Int. J. Radiation Oncology Biol. Phys., Vol. 67, No. 1, pp. 19–30, 2007

0360-3016/07/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2006.08.041

CLINICAL INVESTIGATION **Lymphoma**

INVOLVED-FIELD RADIOTHERAPY FOR PATIENTS IN PARTIAL REMISSION AFTER CHEMOTHERAPY FOR ADVANCED HODGKIN'S LYMPHOMA

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Purpose: The use of radiotherapy in patients with advanced Hodgkin's lymphoma (HL) is controversial. The purpose of this study was to describe the role of radiotherapy in patients with advanced HL who were in partial remission (PR) after chemotherapy.

Methods: In a prospective randomized trial, patients <70 years old with previously untreated Stage III-IV HL were treated with six to eight cycles of mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycine, vinblastine hybrid chemotherapy. Patients in complete remission (CR) after chemotherapy were randomized between no further treatment and involved-field radiotherapy (IF-RT). Those in PR after six cycles received IF-RT (30 Gy to originally involved nodal areas and 18–24 Gy to extranodal sites with or without a boost).

Results: Of 739 enrolled patients, 57% were in CR and 33% in PR after chemotherapy. The median follow-up was 7.8 years. Patients in PR had bulky mediastinal involvement significantly more often than did those in CR after chemotherapy. The 8-year event-free survival and overall survival rate for the 227 patients in PR who received IF-RT was 76% and 84%, respectively. These rates were not significantly different from those for CR patients who received IF-RT (73% and 78%) or for those in CR who did not receive IF-RT (77% and 85%). The incidence of second malignancies in patients in PR who were treated with IF-RT was similar to that in nonirradiated patients.

Conclusion: Patients in PR after six cycles of mechlorethamine, vincristine, procarbazine, prednisone/doxorubicine, bleomycine, vinblastine treated with IF-RT had 8-year event-free survival and overall survival rates similar to those of patients in CR, suggesting a definite role for RT in these patients. **© 2007 Elsevier Inc.**

Hodgkin's lymphoma, Advanced stage, Partial remission, Radiotherapy, Combined modality treatment.

INTRODUCTION

The treatment results of patients with Hodgkin's lymphoma (HL) have improved tremendously during the past decades. The potential role of radiotherapy (RT) after completion of chemotherapy for HL is based on the observation that relapses generally occur at initially involved sites and that RT will lower recurrence rates (1). The use of RT in patients

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Detailed results from the European Organization for Research and Treatment of Cancer Lymphoma Group Trial No. 20884 presented at the Sixth International Symposium on Hodgkin's Lymphoma, September 18–21, 2004; Köln, Germany.

Drs. Aleman and Raemaekers contributed equally to the study.

Supported by the Ank van Vlissingen Foundation, Amsterdam, The Netherlands.

Acknowledgments—This report is dedicated to J. Marion V. Burgers, radiation oncologist at The Netherlands Cancer Institute, Amsterdam, who was involved in the initiation of the trial and died in 1997. We thank J. Yahalom for critically reviewing the manuscript.

Conflict of interest: none.

Received May 22, 2006, and in revised form Aug 21, 2006. Accepted for publication Aug 21, 2006.

in complete remission (CR) or partial remission (PR) after chemotherapy has been a matter of debate for decades. The results for patients in PR after chemotherapy have usually not been specified but have been described with either the results of patients in CR after chemotherapy (2–4) or those of patients with primary progressive disease (PD) or early relapse (5, 6). In a recent intergroup randomized study of advanced-stage HL patients, two chemotherapy regimens (doxorubicine, bleomycine, vinblastine, and dacarbazine vs. mechlorethamine, vincristine, procarbazine, prednisone/doxorubicine, bleomycine, vinblastine [MOPP-ABV]) were compared. Regardless of the response, no RT was used. In patients in PR, the cumulative relapse rate was 40–45% compared with only 20–22% in patients in CR. The overall survival (OS) rate was not reported (7).

The European Organization for Research and Treatment of Cancer Lymphoma Group performed a randomized trial in patients with Stage III-IV HL to evaluate the impact of RT on the relapse rate in patients in CR after six to eight cycles of MOPP-ABV hybrid chemotherapy. Patients in CR after chemotherapy were randomized between no further treatment and involved-field RT (IF-RT) (8). IF-RT did not improve the outcome of patients with advanced-stage HL who were in CR after six to eight cycles of MOPP-ABV hybrid chemotherapy. In this trial, patients in PR after chemotherapy, who were considered to have active residual disease, were all scheduled to receive IF-RT. We report the outcome of this important subset of patients, with special emphasis on the role of IF-RT.

METHODS AND MATERIALS

Patients with previously untreated clinical Stage III or IV HL who were 15–70 years old age were eligible for the study (European Organization for Research and Treatment of Cancer trial No. 20884). The ineligibility criteria were pathologic Stage IIIAs with splenic involvement as the only site of infradiaphragmatic disease; severe cardiac, pulmonary, or metabolic disease; and a previous diagnosis of cancer (except for nonmelanoma skin tumors and cervical carcinoma *in situ*). All pathologic specimens were to be reviewed, but this was not a criterion for eligibility. Of the 649 patients described in this report, representative lymph node biopsy samples were actually reviewed for 583. The diagnosis of HL was confirmed in 559 and could not be confirmed in 24; the diagnosis of HL was uncertain in 9 and excluded in 15 (including 10 patients with non-Hodgkin's lymphoma).

The protocol was submitted to, and approved by, the ethics committee of each participating center; informed consent according to local guidelines was required before enrollment.

Pretreatment workup

The required staging procedures at enrollment are described in Table 1. After four cycles of chemotherapy, all examinations with initially abnormal results had to be repeated.

Bulky disease was defined as a mass of ≥10 cm (largest diameter) or a bulky mediastinum (mediastinum/thorax ratio ≥0.35 at T5-T6) (9). CR after chemotherapy was defined as the disappearance of all disease-related symptoms and measurable lesions, including normalization of abnormal blood parameters and radiologic examination and bone marrow biopsy specimen findings. PR after chemotherapy was defined as a decrease of ≥50% in the product of two perpendicular diameters in all measurable and evaluable lesions, negative bone marrow findings, no disease symptoms, and no new lesions (10). CR after RT could either be identical to the definition of CR after chemotherapy or residual disease without signs of change for a period of >3 months (rendering residual active disease unlikely).

Chemotherapy

MOPP-ABV hybrid chemotherapy was administered to all patients (see previous publication for details [8]). The cycles were repeated every 28 days for a total of six to eight cycles.

Patients were evaluated for response after four cycles of chemotherapy. For those with PD or stable disease, treatment was individualized. All other patients received two additional cycles of MOPP-ABV chemotherapy. Patients who were in CR after four cycles and who remained in CR after six cycles were randomly assigned to receive no further treatment or IF-RT. Patients who were in PR after four cycles and who were in CR after six cycles were given two additional cycles of chemotherapy before undergoing randomization. Patients who remained in PR after six cycles were treated with IF-RT. The last group of patients constituted the target population for the present analysis.

Involved-field RT

All areas involved before the start of chemotherapy were irradiated, bone marrow excepted. Nodal areas in patients in CR received a dose of 24 Gy and those in patients in PR a dose of 30 Gy in 1.5–2.0-Gy fractions (with a boost of 4–10 Gy when indicated). The spleen was included in the radiation field when paraaortic nodes were involved. In the case of splenic involvement in the absence of known paraaortic nodal disease, the spleen and paraaortic nodes were irradiated. In the case of lung involvement, 16 Gy was prescribed after CR and 18 Gy after PR, with a boost of 4–10 Gy when necessary. If the liver was involved, 20 Gy of radiation was given. If bone was involved, 24 Gy was given to the affected areas (with a boost of 10 Gy when indicated). The dose was defined according to the guidelines of the International Commission on Radiation Units and Measurements Report 29 (11). IF-RT was started within 6–8 weeks after the first day of the last cycle of chemotherapy and was administered in one to three courses, depending on the extent of the original involvement.

Pattern of relapse

Recurrence was defined in patients in CR after chemotherapy or RT as the appearance of any new lesion. PD was defined in patients in PR after chemotherapy or RT as an increase by ≥50% in the size of previously involved sites. Recurrence after previous CR and PD after previous PR were considered as relapses in this report.

The involved areas were divided into 11 nodal and 5 extranodal sites. Relapses are described with respect to localization, initial involvement, time to relapse, irradiation, radiation dose, and adherence to radiation protocol (12). Major violations of the radiation protocol were defined as no irradiation of an originally involved area or a total dose of <90% of the prescribed dose.

Statistical analysis

The main aim of the present study was to evaluate the outcome of patients in PR after chemotherapy who were subsequently treated with IF-RT. The response to RT, pattern of relapse, event-free survival (EFS), and OS were the main endpoints analyzed.

Table 1. Clinical characteristics versus response to chemotherapy

Characteristic	All (n = 739)	PR-RT (n = 227)	CR-no RT (n = 246)	CR-RT (n = 176)
Male/female ratio	1.79	1.58	2.00	1.44
Age (y)				
Median	33	30	33	34
Range	14–71	15–70	15–70	14–70
Age >45 y	192 (26)	38 (17)	64 (26)	50 (28)
Topography				
Supradiaphragmatic	106 (14)	42 (18)	27 (11)	29 (16)
Infradiaphragmatic	18 (3)	1 (<1)	7 (3)	5 (3)
Both	615 (83)	184 (81)	212 (86)	142 (81)
Stage*				
IIIA	191 (26)	73 (32)	63 (26)	43 (24)
IIIB	238 (32)	69 (30)	72 (29)	66 (38)
IVA	96 (13)	31 (14)	35 (14)	21 (12)
IVB	214 (29)	54 (24)	76 (31)	46 (26)
Bulky disease†	311 (42)	116 (51)	79 (32)	72 (41)
Mediastinal involvement	598 (81)	201 (89)	194 (82)	142 (83)
Bulky mediastinum‡	208 (28)	91 (40)	44 (18)	49 (28)
≥5 Nodal localizations§	310 (42)	95 (42)	112 (46)	62 (35)
Extranodal localizations				
Lung	132 (18)	48 (21)	37 (15)	30 (17)
Liver	77 (10)	12 (5)	28 (11)	16 (9)
Bone	32 (4)	6 (2)	9 (5)	8 (4)
Bone marrow	83 (11)	7 (3)	45 (18)	18 (10)
Visceral localizations among patients with Stage IV *(n)*				
1	203 (66)	61 (72)	78 (70)	37 (55)
2	75 (24)	17 (20)	24 (22)	24 (36)
≥3	32 (10)	7 (8)	9 (8)	6 (9)
Albumin <40 g/L (n = 596)	297 (50)	76 (41)	100 (51)	73 (51)
Hb <10.5 g/dL (n = 712)	164 (23)	42 (19)	55 (23)	42 (24)
WBC ≥15.0 × 10^9/L (n = 711)	125 (18)	50 (22)	36 (15)	25 (15)
IPI‖ ≥3	231/579¶ (40)	57/182¶ (31)	79/187¶ (42)	53/141¶ (38)

Abbreviations: PR = partial remission; RT = radiotherapy; CR = complete remission; Hb = hemoglobin; WBC = white blood cell count; IPI = International Prognostic Index.

Data presented as number of patients, with percentages in parentheses, unless otherwise noted.

* Stage determined by physical examination, complete blood count, erythrocyte sedimentation rate, serum biochemical tests, plain chest X-ray, CT of chest, ultrasonography of liver and spleen, bipedal lymphangiography in early years of trial, later fully replaced by abdominal CT, and unilateral bone marrow biopsy. Liver biopsy, bone scan, and gallium scintigraphy performed only if indicated but were not required.

† Bulky disease defined as mass of ≥10 cm (largest diameter) or bulky mediastinum.

‡ Bulky mediastinum defined, in patients with mediastinal involvement, as mediastinum/thorax ratio of ≥0.35 at T5–T6 with patient standing.

§ Median of initial nodal localizations was 4 for all groups.

‖ Only 6 of 7 prognostic parameters available in database because no information on lymphocytopenia collected.

¶ Patients for whom IPI could be determined.

Patients treated with IF-RT after reaching PR with chemotherapy were compared with those in CR after chemotherapy stratified into those treated with IF-RT (both randomized and nonrandomized) and those not treated with IF-RT. EFS was calculated from the start of chemotherapy to the first event (disease progression, relapse, or death from any cause), the time of the last examination, or March 1, 2005, whichever came first. OS was calculated from the start of chemotherapy to death, the last examination, or March 1, 2005, whichever came first. The interval to a second malignancy was calculated from the start of chemotherapy to the diagnosis of a second cancer, death, last examination, or March 1, 2005, whichever came first. The cumulative probability of relapse was calculated as one minus the probability of surviving without developing relapse. The cumulative probability of a second malignancy was calculated as one minus the probability of surviving without developing a second malignancy.

An analysis of the prognostic factors with regard to the response to chemotherapy was performed using Fisher's exact test (univariate analysis) and logistic regression (multivariate analysis). The factors analyzed were gender, stage (III vs. IV), bulky disease (absent vs. present), bulky mediastinal disease (absent vs. present), number of nodal areas involved (<5 vs. ≥5), bone marrow involvement (absent vs. present), albumin level (<40 g/L vs. ≥40 g/L), hemoglobin (<10.5 g/dL vs. ≥10.5 g/dL or <6.5 mmol/L vs. ≥6.5 mmol/L), white blood cell count (<15 × 10^9/L vs. ≥15 × 10^9/L), International Prognostic Index (<3 vs. ≥3) (13).

Event-free survival, OS, and the probability of a second cancer were estimated according to the Kaplan-Meier method, and the rates between groups were compared using the log–rank test. Ninety-five percent confidence intervals (CIs) for the rates were estimated using the method of Rothman and Boice (14). Two-sided tests were used in reporting the results. Statistical significance was defined as $p < 0.01$.

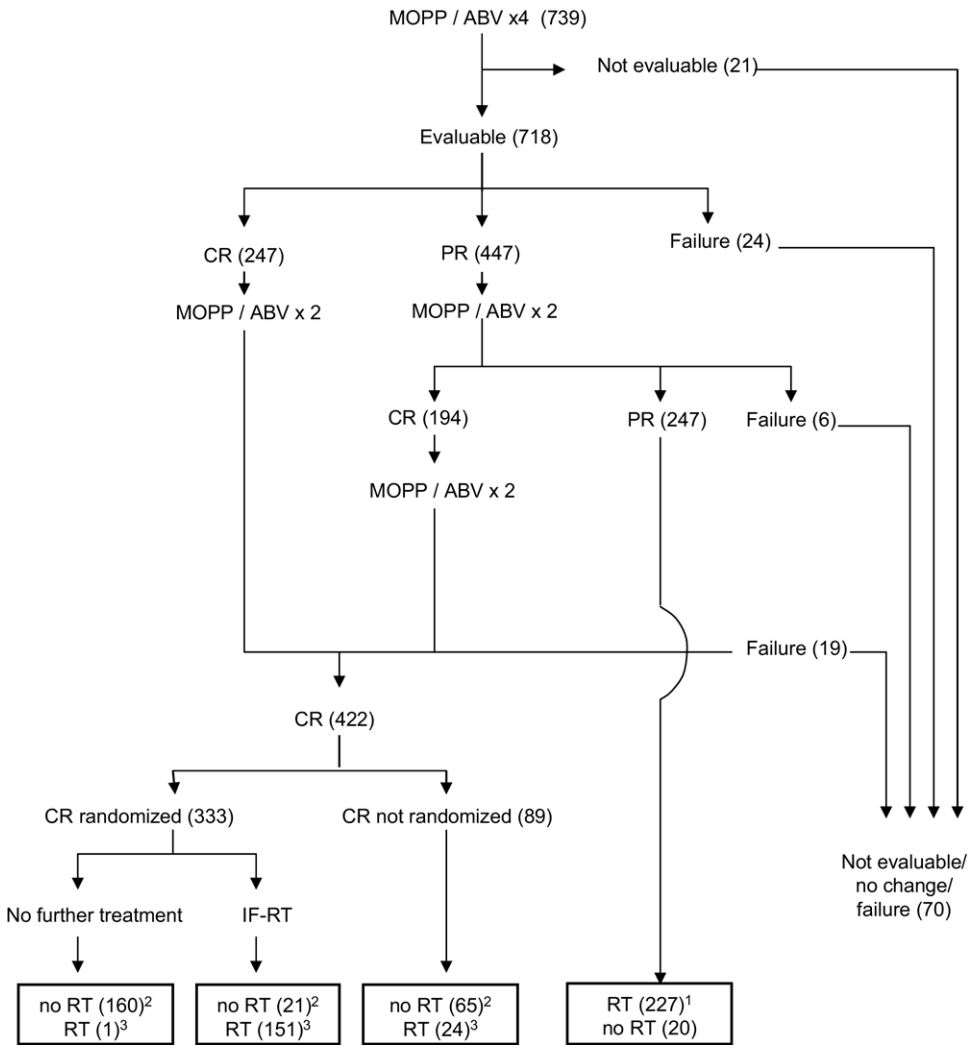

Fig. 1. Flow chart of European Organization for Research and Treatment of Cancer trial No. 20884, including numbers of patients according to response to chemotherapy and application of radiotherapy. MOPP-ABV = mechlorethamine, vincristine, procarbazine, prednisone/doxorubicine, bleomycin, and vinblastine; PR = partial remission after chemotherapy; CR = complete remission after chemotherapy; IF-RT = involved-field radiotherapy; PR-RT = patients in partial remission who received radiotherapy (n = 227); CR-no RT = patients in complete remission who did not receive RT (n = 246); CR-RT = patients in complete remission who received RT (n = 176). *Of 247 patients in PR after chemotherapy, 20 did not undergo RT because of progressive disease between end of chemotherapy and start of RT (n = 4), doctor refusal (n = 8), patient refusal (n = 4), mistake (n = 1), and unknown reasons (n = 3).

Stata statistical software (STata Corp LP, College Station, TX) (release 8.2) and Statistical Package for Social Sciences software (release 11.5) (SPSS Inc., Chicago, IL) were used to analyze the data.

Forty-two centers in Europe participated. Randomization was done by telephone or facsimile, stratified by center. The data were stored using a specific data management program (PIGAS) developed at the Institut Gustave Roussy, Villejuif, France (15). The data were updated on March 1, 2005. The median follow-up period was 94 months (range, 9–190 months).

RESULTS

Clinical characteristics and response to chemotherapy

Between September 1989 and April 2000, a total of 739 patients were enrolled to receive chemotherapy (Fig. 1). Of these, 422 were in CR and 247 PR. Of the remaining 70 patients, 7 had no change, 28 had PD after chemotherapy, 14 had died during therapy, and 21 could not be evaluated.

Of the 247 patients in PR after chemotherapy, 20 did not undergo RT (Fig. 1). The characteristics and outcomes of patients in PR treated with IF-RT (PR-RT; n = 227) were compared with those of patients in CR after chemotherapy who were not treated with RT (CR-no RT; n = 246) and those of patients in CR after chemotherapy who were treated with RT (CR-RT; n = 176; Fig. 1).

Compared with all patients in CR after chemotherapy, the patients in the PR-RT group had bulky disease significantly more often ($p < 0.001$), especially bulky mediastinal disease ($p = 0.001$), were >45 years less often ($p = 0.003$), and had bone marrow involvement less often ($p < 0.001$; Table 1).

Table 2. Number of nodal areas with residual abnormalities versus location of residual disease and number of extranodal sites with residual abnormalities in 227 patients in PR after chemotherapy

Nodal areas in PR* (*n*)	Residual abnormalities in mediastinum		Residual abnormalities in paraaortic area		Extranodal areas in PR after chemotherapy	
	No	Yes	No	Yes	No	Yes
0	2	0	2	0	0	2
1	23	118	131	10	127	14
2	14	35	29	20	46	3
≥3	6	29	13	22	32	3
Total	45 (20)	182 (80)	175 (77)	52 (23)	205 (91)	22 (9)†

Abbreviations: PR = partial remission; IF-RT = involved-field radiotherapy.
Data in parentheses are percentages of all patients in PR treated with IF-RT.
* Irrespective of number of extranodal areas in PR.
† Fourteen of 22 residual abnormalities in lungs.

After chemotherapy, residual abnormalities were observed in the mediastinum in 182 (80%) of 227 patients in the PR-RT group. The number of nodal areas in patients with residual abnormalities varied from zero to five (one in 62%; Table 2). The mediastinum was the only site of residual abnormalities in 104 of the 127 patients with only one nodal site and no extranodal sites of residual abnormality. In all 22 patients with extranodal remnants, the abnormalities were limited to one extranodal site.

The 24 patients in whom the diagnosis of HL could not be confirmed on central review were equally distributed among the three subgroups of patients.

Toxicity of IF-RT (World Health Organization toxicity criteria)

Grade 3-4 radiation-related hematologic toxicity occurred in 53% of patients and correlated with previous severe toxicity due to chemotherapy ($p = 0.01$). No differences were found in Grade 3-4 radiation-related hematologic, neurologic, or digestive tract toxicity between patients irradiated after reaching PR or CR with chemotherapy. Grade 3-4 radiation pneumonitis was observed in <1% of the PR and CR patients undergoing RT (Table 3). No toxic deaths were observed after RT. During long-term follow-up, radiation pneumonitis was reported in <1% in the PR-RT group and in 2% in the CR-RT group.

Outcome

The outcome of patients who were in PR after chemotherapy and received IF-RT was similar to that of patients who were in CR after chemotherapy, confirming the results of our previous reports (8, 16). The 8-year EFS rate was 76%, 77%, and 73% for patients in the PR-RT, CR-no RT, and CR-RT groups, respectively. The corresponding 8-year OS rates were 84%, 85%, and 78% (Table 4 and Fig. 2).

On evaluation 2–3 months after RT, 154 of 227 patients were in CR. After 3–38 months, 209 of 227 patients were considered to be in CR without additional treatment, reflecting either slow improvement of residual abnormalities or stable residual abnormalities interpreted as fibrosis. For the 209 patients in CR after RT, the 8-year EFS and OS rate was 82% (95% CI, 75–87%) and 90% (95% CI, 84–94%), respectively. The corresponding rates were much poorer in patients who never reached CR (6% [95% CI, 0–22%] and 7% [95% CI, 0–26%]). Of the 18 patients who never reached CR after RT, 15 developed PD, of whom 13 died. Of the remaining 2 patients, 1 died of complications and 1 of an intercurrent cause. In those who did not achieve CR, most events occurred within the first 2 years after RT completion.

In the logistic regression analysis of the overall population ($n = 739$), bone marrow involvement was associated with a greater chance of CR after chemotherapy (odds ratio

Table 3. Treatment-related acute WHO grade 3 or 4 toxicity by patient group

Toxicity	PR-RT ($n = 227$)	CR-no RT ($n = 246$)	CR-RT ($n = 176$)
Chemotherapy related			
Hematologic	105 (46)	143 (58)	97 (55)
Neurologic	9 (4)	11 (4)	15 (9)
Digestive*	16 (7)	32 (13)	23 (13)
Radiotherapy related			
Hematologic	35 (15)	—	31 (18)
Pulmonary	1 (<1)	—	2 (1)
Digestive*	12 (5)	—	14 (8)

Abbreviations: WHO = World Health Organization; other abbreviations as in Table 1.
Data in parentheses are percentages.
* WHO Grade 3 digestive toxicity includes, among other issues, vomiting requiring therapy and intolerable diarrhea requiring therapy; WHO Grade 4 digestive toxicity includes, among other issues, intractable vomiting or diarrhea, leading to hemorrhagic dehydration.

Table 4. Cause of death and incidence of second cancers by patient group

Variable	PR-RT (n = 227)	CR-no RT (n = 246)	CR-RT (n = 176)
All deaths *(n)*	32 (14)	31 (13)	34 (19)
Progressive disease	17	17	6
Treatment-related	2	3	6
Initial treatment	2	1	2
Salvage treatment	0	2	4
Second cancer	7	8	15
Intercurrent	5	3	6
Cause unspecified	1	0	1
8-y EFS (95% CI)	76 (69–81)	77% (70–82)	73% (65–80)
8-y OS (95% CI)	84 (78–89)	85% (79–89)	78% (70–84)
All second malignancies	9	11	18
Type			
Acute leukemia or myelodysplasia	2	3	10
Non-Hodgkin's lymphoma	0	1	2
Solid tumor outside radiation field	3	7	3
Solid tumor within radiation field	3	0	3
Myeloma	1	0	0
Occurrence of second malignancy			
After 6 cycles	9/208	6/153	13/106
After 8 cycles*	0/19	5/93	5/70
8-y Cumulative second cancer rate (95% CI)†	5.7 (3.0–10.8)	5.6 (3.0–10.1)	12.9 (8.0–20.3)

Abbreviations: EFS = event-free survival; OS = overall survival; CI = confidence interval; other abbreviations as in Table 1.

Data in parentheses are percentages, unless otherwise noted.

* Of 227 patients, 19 received eight cycles of chemotherapy by mistake instead of six as prescribed in protocol.

† Comparison among three groups, $p = 0.0177$.

2.57, 95% CI, 1.47–4.53, $p < 0.001$), and bulky mediastinal disease was associated with a lower chance of reaching CR after chemotherapy (odds ratio 0.49, 95% CI, 0.35–0.69, $p < 0.001$).

Pattern of relapse

After a median follow-up of 94 months, 108 of the 649 patients discussed in this report had disease relapse (Table 5).

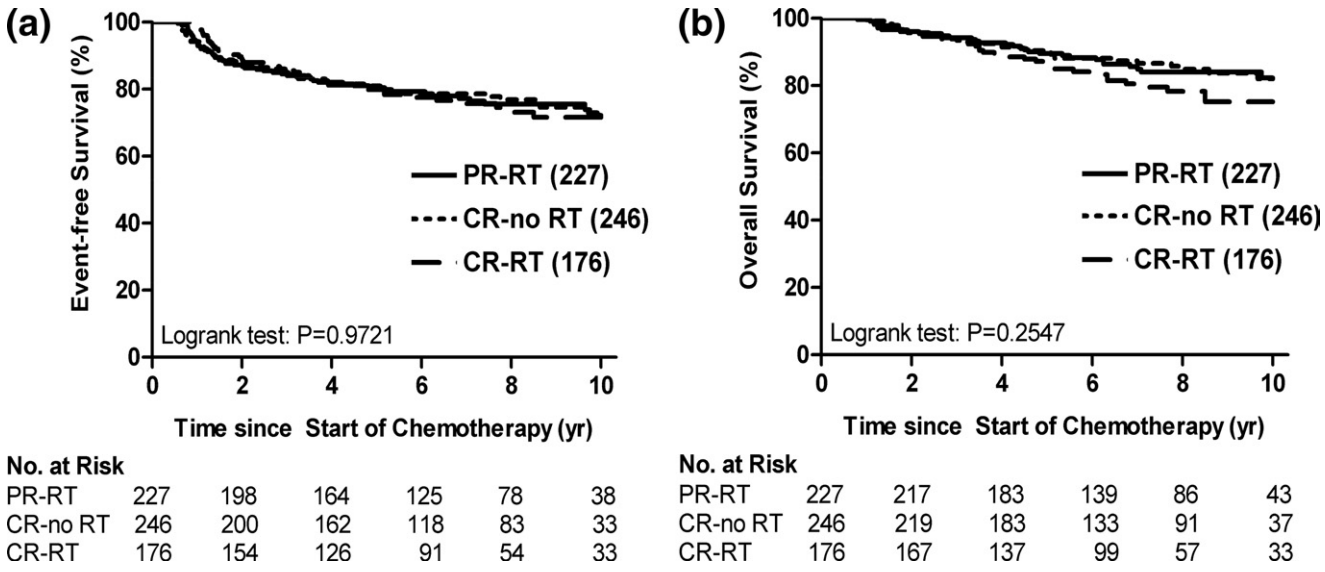

Fig. 2. Patients in complete remission (CR) or partial remission (PR) after chemotherapy. Kaplan-Meier estimates of (a) event-free and (b) overall survival for patients in PR after chemotherapy who underwent radiotherapy (PR-RT, solid line, $n = 227$), patients in CR who did not (CR-no RT, dotted line, $n = 246$), and patients in CR who did undergo RT (CR-RT, dashed line, $n = 176$).

Table 5. Patterns of relapse

Relapse	PR-RT (n = 227)	CR-no RT (n = 246)	CR-RT (n = 176)
Incidence *(n)*	40 (18)	43 (17)	25 (14)
Site			
Nodal only	20 (9)	28 (11)	16 (9)
Extranodal only	2 (1)	2 (1)	2 (1)
Both	18 (8)	13 (5)	7 (4)
Original involvement*			
Involved, irradiated	28 (12)	0 (0)	14 (8)
Involved, not irradiated	9† (4)	35 (14)	2† (1)
Previously uninvolved, not irradiated	25 (11)	24 (10)	18 (10)
Previously involved, irradiated, and previously uninvolved, not irradiated	15 (7)	0 (0)	7 (4)
8-y Cumulative relapse rate			
No major violations of RT protocol	27/156 (18)	—	17/123 (16)
95% CI	12–26		10–26
≥1 Major violations of RT protocol	13/71 (19)	—	8/53 (16)
95% CI	11–30		8–29

Abbreviations: CI = confidence interval; other abbreviations as in Table 1.
Data in parentheses are percentages.
* Patients can be listed in more than one category.
† Major violations of radiotherapy protocols: no irradiation of an originally involved area or total dose <90% of the prescribed dose.

The evaluation of the adherence to protocol showed that violations to the radiation protocol had no influence on the relapse rate in PR patients after chemotherapy or CR-RT patients (12).

Second malignancies

The incidence rates of second malignancies did not differ significantly from those published previously (8). The distribution of the 15 patients with acute leukemia/myelodysplasia is shown in Table 4. No differences were found in the extent of radiation between the CR-RT and PR-RT groups. The radiation dose in the PR-RT group was greater. No relationship was noted between the number of chemotherapy cycles and the risk of acute leukemia, although the number of events was small.

DISCUSSION

After a median follow-up of almost 8 years, the outcome of patients with advanced HL in PR after six cycles of MOPP-ABV hybrid chemotherapy who received IF-RT was as good as that of patients in CR after chemotherapy, suggesting a definite role for RT in patients in PR after adequate chemotherapy.

The optimal treatment of adult patients with advanced HL has been controversial for many decades. In Table 6, a selection of the most recently published trials considering patients with advanced HL is summarized. Comparisons between trials must be made with caution because the characteristics of the patients included in the trials may differ. Also, for some trials, the overall results were presented and, for others, the results were given for patients with a certain response to chemotherapy only. In general, agreement has been reached on the use of anthracycline-containing chemotherapy for patients with advanced HL. The value of additional RT, however, has long been debated. Some investigators have advocated primary treatment with chemotherapy alone to avoid the toxicity of RT, accepting lower EFS rates (2, 7). Others, however, have favored a combined modality consisting of chemotherapy and RT (2–4, 8, 16–18) (Table 6).

Furthermore, other investigators have recommended treatment intensification in the case of a response of <75% (5). In the present trial, we have shown that RT does not improve the outcome of patients in CR after chemotherapy. Patients in PR after chemotherapy received IF-RT to all initially involved disease sites, and their outcome was similar to that of patients in CR. Importantly, most patients in PR only had one nodal area displaying residual abnormalities. Thus, RT to remnants can probably replace IF-RT (19), significantly reducing the exposure of normal tissue. Limiting the radiation volume and dose are expected to decrease the risks of cardiovascular toxicity (20) and second cancers (21, 22).

Data on the optimal treatment strategy in advanced stages of HL are difficult to interpret. First, the response has not been not uniformly defined. Although some investigators have defined PR as a ≥50% decrease, others have used a ≥75% decrease in the product of two perpendicular diameters in all measurable and evaluable lesions, in conjunction with negative bone marrow findings, no disease symptoms, and no new lesions. Furthermore, patients in PR after chemotherapy are often analyzed together with patients with primary PD and those with early relapse after reaching CR with chemotherapy, with or without RT. For instance, the Groupe d'études des Lymphomes de l'Adulte (5) has advo-

Table 6. Overview of studies that included adult patients with advanced Hodgkin's lymphoma

Treatment	Investigator	Eligible patients	Regimen	*n*	5-y failure rate (%)	*p*	5-y OS rate (%)	*p*
CHT only	Canellos *et al.* (2)	Stage IIIA2, IIIB, IVA, or IVB	(a) 6–8 MOPP alone, no RT	123	FFS 50%	0.02 (MOPP vs. other)	66%	0.28 (MOPP vs. other)
			(b) MOPP alternating with ABVD, 12, no RT	123	FFS 65%		75%	
			(c) 6–8 ABVD alone, no RT	115	FFS 61%		73%	
	Duggan *et al.* (7)	Stage III2A, IIIB or IV or relapse after definitive RT	(a) 8–10 ABVD, no RT	433	FFS 63%	0.42	82%	0.82
			(b) 8–10 MOPP-ABV hybrid, no RT	419	FFS 66%		81%	
CHT with or without RT (by randomization)	Fabian (39)	Stage III-IV in CR after CHT	(a) 6 MOP-BAP, no RT	143*	RFS 66%	>0.2	79%	0.14
			(b) 6 MOP-BAP + IF-RT	135†	RFS 74%		86%	
	Fermé (40, 41)	Stage IIIB-IV, CR or good PR after 6 cycles CHT	(a) 6 MOPP-ABV hybrid + 2 MOPP-ABV hybrid	92	DFS 80%	0.01 (comparison of 4 treatment arms); 0.07 (between 2 consolidation arms after stratification of induction regimen)‡	85%	0.01 (comparison of 4 treatment arms); 0.2 (a) vs. (c); 0.002 (b) vs. (d)‡
			(b) 6 MOPP-ABV hybrid + (S)TNI	114	DFS 82%		88%	
			(c) 6 ABVPP + 2 ABVPP	116	DFS 68%		94%	
			(d) 6 ABVPP + (S)TNI	96	DFS 75%		78%	
	Aleman *et al.* (8)	Stage IIIA-IV, CR after CHT	(a) 6–8 MOPP-ABV, no further treatment	161	EFS 84%	0.35	91%	0.07
			(b) 6–8 MOPP-ABV + IF-RT	172	EFS 79%		85%	
CHT and RT on indication	Horning *et al.* (17)	Stage III-IV or bulky mediastinal disease	Stanford V + RT in case of bulky mediastinal disease, nodal masses ≧5 cm, macroscopic nodules in intact spleen on CT (87% plus RT)	47	FFS 83%	NA	6%	NA
	Diehl *et al.* (3)	Unfavorable Stage IIB-IIIA or Stage IIIB-IV	(a) COPP-ABVD + RT for originally bulky disease or residual tumor (64% plus RT)	260	FFTF 69%		83%	
			(b) BEACOPP baseline + RT on originally bulky disease or residual tumor (71% plus RT)	469	FFTF 76%§		88%	
			(c) BEACOPP escalated + RT for originally bulky disease or residual tumor (71% plus RT)	466	FFTF 87%‖¶		91%#**	
	Radford *et al.* (4)	Unfavorable Stage I-II or Stage III-IV	ChlVPP/EVA hybrid + RT on originally bulky disease or residual abnormalities	144††	EFS 78%	0.0006	89%	0.04
			VAPEC-B + RT on originally bulky disease or residual abnormalities	138‡‡	EFS 58%		79%	

continued

Table 6. Overview of studies that included adult patients with advanced Hodgkin's lymphoma (*Continued*)

Treatment	Investigator	Eligible patients	Regimen	*n*	5-y Failure rate (%)	*p*	5-y OS rate (%)	*p*
	Federico *et al.* (23)	Advanced unfavorable, in CR or PR after 4 ABVD or other anthracycline-containing regimen	(a) HDT + ASCT + IF-RT in case of initial bulky disease of residual masses	83	FFS All: 75% PR: 66%	0.4 (all); 0.4 (PR)	All: 88% PR: 86%	0.99 (all); 0.6 (PR)
			(b) 4 Cycles conventional CHT + IF-RT in case of initial bulky disease of residual masses	80	FFS All: 82% PR: 77%		All: 88% PR: 88%	
	Gobbi (42)	Stage IIB, III or IV	(a) ABVD + RT for previously bulky or partially remitting disease	122	FFS 78%	<0.01 (Stanford V vs. other 2 regimens)	90%	0.33 (a vs. c); 0.04 (a vs. b); 0.33 (c vs. b)
			(b) Stanford V + RT for previously bulky or partially remitting disease[§§]	107	FFS 54%		82%	
			(c) MOPPEBVCAD + RT for previously bulky or partially remitting disease	106	FFS 81%		89%	

Abbreviations: OS = overall survival; CHT = chemotherapy; MOPP = mechlorethamine, vincristine, procarbazine, prednisone; FFS = failure-free survival; RT = radiotherapy; ABVD = doxorubicin, bleomycin, vinblastine and dacarbazine; MOPP-ABV = mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine; CR = complete remission; MOP-BAP = nitrogen mustard, vincristine, prednisone, bleomycin, doxorubicin, and procarbazine; RFS = relapse-free survival; IF-RT = involved-field RT; PR = partial remission; DFS = disease-free survival; (S)TNI = (Sub)total nodal irradiation; ABVPP = doxorubicin, bleomycin, vinblastine, procarbazine, prednisone; EFS = event-free survival; Stanford V = doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone; NA = not applicable; COPP-ABVD = cyclophosphamide, vincristine, procarbazine, and prednisone alternating with doxorubicin, bleomycin, vinblastine, dacarbazine; FFTF = freedom from treatment failure; BEACOPP = bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone; ChlVPP/EVA = chlorambucil, vinblastine, procarbazine, prednisone/etoposide, vincristine, doxorubicin; VAPEC-B = doxorubicin, cyclophosphamide, etoposide, vincristine, bleomycin, prednisolone; HDT + ASCT = high-dose therapy with autologous stem-cell transplantation; MOPPEBVCAD = mechlorethamine, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, vindesine.

* Of 143 patients, 130 received no further therapy.

† Of 135 patients, 104 received IF-RT.

‡ Long-term follow-up data confirmed conclusion (41).

§ In comparison with COPP-ABVD group, $p = 0.04$.

‖ In comparison with COPP-ABVD group, $p < 0.001$.

¶ In comparison with standard BEACOPP group, $p < 0.001$.

In comparison with COPP-ABVD group, $p = 0.002$.

** In comparison with standard BEACOPP group, $p = 0.06$.

†† Of whom, 76 had Stage III or IV.

‡‡ Of whom, 79 had Stage III or IV.

§§ This regimen deviated from original Stanford V schedule; RT only given to originally bulky sites and sites in PR after CHT.

cated high-dose chemotherapy with peripheral stem cell support for patients in PR of <75% after chemotherapy, based on their results from 157 patients with failure after induction chemotherapy ($n = 67$), relapse ($n = 68$) or PR of <75% ($n = 22$). We believe the power of this study was too limited to advise treatment intensification for patients in PR after induction chemotherapy. Furthermore, in the Intergroup HD01 trial (23) and the Scotland and Newcastle Lymphoma Group HD3 trial (24), no benefit from early intensification with high-dose chemotherapy and autologous stem-cell transplantation could be demonstrated over standard treatment in groups of patients assumed to be at high risk of failure. Additionally, high-dose chemotherapy with stem cell support is accompanied by acute treatment-related death in ≤8% of the patients (5, 23–26). The long-term toxicity could also be considerable (27).

To *a priori* identify a group of patients who might benefit from more or less intensive therapy, the pretreatment clinical characteristics of the patients in CR after six cycles of MOPP-ABV hybrid chemotherapy were examined. The multivariate analysis of CR after chemotherapy performed on the overall data set showed a significantly decreased probability of CR in the case of bulky mediastinal disease. As expected when comparing patients in PR after chemotherapy who received RT with those in CR, significantly more patients with bulky (mediastinal) disease at the start of treatment were found in the PR group. However, the only factor that correlated with the final treatment outcome was the response to RT. The 18 who never reached CR after RT had a distinctly poor outcome. Apparently, we need other, probably biologic, parameters to predict the treatment outcome (28–32).

It is likely that among patients in PR, a substantial proportion did not truly have active residual disease and were possibly overtreated with IF-RT. Although more sophisticated imaging techniques are now available, it is still difficult to discriminate between active disease and fibrosis. During the inclusion period of the present study, the imaging techniques evolved. Lymphography was replaced by CT, and the image quality of CT improved significantly. Furthermore, the diagnostic accuracy of the now frequently used [(18)F]fluorodeoxyglucose-positron emission tomography (FDG-PET) scan is significantly greater than that of CT, with a high negative predictive value reported in most studies (33). Negative FDG-PET findings after therapy completion, however, do not exclude the presence of residual microscopic disease (34). In addition, although positive posttreatment FDG-PET findings are a strong indicator of residual active disease, all series have identified false-positive results in 5–10% of patients (35–37). The value of FDG-PET will be clarified by studies such as the German Hodgkin Study Group ongoing study in patients with advanced HL (38).

In the present evaluation, we observed differences in the cumulative rates of second malignancies, especially leukemia/myelodysplastic syndrome, among the different treatment groups. However, this remarkable finding could not be satisfactorily explained by a more detailed analysis of this relatively small number of events. Apparently, the regimen itself and/or the extent of treatment cannot be held responsible for the observed differences. Therefore, we could not rule out that this finding occurred by chance.

CONCLUSION

The results of our study have shown that patients with advanced HL in CR after six to eight cycles of adequate anthracycline-based chemotherapy do not benefit from additional RT. Those with residual abnormalities after six cycles of chemotherapy had an excellent clinical outcome with additional RT delivered to these remnants. After a median follow-up of 8 years, no excess toxicity emerged. Treatment adaptations according to the results of more reliable response assessments will further refine the treatment decisions to restrict RT to those patients who really need it.

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APPENDIX

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