

ORIGINAL ARTICLE

Chemotherapy plus Involved-Field Radiation in Early-Stage Hodgkin's Disease

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ABSTRACT

BACKGROUND

Treatment of early-stage Hodgkin's disease is usually tailored in line with prognostic factors that allow for reductions in the amount of chemotherapy and extent of radiotherapy required for a possible cure.

METHODS

From 1993 to 1999, we identified 1538 patients (age, 15 to 70 years) who had untreated stage I or II supradiaphragmatic Hodgkin's disease with favorable prognostic features (the H8-F trial) or unfavorable features (the H8-U trial). In the H8-F trial, we compared three cycles of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) combined with doxorubicin, bleomycin, and vinblastine (ABV) plus involved-field radiotherapy with subtotal nodal radiotherapy alone (reference group). In the H8-U trial, we compared three regimens: six cycles of MOPP-ABV plus involved-field radiotherapy (reference group), four cycles of MOPP-ABV plus involved-field radiotherapy, and four cycles of MOPP-ABV plus subtotal nodal radiotherapy.

RESULTS

The median follow-up was 92 months. In the H8-F trial, the estimated 5-year event-free survival rate was significantly higher after three cycles of MOPP-ABV plus involved-field radiotherapy than after subtotal nodal radiotherapy alone (98% vs. 74%, $P < 0.001$). The 10-year overall survival estimates were 97% and 92%, respectively ($P = 0.001$). In the H8-U trial, the estimated 5-year event-free survival rates were similar in the three treatment groups: 84% after six cycles of MOPP-ABV plus involved-field radiotherapy, 88% after four cycles of MOPP-ABV plus involved-field radiotherapy, and 87% after four cycles of MOPP-ABV plus subtotal nodal radiotherapy. The 10-year overall survival estimates were 88%, 85%, and 84%, respectively.

CONCLUSIONS

Chemotherapy plus involved-field radiotherapy should be the standard treatment for Hodgkin's disease with favorable prognostic features. In patients with unfavorable features, four courses of chemotherapy plus involved-field radiotherapy should be the standard treatment. (ClinicalTrials.gov number, NCT00379041.)

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*Other members of the EORTC–GELA (European Organization for Research and Treatment of Cancer–Groupe d'Études des Lymphomes de l'Adulte) H8 Trial are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

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DURING THE PAST TWO DECADES, THE treatment of Hodgkin's disease has evolved considerably. Staging laparotomy has been abandoned, management has been adjusted to reduce the risk of treatment failure, and clinical trials have defined the value of radiation therapy alone, chemotherapy alone, and therapy that combines the two approaches. The goal of current treatment is a maximum cure rate with a minimum of long-term toxic effects.

The results of the European Organization for Research and Treatment of Cancer (EORTC) Lymphoma Group H7 trial (1988–1993),¹ which was based on clinical prognostic factors,² led to three major conclusions: clinical staging is sufficient for stratifying early stages of the disease, chemotherapy followed by involved-field radiotherapy should be the standard treatment, and the duration of chemotherapy should be adapted to the severity of the disease.

The EORTC–GELA (Groupe d'Études des Lymphomes de l'Adulte) H8 trial, which we report on here, was based on the same prognostic factors that were used in the H7 trial.² In patients with favorable prognostic features, we compared subtotal nodal radiotherapy with a combination of chemotherapy and radiotherapy. In patients with unfavorable prognostic features, we compared the duration of chemotherapy and the extent of radiation fields. In the H7 trial, the combination of epirubicin, bleomycin, vinblastine, and prednisone (EBVP) had poor short-term efficacy. In our trial, patients received mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) in combination with doxorubicin, bleomycin, and vinblastine (ABV).³ We report on the results of the H8 trial as of January 2006.

METHODS

PATIENTS

Patients between the ages of 15 and 70 years who had untreated clinical stage I or II supradiaphragmatic Hodgkin's disease were eligible for the study. The exclusion criteria were previous laparotomy, a concomitant or previous cancer other than basal-cell carcinoma of the skin or in situ carcinoma of the cervix, a concomitant severe illness that would reduce life expectancy, social circumstances not allowing for proper treatment and follow-up, and positivity for the human immunodeficiency virus. The protocol was approved by the ethics committee at each participating center

or country, according to local laws. All patients provided written informed consent before enrollment. Pathological specimens were reviewed by an international panel of pathologists.

PRETREATMENT WORKUP

Clinical staging included physical examination, complete blood count, measurement of the erythrocyte sedimentation rate, serum biochemical tests, chest radiography, computed tomography of the chest and abdomen, and unilateral iliac bone marrow biopsy. Bulky disease was defined as a mediastinal mass with a maximum width on a standard chest radiograph of at least one third of the internal transverse diameter of the thorax at the level of T5 through T6 or any mass of at least 10 cm in the largest dimension.⁴ The H7 trial prognostic score, which was based on clinical and laboratory features, was used for stratification of the patients into two prognostic groups: favorable prognosis (the H8-F trial) and unfavorable prognosis (the H8-U trial) (Fig. 1).

STUDY DESIGN

Patients were enrolled in 91 centers (60 from the EORTC and 31 from the GELA) in Belgium, France, Italy, the Netherlands, Poland, Portugal, Slovenia, and Spain. Registration, randomization, and data collection were performed at the Clinical Research Unit at Centre François Baclesse in Caen, France. Randomization was stratified according to center. All data were updated on January 1, 2006. The median follow-up period was 92 months (range, 1 to 147).

Patients in the H8-F trial were randomly assigned to receive either subtotal nodal radiotherapy or combination therapy consisting of three cycles of MOPP-ABV plus involved-field radiotherapy. Patients in the H8-U trial were randomly assigned to one of three regimens: six or four cycles of MOPP-ABV plus involved-field radiotherapy or four cycles of MOPP-ABV plus subtotal nodal radiotherapy. MOPP-ABV was administered every 28 days.³ (Doses and schedules of the chemotherapy combinations are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.)

Radiotherapy was begun within 1 month after assignment to subtotal nodal radiotherapy or 3 to 4 weeks after the last cycle of chemotherapy. Target volumes for involved-field radiotherapy initially included involved nodal regions, and those for subtotal nodal radiotherapy included the man-

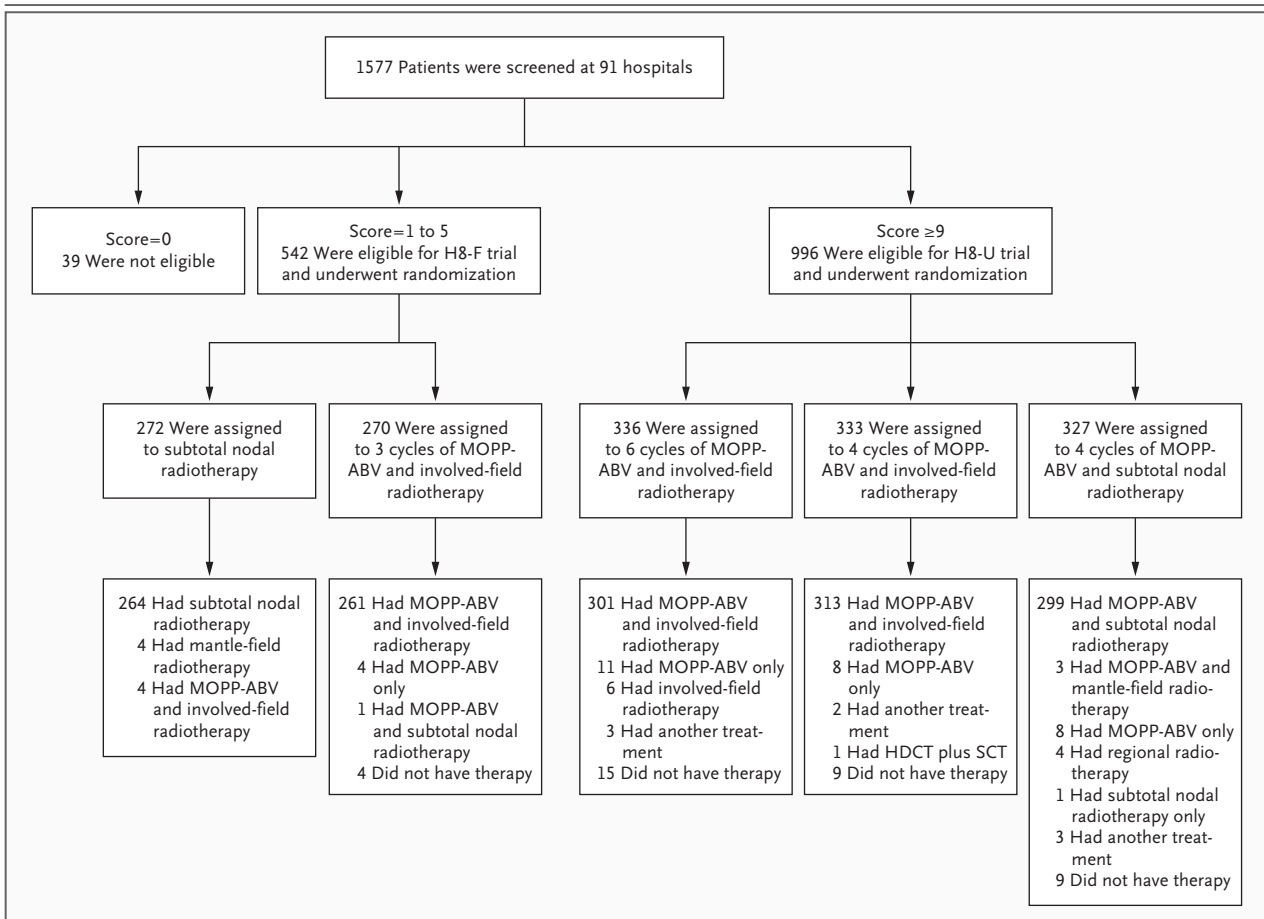


Figure 1. Enrollment and Outcomes.

Patients in the H8 trial were categorized as having a favorable prognosis (H8-F) or an unfavorable prognosis (H8-U) on the basis of a prognostic score. The prognostic score was calculated according to initial clinical and biologic features as follows: age (<40 years, 0 points; 40 to 49 years, 1; ≥50 years, 9), sex (female, 0; male, 1), disease stage (stage I, 0 points; stages II₂ to II₃, 1; stages II₄ to II₅, 9), presence or absence of mediastinal involvement or ratio of mediastinum to thorax (no involvement or ratio <0.35, 0 points; ratio ≥0.35, 9), presence or absence of systemic symptoms (e.g., fever, night sweats, weight loss) and erythrocyte sedimentation rate (no symptoms and rate <50 mm per hour, 0 points; symptoms and rate <30 mm per hour, 1; no symptoms and rate ≥50 mm per hour or symptoms and rate ≥30 mm per hour, 9), and histologic type (lymphocyte predominance and nodular sclerosis, 0 points; mixed cellularity and lymphocyte depletion, 1). MOPP-ABV denotes mechlorethamine, vincristine, procarbazine, and prednisone plus doxorubicin, bleomycin, and vinblastine; HDCT high-dose chemotherapy; and SCT stem-cell transplantation.

tle field, spleen, and para-aortic nodes. Patients who were in complete remission after chemotherapy received 36 Gy, and those in partial remission received 40 Gy (with a boost of 4 Gy if needed) in fractions of 2 Gy. Patients who were treated with subtotal nodal radiotherapy received 36 Gy of radiation to nodal regions with a boost of 4 Gy in initially involved nodal regions.

Complete remission, unconfirmed complete remission, partial remission, and no change were defined according to the criteria of Lister et al.⁵ Patients with a partial response were not given additional treatment unless progression of the

disease was confirmed by appropriate imaging tests, biopsy, or both. All patients were to be followed during each cycle of chemotherapy, after radiotherapy, and every 3 months thereafter during the first 2 years, then every 6 months until the fifth year, and annually thereafter. No recommendations were made for the treatment of patients with disease progression or relapse.

PRIMARY AND SECONDARY OUTCOMES

The primary end point was event-free survival (with events defined as disease progression during treatment, lack of complete remission at the

end of treatment, relapse, or death from any cause). Secondary end points were overall survival and the incidence of late severe complications (i.e., a second cancer, cardiac toxic effects, radiation pneumonitis, chemotherapy-related pulmonary dysfunction, and severe infection). The event-free and overall survival were calculated from the day of randomization to the date of the first event, the date of the last examination, or January 1, 2006, whichever came first. The time to the development of a late severe complication was calculated from the date of randomization to the date on which the complication was diagnosed.

STATISTICAL ANALYSIS

The cumulative probability of a late severe complication was calculated as 1 minus the probability of survival without the development of a complication. The probabilities of event-free and overall survival and the cumulative probability of a late severe complication were estimated with the use of the Kaplan–Meier method, and estimates in the treatment groups were compared by the log-rank test. Comparisons of the probability of a second cancer were made with the use of the log-rank test adjusted for age and sex. Ninety-five percent confidence intervals for survival and cumulative probability estimates were calculated with the use of the method of Rothman and Boice⁶ and a binomial distribution of the probability, respectively. All analyses were performed according to the intention-to-treat principle. Reported results are based on two-sided tests. Stata statistical software was used to analyze the data.⁷

In the H8-F trial, the objective was to assess the equivalence of results in the group receiving three cycles of MOPP-ABV plus involved-field radiotherapy and the group that received subtotal nodal radiotherapy (reference group). Assuming a 5-year event-free survival rate of 80% in both groups, we needed to enroll 552 patients to have the statistical power to show that the true difference between the two groups did not exceed 10% (with an alpha level of 0.05, a beta level of 0.20, and a two-sided test comparing two binomial distributions).⁸ In the H8-U trial, the objective was to assess the equivalence of results in three groups: one receiving six cycles of MOPP-ABV plus involved-field radiotherapy (reference group), one receiving four cycles of MOPP-ABV plus involved-field radiotherapy, and one receiving four cycles of MOPP-ABV plus subtotal nodal radiotherapy.

Assuming a 5-year event-free survival rate of 90% in the three groups, we needed to enroll 863 patients to achieve the statistical power described for the H8-F trial. We used an unconditional test of equivalence according to the difference of two independent binomial proportions, which produced corresponding confidence intervals. In the H8-F trial and the H8-U trial, an event rate of 20% or more in either group was considered unacceptable. Stopping rules were based on the binomial distribution of events assessed 2 years after randomization with fixed blocks of 20 patients in each group.⁹

RESULTS

PATIENTS

From August 1993 to March 1999, a total of 1577 patients were referred to the 91 participating centers (Fig. 1). Thirty-nine patients with very favorable prognostic features (a prognostic score of 0) were not eligible for randomization; they were treated only with mantle-field radiotherapy. Of the remaining 1538 eligible patients, 542 (35%) were categorized as having a favorable prognosis and 996 (65%) were categorized as having an unfavorable prognosis. The characteristics of the two groups of patients were well balanced (Table 1).

H8-F TRIAL

After completion of the assigned treatment, response rates were similar in the two groups. Among the 446 patients in both groups who had a confirmed or unconfirmed complete remission, 5 had a relapse after combination therapy and 61 after subtotal nodal radiotherapy ($P < 0.001$) (Table 2). The difference in the estimated 5-year event-free survival rate was 24 percentage points (95% confidence interval [CI], 18 to 29; $P < 0.001$), favoring the combination-therapy group (Fig. 2A and Table 2). There were 19 deaths in the group receiving subtotal nodal radiotherapy and 4 in the combination-therapy group (Table 2). The 10-year overall survival estimate was significantly higher in the combination-therapy group (97%) than in the group receiving subtotal nodal radiotherapy (92%, $P = 0.001$) (Fig. 2B and Table 2).

H8-U TRIAL

After chemotherapy, complete-remission rates (certain and uncertain) were 69% in the group receiving six cycles of MOPP-ABV plus involved-field

Table 1. Characteristics of 542 Patients with a Favorable Prognosis and 996 Patients with an Unfavorable Prognosis.*

Variable	Favorable Prognosis (H8-F Trial)		Unfavorable Prognosis (H8-U Trial)		P Value†
	Subtotal Nodal Radiotherapy (N=272)	3 Cycles of MOPP-ABV plus Involved-Field Radiotherapy (N=270)	6 Cycles of MOPP-ABV plus Involved-Field Radiotherapy (N=336)	4 Cycles of MOPP-ABV plus Subtotal Nodal Radiotherapy (N=327)	P Value‡
Age — yr					
Median	30	30	33	31	0.73
Range	15–50	15–50	16–69	15–70	
Male:female ratio	1.54:1	1.81:1	0.81:1	0.88:1	0.81
Systemic symptoms — no. (%)‡	18 (7)	17 (6)	136 (44)	137 (45)	0.90
Erythrocyte sedimentation rate — mm/hr					
Median	13	14	50	52	0.81
Range	1–57	1–49	1–160	3–167	
Lymph-node regions involved — no. (%)					
≤3	270 (99)	270 (100)	291 (87)	282 (86)	0.99
≥4	2 (1)	0	45 (13)	46 (14)	
Mediastinal involvement — no. (%)					
Any involvement	124 (46)	139 (51)	263 (78)	252 (77)	0.92
Bulky mediastinum§	1 (<1)	1 (<1)	121 (36)	129 (39)	0.66
Histologic analysis¶					
No. of patients	242	234	299	282	
Type of disease — no. (%)					
Lymphocyte predominant	14 (6)	15 (6)	2 (1)	2 (1)	0.76
Nodular sclerosing	175 (72)	176 (75)	258 (86)	248 (88)	
Mixed cellularity	42 (17)	39 (17)	26 (9)	21 (7)	
Hodgkin's disease of unspecified type	4 (2)	2 (1)	10 (3)	12 (4)	
Non-Hodgkin's lymphoma	2 (1)	0	1 (<1)	4 (1)	
Not Hodgkin's disease	5 (2)	2 (1)	2 (1)	2 (1)	
Overall treatment duration — mo					
Median	3.2	4.3	7.2	5.3	<0.001
Range	1.1–6.9	2.0–9.1	0.9–10.3	0.9–10.9	0.9–10.3

* Because of rounding, percentages may not total 100. MOPP-ABV denotes mechlorethamine, vincristine, procarbazine, and prednisone plus doxorubicin, bleomycin, and vinblastine.

† In the H8-U trial, P values are for all comparisons among the three groups.

‡ Systemic symptoms included fever, night sweats, and weight loss. In the H8-U trial, data were available for 312 of 336 patients in the group receiving six cycles of MOPP-ABV plus involved-field radiotherapy, for 315 of 333 patients in the group receiving four cycles of MOPP-ABV plus involved-field radiotherapy, and for 306 of 327 patients in the group receiving four cycles of MOPP-ABV plus subtotal nodal radiotherapy.

§ Bulky mediastinum was defined as a ratio of mediastinum to thorax of at least 0.35 at the level of T5 through T6 while the patient was standing.

¶ In the H8-F trial, the diagnosis of Hodgkin's disease was confirmed in 461 of the 476 patients (96.8%) whose data were reviewed; the condition was ruled out in 15 patients (including 2 patients with non-Hodgkin's lymphoma). In the H8-U trial, the diagnosis of Hodgkin's disease was confirmed in 833 of the 873 patients (95.4%) whose data were reviewed; the condition was ruled out in 40 patients (including 5 patients with non-Hodgkin's lymphoma).

|| The overall duration of treatment was defined as the time from randomization to the end of radiotherapy.

radiotherapy, 64% in the group receiving four cycles of MOPP-ABV plus involved-field radiotherapy, and 64% in the group receiving four cycles of MOPP-ABV plus subtotal nodal radiotherapy ($P=0.38$ for all comparisons) (Table 2). After radiotherapy, the rates were, respectively, 83%, 85%, and 86% ($P=0.43$ for all comparisons). Of the 270 patients who had a partial response to initial chemotherapy and who were assigned to receive radiotherapy, 260 received radiotherapy, 2 declined treatment, 6 stopped treatment, and 2 received another treatment. Of the 260 patients who received radiotherapy, 166 had a confirmed or unconfirmed complete remission after radiotherapy: 44 of 77 patients (57%) in the group receiving six cycles of MOPP-ABV plus involved-field radiotherapy, 63 of 95 patients (66%) in the group receiving four cycles of MOPP-ABV plus involved-field radiotherapy, and 59 of 88 patients (67%) in the group receiving four cycles of MOPP-ABV plus subtotal nodal radiotherapy ($P=0.36$ for all comparisons) (data not shown). Among the 766 patients who had a confirmed or unconfirmed complete remission after radiotherapy, 42 (5%) had a relapse: 15 of 253 patients (6%) in the group receiving six cycles of MOPP-ABV plus involved-field radiotherapy, 14 of 259 patients (5%) in the group receiving four cycles of MOPP-ABV plus involved-field radiotherapy, and 13 of 254 patients (5%) in the group receiving MOPP-ABV plus subtotal nodal radiotherapy (Table 2).

The three groups had similar event-free survival estimates. Of the 42 patients who had a relapse, 31 were among the 561 patients who were in complete remission after chemotherapy (11 of 194 patients in the group receiving six cycles of MOPP-ABV plus involved-field radiotherapy, 10 of 190 patients in the group receiving four cycles of MOPP-ABV plus involved-field radiotherapy, and 10 of 177 patients in the group receiving MOPP-ABV plus subtotal nodal radiotherapy); 11 of the patients with relapse were among 168 patients who had a partial response after chemotherapy and who received the planned radiotherapy (4 of 45 patients, 4 of 63 patients, and 3 of 60 patients, respectively).

There were no significant differences in the 5-year event-free survival estimates among the three groups (Fig. 3A and Table 2). Among the 107 patients who died, the proportion who died from Hodgkin's disease or acute toxic effects was significantly lower ($P=0.046$) in the group receiving

four cycles of MOPP-ABV than in the group receiving six cycles of MOPP-ABV: 38 of 70 patients (54%; 95% CI, 42 to 66) versus 27 of 37 patients (73%; 95% CI, 56 to 86) (data not shown). Causes of death are listed in Table 2. There were no significant differences among the three groups in the estimated overall survival (Fig. 3B and Table 2). There were also no significant differences in overall survival between patients who had a confirmed or unconfirmed complete remission and those who had a partial remission after chemotherapy.

ACUTE TOXIC EFFECTS

In the overall population, grade 3 or 4 hematologic toxic effects developed in 49% of patients during chemotherapy and in 9% of patients during or after radiotherapy. Among patients in the H8-U trial, grade 3 or 4 neutropenia was reported in 430 patients (43%) and resulted in transient interruption of chemotherapy in 2 patients and permanent interruption of chemotherapy in 8 patients.

LONG-TERM TOXIC EFFECTS

A second cancer developed 1 to 146 months after randomization in 55 patients (Table 2). Of 12 patients with acute leukemia or myelodysplasia that developed 13 to 91 months after randomization, 6 patients were over the age of 50 years at diagnosis; 3 patients had received salvage treatment, including 1 patient who received high-dose chemotherapy and autologous stem-cell transplantation. Of 36 patients with solid tumors that developed 5 to 127 months after randomization, 13 were over the age of 50 years at diagnosis; in 21 of the patients, solid tumors developed within involved irradiated areas; in 15 patients, tumors developed outside irradiated areas.

The cumulative estimate for a second cancer was compared between the H8-F trial and the H8-U trial, since no significant differences were observed among the study groups within the prognostic category. After adjustment for sex and age at diagnosis (15 to 39, 40 to 49, and ≥ 50 years), the 10-year cumulative estimates for the development of a second cancer were 1.5% in the H8-F trial (95% CI, 0 to 4.5) and 2.4% in the H8-U trial (95% CI, 0.4 to 5.2) ($P=0.08$) (data not shown).

Cardiac toxic effects were reported in 21 patients; of those patients, 7 had a myocardial infarction. The 10-year cumulative estimate for cardiac toxic effects was 2.3% (95% CI, 1.4 to 4.0). In 25 patients, pneumonitis developed after radiotherapy

Table 2. Clinical Outcome for Patients with a Favorable Prognosis and Patients with an Unfavorable Prognosis.*

Outcome	Favorable Prognosis (H8-F Trial)		Unfavorable Prognosis (H8-U Trial)		P Value†
	Subtotal Nodal Radiotherapy (N = 272)	3 Cycles of MOPP-ABV plus Involved-Field Radiotherapy (N = 270)	6 Cycles of MOPP-ABV plus Involved-Field Radiotherapy (N = 336)	4 Cycles of MOPP-ABV plus Subtotal Nodal Radiotherapy (N = 327)	
Response at the end of chemotherapy					
No. of patients	NA	236	295	299	281
Complete remission — no. (%)	NA	133 (56)	115 (39)	110 (37)	90 (32)
Unconfirmed complete remission — no. (%)	NA	47 (20)	88 (30)	82 (27)	90 (32)
Partial remission — no. (%)	NA	56 (24)	79 (27)	100 (33)	91 (32)
Progression — no. (%)	NA	0	11 (4)	5 (2)	9 (3)
Early death — no. (%)	NA	0	2 (1)	2 (1)	1 (<1)
Response at the end of treatment					
No. of patients	226	250	306	304	296
Complete remission — no. (%)	164 (73)	197 (79)	161 (53)	168 (55)	144 (49)
Unconfirmed complete remission — no. (%)	50 (22)	35 (14)	92 (30)	91 (30)	110 (37)
Partial remission — no. (%)	7 (3)	16 (6)	33 (11)	31 (10)	27 (9)
Progression — no. (%)	5 (2)	2 (1)	20 (7)	14 (5)	15 (5)
Progression or relapse — no. (%)‡	66 (24)	7 (3)	41 (12)	31 (9)	31 (9)
Progression — no.	5	2	20	14	15
Relapse — no.	61	5	21	17	16
Site of progression or relapse					
Nodal only					
Relapse within irradiated field — no. (%)	18 (27)	1 (14)	4 (10)	8 (26)	3 (10)
Progression — no.	1	0	1	3	0
Relapse — no.	17	1	3	5	3
Relapse outside irradiated field — no. (%)	19 (29)	3 (43)	19 (46)	11 (35)	8 (26)
Progression — no.	2	2	12	4	6
Relapse — no.	17	1	7	7	2
Extranodal — no. (%)					
Progression — no.	0	0	2	2	4
Relapse — no.	24	3	10	4	9
Unspecified — no. (%)					
Progression — no.	2	0	5	5	5
Relapse — no.	3	0	1	1	2

Complete remission or unconfirmed complete remission									
No. of patients	214	232	253	259	254				
No. of patients with relapse	50	5	15	14	13				
Relapse-free survival — % (95% CI)									
At 5 yr	78 (71–83)	99 (97–100)	94 (91–97)	95 (92–97)	96 (92–98)				
At 10 yr	75 (69–81)	95 (86–98)	93 (89–96)	93 (87–96)	94 (90–97)	0.91			
Partial remission									
No. of patients	7	16	33	31	27				
No. of patients with disease progression	1	0	5	3	1				
No. of patients with events	75	10	54	51	48				
At ≤5 yr	68	4	51	38	41				
At >5 yr	7	6	3	13	7				
Event-free survival — % (95% CI)									
At 5 yr [†]	74 (68–79)	98 (96–99)	84 (80–88)	88 (84–91)	87 (83–90)				
At 10 yr	68 (64–76)	93 (85–97)	82 (77–86)	80 (75–85)	80 (71–86)	0.80			
Deaths — no. (%)	19 (7)	4 (1)	37 (11)	36 (11)	34 (10)				
Cause of death — no. (%)									
Non-Hodgkin's lymphoma or solid tumor after pathological review	0	0	0	0	2 (6)				
Hodgkin's disease uncertain after pathological review	0	0	0	2 (6)	2 (6)				
Progressive disease	7 (37)	1 (25)	24 (65)	12 (33)	13 (38)				
Treatment-related disorder	4 (21)	2 (50)	3 (8)	3 (8)	6 (18)				
Coexisting illness	3 (16)	1 (25)	1 (3)	7 (19)	3 (9)				
Second cancer	2 (11)	0	8 (22)	7 (19)	5 (15)				
Unspecified cause	3 (16)	0	1 (3)	5 (14)	3 (9)				
Overall survival — % (95% CI)									
At 5 yr [†]	94 (91–97)	99 (97–100)	89 (85–92)	93 (89–95)	92 (88–94)				
At 10 yr	92 (87–95)	97 (92–99)	88 (84–91)	85 (78–90)	84 (74–90)	0.93			

Table 2. (Continued.)

Outcome	Favorable Prognosis (H8-F Trial)		Unfavorable Prognosis (H8-U Trial)		P Value†
	Subtotal Nodal Radiotherapy (N=272)	3 Cycles of MOPP-ABV plus Involved-Field Radiotherapy (N=270)	6 Cycles of MOPP-ABV plus Involved-Field Radiotherapy (N=336)	4 Cycles of MOPP-ABV plus Subtotal Nodal Radiotherapy (N=327)	
Second cancer					
Any — no. (%)	6 (2)	5 (2)	12 (4)	18 (5)	14 (4)
Acute leukemia or myelodysplasia — no. (%)	0	0	6 (2)	3 (1)	3 (1)
Non-Hodgkin's lymphoma — no. (%) **	0	0	0	5 (2)	3 (1)
Solid tumor — no. (%) †	6 (2)	5 (2)	6 (2)	11 (3)	8 (2)
Cumulative probability — % (95% CI)					
At 5 yr	1.5 (0.6–4.0)	0.8 (0.2–3.1)	3.4 (1.9–6.3)	2.4 (1.1–4.9)	1.7 (0.7–4.0)
At 10 yr	3.4 (1.3–8.4)	3.2 (1.2–8.0)	4.5 (2.5–7.9)	7.1 (4.3–11.6)	8.8 (4.3–17.3)

* Because of rounding, percentages may not total 100. MOPP-ABV denotes mechlorethamine, vincristine, procarbazine, and prednisone plus doxorubicin, bleomycin, and vinblastine. In the H8-U trial, P values are for all comparisons among the three groups.

† Progression was defined as disease progression during therapy. Relapse was defined as progression that occurred more than 3 months after the end of treatment in patients who had complete remission, unconfirmed complete remission, or partial remission after radiotherapy.

‡ An unconditional test of equivalence with asymptotic methods was performed to calculate the difference between two independent binomial proportions, with data censored at 5 years of follow-up (the primary outcome) and a two-sided 95% CI. In the H8-F trial, the 95% CI was 18.4% to 29.1%, not excluding a difference in 5-year event-free survival estimates of more than 10%. In the H8-U trial, the 95% CI was 1.4% to 9.0%, excluding a difference in 5-year event-free survival estimates of more than 10% between the group receiving four cycles of MOPP-ABV plus involved-field radiotherapy and the group receiving six cycles of MOPP-ABV plus involved-field radiotherapy; and 3.9% to 6.2%, excluding a difference in 5-year event-free survival estimates of more than 10% between the group receiving four cycles of MOPP-ABV plus involved-field radiotherapy and the group receiving four cycles of MOPP-ABV plus subtotal nodal radiotherapy.

¶ In the H8-F trial, the median follow-up of the patients who survived was 92 months (range, 2 to 140) for the 253 patients who received subtotal nodal radiotherapy and 90 months (range, 4 to 146) for the 266 patients who received MOPP-ABV plus involved-field radiotherapy. In the H8-U trial, the median follow-up of the 883 patients who survived was 89 months (range, 1 to 140), with no significant differences among the study groups.

|| In the H8-F trial, among the 11 patients with a second cancer, 9 initially presented with Hodgkin's disease of the nodular sclerosing type and one with Hodgkin's disease of mixed-cellularity type; the initial histologic material was not reviewed for one patient. In the H8-U trial, a non-Hodgkin's lymphoma and a solid tumor developed in succession in one patient in the group receiving four cycles of MOPP-ABV plus involved-field radiotherapy; the initial histologic material was not reviewed for this patient.

** In the H8-U trial, of the eight patients in whom non-Hodgkin's lymphoma secondarily developed, five initially presented with Hodgkin's disease of nodular sclerosing type, and one with a disease not diagnosed as Hodgkin's disease; for the remaining two patients, the initial histologic material was not reviewed.

†† In the H8-U trial, of the 25 patients in whom a solid tumor secondarily developed, 21 initially presented with Hodgkin's disease of the nodular sclerosing type, and 1 with Hodgkin's disease of mixed-cellularity type; initial histologic material was not reviewed for 3 patients.

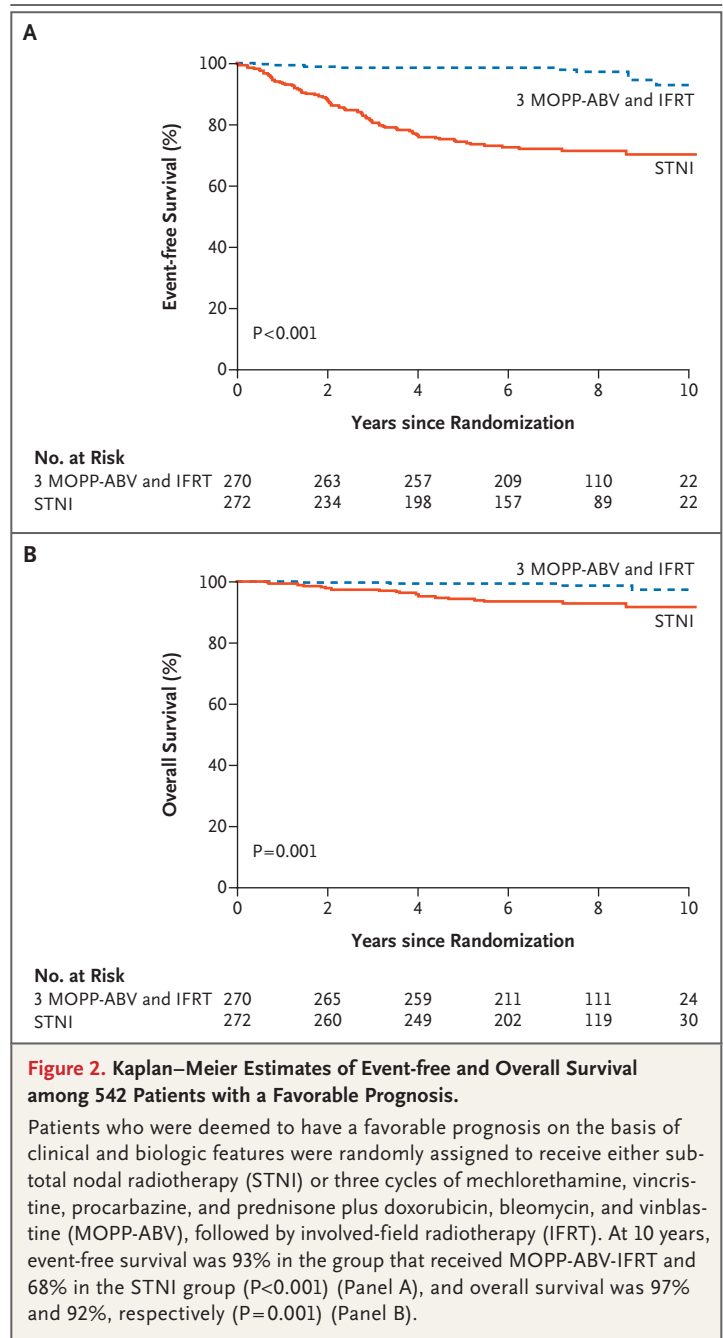
(10-year cumulative estimate, 1.7%; 95% CI, 1.1 to 2.5), and 40 patients had chronic dyspnea, including 15 patients with altered pulmonary function (10-year cumulative estimate, 3.5%; 95% CI, 2.3 to 5.3). The incidence of long-term dyspnea was independent of the extent of radiotherapy delivered to the upper diaphragmatic area. In contrast, the incidence of long-term dyspnea increased significantly with the total dose of bleomycin administered ($P=0.002$). Among patients who received MOPP-ABV, the 10-year cumulative estimates for long-term dyspnea were 0.8% after three cycles (95% CI, 0.2 to 3.0), 2.5% after four cycles (95% CI, 1.5 to 4.2), and 8.8% after six cycles (95% CI, 4.1 to 18.3). Sixty-six patients had a severe infection (10-year cumulative estimate, 4.4%; 95% CI, 3.5 to 5.6).

DISCUSSION

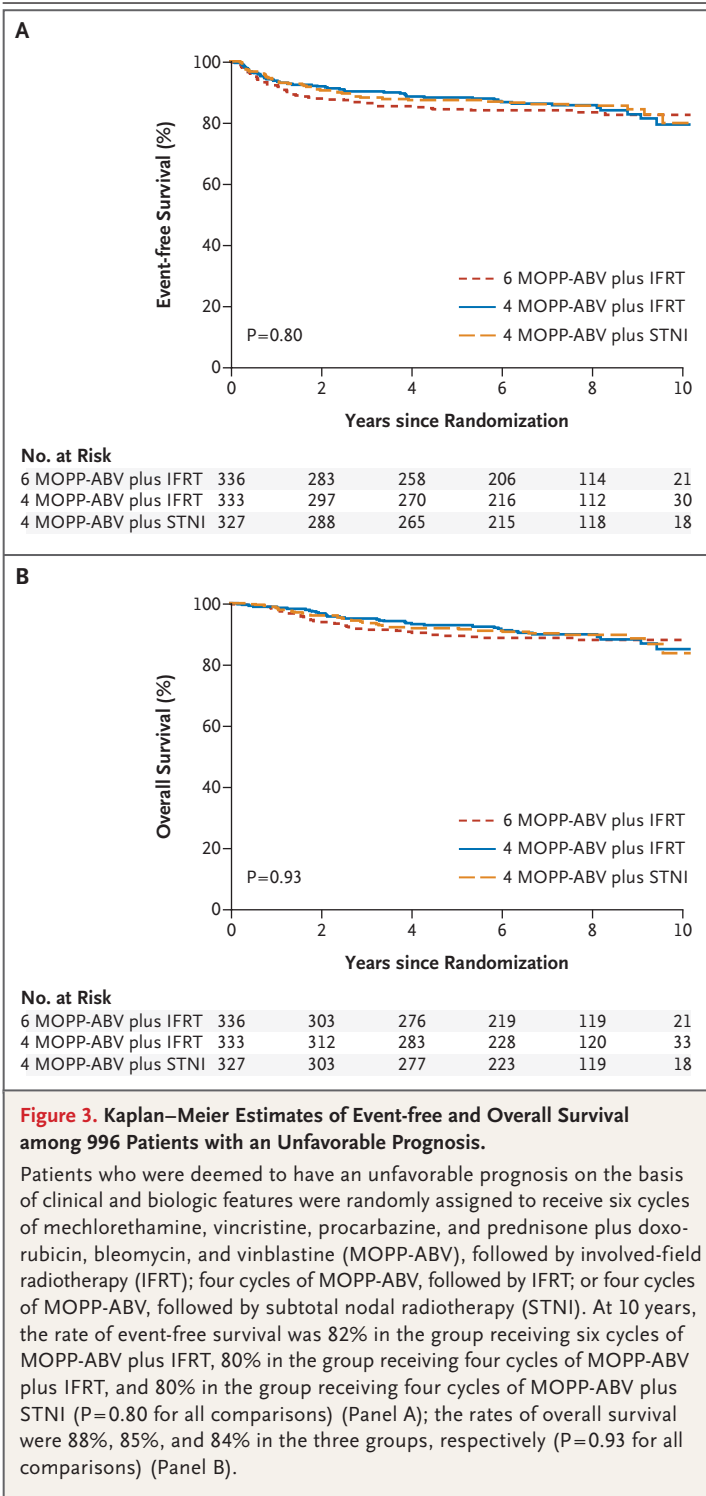
Our study showed that a combination of chemotherapy and radiotherapy should now be considered the standard treatment for all patients with localized stage supradiaphragmatic Hodgkin's disease and that subtotal nodal radiotherapy alone can no longer be recommended. Among patients without risk factors for a poor outcome, the group treated with subtotal nodal radiotherapy had a lower event-free survival rate than predicted, and combination therapy was superior in terms of disease control and overall survival.

The superiority of radiotherapy combined with chemotherapy of short duration over radiotherapy alone in terms of disease control has been shown previously. Press et al.¹⁰ reported superior failure-free survival after three cycles of doxorubicin and vinblastine plus subtotal nodal radiotherapy, as compared with subtotal lymphoid radiotherapy alone, for Hodgkin's disease in stages IA, I_EA, IIA, and II_EA. In the German Hodgkin's Study Group HD7 trial, two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by subtotal nodal radiotherapy resulted in a higher rate of event-free survival than did subtotal nodal radiotherapy alone, with no significant differences in terms of overall survival rates.¹¹

Our results with subtotal nodal radiotherapy alone compared favorably with these two trials in which subtotal nodal radiotherapy was combined with chemotherapy; in our trial, involved-field radiotherapy was used. The main difference between the results of the EORTC H7-F trial and our results concerns the significant difference in



overall survival between the two H8-F groups, which favors combination therapy.¹ In patients without risk factors, the standard treatment is three courses of a doxorubicin-containing regimen followed by involved-field radiotherapy (at a dose of 30 to 36 Gy). In patients with risk factors, the H8-U trial shows equivalent results for both experimental groups as compared with the reference group; four cycles of a doxorubicin-containing regimen are as effective as six cycles, and



involved-field radiotherapy yields a disease-control rate similar to that with subtotal nodal radiotherapy. For these patients, the results of the H8-U trial support the recommendation that four

courses of a doxorubicin-containing regimen and involved-field radiotherapy should be the standard treatment.

The results of both the H8-F and H8-U trials show that involved-field radiotherapy is sufficient treatment after a chemotherapy-induced complete remission has been obtained and that subtotal nodal radiotherapy after chemotherapy can no longer be recommended. Our study confirmed the efficacy of a reduced volume of radiotherapy after chemotherapy, from extended fields to involved fields. This regimen was previously shown to be effective in randomized studies after either four cycles of ABVD^{12,13} or cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) plus ABVD for two cycles in patients with early-stage Hodgkin's disease with an unfavorable prognosis.¹⁴

In patients with a poor prognosis, the response (complete remission or partial response) to chemotherapy was not linked to the risk of later relapse. However, because a small proportion of patients underwent restaging with the use of modern imaging or biopsy to discriminate between active disease and residual fibrosis, we can make no definitive conclusions about the optimal treatment of patients with a partial response or complete remission after initial chemotherapy.

The cumulative estimate of the development of a second cancer in our study is consistent with the findings in other series,^{12,15} but a longer follow-up will be necessary to determine whether there is a significant reduction in long-term side effects owing to a reduction in the volume irradiated.

The results of our trial show that it is possible to tailor the duration of chemotherapy according to risk factors.¹⁶ Moreover, our findings point to a new role for adjuvant radiotherapy with smaller radiation fields, allowing for the reduction of toxic effects associated with large fields.¹⁷ A remaining question now under investigation is whether patients with early-stage Hodgkin's disease can be cured with chemotherapy alone.¹⁸⁻²¹

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APPENDIX

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