Low-Dose Radiation Is Sufficient for the Noninvolved Extended-Field Treatment in Favorable Early-Stage Hodgkin's Disease: Long-Term Results of a Randomized Trial of Radiotherapy Alone

By Eckhart Dühmke, Jeremy Franklin, Michael Pfreundschuh, Susanne Sehlen, Norman Willich, Ursula Rühl, Rolf-Peter Müller, Peter Lukas, Anton Atzinger, Ursula Paulus, Bernd Lathan, Ulrich Rüffer, Markus Sieber, Jürgen Wolf, Andreas Engert, Axel Georgii, Susanne Staar, Richard Herrmann, Maria Beykirch, Hartmut Kirchner, Adelheid Emminger, Richard Greil, Esther Fritsch, Peter Koch, Angelika Drochtert, Oana Brosteanu, Dirk Hasenclever, Markus Loeffler, and Volker Diehl

Purpose: **To show that radiotherapy (RT) dose to the noninvolved extended field (EF) can be reduced without loss of efficacy in patients with early-stage Hodgkin's disease (HD).**

Patients and Methods: **During 1988 to 1994, pathologically staged patients with stage I or II disease who were without risk factors (large mediastinal mass, extranodal lesions, massive splenic disease, elevated erythrocyte sedimentation rate, or three or more involved areas) were recruited from various centers. All patients received 40 Gy total fractionated dose to the involved field areas but were randomly assigned to receive either 40 Gy (arm A) or 30 Gy (arm B) total fractionated dose for the clinically noninvolved EF. No chemotherapy was given. RT films were prospectively reviewed for protocol violations and recurrences retrospectively related to the applied RT.**

Results: **Of 382 recruited patients, 376 were eligible for randomized comparison, 190 in arm A and 186 in arm B. Complete remission was attained in 98% of patients in each arm. With a median follow-up of 86 months, 7-year relapse-free survival (RFS) rates were 78% (arm A) and 83% (arm B) (*P* = .093). The upper 95% confidence limit for the possible inferiority of arm B in RFS was 4%. Corresponding overall survival rates were 91% (arm A) and 96% (arm B) (*P* = .16). The most common causes of death (n = 27) were cardiorespiratory disease/pulmonary embolisms (seven), second malignancy (six), and HD (five). Protocol violation was associated with significantly poorer RFS. Nonirradiated nodes were involved in 42 of 52 reviewed relapses, infield areas in 18, marginal areas in 17, and extranodal sites in 16.**

Conclusion: **EF-RT alone attains good survival rates in favorable early-stage HD. The 30-Gy dose is adequate for clinically noninvolved areas. Protocol violation worsens the subsequent prognosis. Relapse patterns suggest that systemic therapy can reduce the 20% long-term relapse rate.**

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THE ASSIGNMENT OF a patient with untreated Hodgkin's disease (HD) to one of three treatment categories, namely early-stage favorable, early-stage unfavorable, and advanced stage, has become a widespread practice.[1-3] Unfavorable early-stage patients, defined as patients with stage I and II disease and an adverse prognostic factor (the list of recognized factors differs between study groups and institutions) are presumed to have a higher risk of recurrence if given radiotherapy (RT) alone and therefore receive combined chemoradiotherapy. Favorable early-stage patients, without adverse factors, are assumed by some groups to need only RT,[4,5] whereas in other centers they also receive some chemotherapy.[3,6,7] The addition of chemotherapy has been shown to reduce the relapse rate, but no overall survival advantage has been demonstrated.[8] Thus a case can still be made for RT alone for these favorable early-stage patients, which must then, however, be applied in extended-field (EF) technique. EF refers both to areas of detected disease and neighboring nodal areas. In numerous investigations of patterns of presentation, these neighboring areas have been shown to be susceptible to associated involvement, which at the time of staging is too small to be detected. This radiation-only policy spares some acute and late drug-related toxicity and, by avoiding drug resistance,

From the Canton Hospital, Basel, Switzerland; Radiotherapy and Internal Medicine Departments, Münich University, Münich; Biometry, Radiotherapy, and Internal Medicine Departments, Cologne University, Cologne; Munster University, Munster; Moabit Hospital, Berlin; Innsbruck University, Innsbruck; Klinikum Passau, Passau; and Pathology Department, Hannover Medical School, Hannover, Germany.

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Address reprint requests to Jeremy Franklin, PhD, Klinik I für Innere Medizin, Cologne University, Josef-Stelzmann-Str 9, 50924 Köln, Germany; email: j.franklin@biometrie.uni-koeln.de.

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may well enable relapsing patients to be successfully treated with salvage therapy using conventional chemotherapy regimens.

EF-RT as the sole treatment modality was in recent years usually administered to a total dose of 40 Gy. This was due largely to Kaplan's meta-analysis of data in the literature on doses between 5 and 40 Gy, which showed a marked, continuous reduction in recurrence rates up to 40 Gy, above which toxicity becomes excessive.[9] Subsequent dose-response analyses,[10-12] however, indicate a plateau in cure rates beginning at approximately 30 Gy. Vijayakumar and Myrianthopoulos[11] derived site-specific dose-response curves separately for subclinical disease, nonbulky clinical disease, and bulky disease. These curves suggest a wide plateau between 30 and 40 Gy for subclinical disease but a steep fall-off in permanent control on reducing dosage from 40 to 30 Gy for bulky disease, with nonbulky clinical disease intermediate between the two.

Although acute side effects are no longer considered of major concern with modern high-voltage irradiation techniques, late sequelae such as second cancers, cardiac disease, pulmonary toxicities, and hypothyroidism compete with HD recurrence as causes of death and reduced quality of life.[13] Various reports have indicated that a dose reduction from 40 Gy to, for example, 30 Gy might decrease the frequency and severity of late radiation toxicities. The cumulative risk of secondary solid tumors, predominantly of the lung, gastrointestinal tract, and female breast, seems to increase continuously even 10 to 20 years after treatment, as demonstrated by pediatric trial results.[14-16] Although a positive correlation between radiation dose and risk of late toxicity may be suspected, investigations published to date give varying results. For second solid tumors, a dose-risk relationship at therapeutic doses has been identified in certain studies[16] but not consistently. Two reports found late cardiac toxicities to be related to total mediastinal dose,[17,18] whereas a third study did not find any mediastinal dose effect, neither for cardiac nor pulmonary late effects.[19] Other studies of pulmonary toxicities have shown moderate dose effects on pulmonary dysfunction,[20,21] but the clinical relevance is unclear. The relative importance of factors such as daily fraction dose, total dose, and treated volume also remains uncertain. The incidence of hypothyroidism was shown to be dose-dependent in a large series of Stanford University Medical Center patients.[22]

Several studies have suggested that not only the quantity but also the quality of irradiation is important for treatment success and for the balance between efficacy and toxicity in HD. For instance, a patterns-of-care study in United States institutions revealed high local and overall relapse rates in cases where inadequate coverage of disease was detected by independent reviewers.[23] The same study also suggested differences in work-up quality and in relapse rates both between various larger institutions and between smaller and larger institutions.[24] Good results obtained in specialist RT centers have not always been maintained when the same protocols are used more widely.

Despite the aforementioned indirect evidence for a beneficial effect of RT dose reduction, no prospective randomized study had been performed. Therefore, the German Hodgkin's Lymphoma Study Group (GHSG) planned a multicenter randomized controlled trial, HD4, to test whether subclinical disease can be adequately controlled by a total radiation dose of 30 Gy to the clinically noninvolved portions of the EF. Areas where tumor was detected by clinical and/or obligatory pathologic staging methods were irradiated with a total dose of 40 Gy. This strategy was compared with the standard treatment, in which 40 Gy was applied uniformly to the entire extended field. The objective of HD4 was to test the hypothesis that a dose reduction from 40 to 30 Gy in the noninvolved EF is possible without a clinically relevant increase in the recurrence rate. An RT review panel was established to evaluate the quality of irradiation in each patient and thus to allow irradiation quality to be related to treatment outcome. Preliminary results of HD4, with a median follow-up of 3.5 years, were reported in 1996[25]; the present account presents the definitive analysis with 7 years median follow-up and observation of approximately 80% of expected follow-up events.

PATIENTS AND METHODS

From 1988 to 1993, patients aged 15 to 75 years with untreated, biopsy-confirmed, clinical stage I and II HD were pathologically staged by laparotomy with splenectomy. Clinical staging included history of disease, physical examination, complete blood cell count, x-ray, computed tomography (CT), ultrasound, bone scan, and bone marrow biopsy. Patients with disease that proved to be Ann Arbor pathologic stage I or II, with or without "B" symptoms, were enrolled onto the HD4 trial if none of the following adverse prognostic factors were present: mediastinal mass larger than one third of thorax diameter, extranodal lesions, massive splenic involvement (ie, diffuse infiltration or more than five focal lesions), erythrocyte sedimentation rate more than 50 mm/h without B symptoms or more than 30 mm/h with B symptoms, or three or more involved nodal areas. The diagnosing pathologist was requested to send a paraffin block biopsy sample to the pathology review panel, who reclassified the case; in the event of a diagnosis other than HD, that case was removed from HD4.

Stratified randomization was performed at the GHSG coordination center in Cologne, Germany, on receipt of staging documentation and patient's written consent. Patients with supradiaphragmatic disease were assigned to one stratum, those with infradiaphragmatic disease to the other. Each patient was randomized onto arm A or arm B by considering the balance between A and B patients in the patient's stratum and in the patient's treatment center. The arm was assigned first to equalize the number of patients in each arm in the patient's stratum. If the stratum arm numbers were already equal, then the arm was

chosen to equalize the numbers per arm in the patient's center. If both these ratios were already in balance, then a coin was tossed. No blinding was possible in this trial.

Each patient's irradiation plan was drawn up by the RT reference center in Munich, Germany, based on the staging documentation and assigned arm. Prerequisites included the use of megavoltage equipment, large-field techniques, and pretreatment planning, including simulation and repeated port film verification during therapy. Patients in arm A received a total dose of 40 Gy to all involved and EF areas in single doses of 1.8 to 2.0 Gy over 4 to 6 weeks. In arm B, irradiation beyond 30 Gy was restricted to the involved field.

The EF for supradiaphragmatic disease comprised a mantle field including all cervical, supraclavicular, infraclavicular, axillary, mediastinal, and hilar lymph nodes, followed (after an interval of 3 to 4 weeks for bone marrow recovery) by irradiation of the para-aortic and splenic pedicle nodes. The para-aortic–pedicle field was not irradiated if initial disease was restricted to the upper cervical nodes. Waldeyer's lymphatic ring was included only if upper cervical nodes were involved. For infradiaphragmatic disease, an inverted-Y field was irradiated, covering the femoroinguinal, iliac, and paraaortic nodes, followed by a T field to the supraclavicular nodes and the mediastinum. The T field was not irradiated if initial disease was restricted to the femoroinguinal nodes.

Six weeks after completion of RT, a restaging examination was performed with assessment of all initial sites of clinical disease using the techniques described under staging as appropriate. For patients in complete remission, follow-up examinations four times per year in the first 2 years, three times per year in the third and fourth years, and twice per year thereafter were specified. If a recurrence of HD was detected, a full staging was performed. For nodal relapse outside the initial RT volume, salvage RT was recommended. Otherwise, for late relapses (relapse-free survival [RFS] $>$ 12 months) salvage treatment with cyclophosphamide, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vincristine, dacarbazine (COPP/ABVD) was recommended, and for early relapses a salvage chemotherapy regimen was recommended, involving high-dose chemotherapy with autologous bone-marrow transplantation where feasible.[26]

The pathology review panel of the GHSG, consisting of four lymphoma specialists, retrospectively re-examined paraffin blocks of biopsy material to confirm the diagnosis of HD and to determine the histologic type. The panel aimed to review all cases.

RT Quality Control

All participating radiotherapists were required to send simulation and port verification films to the Radiotherapy Review Center in Munich, where they were assessed by a panel of four experienced radiation oncologists. Images were evaluated with regard to four categories of protocol violation (PV) as follows: incomplete coverage of tumor or inadequate safety margin (V−), excessive coverage (V+), total dose less than 90% of protocol (D−), total dose more than 110% of protocol (D+), dose administered too slowly (Ds; $<$ 1.8 Gy/d or $>$ 2 weeks delay during treatment to one volume or $>$ 4 weeks interval between large fields), and technical deficiency (T; lack of megavoltage equipment or large-field method).

Each panelist decided on the presence or absence of PV within each category. The overall result for a given patient was designated PV for those categories (if any) in which at least three of the four panelists voted for a PV. This assessment was prospective in the sense that it took place without knowledge of treatment results or remission duration.

Radiologic Assessment of Relapses

The Radiotherapy Review Center was informed by the trial coordination center of any relapse. CT images were obtained and compared with the RT planning documents and simulator and port films to classify the recurrence as follows: infield local on site of primary disease (IFL), infield new on irradiated but previously uninvolved site (IFN), outfield local on nonirradiated primary site (OFL; should not exist), outfield new on noninvolved and nonirradiated site (OFN), and marginal recurrence on the radiation field boundaries, defined as relapse arising at the steep dose decrease at the field margins (MR).

This assessment was retrospective in the sense that irradiation was evaluated in relation to the known relapse pattern.

Statistics

The primary end point of the trial was RFS, defined as the time from attainment of complete remission (CR) after completed HD4 therapy until relapse or date of last information. RFS was not defined for those few patients who did not reach a CR. Secondary end points were CR rate and overall survival (OS; deaths from any cause count as events).

The target recruitment for HD4 was approximately 360 patients over 4 years, which was calculated to provide a power of 80% to detect a difference in RFS of 10% to 15% at the 5% level of significance (one-sided test), given the expected RFS rate of approximately 80% in the standard arm A.[27]

An intent-to-treat analysis was planned, including all randomized, qualified patients who began therapy. Those patients who dropped out without beginning treatment were included in the overall results but not in the randomized comparison. Total doses as documented on the RT forms were analyzed per arm to assess the extent to which the planned dose reduction to 30 Gy was actually carried out.

Survival data (RFS, OS) were analyzed using the Kaplan-Meier method and compared between treatment arms using the log-rank test. A multivariate analysis of RFS using Cox proportional hazards regression was also performed, including age, sex, histologic subtype, stage, B symptoms, the international prognostic index for advanced HD,[28] and RT PV as possible cofactors, together with treatment arm. For this purpose, only those PVs that reduced the amount, intensity, or adequacy of treatment (V−, D−, Ds, T, designated relevant PVs) were considered. The aim of the multivariate analysis was to test for the presence of prognostic factors, including the prognostic relevance of PV, and to reassess the treatment arm comparison allowing for the effect of such factors.

RESULTS

In total, 382 patients were randomized onto HD4. The pathology review panel, which has assessed 71% of all HD4 cases, diagnosed a non-Hodgkin's lymphoma (NHL) instead of HD in four of these cases, resulting in retrospective exclusion of these four cases from the trial, leaving 378 qualified patients for the overall analysis. Two qualified patients were excluded from the arm comparisons because they did not begin HD4 treatment: one suffered HD progression before radiation could begin (2 weeks after randomization), and the other refused all HD4 treatment (he received involved-field irradiation). Thus 376 patients, 190 in arm A and 186 in arm B, were available for arm comparisons. Contact was lost with two of the arm A

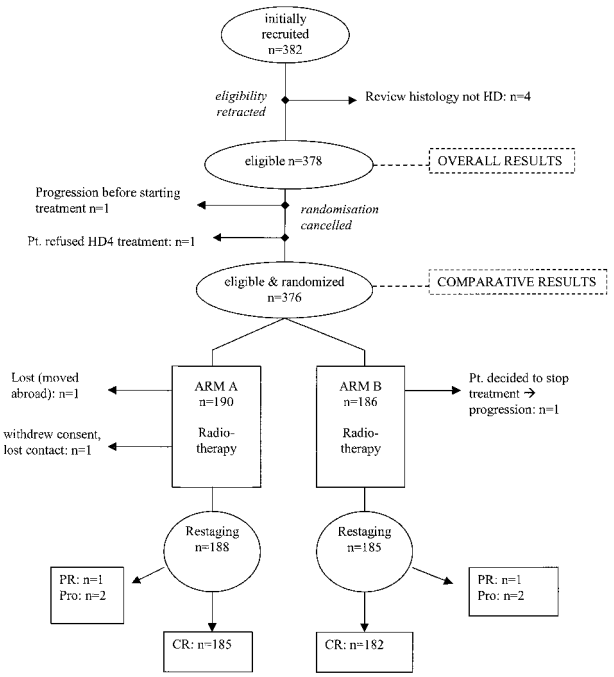

Fig 1. Flowchart of the HD4 trial.

patients during therapy (one moved abroad and another refused further participation): the exclusion of these patients had only a negligible effect (< 1%) on the CR rate, and due to lack of follow-up made no contribution to OS and RFS rates. One arm B patient decided to stop treatment and later experienced disease progression; he was counted as a progression under treatment. This information is listed as a flowchart in Fig 1.

Overall, the median patient age at randomization was 32 years; 62% of patients were male. At histologic review, 15% of the reviewed cases were lymphocyte predominant, 47% nodular sclerosing, 28% mixed cellularity, and none were lymphocyte depleted; the remaining 10% were unclassified or HD could not be definitely confirmed. Almost all patients were in good general condition (99% had Karnofsky status of 9 or 10). Stages I and II were almost equally frequent, and B symptoms were rare (5%). Patient characteristics were well balanced between treatment arms (Table 1).

Nearly all patients (98% in each arm) attained a CR at the end of HD4 protocol treatment, with partial remission in one patient in each arm (Table 2). Progression during or immediately after treatment was seen in two arm A patients and three arm B patients (1.3% overall). Progression occurred as follows: cervical nodes during mantle field RT, inguinal nodes after mantle field RT, iliac nodes after mantle–para-aortic RT; pericardia during mantle field RT, and skeletal disease (os sacrum) after mantle–para-aortic RT. There were 41 relapses in arm A and 29 in arm B, occurring up to 8 years after treatment.

Table 1. Patient Characteristics (percentage of cases with nonmissing data)

	Arm A, % (n = 190)	Arm B, % (n = 186)
Age		
< 20 years	7	11
20-30 years	33	36
30-40 years	31	26
40-50 years	15	15
50-60 years	12	10
60-70 years	2	3
Sex		
Female	37	39
Male	63	61
Reference histology (available for 71%)		
LP	15	14
NS1	37	41
NS2	6	9
MC	30	26
LD	—	—
UC (HD)	3	4
HD?	10	6
Karnofsky (available for 96%)		
6-8	1	1
9-10	99	99
International prognostic score (available for 76%)		
0	23	24
1	53	52
2	21	19
3-4	3	5
Stage		
IA	47	44
IB	3	1
IIA	49	53
IIB	2	3

NOTE. Data were complete except where indicated.

Abbreviations: LP, lymphocyte predominant; NS, nodular sclerosing; MC, mixed cellularity; LD, lymphocyte depleted; UC, unclassified.

To date, at a median observation time of 86 months, 27 deaths have been recorded (Table 3 lists causes of death). Only five patients, all in arm A, died of HD. One died of complications of laparotomy, but there were no other first-line acute toxicity deaths. Two patients experienced fatal acute salvage toxicity. Six patients died from second malignancies (leukemia, one patient; NHL, two patients; solid tumors, two patients; unspecified, one patient), four died from cardiopulmonary-related causes (cardiomyopathy, one patient; myocardial infarction, one patient; decom-

Table 2. Treatment Outcome

	Arm A (n = 190)		Arm B (n = 186)	
	No. of Patients	%	No. of Patients	%
End of therapy				
CR	185	98	182	98
PR	1	< 1	1	< 1
Pro	2	1	3	2
NA	2	< 1	—	—
Relapses	41	22	29	16
Deaths (all)	17	9	10	5

Abbreviations: PR, partial remission; Pro, progression; NA, not assessed.

pensated heart failure, one patient; unspecified, one patient), and three died from pulmonary embolisms.

The incidence of acute radiation toxicity in each treatment arm is listed in Table 4. World Health Organization grades 3 to 4 were rare (at most, 4% of patients) with the exception of nausea (5% in each arm). No significant differences between the two treatment arms were seen. Of the possible late sequelae, only the secondary malignancies were reliably documented. Three patients with leukemias, four with NHL, and eight with solid tumors and one unspecified malignancy were reported, eight in each arm, in 4.3% of all patients. Of these malignancies, one leukemia, one NHL, and one breast cancer occurred after relapse therapy (four chemotherapy cycles in each case); the remaining cases occurred in continuous CR. Secondary solid tumors were localized as follows (with type of first-line RT): two malignant melanomas on the back (mantle–para-aortic), two breast cancers (mantle), one lung adenocarcinoma (mantle), one gastric carcinoma (mantle–para-aortic), one carcinoma of the colon descendens (mantle–para-aortic), and one astrocytoma (mantle–para-aortic).

Table 3. Causes of Death (number of cases)

	Arm A (n = 190)	Arm B (n = 186)
HD	5	—
Laparotomy toxicity	1	—
Acute salvage toxicity	2	—
Second malignancy*	2	4
Cardiopulmonary/lung embolism†	4	3
Other illness	1	2
Suicide/accident	1	1
NA	1	—
All deaths	17	10

*Leukemia (n = 1), non-Hodgkin's lymphoma (n = 2), solid tumors (n = 2), unspecified (n = 1).

†Lung embolia (n = 3), cardiomyopathy (n = 1), myocardial infarction (n = 1), decompensated heart deficiency (n = 1), unspecified (n = 1).

The frequency distribution of documented total dose to the noninvolved EF in each treatment arm is listed in Table 5 for supradiaphragmatic and infradiaphragmatic fields separately. One patient without RT documentation was excluded from this analysis. In total, 28 patients received no supradiaphragmatic RT and 31 received no infradiaphragmatic RT, correctly in each case, because the initial disease was restricted to the inguinal or upper cervical nodes, respectively. Further, four patients incorrectly went without supradiaphragmatic RT and 27 without infradiaphragmatic RT, because of the patients' wishes in most cases. There were 19 such cases in arm A and 12 in arm B. The distribution of total dose is described for all patients with documented irradiation to the corresponding field. For supradiaphragmatic fields, the documented dose was within $\pm$ 2 Gy of the planned dose in 95% of cases in each arm, and only 4% of arm B patients received 32 Gy or more supradiaphragmatically. In the infradiaphragmatic field, 13% of arm A patients received less than 39 Gy (6% received circa 30 Gy), whereas 3% of arm B patients were irradiated with 32 Gy or more. Four arm B patients received doses less than 20 Gy because of disease progression, intercurrent disease, or the patient's wish.

For all trial patients, the overall survival rate at 7 years after recruitment was 93% (95% confidence interval, 91% to 96%). RFS for all trial patients in CR at completion of protocol treatment was 80% (95% confidence interval, 75% to 84%). No significant difference between the treatment arms was seen for either of these end points (Figs 2 and 3); both rates were slightly higher in the reduced-dose arm B ($P = .093$ for RFS; $P = .16$ for OS).

Information on salvage therapy for first relapse was available for all 70 relapsing patients; 53 (76%) received COPP/ABVD or a similar chemotherapy; nine received bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone, five had radiation alone, and three were given COPP. Overall survival of all relapsing patients, measured from time of relapse, was 82% at 5 years, without a significant difference between treatment arms ($P = .23$; data not shown).

None of the patient or disease characteristics tested showed a significant association with RFS in multivariate analysis. However, the presence of a relevant PV significantly increased the risk of relapse ($P = .0087$). The treatment arm effect was nonsignificant in the Cox regression ($P = .15$), in agreement with the univariate Kaplan-Meier analysis reported above.

RT Quality Control

The Radiotherapy Review Center was able to assess the RT treatment films of 368 (98%) of 376 randomized

Table 4. Acute First-Line Radiation Toxicity According to WHO Grade

	Arm A* (%)				Arm B† (%)			
	1	2	3	4	1	2	3	4
Leukopenia	12	4	—	—	10	5	1	—
Thrombopenia	3	—	—	—	1	—	—	—
Anemia	3	1	—	—	3	—	—	—
Infection	3	3	1	—	1	3	—	—
Skin	30	16	4	1	35	15	1	—
Pharynx	29	15	2	—	33	8	1	—
Larynx	18	3	—	—	23	3	—	—
Nausea	43	13	8	1	42	16	9	—
Esophagus	24	8	1	1	25	8	—	—
Lung	3	1	—	1	3	—	—	—
Heart	—	1	—	—	—	—	—	—
Pericardia	1	1	—	—	1	—	—	—
Stomach	11	5	3	—	13	35	1	—
Kidney	1	—	—	—	1	—	—	—
L'Hermitte	1	1	—	—	—	—	—	—

NOTE. Cases without any documentation of acute toxicity (n = 72) were excluded.
Abbreviation: WHO, World Health Organization.
*Cases included, 158; cases excluded, 32.
†Cases included, 146; cases excluded, 40.

patients. Thirty-seven percent of patients had at least one PV. Table 6 shows the frequency of PVs per treatment arm. Category V− (incomplete coverage of tumor or inadequate safety margin) was by far the most frequent, with 29% and 28% in the 40-Gy arm and 30-Gy arm, respectively. Prolonged administration (Ds, overall frequency 6%), inadequate dose (D−, overall frequency 5%), and technical deficiency (T, overall frequency 4%) followed; too large a volume or dose was rare (V+, D+, overall frequency of each was 1%). No significant differences in PV frequencies between arms were observed.

Relevant PV (V−, D−, Ds, T) was associated with a significantly lower RFS (Fig 4) of 72% at 7 years, compared with 84% for patients without such a PV ($P = .0043$). Note that only patients attaining a CR are included for RFS, so patients incurring a PV because of adverse disease course, which would bias the comparison, were not included.

Table 5. Total Given Radiation Dose to the Noninvolved EF as Documented

	Arm A (n = 190)		Arm B (n = 186)	
	Supra	Infra	Supra	Infra
RT not planned to this field, n	15	17	13	14
RT planned but not given, n*	3	16	1	11
Included in dose analysis, n	171	156	172	161
Total given dose, % of patients				
10-19 Gy	—	—	2	< 1
20-28 Gy	—	1	< 1	—
29-31 Gy	1	6	94	96
32-38 Gy	4	5	2	2
39-41 Gy	95	88	2	1
> 42 Gy	< 1	—	—	—

NOTE. One patient without RT documentation was excluded. Percentages refer to all patients receiving documented radiation to the respective field (supradiaphragmatic or infradiaphragmatic), as detailed in the upper part of the table.
*Patient's wish was the most common reason given for not irradiating prescribed fields.

Radiologic Assessment of Relapse

As of May 2000, CT images from 52 of the 70 reported relapsed patients had been evaluated. Figure 5 describes the location of 47 relapses among patients with primary supradiaphragmatic disease and five among those with primary infradiaphragmatic disease. All patients with infradiaphragmatic disease experienced relapse in supradiaphragmatic nodal sites, one also in the lung, and one also in infradiaphragmatic sites. The majority of patients with supradiaphragmatic disease had recurrence in infradiaphragmatic nodes (n = 27); 18 of these were solely infradiaphragmatic nodal relapses and seven also had involved supradiaphragmatic nodes. There were a smaller number of pure supradiaphragmatic relapses (n = 8). Overall, 16 of the patients experienced relapses involving extranodal organs, the most common being the lung (n = 8) and the liver (n = 5).

Table 7 describes the frequencies of types of relapse sites in each arm with respect to primary involvement and radiation field (note that each relapse may be counted in > one category). Most frequent were new outfield (OFN) sites

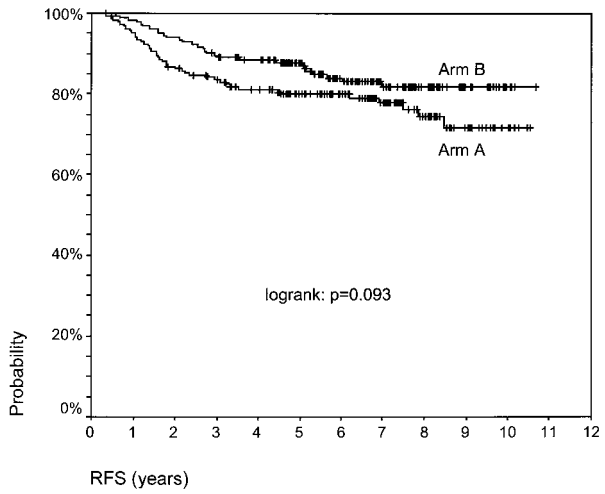

Fig 2. RFS in each treatment arm, including all eligible, randomized patients who attained a CR under protocol therapy (arm A, n = 185; arm B, n = 182).

(71 sites in 42 patients), then marginal (MR) relapses (30 sites in 17 patients). Recurrences within the radiation field (IFN, 16 sites in nine patients; IFL, 10 sites in nine patients) were less common. The treatment arms do not seem to show different patterns of relapse.

DISCUSSION

EF-RT alone for pathologic stage I and II HD patients without adverse prognostic factors was able, in the multicenter setting of the HD4 trial, to induce a CR in 98% of patients, 80% of whom remained free of recurrence for at least 7 years. These results reflect the effectiveness of EF-RT alone as a first-line modality as well as the effectiveness of salvage therapy for patients who experienced relapse, who had more than an 80% chance of surviving 5 or more years through salvage treatment with a COPP/ABVD-like regimen in the majority of cases. These results compare well with those obtained by other groups using EF-RT in similar patients.[2,29-31] Further, EF-RT causes little severe acute toxicity. The observed second cancer rate of 4.3% with 7 years median follow-up was moderate but is expected to increase because of late solid tumors.[14,15]

The 7-year RFS rate in HD4 was lower than the 89% seen in the parallel GHSG trial HD5 for stage I to IIIA HD with risk factors,[32] in which four chemotherapy cycles preceded irradiation. However, HD4 was superior to HD5 with respect to CR rate (HD5, 91%) and 7-year OS rate (HD5, 90%). The more durable remissions obtained with com-

Table 6. PVs as Prospectively Assessed by the Radiotherapy Review Center

	Arm A, % (n = 190)	Arm B, % (n = 186)
Technical (T)	2	6
Volume too large (V+)	2	1
Volume too small (V−)	29	28
Dose too large (D+)	—	2
Dose too small (D−)	6	5
Dosage too slow (Ds)	5	6
Any protocol violation	38	37

NOTE. A total of 183 of 190 cases in arm A and 186 of 186 cases in arm B were assessed (98% overall). Each case may be counted in more than one PV category.

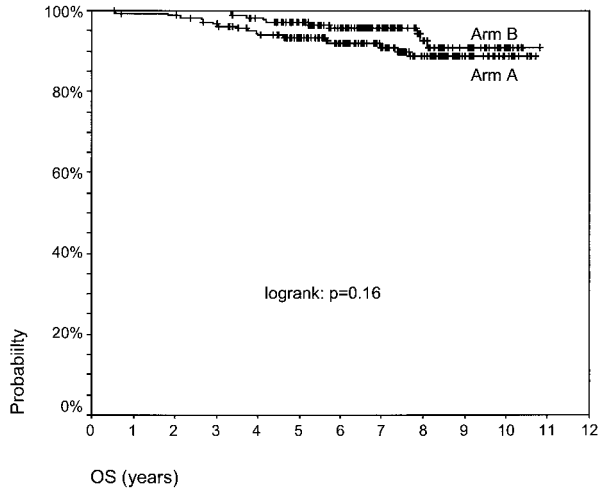

Fig 3. OS in each treatment arm, including all eligible, randomized patients (arm A, n = 190; arm B, n = 186).

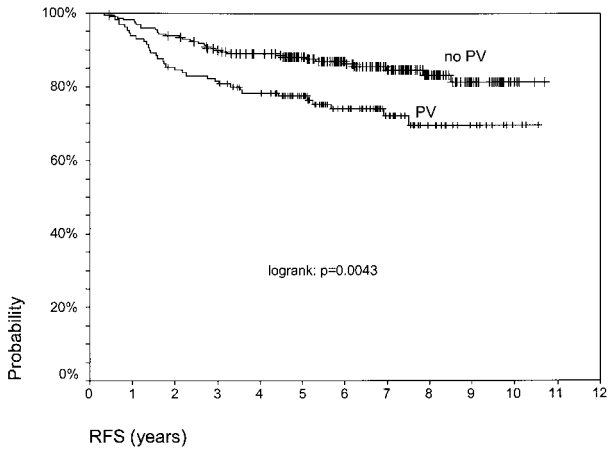

Fig 4. RFS according to presence (n = 127) or absence (n = 242) of a relevant RT PV. Relevant PVs are defined in Patients and Methods, under Statistics.

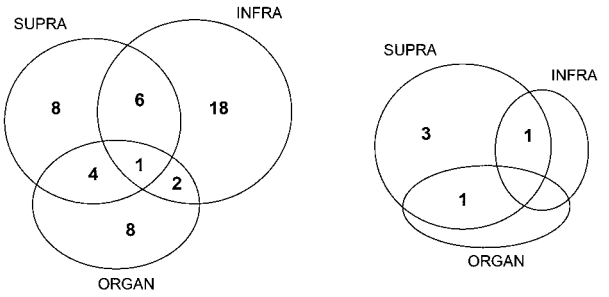

Fig 5. Supradiaphragmatic nodal, infradiaphragmatic nodal, and organ involvement (lung [n = 8], liver [n = 5], bone [n = 3], bone marrow [n = 2], pericardia [n = 2], pleura [n = 1]) at relapse, separately for patients with primary disease as supradiaphragmatic (left, n = 47) and infradiaphragmatic (right, n = 5), respectively.

bined modality must be set against the greater difficulty of salvage treatment and greater toxicity. The higher rate of patients who experienced incomplete responses in HD5 is presumably due to the unfavorable nature of disease (presence of adverse prognostic factors) in the HD5 cohort.

The treatment arm comparison results suggest that 30 Gy in the clinically noninvolved EF is equivalent in efficacy to 40 Gy. The 95% confidence interval for the true difference in 7-year RFS between the 30 Gy and 40 Gy schemes extends from −4% to 14%, indicating a worst-case value of 4% inferiority due to the dose reduction. This result was confirmed by a multivariate analysis in which the effect of prognostic factors and PVs were considered. Similarly, OS seems to be at least equivalent with the 30 Gy scheme. The number of deaths not directly attributable to HD was approximately equal in both arms (Table 3), but all deaths attributable to HD (n = 5) or to acute salvage toxicity (n = 2) occurred in the 40 Gy arm. No plausible explanation could be found for this imbalance: because it seems unlikely that 30 Gy could achieve better tumor control than 40 Gy, we assume that the imbalance in HD deaths was due to chance.

Table 7. Relapse Sites in Relation to Initial Disease and Field Irradiated in HD4

	Arm A (n = 190)	Arm B (n = 186)
IFL	6	3
IFN	6	3
OFL	1	0
OFN	26	16
MR	11	5
Total assessed	33	19
All relapses	41	29

NOTE. Data represent number of patients with at least one relapse site of the given type (according to reference radiotherapy panel up until May 2000). Each relapse case may be counted in more than one category.

Furthermore, the intended dose reduction to 30 Gy in the noninvolved field was actually achieved in the great majority of cases: only 4% of arm B patients received a dose of 32 Gy or more, whereas just 6% of arm A patients received less than 32 Gy (Table 5). The observed equivalence is therefore not due to a blurring of the distinction between the assigned dose levels. However, it must be remembered that the trial was not blind—the possibility cannot be excluded that either the treating clinician or the patient in arm B, being aware of the reduced dose, consciously or unconsciously compensated by, for instance, more careful radiotherapeutic technique, wider field margins, or more regular or thorough follow-up examinations. With respect to radiation technique, comparison of the number of PVs in each arm revealed no consistent or relevant differences between the treatment arms. In particular, inadequate field volumes were seen in 29% of patients in arm A and in 28% of patients in arm B, and excessive field volumes were seen in 2% and 1% of patients, respectively. With respect to follow-up, differences here would not influence RFS.

What is the clinical significance of this result? It is plausible that a 10 Gy dose reduction in the noninvolved EF should reduce the burden of acute and late toxicities associated with radiation. No reduction in acute toxicities, which are in any case relatively minor, could be demonstrated in this trial. Of greater relevance are the late sequelae such as second cancers, cardiorespiratory disease, pulmonary toxicity, and thyroid effects,[13] all of which have been clearly related to irradiation in HD patients. Regrettably, assessment and documentation of late effects in HD4 were inadequate for a reliable analysis because of incomplete data. However, as described in the introduction, correlation between incidence and radiation dose has been inferred elsewhere for certain late toxicities.

The review and assessment of RT simulation and verification films led to identification of prognostically relevant PV in a considerable proportion of cases. The multicenter nature of the trial should be taken into account when assessing this result. The proportion of patients with PV varied considerably between participating centers, with statistically significant differences in this proportion between the 10 centers that contributed 10 or more cases (P = .005). However, no association between PV frequency and type of center could be discerned. Information on the nature, frequency, and prognostic relevance of PV is provided back to participating radiotherapists at annual GHSG meetings, thus forming a quality control cycle with the potential to improve standards and treatment outcome.

Treatment strategies for favorable early-stage HD have evolved considerably since HD4, although EF-RT alone is still regarded as standard in some institutions. A major influence has been the availability of less toxic chemotherapy regimens and the improvement in noninvasive staging techniques. This has led to abandonment of laparotomy staging in most centers, coupled with the insertion of limited chemotherapy before radiation. The additional systemic therapy is designed to control undetected abdominal disease. A large reduction in the risk of recurrence has been demonstrated, even with minimal chemotherapy,[8] although no improvement in OS has been demonstrated. Salvage by conventional chemotherapy such as COPP/ABVD or bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone is highly effective after first-line radiation alone, as our present results show, but has not yet been accurately assessed after a combined-modality strategy. Also important is the additional late toxicity owing to the chemotherapy, although the hope is, by choice of a mild regimen and low doses, to keep this toxicity to a minimum. This strategy is particularly attractive if radiation is limited to the involved field, which leads to a marked reduction in irradiated volume in these early-stage patients and thus to a potential toxicity benefit. Essentially, the control of subclinical disease is thus delegated to chemotherapy, whereas irradiation (supported by chemotherapy) controls clinical disease. The observed relapse pattern in HD4 (Fig 5) emphasizes an advantage of this strategy: chemotherapy is effective against the many outfield and extranodal recurrences that lie outside the range of EF radiation. Further, because the drugs are also active in involved areas, the radiation dose to involved areas may also be reduced from the previous 40-Gy standard.[33]

In the GHSG, these developments are apparent in the successor trials for favorable early-stage HD. In HD7 (recruitment 1994-1998), clinically staged patients were treated with EF-RT as in HD4, according to randomization with or without the insertion of two ABVD cycles before RT. Interim analyses[34] have already demonstrated a worthwhile improvement in failure-free survival without a relevant increase in acute toxicity. Patients in the radiation-alone arm of HD7, however, fared slightly worse than those in HD4, presumably because of the lack of laparotomy staging and consequently the presence of some untreated occult abdominal disease. In the current trial (HD10), all patients receive chemotherapy (two or four cycles of ABVD) and only involved-field RT is given to a dose of 30 or 20 Gy.[35]

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