCLUSION HL survivors continue to have a reduced life expectancy due to an increased risk of dying of SMNs and/or CVDs, although it was lower among patients treated in the most recent calendar period studied (2002-2014).

ACCOMPANYING CONTENT

Appendix

Accepted March 25, 2025
Published May 5, 2025

JCO Global Oncol 11:e2400344

INTRODUCTION

Classic Hodgkin lymphoma (cHL) is the first advanced malignancy to be cured by a combination of chemotherapy (CT) and radiotherapy (RT).[1-3] Although the treatment of cHL has been one of the major successes in the fight against cancer, the cure has come at a price because the treatment itself has been shown to increase the risk of subsequent second malignant neoplasms (SMNs) and cardiovascular diseases (CVDs).[4-14] Overall, adverse effects can be seen long after treatment, even 40 years later, and can translate into excess mortality in patients with Hodgkin lymphoma (HL) cured of their disease. However, only a few studies have thus far assessed cause-specific mortality beyond 20 years and quantified to what extent such morbidity translates into long-term excess mortality in patients with HL.[1,6,7,9,12-14]

In this study, we investigated the outcome of a large cohort of patients with cHL treated in Chile between 1985 and 2014. Our research originates from a Latin American country and includes cases from across the nation without exclusions. It spans a period when extended RT was routinely administered, even for advanced stages, a practice that has since shifted toward more selective use of CT and RT, addressing the impact of these now-outdated treatment techniques. This study complements well a Dutch study conducted by Aleman and colleagues dealing with long-term cause-specific mortality of patients treated for HL,[15] offering region-specific data to refine and validate follow-up guidelines. It may also help other countries to benefit from our finding and improve treatment practices for HL, given that only few studies dealing with the outcome of patients with HL in Latin America have been published so far.[16,17]

Here we present the results of long-term, cause-specific mortality, including HL progression, treatment-related infections, SMNs, and CVDs.

PATIENTS AND METHODS

Eligible patients for this report were over age 15 years, treated between 1985 and 2014 at 18 different public cancer

CONTEXT

Key Objective
Hodgkin lymphoma (HL) survivors continue to have a reduced life expectancy due to an increased risk of dying of second malignant neoplasms (SMNs) or of cardiovascular diseases (CVDs).

Knowledge Generated
The present study confirms that HL survivors continue to have a reduced life expectancy compared with the general population due to an increased risk of dying of SMNs or of CVDs. Awareness of the increased risk remains crucial; risk-reduction strategies are welcome to lessen the impact of late adverse events on HL survivors.

Relevance
It is expected that current treatment practice will end up with a smaller number of SMNs and CVDs in the next future.

centers in Chile belonging to the network of Adult Cancer Program, and registered in a prospective database located at the Cancer Unit of the Ministry of Health in Santiago, Chile. In 1985, the National Cancer Program began registration at the national level. Cases had adequate tissue biopsy specimens for diagnosis and available clinical data, including baseline information on disease staging, laboratory parameters at diagnosis, treatment regimens received, and follow-up. All stages and all subtypes of HL were included. In summary, the protocols were from 1985 to 1994: cyclophosphamide, vincristine, procarbazine, prednisone (C-MOPP) three to six cycles + 40 Gy extended-field RT (EFRT; 40 Gy mantle and inverted Y); from 1995 to 1999: mitoxantrone, vincristine, vinblastine, prednisone (NOVP)/C-MOPP/doxorubicin, bleomycin, and vinblastine (ABV) three to six cycles + 40 Gy EFRT; and from 2000 to 2014: doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) three to six cycles + 30 Gy involved-field RT.

The study was done in compliance with the Declaration of Helsinki and approved by research ethics committees and institutional review boards at each participating institution. All patients provided written informed consent before study entry.

The primary aim of the study was to analyze causes of death, the principal end point being overall survival (OS), measured from the date of diagnosis until death from any cause or the date of the last known contact (April 30, 2023) for living patients.

The cause of death was taken from Civil Registry Death Certificates, filed by the physician who assisted the patient or the one who last saw him/her, and stored at the Department of Statistics and Health Information (Departamento de Estadisticas e Información en Salud) of the Ministry of Health.

Survival curves were calculated with the Kaplan-Meier method, and time-to-event distributions were compared with the log-rank test (univariable regression). Cox models were used to investigate the association between survival outcomes, and covariates with hazard ratios (HRs) with 95% CIs were used as summary measure. Cumulative incidence functions were estimated by Fine-Gray methods. All reported tests were two-sided, and a *P* value of .05 was considered to indicate moderate strength of evidence against the null hypothesis. *P* values were not adjusted for multiple comparisons. Statistical analyses were performed using SPSS (version 29.0).

RESULTS

Patient Characteristics

Between 1985 and 2014, 1,435 patients were registered and treated at the network centers. Patient characteristics are summarized in Table 1. The median age was 38 years (range, 15-86), with a slight male predominance (54.5%). According to histology, 18 patients (1.3%) were nodular lymphocyte–predominant, 67 (4.7%) lymphocyte-rich, 618 (43.1%) nodular sclerosis, 629 (43.9%) mixed cellularity, 100 (7%) lymphocyte-depleted, and two (0.1%) unclassified. Systemic B symptoms were present in 69% of patients. According to disease extension, 592 (41.3%) and 843 (58.7%) patients were classified as stage I-II and III-IV, respectively.

Patients received treatment according to the protocols in use at any given time. Information on initial treatment with CT was available in all but two patients, whereas information on initial RT was available in 1,306 patients (91%). Table 2 shows the cause of death of 687 patients. Among the 1,306 patients with full information on initial therapy, 25 (1.7%) were treated with RT alone, 597 (45.7%) with CT and RT, and 684 (52.4%) with CT alone. Moreover, information on RT was lacking for 127 additional patients who received CT. Overall, 139 patients (9.7%) received C-MOPP and 81 (5.6%) received NOVP (these two regimens were mainly used in the period 1985-1998). Thereafter, 928 patients (64.7%) were treated with ABVD; C-MOPP alternating with ABV was delivered to 258 patients (18%), and bleomycin, etoposide,

TABLE 1. Baseline Characteristics of 1,435 Patients Treated With Hodgkin Lymphoma

Characteristic	Patients	No. (%)
Age, years, median (range)	1,435	38 (15-86)
Male, No. (%)	1,435	781 (54.4)
Histology, No. (%)	1,435	
NLPHL		18 (1.3)
Lymphocyte-rich		67 (4.7)
Nodular sclerosis		618 (43.1)
Mixed cellularity		629 (43.9)
Lymphocyte-depleted		100 (7)
Unclassified		2 (0.1)
B symptoms, No. (%)	1,435	
No		450 (31)
Yes		985 (69)
Extranodal sites, No. (%)	1,435	332 (23)
Bone marrow		277 (19.3)
Lung		185 (12.9)
Liver		114 (8)
Bone		74 (5)
GI		4 (0.3)
Nervous central system		2 (0.1)
Stage, No. (%)	1,435	
I-II		592 (41.3)
III-IV		843 (58.7)
Therapy first line, No. (%)	1,433	
ABVD		926 (63.9)
C-MOPP		139 (9.5)
C-MOPP/ABV		258 (19)
NOVP + RT		72 (5)
NOVP		9 (0.6)
RT alone		25 (1.7)
BEACOPP		4 (0.3)
RT, No. (%)	1,435	
No		684 (48)
Yes		622 (43)
Unknown		129 (9)
Response to therapy, No. (%)	1,411	
CR		1,008 (71.4)
PR		253 (17.9)
PD		150 (10.6)
Therapy second line, No. (%)	252	
ESHAP		220 (87.3)
ICE		5 (2)
Other		27 (10.7)
First relapse, No. (%)	1,008	207 (20.7)
Therapy first relapse, No. (%)	252	
ESHAP		220 (87)
MOPP/MOPP-ABV		25 (10)
Other		7 (3)
Response to therapy (first relapse), No. (%)	372	
CR		196 (52)
PR		79 (21)
PD		97 (26)
Second relapse, No. (%)	104	47 (3.2)
Therapy second relapse	122	
CHT		46 (38)
ASCT		76 (62)
Response to therapy second line, No. (%)	109	
CR		70 (63.6)
PR		16 (15.4)
PD		23 (21.0)
Third relapse, No. (%)	70	9 (12.8)
Status at last follow-up, No. (%)	1,435	
Alive		748 (52)
Dead		687 (48)

(continued in next column)

Abbreviations: ABV, doxorubicin, bleomycin, and vinblastine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ASCT, autologous stem cell transplantation; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine; CHT, chemotherapy; C-MOPP, cyclophosphamide, vincristine, procarbazine, prednisone; CR, complete remission; ESHAP, etoposide, methylprednisolone, high-dose cytarabine (ara-C), and cisplatin; ICE, ifosfamide, carboplatin, etoposide; NLPHL, doxorubicin, bleomycin, vincristine, cyclophosphamide, procarbazine, prednisone; NOVP, mitoxantrone, vincristine, vinblastine, prednisone; PD, progressive disease; PR, partial response; RT, radiotherapy.

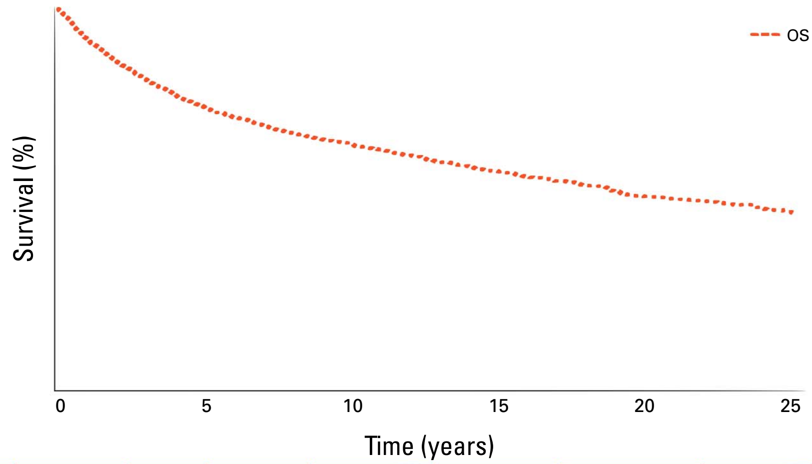
doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine was prescribed in four patients (0.3%) only.

Overall, information on relapse was available for 252 patients who relapsed 3-192 months (median 25 months) after the end of induction therapy.

Salvage therapy was mainly etoposide, methylprednisolone, high-dose cytarabine (ara-C), and cisplatin (220 patients, 87.3%). Autologous stem cell transplantation (ASCT) was performed in 76 patients as consolidation of second-line therapy. From this cohort, 74% (56/76) are alive, with a median follow-up after transplant of 143 months (97-226) or 12.1 years. Regarding the patients who were refractory/

TABLE 2. Cause of Death of 687 Patients With Hodgkin Lymphoma

Causes of Death	No. (%)
Lymphoma/treatment-related infections	501 (73)
Second malignant neoplasms	72 (10)
Cardiovascular diseases	54 (8)
Other causes	60 (9)



No. at risk:							
OS	1435	1062	901	594	348	187	76

FIG 1. OS for all 1,435 patients with Hodgkin lymphoma. OS, overall survival.

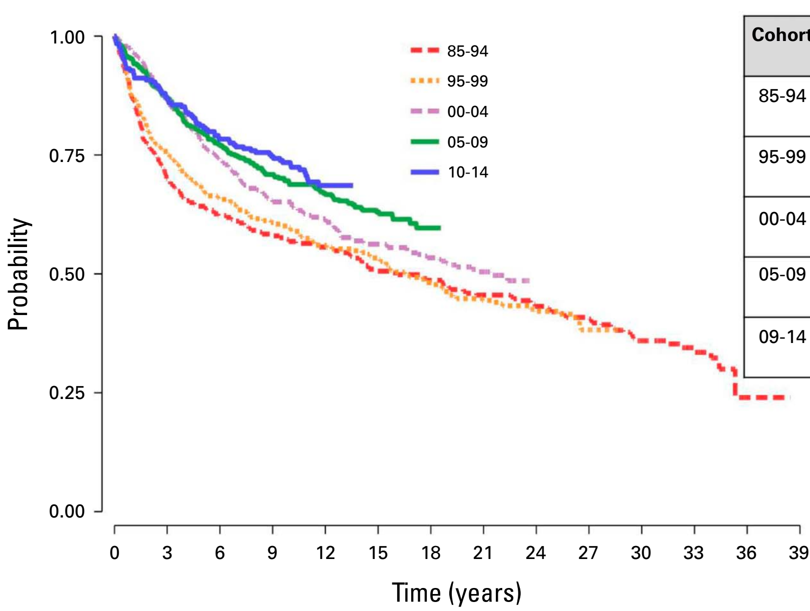
relapsed and not transplanted, only 23% (122/533) are alive. Most of the remaining patients died of lymphoma.

Mortality Rates

After a median follow-up of 268 months or 22.3 years (95% CI, 235 to 300), 748 patients were still alive at the date of last contact, whereas 687 (47.9%) patients had died, resulting in a 30-year OS of 42% (Fig 1). Survival significantly improved over time, from the beginning to the end of the study period (Fig 2).

Cause-Specific Mortality

Causes of death were assessed in 680 (99%) of 687 patients. As summarized in Table 2, the main causes were lymphoma and treatment-related toxicities, mainly infections (73%), followed by SMNs (10%), CVDs (8%), and other causes (9%).



Cohort	N (fail)	5-year OS, % (95%CI)	HR (95%CI)	*P*
85-94	257 (170)	64 (58-70)	1.00	
95-99	268 (160)	68 (62-73)	0.99 (0.79-1.23)	.908
00-04	281 (140)	77 (71-81)	0.80 (0.64-1.01)	.063
05-09	378 (144)	80 (75-84)	0.67 (0.53-0.84)	.001
09-14	249 (74)	81 (76-85)	0.60 (0.45-0.79)	<.001

FIG 2. OS by cohort by years (n = 1,433). HR, hazard ratio; OS, overall survival.

Other causes included chronic pulmonary failure (26 patients, 3%), pulmonary fibrosis associated with bleomycin (eight patients, 1.2%), accident (nine patients, 1.3%), metabolic disease (seven patients, 1%), COVID (four patients, 0.6%), intestinal perforation (three patients, 0.4%), suicide (three patients, 0.4%), dementia and pancreatitis/hepatitis (two patients each, 0.3%), and malnutrition (one patient, 0.1%). In seven patients (1%), the cause was not reported.

Infections associated with treatment-related neutropenia proved to be a relevant cause of death only in the oldest cohort (1985-1994), but they decreased dramatically after the introduction of granulocyte colony-stimulating factor (G-CSF) as part of treatment-related neutropenia.

Cumulative incidence of death (CID) due to lymphoma and treatment-related toxicities, SMNs, and CVDs is reported in Figure 3. The difference between patients who died of lymphoma/treatment-related toxicities and patients who died of SMNs and CVDs was significant (P = .001; HR, 0.6 [95% CI, 0.6 to 0.7]).

Treatment-Specific Mortality

Cumulative mortality risk was higher for patients treated with MOPP/MOPP-like versus ABVD (HR, 1.4 [95% CI, 1.2 to 1.7]; P = .001; Fig 4A), and the difference was evident also for the cohort of patients treated between 1985 and 2002 (HR, 1.27 [95% CI, 1.01 to 1.6]; P = .001; Fig 4B).

Of note, no differences emerged in the cumulative risk of death for patients treated with ABVD before 2002 and after 2002 (HR, 1.27 [95% CI, 0.7 to 2.6]; P = .12), thus excluding a time-dependent bias in the differences observed in the comparison of ABVD with MOPP/MOPP-like therapies.

The risk of death of 76 patients receiving ASCT as consolidation of salvage therapy was significantly lower compared with those 46 patients achieving complete remission (CR) with salvage therapy and not transplanted (HR, 0.3 [95% CI, 0.1 to 0.4]; P = .001; Fig 5).

SMNs

Overall, 61 patients (8.9%) with solid tumors (STs) and 11 patients with hematological malignancies (HMs) were reported, as summarized in Appendix Table A1. The most common STs were GI (41%), lung (25%), breast (10%), undifferentiated carcinoma (6.5%), prostate (3%), female genital organ (3%), and 2% of other tumors (urethra, skin, thyroid, primitive neuroectodermal tumor sarcoma, mesothelioma, meningioma, melanoma; one case, 1.6%). In one case, the origin was not identified.

In patients who developed a secondary ST, the median age at diagnosis of HL was 48 years (range, 18-80). STs occurred at a median of 12 years (range, 1-32) from the start of HL treatment.

There were 11 patients (1.7%) with secondary HM: six acute leukemias and five non-HLs. In these patients, the median age at diagnosis of HL was 39 years (range, 18-61), and secondary HM occurred at a median of 6 years (range, 1-18) after HL treatment.

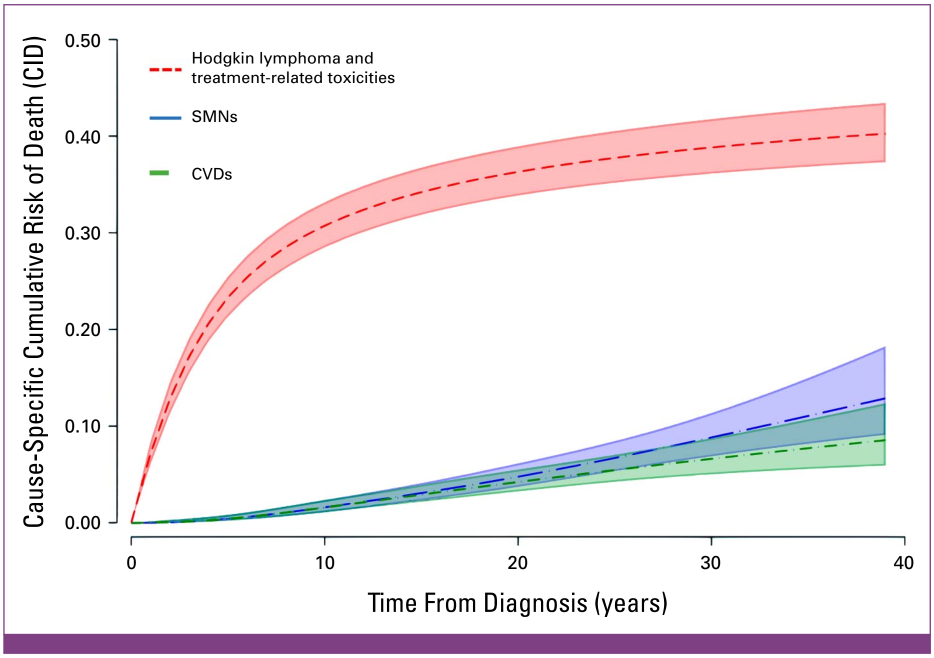
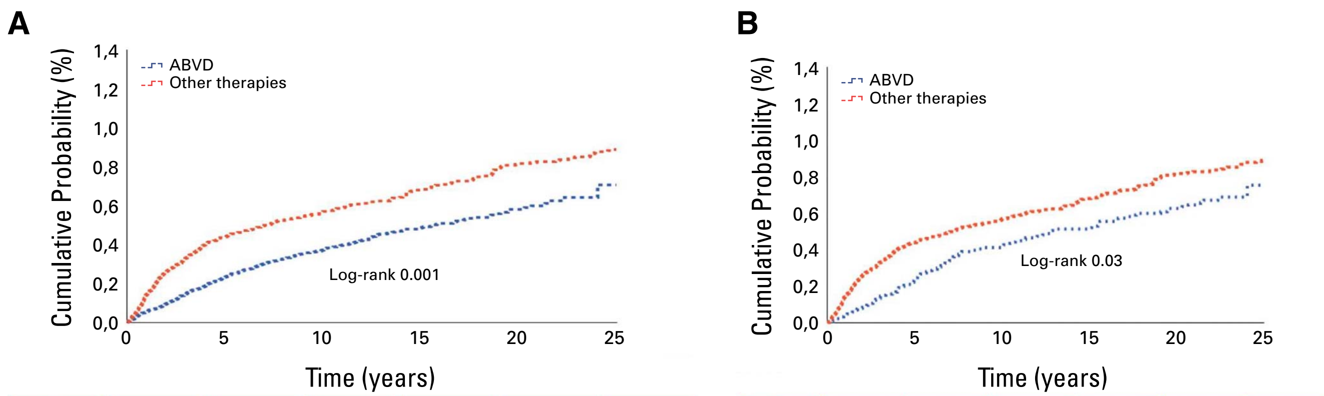


FIG 3. Cause-specific cumulative incidence function of deaths. CID, cumulative incidence of death; CVDs, cardiovascular diseases; SMNs, second malignant neoplasms.

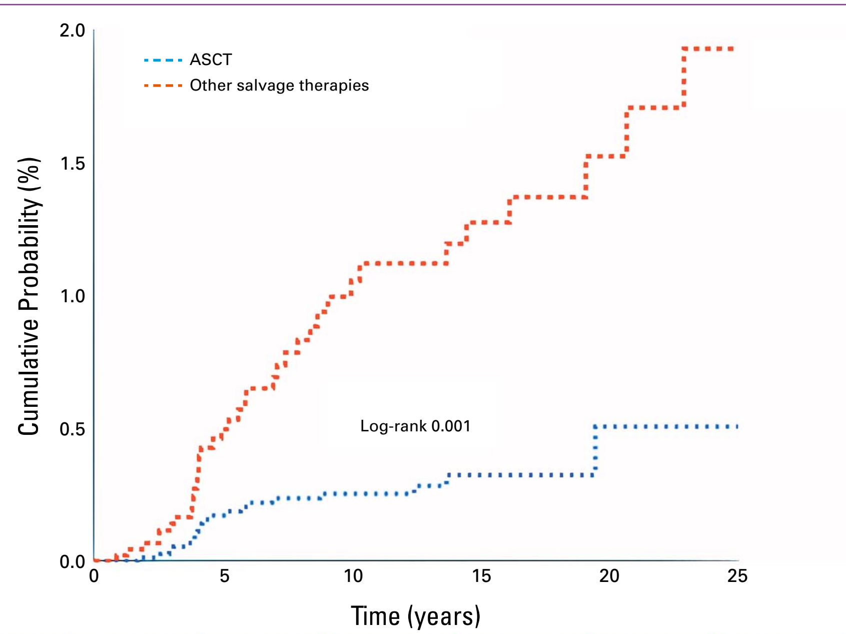


No. at risk:						
ABVD therapy	928	717	497	236	68	7
Other therapies	478	308	271	242	197	93

No. at risk:						
ABVD therapy	200	154	131	117	60	7
Other therapies	478	308	271	242	197	93

FIG 4. (A) Cumulative incidence of death according to type of initial chemotherapy. (B) Cumulative mortality risk for patients treated with ABVD (n = 200) versus other (n = 478; only cases treated between 1985 and 2002). ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine.

CID due to SMNs was HR, 0.5 (95% CI, 0.2 to 0.9), HR, 1.6 (95% CI, 1.1 to 2.4), HR, 3.1 (95% CI, 2.3 to 4.1), and HR, 4.7 (95% CI, 3.7 to 6.1) at 5, 10, 15, and 20 years, respectively. CID resulted significantly higher in patients treated with MOPP/MOPP-like regimens than with ABVD (HR, 1.2 [95% CI, 1 to 1.426]; P = .048). Ten-year cumulative incidence of SMNs was 0.7, 4.1, and 8.0 for patients age <45, 45-59, and 60 years or over at the time of HL diagnosis, respectively; the



No. at risk:						
ASCT	76	60	35	11	2	0.5
Other salvage therapies	46	28	15	9.5	5.5	1.5

FIG 5. Cumulative incidence of death for patients with transplant as salvage therapy versus other salvage therapies. ASCT, autologous stem cell transplantation.

difference was statistically significant ($P < .001$). Regarding secondary malignancies, stomach cancer accounted for nearly one third of the secondary GI cancers in our study. Of these patients, 71% received 30-40 Gy EFRT in addition to CT, and both esophageal cancer had mediastinal radiation. For colorectal cancer (CRC), the majority (67%) of patients were treated with 30-40 Gy EFRT. Similarly, 66% of patients diagnosed with secondary breast cancer underwent 30-40 Gy mantle RT.

CVDs

CVDs were reported as the cause of death in 54 instances (8%): 26 heart failure (HF), 18 acute myocardial infarction (AMI), seven strokes, and three pulmonary thromboembolism. The median age at diagnosis of the 26 patients who died of HF was 56 years (range, 17-77), with a median time post-treatment of 11 years (range, 1-34).

The median age at diagnosis of the 18 patients who died of AMI was 48 years (range, 22-69), with a median time post-treatment of 13 years (range, 4-26); the median age at death was 60 years (range, 37-78).

The median age at diagnosis of the seven patients who died of stroke was 61 years (range, 37-73), with a median time post-treatment of 7 years (range, 3-11). The median age at death was 76 years (range, 41-84).

Half of the patients who died of CVD received 30-40 Gy RT including the mediastinum and also half (54%) received anthracycline-containing regimen (ABDV).

CID due to CVDs was 0.4 (0.2-0.8), 1.5 (1.0-2.3), 2.9 (2.1-3.8), and 4.1 (3.2-5.4) at 5, 10, 15, and 20 years, respectively, with no difference according to the year of diagnosis (before or after 2002; HR, 1.2 [95% CI, 0.6 to 1.4]; $P = .45$) or type of CT (MOPP/MOPP-like *v* ABVD; HR, 2.3 [95% CI, 0.56 to 3.5]; $P = .78$).

DISCUSSION

In this study, conducted in a series of 1,435 patients with HL with a very long follow-up and with the cause of death established in 100% of cases, we found that the majority of patients succumbed to lymphoma and treatment-related toxicities within the first decade, whereas HL survivors faced an elevated risk of death for SMNs and CVDs, especially when HL was diagnosed in adulthood.

The findings of the present study complement the few data coming from other South American Countries. In a study of 498 patients treated in Argentina with ABVD, after a median follow-up of 37 months, a 5-year OS of 85% was found.[16] More recently, Biasoli updated the outcome of 1,329 patients with HL from the Brazilian Hodgkin Lymphoma Registry, treated between 2009 and 2018 with ABVD plus 30 Gy RT. After a median follow-up of 56 months, she reported a 5-year OS of 100%, 94%, and 80% for patients with limited, intermediate, and advanced stage, respectively. Biasoli also emphasized the impact on outcome of socioeconomic status (SES), with a 5-year OS of 90% and 77% for patients with higher and lower SES, respectively ($P < .0001$).[17]

The present study also demonstrates that survival significantly improved over time, from 64% at 5 years observed in those diagnosed between 1985 and 1994 to 81% for those diagnosed between 2009 and 2014, confirming the effectiveness of the changes in treatment strategy adopted in the last 20 years.

However, despite the improvement documented by a 30-year OS of 42%, patients with HL still exhibit higher risk of death compared with the general population.[5,12,13,18,19] Long-term HL outcome remains challenging, although it is difficult to compare the survival rates in different studies. For example, in a recent Danish cohort study including only patients age 15-40 years and a shorter median follow-up, the analysis revealed that OS was 89.9% at 15 years after diagnosis.[18] Moreover, in a Norwegian population-based case-control study with a median follow-up of 10.4 years (95% CI, 6.0 to 22.0), 73% of patients died, and the study population included only people age >60 years at the time of HL diagnosis.[19]

In our study, differently from older studies dealing with the role of HL and ASCT, where the latter was associated with lower OS, the risk of death of patients transplanted as consolidation after second-line salvage therapy was much lower than that of the 46 patients who achieved CR and were not transplanted (Fig 5), suggesting that ASCT had a positive impact not only on HL-specific survival but also reduced the risk of death for causes such as SMNs and CVDs.[20-22]

In our study, the number of SMN-related deaths increased consistently over time, particularly for second STs, with a median onset at 12 years after lymphoma treatment, extending up to 32 years. Other reports also showed that the risk of secondary STs peaked between 5 and 15 years and remained high for at least 40 years.[7,13]

The substantially higher 10-year cumulative incidence of SMN in older patients (8.0 for ≥60 years) compared with younger individuals (0.7 for <45 years) underscores the compounding effects of aging and treatment exposures. The spectrum of ST types, including GI, lung, and breast cancers, aligns with the well-known carcinogenic effects of these treatment. Aleman et al[5] noted a significant rise in ST incidence and mortality in patients treated before age 21 years. Age at diagnosis affects long-term consequences, with hematological neoplasia occurring at a younger median age (39 years), followed by STs.[5] Kumar et al[9] observed a decline in secondary cancer incidence over time, specifically in digestive tract and breast cancers, among patients treated between 1973 and 1986 compared with those treated in the period 1987-2000. However, the decrease was not consistent across all STs and HMs.

We tried to assess the role of different regimens with respect to the incidence of SMNs. Patients who received MOPP or C-MOPP/ABV had twice the incidence of an SST compared with those who received ABVD (7.28% *v* 3.44%).

Secondary GI cancers following HL treatment are significantly prevalent, with stomach cancer representing 27% of secondary GI malignancies in our study. This mirrors national Chilean trends, where stomach cancer ranks as a leading cause of cancer mortality,[23,24] as well as the potential role of RT in these cases. In fact, 70% of these patients besides CT received extended-field RT (30 Gy). Morton et al[25] found a significant increase in the risk of stomach cancer with stomach radiation ≥25 Gy and procarbazine ≥5,600 mg/m^2.[20] Elevated risks were also noted with radiation alone (≥25 Gy) without procarbazine and with dacarbazine-containing CT. van Eggermond et al[26] found an elevated risk of CRC with high-dose procarbazine and infradiaphragmatic irradiation. Notably, there are no reports associating GI with dacarbazine in ABVD regimens. Regarding CRC, the third leading cause of cancer-related mortality in both sexes in Chile,[24,27] EFRT (mantle and inverted Y) was administered to the majority (67%) of patients with CRC. These patients were younger than the median age of CRC diagnosis in Chile (57 *v* 66 years).[27]

To our knowledge, our findings may be among the first to suggest a potential link between ABVD and an elevated CRC risk, as dacarbazine, similar to procarbazine, has demonstrated carcinogenic potential in animal models. Additionally, 75% of esophageal cancer cases involved radiation to the mediastinum.

We also observed an association between large-field RT and breast cancer, with 75% of these patients having this form of treatment. This is consistent with previous findings from the British Columbia Cancer Agency, which demonstrated that women treated for HL with mantle-field RT have a higher risk of secondary breast cancer compared with those treated with CT alone or small-field RT.[28] In our study, second HMs, though less frequent, occurred earlier, with a median onset at 6 years after diagnosis, extending up to 18 years. The 1.7% of SHM is also within the expected range for this patient population.[18]

The relatively shorter median latency of 6 years confirmed that, despite the many factors involved in the development of SMN (such as genetic alterations, immunological, hormonal, lifestyle, and environmental factors), the impact of chemo-RT itself seems eminent.

From several published data, infections, the second highest cause of absolute excess risks, affected half of the patients over age 60 years at diagnosis, with five of seven deaths within the first year in that age group.[29] Among the causes of deaths in this HL cohort, infections proved to be a relevant cause only in the earliest part of the study period. Of note, infections decreased dramatically with the introduction of G-CSF support, which suggests that improvements in supportive care over time have played a crucial role in reducing treatment-related mortality rates.

In our study, CVDs were reported as the cause of death in 8% of cases, in line with published reports on increased CVD mortality[5,10,11,30]; furthermore, they continue to increase over time, reaching up to 34 years after diagnosis. Cardiac failure and CVDs occurred at older ages at diagnosis, aligning with expectations for later-life occurrences.[10,31,32]

Unlike some findings, our study did not observe a decrease in risk in the later period. The cumulative incidence of CVD-related deaths increased over time, reaching 4.1 at 20 years post-treatment. This risk did not differ on the basis of year of diagnosis or CT. Moreover, this risk is similar to that in the Aleman et al[5] study (4% after 20 years). For patients who died of HF, the median age was 56 years, and the median time from treatment to death was 11 years. This suggests HF is a relatively long-term complication in this population.

AMI occurred at a median age of 48 years, whereas HF and stroke occurred at 56 and 61 years, respectively. The median time from treatment to death was 13 and 7 years for AMI and HF, respectively. Notably, 37% of cases were under age 40 years at diagnosis, and half of AMI deaths occurred in patients younger than age 60 years. This finding shows relatively young median ages at diagnosis and indicates premature cardiovascular aging compared with the general population.

Given that the data are based on older treatment techniques and span over 30 years, making current follow-up recommendations is challenging. However, this information is unique due to its geographical context and period of time involved. For contemporary management, patients with localized HL now typically receive CT without procarbazine and may undergo involved-site RT or none at all, guided by interim positron emission tomography/computed tomography after two to three cycles of CT. Modern RT delivery techniques, including intensity-modulated RT and deep inspiration breath-hold solutions, are changing the scenario of radiation-induced secondary cancers and cardiac toxicities among patients with mediastinal classical HL.[33] For patients treated in the past, GI symptoms should be evaluated promptly. Early diagnosis of CRC is crucial and should be managed through established screening programs. Additionally, it is important to confirm existing recommendations by initiating breast cancer screening with annual mammography starting at age 40 years or 10 years after the primary treatment for HL, as part of a comprehensive follow-up strategy.[34-39]

In conclusion, regardless of the fact that advances in HL treatment resulted in a relevant improvement of cure rate, the present study confirms that HL survivors continue to have a reduced life expectancy compared with the general population due to an increased risk of dying of SMN or of CVD. However, it is expected that current treatment practice locally and globally, with less patients treated with RT and, when indicated, with less extensive radiation fields and avoidance of some CT drugs like cyclophosphamide and procarbazine, will end up with a smaller number of SMN and CVD in the future. So future studies comparing with currently treated patients may show a reduced risk of these long-term adverse events. An ongoing challenge is the crucial need for optimal patient selection for treatment approaches aimed at achieving durable remission and minimizing treatment-related toxicity.

The present study confirms that HL survivors continue to have a reduced life expectancy compared with the general population due to an increased risk of dying of SMN or of CVD. However, it is expected that current treatment practice will end up with a smaller number of SMN and CVD in the next future.

AFFILIATIONS

[1]Hospital del Salvador, Universidad de Chile, Santiago de Chile, Chile
[2]CHIMOMO Department, University of Modena and Reggio Emilia, Modena, Italy
[3]Hematology Department, Jules Bordet Institute, Brussels, Belgium
[4]Oncology Nurse, Public Health Magister, Universidad de Chile, Universidad Mayor, Santiago de Chile, Chile
[5]Hematology Unit, IRCCS Istituto Tumori Giovanni Paolo II, Bari, Italy
[6]Hospital Barros Luco Trudeaux, Santiago, Chile
[7]Hospital San Juan de Dios, Santiago, Chile
[8]Hospital Regional de Valdivia, Valdivia, Chile
[9]Hospital Sótero del Río, Santiago, Chile
[10]Hospital San Borja Arriarán, Santiago, Chile
[11]Hospital Regional de Talca, Talca, Chile
[12]Hospital Regional de Concepcion, Concepcion, Chile
[13]Hospital Gustavo Fricke, Viña del Mar, Chile
[14]Hospital Las Higueras de Talcahuano, Talcahuano, Chile
[15]Hospital Regional de La Serena, La Serena, Chile
[16]Hospital Carlos van Buren, Valparaiso, Chile
[17]Department of Physics and Chemistry, University of Palermo, Palermo, Italy
[18]Fondazione Italiana Linfomi, Trial Office Modena, Modena, Italy

CORRESPONDING AUTHOR

Maria Elena Cabrera, MD, PhD; e-mail: mecabrera1950@gmail.com.

AUTHOR CONTRIBUTIONS

Conception and design: Maria Elena Cabrera, Yana Stepanishyna, Lea Derio, Vivianne Lois, Massimo Federico
Financial support: Valeska Vega, Christine Rojas
Administrative support: Lea Derio, Tetiana Skrypets, Valeska Vega, Marvila Intriago, Luigi Marcheselli
Provision of study materials or patients: Vivianne Lois, Valeska Vega, Susana Calderon, Hernán Rojas, Alvaro Pizarro, M. Gabriela Mendoza, Christine Rojas, Jacqueline Oliva, Bernardita Rojas
Collection and assembly of data: Vivianne Lois, Valeska Vega, Susana Calderon, Hernán Rojas, Alvaro Pizarro, M. Gabriela Mendoza, Monica Romero, Christine Rojas, Jacqueline Oliva, Marvila Intriago
Data analysis and interpretation: Monica Civallero, Yana Stepanishyna, Tetiana Skrypets, Vivianne Lois, Bernardita Rojas, Luana Conte, Luigi Marcheselli, Massimo Federico
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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/go/authors/author-center.
Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Tetiana Skrypets
Honoraria: Takeda, AbbVie, Menarini

Monica Romero
Honoraria: Novartis
Consulting or Advisory Role: Pfizer, Bristol Myers Squibb/Pfizer
Speakers' Bureau: Novartis, Pfizer, AbbVie, Astellas Pharma

Christine Rojas
Honoraria: Roche, Janssen, Novartis, AstraZeneca, Bristol Myers Squibb/Celgene
Consulting or Advisory Role: Janssen, BMSi, Roche
Travel, Accommodations, Expenses: Roche, Janssen, AstraZeneca

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

Our thanks to all the physicians who treated these patients at each cancer center. Our thanks also to the Investigation Unit and Clinical Trials of the Instituto Nacional del Cance, as well as Dr Sebastian Sole, who looked for the radiation information of some patients.

REFERENCES

1. Connors JM, Cozen W, Steidl C, et al: Hodgkin lymphoma. Nat Rev Dis Prim 6:61, 2020
2. Ansell SM: Hodgkin lymphoma: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol 97:1478-1488, 2022
3. Johnson PWM: Are we reaching the maximum cure rate for Hodgkin lymphoma? Hematol Oncol 41:57-61, 2023 (suppl 1)
4. Swerdlow AJ, Higgins CD, Smith P, et al: Second cancer risk after chemotherapy for Hodgkin's lymphoma: A collaborative British cohort study. J Clin Oncol 29:4096-4104, 2011
5. Aleman BMP, van den Belt-Dusebout AW, Klokman WJ, et al: Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol 21:3431-3439, 2003
6. Núñez-García B, Clemente MB, Sánchez JC, et al: Long-term outcomes in Hodgkin lymphoma survivors. Temporary trends and comparison with general population. Hematol Oncol 41:407-414, 2023
7. 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 Med 373:2499-2511, 2015
8. van Leeuwen FE, Klokman WJ, van't Veer MB, et al: Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. J Clin Oncol 18:487-497, 2000
9. Kumar V, Garg M, Chandra AB, et al: Trends in the risks of secondary cancers in patients with Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk 18:576-589.e1, 2018
10. van Nimwegen FA, Schaapveld M, Janus CPM, et al: Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. JAMA Intern Med 175:1007-1017, 2015
11. Andersson A, Melin B, Enblad G, et al: High risk of cardiovascular side effects after treatment of Hodgkin's lymphoma—Is there a need for intervention in long-term survivors? Ups J Med Sci 10:126, 2021
12. de Vries S, Schaapveld M, van Nimwegen FA, et al: High burden of subsequent malignant neoplasms and cardiovascular disease in long-term Hodgkin lymphoma survivors. Br J Cancer 118: 887-895, 2018
13. de Vries S, Schaapveld M, Janus CPM, et al: Long-term cause-specific mortality in Hodgkin lymphoma patients. J Natl Cancer Inst 113:760-769, 2021
14. Gao J, Chen Y, Wu P, et al: Causes of death and effect of non-cancer-specific death on rates of overall survival in adult classic Hodgkin lymphoma: A populated-based competing risk analysis. BMC Cancer 21:955, 2021
15. Aleman BMP, van den Belt-Dusebout AW, Klokman WJ, et al: Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol 21:3431-3439, 2003
16. Mahuad C, Victoria O, Laura K, et al: Retrospective multicenter real-life study on the first-line treatment of classical Hodgkin lymphoma in Argentina. Clin Hematol Int 4:44-51, 2022
17. Biasoli I, Castro N, Villarim CC, et al: Treatment outcomes in classic Hodgkin lymphoma: 5-year update from the Brazilian Hodgkin Lymphoma Registry. EJHaem 4:1191-1195, 2023
18. Rossetti S, Juul SJ, Eriksson F, et al: Long-term cause-specific mortality in adolescent and young adult Hodgkin lymphoma patients treated with contemporary regimens—A nationwide Danish cohort study. Br J Haematol 205:1374-1382, 2024
19. Lia K, Jørgensen RRK, Wold BL, et al: Overall survival and causes of death in elderly patients with Hodgkin lymphoma: A Norwegian population-based case-control study. Haematologica 109: 1403-1412, 2024
20. Mauch PM, Kalish LA, Marcus KC, et al: Long-term survival in Hodgkin's disease relative impact of mortality, second tumors, infection, and cardiovascular disease. Cancer J Sci Am 1:33-42, 1995
21. Hodgson DC, Gilbert ES, Dores GM, et al: Long-term solid cancer risk among 5- year survivors of Hodgkin's lymphoma. J Clin Oncol 25:1489-1497, 2007
22. Ng AK, Bernardo MP, Weller E, et al: Long-term survival and competing causes of death in patients with early-stage Hodgkin's disease treated at age 50 or younger. J Clin Oncol 20:2101-2108, 2002
23. Csendes A, Figueroa M: Situación del cáncer gástrico en el mundo y en Chile. Revista chilena de cirugía 69:502-507, 2017
24. Bray F, Laversanne M, Sung H, et al: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74:229-263, 2024
25. Morton LM, Dores GM, Curtis RE, et al: Stomach cancer risk after treatment for Hodgkin lymphoma. J Clin Oncol 31:3369-3377, 2013
26. van Eggermond AM, Schaapveld M, Janus CP, et al: Infradiaphragmatic irradiation and high procarbazine doses increase colorectal cancer risk in Hodgkin lymphoma survivors. Br J Cancer 117: 306-314, 2017
27. Mondschein S, Subiabre F, Yankovic N, et al: Colorectal cancer trends in Chile: A Latin-American country with marked socioeconomic inequities. PLoS One 17:e0271929, 2022
28. Conway JL, Connors JM, Tyldesley S, et al: Secondary breast cancer risk by radiation volume in women with Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 97:35-41, 2017
29. Dores GM, Curtis RE, Dalal NH, et al: Cause-specific mortality following initial chemotherapy in a population-based cohort of patients with classical Hodgkin lymphoma, 2000-2016. J Clin Oncol 38: 4149-4162, 2020
30. Lu Z, Teng Y, Ning X, et al: Long-term risk of cardiovascular disease mortality among classic Hodgkin lymphoma survivors. Cancer 128:3330-3339, 2022
31. Oliva S, Puzzovivo A, Gerardi C, et al: Late cardiological sequelae and long-term monitoring in classical Hodgkin lymphoma and diffuse large B-cell lymphoma survivors: A systematic review by the Fondazione Italiana Linfomi. Cancers (Basel) 14:61, 2021
32. van Nimwegen FA, Schaapveld M, Cutter DJ, et al: Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. J Clin Oncol 34:235-243, 2016
33. Iorio GC, Salvestrini V, Borghetti P, et al: The impact of modern radiotherapy on radiation-induced late sequelae: Focus on early-stage mediastinal classical Hodgkin Lymphoma. A critical review by the Young Group of the Italian Association of Radiotherapy and Clinical Oncology (AIRO). Crit Rev Oncol Hematol 161:103326, 2021
34. Mulder RL, Hudson MM, Bhatia S, et al: Updated breast cancer surveillance recommendations for female survivors of childhood adolescent, and young adult cancer from the international guideline harmonization group. J Clin Oncol 38:4194-4207, 2020
35. Eisenberg ER, Weiss A, Prakash I, et al: Surgical management and contralateral breast cancer risk in women with history of radiation therapy for Hodgkin lymphoma: Results from a population-based cohort. Ann Surg Oncol 29:6673-6680, 2022
36. Wong SM, Ajjamada L, Weiss AC, et al: Clinicopathologic features of breast cancers diagnosed in women treated with prior radiation therapy for Hodgkin lymphoma: Results from a population-based cohort. Cancer 128:1365-1372, 2022
37. National Comprehensive Cancer Network (NCCN) guidelines, version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/hodgkin_blocks.pdf
38. Ciavarella S, Minoia C, Quinto AM, et al: Improving provision of care for longterm survivors of lymphoma. Clin Lymphoma Myeloma Leuk 17:e1-e9, 2017
39. Stepanishyna Y, Meunier F, Bron D: Survivorship after Hodgkin lymphoma and the right to be forgotten. Curr Opin Oncol 36:360-368, 2024

APPENDIX

TABLE A1. Second Cancer ICD Code

Second Solid/Cancer Site	ICD Code	Number of Patients (%)
GI tract	C15-C26	25 (41)
Lung	C34	15 (24)
Breast	C50	6 (10)
Prostate	C61	2 (4)
Female genital organ	C51-C58	2 (3.2)
Urethra	C64-C68	1 (1.6)
Skin	C43-C44	1 (1.6)
Thyroid	C73	1 (1.6)
PNET sarcoma	C96	1 (1.6)
Mesothelioma	C45	1 (1.6)
Meningioma	C70	1 (1.6)
Melanoma	C43	1 (1.6)
Carcinoma undifferentiated	C76-C80	4 (6.6)
Second hematological malignancies		
NHL	C82-88	5 (45)
Leukemia	C91-96	6 (55)

Abbreviations: ICD, International Classification of Diseases, 10th revision; NHL, non-Hodgkin lymphoma; PNET, primitive neuroectodermal tumor.