Published Ahead of Print on August 11, 2003 as 10.1200/JCO.2003.03.023

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

By Andreas Engert, Petra Schiller, Andreas Josting, Richard Herrmann, Peter Koch, Markus Sieber, Friederike Boissevain, Maike de Wit, Jörg Mezger, Eckhart Dühmke, Normann Willich, Rolf-Peter Müller, Bernhard F. Schmidt, Helmut Renner, Hans Konrad Müller-Hermelink, Beate Pfistner, Jürgen Wolf, Dirk Hasenclever, Markus Löffler, and Volker Diehl

Purpose: **To investigate whether radiotherapy can be reduced without loss of efficacy from extended field (EF) to involved field (IF) after four cycles of chemotherapy.**

Patients and Methods: **Between 1993 and 1998, patients with newly diagnosed early-stage unfavorable HD were enrolled onto this multicenter study. Patients were randomly assigned to receive cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) + doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) for two cycles followed by radiotherapy of 30 Gy EF + 10 Gy to bulky disease (arm A) or 30 Gy IF + 10 Gy to bulky disease (arm B).**

Results: **Of 1,204 patients randomly assigned to treatment, 1,064 patients were informative and eligible for the arm comparison (532 patients in arm A; 532 patients in arm B). The median observation time was 54 months. Five years after random assignment, the overall survival (OS_{ran}) for all eligible patients was 91% and freedom from treatment failure ($FFTF_{ran}$) was 83%. Survival rates at 5 years after start of radiotherapy revealed no differences for arms A and B, respectively, in terms of FFTF (85.8% and 84.2%) and OS at 5 years (90.8% and 92.4%). There also were no differences between arms A and B, respectively, in terms of complete remission (98.5% and 97.2%), progressive disease (0.8% and 1.9%), relapse (6.4% and 7.7%), death (8.1% and 6.4%), and secondary neoplasia (4.5% and 2.8%). In contrast, acute side effects including leukopenia, thrombocytopenia, nausea, gastrointestinal toxicity, and pharyngeal toxicity were more frequent in the EF arm.**

Conclusion: **Radiotherapy volume size reduction from EF to IF after COPP + ABVD chemotherapy for two cycles produces similar results and less toxicity in patients with early-stage unfavorable HD.**

J Clin Oncol 21.

IN EUROPE, depending on stage and risk factors, patients with Hodgkin's lymphoma (HD) are allocated to early-stage favorable, early-stage unfavorable, and advanced-stage risk groups. The early-stage favorable group usually comprises stages IA and IIA without risk factors. Early-stage unfavorable includes those patients in stages I and II with risk factors such as large mediastinal mass, three or more involved lymph node areas, high erythrocyte sedimentation rate (ESR), advanced age, and B symptoms as well as selected patients with stage IIIA disease. Most stage III and IV patients are classified in the advanced-stage risk group. These definitions vary slightly among study groups and study generation, but in general, have become comparable.[1]

For patients with early-stage unfavorable HD, a number of clinical trials comparing radiotherapy, chemotherapy, or combined-modality treatment identified a combined approach of four to six cycles of chemotherapy followed by radiotherapy as superior in terms of response rates and long-term outcome.[2-4] Disease-free survival with combined-modality treatment in these patients ranges from 65% to 75% and overall survival (OS) is approximately 80% at 5 years.

The basic principles of modern radiotherapy in HD were developed by Henry Kaplan at Stanford University in the early 1960s.[5,6] His studies revealed that lymph nodes adjacent to clinically involved sites were at high risk for subsequent involvement if left untreated. These findings were used for a better definition of radiation fields and still represent the current standard in modern radiotherapy. The smallest volume commonly used is the involved-field (IF) volume in which all clinically involved lymph nodes of a given region are irradiated.

From the First Department of Internal Medicine, University Hospital of Cologne and Department of Radiotherapy, University Clinic of Cologne, Cologne; Medical Department and Department of Radiotherapy, University Clinic Münster, Münster; University Clinic Nürnberg, Nürnberg; University Clinic Hamburg, Hamburg; St Vincentius Hospital Karlsruhe, Karlsruhe; Department of Radiation Oncology, Ludwig Maximilian Universität München, München; Center of Radiotherapy, Katharinenhospital, Stuttgart; Center of Radiotherapy, Klinikum Nord, Nürnberg; Institute of Pathology, University of Würzburg; Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany; and University Hospital, Basel, Switzerland, for the Swiss Group for Clinical Cancer Research.

Submitted March 4, 2003; accepted July 16, 2003.

Supported in part by the Deutsche Krebshilfe and by the Swiss Group for Clinical Cancer Research.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Volker Diehl, MD, Department I of Internal Medicine, University Hospital Cologne, Cologne 50924, Germany; e-mail: v.diehl@uni-koeln.de.

0732-183X/03/2119-1/$20.00

Pages 3601 – 3608

The extended field (EF) includes the IF as well as all adjacent lymph node regions. When radiotherapy alone was given, a superior outcome was documented in prospectively randomized studies for those patients treated with the EF technique compared with the IF technique.[6,7]

During the last decades, most clinical trials in early-stage unfavorable patients aimed to improve both chemotherapy and radiotherapy to possibly reduce toxicity, thereby maintaining response rates and OS. The good prognosis of these patients (with many sustained complete remissions) created an increasing need to consider long-term side effects of treatment, including second cancers, infertility, or other organ damage.

On the basis of prior results of our group,[8] the aim of this HD8 study was to evaluate a possible reduction in the volume of tissue irradiated in patients with early-stage unfavorable HD. We report the final results of this multicenter study in which 1,204 patients were prospectively randomly assigned to receive either cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) + doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) for two cycles followed by 30 Gy EF + 10 Gy bulk or COPP + ABVD for two cycles followed by 30 Gy IF + 10 Gy bulk.

PATIENTS AND METHODS

Patients

Between February 1993 and March 1998, newly diagnosed patients with histology-proven HD in clinical stages I and II with one or more risk factors as well as patients in clinical stage IIIA without any risk factors were enrolled onto this multicenter study. Risk factors included large mediastinal mass (at least one third of maximal thorax diameter), extranodal disease, massive splenic involvement (diffuse infiltrations or more than five focal lesions), elevated ESR (≥ 50 mm/h in patients without B symptoms; ≥ 30 mm/h in patients with B symptoms), and more than two lymph node areas of involvement. Patients in stage IIB were included onto this study if they had an elevated ESR or more than two involved lymph node areas and none of the other risk factors. In addition, patients had to be between 16 and 75 years of age, in good general condition (Karnofsky performance status > 70%), not previously treated, and free of concurrent disease. Patients with impaired heart, lung, liver, or kidney function; previous malignant disease; or HIV-positive status were not included. Minimal hematologic requirements included a WBC count more than 3,000/μL and platelet count more than 100,000/μL. Patients were also excluded from the study if they had chronic obstructive lung disease, if they were pregnant or lactating, or if they had HD as part of a composite lymphoma. Biopsy material was centrally reviewed by at least one member of a panel of six HD expert pathologists. All patients had to give written informed consent before study entry. Routine staging procedures included medical history; physical examination; chest radiography; computed tomography of the chest, abdomen, and pelvis; bone marrow biopsy; CBC; serum chemistry; lung function tests; and echocardiography.

Study Design

Patients were registered and treated in 212 hospitals and practices in Germany, Switzerland, Austria, and the Czech Republic. After clinical staging was performed, patients were centrally randomly assigned via telephone to one of the two arms as follows: arm A, two cycles of COPP alternating with two cycles of ABVD followed by 30 Gy radiotherapy in the extended-field (EF) volume + 10 Gy to initial bulky disease; arm B, COPP + ABVD for two cycles followed by 30 Gy radiotherapy in the involved-field (IF) volume + 10 Gy to initial bulky disease. Each patient was randomly assigned to arm A or B at a ratio of 1:1. Stratified random allocation of patients was performed using a computerized random number generator according to the process of minimization described by Pocock.[9]

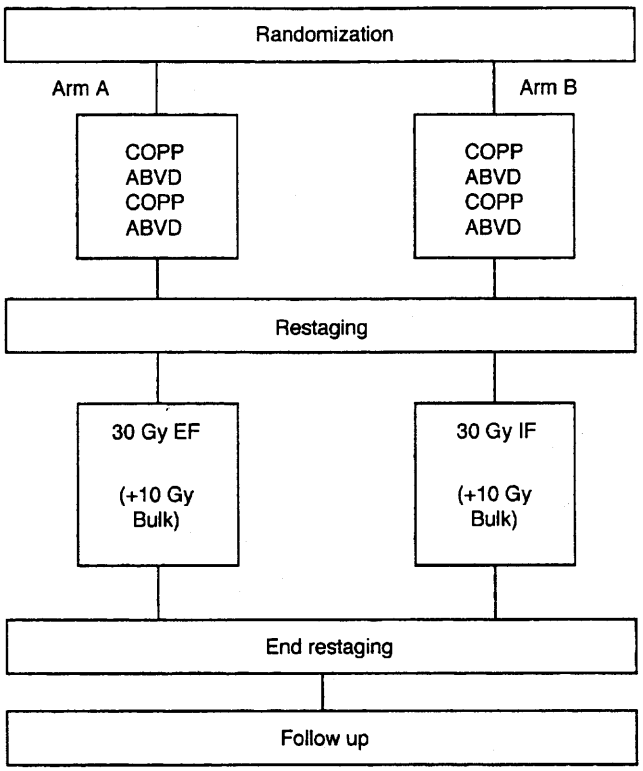


Fig 1. Design of the HD8 trial. Patients with histology-proven Hodgkin's lymphoma in following stages were included. EF, extended field; IF, involved field; COPP, cyclophosphamide 650 mg/m² days 1 + 8, vincristine 1.4 mg/m² days 1 + 8, procarbazine 100 mg/m² days 1 to 14, and prednisone 40 mg/m² day 1 to 14; ABVD, doxorubicin 25 mg/m² days 29 + 43, bleomycin 10 mg/m² days 29 + 43, vinblastine 6 mg/m² day 29 + 43, and dacarbazine 375 mg/m² day 29 + 43.

Stratification factors included center, stage (supradiaphragmatic stage I and II, infradiaphragmatic stage I and II, or stage IIIA) and laparotomy (yes or no).

Chemotherapy

The design of the HD8 trial is shown in Figure 1. Patients were scheduled to receive a total of two cycles of COPP, a regimen previously reported by our group, alternating with two cycles of ABVD.[8] COPP was given from days 1 to 14 followed by ABVD on days 29 and 43 (Table 1). Treatment was repeated on day 57 and postponed if the leukocyte count was less than 2,500/μL or the platelet count was less than 80,000/μL on the day the patient was scheduled for re-treatment. For these patients, therapy was postponed between 3 and 14 days until recovery. In patients with continuing leucopenia or thrombocytopenia after a 2-week delay, all drugs with the exception of vincristine, prednisone, and bleomycin were reduced to 75% of the planned dose. Granulocyte colony-stimulating factor was given if clinically indicated according to the American Society of Clinical Oncology guidelines until leukocyte recovery.[10]

Radiotherapy

Before treatment, all sites of disease were defined and documented after consent among the treating physicians. Appropriate radiotherapy according to treatment arm was then planned centrally by the expert radiation oncology review panel. Allocated radiotherapy was initiated only in those patients who received protocol chemotherapy, had sufficient hematopoietic reserves, and did not show progressive disease after the end of chemotherapy. Patients received 30 Gy in either the EF technique (arm A) or IF technique (arm B) over a period of 3 to 3.5 weeks. Additional radiotherapy of 10 Gy was given during the fourth week to areas of initial bulky disease. Single-fraction size was 1.8 to 2.0 Gy given five times a week.

Table 1. COPP + ABVD Regimen

Regimen	Dosage (mg/m²)
COPP	
Cyclophosphamide*	650 IV days 1 + 8
Vincristine†	1.4 IV days 1 + 8
Procarbacine	100 PO days 1-14
Prednisone	40 PO days 1-14
ABVD	
Doxorubicin	25 IV days 29 + 43
Bleomycin	10 IV days 29 + 43
Vinblastine	6 IV days 29 + 43
Dacarbazine	375 IV days 29 + 43

Abbreviations: COPP, cyclophosphamide, vincristine, procarbazine, and prednisone; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; IV, intravenous; PO, oral.

*Uromitexan also is required, with 20% of cyclophosphamide dose IV hour 0 and hours 4 and 8. Under any circumstances, the patient should drink 2.5 L of liquids on the day of therapy.

†Maximum 2 mg total.

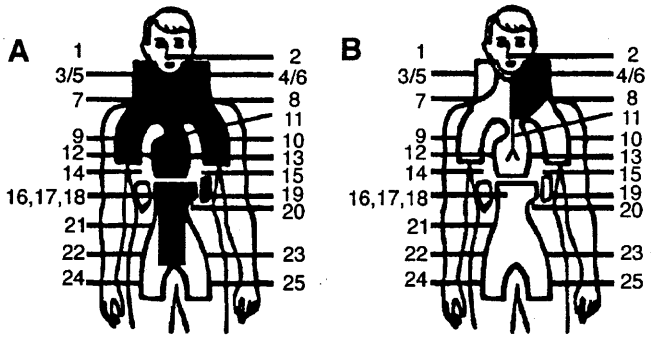


Fig 2. Radiotherapy (RT) volume for a patient with Hodgkin's disease stage I in the left neck: disease involvement lower cervical region on the left side. (A) Typical extended-field RT volume (mantle field plus the paraaortic area, splenic hilar region, and spleen); (B) for the same patient the involved-field RT volume includes the whole left neck (upper and lower cervical region plus the supra- and infraclavicular lymph node regions).

EF radiation therapy (EF-RT) included the involved lymph node region as well as all anatomic and functional adjacent but clinically uninvolved lymph node regions. Generally, EF-RT indicated treatment delivered to regions on both sides of the diaphragm. For a supradiaphragmatic involvement (such as the mediastinal nodes), the EF-RT volume included a mantle field and also the paraaortic area (inferior border L4–5 interspace), the splenic hilar region, and the spleen if necessary. The mantle field extended from the inferior portion of the mastoid to the level of the insertion of the diaphragm. Individually contoured lung blocks were designed to conform to the patient's anatomy and tumor extension. The first group of treatments adding up to 16 Gy total radiation were delivered to the initial mediastinal-hilar lymph node enlargement. Subsequently, the mediastinal-hilar contour was modified and included only the extension after chemotherapy. A subdiaphragmatic radiation field was similar to an inverted Y, including the retroperitoneal and pelvic lymph nodes and the spleen. In addition, a mantle field without the upper cervical and axillary region was irradiated (T field).

If there was an involvement in the upper cervical region or the Waldeyer's ring only, radiation therapy was administered to supradiaphragmatic regions only. The EF-RT consisted of a mantle field plus additional Waldeyer fields. If only the inguinal nodes were involved, the EF-RT was applied in the inverted-Y technique.

IF radiotherapy (IF-RT) was administered to all initially involved lymph node regions. All of these regions were treated in one field, if possible (for example, a T field for supraclavicular and mediastinal involvement). The procedure for the design of the field contour of bulky mediastinal disease was the same as for EF-RT.

Examples of radiotherapy for a patient with stage I disease in the left neck are given in Figure 2 for EF-RT (A) and IF-RT (B), respectively.

Evaluation of Response and Follow-Up

Patients were monitored during therapy by physical examination, chest x-ray, and routine blood tests. The first restaging including control of all initially enlarged lymph-nodes by computed tomography scans was performed 2 weeks after the last chemotherapy and was immediately followed by radiotherapy. The final restaging was conducted 8 weeks after the end of radiotherapy. Patients were then observed at 3-month intervals during the first year, every 4 months in the second year, every 6 months in the third and fourth year, and annually thereafter. Treatment outcome was assessed at 3 months after the end of protocol treatment. Freedom from treatment failure (FFTF) for the arm comparison was defined as the time from the start of radiotherapy to the first of the following events: progression during radiotherapy, lack of complete remission (or complete remission with residual abnormalities) at the end of protocol treatment, relapse, or death from any cause.

The arm comparison for OS was also based on the time calculated from the start of radiotherapy until death from any cause or date of last information, respectively. In addition, FFTF and OS for all eligible patients were calculated as the time from random assignment to treatment ($FFTF_{ran}$ and OS_{ran}, respectively). Definitions of complete remission, partial remission, and no change were used as previously described.[8] Progressive disease was defined as appearance of new lesions or B symptoms, or increase in any lesion of 25% in the largest diameter under treatment or within 3 months after the end of treatment. Relapse was defined as appearance of new lesions, or as reappearance of initial lesions or B symptoms after a period of at least 3 months of complete remission.

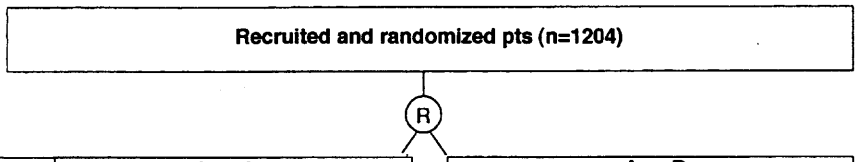
Statistical Analysis

The trial was designed to test the hypothesis that 30 Gy in the IF technique was equivalent to 30 Gy in the EF technique in patients responding to two cycles of COPP + ABVD. To exclude an inferiority of arm B of $\geq$ 8% in terms of FFTF at 5 years after start of radiotherapy (significance level of 5%), an initial target recruitment of more than 500 patients was calculated to provide a statistical power of 80% given a true difference of 0%.[11] Subsequently, an independent model calculation was developed to estimate FFTF rates after combined-modality treatment depending on the irradiated volume and the number of chemotherapy cycles. The model indicated a small true difference between IF-RT and EF-RT after four cycles of chemotherapy. To meet the objectives and still discriminate an 8% difference from a true difference of approximately 2% to 3% in this trial, a more precise estimation of the difference between the treatment arms, and therefore at least 1,000 patients were required. As a consequence, the steering committee extended the target recruitment to 1,100 patients.

Interim analyses were planned after 3, 4, and 5 years, and the final analysis was planned after 7.5 years. A restricted procedure as proposed by Whitehead[12] was designed to monitor the trial and to regulate possible early stopping.

The main end point of the trial was FFTF after the start of radiotherapy. Thus, only patients who received chemotherapy and subsequently proceeded to radiotherapy were included in the treatment comparison (informative patients). Patients with progressive disease before radiotherapy or those who discontinued chemotherapy for other reasons were not included in this comparison and were replaced in the randomization process. Comparisons between treatment groups including outcome, cause of death, and number of secondary malignancies were performed for informative patients on an intention-to-treat basis.

Analysis of acute toxicities only included informative patients who had sufficient documentation. Furthermore, the analysis of acute toxicities during radiotherapy did not include patients who switched treatment arms or discontinued radiotherapy because of reasons other than toxicity (0.5%).



	Arm A 2x (COPP+ABVD) + 30Gy EF (+10 Gy Bulk)	Arm B 2x (COPP+ABVD) + 30Gy IF (+10 Gy Bulk)
Number randomized	**602**	**602**
Exclusions from overall analysis: not eligible	14 Review not HD 22 Clinical exclusion criteria 1 No pts consent	11 Review not HD 20 Clinical exclusion criteria
=> Number eligible and includes in overall results	**565**	**571**
Did not receive the intended chemotherapy:	5 Patients wish 28 substantially more or other therapy	6 Patients wish 33 substantially more or other therapy
=>Not informative for arm comparison	33	39
Received chemotherapy and started Radiotherapy (informative)	518 Fully 14 Partially	519 Fully 10 Partially
=>Number Informative for arm comparison	**532**	**532**

Fig 3. Flow of participants through the HD8 study. EF, extended field; IF, involved field; COPP, cyclophosphamide, vincristine, procarbazine, and prednisone; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; HD, Hodgkin's disease.

Therefore, 914 patients (86%) were included. The Mann-Whitney *U* test was used for arm comparisons of acute toxicity (WHO grades 1 to 4).

Survival data (FFTF, $FFTF_{ran}$, OS, and OS_{ran}) were analyzed using the Kaplan-Meier method.[13] The log-rank test was used for comparison of survival time data between treatment arms. Furthermore, a multivariate analysis of FFTF was performed using Cox proportional hazards regression to reassess the treatment comparison and allow for the influence of prognostic factors.[14] To confirm the results gained by informative patients only, arm comparisons were repeated for all eligible patients $FFTF_{ran}$ and OS_{ran} were applied.

RESULTS

Patient Characteristics

A total number of 1,204 patients were randomly assigned to treatment arms. Figure 3 presents the flow of patients through the various stages of the trial. Sixty-eight patients were not qualified and were excluded: reasons for exclusion were incorrect staging (n = 33), review pathology diagnosis indicated that disease was not HD (n = 25), severe concomitant disease (n = 4), patient's wish (n = 1), and other clinical exclusion criteria (n = 5). From a total of 1,136 eligible patients, 72 patients discontinued the study before starting radiotherapy because of progressive disease (n = 27), severe protocol violation (n = 19), patient's wish (n = 11), concomitant disease or incorrect staging at time of inclusion (n = 14), and unknown reason (n = 1). The characteristics of these patients are similar according to treatment arm, as shown in Table 2. Eight informative patients swapped treatment arms (arm A to arm B: patient's wish [n = 2], protocol violation [n = 1]; arm B to arm A: patient's wish [n = 1], protocol violation [n = 4]). These patient cases were included in the analysis according to their randomization arm. Thus, a total of 1,064 patients were informative for arm comparison (532 patients in each arm). Importantly, data on response and follow-up were available for all of these patients (100%). As indicated in Table 3, the characteristics were well balanced between the two arms. Most patients were younger than 50 years (83%), were in stage II (89%), and had a nodular sclerosis histology (55%). A total of 76% of patient cases were reviewed by the expert pathology reference panel.

Toxicity

The most commonly observed toxicities during chemotherapy in arms A and B, respectively, included WHO grade 3 to 4 leucopenia (60.1% and 56.3% of patients), alopecia (25.2% and 24.1% of patients), and nausea (10.1% and 11.0% of patients; data not shown). Each other type of acute toxicity occurred in less than 2% of patients. In keeping with the fact that all patients received identical treatment during this phase of the study, no difference was observed between the two treatment arms.

Table 2. Patient Characteristics and Reason for Therapy Discontinuation of Eligible Patients (noninformative patients)

Characteristic	No. of Patients in Arm A (n = 33)	No. of Patients in Arm B (n = 39)
Age, years		
15-49	22	29
50-75	11	10
Sex		
Female	14	20
Male	19	19
Stage		
I	5	4
II	28	32
III		3
B symptoms present	17	13
Laparotomy performed	1	4
Reason for discontinuation		
Progression	11	16
Protocol violation	9	10
Patient's wish	5	6
Concomittant disease or incorrect staging at time of inclusion	8	6
Accident (drowned)	—	1

Table 3. Characteristics of Informative Patients According to Treatment Arm

Characteristic	% of Patients in Arm A (n = 532)	% of Patients in Arm B (n = 532)
Age, years		
< 20	10.3	9.0
20-29	35.1	36.8
30-39	24.6	26.9
40-49	12.8	11.8
50-59	8.6	7.5
60-75	8.5	7.9
Median	31.3	30.7
Sex		
Female	51.9	49.7
Male	48.1	50.2
Stage		
IA	5.6	4.5
IB	3.4	2.6
IIA	66.5	67.5
IIB	22.0	23.1
IIIA	2.4	2.3
Risk factor		
Large mediastinal mass	17.3	19.4
Massive spleen involvement	0.4	0.4
Extranodal involvement	7.1	7.5
High ESR	47.4	49.6
≥ 3 lymph node areas	65.8	64.3
Laparotomy performed	4.5	3.2
Karnofsky performance status		
90-100	93.0	93.2
70-80	4.7	4.9
Review histology		
Lymphocyte predominant	1.3	1.5
Lymphocyte rich	0.6	0.4
Nodular sclerosis	53.9	56.1
Mixed cellarity	13.9	13.5
Lymphocyte depleted	0.6	0.2
Unclassifiable or other	5.6	3.9

Abbreviation: ESR, erythrocyte sedimentation rate.

The acute toxicities during radiotherapy are summarized in Table 4. Patients treated with EF radiotherapy (arm A) compared with IF radiotherapy (arm B), respectively, more often developed nausea (62.5% and 29.1%; $P < .001$), pharyngeal toxicity (49.1% and 40.5%; $P = .001$), leukopenia (49.1% and 33.3%; $P < .001$), thrombocytopenia (16.7% and 5.5%; $P < .001$), and gastrointestinal toxicity (17.5% and 4.1%; $P < .001$).

Causes of death during the study and in the follow-up period are shown in Table 5. A total of 43 informative patients in arm A died (8.1%) compared with 34 informative patients in arm B (6.4%; $P = .344$). There were 12 patients in each arm who died as a result of progressive disease. Twenty patients died as a result of secondary malignancies (12 and eight patients in arms A and B, respectively). The total number of secondary malignancies included with acute myelocytic leukemia or myelodysplastic syndrome (seven and two), nine non-Hodgkin's lymphoma (five and four), and 21 solid tumors (12 and nine). As shown in Table 6, there were a total of 24 secondary malignancies in arm A (4.6%) compared with 15 in arm B (2.8%; $P = .191$).

Table 4. Acute Toxicity During Radiotherapy

Toxicity	Grade	% of Patients in Arm A (n = 470)	% of Patients in Arm B (n = 444)	P
Skin	1-2	47.0	48.4	
	3-4	1.9	2.0	
Nausea or emesis	1-2	54.9	27.9	< .001
	3-4	7.7	1.4	
Pharynx	1-2	47.9	39.6	.001
	3-4	1.3	0.7	
Esophagus	1-2	44.3	43.0	
	3-4	1.5	0.9	
Leukopenia	1-2	44.5	31.1	< .001
	3-4	4.5	2.3	
Larynx	1-2	24.7	21.4	
	3-4	0.4	0.2	
Thrombopenia	1-2	15.3	5.4	< .001
	3-4	1.3	0.2	
Gastrointestinal	1-2	16.6	4.1	< .001
	3-4	0.9	0.2	
Anemia	1-2	9.1	6.5	
	3-4	0.6	0.0	
Pulmonary	1-2	6.2	4.1	
	3-4	0.2	—	
Infection	1-2	5.3	2.3	
	3-4	0.6	0.2	

Treatment Outcome and Survival Rates

The median observation time was 55 months in both treatment groups (range, 0.7 to 100.7 months). The OS_{ran} of all 1,136 eligible patients in this study was 91.1% after 5 years, with an $FFTF_{ran}$ of 82.6%. From the group of informative patients (n = 1,064) treated with COPP + ABVD for two cycles followed by radiotherapy, 524 of 532 (98.5%) of patients in arm A achieved complete remission compared with 517 of 532 (97.2%) patients in arm B. In addition, there also was no difference in terms of partial remission (0.6% in arm A and 0.4% in arm B) or progressive disease (0.8% in arm A and 1.9% in arm B), as shown in Table 7. Survival rates at 5 years after start of radiotherapy revealed no difference between arms A and B, respectively, in terms of OS (90.8% and 92.4%; difference [EF − IF] = −1.6; 95% confidence interval −5.6 to 2.5) or FFTF (85.8% and 84.2%). The difference (EF − IF) in FFTF was 1.6% with an upper 95% confidence limit of 5.9%. Thus, an inferiority of IF of more than 6% compared with EF can be ruled out. The Kaplan-Meier plots for FFTF and OS are shown in Figures 4 and 5, respectively.

Regarding the quality of radiotherapy, there were no significant differences between EF and IF techniques in terms of

Table 5. Causes of Death of Informative Patients According to Treatment Arm

Cause of Death	Arm A (n = 532)		Arm B (n = 532)	
	No.	%	No.	%
Hodgkin's disease	12	2.3	12	2.3
Acute toxicity (primary therapy)	2	0.4	—	—
Acute toxicity (salvage therapy)	2	0.4	3	0.6
Secondary malignancy	12	2.3	8	1.5
Heart or lung	5	0.9	7	1.3
Other or unknown	10	1.9	4	0.8
Overall	43	8.1	34	6.4

Table 6. Secondary Malignancies of Informative Patients According to Treatment Arm

Malignancy	Arm A (n = 532)		Arm B (n = 532)	
	No.	%	No.	%
AML or MDS	7	1.3	2	0.4
NHL	5	0.9	4	0.8
Solid tumor	12	2.3	9	1.7
Overall	24	4.5	15	2.8

Abbreviations: AML, acute myelocytic leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma.

technical aspects, radiated volume, or dose volume. In addition, when patients with protocol violations during radiotherapy were compared with those without protocol violation, there was no difference in terms of response, FFTF, or OS.

DISCUSSION

In the HD8 study reported in this article, 1,204 patients with early-stage unfavorable HD were randomly assigned to receive COPP + ABVD for two cycles and either 30 Gy EF + 10 Gy on bulky sites (arm A) or 30 Gy IF + 10 Gy on bulky sites (arm B). A total of 1,136 patients were eligible for the final analysis. The following findings emerge from this study. First, there was no difference in treatment outcome between the two arms, both when only those 1,064 patients were considered who proceeded to the radiotherapy part of the treatment and when all 1,136 eligible patients were included in the intent-to-treat analysis patients. The OS at 5 years was 90.8% in arm A and 92.4% in arm B; FFTF was 85.8% in arm A and 84.2% in arm B. An inferiority of IF in terms of FFTF of more than 6% can therefore be ruled out. Second, there also were no differences in terms of overall response rates, early progression rates, or relapse. Third, more toxicity during radiotherapy (including leukopenia, thrombocytopenia, gastrointestinal toxicity, pharyngeal toxicity, and nausea) was observed in the EF arm. On the basis of these results, the German Hodgkin's Study Group (GHSG) regards IF radiotherapy as the standard in the context of four courses of chemotherapy in early-stage unfavorable HD.

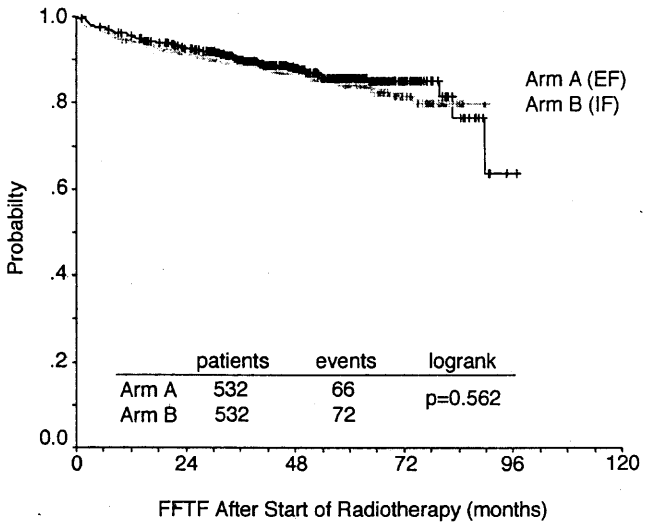


Fig 4. Kaplan-Meier analysis of freedom from treatment failure (FFTF) after start of radiotherapy according to treatment arm. Number of patients and events in each arm are given. EF, extended field; IF, involved field.

The risk of severe long-term toxicity for HD patients undergoing combined-modality treatment includes coronary artery disease,[15] pericarditis,[15] gonadal dysfunction,[16] and other complications such as fatigue.[17] In recent years, however, most concern has been attributed to the induction of second malignancies comprising acute leukemias, non-Hodgkin's lymphoma, and solid tumors.[18-23] The combined use of radiotherapy and chemotherapy generally might be associated with an increased risk for secondary malignancies when compared with one modality alone. However, there is a more pronounced risk when chemotherapy is combined with large-field radiotherapy such as

Table 7. Treatment Outcome, Events for FFTF, and Survival Rates After 5 Years According to Treatment Arm

	Arm A (n = 532)		Arm B (n = 532)	
	No.	%	No.	%
Treatment outcome				
CR	524	98.5	517	97.2
PR	3	0.6	2	0.4
NC	—	—	1	0.2
Progression	4	0.8	10	1.9
Unknown	1	0.2	2	0.4
Relapse	34	6.4	41	7.7
Event for FFTF	66	12.4	72	13.5
Survival				
FFTF				
Rate	85.8		84.2	
95% CI	82 to 88		80 to 88	
OS				
Rate	90.8		92.4	
95% CI	88 to 94		90 to 95	

Abbreviations: FFTF, freedom from treatment failure; CR, complete remission; PR, partial remission; NC, no change; OS, overall survival.

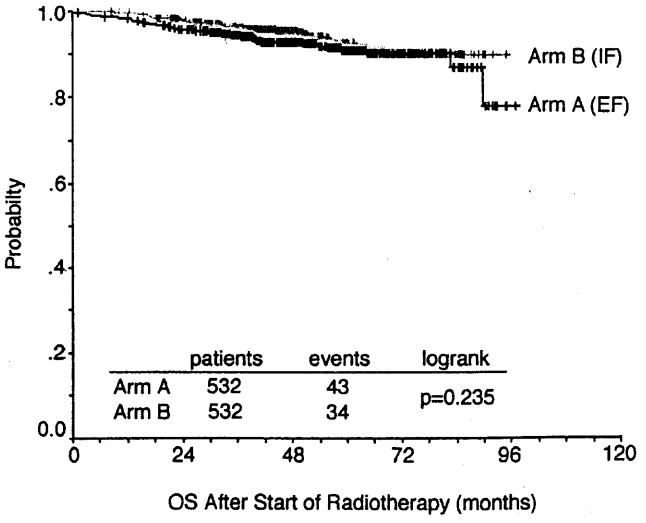


Fig 5. Kaplan-Meier analysis of overall survival (OS) after start of radiotherapy according to treatment arm. Number of patients and events in each arm are given. EF, extended field; IF, involved field.

EF or subtotal nodal radiotherapy (STLI). The relative risk is estimated to range from 2 to 6. This risk may be worse in younger patients, particularly for the development of breast cancer.[24] More recently, van Leeuwen et al[25] showed that the risk of breast cancer grossly depends on the menopausal status and, more importantly, on the radiation dose given. Patients receiving more than 38.5 Gy had a relative risk for breast cancer of 7.3 compared with a relative risk of 1.8 for those receiving less than 24 Gy ($P < .05$). Thus, there is a strong need to improve on the combined-modality treatment concepts, in terms of both chemotherapy and radiotherapy.

To date, the number of second malignancies observed in the HD8 study, with a total of 1,204 patients included, was 24 in the EF arm (4.5%) and 15 in the IF arm (2.8%). Among these were solid tumors (12 and nine patients, respectively), non-Hodgkin's lymphoma (five and four patients), and acute leukemias (seven and two patients). Although this study indicates that the reduction of field size has not compromised the efficacy of treatment, it might take more time to distinguish a significant reduction of long-term side effects because of the smaller volume irradiated.

In preceding studies, the GHSG had randomly assigned responding patients in early unfavorable stages to either 40 or 20 Gy EF + 20 Gy IF (HD1) with no outcome difference.[26] In the follow-up trial (HD5), patients received 30 Gy EF + 10 Gy on bulky sites.[8] These trials demonstrated that radiation dose in the EF can safely be reduced to at least 30 Gy (with 10 Gy on bulky tumors) when given after COPP + ABVD for two cycles. Similar to the study reported in this article, other groups have aimed at improving combined-modality treatment for HD patients in early unfavorable stages. The cooperative study reported by Zittoun et al[27] compared six cycles of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) sandwiched around 40 Gy of radiotherapy applied either with the IF or EF technique. In a total of 173 patients evaluated, there was no difference in terms of disease-free survival (87% for IF and 93% for EF) and overall survival (92% for IF and 91% for EF). An Italian study headed by the Milan group entered 140 patients onto a randomized study comparing STLI with IF radiotherapy after four cycles of ABVD. With a median follow-up of 87 months, treatment outcome was similar in both arms (freedom from progression 97% and 94%; survival 93% and 94%, respectively).[28] In the H8U trial, the European Organization for Research and Treatment of Cancer compared six cycles of MOPP + doxorubicin, bleomycin, and vinblastine (ABV) + 36 Gy IF with four cycles of MOPP + ABV + 36 Gy IF and four cycles MOPP + ABV + STLI. Again, there was no difference among the three arms in terms of response rates, failure-free survival, and OS, although the median follow-up was still rather short (39 months).[29]

With the demonstration of ABVD being superior to MOPP or a MOPP-like regimen in advanced stages,[30] four cycles of ABVD have become standard for HD patients in early unfavorable stages, although the MOPP + ABVD variants were equally effective.[31] Although no formal randomized comparison has been performed, the MOPP variant used by the GHSG (COPP) has produced similar results when alternated with ABVD. Thus, two cycles of COPP alternating with two cycles of ABVD as used in the HD8 and in the preceding HD5 study of the GHSG[10] was clearly an appropriate and timely standard treatment.

For patients with HD in advanced stages, the GHSG developed a new polychemotherapy program: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) in two dose variants.[32] With this regimen, the results in patients with advanced HD have become superior to those reported for early unfavorable stages: When treated with escalated-dose BEACOPP, the FFTF was 87% after 5 years (HD9 arm C) compared with 82.6% overall in the current HD8 study. These data suggest that further studies in early unfavorable stages could aim at improving the long-term results by dose escalation. Thus, the GHSG follow-up study for this group of patients (HD11) compared four cycles of BEACOPP in the baseline version with four cycles of ABVD. Radiotherapy consists of 30 or 20 Gy, respectively. This study recruited 1,400 patients between April 1998 and January 2003. The recently opened current HD14 trial introduces escalated-dose BEACOPP into early unfavorable stages. Two cycles of BEACOPP followed by two cycles of ABVD are being compared with four cycles of ABVD followed by 30 Gy IF radiotherapy.

In summary, the prospectively randomized HD8 study of the GHSG comparing 30 Gy radiotherapy in the EF or IF technique defines a new standard of treatment for patients in early-stage unfavorable HD; that is, four cycles of effective chemotherapy followed by IF radiotherapy.

ACKNOWLEDGMENT

We are indebted to all hospitals and practices who contributed to this study. We also thank Hiltrud Nisters-Backes and Tina Koch for the excellent data management, Thomas Schober for managing the database, and Ursula Paulus and Oana Brosteanu for additional statistics and their valuable comments. In addition, we thank Hans Eich for his helpful support for the Radiotherapy section.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflict of interest.

APPENDIX 1

Persons responsible for the trial HD8 included: V. Diehl, trial chairman; A. Engert, J. Wolf, A. Josting, H. Tesch, M. Sieber, U. Rueffer, D. Hasenclever, U. Paulus, M. Loeffler, trial coordinators; T. Koch, H. Nisters-Backes (Köln), data management; T. Schober (Köln), database; P. Schiller (Köln), B. Pfistner (Köln), U. Paulus (Köln), O. Brosteanu (Leipzig), D. Hasenclever (Leipzig), M. Loeffler (Leipzig), statistics; A. Georgii (Hannover), H.-C. Müller-Hermelink (Frankfurt), pathology review; E. Dühmke (München), radiotherapy review; and A. Engert (Köln), P. Schiller (Köln), A. Josting, writing committee.

APPENDIX 2

The following participating institutions recruited patients in HD8, in descending order of recruitment (unless otherwise noted, all institutions are located in Germany): Bern, Swiss Group for Clinical Cancer Research (centers in Bern, Basel, Lausanne, St Gallen, and Ticino), Switzerland; Münster, Universitätsklinik Münster, Onkologische Ambulanz 15 A West; Köln, Universitätsklinik Köln, Klinik I für Innere Medizin, Ambulanz; Nürnberg, Klinikum Nürnberg, Klinik V Onkologie/Hämatologie; Hamburg, Universität Krankenhaus Eppendorf, Abteilung Hämatologie/Onkologie; Karlsruhe, St Vincentius Krankenhäuser, Zentrum für Innere Medizin; Chemnitz, Klinikum Chemnitz/Krankenhaus Küchwald, Klinik für Hämatologie Station 271; Heidelberg, Universitätsklinikum Heidelberg, Med. Klinik u. Poliklinik V; Freiburg, Med. Universitätsklinik Freiburg, Innere Medizin I, Abteilung Hämatologie/Onkologie; München, Klinikum Groβhadern, Klinik III für Hämatologie/Onkologie; Berlin, HELIOS Klinikum Berlin, Innere Medizin; Dresden, Universitätsklinik C.G. Carus, Medizinische Klinik I; Magdeburg, Otto von Guericke Universität Magdeburg, Abteilung für Hämatologie; München, Klinikum "Rechts der Isar," Medizinische Klinik III; Berlin, Campus Virchow Klinikum, Hämatologie/Onkologie; Mannheim, Klinikum der Stadt Mannheim, III. Medizinische Klinik; Homburg, Med. Universitätsklinik Homburg, Innere Medizin I; Stuttgart, Robert-Bosch-Krankenhaus, Innere Med. II Hämatologie/Onkologie; Tübingen, Eberhard-Karls-Universität, Abteilung Innere Med. II Hämatologische Ambulanz; Kiel, Städtisches Klinikum der Christian-Albrechts-Universität, II. Medizinische Klinik; München, Akademisches Lehrkrankenhaus, I. Med. Abteilung; Berlin, Universitätsklinikum Charité Mitte, Hämatologie/Onkologie; Ulm, Universitätsklinik Ulm, Innere Abteilung III; Jena, Friedrich-Schiller-Universität, Klinik für Innere Medizin; Berlin, Klinikum Berlin-Neukölln, Abteilung Hämatologie/Onkologie; Gieβen, Justus-Liebig-Universität Gieβen, Med. Klinik IV, Hämatologie/Onkologie; Berlin, Universitätsklinikum Benjamin Franklin, Hämato-Onkologische Ambulanz; Eschweiler, St Antonius Hospital, Abteilung für Hömatologie/Onkologie; Essen, Universitätsklinik Essen, Hämatologische Tagesklinik; Ravensburg, Oberschwabenklinik, Innere Abteilung; Erlangen, Universitätsklinik Erlangen, Med. Klinik u. Poliklinik III; Hagen, Marienhospital Hagen, Hämatologisch/Onkologische Station; Marburg, Klinikum der Philipps-Universität, Innere Medizin Hämatologie/Onkologie; Fakultni Nemocnice, Oddelení klinické hematologia, Prague, Czech Republic; Krefeld, Städt. Krankenanstalten Krefeld, Medizinische Klinik II; Essen, Evangelisches Krankenhaus, Innere Medizin; Göttingen, Georg-August-Universität, Med. Klinik Abteilung Hämatologie/Onkologie; Minden, Klinikum Minden, Abteilung Hämatologie/Onkologie; Hannover, Med. Hochschule Hannover, Abteilung Hämatologie/Onkologie; Bad Sarow, Humaine Klinikum Bad Sarow, Abteilung Hämatologie/Onkologie; Braunschweig, Städtisches Klinikum Braunschweig, Med. Klinik-IKO; Stuttgart, Bürgerhospital Stuttgart, Medizinische Klinik I; Schweinfurt, Leopoldiner Krankenhaus, Medizinische Klinik II; Offenburg, Klinikum Offenburg, Medizinische Klinik II; München, Hämatologie/Onkologie Gemeinschaftspraxis, Onkologie; Lübeck, Med. Universität Lübeck, Innere Medizin Hämatologie/Onkologie; Kaiserslautern, Westpfalz Klinikum GmbH, Innere med. I/Hämatologie; Innsbruck, Universitätsklinikum Innsbruck, Inst. für Epidemiologie, Austria; Hildesheim, St Bernward-Krankenhaus, Medizinische Klinik II; Heilbronn, Städtisches Krankenhaus Heilbronn, I. Medizinische Klinik; Duisburg, St Johannes Hospital, Medizinische Klinik II; Berlin, Vivantes, Hämatologisch- Onkologische Beratung; Sindelfingen, Städtisches Krankenhaus Sindelfingen, Innere Medizin; Wiesbaden, Dr Horst-Schmidt-Kliniken Wiesbaden, Innere Med. III, Hämatologie/Onkologie; Stuttgart, Diakonissenkrankenhaus, Innere Med. II; Stade, Klinik Dr. Hancken, Abteilung für Hämatologie; Karlsruhe, Städtisches Klinikum Karlsruhe, Med. Klinik II/Hämatologie; Regensburg, Universitätsklinik Regensburg, Klinik I für Innere Medizin; Frankfurt, Krankenhaus Nordwest, II. Medizinische Klinik; Würzburg, Universitätsklinik u. Poliklinik Würzburg, Onkologische Abteilung; Reutlingen, Kreiskrankenhaus Reutlingen, Med. Klinik; Regensburg, Krankenhaus d. Barmherzigen Brüder, Klinik für internistische Onkologie u. Hämatologie; Lübeck, Städt. Krankenhaus Süd, Abteilung Hämatolog./Onkologie; Hamm, Ev. Krankenhaus Hamm, Innere Medizin/Hämato-Onkologie; Lebach, Caritas-Krankenhaus, Innere Medizin; Heidelberg, Thorax-Klinik der LVA Baden, Internistisch-Onkologische Abteilung; Aachen, Gemeinschaftspraxis, Hämatologie/Onkologie; Duisburg, Johanniter-Krankenhaus Rheinhausen, Med. Klinik II/Onkologie; Dresden, Krankenhaus Dresden-Friedrichstadt, I. Med. Klinik; Bonn, Medizinische Poliklinik, Innere Medizin; Freiburg, Ev. Diakoniekrankenhaus, Innere Abteilung; Trier, Krankenanstalt Mutterhaus d. Borromäerinnen, Medizinische Klinik; Rostock, Universität Rostock, Innere Medizin Onkologie/Hämatologie,; Neubrandenburg, Klinikum Neubrandenburg, Innere Med./Hämatol. Abteilung; München, Klinikum Innenstadt der LMU, Med. Klinik Abteilung Hämatologie; Mönchengladbach, Kliniken Maria Hilf, Abteilung I; Kassel, Klinikum Kassel, Hämatologie/Onkologie; Jena, Hämatologie/Onkologie Gemeinschaftspraxis, Innere Medizin; Freiburg, Klinik für Tumorbiologie, Klinik für Internistische Onkologie; Flensburg, St Franziskus Hospital, Innere V; Bad Friedrichshall, Kreiskrankenhaus am Plattenwald, Innere Abteilung; Dortmund, St Johannes Hospital, Medizinische Klinik; Hamburg, Gemeinschaftspraxis Prof Dr Kleeberg, Innere Medizin/Hämatologie; Schwäbisch Hall, Diakonie-Krankenhaus Schwäbisch Hall, Innere Abteilung; Oldenburg, Städtische Kliniken, Innere Med. II; Neumarkt I.D. Oberpfalz, Kreiskrankenhaus Neumarkt, Innere Medizin II; Münster, Hämatologie/Onkologie Gemeinschaftspraxis, Hämato-Onkologisch; München, Städtisches KH Harlaching, IV Med. Abteilung; Hannover, Hämatologie/Onkologie Gemeinschaftspraxis, Hämatologie/Intern. Onkologie; Hof/Saale, Klinikum Hof/Saale, Med. Klinik Innere Medizin; Hameln, Krankenhaus d. Kreises Hameln/Pyrmont, Innere Abteilung; Bonn, Universitätsklinik Bonn, Med. Klinik u. Poliklinik; Frankfurt/Oder, Klinikum Frankfurt/Oder, Klinik für Innere Med.; Bochum, Knappschaftskrankenhaus, Med. Klinik; Aschaffenburg, Klinikum Aschaffenburg, II Med. Klinik; Aurich, Kreiskrankenhaus Aurich, Innere Med./Hämatologie; Wolfsburg, Stadtkrankenhaus Wolfsburg, I. Medizinische Klinik; Waldbröl, Kreiskrankenhaus Waldbröl, Medizinische Klinik; Stuttgart, Katharinenhospital Stuttgart, Klinik für Onkologie; Schwerin, Klinikum Schwerin, Abteilung Hämatologie/Onkologie; Oldenburg, Gemeinschaftspraxis Innere Medizin, Ärzte für innere Medizin; Limburg, St Vincentius Krankenhaus, Abteilung Hämatologie; Lemgo, Klinikum Lippe-Lemgo, Medizinische Klinik II; Leipzig, Universitätsklinik Leipzig, Med. Klinik II/Abteilung Hämatologie; Köln, Krankenhaus Merheim, Lungenklinik Onkologische Abteilung; Herne, Marienhospital Herne, Abteilung Hämatologie/Onkologie; Günzburg, Kreiskrankenhaus Günzburg, Innere Medizin; Greifswald, Ernst-Moritz-Arndt-Universität, Innere Medizin C Abteilung Hämatologie/Onkologie; Bremen, Evang. Diakonissenanstalt, Med. Klinik Abteilung Hämatologie/Onkologie; Bocholt, St Agnes Hospital, Med. Klinik II; Bayreuth, Klinikum Bayreuth, Medizinische Klinik I; Bamberg, Klinikum Bamberg, II. Medizinische Klinik; Bad Oeynhausen, Gemeinschaftspraxis Innere Medizin, Innere Medizin; Aalen, Kreiskrankenhaus Ostalb-Klinikum, Innere Abteilung; Bielefeld, Städt. Krankenhaus Bielefeld-Mitte, I. Medizinische Klinik; Bochum, Onkologische Schwerpunktpraxis, Innere Medizin; Wuppertal, Ärztehaus am St Josef, Hämatologie, Hämatologie; Wuppertal, Klinikum Wuppertal/Klinikum Barmen, Med. Klinik Hämatologie/Onkologie; Wuppertal, Bethesda Krankenhaus, Innere Abteilung; Trier, Krankenanstalt Mutterhaus d. Borromäerinnen, Abteilung Strahlentherapie; Siegen, St Marien-Krankenhaus, Med. Klinik III Hämatologie/Onkologie; Siegen, Evang. Jung-Stilling-Krankenhaus, Med. Klinik; Radebeul, Kreiskrankenhaus Radebeul, Innere Abteilung; Pforzheim, Städtisches Krankenhaus, Med. Klinik II; Paderborn, Brüderkrankenhaus St Josef, Abteilung für Radiologische Diagnostik; Mühlheim/Ruhr, St Marienhospital, I. Med. Klinik; Mainz, St Hildegardis-Krankenhaus, Innere/Onkologie; Magdeburg, Städt. Klinikum Magdeburg, Innere Medizin Abteilung Hämatologie/Onkologie; Lüdenscheid, Kreiskrankenhaus Lüdenscheid, Innere Abteilung/Onkologie; Ludwigshafen, Klinikum der Stadt Ludwigshafen, Medizinische Klinik A; Lippstadt, Evang. Krankenhaus Lippstadt, Innere Medizin; Lahr, Klinikum Lahr, Med. Klinik/Gastroenterologie; Köln, Krankenhaus Köln Holweide, Innere Abteilung; Kronach, Praxis Innere Medizin, Innere Medizin; Koblenz, Evang. Stift St Martin Koblenz, Innere Medizin; Holzminden, Ev. Krankenhaus Holzminden, Innere Abteilung; Hildesheim, Städtisches Krankenhaus, Medizinische Klinik I; Herford, Klinikum Kreis Herford,

APPENDIX 2 (Continued)

Medizinische Klinik II; Heidenheim, Kreiskrankenhaus Heidenheim, Innere Medizin; Hannover, Therapiebereich Siloah, Klinik für Hämatologie u. Onkologie; Hannover, Friederikenstift Hannover, Med. Klinik; Hagen, Onkologische Praxis, Innere Medizin; Gütersloh, Städtisches Krankenhaus Gütersloh, Med. Klinik/Hämatologie; Fürth, Praxis im Klinikum, Med. Klinik II; Düsseldorf, Diakoniewerk Kaiserswerth, Innere Medizin; Darmstadt, Städt. Kliniken Darmstadt, Med. Klinik V/Hämatologie; Cottbus, Carl-Thiem-Klinikum, II Med. Klinik; Celle, Allgemeines Krankenhaus, Gastroenterolog. Abteilung; Bietigheim-Bissingen, Krankenhaus Bietigheim, Innere Medizin I; Berlin, Praxis Innere Medizin, Innere Medizin; Berlin, Gemeinschaftspraxis Innere Medizin, Innere Medizin; Aachen, Med. Fakultät der RWTH Aachen, Medizinische Klinik IV; Neuss, Johanna Etienne Krankenhaus, Innere Abteilung; Nettetal, Städtisches Krankenhaus, Innere Medizin; Münster, Fachklinik Hornheide, Internistische Onkologie; München, Klinikum Großhadern, Klinik für Strahlentherapie,; München, Internist-Hämatologe, Hämatologe; Mülheim A.D. Ruhr, Ev. Krankenhaus Mülheim/Ruhr, Medizinische Klinik; Meschede, St Walburga-Krankenhaus, Innere Medizin II, Hämatologie/Onkologie; Mayen, Hämatologie/Onkologie Schwerpunktpraxis, Innere Medizin; Ludwigshafen, St Marienkrankenhaus, Medizinische Klinik; Worms, Onkologische Schwerpunktpraxis, Hämatologe; Witten, Marienhospital Witten, Innere Medizin; Wiesbaden, Klinik für Innere Medizin u. Gastroenterologie, Hämatologie/Onkologie; Wesel, Marienhospital Wesel, II Med. Klinik; Viersen, Irmgardis Krankenhaus, Innere Abteilung, Tübingen, Internistische Praxis, Innere Medizin; Trier, Onkologische Schwerpunktpraxis, Innere Medizin; Siegburg, Internistische Praxis, Onkologie; Schleswig, Martin-Luther-Krankenhaus, Innere Abteilung II; Saarlouis, St Elisabeth Krankenhaus, Med. Klinik I, Saarbrücken, Klinikum Saarbrücken gGmbH, Klinik für Radioonkologie; Saarbrücken, Caritasklinik St Theresia, Klinik für Onkologie und Immunologie; Rottweil, Kreiskrankenhaus, Med. Klinik; Rostock, Klinikum Südstadt, Onkologische Klinik; Rosenheim, Praxis Innere Medizin, Innere Medizin; Rosenheim, Klinikum Rosenheim, Innere Medizin; Stuttgart, Marienhospital, Innere Med. II; Stadtlohn, Krankenhaus Maria Hilf, Innere Abteilung; Solingen, St Lukas Klinik, Innere Medizin; Rheine, Jacobi-Krankenhaus, Innere Abteilung; Remscheid, Klinikum Remscheid-Lennep, Med. II Innere Abteilung; Recklinghausen, Knappschaftskrankenhaus, Innere Medizin; Ostfildern/Ruid, Paracelsus Krankenhaus Ruid, Med. Klinik Hämatologie/Onkologie; Osnabrück, Paracelsus Klinik, Hämatologie/Onkologie; Olpe, St Martinus-Hospital, Medizinische Klinik; Oberhausen, Evang. Krankenhaus Oberhausen, Innere Medizin; Neuwied, DRK Krankenhaus Neuwied, Innere Medizin; Lippstadt, Dreifaltigkeitshospital, Onkologie; Landshut, Praxis Innere Medizin, Innere Medizin; Landau/Pfalz, St Vinzentius Krankenhaus, Innere Medizin; Köln, Universitätsklinik Köln, Innere Medizin II; Köln, St Elisabeth-Krankenhaus, Innere Medizin; Koblenz, Städt. Krankenhaus Kemperhof, II Med. Klinik; Hamm, St Marien Hospital, Innere Abteilung; Hamburg, Univ. Krankenhaus Eppendorf, Radiol. Klinik u. Strahleninstitut; Lörrach, Kreiskrankenhaus Lörrach, Innere Abteilung; Hamburg, Praxis Innere Medizin, Innere Medizin; Hamburg, Allg. Krankenhaus Barmbeck, Onkologische Abteilung; Göttingen, Gemeinschaftspraxis Innere Medizin, Innere Medizin; Frechen, St Katharinenhospital Frechen, Innere; Frechen, Praxis Innere Medizin, Innere Medizin; Essen, Praxis Innere Medizin, Innere Medizin; Emden, Hans-Susemihl-Klinik, Med. Klinik I; Düsseldorf, Kliniken der Landeshauptstadt Düsseldorf, Med. Klinik; Dortmund, Kliniken Dortmund GmbH, Med. Klinik/Onkologie; Bünde, Lukas Krankenhaus, Med. Klinik; Bremerhaven, ZKH Reinkenheide, Med. Klinik I; Bielefeld, St Franziskus Hospital, Med. Klinik II Abteilung Hämatologie/Onkologie; Dormagen, Kreiskrankenhaus Dormagen, Medizinische Klinik; Bremen, Zentralkrankenhaus "Links der Weser," Medizinische Klinik; Bochum, Universitätsklinik St Josef-Hospital, Med. Klinik.

REFERENCES

1. Diehl V, Mauch P, Harris NL: Hodgkin's disease, in De Vita V (ed): Cancer Principles and Practice of Oncology. Philadelphia, PA Lippincott Williams & Wilkins, 2001, pp 2339-2387
2. Kaplan H: Hodgkin's Disease. Cambridge, MA, Harvard University Press, 1980
3. Hoppe RT, Coleman CN, Cox RS, et al: The management of stage I-II Hodgkin's disease with irradiation alone or combined modality therapy: The Stanford experience. Blood 59:455-465, 1982
4. Carde P, Burgers JM, Henry-Amar M, et al: Clinical stages I and II Hodgkin's disease: A specifically tailored therapy according to prognostic factors. J Clin Oncol 6:239-252, 1988
5. Kaplan H: The radical radiotherapy of Hodgkin's disease. Radiology 78:553-561, 1962
6. Kaplan H: Survival and relapse rates in Hodgkin's disease: Stanford experience, 1961-71. Natl Cancer Inst Monogr 36:487-496, 1973
7. Specht L, Gray RG, Clarke MJ, et al: Influence of more extensive radiotherapy and adjuvant chemotherapy on long-term outcome of early-stage Hodgkin's disease: A meta-analysis of 23 randomized trials involving 3,888 patients. J Clin Oncol 16:830-843, 1998
8. Loeffler M, Diehl V, Pfreundschuh M, et al: Dose-response relationship of complementary radiotherapy following four cycles of combination chemotherapy in intermediate-stage Hodgkin's disease. J Clin Oncol 15:2275-2287, 1997
9. Pocock SJ: Clinical Trials: A Practical Approach. New York, NY, Wiley, 1984
10. Bennett CL, Smith TJ, Weeks JC, et al: Use of hematopoietic colony-stimulating factors: The American Society of Clinical Oncology survey—The Health Services Research Committee of the American Society of Clinical Oncology. J Clin Oncol 14:2511-2520, 1996
11. Makuch R, Simon R: Sample size requirements for evaluating a conservative therapy. Cancer Treat Rep 62:1037-1040, 1978
12. Whitehead J: The Design and Analysis of Sequential Clinical Trials (ed 2). Chichester, United Kingdom, Ellis Horwood, 1992
13. Kaplan EL, Meier P: Non parametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958
14. Cox DR: Regression models and life tables. J R Stat Soc 34:187-220, 1972
15. Hancock SL, Donaldson SS, Hoppe RT: Cardiac disease following treatment of Hodgkin's disease in children and adolescents. J Clin Oncol 11:1208-1215, 1993
16. Blumenfeld Z, Dann E, Avivi I, et al: Fertility after treatment for Hodgkin's disease. Ann Oncol 13:138-147, 2002
17. Knobel H, Havard Loge J, Brit Lund M, et al: Late medical complications and fatigue in Hodgkin's disease survivors. J Clin Oncol 19:3226-3233, 2001
18. Prosnitz LR: Reducing treatment-related morbidity and mortality in early-stage Hodgkin's disease and why the recent Southwest Oncology Group Trial is not the way to go. J Clin Oncol 20:2225-2228, 2002
19. Boivin JF, Hutchison GB, Zauber AG, et al: Incidence of second cancers in patients treated for Hodgkin's disease. J Natl Cancer Inst 87:732-741, 1995
20. Metayer C, Lynch CF, Clarke EA, et al: Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. J Clin Oncol 18:2435-2443, 2000
21. Swerdlow AJ, Barber JA, Hudson GV, et al: Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: The relation to age at treatment. J Clin Oncol 18:498-509, 2000
22. Rueffer U, Josting A, Franklin J, et al: Non-Hodgkin's lymphoma after primary Hodgkin's disease in the German Hodgkin's Lymphoma Study Group: Incidence, treatment, and prognosis. J Clin Oncol 19:2026-2032, 2001

23. Josting A, Wiedenmann S, Franklin J, et al: Secondary myeloid leukemia and myelodysplastic syndromes in patients treated for Hodgkin's disease: A report from the German Hodgkin's Lymphoma Study Group. J Clin Oncol 21:10.1200/JCO.2003.07.160

24. Hancock SL, Tucker MA, Hoppe RT: Breast cancer after treatment of Hodgkin's disease. J Natl Cancer Inst 85:25-31, 1993

25. van Leeuwen FE, Klokman WJ, van't 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

26. Diehl V, Loeffler M, Pfreundschuh M, et al: Further chemotherapy versus low-dose involved-field radiotherapy as consolidation of complete remission after six cycles of alternating chemotherapy in patients with advance Hodgkin's disease: German Hodgkins' Study Group (GHSG). Ann Oncol 6:901-910, 1995

27. Zittoun R, Audebert A, Hoerni B, et al: Extended versus involved fields irradiation combined with MOPP chemotherapy in early clinical stages of Hodgkin's disease. J Clin Oncol 3:207-214, 1985

28. Bonvante V, Viviani S, Devizzi L, et al: Ten years experience with ABVD plus radiotherapy: Subtotal nodal (STNI) vs involved-field (IFRT) in early stage Hodgkin's disease. Proc Am Soc Clin Oncol 20:281a, 2001 (abstr 1120)

29. Ferme C, Eghbali H, Habenbeek A, et al: MOPP/ABV (M/A) hybrid and irradiation in unfavorable supradiaphragmatic clinical stages I-II HD: Comparison of three treatment modalities, preliminary results of the EORTC-GELA H8-U randomized trial in 995 patients. Blood 96:576a, 2000

30. Canellos GP, Niedzwiecki D: Long-term follow-up of Hodgkin's disease trial. N Engl J Med 346:1417-1418, 2002

31. Canellos GP, Anderson JR, Propert KJ, et al: Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 327:1478-1484, 1992

32. Diehl V, Franklin J, Pfreundschuh M, et al: Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med 348:2386-2395, 2003