

Meta-Analysis of Chemotherapy Versus Combined Modality Treatment Trials in Hodgkin's Disease

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Design: To perform a meta-analysis of all randomized trials that compared chemotherapy (CT) alone versus combined modality treatment (CT + radiotherapy [RT]) for which individual patient data could be made available.

Patients and Methods: Data on 1,740 patients treated on 14 different trials that included 16 relevant comparisons have been analysed. Eight comparisons were designed to evaluate the benefit of additional RT after the same CT (CT₁ v CT₁ + RT; additional RT design). Eight comparisons were designed to evaluate whether RT in a combined modality setting can be substituted by CT using either more cycles of the same CT or regimens that contain additional drugs (CT₁ + CT₂ v CT₁ + RT or CT₁ v CT₂ + RT; parallel RT/CT design).

Results: Additional RT showed an 11% overall improvement in tumor control rate after 10 years ($P = .0001$; 95% confidence interval [CI], 4% to 18%). No difference could be detected with respect to overall

survival ($P = .57$; 95% CI, -10% to 4%). In contrast, when combined modality treatment was compared with CT alone in the parallel-design trials, no difference could be detected in tumor control rates ($P = .43$; 95% CI, -6% to 9%), but overall survival was significantly better after 10 years in the group that did not receive RT ($P \neq .045$; 8% difference; 95% CI, 1% to 15%). There were significantly fewer fatal events among patients in continuous complete remission (relative risk [RR], 1.73; 95% CI, 1.17 to 2.53; $P = .005$) if no RT was given.

Conclusion: Combined modality treatment in patients with advanced-stage Hodgkin's disease overall has a significantly inferior long-term survival outcome than CT alone if CT is given over an appropriate number of cycles. The role of RT in this setting is limited to specific indications.

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SYSTEMIC POLYCHEMOTHERAPY and local radiation (RT) are two well-established treatment principles for Hodgkin's disease. Since the invention of the mechlorethamine, vincristine, procarbazine, and prednisone (MOPP)¹ and doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) schemes,² polychemotherapy has become indispensable for the treatment of advanced-stage disease. Many efforts presently concentrate on improving this treatment principle by variation of substances, timing, dosing, etc.³⁻⁸

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The role of RT in combination with chemotherapy (CT) has remained controversial.⁹⁻¹⁸ Many trials involved too few patients to detect relevant differences reliably and remained inconclusive. Furthermore, little information was available in single trials on long-term outcomes.

To obtain a more detailed understanding of the role of RT in advanced-stage Hodgkin's disease, we initiated a systematic meta-analysis of all accessible randomized trials that compared CT alone versus a combined modality strategy (CT + RT). To adjust for different treatment policies and inclusion criteria among trial groups, submission of individual patient records was requested for each patient in such a trial. A joint analysis of all of these data was undertaken with respect to the end points of disease control, overall survival, survival in continuous complete remission, and survival after treatment failure.

PATIENTS AND METHODS

Organization of the Meta-Analysis

Screening literature, data bases, and conference proceedings led to the identification of 30 potentially relevant randomized trials to be incorporated into the meta-analysis. A detailed study protocol was then elaborated that included a description of the project objectives and methodologies. The protocol included a detailed instruction for data abstraction of individual patient records with specific coding instructions and definitions. Initial patient characteristics requested were date of birth, sex, histology, laparotomy, stage, systemic symptoms, medias-

tinal involvement (no, yes, large), and bulky disease (no, yes). Definitions for large mediastinal mass and bulky disease were requested from the study groups. Treatment information requested included date of initiation of treatment, date of randomization, and randomization arm (ie, treatment intended). Treatment outcome variables included date of end of treatment, remission status, date of relapse, last follow-up date, last known vital status, and cause of death. Previous experience with submission of individual patient records from many trial groups had been encouraging in the International Database on Hodgkin's disease (IDHD)¹⁹ and suggested that the project should be feasible. However, no laboratory parameters, such as erythrocyte sedimentation rate, serum albumin, hemoglobin, etc, were requested, because the IDHD experience has shown that these data are unstandardized and incomparable between and even within trial groups. The protocol descriptions were sent out with covering letters to the trial groups or individuals assumed to have been involved.

Trials Included

Of 26 trial candidates initially deemed to be suitable and completed at the time the meta-analysis was initiated, data for 14 were finally included that contained information on more than 70% of all patients treated in randomized CT versus CT + RT trials. Four trials were still ongoing and no unblinded data could be provided (European Organization for Research and Treatment of Cancer [EORTC] H34, British National Lymphoma Investigation Group,²⁰ and Pediatric Oncology Group 8725²¹ and 8625/26). Original data from eight trials were definitively destroyed, lost, or not accessible (Roswell Park Memorial Hospital, Buffalo, NY²²; Cancer and Leukemia Group B [CALGB] 7751, 7451, and 6609^{23,24}; Southwest Oncology Group [SWOG] 774/775; Yale University HIC 3281; Western Cancer Study Group 131; and Children's Cancer Study Group 521). Data could not be provided by two trial groups (CALGB 7551²³ and Southeastern Cancer Study Group [SEG] HD81328.²⁵ Two trial groups could only provide cumulative outcome data instead of individual patient data (St Jude Children's Research Hospital and Cape Town University).

On the basis of their objectives and designs, two principally different types of trials that deserve separate consideration in the analysis must be distinguished (Table 1).

Additional RT design. Eight comparisons were designed to evaluate the benefit of additional RT after the same CT (CT₁ v CT₁ + RT). The trials were hence planned to show differences (ie, RT v no RT) and their objective was to quantify the magnitude of benefit due to additional RT. In most cases, six cycles of CT were planned, except in two trials. Randomization took place at the beginning of treatment in six trials and was conditional on remission induction in two trials. CT was based on MOPP or MOPP variants (seven trials) and only one recent trial used an anthracycline-containing regimen (SWOG 78-08). Extended-field RT was planned in three trials that involved only 151 patients, and involved-field radiation in five trials.

Parallel RT/CT design. Eight comparisons were designed to evaluate whether RT after CT can be substituted by CT using either more cycles of the same CT or regimens that contain additional drugs (CT₁ + CT₂ v CT₁ + RT or CT₁ v CT₂ + RT). Although different in detail, all of these trials had the common objective to examine whether prolonged CT can be substituted for RT in a combined modality program. Hence, the trials were planned to examine equivalence. In most cases, six cycles of CT were planned before RT, compared with eight to 12 cycles if no RT was given. CT was entirely based on MOPP or MOPP variants in only three trials, while anthracyclines were used in some form in five trials, although not necessarily in both arms. Randomization took place initially in five trials and was conditional on

remission induction in three trials. Extended-field RT was planned in five trials and involved-field RT in three. In the trials analyzed, there was a tendency to contrast extended-field RT with more CT cycles in the CT arm alone than involved-field RT.

It should be noted that two trials had a randomization between three arms (Eastern Cooperative Oncology Group [ECOG] 14-81, eight to 12 cycles of carmustine, cyclophosphamide, vinblastine, procarbazine, and prednisone [BCVPP] v eight to 12 cycles of MOPP-ABVD v eight to 12 cycles of BCVPP + RT; National Cancer Institute of Canada [NCIC], six cycles of MOPP v 10 MOPP v six cycles of MOPP + RT). These trials involved both an additional RT question, as well as a parallel RT/CT question, and we decided to analyze the arm comparisons separately according to their objective. Consequently, the combined modality arm of these two trials was used in both analyses (additional RT design and parallel RT/CT design). In addition, it should be mentioned that the NCIC trial had a more complex design with a first randomization after three MOPP cycles to extended radiation or to further MOPP therapy (with subsequent randomization in this arm to the three alternatives previously mentioned). However, several patients initially randomized to receive further MOPP therapy did not undergo a second randomization and could therefore not be clearly classified with respect to their intention to treat (whether or not RT was planned). Therefore, in accordance with the study group, only the three arms of the second randomization were used.

Patients Included

Data from 1,740 patients were analyzed. It should be noted that some of the trial groups submitted data with either more patients or longer follow-up periods than published in previous reports (SWOG 7518, ECOG 1476, and Manchester) and one trial group submitted unpublished data (Southeastern Cancer Study Group [SEG] 77 HD320). Almost complete data were available for sex, age, stage, systemic symptoms, histology, laparotomy, randomization arm, primary treatment outcome, relapse, date of last follow-up evaluation, and death. Information was only partly available on mediastinal involvement (92%), large mediastinal mass (58%), bulky disease (65% in additional RT trials and 0% in parallel RT/CT trials), date of relapse (92%; lacking in the Canadian trial), and cause of death (48% of all deaths). Hence, 1,740 patients could be included for analysis of overall survival and 1,610 for analysis of time to failure of disease control. Cause of death was not available from the two ECOG trials and appeared to be lacking at random in the other data sets. The definition of large mediastinal mass differed substantially among trial groups; therefore, this parameter could not be analyzed.

Table 2 lists patient characteristics. The patient populations differed remarkably between the two trial designs. Trials with an additional RT design tended to include more patients with intermediate-stage disease (stage I to IIA, 14% v 0%; stage IIB to IIIA, 31.5% v 17%; and stage IIIB to V, 54.5% v 83%), with less mediastinal involvement and less frequent laparotomy than trials with a parallel RT/CT design. Minor imbalances between the randomized arms (eg, age, histology, and mediastinal involvement) can be adjusted for in multivariate analyses.

End Points

Five end points were used in the subsequent analysis in an attempt to assess separately biologically different effects. The clinically most important end point was overall survival, which is defined as time to death of any cause. The efficacy of treatment to control Hodgkin's disease was measured by the time to failure of disease control, which is defined as the occurrence of either progression during treatment, no complete remission at the end of treatment, or relapse, with deaths in

Table 1. Description and Results of Individual Trials

Trial	Inclusion Period	n	Design	n per arm	Disease Control		Overall Survival		
					Log Hazards Ratio	95% CI	Log Hazards Ratio	95% CI	
Additional RT design: CT ₁ v CT ₁ + RT									
SEG 77 HD320*	1974-76	38	R	6 BCVPP (19)	-1.64	-3.19-0.09	-0.74	-2.13-0.65	
Manchester Lymphoma Group ²⁶	1975-82	63	R	6 BCVPP (19)	-0.49	-1.64-0.66	-0.22	-1.12-0.73	
			7-10 MVPP (31)	IF 30 Gy					
GATLA HD77 ^{27,28}	1977-86	255	R	7-10 MVPP (32)	-0.81	-1.16-0.46	-0.63	-1.12-0.15	
			6 CVPP (111)	IF 30 Gy					
SWOG 78-08 ²⁹	1978-88	278	R	6 CVPP (144)	-0.38	-0.83-0.08	0.40	-0.14-0.93	
			6 MOP-BAP (143)	IF 30 Gy					
ECOG 14-81 ^{30,31}	1981-86	218	R	8-12 BCVPP (135)	-0.01	-0.39-0.36	0.20	-0.26-0.67	
			8-12 BCVPP (71)	IF 20 Gy					
Stanford H7/K7 ³²	1968-74	33	R	8-12 BCVPP (147)	-0.11	-1.16-0.94	-0.01	-0.85-0.83	
			6 MOPP (15)	IF 15-20 Gy					
Baltimore Cancer Research Program ³³	1972-75	36	R	6 MOPP (18)	-0.82	-2.04-0.41	-0.60	-2.38-1.19	
			6 MOPP (17)	TNI 35-44 Gy					
NCIC HD1 ³⁴	1972-76	82	R	6 MOPP (19)	No data		-0.01	-0.67-0.65	
			6 MOPP (27)	EF 40 Gy					
			R	6 MOPP (55)					
				EF 20-30 Gy					
Parallel RT/CT design: CT ₁ + CT ₂ v CT ₁ + RT or CT ₁ v CT ₂ + RT									
ECOG 14-76 ^{35,36}	1976-81	198	R	6 BleoMOPP (103)	0.05	-0.37-0.48	0.38	-0.06-0.83	
ECOG 14-81 ^{30,31}	1981-86	288	R	4-6 [MOPP-ABVD] (95)	0.35	0.02-0.69	0.47	0.07-0.87	
			8-12 BCVPP (141)	IF 15-20 Gy					
GHSG HD3 ³⁷	1984-88	100	R	3[COPP-ABVD] (147)	-0.03	-0.81-0.75	-0.75	-1.98-0.48	
			8-12 BCVPP (49)	IF 15-20 Gy					
NCIC HD1 ³⁴	1972-76	84	R	6 MOPP (51)	No data		-0.12	-0.72-0.48	
			3[COPP-ABVD] (29)	IF 20 Gy					
SWOG 75-18 ^{38,39}	1975-80	137	R	6 MOPP (55)	-0.39	-1.03-0.25	-0.09	-0.67-0.49	
			10 BleoMOPP (68)	EF 20-30 Gy					
Lyon LMS80 ⁴⁰	1980-84	58	R	3 BleoMOPP (69)	0.30	-0.63-1.23	0.97	-0.12-2.06	
			6 [MOPP-CVPP] (30)	TNI 30-40 Gy					
Stanford C7-10 ³²	1980-84	37	R	6 MOPP (28)	-0.51	-1.53-0.51	0.77	-1.98-0.44	
			6 [PAVe-ABVD] (20)	EF 30 Gy					
Stanford C12-15 ³²	1981-88	37	R	6 PAVe (17)	-0.40	-1.83-1.03	0.54	-0.73-1.81	
			6 [MOPP-ABVD] (20)	TNI 40-44 Gy					
			R	6 PAVe (17)	No data		No data		

NOTE. Table provides a short description of each trial entered into the joint meta-analysis, which identifies study group, trial code number, inclusion period, flow sheet with type of CT, RT field, time and condition of randomization, and number of randomized patients included. Last column gives the point estimate (with 95% CI) of the log hazards ratio for each trial with respect to the end points disease control and overall survival. Trials are grouped into 2 different classes depending on the type of design used. The objective of comparisons with additional RT design CT₁ v CT₁ + RT was to evaluate the benefit of additional RT after the same number of cycles of the same CT. The objective of comparisons with parallel RT/CT design (CT₁ + CT₂ v CT₁ + RT) or (CT₁ v CT₂ + RT) was to evaluate whether RT after CT can be substituted by CT using either more cycles of the same CT or regimens that contain additional drugs.

Abbreviations: DC, disease control; OS, overall survival; R, randomization; R(CR), randomization conditional on complete remission; R(CR, PR), randomization conditional on complete or partial remission; IF, involved field; EF, extended field; TNI, total-nodal irradiation; BCVP, carmustine, cyclophosphamide, vinblastine, procarbazine, and prednisone; MVPP, mechlorethamine, vinblastine, procarbazine, and prednisone; CVPP, cyclophosphamide, vinblastine, procarbazine, and prednisone; MOP-BAP, mechlorethamine, vincristine, procarbazine, bleomycin, doxorubicin, and prednisone; MOP, mechlorethamine, vincristine, procarbazine, and prednisone; BleoMOP, bleomycin, mechlorethamine, vincristine, procarbazine, and prednisone; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; COPP, cyclophosphamide, vincristine, procarbazine, and prednisone; CVPP, lomustine, vinblastine, procarbazine, and prednisone; PAVe, procarbazine, melphalan, and vinblastine; SEG, Southeastern Cancer Study Group; GATLA, Grupo Argentino de Tratamiento de Leucemia Aguda; SWOG, Southwest Oncology Group; ECOG, Eastern Cooperative Oncology Group; NCIC, National Cancer Institute of Canada; GHSG, German Hodgkin's Study Group.

*No publication on this trial.

continuous complete remission censored. Survival in continuing complete remission was defined as time to death in complete remission, with any relapse censored. These three end points were measured since the start of treatment. Survival after treatment failure was defined as time to death of any cause after failure of disease control. Finally, time to leukemia-related death was defined as time from initiation of therapy to death from leukemia, with all deaths from other or unknown causes censored.

Statistical Analysis

Kaplan-Meier estimates were used to obtain univariate survival time estimates. Cumulative incidence plots⁴¹ were used for the univariate

description of leukemia-related deaths. Tests for heterogeneity were performed separately for the two sets of trials (additional and parallel design). No significant heterogeneity was detected. All analyses were performed separately for the additional RT and for the parallel RT/CT design trials.

To accommodate for different baseline hazards functions in different trials, to adjust for slight imbalances in the patient populations, and to permit estimation of treatment effects in specific subgroups, multivariate analyses were performed using the proportional hazards model. The models were fitted to the data pooled from different trials stratified by trial. Besides the treatment arm (CT + RT = 1, CT = 0), the model

Table 2. Patient Characteristics

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Characteristic	Additional RT				Parallel RT/CT				Completeness (%)
	CT (n = 434)		CT + RT (n = 569)		CT (n = 460)		CT + RT (n = 479)		
	No.	%	No.	%	No.	%	No.	%	
Male	279	64	370	65	303	66	331	69	99.9
Age, years									99.7
< 30	191	46	260	46	232	50	251	52	
30-45	119	30	171	30	124	27	133	28	
45-60	83	15	86	15	72	16	66	14	
> 60	39	9	48	9	32	7	27	6	
Stage									99.8
I, IIA	56	13	86	15	—	—	1	—	
IIB, IIIA	149	34	165	29	79	17	78	17	
IIIB, IV	228	53	316	56	381	83	398	83	
Histology									99.9
LP	22	5	35	6	9	2	10	2	
NS	205	47	308	54	267	58	293	61	
MC	189	43	183	32	138	30	122	25	
LD	16	4	30	5	12	3	17	4	
Unclassified	2	1	13	3	32	7	37	8	
Laparotomy	111/412	27	139/545	25	186/418	44	186/441	42	92.9
Mediastinal involvement	195/400	49	266/507	52	249/424	59	243/415	59	92.1
Large mediastinal mass	39/319	12	58/338	17	59/174	34	65/171	38	57.6
Bulky disease*	93/316	29	100/335	30	No data		No data		64.9 additional RT 0 parallel RT/CT

*Definition of bulky disease: ≥ 10 cm (Baltimore trial, Manchester trial), ≥ 5 to 6 cm (SWOG 78-08, GATLA HD77, and SEG 77 HD320).

incorporated stage (two variables for stage I/II, and stage IV, respectively), systemic symptoms, histology, mediastinal involvement, and bulky disease (only in the additional RT trials) as explanatory variables. All explanatory variables were coded according to their frequency in the data set (no = 0 [frequency of the variable]; yes = 1 - [frequency of the variable]). Due to this coding, an averaged population-based baseline hazards function was defined, and the estimated arm effect in the model could be interpreted as the averaged arm effect in the population. In addition, interaction terms were introduced between the arm and the explanatory variables, which allowed estimation of subgroup-specific arm effects different from the overall arm effect.

All analyses were performed according to treatment intended.

RESULTS

Disease Control and Overall Survival

Trials that compared additional RT versus no RT. A pooled analysis of 918 patients from seven trials with additional RT design showed a clear benefit for RT in the rate of continuous complete remission in the order of 11% at 10 years, with a 95% confidence interval (CI) of 4% to 18% (Fig 1A). A stratified log-rank test for arm comparison was highly significant ($P < .001$).

Multivariate analysis confirmed this finding. The hazards rate for Hodgkin's disease treatment failure was reduced by nearly 40% using additional RT (relative risk [RR], 0.63; 95% CI, 0.50 to 0.78) (Fig 1B). However, the magnitude of this beneficial RT effect varied between subgroups with different prognostic factors. It was more pronounced in patients with mediastinal involvement (RR, 0.51; 95% CI,

0.31 to 0.85), less pronounced in patients with mixed cellularity (MC) or lymphocyte-depleted (LD) histology (RR, 0.76; 95% CI, 0.46 to 1.23), and virtually absent in patients with stage IV disease (RR, 1.08; 95% CI, 0.63 to 1.86). There was no additional benefit of RT in patients with bulky disease. However, with respect to overall survival (1,003 patients, eight trials), no beneficial effect could be identified by additional RT (Fig 1C; stratified log-rank test, $P = .6$).

Trials that compared additional RT versus additional CT. A pooled analysis of 837 patients from seven trials with parallel design showed almost identical behavior in the rate of continuous complete remissions (Fig 2A). A stratified log-rank test for arm comparison was not significant ($P = .43$).

Multivariate analysis confirmed this finding. The relative risk for Hodgkin's disease treatment failure was not reduced by RT (estimate, 1.07; 95% CI, 0.85 to 1.34). A check for significant interaction terms between treatment arm and prognostic factors show no deviations from this general finding in subgroups. The only exception was a moderate, but nonsignificant trend for an interaction of arm effect and mediastinal involvement (RR, 0.92; 95% CI, 0.55 to 1.57; Fig 2B).

Remarkably, the overall survival in this group of patients (939 patients, eight trials) showed a significant benefit for patients who received CT only (Fig 2C; stratified log-rank

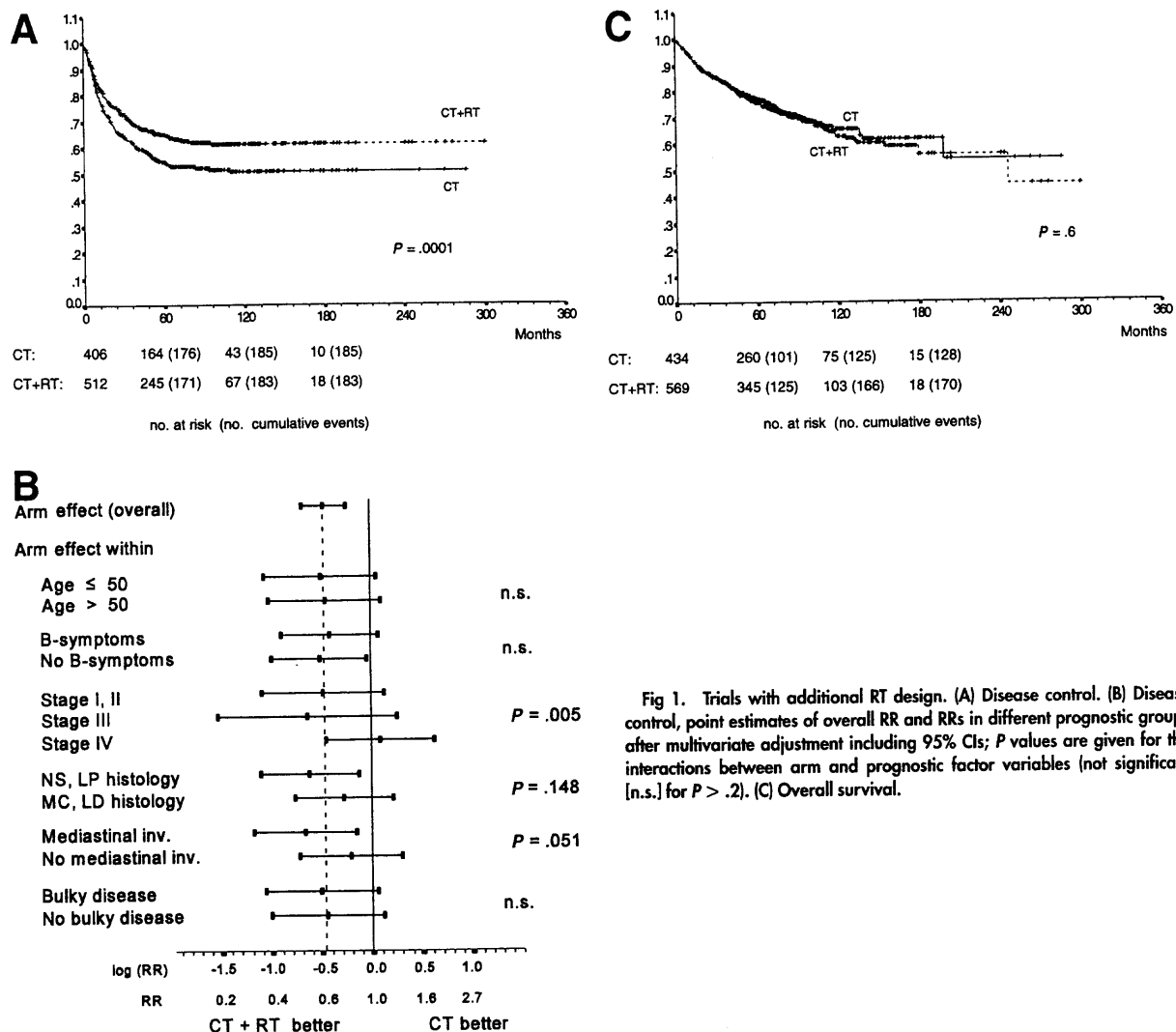


Fig 1. Trials with additional RT design. (A) Disease control. (B) Disease control, point estimates of overall RR and RRs in different prognostic groups after multivariate adjustment including 95% CIs; P values are given for the interactions between arm and prognostic factor variables (not significant [n.s.] for $P > .2$). (C) Overall survival.

test, $P = .045$). Ten years after the start of treatment, overall survival rates were 8% better if CT alone instead of a combined modality treatment was given (95% CI, 1% to 15%).

Causes of Death

To understand better the discordance between the end points disease control and overall survival, a more detailed analysis of the causes of death was undertaken. Table 3 lists treatment outcomes and causes of death as far as they were documented. Of these, only about two thirds were due to Hodgkin's disease. Unfortunately, one trial group was unable to report detailed causes of death, which explains the high rate of missing data. Other missing data appeared to occur at random, and therefore did not bias the subsequent analyses.

An analysis of survival in continuous complete remission particularly highlights death hazards not due to Hodgkin's disease progression or relapse. For this end point, any progression, existence, or recurrence of Hodgkin's disease is censored. Adjustment for prognostic factors was only significant with respect to age in both trial design types. There was no effect of splenectomy on survival in continuous complete remission. The analysis shows a remarkably large overall benefit in favor of CT alone (Fig 3). The age-adjusted RR of death not related to Hodgkin's disease after CT + RT was 1.64 (95% CI for RR, 0.94 to 2.85; $P = .08$) in additional RT trials, and 1.72 (95% CI for RR, 1.04 to 2.82; $P = .03$) in parallel RT/CT trials. The magnitude of the benefit is almost identical in both trial designs, which indicates this finding is valid, independent of trial design. Therefore, a joint analysis of all trials was performed, which led to an estimate of the

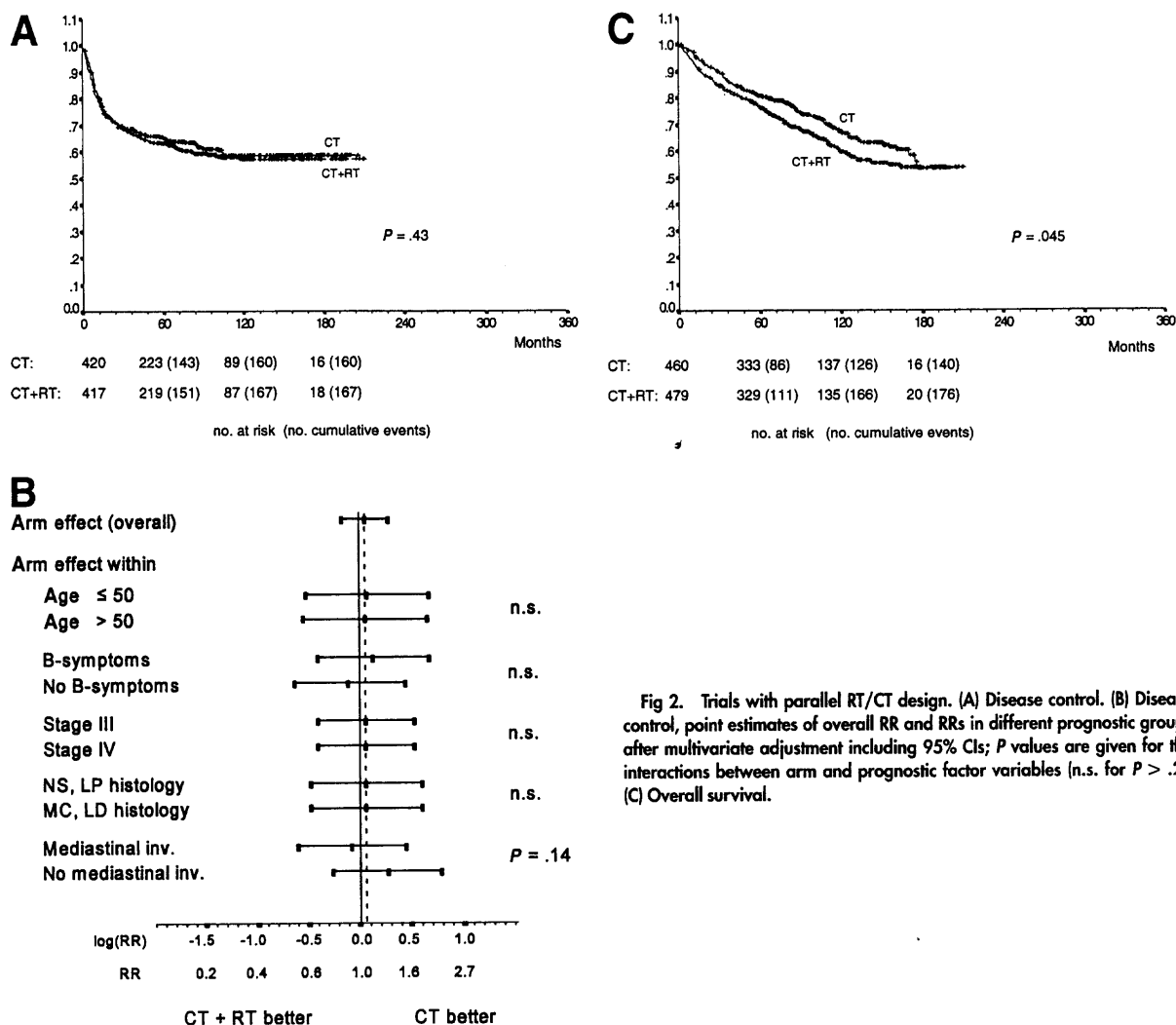


Fig 2. Trials with parallel RT/CT design. (A) Disease control. (B) Disease control, point estimates of overall RR and RRs in different prognostic groups after multivariate adjustment including 95% CIs; P values are given for the interactions between arm and prognostic factor variables (n.s. for $P > .2$). (C) Overall survival.

age-adjusted RR of death not related to Hodgkin's disease after CT + RT of 1.73 (95% CI, 1.17 to 2.53; $P = .0051$). The ECOG 14-81 trial counted in the joint analysis as one trial, with the two CT arms pooled. Hence, this analysis suggests that patients with combined modality treatment experience a higher risk for fatal events not related to the original disease, but somehow related to treatment. It is likely that several causes contribute to the overall effect (eg, leukemia, other second neoplasms, cardiac events, late infections, and other causes). However, due to the small number of events, nonspecific coding, and too short follow-up duration for, eg, solid tumors, the data set does not permit identification of the relative contributions of the different causes of death, except for leukemia-related deaths.

The role of combined modality treatment for induction of secondary leukemia was investigated by analyzing time to leukemia-related death (censoring all deaths of other or of

unspecified causes). All analyses of time to leukemia-related death were performed on the entire data set, excluding the ECOG trials because of systematically missing causes of death. The NCIC trial counted here as one trial, with the two CT arms pooled. The cumulative incidence of leukemia-related death is displayed in Fig 4. Multivariate age-adjusted analysis shows a significant adverse effect of combined modality treatment (RR, 2.48; 95% CI, 1.05 to 5.87; $P = .038$). The analyses were repeated with respect to time to leukemia in continuous complete remission, censoring all relapses, and yielded similar results (multivariate RR, 2.79; 95% CI, 1.04 to 7.54; $P = .042$).

A similar analysis of time to solid tumor was not performed because of insufficient data due to two reasons. First, the median follow-up duration in the analyzed data set was 8.5 years, and it is known that secondary solid tumors occur 10 to 15 years after therapy.⁴² Furthermore, only

Table 3. Treatment Outcomes and Causes of Death

Variable	Additional RT				Parallel RT/CT				Completeness (%)
	CT (n = 434)		CT + RT (n = 569)		CT (n = 460)		CT + RT (n = 479)		
	No.	%	No.	%	No.	%	No.	%	
Outcome									
Complete remission	378	87	486	86	374	83	385	82	98.9
Progression	6	1	18	3	21	5	23	5	
Partial remission/other	49	12	63	11	54	12	64	13	
Relapse	147	34	128	23	103	23	106	22	98.9
Death (all)	129	30	172	30	140	30	176	37	100
Hodgkin's disease	65		65		35		35		
Treatment-related	7		7		2		1		
Leukemia	3		10		5		10		
Non-Hodgkin's lymphoma	—		4		2		—		
Solid tumor	7		7		2		3		
Cardiovascular	5		1		1		3		
Other known	9		13		9		12		
Unknown	7		6		8		10		
Not available*	26		59		76		102		

*Causes of death were systematically not available from the 2 ECOG trials. ECOG 14-81a was randomized 1:2.

information on causes of death was available. The median survival time after a secondary neoplasm is up to 5 years, which indicates that secondary solid tumors are not necessarily fatal.⁴²

The chance of successful salvage therapy in patients after Hodgkin's disease treatment failure depending on the preceding treatment strategy is considered in the analysis of death hazards after relapse. Multivariate age-adjusted analysis shows an overall benefit in favor of CT alone (Fig 5), as shown by a RR for Hodgkin's disease-related death after initial disease progression or relapse after initial CT + RT of 1.37 (95% CI for RR, 1.01 to 1.86) in additional RT trials and of 1.33 (95% CI for RR, 0.99 to 1.79) in parallel RT/CT trials. Here again, the magnitude of the benefit in favor of CT alone does not differ between the two design types. However, these results should be interpreted carefully. In the additional RT design setting, the effect may be due to a

selection bias because of significant better disease control in the combined modality arm. The effect in the parallel RT/CT trials is mainly attributable to one trial (ECOG 14-81b).

Additional Analyses

To investigate whether the results obtained depended on particular trials, a stability analysis was performed for the main end points (disease control, overall survival, survival in continuous complete remission, and survival after failure) by leaving out one trial. The results remained qualitatively stable, except in the analysis of survival after failure in parallel RT/CT design trials, as mentioned earlier (RR, 1.07; 95% CI, 0.74 to 1.55 if ECOG 14-81b is excluded).

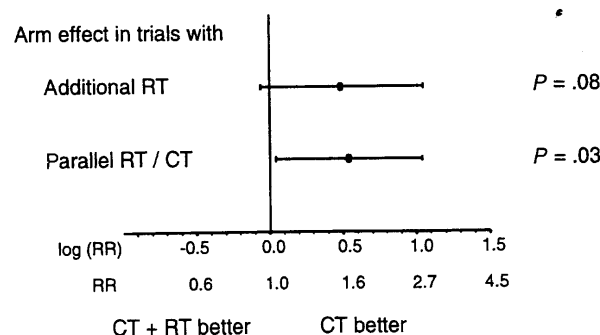


Fig 3. Survival in continuous complete remission. RR of CT + RT versus CT after multivariate adjustment for age for trials with additional RT resp. parallel RT/CT design with 95% CIs.

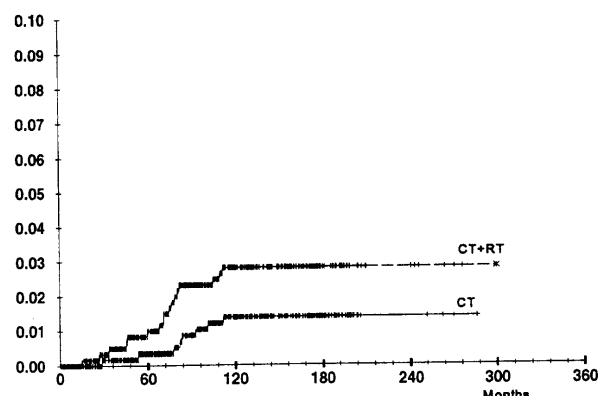


Fig 4. Cumulative incidence of leukemia-related death. Results of the joint analysis of 1,183 patients from 12 trials with respect to the endpoint leukemia-related death. The ECOG trials were excluded here because of systematically missing causes of death.

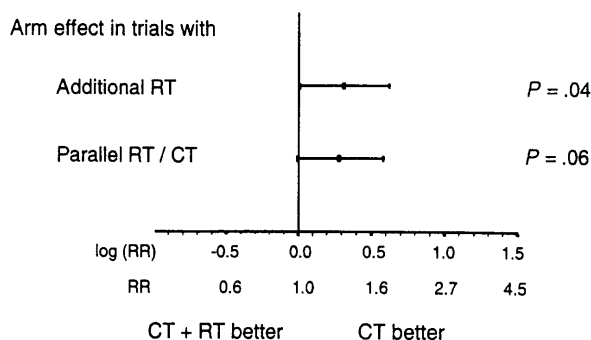


Fig 5. Survival after HD-failure. RR of CT + RT versus CT after multivariate adjustment for age for trials with additional RT resp. parallel RT/CT design with 95% CIs.

DISCUSSION

This meta-analysis is the most comprehensive and systematic analysis of trials that compared combined modality versus CT strategies in advanced- and intermediate-stage Hodgkin's disease performed to date. It contains individual patient information from more than 70% of all patients treated in corresponding trials since the early 1970s. Several study groups have submitted more detailed data (longer follow-up, more patients assessable) to this meta-analysis than reported in publications by these groups (SWOG 75-18, ECOG 14-76, ECOG 14-81, and the Manchester trial).

The meta-analysis provides several novel insights with implications for modern treatment strategies. The trials that compared additional RT versus no RT clearly showed that RT is an effective treatment principle in intermediate- and advanced-stage Hodgkin's disease with respect to disease control. However, the trials that compared parallel RT versus further CT also showed that pure CT strategies gave the same disease control as combined modality treatments. However, the unexpected finding was that in this setting, the use of RT was associated with a significantly worse overall survival (-8% after 10 years). This was mainly due to a higher hazard for disease-unrelated fatal events in continuous complete remission. A second mechanism could be a compromised possibility to rescue patients from first disease progression or relapse if they were treated with RT beforehand.

The findings of the multivariate analyses can be interpreted consistently. In the trials that used additional RT designs, a large heterogeneity of the RT effect was observed depending on the profile of the patients. As might be expected, after six cycles of MOPP-like CT, patients with more systemic disease (stage IV) benefit much less than patients with localized disease (low stage, mediastinal involvement). In contrast, in the trials with parallel design

(ie, with more extensive and partly anthracycline-containing CT) such a heterogeneity was remarkably reduced. This finding further suggests that the CT usually given in the additional RT design trials (generally six cycles of mostly MOPP or MOPP variants) did not fully exploit its potential. This finding strongly suggests that the spectrum of prognostic factors is treatment-dependent and can to a large degree be narrowed by appropriate CT. Previous analyses of prognostic factors were unable to detect this panorama change, as they disregarded the treatments in their analyses.^{43,44}

An attempt was made to analyze the independent effects of the duration of CT, of the composition of CT (eg, anthracycline-containing), and of RT dose and field sizes. No significant effects were found. As RT doses and field sizes and CT cycles do not vary systematically enough between trials to allow a reliable analysis, the nonsignificant results must be interpreted with caution. There are, at present, not enough trials that evaluated the effect of involved- or extended-field RT after more than six cycles of MOPP-like or modern anthracycline-containing chemotherapy. Such data for both types of trial designs (additional and parallel) would be interesting. To our knowledge, presently ongoing trials by the EORTC (H34) and the Pediatric Oncology Group (8625/26) will soon provide information on additional RT after more than six cycles of anthracycline-containing regimens and involved-field total-nodal RT. A further trial of the Pediatric Oncology Group has recently been published.²¹ This trial shows no benefit of additional total-nodal RT after four cycles of MOPP-ABVD in either event-free survival or overall survival. A forthcoming trial by the French Groupe d'Etudes des Lymphomes de l'Adulte (GELA) group will contribute to the understanding of parallel design trials with anthracycline-containing regimens and high-dose RT.⁴⁵

Although it remains somewhat speculative to extrapolate from trials conducted more than 10 years ago, it can be assumed with reasonable confidence that the treatment regimens introduced in the last decade (ie, anthracycline-containing regimens, ABVD, MOPP/ABVD, and MOPP-ABV variants) in patients with advanced- and intermediate-stage disease may be (slightly) more effective in terms of tumor control than the regimens used in the trials analyzed here. Hence, one can assume that the beneficial effects of RT on tumor control have diminished further. It seems unrealistic to expect an 11% difference in continuous complete remission rates with or without radiation after more than six cycles of modern treatments. Furthermore, it can be assumed that modern CT strategies do not induce more secondary leukemias than those used in the MOPP era.⁴⁶⁻⁴⁹ In contrast,

the hazardous effect of combined modality treatment for solid tumor induction^{50,51,47} and the toxic effects on organs, like myocardial failure,^{50,52} have been documented. Taking these aspects into consideration, the RR estimates obtained in this meta-analysis with respect to disease control, overall survival, and survival in continuous complete remission are likely to be conservative, which implies that long-term results of CT alone may be even better today than estimated from the data analyzed.

The present meta-analysis was undertaken with respect to treatment intended. Information on treatment actually given was not requested. However, it is known from some of the publications of trials included that deviations from the randomized treatment did occur (SWOG²⁹ and the German Hodgkin's Study Group³⁷). There is a tendency not to give patients with rapid remission the RT they were randomized to receive and, vice versa, patients with a slow response may receive RT although they were not randomized to this treatment. Both effects tend to diminish real treatment differences.

The main end point of this analysis was overall survival, which is clearly the clinically most important end point. Overall survival is a composite end point that combines death from Hodgkin's disease, acute, and late toxicity, and intercurrent death. To understand the respective separate impacts of these risks, specific end points were used. The end point "time to failure of disease control" assesses the efficacy of treatment in controlling Hodgkin's disease, not confounded by deaths due to late side effects of treatment. To describe such competing risk situations (failure of disease control, non-disease-related death), methods other than the Kaplan-Meier plots have been proposed,⁵³ including cumulative incidence and conditional probability plots. In this special situation, where the hazards for the two different failure types almost do not overlap (failure of disease control is an early event, while death due to late toxicity is a late effect), these alternative descriptive methods lead to almost identical results (data not shown). *

This meta-analysis included individual patient data from 14 trials with 1,740 patients. Data on two small trials have been submitted in cumulative format. A trial by the St Jude's Children Research Hospital, Memphis included 34 patients between 1972 and 1976 who were randomized 18 months to receive cyclophosphamide, vincristine, and procarbazine (COP) versus COP plus extended-field RT. While the rate of failure slightly favored CT + RT (12 of 15 v seven of 19), no difference could be found for survival (four of 15 v five of 19). Another trial from the University of Cape Town included 15 patients randomized between 1980 and 1983 to six cycles of mechlorethamine, vinblastine, vincristine, procarbazine, and prednisone (MVOPP) versus six MVOPP

plus involved-field radiation. No difference could be found with respect to failure data (seven of 10 v five of five) or survival (five of 10 v three of five). Hence, the data are consistent with the meta-analysis. The only contradictory result known to us stems from one of the trials not submitted to this meta-analysis (SEG 81-328²⁵). In this trial, 30 patients were randomized to receive BCVPP versus BCVPP plus involved-field RT; a significant difference in overall survival ($P = .05$) was reported in favor of combined modality. Given the clear findings in Fig 1 on a much larger cohort this finding can be judged as false-positive.

Meta-analysis of the kind reported here, with individual patient data and involving partly unpublished data, represent an objective quantitative review of all available evidence and are therefore superior in many respects to literature reviews or literature-based meta-analyses.^{54,55} One major advantage is that the same methodology of analysis is applied to all data, using the same definitions for end points, etc. Adjustments can be made for heterogeneity in the composition of patient populations between different trials groups. Furthermore, the statistics on rare events like long-term hazards become more solid.

Meta-analysis of many necessarily not identical trials have their obvious limitations. It is clear that they cannot replace single large and conclusive trials, which, per se, can achieve a much higher degree of standardization, quality control, and consistency.^{56,57} For example, we could not include serum parameters into the prognostic factors, as we could not find a way to identify the correct reference interval for each measurement. Likewise, the definitions for some clinical parameters (eg, large mediastinal mass) are not standardized. We also had only a limited possibility to check whether histology had undergone a central review process. For some study groups, we know that this was the case for many specimens. Furthermore, no information about quality maintenance and control procedures was available with respect to RT fields and doses.

On the other hand, one of the limitations of such a meta-analysis are also one of its biggest advantages. The result of a single large trial may be clear, but it may still be debatable whether the results generalize to other variants of the treatment or to other patient cohorts. A meta-analysis overcomes this problem of generalizability and investigates whether the general treatment principle is active and valid across a variety of countries, study groups, treatment traditions, prognostic factors, and definitions, irrespective of the fine details.⁵⁴ A more systematic discussion of this aspect was reported by Peto.⁵⁸ According to his uncertainty principle, we decided to request and analyze data from all trials that compared CT versus CT + RT, irrespective of the inclusion criteria adopted by the respective study group. The

essential eligibility criterion was whether physicians had decided that a CT versus CT + RT study design was appropriate for a certain spectrum of patients. Therefore, we obtained a rather broad range of stages (Table 2). Furthermore, some of the patients were children younger than 15 years of age and others were elderly patients up to the age of 83 years. None of these patients was excluded from analysis. The number of children included in the data set was too small to draw any firm conclusions, and the results basically apply to adults.

In conclusion, the results of our meta-analysis suggest that combined modality treatment of patients with advanced- and intermediate-stage Hodgkin's disease overall

has a significantly inferior long-term outcome than CT alone if CT is given over an appropriate number of cycles (eg, eight). Despite its effectiveness in local disease control, RT induced long-term hazards and might compromise possibilities to rescue patients from relapse. Hence, we conclude that RT in this setting should be limited to specific indications.

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APPENDIX

The following trial groups and trialists collaborated in this meta-analysis:

Baltimore Cancer Research Program: P.J. O'Dwyer, P.H. Wiernik
Cape Town Leukemia Centre: P. Jacobs, C.A. Johnson
Eastern Cooperative Oncology Group: P.A. Cassileth, J.H. Glick, L.A. Kalish (biometry)
German Hodgkin Study Group: V. Diehl, M. Loeffler, D. Hasenclever (biometry)
Grupo Argentino de Tratamiento de la Leucemia Aguda: S. Pavlovsky
Groupe Lyon, Marseille, St. Etienne (LMS): D. Assouline
Manchester Lymphoma Group: D. Crowther, R. Swindell (biometry)
National Cancer Institute of Canada: D. Bergsagel, M. Gospodarowicz, J.L. Pater
St Jude Children's Research Hospital: E.I. Thompson
Southeastern Cancer Study Group: A.A. Bartolucci, D.M. Brizel
South West Oncology Group: C.A. Coltman, R.I. Fisher, S. Dahlberg (biometry)
Stanford: R.T. Hoppe, S. Rosenberg

Members of the Overview Study Group of the IDHD were as follows: J. Cosset, S. Dahlberg, R. Fisher, R. Gray, D. Hasenclever, M. Henry-Amar, R. Hoppe, M. Loeffler, L. Specht, and R. Somers.

Study design, data collection and checks, statistical analyses, and manuscript preparation were the responsibilities of the writing committee: M. Loeffler, O. Brosteanu, D. Hasenclever (all Leipzig, Germany), and M. Sextro (Cologne, Germany).

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