Response-adapted omission of radiotherapy in children and adolescents with early-stage classical Hodgkin lymphoma and an adequate response to vincristine, etoposide, prednisone, and doxorubicin (EuroNet-PHL-C1): a titration study

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Summary

Background Children and adolescents with early-stage classical Hodgkin lymphoma have a 5-year event-free survival of 90% or more with vincristine, etoposide, prednisone, and doxorubicin (OEPA) plus radiotherapy, but late complications of treatment affect survival and quality of life. We investigated whether radiotherapy can be omitted in patients with adequate morphological and metabolic responses to OEPA.

Methods The EuroNet-PHL-C1 trial was designed as a titration study and recruited patients at 186 hospital sites across 16 European countries. Children and adolescents with newly diagnosed stage IA, IB, and IIA classical Hodgkin lymphoma younger than 18 years of age were assigned to treatment group 1 to be treated with two cycles of OEPA (vincristine 1·5 mg/m² intravenously, capped at 2 mg, on days 1, 8, and 15; etoposide 125 mg/m² intravenously, on days 1–5; prednisone 60 mg/m² orally on days 1–15; and doxorubicin 40 mg/m² intravenously on days 1 and 15). If no adequate response (a partial morphological remission or greater and PET negativity) had been achieved after two cycles of OEPA, involved-field radiotherapy was administered at a total dose of 19·8 Gy (usually in 11 fractions of 1·8 Gy per day). The primary endpoint was event-free survival. The primary objective was maintaining a 5-year event-free survival rate of 90% in patients with an adequate response to OEPA without radiotherapy. We performed intention-to-treat and per-protocol analyses. The trial was registered at ClinicalTrials.gov (NCT00433459) and with EUDRACT, (2006–000995-33) and is completed.

Findings Between Jan 31, 2007, and Jan 30, 2013, 2131 patients were registered and 2102 patients were enrolled onto EuroNet-PHL-C1. Of these 2102 patients, 738 with early-stage disease were allocated to treatment group 1. Median follow-up was 63·3 months (IQR 60·1–69·8). We report on 714 patients assigned to and treated on treatment group 1; the intention-to-treat population comprised 713 patients with 323 (45%) male and 390 (55%) female patients. In 440 of 713 patients in the intention-to-treat group who had an adequate response and did not receive radiotherapy, 5-year event-free survival was 86·5% (95% CI 83·3–89·8), which was less than the 90% target rate. In 273 patients with an inadequate response who received radiotherapy, 5-year event-free survival was 88·6% (95% CI 84·8–92·5), for which the 95% CI included the 90% target rate. The most common grade 3–4 adverse events were neutropenia (in 597 [88%] of 680 patients) and leukopenia (437 [61%] of 712). There were no treatment-related deaths.

Interpretation On the basis of all the evidence, radiotherapy could be omitted in patients with early-stage classical Hodgkin lymphoma and an adequate response to OEPA, but patients with risk factors might need more intensive treatment.

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Introduction

Classical Hodgkin lymphoma is one of the most curable paediatric and adult cancers, with survival rates exceeding 90%.[1–6] However, individuals who survive are at a high risk of secondary cancers and cardiovascular disease after chemoradiotherapy.[7–9]

The current challenge is to tailor therapy to avoid overtreatment or undertreatment. Patient subgroups,

Research in context

Evidence before this study

Children and adolescents who survive classical Hodgkin lymphoma bear a high risk for secondary cancers and cardiovascular disease later in life after successful chemoradiotherapy combination treatment. The challenge is to sustain high cure rates while reducing long-term side-effects by reducing radiotherapy and chemotherapy exposure. We searched MEDLINE between Jan 1, 2005, and March 31, 2022, in the English language using the terms "Hodgkin lymphoma", "low risk disease", "radiotherapy-induced late effects", "interim PET", and "chemotherapy". PET after one to three cycles of chemotherapy is used for response-adapted therapy in patients with early-stage classical Hodgkin lymphoma. Chemotherapy treatment usually contains anthracyclines, such as doxorubicin, either in combination with bleomycine, vincristine, and dacarbazine; vincristine, prednisone, and cyclophosphamide; or vincristine, etoposide, and prednisone (OEPA).

Added value of this study

In our large, multinational trial (EuroNet-PHL-C1) in patients younger than 18 years with early-stage classical Hodgkin lymphoma, we have shown that radiotherapy could safely be avoided in a large number of patients with early-stage disease who have an adequate PET response to an intensified induction with two cycles of OEPA chemotherapy. The low proportion of patients with an inadequate response who received involved-field radiotherapy also had excellent event-free-survival. In a subgroup of patients with early-stage bulky disease or an elevated erythrocyte sedimentation rate, considered to be risk factors within this regimen, stratification to an intermediate treatment group might be more appropriate for achieving higher event-free survival and progression-free survival.

Implications of all the available evidence

The omission of radiotherapy in patients with an adequate response is likely to reduce the late-effects of treatment, such as second malignancies, and has become the current treatment approach for young patients with classical Hodgkin lymphoma in the EuroNet-PHL consortium. The reduction of radiotherapy in a large proportion of patients according to their adequate metabolic response after two intensive induction chemotherapy cycles removes a substantial part of their treatment burden. For patients with early-stage disease with risk factors, or else with early unfavourable disease stage, treatment de-escalation might not be adequate with regards to progression-free survival outcomes. Similar to other consortia, risk-adapted treatment in the intermediate-stage treatment group might be considered. The hope is that, with this approach, radiotherapy-induced secondary cancers in children who survive early-stage Hodgkin lymphoma can be avoided. The results of this trial might change the current treatment frameworks for early-stage classical Hodgkin lymphoma in children and adolescents throughout the EuroNet-PHL consortium and in other international paediatric Hodgkin lymphoma study groups.

which differ in their responses to treatment, should have the same high cure rate with the least amount of treatment possible. Building on a series of treatment optimisation trials[1,2,10] done since 1978, the European Network for Paediatric Hodgkin Lymphoma (EuroNet-PHL) has adopted a common comprehensive treatment strategy on the basis of a combined-modality scheme for children and adolescents with early-stage Hodgkin lymphoma.

All patients in these former series received two intensive induction cycles with vincristine, etoposide, prednisone, and doxorubicin (OEPA), after which patients with early-stage Hodgkin lymphoma received involved-field radiotherapy to all initially involved tumour sites; the 5-year event-free survival was 90%.[10] Treatment reduction, in the form of radiotherapy omission, might be justified, even if it leads to a minor decrease in efficacy, as long as the outcome is consistent with the target outcome rate and treatment toxicity is reduced appreciably. Therefore, the primary objective of this titration study (EuroNet-PHL-C1) for patients with early-stage Hodgkin lymphoma was to analyse whether in patients with an adequate PET and morphological response after two cycles of OEPA, radiotherapy could be safely omitted and the 90% 5-year event-free survival still be maintained. An important secondary objective for the patients was to investigate whether those with an inadequate response to OEPA who were scheduled to receive standard radiotherapy after consolidation chemotherapy would still meet the 90% 5-year event-free survival target.

Methods

Study design and participants

This trial was designed as a titration study[11] and recruited at 186 hospital sites across 16 European countries (Czech Republic, England, France, Germany, Austria, Ireland, Slovakia, Sweden, Norway, Poland, Belgium, Switzerland, Denmark, Spain, Slovenia, and The Netherlands (appendix pp 2, 5–9). This study recruited patients to three treatment groups on the basis of disease stage and the presence or absence of B symptoms, defined as weight loss, fever, or night sweats, or a combination. Patients with Ann Arbor disease stages IA or IB and IIA were assigned to treatment group 1 and were included in this analysis.

Previously untreated patients younger than 18 years with classical Hodgkin lymphoma were included and stratified according to risk using Ann Arbor disease stages IA or IB and IIA, as assessed by local investigators (France) or by central review (all other countries). Reference pathology was mandatory and required a centralised review of all local histopathology specimens

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See Online for appendix

in trial patients by a second expert. Exclusion criteria included the following: any pre-treatment of Hodgkin lymphoma, except for steroid pre-phase therapy, for example for a bulky mediastinal tumour; known hypersensitivity or contraindication to the study drugs; the diagnosis of nodular lymphocyte-predominant Hodgkin lymphoma; previous chemotherapy or radiotherapy; other or simultaneous malignancies; pregnancy, lactation, or both; female patients who were sexually active and refused the use of effective contraception (oral contraception, intrauterine devices, a barrier method of contraception in conjunction with spermicidal gel, or surgical sterilisation); current or recent (within 30 days of the start of trial treatment) treatment with another investigational drug or participation in another investigational trial; severe concomitant diseases, such as immune deficiency syndromes; and known HIV positivity. All patients or their guardians provided written informed consent. Local and central ethical boards in each country approved the study, and the study was performed in accordance with good clinical practice and the Declaration of Helsinki.

Procedures

The initial disease staging comprised a clinical assessment, cross-sectional diagnostic imaging, and [^{18}F]fluorodeoxyglucose ([^{18}F]FDG)-PET scanning. Diagnostic imaging included intravenous contrast-enhanced, cross-sectional imaging from the skull base to the symphysis. Investigation of the neck, abdomen, and pelvis was performed either by CT or MRI, and a chest CT was mandatory. Patients were assigned to treatment groups according to the reference staging, defined by the real-time central review board or by local staging. All patients received two cycles of OEPA (1·5 mg/m^2 vincristine intravenously, capped at 2 mg, on days 1, 8, and 15 of a 28-day cycle; 125 mg/m^2 etoposide intravenously, on days 1–5; 60 mg/m^2 prednisone orally, on days 1–15; and 40 mg/m^2 doxorubicin intravenously, on days 1 and 15). The subsequent chemotherapy cycle started on day 29 of each cycle when the following criteria were fulfilled: a satisfactory general condition, a white blood cell count of more than 2000 cells per mm^3, an absolute neutrophil count of more than 500 cells per mm^3, platelets more than 80 000 per mm^3, and no contraindication to any of the prescribed drugs.

If patients had an expected treatment delay of more than 1 week, for example due to febrile neutropenia, the protocol recommended contacting the regional study chairperson, since the treatment delay might affect efficacy. Before the start of each chemotherapy cycle, differential blood count and alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, bilirubin, and creatinine were assessed. Additionally, blood counts were measured at least twice during each cycle to capture the highest haematotoxic effects of chemotherapy. The patient's general condition, assessed with the Lansky or Karnofsky performance scores, was documented before therapy and regularly during therapy. Chemotherapy-related toxicity was categorised according to Common Terminology Criteria for Adverse Events (CTCAE; version 2.0).[12] Adverse events were documented and graded concomitantly to each chemotherapy cycle using a prespecified list of expected adverse events and by describing unexpected adverse events. Long-term sequelae were documented on follow-up case report forms.

The premature termination of trial therapy in an individual patient was considered for the following reasons: adverse events or serious adverse events, no response to therapy according to protocol definition, excessive toxicity, investigator request, a severe protocol violation, non-compliance of the patient, and administrative problems. In addition, the trial therapy could be terminated by request of the patient, in the case of withdrawal of consent, or in the case of loss to follow-up. Additional criteria for a patient to be removed from the study are described in the appendix (p 3).

The decision to administer radiotherapy was established after the early response assessment results were obtained. Early response assessment was performed after the completion of chemotherapy on day 29–31 of the second cycle of OEPA. All early response assessment PET, CT, and MRI scans of all patients in all participating countries were immediately sent to the central review board (in Halle, Germany) for a real-time review, except for France, which had their own regional assessment for decisions on the further stratification of their patients. The early response assessment was based on morphological tumour volume response and PET response.[10,11] Partial remission corresponded to an at least 50% tumour volume reduction in any involved nodal site. For the evaluation of the PET response, the International Harmonization Project Criteria were used, which defined the standard at the time the study was done.[13] The PET was interpreted as negative if the highest remaining FDG uptake did not exceed either the uptake in the mediastinal blood pool (for minimal residual volumes that were ≥2 cm at the largest diameter) or the uptake of the surrounding background (for minimal residual volumes that were <2 cm at the largest diameter).

An adequate response at the early response assessment was defined as a partial morphological remission or greater and PET negativity. Radiotherapy was omitted in patients who responded adequately to induction chemotherapy with two cycles of OEPA. Patients with an inadequate response received radiotherapy at a total dose of 19·8 Gy (usually in 11 fractions of 1·8 Gy per day) to all initially involved tumour sites. Residual masses of more than 100 mL at the early response assessment and sites that responded slowly to treatment (<75% volume reduction at the early response assessment in lesions with a minimal residual volume of >5 mL) received an additional boost of 10·8 Gy (divided into six fractions of 1·8 Gy per day). Further details on radiotherapy

techniques are outlined in detail in the radiotherapy manual (appendix pp 25–63).

Outcomes

The primary endpoint was event-free survival, defined as the time from the start of treatment until whichever of the following events occurred first: death from any cause, progression or relapse of classical Hodgkin lymphoma, or occurrence of a secondary malignancy. Secondary endpoints in all patients were overall survival, defined as the time from the start of treatment to death from any cause; and progression-free survival, defined as the time from the start of treatment to the first of the following events: death from any cause, progression of classical Hodgkin lymphoma, or relapse of classical Hodgkin lymphoma. The additional secondary endpoint of gonadotoxicity or fertility assessment in patients in treatment group 2 and treatment group 3 (patients with intermediate and advanced-stage disease) has been reported in our previous publication of the EuroNet-PHL-C1 trial.[11]

Statistical analysis

The trial aimed to include all available patients within an enrolment period of 6 years to maximise power in the relevant subgroups (treatment group 1 with an adequate response and inadequate response), with at least 684 patients expected for treatment group 1. With the expected number of patients, we made sure that half the width of the 95% CIs in the two groups would be less than 5%. We estimated a 5-year event-free survival in the two subgroups with a two-sided 95% CI, which corresponded to a power of 80% to detect a difference of 6%. Subgroup outcome was considered to be consistent with the target rate if the CI included or was more than 90%. The main results of the trial were compiled in a forest plot. The primary objective was to confirm that the 5-year event-free survival was consistent with a 90% target rate in patients with an adequate response, in whom standard radiotherapy was omitted. The secondary objective was to confirm that the 5-year event-free survival was still consistent with the 90% target rate in patients with inadequate response. Only events that occurred within a follow-up period of 72 months were considered.

We performed an intention-to-treat analysis, which was prespecified in the protocol, and a post-hoc per-protocol analysis. The per-protocol analysis set excluded patients who had disease progression or died or withdrew before the response assessment with [^{18}F]FDG-PET, as well as patients who received no radiotherapy despite an inadequate response at the early response assessment, and patients who received radiotherapy but had an adequate response at the early response assessment. In addition, patients were excluded if they had been treated according to treatment group 1 but had been confirmed by the central review board as having intermediate or advanced stage lymphoma. Toxicity profiles of the OEPA regimen are described for all patients in the intention-to-treat analysis. Analyses were performed using R version 4.03.

Estimates of 5-year rates with two-sided 95% CIs were obtained with the Kaplan-Meier product-limit estimator for all time-to-event endpoints (event-free survival, overall survival, and progression-free survival). The results of all subgroups defined by early response assessment results (adequate response or inadequate response) or the presence or absence of prognostic factors were analysed, with the primary focus on patients with an adequate response in whom standard radiotherapy was omitted.

In most adult and paediatric trials on early-stage classical Hodgkin lymphoma, early favourable and early unfavourable stages of Hodgkin lymphoma are distinguished, since the unfavourable subgroup is usually assigned to receive more intensive treatment.[4,14] We therefore performed an unplanned subgroup analysis to establish whether patients with early unfavourable stage classical Hodgkin lymphoma would still meet the 90% 5-year event-free survival target when treated similarly to patients with early favourable stage lymphoma. We distinguished patients with the risk factors of bulky disease or an increased erythrocyte sedimentation rate, or both, from those without risk factors or those with undetermined risk factor status (mainly due to undocumented erythrocyte sedimentation rate values or missing bulky disease measurement). We defined bulky disease as a contiguous tumour volume of 200 mL or more. The purpose of this definition was to identify patients in treatment group 1 with large nodal masses. A volume of 200 mL approximately corresponds to the median maximum contiguous volume in patients with advanced stages (data not shown). We did not use the two-dimensional definition of mediastinal bulk of more than 33% of the thoracic aperture on x-ray, because more advanced methods for three-dimensional volumetry were part of the study procedures. In addition, Hodgkin lymphoma study groups of adults use a threshold of erythrocyte sedimentation rate of more than 50 mm in the first hour in patients without B symptoms and an erythrocyte sedimentation rate of more than 30 mm in the first hour in those with B symptoms as a risk factor. We decided an erythrocyte sedimentation rate of 30 mm or more in the first hour, independent of the presence of B symptoms, was a risk factor in patients in treatment group 1, since erythrocyte sedimentation rate is potentially lower in younger patients.[15,16] The outcome within these subgroups was considered to be consistent with the target rate, if the 95% CI included or was higher than 90%. The main results of the titration trial, including the subgroup analyses with and without risk factors or with undetermined risk factor status, were compiled in a forest plot for event-free survival. Thyroid disorders and cardiovascular disorders as particular late toxicities of treatment were documented during follow-up visits. We reported the numbers of patients with documented late

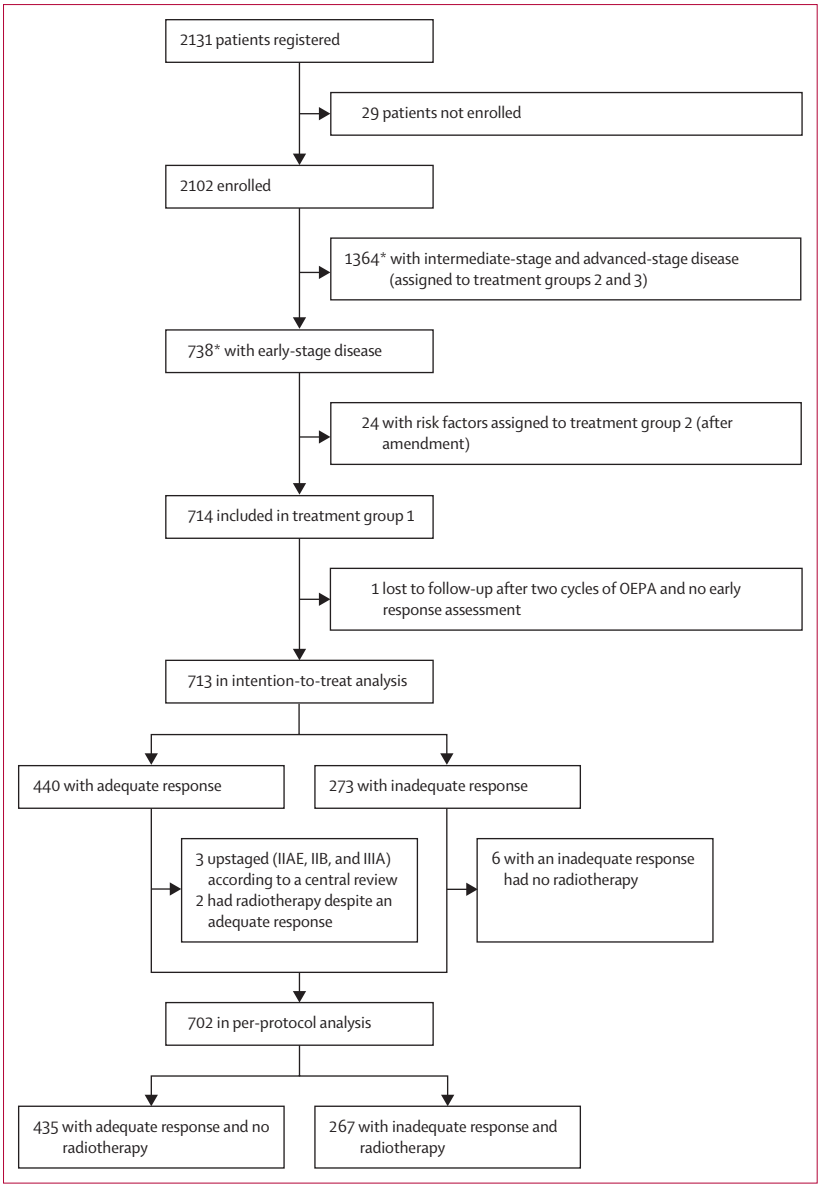

Figure 1: **Consort flowchart**
*One patient included in the treatment group 1 per-protocol analysis was randomly assigned to treatment group 2 on the investigator's discretion, but downstaged to treatment group 1 by the central review.

	All patients (n=713)
Age, years	
≥13 years	477 (67%)
<13 years	236 (33%)
Median	14·6 (12·0–16·0)
Sex	
Male	323 (45%)
Female	390 (55%)
Combined stage	
IA	40 (6%)
IB	5 (1%)
IIA	665 (93%)
IIAE	1 (<1%)
IIB	1 (<1%)
IIIA	1 (<1%)
Bulky disease*	
No	571 (80%)
Yes	110 (15%)
Undetermined	32 (4%)
Erythrocyte sedimentation rate in the first hour	
<30 mm	302 (42%)
≥30 mm	185 (26%)
Undetermined	226 (32%)
Risk factors present†	
Yes	252 (35%)
No	272 (38%)
Undetermined	189 (27%)
Response group at early response assessment	
Adequate response	440 (62%)
Inadequate response	273 (38%)
Early response assessment and risk factors†	
Adequate response and risk factors present	132 (19%)
Inadequate response and risk factors present	120 (17%)
Adequate response and no risk factors present	183 (26%)
Inadequate response and no risk factors present	89 (12%)
Adequate response undetermined	125 (18%)
Inadequate response undetermined	64 (9%)

Data shown as n (%) or median (IQR).* Bulky disease defined as a contiguous tumour volume of 200 mL or more. †Risk factors were elevated erythrocyte sedimentation rate or bulky disease or both.

Table 1: **Demographic data of intention-to-treat patients in treatment group 1**

toxicities before relapse as descriptive endpoints both in patients with an adequate response and without radiotherapy, and with an inadequate response; no statistical tests were done, and this was done post-hoc. This trial was registered at ClinicalTrials.gov, NCT00433459 and with EUDRACT, 2006–000995-33. Details of the Data Monitoring Committee are described in the study protocol (appendix pp 84–85).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 31, 2007, and Jan 30, 2013, 2131 patients were registered and 2102 patients were enrolled onto EuroNet-PHL-C1 (appendix p 4). Of these 2102 patients, 738 had early-stage disease and were allocated to treatment group 1 (figure 1), including one patient who was assigned to treatment group 2 at the investigator's discretion, but was downstaged to treatment group 1 by central review and was treated in treatment group 1 and included in the treatment group 1 per-protocol analysis. This patient has been included previously in the intention-to-treat analysis of patients in treatment group 2 and treatment group 3.[11]

After a major protocol amendment (sixth amendment, Nov 12, 2012) considering an elevated erythrocyte sedimentation rate of 30 mm or more in the first hour or a bulky mass of 200 mL or more as risk factors, 24 consecutive patients were considered early stage with an unfavourable risk (intermediate risk), and were assigned to treatment in treatment group 2. Of the 714 remaining patients assigned to treatment group 1, 713 were included in the intention-to-treat analysis and 702 were included in the per-protocol analysis (figure 1). The demographics of the patients in the intention-to-treat analysis are described in table 1. We did not collect data on race or ethnicity

At the early response assessment, 440 (62%) of 713 patients in the intention-to-treat analysis had an adequate response and received no radiotherapy. 273 (38%) of 713 patients in the intention-to-treat analysis with an inadequate response at the early response assessment received involved-field radiotherapy.

Among 440 patients with an adequate response, only 50 (11%) had a partial morphological response. Of these 50, five (10%) patients had a relapse, compared with 50 (13%) of 389 patients who had a relapse with a complete morphological response. The follow-up was 5 years for 80% of all patients. Median follow-up was 63·3 months (IQR 60·1–69·8) months. Within 72 months after the start of the trial, there were 91 events in the intention-to-treat analysis set, with recurrent classical Hodgkin lymphoma as the first event in 84 patients. In six patients, secondary malignancies as first events occurred between 5·4 and 70·1 months after the start of treatment with the following diagnoses: one thyroid carcinoma, one osteosarcoma, one chondroblastoma, two acute myeloid leukaemias, and one chronic myeloid leukaemia (appendix p 10). Six patients in the intention-to-treat cohort died, two after recurrent disease, one after a secondary malignancy, two from toxic death during salvage treatment, and one patient died by suicide 51·5 months after the start of treatment (appendix p 10). 1306 (92%) of 1426 of all OEPA chemotherapy cycles were administered with at least 90% of all the prescribed drug doses (appendix p 11). The treatment delay between the first and second OEPA cycle was not longer than 1 week in more than 90% of all chemotherapy cycles (appendix p 11). In all patients, the study chemotherapy was administered as prescribed by the protocol.

5-year event-free survival in patients with an adequate response in the intention-to-treat population was 86·5% (95% CI 83·3–89·8; 59 events in 440 patients; figure 2), which was less than the 90% target rate. 5-year event-free survival in the per-protocol analysis of patients with an adequate response was 87·1% (95% CI 83·9–90·3; 56 events in 435 patients; appendix p 20), which met the 90% target rate. 5-year progression-free survival and overall survival of patients with an adequate response in the intention-to-treat population was similar to those in the per-protocol population (appendix pp 19, 21).

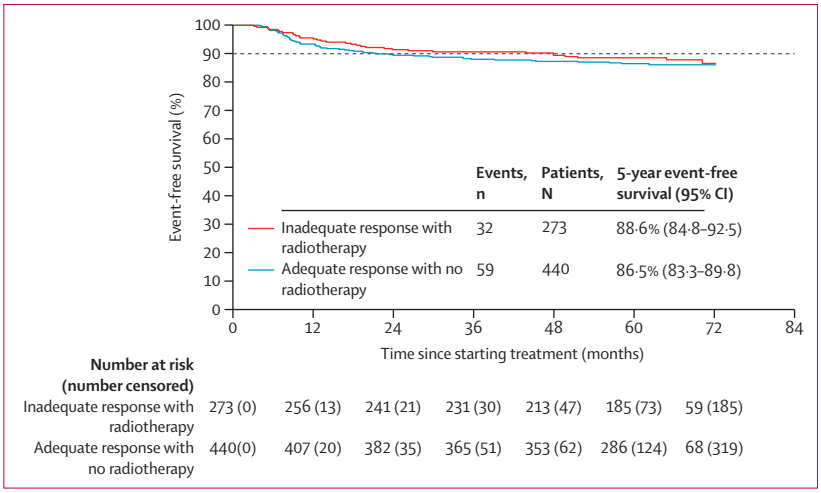

Figure 2: **5-year event-free survival of patients in the intention-to-treat group with an adequate or inadequate response**

	Grade 1–2	Grade 3	Grade 4
Decreased haemoglobin	476 (67%)	54 (8%)	9 (1%)
Decreased white blood cells	238 (33%)	275 (39%)	162 (23%)
Decreased neutrophils	56 (8%)	90 (13%)	507/680 (75%)
Decreased platelets	95 (13%)	22 (3%)	1 (<1%)
Creatinine increase	38 (5%)	0	0
Bilirubin increase	48 (7%)	1 (<1%)	0
Liver enzymes increase	380/690 (55%)	31/690 (4%)	0
Fever	206 (29%)	3 (<1%)	0
Infection	224/690 (32%)	40 (6%)	2 (<1%)
Stomatitis or pharyngitis	248 (35%)	25 (4%)	1 (<1%)
Vomiting	260/690 (38%)	12 (2%)	2 (<1%)
Diarrhoea	97 (14%)	12 (2%)	3 (<1%)
Constipation	240 (34%)	15 (2%)	2 (<1%)
Neuropathy (sensory)	156 (22%)	12 (2%)	0
Neuropathy (motor activity)	101 (14%)	12 (2%)	0

Data shown as n (%). The major toxicities or selected adverse events of 713 patients in treatment group 1 receiving vincristine, etoposide, prednisone, and doxorubicin cycles for induction treatment are listed here. For adverse events of grade 1–2, any occurring in 10% or more of patients are shown. All grade 3 and 4 events are shown. Using the Common Terminology Criteria for Adverse Events version 2.0, grade 0–4 toxicities were documented; grade 5 toxicities were not specified. No grade 5 toxicities (ie, treatment-related deaths) occurred.

Table 2: **Adverse events during treatment with vincristine, etoposide, prednisone, and doxorubicin in the intention-to-treat population (n=713)**

5-year event-free survival in patients with an inadequate response (n=273) was 88·6% (95% CI 84·8–92·5; 32 events in 273 patients), and the 95% CI included the 90% target rate (figure 2). Similar 5-year event-free survival was shown in the per-protocol analysis (appendix p 20). 5-year progression-free survival and overall survival were similar in the per-protocol and intention-to-treat

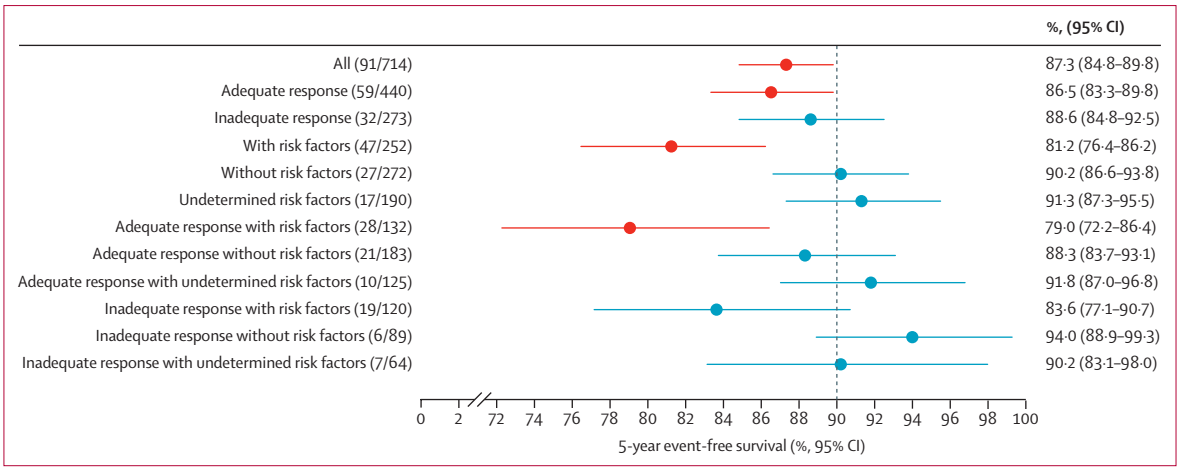

***Figure 3*: Forest plot of subgroup analyses**
Data in parentheses in each subgroup are number of events/number of patients. Of the 714 patients in the intention-to-treat analysis, one patient had no information at the early response assessment and therefore is not included in the adequate response or inadequate response groups, resulting in a denominator of 713 patients in the second, third, and fourth line of the forest plot. Risk factors were either bulky disease or elevated erythrocyte sedimentation rate, or both. Red lines represent results with percentages and 95% CIs less than the 90% target rate, and blue lines represent results more than the 90% target rate.

analyses of these patients as well, and were all consistent with the 90% target rate (appendix pp 19, 21).

No patients discontinued treatment for drug-related toxicity. Most adverse events occurred as haematological toxicity (table 2), with the most common CTCAE event of grade 3 or worse being neutropenia (597 [88%] of 680) and leukopenia (437 [61%] of 712). All adverse reactions of CTCAE grades 1–4 are listed in the appendix (pp 12–18). For late toxicities, as prespecified in the protocol, thyroid gland disorders were reported in 14 (3%) of 440 patients with an adequate response (of whom 173 had their thyroid assessment documented) and 54 (20%) of 273 patients with an inadequate response (of whom 230 had their thyroid assessment documented). In 46 (68%) of the 68 patients with reported thyroid disorders, subclinical hypothyroidism was diagnosed. Cardiovascular disorders were reported in eight (2%) of 439 patients with an adequate response and eight (3%) of 271 patients with an inadequate response. Among the 24 patients who had early-stage disease assigned to treatment group 2 after the protocol amendment, only one patient relapsed (data not shown).

In an unplanned subgroup analysis of the intention-to-treat and per-protocol populations, we compared 5-year event-free survival in patients with risk factors (bulky disease or increased erythrocyte sedimentation rates, or both) versus those without risk factors or those with an undetermined risk factor status (figure 3; appendix p 24). The rate of mediastinal involvement was 74% (526/713) in all patients and did not seem to differ between patients with an adequate response and those with an inadequate response (appendix p 24). However, the rate of bulky disease and mediastinal involvement was lower in patients with an adequate response than in patients with an inadequate response (appendix p 24).

Discussion

EuroNet-PHL-C1 was a large, multinational trial performed in 16 European countries. The participating national paediatric consortia on classical Hodgkin lymphoma agreed on a comprehensive treatment strategy for all stages of the disease. Here, we present the results of patients younger than 18 years with early-stage classical Hodgkin lymphoma. On the basis of all the evidence, radiotherapy could be safely be avoided in patients with early-stage disease who have an adequate response to OEPA induction treatment without compromising 5-year event-free survival or overall survival. In addition, we have shown that in patients with early-stage disease with an increased erythrocyte sedimentation rate or bulky disease, or both, 5-year event-free survival was less than the 90% target rate both in patients with an adequate response as well as in patients with an inadequate response with consolidating radiotherapy after OEPA induction treatment.

Our first objective was to investigate whether radiotherapy can be safely omitted in patients with an adequate response to intensive OEPA induction chemotherapy. We implemented the PET-guided omission of radiotherapy in adequate responders without randomly assigning patients to standard radiotherapy, to gain sufficient power for the titration question. This concept is fully in line with the treatment titration strategy of our consortium, in which the reduction of serious treatment-related events is traded off with minor reductions in treatment efficacy.[11] In previous studies of the German-Austrian Leukemia and Lymphoma Working Group and German Pediatric Oncology and Hematology Society-Hodgkin Disease Study Group consortium, we observed a 5-year event-free survival of more than 90% with OEPA and radiotherapy in all patients with early-stage disease. Therefore, in the titration design we used a target rate of 90% event-free

survival at 5 years with a lower treatment burden in patients with an adequate response to OEPA. With the treatment titration design, we have shown that radiotherapy can be avoided in approximately two-thirds of patients while keeping the 5-year event-free survival consistent with the 90% target rate.

There is no doubt that radiotherapy is an effective treatment for classical Hodgkin lymphoma, as confirmed in the randomised CCG 5942 trial[17] and the response-adaptation trial GPOH-HD 95.[18] One limitation of our study is that we did not randomly assign patients to receive radiotherapy or not, meaning that the comparison of radiotherapy versus no radiotherapy is biased in our study, because only patients who were prognostically worse received radiotherapy. With identical treatment, patients with an adequate response would probably have had a better outcome than patients with an inadequate response to OEPA. Our data suggest, but do not prove, that we might have had approximately 5% more relapses in patients with an adequate response by omission of radiotherapy. This finding is one reason why we will be adding one consolidating cycle of cyclophosphamide, vincristine, prednisone, and dacarbazine after an adequate response in treatment group 1 in the subsequent study EuroNet-PHL-C2, with the aim to preserve 5-year event-free survival rates of more than 90% in this group. The novelty factor of our trial compared with the two aforementioned trials is that the response adaptation was based on a metabolic response assessment and not on morphological response alone.

In the GPOH-HD 2002 trial, the event-free survival results for patients with or without radiotherapy were slightly better than those in this trial. However, the number of patients selected for morphological complete response and the subsequent omission of radiotherapy in the GPOH-HD 2002 trial comprised only a third of the number of patients in treatment group 1 (62 [31·8%] of 195 patients). In the present study, using a combination of morphological and PET criteria for adequate responses and the subsequent omission of radiotherapy, approximately two thirds of all treatment group 1 patients did not receive radiotherapy. This absence of radiotherapy could explain the slightly inferior event-free survival of patients with an adequate response in this study compared with the GPOH-HD 2002 trial. In addition, the cohort of patients with an inadequate response in the present trial contained a prognostically worse group of patients. This selection might also explain the slightly inferior outcome of these patients compared with the GPOH-HD 2002 trial.

Our results are superior to those of another published limited-stage paediatric classical Hodgkin lymphoma trial by Keller and colleagues,[19] the AHOD0431 trial. The investigators studied a response-adapted approach with three cycles of doxorubicin, vincristine, prednisone, and cyclophosphamide with or without radiotherapy and reached a 4-year event-free survival of 79·9%, and only 49·0% of patients had received no radiotherapy compared with 62% in our trial. The AHOD0431 trial included only low-risk patients without bulky masses, but patients with elevated inflammatory markers, such as increased erythrocyte sedimentation rate or increased C-reactive protein and patients with multiple sites of disease were not excluded.

For adults at a median age of 34 years with early-stage classical Hodgkin lymphoma, Radford and colleagues[20] showed that after three cycles of doxorubicin, bleomycine, vincristine, and dacarbazine (ABVD), patients with negative PET findings had a similarly good prognosis with or without consolidation radiotherapy. Another limitation of our study is that secondary malignancies occurred in 1% of patients, whereas Mittal and colleagues[21] showed that, in a cohort of 154 children with all-stage classical Hodgkin lymphoma treated with ABVD, no secondary malignancies occurred. This difference might be because of chance fluctuation. However, Mittal and colleagues found a decreased left ventricular function in 5·9% of patients and abnormal spirometry in 43·2% of patients, or a reduced diffusion capacity of the lung for carbon monoxide in 42·0% of patients. These late effects are likely to be associated with the high cumulative anthracycline load of approximately 200 mg/m² and to the abundant use of bleomycin in ABVD, which is a main difference between the dose-dense two cycles of OEPA and four cycles of ABVD. The question of using OEPA versus ABVD is not only an open question of efficacy and toxicity, it is also an open question of trading off higher relapse rates versus less radiotherapy use to avoid radiotherapy-induced secondary malignancies and other late effects. However, the aim of our study was not focused to actually capture the late effects of treatment.

In other Hodgkin lymphoma study groups, both in the paediatric and adult setting, the definitions of early-stage classical Hodgkin lymphoma differed substantially from the definition in our treatment group 1.[22] In the EuroNet-PHL-C1 trial, treatment group 1 comprises approximately 40% of all recruited patients with classical Hodgkin lymphoma, whereas patients with early-stage disease in other study groups comprise only 20–25%. These differences are most probably because of two factors: the presence of bulky disease or large mediastinal mass, or signs of systemic inflammation, or both, in our early-stage cohort. Therefore, in this study, an unplanned subgroup analysis of patients with and without these risk factors was initiated. In contrast to other study groups, we defined bulky disease by three-dimensional volumetry on cross-sectional imaging compared with the two-dimensional x-ray definition. In addition, non-paediatric study groups use a threshold of an erythrocyte sedimentation rate of more than 50 mm in the first hour in patients without B symptoms and an erythrocyte sedimentation rate of more than 30 mm in the first hour in those with B symptoms to define higher risk.[23] We decided to define a high erythrocyte sedimentation rate as 30 mm or more in

the first hour, independent of the presence of B symptoms, since erythrocyte sedimentation rate is potentially lower in younger patients[15] and B symptoms were generally not present in treatment group 1 patients. For this analysis, we hypothesised that the group with any of the factors used by other study groups to define early unfavourable stages—namely, with bulky disease or a high erythrocyte sedimentation rate of 30 mm or more in the first hour, or both—would differ in prognosis when given the treatment group 1 strategy. We showed, in the intention-to-treat analysis, that the 90% target rate was only reached in patients with early-stage disease without risk factors and those with undetermined risk factor status, whereas in patients with risk factors, the 90% target was not reached in those with an adequate response to OEPA. For the subgroup with an inadequate response and radiotherapy, the point estimate was less than 90%, whereas the 95% CI still included the 90% target rate. Consequently, the sixth amendment in the last year of the recruitment period was made, and subsequently patients with early-stage disease with risk factors were treated as patients with intermediate-stage disease. Until the closure of recruitment, 24 patients with early-stage disease with risk factors were treated in the intermediate risk group (treatment group 2) and only one patient relapsed. Thus, these patients with early unfavourable stages might be safely treated in treatment group 2, similar to reports from other study groups.[24]

At the time the EuroNet-PHL-C1 study was designed, the International Harmonisation Project criteria were the standard for definition of an adequate PET response in lymphoma. Deauville scores were not yet established and there were no studies published in which radiotherapy had been omitted by using PET response. An international consensus was reached in 2014 with the Lugano criteria, by accepting a residual uptake not exceeding the liver avidity, according to Deauville grades 1–3, as complete metabolic remission. However, in trials involving PET where de-escalation is investigated, it might be preferable to consider a Deauville grade of 3 as an inadequate response to avoid under-treatment.[25] Consequentially, many studies that started at that time have applied similar criteria; for example, EORTC-HD10,[24] AHOD0431,[19] and RAPID.[20] According to the international consensus, in the subsequent EuroNet-PHL-C2 trial, patients with a Deauville score higher than 3 after two OEPA courses will receive radiotherapy, and patients with a Deauville score lower than 3 will receive one course of cyclophosphamide, vincristine, prednisone, and dacarbazine consolidation. This strategy has been taken forward as the standard treatment for patients with early-stage disease without risk factors.[26] Patients with early-stage disease and risk factors will be treated within the intermediate-risk treatment group 2. The aim of the research is to clarify whether the results in patients with early-stage disease without risk factors can be further improved by minor treatment intensification and whether patients with early-stage disease with risk factors will have an event-free survival of more than 90% when treated as intermediate-risk disease.

Contributors

CM-K, DK, DH, WHW, and RK verified the underlying data and wrote the first draft of the manuscript and with JL-P, AF-T, WB, AA, JMB, AB, SB, MC, FC, AC, SD, KD, AF, SG, TG, LLH, AH, JK, LK, TL, GM, FM, JP, TP, VR, ADR, DS, AU, and DV were responsible for the trial design, data interpretation, analysis, critical review, editing, and final review. All authors had access to all the data reported in the study. The corresponding author had full access to all the data and the final responsibility to submit for publication.

Declaration of interests

CM-K declares a research grant to their institution from MSD, and an unpaid leadership role as the Scientific Secretary of the EuroNet-PHL group. WB declares support for attending meetings or travel from Amgen, eusapharma, Gilead Roche, Jazz pharma, and Takeda; and has also participated on a drug safety monitoring board or advisory board for Amgen, Novartis, Roche, and Takeda. MC declares funding for the MK-3475 trial from MSD. AF-T declares support from Takeda for attending a meeting in 2016. JL-P declares a grant support from programme hospitalier de recherche clinique en cancerologie and participation on data monitoring committee for Bristol Myers Squibb and Boehringer. TL declares participation in data monitoring committees for MSD. All other authors declare no competing interests.

Data sharing

The study protocol is available in the appendix (p 64). Individual participant data that underlie the results reported in this Article (text, tables, figures, and appendices) will be shared after deidentification to researchers who provide a methodologically sound and ethically approved proposal. Proposals can be submitted up to at least 36 months after Article publication. Proposals should be directed to dirk.hasenclever@imise.uni-leipzig.de. To gain access, data requestors will need to sign a data-access agreement. This manuscript describes only one treatment group, treatment group 1.

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References

1 Schellong G, Brämswig J, Ludwig R, et al. Combined treatment strategy in over 200 children with Hodgkin's disease: graduated chemotherapy, involved field irradiation with low dosage and selective splenectomy. A report of the cooperative therapy study DAL-HD-82. *Klin Padiatr* 1986; **198:** 137–46.

2 Schellong G, Pötter R, Brämswig J, et al. High cure rates and reduced long-term toxicity in pediatric Hodgkin's disease: the German-Austrian multicenter trial DAL-HD-90. *J Clin Oncol* 1999; **17:** 3736–44.

3 Weiner MA, Leventhal B, Brecher ML, et al. Randomized study of intensive MOPP-ABVD with or without low-dose total-nodal radiation therapy in the treatment of stages IIB, IIIA2, IIIB, and IV Hodgkin's disease in pediatric patients: a Pediatric Oncology Group study. *J Clin Oncol* 1997; **15:** 2769–79.

4 Donaldson SS, Hudson MM, Lamborn KR, et al. VAMP and low-dose, involved-field radiation for children and adolescents with favorable, early-stage Hodgkin's disease: results of a prospective clinical trial. *J Clin Oncol* 2002; **20:** 3081–87.

5 Schwartz CL, Constine LS, Villaluna D, et al. A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate- and high-risk Hodgkin lymphoma: the results of P9425. *Blood* 2009; **114:** 2051–59.

6 Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. *J Clin Oncol* 2014; **32:** 3651–58.

7 Bhatia S, Robison LL, Oberlin O, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. *N Engl J Med* 1996; **334:** 745–51.

8 Schellong G, Riepenhausen M, Ehlert K, et al. Breast cancer in young women after treatment for Hodgkin's disease during childhood or adolescence--an observational study with up to 33-year follow-up. *Dtsch Arztebl Int* 2014; **111:** 3–9.

9 van Nimwegen FA, Ntentas G, Darby SC, et al. Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. *Blood* 2017; **129:** 2257–65.

10 Mauz-Körholz C, Hasenclever D, Dörffel W, et al. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: the GPOH-HD-2002 study. *J Clin Oncol* 2010; **28:** 3680–86.

11 Mauz-Körholz C, Landman-Parker J, Balwierz W, et al. Response-adapted omission of radiotherapy and comparison of consolidation chemotherapy in children and adolescents with intermediate-stage and advanced-stage classical Hodgkin lymphoma (EuroNet-PHL-C1): a titration study with an open-label, embedded, multinational, non-inferiority, randomised controlled trial. *Lancet Oncol* 2022; **23:** 125–37.

12 Trotti A, Byhardt R, Stetz J, et al. Common toxicity criteria: version 2.0. an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. *Int J Radiat Oncol Biol Phys* 2000; **47:** 13–47.

13 Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007; **25:** 579–86.

14 Klimm B, Goergen H, Fuchs M, et al. Impact of risk factors on outcomes in early-stage Hodgkin's lymphoma: an analysis of international staging definitions. *Ann Oncol* 2013; **24:** 3070–76.

15 Miller A, Green M, Robinson D. Simple rule for calculating normal erythrocyte sedimentation rate. *Br Med J (Clin Res Ed)* 1983; **286:** 266.

16 Specht L, Hasenclever D. Prognostic factors. In: Engert A, Younes A, eds. Hodgkin lymphoma: a comprehensive overview. Cham: Springer International Publishing, 2015: 131–55.

17 Wolden SL, Chen L, Kelly KM, et al. Long-term results of CCG 5942: a randomized comparison of chemotherapy with and without radiotherapy for children with Hodgkin's lymphoma--a report from the Children's Oncology Group. *J Clin Oncol* 2012; **30:** 3174–80.

18 Dörffel W, Rühl U, Lüders H, et al. Treatment of children and adolescents with Hodgkin lymphoma without radiotherapy for patients in complete remission after chemotherapy: final results of the multinational trial GPOH-HD95. *J Clin Oncol* 2013; **31:** 1562–68.

19 Keller FG, Castellino SM, Chen L, et al. Results of the AHOD0431 trial of response adapted therapy and a salvage strategy for limited stage, classical Hodgkin lymphoma: a report from the Children's Oncology Group. *Cancer* 2018; **124:** 3210–19.

20 Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med* 2015; **372:** 1598–607.

21 Mittal A, Bhethanabhotla S, Ganguly S, et al. Late effects in pediatric Hodgkin lymphoma survivors after uniform treatment with ABVD with or without radiotherapy. *Pediatr Blood Cancer* 2021; **68:** e29293.

22 Mauz-Körholz C, Metzger ML, Kelly KM, et al. Pediatric Hodgkin lymphoma. *J Clin Oncol* 2015; **33:** 2975–85.

23 Engert A, Plütschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med* 2010; **363:** 640–52.

24 André MPE, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: final results of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol* 2017; **35:** 1786–94.

25 Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014; **32:** 3059–68.

26 Korholz D. Second international inter-group study for classical Hodgkin lymphoma in children and adolescents. Feb 18, 2016. https://clinicaltrials.gov/ct2/show/NCT02684708 (accessed Feb 18, 2022).