Overall survival and causes of death in elderly patients with Hodgkin lymphoma: a Norwegian population-based case-control study

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Abstract

Elderly Hodgkin lymphoma (HL) patients are poorly characterized and under-represented in studies. In this national population-based study, we investigated cause-specific survival using competing-risk analysis in elderly HL patients compared to the normal population. Patients ≥60 years of age diagnosed between 2000-2015 were identified by the Cancer Registry of Norway, and records were reviewed in detail and compared to data from the Norwegian Cause of Death Registry for patients and cancer-free controls. Of 492 patients, 81 (17%) were ineligible for treatment directed specifically towards HL, mostly because of an underlying other lymphoma entity, whereas 74 (15%) and 337 (69%) were treated with palliative or curative intent, respectively. Median overall survival in patients ineligible for assessment of HL-directed therapies was 0.5 years (95% Confidence Interval [CI]: 0.4-0.6), and for palliatively and curatively treated patients 0.8 (0.4-1.2) and 9.1 (7.5-10.7) years, respectively. After correction of discrepancies in registry data, with 359 deaths, 108 (30%) died of HL, the most common cause of death. In curatively treated patients, treatment-related mortality was 6.5% and the risk difference of dying from HL compared to controls was 28% (95% CI: 23-33%) after ten years. These numbers indicate disease control in a majority of elderly patients eligible for curative treatment, compared to risk differences for death from HL of 59% (48-71%) and 42% (31-53%) after ten years in the palliative and ineligible groups, respectively. There was an increased risk of dying from hematologic malignancies other than HL in all groups, but not from other competing causes of death, showing no excess mortality from long-term treatment complications.

Introduction

Hodgkin lymphoma (HL) is one of the most common lymphoma entities in younger adults, but a second peak in incidence occurs in elderly patients.[1-3] Currently 20-25% of HL patients are >60 years at presentation, a proportion that may rise with increasing life expectancy in most Western populations. HL is one of the most curable cancers in younger patients with 5-year relative survival rates of around 90%.[4] For elderly HL patients, however, the outcome after treatment remains inferior to that in younger patients, probably because of poorer tolerance to modern intensive chemotherapy, different disease biology, and more comorbidities.[5-8] As a consequence, elderly patients are frequently excluded from clinical trials and the optimal therapy for first-line treatment for the elderly is poorly defined.[2] Because of inferior outcome, the majority of deaths from HL in the modern era occur in the elderly patients.[9] Trials specifically recruiting elderly HL patients have been difficult to perform and are probably subject to selection bias.[10] Therefore, HL patients >60 years of age remain poorly characterized in terms of demographic and clinical factors at presentation, as do choice of treatment and outcome outside selected and small studies.[11-15] As the

human lifespan increases, cancer will disproportionately affect the elderly, and malignant disorders in this age group will become increasingly important in oncology.[16]

To our knowledge, few have attempted to describe in detail the whole scope of elderly HL patients in a population-based manner. Here, we aim to combine population-based identification of patients from the Cancer Registry of Norway (CRN) and individual patient record review to describe demographic and clinical characteristics at presentation, treatment choice, and outcome in a comprehensive cohort of HL patients diagnosed in the modern era between 2000 and 2015. To better address the higher risk of death from other diseases common in elderly individuals, we compare survival and causes of death to a matched normal population using competing risk analysis. A large, unbiased selection of patients with relevant individual data may provide important knowledge about this cohort of patients and aid improvement of current practice, as well as planning of future studies.

Methods

Study design

Patients with HL diagnosed from January 1995 to December 2015 and aged >60 years at diagnosis were identified through the CRN (*Online Supplementary Methods*). Clinical data were retrieved on diagnosis, treatment, and follow-up from medical records at local and regional hospitals and from general practitioners by the co-authors aided by study nurses.

Patients were divided into three groups based on treatment given.

1) Patients ineligible for HL treatment had other concomitant severe diseases, such as other cancers, cardiovascular disease (CVD) or dementia that precluded any treatment directed specifically at HL, had died before the diagnostic biopsy was reviewed, or HL was diagnosed at autopsy. Patients with a previous or simultaneous diagnosis of another lymphoproliferative disease, mostly chronic lymphocytic leukemia (CLL) or a non-Hodgkin lymphoma (NHL, referred to as mixed lymphomas) could receive treatment targeting both disease categories.

2) Patients treated with palliative intent either received no chemotherapy (steroids or palliative radiotherapy allowed) or chemotherapy directed at HL at doses <50% of the dose of central drugs in recommended regimens.

3) All other patients (i.e., those treated with curative intent) received typical regimens directed towards HL at >50% dose of central drugs or curatively intended radiation therapy.

The most likely cause of death was concluded from medical records and specified using the International Classification for Disease (ICD-10).[17] Death occurring during and up to three months after the last antineoplastic treatment and not due to progression of HL, was deemed treatment-related mortality (TRM).

The Norwegian Cause of Death Registry (DAAR) provided date and cause of death for patients and 10 cancer-free controls, matched on age, sex and community of residence at the time of HL diagnosis. Causes of death in DAAR are specified using ICD-10 at the level of the immediate and the underlying cause of death. Inconsistencies regarding improbable deaths from hematologic diseases other than HL in the patients were observed and corrected.

The study was approved by the Norwegian Regional Committees for Medical and Health Research Ethics (REK 2016/1202) and Data Protection Officers at all participating hospitals, and performed according to the Declaration of Helsinki.

Statistical analysis

Overall survival (OS) for patients and controls was estimated from date of diagnosis or matching, respectively, to death of any cause, or censored at last date of follow-up (December 31st 2021). Cause-specific survival (CSS) in patients was estimated from diagnosis to death of HL, censored for other causes of death or date of last follow-up. OS and CSS were analyzed by Kaplan-Meier statistics, and groups compared using the log-rank test.

Cumulative incidence functions (CIF) for different causes of death (grouped as HL, hematologic malignancies other than HL, other cancers, dementia, CVD, infections or all other causes) were calculated from date of diagnosis to death from the respective cause using the Aalen-Johansen estimator and compared using Gray's test. Risk differences between patients and controls were calculated for each competing event at 2, 5, and 10 years with 95% Confidence Intervals (CI) (*Online Supplementary Methods* and *Online Supplementary Table S1*).

Results

Patients' characteristics

Through the CRN, we identified 561 patients with HL >60 years of age in Norway from the time period 1995-2015 (*Online Supplementary Figure S1*). In addition, 17 were identified from the Lymphoma Registry of Oslo University Hospital. After initial attempts to retrieve data, we excluded all 86 patients diagnosed between 1995 to 1999, due to insufficient data in a larger number of patients from these years. The final study population thus consisted of 492 patients diagnosed from 2000-2015. Eighty-one (17%) patients were ineligible for the analysis of outcomes after HL treatment, due to either presence of mixed lymphoma (N=54), HL diagnosed after death or at autopsy (N=13), severe comorbidity precluding HL treatment (N=7), and incomplete patient data (N=7). Mixed lymphoma was defined as previous or concomitant presence of a second malignant lymphoproliferative disease other than HL. Of the 54 cases

(11% of all patients), 20 had preceding diagnosis of a NHL or myeloma, 14 cases were diagnosed as a transformation of CLL, and 14 cases showed presence of two separate lymphoma entities at diagnosis. Six cases remained difficult to classify as either HL or another lymphoma after review and were not treated as HL. Seventy-four (15%) of the patients were treated with palliative intent and 337 (69%) received treatment with intent to cure.

Median age of the whole cohort was 71 years (range 60-94), and 58% were male (*Online Supplementary Table S2*). Median age in the ineligible group and in palliatively and curatively treated patients was 73 years (range 61-94), 81 years (range 61-94), and 69 years (range 60-90), respectively. Data concerning patient-, disease- and treatment-related variables were missing in a larger proportion of the ineligible cases, and a formal comparison was made for the palliative and curative groups only. Patients in the curatively treated group were significantly younger, had better performance status, were more often fully independent in personal activities of daily living, and had a lower burden of comorbidities at the time of diagnosis of HL. For disease-related parameters, curatively treated patients more often had nodular lymphocyte predominant HL (NLPHL), more often had stage I or II disease, and less often had B symptoms. A total of 89% of biopsies were reviewed at university hospitals: 84% of biopsies from palliatively and 90% from the curatively treated patients.

Nineteen of the palliatively treated patients did not receive any lymphoma-directed chemotherapy due to frailty, age, and/or patient choice. The remaining patients were treated with palliatively intended chemotherapy, either anthracyline-free regimens or dose-reduced CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone). Radiotherapy was part of the palliative treatment in 14 of the patients. The majority of patients included in the curatively treated group had multi-agent chemotherapy. The most common first-line regimen was CHOP (74%), followed by ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine; 20%). Seventeen patients had curatively intended radiotherapy as their sole first-line treatment, and 14 of these had NLPHL.

Overall survival

The median follow-up for all patients still alive at end of study was 10.4 years (95% CI: 6.0-22.0). During the course of follow-up, 359 (73%) patients in the study population died. Of them, there were 74 (91%) deaths in the ineligible groups, 73 (99%) in the palliative group, and 212 (63%) in the curative group. Median OS for ineligible, palliatively and curatively treated patients were 0.5 (95% CI: 0.4-0.6), 0.8 (0.4-1.2), and 9.1 (7.5-10.7) years, respectively, significantly lower in the ineligible and palliative group compared to the curative group (P<0.001 for both comparisons) (Figure 1). The 2- and 5-year OS rates were 27% (95% CI: 19-39%) and 20% (13-31%) for the ineligible group, 23% (15-35%) and 9% (5-19%) for the palliative group, and 80% (76-84%) and 64% (59-70%) for the curative group.

Median OS was lower compared to controls for all patients and for each of the groups (P<0.01 for all comparisons) (Figure 2). For the ineligible and palliatively treated patients, median OS was 0.5 and 0.8 compared to 8.3 and 11.9 years in the respective control populations. For the curatively treated patients, the median survival for the study group was 9.1 years, compared to 14.2 years for the matched population. CSS at 2, 5, and 10 years for curatively treated patients were 83.4%, 76.2%, and 69.4%, respectively, considerably higher than for the other subgroups (*Online Supplementary Table S3* and *Online Supplementary*

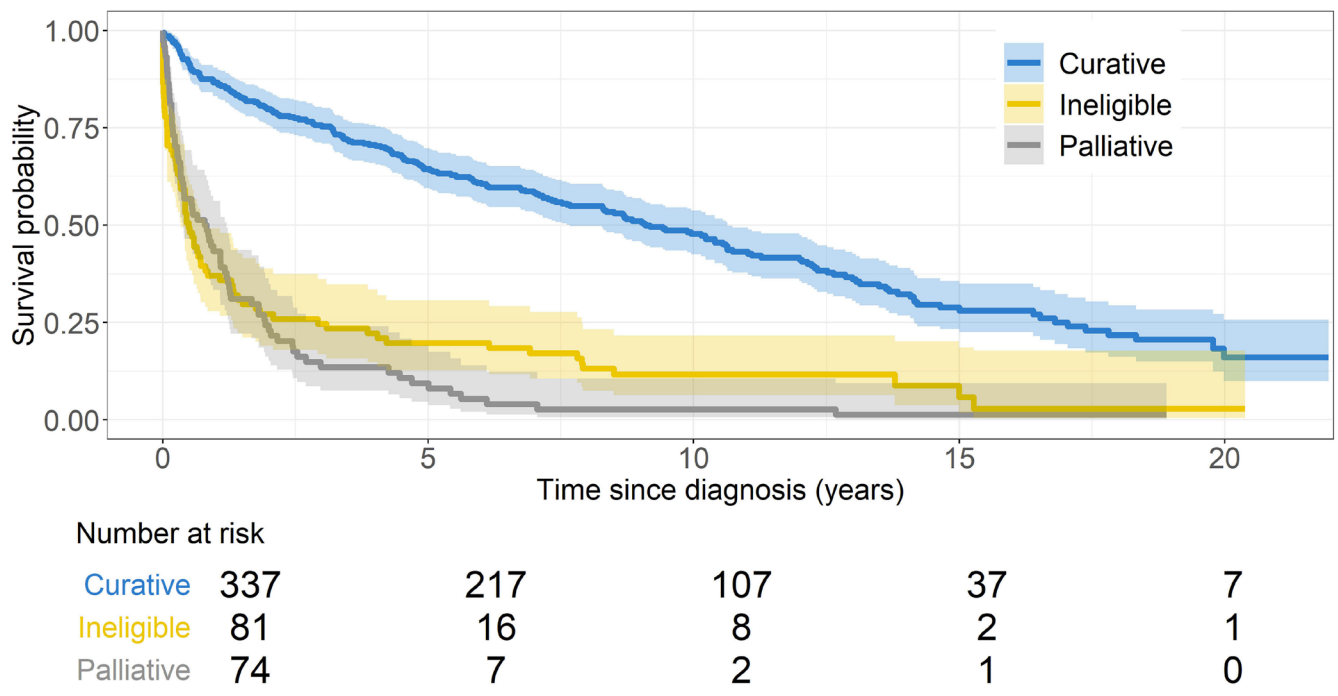

Figure 1. Overall survival according to treatment groups. Overall survival was analyzed by Kaplan-Meier statistics and groups compared using the log-rank test. Overall survival was significantly lower in the ineligible and palliative group compared to the curative group (P<0.001 for both comparisons).

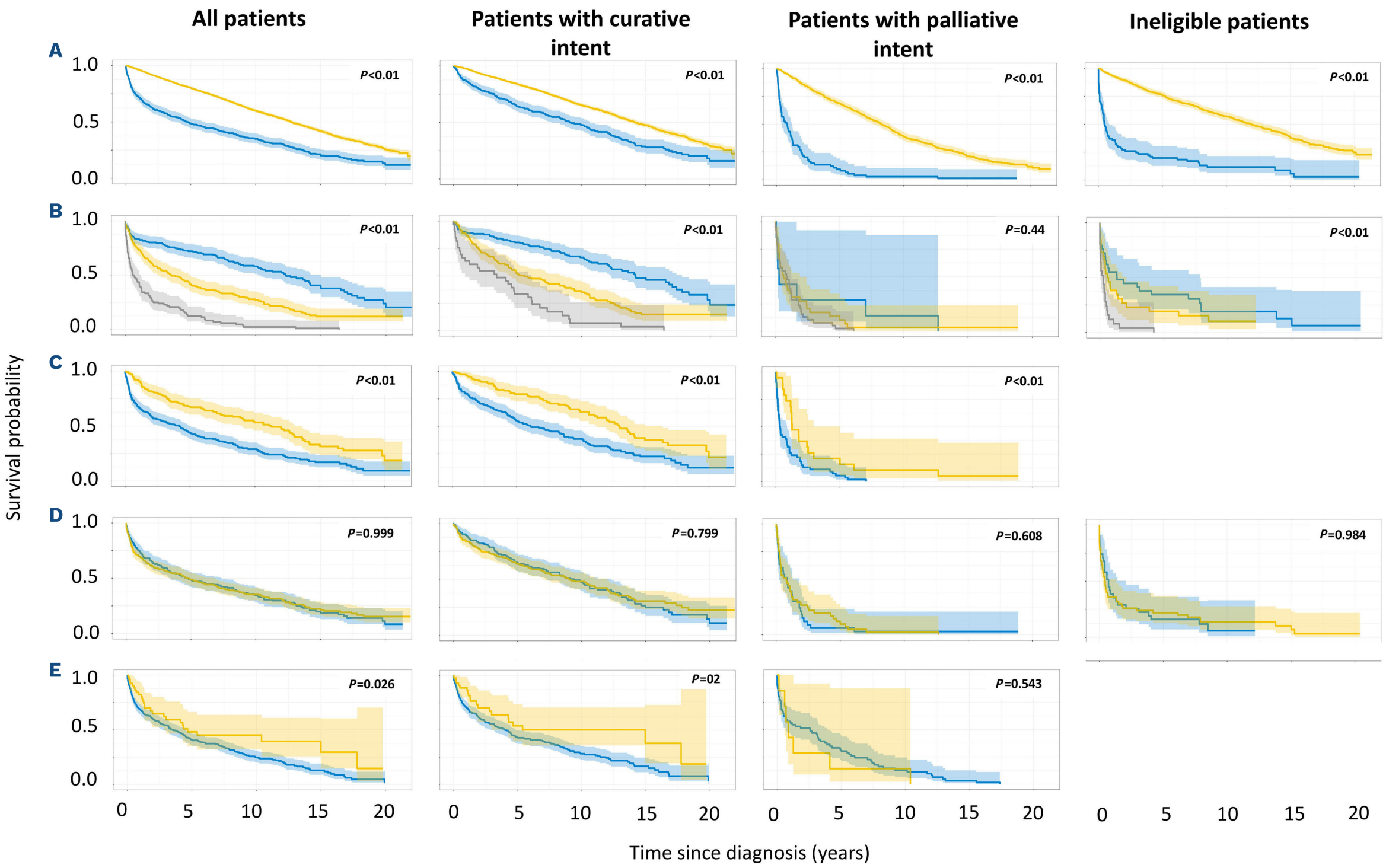

Figure 2. Overall survival in elderly Hodgkin lymphoma patients and controls. (A) Overall survival of patients (blue line) and matched cancer-free controls (yellow line). (B) Overall survival by age group at diagnosis with 60-69 years (blue line), 70-79 years (yellow line) and ≥80 years (gray line). (C) Overall survival by stage with early stage (I-IIA; yellow line) and advanced stage (IIB-IV, blue line). Staging incomplete in most patients in the ineligible group. (D) Overall survival by sex with male patients (yellow line) and female patients (blue line). (E) Overall survival by histological subgroup with Nodular Lymphocyte Predominant Hodgkin Lymphoma (yellow line) and Classical Hodgkin Lymphoma (blue line). Overall survival was analyzed by Kaplan-Meier statistics and groups compared using the log-rank test.

Figure S2).

Younger age, early stage disease, and NLPHL histology were significantly associated with better survival in all patients and in the groups with sufficient data for analysis ($P<0.01$) (Figure 2). Sex was not associated with survival in all patients combined nor in any of the groups.

Causes of death

With 359 deaths, the frequency of different causes, as extracted from records or underlying or immediate causes of death from DAAR, is shown in Table 1. From records, 108 (30% of all deaths) were assigned to HL, 28 (8%) to TRM, and 223 (44%) to all other causes combined. There was inadequate information in the records regarding cause of death in 18% of the patients. After correction for ambiguities concerning type of hematologic malignancy (see *Online Supplementary Methods* for details), DAAR reported a higher proportion of deaths attributed to HL, both for all patients combined (49 *vs*. 30%) and in the three groups. DAAR reported death from hematologic malignancies other than HL at a similar level in all patients as compared to record-based data, but with differences between the three groups: 27%, 7%, and 6% of deaths in the ineligible, palliative and curative groups, compared to 38%, 1%, and <1% in the record-based review. Accepting that unknown causes and TRM are not valid entries on death certificates, the proportions of patients dying from other cancers, dementia, CVD, infections, and other causes combined were similar when based on patient records and DAAR.

Individual patient data on causes of death from records seemed to match better with the underlying cause from DAAR than with the immediate cause (*Online Supplementary Figure S3*). For HL as the underlying cause of death, 82% were classified as either HL (51%), TRM (13%), or unknown (18%) in the record-based review. Eighteen percent of deaths with HL as the underlying cause in DAAR were differently classified by review of records, mostly as other hematologic malignancies (6%) and CVD (5%). Concerning other causes of death, the best agreement on an individual patient basis was seen for other hematologic malignancies, other cancers, and CVD, all with an approximate 50% agreement between the underlying cause from DAAR and review of records.

Competing risk analysis

Using the corrected underlying cause of death from DAAR, CIF estimates for the marginal probability for each competing event in the whole patient population, and separately in the ineligible, palliative and curative groups, were compared to the matched population (Figure 3). The differences in calculated cumulative incidences compared to controls at 2, 5, and 10 years for each competing cause of death are shown in Table 2. The risk of dying from HL rises from 16% at two years to 28% after ten years for the curatively treated patients, compared to 59% and 42% after ten years in the ineligible and palliative groups, respectively. Overall, and in all three groups, the risk of dying from another hematologic malignancy was higher than in the normal population, with the highest difference seen for the ineligible patients; 20% and 23% at two and five years, respectively. The risk of death from CVD, dementia, and other causes was significantly lower in the whole cohort of patients, whereas the risk of dying from other cancers or infections was similar to the normal population.

Table 1. Causes of death according to Norwegian Cause of Death Registry and patient records.

	All patients N=492			Ineligible group N=81		Palliative group N=74		Curative group N=337	
Number of deaths, all causes, N (%)	**359 (73.0)**			**74 (91.4)**		**73 (98.6)**		**212 (62.9)**	
Cause of death	**DAAR[a]**	**Patient records**	***P*[b]**	**DAAR**	**Patient records**	**DAAR**	**Patient records**	**DAAR**	**Patient records**
Hodgkin lymphoma	175 (48.7)	108 (30.1)	<0.001	34 (46.0)	15 (20.3)	44 (60.3)	37 (50.7)	97 (45.8)	56 (26.4)
Other hematologic malignancies	38 (10.6)	30 (8.4)	0.31	20 (27.0)	28 (37.8)	5 (6.8)	1 (1.4)	13 (6.1)	1 (0.5)
Other cancers	39 (10.7)	45 (12.5)	0.49	3 (4.1)	5 (6.8)	8 (11.0)	8 (11.0)	28 (13.2)	32 (15.1)
Other causes	30 (8.4)	20 (5.6)	0.14	5 (6.8)	1 (1.4)	8 (11.0)	3 (4.1)	17 (8.0)	16 (7.5)
Dementia	9 (2.5)	4 (1.1)	0.16	0 (0)	0 (0)	0 (0)	0 (0)	9 (4.2)	4 (1.9)
Cardiovascular diseases	39 (10.7)	38 (10.6)	0.90	4 (5.4)	4 (5.4)	5 (6.8)	6 (8.2)	30 (14.2)	28 (13.2)
Infections	29 (8.1)	21 (5.8)	0.24	8 (10.8)	4 (5.4)	3 (4.1)	5 (6.8)	18 (8.5)	12 (5.7)
Treatment-related mortality	-	28 (7.8)	-	-	1 (1.4)	-	5 (6.8)	-	22 (10.4)
Unknown causes	-	65 (18.1)	-	-	16 (21.6)	-	8 (11.0)	-	41 (19.3)

Categorical data are described with numbers and proportions. Groups of patients are compared by Fisher Exact test as two independent groups. [a]DAAR: The Norwegian Cause of Death Registry. [b]*P*-values for comparison of DAAR and patients records for the given cause *versus* all other different causes of death.

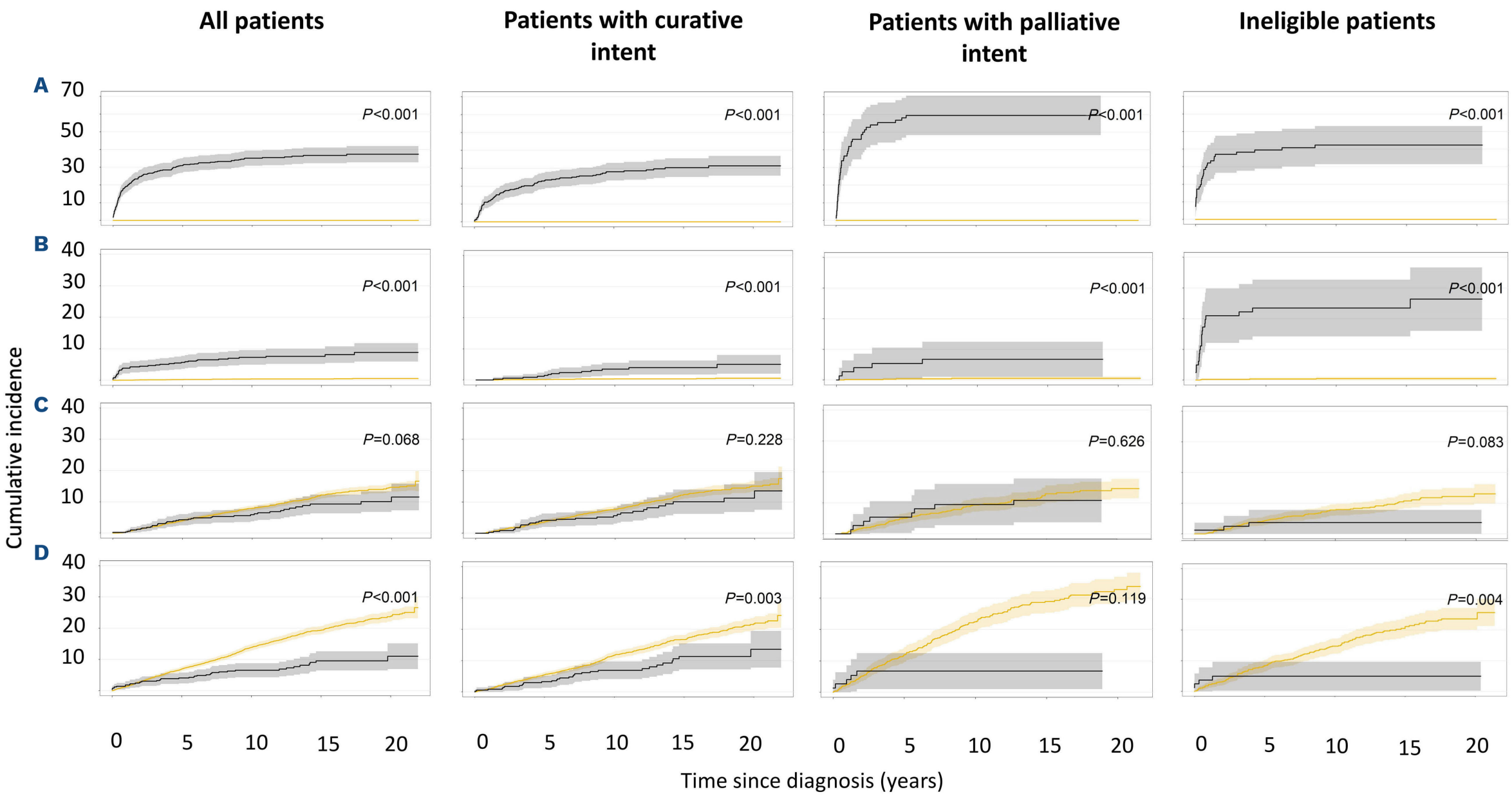

Figure 3. Cumulative incidence functions for competing causes of death in elderly Hodgkin lymphoma patients (black lines) and controls (yellow lines). (A) Death from Hodgkin lymphoma. (B) Death from other hematologic malignancies. (C) Death from other cancers. (D) Death from cardiovascular diseases cumulative incidence rates for different causes of death were calculated from date of diagnosis to death from the respective cause using the Aalen-Johansen estimator and compared using Gray's test.

Discussion

Using individual patient records, we report a population-based retrospective analysis of all patients diagnosed with HL at ≥60 years of age in Norway between 2000-2015. For curatively treated patients, OS at two and five years was 80% and 64%, with 26% and 10% of deaths attributed to HL or TRM, respectively. Compared to the general population, and correcting for competing causes of death, the cumulative incidence of death from HL at five years in curatively treated patients was 23%, compared to 58% for palliatively treated patients. Furthermore, patients with HL had an elevated risk of dying from other hematologic malignancies in the years after diagnosis, but not from other causes, indicating low, long-term excess mortality from treatment.

To improve outcome for elderly patients, better understanding of the heterogeneity of this cohort in terms of disease biology, clinical presentation, and treatment options appears to be important.[5,6,8,18,19] In addition, patients' frailty and comorbidities are associated with choice of treatment and one-year all-cause mortality.[20-22] By review of individual records, we found 30% of deaths in the whole cohort occurring from HL, and 48% of these were seen in the 32% of patients that could not receive curatively intended treatment. Competing risk analysis demonstrates that death from HL is a proportionately larger problem in patients not receiving curative treatment, with a cumulative incidence of death from HL in the two groups either not eligible for typical HL treatment or receiving palliative treatment only of 37.0-50.0% and 39.5-58.1% at two and five years, respectively. To prevent deaths from HL in the elderly, more focus should be put on the patients who never receive curative treatment, who account for approximately one-third of the population in our cohort. Several reports demonstrate improved outcomes in recent decades for patients with HL >60 years of age, and most of this improvement is probably seen for the curatively

Table 2. Differences in calculated cumulative incidences of Cause of Death Registry for patients compared to controls.

Cause of death	Time, years	All patients			Patients treated with curative intent			Patients treated with palliative intent			Ineligible patients		
		Risk difference	95% CI	*P*	Risk difference	95% CI	*P*	Risk difference	95% CI	*P*	Risk difference	95% CI	*P*
Hodgkin lymphoma	2	24.8	21.0-28.6		16.3	12.4-20.3		50	38.6-61.4		37.0	26.5-47.6	
	5	30.9	26.8-35.0	<0.01	22.8	18.3-27.3	<0.01	58.1	46.9-69.4	<0.01	39.5	28.9-50.2	<0.01
	10	35.1	30.8-39.4		28.0	23.1-32.9		59.5	48.3-70.7		42.3	31.5-53.1	
Other hematologic malignancies	2	4.3	2.5-6.2		0.5	-0.4-1.3		3.9	-0.6-8.4		20.8	11.9-29.6	
	5	5.5	3.4-7.5	<0.01	1.3	0.0-2.6	<0.01	5.0	-0.2-10.2	<0.01	23.1	13.9-32.3	<0.01
	10	6.8	4.5-9.2		3.1	1.1-5.2		6.2	0.5-11.9		23.0	13.7-32.2	
Other cancers	2	0.0	-1.1-1.1		-0.4	-1.4-0.7		2.2	-2.4-6.8		-0.3	-2.8-2.3	
	5	0.2	-1.6-2.1	0.07	0.4	-1.8-2.6	0.23	0.4	-5.0-5.8	0.63	-0.6	-5.0-3.7	0.08
	10	-2.0	-4.3-0.3		-2.0	-4.7-0.7		0.2	-6.9-7.2		-4.1	-8.6-0.5	
Other causes	2	-0.2	-1.5-1.1		-1.2	-2.2 to -0.3		6.1	-0.7-12.9		-1.6	-4.3-1.1	
	5	-1.6	-3.2-0.0	<0.01	-2.5	-4.0 to -0.9	<0.01	3.9	-3.4-11.2	0.39	-3.1	-5.9 to -0.3	0.11
	10	-4.9	-7.1-2.7		-5.6	-7.9 to -3.3		-3.8	-11.3-3.8		-3.2	-8.5-2.1	
Dementia	2	-0.6	-0.8 to -0.4		-0.2	-0.4-0.1		-1.49	-2.4 to -0.6		-1.1	-1.8 to -0.4	
	5	-0.9	-1.5 to -0.2	<0.01	-0.2	-1.0-0.7	0.37	-2.8	-4.0 to -1.6	0.06	-2.0	-2.9 to -1.0	0.03
	10	-1.3	-2.5-0.0		0.1	-1.6-1.9		-5.2	-6.8 to -3.5		-3.3	-4.53 to -2.0	
Cardiovascular diseases	2	-0.2	-1.7-1.3		-1.0	-2.3-0.2		1.6	-4.3-7.6		1.7	-3.1 to -6.6	
	5	-2.9	-4.8 to -1.0	<0.01	-2.2	-4.3 to -0.2	<0.01	-5.3	-11.5-0.9	0.12	-3.5	-8.6-1.6	<0.01
	10	-7.3	-9.8 to -4.9		-4.8	-7.8 to -1.8		-15.7	-22.2 to -9.2		-9.8	-15.1 to -4.5	
Infections	2	0.9	-0.4-2.2		-0.2	-1.0-0.7		0.8	-3.0-4.6		5.6	-0.2-11.3	
	5	0.2	-1.3-1.7	0.33	-0.2	-1.6-1.2	0.72	-0.4	-5.1-4.3	0.16	2.5	-3.4-8.4	0.88
	10	-1.5	-3.3-0.4		-1.3	-3.1-0.6		-4.7	-9.7-0.3		0.6	-5.9-7.0	

Cumulative incidence rates for different causes of death were calculated from date of diagnosis to death from the respective cause using the Aalen-Johansen estimator. Risk differences between patients and controls were calculated for each competing event at two, five, and ten years with 95% Confidence Intervals (CI).

treated patients.[15,23] With differences in patient selection and definitions of curatively intended treatment, CSS was 76% at five years in our cohort, comparable to the 85% reported for patients treated between 2000 and 2017 in 15 Swiss referral centers.[19] Also, Surveillance Epidemiology and End Result (SEER) data show that CSS is higher in patients treated with more intensive regimens.[24] In the presence of competing risks of death, the cumulative incidence function may prevent the bias seen in the complement of the Kaplan-Meier survival function and may better estimate patients' prognosis.[25,26] In our data, this is reflected in the lower competing risk of dying of HL compared to DSS in all groups, but with greater differences compared to DSS for those not treated with curative intent (Table 1 and *Online Supplementary Table S3*).

Treatment-related mortality is generally higher for older patients with HL, presumably related to age itself, poor performance status at diagnosis, underlying comorbidities, and reduced organ function.[16,27-29] Using a broad definition of TRM, we found a rate of 5.7% in all patients combined and 6.5% in the curatively treated patients. This is in line with the 5% TRM reported in a population-based study in British Columbia, Canada, also in the modern era, but the latter study provided no clear definition of TRM.[28] Prospective studies of combination chemotherapy in elderly HL patients have reported rates ranging from 7% to 18%.[14,15,27,30] Regimens that include novel drugs, such as brentuximab vedotin or programmed cell death protein-1 inhibitors are also studied in selected elderly patients. Of note, the BCAP trial by the Nordic and German Hodgkin study groups, substituting vincristine with brentuximab vedotin in CHOP, reported TRM at 2%.[31] The Echelon-1 trail provided a subanalysis of patients >60 years of age, encompassing 181 of the original study population of 1,334 adults with a rate of TRM of 4%.[32] Data from the elderly cohort of the GHSG HD21 study, evaluating BrECADD, are still awaited. With 10% and 26% of the deaths in curatively treated patients resulting from TRM and HL, respectively, less toxic but equally effective novel treatments would likely benefit survival, especially in those eligible for curative treatment.

With improved lymphoma treatment, increased mortality from causes other than HL, e.g., CVD, other cancers, and infections, has been a major concern in younger patients.[18,28] More recent treatment protocols hold promise to reduce non-cause mortality in adult HL patients in general.[30,33] In a study based on the SEER database, Gao *et al.*[34] demonstrated a higher cumulative incidence of death from causes other than HL in patients >60 years of age compared to younger patients. However, as older individuals have a naturally higher risk of dying from a variety of causes, comparison to young patients alone, even with competing risk approaches, may not be fully informative. In our cohort, treatment with contemporary chemotherapy regimens and limited use of radiotherapy did not lead to an increased long-term risk of death neither from other cancers, CVD nor infections compared to the more relevant general elderly population. In another SEER study including elderly HL patients, Dores *et al.*[35] reported significantly elevated standardized mortality rates from both heart disease, pulmonary disease, infections, myeloid malignancies and solid neoplasms. However, in a population mostly treated with ABVD, the excess risk seemed to decrease with time and, after one year, was noticeable only in patients with advanced disease. The reasons for these discrepancies may relate to differences in background risk of cardiac disease, more frequent use of ABVD in the SEER cohort, and the larger sample size of the latter study. Furthermore, morbidity from adverse effects may be a problem; we plan to assess the intermediate- or long-term prevalence of the abovementioned conditions in older survivors of HL as part of the current national project.

In our cohort of elderly patients, we show elevated risk of dying from hematologic malignancies other than HL compared to the general population. This increase in risk is most pronounced in the group of patients ineligible for typical HL treatment. In the latter group, 20 of 74 deaths were related to hematologic malignancies other than HL, 13 of which were due to NHL and 4 to CLL. This group comprised a high number of cases with mixed lymphoproliferative diseases at diagnosis: 54 of 81 patients. In their study of elderly classical HL patients, Cheng *et al.*[28] excluded 69 out of 893 patients (7.7%) due to other underlying CLL, small lymphocytic leukemia, or other NHL. To the best of our knowledge, similarly high rates of mixed lymphoproliferative disorders in younger patients with HL have not been reported. Both the high occurrence of multiple lymphoma entities at diagnosis and death from other hematologic malignances may be a matter of chance as the incidence of other lymphoproliferative diseases and myeloid neoplasia increases sharply with age.[9] This can not, however, explain the increased risk of death in patients with HL compared to the general population, and may suggest a different biology of some cases of HL in elderly patients. For patients with such mixed lymphomas, defining better treatment options that encompass complex entities seems warranted, and our data show that some may become long-term survivors. For deaths from myeloid neoplasia occurring after treatment, both pre-existing myelodysplasia and effects of chemotherapy, especially alkylating agents, may be involved.

In general, assessing causes of death is difficult, especially retrospectively, and the quality of registry data may vary.[36,37] The latter may be particularly relevant in rare and potentially curable malignant diseases, where uncertainties about diagnostic codes for different lymphoproliferative diseases and unclear remission status at time of death may reduce the accuracy of information on death certificates. We observed such possible discrepancies in two ways. First, a proportion of patients were registered as dying from different hematologic diseases without any prior diagnosis other than HL, either by the CRN or record review.

These deaths were most commonly registered in DAAR as C85.9, i.e., NHL without further specification. The opposite, i.e., death from HL in the absence of a prior diagnosis in the CRN, did not occur in the general population. We believe such discrepant classification of HL patients by DAAR results from uncertainties about the exact lymphoma entity at the time of death, details that are not always known to the physician signing the death certificate. For our analysis, we therefore reclassified such cases as deaths from HL. Secondly, there were a number of discrepancies between the assumed cause of death as assessed by record review and both the underlying or immediate cause of death from DAAR. Reassuringly, most cases of TRM and unknown causes from chart reviews were classified by DAAR as HL as the underlying cause of death. Furthermore, approximately 50% agreement was seen for other hematologic malignancies (after corrections had been made; see above), CVD, and second cancers. Compared to the report from Goa *et al.*,[34] we report a similar distribution of HL as the underlying cause of death (52.2% of all deaths in patients >60 years of age compared to our 48.7%), but different rates of death from CVD (20.0% *vs*. 10.7%), secondary neoplasms (6.0% *vs*. 10.7%), and infections (4.1% *vs*. 8.1%). Comparison across studies is difficult; Goa *et al*.[34] included patients diagnosed between 1983 and 2005, most of whom were probably treated with now outdated protocols. The marked drop in mortality for CVD observed for the general Norwegian population over the last three decades may also explain some of these discrepancies.[38] Corresponding numbers in the British Columbia cohort treated since 2000, where 160 deaths had occurred in the 327 patients treated with curative intent, were 49.4% for deaths from HL (including deaths from immediate treatment toxicity), 19.4% for secondary malignancies (including other hematologic malignancies), and 8.8% for CVD, all possibly more representative comparators to our data.[28]

The optimal treatment for elderly patients with HL remains controversial with no established standard of care. Norwegian recommendations have advocated CHOP for most patients, and ABVD for selected patients 60-70 years of age.[14] For early stages, both with or without risk factors, the use of radiotherapy to sites involved by lymphoma has been standard.[14] For advanced disease, only residual disease or areas of initial bulk routinely received irradiation. It is encouraging that OS is better in early stages, with no increased long-term risk of death from either CVD or secondary cancers in the whole cohort. Altogether, OS of our curative cohort was similar to the equally large and also population-based study from British Columbia, both with a 5-year OS rate of 60%, treated with ABVD.[28] Concerns have been raised about exaggerated risks of pulmonary toxicity from bleomycin in the elderly. Five patients in our cohort (7% of those treated with ABVD in the curative group) died of pulmonary toxicity possibly associated with bleomycin. Recent Nordic data suggest that ABVD/AVD may be superior to CHOP for patients with advanced stages, but no randomized comparison has ever been undertaken.[39]

Our retrospective study is one of the largest population-based studies evaluating older patients with HL, including matched controls from the general population. With the high coverage of CRN, selection bias was minimized. Despite being retrospective in nature, access to individual patient records from multiple health-care resources has allowed retrieval of detailed data, with data on causes of death from DAAR, competing risk analysis of patients, and controls being examined together for the first time.

Disclosures

No conflicts of interest to disclose.

Contributions

KL and AF are responsible for study conception and design. KL, BLW, ØF, UMF, HB, IBB and AF are responsible for data collection and assembly. KL, RRKJ and AF are responsible for data analysis and interpretation. KL, RRKF and AF created the figures and tables. SB and AF supervised the study. KL and AF wrote the manuscript. All authors contributed to writing the manuscript, and reviewed and approved the final version.

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Data-sharing statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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