Dose-Response Relationship of Complementary Radiotherapy Following Four Cycles of Combination Chemotherapy in Intermediate-Stage Hodgkin's Disease

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Purpose: **To determine the appropriate irradiation dose after four cycles of modern combination chemotherapy in nonbulky involved field (IF/BF) and noninvolved extended-field (EF/IF) sites in patients with intermediate-stage Hodgkin's disease (HD).**

Materials and Methods: **HD patients in stage I to IIIA with a large mediastinal mass, E stage, or massive spleen involvement were treated with two double cycles of alternating cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) plus doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by EF irradiation in two successive trials (HD1 and HD5). In the HD1 trial (1983 to 1988), 146 patients who responded to chemotherapy were randomized to receive 20 Gy (70 patients) or 40 Gy (76 patients) of EF irradiation in all fields outside bulky disease sites. A cohort of 111 patients who fulfilled the same inclusion criteria in the subsequent trial HD5 (1988 to 1993) were treated with 30 Gy. Bulky disease always received 40 Gy.**

Results: **Freedom-from-treatment-failure (FFTF) and survival (SV) curves showed no differences between the 20-, 30-, and 40-Gy groups. However, acute toxicities were more frequent in the 40-Gy arm. Analysis of relapse patterns showed that 18 of 26 relapsing patients either failed to respond in initial bulky sites (n = 5) or had an extranodal relapse (n = 9) or both (n = 4). After 5 years, the cumulative risk for relapse in bulky sites is 10%, despite 40 Gy of radiation.**

Conclusion: **Our results strongly suggest that there is no relevant radiotherapy dose effect in the range between 20 Gy and 40 Gy in IF/BF and EF/IF after 4 months of modern polychemotherapy in patients with intermediate-stage HD. Relapse patterns indicate that patients destined to relapse need more systemic, rather than local, treatment. Based on our data, we conclude that 20 Gy is sufficient in EF/IF of intermediate-stage HD following four cycles of modern polychemotherapy.**

J Clin Oncol 15:2275-2287. © 1997 by American Society of Clinical Oncology.

IT IS WIDELY ACCEPTED that intermediate-stage Hodgkin's disease (HD) patients in pathologic or clinical stage (PS/CS) I, II, and limited-stage III with additional prognostically adverse factors may qualify for a combination of chemotherapy and radiotherapy. The precise definition of this group varies between trial groups.[1] Such adverse prognostic factors are as follows: a large mediastinal mass,[2] massive splenic involvement,[3] a large number of involved lymph node areas,[4-5] an enhanced erythrocyte sedimentation rate,[6-8] anemia,[9,10] tumor burden,[11-13] and nodular sclerosis grade II histology.[10,14] It is generally believed that such patients should receive four to six cycles of modern multidrug chemotherapy and in addition radiotherapy to the involved field (IF) or the extended field (EF). The combination of the number of chemotherapy cycles, the field sizes, and the dosage of radiation within these fields are subject of debate.[15]

There is little debate that bulky disease like a large mediastinal mass should receive radiotherapy and 40 to 45 Gy is generally given. With respect to the optimal dosage of radiotherapy in nonbulky involved-field areas (IF/BF) and in noninvolved extended-field areas (EF/IF) after chemotherapy, only parsimonious data are available and, to our knowledge, no conclusive studies have been undertaken (see Discussion).

The German Hodgkin Lymphoma Study Group (GHSG) in 1982 designed the HD1 trial to investigate in greater detail which dose of radiation would be required in nonbulky involved fields (IF/BF) and noninvolved extended fields (EF/IF) following only two dou-

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Submitted January 13, 1997; accepted March 10, 1997.

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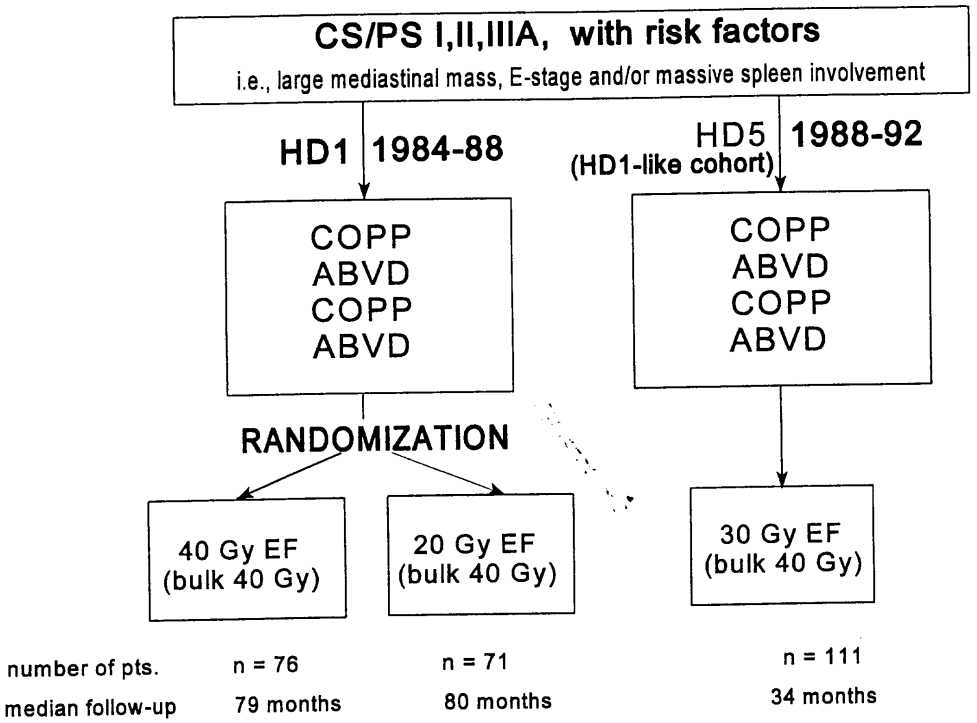

Fig 1. Flowsheets of the HD1 trial and of the corresponding historical control group of the HD5 trial.

ble cycles of cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) plus doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). For areas with bulky disease, 40 Gy of irradiation was given, while in the other areas, 40 Gy was compared with 20 Gy (Fig 1).

Additional data about a dose of 30 Gy became available recently from the HD5 trial of the GHSG. This trial was initiated in March 1988 to compare two polychemotherapies in a combined modality setting. One of these chemotherapies was the COPP plus ABVD scheme also used in the HD1 trial (the other scheme consisted of a rapidly alternating COPP/ABV/ifosphamide, methotrexate, etoposide, and prednisone [IMEP] scheme). Chemotherapy was followed by a similar radiation strategy as in the HD1 trial, including EF irradiation. While the dose remained 40 Gy to bulky sites, a dose of 30 Gy was chosen for the nonbulky nodal sites. Here, we present the data on 20-, 30-, and 40-Gy EF radiation (bulky 40 Gy) after four cycles of combination chemotherapy in intermediate-stage HD.

MATERIALS AND METHODS

The following abbreviations regarding radiation fields are used throughout: BF, bulky site field; IF/BF, involved field outside the BF field (ie, nonbulky nodal disease sites); EF/IF, extended field outside the IF field (ie, areas of suspected subclinical disease); EF/BF, extended field outside the BF field; and OF, nodal outfield (ie, all nodal areas outside the extended field).

Study Design

Eligibility. Untreated patients between 15 and 60 years of age with histologically proven HD were eligible. Patients in PS/CS I, II, and IIIA with one or more of the following three adverse prognostic factors were entered: large mediastinal mass with more than one third of the maximum thoracic diameter, massive spleen involvement with diffuse infiltrations, or more than five focal lesions or extranodal involvement (according to the Ann Arbor staging system). Patients with impaired heart, lung, liver, or kidney function or previous malignant diseases were excluded.

Patients were asked to sign a document about informed consent before entry onto the study. The document had beeen aproved by the Institutional Review Board of the GHSG.

For completeness, it should be noted that the HD5 trial had a broader inclusion spectrum than the HD1 trial by taking two additional risk factors into account: elevated erythrocyte sedimentation rate and three or more lymph node areas involved. We restrict our attention only to HD5 patients who fulfill the inclusion criteria for the HD1 trial and who were randomized to the COPP plus ABVD scheme.

Recruitment. Patients were entered to the HD1 trial between January 1984 and February 1988. The median observation time is 6.5 years. Between March 1988 and January 1993, patients were entered onto the HD5 trial. The median observation time is 3 years.

Staging procedure. The staging procedures included the following mandatory examinations: size of all enlarged lymph nodes, size of liver and spleen, presence and duration of symptoms, chest x-

ray, thoracic computed tomographic (CT) scan, abdominal CT scan and ultrasound, bone marrow biopsy, liver biopsy, radioisotope scan of the skeletal system, and a number of laboratory tests (erythrocyte sedimentation rate, alkaline phosphatase, WBC, hemoglobin, thrombocytes, differential blood counts, and liver enzymes); liver and spleen scintiscan, bipedal lymphangiography, and x-ray of the skeleton were optional examinations. A massive mediastinal mass was diagnosed if a mediastinal tumour was greater than one third of the maximum thoracic diameter.

Histologic diagnosis was made by regional pathologists and copies of the reports were sent to the study center. Staging laparotomy was recommended in the HD1 trial, but not in the HD5 trial. Laparotomy (CS I to IIIA) was performed according to international standards.[16]

Treatment protocol. The study designs are summarized in Fig 1. Patients received two double cycles of alternating COPP plus ABVD followed by careful restaging and subsequent radiotherapy.

Chemotherapy. COPP was given as a modification of the MOPP scheme reported by De Vita et al[17] with mustargen being substituted by cyclophosphamide: cyclophosphamide 650 mg/m^2 intravenously (IV) on days 1 and 8, vincristine 1.4 mg/m^2 (maximum, 2 mg) IV on days 1 and 8, procarbazine 100 mg/m^2 orally on days 1 to 14, and prednisone 40 mg/m^2 orally on days 1 to 14, with recycling on day 29.

ABVD was given according to the Milan protocol[18]: doxorubicin 25 mg/m^2 IV on days 1 and 15, bleomycin 10 mg/m^2 IV on days 1 and 15, vinblastine 6 mg/m^2 IV on days 1 and 15, dacarbazine 375 mg/m^2 IV on days 1 and 15, with recycling on day 29.

Radiotherapy. Before chemotherapy was started, all clinical and pathologic sites of disease were mapped. If the patient was given radiation, all initially involved nodal sites had to be included in the treatment ports. Centers that participated in the trial were requested to use megavoltage EF techniques with customized blocks. Use of a simulator was mandatory. Techniques for compensation of local dose excess were recommended. Radiotherapy was also given to the spleen if the spleen or paraaortic lymph nodes were involved. No routine radiation was recommended for liver or lung involvement. Doses had to be delivered in 1.8- to 2.0-Gy daily fractions with megavoltage radiation or cobalt 60. Kidney blocks were used when necessary. The radiation volume of a massive mediastinal mass encompassed the original volume up to 16 Gy total dose. Reduced volumes were recommended for subsequent fractions. A heart block was recommended if doses were greater than 16 Gy. EF irradiation implied the following volumes: upper cervical involvement only Waldeyer's ring and mantle field; supradiaphragmatic involvement only mantle field, paraaortic spade, and spleen; supradiaphragmatic and paraaortic involvement mantle field, inverted-Y field, and spleen; Infradiaphragmatic involvement only T-field, inverted-Y field, and spleen; inguinal involvement only inverted-Y field and spleen; and IIIA, total nodal irradiation.

Bulky disease was defined as a tumor location with a tumor diameter greater than 7.5 cm in one axis. Massive mediastinal tumor was defined as a tumor greater than one third of the maximum thoracic diameter.

BF were planned to receive 40 Gy in any case for both the HD1 and HD5 trials. The dose in the EFs and IFs outside BF was 40 Gy in arm A and 20 Gy in arm B of the HD1 trial, and 30 Gy in the HD5 trial. To describe the extent of radiotherapy given to the patient cohorts, the dose planned and actually given was determined for each potential nodal disease site. Fourteen such nodal sites were distinguisted for the HD1 patients: Waldeyer's ring (n = 1), cervical (n = 2), supraclavicular (n = 2), axillary (n = 2), mediastinum (n = 1) spleen hilus (n = 1), paraaortic (n = 1), iliacal (n = 2), and inguinal (n = 2).

Twenty nodal sites were distinguished for the HD5 patients: Waldeyer's ring (n = 2), upper cervical (n = 2), cervical (n = 2), supraclavicular (n = 2), axillary (n = 2), lung hilus (n = 2), mediastinum (n = 1) spleen hilus (n = 1), spleen (n = 1), paraaortic (n = 1), iliacal (n = 2), and inguinal (n = 2).

Treatment allocation. Patients who had undergone chemotherapy according to protocol and did not progress during chemotherapy were eligible for randomization to one of the two treatment arms in the HD1 trial (arm A, 40 Gy EF; arm B, 20 Gy EF). Of 183 patients registered to the HD1 trial, 22 were not eligible. The reasons for noneligibility were as follows: HD not confirmed by reference pathology (three cases); progressive disease during or immediately after chemotherapy (six cases; two died within 1 year, three within 3 years, and one achieved a clinical complete remission [CR] with further chemotherapy); premature termination at patient's request (four cases); and protocol violation of chemotherapy (nine cases; one received a different polychemotherapy after two courses of COPP plus ABVD, and eight received three courses of COPP plus ABVD). Randomization was refused by a further 14 patients, which left 147 patients actually randomized in the HD1 trial. A total of 111 comparable patients registered to the HD5 trial are currently assessable.

Randomization. Randomization was performed by the random permuted block method with stratification according to stage and centers.

Documentation

Report of treatment. Treatment was documented after each chemotherapy cycle and after radiotherapy. This included dose scheduled, dose given, toxicity, and reasons for dose reductions or extensions of the time frame. Furthermore, documentation was requested after each restaging and at regular intervals in the follow-up period.

All data forms were carefully checked by two data managers and a physician and were entered into a data base with interactive programs that provided consistency checks. Data on the vital status of patients were cross-checked with public death registries. At regular intervals, follow-up forms were requested.

Evaluation of treatment outcome. The success of treatment was determined by restaging 4 weeks after chemotherapy and 4 to 8 weeks after the termination of the protocol treatment. It consisted of a control and careful documentation of all initial disease manifestations by adequate clinical and histological methods. CR was defined as the disappearence of all clinical disease manifestations for at least 4 weeks. Partial remission (PR) was defined as reduction in all disease localizations by at least 50% compared with the initial involvement. Patients with questionable persisting disease were classified as partial responders, which also included the status of uncertain CR (eg, with residual mass).

Central Reviews

Pathology review. Histologic diagnosis was made initially by local pathologists, who were asked to submit material to a central panel of pathologists for review. Registration to the trial occurred on the basis of the initial diagnosis. Cases with the review diagnosis "not HD" were excluded from analysis. In the absence of a review

diagnosis, or in cases in which the review was inconclusive (due either to inadequate material or to unusual results), the initial diagnosis of HD was deemed sufficient for eligibility.

In total, 151 of the original 183 HD1 patients underwent central histologic review. Eight of these 151 cases could not be conclusively reviewed because of inadequate sample material. HD was confirmed in 132 of the 143 reviews based on adequate samples. Three patients were excluded from the analysis because the review panel diagnosed not HD. In eight cases, HD could not be proven or disproven. These cases were included in the analysis, on the basis of the initial diagnosis, but special attention is given to them (see Subgroups Analysis). Based on this experience, we can assume that the 32 HD1 cases (of 183 assessable cases) not reviewed may contain a maximum of two lymphomas other than HD.

Radiotherapy review. A central review of all documentation forms of the radiotherapy intended and actually given has been undertaken. However, no CT scans and verification films were requested for this review. Protocol violations were classified in terms of field sizes, dose, and timing. Major protocol violations (MPV) were defined as cases in which IFs had not been irradiated at all. All other deviations in field margins, dosage, timing, and technical modalities were classified as minor protocol violations. In case of relapse, the reported relapse sites were classified with respect to the radiation field actually treated. This provided information on whether a relapse occurred at a known initially involved site or at a new initially uninvolved site and whether this was within or outside the radiation field.

Biometry

End points. The CR rate was defined as the ratio of all patients in CR to all assessable patients. Freedom from treatment failure (FFTF) was defined as the time from the start of therapy (including laparotomy) to the first of the following events: death, progressive disease, non-CR status (PR or no change) at the end of the protocol treatment (disregarding the restaging following chemotherapy treatment), or relapse.[19] Survival times were obtained and included all deaths whether disease-related or not. All time-to-event data were recorded from the start of treatment. Kaplan-Meier estimates are given for the probabilities to survive beyond a given time. Pairwise comparisons of failure time data used the log-rank test. Comparisons of treatment groups were performed according to intention to treat. To evaluate local field-specific relapse rates, only patients with proven CR were considered and time to first appearance of tumor was recorded seperately for BF, IF/BF, and EF/IF in each patient. This implied true recurrence or new appearance of tumor. Kaplan-Meier estimates were undertaken for each of these fields and cumulative local relapse rates were estimated for two time points (30 and 60 months) after CR.

Proportional hazards models. To evaluate the independent contributions of potential prognostic factors, proportional hazards models were set up for FFTF and overall survival (SV) as end points. Proportional hazards models were constructed for all HD1 patients and for all randomized HD1 patients. Covariates considered were age (0 if $\leq$ 40, 1 if $>$ 40 years), stage (0 if I or IIA, 1 if IIB or IIIA), large mediastinal mass (yes/no), erythrocyte sedimentation rate, alkaline phosphatase, and hemoglobin. The latter parameters were dichotomized using as cutpoints 80 mm/h for erythrocyte sedimentation rate, 230 U/L for alkaline phosphatase, and 12 g/L for hemoglobin for males and 10.5 g/L for females. This corresponds to published cutpoints used by us[17] or others.[19] In addition, models were fitted to the entire data set of all HD1 and HD5 patients with the previous covariates, including also a linear and quadratic term to account for possible dose responses of the radiation dose. Regression models with all parameters included were built up, and step-down regression was performed. All regression models were restricted to patients with complete data sets.

Table 1. Patient Characteristics

Characteristic	HD1 Arm A (40 Gy) No.	%	HD1 Arm B (20 Gy) No.	%	HD5 (30 Gy) No.	%
Assessable	76		71		111	
Sex						
Male		55		52		56
Age, years						
Median	29		27		31	
Range	16-56		15-60		16-62	
Histology						
LP	1	1	2	3	6	5
NS	51	67	49	69	73	66
MC + EP	14	18	8	11	19	9
LD	1	1	0	0[a]	0	0
Not classified	9	12	12	17	13	12
Reference pathology	53	70	59	83	74	67
Laparotomy	38	50	32	45	25	23
Stage (CS/PS)						
I	0	0	4	6	8	7
II	49	64	41	58	65	59
III	27	36	27	38	38	34
B symptoms	18	24	19	27	33	30
Risk factors						
Massive spleen*	22	29	26	37	29	26
Extranodal*	19	25	12	17	30	27
Large mediastinal mass*	49	64	40	56	64	58
Bulky disease (> 7.5 cm)	51	67	46	65	70	63

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

*Not mutually exclusive.

Patient Population

Study centers. Patients for the HD1 trial were recruited from 41 study centers, with one center providing 38 patients and 18 others only one patient. Patients for the subset of the HD5 trial were recruited from 26 study centers, with one center providing nine patients and seven others only one patient. Participating centers are listed in the Appendix.

Patient characteristics. Table 1 lists patient characteristics of the two randomized groups of the HD1 trial (arm A, 40 Gy EF; arm B, 20 Gy EF) and of the respective treatment arm of the HD5 trial that received 30 Gy EF. For simplicity, we shall refer to this cohort as the HD5 group.

There are no apparent differences between the three groups, except for the frequency of laparotomy. This is due to the fact that staging laparotomy was recommended in the HD1 trial, but not in the HD5 trial. The laparotomies performed in the HD5 group are largely due to patients in stage CS I and IIA, who would have qualified for a pure radiotherapy strategy in case of negative outcome.

Table 2. Irradiation Volume Given

Initial Disease Localization	Fields to be Irradiated	Patients to be Treated: HD1 Arm A No.	HD1 Arm A %	HD1 Arm B No.	HD1 Arm B %	HD5 No.	HD5 %
Upper cervical	WR + Mantle	0	0	0	0	1	1
Supradiaphragmatic	Mantle + spleen + paraaortic	45	59	41	58	65	59
Supradiaphragmatic + infradiaphragmatic	Mantle + spleen + Inv-Y	27	36	27	38	39	35
Infradiaphragmatic	T field + spleen + Inv-Y	4	5	3	4	6	5
Inguinal	Spleen + Inv-Y	0	0	0	0	0	0
Total		76	100	71	100	111	100

Abbreviations: WR, Waldeyer's ring; Inv-Y, inverted-Y field.

RESULTS

Chemotherapy

Generally, scheduled chemotherapy could be given without problems. Patients in the three groups received 98% of the scheduled average dose. The mean dose-intensity given (ie, dose/time) was 85% in the HD1 groups and 89% in the HD5 group.

Radiotherapy

Table 2 shows that the three treatment groups were comparable with respect to the different irradiation volumes planned. The combination of mantle-field plus paraaortic spade and spleen irradiation is the dominant one, followed by the combination of mantle-field, inverted-Y field, and spleen irradiation.

Tables 3 and 4 list the radiation doses actually delivered to the various nodal sites. The frequencies refer to the total number of sites (summed over all patients) in a given field (OF, EF/BF, or BF) that received a particular radiation dose. Information was available about doses given to 2,058 nodal sites in 147 HD1 patients (ie, 14 sites per patient) and on 2,120 sites in 106 HD5 patients (ie, 20 sites per patient).

Tables 3 and 4 illustrate that the 20-Gy difference in dose intended in the EF/BF fields was, on average, actually established. There were some deviations in the 40-Gy arm, ie, lowering the scheduled dose, and some deviations in the 20-Gy arm, ie, exceeding the scheduled dose. Hence, the difference achieved between the two trial arms was somewhat smaller than intended, but still large enough to draw valid conclusions. Unplanned dose reductions and dose increases were roughly balanced for the 30-Gy arm. Thus, a dose-response relationship between the 20-, 30-, and 40-Gy settings appears testable.

The radiation dose to bulky disease was exactly 40 Gy

Table 3. Irradiation Dosage Given: HD1 Randomized Patients Only

Dose (Gy)	Sites: OF (0 Gy intended) No.	OF (0 Gy intended) %	Arm A EF/BF (40 Gy intended) No.	Arm A EF/BF (40 Gy intended) %	Arm B EF/BF (20 Gy intended) No.	Arm B EF/BF (20 Gy intended) %	BF (40 Gy intended) No.	BF (40 Gy intended) %
0-10	462	92	39	5	50	7	1†	1
> 10-19	1	< 1	16	2	6	1	—	—
> 19-21	7	1	6	1	524	74	—	—
> 21-30	2	< 1	26	3	36	5	1*	1
> 30-35	1	< 1	2	< 1	7	1	—	—
> 35-39	4	1	65	9	9	1	7	7
> 39-41	20	4	593	79	76	11	83	85
> 41-45	4	1	2	< 1	1	< 1	4	4
> 45	—	—	—	—	1	< 1	2	2
Total	501	100	749	100	710	100	98	100

*One mediastinal bulk received irradiation with 9 Gy at diagnosis; received a further 20 Gy during therapy.

†One patient (arm B) refused further irradiation when only 10 Gy had been delivered.

Table 4. Irradiation Dosage Given: HD5 Patients

	Sites					
	OF (0 Gy intended)		EF/BF (30 Gy intended)		BF (40 Gy intended)	
Dose (Gy)	No.	%	No.	%	No.	%
0-10	458	92	68	4	1*	< 1
> 10-25	—	—	15	1	—	—
> 25-29	—	—	3	—	—	—
> 29-31	39	8	1,316	86	6	7
> 31-35	—	—	21	2	—	—
> 35-39	—	—	17	2	—	—
> 39-41	—	—	83	5	82	89
> 41-45	—	—	4	—	3	4
> 45	—	—	4	—	—	—
Total	497	100	1,531	100	92	100

NOTE. Patients include 111 in HD5 analog to HD1; 5 of these patients did not have documented dosages. Therefore, this table presents the data of 106 patients.

*One left iliac site was not irradiated.

Table 5. Toxicity: Number of Patients Showing Documented Side Effects During Radiotherapy

Side Effect	Arm A (40 Gy), n = 76	Arm B (20 Gy), n = 71	HD5 (30 Gy)†, n = 111
Leukopenia	20	10	31
Thrombocytopenia	15*	6*	17
Nausea	40	27	23
Vomiting	14	8	NA
Diarrhea	8	4	NA
Stomatitis	4	6	NA
Cystitis	0	1	NA
Dysphagia	24*	12*	12
Heart	1	1	0
Lung	2	3	2
Skin	26*	12*	13

Abbreviation: NA, not available.

*Due to differences in toxicity data collection, HD5 data are not strictly comparable with HD1 data. However, the differences between the 20-Gy and 40-Gy arms were significant ($P < .05$).

†Toxicity data in the HD5 trial were categorized according to WHO grade. The frequencies in the HD5 column are for toxicities ≥ grade 2.

to 85% of all bulky sites, and was between 35 Gy and 45 Gy in 96% of such sites in HD1 patients. Four exceptions occurred. In one case, radiotherapy was terminated at 10 Gy at the patient's request. In a second case, the exact dose to the mediastinum is unknown, but was at least 20 Gy. One patient received 52 Gy to the mediastinum due to a large residual tumor that remained after 40 Gy. One patient received 48 Gy to the mediastinum without apparent clinical justification. The radiation dose in HD5 was exactly 40 Gy to 89% of all bulky sites, and was between 35 Gy and 45 Gy in 92% of such sites. One left iliacal bulky site was not irradiated, and seven bulky sites were treated with only 30 Gy.

Toxicity

Tables 5 and 6 list acute toxicities of World Health Organization (WHO) grade 2 or higher reported to the study center. Although the assessment of the acute toxicities during radiotherapy lacked formal monitoring, we believe that the differences reported are clinically correct. Hence, the higher radiation dose is associated with a significantly higher rate of thrombocytopenia, dysphagia, and skin irritations. Taken together, the 40-Gy arm was associated with more acute side effects during radiotherapy.

The long-term toxicities showed similar rates of documented serious infections (mostly herpes zoster) independent of the radiation dose (Tables 5 and 6). The rate observed in the HD5 group was not reported, as it has a shorter follow-up time. There is, at present, only a small number of secondary neoplasias without preference of one group. Further late complications are listed in Tables 5 and 6, and indicate that there is an overall higher rate in the 40-Gy arm.

Treatment Outcomes

Table 7 lists the treatment outcomes for the two HD1 groups, for the entire HD1 cohort, and for the HD5 group.

After the entire HD1 treatment, 158 of 180 patients (88%) achieved a CR (95% confidence interval, 82% to 92%). Thirteen patients suffered from progressive disease. Two patients have achieved a PR after full treatment and another seven terminated treatment prematurely without having achieved a CR. Of 158 patients in CR, 25 have relapsed.

Table 6. Toxicity: Number of Patients With Late Complications Documented During Follow-Up (HD1 only)

Complication	Arm A (40 Gy), n = 76	Arm B (20 Gy), n = 71
Secondary neoplasm	2†	1†
Ileus	1	0
Serious infections	6	5
Fibrosis, pneumonitis	8	5
Amenorrhea	3	1
Polyneuropathy	1	2
Diabetes	1	—
Other	12	6
Total	34*	20*

*Significant difference, $P = .04$.

†One immunoblastic lymphoma, 1 carcinoma of the tongue base, and 1 thyroid cancer.

Table 7. Treatment Outcome

Outcome	HD1 Arm A (40 Gy)	HD1 Arm B (20 Gy)	HD1 All	HD5 (30 Gy)
CR	70	67	158	102
95% CI*	92%	94%	88%	92%
95% CI	84%-97%	86%-98.5%	82%-92%	85%-96%
PR	1	2	9	5
Progression	5	2	13	4
Treatment-related death	0	1	1	1
Relapse	11	11	25	5
Death	12	7	29	6
Total	76	71	180	111

NOTE. Causes of death: HD1 (all)—18 due to HD, 1 acute toxicity in primary radiotherapy (septic shock), 2 acute toxicity in salvage therapy, 1 due to autologous bone marrow transplantation, 3 secondary neoplasms (immunoblastic lymphoma, non-Hodgkin's lymphoma, acute myelogenous leukemia (French-American-British stage M4), 3 organ failure (lungs, heart, circulation), 1 cause unknown; HD5—4 due to HD, 1 acute toxicity in primary radiotherapy (infection), 1 acute toxicity in salvage (sepsis).

*95% confidence interval for the percentage of patients attaining CR.

The CR rates in the 40-Gy, 30-Gy and 20-Gy groups are 92%, 94%, and 92%, respectively. They are statistically not significantly different. The 95% confidence intervals show almost complete overlap. It should be noted that all initial extranodal lesions achieved a local CR due to chemotherapy alone and none of the patients relapsed.

Figure 2A shows no significant difference with respect to the end point FFTF between the three treatment groups when analyzed by intention to treat.

At 4 years after the start of treatment, the estimated probabilities of FFTF for the 20-, 30-, and 40-Gy groups are 79%, 86%, and 80% with corresponding 95% confidence intervals of 69% to 89%, 79% to 94%, and 70% to 89%, respectively. We calculate an upper 95% confidence limit for the difference in 4-year FFTF between the two extreme treatments to be 9%. Hence, treatment with 20 Gy of radiation is unlikely to be more than 9% inferior to 40 Gy.

This analysis was repeated with the 11 patients in HD1 arm B who received 40 Gy radiation to IF/BF sites being excluded (ie, analysis by treatment given). FFTF and SV curves still overlap, and there is no indication of any difference in efficacy between the 20-Gy and 40-Gy treatments. The upper 95% confidence interval for the FFTF inferiority of the 20-Gy treatment at 4 years compared with 40 Gy is 11% in this case.

Figure 2B shows no statistically significant difference with respect to overall SV between the three treatment groups if analyzed by intention to treat.

At 4 years after the start of treatment, the estimated probability of survival is 88% in the 40-Gy arm, 93% in the 30-Gy arm, and 94% in the 20-Gy arm, with the 95% confidence intervals being 81% to 95%, 88% to 98%, and 88% to 99.7%, respectively.

At 4 years, the 95% confidence limit for the difference in survival rates between the 20-Gy and 40-Gy two extreme treatments is +15% to −3%. Hence, the 20-Gy treatment is unlikely to be more than 3% inferior to the 40-Gy treatment with respect to 4-year SV.

Pattern of Relapse

Furthermore, we analyzed the pattern of relapses. A total of 30 patients relapsed in the HD1 and HD5 trials. Of the 25 relapses in the HD1 trial, three occurred in patients not randomized. In one patient, the information about site of relapse could not be obtained. Hence, 26 relapses could be analyzed in detail. The analysis shows that 18 of 26 relapsing patients either failed to respond in initial bulky sites (n = 5) or had an extranodal relapse (n = 9) or both (n = 4). Of the eight patients who relapsed in nonbulky nodal sites only, four relapses occurred in unirradiated sites only. Of these, one was associated with an MPV of radiotherapy fields. Hence, the pattern of relapse suggests that only a minority of relapses was potentially preventable by a different dosage of radiotherapy in the EF. Twenty-two of 26 relapsing patients showed relapses in bulky sites, extranodal sites, or outfield sites.

The relapse process is further highlighted by an analysis of the local relapse rate. In all patients who achieved a CR, we evaluated time to first appearance or reappearance of tumor separately in the BF, IF/BF, and EF/IF.

Table 8 lists estimates and 95% confidence limits for the local relapse rates after 30 and 60 months according to doses intended and fields actually irradiated. It is apparent that there is no statistically significant difference between the doses. Furthermore, the relapse rates in the IF/BF and in the EF/IF do not appear to differ. It should be mentioned that the relapse rate for the sites with initial bulky disease was 4.6% (95% confidence interval, 1% to 9%) after 30 months and greater than 10% after 60 months. The nodal outfield relapse rate, on the other hand, amounted to 0.8% after 6.5 years in the HD1 trial.

Survival After Relapse

Figure 3 displays the overall SV of all HD1 patients who relapsed. SV information is not available for one

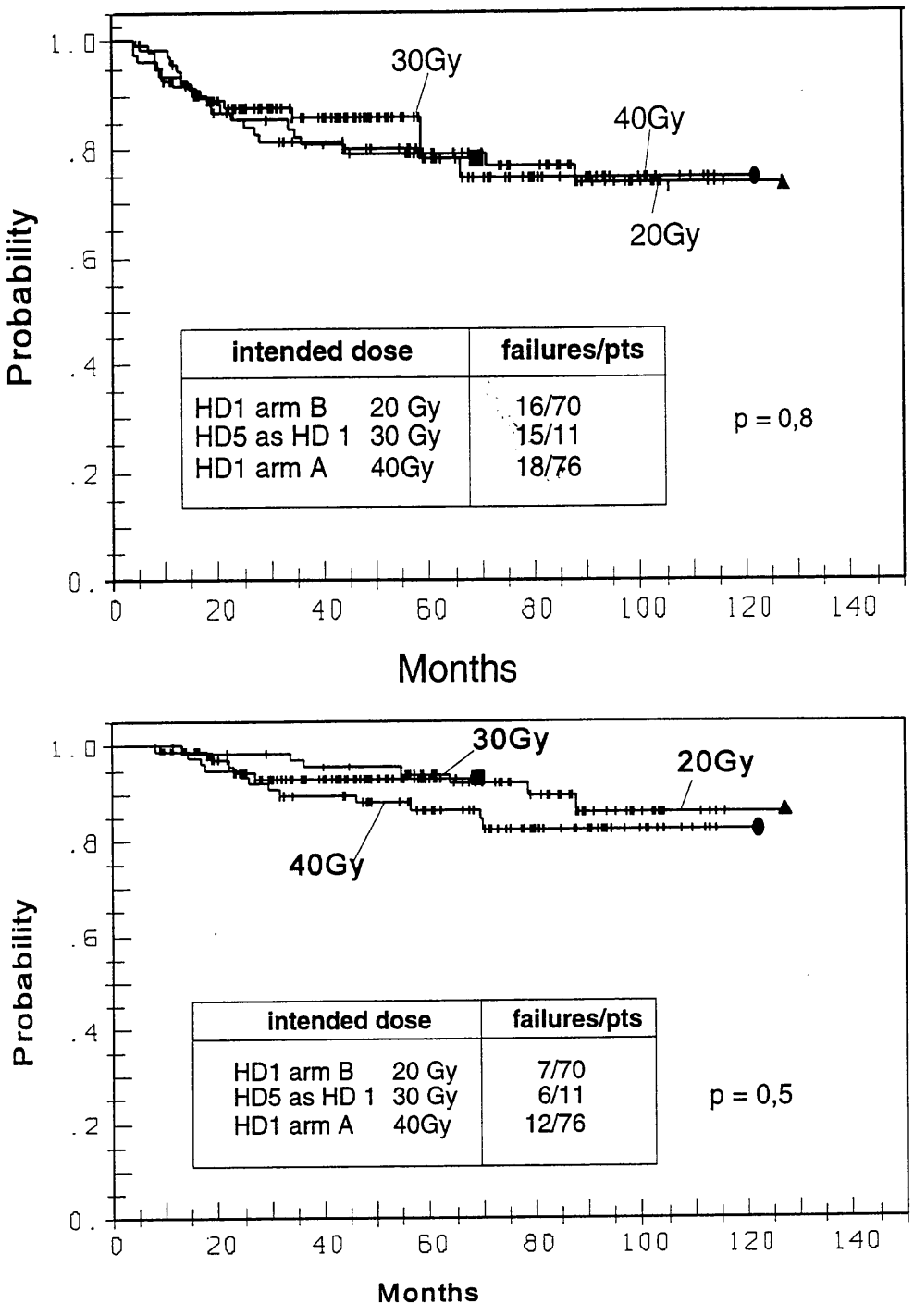

Fig 2. Time-to-event estimates. (A) FFTF and (B) Overall SV. Kaplan-Meier estimates are given for the 3 treatment groups. No statistically significant differences could be detected.

patient after relapse. The Kaplan-Meier estimate shows that the median SV time after a relapse is approximately 3 years. Thus, relapse is associated with a remarkable worsening of prognosis.

Subgroup Analysis

Figure 4 gives the Kaplan-Meier estimates for overall SV and FFTF for all HD1 patients according to stages. It is noteworthy that patients with stage IA and IIA have a good prognosis with respect to SV. The test for heterogeneity of the population is highly significant.

Furthermore, we investigated whether there is a diffence between patients who underwent a laparotomy compared with those who did not. We could not find any statistically significant diffence in CR rate, FFTF, or SV end points.

Table 8. Field-Specific Relapse Rates Estimated at 30 and 60 Months (HD1 only) after CR

	Field Specific Relapse Rate (Kaplan-Meier estimate)					
	20 Gy		30 Gy		40 Gy	
Fields Irradiated	%	95% CL	%	95% CL	%	95% CL
IF/BF						
At 30 months	5.7	1-13	5.7	1-12	8.0	1-17
At 60 months	6.7	5-15	0	0	10.2	2-18
EF/IF						
At 30 months	7.7	2-14	5.7	1-12	5.8	1-12
At 60 months	9.0	1-17	0	0	10.8	3-19
BF						
At 30 months					4.6	1-9
At 60 months					10.3	4-16

Abbreviation: CL, confidence limit.

Prognostic Factor Analysis

A multivariate proportional hazards model was fitted on the pooled data set of the HD1 and HD5 groups to double check that there is no relevant dose-effect relationship with respect to FFTF. To adjust for possible imbalances between the HD1 and HD5 groups, a variety of covariates was included in this model. These were age, stage, laparotomy, mediastinal tumor, erythrocyte sedimentation rate, alkaline phophatase, and hemoglobin. Dose was modeled to allow for a nonlinear dose-response characteristic. None of these covariates was statistically significant, except stage. In particular, no evidence for a dose effect could be found. The corresponding model coefficients were not significantly different from zero (linear and quadratic terms).

DISCUSSION

The major results of the HD1 and HD5 trials can be summarized as follows. First, with respect to local control rates, 20, 30, and 40 Gy radiation seem to have similar effectivities in EF/IF. With 95% confidence, the low-dose radiation with 20 Gy is at most 9% worse than the high-dose radiation with respect to failure rate at 4 years, and at most 3% worse with respect to overall SV.

Second, the relapse pattern shows that multisite relapses are frequent and in most cases cannot be linked to protocol violations. The majority of relapses involves extranodal sites and/or the site of the initial bulky disease. Only a few nodal relapses occurred in previously uninvolved and unirradiated localizations. Hence, the relapse pattern indicates that relapses in chemotherapy-treated intermediate-stage HD is not a problem of local radiotherapy and that these patients might have benefited from more systemic treatment.

On the other hand, it is noteworthy that relapse rate of bulky sites that received 40 Gy radiation is estimated to

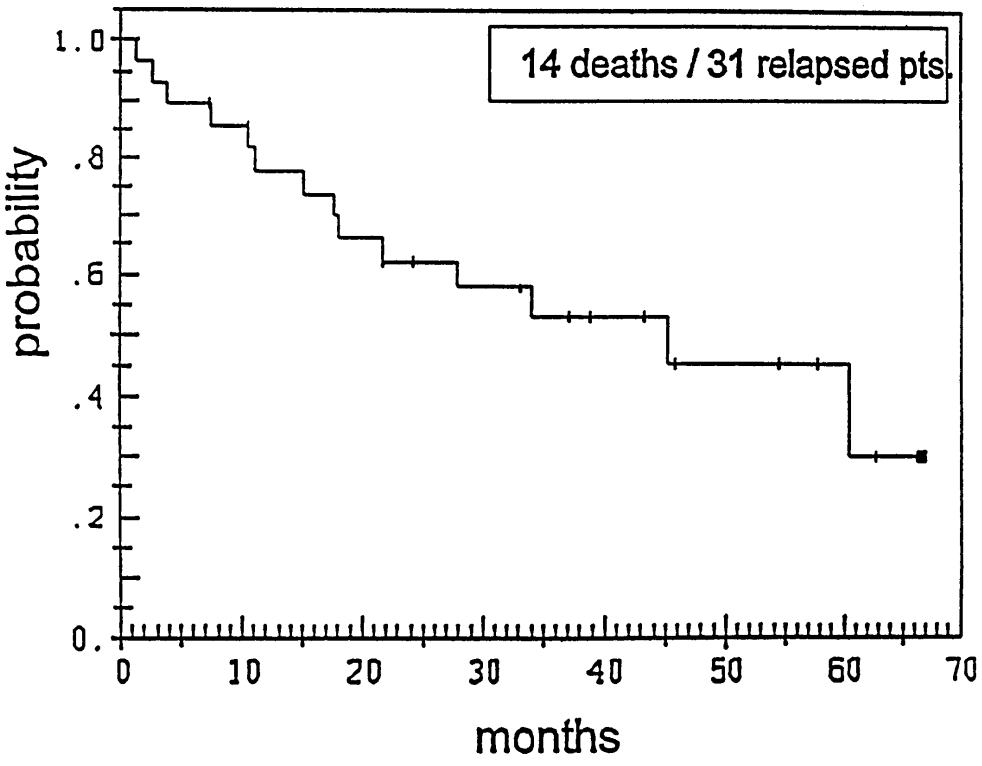

Fig 3. SV after relapse for all patients who relapsed in the HD1 and HD5 trials. Only approximately half of the patients survived 3 years.

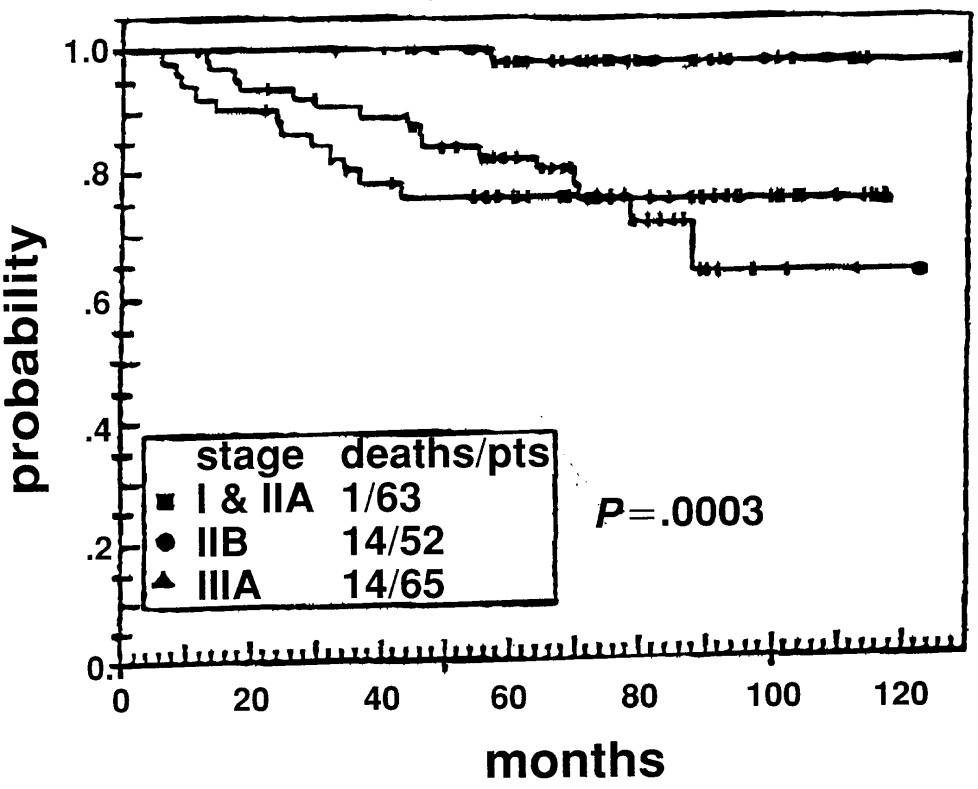

Fig 4. Overall SV according to stage in the HD1 trial, which provides information about the prognostic impact of stage on long-term outcome. The SV of patients in stage I with risk factors is excellent (only 1 patient dead), while stage II and III patients do significantly worse.

be approximately 10% after 5 years. This fact suggests that the options for reducing radiotherapy dose are limited for bulky disease sites.

Third, the need to prevent a relapse is highlighted by the poor prognosis observed for relapses in the HD1 trial, which is similar to the one observed in patients who relapsed after intensive treatment of advanced-stage disease.[20] Therefore, primary treatment in intermediate stages should aim at initial disease control.

Fourth, there is an indication from our data that 40 Gy of radiotherapy is associated with a higher rate of acute and late complications.

We therefore conclude that there are no conclusive arguments to recommend routinely 40 Gy of irradiation on IF/BF and EF/IF fields if four cycles of an effective polychemotherapy are given before hand. Our data rather suggest that 20 Gy of radiation may be sufficient for patients with CS/PS I, II, and IIIA disease with risk factors. However, this is based on a limited series of observations among 76 patients. Collection of further data with 20 Gy might be appropriate to obtain even more precise quantitative estimates. The ongoing follow-up study on the HD5 trial will provide a precise quantitative estimate on the 30-Gy dose, as we expect 100 additional patients to become assessable in the next years (HD5 accrual terminated in 1993).

The data on the 30-Gy arm in the HD5 trial have been included to strengthen the argument about an irrelevant dose effect between 20 Gy and 40 Gy. The multivariate analysis of the pooled data set adjusting for imbalances in risk factors did not show any evidence of a dose effect. Addition of the HD5 data to the analysis increased the precision of these estimates.

In the present HD1 trial, approximately half of the patients did not undergo laparotomy and splenectomy. It is hence likely that the CS cases did contain a number of advanced-stage IIIB patients, who are more likely to fail to respond to the HD1 treatment due to insufficient chemotherapy. Therefore, the relapse rate estimates may actually be somewhat overestimated if referred to a patient population that received routine laparotomy. However, this difference does not seem remarkable, as the FFTF curves for the CS and PS groups did not differ significantly and no effect was seen in the multivariate analysis.

A number of extranodal disease localizations were not routinely irradiated (eg, lung and pleura). In total, 61 patients initially presented with extranodal involvement. However, all patients with initial extranodal lesions (100%) achieved a local CR due to chemotherapy and none relapsed. All relapses in extranodal sites were new manifestations. Hence, four cycles of chemotherapy pro-

vided an effective control of inital extranodal disease in this setting.

In summary, we conclude that a large part of the patients in stage CS/PS I, II, and IIA can suffiently be treated by two courses of COPP plus ABVD and 20 Gy EF (bulky disease, 40 Gy) irradiation. There appears to be only a small group of patients that develops more systemic disease and may require more intensive chemotherapy to prevent later relapse. With respect to the poor prognosis of relapsed patients, the GHSG decided to allocate pa-tients with CS IIB and massive mediastinal mass, massive spleen involvement, and extranodal involvement, as well as all CS IIIA patients with risk factors, to intensive chemotherapy protocols with eight cycles of chemotherapy. Of the 30 relapses reported, more than 23 patients would have undergone more intensive treatment due to these modified inclusion criteria.

Hence, we conclude that low-dose radiation in a combined modality setting appears to be a safe strategy for patients with intermediate localized stages. Similar arguments appear to hold for the use of combined modality in advanced-stage HD.[21]

Reduced doses of radiation are likely to reduce long-term side effects. Analyzing data from pattern-of-care outcome studies, Coia and Hanks[22] reported that the cumulative incidence of gastrointestinal injury in patients who received infradiaphragmatic radiation to the paraaortic and iliac regions was clearly related to total dose. In our series, approximately 40% of patients would have benefited from a reduced abdominal radiation dose. Data on dose dependence of toxicity to thoracic organs is largely missing and deserves further investigation. Furthermore, the role of EF radiation for the induction of solid tumors as secondary neoplasias has been well documented.[23] Reduction of field sizes was reported to reduce second cancer risks. It will remain a challenge for future investigations to determine whether one can further reduce radiotherapy fields and doses, as well as chemotherapy toxicity, without compromising treatment outcomes.

The obvious question for future research is whether any radiation is required in the EF/IF sites after four cycles of modern polychemotherapy. This question is currently being addressed by the HD8 trial of the GHSG, which started in March 1993. This protocol includes patients with CS IA, IB, and IIA with any of the five risk factors mentioned earlier, CS IIB with high erythrocyte sedimentation rate and/or more than three lymph node areas, as well as CS/PS IIIA without any risk factor. These patients all receive two courses of COPP plus ABVD and are randomized between 30 Gy EF and 30 Gy IF. Bulky sites receive 40 Gy in any case. Hence, this trial investigates whether radiation is needed at all in the EF/IF fields and hence is a consequent extension of the question discussed in this report. The decision to use 30 Gy in this trial was made before the data reported here were available.

Zittoun et al[24] reported a trial in which patients in CS I, II, or IIIA with risk factors (two or more of five: age $\geq$ 40 years, histology, mediastinal involvement, extranodal involvement, and B symptoms) received either 40 Gy EF or IF combined with six cycles of MOPP chemotherapy. Hence, the radiation dose in the IF areas was identical in both groups, but in the EF/IF field, the trial investigated 0 Gy versus 40 Gy. No difference between the radiation regimens could be detected on the basis of 245 patients.

Recently, preliminary data have been published from the Milan group on 73 patients treated with four courses of ABVD followed by either IF or EF with 30 to 36 Gy.[25] All patients achieved a CR and no relapse was observed with a median follow-up duration of 2 years. However, the follow-up time and the number of patients on the trial are too small to draw any firm conclusions.

Hence, we can see that within the last decade, there is a certain progress toward less intensive treatment strategies with less chemotherapy and less radiotherapy for patients with intermediate-stage HD. We consider it useful to undertake more studies to evaluate the dose-response characteristics of radiotherapy after chemotherapy in localized disease.

ACKNOWLEDGMENT

We thank the Federal Minister for Science and Technology in Germany for a generous grant that enabled this study and Dr George Canellos and anonymous reviewers for helpful comments.

APPENDIX
GHSG Study Participants

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Hinterberger; Mainz, Universitätsklinik (B. Krüger, K. Kutzner); Erlangen, Universitätsklinik (J. König, S. Petsch, R. Sauer); Frankfurt, Universitätsklinik (K. Schalk, Szepesi); Bonn, Universitätsklinik (U. Loos, I. Boldt); Ravensburg, St. Elisabethen Krankenhaus (W. Mende); Berlin-Steglitz (H. Ernst, J. Teichmann); Kiel, Städt. Krankenhaus (W. Gaßmann, T. Brix); München r.d. Isar (H.D. Schick); Duisburg, St. Johannes-Hospital (M. Westerhausen, R. Fuchs, B. Makoski); Berlin-Moabit (H. Hellriegel, G. Kühn, U. Rühl); Mannheim, Klinikum (P. Worst, P. Diezler); Roma, La Sapienza (C. Cartoni, Anselmo); Krefeld, Städt. Krankenhaus (M. Planker, U. Schulz); Karlsruhe, St. Vincentius Krankenhäuser (S. Theml, R. Staiger, W. Haase); Lübeck, Medizinische Hochschule (T. Wagner, G. Schwieder, Brandenburg); Wiesbaden, Praxis Dr. Schmitz; Köln, Med. Universitätsklink II (B. Mödder); Trier, Krankenhaus d. Barmherzigen Brüder (H. Hennekeuser); Augsburg, Zentralklinikum (G. Schlimok, Doukas, A.-C. Voss); Stuttgart, Robert-Koch-Klinik (Schalk, Schlegel); Heidelberg, Thoraxklinik (Ch. Manegold, Flentje); Essen-Werden, Evangelisches Krankenhaus (Tivier, Hoederath); Oldenburg, Evangelisches Krankenhaus (F. Hinrichs, A. Temmesfeld); Berlin, Praxis Dr. Weißenfels; Hildesheim Städt. Krankenhaus (J. Preiß, W. Gärtner); München-Harlaching, Städt. Krankenhaus (Hoffmann, Rübe); Hildesheim, St. Bernward Krankenhaus (D. Urbanitz, Heide); Trier, Mutterhaus der Borromäerinnen (H. Siebner, K.H. van de Weyer, D. Dornoff); Neuss, Lukaskrankenhaus (P. Czygan); Hannover, Praxis Dr. Wysk; Herford, Kreiskrankenhaus (M. Rochell); Heilbronn, Städt. Krankenhaus (K. Koniczek);

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REFERENCES

1. Loeffler M, Mauch P, Laclennan K, et al: Review on prognostic factors on Hodgkin's disease. Ann Oncol 3:563-566, 1992 (suppl 4)

2. Mauch P, Goodman R, Hellman S: The significance of mediastinal involvement in early stage Hodgkin's disease. Cancer 42:1039-1045, 1978

3. Lee CKK, Bloomfield CD, Goldman AI, et al: Prognostic significance of mediastinal involvement in Hodgkin's disease treated with curative radiotherapy. Cancer 46:2403-2409, 1980

4. Tubiana M, Henry-Amar M, Hayat M, et al: Prognostic significance of the number of involved areas in the early stages of Hodgkin's disease. Cancer 54:885-894, 1984

5. Tubiana M, Henry-Amar M, Van Der Werf-Messing B, et al: A multivariate analysis of prognostic factors in early stage Hodgkin's disease. Int J Radiat Oncol Biol Phys 11:23-30, 1985

6. Gobbi PG, Cavalli C, Frederico M, et al: Hodgkin's disease prognosis: A directly predictive equation. Lancet 3:675-678, 1988

7. Loeffler M, Pfreundschuh M, Hasenclever D, et al: Prognostic risk factors in advanced Hodgkin's lymphoma. Report of the German Hodgkin Study Group. Blut 56:273-281, 1988

8. Tubiana M, Henry-Amar M, Burgers MV, et al: Prognostic significance of erythrocyte sedimentation rate in clincal stages I-II of Hodgkin's disease. J Clin Oncol 2:194-200, 1984

9. Gobbi PG, Gendarini A, Crema A, et al: Serum albumin in Hodgkin's disease. Cancer 55:389-393, 1985

10. Haybittle JL, Easterling MJ, Bennet MH, et al: Review of British National Lymphoma Investigation studies of Hodgkin's disease and development of prognostic index. Lancet 1:967-972, 1985

11. Specht L, Nissen NI: Hodgkin's disease stages I and II with infradiaphragmatic presentation: A rare and prognostically unfavourable combination. Eur J Haematol 40:396-402, 1988

12. Specht L, Nordentoft AM, Cold S, et al: Tumor burden as the most important prognostic factor in early stage Hodgkin's disease. Relations to other prognostic factors and implications for choice of treatment. Cancer 61:1719-1727, 1988

13. Specht L, Lauritzen AF, Nordentoft AM, et al: Tumor cell concentration and tumor burden in relation to histopathologic subtype and other prognostic factors in early stage Hodgkin's disease. Cancer 65:2594-2601, 1990

14. MacLennan KA, Bennett MH, Tu A, et al: Relationship of histopathologic features to survival and relapse in nodular sclerosing Hodgkin's disease. A study of 1659 patients. Cancer 64:1686-1693, 1989

15. Pfreundschuh M, Lathan B, Loeffler M, et al: Recommendations for future clinical trials on Hodgkin's disease. Ann Oncol 3:101-104, 1992 (suppl 4)

16. Paglia MA, Lachner MJ, Hertz RE, et al: Surgical aspects and results of laparotomy and splenectomy in Hodgkin's disease. Am J Roentgenol 117:12-18, 1973

17. DeVita VT, Serpick AA, Carbone PP: Combination chemotherapy in the treatment of advanced Hodgkin's disease. Ann Intern Med 73:881-895, 1970

18. Bonadonna G, Zucali R, De Lena M, et al: Combination chemotherapy of Hodgkin's disease with Adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. Cancer 36:252-259, 1975

19. Loeffler M, Hasenclever D: Probleme der Konzeption und Auswertung von Therapiestudien bei langer Behandlungsdauer, mittlerer CR-Rate und langer Überlebensdauer, in Selbmann HK, Dietz (eds): Medizinische Informationsverarbeitung und Epidemiologie im Dienste der Gesundheit, 32. Jahrestagung der GMDS, Tübingen, Germany, October 1987

20. Fuchs R, Loeffler M, Pfreundschuh M, et al: Prognosis of high dose chemotherapy/autologous bone marrow transplantation candidates not receiving this treatment after failure of primary therapy of Hodgkin's disease. Leuk Lymphoma (in press)

21. Proswitz LR, Roberts KB: Combined chemotherapy and radiotherapy for Hodgkin's disease. Oncology 6:113-128, 1992

22. Coia LR, Hanks GE: Complications from large field intermediate dose infradiaphragmatic radiation: An analysis of the Patterns of Care Outcome Studies for Hodgkin's disease and seminoma. Int J Radiat Oncol Biol Phys 15:29-35, 1988

23. Somers R, Henry-Amar, M, Meerwaldt JK, et al: Treatment strategy in Hodgkin's disease. Colloque INSERM vol 196. Paris, France, Libbey, 1990

24. 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

25. Bonfante V, Santoro A, Viviani S, et al: ABVD plus radiotherapy (subtotal nodal vs involved field) in early stage Hodgkin's disease. Proc Am Soc Clin Oncol 13:373, 1994 (abstr 1262)