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ORIGINAL REPORT

Eight Cycles of Escalated-Dose BEACOPP Compared With Four Cycles of Escalated-Dose BEACOPP Followed by Four Cycles of Baseline-Dose BEACOPP With or Without Radiotherapy in Patients With Advanced-Stage Hodgkin's Lymphoma: Final Analysis of the HD12 Trial of the German Hodgkin Study Group

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See accompanying editorial on page 4215 and article on page 4227

A B S T R A C T

Purpose

Eight cycles of BEACOPP$_{escalated}$ (escalated dose of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) followed by radiotherapy (RT) to initial bulk or residual tumor mass is the German Hodgkin Study Group standard of care for advanced-stage Hodgkin's lymphoma (HL). However, treatment-related toxicity is a concern, and the role of RT in this setting is unclear. The HD12 study thus aimed to reduce toxicity while maintaining efficacy.

Patients and Methods

In this prospectively randomized multicenter trial, eight cycles of BEACOPP$_{escalated}$ was compared with four cycles of BEACOPP$_{escalated}$ followed by four cycles of the baseline dose of BEACOPP (BEACOPP$_{baseline}$; 4 + 4), and RT with no RT in the case of initial bulk or residual disease. The study was designed to exclude a difference in 5-year freedom from treatment failure (FFTF) rate of 6%.

Results

Between January 1999 and January 2003, 1,670 patients age 16 to 65 years were enrolled onto the HD12 study. At 5 years, FFTF was 86.4% in the BEACOPP$_{escalated}$ arm and 84.8% in the 4 + 4 arm (difference, −1.6%; 95% CI, −5.2% to 1.9%), and overall survival was 92% versus 90.3% (difference, −1.7%; 95% CI, −4.6% to 1.1%). Deaths related to acute toxicity of chemotherapy were observed in 2.9% of patients (BEACOPP$_{escalated}$, n = 19; 4 + 4, n = 27). FFTF was inferior without RT (90.4% *v* 87%; difference, −3.4%; 95% CI, −6.6% to −0.1%), particularly in patients who had residual disease after chemotherapy (difference, −5.8%; 95% CI, −10.7% to −1.0%), but not in patients with bulk in complete response after chemotherapy (difference, −1.1%; 95% CI, −6.2% to 4%).

Conclusion

The reduction of BEACOPP to the 4 + 4 regimen did not substantially reduce severe toxicity but might decrease efficacy. Our results do not support the omission of consolidation RT for patients with residual disease. Alternative strategies for improving the risk-to-benefit ratio for patients with advanced HL are needed.

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INTRODUCTION

Hodgkin's lymphoma (HL) has become a curable malignancy for the majority of patients. For those diagnosed with advanced-stage disease, chemotherapy (CT) with six to eight cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) followed by radiotherapy (RT) to areas of initial bulk or residual disease was regarded as standard of care for many years. With this approach, 5-year failure-free survival rates of up to 65% were reported with long-term survival of

75%.[1-5] Approximately 50% of relapsing patients can be rescued by high-dose CT.[6,7]

To improve the prognosis for advanced-stage HL, the German Hodgkin Study Group (GHSG) developed the dose-dense BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) in both a standard-dose and an escalated-dose version. Both of these versions were subsequently compared with the standard at that time, which was COPP (cyclophosphamide, vincristine, procarbazine, and prednisone) alternating with ABVD.[8] The escalated-dose version of BEACOPP ($BEACOPP_{escalated}$) improved the 5-year freedom from treatment failure (FFTF) from 68% for COPP-ABVD to 88% and demonstrated a clear survival benefit of 11% at 10 years.[9]

Although tumor control with $BEACOPP_{escalated}$ is excellent, there is some concern about acute and late toxicity.[10] $BEACOPP_{escalated}$ induced severe neutropenia in most patients, with WHO grade 4 infections in 8% and treatment-related mortality in 1.7%.[8,9] In addition, an increased rate of secondary leukemia compared with treatment by COPP-ABVD was documented (cumulative incidence, 3.2% *v* 0.4% at 10 years). Late toxicity of combined-modality treatment in patients with HL also includes other second malignancies such as solid tumors, which are at least in part due to RT.[11,12] Thus,

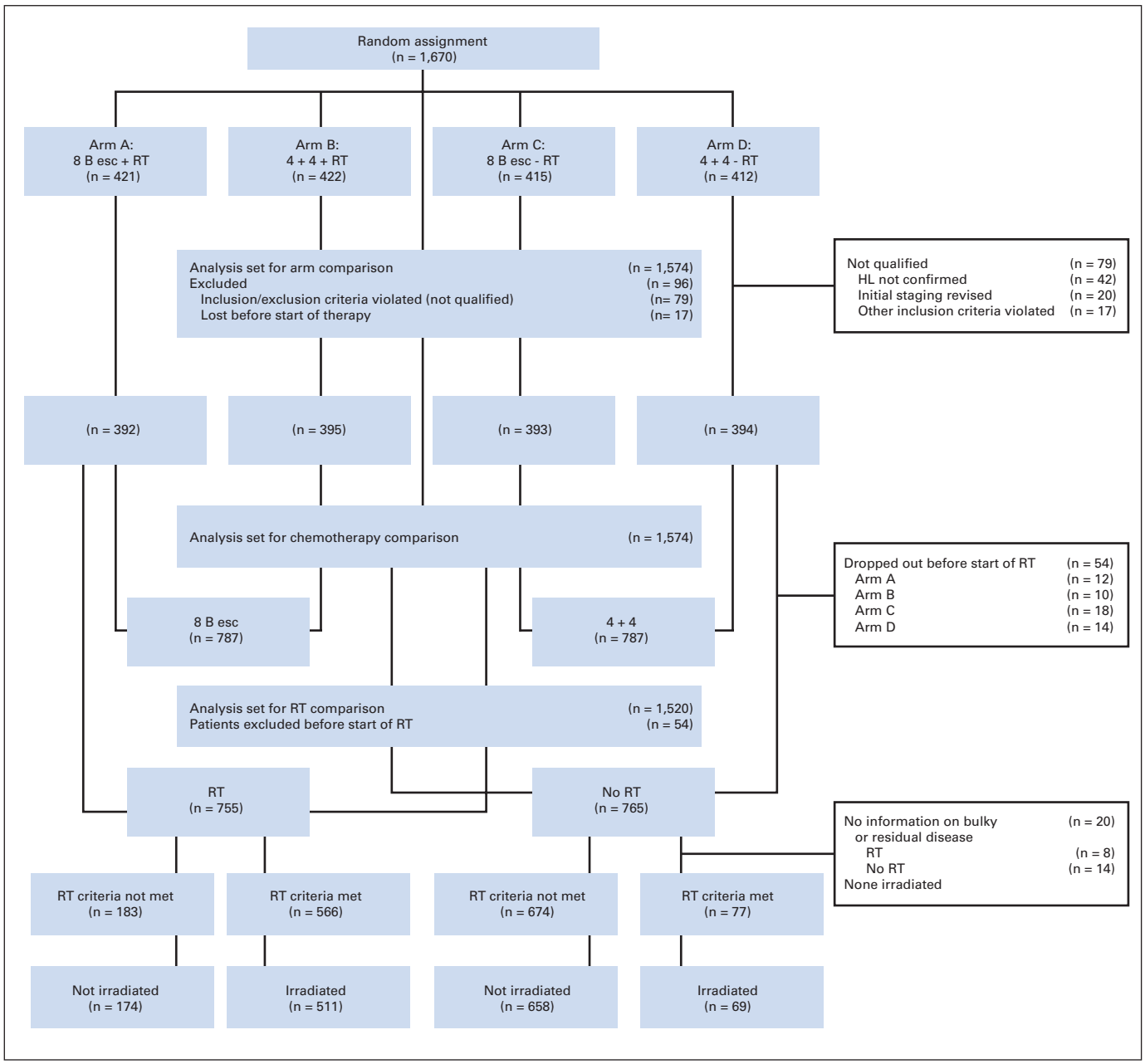

Fig 1. CONSORT diagram. Patient flow of the HD12 study. Radiotherapy (RT) criteria: bulky disease ≥ 5 cm or residual disease ≥ 1.5 cm in the restaging after chemotherapy, skeletal involvement with instability risk in the RT arms, or inadequate response to chemotherapy or skeletal involvement with instability risk in the no-RT arms. Criteria are based on the central review decision, if available. Otherwise, documentation of the study center is the relevant source. 8 B esc, eight cycles of escalated-dose BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone); 4 + 4, four cycles of escalated-dose BEACOPP plus four cycles of baseline-dose BEACOPP; HL, Hodgkin's lymphoma.

reducing treatment-related toxicity associated with $BEACOPP_{escalated}$ and additional RT while maintaining efficacy of this regimen has become a major challenge.

Therefore, the rationale of the HD12 study was to decrease toxicity associated with eight cycles of $BEACOPP_{escalated}$ and RT while maintaining efficacy. We thus compared eight cycles of $BEACOPP_{escalated}$ with four cycles of $BEACOPP_{escalated}$ followed by four cycles of the baseline dose of BEACOPP ($BEACOPP_{baseline}$; 4 + 4) as well as consolidation RT to initial bulk and residual disease with no additional RT to these locations in a 2 × 2 factorial design.

PATIENTS AND METHODS

Patients

Newly diagnosed patients with histology-proven HL in the following clinical stages were included: Ann Arbor stage IIB with a large mediastinal mass (≥ one third of the maximal thoracic diameter) or extranodal lesions and stages III or IV. Inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, age 16 to 65 years, HIV negativity, and freedom from concurrent disease disallowing protocol treatment. Patients were registered and treated in 320 hospitals and outpatient centers in Germany, Czech Republic, Switzerland, Austria, and the Netherlands. Review of biopsy specimens by a panel of expert lymphoma pathologists was part of the protocol and was performed in 1,368 patients (86.9%). Staging and pretreatment evaluation included medical history; physical examination; chest radiography; computed tomography scans of the neck, chest, and abdomen; ultrasound of the abdomen; bone marrow biopsy; skeletal scintigraphy; serum chemistry; lung function test; ECG; and echocardiography. Written informed consent was approved by the local ethics committee and was signed by each patient before enrollment. The study was conducted in accordance with the Declaration of Helsinki.

Study Design and CT

The study had two major objectives: first, concerning CT, to assess the influence of replacing the last four of the eight cycles of $BEACOPP_{escalated}$ with four cycles of $BEACOPP_{baseline}$. Second, concerning RT, to evaluate the impact of consolidating RT in patients responding to CT who had initial bulky disease (> 5 cm) or residual disease ≥ 1.5 cm. Consequently, patients were randomly assigned to one of four arms: arm A: eight cycles of $BEACOPP_{escalated}$ followed by RT for responding patients with initial bulk or residual tumor; arm B: eight cycles of $BEACOPP_{escalated}$ without consolidation RT to such lesions; arm C: four cycles of $BEACOPP_{escalated}$ followed by four cycles of $BEACOPP_{baseline}$ (4 + 4) with consolidation RT for responding patients with initial bulk or

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Treatment Arm								CT Comparison				RT Comparison			
	8 $B_{escalated}$ + RT (n = 392)		8 $B_{escalated}$ − RT (n = 395)		4 + 4 + RT (n = 393)		4 + 4 − RT (n = 394)		8 $B_{escalated}$ ± RT (n = 787)		4 + 4 ± RT (n = 787)		Chemotherapy + RT (n = 755)		Chemotherapy − RT (n = 765)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years																
Mean	35.6		35.3		35.7		35.4		35.5		35.5		35.2		34.8	
Standard deviation	12.9		12.8		12.8		12.9		12.8		12.8		12.5		12.5	
Female	153	39.0	153	38.7	157	39.9	147	37.3	306	38.9	304	38.6	300	39.7	296	38.7
Ann Arbor stage*																
IIB	67	17.1	63	15.9	67	17.0	58	14.7	130	16.5	125	15.9	134	17.7	121	15.8
IIIA	78	19.9	92	23.3	88	22.4	89	22.6	170	21.6	177	22.5	159	21.1	177	23.1
IIIB	100	25.5	108	27.3	105	26.7	109	27.7	208	26.4	214	27.2	193	25.6	207	27.1
IVA	40	10.2	30	7.6	41	10.4	38	9.6	70	8.9	79	10.0	79	10.5	67	8.8
IVB	107	27.3	102	25.8	91	23.2	100	25.4	209	26.6	191	24.3	189	25.0	193	25.2
Risk factors																
Large mediastinal mass	117	29.8	113	28.6	112	28.5	105	26.6	230	29.2	217	27.6	225	29.8	216	28.2
Extranodal involvement	77	19.6	79	20.0	88	22.4	86	21.8	156	19.8	174	22.1	157	20.8	161	21.0
At least three nodal areas involved	328	83.7	335	84.8	322	81.9	320	81.2	663	84.2	642	81.6	622	82.4	635	83.0
High ESR	268	68.4	272	68.9	262	66.7	276	70.1	540	68.6	538	68.4	510	67.5	534	69.8
Bulk ≥ 5 cm	253	64.5	231	58.5	249	63.4	246	62.4	484	61.5	495	62.9	487	64.5	467	61.0
WHO activity index of 2	21	5.4	30	7.7	30	7.7	21	5.3	51	6.5	51	6.5	46	6.1	45	5.9
IPS (90.9%, n = 1,430)																
0-1	118	32.8	118	33.6	117	33.0	103	28.3	236	33.2	220	30.6	228	33.1	220	31.6
2-3	188	52.2	169	48.1	172	48.5	208	57.1	357	50.2	380	52.9	350	50.8	369	53.0
4-7	54	15.0	64	18.2	66	18.6	53	14.6	118	16.6	119	16.6	111	16.1	107	15.4
Reference histology (86.9%; n = 1,368)																
Nodular sclerosing cHL	198	58.8	203	58.0	179	53.8	202	58.0	401	58.4	381	55.9	369	56.9	396	58.3
Mixed cellularity cHL	86	25.5	100	28.6	98	29.4	91	26.1	186	27.1	189	27.8	177	27.3	183	27.0
Nodular lymphocyte–predominant HL	19	5.6	6	1.7	8	2.4	15	4.3	25	3.6	23	3.4	25	3.9	19	2.8
Lymphocyte-rich cHL	7	2.1	8	2.3	10	3.0	8	2.3	15	2.2	18	2.6	15	2.3	16	2.4
Lymphocyte-depleted cHL	4	1.2	5	1.4	6	1.8	6	1.7	9	1.3	12	1.8	9	1.4	11	1.6
HL, not classified	20	5.9	24	6.9	31	9.3	24	6.9	44	6.4	55	8.1	49	7.6	48	7.1
HL, uncertain	3	0.9	4	1.1	1	0.3	2	0.6	7	1.0	3	0.4	4	0.6	6	0.9

Abbreviations: 8 $B_{escalated}$, eight cycles of escalated-dose BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone); 4 + 4, four cycles of escalated-dose BEACOPP plus four cycles of baseline-dose BEACOPP; cHL, classical Hodgkin's lymphoma; CT, chemotherapy; ESR, erythrocyte sedimentation rate; HL, Hodgkin's lymphoma; IPS, International Prognostic Score; RT, radiotherapy.
*One patient reclassified as stage IIA.

residual tumor; or arm D: four cycles of $BEACOPP_{escalated}$ followed by four cycles of $BEACOPP_{baseline}$ without consolidation RT to such lesions (Fig 1). Randomization was stratified according to participating center, tumor stage (IIB or IIIA *v* IIIB or IV), age (< 50 *v* ≥ 50 years), International Prognostic Score (IPS; < 3 *v* ≥ 3), and bulky disease. BEACOPP CT was administered as described elsewhere.[8]

RT

A central diagnostic panel monitored the trial as previously described.[13] To protect against bias, panel members were blinded for the treatment arm, reviewed the baseline and interim CT scans, and gave consensus recommendations regarding consolidation RT: either not to irradiate the patient irrespective of randomly assigned arm (responding patients without initial bulk and without residual tumor $\geq$ 1.5 cm), to continue as randomly assigned (responding patients with initial bulk or residual tumor), or to irradiate the patient irrespective of randomly assigned arm (patients with inadequate response, ie, $<$ 50% tumor reduction in case of bulky disease). Patients in the second group were randomly assigned to additional RT (arms A and C) and all inadequately responding patients received 30 Gy RT to the sites of initial bulky disease and/or any residual tumor $\geq$ 1.5 cm. In addition, patients with bone lesions with instability risk always received a recommendation for RT.

Assessment of Response and Toxicity

Restaging was performed after four and eight cycles of BEACOPP and 4 to 6 weeks after the end of RT. Complete remission (CR) was defined as disappearance of all clinical and radiologic disease. Partial remission was defined as reduction of at least 50% of maximal diameter in major lesions. No change was either a decrease of less than 50% or an increase of less than 25%. An increase of more than 25% or any new lesions occurring during or within 3 months after the end of treatment was classified as progressive disease. Toxicities were documented according to the WHO toxicity criteria and National Cancer Institute Common Toxicity Criteria (NCI-CTC) criteria adapted for RT.

Statistical Methods

The primary end point of the trial was FFTF defined as progression during treatment, salvage treatment after lack of CR, considerable additional nonstudy treatment (but not additional RT in the no-RT arms), relapse, and death from any cause counted as failure events. PFS (progression-free survival) was also calculated (progression or relapse of HL and death from any cause).

A 2 $\times$ 2 factorial design with pooling of treatment arms was used to test the hypotheses of noninferiority of the experimental interventions (4 + 4, no RT): arms A and B versus arms C and D for the CT comparison, and arms A and C versus arms B and D for the RT comparison. Assuming a 5-year FFTF rate of 80% to 85% for the standard treatment, the study was designed to exclude a difference in 5-year FFTF rates of 6% in pooled comparisons for both treatment modalities assuming no interaction. Analysis was based on the intention-to-treat principle, with nonqualified patients being excluded on the basis of information available before random assignment or when no study treatment was given. FFTF, PFS, and overall survival (OS) were compared between groups with the Kaplan-Meier method and the log-rank test, stratified by other treatment modality in pooled comparisons. Hazard ratios (HRs) were calculated by using the Cox regression model, always adjusting for other modality. Outcomes were compared by using Fisher's exact test. An unplanned analysis was performed to identify subgroups that required RT. All calculations were made by using SAS, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Between January 1999 and January 2003, a total of 1,670 patients age 16 to 65 with a median follow-up of 78 months were randomly assigned to treatment groups. Ninety-six patients were excluded (Fig 1) resulting in 1,574 eligible patients (787 in each of two groups). Fifty-four additional patients were excluded from the RT comparison because of disease progression or death before restaging after CT and central review (1,520 evaluable patients; 755 in the RT group and 765 in the no-RT group). Characteristics and risk factors were equally distributed between treatment arms (Table 1).

Central Panel Review and RT

In total, 1,085 of 1,520 patients (71%) were reviewed by the central diagnostic panel to evaluate their need for additional RT. Of these, 19% (n = 207) did not have bulky disease or residual tumors and thus did not require RT. RT performed on the basis of inadequate CT response had to be performed in 148 patients (14%), including 25 patients with bone involvement and risk of fracture. From the remaining 730 patients (67%) with treatment strategies based on random assignment, 93% (n = 608) had bulky disease at baseline, and 65% had residual tumors $\geq$ 1.5 cm. Adherence to recommended treatment strategies was good, with 94% of patients being treated according to protocol on the basis of central panel review or local center diagnostics (Fig 1).

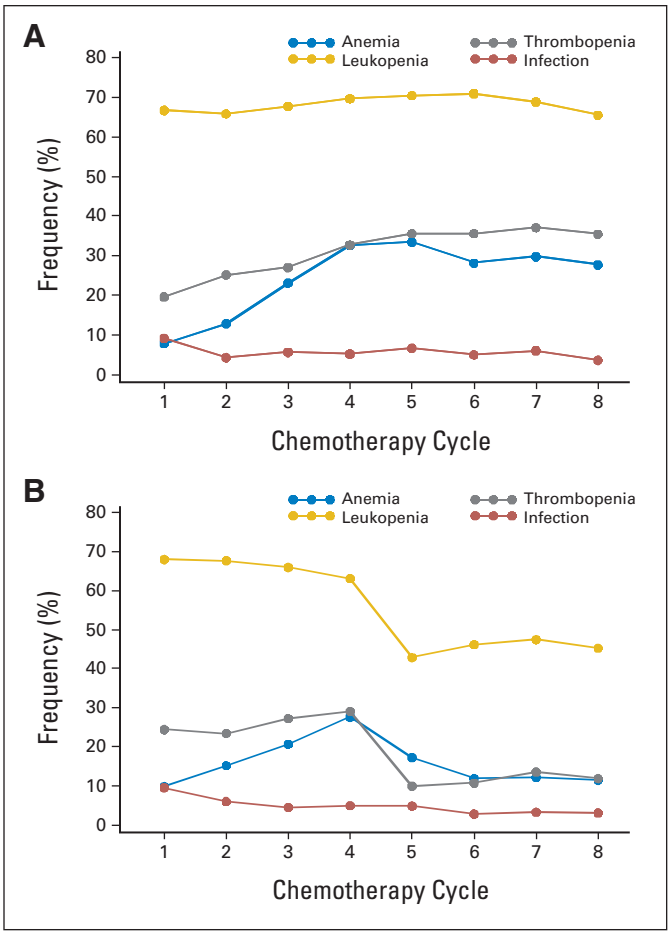

Fig 2. Acute toxicity (grade 3 or 4) per cycle. (A) Eight cycles of escalated-dose BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone). (B) Four cycles of escalated-dose BEACOPP followed by four cycles of baseline-dose BEACOPP.

Toxicity

WHO grade 3 to 4 toxicity related to CT was observed in 1,440 (97%) of 1,479 patients. The most prominent differences between pooled CT arms were anemia (65% [$BEACOPP_{escalated}$] *v* 50% [4 + 4]) and thrombocytopenia (66% *v* 51%). Other frequent toxicities were leukocytopenia (91%) and infections (28%). The proportion of patients with severe hematologic toxicities decreased in the last four cycles of the 4 + 4 regimen (Fig 2). Death related to acute toxicity during CT was observed in 2.9% of patients: 19 during $BEACOPP_{escalated}$ and 27 during 4 + 4 treatment (Table 2). The majority of deaths in the 4 + 4 group (21 of 27; 78%) occurred during the first four cycles of $BEACOPP_{escalated}$, although six deaths

Table 2. Causes of Death, Secondary Malignancies, and Outcome Parameters

	Treatment Arm														CT Comparison						RT Comparison					
	8 $B_{escalated}$ + RT (n = 392)				8 $B_{escalated}$ − RT (n = 395)				4 + 4 + RT (n = 393)				4 + 4 − RT (n = 394)				8 $B_{escalated}$ ± RT (n = 787)		4 + 4 ± RT (n = 787)		Difference		Chemotherapy + RT (n = 755)		Chemotherapy − RT (n = 765)		Difference	
Variable	No.	%	%	95% CI (%)	No.	%	%	95% CI (%)	No.	%	%	95% CI (%)	No.	%	%	95% CI (%)	No.	%	No.	%	%	95% CI (%)	No.	%	No.	%	%	95% CI (%)
Total No. of deaths	36	9.2			37	9.4			42	10.7			41	10.4			73	9.3	83	10.5			50	6.6	54	7.1		
Toxicity of primary chemotherapy	8	2.0			11	2.8			17	4.3			10	2.5			19	2.4	27	3.4			2	0.3	5	0.7		
Infection	7	1.8			7	1.8			11	2.8			9	2.3			14	1.8	20	2.5			1	0.1	4	0.5		
Cardiovascular					2	0.5			3	0.8							2	0.3	3	0.4								
Bleomycin toxicity					1	0.3			1	0.3			1	0.3			1	0.1	2	0.3			1	0.1	1	0.1		
Cerebral bleeding									1	0.3									1	0.1								
Unclear	1	0.3			1	0.3			1	0.3							2	0.3	1	0.1								
Hodgkin's lymphoma	8	2.0			7	1.8			7	1.8			16	4.1			15	1.9	23	2.9			12	1.6	18	2.4		
Secondary malignancy	14	3.6			9	2.3			10	2.5			3	0.8			23	2.9	13	1.7			24	3.2	12	1.6		
Toxicity of salvage treatment	1	0.3			2	0.5			2	0.5			3	0.8			3	0.4	5	0.6			2	0.3	5	0.7		
Cardiovascular					1	0.3			3	0.8			4	1.0			1	0.1	7	0.9			3	0.4	4	0.5		
Other	5	1.3			7	1.8			3	0.8			5	1.3			12	1.5	8	1.0			7	0.9	10	1.3		
Total No. of secondary malignancies	24	6.1			19	4.8			20	5.1			13	3.3			43	5.5	33	4.2			44	5.8	32	4.2		
AML/MDS	8	2.0			4	1.0			4	1.0			6	1.5			12	1.5	10	1.3			12	1.6	10	1.3		
5-year cumulative incidence*		1.6				0.8				0.8				1.3				1.2		1.0				1.2		1.1		
NHL	5	1.3			6	1.5			3	0.8			2	0.5			11	1.4	5	0.6			8	1.1	8	1.0		
Solid tumor	11	2.8			9	2.3			13	3.3			5	1.3			20	2.5	18	2.3			24	3.2	14	1.8		
Final treatment outcome†																												
CR/CRu	366	93.4			366	92.7			361	91.9			356	90.4			732	93.0	717	91.1			725	96.0	721	94.2		
PR	3	0.8			10	2.5			1	0.3			12	3.0			13	1.7	13	1.7			4	0.5	20	2.6		
NC					1	0.3			1	0.3			.	.			1	0.1	1	0.1			1	0.1	1	0.1		
Progression	7	1.8			2	0.5			13	3.3			13	3.3			9	1.1	26	3.3			15	2.0	11	1.4		
Death without staging	9	2.3			8	4.1			15	3.8			10	2.5			17	2.2	25	3.2			1	0.1	1	0.1		
Unknown/not done	7	1.8			8	4.1			2	0.5			3	0.8			15	1.9	5	0.6			9	1.2	11	1.4		
Recurrence																												
Progression including late progression	7	1.8			8	2.0			13	3.3			16	4.1			15	1.9	29	3.7			15	2.0	20	2.6		
Relapse	16	4.1			22	5.6			14	3.6			27	6.9			38	4.8	41	5.2			30	4.0	49	6.4		
Kaplan-Meier estimates																												
5-year OS rate			92.1	89.4 to 94.8			91.9	89.1 to 94.6			90.7	87.8 to 93.6			89.9	86.9 to 92.9					−1.7	−4.6 to 1.1					−1.1	−3.5 to 1.3
5-year PFS rate			88.5	85.3 to 91.8			86.5	83.0 to 90.0			86.6	83.2 to 90.0			83.5	79.7 to 87.2					−2.5	−6.0 to 1.0					−3.4	−6.6 to −0.2
5-year FFTF rate			87.2	83.8 to 90.6			85.6	82.0 to 89.2			86.6	83.1 to 90.0			83.1	79.3 to 86.8					−1.6	−5.2 to 1.9					−3.4	−6.6 to −0.1

Abbreviations: 8 $B_{escalated}$, eight cycles of escalated-dose BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone); 4 + 4, four cycles of escalated-dose BEACOPP plus four cycles of baseline-dose BEACOPP; AML, acute myeloid leukemia; CR, complete response; CRu, unconfirmed complete response; CT, chemotherapy; FFTF, freedom from treatment failure; MDS, myelodysplastic syndrome; NC, no change; NHL, non-Hodgkin's lymphoma; OS, overall survival; PFS, progression-free survival; PR, partial response; RT, radiotherapy.

*Allowing for death as competing risk.

†Final treatment outcome was defined as Hodgkin's lymphoma status at final restaging 4 to 6 weeks after completion of study treatment. If no additional treatment was given after non-CR and there was no progression of disease within 6 months, the final treatment outcome was retrospectively redefined as CRu.

occurred during or after the four cycles of $BEACOPP_{baseline}$. To a lesser extent, this also holds true for the first four cycles in the group assigned to eight cycles of $BEACOPP_{escalated}$ (11 of 19; 58%). Most deaths related to toxicity were due to infections (n = 34) or occurred in patients age ≥ 40 years. The highest mortality was observed in patients age 60 to 65 years (17 of 99; 17.2%) and in those with an IPS of 4 to 7 (data not shown). For patients younger than age 60 years, the rate was 2.0% (29 of 1,475 patients). By decade, the rate was lowest in the 16- to 19-year-old age group, and it increased for each decade. RT was well tolerated with only three grade 4 NCI-CTC toxicities in 575 patients (0.5%).

Secondary Malignancies

There were 76 (4.8%) secondary malignancies: 38 patients with solid tumors, 16 with non-Hodgkin's lymphoma, and 22 with acute myeloid leukemia. No differences in secondary neoplasia were observed between treatment arms or modalities (Table 2).

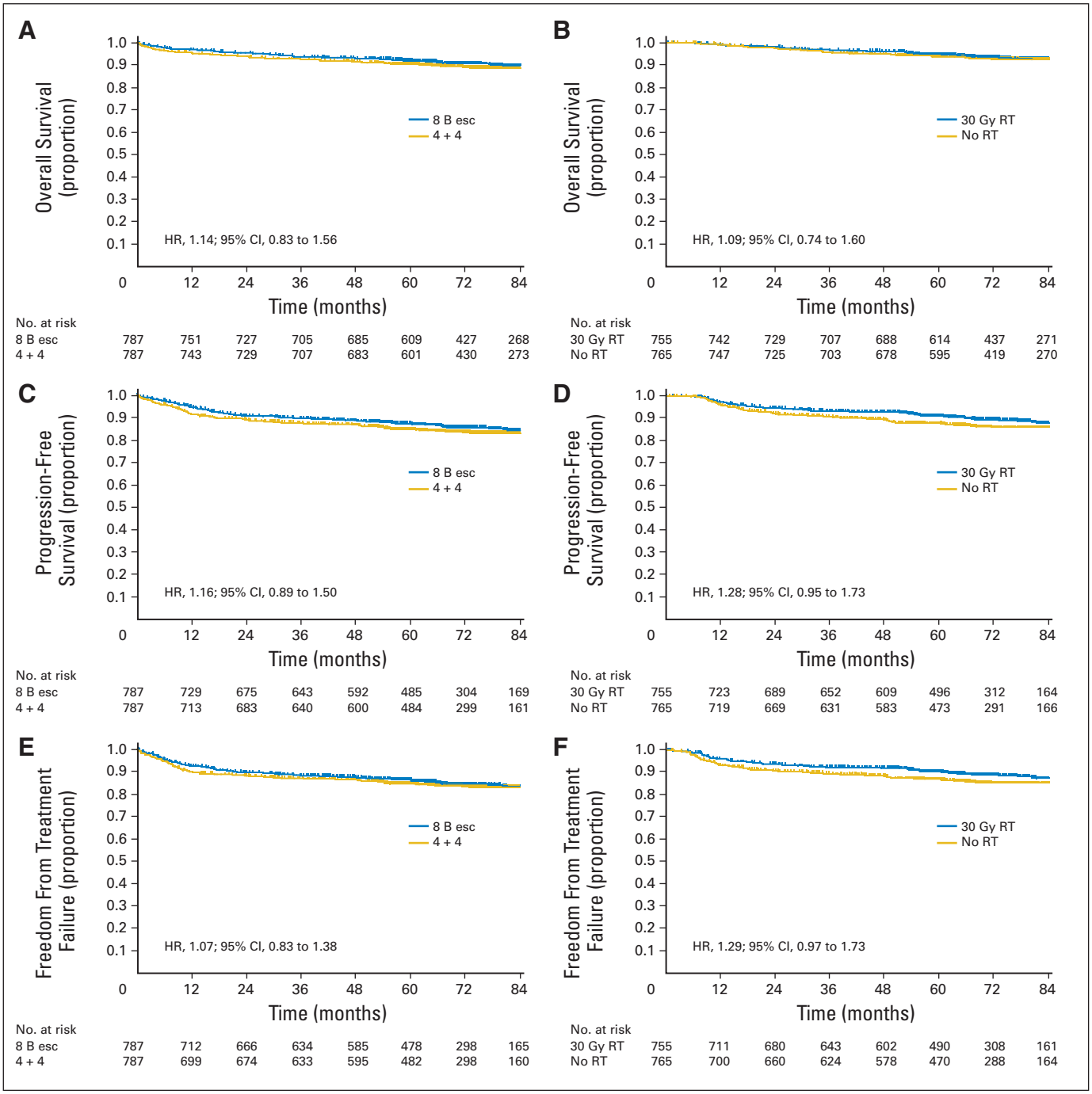

Fig 3. Kaplan-Meier estimates for (A, B) overall survival, (C, D) progression-free survival, and (E, F) freedom from treatment failure. Hazard ratios (HRs) adjusted for other treatment modality. 8 B esc, eight cycles of escalated-dose BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone); 4+4, four cycles of escalated-dose BEACOPP plus four cycles of baseline-dose BEACOPP; RT, radiotherapy.

Mortality

With a median follow-up for survival of 78 months, a total of 156 patients (9.9%) have died. Most frequent events were CT-related toxicity, followed by HL, secondary neoplasia, toxicity of salvage therapy, and cardiovascular mortality. There was no difference in terms of mortality between arms or modalities (Table 2).

Efficacy Outcome Parameters

Response rates after treatment were similar between both pooled CT and RT arms. Progressions, relapses, and number of deaths observed after a median of 69 months for efficacy outcomes are shown in Table 2. Only the rate of early progressive disease was significantly different (1.1% for $BEACOPP_{escalated}$ and 3.3% for 4 + 4; $P = .006$). At 5 years, FFTF was 85.6% (95% CI, 83.8% to 87.4%), and OS was 91.1% (95% CI, 89.7% to 92.6%) for the entire study cohort. The Kaplan-Meier plots for the CT and RT comparisons (OS, FFTF, and PFS) are shown in Figure 3. For the CT comparison, FFTF was 86.4% for $BEACOPP_{escalated}$ and 84.8% for 4 + 4 (difference, −1.6%; 95% CI, −5.2% to 1.9%); PFS was 87.5% and 85%, respectively (difference, −2.5%; 95% CI, −6% to 1%). 5-year OS was not different (92% [$BEACOPP_{escalated}$] *v* 90.3% [4+4]; difference, −1.7%; 95% CI, −4.6% to 1.1%). Analysis of PFS and OS by IPS groups and age decades revealed no significant difference between $BEACOPP_{escalated}$ and 4 + 4 treatment (data not shown).

For the RT comparison, the FFTF was 87% in the no-RT arms compared with 90.4% in the RT arms (difference, −3.4%; 95% CI, −6.6% to −0.1%; log-rank $P = .08$). Eleven percent of patients in the no-RT arms received RT according to the prespecified criteria (Fig 4). Subgroup analyses showed an inferior FFTF for patients with residual disease after CT without RT (difference, −5.8%; 95% CI, −10.7% to −1.0%; Fig 5); altogether, 22.9% of patients were irradiated in the no-RT arms. In contrast, omitting RT in patients with bulky disease in CR after CT was not detrimental (Fig 5).

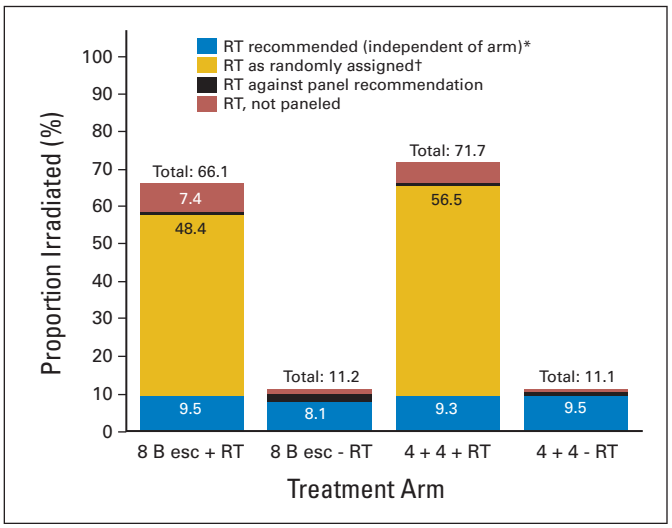

Fig 4. (*) Radiotherapy (RT) patients with inadequate chemotherapy response or bone involvement with fracture risk. (†) Responding patients with bulk ≥ 5 cm or residual tumor ≥ 1.5 cm. 8 B esc, eight cycles of escalated-dose BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone); 4+4, four cycles of escalated-dose BEACOPP plus four cycles of baseline-dose BEACOPP.

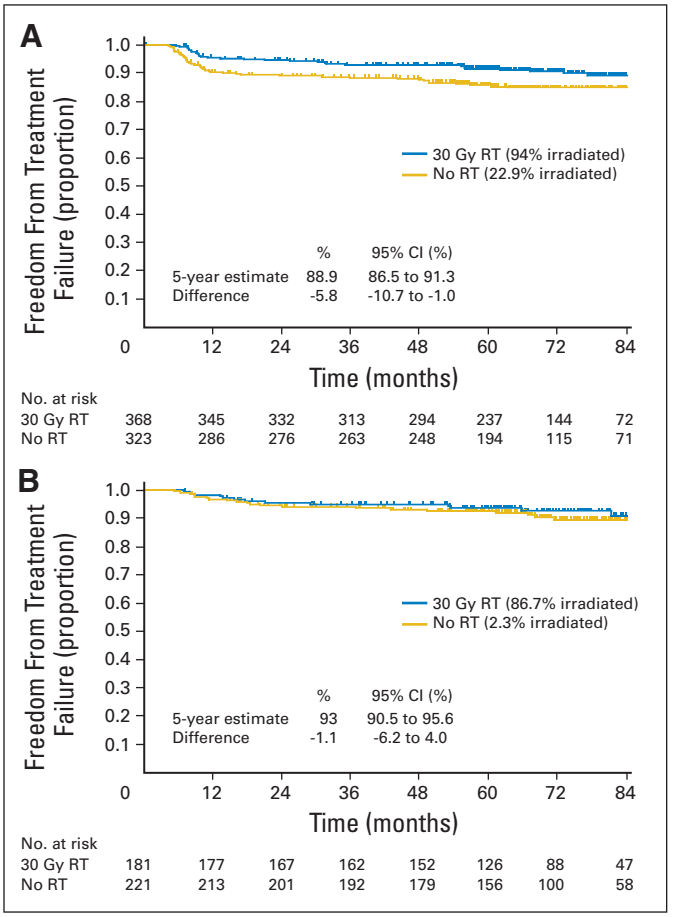

Fig 5. Subgroup analysis for radiotherapy (RT). (A) Patients with residual disease after chemotherapy (with or without bulky disease). (B) Bulky disease without residual disease after chemotherapy.

DISCUSSION

The HD12 trial evaluated the reduction of therapy intensity while maintaining efficacy. A total of 320 centers from five European countries included 1,670 patients in this randomized trial. Major findings to emerge from this trial are as follows: (1) The efficacy of $BEACOPP_{escalated}$ reported in the prior HD9 study was confirmed in the HD12 study, with an overall FFTF of 86% at 5 years. (2) The reduction of dose intensity from eight cycles of $BEACOPP_{escalated}$ to 4 + 4 resulted in a nonsignificant decrease in FFTF of 1.6%. However, significantly more patients experienced progressive disease with the 4 + 4 regimen (3.3% *v* 1.1%; $P = .006$). (3) Although the reduced dose of 4 + 4 resulted in less acute hematologic toxicity during cycles five to eight, this had no impact on the number of deaths related to acute toxicity. (4) Patients with residual disease after $BEACOPP_{escalated}$ benefited from consolidation RT, whereas this effect was not seen in patients with initial bulk who were in CR after CT.

HD12 confirmed the efficacy of $BEACOPP_{escalated}$ reported in the preceding HD9 trial.[8] In HD9, the improved outcome was largely due to the lower number of patients suffering from primary progression observed in 2% for eight cycles of $BEACOPP_{escalated}$ and 10% with eight cycles of COPP-ABVD. These patients have a particularly poor

outcome.[6] Compared with the standard arm of eight cycles of $BEACOPP_{escalated}$, there were also significantly more patients with early progression in the experimental 4 + 4 arm in HD12. Although this did not result in a significant difference in the primary end point of this study (FFTF $P = .6$), there is some concern about efficacy. This is supported by a randomized study recently published by Federico et al[14] who reported a PFS at 5 years of 81% (95% CI, 70% to 89%) by using four cycles of $BEACOPP_{escalated}$ followed by two cycles of $BEACOPP_{baseline}$. To avoid a gradual loss of efficacy, a more individualized and risk-adapted strategy might be needed. Therefore, the GHSG has introduced a personalized treatment strategy in its current HD18 trial, which uses a response-adapted design guided by positron emission tomography.[15-17]

Importantly, the cautious reduction of CT did not reduce treatment-related mortality. Although the number of events is too small to detect significant differences, surprisingly there were more events in the 4 + 4 arm. Overall treatment-related mortality was mainly because of neutropenic infections (74% of all CT-related deaths). The risk of treatment-related mortality steeply increased with age, ranging from less than 1% in patients younger than 40 years to 17.2% in those age 60 to 65 years. Consequently, the upper age limit within the GHSG was changed to 60 years, the internationally accepted lower age limit for so called "elderly" patients with HL. It is well known that the reduced tolerability of conventional CT of older patients with HL results in more severe toxicities, including fatal outcomes and the inability to maintain the scheduled dose density.[18-23] Aggressive approaches are obsolete in this patient cohort.[24] The GHSG has therefore changed the treatment strategy by introducing new and presumably less toxic drugs (gemcitabine, lenalidomide) in protocols for elderly patients.[25]

To reduce acute treatment-related toxicity for patients younger than age 60 years in the ongoing HD18 trial, an antibiotic prophylaxis has become mandatory, and pretreatment with dexamethasone in analogy to non-Hodgkin's lymphoma patients is allowed.[26] These measures might reduce the mortality associated with $BEACOPP_{escalated}$.

Other adverse effects such as secondary malignancies or infertility and hypogonadism are also of concern in the treatment of patients with HL. These toxicities are not necessarily reflected in the efficacy-related outcome parameters (FFTF, PFS, and OS), but they might substantially compromise patients' health and quality of life. With a median follow-up of 69 months, a comprehensive assessment of secondary malignancies in this trial is not possible. However, acute leukemia usually occurs within few years after completion of CT. In HD9, the 5-year cumulative incidence of acute leukemia was 2.2% after $BEACOPP_{escalated}$. This number is lower in HD12 (1.1%) but the total numbers are too small to allow sound conclusions. Undoubtedly, the leukemic risk of $BEACOPP_{escalated}$ is higher than with ABVD, warranting further critical observation. This is also true for gonadal toxicity caused by the alkylating agents in this regimen.[27-29] Although we did not prospectively investigate the gonadal function in this trial, the dose reduction in the 4 + 4 schedule might not be sufficient to substantially reduce infertility for both male and female patients.[29,30]

On the basis of the comparison of 5-year FFTF, the strategy to confine RT to patients with inadequate response only was inferior to irradiating all sites of initial bulk and residual disease (difference, −3.4%; lower bound of 95% CI, −6.6%). Although secondary comparisons were not significant (log-rank $P = .08$; HR, 1.29; 95% CI, 0.97 to 1.73), this is especially true because patients in all arms who had poor CT response were irradiated (11%). Their outcome would likely have suffered most without RT and thus, the HD12 results likely underestimate the total effect of additional RT. This means that consolidation RT cannot be entirely abandoned in advanced-stage HL, even after intensive CT. In addition, only 72% of all patients were centrally reviewed. This might bias the results for the entire study cohort. Consequently, we performed subgroup analyses that revealed a clearly inferior FFTF of −5.8% (95% CI, −10.7% to −1.0%) for patients without consolidation RT of residual disease after CT. This finding is in line with the recently published retrospective analysis of the United Kingdom Lymphoma Group (UKLG) LY09 trial.[31] There was, however, no FFTF difference between the two different RT strategies for patients with initial bulky disease who achieved CR after CT. In contrast, this cohort showed the best PFS of all subgroups indicating the predictive value of responsiveness to CT. Interestingly, this patient subgroup also had no significant benefit from additional RT in the UKLG LY09 trial (HR, 0.52; 95% CI, 0.21 to 1.27). Thus, these findings challenge the indication of RT for patients with initial bulk who achieve a CR after CT.

In conclusion, our results support neither the reduction of $BEACOPP_{escalated}$ to the 4 + 4 regimen nor the omission of RT for patients with residual disease after CT. However, our results show that consolidation RT can be safely omitted in patients with initial bulky disease who achieve a CR after CT. To optimize the risk-to-benefit ratio for individual patients with advanced HL, alternative strategies must be evaluated. An individual de-escalation strategy that uses interim positron emission tomography after two cycles of $BEACOPP_{escalated}$ is currently being tested in the GHSG HD18 trial. This concept will be challenged by ongoing studies investigating an escalation strategy after two cycles of ABVD.[32] However, both approaches have the potential to restrict aggressive CT to those patients who need it and will therefore hopefully further improve the outcome of patients with HL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Data analysis and interpretation: Peter Borchmann, Heinz Haverkamp
Manuscript writing: All authors
Final approval of manuscript: All authors

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