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

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Supplementary Material

Table of contents

Supplementary methods

Patients

Patients diagnosed with Hodgkin Lymphoma (HL) from January 1995 to December 2015 and aged 60 years or older were identified through Cancer Registry of Norway (CRN). The CRN has an estimated 98.8% completeness on all cancer diagnoses in Norway based on accumulated information from pathology reports, discharge hospital records and death certificates [1]. For the present study, additional patients were retrieved from the Lymphoma registry at Oslo University Hospital, the referral institution or the South-Eastern part of Norway. As detailed below, 8 additional HL patients (4 with mixed lymphomas, 4 with HL treated with curative intent) were identified in this registry from 2000-2015, for an estimated coverage of 97.1% (266/274) for elderly HL patients in this region alone. Similar hospital based registries were not available in the other regions. Diagnoses from the CRN were cross-checked with original pathology reports to exclude any errors in registration.

Data retrieval

Clinical data were retrieved from the time of diagnosis, treatment and follow-up from medical records at local and regional hospitals as well as from general practitioners.

Collected data were reviewed by the coauthors, aided by study nurses.

For each HL patient, we retrieved information on age, sex, performance status by Eastern Cooperative Oncology Group (ECOG) classification [2], independency of help in personal activity of daily living (pADL) [3], comorbidities using the Modified Cumulative Illness Rating Scale for Geriatrics (CIRS-G) [4], presence of human immunodeficiency virus (HIV) infection, concomitant medications at diagnosis and smoking habits. Patients underwent staging and treatment evaluation for HL according to national guidelines at the time, mostly consisting of computed tomography (CT) scanning and a bone marrow trephine biopsy at diagnosis and repeated during treatment and after treatment for response assessment. Positron emission tomography-CT (PET-CT) was introduced gradually for staging and evaluation from 2008 onwards. Captured disease-related parameters included extent of disease by Ann Arbor stage, presence or absence of bulky disease (defined as any lesion ≥ 10 cm in largest diameter on CT scans), presence of B symptoms (unexplained fever, weight loss, night sweats). For stage I-IIA disease, risk factors were recorded as presence of any bulky lesions, erythrocyte sedimentation rate > 50 mm/h, involvement of more than two or two non-contiguous lymphatic regions, infradiaphragmal disease except singular inguinal lesions, differentiating early favorable (no risk factor) and unfavorable disease (≥1 risk factor) [5]. For stage IIB, III or IV disease, risk factors were registered according to the International Prognostic Score (IPS) [6]. From histology reports, we recorded whether a review had been undertaken at a university referral pathology department, histologic subtype of HL and presence of Ebstein Barr Virus (EBV) in tumor cells by EBV encoded small RNAs (EBER) in-situ hybridization. Information concerning choice of chemotherapy regimens, dates of treatment, doses, number of cycles and complications, recorded retrospectively by the study team and expressed by CTC-AE criteria, were detailed. For patients not receiving treatment directed to HL or those treated with dose-reduced regimens, the reason for these adaptations was documented.

Patients were classified into one of three groups based on treatment and treatment intent:

1. Patients ineligible for HL treatment and/or outcome had other concomitant severe diseases, such as other cancers, severe cardiovascular disease (CVD) or dementia that precluded any treatment directed specifically at HL, died before the diagnostic biopsy was reviewed or HL was diagnosed at autopsy.

Patients with a previous or simulations diagnosis of Non-Hodgkin Lymphoma (NHL) or chronic lymphocytic leukemia (CLL) were referred to as having a mixed lymphoma (Supplementary Figure S1) and could receive treatment aimed at both the HL and NHL/CLL component of their disease, including combination chemotherapy regimens that would be considered adequate for HL. Due to the complexity of the lymphoma, they were however considered ineligible for outcome of HL alone;

2. Patients treated with palliative intent either received no definitive treatment (steroids or palliative radiotherapy allowed) or chemotherapy directed at HL at doses less than 50% of the dose of central drugs in recommended regimens (i.e. < 50% doxorubicin and/or cyclophosphamide) in CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) and standard BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone), less than 50% doxorubicin and/or dacarbacine in ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), less than 50% of chlorambucil ChlOPP (chlorambucil, vincristine, procarbazine, prednisolone), or records clearly expressed the intent to be palliative;

3. All other patients, i.e. those treated with curative intent, received typical regimens directed towards HL at more than 50% dose of central drugs or curatively intended radiation therapy. Radiotherapy as the primary treatment was deemed curative when applied as extended field in patients with classical HL or as involved field in patients with nodular lymphocyte predominant HL (NLPHL) and doses exceeded 30 Gy, otherwise deemed palliative.

Treatment principles for patients with HL over the age of 60 years are detailed in national recommendations issued by the Norwegian Directorate of Health [7]. Because of toxicity problems seen with regimens used to younger patients, CHOP given every third week was standard from 2000-2015 for curatively treated patients. Patients deemed fit could receive ABVD, and bleomycin could be omitted if pulmonary toxicity was a concern. Patients with early favorable disease (for definition see above) would normally receive two courses of chemotherapy followed by consolidative involved-field radiotherapy, those with early unfavorable disease would receive 4 cycles before radiotherapy. Patients with IIB-IV disease would receive 6-8 cycles of either CHOP or ABVD, with localized radiotherapy to be considered for sites with initial bulk or remaining visible lesions. Other options for curative chemotherapy were BEACOPP or, in cases with concern over cardiac toxicity, anthracyline-free regimens in the form of ChlOPP. Radiotherapy alone was not recommended for classical HL, but was given to extended fields to a low number of patients with stage I-IIA disease without risk factors according to guidelines before 2000. For palliative treatment, dose-reductions of the regimens listed above (for instance CHOP without doxorubicin, referred to as CVP), single agent chemotherapy (mostly trofosfamide) or radiotherapy were listed options. Treatment recommendations for patients with NLPHL were generally similar, except involved field radiotherapy RT to 30-35 Gy was an option for stage I-IIA patients without risk factors and Rituximab could be added to chemotherapy in patients with stage IIB-IV.

For all patients, the most likely cause of death was contracted from medical records specified using the International Classification for Disease (ICD-10) [8]. Any 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), not classified in more detail.

Matched controls

Norwegian Cause of death Registry (DAAR) provided the date and cause of death for all patients and 10 cancer-free controls for every included patients, matched on age, sex and community of residence

at the time of HL diagnosis. Causes of death in DAAR are specified using the ICD-10 and at the level of the immediate and the underlying cause of death. These data are collected from death certificates issued by physicians at the time of death of any Norwegian citizen.

For competing risk analysis the underlying cause of death from DAAR was used in patients and controls with the following correction concerning death from different kinds of hematological malignancies. We assume that the discrepancies likely resulted from lack of information of the exact lymphoma diagnosis by the physician issuing the death certificate. These inconsistencies were observed in patients dying of HL according to review of records, but from hematological malignancies other than HL (C82-C96 or D46-47) in data from DAAR. Patients never diagnosed with a hematological malignancy other than HL according to neither patient records nor CRN reports were deemed unlikely to have died of any such conditions. These cases were recoded before further comparison. We therefore recoded the DAAR data from other hematological malignancies (C82-C96 or D46-47) to HL (C81) in 14 cases in the ineligible group, 7 cases in the palliative group and 14 cases in the curative group. Otherwise, only underlying causes of death from DAAR were used for the competing risk analysis in both patients and controls.

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. The approval allowed retrieval of data from CRN, DAAR and patients' records for deceased patients. All patients alive by January 2017 were notified of the study by written mail. Survivors who did not consent to participation were instructed to reply by returning the informed consent form to the study team. Positive consent would not require any action on the part of the survivor. The study team did not get any objections in return.

Statistical analysis

Continuous variables were described using median and range, whereas categorical data were described with proportions. Groups of patients were compared using the Mann-Whitney or Kruskal-Wallis tests, Chi-Square and Fisher Exact tests, as appropriate.

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, for those alive by the time of last data retrieval from the CRN. Cause-specific survival (CSS) was estimated from diagnosis to death of HL, censored for all 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, hematological 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. Causes of death were grouped as HL (C81), hematological malignancies other than HL (C82-C96, D46-D47 by ICD-10), other cancers (C02-C80, D37-D43), dementia (F01-03, G30-31, R54) cardiovascular diseases (I06-I74), infections (J09-J96, K26-K83, L97-L98, M16-M86, N12-N39, U07), or other causes (all other causes of death). Risk differences between patients and controls were calculated for each competing event at 2, 5 and 10 years with 95% confidence intervals (CI).

All statistical analyses were two sided and p-values of < 0.05 considered statistically significant. We used International Business Machines Statistical package for social services (IBM SPSS®) version 28.0 (Armonk, NY) and R software version 4.1.1. (Supplementary Table S1).

Supplementary Table S1: Specific packages used for R software version 4.1.1.

Package	Functions	Package Versions
haven	read_sav	2.43
survminer	ggsurvplot	0.4.9
survival	survfit, survdiff	3.4-0
networkD3	sankeyNetwork	0.4
prodlim	prodlim	2019.11.13
cmprsk	cuminc	2.2-11

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Supplementary Table S2: Patient, disease and treatment characteristics of the study population according to the three study groups.

Characteristic	All	Ineligible group	Palliative group	Curative group	P
Number of patients (%)	492	81 (16.5)	74 (15.0)	337 (68.5)	
Sex					0.545
Male	283 (57.5)	51 (63)	41 (55.5)	191 (56.7)	
Female	209 (42.5)	30 (37)	33 (44.5)	146 (43.3)	
Age at diagnosis/ years					**<0.001**
Median (range)	71 (60-94)	73 (61-94)	81 (61-94)	69 (60-90)	
60 – 69	202 (41.1)	29 (35.8)	7 (9.5)	166 (49.3)	
70 – 79	194 (39.4)	26 (32.1)	28 (37.8)	140 (41.5)	
≥ 80	96 (19.5)	26 (32.1)	39 (52.7)	31 (9.2)	
Histology					**0.004**[a]
Nodular lymphocyte predominant	54 (11.6)	0 (0)	7 (9.6)	47 (13.9)	
Nodular sclerosis	158 (34.1)	0 (0)	27 (37.0)	131 (38.9)	
Mixed cellularity	62 (13.4)	0 (0)	11 (15.1)	51 (15.1)	
Lymphocyte-depleted	14 (3.0)	0 (0)	8 (10.8)	6 (1.8)	
Lympocyte-rich	36 (7.6)	0 (0)	5 (6.8)	31 (9.2)	
Classical nos	71 (15.3)	0 (0)	12 (16.4)	59 (17.5)	
Hodgkin lymphoma nos	15 (3.2)	16 (22.9)	3 (4.1)	12 (3.6)	
Mixed lymphoma	54 (11.6)	54 (77.1)	0 (0)	0 (0)	
EBV staining in biopsy					**<0.001**
Positive	33 (7.6)	4 (16.7)	12 (16.2)	17 (5.0)	
Negative	103 (23.7)	9 (37.5)	10 (13.5)	84 (24.9)	
Not described	299 (68.7)	11 (45.8)	52 (70.3)	236 (70.0)	
Pathology review at university hospital					0.093
Yes	398 (88.8)	38 (86.4)	61 (83.6)	299 (90.3)	
No	50 (11.2)	6 (13.6)	12 (16.4)	32 (9.7)	
Stage (Ann Arbor)					0.308
I - II	199 (44.7)	16 (47.1)	29 (39.2)	154 (45.7)	
III - IV	246 (55.3)	18 (52.9)	45 (60.8)	183 (54.3)	
B-symptoms					**0.019**
Absent	244 (55.0)	16 (48.5)	32 (43.2)	196 (58.2)	
Present	200 (45.0)	17 (51.5)	42 (56.8)	141 (41.8)	
ECOG status					**<0.001**
0 - 1	310 (71.6)	18 (66.7)	27 (37.5)	265 (79.3)	
≥ 2	123 (28.4)	9 (37.0)	45 (62.5)	69 (20.7)	
HL risk groups					0.068
Early favorable	94 (21.6)	7 (26.0)	8 (10.8)	79 (23.6)	
Early unfavorable	60 (13.8)	3 (11.1)	11 (14.9)	46 (13.7)	
Advanced					0.162
IPS (0 - 2)	94 (21.6)	5 (18.5)	13 (17.6)	76 (22.7)	
IPS (3 - 4)	139 (31.9)	6 (22.2)	30 (40.5)	103 (30.7)	
IPS (5 - 7)	49 (11.2)	6 (22.2)	12 (16.2)	31 (9.3)	
Personal activities of daily living					**<0.001**
Independent	318 (77.6)	6 (82.2)	29 (40.3)	283 (85.8)	
Dependent	92 (22.4)	2 (2.7)	43 (60.0)	47 (14.2)	
CIRS-G total					**<0.001**
Median (range)	7 (0-25)	6 (0-18)	10 (0-25)	6 (0-23)	
CIRS - G (≤ 7)	259 (62.0)	7 (63.6)	26 (35.1)	226 (67.9)	
CIRS - G (≥ 8)	159 (38.0)	4 (36.4)	48 (64.9)	107 (32.1)	
Treatment directed at HL					**<0.001**
Chemotherapy and/or irradiation	392 (84.7)	0 (0)	55 (74.3)	337 (100)	
No treatment given (other than steroids)	46 (9.9)	27 (52.0)	19 (25.7)[b]	0 (0)	
Other lymphoma treatments	25 (5.4)	25 (48.1)	0 (0)	0 (0)	
Treatment regimen (primary treatment)					**<0.001**
CHOP	270 (69.1)	20 (80.0)[c]	12 (26.1)	238 (74.4)	
ABVD/AVD/ABOP	64 (16.4)	1 (4.0)[d]	0 (0)	63 (19.7)	

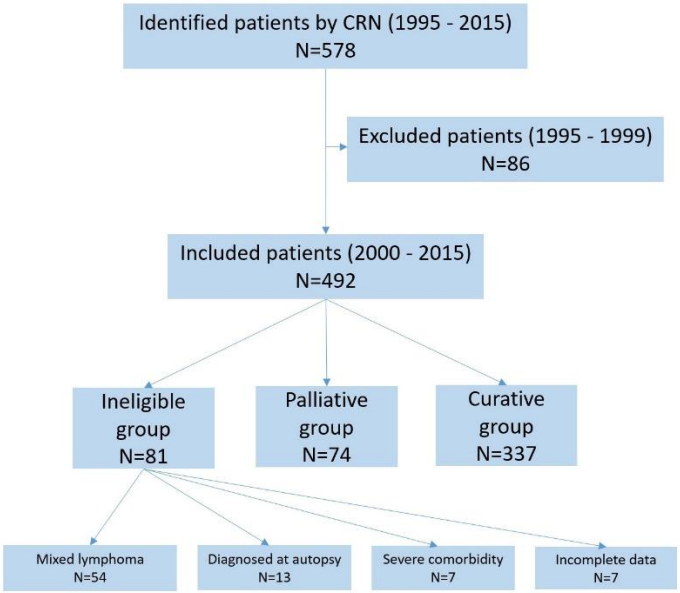
BEACOPP	5 (1.3)	0 (0)	1 (2.2)[e]	4 (1.3)	
Anthracycline-free regimens	52 (13.3)	4 (16.0)	33 (71.7)	15 (4.7)	
Irradiation as part of primary treatment					**<0.001**
Curative radiotherapy only	17 (10.1)	0 (0)	0 (0)	17 (11.0)	
Consolidation limited disease	96 (57.1)	0 (0)	0 (0)	96 (62.3)	
Consolidation advanced disease	41 (24.4)	0 (0)	0 (0)	41 (26.6)	
Palliation	14 (8.3)	0 (0)	14 (100)	0 (0)	

Continuous variables were described using median and range, whereas categorical data were described with proportions. Groups of patients were compared by Pearson's chi-squared test. Statistically significant P-values are indicated in bold. Across variables, data were missing in between 1 and 72 cases, mostly in the ineligible group, and only numbers with valid data are shown. Sums may not add to the total in each group, percentages are given for valid cases only. [a] Data were missing in a larger proportion of the ineligible cases and a formal comparison was therefore done for the palliative and curative groups only, excluding missing cases. [b] Chemo- or radiotherapy not given due to reduced general condition (n=5), patients wish (n=3), comorbidities (n=5), age (n=2), or considered in no need of treatment other than steroids (n=4). [c] CHOP given with or without rituximab. [d] AVD given after lobectomy for lung carcinoid. [e] The palliative patient with BEACOPP had reduced dosages of chemotherapy. NOS: not otherwise specified; Mixed lymphoma defined as previous or concomitant second malignant lymphoproliferative disease other than Hodgkin lymphoma; ECOG: Performance status by Eastern Cooperative Oncology Group; EBV: Ebstein Barr Virus; HL: Hodgkin lymphoma; IPS: International prognostic score; CIRS- G: Modified Cumulative Illness Rating Scale for Geriatrics; CHOP: cyclophosphamid, doxorubicin, vincristine and prednisolone; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; AVD: doxorubicin, vinblastine, and dacarbazine; ABOP: doxorubicin, bleomycin, vincristine and prednisolone; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; Antracycline-free regimes included COP: cyclophosphamide, vincristine and prednisolone, ChlVPP: chlorambucil, vinblastine, procarbazine and prednisolone, CEPK: carmustine, etoposide, prednisolone and chlorambucil; trophosphamide or occasional treatment based on bendamustin or gemcitabine.

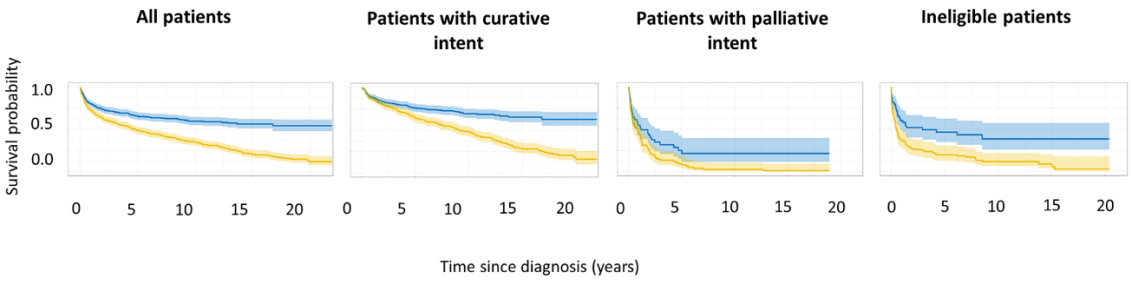
Supplementary Table S3: Cause-specific survival in all patients combined and according to subgroup

	All patients		Patients with curative intent		Patients with palliative intent		Ineligible patients	
Time	Survival %	95% CI	Survival %	95% CI	Survival %	95% CI	Survival %	95% CI
2	73.5	69.5;77.6	83.4	79.5;87.5	42.6	31.7;57.4	51.8	40.3;66.7
5	65.9	61.6;70.5	76.2	71.7;81.0	25.0	14.6;42.7	46.5	34.6;62.4
10	59.5	54.7;64.6	69.4	64.1;75.0	21.4	11.6;39.6	38.6	25.9;57.4

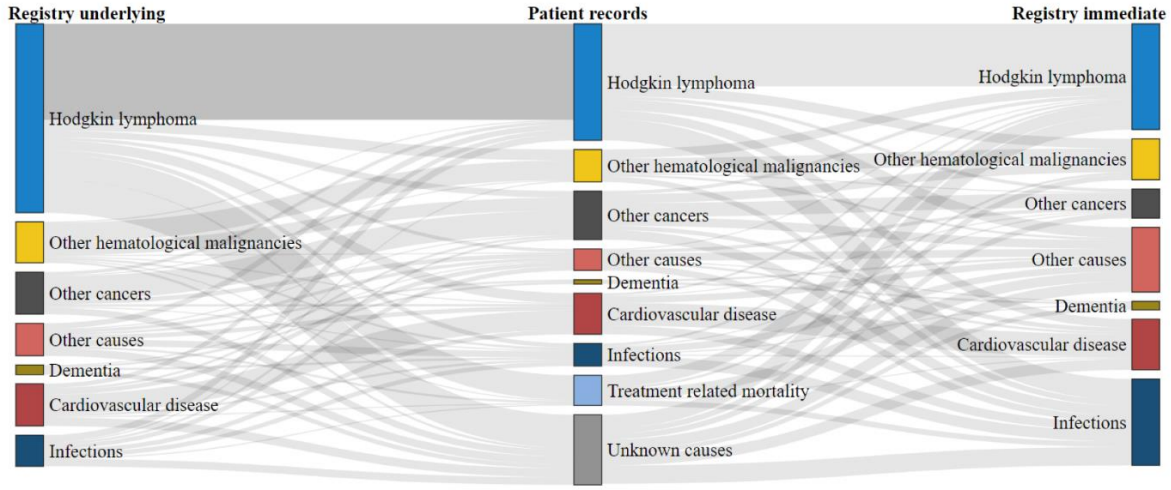
Cause-specific survival rates for death due to Hodgkin Lymphoma (HL) were calculated from date of diagnosis to death from HL using Kaplan-Meier statistics at 2, 5 and 10 years with 95% confidence intervals (CI).



Supplementary Figure S1: Flowchart of included patients with Hodgkin lymphoma in Norway 1995-2015. CRN: Cancer Registry in Norway. Mixed lymphoma defined as a previous or concomitant presence of a second malignant lymphoproliferative disease other than Hodgkin lymphoma.



Supplementary Figure S2: Cause-specific survival (blue line) and compared to overall survival (yellow line) for all patients combined and subgroups.



Supplementary Figure S3: Individual patient information regarding cause of death as the underlying or immediate cause from the Norwegian Cause of Death Registry compared to patient records.