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Clinical Investigation

Comparison of 36 Gy, 20 Gy, or No Radiation Therapy After 6 Cycles of EBVP Chemotherapy and Complete Remission in Early-Stage Hodgkin Lymphoma Without Risk Factors: Results of the EORT-GELA H9-F Intergroup Randomized Trial

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Conflict of interest: none.

The study is registered with ClinicalTrials.gov and may be viewed online at https://clinicaltrials.gov/ct2/show/record/NCT00005584.

Supplementary material for this article can be found at www.redjournal.org.

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Summary

Patients with early-stage Hodgkin lymphoma, without risk factors, in complete remission after 6 cycles of epirubicin, bleomycin, vinblastine, and prednisone chemotherapy, were randomized to 36 Gy or 20 Gy of involved-field radiation therapy or to no radiation therapy (open-label, multicenter noninferiority trial). The 5-year relapse-free survival rate in the 20-Gy arm was not inferior to the 5-year relapse-free survival rate in the 36-Gy arm. However, omitting radiation therapy may jeopardize the treatment outcome.

Purpose: While patients with early-stage Hodgkin lymphoma (HL) have an excellent outcome with combined treatment, the radiation therapy (RT) dose and treatment with chemotherapy alone remain questionable. This noninferiority trial evaluates the feasibility of reducing the dose or omitting RT after chemotherapy.

Methods and Materials: Patients with untreated supradiaphragmatic HL without risk factors (age $\geq$ 50 years, 4 to 5 nodal areas involved, mediastinum-thoracic ratio $\geq$ 0.35, and erythrocyte sedimentation rate $\geq$ 50 mm in first hour without B symptoms or erythrocyte sedimentation rate $\geq$ 30 mm in first hour with B symptoms) were eligible for the trial. Patients in complete remission after chemotherapy were randomized to no RT, low-dose RT (20 Gy in 10 fractions), or standard-dose involved-field RT (36 Gy in 18 fractions). The limit of noninferiority was 10% for the difference between 5-year relapse-free survival (RFS) estimates. From September 1998 to May 2004, 783 patients received 6 cycles of epirubicin, bleomycin, vinblastine, and prednisone; 592 achieved complete remission or unconfirmed complete remission, of whom 578 were randomized to receive 36 Gy (n = 239), 20 Gy of involved-field RT (n = 209), or no RT (n = 130).

Results: Randomization to the no-RT arm was prematurely stopped ($\geq$20% rate of inacceptable events: toxicity, treatment modification, early relapse, or death). Results in the 20-Gy arm (5-year RFS, 84.2%) were not inferior to those in the 36-Gy arm (5-year RFS, 88.6%) (difference, 4.4%; 90% confidence interval [CI] −1.2% to 9.9%). A difference of 16.5% (90% CI 8.0%-25.0%) in 5-year RFS estimates was observed between the no-RT arm (69.8%) and the 36-Gy arm (86.3%); the hazard ratio was 2.55 (95% CI 1.44-4.53; P <.001). The 5-year overall survival estimates ranged from 97% to 99%.

Conclusions: In adult patients with early-stage HL without risk factors in complete remission after epirubicin, bleomycin, vinblastine, and prednisone chemotherapy, the RT dose may be limited to 20 Gy without compromising disease control. Omitting RT in these patients may jeopardize the treatment outcome.

Introduction

For patients with early-stage Hodgkin lymphoma (HL), the standard of care has become a combination of chemotherapy and radiation therapy (RT) (1, 2). The European Organisation for Research and Treatment of Cancer (EORTC) has investigated several risk-adapted strategies based on prognostic factors to distinguish between favorable and unfavorable subgroups that might benefit from different approaches. Risk factors used in previous trials were applied to the trial design (2, 3).

To reduce the toxic effects of treatment while maintaining disease control, we conducted a randomized multicenter phase 3 trial in which 2 experimental arms were compared with a standard arm. On the basis of the H7-F trial results, a combination of 6 courses of epirubicin, bleomycin, vinblastine, and prednisone (EBVP) followed by 36 Gy of involved-field radiation therapy (IFRT) (36-Gy arm) was the control arm for patients in complete remission (CR) or unconfirmed complete remission (CRu) after chemotherapy (3). In combined-modality therapy, an in-field control rate of 85% to 95% could be obtained using IFRT doses of 15 to 25 Gy in pediatric series (4-7). Therefore, the first experimental arm of the trial consisted of 6 courses of EBVP followed by 20 Gy of IFRT (20-Gy arm). In the late 1990s, to limit cardiovascular damage or second cancers after RT and to prevent quality-of-life impairment (8-10), the use of chemotherapy alone had been considered a promising approach (11-13); whether RT can be omitted remains an unsolved question (14, 15). Therefore, the second experimental arm of the trial consisted of 6 courses of EBVP without RT (no-RT arm). We report on the results of the randomized, open-label, multicenter noninferiority trial for patients with early-stage HL without risk factors who achieved CR or CRu after EBVP chemotherapy.

Methods and Materials

Patients

Patients who had untreated stage I or II supradiaphragmatic classical HL without risk factors (age $\geq$ 50 years, stage II with 4 to 5 involved nodal areas, mediastinum-thoracic ratio $\geq$ 0.35, and erythrocyte sedimentation rate [ESR] $\geq$ 50 mm in first hour with no B symptoms or ESR $\geq$ 30 mm in first hour with B symptoms) were eligible for the study (Fig. 1). Inclusion was based on the diagnosis made by the local pathologist; the material was reviewed by a panel of pathologists (Appendix E1; available online at www.redjournal.org). Patients with lymphocyte predominant nodular HL subtype were not eligible. The exclusion criteria were concomitant or previous malignancies other than basal skin or in situ carcinoma of the cervix, concomitant other severe illness, or human immunodeficiency virus positivity. Clinical staging included the following: physical examination, complete blood count, ESR after 1 hour, chest film with measurement of mediastinum-thoracic ratio, computed tomography (CT) scan of thorax and abdomen, and bone marrow biopsy (optional in patients without B symptoms) (16).

The trial was approved by a protocol review committee and by the ethics committee of each participating center or country according to local laws. All patients gave written informed consent before study entry.

Treatment

All patients received 6 courses of EBVP (epirubicin, 70 mg/m^2 intravenously [IV] on day 1; bleomycin, 10 mg/m^2 IV or intramuscularly on day 1; vinblastine, 6 mg/m^2 IV on day 1; and prednisone, 40 mg/m^2 orally on days 1 through 5) administered every 21 days. Patients who achieved CR or CRu were randomly assigned to receive either 36 Gy of IFRT, 20 Gy of IFRT, or no further RT. Classical IFRT was begun within 3 to 4 weeks after the end of the last cycle of chemotherapy. The field borders were defined based on body anatomy (except for the mediastinum). Patients were treated mostly through parallel opposed fields. Adjacent clinically negative areas were not irradiated. Patients in partial remission (PR) received 36 Gy of IFRT (with a 4-Gy boost in sites of partial response). All RT regimens were applied in fractions of 1.75 to 2.0 Gy, with 5 fractions per week, with all fields treated each day.

Study design

Patients achieving CR or CRu after EBVP chemotherapy were randomly assigned in equal ratios to 1 of the 3 treatment modalities defined in the previous section. The primary endpoint was the 5-year relapse-free survival estimate (time to relapse after CR or CRu or death) assuming that $\geq$90% of all expected events will occur within 5 years of randomization. The secondary endpoints were event-free survival (time to disease progression during treatment, relapse, or death), overall survival, and incidence of late complications (second cancer, cardiac toxic effects, radiation pneumonitis, or chemotherapy-related pulmonary dysfunction occurring $>$12 months after treatment initiation). Relapse-free, event-free, and overall survival estimates were calculated from the date of the start of chemotherapy to the date of the first event; the date of the last examination; or December 31, 2010. The time to the development of a late complication was calculated from the date of the start of chemotherapy to the date on which the first complication was diagnosed.

Response to treatment (CR, CRu, PR, and no change) was defined according to Cotswolds recommendations using CT scan assessment (17). Response was evaluated after chemotherapy and after RT. Patients with stable or progressive disease after chemotherapy were treated off protocol. All patients were to be followed up at regular intervals after the end of treatment.

Patients were enrolled in 104 centers from 9 European countries. Registration, randomization, and data collection were performed at a unique clinical research unit. Patients were randomized in a 1:1:1 ratio for the 3 arms. Randomization was performed centrally by telephone and stratified by center with fixed blocks of 6 patients. The median follow-up time was 91 months (range, 4-147 months).

Statistical analysis

A noninferiority test was used to compare each of the 2 experimental arms with the control arm in terms of relapse-free survival rate at 5 years (18). The noninferiority margin was set to 10% in terms of the difference of 2 rates. Assuming that 80% of patients would achieve CR or CRu after chemotherapy and assuming a 5-year relapse-free

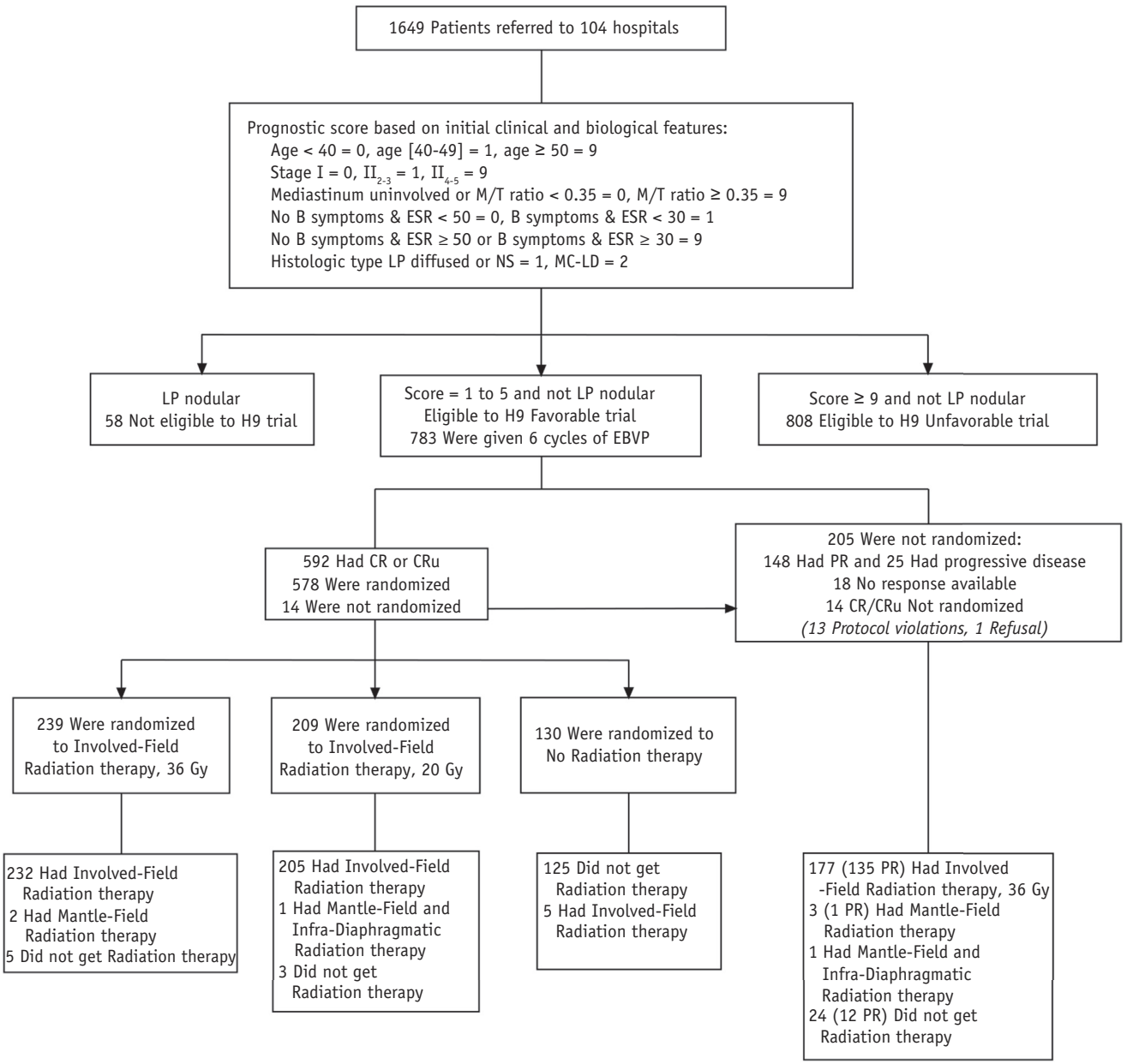


Fig. 1. CONSORT (Consolidated Standards of Reporting Trials) diagram showing study protocol and numbers of patients by treatment arm. Enrollment in the H9-F trial lasted from September 1998 to May 2004. Five major lymph node areas were defined: the whole neck including the supraclavicular area (left and right); the axilla including the infraclavicular area (left and right); and the whole mediastinum including the hilar nodes on both sides (one area). *Abbreviations:* CR = complete remission; CRu = unconfirmed complete remission; EBVP = epirubicin, bleomycin, vinblastine, and prednisone; ESR = erythrocyte sedimentation rate; LP = lymphocyte predominant nodular histologic subtype; MC-LD = mixed cellularity - lymphocytic-depleted histologic subtypes; M/T = mediastinum-thoracic; NS = nodular sclerosing histologic subtype; PR = partial remission.

survival rate of 90% in the control arm, we determined that a minimal sample size of 417 patients was necessary to have 80% power to conclude to noninferiority at a 5% significance level. The upper bound of the 2-sided 90% confidence interval (CI) of the difference (control arm minus experimental arm) was compared with the noninferiority margin of 10% (18, 19). A univariate Cox regression analysis was also performed to estimate the hazard ratio (HR) between 2 arms and its corresponding *P* value. The comparison of the control arm with the experimental no-RT arm was limited to patients randomized before the no-RT arm was closed to entry. No interim analysis was planned. Two stopping rules were defined: The first was made to stop chemotherapy if ≤70% of patients were in CR or CRu after EBVP chemotherapy. The second stopping rule was based on the occurrence of the following: modification of planned RT, severe treatment-related toxicity within 18 months after randomization, no CR or CRu after RT, and relapse or early death from any cause. A ≥20% rate of these occurrences (all events combined) in either arm was considered unacceptable. The stopping rules were based on the binomial distribution of events assessed 2 years after randomization (20).

The probabilities of relapse-free, event-free, and overall survival and the cumulative probability of a late complication or second cancer were estimated with the Kaplan-Meier method. The cumulative probability of a late complication was calculated as 1 minus the probability of survival without the development of that complication. All randomized patients were included in the primary analysis, in the arm to which they were allocated by randomization.

Results

Patients

Overall, 783 patients without risk factors were enrolled in the trial from September 1998 to May 2004 (Fig. 1). The proportion of CR or CRu after EBVP chemotherapy was 77% (95% CI 74%-80%), allowing accrual in the trial to continue (first stopping rule, Fig. 2A). Of the 592 CR or CRu patients, 578 (98%) were randomized, 239 to 36-Gy IFRT, 209 to 20-Gy IFRT, and 130 to no RT; 205 patients were not randomized (Fig. 1). Protocol violations occurred in 16 patients (3%): 8 did not receive RT, 3 received more extensive RT, and 5 received IFRT while randomized in the no-RT arm. Seventeen percent of patients were lost to follow-up within 5 years. Patient characteristics were well balanced among the 3 arms (Table 1).

Results of patients randomized in trial

Response to treatment, progression, and relapse

Of the patients responding to EBVP chemotherapy, 66% were classified as having CR and 34% as having CRu

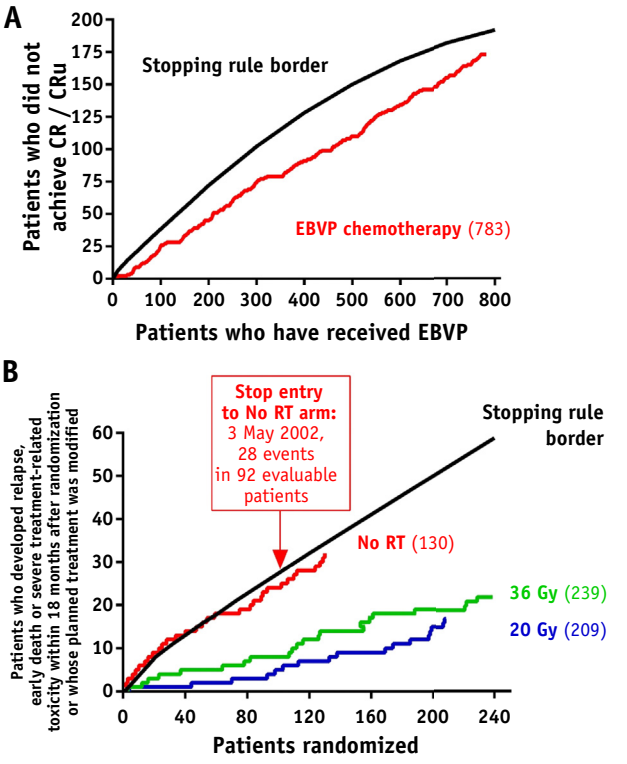


Fig. 2. Stopping rules for initial epirubicin, bleomycin, vinblastine, and prednisone (EBVP) chemotherapy with partial remission, no change, or progressive disease accounting for event. A, Application of stopping rule after complete remission (CR) or unconfirmed complete remission (CRu) was achieved. B, The second stopping rule was based on the occurrence of the following: modification of planned treatment (ie, 36 Gy instead of 20 Gy or any irradiation instead of no irradiation), severe treatment-related toxicity, no CR or CRu after radiation therapy, and relapse or early death accounting for event. Patients were randomly assigned to receive 6 cycles of EBVP plus 36 Gy of involved-field radiation therapy, 20 Gy of involved-field radiation therapy, or no radiation therapy (RT).

(Table 2). Of the patients randomized, 20 progressed: 5 (1%) during RT and 15 (3%) within 3 months after the end of therapy. In an additional 40 patients (7%), early relapse occurred (4-12 months after the end of therapy), whereas 34 (6%) had late relapses. Most relapses were of nodal type located in previously involved areas and occurred in the no-RT arm. The no-RT arm was closed to entry in May 2002 because the proportion of patients with modification of planned therapy, no CR or CRu after RT, relapse, early death from any cause, or severe treatment-related toxicity within 18 months after randomization exceeded 20% (second stopping rule, Fig. 2B).

Relapse-free survival and overall survival

In CR or CRu patients after EBVP chemotherapy, the difference in 5-year relapse-free survival estimates between the 36-Gy arm and 20-Gy arm (88.6% and 84.2%,

Table 1 Baseline demographic and clinical characteristics of 783 patients without risk factors*

Demographic or clinical characteristics	Total (N=783)	6 Cycles of EBVP plus 36 Gy of IFRT (n=239)	6 Cycles of EBVP plus 20 Gy of IFRT (n=209)	6 Cycles of EBVP and no RT (n=130)	Patients not in complete remission after 6 cycles of EBVP or not randomized (n=205)
Age, y					
Median	31	31	30	31	32
Range	15-49	15-49	16-49	16-49	16-49
Male-female ratio	1.2:1	1.3:1	1.2:1	1.2:1	1.3:1
B symptoms present, n (%)	46 (6)	15 (7)	10 (5)	7 (6)	14 (7)
ESR, mm in first hour					
Median	13	12	14	12	17
Range	1-64	1-64	1-49	1-60	1-49
No. of lymph node areas involved, n (%)					
1	276 (37)	94 (42)	72 (36)	54 (44)	56 (29)
2	314 (43)	88 (39)	87 (44)	49 (39)	90 (47)
≥3	151 (20)	44 (19)	41 (20)	21 (17)	45 (24)
Mediastinal involvement, n (%)	407 (55)	111 (49)	108 (54)	60 (48)	128 (67)
Large mediastinal mass,† n (%)	2 (<1)	0 (0)	1 (<1)	0 (0)	1 (<1)
Histologic analysis					
No. of patients	507	150	132	84	141
Type of disease,‡ n (%)					
Lymphocyte predominant nodular	6 (1)	2 (1)	1 (1)	1 (1)	2 (1)
Nodular sclerosing	449 (89)	136 (91)	112 (85)	75 (90)	126 (90)
Mixed cellularity	36 (7)	7 (5)	14 (10)	6 (7)	9 (7)
Hodgkin lymphoma of unspecified type	7 (1)	2 (1)	3 (2)	0 (0)	2 (1)
Non-Hodgkin lymphoma	3 (1)	1 (1)	1 (1)	1 (1)	0 (0)
Not Hodgkin lymphoma	6 (1)	2 (1)	1 (1)	1 (1)	2 (1)
Overall treatment duration,§ mo					
Median	6.3	6.8	6.7	4.2	6.4
Range	0-19	0-15	0-19	3-7	0-19
Follow-up duration‖					
Median, mo	91	86	90	99	94
Range, mo	1-147	4-142	4-141	4-147	1-139
0-2 y, n (%)	66 (8)	19 (8)	18 (9)	9 (7)	20 (10)
3-4 y, n (%)	68 (9)	25 (10)	22 (10)	7 (5)	14 (7)
≥5 y, n (%)	649 (83)	195 (82)	169 (81)	114 (88)	171 (83)

Abbreviations: EBVP = epirubicin, bleomycin, vinblastine, and prednisone; ESR = erythrocyte sedimentation rate; IFRT = involved-field radiation therapy; RT = radiation therapy.

* Because of rounding, percentages may not total 100%.

† A large mediastinal mass was defined, in patients with mediastinal involvement, as a ratio of the mediastinum to the thorax of at least 0.35 at the level of T5 through T6 while patients were standing.

‡ The histologic type was determined after review by 2 panels of pathologists (panel A, 318 of 425 cases reviewed [75%]; panel B, 189 of 358 cases reviewed [53%]). However, inclusion was based on the diagnosis made by the local pathologist.

§ The overall duration of treatment was defined as the time from the first day of chemotherapy to the end of RT or the end of chemotherapy in the no-RT arm.

‖ The follow-up duration was defined as the time from the first day of chemotherapy to the date of most recent follow-up or January 1, 2011, whichever came first.

respectively) was 4.4% (90% CI −1.2% to 9.9%), demonstrating noninferiority of 20-Gy IFRT relative to 36-Gy IFRT; the HR estimate was 1.53 (95% CI 0.92-2.55; $P=.102$). In patients randomized before May 2002, the study could not demonstrate noninferiority of the no-RT arm (5-year relapse-free survival estimate, 69.8%) compared with the 36-Gy arm (86.3%) with a difference of 16.5% (90% CI 8.0%-25.0%) between the 2 arms since the upper bound of the 90% CI exceeded the prespecified noninferiority margin (10%); the HR estimate was 2.55 (95% CI 1.44-4.53; $P<.001$) (Table 2, Fig. 3A). The number of deaths related (n=8) or unrelated (n=6) to HL was limited and equally distributed in the 3 treatment arms, leading to superimposable overall survival curves (Fig. 4A).

Table 2 Clinical outcome of patients without risk factors*

	Total (N = 783)	6 Cycles of EBVP plus 36 Gy of IFRT (n = 239)	6 Cycles of EBVP plus 20 Gy of IFRT (n = 209)	6 Cycles of EBVP and no RT (n = 130)	Patients not in CR after 6 cycles of EBVP or not randomized (n = 205)
Response at end of chemotherapy, n (%)					
Patients with information available, n	765	239	209	130	187
CR	389 (51)	161 (67)	132 (63)	88 (68)	8 (4)
CRu	203 (27)	78 (33)	77 (37)	42 (32)	6 (3)
PR	148 (19)	0 (0)	0 (0)	0 (0)	148 (80)
Progression	25 (3)	0 (0)	0 (0)	0 (0)	25 (13)
Response at end of treatment, n (%)					
Patients with information available, n	767	239	209	130	189
Responders (CR and CRu), % (95% CI)	89 (87-91)	99 (98-100)	98 (95-99)	100 (97-100)	59 (51-66)
CR, n (%)	498 (65)	194 (81)	163 (78)	88 (68)	53 (28)
CRu, n (%)	186 (24)	44 (18)	42 (20)	42 (32)	58 (31)
PR, n (%)	50 (7)	0 (0)	0 (0)	0 (0)	50 (26)
Progression, n (%)	33 (4)	1 (1)	4 (2)	0 (0)	28 (15)
Progression early† and late relapse, n	53/54 + 45	6/9 + 10	7/8 + 17	7/23 + 7	33/14 + 11
% (95% CI)	19 (17-22)	10 (7-15)	15 (11-21)	28 (21-37)	29 (23-35)
Site of progression/relapse					
Nodal only, within irradiated field	4/9 + 17 (4)	0/1 + 5 (2)	1/5 + 7 (6)	NA	3/3 + 5 (5)
Nodal only, outside irradiated field	38/32 + 15 (11)	6/7 + 4 (7)	1/2 + 3 (3)	6/21 + 6 (25)	25/2 + 2 (14)
Extranodal with or without nodal	7/13 + 10 (4)	0/1 + 0 (<1)	4/1 + 6 (5)	1/2 + 1 (3)	2/9 + 3 (7)
Unspecified	4/0 + 3 (1)	0/0 + 1 (<1)	1/0 + 1 (1)	0/0 + 0 (0)	3/0 + 1 (2)
Duration of response,‡ mo					
Median	76	77	76	71	79
Range	1-143	1-134	1-132	1-143	1-129
CR or CRu patients at end of treatment, n	684	238	205	130	111
Early and late relapse, n	107	24	28	37	18
5-y relapse-free survival, % (95% CI)	80 (77-83)	89 (84-92)	84 (78-89)	70 (61-77)	71 (64-77)
PR patients at end of treatment					
No. of progressions relapses (%)	2/4 + 5 (22)	NA/NA	NA/NA	NA/NA	2/4 + 5 (22)
5-y progression-free survival, % (95% CI)	74 (58-85)	NA (NA)	NA (NA)	NA (NA)	74 (58-85)
Patients with CR or CRu after EBVP					
5-y relapse-free survival, % (90% CI)	-	88.6 (84.6-91.6)	84.2 (79.3-88.0)	69.8 (62.4-75.9)	-
In patients randomized before May 4, 2002§	-	86.3 (80.2-90.6)	-	69.8 (62.4-75.9)	-
5-y difference for 36 Gy vs 20 Gy, % (90% CI)	-	4.4 (−1.2 to 9.9)	-	-	-
5-y difference for 36 Gy vs no RT, % (90% CI)	-	-	-	-	-
In patients randomized before May 4, 2002	-	16.5 (8.0-25.0)	-	-	-
All patients					
5-y event-free survival, % (95% CI)	79 (76-82)	88 (83-92)	84 (78-88)	69 (60-77)	70 (63-76)

(*continued on next page*)

Table 2 (*continued*)

	Total (N=783)	6 Cycles of EBVP plus 36 Gy of IFRT (n=239)	6 Cycles of EBVP plus 20 Gy of IFRT (n=209)	6 Cycles of EBVP and no RT (n=130)	Patients not in CR after 6 cycles of EBVP or not randomized (n=205)
Death, n (%)	31 (4)	6 (2)	4 (2)	4 (3)	17 (8)
Progressive disease	20 (2)	3 (1)	2 (1)	2 (2)	13 (6)
Treatment related	4 (<1)	1 (<1)	0 (0)	0 (0)	3 (1)
Not related to HL	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
Second cancer	2 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)
Unspecified cause	4 (<1)	1 (<1)	2 (1)	1 (<1)	0 (0)
5-y overall survival,‖ % (95% CI)	97 (95-98)	98 (95-99)	99 (96-100)	97 (92-99)	93 (88-95)
10-y overall survival, % (95% CI)	94 (91-96)	95 (86-98)	97 (93-99)	95 (85-98)	90 (84-93)

Abbreviations: CI = confidence interval; CR = complete remission; CRu = unconfirmed complete remission; EBVP = epirubicin, bleomycin, vinblastine, and prednisone; HL = Hodgkin lymphoma: IFRT = involved-field radiation therapy; NA = not applicable; PR = partial remission; RT = radiation therapy.

* Because of rounding, percentages may not total 100%.

† Early relapse denotes relapse occurring within 3 to 12 months after treatment completion; late relapse denotes relapse occurring >12 months after treatment completion.

‡ The analysis of duration of response was confined to the 684 patients who had CR or CRu.

§ Primary endpoint of trial. The comparison of the arm receiving EBVP plus 36-Gy IFRT (control arm) with the arm receiving EBVP and no RT (experimental arm) was limited to patients in CR or CRu after chemotherapy who were randomized before the experimental no-RT arm was closed to entry.

‖ The median follow-up period of the patients who survived was 86 months (range, 4-142 months) in the arm receiving 6 cycles of EBVP plus 36-Gy IFRT, 88 months (range, 4-139 months) in the arm receiving 6 cycles of EBVP plus 20-Gy IFRT, 99 months (range, 1-147 months) in the arm receiving 6 cycles of EBVP with no RT, and 92 months (range, 1-139 months) in patients who were not randomized.

Characteristics and outcome of patients not randomized in trial

Compared with randomized patients, nonrandomized patients less often had stage I HL (29% vs 40%, $P=.009$) and more often had mediastinal involvement (67% vs 51%, $P<.001$) (Table 1). During EBVP chemotherapy, 25 patients (13%) progressed (Table 2). Of these patients, 1 received only IFRT; 2 received MOPP-ABV (mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine) chemotherapy followed by IFRT; 3 received BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) chemotherapy followed by IFRT in 1; and 2 received high-dose chemotherapy and bone marrow transplantation. Salvage treatment was not specified in the remaining 17 patients. Of the 148 PR patients after EBVP chemotherapy, 42 (28%) achieved CR after RT, 54 (36%) achieved CRu, 48 (32%) remained in PR, and 4 (3%) had disease progression.

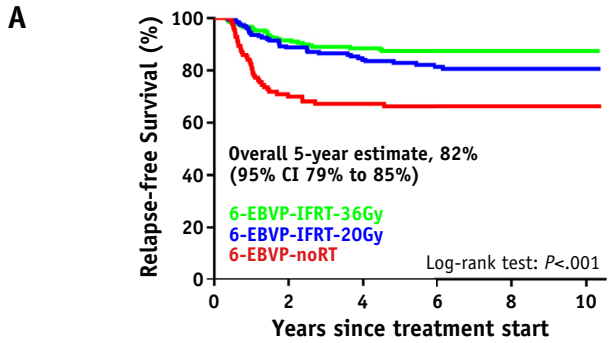
The number and type of progressions and relapses were close to those of patients randomized in the no-RT arm. Despite the finding that the event-free curve of nonrandomized patients was superimposable onto the relapse-free survival curve of patients randomized to the no-RT arm (Fig. 3B), overall survival of the former group was lower than that of randomized patients and even lower than that of patients randomized in the no-RT arm (Fig. 4B). However, among the 148 PR patients after EBVP, the 5-year event-free and overall survival estimates were 81% (95% CI 74%-87%) and 95% (95% CI 90%-98%), respectively.

Toxicity of treatment, supportive measures, and late adverse events

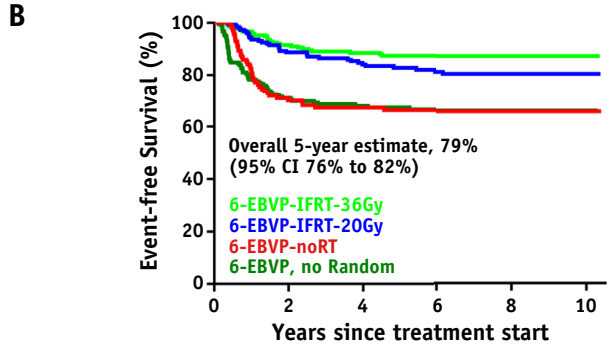
In the overall population, grade 3 or 4 hematologic toxicity—mostly leucopenia—developed in 44% of patients during chemotherapy (Table 3). Grade 3 or 4 neutropenia was reported in 26% of patients, and 5% of patients had serious adverse events that led to 1 chemotherapy-related death. During or after RT, grade 3 or 4 hematologic and nonhematologic toxicities developed in very few patients: 2 patients and 16 patients, respectively. As a late adverse event, cardiovascular toxicity was reported in 1% of patients, giving a 5-year cumulative estimate of 0.6% (95% CI 0.2%-1.5%). A pulmonary complication was reported in 1% of patients, with an overall 5-year cumulative estimate of 0.9% (95% CI 0.5%-2.0%). A second malignancy developed in 14 patients 16 to 134 months after the start of chemotherapy, giving a 5-year cumulative incidence estimate of second cancer of 1.2%.

Discussion

The aim of the trial was to assess whether, in patients in CR or CRu after 6 cycles of EBVP, IFRT to a lower dose than 36 Gy or no RT after chemotherapy could be used without compromising the high rate of disease control in those with

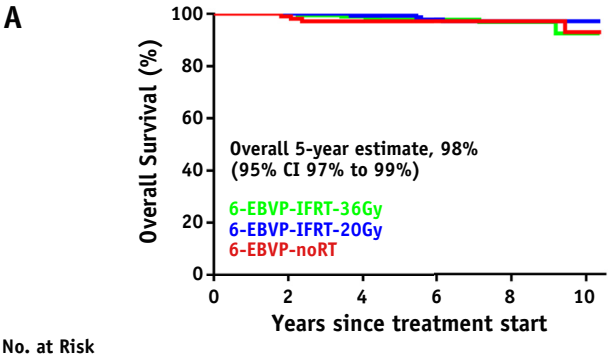


No. at Risk						
6-EBVP-IFRT-36Gy	239	209	186	149	73	33
6-EBVP-IFRT-20Gy	209	179	156	127	66	25
6-EBVP-noRT	130	91	82	67	50	21

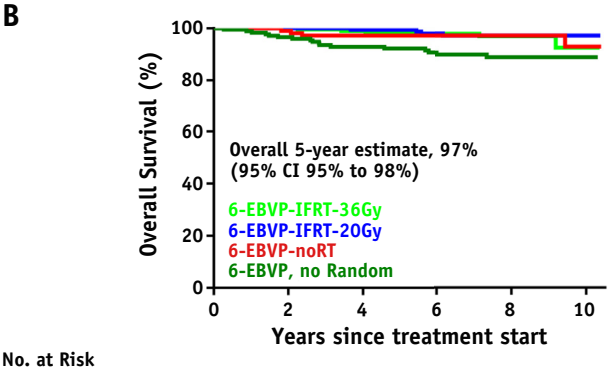


No. at Risk						
6-EBVP-IFRT-36Gy	239	209	186	149	73	33
6-EBVP-IFRT-20Gy	209	179	156	127	66	25
6-EBVP-noRT	130	91	82	67	50	21
6-EBVP, no Random	*205*	*136*	*122*	*102*	*63*	*21*

Fig. 3. A, Kaplan-Meier estimates of relapse-free survival among patients enrolled in H9-F trial who were randomly assigned to receive 6 cycles of epirubicin, bleomycin, vinblastine, and prednisone (6-EBVP) plus 36 Gy of involved-field radiation therapy (IFRT), 20 Gy of IFRT, or no adjuvant radiation therapy (RT). B, Same figure with projection of event-free survival in patients who did not achieve complete remission or unconfirmed complete remission or who were not randomized; of these 205 patients, 181 were given RT. *Abbreviation:* CI = confidence interval.



No. at Risk						
6-EBVP-IFRT-36Gy	239	227	205	166	77	33
6-EBVP-IFRT-20Gy	209	198	182	150	78	31
6-EBVP-noRT	130	124	113	96	70	27



No. at Risk						
6-EBVP-IFRT-36Gy	239	227	205	166	77	33
6-EBVP-IFRT-20Gy	209	198	182	150	78	31
6-EBVP-noRT	130	124	113	96	70	27
6-EBVP, no Random	*205*	*182*	*162*	*134*	*84*	*29*

Fig. 4. A, Kaplan-Meier estimates of overall survival among patients enrolled in H9-F trial who were randomly assigned to receive 6 cycles of epirubicin, bleomycin, vinblastine, and prednisone (6-EBVP) plus 36 Gy of involved-field radiation therapy (IFRT), 20 Gy of IFRT, or no adjuvant radiation therapy (RT). B, Same figure with projection of overall survival in patients who did not achieve complete remission or unconfirmed complete remission or who were not randomized; of these 205 patients, 181 were given RT. *Abbreviation:* CI = confidence interval.

early-stage HL without risk factors. With the number of patients accrued and the available follow-up, the primary endpoint of the trial (5-year relapse-free survival estimate) demonstrates that 20 Gy of IFRT is not inferior to 36 Gy of IFRT (control arm). In contrast, treatment omitting RT provides a worse relapse-free survival estimate, and premature closing of recruitment in the no-RT arm was needed. However, the overall survival curves of the 3 treatment arms are similar. No interpretation of the results should be performed without considering the design of the trial. First, randomization done after CR or CRu was achieved with EBVP chemotherapy might have resulted in a higher overall response rate at the end of treatment than if randomization was performed up front. Second, selection of the EBVP regimen instead of the current standard—doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)—limits the impact of the results of the no-RT arm for daily clinical practice.

The administration of 6 cycles of EBVP followed by 36 Gy of IFRT provides a 5-year relapse-free survival estimate of 88.6% (95% CI 84.6%-91.6%), a result that differs from that of the H8-F trial (with similar inclusion criteria and randomization performed before chemotherapy), in which 3 cycles of MOPP-ABV and 36-Gy IFRT resulted in a 5-year relapse-free survival estimate of 98% (95% CI 96%-99%) (2). The control arm did not yield the results of the German Hodgkin Study Group (GHSG) HD10 trial, which reported a 5-year freedom—from—treatment failure estimate of 92.8% (95% CI 89.1%-95.3%) after 4 cycles of ABVD and 30-Gy IFRT

Table 3 Toxicity of treatment, supportive measures, and late adverse events* in patients without risk factors†

Toxicity, treatment effects, and cumulative estimates	Total (N=783)	6 Cycles of EBVP plus 36 Gy of IFRT (n=239)	6 Cycles of EBVP plus 20 Gy of IFRT (n=209)	6 Cycles of EBVP and no RT (n=130)	Patients not in CR after 6 cycles of EBVP or not randomized (n=205)
Acute toxicity related to chemotherapy					
Patients with information available	734	-	-	-	-
Toxicity grade 1-2/grade 3-4	-	NA	NA	NA	NA
At least 1 hematologic toxicity	29%/25%	-	-	-	-
Anemia	14%/0%	-	-	-	-
Thrombopenia	2%/<1%	-	-	-	-
Leucopenia	35%/8%	-	-	-	-
Neutropenia	18%/24%	-	-	-	-
Blood transfusion, n	0 (0%)	-	-	-	-
Growth factors used, n	32 (4%)	-	-	-	-
Administration of antibiotics, n	34 (5%)	-	-	-	-
Hospitalization, n	70 (10%)	-	-	-	-
Serious adverse event, n	40 (5%)	-	-	-	-
Chemotherapy stopped definitively,‡ n	17 (2%)	-	-	-	-
Acute toxicity related to RT					
Patients with information available	568	215	191	1	161
Toxicity grade 1-2 grade 3-4	-	-	-	-	-
At least 1 toxicity	54%/3%	52%/2%	40%/2%	(1)/(0)	63%/6%
Hematologic	4%/<1%	4%/0%	5%/0%	-	4%/1%
Nonhematologic					
Pulmonary	21%/2%	24%/1%	12%/1%	-	29%/2%
Mucositis	6%/<1%	6%/<1%	4%/0%	-	8%/0%
Cutaneous	29%/1%	31%/1%	25%/1%	-	30%/3%
Nausea or vomiting	24%/<1%	27%/<1%	9%/0%	-	38%/0%
RT stopped definitively, n	5 (1%)	1 (<1%)	0 (0%)	-	4 (2%)
Late cardiovascular toxicity, n (%)	6 (1)	2 (1)	2 (1)	2 (1)	0 (0)
Myocardial infarction or angina pectoris, n (%)	2 (<1)	1 (<1)	1 (<1)	0 (0)	-
Congestive heart failure, n (%)	2 (<1)	0 (0)	1 (<1)	1 (<1)	-
Constrictive pericarditis, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	-
Stroke, n (%)	1 (<1)	0 (0)	0 (0)	1 (<1)	-
Arterial peripheral vasculopathy, n (%)	1 (<1)	1 (<1)	0 (0)	0 (0)	-
5-y cumulative rate of late cardiovascular toxicity, % (95% CI)	0.6 (0.2-1.5)	-	-	-	-
10-y cumulative rate of late cardiovascular toxicity, % (95% CI)	0.8 (0.3-1.9)	-	-	-	-
Late pulmonary toxicity, n (%)	7 (1)	0 (0)	1 (<1)	2 (2)	4 (2)
Pneumonitis, n (%)	6 (1)	0 (0)	1 (<1)	2 (2)	3 (1)
Dyspnea, n (%)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
Functional test altered, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
5-y cumulative rate of late pulmonary toxicity, % (95% CI)	0.9 (0.5-2.0)	-	-	-	-
10-y cumulative rate of late pulmonary toxicity, % (95% CI)	0.9 (0.5-2.0)	-	-	-	-
All second cancers, n (%)	14 (2)	3 (1)	6 (3)	2 (2)	3 (1)
Type of second cancer					
Acute leukemia, n (%)§	1 (<1)	0 (0)	0 (0)	1 (1)	0 (0)

(*continued on next page*)

Table 3 (*continued*)

Toxicity, treatment effects, and cumulative estimates	Total (N = 783)	6 Cycles of EBVP plus 36 Gy of IFRT (n = 239)	6 Cycles of EBVP plus 20 Gy of IFRT (n = 209)	6 Cycles of EBVP and no RT (n = 130)	Patients not in CR after 6 cycles of EBVP or not randomized (n = 205)
Non-Hodgkin lymphoma, n (%)‖	2 (<1)	1 (<1)	0 (0)	0 (0)	1 (<1)
Solid tumor, n (%)¶	11 (2)	2 (1)	6 (3)	1 (1)	2 (1)
5-y cumulative rate of second cancers, % (95% CI)	1.2 (0.6-2.3)	0.5 (0.0-3.7)	2.7 (1.1-6.3)	0.8 (0.1-5.8)	0.5 (0.0-3.7)
10-y cumulative rate of second cancers, % (95% CI)	2.7 (1.5-4.8)	-	-	-	-

Abbreviations: CI = confidence interval; EBVP = epirubicin, bleomycin, vinblastine, and prednisone; IFRT = involved-field radiation therapy; NA = not applicable; RT = radiation therapy.

* Late adverse effect denotes toxicity occurring >12 months after treatment completion.

† Because of rounding, percentages may not total 100%.

‡ EBVP chemotherapy was stopped definitively in 1 patient in the arm receiving 36-Gy IFRT (5 cycles administered) and in 16 patients with partial remission.

§ An acute lymphocytic leukemia developed 24 months after the sixth EBVP cycle in a 27-year-old male patient.

‖ Non-Hodgkin lymphoma developed in 1 complete responder (37-year-old male patient) 99 months after 6 cycles of EBVP and 36-Gy IFRT. One patient (43-year-old male patient) in partial remission after 6 cycles of EBVP was given 36-Gy IFRT, and non-Hodgkin lymphoma developed 6 months later.

¶ Of the 11 cases of solid tumors that occurred 21 to 134 months after randomization, 6 developed within involved irradiated areas (in field) and 5 developed outside irradiated areas (out of field): 1 in-field and 1 out-of-field solid tumor in the arm receiving 6 cycles of EBVP and 36-Gy IFRT; 4 in-field and 2 out-of-field solid tumors in the arm receiving 6 cycles of EBVP and 20-Gy IFRT; 1 out-of-field solid tumor in the arm receiving 6 cycles of EBVP and no RT; and 1 in-field and 1 out-of-field solid tumor in patients in partial remission after 6 cycles of EBVP who were administered IFRT.

(21). We conclude that administration of 6 cycles of EBVP chemotherapy results in a lower disease control rate than ABVD chemotherapy, and we do not recommend EBVP in adult patients with early-stage HL without risk factors.

In CR or CRu patients after 6 cycles of EBVP who received the experimental 20 Gy of IFRT, the clinical outcome is not inferior to that of patients treated with 6 cycles of EBVP and 36 Gy of IFRT. Despite noninferiority between 20 Gy and 36 Gy of IFRT, a higher number of late relapses occurred after 20 Gy and the role of the EBVP chemotherapy remains questionable. In the GHSG HD10 trial, 2 cycles of ABVD were compared with 4 cycles of ABVD followed by 30 Gy of IFRT or 20 Gy of IFRT given at random. The 5-year freedom−from−treatment failure rates were 93.4% and 92.9% with 30 Gy of IFRT and 20 Gy of IFRT, respectively. The noninferiority of the lower dose of radiation was the main argument to recommend 20 Gy of RT in early-stage HL without risk factors as defined by the GHSG (21). Although the EBVP chemotherapy used instead of standard ABVD may explain the poorer disease control rate observed, our study contributes to the assessment of 20 Gy as the recommended irradiation dose after initial ABVD chemotherapy in early-stage HL without risk factors.

The experimental no-RT arm ends up having worse results for relapse-free survival compared with combined-modality treatment, while similar overall survival estimates are obtained. The trial protocol design is to randomize the patients once CR or CRu to chemotherapy is achieved. After 6 cycles of EBVP, the evaluation of response based on clinical examination and CT scan findings without a centralized review and without a positron emission tomography (PET) scan could bias the population selected for randomization. To take this possible bias into account, stopping rules were applied to EBVP chemotherapy and to EBVP followed or not followed by RT with all possible events considered. The stopping rules led us to prematurely stop enrollment of patients in the no-RT arm. The conclusion is that 6 cycles of EBVP chemotherapy alone are not sufficient to achieve a satisfactory disease control rate. The study also indicates that in patients who do not achieve CR or CRu after EBVP chemotherapy, additional IFRT can compensate for disease control although expected overall survival is unsatisfactory. The choice of EBVP instead of ABVD hampers our conclusion on a treatment omitting RT. A 12-year freedom−from−disease progression rate of 87% has been reported in limited-stage HL after ABVD alone (22). Since the design of the trial, both the standard systemic therapy and RT strategies of early-stage HL without risk factors have changed. RT volumes have been reduced from IFRT to involved-node or involved-site RT (23, 24). The rationale for this target volume reduction is that most relapses after chemotherapy are seen only in originally involved sites (25). Recent changes in RT modalities, including reduction of radiation dose and radiation target volumes, and the use of modern RT techniques (intensity modulated RT, deep inspirational breath hold, and so on) are aimed at minimizing (late) toxicity while maintaining treatment efficacy (24). In this trial we did not observe any unexpected acute toxicity, but the follow-up is still too short to evaluate long-term toxicity.

Early PET assessment is used in clinical trials to select patients who might benefit from chemotherapy alone. The initial results of the Cancer and Leukemia Group B/Alliance trial suggest that interim PET is a useful marker to limit the treatment to chemotherapy alone (ABVD) after negative interim PET findings; patients with positive interim PET findings might benefit from more intensive chemo-RT (26). In the EORTC/Lymphoma Study Association/Fondazione Italiana Linfomi H10 trial, experimental treatment driven by PET scan findings after 2 cycles of ABVD is compared with 3 cycles of ABVD and 30-Gy IFRT in early-stage disease without risk factors. In patients with negative PET scan findings after 2 cycles of ABVD, the risk of relapse is significantly increased when RT is omitted, but the overall outcome is excellent both after combined-modality treatment and after only chemotherapy (27). Similarly, the Randomised Phase III Trial to Determine the Role of FDG-PET Imaging in Clinical Stages IA/IIA Hodgkin's Disease shows that patients with nonbulky early-stage HL with negative PET findings after 3 cycles of ABVD have a good prognosis either with or without consolidation RT (28). The results of our experimental no-RT arm are consistent with the results of the EORTC/LYSA/FIL H10 trial and the RAPID trial. On the basis of our hypothesis on the 5-year relapse-free survival rate and the choice of the noninferiority margin, the null hypothesis that the no-RT arm is inferior to the 36-Gy arm could not be rejected. The GHSG HD16 trial is currently testing a strategy limited to ABVD alone in early-stage HL with negative PET findings after 2 cycles of chemotherapy (29).

In conclusion, in HL patients without risk factors in CR after chemotherapy (EBVP), the RT dose may be limited to 20 Gy without compromising disease control. Omitting RT in these patients, however, may jeopardize the treatment outcome.

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