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ORIGINAL ARTICLE

Impact of individualized treatment on recovery from fatigue and return to work in survivors of advanced-stage Hodgkin's lymphoma: results from the randomized international GHSG HD18 trial☆

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Background: Persisting cancer-related fatigue impairs health-related quality of life (HRQoL) and social reintegration in patients with Hodgkin's lymphoma (HL). The GHSG HD18 trial established treatment de-escalation for advanced-stage HL guided by positron emission tomography after two cycles (PET-2) as new standard. Here, we investigate the impact of treatment de-escalation on long-term HRQoL, time to recovery from fatigue (TTR-F), and time to return to work (TTR-W).

Patients and methods: Patients received European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and life situation questionnaires at baseline, interim, end of treatment, and yearly follow-up. TTR-F was defined as time from the end of chemotherapy until the first fatigue score <30. TTR-W was analyzed in previously working or studying patients and measured from the end of treatment until the first documented work or education. We compared duration of treatment on TTR-F and TTR-W using Cox proportional hazards regression adjusted for confounding variables.

Results: HRQoL questionnaires at baseline were available in 1632 (83.9%) of all randomized patients. Overall, higher baseline fatigue and age were significantly associated with longer TTR-F and TTR-W and male sex with shorter TTR-W. Treatment reduction from eight to four chemotherapy cycles led to a significantly shorter TTR-F [hazard ratio (HR) 1.41, $P = 0.008$] and descriptively shorter TTR-W (HR 1.24, $P = 0.084$) in PET-2-negative patients. Reduction from six to four cycles led to non-significant but plausible intermediate accelerations. The addition of rituximab caused significantly slower TTR-F (HR 0.70, $P = 0.0163$) and TTR-W (HR 0.64, $P = 0.0017$) in PET-2-positive patients. HRQoL at baseline and age were the main determinants of 2-year HRQoL.

Conclusions: Individualized first-line treatment in patients with advanced-stage HL considerably shortens TTR-F and TTR-W in PET-2-negative patients. Our results support the use of response-adapted shortened treatment duration for patients with HL.

Key words: Hodgkin's lymphoma, fatigue, return to work, recovery, quality of life, survivorship

INTRODUCTION

Hodgkin's lymphoma (HL) has become a highly curable hematologic malignancy even in advanced stages, leading to increasing numbers of mostly young long-term survivors and shifting scientific focus toward late sequelae and health-related quality of life (HRQoL).

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Cancer-related fatigue is a persisting feeling of extreme exhaustion and associated with reduced energy levels, muscle strength, and cognitive function, and is highly prevalent among patients with and survivors of HL.[1] Approximately 20% of patients with HL experience severe and persisting cancer-related fatigue, which is largely independent of tumor stage and treatment.[2] Importantly, cancer-related fatigue prevents cancer survivors from social reintegration.[3]

The randomized, international, multicenter trial HD18 investigated individualized treatment for patients with advanced-stage HL and established reduction of chemotherapy to only four cycles of eBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses) in positron emission tomography (PET)-negative patients after two cycles. Four cycles of eBEACOPP in these patients were equally effective compared to the previous standard of eight or six cycles.[4,5] Escalation of treatment from eBEACOPP to eBEACOPP plus intravenous rituximab (R-eBEACOPP) was studied for PET-positive patients but did not demonstrate superior progression-free survival.[6] However, fewer chemotherapy cycles in positron emission tomography (PET-2)-negative patients have led to improvements in tolerability and overall survival[4] but effects on patient-reported outcomes (PROs) and survivorship are still unknown.

We therefore analyzed HRQoL and life situation from the HD18 trial to determine whether shorter treatment duration affects long-term quality of life, TTR-F, and TTR-W.

PATIENTS AND METHODS

Patients

HD18 was an international, open-label, randomized, phase III trial carried out in 301 hospitals and private practices in five European countries. Patients aged 18-60 years with newly diagnosed, advanced-stage HL and an Eastern Cooperative Oncology Group performance status of 0-2 were recruited. Detailed enrollment criteria and trial procedures were described previously.[4,5] In brief, patients received two cycles of eBEACOPP followed by metabolic response assessment using PET after two cycles (PET-2). Patients with positive PET-2 were randomly assigned to receive six further cycles of eBEACOPP (arm A) or an additional six cycles of R-eBEACOPP (arm B) until 1 June 2011. After 1 June 2011, all patients with positive PET-2 were assigned to the updated standard therapy with an additional four cycles of eBEACOPP (arm A6). Patients with negative PET-2 were randomized to standard therapy [additional six cycles of eBEACOPP until 1 June 2011 (arm C); an additional four cycles of eBEACOPP after 1 June 2011 (arm C6)] or experimental therapy [an additional two cycles of eBEACOPP (arm D and arm D4)]. The study was carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. All patients provided written informed consent before study entry. The trial is registered with ClinicalTrials.gov, NCT00515554, and is completed.

Patient-reported outcomes

As part of the scientific program, patients received a quality-of-life questionnaire, including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30),[7] and the life situation questionnaire to assess the current work status.[8] Patients and survivors completed this questionnaire at the following time points: immediately after diagnosis (baseline); after two to four cycles of chemotherapy; after the end of first-line treatment including chemotherapy and, if applicable, radiotherapy (RT); and at follow-up examinations every 3 months in the first year and every 6 months until the fifth year after the end of treatment.

Statistics

Recovery from cancer-related fatigue and return to work were analyzed and compared using time-to-event methods including inverse Kaplan—Meier curves and Cox proportional hazards models, as recommended for PROs by the SISAQOL consortium.[9] The use of Kaplan—Meier statistics and Cox proportional hazards regression implies that relapses and other comparable events are not separately counted and analyzed as competing risk events. In case of death, the individual observation time ends and is right-censored if recovery from cancer-related fatigue or return to work was not observed before. This statistical approach is adequate for etiological questions in the presence of competing risks.[10]

Comparisons of TTR-F and TTR-W were done between directly randomized treatment arms, i.e. arm A versus arm B for PET-2-positive patients (comparison A) and arm C versus arm D (comparison B) and arm C6 versus arm D4 (comparison C) for PET-2-negative patients. Time to recovery from fatigue (TTR-F) was defined as time from the end of chemotherapy until the first EORTC QLQ-C30 fatigue score <30 or the time of last questionnaire (censored). Only patients who were working or in education before treatment were included in the return-to-work analysis. Time to return to work (TTR-W) was defined as time from the end of chemotherapy until the first report of working or in education or time of last questionnaire (censored). We compared TTR-F and TTR-W in randomized treatment groups using Cox proportional hazards regression with adjustment for age, sex, and baseline scores of fatigue. The 2-year rates of survivors with fatigue <30 and return to work were estimated with Kaplan—Meier statistics. Effects of disease and patient and treatment characteristics on 2-year HRQoL domains were analyzed using a predefined and previously established regression model.[11] No imputation for missing data was carried out. Treatment effects on HRQoL scores were estimated in separate multiple linear regressions with adjustment for age, sex, and baseline fatigue at 2 years after the end of treatment. Only randomized comparisons were tested for significance with a

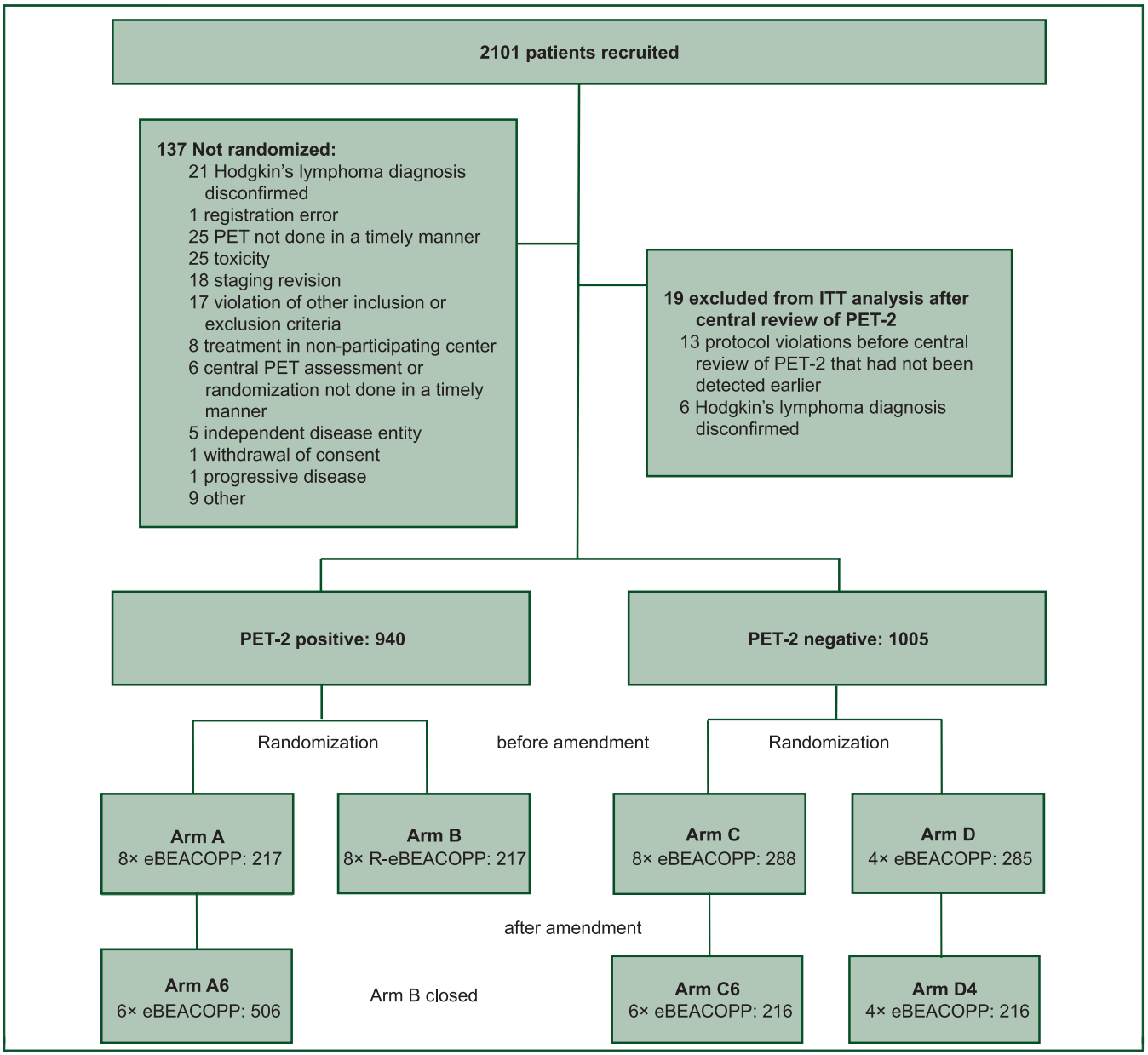

Figure 1. CONSORT flowchart.
CONSORT, Consolidated Standards of Reporting Trials; eBEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses; ITT, intention-to-treat; PET, positron emission tomography.

two-sided αerror of 0.05 and without adjustment for multiple testing.

RESULTS

Patients

A total of 2101 patients aged 18-60 years with advanced-stage HL were recruited in HD18; of whom 156 were found ineligible. Figure 1 shows a Consolidated Standards of Reporting Trials (CONSORT) flowchart of patient recruitment in HD18. The intention-to-treat (ITT) cohort therefore consisted of 1945 patients. PET-2-negative patients were randomized between 8× eBEACOPP (arm C, $n = 288$) and 4× eBEACOPP (arm D, $n = 285$), and between 6× eBEACOPP (arm C6, $n = 216$) and 4× eBEACOPP (arm D4, $n = 216$). PET-2-positive patients were randomized to receive 8× eBEACOPP (arm A, $n = 217$) or 8× R-eBEACOPP (arm B, $n = 217$). Five hundred and six PET-2-positive patients received 6× eBEACOPP (arm B6) after protocol amendment.

Time to recovery from fatigue

A total of 1453 patients provided at least one follow-up quality-of-life questionnaire and were thus available for TTR-F analysis. Overall, higher baseline fatigue and age were significantly associated with prolonged TTR-F, whereas sex was not (Table 1). Treatment reduction from eight to four cycles of eBEACOPP led to a significantly shorter TTR-F (HR 1.41, $P = 0.008$). Reducing the cycle number of

Table 1. Cox regression analysis of time to recovery from fatigue (TTR-F) in three randomized treatment comparisons A-C

No.	Experimental treatment[a]	Fatigue at baseline[b]		Experimental treatment		Male sex		Age[b]	
		HR	P	HR	P	HR	P	HR	P
A	PET-2+, 8× R-eBEACOPP[c]	0.99	<0.0001	0.70	0.0163	1.00	0.98	0.96	<0.0001
B	PET-2−, 4× versus 8× eBEACOPP	0.99	0.0002	1.41	0.0080	1.19	0.20	0.97	<0.0001
C	PET-2−, 4× versus 6× eBEACOPP	0.99	0.0004	1.22	0.18	0.96	0.78	0.97	<0.0001

eBEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses; HR, hazard ratio; PET-2, positron emission tomography; R-eBEACOPP, eBEACOPP plus intravenous rituximab.
[a]PET-2 positivity with uptake > mediastinum: Deauville Score ≥3.
[b]Continuous variable.
[c]Randomized comparison to 8× eBEACOPP.

eBEACOPP from six to four cycles (HR 1.22, $P = 0.18$) speeded TTR-F accordingly but was not statistically significant. In PET-2-positive patients, a significantly slower TTR-F was observed after the addition of rituximab (HR 0.70, $P = 0.0163$). Cox regression results of TTR-F are outlined in Table 1; Figure 2 shows inverse Kaplan—Meier curves of TTR-F for the compared treatments. In PET-2-negative patients, median TTR-F was 19.1 months [95% confidence interval (CI) 13.3-28.3 months] in arm C (eight cycles), 12.9 months (95% CI 9.7-19.7 months) in arm C6 (six cycles, post-amendment), 11.8 months (95% CI 7.8-15.4 months) in arm D (four cycles), and 9.9 months (95% CI 7.9-13.3 months) in arm D4 (four cycles, post-amendment). Two years after chemotherapy, recovery rates from fatigue were 53.9% (95% CI 46.3% to 61.4%) in arm C, 64.2% (95% CI 55.3% to 73.1%) in arm C6, 62.9% (95% CI 55.9% to 69.9%) in arm D, and 71.3% (95% CI 63.5% to 79.0%) in arm D4.

Time to return to work

A total of 1049 patients who reported to work or being in education before therapy provided at least one questionnaire during follow-up and thus were available for the TTR-W analysis. Similar to the TTR-F analysis, fatigue baseline scores and patients' age were significant determinants of TTR-W (Table 2) and the addition of rituximab resulted in longer TTR-W (HR 0.64, $P = 0.0017$) in PET-2-positive patients. Interestingly, male sex was significantly associated with shorter TTR-W. Among PET-2-negative patients, the highest observed HR (HR 1.24, $P = 0.084$) was seen when comparing four versus eight cycles of eBEACOPP, but this was not statistically significant. Cox regression results of TTR-W are outlined in Table 2 and inverse Kaplan—Meier curves describe TTR-W in Figure 3. In PET-2-negative patients, median TTR-W was 18.1 months (95% CI 13.2-24.6 months) in arm C (eight cycles), 15.2 months (95% CI 12.5-21.8 months) in arm C6 (six cycles, post-amendment), 13.7 months (95% CI 11.5-17.8 months) in arm D (four cycles), and 15.0 months (95% CI 9.2-19.6 months) in arm D4 (four cycles, post-amendment). Two years after chemotherapy, 47.6% (95% CI 38.8% to 56.4%) of patients in arm C returned to work, 57.3% (95% CI 46.4% to 68.3%) in arm C6, 57.1% (95% CI 48.4% to 65.7%) in arm D, and 61.4% (95% CI 51.8% to 71.1%) in arm D4.

Two-year HRQoL in detail

HRQoL questionnaires at baseline were available in a total of 1632 (83.9%) of all patients of the ITT cohort in HD18. Follow-up questionnaires in the second year after treatment were available in 958 (49.3%) patients. Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.11.014, details available questionnaires at given timepoints. HRQoL at baseline and age were the leading determinants of HRQoL in the second year after treatment. Experimental treatment, i.e. addition of rituximab for PET-2 positive or cycle reduction to four cycles from eight (pre-amendment) or six (post-amendment) cycles, did not significantly impact the scores 2 years after therapy. Detailed multiple regression results of eight relevant HRQoL domains, five functioning and three symptom scales of the EORTC QLQC30, are stated in Supplementary Tables S2-S4, available at https://doi.org/10.1016/j.annonc.2023.11.014.

DISCUSSION

The focus of our present analysis was to determine the impact of individualized (i.e. metabolic response adapted) treatment on the recovery from cancer-related fatigue and social reintegration of survivors from advanced-stage HL. We determined treatment effects using randomized comparisons of PROs provided within the phase III GHSG HD18 trial.

The following two major findings emerge from this analysis. Firstly, TTR-F is dependent on treatment duration in advanced-stage HL patients with shorter recovery after fewer cycles of chemotherapy. Secondly and accordingly, differences in fatigue recovery translate into differences in social integration of survivors reflected by time of return to work, indicating an earlier return to 'day-to-day life' with shorter treatment time.

To our knowledge, this is the first analysis showing an impact of PET-guided first-line treatment on the quality of life and social reintegration of HL survivors. In this setting, this is the first report based on time-to-event analyses of HRQoL measures, in line with recommended objectives and statistical methods for PROs in randomized controlled trials (RCTs) stated by the SISAQOL consortium.[9] Our results confirm that these methods are well suited to study the recovery process of HL survivors and to inform clinicians of HRQoL in a familiar statistical format.

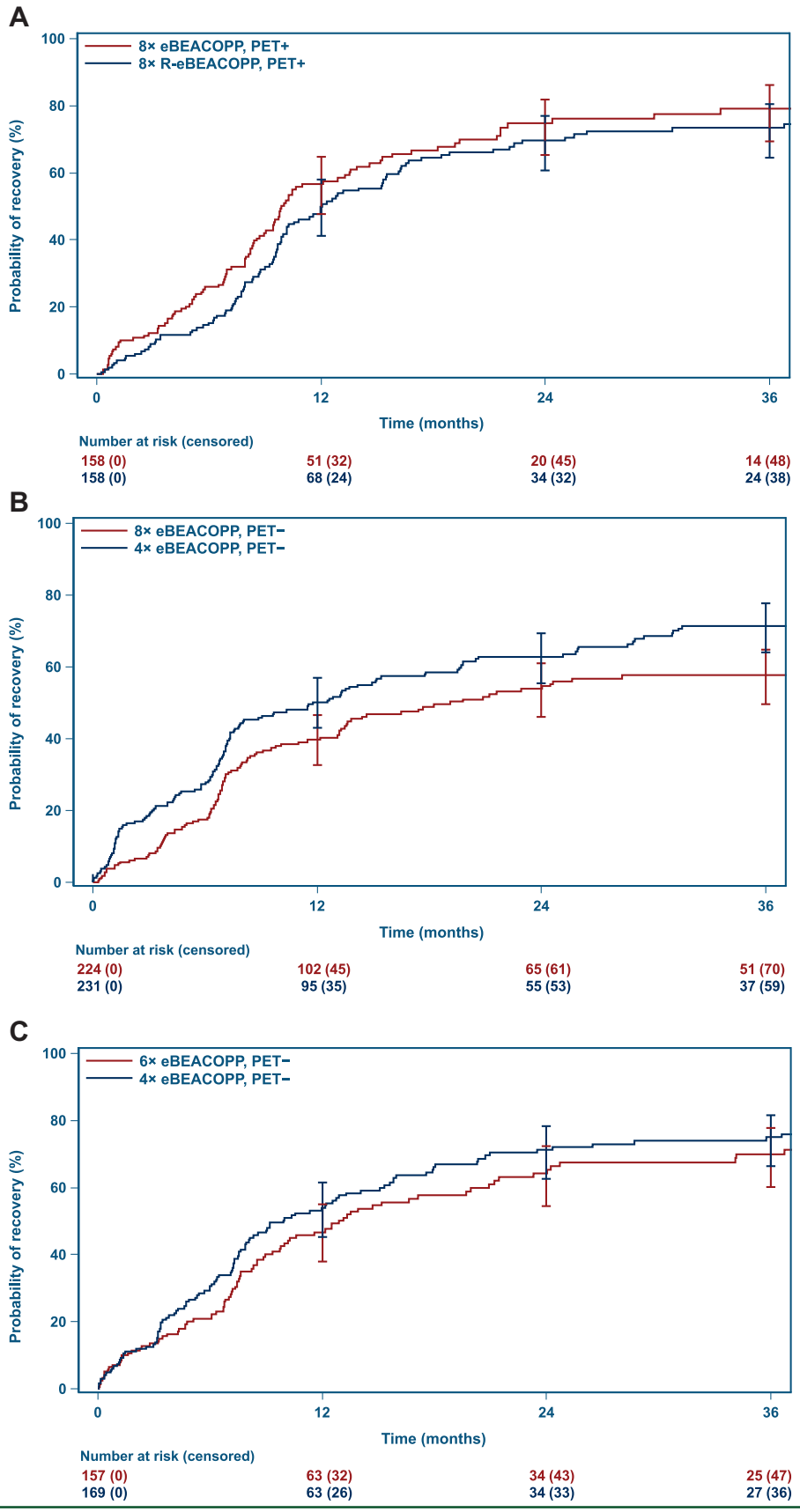

Figure 2. Time to recovery from fatigue (TTR-F).
eBEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses; PET, positron emission tomography; R-eBEACOPP, eBEACOPP plus intravenous rituximab.

Table 2. Cox regression analysis of time to return to work (TTR-W) in three randomized treatment comparisons A-C

No.	Experimental treatment[a]	Fatigue at baseline[b]		Experimental treatment		Male sex		Age[b]	
		HR	*P*	HR	*P*	HR	*P*	HR	*P*
A	PET-2+, 8× R-eBEACOPP[c]	0.99	0.0001	0.64	0.0017	1.40	0.028	0.96	<0.0001
B	PET-2−, 4× versus 8× eBEACOPP	0.99	0.0301	1.24	0.084	1.32	0.031	0.96	<0.0001
C	PET-2−, 4× versus 6× eBEACOPP	1.00	0.11	1.20	0.23	1.63	0.003	0.96	<0.0001

eBEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses; HR, hazard ratio; PET-2, positron emission tomography; R-eBEACOPP, eBEACOPP plus intravenous rituximab.
[a]PET-2 positivity with uptake > mediastinum: DS ≥3.
[b]Continuous variable.
[c]Randomized comparison to 8× eBEACOPP.

In this analysis, all patients have received eBEACOPP or R-eBEACOPP, which is the standard of care (SOC) for advanced-stage HL in Germany and many other European countries. At present, comparisons to other regimens such as doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) can only be made indirectly and should therefore be interpreted with caution as other socioeconomic factors (e.g. social security and labor market conditions in the country of residence) may play a confounding role. Very recently, Juul et al. provided a comprehensive analysis on work and education interruption in HL survivors treated predominantly with ABVD within EORTC-LYSA trials. Fortunately, they found that 86% of survivors resumed work within 24 months.[12] However, a majority (68%) of them had early-stage disease which limits comparability with our data in advanced-stage HL. Glimelius et al. found that the mean annual number of lost work days following treatment in patients with advanced-stage HL is indeed significantly higher compared to that in patients with early-stage disease.[13] Stratified by treatment regimen, mean number of lost days in the fifth year of follow-up was comparable between 6-8× ABVD ± RT (62 days, 95% CI 43-82 days) and 6-8× BEACOPP ± RT (60 days, 95% CI 29-89 days).[13] In our own trial database, we observed similar levels of fatigue during and following treatment in patients receiving 4× ABVD for early-unfavorable HL (HD14 trial) compared to patients receiving 6× eBEACOPP for advanced-stage HL (HD15 trial), indicating that there are no substantial differences between these regimens in terms of fatigue (see Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2023.11.014).

Our analysis stresses the need for effective interventions to improve cancer-related fatigue in patients with HL. Patients in the HD18 trial did not receive additional counseling outside of routine clinical care. The German guideline on diagnostics, therapy, and aftercare of adult patients with HL recommends assessment of cancer-related fatigue in aftercare and moderate exercise, such as endurance training based on individual exercise capacities.[14] If these recommendations are followed is heavily depending on the treating physician. Furthermore, a general structure to provide adequate counseling or even dedicated interventions to improve recovery following chemotherapy and prevent persisting cancer-related fatigue is missing. For patients with manifest fatigue following treatment for HL, cognitive behavioral therapy and other psychosocial interventions are promising options.[15-18] Persisting cancer-related fatigue is an important factor preventing survivors from social reintegration. Previous analyses found a significant negative association between severe cancer-related fatigue and employment in survivors and a strong link between cancer-related fatigue and financial problems.[3] Approximately one-third of young survivors of cancer report troubles keeping up with work or education 15-35 months after diagnosis.[19] A recent analysis of the EORTC-LYSA trials found that work or education is commonly interrupted in patients with HL.[12] However, social reintegration is clearly affected by socioeconomic variables. While most of the survivors return to work or education within 2 years, female sex, higher age, and a lower level of education were associated with not returning to work after treatment.[12] Our study confirms the influence of sex and age on TTR-W but also identifies differences between trial arms. In contrast to TTR-F, which was not determined by sex, treatment effect on TTR-W may be more prone to the influence of socioeconomic variables such as gender or level of education. Lastly, we found that baseline fatigue has a significant negative influence on TTR-W.

HD18 was a treatment optimization trial demonstrating that four cycles of chemotherapy in PET-2-negative patients are sufficient for tumor control and result in improvements in tolerability.[4] Treatment de-escalation should primarily serve to improve the quality of life of patients and survivors. However, previous HRQoL analyses found no impact of treatment intensity and cancer stage on long-term fatigue and quality of life of patients with HL in general.[11] This result might be explained by the larger influence of psychosocial factors as perpetuating factors for persisting cancer-related fatigue.[20] Accordingly, treatment intensity had no significant effect on fatigue levels and other HRQoL scales in year 2 of survivorship in the present study. Even the reduction from eight to four cycles of eBEACOPP had no significant effect. Instead, HRQoL at baseline and age were the main determinants of later HRQoL, again underscoring the effect of psychosocial factors on long-term survivorship.

As cancer and its treatment inevitably cause significant acute cancer-related fatigue,[2] treatment duration may affect the transition from patient to former patient. Indeed,

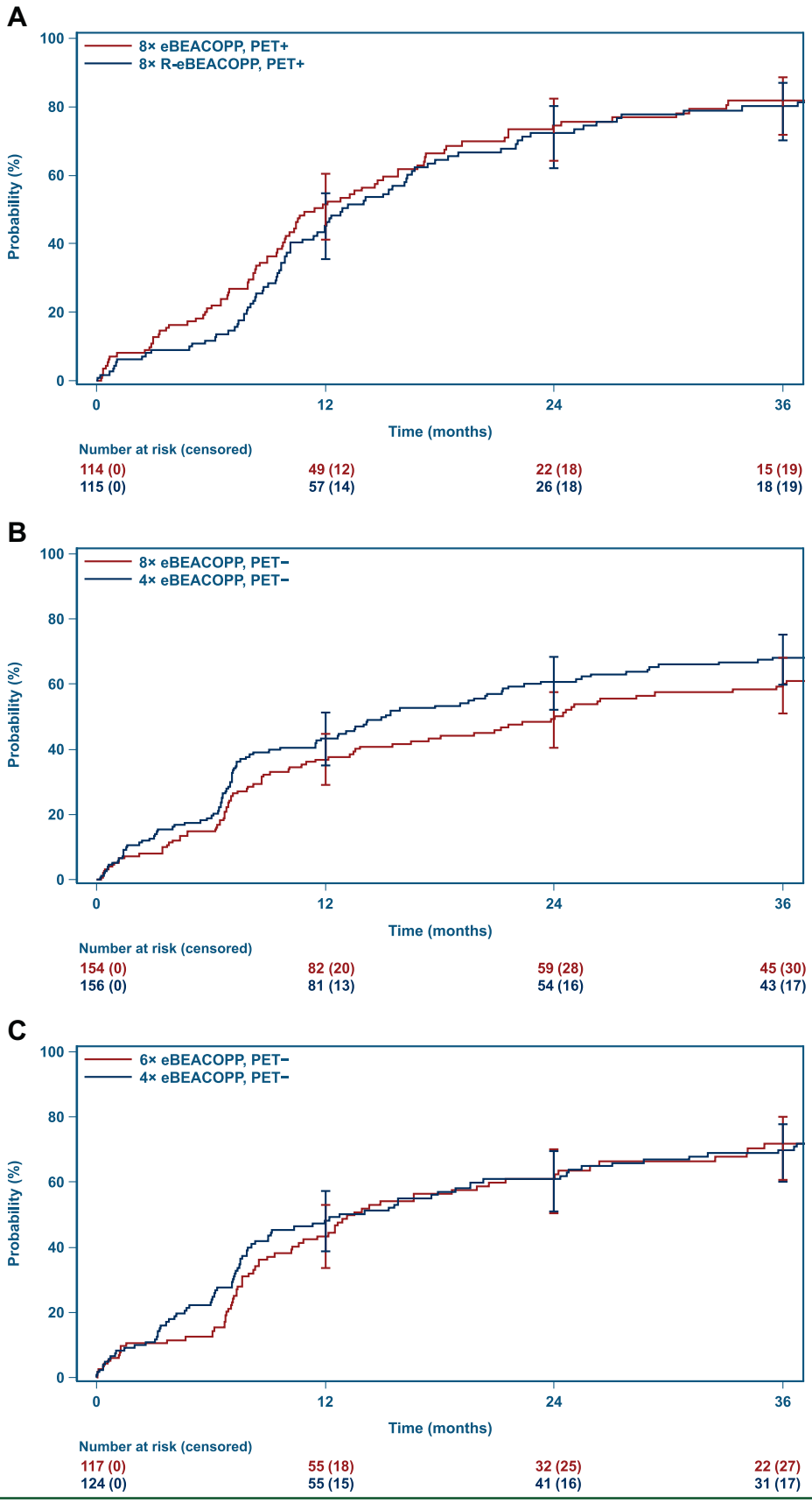

Figure 3. Time to return to work (TTR-W).
eBEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses; PET, positron emission tomography; R-eBEACOPP, eBEACOPP plus intravenous rituximab.

using time-to-event analyses, we observed slower recovery of cancer-related fatigue and prolonged social reintegration after more intense treatment with more cycles of chemotherapy or addition of rituximab. This underscores the importance of selecting adequate methods to detect meaningful HRQoL differences between trial arms. Incorporating PROs should become standard in oncology trials, especially in highly curable diseases such as HL since they allow quantification of the advantages and disadvantages of cancer treatments from the patient's perspective. They can therefore inform caregivers and improve decision making and treatment selection. However, statistical methods for analyzing HRQoL data are often inconsistent.[21] Consequently, the SISAQOL consortium makes continuous efforts to harmonize methodological approaches to PRO assessements.[9] Here, we followed their recommendation to describe PRO outcomes in HD18, which defined the current SOC for advanced-stage HL in several countries, hopefully encouraging standardized reporting of PROs in other pivotal RCTs in HL.

Notably, we observed significantly prolonged TTR-F (HR 0.70, $P = 0.0163$) and TTR-W (HR 0.64, $P = 0.0017$) for patients randomized to receive additional CD20-targeted treatment with rituximab together with chemotherapy. This was not expected, as investigator-reported toxicities according to the National Cancer Institute Common Terminology Criteria for Adverse Events occurred with similar frequency in the experimental (arm A) and SOC (arm B) groups.[6] This observation challenges the assumption that immunotherapy is better tolerated and thus might have less impact on PROs than chemotherapy. Given that antibodies targeting CD30 or programmed cell death protein 1 are already approved or in clinical development for first-line treatment of HL,[22,23] our results therefore call for inclusion and reporting of PROs as key endpoints to detect their impact on HRQoL.

This study comes with limitations. Firstly, there is a considerable amount of missing data, especially at later time points. This is typical for longitudinal studies of HRQoL and may introduce bias. However, the primary focus of this work lies on time-to-event analyses, which do not depend on available data at fixed timepoints and account for missing values with an adequate method for data missing at random: censoring at the date of last information. Accordingly, 74.7% of the ITT cohort in HD18 were available for analysis of TTR-F compared to 49.3% who were available for 2-year HRQoL outcomes. Nevertheless, the high amount of missing data and increasing dropout over time limit the precision of our results. Although we are not aware of any relevant imbalance between the compared and randomized treatment groups and applied standard methods to account for missing values, the necessary statistical assumption—missingness at random—cannot be proven. This basic statistical limitation and the considerable amount of missing values can therefore affect our estimates to a certain degree. Secondly, the one-dimensional fatigue scale of the EORTC QLQ-C30 questionnaire does not measure different dimensions of cancer-related fatigue and in fact is composed of only three items. Other more dedicated modules of the questionnaire such as the QLQ-FA12[24] enable a more nuanced assessment of TTR-F, but were not available at the time of the HD18 trial. Thirdly, this is a *post hoc* analysis of HRQoL data and the threshold of fatigue <30 to define fatigue recovery is not predefined. We tested different options to define fatigue recovery in independent data of the HD15 trial, where the here applied cut-off differentiated best between the randomized treatment groups (unpublished results). Although this simplified approach is certainly not the most precise psychometric method in individual cases, we consider it appropriate and sufficient at the group level. It enables easy use and hopefully replication of our results in future independent studies.

In conclusion, the individualized PET-2-guided de-escalation of first-line treatment for patients with advanced-stage HL accelerated the time to recovery from cancer-related fatigue and return to work. De-escalating and shortening chemotherapies enable thus a faster social reintegration of HL survivors and reduce the psychosocial burden of disease. This finding is relevant when having in mind that HL survivors are mostly young and need to return to their 'normal lives' as soon as possible to prevent long-term socioeconomic consequences. Our results encourage implementing time-to-event analyses of PROs in randomized clinical trials of HL and development of shorter treatments to improve recovery from cancer-related fatigue and social reintegration of survivors.

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DISCLOSURE

The authors have declared no conflicts of interest.

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