Comparison of outcomes between Hodgkin's lymphoma patients treated in and outside clinical trials: a study based on the EORTC-Dutch late effects cohort-linked data

Juul, S.J.; Kicinski, M.; Schaapveld, M.; Rossetti, S.; Aleman, B.M.P.; Liu, L.F.; ... ; Maraldo, M.V.

Received: 30 August 2022 | Revised: 9 November 2022 | Accepted: 10 November 2022

DOI: 10.1111/ejh.13899

ORIGINAL ARTICLE

European Journal of Haematology

WILEY

Comparison of outcomes between Hodgkin's lymphoma patients treated in and outside clinical trials: A study based on the EORTC-Dutch late effects cohort-linked data

Sidsel Jacobsen Juul[1] | Michal Kicinski[2] | Michael Schaapveld[3] | Sára Rossetti[4] | Berthe M. P. Aleman[5] | Lifang Liu[2] | Flora E. van Leeuwen[3] | Paul Meijnders[6] | Augustinus D. G. Krol[7] | Cécile P. M. Janus[8] | Martin Hutchings[4] | Maja V. Maraldo[1]

[1]Department of Oncology, Rigshospitalet, Copenhagen, Denmark

[2]EORTC Headquarters, Brussels, Belgium

[3]Department of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

[4]Department of Haematology, Rigshospitalet, Copenhagen, Denmark

[5]Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

[6]Department of Radiation Oncology, Iridium Network, University of Antwerp, Antwerpen, Belgium

[7]Department of Radiation Oncology, Leiden University Medical Centre, Leiden, The Netherlands

[8]Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

Correspondence
Sidsel Jacobsen Juul, Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen, Denmark.
Email: sidsel.jacobsen.juul@regionh.dk

Funding information
Innovative Medicines Initiative Joint Undertaking, Grant/Award Number: 115546; European Union's Seventh Framework Programme, Grant/Award Number: FP7/2007/2013; The Danish Cancer Society

Abstract

Studies have shown higher survival rates for patients with Hodgkin lymphoma (HL) treated within clinical trials compared to patients treated outside clinical trials. However, endpoints are often limited to overall survival (OS). In this retrospective cohort study, we investigated the effect of trial participation on OS, the incidence of relapse, second cancer, and cardiovascular disease (CVD). The study population consisted of patients with HL, aged between 14 and 51 years at diagnosis, who started their treatment between 1962 and 2002 at three Dutch cancer centres. Patients were either included in the EORTC Lymphoma Group trials (H1–H9) or treated according to standard guidelines at the time. After adjusting for differences in baseline characteristics, trial participation was associated with longer OS (median OS: 29.4 years [95%CI: 27.0–31.6] for treatment inside trials versus 27.4 years [95%CI: 26.0–28.5] for treatment outside trials, $p = .046$), a lower incidence of relapse (HR = 0.79, 95%CI: 0.63–0.98, $p = .036$) and a higher incidence of CVD (HR = 1.49, 95%CI: 1.23–1.79, $p < .001$). The trial effect for CVD was present only for patients treated before 1983. No evidence of differences in the incidence of second cancer was found. Consequently, essential results from clinical trials should be implemented into standard practice without undue delay.

KEYWORDS
clinical trials, data linkage, EORTC, Hodgkin lymphoma, late effects

Novelty statement

1. What is the new aspect of your work? In this retrospective cohort study of long-term Hodgkin lymphoma survivors, we investigated the effect of trial participation on overall survival including endpoints not previously studied in this patient population (incidence of relapse, second cancer and cardiovascular disease).

2. What is the central finding of your work? Increased overall survival and a lower incidence of relapse among trial patients.
3. What is (or could be) the specific clinical relevance of your work? Historical data and survivorship research are important to ensure optimal treatment and care for future patients.

1 | INTRODUCTION

Between 1964 and 2004, the European Organization for Research and Treatment of Cancer (EORTC) Lymphoma Group conducted a series of phase III randomized clinical trials (referred to as the H1–H9 trials) with the aim of improving the efficacy of treatment for Hodgkin Lymphoma (HL), while reducing treatment-related long-term toxicity.[1–12] The 10-year relative survival rate of patients with HL (diagnosed in the same period) eventually improved, with an increase from 72% to 93% for early-stage disease and from 63% to 78% for advanced-stage disease.[1,13] However, survival rates estimated from population-based registries appeared to be lower, suggesting better outcomes among patients treated within the clinical trials.[1,14]

Differences in baseline characteristics between the two populations could perhaps explain the survival gap,[15,16] as trial participants often consist of a prognostically favourable subset of patients.[17] However, a recent study observed no differences in survival between patients with HL treated in and outside of trials, adjusting for baseline characteristics.[1] Consequently, it would be warranted to see how data acquired from clinical trial series compare to data gained from population-based registries, and hence the extent to which trial outcomes may reflect prognoses for patients in general.[14]

Among patients with HL, little is known about the effect of trial participation on endpoints other than overall survival (OS). In this retrospective cohort study based on the deterministic linkage of two large databases, we investigated the effect of trial participation on overall survival, the incidence of relapse, second cancer, and cardiovascular disease (CVD).

2 | MATERIAL AND METHODS

2.1 | Data collection and study population

The study population consisted of patients with HL between 14 and 51 years without a previous history of cancer, who started their treatment between 1962 and 2002 at three Dutch cancer centres: Netherlands Cancer Institute (NKI) Amsterdam, the Erasmus Medical Cancer Center Institute Rotterdam (Daniel den Hoed Kliniek, DDHK), and the Leiden University Medical Center (LUMC). These three centres were chosen because of their long-term involvement in the clinical trials of the EORTC Lymphoma Group and because of their contribution to the Dutch late-effects cohort.

The methods of data collection for this cohort have been described elsewhere.[18–20] In short, information on baseline patient demographics and treatment characteristics was extracted from medical records. Information on the incidence of relapse, the development of second malignancies, and CVD was acquired from mailed questionnaires to the patient's general practitioner, by review of hospital records, and record linkage with the Netherlands Cancer Registry. End of the follow-up was between 2010 and 2015. The rationale and procedure of the deterministic data linkage including the retrospective identification of patients treated in the EORTC clinical trials have been described in detail elsewhere.[1] Of note, trial participants were all primarily treated at the participating centres, whereas a smaller number of non-trial participants could have been referred. Also, the majority of the H1–H9 trials (7 out of 9) were conducted in stage I-II patients. Only H9 did not include lymphocytic predominant nodular subtype for randomization, otherwise, all HL subtypes were included in both study groups.

2.2 | Criteria of evaluation

The overall survival duration was defined as the time from treatment start until death from any cause. Time until relapse was defined as the time between treatment start and the start of a second line-treatment (as the date of relapse was not available for all patients). Time until second cancer was defined as the time between treatment start and the first diagnosis of second cancer. Time until CVD was defined as the time between treatment start and the first diagnosis of CVD (defined as angina pectoris, myocardial infarction, valve disease, cardiomyopathy, or congestive heart failure).

2.3 | Statistical analysis

Unadjusted survival curves among patients treated in and outside clinical trials were described using the Kaplan–Meier approach[21] and compared with the log-rank test.[22] Confidence intervals were estimated using the normal approximation of the distribution of log(−log (survival)) and the Greenwood variance formula.[23] Unadjusted hazard ratio of death was obtained using Cox regression.[24] The cumulative incidence of disease progression, second cancer, and CVD among patients treated in and outside clinical trials was described using the Aalen-Johansen estimator[25] and compared with the Gray test.[26] The unadjusted sub-distribution hazard ratio was estimated by a proportional sub-distribution hazards model.[27]

The inverse probability of treatment weighted (IPTW) Kaplan–Meier method and a weighted log-rank test was used to describe and compare adjusted survival curves.[28] Additionally, the adjusted sub-distribution hazard ratios were estimated using IPTW proportional

sub-distribution hazard models.[27,29] Patients without events were censored at the time of the last update. Death was considered as a competing event in the analyses of disease progression, second cancer, and CVD.

Whether the effect of trial participation changed over time was investigated by testing the interaction between trial participation and log(time) modelled with restricted cubic splines with three knots located at the 5th, 50th, and 95th percentiles (using a Wald test with two degrees of freedom).[30] In case of evidence of non-proportional hazards, the interaction between trial participation and log(time) was introduced to the model. Log(time) was modelled using the splines in the case of evidence of a nonlinear association between log(HR) and log(time) (tested using a Wald test with one degree of freedom) or using log(time) term only otherwise.

The estimates of the probabilities of trial participation were based on a logistic regression model with age (continuous), sex, disease stage (I vs. II vs. III vs. IV), date of treatment start (continuous), and hospital used as covariates. The model included all first-order terms and interactions. To allow for non-linear effects, age and date of treatment start were modelled using restricted cubic splines with three knots located at the 5th, 50th, and 95th percentiles.

To examine the robustness of the conclusions from the main analysis, a sensitivity analysis was made using an individual matching approach. Trial patients were matched one to one by age (±2 years), sex, stage, and date of treatment start (±5 years) with non-trial patients.

All tests were performed at a two-sided significance level of 0.05. Details about the statistical analyses (including sensitivity and exploratory analyses) are available in the supplement.

3 | RESULTS

A total number of 2864 patients with HL treated between 1962 and 2002 at three Dutch hospitals were included in the analyses. Of these,

TABLE 1 Characteristics of the study population

	Trial participants		Non-trial participants		
	N (%)	Median (range)	N (%)	Median (range)	*p*-value*
Total no. of patients	1123 (100)		1741 (100)		
Sex					
Male	616 (54.9)		1018 (58.5)		.056
Female	507 (45.1)		723 (41.5)		
Age		28.0 (15.1–51.0)		29.0 (14.8–50.9)	.011
Treatment year		1986 (1964–2002)		1980 (1962–2000)	<.001
Center					
NKI	370 (32.9)		625 (35.9)		.079
DDHK	520 (46.3)		732 (42.0)		
LUMC	233 (20.7)		384 (22.1)		
Stage					
I	304 (27.1)		318 (18.3)		<.001
II	633 (56.4)		644 (37.0)		
III	125 (11.1)		376 (21.6)		
IV	59 (5.3)		285 (16.4)		
Missing	2 (0.2)		118 (6.8)		
Chemotherapy in primary treatment					
No	401 (35.7)		636 (36.5)		.653
Yes	721 (64.2)		1101 (63.2)		
Missing	0 (0.0)		4 (0.2)		
Radiotherapy in primary treatment					
No	56 (5.0)		308 (17.7)		<.001
Yes	1067 (95.0)		1430 (82.1)		
Missing	0 (0.0)		3 (0.2)		
Splenectomy					
No	856 (76.2)		1205 (69.2)		.004
Yes	249 (22.2)		456 (26.2)		
Missing	18 (1.6)		80 (4.6)		

*p-value of the chi-square test is given for the categorical variables and of the Wilcoxon-Mann–Whitney test for the continuous variables.

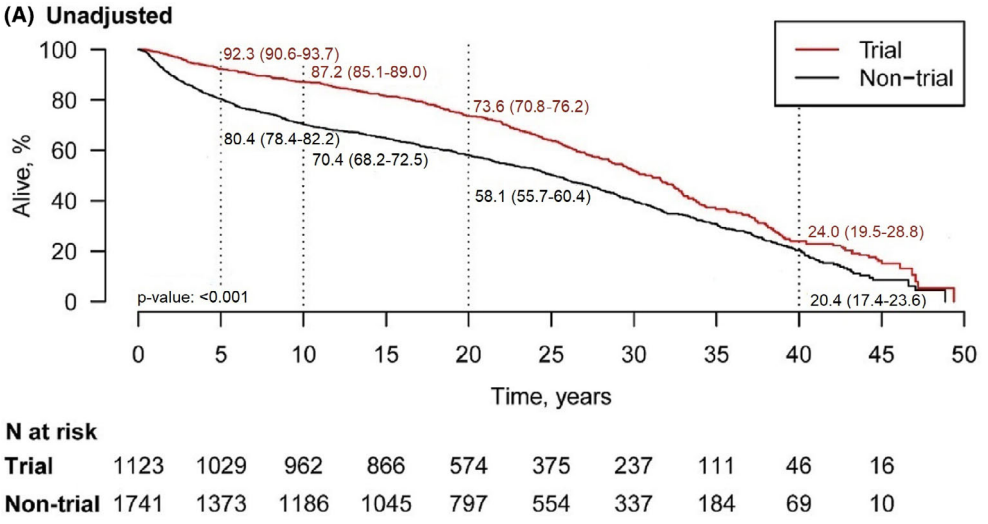
1123 (39.2%) participated in the EORTC H1–H9 trials (for detailed trial information see supplement). The median follow-up time for the whole cohort was 28.2 years.

Characteristics of the study population are presented in Table 1. Among patients treated in trials, 54.9% were male, the median age was 28.0 years (range: 15.1–51.0 years) and the median treatment year was 1986 (range: 1964–2002). Most of the trial participants were treated for stage I or II disease (27.1% and 56.4%, respectively), and only 16.4% for stage III or IV disease (11.1% and 5.3%, respectively). The vast majority had been treated with radiotherapy as part of their primary treatment (95.0%) whereas chemotherapy as part of the primary treatment only applied for 64.2%. Unlike patients treated in trials, a greater proportion of the non-trial participants had stage III or IV disease (21.6% and 16.4%, respectively). Also, only 82.1% had been treated with radiotherapy as part of their primary treatment and the median treatment year was 1980 (range: 1962–2000). Otherwise, the two groups were generally comparable. In the weighted samples, the distribution of all baseline characteristics (age, sex, disease stage, date of treatment start, and hospital) was also balanced between trial and non-trial participants (data not shown).

3.1 | Comparison of outcomes by trial participation

Unadjusted analysis showed longer overall survival for patients treated in clinical trials (median OS 31.1 years [95% CI: 29.4–32.4] for treatment in trials versus 25.2 years [95% CI: 24.0–26.3] outside trials, $p < .001$, Figure 1A). After adjustment for baseline characteristics, trial participation was still associated with a longer overall survival time (median OS 29.4 years [95% CI: 27.0–31.6] for treatment in trials versus 27.4 years [95% CI: 26.0–28.5] outside trials, $p = .046$), albeit to a smaller degree (Figure 1B). The effect of trial participation on the hazard of death decreased over time, with differences most apparent in the first years after diagnosis (Table 2). No evidence of effect modification by disease stage ($p = .92$) or time of treatment ($p = .29$) was found. Like the main analysis, the sensitivity analysis using matching showed that trial participation was associated with a small rise in OS time ($p = .016$), see supplement.

Results also showed a significantly lower incidence of relapse for patients treated in clinical trials (sub-distribution HR 0.50, 95% CI: 0.43–0.57, $p < .001$). The cumulative incidence at 40 years was 25.1% (95% CI: 22.6%–27.8%) for treatment in trials versus 44.2% (95% CI:



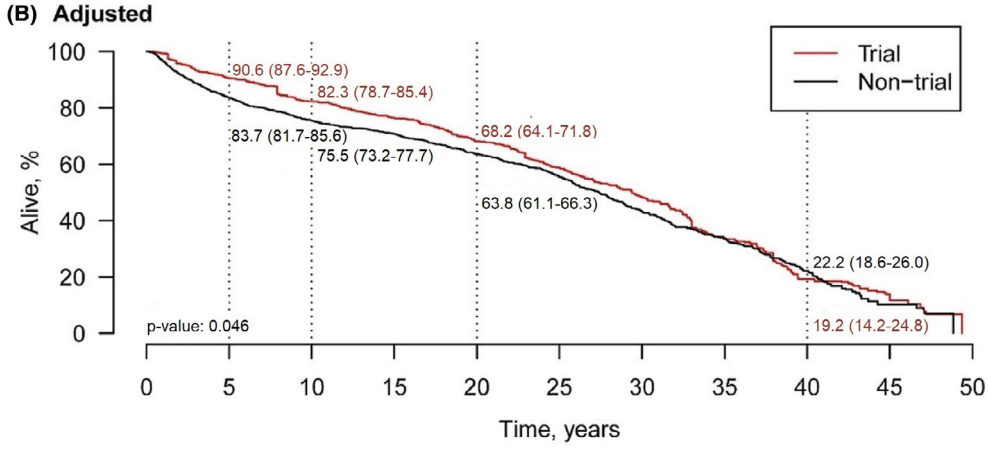


FIGURE 1 Overall survival among trial and non-trial patients (A) and by trial participation adjusting for baseline characteristics (B). Estimates at 5, 10, 20, and 40 years with 95% confidence intervals are indicated on the plots.

TABLE 2 Associations between trial participation and patients' outcomes in the adjusted and unadjusted analyses

	Unadjusted analysis		Adjusted analysis	
	HR	(95% CI)	HR	(95% CI)
Overall survival				
0–1 year	0.26	(0.19–0.34)	0.50	(0.30–0.81)
≥ 1–5 years	0.49	(0.42–0.56)	0.73	(0.57–0.93)
≥ 5–10 years	0.64	(0.57–0.71)	0.86	(0.72–1.02)
≥ 10–20 years	0.84	(0.75–0.95)	1.02	(0.86–1.19)
≥ 20–40 years	1.11	(0.94–1.31)	1.20	(0.96–1.50)
Relapse	0.50	(0.43–0.57)	0.79	(0.63–0.98)
Second cancer				
0–1 year	0.42	(0.22–0.78)	0.30	(0.11–0.80)
≥ 1–5 years	0.73	(0.54–0.98)	0.64	(0.45–0.91)
≥ 5–10 years	0.92	(0.77–1.10)	0.87	(0.67–1.13)
≥ 10–20 years	1.17	(1.01–1.35)	1.05	(0.86–1.29)
≥ 20–40 years	1.48	(1.17–1.87)	1.13	(0.73–1.75)
Cardiovascular disease	1.67	(1.45–1.92)	1.49	(1.23–1.79)

Note: The effect of trial participation on the hazard of death changed over time ($p < .001$ for the unadjusted and $p = .042$ for the adjusted analysis). The effect of trial participation on the sub-distribution hazard of second cancer changed over time ($p = .011$ for the unadjusted analysis and $p = .030$ for the adjusted analysis). There was no evidence of non-proportional hazards either in the adjusted or in the unadjusted analyses of relapse or cardiovascular disease. Hazard ratio is provided for overall survival and the sub-distribution hazard ratio for relapse, cardiovascular disease, and second cancer.
Abbreviation: HR, Hazard ratio.

41.8%–46.6%) for treatment outside trials (Figure 2A). Adjusting for baseline characteristics, trial participation was still associated with a lower incidence of relapse, but the trial effect was weaker (sub-distribution HR 0.79, 95% CI: 0.63–0.98, $p = .036$). In the adjusted analysis, a cumulative incidence of relapse at 40 years was 30.4% (95% CI: 25.6%–35.8%) for treatment in trials versus 37.9% (95% CI: 35.4%–40.4%) for treatment as a part of the routine clinical practice (Figure 2B). An additional adjustment for radiotherapy use in the primary treatment resulted in a somewhat lower effect of trial participation (sub-distribution HR 0.83 95% CI: 0.65–1.03). There was no evidence of non-proportional hazards ($p = .34$ for unadjusted analysis and $p = .077$ for adjusted analysis), nor effect modification by disease stage ($p = .97$) or time of treatment ($p = .48$). The sensitivity analysis using matching showed a somewhat greater effect of trial participation on the cumulative incidence of relapse compared to the main analyses (sub-distribution HR = 0.71, 95% CI: 0.60–0.84, see supplement).

Evaluating the incidence of second cancer, no evidence of differences between patients treated in and outside clinical trials was observed (Figure 3A). This was also applied after adjustment for baseline characteristics (Figure 3B) including sensitivity analysis using matching ($p = .68$, see supplement). Results from the adjusted analysis showed a cumulative incidence of second cancer at 40 years of 41.2% (95% CI: 35.3%–47.2%) for patients treated in clinical trials versus 40.5% (95% CI: 37.1%–44.0%) outside trials, $p = .89$ (Figure 3B). No evidence of effect modification by disease stage ($p = .33$) or time of treatment ($p = .83$) was found.

Finally, the incidence of CVD was investigated. In the unadjusted analysis, patients treated in clinical trials showed a higher incidence of CVD than those treated as part of the routine clinical practice (sub-distribution HR = 1.67, 95% CI: 1.45–1.92, $p < .001$). Adjusting for baseline characteristics, trial participation was still associated with a higher incidence of CVD (HR = 1.49, 95% CI: 1.23–1.79, $p < .001$). The cumulative incidence of CVD at 40 years adjusting for baseline characteristics was 50.8% (95% CI: 43.6%–57.4%) for treatment in clinical trials versus 37.3% (95% CI: 33.7%–41.0%) for treatment as a part of the routine clinical practice (Figure 4B). After additional adjustments for radiotherapy use as part of primary treatment, the estimated trial effect on the incidence of CVD was weaker (sub-distribution HR 1.37, 95% CI: 1.14–1.66). There was no significant evidence of effect modification by disease stage ($p = .08$), and results from a cause-specific IPTW hazard model were consistent with the main analysis (cause-specific HR for CVD 1.34, 95% CI: 1.13–1.58). The sensitivity analysis using matching also indicated a smaller but statistically significant association between trial participation and CVD (HR 1.34, 95% CI: 1.14–1-58, see supplement). No evidence of non-proportional hazards was apparent ($p = .33$ for unadjusted analysis and $p = .28$ for adjusted analysis). However, the association between trial participation and the incidence of CVD was different for patients treated before and after 1982 (p-value for interaction = .024, sub-distribution HR = 1.76, 95% CI: 1.26–2.45 for ≤1982 corresponding to patients treated in the H1-H5 trials and sub-distribution HR = 1.09, 95% CI: 0.85–1.40 for ≥1983 corresponding to patients treated in the H6–H9 trials).

4 | DISCUSSION

Demonstrating a potential gap in the outcomes for patients with HL treated in and outside clinical trials has important implications. Superior outcomes for patients treated within the trials would suggest that more attention is needed to timely incorporate novel strategies in routine clinical practice.

To the best of our knowledge, this study is the first to describe the relative effectiveness of HL treatment in versus outside clinical trials for outcomes other than OS and with a median follow-up time of >28 years. Our findings showed that trial participation was associated with longer OS, a lower incidence of relapse and a higher incidence of CVD (the latter only applicable to those treated before 1983). However, after adjustment for baseline characteristics, the trial effect became smaller but remained statistically significant.

The survival gap between trial and non-trial participants could thus be explained, partly, by the imbalance in the baseline characteristics between the two populations, which is in line with previous findings.[1,17] However, the results suggest an additional benefit of trial participation (up to 10 years), which might be explained by extended and more structured follow-up, improved and better staging, as well

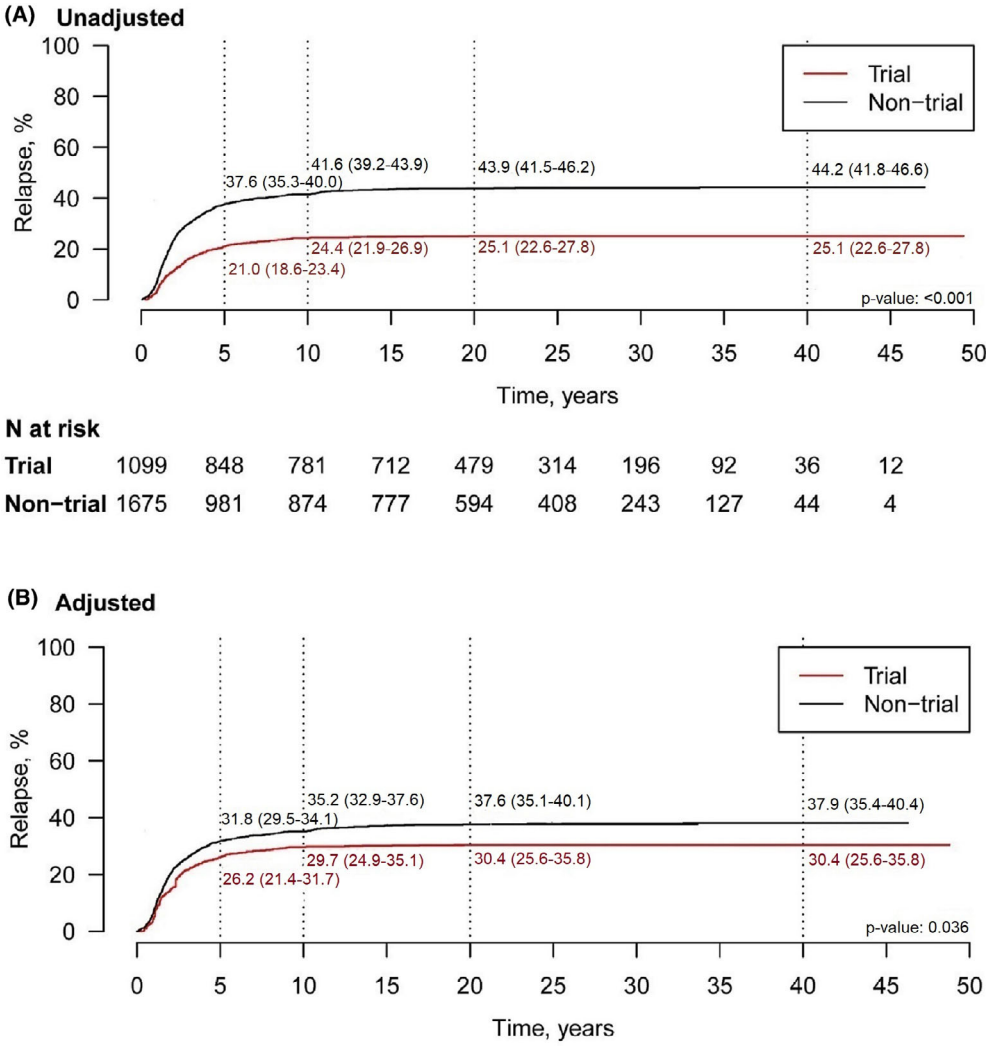


FIGURE 2 Incidence of relapse among trial and non-trial patients (A) and by trial participation adjusting for baseline characteristics (B). Estimates at 5, 10, 20, and 40 years with 95% confidence intervals are indicated on the plots.

as the availability of new and more effective anti-cancer treatments offered within a trial setting.[1,31]

Also, a lower incidence of relapse was observed among trial participants. It would be plausible to think that this was due to the predominance of better prognostic groups treated in the trials; however, the difference in the incidence of relapse remained substantial in the analysis adjusted for baseline characteristics including disease stage. The difference is therefore more likely due to more effective treatment regimens in the trials (and a delay in the implementation of these more effective treatment regiments into the routine clinical practice). By extension, we observed an important variation in median treatment year between the two groups (6 years), suggestive of an overabundance of trial patients in the second half of the study period, where HL treatment is significantly improved. However, selection bias cannot be excluded.

We found no evidence of differences in the incidence of second cancer between patients treated in and outside clinical trials, nor did we see effect modification by the period of treatment. Since radiotherapy has consistently been reported as the main risk factor for second solid cancers,[20,32,33] the first was rather unexpected (due to the greater use of radiotherapy in the primary treatment in the H1–H9 trials). On the other hand, it is well known that chemotherapy also leads to a raised risk of second cancers,[34] and we must assume that patients treated outside trials have received alkylating-based treatment to a greater extent than anthracycline-based treatment, tested within the trials, which likewise carries a higher risk of developing second cancer[32,34,35] (for detailed description of the standard treatment of HL in the Netherlands during the study period, see supplement).

To see no effect modification by the time of treatment was also rather unexpected since efforts to reduce treatment toxicity were initiated within the trial setting from the late 1980s onwards.[36] This was due to prior studies revealing that the main complications (CVD and secondary malignancies) were caused by the amount of radiotherapy used.[36] It is difficult to explain why we did not see a trial effect after the reduction of radiation exposure in the later trials. Maybe the exposure reduction was too small. Maybe the results were biased by an increase in smoking rates among women during the same period, leading to an increased incidence of lung cancers among female survivors[32,37] or maybe the advantage of using smaller radiotherapy volumes disappeared, as a result of the increased usage of anthracyclines.[38,39] Also, because of the long latency to second cancers, the lack of trial effect could simply be due to a shorter

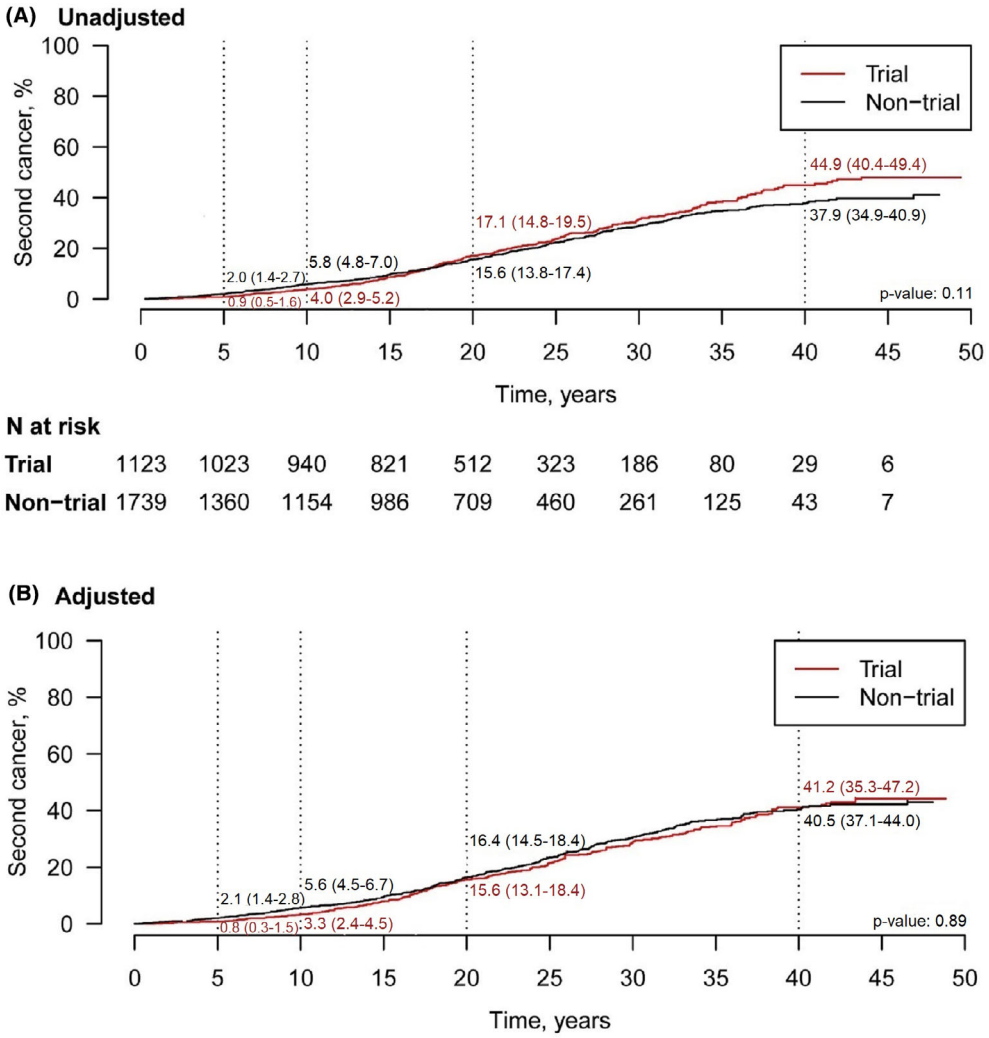


FIGURE 3 Incidence of second cancer among trial and non-trial patients (A) and by trial participation adjusting for baseline characteristics (B). Estimates at 5, 10, 20, and 40 years with 95% confidence intervals are indicated on the plots.

observation time.[20] According to Schaapveld et al., the risk of second cancer is still elevated 35 years or more after treatment.[32] The current standard of care in radiation oncology (including involved-node or involved-site radiotherapy, 3D-conformal treatment planning, and radiation doses of less than 36 Gy) was not used in our study population.[32] However, clinical information confirming the reduced risks of late toxicities from modern radiotherapy is slowly accumulating.[40] The expectation is therefore that these significant treatment improvements (along with less toxic chemotherapy regimens) may lead to a reduced risk of second cancers among the patients treated after 2002.[32,37,41] In general, the incidence of all radiotherapy-induced late morbidity is expected to fall as current treatment (including treatment tailoring) gains traction.[40]

The greater use of radiotherapy as a primary treatment in the H1–H9 trials could be a possible explanation for the observed higher incidence of CVD. However, the association was still found after adjustment for radiotherapy use in the exploratory analyses, so this would only explain part of the association. Also, since only surviving patients could suffer from long-term treatment toxicities, another possible explanation was a lower incidence of competing events. However, results from a cause-specific IPTW hazard model were consistent with the main analysis, suggesting that this was not the case. Unfortunately, we were not able to adjust for other risk factors associated with CVD, such as hypertension, hypercholesterolemia, diabetes, or smoking.[42] Likewise, the results could have been influenced by the different chemotherapy regimens (with varying risk profiles for CVD) used during the study period.[19,20] The trial effect for CVD, however, was present only for patients treated before 1983. The finding, therefore, has no clinical implications as data originated from patients treated with outdated treatment protocols.

A possible trial effect has previously been difficult to quantify because of methodological difficulties with most published work.[17,31] The main strength of our study is the unique dataset; a large sample size consisting of thousands of HL survivors, treated across a period of four decades and with a median follow-up time of almost 30 years, which enables the evaluation of long-term effects of trial participation. Also, the trial effect was studied by direct linkage of clinical trial data with its source population, which minimizes misclassification of trial participation, thus improving the validity of the results.[1] There are, however, certain limitations. Some are inherent in the retrospective design, such as lack of information regarding relevant baseline characteristics (including HL-specific prognostic factors, comorbidities,

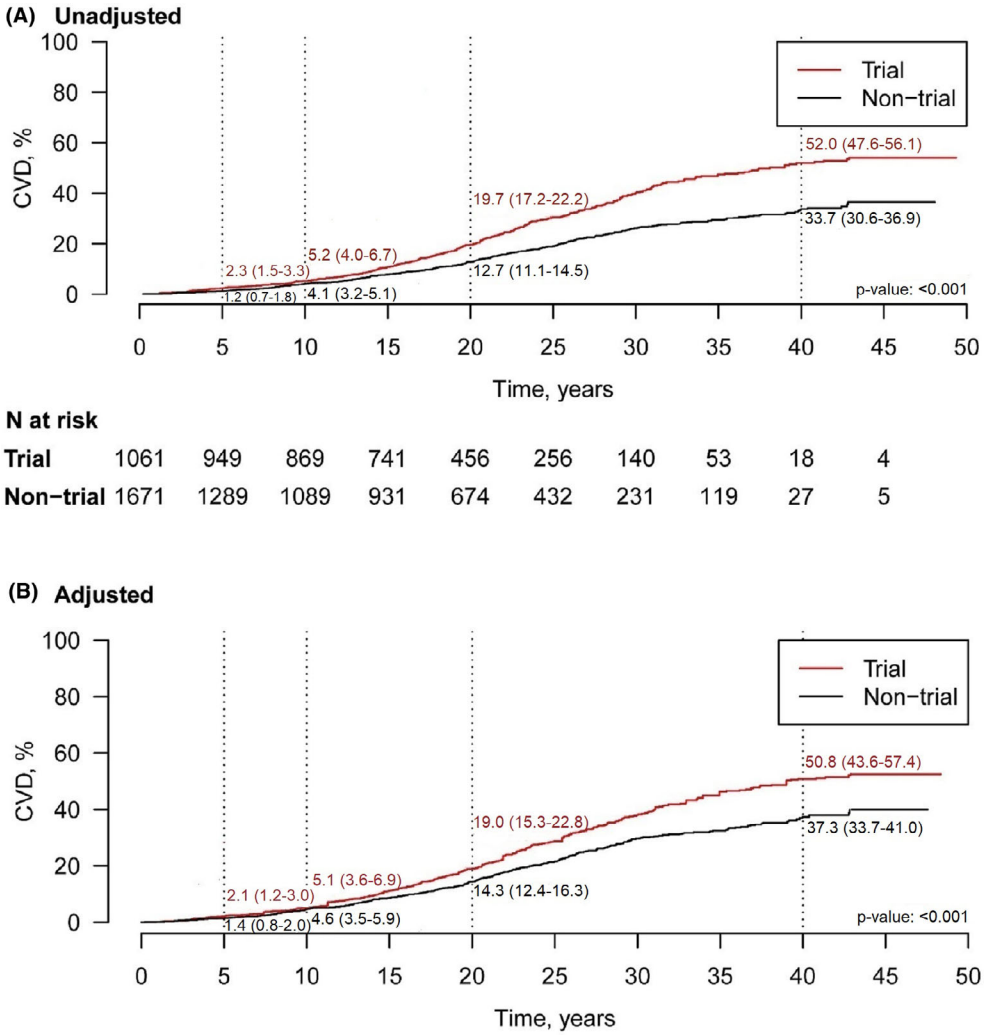


FIGURE 4 Incidence of cardiovascular disease (CVD) among trial and non-trial patients (A) and by trial participation adjusting for baseline characteristics (B). Estimates at 5, 10, 20, and 40 years with 95% confidence intervals are indicated on the plots.

socioeconomic status, and family history). By extension, patients with worse performance scores and poor compliance are often excluded from clinical trials and we do not know the exact reasons why non-trial patients were not included in a protocol. Also, the exact treatment information was unknown for non-trial patients. These factors could potentially confound the association between trial effect and patient outcomes.[1] The observed trial effect was, however, rather strong, suggesting that confounding is unlikely to explain the entire effect. Furthermore, we cannot rule out the possibility of some patients being misclassified as non-trial participants. However, if this were the case, an underestimation of the trial effect would likely have occurred. In addition, a 'hospital trial participation effect' may exist, meaning that all patients treated in the included institutions receive above-average quality care.[43,44] Finally, detection bias, that is, different standards of measurement of outcomes in and outside clinical trials, may have skewed the results.[31] As an example, an underestimation of the trial effect for the incidence of relapse is expected, due to more stringent disease evaluation within the trial setting.

Historically, the treatment of HL has improved over time based on well-conducted clinical trials. It is also well established that dissemination of trial results and subsequent implementation into standard practice have resulted (with some time lag) in non-trial patients benefitting too.[1] In this cohort, we observed not only a longer OS time associated with treatment within a randomized clinical trial for HL but also a beneficial effect on the incidence of relapse. No evidence of differences in the incidence of second cancer was found, nor for the risk of CVD after 1982. However, as our study period does not reflect the era of novel treatment agents, our findings may not be directly applicable to patients treated with more contemporary regimens. Nevertheless, our results have shown no harmful outcomes for trial patients in this cohort, despite treatment de-escalation within the trial setting during the study period. This supports the value of continuously carrying out clinical trials in this patient population with the aim of maintaining high cure rates while minimizing long-term toxicity. Also, the finding of a longer OS time truly underscores the importance of implementing significant results from clinical trials into standard practice without undue delay. Furthermore, the importance of thorough long-term care and follow-up cannot be emphasized enough, as potential late effects related to new treatments may be unknown at the time of study evaluation (as exemplified by the higher incidence of CVD among trial patients treated in the earlier study period). The historical findings of

unexpected consequences of treatment thereby highlight the importance of continuously carrying out survivorship research. Only by doing so, optimal treatment and care for future patients will be ensured.

AUTHOR CONTRIBUTIONS

Lifang Liu designed the study. Maja V. Maraldo acted as study coordinator. Michael Schaapveld, Flora E. van Leeuwen, Cécilie P.M. Janus, and Augustinus D.G. Krol aquired data. Michael Schaapveld carried out data linkage. Michal Kicinski performed the statistical analyses. Sidsel J. Juul interpreted data and results and drafted the first manuscript. Maja V. Maraldo, Martin Hutchings, Michal Kicinski, Berthe M.P. Aleman, Sára Rossetti, Paul Meijnders, Michael Schaapveld, Cécilie P.M. Janus, Agustinus D.G. Krol, and Flora E. van Leeuwen critically reviewed the paper. All authors commented, revised, and approved the final manuscript.

ACKNOWLEDGEMENTS

The work leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking (under grant agreement no. 115546), resources that are composed of a financial contribution from the European Union's Seventh Framework Programme (FP7/2007/2013) and in-kind contribution from EFPIA companies. This publication reflects the authors' view, and neither IMI nor the EU nor EFPIA are responsible for any use that may be made of the information contained therein. Also, this publication was supported by a donation from the Danish Cancer Society in Denmark.

CONFLICT OF INTEREST

The authors report no conflict of interest of relevance to this study.

DATA AVAILABILITY STATEMENT

All data used in this analysis is provided by The Netherlands Cancer Institute. Request for access to the data supporting the results of this study must be made via the corresponding author (who will then provide the contact).

ORCID

Sidsel Jacobsen Juul https://orcid.org/0000-0002-2654-5194
Michal Kicinski https://orcid.org/0000-0002-7066-0587
Michael Schaapveld https://orcid.org/0000-0003-4390-7182
Sára Rossetti https://orcid.org/0000-0003-0508-5843
Berthe M. P. Aleman https://orcid.org/0000-0003-2306-6590
Flora E. van Leeuwen https://orcid.org/0000-0002-5871-1484
Paul Meijnders https://orcid.org/0000-0003-1242-6546
Martin Hutchings https://orcid.org/0000-0003-3873-1741
Maja V. Maraldo https://orcid.org/0000-0001-6159-5907

REFERENCES

1. Liu L, Giusti F, Schaapveld M, et al. Survival differences between patients with Hodgkin lymphoma treated inside and outside clinical trials. A study based on the EORTC-Netherlands cancer registry linked data with 20 years of follow-up. *Br J Haematol*. 2017;176(1):65-75.
2. Aleman BMP, Raemaekers JMM, Tirelli U, et al. Involved-field radiotherapy for advanced Hodgkin's lymphoma. *N Engl J Med*. 2003;348(24):2396-2406.
3. Carde P, Burgers JM, Henry-Amar M, et al. Clinical stages I and II Hodgkin's disease: a specifically tailored therapy according to prognostic factors. *J Clin Oncol*. 1988;6(2):239-252.
4. Carde P, Hagenbeek A, Hayat M, et al. Clinical staging versus laparotomy and combined modality with MOPP versus ABVD in early-stage Hodgkin's disease: the H6 twin randomized trials from the European Organization for Research and Treatment of Cancer Lymphoma Cooperative Group. *J Clin Oncol*. 1993;11(11):2258-2272.
5. Fermé C, Eghbali H, Meerwaldt JH, et al. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. *N Engl J Med*. 2007;357(19):1916-1927.
6. Fermé C, Thomas J, Brice P, et al. ABVD or BEACOPP baseline along with involved-field radiotherapy in early-stage Hodgkin lymphoma with risk factors: results of the European Organisation for Research and Treatment of Cancer (EORTC)–Groupe d'Étude des Lymphomes de l'Adulte (GELA) H9-U intergroup randomised trial. *Eur J Cancer*. 2017;81:45-55.
7. Noordijk EM, Carde P, Dupouy N, et al. Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials. *J Clin Oncol of J Am Soc Clin Oncol*. 2006;24(19):3128-3135.
8. Somers R, Carde P, Tarayre M, et al. A randomized study in stage IIIB and IV Hodgkin's disease comparing eight courses of MOPP versus an alteration of MOPP with ABVD: a European Organization for Research and Treatment of cancer lymphoma cooperative Group and Groupe Pierre-et-Marie-curie cont. Henry-Amar M, editor. *J Clin Oncol*. 1994;12(2):279-287.
9. Thomas J, Fermé C, Noordijk EM, et al. Comparison of 36 Gy, 20 Gy, or No radiation therapy after 6 cycles of EBVP chemotherapy and complete remission in early-stage Hodgkin lymphoma without risk factors: results of the EORT-GELA H9-F intergroup randomized trial. *Int J Radiat Oncol*. 2018;100(5):1133-1145.
10. Tubiana M, Henry-Amar M, Hayat M, Breur K, van der Werf-Messing B, Burgers M. Long-term results of the E.O.R.T.C. randomized study of irradiation and vinblastine in clinical stages I and II of Hodgkin's disease. *Eur J Cancer*. 1979;15(5):645-657.
11. Tubiana M, Hayat M, Henry-Amar M, Breur K, van der Werf MB, Burgers M. Five-year results of the E.O.R.T.C. randomized study of splenectomy and spleen irradiation in clinical stages I and II of Hodgkin's disease. *Eur J Cancer*. 1981;17(3):355-363.
12. Tubiana M, Henry-Amar M, Carde P, et al. Toward comprehensive management tailored to prognostic factors of patients with clinical stages I and II in Hodgkin's disease. The EORTC Lymphoma Group controlled clinical trials: 1964–1987. *Blood*. 1989;73(1):47-56.
13. 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.
14. Roy P, Vaughan Hudson G, Vaughan Hudson B, Esteve J, Swerdlow AJ. Long-term survival in Hodgkin's disease patients: a comparison of relative survival in patients in trials and those recorded in population-based cancer registries. *Eur J Cancer*. 2000;36(3):384-389.
15. Björkholm M, Svedmyr E, Sjöberg J. How we treat elderly patients with Hodgkin lymphoma. *Curr Opin Oncol*. 2011;23(5):421-428.
16. Terschüren C, Gierer S, Brillant C, Paulus U, Löffler M, Hoffmann W. Are patients with Hodgkin lymphoma and high-grade non-Hodgkin lymphoma in clinical therapy optimization protocols representative of these groups of patients in Germany? *Ann Oncol*. 2010;21(10):2045-2051.

17. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet*. 2004;363(9405):263-270.
18. van Nimwegen FA, Schaapveld M, Janus CPM, et al. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. *JAMA Intern Med*. 2015;175(6):1007-1017.
19. Aleman BMP, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood*. 2007;109(5):1878-1886.
20. van Leeuwen FE, Klokman WJ, Hagenbeek A, et al. Second cancer risk following Hodgkin's disease: a 20-year follow-up study. *J Clin Oncol*. 1994;12(2):312-325.
21. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53(282):457-481.
22. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J R Stat Soc Ser Gen*. 1972;135(2):185.
23. Greenwood M. The natural duration of cancer. *Rep Public Health Med Subj Lond*. 1926;33:1-26.
24. Cox DR. Regression models and life-tables. *J R Stat Soc Ser B Methodol*. 1972;34(2):187-220.
25. Aalen OO, Johansen S. An empirical transition matrix for non-homogeneous Markov chains based on censored observations. *Scand J Stat*. 1978;5(3):141-150.
26. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat*. 1988;16(3):1141-1154.
27. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509.
28. Xie J, Liu C. Adjusted Kaplan-Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. *Stat Med*. 2005;24(20):3089-3110.
29. Aimyong N. *Propensity Score Methods for Competing Risks*. 2014. doi:10.17615/ch1v-a404.
30. Harrell F. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. Springer; 2001.
31. Braunholtz DA, Edwards SJL, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a 'trial effect'. *J Clin Epidemiol*. 2001;54(3):217-224.
32. Schaapveld M, Aleman BM, van Eggermond AM, et al. Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. *N Engl J Med*. 2015;373(26):2499-2511.
33. Ng AK, Bernardo MVP, Weller E, et al. Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: long-term risks and risk factors. *Blood*. 2002;100(6):1989-1996.
34. Swerdlow AJ, Higgins CD, Smith P, et al. Second cancer risk after chemotherapy for Hodgkin's lymphoma: a collaborative British cohort study. *J Clin Oncol*. 2011;29(31):4096-4104.
35. Demoor-Goldschmidt C, de Vathaire F. Review of risk factors of secondary cancers among cancer survivors. *Br J Radiol*. 2019;92(1093):20180390.
36. Eghbali H, Raemaekers J, Carde P, Group EL. The EORTC strategy in the treatment of Hodgkin's lymphoma. *Eur J Haematol*. 2005;75(s66):135-140.
37. Ng A. Current survivorship recommendations for patients with Hodgkin lymphoma: focus on late effects. *Blood*. 2014;124:3373-3379.
38. Neppelenbroek SIM, Geurts YM, Aleman BMP, et al. Anthracycline exposure and breast cancer risk in female Hodgkin lymphoma survivors. *J Clin Oncol*. 2021;39(15_suppl):12074-12074.
39. Teepen JC, van Leeuwen FE, Tissing WJ, et al. Long-term risk of subsequent malignant neoplasms after treatment of childhood cancer in the DCOG LATER study cohort: role of chemotherapy. *J Clin Oncol*. 2017;35(20):2288-2298.
40. Milgrom SA, Bakst RL, Campbell BA. Clinical outcomes confirm conjecture: modern radiation therapy reduces the risk of late toxicity in survivors of Hodgkin lymphoma. *Int J Radiat Oncol*. 2021;111(4):841-850.
41. Girinsky T, van der Maazen R, Specht L, et al. Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: concepts and guidelines. *Radiother Oncol*. 2006;79(3):270-277.
42. van Nimwegen FA, Schaapveld M, Cutter DJ, et al. Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. *J Clin Oncol*. 2016;34(3):235-243.
43. Majumdar SR, Roe MT, Peterson ED, Chen AY, Gibler WB, Armstrong PW. Better outcomes for patients treated at hospitals that participate in clinical trials. *Arch Intern Med*. 2008;168(6):657-662.
44. Bois AD, Rochon J, Lamparter C, for the AGO Organkommission OVAR PFisterer J. Pattern of care and impact of participation in clinical studies on the outcome in ovarian cancer. *Int J Gynecol Cancer*. 2005;15(2):183-191.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Juul SJ, Kicinski M, Schaapveld M, et al. Comparison of outcomes between Hodgkin's lymphoma patients treated in and outside clinical trials: A study based on the EORTC-Dutch late effects cohort-linked data. *Eur J Haematol*. 2023;110(3):243-252. doi:10.1111/ejh.13899