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ORIGINAL REPORT

Long-Term Follow-Up of Contemporary Treatment in Early-Stage Hodgkin Lymphoma: Updated Analyses of the German Hodgkin Study Group HD7, HD8, HD10, and HD11 Trials

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ABSTRACT

Purpose

Combined-modality treatment is widely considered the standard of care in early-stage Hodgkin lymphoma (HL), and treatment intensity has been reduced over the last years. Long-term follow-up is important to judge both efficacy and safety of the different therapies used.

Patients and Methods

We analyzed updated follow-up data on 4,276 patients treated within the German Hodgkin Study Group trials HD7 and HD10 for early-stage favorable HL and HD8 and HD11 for early-stage unfavorable HL between 1993 and 2003.

Results

In HD7 (N = 627; median follow-up, 120 months), combined-modality treatment was superior to extended-field radiotherapy (RT), with 15-year progression-free survival (PFS) of 73% versus 52% (hazard ratio [HR], 0.5; 95% CI, 0.3 to 0.6; $P < .001$), without differences in overall survival (OS). In HD10 (N = 1,190; median follow-up, 98 months), noninferiority of two cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) plus 20 Gy involved-field (IF)–RT to more intensive four cycles of ABVD plus 30 Gy IF-RT was confirmed with 10-year PFS of 87% each (HR, 1.0; 95%, 0.6 to 1.5) and OS of 94% each (HR, 0.9; 95% CI, 0.5 to 1.6), respectively. In both trials, no differences in second neoplasias were observed. In HD8 (N = 1,064; median follow-up, 153 months), noninferiority of involved-field RT to extended-field RT regarding PFS was confirmed (HR, 1.0; 95% CI, 0.8 to 1.2). In HD11 (N = 1,395; median follow-up, 106 months), superiority of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone at baseline over ABVD was not observed. After $BEACOPP_{baseline}$, 20 Gy IF-RT was noninferior to 30 Gy (10-year PFS, 84% *v* 84%; HR, 1.0; 95% CI, 0.7 to 1.5). In contrast, PFS was inferior in ABVD-treated patients receiving 20 Gy instead of 30 Gy IF-RT (10-year PFS, 76% *v* 84%; HR, 1.5; 95% CI, 1.0 to 2.1). No differences in OS or second neoplasias were observed in in both trials.

Conclusion

Long-term follow-up data of the four randomized trials largely support the current risk-adapted therapeutic strategies in early-stage HL. Nevertheless, continued follow-up is necessary to assess the long-term safety of currently applied therapeutic strategies.

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INTRODUCTION

In patients with early-stage Hodgkin lymphoma (HL), combined-modality treatment (CMT) is widely considered the standard of care because of better tumor control compared with radiotherapy (RT).[1,2] Despite high cure rates, treatment-related toxicity is a major concern in this rather young patient population. Depending on the intensity of chemotherapy and RT, the risk of late events, such as second neoplasias (SN) and organ toxicity, might be increased.[3-8] These potentially treatment-related morbidities might have an effect on long-term treatment outcome and significantly contribute to late mortality.[7,9] Therefore, subsequent trials evaluated a reduction of the RT field size and dose, as well as chemotherapy intensity, aiming at achieving sufficient tumor control while potentially reducing treatment-associated toxicity.

ASSOCIATED CONTENT

Data Supplements
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In early-stage favorable HL, two cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) followed by 20 Gy IF-RT is widely considered the standard of care on the basis of the German Hodgkin Study Group (GHSG) HD10 trial showing noninferiority compared with more intensive therapy.[10] On the basis of the results of the European Organisation for Research and Treatment of Cancer (EORTC) H8U and the GHSG HD8 trial, four cycles of chemotherapy followed by 30 Gy IF-RT are being regarded as the standard of care in patients with early-stage unfavorable HL.[11,12] In HD8, noninferiority of IF-RT compared with extended field (EF)–RT was confirmed with 10-year follow-up.[13] A moderate increase of chemotherapy intensity using bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone at baseline dosage ($BEACOPP_{baseline}$) compared with ABVD did not improve outcomes in the GHSG HD11 trial.[14]

So far, long-term data in HL is limited to retrospective, database-driven analyses or smaller prospective trials. To learn more on the long-term safety and efficacy of currently applied risk-adapted CMT strategies in early-stage HL, we updated our relevant GHSG phase III trials with 10 and 15 years of follow-up, respectively.

PATIENTS AND METHODS

Patients and Study Design

Between February 1, 1993, and January 13, 2003, 4,794 patients ages 16 to 75 years with newly diagnosed, biopsy-proven, early-stage HL were included in the GHSG trials HD7, HD8, HD10, and HD12 (Data Supplement). The studies were carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice. All patients provided written informed consent before study entry. The more recent HD10 and HD11 trials were registered at ClinicalTrials.gov (NCT00265018, NCT00264953).

Patients were assigned to trials for early-stage favorable (HD7, HD10) or unfavorable (HD8, HD11) disease, depending on the presence of the following risk factors: (a) large mediastinal mass, (b) extranodal disease, (c) elevated erythrocyte sedimentation rate, (d) three or more lymph node areas, and (e) massive spleen involvement as follows: HD7 – clinical stage (CS) I or II without (a)-(e); HD8— CS IA, IB, or IIA and one or more of (a)-(e), CS IIB and (c) and/or (d) only, or CS IIIA without any risk factors; HD10—CSI-II without (a)-(d); HD11—CS IA, IB, or IIA and one or more of (a)-(d), or CS IIB and (c) and/or (d), but not (a) or (b).

Patients received risk-adapted treatment. In HD7, patients were randomly assigned to receive 30 Gy EF-RT plus 10 Gy IF-RT either without (EF-RT group) or with (CMT-group) preceding chemotherapy of two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). In HD8, patients were randomly assigned to receive 30 Gy of either EF-RT or IF-RT after two alternating cycles of cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) and ABVD. In HD10, patients were randomly assigned to receive either four or two cycles of ABVD, followed by either 30 or 20 Gy IF-RT in a 2 × 2 factorial design. In HD11, patients were randomly assigned to receive four cycles of either ABVD or $BEACOPP_{baseline}$, followed by either 30 or 20 Gy IF-RT in a 2 × 2 factorial design.

Final results of the trials and a first follow-up analysis of HD8 have been published.[1,10,11,13,14] Follow-up assessment was similar across trials, with appointments at increasing intervals after therapy completion and computed tomography (CT) only performed at the investigators' discretion. Relapse of HL or occurrence of SN were confirmed by biopsy locally, and reports were verified by GHSG trial physicians before database entry. Our present analyses are based on all patients included in the most recent analysis of each respective study. To present results comparable with those of more recent trials, main analyses were also conducted within the subgroup of patients with classical HL (all patients with nodular lymphocyte-predominant HL and missing reference histology were excluded; Data Supplement).

Statistical Analysis

To assess long-term treatment outcome, we report progression-free survival (PFS; time from first diagnosis to progressive disease, relapse, or death from any cause or censored at the date of last information on disease status) and overall survival (OS; time from first diagnosis to death from any cause or censored at the date of last information; in cases of information lag of more than 12 months, information on survival status was obtained from residents' registration offices wherever possible). Survival outcomes were analyzed according to Kaplan-Meier and compared between treatment groups using log-rank test for the superiority objectives in HD7 (EF-RT *v* CMT) and HD11 (ABVD *v* $BEACOPP_{baseline}$) and hazard ratios (HRs) with 95% CIs obtained from Cox regression models. Because margins for the noninferiority objectives in HD8 (EF-RT *v* IF-RT), HD10 (four *v* two cycles of ABVD and 30 *v* 20 Gy IF-RT), and HD11 (30 *v* 20 Gy IF-RT) were defined as absolute differences in 5-year estimates in the trial protocols, we calculated margins for the HR using the currently observed 5-year estimate for PFS and subtracted the original margin. In the factorially designed HD10 trial, analyses of the chemotherapy comparison were stratified by RT group and vice versa. In HD11, treatment arms were analyzed separately because of the interaction between chemotherapy regimen and IF-RT dose observed in the 5-year analysis.

Cumulative incidence of SN was estimated according to Kaplan-Meier, accounting for death without preceding SN as a competing risk, and compared between treatment groups using subdistribution HRs and 95% CIs obtained from Cox regression models. We estimated standardized incidence ratios (SIRs) for SN using age- and sex-specific reference values for the German population.[15] Patient characteristics and therapies were analyzed descriptively. Statistical computations were performed with SAS (version 9.4; SAS Institute, Cary, NC).

RESULTS

Early-Stage Favorable HL

A total of 650 and 1,370 patients with early-stage favorable HL had been assigned to the GHSG HD7 and HD10 trials from 1993 to 1998 and 1998 to 2001, respectively; 627 and 1,190 of them could be included in the present analysis (Table 1; Data Supplement). Updated follow-up data beyond the previous analysis (in December 2005 and June 2009, respectively) were available for 56% and 44% of patients alive by the time of this last analysis and obtained from residents' registries in 26% and 11% of these patients. The median follow-up time for OS was 136 and 113 months, respectively, and did not differ between trial arms.

HD7 Long-Term Follow-Up

With 15-year PFS estimates of 52% and 73% and an HR of 0.5 (95% CI, 0.3 to 0.6), superiority of CMT compared with EF-RT was confirmed ($P < .001$). OS did not differ significantly between trial arms ($P = .3$), with 15-year estimates of 77% versus 80% and an HR of 0.8 (95% CI, 0.6 to 1.2; Figs 1A and 1B). As depicted in Table 2 and the Data Supplement, 15-year estimates for the cumulative incidence of any SN were 16% and 14%, respectively, with a comparable distribution of solid and hematologic malignancies and SIRs of 2.7 (95% CI, 1.9 to 3.6) and 3.0 (95% CI, 2.2 to 4.0).

Table 1. Characteristics of Patients in the German Hodgkin Study Group Trials HD7, HD10, HD8, and HD11 in Early-Stage Hodgkin Lymphoma

Characteristic	Early-Stage Favorable HL		Early-Stage Unfavorable HL	
	HD7 (N = 627)	HD10 (N = 1,190)	HD8 (N = 1,064)	HD11 (N = 1,395)
Age				
Median (range), years	36 (16-75)	36 (16-75)	30 (16-75)	33 (16-75)
≥ 60	63 (10)	138 (12)	89 (8)	101 (7)
Male sex	373 (59)	726 (61)	524 (49)	684 (49)
Ann Arbor stage				
IA	262 (42)	361/1,189 (30)	54 (5)	47 (3)
IB	19 (3)	24/1,189 (2)	32 (3)	38 (3)
IIA	327 (52)	738/1,189 (62)	713 (67)	942 (68)
IIB	19 (3)	66/1,189 (6)	240 (23)	368 (26)
IIIA			25 (2)	
Risk factors				
Large mediastinal mass	0 (0)	0 (0)	195 (18)	274 (20)
Extranodal involvement	0 (0)	0 (0)	78 (7)	142 (10)
≥3 nodal areas	0 (0)	0 (0)	692 (65)	943 (68)
Elevated ESR	0 (0)	0 (0)	517/1061 (49)	714/1,393 (51)
Massive spleen involvement	0 (0)	n.d.	4 (< 1)	n.d.
Infradiaphragmatic disease present	55 (9)	96/1187 (8)	107 (10)	106 (8)
Performance status				
ECOG = 0	n.d.	1,073/1,184 (91)	n.d.	1,021/1,392 (73)
ECOG = 1	n.d.	110/1,184 (9)	n.d.	356/1,392 (26)
ECOG = 2	n.d.	1/1,184 (< 1)	n.d.	15/1,392 (1)
Karnofsky index, median (range)	10 (7-10)*	n.d.	10 (7-10)†	n.d.
Histology				
NS	198/432 (46)	420/1,079 (39)	586/807 (73)	870/1,265 (69)
MC	141/432 (33)	434/1,079 (40)	146/807 (18)	241/1,265 (19)
NLPHL	63/432 (15)	81/1,079 (8)	15/807 (2)	37/1,265 (3)
Other	30/432 (7)	144/1,079 (13)	60/807 (7)	117/1,265 (9)

NOTE. Data given as No. (%) or No./total (%) unless otherwise indicated.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESR, erythrocyte sedimentation rate; HL, Hodgkin lymphoma; MC, mixed cellularity; n.d., not done; NLPHL, nodular lymphocyte-predominant HL; NS, nodular sclerosis.
*Information missing in 31 patients.
†Information missing in 22 patients.

Only a minority of deaths was HL-related (2% of analyzed patients in each arm) but instead attributed to SN (5% *v* 6%), cardiovascular disease (3% each), or respiratory disease (2% *v* 1%; Table 2)

HD10 Long-Term Follow-Up

Comparison of pooled chemotherapy and RT groups did not reveal any differences in terms of efficacy (data not shown). Noninferiority of the least intensive (two cycles of ABVD plus 20 Gy) to the most intensive (four cycles of ABVD plus 30 Gy) arm was confirmed with 10-year PFS estimates of 87% each and an HR of 1.0 (95% CI, 0.6 to 1.5 within the calculated margin for noninferiority of 2.2). The 10-year OS estimates were excellent, with 94% each and an HR of 0.9 (95% CI, 0.5 to 1.6; Fig 1C and 1D). With SIRs of 2.1 each and a 10-year cumulative incidence of 8% and 9% in arms A and D, respectively, no difference in terms of incidence and type of SN was observed (Table 2; Data Supplement). SN accounted for the majority of deaths (2% of analyzed patients), whereas HL-related death was reported in 1% of patients (Table 2).

Early-Stage Unfavorable HL

From 1993 to 1998 and 1998 to 2003, a total of 1,204 and 1,570 patients with early-stage unfavorable HL had been enrolled in the GHSG HD8 and HD11 trials, respectively, and 1,064 and 1,395 of them were analyzed (Table 1; Data Supplement). For 41% and 47% of patients alive at the time of the previous analysis (in January 2011 and July 2009, respectively), updated follow-up data, obtained from residents' registries in 28% and 12% of these patients, were available, resulting in a median follow-up for OS of 174 and 117 months, respectively, without differences between trial arms.

HD8 Long-Term Follow-Up

In terms of both PFS and OS, noninferiority of IF-RT versus EF-RT was confirmed, with an HR of 1.0 (95% CI, 0.8 to 1.2 within the calculated noninferiority margin of 1.6) and 0.9 (95% CI, 0.7 to 1.2), respectively (Figs 3A and 3B). Overall, a nonsignificant trend toward more SN after EF-RT versus IF-RT was observed, with 15-year cumulative incidence estimates of 17% versus 14% ($P = .3$; Data Supplement). This trend is more pronounced when examining only the incidence of acute myeloid leukemia or myelodysplastic syndromes (2.4% *v* 0.8%; $P = .1$), but not in non-Hodgkin lymphoma (2.6% *v* 2.9%; $P = 1.0$). In solid SN, the trend became more pronounced with longer follow-up but did not meet statistical significance (12% *v* 10.4%; $P = .7$, Table 2; Data Supplement). In both arms, SN accounted for the majority of deaths (6% *v* 5% of patients), followed by HL (3% each) and cardiovascular disease (2% *v* 3%; Table 2).

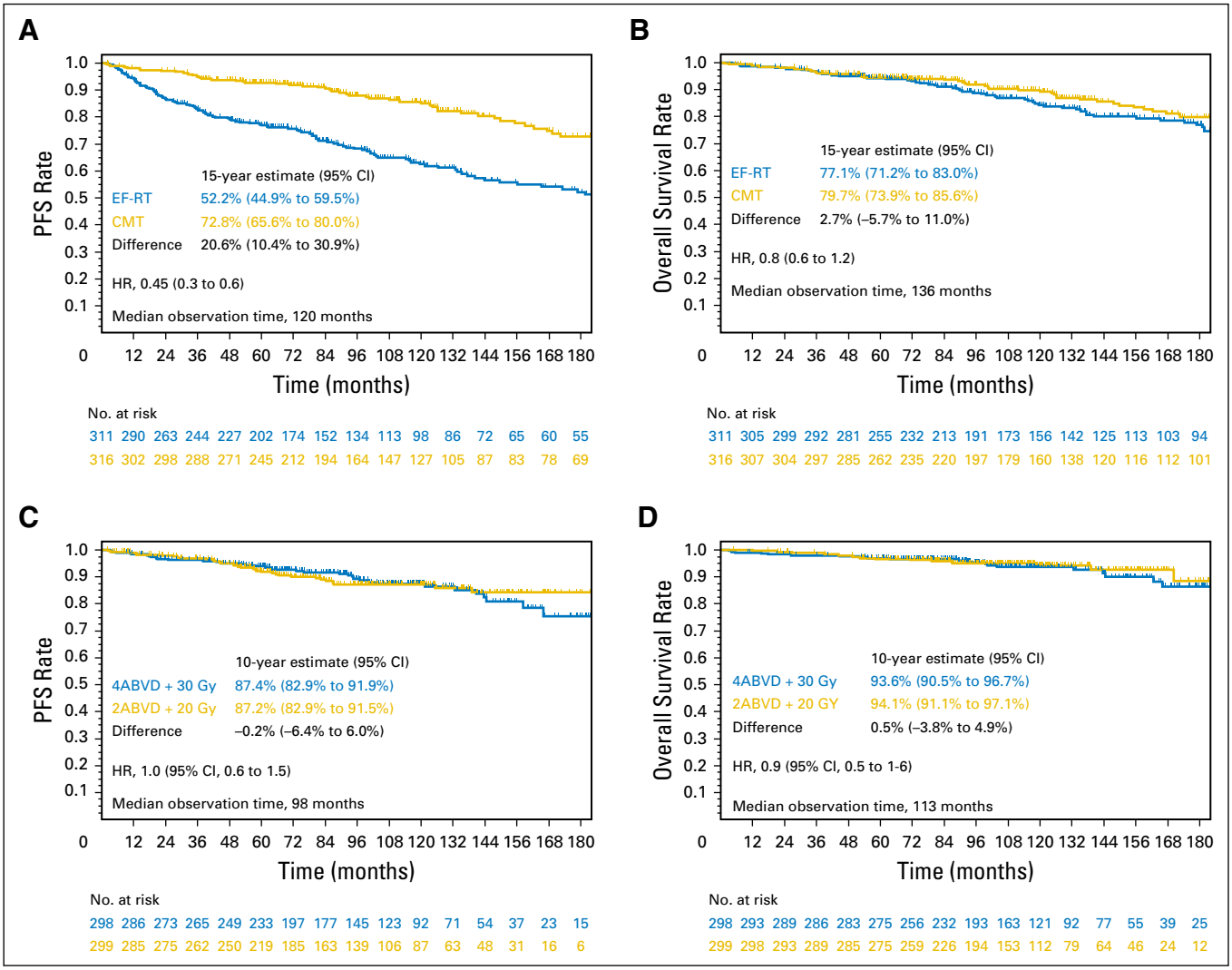

Fig 1. Long-term efficacy data for the German Hodgkin Study Group HD7 and HD10 trials in early-stage favorable Hodgkin lymphoma. (A) PFS in the HD7 trial; (B) overall survival in the HD7 trial; (C) PFS of arms A and D of the HD10 trial (analysis set for chemotherapy comparison); (D) overall survival of arms A and D of the HD10 trial (analysis set for chemotherapy comparison). Abbreviations: 2ABVD, two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine; 4ABVD, four cycles of doxorubicin, bleomycin, vinblastine and dacarbazine; CMT, combined-modality treatment; EF-RT, extended-field radiotherapy; HR, hazard ratio; PFS, progression-free survival.

HD11 Long-Term Follow-Up

With prolonged follow-up, no difference in PFS was found with $BEACOPP_{baseline}$ compared with standard ABVD when consolidated with 30 Gy (HR, 1.1; 95% CI, 0.7 to 1.5; $P = .8$; Fig 2A to 2E). In contrast to the 5-year analysis, $BEACOPP_{baseline}$ was no longer found to be significantly superior when followed by 20 Gy IF-RT (HR, 0.8; 95% CI, 0.6 to 1.1; $P = .1$; Fig 2B). When examining RT dose, there was a difference of −8.3% (−15.2% to −1.3%) in 10-year PFS for ABVD-treated patients receiving 20 Gy instead of 30 Gy IF-RT, with an HR of 1.5 (95% CI, 1.0 to 2.1, exceeding the calculated non-inferiority margin of 1.6; Fig 2C). After $BEACOPP_{baseline}$, 20 Gy IF-RT was found to be noninferior to 30 Gy IF-RT, with an HR of 1.0 (95% CI, 0.7 to 1.5 within the calculated noninferiority margin of 1.7) for PFS (Fig 2D). In terms of OS (Fig 2E) or SN (Table 2; Data Supplement), no significant differences or relevant trends could be observed between trial arms. Most frequent causes of death were HL (3%), SN (2%), and cardiovascular disease (1%; Table 2).

DISCUSSION

Multiagent chemotherapy followed by RT has significantly improved the outcome of patients with early-stage HL.[1,2,10-12] Nevertheless, SN and organ toxicity especially contribute to long-term morbidity and mortality,[5-7,9] and one aim of current research in early-stage HL is to reduce treatment-associated toxicity. Despite the HD.6 trial reporting 10-year median follow-up comparing mantle-field RT-containing treatment with ABVD alone,[16] long-term follow-up analyses of large randomized prospective trials evaluating current treatment strategies with regard to long-term efficacy and safety have not been published thus far. Here, we report the updated results of HD7 and HD10 in early-stage favorable HL and HD8 and HD11 in early-stage unfavorable HL, with a follow-up of 10 to 15 years.

Table 2. Second Neoplasias and Causes of Death After Treatment for Early-Stage Hodgkin Lymphoma in the German Hodgkin Study Group Trials HD7, HD10, HD8, and HD11

	Early-Stage Favorable HL						Early-Stage Unfavorable HL					
	HD7		HD10				HD8		HD11			
Variable	EF-RT N = 311	CMT N = 316	4ABVD + 30 Gy N = 298	4ABVD + 20 Gy N = 298	2ABVD + 30 Gy N = 295	2ABVD + 20 Gy N = 299	COPP/ABVD + EF-RT N = 532	COPP/ABVD + IF-RT N = 532	ABVD + 30 Gy N = 356	ABVD + 20 Gy N = 347	$BEACOPP_b$ + 30 Gy N = 341	$BEACOPP_b$ + 20 Gy N = 351
Median follow-up disease status, months	123	118	101	92	99	99	163	144	107	101	111	105
Median follow-up survival, months	144	132	117	113	115	111	177	172	118	115	118	117
Second neoplasia												
AML/MDS/ALL	1 (< 1)	3 (1)	2 (1)	0 (0)	0 (0)	0 (0)	12 (2)	4 (1)	0 (0)	1 (< 1)	1 (< 1)	2 (1)
NHL/myeloma	12 (4)	7 (2)	8 (3)	5 (2)	5 (2)	8 (3)	12 (2)	12 (2)	4 (1)	5 (1)	6 (2)	0 (0)
Solid tumor	28 (9)	32 (10)	17 (6)	12 (4)	14 (5)	16 (5)	57 (11)	41 (8)	11 (3)	16 (5)	17 (5)	18 (5)
Total	41 (13)	42 (13)	27 (9)	17 (6)	19 (6)	24 (8)	81 (15)	57 (11)	15 (4)	22 (6)	24 (7)	20 (6)
10-year cumulative incidence, % (95% CI)	n.d.	n.d.	8 (5-12)	6 (3-10)	8 (4-11)	9 (5-13)	n.d.	n.d.	6 (3-9)	7 (4-9)	7 (4-10)	5 (3-8)
15-year cumulative incidence, % (95%-CI)	16 (11-22)	14 (9-19)	n.d.	n.d.	n.d.	n.d.	17 (13-21)	14 (10-18)	n.d.	n.d.	n.d.	n.d.
SIR (95% CI)	2.7 (1.9-3.6)	3.0 (2.2-4.0)	2.1 (1.4-3.1)	1.5 (0.9-2.3)	1.6 (1.0-2.5)	2.1 (1.4-3.2)	3.6 (2.9-4.5)	2.6 (2.0-3.3)	1.4 (0.8-2.3)	2.4 (1.5-3.7)	2.2 (1.4-3.3)	1.7 (1.0-2.6)
Second neoplasia without prior progression or relapse of HL	34 (11)	41 (13)	24 (8)	14 (5)	17 (6)	22 (7)	75 (14)	48 (9)	13 (4)	19 (5)	22 (6)	19 (5)
Causes of death												
Hodgkin lymphoma	6 (2)	5 (2)	3 (1)	2 (1)	3 (1)	2 (1)	17 (3)	18 (3)	9 (3)	10 (3)	10 (3)	12 (3)
Second neoplasia	16 (5)	18 (6)	6 (2)	4 (1)	6 (2)	4 (1)	34 (6)	24 (5)	5 (1)	8 (2)	8 (2)	6 (2)
Cardiovascular disease	9 (3)	9 (3)	4 (1)	3 (1)	0 (0)	3 (1)	13 (2)	18 (3)	6 (2)	3 (1)	5 (1)	3 (1)
Pulmonary disease	6 (2)	3 (1)	1 (< 1)	2 (1)	0 (0)	1 (< 1)	6 (1)	1 (< 1)	1 (< 1)	0 (0)	0 (0)	1 (< 1)
Other disease	4 (1)	4 (1)	0 (0)	2 (1)	2 (1)	3 (1)	9 (2)	3 (1)	1 (< 1)	3 (1)	1 (< 1)	2 (1)
First-line toxicity	3 (1)	1 (< 1)	3 (1)	3 (1)	1 (< 1)	0 (0)	2 (< 1)	0 (0)	3 (1)	1 (< 1)	2 (1)	1 (< 1)
Salvage toxicity	4 (1)	1 (< 1)	0 (0)	0 (0)	4 (1)	1 (< 1)	3 (1)	5 (1)	2 (1)	1 (< 1)	3 (1)	2 (1)
Accident/Suicide	0 (0)	1 (< 1)	0 (0)	3 (1)	0 (0)	0 (0)	3 (1)	1 (< 1)	2 (1)	1 (< 1)	0 (0)	1 (< 1)
Unclear	13 (4)	9 (3)	4 (1)	1 (< 1)	5 (2)	3 (1)	18 (3)	20 (4)	3 (1)	7 (2)	3 (1)	5 (1)
Total	61 (20)	51 (16)	21 (7)	20 (7)	21 (7)	17 (6)	105 (20)	90 (17)	32 (9)	34 (10)	32 (9)	33 (9)

NOTE. Data given as No. (%) unless otherwise indicated.

Abbreviations: 2ABVD, two cycles of doxorubicin, bleomycin, vinblastine and dacarbazine; 4ABVD, four cycles of doxorubicin, bleomycin, vinblastine and dacarbazine; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; $BEACOPP_b$, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone at baseline dosage; CMT, combined-modality treatment; COPP/ABVD, cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, and dacarbazine; EF-RT, extended-field radiotherapy; HL, Hodgkin lymphoma IF-RT, involved-field radiotherapy; MDS, myelodysplastic syndrome; n.d., not done; NHL, non-Hodgkin lymphoma; SIR, standardized incidence ratio compared with the age- and sex-matched general German population.

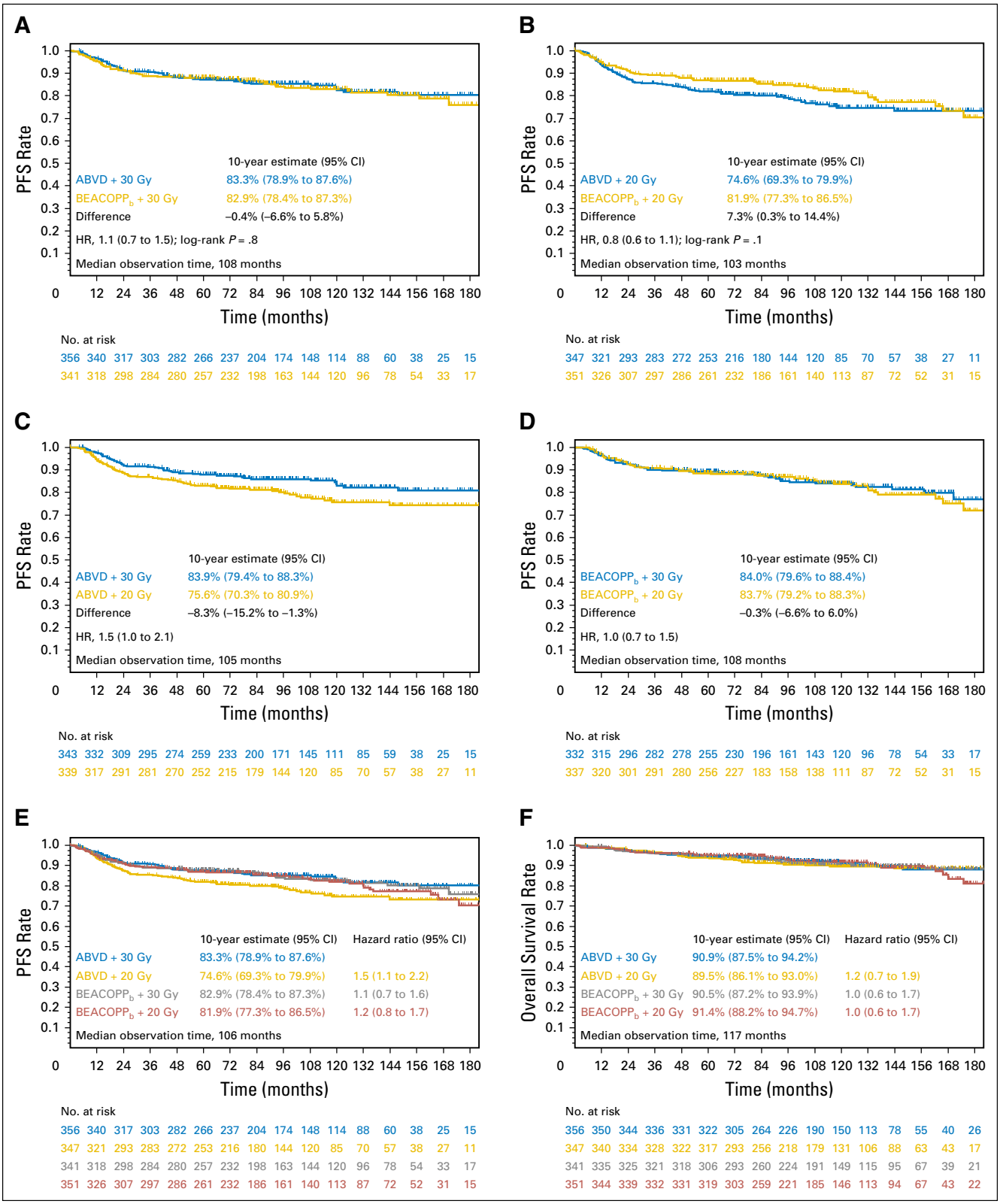

Fig 2. Long-term efficacy data for the German Hodgkin Study Group HD11 trial in early-stage unfavorable Hodgkin lymphoma. (A) Chemotherapy comparison: PFS for ABVD versus BEACOPP$_b$ with consolidative 30 Gy IF-RT. (B) Chemotherapy comparison: PFS for ABVD versus BEACOPP$_b$ with consolidative 20 Gy IF-RT. (C) Radiotherapy comparison: PFS for ABVD either followed by 30 or 20Gy IF-RT. (D) Radiotherapy comparison: PFS for BEACOPP$_b$ either followed by 30 or 20 Gy IF-RT. (E) PFS for all four trial arms of the HD11 trial (analysis set for chemotherapy comparison). (F) OS for all four trial arms of the HD11 trial (analysis set for chemotherapy comparison). Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP$_b$, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone at baseline dosage; HR, hazard ratio; IF-RT, involved-field radiotherapy; OS, overall survival; PFS, progression-free survival.

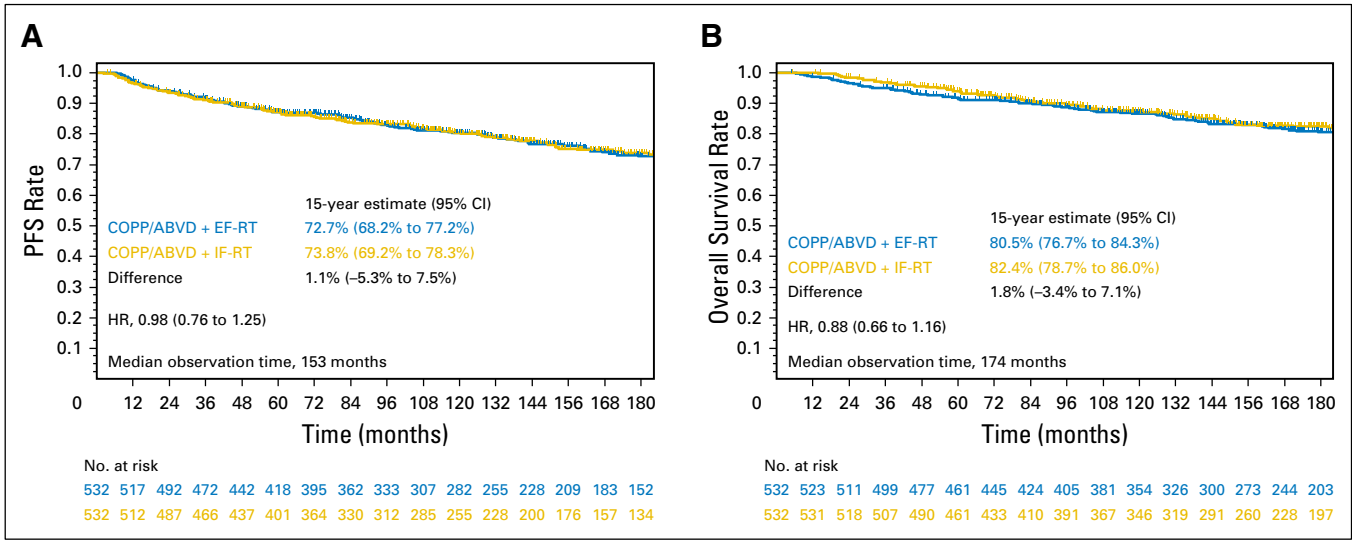

Fig 3. Long-term efficacy data for the German Hodgkin Study Group HD8 trial in early-stage unfavorable Hodgkin lymphoma. (A) PFS in the HD8 trial; (B) OS in the HD8 trial. Abbreviations: COPP/ABVD, cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, and dacarbazine; EF-RT, extended-field radiotherapy; HR, hazard ratio; IF-RT, involved-field radiotherapy; OS, overall survival; PFS, progression-free survival.

The presented analyses strongly support the current risk-adapted treatment strategy in early-stage favorable HL: the 15-year follow-up analysis of our HD7 trial confirmed the superiority of CMT, with a 15-year PFS difference of 21% over EF-RT (73% *v* 52%). A relevant OS difference could not be detected, either in the 7-year analysis[1] or in the present update, indicating a reasonable chance of a second long-term remission in case of relapse. With prolonged follow-up, OS rates decreased from over 90% after 7 years to 80% and 77% after 15 years. Only a minority of deaths was related to HL; instead, SN, cardiovascular, and respiratory events accounted for most deaths, underlining the prognostic relevance of treatment-associated long-term toxicity.[7,9]

Retrospective analyses indicate that both RT dose[8,17,18] and field size, as well as intensity of chemotherapy—particularly alkylating agents and etoposide—correlate with an increased incidence of SN.[19] Subsequently, less intensive CMT approaches have been evaluated in HD10. In terms of disease control, the present analysis confirmed noninferiority of two cycles of ABVD followed by 20 Gy IF-RT to more intensive approaches, with excellent 10-year PFS and OS estimates of 87% and 94%, respectively.[10] A further reduction of chemotherapy intensity by omission of dacarbazine and/or bleomycin from ABVD cannot be generally recommended because of poorer tumor control observed in the GHSG HD13 trial.[20]

In early-stage unfavorable HL, four cycles of chemotherapy followed by 30 Gy IF-RT are regarded as standard treatment.[11,12] Our long-term HD8 analysis confirms noninferiority of 30 Gy IF-RT to 30 Gy EF-RT after two cycles of COPP/ABVD, but 15-year PFS and OS rates of 74% and 82%, respectively, leave room for improvement. In the long-term analyses of the subsequent HD11 trial, no significant superiority of $BEACOPP_{baseline}$ over ABVD was observed when combined with 30 or 20 Gy IF-RT. Regarding RT, initial and long-term analyses strongly suggest that moderately increased chemotherapy allows a dose reduction of IF-RT, with noninferiority of 20 Gy compared with 30 Gy observed after $BEACOPP_{baseline}$. A further intensification of chemotherapy in early-stage unfavorable HL was evaluated in the more recent HD14 trial; here, the combination of two cycles of $BEACOPP_{escalated}$ and two cycles of ABVD resulted in a significant PFS advantage compared with four cycles of ABVD at 5 years. Although there has been more acute toxicity and no improvement in OS so far, the improved tumor control is a relevant outcome parameter for patients.[21,22] Furthermore, the intensified regimen might enable positron emission tomography (PET)-guided RT and reduction of RT dose.

The role of RT in the treatment of early-stage HL has been frequently addressed.[16,23] To date, there are no conclusive data that support a response-adapted, PET-guided RT approach; both the the UK National Cancer Research Institute RAPID trial[24] and the EORTC/Group des Etudes des Lymphomes de l'Adulte (GELA)/Fondazione Italiana Linfomi (FIL) H10 trial[25] failed to demonstrate noninferiority in patients who were PET negative after chemotherapy and did not receive RT. Currently, the GHSG HD16 and HD17 trials are evaluating a similar PET-guided RT approach. The impact of consolidating RT on outcome is supported by a National Cancer Database analysis of 20,600 patients with early-stage HL and by a Cochrane analysis, both showing inferior tumor control and OS with chemotherapy alone compared with CMT.[23,26] Thus, to date, two cycles of ABVD followed by 20 Gy IF-RT are still considered standard of care in early-stage favorable HL.[2,23] Omission of RT in patients who are PET negative and have a favorable risk profile can be justified only in selected individual patients after weighing the risk-benefit ratio of tumor control and toxicity.

The detailed analysis of incidence rates and subtypes of SN has not shown any significant differences between treatment arms so far. In line with prior reports,[13,27,28] the 15-year analysis of HD8 shows a trend toward a higher incidence of solid SN and secondary acute myeloid leukemia or myelodysplastic syndromes in patients treated with EF-RT compared with IF-RT. With regard to the latency of several years or even decades until manifestation of SN—especially of potentially RT-associated secondary solid

tumors, as shown in the Data Supplement and as reported by several retrospective analyses—the follow-up period of HD8, HD10, and HD11 is probably still too short to confidentially assess the risk of SN with reduced RT doses and a reduced field size, respectively.[29] With the current follow-up of HD10 and HD11, no difference in cumulative incidence of SN was detected between 20 or 30 Gy IF-RT. Subsequent analyses with even longer follow-up will have to confirm that the reduction of RT field size or dose indeed translates into a reduced risk of SN.

The present data suggest a lower risk of smaller RT field size on SN; however, there is no such benefit detectable yet in patients who have received a lower RT dose. To what extent the increased SIRs of SN, even after two cycles of ABVD and 20 Gy IF-RT, is attributable to RT and/or chemotherapy remains unclear. A recent EORTC analysis reported significantly increased cardiovascular disease per 1 Gy increase of mean heart radiation dose and per a 50-mg/m^2 increase of cumulative anthracycline dose.[30] Another recent study focusing on serious cardiac events in younger HL survivors found an increase of grade 3 to 5 events after cardiac RT doses $\geq$ 35 Gy but not after doses of 15 to 35 Gy or with cumulative anthracycline doses of $\geq$ 250 mg/m.[2,6] These findings emphasize the need for thorough and prolonged follow-up after initial HL therapy and a critical re-evaluation of the available follow-up data.

The reported analyses are limited by the fact that updated information beyond the last previous analysis has been provided for only approximately half of the eligible patients. Lack of long-term follow-up is an issue observed in many trials, particularly for early-stage HL. Many years after successful therapy, patients tend to continue follow-up with their general practitioners, and some do not attend follow-up visits at all after a certain time. To ensure that results of the main study objectives are not significantly biased by this information lag, we compared patients with and without new information and found no relevant differences in baseline characteristics or allocation between treatment arms. We also found only a few patients ($<$ 1%) with the only new information being the diagnosis of an adverse event, making over-reporting of relapses, SN, or deaths unlikely. Hence, we feel that our analysis contributes significantly to the understanding of the long-term course of disease after contemporary first-line strategies in early-stage HL.

In conclusion, our updated analyses confirm the excellent efficacy of two cycles of ABVD followed by 20 Gy IF-RT in early-favorable HL and support the approach to apply an intensified chemotherapy regimen in early-unfavorable HL to improve tumor control and to enable a reduction of RT intensity. The documented impact of treatment-related SN and organ toxicity on long-term survival in all four trials underlines the persistent need to develop less toxic but equally effective approaches for the treatment of HL.

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REFERENCES

1. Engert A, Franklin J, Eich HT, et al: Two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine plus extended-field radiotherapy is superior to radiotherapy alone in early favorable Hodgkin's lymphoma: Final results of the GHSG HD7 trial. J Clin Oncol 25:3495-3502, 2007
2. Noordijk EM, Carde P, Dupouy N, et al: Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: Long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials. J Clin Oncol 24:3128-3135, 2006
3. Behringer K, Josting A, Schiller P, et al: Solid tumors in patients treated for Hodgkin's disease: A report from the German Hodgkin Lymphoma Study Group. Ann Oncol 15:1079-1085, 2004
4. Ng AK, Bernardo MV, Weller E, et al: Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: Long-term risks and risk factors. Blood 100:1989-1996, 2002
5. Schaapveld M, Aleman BM, van Eggermond AM, et al: Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. N Engl J Med 373:2499-2511, 2015
6. Bhakta N, Liu Q, Yeo F, et al: Cumulative burden of cardiovascular morbidity in paediatric, adolescent, and young adult survivors of Hodgkin's lymphoma: An analysis from the St Jude Lifetime Cohort Study. Lancet Oncol 17:1325-1334, 2016
7. Ng AK, Bernardo MP, Weller E, et al: Long-term survival and competing causes of death in patients with early-stage Hodgkin's disease treated at age 50 or younger. J Clin Oncol 20:2101-2108, 2002
8. Schneider U, Sumila M, Robotka J, et al: Dose-response relationship for breast cancer induction at radiotherapy dose. Radiat Oncol 6:67, 2011
9. Aleman BM, van den Belt-Dusebout AW, Klokman WJ, et al: Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol 21:3431-3439, 2003
10. Engert A, Plütschow A, Eich HT, et al: Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med 363:640-652, 2010
11. Engert A, Schiller P, Josting A, et al: Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: Results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. J Clin Oncol 21:3601-3608, 2003
12. Fermé C, Eghbali H, Meerwaldt JH, et al: Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. N Engl J Med 357:1916-1927, 2007
13. Sasse S, Klimm B, Görgen H, et al: Comparing long-term toxicity and efficacy of combined-modality treatment including extended- or involved-field radiotherapy in early-stage Hodgkin's lymphoma. Ann Oncol 23:2953-2959, 2012
14. Eich HT, Diehl V, Görgen H, et al: Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: Final analysis of the German Hodgkin Study Group HD11 trial. J Clin Oncol 28:4199-4206, 2010
15. Pulte D, Jansen L, Gondos A, et al: Improved population level survival in younger Hodgkin lymphoma patients in Germany in the early 21st century. Br J Haematol 164:851-857, 2014
16. Meyer RM, Gospodarowicz MK, Connors JM, et al: ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. N Engl J Med 366:399-408, 2012
17. Franklin J, Pluetschow A, Paus M, et al: Second malignancy risk associated with treatment of Hodgkin's lymphoma: Meta-analysis of the randomised trials. Ann Oncol 17:1749-1760, 2006

18. Kumar S: Second malignant neoplasms following radiotherapy. Int J Environ Res Public Health 9:4744-4759, 2012

19. Swerdlow AJ, Higgins CD, Smith P, et al: Second cancer risk after chemotherapy for Hodgkin's lymphoma: A collaborative British cohort study. J Clin Oncol 29:4096-4104, 2011

20. Behringer K, Goergen H, Hitz F, et al: Omission of dacarbazine or bleomycin, or both, from the ABVD regimen in treatment of early-stage favourable Hodgkin's lymphoma (GHSG HD13): An open-label, randomised, non-inferiority trial. Lancet 385:1418-1427, 2015

21. Buerkle C, Goergen H, Muller H, et al: Patient preferences - survey of Hodgkin lymphoma survivors on treatment-associated burden and side effects. Presented at the European Hematology Association 2016, Copenhagen, Denmark, 2016

22. von Tresckow B, Plütschow A, Fuchs M, et al: Dose-intensification in early unfavorable Hodgkin's lymphoma: Final analysis of the German Hodgkin Study Group HD14 trial. J Clin Oncol 30:907-913, 2012

23. Olszewski AJ, Shrestha R, Castillo JJ: Treatment selection and outcomes in early-stage classical Hodgkin lymphoma: Analysis of the National Cancer Data Base. J Clin Oncol 33:625-633, 2015

24. 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 372:1598-1607, 2015

25. Raemaekers JM, André MP, Federico M, et al: Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: Clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol 32:1188-1194, 2014

26. Herbst C, Engert A: Meta-analyses of early-stage Hodgkin lymphoma. Acta Haematol 125:32-38, 2011

27. De Bruin ML, Sparidans J, van't Veer MB, et al: Breast cancer risk in female survivors of Hodgkin's lymphoma: Lower risk after smaller radiation volumes. J Clin Oncol 27:4239-4246, 2009

28. Gilbert ES, Stovall M, Gospodarowicz M, et al: Lung cancer after treatment for Hodgkin's disease: Focus on radiation effects. Radiat Res 159:161-173, 2003

29. van Leeuwen FE, Klokman WJ, Veer MB, et al: Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. J Clin Oncol 18:487-497, 2000

30. Maraldo MV, Giusti F, Vogelius IR, et al: Cardiovascular disease after treatment for Hodgkin's lymphoma: An analysis of nine collaborative EORTC-LYSA trials. Lancet Haematol 2:e492-e502, 2015

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Long-Term Follow-Up of Contemporary Treatment in Early-Stage Hodgkin Lymphoma: Updated Analyses of the German Hodgkin Study Group HD7, HD8, HD10, and HD11 Trials

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