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

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Disclosures

No conflicts of interest to disclose.

Contributions

KL and AF: conception and design of the study; KL, BLW, ØF, UMF, HB, IBB and AF: data collection and assembly; KL, RRKJ and AF: data analysis and interpretation; KL, RRKF and AF: created figures and tables; SB and AF: supervised; KL and AF: wrote the manuscript. All authors took part in writing the manuscript and reviewed and approved the final version.

Data-sharing statement

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

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Abstract

Elderly Hodgkin Lymphoma (HL) patients are poorly characterized and underrepresented 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 diagnosed between 2000-2015 were identified by Cancer Registry of Norway, records reviewed in detail and compared to data from 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 10 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 10 years in the palliative and ineligible groups, respectively. There was an increased risk of dying from hematological 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 over 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 area occurs 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, the HL patients older than 60 years remains 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 elderly 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 and yet at the same time detailed manner. Herein, we aim to combine population-based identification of patients from 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 area between 2000 and 2015. To better address the higher risk of death from other diseases common in the 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 or older at diagnosis were identified through CRN (Online Supplementary Methods).

Clinical data were retrieved from diagnosis, treatment and follow-up from medical records at local and regional hospitals and from general practitioners by the coauthors 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, 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 less than 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 more than 50% dose of central drugs or curatively intended radiation therapy.

The most likely cause of death was contracted from medical records and specified using the International Classification for Disease (ICD-10) [17]. Death occurring during and up to 3 months after the last antineoplastic treatment and not due to progression of HL, was deemed treatment related mortality (TRM).

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 hematological 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, 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. 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 Supplementary Table S1).

Results

Patient characteristics

Through the CRN, we identified 561 patients with HL over 60 years of age in Norway from the time period 1995-2015 (Online supplementary Figure S1). Additionally, 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 (11% of all patients), 20 cases 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 a palliative intent and 337 (69%) received treatment with an intent to cure the patient.

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 (61-94), 81 (61-94) and 69 years (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 done 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 patients' 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 (95% Cl 6.0-22.0) years. 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 overall survival rates were 27% (95% Cl 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 the 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 year, 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%, respecivley, considerably higher than for the other subgroups (Supplementary Figure S2 and Supplementary Table S3).

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, neither 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. Records lacked adequate information on cause of death in 18% of the patients. After correction for ambiguities concerning type of hematological malignancy (details Online Supplementary Methods), DAAR reported, a higher proportion of deaths attributed to HL, both for all patients combined (49 versus 30%) and in the three groups. DAAR reported death from hematological 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 precent of deaths with HL as the underlying cause in DAAR were differently classified by review of records, mostly other hematological malignancies (6%) and CVD (5%). Concerning other causes of death, the best agreement on individual patient basis was seen for other hematological malignancies, other cancers and CVD, all with about 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 2 years to 28% after 10 years for the curatively treated patients, compared to 59% and 42% after 10 years in the ineligible and palliative groups, respectively. Overall, and in all three groups, the risk of dying from another hematological malignancy was higher than in the normal population, with the highest difference seen for the ineligible patients; 20% and 23% at 2 and 5 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.

Discussion

Using individual patient records, we report a population-based retrospective analysis of all patients diagnosed with HL at age ≥ 60 years in Norway between 2000-2015. For curatively treated patients, OS at 2 and 5 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 5 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 hematological 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 important [5, 6, 8, 18, 19]. Also, patients' frailty and comorbidities are associated with choice of treatment and one-year all-cause mortality [20, 21, 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 demonstrate 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 2 and 5 years, respectively. To prevent deaths from HL in the elderly, more focus should be put on the patients never receiving curative treatment, accounting for about 1/3 of the population in our cohort.

Several reports demonstrate improved outcomes in recent decades for patient with HL over the age of 60, and most of this improvement is probably seen for the curatively treated patients [15, 23]. With differences in patient selection and definitions of curatively intended treatment, CSS was 76% at 5 years in our cohort, comparable to 85% reported for patients treated between 2000 and 2017 in 15 Swiss referal 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 bias seen in the complement of the Kaplan-Meier survival function and may better estimate patients' prognosis [25, 26]. In our data, this is refleced 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 Supplementary Table S3).

TRM 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 in line with the 5% TRM reported in a population-based study in British Columbia also from the modern area, 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 trail 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 over the age of 60, encompassing 181 of the original study population of 1334 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 over 60 years 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 normal 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 difference 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 and 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 hematological 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 hematological 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, i.e. 54 of 81 patients. In their study of elderly classical HL patients, Cheng et al [28] excluded 69 out 893 patients (7.7%) due 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 hematological malignances may be a matter of chance as the incidence of other lymphoproliferative diseases and myeloid neoplasia increases sharply with age [9]. This should 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 preexisting 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 hematological diseases without any prior diagnosis other than HL, neither by CRN nor 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 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. Further, about 50% agreement was seen for other hematological malignancies (after corrections done as 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 over 60 years, compared to our 48.7%), but different

rates of death from CVD (20.0% versus 10.7%), secondary neoplasms (6.0% versus 10.7%) and infections (4.1 versus 8.1%). Comparison across studies is difficult, but by 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 from year 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 hematological 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 received irradiation routinely. It is encouraging that OS is better in early stages, with no increased long-term risk of death from neither CVD nor 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 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 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 has been done for the first time.

References:

1. Cancer Registry of Norway. Norwegian Registry of Lymphoid Malignancies https://www.kreftregisteret.no/en/The-Registries/clinical-registries/norwegian-registry-of-lymphoid-malignancies/ Accessed June 2, 2023.
2. Ansell SM. Hodgkin lymphoma: A 2020 update on diagnosis, risk□stratification, and management. Am J Hematol. 2020;95(8):978-989.
3. Mathas S, Hartmann S, Küppers R. Hodgkin lymphoma: Pathology and biology. Semin Hematol. 2016;53(3):139-147.
4. Eichenauer DA, Engert A, André M, et al. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Supp 3:iii70-75.
5. Bachanova V, Connors JM. Hodgkin lymphoma in the elderly, pregnant, and HIV-infected. Semin Hematol. 2016; 2016;53(3):203-208.
6. Sjöberg J, Halthur C, Kristinsson SY, et al. Progress in Hodgkin lymphoma: a population-based study on patients diagnosed in Sweden from 1973-2009. Blood. 2012;119(4):990-996.
7. Stark GL, Wood KM, Jack F, et al. Hodgkin's disease in the elderly: a population-based study. Br J Haematol. 2002;119(2):432-440.
8. Walker A, Schoenfeld ER, Lowman JT, Mettlin CJ, MacMillan J, Grufferman S. Survival of the older patient compared with the younger patient with Hodgkin's disease. Influence of histologic type, staging, and treatment. Cancer. 1990;65(7):1635-1640.
9. Jagadeesh D, Diefenbach C, Evens AM. XII. Hodgkin lymphoma in older patients: challenges and opportunities to improve outcomes. Hematol Oncol. 2013;31 Suppl 1:69-75.
10. Engert A, Ballova V, Haverkamp H, et al. Hodgkin's Lymphoma in Elderly Patients: A Comprehensive Retrospective Analysis From the German Hodgkin's Study Group. J Clin Oncol. 2005;23(22):5052-5060.
11. Böll B, Bredenfeld H, Goergen H, et al. Phase 2 study of PVAG (prednisone, vinblastine, doxorubicin, gemcitabine) in elderly patients with early unfavorable or advanced stage Hodgkin lymphoma. Blood. 2011;118(24):6292-6298.
12. Böll B, Görgen H, Fuchs M, et al. ABVD in older patients with early-stage Hodgkin lymphoma treated within the German Hodgkin Study Group HD10 and HD11 trials. J Clin Oncol. 2013;31(12):1522-1529.
13. Halbsguth TV, Böll B, Borchmann P, Diehl V. The unique characteristics and management of patients over 60 years of age with classic Hodgkin lymphoma. Curr Hematol Malig Rep. 2011;6(3):164-171.
14. Kolstad A, Nome O, Delabie J, Lauritzsen G, Fossa A, Holte H. Standard CHOP-21 as first line therapy for elderly patients with Hodgkin's lymphoma. Leuk Lymphoma. 2007;48(3):570-576.
15. Proctor SJ, Wilkinson J, Jones G, et al. Evaluation of treatment outcome in 175 patients with Hodgkin lymphoma aged 60 years or over: the SHIELD study. Blood. 2012;119(25):6005-6015.
16. Proctor SJ, White J, Jones GL. An international approach to the treatment of Hodgkin's disease in the elderly: launch of the SHIELD study programme. Eur J Haematol. 2005;75(s66):63-67.
17. World Health O. International statistical classification of diseases and related health problems. 10th revision, Fifth edition, 2016 ed. Geneva: World Health Organization, 2015.
18. Proctor SJ, Taylor P, Mackie M, et al. A numerical prognostic index for clinical use in identification of poor-risk patients with Hodgkin's disease at diagnosis. Leuk Lymphoma. 1992;7 Suppl:17-20.
19. Moccia AA, Aeppli S, Güsewell S, et al. Clinical characteristics and outcome of patients over 60 years with Hodgkin lymphoma treated in Switzerland. Hematol Oncol. 2021;39(2):196-204.
20. Carter J, David KA, Kritharis A, Evens AM. Current Treatment Options for Older Patients with Hodgkin Lymphoma. Curr Treat Options Oncol. 2020;21(5):42.
21. Rodday AM, Hahn T, Kumar AJ, et al. First-line treatment in older patients with Hodgkin lymphoma: a Surveillance, Epidemiology, and End Results (SEER)-Medicare population-based study. Br J Haematol. 2020;190(2):222-235.
22. Kumar AJ, Nelson J, Rodday AM, et al. Development and validation of a prediction model for 1-year mortality among older adults with Hodgkin Lymphoma who receive dose-intense chemotherapy. J Geriatr Oncol. 2021;12(8):1233-1239.

23. Böll B, Görgen H. The treatment of older Hodgkin lymphoma patients. Br J Haematol. 2019;184(1):82-92.
24. Rodday AM, Hahn T, Kumar AJ, et al. Association of Treatment Intensity With Survival in Older Patients With Hodgkin Lymphoma. JAMA Netw Open. 2021;4(10):e2128373.
25. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation. 2016;133(6):601-609.
26. Berry SD, Ngo L, Samelson EJ, Kiel DP. Competing Risk of Death: An Important Consideration in Studies of Older Adults. J Am Geriat Soc. 2010;58(4):783-787.
27. Evens AM, Hong F, Gordon LI, et al. The efficacy and tolerability of adriamycin, bleomycin, vinblastine, dacarbazine and Stanford V in older Hodgkin lymphoma patients: a comprehensive analysis from the North American intergroup trial E2496. Br J Haematol. 2013;161(1):76-86.
28. Cheng PTM, Villa D, Gerrie AS, et al. The outcome of older adults with classic Hodgkin lymphoma in British Columbia. Blood Adv. 2022;6(22):5924-5932.
29. Kiserud C, Loge J, Fosså A, Holte H, Cvancarova M, Fosså S. Mortality is persistently increased in Hodgkin's lymphoma survivors. Eur J Cancer. 2010;46(9)1632-1639.
30. Favier O, Heutte N, Stamatoullas-Bastard A, et al. Survival after Hodgkin lymphoma: causes of death and excess mortality in patients treated in 8 consecutive trials. Cancer. 2009;115(8):1680-1691.
31. Boell B, Fosså A, Goergen H, et al. B-CAP (brentuximab vedotin, cyclophosphamide, doxorubicin and predniso(lo)Ne) in Older Patients with Advanced-Stage Hodgkin Lymphoma: Results of a Phase II Intergroup Trial By the German Hodgkin Study Group (GHSG) and the Nordic Lymphoma Group (NLG). Blood. 2018;132(Supplement 1):926.
32. Evens AM, Connors JM, Younes A, et al. Older patients (aged ≥60 years) with previously untreated advanced-stage classical Hodgkin lymphoma: a detailed analysis from the phase III ECHELON-1 study. Haematologica. 2022;107(5):1086-1094.
33. Provencio M, Millán I, España P, et al. Analysis of Competing Risks of Causes of Death and their Variation Over Different Time Periods in Hodgkin's Disease. Clin Cancer Res. 2008;14(16):5300-5305.
34. 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. 2021;21(1):955.
35. Dores GM, Curtis RE, Dalal NH, Linet MS, Morton LM. Cause-Specific Mortality Following Initial Chemotherapy in a Population-Based Cohort of Patients With Classical Hodgkin Lymphoma, 2000-2016. J Clin Oncol. 2020;38(35):4149-4162.
36. Pedersen AG, Ellingsen CL. Data quality in the Causes of Death Registry. Tidsskr Nor Laegeforen. 2015;135(8):768-770.
37. Foss Abrahamsen A, Egeland T, Hansen S, Langholm R, Holte H, Kvaløy S. Hodgkin's disease in a national and hospital population: trends over 20 years. Eur J Cancer. 1997;33(14):2380-2383.
38. Norwegian Institute of Public Health. Cardiovascular disease in Norway. https://www.fhi.no/en/op/hin/health-disease/cardiovascular-disease-in-norway---/ Accessed April 25, 2023
39. Övergaard N, Lia K, Asdahl P, et al. T082: AVD - a possible golden standard in the first-line treatment of older classical Hodgkin lymphoma patients. Hemasphere. 2022;6(Suppl):37-38.

Table 1: Causes of death according to Norwegian causes 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 hematological 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. Statistically significant P-values are indicated in bold. [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.

Table 2: Differences in calculated cumulative incidences of cause of death for patients compared to controls.

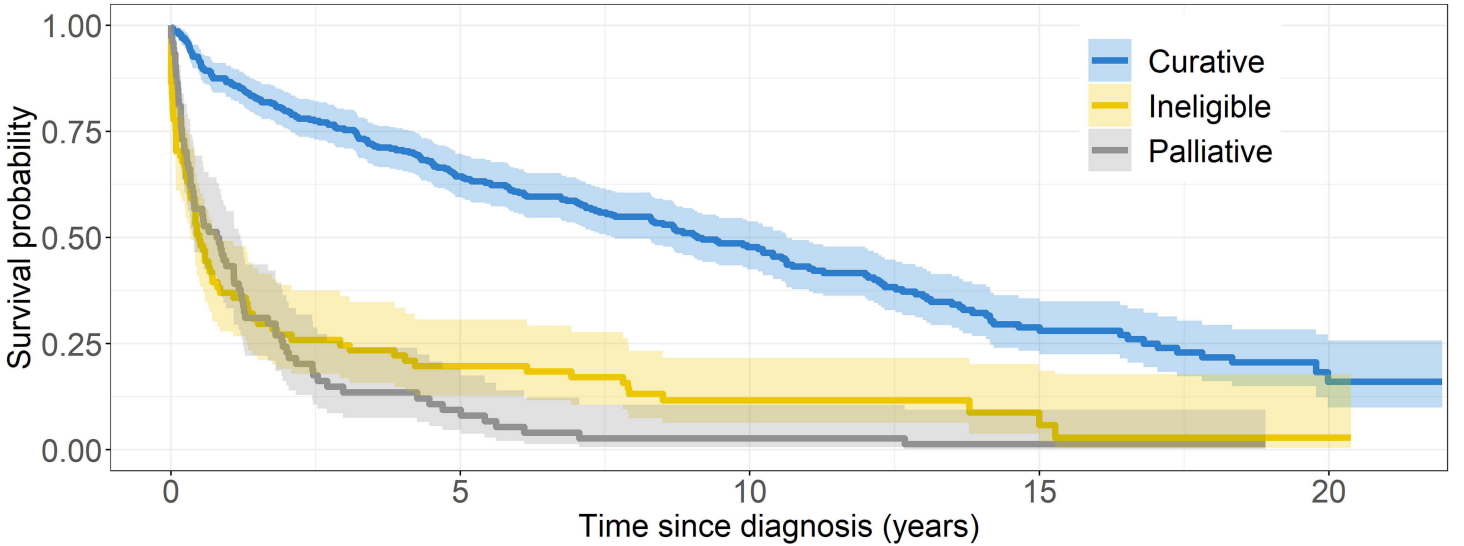
		All patients			Patients with curative intent			Patients with palliative intent			Ineligible patients		
Cause of death	Time	Risk difference	95% CI	P-value	Risk difference	95% CI	P-value	Risk difference	95% CI	P-value	Risk difference	95% CI	P-value
Hodgkin lymphoma	2	24.8	21.0;28.6		16.3	12.4;20.3		50	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 hematological 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;-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;-0.9	**<0.01**	3.9	-3.4;11.2	0.39	-3.1	-5.9;-0.3	0.11
	10	-4.9	-7.1;2.7		-5.6	-7.9;-3.3		-3.8	-11.3;3.8		-3.2	-8.5;2.1	
Dementia	2	-0.6	-0.8;-0.4		-0.2	-0.4;0.1		-1.49	-2.4;-0.6		-1.1	-1.8;-0.4	
	5	-0.9	-1.5;-0.2	**<0.01**	-0.2	-1.0;0.7	0.37	-2.8	-4.0;-1.6	0.06	-2.0	-2.9;-1.0	**0.03**
	10	-1.3	-2.5;0.0		0.1	-1.6;1.9		-5.2	-6.8;-3.5		-3.3	-4.53;-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;6.6	
	5	-2.9	-4.8;-1.0	**<0.01**	-2.2	-4.3;-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;-4.9		-4.8	-7.8;-1.8		-15.7	-22.2;-9.2		-9.8	-15.1;-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 2, 5 and 10 years with 95% confidence intervals (CI). Statistically significant P-values are indicated in bold.

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).

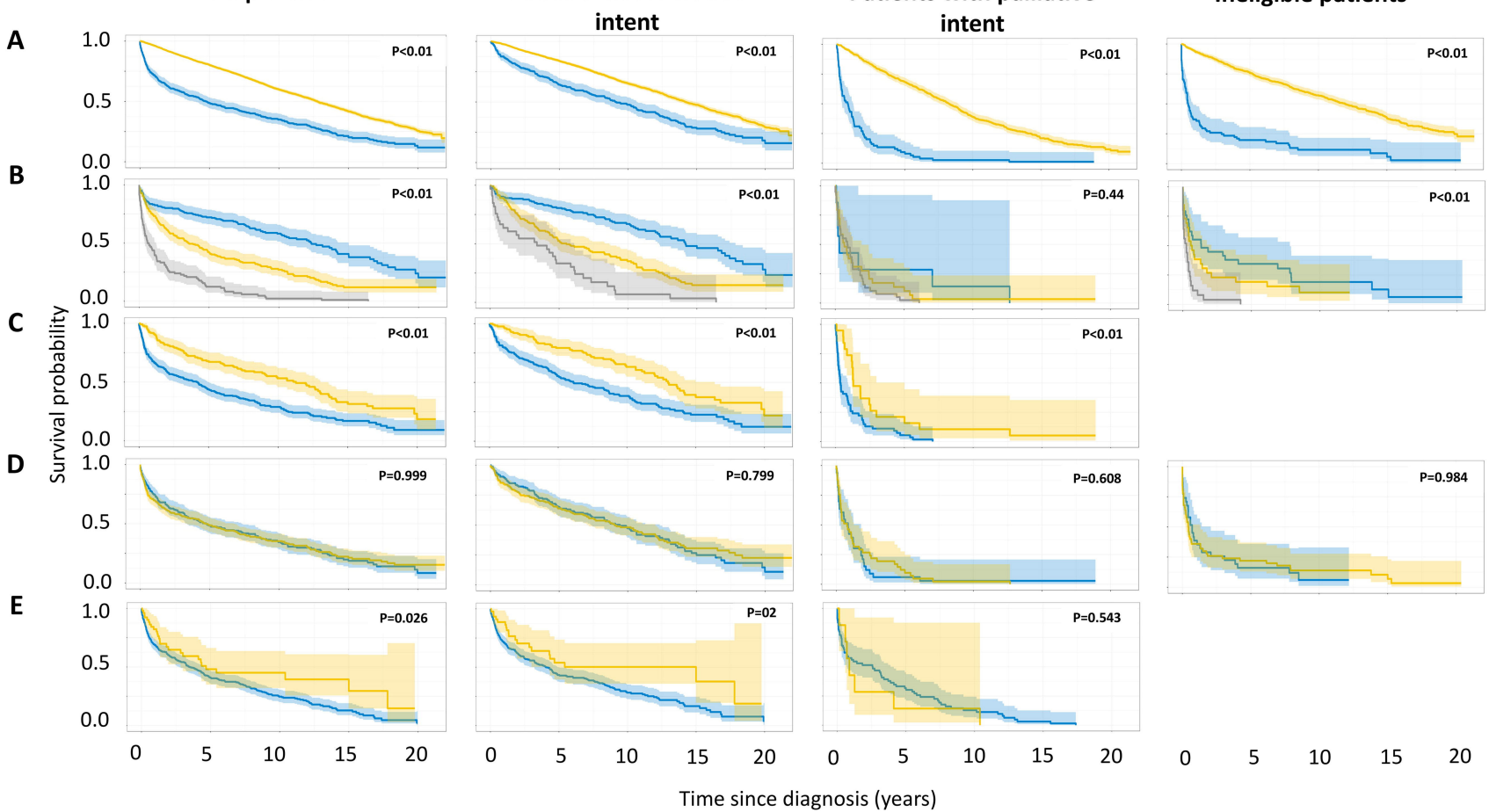
Figure 2: Overall survival in elderly Hodgkin Lymphoma patients and controls. (A) Overall survival of patients (blue line) and matched cancer-free controls (yellow line). (B) Overall survival by age group at diagnosis with 60-69 years (blue line), 70-79 years (yellow line) and ≥ 80 years (grey line). (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.

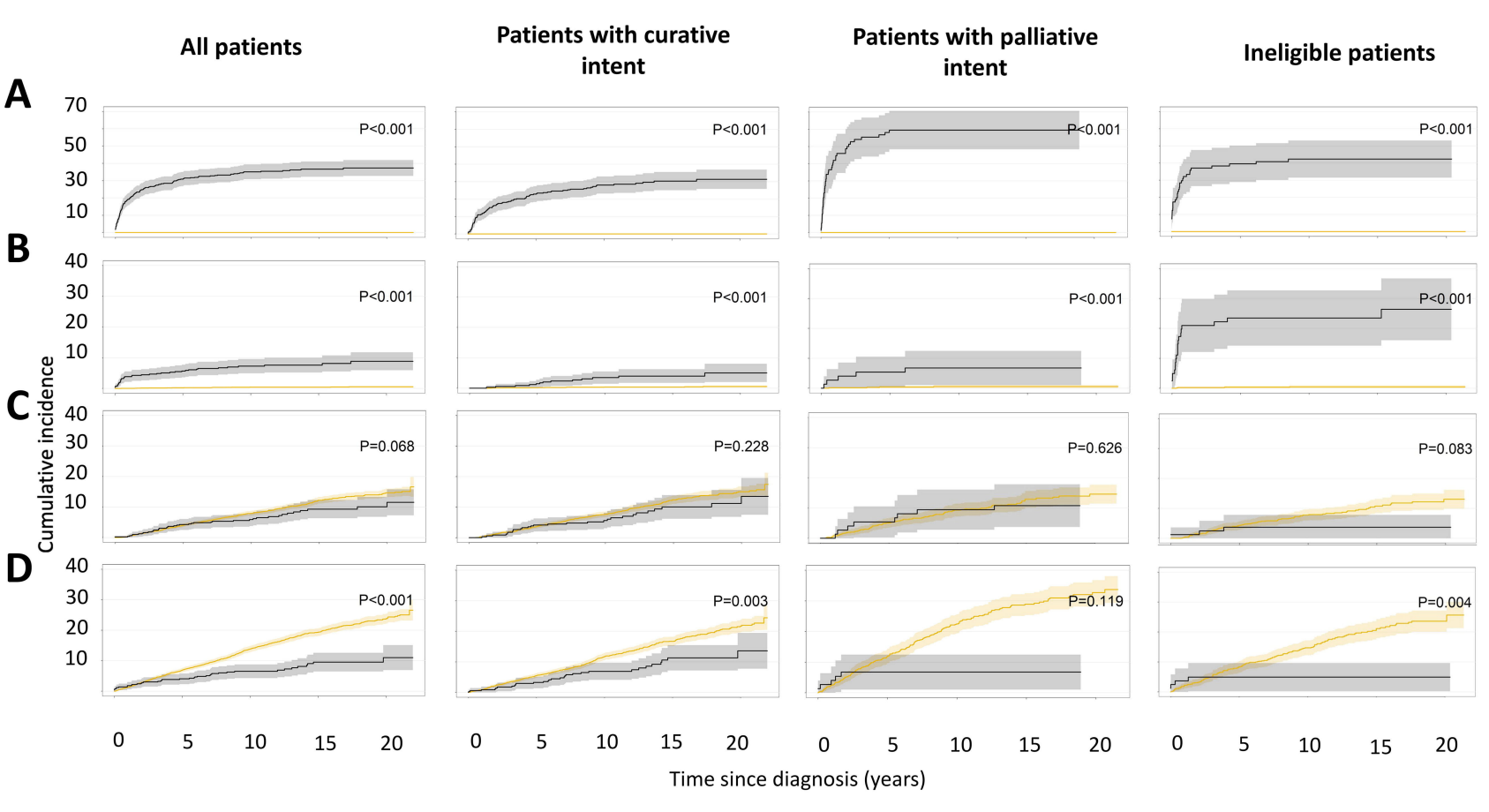
Figure 3: Cumulative incidence functions for competing causes of death in elderly Hodgkin Lymphoma patients (black lines) and controls (yellow lines). (A) Death from Hodgkin Lymphoma (B) Death from other hematological malignancies (C) Death from other cancers (D) Death from cardiovascular diseases cumulative 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.



Number at risk

Curative	337	217	107	37	7
Ineligible	81	16	8	2	1
Palliative	74	7	2	1	0


All patients
Patients with curative intent
Patients with palliative intent
Ineligible patients
A
B
C
D
E
Survival probability
1.0
0.5
0.0
P<0.01
P<0.01
P<0.01
P<0.01
P<0.01
P<0.01
P=0.44
P<0.01
P<0.01
P<0.01
P<0.01
P=0.999
P=0.799
P=0.608
P=0.984
P=0.026
P=02
P=0.543
0
5
10
15
20
Time since diagnosis (years)


All patients
Patients with curative intent
Patients with palliative intent
Ineligible patients
A
B
C
D
Cumulative incidence
P<0.001
P<0.001
P<0.001
P<0.001
P<0.001
P<0.001
P<0.001
P<0.001
P=0.068
P=0.228
P=0.626
P=0.083
P<0.001
P=0.003
P=0.119
P=0.004
0
5
10
15
20
Time since diagnosis (years)

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

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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

References:

1. Larsen IK, Småstuen M, Johannesen TB, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer. 2009;45(7):1218-1231.
2. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-655.
3. Wallace M, Shelkey M. Monitoring Functional Status in Hospitalized Older Adults. Am J Nurs. 2008;108(4):64-72.
4. Salvi F, Miller MD, Grilli A, et al. A Manual of Guidelines to Score the Modified Cumulative Illness Rating Scale and Its Validation in Acute Hospitalized Elderly Patients. J Am Geriatr Soc. 2008;56(10):1926-1931.
5. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol. 2014;32(27):3059-3068.
6. Hasenclever D, Diehl V, Armitage JO, et al. A Prognostic Score for Advanced Hodgkin's Disease. N Engl J Med. 1998;339(21):1506-1514.
7. Helsedirektoratet (2019). Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av maligne lymfomer [nettdokument]. Oslo: Helsedirektoratet (sist faglig oppdatert 06. mars 2023, lest 29. august 2023). Tilgjengelig fra https://www.helsedirektoratet.no/retningslinjer/lymfekreft-handlingsprogram
8. World Health O. International statistical classification of diseases and related health problems. 10th revision, Fifth edition, 2016 ed. Geneva: World Health Organization, 2015.

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)	

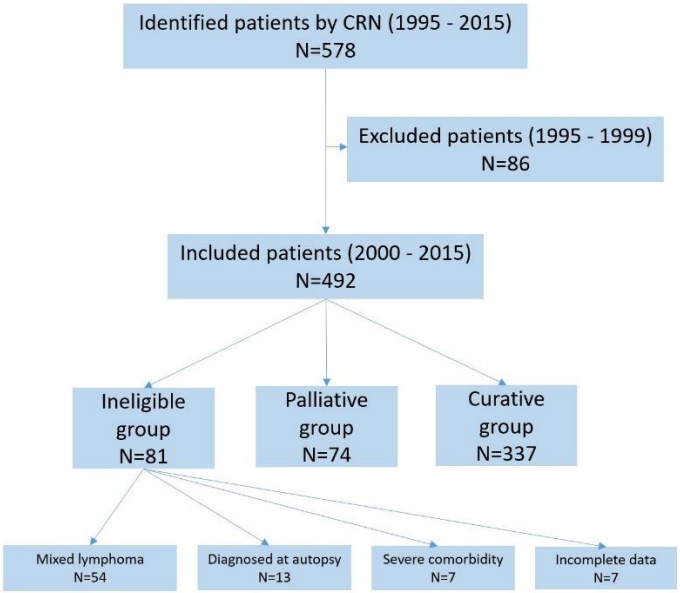
BEACOPP	5 (1.3)	0 (0)	1 (2.2)[e]	4 (1.3)	
Anthracycline-free regimens	52 (13.3)	4 (16.0)	33 (71.7)	15 (4.7)	
Irradiation as part of primary treatment					**<0.001**
Curative radiotherapy only	17 (10.1)	0 (0)	0 (0)	17 (11.0)	
Consolidation limited disease	96 (57.1)	0 (0)	0 (0)	96 (62.3)	
Consolidation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

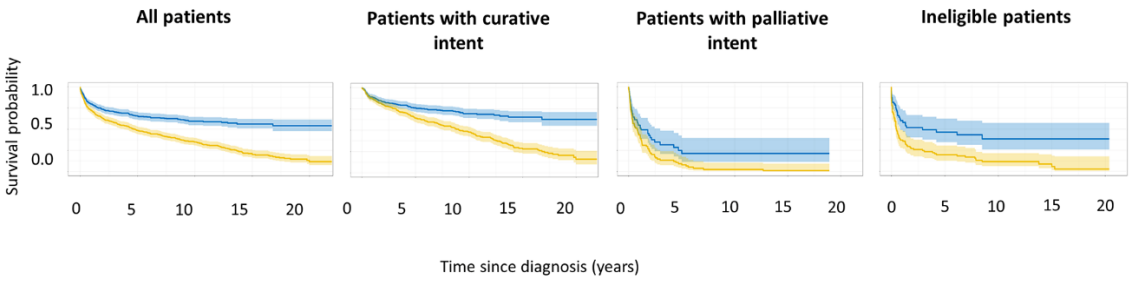
Supplementary Table S3: Cause-specific survival in all patients combined and according to subgroup

	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

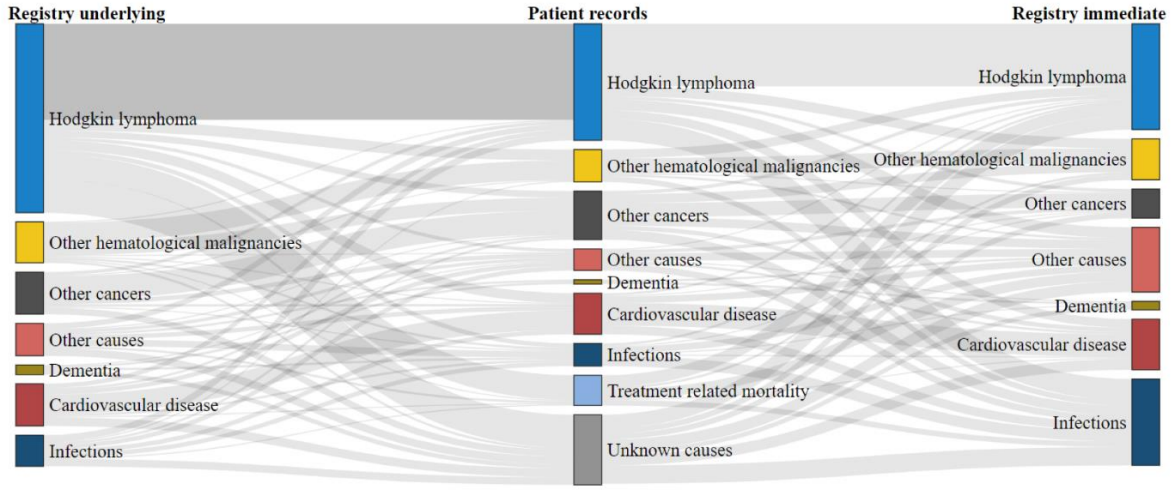
Cause-specific survival rates for death due to Hodgkin Lymphoma (HL) were calculated from date of diagnosis to death from HL using Kaplan-Meier statistics at 2, 5 and 10 years with 95% confidence intervals (CI).



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.