PET-guided omission of radiotherapy in early-stage unfavourable Hodgkin lymphoma (GHSG HD17): a multicentre, open-label, randomised, phase 3 trial

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Summary

Background Combined-modality treatment consisting of chemotherapy and consolidation radiotherapy is standard of care for patients with early-stage unfavourable Hodgkin lymphoma. However, the use of radiotherapy can have long-term sequelae, which is of particular concern, as Hodgkin lymphoma is frequently diagnosed in young adults with a median age of approximately 30 years. In the German Hodgkin Study Group HD17 trial, we investigated whether radiotherapy can be omitted without loss of efficacy in patients who have a complete metabolic response after receiving two cycles of escalated doses of etoposide, cyclophosphamide, and doxorubicin, and regular doses of bleomycin, vincristine, procarbazine, and prednisone (eBEACOPP) plus two cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) chemotherapy (2+2).

Methods In this multicentre, open-label, randomised, phase 3 trial, patients (aged 18–60 years) with newly diagnosed early-stage unfavourable Hodgkin lymphoma (all histologies) and an Eastern Cooperative Oncology Group performance status of 2 or less were enrolled at 224 hospitals and private practices in Germany, Switzerland, Austria, and the Netherlands. Patients were randomly assigned (1:1) to receive either standard combined-modality treatment, consisting of the 2+2 regimen (eBEACOPP consisted of 1250 mg/m² intravenous cyclophosphamide on day 1, 35 mg/m² intravenous doxorubicin on day 1, 200 mg/m² intravenous etoposide on days 1–3, 100 mg/m² oral procarbazine on days 1–7, 40 mg/m² oral prednisone on days 1–14, 1·4 mg/m² intravenous vincristine on day 8 [maximum dose of 2 mg per cycle], and 10 mg/m² intravenous bleomycin on day 8; ABVD consisted of 25 mg/m² intravenous doxorubicin, 10 mg/m² intravenous bleomycin, 6 mg/m² intravenous vinblastine, and 375 mg/m² intravenous dacarbazine, all given on days 1 and 15) followed by 30 Gy involved-field radiotherapy (standard combined-modality treatment group) or PET4-guided treatment, consisting of the 2+2 regimen followed by 30 Gy of involved-node radiotherapy only in patients with positive PET at the end of four cycles of chemotherapy (PET4; PET4-guided treatment group). Randomisation was done centrally and used the minimisation method and seven stratification factors (centre, age, sex, clinical symptoms, disease localisation, albumin concentration, and bulky disease), and patients and investigators were masked to treatment allocation until central review of the PET4 examination had been completed. With the final analysis presented here, the primary objective was to show non-inferiority of the PET4-guided strategy in a per-protocol analysis of the primary endpoint of progression-free survival. We defined non-inferiority as an absolute difference of 8% in the 5-year progression-free survival estimates between the two groups. Safety analyses were done in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, NCT01356680.

Findings Between Jan 13, 2012, and March 21, 2017, we enrolled and randomly assigned 1100 patients to the standard combined-modality treatment group (n=548) or to the PET4-guided treatment group (n=552); two patients in each group were found ineligible after randomisation. At a median follow-up of 46·2 months (IQR 32·7–61·2), 5-year progression-free survival was 97·3% (95% CI 94·5–98·7) in the standard combined-modality treatment group and 95·1% (92·0–97·0) in the PET4-guided treatment group (hazard ratio 0·523 [95% CI 0·226–1·211]). The between-group difference was 2·2% (95% CI –0·9 to 5·3) and excluded the non-inferiority margin of 8%. The most common grade 3 or 4 acute haematological adverse events were leucopenia (436 [83%] of 528 patients in the standard combined-modality treatment group *vs* 443 [84%] of 529 patients in the PET4-guided treatment group) and thrombocytopenia (139 [26%] *vs* 176 [33%]), and the most frequent acute non-haematological toxic effects were infection (32 [6%] *vs* 40 [8%]) and nausea or vomiting (38 [7%] *vs* 29 [6%]). The most common acute radiotherapy-associated adverse events were dysphagia (26 [6%] in the standard combined-modality treatment group *vs* three [2%] in the PET4-guided treatment group) and mucositis (nine [2%] *vs* none). 229 serious adverse events were reported by 161 (29%) of 546 patients in the combined-modality treatment group, and 235 serious adverse events were reported by 164 (30%) of 550 patients in the PET4-guided treatment group. One suspected unexpected serious adverse reaction (infection) leading to death was reported in the PET4-guided treatment group.

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Interpretation PET4-negativity after treatment with 2+2 chemotherapy in patients with newly diagnosed early-stage unfavourable Hodgkin lymphoma allows omission of consolidation radiotherapy without a clinically relevant loss of efficacy. PET4-guided therapy could thereby reduce the proportion of patients at risk of the late effects of radiotherapy.

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Introduction

Standard combined-modality treatment of patients with early-stage unfavourable Hodgkin lymphoma includes four cycles of chemotherapy and consolidation radiotherapy with a dose of 30 Gy.[1,2] The well tolerated doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) regimen is widely used as the systemic backbone of this strategy, yielding 5-year progression-free survival rates of approximately 85%.[3] The German Hodgkin Study Group (GHSG) HD14 trial aimed to improve progression-free survival in these patients by introducing an intensified chemotherapy regimen consisting of two cycles of escalated doses of etoposide, cyclophosphamide, and doxorubicin, and regular doses of bleomycin, vincristine, procarbazine, and prednisone (eBEACOPP) plus two cycles of ABVD (2+2).[4] This trial showed that there was a significant difference in progression-free survival in favour of the short, but more intensive, 2+2 regimen compared with four cycles of ABVD.[4] The 2+2 regimen was then adopted as the new standard of care within the GHSG, and is regarded as a treatment option by National Comprehensive Cancer Network and European Society for Medical Oncology guidelines.[5,6] However, the overall treatment intensity of 2+2 followed by 30 Gy involved-field radiotherapy is high and raises concerns about the long-term sequelae. It is well known that extended-field consolidation radiotherapy in patients with early-stage unfavourable Hodgkin lymphoma increases the risk of second primary malignancies.[7,8] Of particular concern is the high cumulative incidence of breast cancer following radiotherapy in young (ie, aged <30 years), female patients with Hodgkin lymphoma.[7,8] Radiotherapy can also induce organ dysfunction, such as as hypothyroidism and cardiovascular disease in the long-term.[9–13] Even though these complications can occur many years after radiotherapy, they are still relevant because Hodgkin lymphoma is a malignancy of young adults, with a median age at diagnosis of around 30 years. Accordingly, omission of radiotherapy is supposed to have a late, but clinically relevant, benefit for patients with newly diagnosed early-stage unfavourable Hodgkin lymphoma.

Research in context

Evidence before this study

We searched MEDLINE on Jan 2, 2020, using the search terms "interim PET" or "PET-2", or "PET-3", or PET-4", and "Hodgkin*". We searched for randomised controlled studies assessing the prognostic effect of interim PET in patients with early-stage Hodgkin lymphoma published between Jan 1, 2005, and Jan 1, 2020, with no language restrictions. We found five studies that had evaluated the predictive value of interim ^{18}F-flurodeoxyglucose (^{18}F-FDG)-PET in patients with early-stage favourable Hodgkin lymphoma, unfavourable Hodgkin lymphoma, or both. Interim PET has been shown to have a positive predictive value in patients with early-stage Hodgkin lymphoma after upfront treatment with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy. By comparison, evidence for the negative predictive value of this imaging modality in patients receiving upfront ABVD is less robust. Omission of radiotherapy in interim PET-negative patients after ABVD chemotherapy results in loss of efficacy when compared with standard combined-modality treatment. We found no evidence from controlled trials on the prognostic effect of interim PET in patients with early-stage Hodgkin lymphoma receiving upfront escalated doses of etoposide, cyclophosphamide, and doxorubicin, and regular doses of bleomycin, vincristine, procarbazine, and prednisone (eBEACOPP).

Added value of this study

We found a high negative predictive value of interim PET after intensive systemic treatment with two cycles of eBEACOPP and two cycles of ABVD in patients with early stage unfavourable Hodgkin lymphoma, thus consolidation radiotherapy can be omitted without the loss of tumour control in these patients. To our knowledge, this is the first randomised controlled trial to show that a chemotherapy-alone treatment strategy is as efficacious as the established combined-modality treatment strategy in patients with early stage unfavourable Hodgkin lymphoma.

Implications of all the available evidence

Omission of consolidation radiotherapy shortens the overall treatment duration in patients with early-stage unfavourable Hodgkin lymphoma and eliminates late effects potentially arising from radiotherapy. The survival outcomes of patients in our study compare favourably with any data from controlled trials published thus far. This new treatment strategy could be applicable to clinical practice, where the medical infrastructure allows administration of eBEACOPP chemotherapy and assessment of metabolic response by ^{18}F-FDG-PET.

On the other hand, omission of radiotherapy could increase the risk of relapse and should therefore be evaluated in patients with a presumably low risk of treatment failure. Unfortunately, the established risk classification systems, which are based on the Ann Arbor staging criteria combined with various clinical risk factors, cannot reliably predict the individual risk of treatment failure.

The introduction of functional imaging using ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET for metabolic response assessment has provided the opportunity for an individualised treatment approach. In advanced-stage Hodgkin lymphoma, interim PET after two cycles of chemotherapy overcomes the prognostic effect of the international prognostic score, which is based on clinical baseline characteristics.[14] Consequently, both interim PET-guided reduction of intensive systemic therapy with eBEACOPP and PET-guided omission of radiotherapy have been successfully established in patients with advanced-stage Hodgkin lymphoma.[3,15–17] Additionally, interim PET-guided escalation of treatment has been investigated in patients with advanced-stage Hodgkin lymphoma after initial therapy with the low-intensity ABVD regimen.[18] We thus hypothesised that PET imaging after four cycles of chemotherapy (PET4) might discriminate between patients with unfavourable Hodgkin lymphoma at a low risk of treatment failure and those with a high risk of treatment failure.

The GHSG HD17 study had two main aims. First, assuming a favourable outcome in presumably low-risk patients with a negative PET result at the end ozotherapy, we aimed to investigate whether omitting consolidation radiotherapy, and thereby reducing the overall treatment intensity, was possible without substantially compromising 5-year progression-free survival. Our second aim was to investigate the prognostic effect of a positive PET4 result in patients receiving combined-modality treatment. This Article reports the results of the final analysis of the GHSG HD17 study.

Methods

Study design and participants

This was a multicentre, open-label, randomised, phase 3 trial done at 224 hospitals and private practices in Germany, Switzerland, Austria, and the Netherlands.

We recruited patients (aged 18–60 years) with newly diagnosed, histologically confirmed, stage IA, IB, or IIA classical Hodgkin lymphoma or nodular lymphocyte-predominant Hodgkin lymphoma, with at least one of the following risk factors: a bulky mediastinal mass (ie, measuring at least a third of the maximum transverse diameter of the thorax); extranodal involvement; either an erythrocyte sedimentation rate of 50 mm/h or higher without B-symptoms, or an erythrocyte sedimentation rate of 30 mm/h or higher with B-symptoms; or involvement of three or more nodal areas. Patients with stage IIB disease with either an erythrocyte sedimentation rate of 50 mm/h or higher without B-symptoms or an erythrocyte sedimentation rate of 30 mm/h or higher with B-symptoms, or involvement of three or more nodal areas, without a bulky mediastinal mass or extranodal involvement, were also included. Histology samples taken by the primary care pathologist at diagnosis were reassessed by at least one of a panel of six lymphoma expert pathologists. Other inclusion criteria were an Eastern Cooperative Oncology Group performance status of 2 or lower and a negative HIV test result. Key exclusion criteria were concurrent diseases precluding protocol treatment and previous chemotherapy or radiotherapy (appendix pp 1–2).

The trial was designed by the GHSG steering committee and approved by the ethics committees of all participating centres. All patients provided written, informed consent before study entry according to the Good Clinical Practice guidelines of the International Conference on Harmonisation and national regulations.

Randomisation and masking

Before starting treatment, patients were registered at the GHSG central office by telephone, where they were then randomly assigned (1:1) to one of two parallel treatment groups: the standard combined-modality treatment group, in which patients received the 2+2 chemotherapy regimen followed by 30 Gy of involved-field radiotherapy, or the PET-guided treatment group, in which patients received the 2+2 chemotherapy regimen followed by 30 Gy of involved-node radiotherapy only in those with a positive PET4 scan. Although not the focus of this study, different modalities of field delineation were used in both groups, with the aim of further reducing the toxicity of radiotherapy with PET-guided treatment. Randomisation was done centrally using the minimisation method with a random component. Stratification factors were centre, age (<45 years *vs* ≥45 years), sex, B-symptoms, disease localisation (supradiaphragmatic *vs* infradiaphragmatic), albumin concentration (<40 g/L *vs* ≥40 g/L), and initial tumour bulk (presence *vs* absence of initial tumour bulk ≥5 cm in largest diameter). Patients and investigators were masked to treatment allocation until central review of the PET4 examination had been completed.

Procedures

The procedures are described in detail in the appendix (pp 2–3). eBEACOPP included 1250 mg/m² cyclophosphamide on day 1, 35 mg/m² doxorubicin on day 1, 200 mg/m² etoposide on days 1–3, 100 mg/m² procarbazine on days 1–7, 40 mg/m² prednisone on days 1–14, 1·4 mg/m² vincristine on day 8 (maximum dose of 2 mg per cycle), and 10 mg/m² bleomycin on day 8; the second cycle of this regimen started on day 22. Granulocyte colony-stimulating factor (G-CSF) had to be administered from day 8 of each eBEACOPP cycle until

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See **Online** for appendix

recovery of white blood cell counts to at least 1000 cells per µL on three consecutive days. ABVD was administered at standard doses consisting of 25 mg/m² doxorubicin, 10 mg/m² bleomycin, 6 mg/m² vinblastine, and 375 mg/m² dacarbazine all given on days 1 and 15; the second cycle of this regimen started on day 29. G-CSF was administered if clinically indicated. Treatment was postponed after the previous chemotherapy cycle until recovery of white blood cell counts to at least 2500 cells per µL and platelet counts to at least 80 000 platelets per µL on the scheduled day of retreatment. For patients requiring treatment postponement for more than 2 weeks or with pronounced toxicity during treatment, dose reductions were done as specified in the trial protocol (described in appendix pp 2–3).

Blood counts were monitored at least twice per week during eBEACOPP and at least once per week during ABVD and radiotherapy. Adverse events during chemotherapy and radiotherapy were assessed and graded, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, for each chemotherapy cycle and during radiotherapy, and the number of CTCAE grade 3–4 events, the number of days in hospital, and whether blood products and G-CSF were administered were documented for each cycle. In addition, all serious adverse events occurring up to 30 days after the end of chemotherapy, or after this timepoint if they were considered as possibly related to chemotherapy, had to be reported as soon as they were known.

CT-based response assessments were scheduled after chemotherapy and then again after radiotherapy, if applicable. CT and PET4 scans were scheduled between day 29 and day 35 (between day 22 and day 29 was allowed for organisational issues) of the fourth chemotherapy cycle, and were assessed by use of a five-point scale, with ^{18}F-FDG uptake higher than the mediastinal blood pool (corresponding to a Deauville score of 3 or higher) defined as positive, and a Deauville score of 1–2 defined as negative.[19] A multidisciplinary panel of experts from medical oncology, nuclear medicine, radiation oncology, and radiology, who were masked to treatment group allocation, centrally reviewed all imaging and clinical information obtained at baseline and after chemotherapy. Patients with progressive disease were taken off study treatment.

Involved-field radiotherapy or involved-node radiotherapy were planned centrally on the basis of initial image-based staging results; initial staging was revised if necessary. The recommended interval between completion of chemotherapy and starting radiotherapy was 4–6 weeks. The total dose of 30 Gy was given in fractions of 1·8–2·0 Gy five times per week.

A data monitoring board consisting of two clinicians and two biostatisticians, with expertise in clinical trials, reviewed recruitment, safety, and efficacy data on a regular basis and agreed with the timing and content of this analysis.

Outcomes

The primary efficacy endpoint was progression-free survival, defined as the time from study entry until disease progression, relapse, or death from any cause. If none of these events had occurred, progression-free survival was censored at the date when the disease status was last assessed. Secondary endpoints were overall survival (defined as time from study entry until death from any cause or censoring at the date when the patient was last known to be alive), the proportion of patients reaching complete remission (defined as the disappearance of all clinical and radiological signs of disease), the proportion of PET4-negative patients (defined as ^{18}F-FDG uptake that did not exceed the mediastinal blood pool), late toxic effects (ie, those occurring after completion of study therapy), and second primary malignancies. Late toxicity will be analysed and reported after the final follow-up visit of the last patient.

Statistical analysis

The study had two independent objectives. The primary objective was to show non-inferiority of PET4-guided treatment over standard combined-modality treatment in terms of progression-free survival. Since a difference in 5-year progression-free survival of 8% or more between the two groups was defined as clinically relevant, non-inferiority was to be established if the upper limit of the two-sided 95% CI for the difference in 5-year progression-free survival, built by normal approximation, was less than 8%.

Assuming an actual inferiority of 1·5 percentage points of PET4-guided treatment compared with standard combined-modality treatment, the non-inferiority test could be done with at least 80% power when at least 35 events for the primary endpoint of progression-free survival had been observed in the per-protocol analysis population. To this end, we planned to recruit 1100 patients within 5 years, assuming that approximately 80% of patients would be evaluable in the per-protocol analysis population. The per-protocol analysis population included all patients in the intention-to-treat analysis population who had a regular central review of the PET4 examination, had complete therapy documentation, and did not have severe protocol deviations, except for progressive disease or death during therapy. Per-protocol analysis was considered as the most conservative analysis for non-inferiority objectives in the trial protocol. If non-inferiority of the PET4-guided strategy was established, the non-inferiority test was planned to be repeated with the same non-inferiority margin for the subgroup of PET4-negative patients, in order to establish whether omission of consolidating radiotherapy does not result in inferior tumour control in this subgroup.

The second prespecified objective of the study was to assess the prognostic effect of PET4. Only patients with a valid PET4 result who were assigned to receive

combined-modality treatment were to be included in this analysis (ie, PET4-positive patients in both groups and PET4-negative patients in the combined-modality treatment group).

We compared time-to-event endpoints using the Kaplan-Meier method, including hazard ratios (HRs) and 95% CIs obtained from univariate Cox regression models. The proportional hazards assumption was tested by visual inspection of survival curves. To assess whether the prognostic effect of PET4 was independent from baseline factors, sensitivity analyses comparing PET4-negative and PET4-positive patients were done, including all stratification factors (except for centre) in the regression model.

Post-hoc analyses were done to examine the prognostic effect of PET4 positivity when a Deauville score of 4 was used as the threshold. Descriptive post-hoc analyses of primary and secondary survival endpoints were done in subsets of PET-positive and PET-negative patients, according to each Deauville score threshold and for the subset of patients in the per-protocol analysis population with initial bulky disease or a large mediastinal tumour.

We did a post-hoc analysis of the standardised mortality ratio, calculated as the number of observed deaths divided by the number of expected deaths in the German population, adjusted for age and sex.

Other secondary endpoints were analysed by means of descriptive statistics. The non-inferiority test was done primarily in the per-protocol population. Sensitivity analyses, safety analyses, and all other analyses were done in the intention-to-treat population, which included all patients who were randomly assigned, except for those with a disconfirmed diagnosis of Hodgkin lymphoma or those who had withdrawn consent for inclusion in the trial and requested anonymisation of study documents. In addition, all patients who dropped out before central review of the PET4 examination had to be excluded from all analyses of the main objectives of the trial. Overall survival was additionally analysed in the per-protocol population.

We used SAS (version 9.4) for all statistical analyses. A p value of 0·05 or less was considered to indicate a significant difference. The trial is registered with ClinicalTrials.gov, NCT01356680.

Role of the funding source

Deutsche Krebshilfe reviewed the trial protocol for adherence to good clinical practice. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Jan 13, 2012, and March 21, 2017, we enrolled and randomly assigned 1100 patients to the standard combined-modality treatment group (n=548) or to the PET4-guided treatment group (n=552; figure 1). Four patients (two in each group) were excluded from the intention-to-treat analysis population due to disconfirmation of their Hodgkin lymphoma diagnosis by pathology review (n=3) or withdrawal of consent before starting treatment (n=1; figure 1). A further 117 (6%) patients (60 in the standard combined-modality treatment group and 57 in the PET4-guided treatment group) dropped out before central review of the PET4 examination, mainly because of revision of initial tumour stage. Thus, centrally reviewed PET4 was available for 979 patients (486 in the standard combined-modality treatment group and 493 in the PET4-guided treatment group). 318 (65%) of 486 patients in the standard combined-modality treatment group and 333 (68%) of 493 patients in the PET4-guided treatment group were PET4-negative. 168 (33%) patients in the standard combined-modality treatment group and

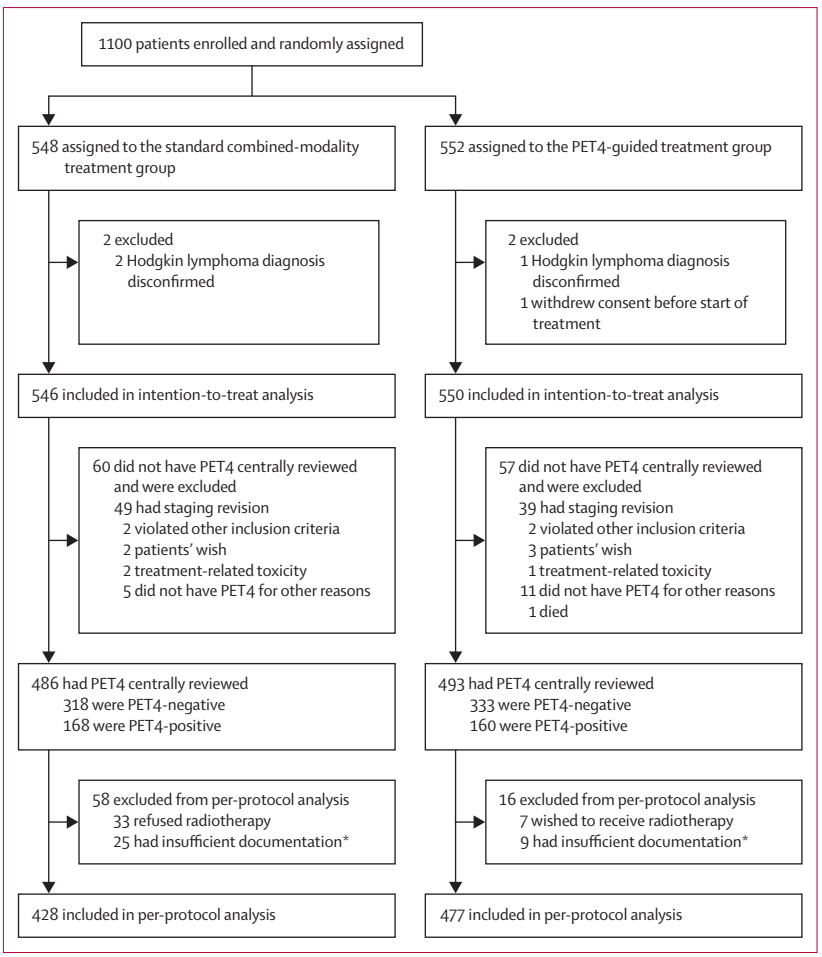

Figure 1: **Trial profile**

PET4=PET scan at the end of four cycles of chemotherapy. *Applies to PET4-positive patients who did not have radiotherapy or restaging documentation after radiotherapy on the respective case report form or PET4-negative patients who were lost to follow-up after PET4 (ie, it was not clear whether the patient received additional radiotherapy or not).

	Standard combined-modality treatment group (n=546)	PET4-guided treatment group (n=550)
Age, years		
Mean	32·8 (11·0)	32·9 (11·0)
Median	30 (24–39)	31 (24–40)
>50	56 (10%)	62 (11%)
Sex		
Female	294 (54%)	294 (53%)
Male	252 (46%)	256 (47%)
Ann Arbor stage		
IA	20 (47%)	18 (3%)
IB	18 (3%)	12 (2%)
IIA	347 (64%)	376 (68%)
IIB	134 (25%)	143 (26%)
IIIA	0	1 (<1%)
ECOG performance status		
1	448 (82%)	444 (81%)
2	98 (18%)	102 (19%)
3	0	4 (1%)
GHSG risk factors		
Large mediastinal mass	98 (18%)	101 (18%)
Extranodal disease	46 (8%)	43 (8%)
Elevated erythrocyte sedimentation rate	243 (45%)	252 (46%)
≥3 nodal areas involved	393 (72%)	400 (73%)
Other risk factors		
Infra-diaphragmatic disease	35 (6%)	33 (6%)
Bulky disease	283 (52%)	305 (55%)
Histological subtype		
Nodular sclerosis	210/339 (62%)	211/323 (65%)
Mixed cellularity	54/339 (16%)	46/323 (14%)
Lymphocyte-depleted	1/339 (<1%)	0
Lymphocyte-rich	8/339 (2%)	7/323 (2%)
Unspecified classical Hodgkin lymphoma	59/339 (17%)	52/323 (16%)
Nodular lymphocyte-predominant Hodgkin lymphoma	7/339 (2%)	7/323 (2%)

Data are mean (SD), median (IQR), n (%), or n/N (%). PET4=PET scan at the end of four cycles of chemotherapy. ECOG=Eastern Cooperative Oncology Group. GHSG=German Hodgkin Study Group.

Table 1: **Baseline characteristics**

160 (32%) patients in the PET4-guided treatment group were PET4-positive, with 42 (9%) patients in the standard combined-modality treatment group and 48 (10%) patients in the PET4-guided treatment group with a Deauville score of more than 3 (including one patient in the standard combined-modality treatment group with primary progressive disease).

A further 58 (12%) of 486 patients in the standard combined-modality treatment group and 16 (3%) of 493 patients in the PET4-guided treatment group dropped out after central review of the PET4 examination. Most dropouts at this stage were due to the patients' own decision; 33 (10%) of 318 PET4-negative patients in the standard combined-modality treatment group refused to have involved-field radiotherapy, whereas seven (2%) of 333 PET4-negative patients in the PET4-guided treatment group requested radiotherapy. Excluding an additional 25 patients in the standard combined-modality treatment group and nine patients in the PET4-guided treatment group with insufficient documentation, the per-protocol population comprised 905 patients (428 in the standard combined-modality treatment group and 477 in the PET4-guided treatment group; figure 1).

Baseline characteristics in the intention-to-treat population are shown in table 1. Median age was 31 years (IQR 24–40; range 18–60), and 508 (46%) of 1096 patients were male.

At a median follow-up of 46·2 months (IQR 32·7–61·2), 25 progression-free survival events had occurred in the per-protocol population (table 2). 5-year progression-free survival was 97·3% (95% CI 94·5 to 98·7) in the combined-modality treatment group and 95·1% (92·0 to 97·0) in the PET4-guided treatment group (HR 0·523 [95% CI 0·226 to 1·211]; figure 2A). The 95% CI for the group difference of 2·2% ranged from –0·9% to 5·3% and excluded the predefined non-inferiority margin of 8%. When restricted to the subgroup of PET4-negative patients, the difference in 5-year progression-free survival was 1·7% (95% CI –1·8 to 5·3; figure 2B). A sensitivity analysis in the intention-to-treat population showed similar results (table 2; appendix p 5).

We analysed the prognostic effect of PET4 in 646 patients who had either a positive PET4 or were assigned to the standard combined-modality treatment group and had a negative PET4. 5-year progression-free survival was significantly higher in the PET-negative group than in the PET-positive subgroups (HR 3·03 [95% CI 1·10–8·33], p=0·024; appendix p 7). In a post-hoc analysis, in which the threshold for PET positivity was increased from a Deauville score of 3 to a Deauville score of 4, the difference in progression-free survival between the groups was greater (HR 10·19 [4·16–25·00]; p<0·0001; appendix p 7). Among those 90 patients with a Deauville score of 4, 5-year progression-free survival was 81·6% (67·9–89·9); 12 of these patients had progression or relapse of Hodgkin lymphoma, one of whom died from primary progression of Hodgkin lymphoma. Multivariable sensitivity analyses, including the PET4 result and baseline factors, showed that the prognostic effect of PET4 positivity, defined as Deauville score of 3 or higher, was not significant in the multivariable model (appendix p 4), whereas PET positivity, defined as a Deauville score of 4 or higher, was a significant risk factor for poor progression-free survival, independent of baseline factors (HR 10·47 [95% CI 4·00–27·38]), p<0·0001; appendix p 4).

A descriptive post-hoc subgroup analysis of patients in the per-protocol analysis population with initial bulky disease or a large mediastinal tumour, showed non-inferiority of PET-guided treatment in this subgroup of patients, with a 5-year progression-free survival of 96% (95% CI 91·0–98·2) in the combined-modality treatment group (n=225), and 96·5% (93·1 to 98·2) in the PET4-guided treatment group (n=267; difference 0·5% [95% CI

–3·6 to 4·6]). Post-hoc sensitivity analyses in PET4-negative patients supported this finding; 5-year progression-free survival in the combined-modality treatment group (n=122) was 96·7% (87·3 to 99·2) and 97·0% (92·2 to 98·9) in the PET4-guided treatment group (n=157), with a difference of 0·4% [–5·0 to 5·8] between the two groups.

At a median follow-up of 48·0 months (IQR 35·4–62·7), 5-year overall survival was 98·8% (95% CI 97·2–99·5) in the per-protocol analysis population (n=905) and 98·6% (97·3–99·3) in the intention-to-treat analysis population (n=1096; appendix p 6). The cause of ten reported deaths in the intention-to-treat population were Hodgkin lymphoma (two patients in the PET4-guided treatment group), primary treatment toxicity (one patient in the PET4-guided treatment group), a second malignancy (two patients in the standard combined-modality treatment group), and a disease unrelated to Hodgkin lymphoma (two patients in the standard combined-modality treatment group and three patients in the PET4-guided treatment group; table 2). The standardised mortality ratio (post-hoc analysis) was 1·7 (95% CI 0·8–3·8) in the intention-to-treat population; 1·4 (0·4–3·6) after combined-modality treatment, and 2·1 (0·8–4·5) after PET4-guided treatment. Thus, survival of patients included in this trial did not differ significantly from the general population in Germany.

Descriptive post-hoc subgroup analyses of overall survival in patients assigned to receive combined-modality treatment (ie, those who were either PET4 positive or were assigned to the standard combined-modality treatment group and PET4 negative) showed no significant difference between PET4-positive and PET4-negative patients, neither with PET4 positivity defined as a Deauville score of 3 or higher (Deauville score of 1–2 *vs* Deauville score of ≥3, p=0·99) nor with PET4 positivity defined as a Deauville score of 4 or higher (Deauville score of 1–3 *vs* Deauville score of ≥4, p=0·49; appendix p 8). 5-year overall survival was 99·0% (95% CI 97·8–100·0) in patients with a Deauville score of less than 4, and 98·9% (96·6–100·0) in those with a Deauville score of 4 or higher.

Final CT-based restaging results after end of study therapy were documented for 1009 patients (502 [92%] in the standard combined-modality treatment group and 507 [92%] in the PET4-guided treatment group), and 348 (69%) of 502 patients in the standard combined-modality treatment group and 290 (57%) of 507 patients in the PET4-guided treatment group had complete remission.

Protocol adherence for 2+2 was good, with a mean relative dose delivery (ie, the percentage of scheduled dose that patients received) of 97·7% (SD 9·7) and a mean delay to complete chemotherapy of 3·0 days (4·8 days). Two patients in the PET-guided treatment group discontinued eBEACOPP and one patient in the standard combined-modality treatment group discontinued ABVD because of drug-related toxicity. Dose reductions because of acute toxic effects were reported in 182 (17%) of 1062 patients during eBEACOPP treatment (79 [15%] of 532 patients in the standard combined-modality treatment group and 103 [19%] of 530 patients in the PET4-guided treatment group) and in 217 (22%) of 1004 patients during ABVD treatment (121 [24%] of 496 patients in the standard combined-modality treatment group and 96 [19%] of 508 patients in the PET4-guided treatment group). Acute grade 3 or 4 adverse events during chemotherapy were reported in 455 (86%) of 528 patients in the standard combined-modality treatment group and 454 (86%) of 529 patients in the PET4-guided treatment group (table 3). The most frequent (ie, those occurring in >25% of patients) acute haematological adverse events were leucopenia (436 [83%] patients in the standard combined-modality

	Standard combined-modality treatment group (n=546)	PET4-guided treatment group (n=550)
Dose reductions during eBEACOPP cycles		
Reduction for any reason	92/532 (17%)	119/530 (23%)
Reduction because of a toxicity event	79/532 (15%)	103/530 (19%)
Dose reductions during ABVD cycles		
Reduction for any reason	100/496 (20%)	91/508 (18%)
Reduction because of a toxicity event	89/496 (18%)	79/508 (14%)
Observation time, months in the per-protocol population		
For disease status	45·8 (32·4–61·0)	46·4 (32·9–61·2)
For survival status	47·4 (35·6–63·0)	48·5 (35·0–62·5)
Tumour events in the per-protocol population		
Any tumour event	5/428 (1%)	15/477 (3%)
Any progression-free survival event	8/428 (2%)	17/477 (4%)
Tumour events		
Progression	2 (<1%)	6 (1%)
Relapse		
≤1 year after end of therapy	3 (<1%)	5 (<1%)
>1 year after end of therapy	6 (1%)	8 (1%)
Any tumour event	11 (2%)	19 (3%)
Any progression-free survival event	15 (3%)	23 (4%)
Cause of death		
Hodgkin lymphoma	0	2 (<1%)
Toxicity of study therapy	0	1 (<1%)
Other disease*	2 (<1%)	3 (<1%)
Second primary malignant neoplasm	2 (<1%)	0
Any death	4 (<1%)	6 (1%)
Second primary malignant neoplasms		
Acute myeloid leukaemia or myelodysplastic syndrome	0	1 (<1%)
Non-Hodgkin lymphoma	1 (<1%)	1 (<1%)
Solid tumour†	6 (1%)	6 (1%)
Any event	7 (1%)	8 (1%)

Data are n/N (%), n (%), or median (IQR). PET4=PET scan at the end of four cycles of chemotherapy. eBEACOPP=escalated doses of etoposide, cyclophosphamide, and doxorubicin, and regular doses of bleomycin, vincristine, procarbazine, and prednisone. ABVD=doxorubicin, bleomycin, vinblastine, dacarbazine. *Included cardiovascular disease (n=2), subarachnoid haemorrhage (n=1), HIV-related cachexia (n=1), and an unknown disease unrelated to Hodgkin lymphoma (n=1). †Included malignant melanoma (n=2), mammary carcinoma (n=2), colorectal cancer (n=1), prostate cancer (n=1), and other rare solid cancers (n=5).

Table 2: **Outcomes of the intention-to-treat population**

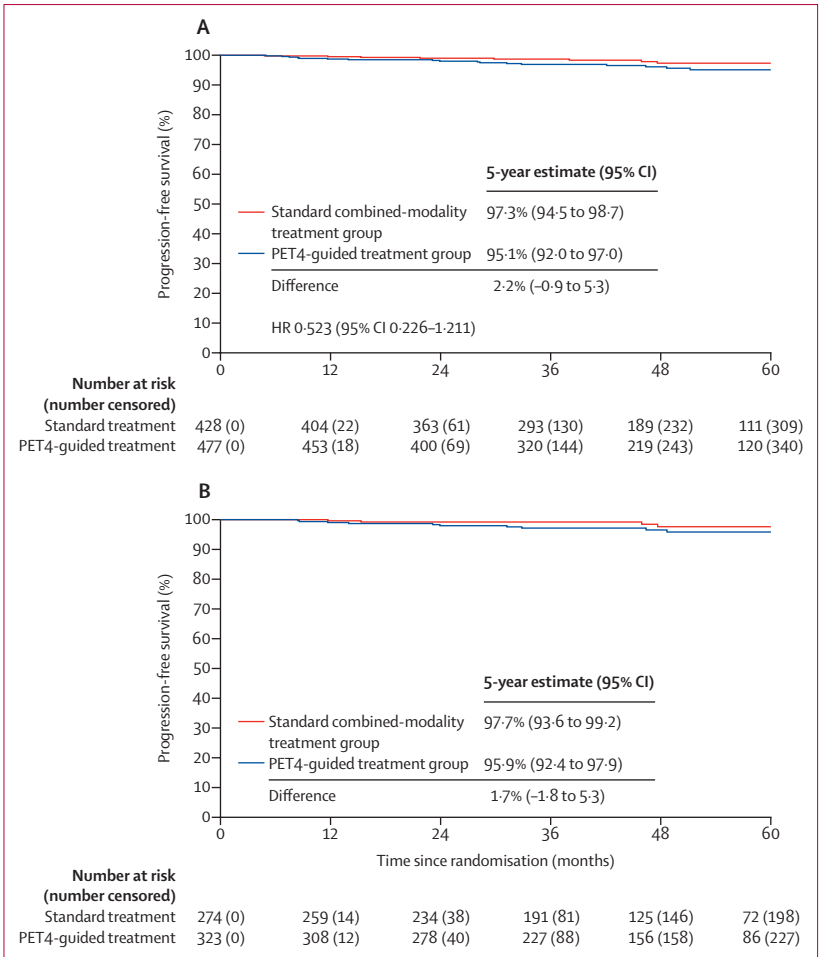

Figure 2: **Kaplan-Meier estimates of 5-year progression-free survival in the per-protocol analysis population (A) and in a subset of PET4-negative patients in the per-protocol analysis population (B)**
PET4=PET scan at the end of four cycles of chemotherapy.

treatment group *vs* 443 [84%] patients in the PET4-guided treatment group), and thrombocytopenia (139 [26%] *vs* 176 [33%]), and the most frequent acute non-haematological adverse events were infection (32 [6%] *vs* 40 [8%]) and nausea or vomiting (38 [7%] *vs* 29 [6%]).

The mean dose of consolidation radiotherapy administered was 30·0 Gy (SD 1·7). Acute grade 3 or 4 radiotherapy-associated adverse events were reported in 37 (9%) of 429 patients in the standard combined-modality treatment group with available documentation, and four (3%) of 155 patients in the PET-guided treatment group with available documentation (table 4); the most frequently observed events were dysphagia (26 [6%] in the standard combined-modality treatment group *vs* three [2%] in the PET4-guided treatment group; one patient in the standard combined-modality treatment group had grade 4 dysphagia) and mucositis (nine [2%] *vs* none; one patient had grade 4 mucositis). 161 (29%) of 546 patients had a total of 229 serious adverse events in the standard combined-modality treatment group and 164 (30%) of 550 patients had a total of 235 serious adverse events in the PET4-guided treatment group. One suspected unexpected serious adverse reaction (infection) that led to death was reported in the PET4-guided treatment group, which was the only treatment-related death. Second primary malignant neoplasms were observed in seven (1%) of 546 patients in the standard combined-modality treatment group (one had non-Hodgkin lymphoma and six had solid tumours) and eight (1%) of 550 patients in the PET4-guided treatment group (one had leukaemia, one had non-Hodgkin lymphoma, and six had solid tumours; table 2).

Discussion

Two major findings emerge from the GHSG HD17 trial involving patients with newly diagnosed early-stage unfavourable Hodgkin lymphoma. First, radiotherapy can be omitted from standard combined-modality treatment without a clinically relevant loss of tumour control in patients with a negative PET after systemic treatment with the 2+2 regimen. Second, a positive PET after 2+2 is a risk factor for poor progression-free survival in patients receiving standard combined-modality treatment, particularly when a Deauville score of 4 is used as the threshold for PET4 positivity.

Extensive radiotherapy used to be the mainstay of treatment in patients with early-stage Hodgkin lymphoma. With the advent of multiagent chemotherapy, large radiation fields (eg, total nodal irradiation) could be reduced to involved fields only.[1,2] However, a reduction in radiation dose was not possible with the ABVD backbone in patients with early-stage unfavourable Hodgkin lymphoma.[3] We hypothesised that the 2+2 chemotherapy regimen, which is more intensive that the ABVD backbone alone, might be effective enough to allow omission of consolidation radiotherapy in patients with a good metabolic response, as determined by PET. The results of the HD17 trial support our hypothesis and non-inferiority of PET-guided omission of consolidation radiotherapy was established.

Our results also suggest that acute toxicity of radiotherapy could be reduced by the involved-node radiotherapy field delineation modality. Since the effect of reducing field delineation on progression-free survival and treatment toxicity was not the focus of this study, radiotherapy-associated data will be analysed separately and published elsewhere. To our knowledge, HD17 is the first prospective, randomised trial to show non-inferiority of a PET-guided chemotherapy approach alone in patients with early-stage Hodgkin lymphoma compared with standard combined-modality treatment. The UK RAPID trial included 571 patients with early-stage favourable and unfavourable Hodgkin lymphoma and tested omission of consolidation radiotherapy in PET-negative patients after three cycles of ABVD.[20] The trial did not reach its primary endpoint and did not show non-inferiority. The larger prospective, randomised H10 trial by The European Organisation for

Research and Treatment of Cancer, Groupe d'Etude Des Lymphomes De l'Adulte, and Fondazione Italiana Linfomi used four cycles of ABVD followed by 30 Gy involved-node radiotherapy in the standard group, whereas PET-negative patients in the experimental group received treatment intensification to six cycles of ABVD alone.[21] The cohort of patients with early-stage unfavourable disease in the H10 trial is similar to the cohort of patients enrolled in the HD17 study. Although six cycles of ABVD chemotherapy, with high cumulative doses of cardiotoxic anthracyclines and lung-damaging bleomycin, are usually administered in patients with advanced-stage Hodgkin lymphoma only, non-inferiority of PET-guided omission of consolidation radiotherapy could not be shown.[21] Different approaches have been used to establish a chemotherapy-alone strategy in patients with early-stage Hodgkin lymphoma, but they have failed to show non-inferiority of this strategy compared with a combined-modality strategy. These previous trials all used ABVD as the chemotherapy backbone; therefore, this regimen does not seem to be effective enough to allow omission of radiotherapy. Consequently, the non-inferiority observed in the HD17 study underlines the importance of the 2+2 regimen, which is shorter but more intensive than ABVD alone, in the success of the trial. This conclusion is supported by an observation from the H10 trial, in which patients with an insufficient metabolic response to two cycles of ABVD had treatment intensification with two cycles of eBEACOPP.[21] This intensification led to a significant and clinically relevant increase in progression-free survival over standard therapy with four cycles of ABVD in this high-risk cohort. Previous studies of PET-guided treatment in patients with advanced-stage Hodgkin lymphoma have shown that upfront dose intensification with two cycles of eBEACOPP allows substantial de-escalation of treatment in patients who have a good response.[15,22] Taking the results of these studies together, effective upfront systemic treatment seems to be necessary to allow relevant de-escalation of therapy without loss of tumour control in patients who respond well to systemic treatment.

However, the important question of whether adverse events caused by the intensified chemotherapy might outweigh any potential benefits of omitting consolidation radiotherapy remains. Importantly, of 1100 patients enrolled in our study, only ten deaths were reported during a median follow-up of approximately 4 years. These events included two Hodgkin lymphoma-related events and one treatment-related death. We also did not identify a significant difference between the mortality of patients included in the HD17 trial and the general population in Germany. We therefore conclude that the HD17 treatment strategy is not only highly efficacious, but also safe.

Despite these findings, we cannot accurately estimate the benefit of omitting consolidation radiotherapy. Radiotherapy is usually tolerated better than chemotherapy in the short term, but long-term sequelae can occur more than 20 years after treatment.[7–13] In general, radiation fields in patients with early-stage unfavourable Hodgkin lymphoma cover three or more lymph node areas or larger mediastinal masses. Therefore, exposure to ionising radiation can have clinically relevant long-term effects, even though we used modern limited radiation fields (involved-field radiotherapy and involved-node radiotherapy) in the HD17 trial.[23,24] Overall, the available

	Standard combined-modality treatment group (n=528)			PET4-guided treatment group (n=529)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Anaemia	41 (8%)	5 (<1%)	0	56 (11%)	8 (2%)	0
Thrombocytopenia	83 (16%)	56 (11%)	0	106 (20%)	70 (13%)	0
Leucopenia	79 (15%)	357 (68%)	0	75 (14%)	368 (70%)	0
Nausea or vomiting	34 (6%)	4 (<1%)	0	26 (5%)	3 (<1%)	0
Mucositis	9 (2%)	2 (<1%)	0	20 (4%)	2 (<1%)	0
Other gastrointestinal tract disorder	14 (3%)	1 (<1%)	0	17 (3%)	6 (1%)	0
Urogenital tract	5 (<1%)	0	0	1 (<1%)	0	0
Respiratory tract	12 (2%)	0	0	11 (2%)	3 (<1%)	0
Drug-related fever	9 (2%)	0	0	7 (1%)	1 (<1%)	0
Allergy	6 (1%)	0	0	6 (1%)	0	0
Heart	2 (<1%)	0	0	0	1 (<1%)	0
Infection	29 (6%)	3 (<1%)	0	33 (6%)	6 (1%)	1 (<1%)
Skin	6 (1%)	0	0	7 (1%)	0	0
Nervous system	15 (3%)	0	0	16 (3%)	1 (<1%)	0

Data are n (%). PET4=PET scan at the end of four cycles of chemotherapy. 2+2=two cycles of escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, and two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine.

Table 3: **Acute grade 3–5 toxic effects during 2+2 chemotherapy**

	Standard combined modality treatment group (n=429)	PET4-guided treatment group (n=155)
	Grade 3–4	Grade 3–4
Any toxicity	37 (9%)	4 (3%)
Anaemia	1 (<1%)	0
Leukopenia	7 (2%)	1 (<1%)
Thrombocytopenia	2 (<1%)	0
Nausea or vomiting	5 (1%)	0
Dysphagia	26 (6%)	3 (2%)
Mucositis	9 (2%)	0
Heart	0	0
Respiratory tract	0	0
Larynx	0	0
Nervous system	0	0
Local skin reaction in radiotherapy field	2 (<1%)	0
Haemorrhage	0	0
Alopecia	1 (<1%)	0
Infection	0	0

Data are n (%). No grade 5 toxic effects occurred during consolidation radiotherapy. PET4=PET scan at the end of four cycles of induction chemotherapy.

Table 4: **Acute grade 3–4 adverse events during consolidation radiotherapy**

evidence suggests that omission of radiotherapy offers a substantial and clinically relevant benefit for patients with Hodgkin lymphoma in the long term.

Finally, the use of eBEACOPP in patients with early-stage Hodgkin lymphoma might raise concerns about toxicity when compared with the less intensive ABVD regimen. In our previous HD14 study, more adverse events were reported in patients who received eBEACOPP in the 2+2 regimen than in those who received four cycles of ABVD; however, no excess in treatment-related mortality was observed.[4] Maintenance of gonadal function and fertility can be of the utmost importance for young patients. A retrospective analysis of the HD14 study showed no difference in the likelihood of giving birth after treatment between these two regimens, and no difference in the likelihood of giving birth for either regimen when compared with the general female population in Germany.[25] In men, recovery of spermatogenesis took longer after 2+2 than after four cycles of ABVD. However, no difference in spermatogenesis between men who had received 2+2 and four cycles of ABVD was observed after recovery.[26] Long-term follow-up also did not identify differences in the risk for second primary malignancies between these two regimens.[27] The available evidence suggests that the benefit of a brief and intensive upfront therapy in terms of efficacy is not counterbalanced by unacceptable toxicity. However, the results of our HD17 study are presumably only applicable if the local infrastructure provides enough resources to safely administer eBEACOPP.

Introducing new drugs into the treatment regimen could result in an even better outcome than solely intensification of chemotherapy from ABVD to eBEACOPP. To increase the efficacy of the well-tolerated ABVD regimen, bleomycin has been replaced with the CD30-specific antibody–drug conjugate brentuximab vedotin.[28] However, the toxicity profile of brentuximab vedotin and doxorubicin, vinblastine, and dacarbazine (BV-AVD) showed a substantial increase in neuropathy and neutropenia compared with ABVD, presumably caused by the combination of two tubulin inhibitors in this regimen. The authors concluded that the results did not encourage further studies of this regimen in patients with early-stage Hodgkin lymphoma.[28] Another option to increase the efficacy of chemotherapy without increasing toxicity could be the use of checkpoint inhibitors, which have shown promising single-agent activity in classical Hodgkin lymphoma.[29–31] The GHSG phase 2 NIVAHL trial indicated high activity of both sequential and concomitant nivolumab–AVD treatment.[32] However, the safety profile of either regimen differed from chemotherapy alone because early-onset and higher grade immune-related adverse events were observed. Follow-up in this phase 2 study is yet too short to draw conclusions about long-term safety or progression-free survival and overall survival. Therefore, improving the ABVD backbone by introducing checkpoint inhibitors is of interest but still needs to be evaluated further in future studies.

The results of our trial showed that metabolic response assessment with PET could be prognostic for progression-free survival. However, the proportion of PET4-positive patients was larger than expected (328 [34%] of 979 patients), which was caused by the conservative cutoff Deauville score used to define high risk (ie, a score of ≥3). The cutoff value was selected to minimise the risk of under-treatment in the PET4-guided treatment group. Retrospective multivariable analysis of patients in the standard combined-modality treatment group revealed that only a Deauville score of 4 was a significant risk factor for poor progression-free survival, which is consistent with the results of studies done in patients with Hodgkin lymphoma published in 2018[15] and 2019.[33] The group of PET4-positive patients, as defined by a Deauville score of 4 or higher, represented only 9% (90 of 979) of the entire patient population. Conversely, 91% (889 of 979) of patients were PET4-negative after 2+2 treatment. Accordingly, many patients with a presumably low risk of treatment failure (ie, with a Deauville score of 3) received combined-modality treatment in our trial.

There are several weaknesses of the HD17 trial that need to be addressed. First, we could not evaluate potential late effects of radiotherapy that might provide quantifiable information on the advantages of omitting radiotherapy, because these side-effects can occur 20 years or more after treatment, which is far beyond our median observation time and also beyond the overall study duration. Radiotherapy techniques have evolved over time, and the incidence of future late effects induced by radiotherapy given to patients today cannot be reliably estimated. Accordingly, the benefit of omitting radiotherapy in patients with early-stage unfavourable Hodgkin lymphoma might be smaller than estimated according to the published evidence. Second, we used a simplified method to estimate the CIs of the differences between treatment groups. However, the non-inferiority margin was clearly excluded, suggesting that our conclusions would be the same with more refined methods than those used in our study. Finally, our study design allowed for the evaluation of the prognostic effect of PET4 positivity only in patients who received combined-modality treatment. Therefore, we could not estimate the therapeutic effect of consolidation radiotherapy on progression-free survival in PET4-positive patients because there was no control group of patients who did not receive radiotherapy in our patient cohort. However, a significant decrease in progression-free survival was observed in patients with a Deauville score of 4 compared with those who had a Deauville score of 3 or lower, even though patients had received consolidation radiotherapy. Consequently, a trial without consolidation radiotherapy for PET4-positive patients is not well justified. On the other hand, our study also did

not include treatment intensification in PET4-positive patients; therefore, it remains unknown whether further treatment intensification could have improved progression-free survival in these patients. However, of all patients with a Deauville score of 4, according to PET4 (n=90), only 12 (13%) had a progression or relapse of Hodgkin lymphoma and required salvage therapy. 11 (92%) of these 12 patients survived without a second progression or relapse during the observation period and might have been successfully treated with second-line therapy. This observation puts the positive prognostic effect of PET4 positivity into perspective. Based on these data, we recommend using a Deauville score of 4 as a cutoff value for PET4 positivity; however, we do not recommend treatment intensification in PET4-positive patients, even though this strategy was not formally tested in our trial.

The strengths of our study include the independent blinded central review of PET examinations, the robust study design, and the large number of patients and contributing centres from several countries included in the study, all of which support the high internal and external validity of the observed effects and conclusions. Since most participating centres were private practices or primary care hospitals, the results reflect a real-world setting in high-income countries.

In conclusion, individualised PET4-guided treatment after 2+2 chemotherapy allows omission of radiotherapy in most patients with newly diagnosed early-stage unfavourable Hodgkin lymphoma. PET-guided therapy therefore substantially reduces the proportion of patients at risk of late effects from irradiation. We recommend this treatment approach for patients with newly diagnosed early-stage unfavourable Hodgkin lymphoma.

Contributors

CK, GK, MD, and CB did the central review of the PET4 examination. AP led the statistical analyses of the data. MF directed activities at the GHSG central office, including data management. AE, PB, and BK led the design of the study protocol. AR led the review of the pathology results. AE is the principal investigator of the study. RG, JM, MST, HO, JD, JM, JT, MS, AK, MA, TVH, SM, UK, SB, TP, MV, AH, MW, JMZ, and AM represent the active study sites involved in data collection. PB and AP verified the data in this study. All authors contributed to data interpretation, reviewed the draft manuscript, and approved the final version of this report.

Declaration of interests

BvT reports personal fees from Amgen, Pfizer, Gilead, Roche, grants from Merck Sharpe & Dohme, Takeda, and Novartis; personal fees from Merck Sharpe & Dohme and Takeda; and non-financial support from Merck Sharpe & Dohme, Takeda, and Novartis outside the submitted work. JM reports non-financial support from Merck Sharpe & Dohme, Bristol Myers Squibb, Takeda, Hexal, and Celgene outside the submitted work. PJB reports grants from Bristol Myers Squibb, Merck Sharpe & Dohme, and Takeda; and personal fees and non-financial support from Bristol-Myers Squibb and Takeda outside the submitted work. MH reports personal fees from AbbVie, Celgene, Gilead Science, Janssen, Mundipharma, Pharmacyclics, and Roche; and speaker's fees from AbbVie, Celgene, Gilead Science, Janssen, Mundipharma, Pharmacyclics, and Roche outside the submitted work. RG reports personal fees from Celgene, Roche, Merck, Takeda, Astra Zeneca, Novartis, Amgen, Bristol Myers Squibb, Merck Sharpe & Dohme, Sandoz, Abbvie, Gilead, Daiichi Sankyo, and Janssen outside the submitted work. All other authors declare no competing interests.

Data sharing

Individual patient data from this trial will not be published in the public domain; however, the trial protocol is provided in the appendix and will be available online for an indefinite period.

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