

CLINICAL INVESTIGATION

Involved-site Radiation Therapy is Equally Effective and Less Toxic Than Involved-field Radiation Therapy in Patients Receiving Combined Modality Treatment for Early-stage Unfavorable Hodgkin Lymphoma—An Analysis of the Randomized Phase 3 HD17 Trial of the German Hodgkin Study Group



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Purpose: Combined modality treatment with chemotherapy followed by consolidation radiation therapy (RT) provides excellent outcomes for patients with early-stage Hodgkin lymphoma. The international standard of care for consolidation RT, involved-site/involved-node radiation therapy (ISRT/INRT), has never been evaluated in a randomized phase 3 trial against the former standard involved-field radiation therapy (IFRT).

Methods and Materials: In the multicenter phase 3 GHSG (German Hodgkin Study Group) HD17 trial, patients with early-stage unfavorable Hodgkin lymphoma were randomized between the standard Combined modality treatment group and a positron-emission tomography (PET)-guided group. In the standard group, patients received 2 cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (eBEACOPP) and 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by 30 Gy IFRT. In the experimental group, patients received no further therapy if postchemotherapy PET was negative and 30 Gy GHSG INRT, comparable to and therefore termed here ISRT, if PET was positive. Here, we analyze the interim PET-positive patients in a post hoc analysis, and therefore the randomized comparison of IFRT versus INRT/ISRT.

Results: A total of 1100 patients were randomized, of which 311 had a positive PET after chemotherapy. Kaplan-Meier estimates of 4-year progression-free survival were 96.8% (95% CI, 91.6%-98.8%) in the IFRT group and 95.4% (95% CI, 89.9%-97.9%; HR, 1.40; 95% CI, 0.44-4.42) in the ISRT group. The pattern of recurrence analyses indicated that none of the cases of disease progression or recurrence in the ISRT group would have been prevented by the use of IFRT. Acute grade 3/4 toxicities occurred in 8.5% of IFRT patients and 2.6% of ISRT patients ($P = .03$).

Conclusions: For the first time, consolidation INRT/ISRT was randomly compared with IFRT in a phase 3 trial. Regarding progression-free survival, no advantage of IFRT could be demonstrated. In summary, our data confirm the status of INRT/ISRT as the current standard of care. © 2024 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC license (<http://creativecommons.org/licenses/by-nc/4.0/>)

Introduction

Combined modality treatment (CMT) consisting of chemotherapy and consolidation radiation therapy (RT) is considered the standard of care for early-stage Hodgkin lymphoma (HL).^{1,2} Although consolidation RT is obsolete in patients with positron-emission tomography (PET)-negative early unfavorable HL after 2 cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (eBEACOPP) followed by 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD),³ it remains the standard of care for patients with early-stage HL after ABVD and for patients with interim PET-positive HL at most centers.⁴⁻⁹

There is an ongoing trend in field de-escalation: After involved-field radiation therapy (IFRT) had replaced extended-field RT as the standard of care in the context of CMT of early-stage HL based on the results of large randomized trials,¹⁰⁻¹³ Girinsky et al developed involved-node radiation therapy (INRT)^{14,15} on the basis of the recurrence patterns observed after chemotherapy alone.¹⁶ In contrast to IFRT,¹⁷ INRT does not irradiate the entire initially affected lymph node region, but only the initially involved lymph nodes.¹⁴ A modification of INRT is the involved-site radiation therapy (ISRT) of the International Lymphoma Radiation Oncology Group (ILROG), which accounts for positional variations between pre- and postchemotherapy imaging.^{18,19} The definition of "INRT" used in the present study more closely aligns with the later established ILROG definition of ISRT¹⁸ rather than the original EORTC INRT definition^{14,15} and henceforth will be termed herein as ISRT.

Although there are retrospective data²⁰⁻²³ and phase 1/2 studies of patients treated with INRT/ISRT²⁴⁻²⁶ and the use

of INRT in both groups of the European Organisation of Research and Treatment of Cancer (EORTC)/Lymphoma Study Association (LYSA)/Fondazione Italiana Linfomi (FIL) phase 3 H10 trial,^{6,27} INRT/ISRT have not yet been compared with IFRT in any randomized trial.

To our knowledge, the GHSG (German Hodgkin Study Group) phase 3 HD17 trial is the first trial that compared INRT/ISRT with IFRT in terms of safety and efficacy in a randomized fashion.

Methods and Materials

Study design and patients

The HD17 study was a multicenter, randomized phase 3 study conducted at 224 sites in Germany, Switzerland, Austria, and the Netherlands. The study was designed by the GHSG steering committee and approved by the responsible ethics committees. Details on inclusion and exclusion criteria and study designs have been published elsewhere.³ Before enrollment in this study, all patients provided written informed consent in accordance with the Good Clinical Practice guidelines of the International Conference on Harmonization and national regulations.

Randomization and treatment

In the standard group, 2 cycles of eBEACOPP followed by 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and 30 Gy IFRT were administered. After completion of chemotherapy, an interim PET (PET4) was

performed, which, however, had no influence on administration of RT as long as there was no progression.

In the experimental group, after the same chemotherapy, the administration of RT depended on the result of PET4. In the case of a negative PET4 (Deauville score 1-2), RT was not applied. In the case of a positive PET4 (Deauville score 3-4), 30 Gy ISRT was performed.

PET4 was centrally reviewed before RT by an interdisciplinary panel (nuclear medicine physician, oncologist, radiation oncologist, and radiologist).

Radiation Therapy procedures

RT was planned to start at a maximum of 4 to 6 weeks after the end of chemotherapy. The prescription was 30.0 to 30.6 Gy in 1.8 to 2 Gy single doses 5 times a week. A RT recommendation was made centrally by the radiation therapy reference institution.

IFRT in the standard group was based on the international standard.¹⁷ Since a pretherapeutic PET-computed tomography (CT) in planning position was recommended but not mandatory for planning ISRT/INRT, inaccuracies in

the transfer of pretherapeutic imaging to the planning CT had to be considered when planning ISRT/INRT. Clinical target volume (CTV) included the affected lymph nodes, considering the initial extension and displacement of normal tissue. Planning target volume was created by geometric expansion around the CTV with axial expansion of 1 to 2 cm and craniocaudal expansion of 3 cm to cover positioning inaccuracies. In summary, the definition of INRT used here is more similar to the definition of ISRT established later by ILROG¹⁸ than to the original INRT definition of the EORTC,^{14,15} so it is termed ISRT (see also Table 1E; Appendix).

The quality of 134 ISRT plans and 42 IFRT plans and the dosimetric differences between 111 ISRT plans and 35 IFRT plans were evaluated centrally after study completion by our radiation oncology panel.²⁸

All cases of disease progression and recurrence were evaluated based on prechemotherapy, RT, and follow-up imaging. They were graded either as infield and/or outfield, and whether they would have been infield and/or outfield in the other respective therapy group. Particular attention was paid to whether a marginal relapse occurred after ISRT, meaning a recurrence/progression after ISRT that would

Table 1 Baseline characteristics

		IFRT (N = 156)	ISRT (N = 155)
Age	Median	28 (22-36)	29 (23-39)
	≥45 y	18 (11.5%)	27 (17.4%)
Sex	Female	84 (53.8%)	81 (52.3%)
	Male	72 (46.2%)	74 (47.7%)
Performance status	ECOG = 0	123 (78.8%)	123 (80.6)
	ECOG = 1	33 (21.2%)	30 (19.4)
Ann Arbor stage	IA	10 (6.4%)	7 (4.5%)
	IB	3 (1.9%)	3 (1.9%)
	IIA	117 (75.0%)	114 (73.5%)
	IIB	26 (16.7%)	31 (20.0%)
GHSG risk factors	Large mediastinal mass	49 (31.4%)	39 (31.6%)
	Extranodal disease	17 (10.9%)	13 (8.4%)
	Elevated erythrocyte sedimentation rate	67 (42.9%)	71 (45.8%)
	≥3 nodal areas	100 (64.1%)	100 (64.5%)
Other risk factors	Infradiaphragmatic disease	11 (7.1%)	10 (6.5%)
	Bulky disease (>5 centimeter)	103 (66.0%)	109 (70.3%)
Histologic subtype	Nodular sclerosis	77 (49.4%)	79 (51.0%)
	Mixed cellularity	13 (8.3%)	18 (11.6%)
	Lymphocyte-rich	1 (0.1%)	0 (0.0%)
	Unspecified classical HL	25 (16.0%)	21 (13.5%)
	Nodular lymphocyte-predominant HL	3 (1.9%)	0 (0.0%)
	not documented	37 (23.7%)	36 (23.2%)

Abbreviations: ECOG = Eastern Cooperative Oncology Group Performance Status; HL = Hodgkin lymphoma; IFRT = involved field radiation therapy; ISRT = involved site radiation therapy.

have been covered by IFRT and thus likely prevented by IFRT.

Statistics

The primary objective of this phase 3 trial was defined as the noninferiority of PET-adapted RT versus standard consolidation RT with respect to progression-free survival (PFS). These results in terms of the primary objective have already been published.³ Here, we present the randomized comparison between IFRT and ISRT in a post hoc analysis.

We evaluated the PFS and overall survival (OS) of patients with PET4-positive results (Deauville score 3-4), that is, patients who had RT, from both treatment groups in a post hoc analysis using the Kaplan-Meier method. Furthermore, we analyzed the subgroup of patients with a Deauville score of 4 in PET4 regarding PFS using the Kaplan-Meier method. Hazard ratios and the corresponding confidence intervals were calculated by Cox regression analyses. Owing to limited power caused by the relatively small patient and event numbers in the PET4-positive subgroups, analyses of PFS and OS are of a descriptive nature. Regarding PFS, progression after initiation of RT, recurrence, or death from any cause were considered events.

Adverse events were documented during chemotherapy and RT according to the Common Terminology Criteria for Adverse Events version 4.0. Acute toxicities of RT were compared using Fisher's exact test. We used SAS (version 9.4) for all statistical analyses.

Results

Patients

Between January 13, 2012, and March 12, 2017, 1100 patients were randomly assigned to the (standard CMT-) IFRT group and the (PET4-guided-) ISRT group (Fig. 1). A total of 4 patients, 2 in each group, were excluded (in 3 patients, the diagnosis of HL could not be confirmed, and 1 patient withdrew consent). PET4 was not reviewed centrally in 60 patients from the IFRT group and 57 patients from the ISRT group (Fig. 1). Thus, in total, PET4 was reviewed centrally in 486 patients from the IFRT group and 493 patients from the ISRT group. In the IFRT and ISRT groups, PET4 was positive in 168 and 160 patients, respectively. Finally, 156 patients with PET4-positive results received IFRT, and 155 received ISRT.

Patient characteristics were similar in both treatment groups (Table 1). The median age in the IFRT and ISRT groups was 28 and 29 years, respectively. There was a slight female predominance in both groups (Group IFRT: female, 53.8% vs male, 46.2%; Group ISRT: female, 52.3% vs male, 47.7%). Patients with stage IIA disease were most common in both groups, accounting for 75.0% (IFRT) and 73.5%

(ISRT) of cases, respectively. There were no relevant differences in the patterns of involvement (Table 2E; Appendix).

Radiation Therapy

Documentation of the dose administered was available in 307 patients overall, 153 in the IFRT group and 154 in the ISRT group (Table 2). A median of 30.0 Gy was applied in both treatment groups in accordance with the protocol. In 1 patient in the ISRT group, RT was stopped at 14 Gy owing to progression in the primary involved region at the beginning of RT. In another patient in the ISRT group, a boost up to 40 Gy was administered to the progressive region, also owing to progression in the primary involved region at the beginning of RT. In the IFRT group, the dose delivered ranged from 28.0 to 30.6 Gy.

Pattern of recurrence

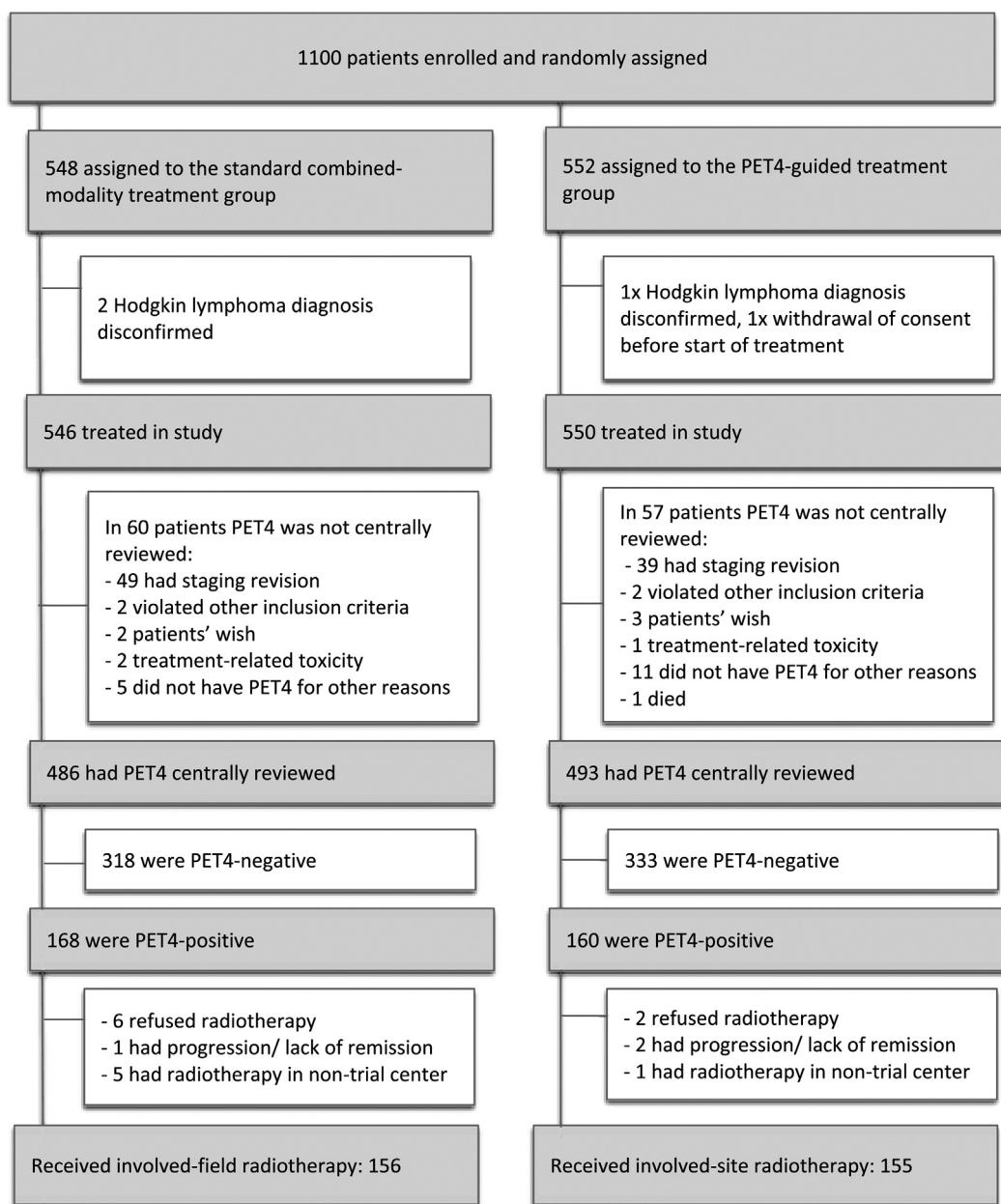
Disease progression after initiation of RT was seen in 3 patients (1.9%) from the ISRT group. Relapses occurred in 3 patients from the IFRT group (1.9%) and in 4 patients from the ISRT group (2.6%). HL-associated deaths were not documented, and no patients died in the ISRT group, whereas 2 patients died in the IFRT group (1 owing to cardiovascular disease and 1 owing to a second primary malignancy). Overall, 5 (3.2%) PFS events occurred in the IFRT group, compared with 7 (4.5%) PFS events in the ISRT group.

Of the 3 recurrences in the IFRT group, 2 were located infield only, and 1 was located both infield and outfield. None of the infield recurrences of the patients from the IFRT group would have been outside the ISRT field.

Of the 3 progressions and 4 recurrences from the ISRT group, only 1 was located infield, 2 were located outfield, and 4 were located both infield and outfield. No marginal relapse occurred in the ISRT group.

Survival

At a median follow-up of 49 months, Kaplan-Meier estimates of 4-year PFS were 96.8% (95% CI, 91.6%-98.8%) in the IFRT group and 95.4% (95% CI, 89.9%-97.9%; HR, 1.40; 95% CI, 0.44-4.42; Fig. 2A) in the ISRT group. For PET4 positivity of Deauville score 4, with only a few patients in long-term follow up (median follow-up of 46 months), Kaplan-Meier estimates of 4-year PFS were 91.6% (95% CI, 76.1%-97.2%) in the IFRT group and 86.4% (95% CI, 69.4%-94.3%; HR, 1.96; 95% CI, 0.49-7.83; Fig. 1E in Appendix) in the ISRT group. At a median follow-up of 52 months, Kaplan-Meier estimates of 4-year OS were 99.1% (95% CI, 93.9%-99.9%) in the IFRT group and 100.0% (95% CI, 100%-100%; Fig. 2B) in the ISRT group.

**Fig. 1.** Consort diagram.**Table 2** Radiation therapy dose

	Patients	Mean (Gy)	SD (Gy)	Minimum (Gy)	Q1 (Gy)	Median (Gy)	Q3 (Gy)	Maximum (Gy)
IFRT	153	30.2	0.3	28.0	30.0	30.0	30.6	30.6
ISRT	154	30.1	1.6	14.0	30.0	30.0	30.0	40.0
Total	307	30.1	1.1	14.0	30.0	30.0	30.6	40.0

Abbreviations: IFRT = involved field radiation therapy; ISRT = involved site radiation therapy; Q1 = first quartile; Q3 = third quartile.

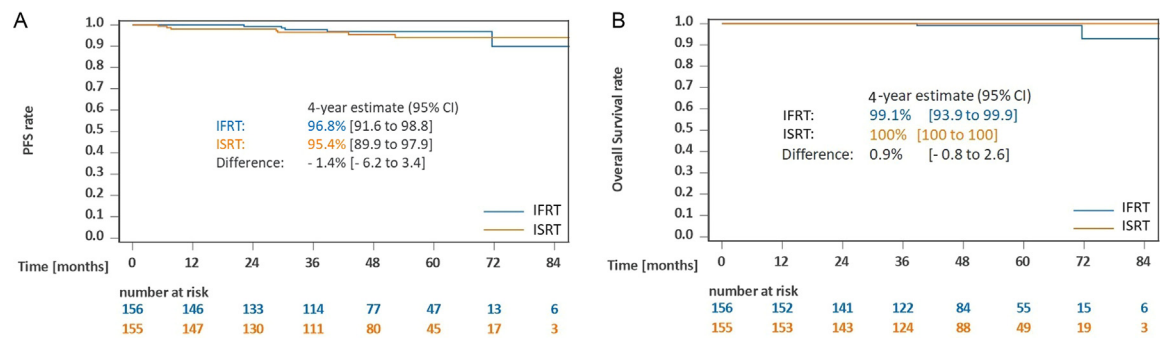


Fig. 2. Kaplan-Meier estimates of 4-year progression-free survival of PET4-positive patients (A); Kaplan-Meier estimates of 4-year overall survival of PET4-positive patients (B). *Abbreviations:* IFRT = involved field radiation therapy; ISRT = involved site radiation therapy.

Acute toxicity during RT

During RT, grade III/IV toxicities occurred in 8.5% of patients in the IFRT group compared with 2.6% in the ISRT group ($P = .03$; Table 3). In particular, grade 3/4 mucositis was more common in patients undergoing IFRT than in those undergoing ISRT (4.6% vs 0.0%, $P = .01$).

Discussion

The GHSG HD17 study was designed to demonstrate the noninferiority of PET4-guided CMT compared with standard CMT in early unfavorable HL and to investigate the prognostic effect of PET4. Here, we present the randomized comparison of ISRT versus IFRT in a post hoc analysis.

Two major findings emerged from our analysis: first, we could not detect a clinically relevant difference between IFRT and ISRT regarding efficacy, keeping in mind that this post hoc analysis was not powered to demonstrate noninferiority of ISRT. Second, none of the recurrences/progresses in

the ISRT group would have been covered and thus prevented by IFRT.

The role of RT in the early stages of HL has been the subject of many studies. In early-stage favorable HL, CMT consisting of 2 or 3 cycles of ABVD and consolidation RT is the standard of care in most centers,^{5,6,9} as a significantly worse PFS is observed without RT.⁵⁻⁷ In contrast for patients with an early-stage unfavorable HL with a negative postchemotherapy PET, consolidation RT can be omitted after $2 \times$ eBEACOPP + $2 \times$ ABVD,³ whereas after ABVD-based chemotherapy, the omission significantly worsens PFS.^{6,7}

For early-stage HL, there has been a progressive reduction in RT field size over time. In contrast to the advanced stages of HL, in which only PET-positive residuals are irradiated after chemotherapy (eg, 4-6 cycles of eBEACOPP or 6 cycles of ABVD),²⁹ the RT fields in early-stage HL are based on the initial extent. Owing to severe side effects, the field size for early-stage HL has already been reduced from total nodal irradiation³⁰ to extended field³¹ and finally to involved field.¹⁰⁻¹² Since studies on recurrence patterns after chemotherapy alone showed that infield recurrences occur primarily in the originally affected lymph nodes,¹⁶ Girinsky et al developed INRT.^{14,15} By definition, INRT requires prechemotherapy imaging to be performed in the RT position for accurate delineation of the target volume.¹⁵ In clinical practice, however, this is not always feasible. Therefore, the concept of ISRT was developed, first by the UK Lymphoma Radiotherapy Group, and affirmed by ILROG, which allows for greater RT margins to compensate for anatomic uncertainties and set-up variation.^{18,32} Thus, INRT can be considered a special case of ISRT but with optimal imaging.¹⁸ When the HD17 study was initiated, the concept of ISRT did not yet exist. However, for better applicability to clinical routine, a prechemotherapy PET in RT position was not obligatory, and therefore, displacement of tissue had to be considered when planning RT.³³ Overall, there are more similarities of INRT in the HD17 trial to the later described ISRT of ILROG¹⁸ than to the original INRT definition of the EORTC.¹⁴ For this reason, the results of the HD17 study are representative for ISRT, so we use the term ISRT.

Table 3 Acute grade 3/4 toxicity during radiation therapy according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

	IFRT N = 153	ISRT N = 154	P value
Any grade 3/4 toxicity	13 (8.5%)	4 (2.6%)	0.03
Leukopenia	2 (1.3%)	1 (0.6%)	0.62
Nausea/vomiting	3 (2.0%)	0 (0.0%)	0.12
Dysphagia	8 (5.2%)	3 (1.9%)	0.14
Mucositis	7 (4.6%)	0 (0.0%)	0.01
Local skin reaction RT field	1 (0.7%)	0 (0.0%)	0.50
Abbreviations: IFRT = involved field radiation therapy; ISRT = involved site radiation therapy.			

There are several studies in which INRT/ISRT was part of CMT, such as the EORTC/LYSA/FIL phase 3 H10 study,^{6,27} the GSHG phase 2 NIVAHL (Nivolumab and AVD in Early-stage Unfavorable Classical Hodgkin Lymphoma) trial,²⁴ the LYSA/FIL/EORTC phase 2 BREACH (Brentuximab Vedotin Associated With Chemotherapy in Untreated Patients With Hodgkin Lymphoma) study,²⁵ and a United States multicenter collaborative phase 1/2 study.²⁶ In all these studies, however, there was no randomized comparison between IFRT and INRT/ISRT, so the safety and efficacy of ISRT compared with IFRT cannot be assessed.

In the EORTC/LYSA/FIL H10 phase 3 trial for patients with early-stage HL, patients received 2 cycles of ABVD followed by an interim PET (PET2). In the standard groups, all patients received INRT after a total of 3 (favorable early-stage) or 4 (unfavorable early-stage) cycles of ABVD. In the experimental groups, only patients with PET2-positive results were treated with INRT (after 2 × ABVD and 2 × eBEACOPP).⁶ The 5-year PFS of the PET2-positive (ie, INRT-irradiated) patients after eBEACOPP was 90.6% (95% CI, 84.7%-94.3%), compared with 77.4% (95% CI, 70.4%-82.9%) after ABVD.⁶ The PFS in our analysis for patients irradiated with ISRT (94.0%; CI:87.3%-97.2%) is comparable to the PFS of the PET2-positive patients treated with 2 × ABVD + 2 × eBEACOPP + INRT in the H10 cohort.

In the GSHG phase 2 NIVAHL trial, patients with early-stage unfavorable HL were randomized into groups receiving either 4 × Nivolumab(N)-AVD or sequential treatment with 4 × N, 2 × N-AVD, and 2 × AVD, followed by 30 Gy ISRT in both treatment arms.²⁴ In the LYSA/FIL/EORTC phase 2 BREACH study, patients were randomized into groups receiving 4 × ABVD and 4 × brentuximab vedotin (BV)-AVD, followed by consolidation RT with 30 Gy INRT in both groups.²⁵ Both studies demonstrate the feasibility of combining ISRT/INRT with nivolumab or BV. However, since ISRT was used in all groups, no statement regarding ISRT in comparison to IFRT can be concluded from the NIVAHL and the BREACH studies.

In the United States multicenter collaborative phase 1/2 study, patients with PET4-negative results were sequentially assigned after 4 cycles of BV-AVD to the following 4 groups: (1) ISRT with 30 Gy, 2) ISRT with 20 Gy, 3) consolidation RT to CT morphologic remnants with 30 Gy, and 4) no RT.²⁶ The 2 ISRT groups of 29 patients showed a 2-year PFS of 93% and 97%, respectively.²⁶ The study demonstrates that the combination of 4 × BV-AVD and ISRT is feasible. However, owing to the small numbers of patients and the lack of an IFRT reference group, it is not possible to draw further conclusions regarding ISRT/INRT from this study.

To date, no prospective studies have directly compared the efficacy of ISRT/INRT to that of IFRT. In contrast, the HD17 study is, to our knowledge, the only study to date that performed a direct randomized comparison between ISRT, the current standard of care, and IFRT, the previous standard of care. Our survival data, combined with the pattern of recurrence analysis, do not suggest a disadvantage of ISRT in terms of PFS. Because ISRT has been already established as the

standard in international guidelines,¹⁸ it is unlikely that another large phase 3 trial will investigate this issue again, especially because our data support the current standard ISRT, even though no noninferiority test could be performed.

Long-term toxicities, such as the occurrence of secondary tumors and cardiovascular events, may significantly limit the life expectancy of HL survivors. But often, they become apparent only after many years or even decades.³⁴ Longer-term follow-up is required to assess the rates of late toxicities from ISRT and the effect of these events on survival. Extrapolating from earlier clinical data, reductions in RT field size are known to be associated with lower risks of late toxicity: for example, reducing the RT field size from the traditional mantle field has been associated with a lower risk of breast cancer.³⁵ As the mean planning target volume of ISRT in the HD17 study was about 200 mL smaller than that of IFRT,²⁸ it can be assumed that patients in the HD17 trial have a lower second tumor risk after ISRT than after IFRT. Furthermore, *in silico* studies show at least a lower risk of second malignancies after ISRT/INRT³⁶⁻³⁸ and premature menopause³⁹ compared with IFRT and a lower risk of myocardial events compared with extended-field RT.⁴⁰ Additionally, we demonstrated that significant fewer acute grade 3/4 toxicities occurred in the ISRT group than in the IFRT group. Collectively, these data suggest that the reduced RT field size of ISRT will likely translate into lower rates of long-term RT-induced toxicities.

The strength of our study compared with the previous data is certainly the randomized multicenter phase 3 design, which provides high internal and external validity. In contrast to the former standard IFRT, which has been established by several randomized studies,¹⁰⁻¹³ no randomized trial randomized INRT versus ISRT so far. There is only one additional phase 3 study, the EORTC/LYSA/FIL H10 study, which incorporated INRT in CMT. However, in the H10 study, INRT was used in all RT groups, and no randomization against IFRT was performed. For this reason, the safety and efficacy of INRT compared with that of IFRT cannot be evaluated in H10 study. In contrast, in the HD17 study HD, ISRT versus IFRT has been randomized, and thus, the HD17 trial is the only study that allows a reliable comparison between INRT/ISRT and IFRT in terms of PFS. Another strength of the HD17 trial is that all PET scans, after 4 cycles of chemotherapy, have been centrally evaluated, and an accurate RT recommendation has been prepared centrally for all patients. On the other hand, there was no real-time central review of the CTVs.

One major limitation of the present analysis is that the comparison of IFRT versus ISRT was not the primary objective of HD17 trial. Furthermore, only PET4-positive patients could be considered to evaluate this question, because PET4-negative patients in the experimental group (PET4-guided and ISRT) have not been irradiated. For this reason, we could only analyze 33.5% of the centrally reviewed patients, which is not enough to perform a noninferiority test. Another limitation is the relatively short follow-up period, which means that no statement could be made about OS or even the long-term toxicity of RT.

In conclusion, in a post hoc analysis of the only phase 3 trial published to date with a randomization between INRT/ISRT and IFRT, we did not detect a clinically relevant difference between IFRT and ISRT regarding efficacy for postchemotherapy PET-positive patients. The results of this randomized study support the already established ILROG standard of ISRT.

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