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Original article

Further chemotherapy versus low-dose involved-field radiotherapy as consolidation of complete remission after six cycles of alternating chemotherapy in patients with advanced Hodgkin's disease

V. Diehl, M. Loeffler, M. Pfreundschuh, U. Ruehl, D. Hasenclever, H. Nisters-Backes, M. Sieber, K. Smith, H. Tesch, W. Geilen, M. Adler, H. Bartels, U. Brandenburg, P. Diezler, G. Doelken, J. Enzian, R. Fuchs, W. Gassmann, H. Gerhartz, U. Hagenaukamp, T. Hecht, E. Hiller, H. Hinkelbein, B. Lathan, H. Kirchner, G. Kuehn, H. Kuerten, U. Loos, B. Makoski, W. Oertel, S. Petsch, R. Pfab, H. Pflueger, M. Planker, R. Rohloff, H. Sack, S. Samandari, R. Sauer, K. Schalk, G. Schmitz, W. Schoppe, G. Schwieder, S. Szepesi, J. Teichmann, W. Wilhelmy, P. Worst, R. Fischer, A. Georgii, K. Huebner & E.-W. Schwarze for the German Hodgkins' Study Group (GHSG)*

Klinik I für Innere Medizin der Universität zu Köln, Cologne, Germany
** See page 909 for list of other participants*

Summary

Objective: It was the aim of this prospective randomized multicenter study to compare chemotherapy and radiotherapy as consolidation treatments in patients achieving complete remission (CR) after 6 cycles of doxorubicin-containing chemotherapy in advanced-stage Hodgkin's disease (HD).

Methods: A total of 288 previously untreated patients aged 18–60 years with stage IIIB or IV HD received induction chemotherapy with 3 × (COPP + ABVD). Patients achieving CR were eligible for randomisation to either 20 Gy radiotherapy to initially involved fields (RT-arm) or to an additional 1 × (COPP + ABVD) (CT-arm). Patients with nodal PR were allocated to more intense radiotherapy (IRT-arm: 20 Gy IF, 40 Gy to persisting tumor). Four patients with persisting organ involvement after induction received salvage chemotherapy.

Results: Of 288 patients, 171 (59%) achieved CR after induction chemotherapy. Of these, 100 patients were successfully randomized to RT or CT. In the CT arm relapses were observed in 10 of 49 patients compared with 13 of 51 patients in the RT arm (p = n.s.). Fifty patients refused randomisation and for them a treatment was chosen, and 21 patients refused any further treatment. Of these 21 patients with no consolidation therapy, 9 relapsed, indicating an approximately 3-fold increased relapse risk compared with those receiving either of the consolidation therapies. No relapse was observed in initially involved lung or liver sites. Adverse prognostic factors for freedom from treatment failure and survival were low hemoglobin and large mediastinal mass at initial presentation.

Conclusions: No statistically significant differences in treatment efficacy were detected between 20 Gy IF radiotherapy and 1 × (COPP + ABVD) chemotherapy following CR after six cycles of alternating chemotherapy in patients with advanced-stage HD. However, limited observations in a non-randomized cohort indicate that patients without consolidation treatment of CR after 6 cycles of chemotherapy may have an elevated risk for relapse.

Key words: chemotherapy, combined modality treatment, Hodgkin's disease, radiotherapy, randomized trial

Introduction

Up to 40% of patients in stage III or IV Hodgkin's disease relapse within 5 years if complete remission (CR) was achieved with current chemotherapy regimens. This was highlighted in a collaborative evaluation of the International Database on Hodgkin's disease [29]. Generally, relapse is associated with a poor prognosis for survival [9, 29]. Thus, prevention of relapse is an important issue.

Because Hodgkin's disease is a radiosensitive tumor it is logical to use radiation in an attempt to eliminate subclinical disease after complete remission following induction chemotherapy. Prosnitz et al. (1982) reported that a good quality of remission could be achieved by combined modality in advanced stages. However, no control group was included in this trial. Several attempts have been made since then to investigate whether the addition of radiotherapy to induction chemotherapy leads to improvement [1, 2, 5, 7, 8, 11, 12, 14, 22, 23, 27, 32]. Most of these trials randomized chemotherapy alone versus combined treatment ab initio [1, 2, 5, 7, 11, 14, 22, 27]. None of them showed a benefit in terms of survival, but one trial showed

that radiotherapy had beneficial effects in reducing the risk for relapse [22]. Other trials investigated the role of radiotherapy restricted to patients in complete or partial remission (CR, PR) after induction chemotherapy. Two trials have compared no further treatment versus RT [8, 12] in CR or CR/PR patients. Significant differences were not detected.

In contrast to these trials comparing radiation versus no further treatment, the objective of the HD3 trial reported here was to compare radiation with further chemotherapy as consolidation. At the time this trial was started no results from comparable trials were available. Trials relating to this question were ongoing within the ECOG group and the NCI-Canada. The ECOG trial used Bleo-MOPP as induction and ABVD as consolidation, while the Canadian study used MOPP throughout. Data from the trials [11, 32] will be discussed below. The results from the ABVD scheme [3, 4] have stimulated the design and use of alternating non-cross-resistant chemotherapy regimens. The German Hodgkin's study group has adopted the COPP/ABVD variant of the MOPP/ABVD scheme in which mustargen is replaced by cyclophosphamide.

It was the objective of the present trial to compare low-dose radiotherapy versus chemotherapy as consolidation treatments in patients with stage IIIB and IV Hodgkin's disease who have achieved complete remission after 6 cycles of alternating non-cross-resistant chemotherapy (i.e., COPP + ABVD).

Material and methods

Study design

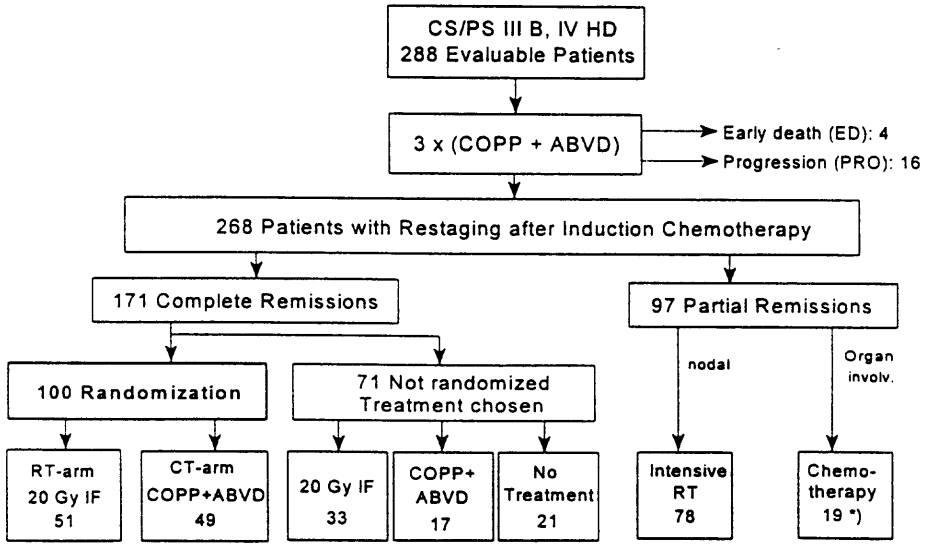
Eligibility. Untreated patients between 15 and 60 years of age with histologically proven HD were eligible. Patients in CS IIIB/IV were entered without laparotomy. In addition, patients exhibiting PS IIIB/IV after a staging laparotomy (routinely performed in CS I–IIIA stage patients) were entered. Written consent was required. Patients with impairment of heart, lung, liver or kidney function or previous malignant diseases were excluded.

Recruitment. Patients were entered between January 1984 and February 1988. The median time of observation is 6 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 CT scan, abdominal CT scan and ultrasound, bone marrow biopsy, liver biopsy, radioisotope scan of the skeletal system and a number of laboratory tests (ESR, AP, WBC, Hb, thrombocytes, differential blood counts, liver enzymes); liver and spleen scinti scan, bipedal lymphangiography and X-ray of the skeleton were optional examinations. A massive mediastinal mass was diagnosed if a mediastinal tumour exceeded 1/3 of the maximum thoracic diameter.

Laparotomy (CS I–IIIA) was performed according to international standards [21]. Histological diagnosis was made by regional pathologists and copies of the reports were sent to the study center.

Treatment protocol. Patients received three double cycles of alternating COPP + ABVD followed by careful restaging. Patients in complete remission (CR) were randomized to receive consolidation by radiotherapy (RT arm: involved field radiotherapy with 20 Gy) or chemotherapy (CT arm: COPP + ABVD). Patients with persisting nodal involvement received intensive radiotherapy (IF 20 Gy, per-



Treatment outcome:								Overall outcome including induction treatment
CR:	51	47	32	16	21	62	6	235 (81,6 %)
PR:	—	—	—	—	—	9	12	21 (7,3 %)
PRO:	—	2	1	1	—	7	1	28 (9,7 %)
ED:	—	—	—	—	—	—	—	4 (1,3 %)

*) 11 of these received CEVD

Fig. 1. Design of the HD3 trial and flowchart of all evaluable patients treated in the HD3 trial including allocation to treatments and treatment outcomes.

sisting tumor 40 Gy). In case of persisting organ involvement four cycles of CEVD were recommended. The relevant part of the study design is summarized in Fig. 1.

Chemotherapy. COPP was given as a modification of the MOPP scheme of DeVita [6] with mustargen being substituted by cyclophosphamide [20]:

Cyclophosphamide	650 mg/m² i.v.	day 1, 8
Vincristin	1.4 mg/m² i.v. (max: 2 mg)	day 1, 8
Procarbacine	100 mg/m² p.o.	day 1–14
Prednisone	40 mg/m² p.o.	day 1–14
Recycle		day 29

ABVD was given according to the Milan protocol [3]:

Doxorubicin	25 mg/m² i.v.	day 1, 15
Bleomycin	10 mg/m² i.v.	day 1, 15
Vinblastine	6 mg/m² i.v.	day 1, 15
DTIC	375 mg/m² i.v.	day 1, 15
Recycle		day 29

CEVD was given as described by our group [24]:

CCNU	80 mg/m² p.o	day 1
Etoposide	120 mg/m² p.o.	day 1–5, 21–26
Vindesine	3 mg/m² i.v.	day 1, 22
Dexamethasone	3 mg/m² p.o.	day 1–8
Dexamethasone	1.5 mg/m² p.o.	day 9–26
Recycle		day 43

The study protocol gave detailed instructions as to the degree of dose reduction if myelopoietic toxicity exceeded given thresholds:

- no reduction if delay of less than 1 week;
- 25% reduction if a 1–2-week delay was caused by the last application of the corresponding cycle;
- 50% reduction if the delay exceeded 2 weeks.

Radiotherapy. Before induction chemotherapy was started all sites of disease were mapped. If the patient was later given radiation, all initially involved nodal sites were included in the treatment ports. Radiotherapy was also given to the spleen if the spleen or paraaortic lymph node were involved. No routine radiation was recommended for liver or lung involvement. All previously involved nodal sites received 20 Gy in 1.5–2.0 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 exceeded 16 Gy. In the RT arm patients received 20 Gy. If a persisting residual tumor was found after induction chemotherapy these areas were given additional radiation up to a total dose of 40 Gy.

Documentation

Report of treatment. The 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 during the follow-up period. The present analysis describes the follow-up until January 1, 1994.

All data forms were carefully checked by two data managers and a physician. Data on the vital status of patients was cross-checked with public death registries.

Evaluation of treatment success. The success of treatment was determined by restaging 4 weeks after the induction chemotherapy and 4–8 weeks after the termination of the protocol treatment. It consisted of a controlled and detailed documentation of all initial disease manifestations by appropriate clinical and histological methods. Complete remission (CR) was defined as the disappearance of all objective disease manifestations and the absence of clinical symptoms for at least four weeks. Partial remission (PR) was defined as reduction in all disease localisations by at least 50% of the initial involvement. Patients with questionable persisting disease were classified as partial responders. For patients with minimal residual nodal disease the designation of CR or PR was left to the discretion of the treating physician. In general, however, such patients were classified as PR and the respective persisting nodal sites received 40 Gy radiation while all other initially involved sites received 20 Gy radiation. Thus, it is likely that some true CR patients have been allocated to the IRT group, rendering treatment results more favourable than is realistic for PR patients.

All patients who started treatment and could be assessed for remission status after (complete or incomplete) induction therapy were considered as evaluable. This was not possible for 1 patient, who was lost to follow-up after 2 cycles. In all other cases the reasons for incomplete treatment were classified as being for one of the following reasons: progression under therapy (PRO), excessive toxicity (ET), violation of protocol, intercurrent death, or patient refusal of further therapy. In all of these cases the remission status was also classified (CR, PR, PRO). These decisions were made by a review committee.

Treatment allocation and randomization. Patients who achieved CR by induction treatment were asked to agree to randomization for further consolidation treatment (see Fig. 1). At this point, 71 of 171 patients refused randomization. Fifty patients preferred to choose a consolidation treatment; 33 of them opted for 20 Gy IF RT and 17 for another COPP + ABVD. Twenty-one patients decided to have no further treatment. The remaining 100 were randomized and all received the treatment to which they were allocated. Randomization was stratified by center and stage (IIIB, IV). Patients with nodal PR after induction therapy were allocated to intensive radiotherapy (IRT) and chemotherapy was recommended for those with persisting organ involvement CEVD.

Central reviews

Pathology review. A pathology review of the biopsies taken before treatment was requested. Local pathologists were asked to submit material to the four central review pathologists, who examined 234 of 293 cases (80%) [10]. The remaining specimens were either not submitted or were of insufficient technical quality. Two NHL were diagnosed and two non-malignant lymphocyte reactions were found. All four were excluded from this analysis. In 230/234 cases the diagnosis of a HD was confirmed. However, in 61 cases review pathologists were unable to agree as to the precise histological subtype. These cases were classified as UC (i.e., unclassified). Further workup of these samples is underway, including immunohistochemistry. Hence, it can be assumed that the 58 cases (of 288 evaluable HD cases) not reviewed contain a maximum of 2 lymphomas other than HD.

Radiotherapy review. All of the forms documenting the radiotherapy actually given have been reviewed. Protocol violations were classified in terms of field sizes, dose and timing. Major protocol violations (MPV) were defined as cases in which involved fields had not been irradiated at all. All other deviations in field margins, dosage, timing and technical modalities were classified as minor protocol violations. 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 inside or outside the radiation field. In the subsequent analyses of the RT arm and IRT group all patients were included regardless of whether major or minor protocol violations had occurred.

Biometry

Endpoints. The complete remission rate was defined as the ratio of all patients in complete remission (CR) to all evaluable 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 (partial remission or no change) at the end of the protocol treatment (disregarding the restaging following induction treatment) or relapse [17]. Survival times were obtained including all deaths whether disease-related or not. All time-to-event data were recorded from the time of patient entry before start of treatment. Kaplan-Meier estimates are given for the probabilities to survive beyond a given time. Comparisons of failure time data were made using the log-rank test. Comparisons of the treatment groups were performed according to intent to treat.

Proportional hazard models. To evaluate the independent contributions of potential prognostic factors proportional hazard models were set up for FFTF and overall survival as endpoints. Proportional hazard models were constructed for all patients and for all randomized patients. Covariates considered were age (0 if ≤40, 1 if >40 years), stage (0 if IIIB, IVA; 1 if IVB) and large mediastinal mass (yes/no), ESR, AP, HB. The latter parameters were dichotomised using as cut-off points 80 mm/h for ESR, 230 U/l for AP (using traditional liquid chemistry), and 12 g/l for hemoglobin for males and 10.5 g/l for females. This corresponds to published cut-off points used by us [18] and others [30]. Regression models with all parameters included were built up, and step-down regression was performed. All regression models were restricted to the patients with complete datasets.

Patient population

Study centers. Patients for the HD3 trial were recruited from 49 study centers, with one center providing 36 patients and others only one patient (ranking see appendix). One center was excluded because it consistently failed to follow the protocol.

Patients excluded from analysis. A total of 293 patients were originally accrued to the trial. Four patients were excluded from analysis because the pathology review had revealed diagnoses other than HD. One patient was not evaluable as no information on the effect of the induction therapy was available. The remaining 288 patients were included in the analysis.

Patient characteristics. Table 1 provides a summary of the characteristics of the overall patient population. In addition, the characteristics are given for the two randomized groups (RT arm, CT arm) and for the patients who have received no consolidation treatment. No significant differences were observed between the groups in univariate comparisons with respect to age, gender, stage, B-symptoms, massive mediastinal mass (MMT), spleen and extranodal organ involvement, ESR, AP, and hematological parameters. With respect to the histology reviewed no differences were found between the three groups of patients who achieved a CR after induction chemotherapy (RT arm, CT arm, no consolidation). However,

Table 1. Characteristics of the entire study population and of specific subpopulations.

	Overall	RT arm (20 Gy IF)	CT arm (COPP+ABVD)	Choice of no consolidation	Patients in PR after induction
					Intensive RT
No. patients	288	51	49	21	78
Age (median)	34	35	38	39	30
Gender (% male)	187	36	36	14	47
Stage					
IIIB	155	28	29	12	45
IVA	32	5	6	1	9
IVB	101	18	14	8	24
Reviewed histology					
LP	1	0	1	0	0
NS	116	23	15	3	38
MC	49	7	12	5	11
LD	3	1	0	1	1
UC[a]	61	12	11	7	8
Not available	58	8	10	5	20
MMT[b]	44	8	9	3	10
Spleen involvement	147	24	27	10	40
ESR (mm/1h)[c]	60	68	61	50	63
AP (U/l)[c]	190	184	181	213	201
HB (g/dl)[c]	13	13	12	13	12
Leukocytes (× 10)[c]	10	10	9	10	12
Thrombocytes (× 10)[c]	356	334	311	340	379
Organ involvement[d]					
Liver	39	6	6	3	11
Bone	17	2	2	2	3
Bone marrow	50	9	9	5	10
Lung	25	3	4	0	8

[a] UC = unclassified.
[b] MMT = massive mediastinal tumor.
[c] Medians.
[d] Not mutually exclusive.

there was a significantly higher percentage of the nodular sclerosis subtype in patients receiving intensive radiation after PR (42% vs. 66%, $p < 0.01$).

Results

Relative dose intensity. A mean number of 5.8 cycles of chemotherapy was given in the induction period. On average, 84% of the scheduled dose intensity could be administered (C: 86%, O: 88%, P: 80%, P: 89%, A: 83%, B: 83%, V: 79%, D: 83%). Only 5% of the patients received less than 60% of the scheduled dose intensity.

Toxicities. Table 2 summarizes the acute toxicities observed during chemotherapy. They are consistent with reports of similar multidrug regimens. In particular ABVD is more hematotoxic than COPP. However, WHO Grade 4 toxicities were rare and included hematologic problems (5 in COPP, 7 in ABVD), skin, heart and brain disorders (one each).

Treatment outcome. Figure 1 summarizes the treatment outcome. After induction chemotherapy of 3 × (COPP + ABVD) 171/288 patients (59%) achieved complete remissions. During induction 16 patients suffered from progressive disease (PRO). Four early deaths (ED) were recorded, two due to complications of laparotomy, one of treatment-related neutropenia (all counted as excessive toxicity) and one of myocardial infarction on day 1 of the first ABVD cycle. The remaining 97 patients were considered to have achieved a partial remission (PR). After conclusion of all treatments, including consolidation and intensive RT or CEVD, a total of 235 (81.6%; 95% confidence interval: [76.6%, 85.9%]) patients had achieved complete remission while 28 (9.7%) were progressive and 21 (7%) had partial remissions at the end of protocol treatment.

Failures and deaths. Table 3 summarizes the treatment failures (FFTF-events) and causes of death. At a median follow-up time of 6 years a total number of 113 failures of first-line treatment and 72 deaths have been observed. The majority of deaths were disease-related (73.6%). Excessive toxicity (ET) in second-line treatment (2° ET) could not be excluded as cause of death in four cases (infections during salvage treatments). Six fatal second neoplasias have been observed so far (2 AML-FAB-M4, 1 AML not subtyped, 1 liver cancer, 1 lung cancer, 1 NHL).

Figure 2 gives a product limit estimate of the overall survival (SV) and FFTF for the entire population. At 7 years the estimates are 76.2% for SV and 59.4% for FFTF with the 95% confidence intervals being [70.9, 81.5%] and [53.3, 65.5%], respectively.

Table 2. Frequency of documented toxicities of chemotherapy.

	COPP	ABVD	Significance
No. cycles	869	839	
Maximum WHO grade			
0	122 (14%)	37 (4%)	
1	401 (46%)	243 (29%)	
2	195 (22%)	283 (34%)	$p < 0.001$
3	121 (14%)	249 (30%)	
4	6 (1%)	9 (1%)	
Cycles with side effects with WHO grade ≥ 1			
Alopecia	54%	64%	$p < 0.001$
Nausea	74%	83%	$p < 0.001$
Vomiting	62%	78%	$p < 0.001$
Leukopenia	38%	62%	$p < 0.001$
Thrombocytopenia	21%	25%	$p < 0.05$
Diarrhoea	28%	30%	n.s.
Neurotoxicity	22%	28%	$p < 0.05$
Other	<20%	<20%	n.s.

Table 3. Treatment failures and causes of deaths.

Events	Overall	RT-arm	CT-arm	No consolidation	Intensive RT	Rest
FFTF events	113	13	12	10	27	51
Deaths	72	4	7	6	21	34
Cause of death						
HD	53	3	5	5	16	24
1° ET	3	–	–	–	–	3
2° ET	4	–	–	–	2	2
Accident	1	–	–	–	–	1
Cardiac failure	2	–	–	–	1	1
Brain failure	1	1	–	–	–	–
Second neoplasia	6	–	1	–	2	3
Unknown	2	–	1	1	–	–

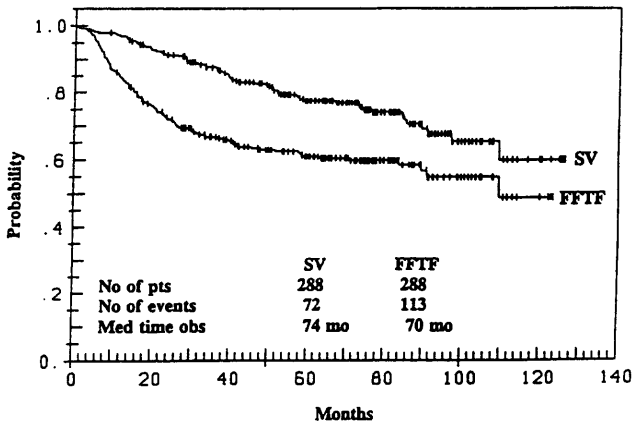


Fig. 2. Kaplan-Meier plots for overall survival (SV), and freedom from treatment failure (FFTF) of 288 evaluable patients.

Radiotherapy as consolidation (RT arm). Thirteen of the 51 patients treated in this arm relapsed all at nodal sites (Table 4). In 4 patients initially uninvolved nodes were affected, and in 6 more than one site was affected. Relapses occurred in 18 previously involved nodal sites, 13 of them in irradiated and 5 in unirradiated areas. These 5 sites occurring in 3 patients have been classified as major protocol violations (MPV). New nodal lesions were observed in 4 cases (3 outside the radiation field). Of 8 patients with initial massive mediastinal tumor (MMT) three relapsed in this site despite radiation. No extranodal relapses were observed.

Chemotherapy as consolidation (CT arm). Among the 49 patients treated with an additional 1 × (COPP + ABVD), 12 FFTF events were recorded. One patient died from a liver cell carcinoma and one of unknown cause. Ten patients relapsed (Table 4), six of them only in nodal sites. In 2 cases only initially involved sites were affected. Of 9 patients with initial MMT four relapsed in the mediastinal site. Extranodal relapses affected the bone (2) and bone marrow (2) as novel sites.

Comparisons between the randomized groups. With respect to the endpoints FFTF and overall survival (SV) no significant differences between the two treatment groups could be detected. Figures 3a and 3b show the Kaplan-Meier estimates for FFTF and SV. Power calculations for the univariate logrank tests show that the tests have a 82% power to detect a difference of 25% in FFTF and 88% power to detect a 20% difference in SV. The estimated difference for FFTF at 5 years is 3% in favor of the CT arm with a 90% confidence interval of [−12%, +18%]. On the other hand, the RT arm and CT arm differ significantly with respect to relapses in initially involved sites (9/13 vs. 2/10, $p < 0.01$ with Fisher's exact test), but the difference is not significant if patients with major protocol violations in the RT arm are excluded from the analysis. Thus, no marked biological differences were revealed between the two randomized treatments (especially if radiation was given according to protocol).

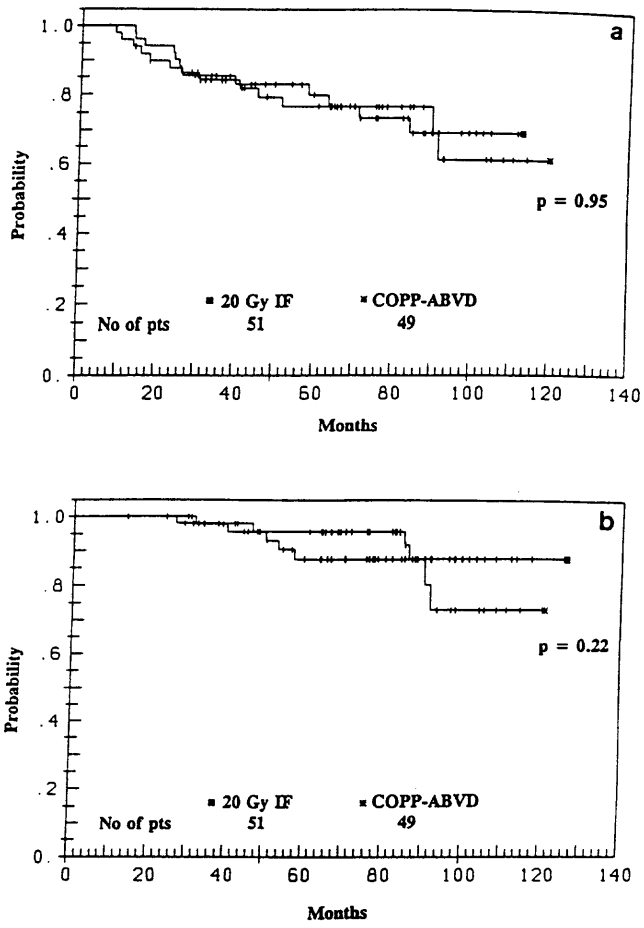


Fig. 3. Comparison of the treatment groups. (a) FFTF; (b) Overall survival. No significant differences were observed.

Table 4. Relapse pattern according to treatment given.

	Patients in CR		
	RT-arm	CT-arm	No consolidation
No. patients in CR	51	49	21
No. patients relapsed	13	10	9
Nodal sites only	13 (100%)	6 (60%)	8 (89%)
Extranodal sites only	0	1	1
Both	0	3	0
Initially involved only	9 (69%)[a]	2 (20%)	3 (33%)
Initially uninvolved only	3	4	1
Both	1	4	5
Relapse			
Within RT field given	7	n.a.	n.a.
Outside RT field given	4[b]	n.a.	n.a.
Both	2[c]	n.a.	n.a.
Pts with relapse in 1 site	7	5	4
Pts with relapse in 2 sites	3	1	2
Pts with relapse in >2 sites	3	4	3

[a] 3 in sites of MPV.
[b] 2 in sites of MPV.
[c] 1 in site of MPV.
[d] 2 in sites of MPV.
[e] 1 in site of MPV.
n.a. = not applicable; MPV = major protocol violation.

Patients without consolidation. Twenty-one patients in CR refused any further consolidation treatment after induction chemotherapy. Nine of these patients relapsed, eight in nodal sites only. In six cases initially uninvolved sites were affected. Figures 4a and 4b gives the Kaplan-Meier estimates for FFTF and SV for this group (no consolidation group) compared with all randomized patients (consolidation group). Thus, patients without consolidation seem to have a higher risk for relapse ($p = 0.02$) and death ($p = 0.013$).

In order to correct for possible imbalances in the non-randomized comparison of these groups a multivariate analysis was performed adjusting for age, stage, MMT, ESR, AP and hemoglobin. In addition to the

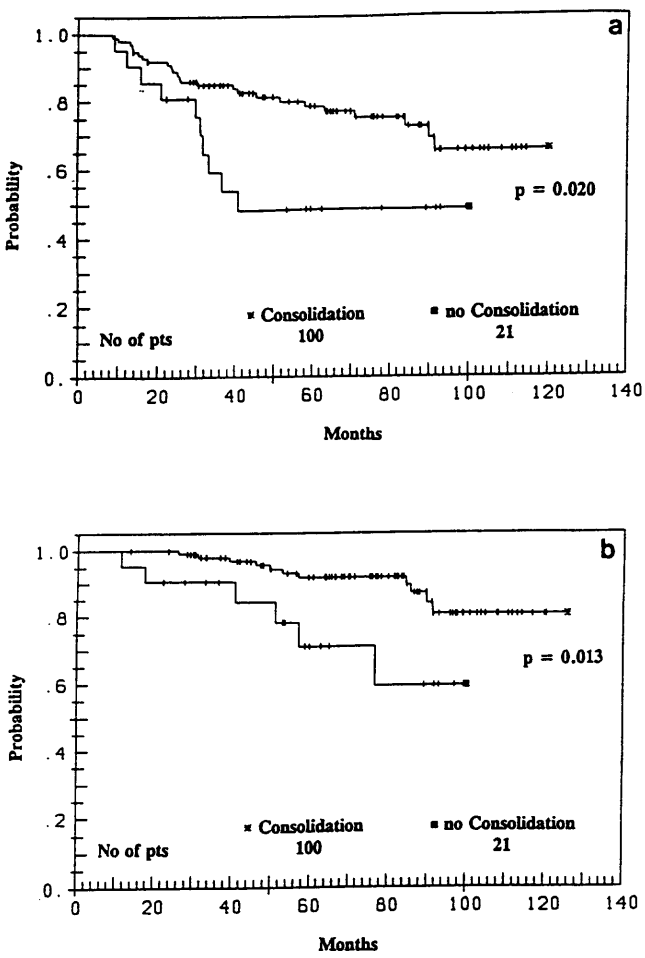


Fig. 4. Comparison of all randomized patients receiving a consolidation treatment (either RT or CT) with the CR patients refusing further consolidation. The difference is highly significant although caution is required since the comparison was not randomized. (a) FFTF; (b) Overall survival.

above covariates a term for consolidation received (yes/no) was included. After backward selection large mediastinal tumor and no consolidation treatment received were significant adverse prognostic factors for both FFTF and survival. After these adjustments the relative risk estimates associated with no consolidation treatment received were 3.67 (95% CI: [1.3; 10.3]) for FFTF and 2.8 (95% CI: [1.13; 5.04]) for survival.

Intensive radiotherapy for nodal disease. Patients with nodal PR after induction therapy received more intensive radiotherapy (IRT group) with 20 Gy to all previously involved sites (IF) and 40 Gy to persisting tumors. Seventy-eight patients were treated according to this strategy, 7 progressed under treatment, 9 remained in PR, and 62 (79%) achieved a final complete remission (Fig. 1). Of these 62 patients in CR one died of heart failure and 10 relapsed.

Chemotherapy for extranodal disease. After induction treatment, 19 patients achieved PR which was not restricted to nodal sites and were allocated to chemotherapy. However, only 11 patients were treated with CEVD. Six patients achieved complete remission after CEVD and two others after CEVD plus additional radiotherapy. Eight of 11 patients of this group are alive with follow-up times from 28 to 108 months. Furthermore, 8 patients were treated with chemotherapies other than CEVD. These cases were considered failures of the intended study strategy (in PR-status) (see Fig. 1).

Prognostic factor analysis. A prognostic factor analysis of the entire cohort showed that only low hemoglobin had prognostic significance for both FFTF and overall survival. The relative risk estimate is 1.94 for FFTF (95% CI: [1.15; 3.27]) and 1.91 for overall survival (95% CI: [1.26; 2.88]) using a dichotomous coding of Hb (12 g/l for males and 10.5 g/l for females as cut-off points). If the analysis was restricted to the randomized patients, only large mediastinal mass was found to be adversely associated with prognosis in both FFTF and overall survival with relative risks of 6.7 for FFTF (95% CI: [1.60; 28.6]) and 3.1 for survival (95% CI: [1.28; 7.5]).

Discussion

To our knowledge this is the first report of a trial comparing low-dose IF radiotherapy versus further chemotherapy in patients who had achieved CR after 6 cycles of modern doxorubicin-containing alternating induction chemotherapy in advanced-stage Hodgkin's disease. In our prospective randomized multicenter trial no statistically significant difference could be detected with respect to failure (i.e., relapse) and overall survival. The power of the trial was sufficient to reveal differences of about 20% after 7 years.

An interesting observation was made in a group of patients who refused consolidation treatment after achieving CR following 6 cycles of induction treatment. These patients showed a markedly elevated relapse risk compared with the two groups who underwent either RT or CT consolidation. However, this comparison is dubious, as no proper randomisation was performed. Hence, we cannot rule out unknown selection effects leading to bias. Clearly the multivariate adjustment performed can only account for known factors. Further randomized studies will be required to clarify whether 6 cycles of alternating doxorubicin-containing induction chemotherapy are sufficient for advanced-stage HD patients.

A third interesting observation is that initially involved extranodal sites were well controlled by the induction chemotherapy. None of the initial lung or liver involvements relapsed although no radiation was administered to these sites in the RT or IRT groups. In the entire study population only one of the initially affected bone marrow involvements relapsed.

It should be noted that no comparison is presented between the groups of patients who received consolidation treatment and those who received intensive radio-

therapy. Due to the design of the trial any such comparison would be biased. Furthermore, the definition of PR is not completely reliable. It is very likely that some of the patients classified as PR in fact exhibited a CR with residual fibrosis. In fact there was a greater proportion of nodular sclerosis subtype in that cohort. Hence, the treatment efficacy of intensive RT for this group of patients (62 out of 78 in CR) may be too optimistic for true PR patients. Sophisticated diagnostic procedures such as gallium scans or tumor mass measurements were not available at the time of the accrual period, nor are they feasible in a multicenter trial.

Therefore, well-designed randomized studies are needed to pursue the question of a dose-response relationship of RT after chemotherapy in CR as well as in PR patients. The potential benefit of a more effective radiotherapy, however, will be limited due to the occurrence of relapses in initially uninvolved nodal sites which in our series made up about half of all relapses. Furthermore, half of the MMT involvements relapsed even after radiation. As a rough estimate an effective radiotherapy avoiding major protocol violations and controlling all known nodal involvements might reduce relapse rates by at most a quarter. However, it is possible that an effective induction and consolidation chemotherapy can restrict this potential gain. Hence, very large trials would be required to reveal any such benefits.

The present trial addresses the question of whether there are differences between low-dose IF-radiation and chemotherapy as consolidation after six cycles of doxorubicin-containing alternating induction treatment. No significant differences were detected in our trial. To our knowledge two other trials investigated the question after induction treatment which did not contain doxorubicin.

A trial conducted by the NCI-Canada compared radiotherapy versus MOPP chemotherapy after a MOPP induction with 3–6 cycles [32]. When adjusted for covariates no differences in relapse rates or survival were observed. However, a significant reduction in nodal infield relapses was noted. This is in line with earlier non-randomized work by Prosnitz et al. (1982) [26].

The ECOG trial No. 1476 had a design similar to that of the HD3 trial [11, 12]. After 6 cycles of Bleo-MOPP 172 patients in CR or PR were randomized to receive 15–20 Gy IF or 3 cycles of ABVD. FFTF and overall survival were significantly better for the ABVD group. However, we would like to argue that Bleo-MOPP may not have been a fully effective induction chemotherapy regimen as it contained no antracycline analogue. Thus, the efficacy of radiation may have been limited, while ABVD was very effective, particularly in PR after MOPP. With a more effective induction treatment such as COPP + ABVD the effectiveness of consolidation chemotherapy and radiotherapy should be more alike, which may explain the lack of a difference in our trial.

Several trials are comparing radiation versus no further treatment after achievement of CR. Interesting observations were made in a recent SWOG trial [8] in which patients in CR after 6 × (MOP + BAP) received either no further treatment or 15–20 Gy IF. A total of 278 patients were randomized (135 for radiation and 143 for no further treatment) before the start of treatment. An analysis by intent-to-treat showed no differences between the treatment groups with respect to remission duration, relapse-free survival and overall survival. However, 44 (16%) of the randomized patients who were complete responders did not receive their assigned treatments. Only 104/135 received radiation and 130/143 received no further treatment. An analysis restricted to the 234 patients who actually received their randomized treatments showed a significant improvement in remission duration in favor of low-dose radiation compared with no further treatment ($p = 0.002$). This was confirmed in a multivariate Cox model adjusting for possible imbalances. The relative risk for relapse for patients receiving no further therapy was estimated to be 1.8 times (CI, 1.0–3.0) that of those receiving low-dose radiation [8]. These results are in good agreement with our findings suggesting an approximately 3-fold higher relapse risk in the non-consolidation group.

Further indications of a beneficial effect of consolidation radiotherapy after 6 cycles of doxorubicin-containing induction chemotherapy come from a retrospective analysis according to treatment actually given to 222 patients treated at the Memorial Sloan-Kettering Cancer Center [31]. The study compared non-randomized patients with full versus partial or no radiation to initially involved sites in patients achieving CR after chemotherapy. Consistent with our finding, in a multivariate analysis adjusting for various covariates the relative risk of relapse was 3-fold higher when only partial or no radiation, as opposed to full IF radiation, was applied. Thus, the SWOG trial, the MSKCC data and our data all suggest that discontinuation of treatment in patients achieving CR after six cycles of antracycline-containing treatment is associated with an increase in risk of relapse. To obtain unequivocal data would, however, require appropriate randomized studies. Whether this is still the case after 8 cycles of chemotherapy is a question being addressed in an ongoing EORTC trial (trial H34, protocol 20884) in which patients in CR after 6 cycles receive 2 further cycles and are then randomized to IF-RT or no further treatment.

There are also some trials in which chemotherapy alone and the same chemotherapy plus RT were randomized before start of treatment without being conditioned on interim remission [1, 2, 5, 7, 11, 14, 22, 27]. One of these trials reported a difference in favour of combined modality [22, 23]. Another trial yields such evidence only if analysed for treatment given, while obtaining no differences if analysed by intent to treat [12]. All other trials showed no differences. However, none of these trials used alternating antracycline-con-

taining regimens. Thus, our study is the first to report similar efficacies of radiotherapy and chemotherapy in consolidation after 6 cycles of alternating chemotherapy. However, further studies are required to investigate more subtle differences in greater detail.

A few remarks on other topics remain to be made. First, the SWOG study reported a favorable effect of radiation in the nodular sclerosis subgroup. We cannot reproduce this finding in our series (data not shown) but the number of events may still be too small. Second, the SWOG study delivered radiation to all initially involved sites including lung and liver. Our study did not include organ radiation but this restriction did not increase the relapse risk. Third, the prognostic factor analysis of the present trial reveals a few factors with some predictive value, in particular low hemoglobin and large mediastinal mass. However, the dataset is too small to provide a reliable indication of the relative risks and thus justify basing treatment decisions on these results. In summary, we conclude that there are no major differences between low dose-involved-field radiotherapy and further chemotherapy in patients with advanced-stage HD who have achieved CR after 6 cycles of an alternating chemotherapy.

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***Study participants**

Hospitals and practitioners (listed according to recruitment): München Großhadern (E. Hiller, H. Gerhartz, R. Rohloff); Köln Med. Universitätsklinik I (V. Diehl, M. Pfreundschuh, H. Sack, M. Adler, B. Lathan); Düsseldorf Universitätsklinik (W. Schoppe, U. Hagen-Aukamp, H. Kürten); Duisburg St. Johannes-Hospital (M. Westerhausen, R. Fuchs, B. Makoski); Marburg Universitätsklinik (H. Pflüger, R. Pfab); Lübeck Städt. Krankenhaus-Süd (H. Bartels, J. Entzian); Freiburg Universitätsklinik (G. Dölken, T. Hecht, H. Hinkelbein); Berlin Steglitz (H. Ernst, J. Teichmann); Erlangen Universitätsklinik (J. König, S. Petsch, R. Sauer); Berlin Moabit (H. Hellriegel, G. Kühn, U. Rühl); Berlin Neukölln (W. Wilhelmy); Frankfurt Universitätsklinik (K. Schalk, Szepesi); Mannheim Klinikum (P. Worst, P. Diezler); Krefeld Städt. Krankenhaus (M. Planker, U. Schulz); B-Charlottenburg (W. Oertel) Karlsruhe St. Vincentius Krankenhäuser (S. Theml, R. Staiger, W. Haase); Lübeck Medizinische Hochschule (T. Wagner, G. Schwieder, Brandenburg); Bonn Universitätsklinik (U. Loos, I. Boldt); Essen Universitätsklinik (S. Samandari); Hannover Med. Hochschule (H. J. Schmoll, H. Kirchner, H. Emminger); Kiel Städt. Krankenhaus (W. Gaßmann, T. Brix); Wiesbaden Praxis Dr. Schmitz; Köln Med. Universitätsklinik II (B. Mödder); Trier Krankenhaus d. Barmherzigen Brüder (H. Hennekeuser); Augsburg Zentralklinikum (G. Schlimok, Doukas, A.-C. Voss); Mainz Universitätsklinik (B. Krüger, K. Kutzner); Oldenburg Evangelisches Krankenhaus (F. Hinrichs, A. Temmesfeld); Berlin Praxis Dr. Weißenfels; Bremen Zentralkrankenhaus links der Weser (T. Luska); München r.d.Isar (H. D. Schick); Hildesheim Städt. Krankenhaus (J. Preiß, W. Gärtner); Aachen Praxis Prof. Essers; Ravensburg St. Elisabethen Krankenhaus (W. Mende); Essen Krupp-Krankenhaus (W. Alberti); München Harlachingen (U. Hoffmann); Hildesheim St. Bernward Krankenhaus (D. Urbanitz, Heide); Trier Mutterhaus der Borromäerinnen (H. Siebner, K. H. van de Weyer, D. Dornoff); Mainz Gemeinschaftspraxis Schniepp/Hinterberger, Köln Krankenhaus Merheim (E. Renner, M. Cohen); Neuss Lukaskrankenhaus (P. Czygan); Olpe St.-Martinus-Hospital (H. W. Scheja); Hannover Praxis Dr. Wysk; Köln Elisabeth Krankenhaus (J. Schoenemann); Herford Kreiskrankenhaus (M. Rochell); Krefeld Maria Hilf (U. Peters); Heilbronn Städt. Krankenhaus (K. Koniczek); Köln Krankenhaus d. Augustinerinnen (D. Mitrenga); Karlsruhe Städt. Kliniken (U. Cammerer); Darmstadt Elisabethenstift (W. Mantel).

Reference radiotherapy: U. Rühl, W. Geilen (Berlin).

Reference Pathology: A. Georgii (Hannover), R. Fischer (Köln), K. Hübner (Frankfurt), E. W. Schwarze (Dortmund).

Data management: H. Nisters-Backes (Köln).

Biometry: M. Loeffler, D. Hasenclever (Leipzig).

Study coordinators: M. Pfreundschuh, M. Loeffler (Köln).

Writing committee: M. Loeffler (responsible secretary), D. Hasenclever, H. Nisters-Backes, M. Sieber, M. Pfreundschuh, U. Rühl, H. Tesch, V. Diehl.

Chairman: Volker Diehl.

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Correspondence to:
Prof. Dr. Volker Diehl
Klinik I für Innere Medizin der Universität zu Köln
Morbus Hodgkin Studiensekretariat
50924 Cologne
Germany