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ABVD Alone versus Radiation-Based Therapy in Limited-Stage Hodgkin's Lymphoma

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ABSTRACT

BACKGROUND

Chemotherapy plus radiation treatment is effective in controlling stage IA or IIA nonbulky Hodgkin's lymphoma in 90% of patients but is associated with late treatment-related deaths. Chemotherapy alone may improve survival because it is associated with fewer late deaths.

METHODS

We randomly assigned 405 patients with previously untreated stage IA or IIA nonbulky Hodgkin's lymphoma to treatment with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) alone or to treatment with subtotal nodal radiation therapy, with or without ABVD therapy. Patients in the ABVD-only group, both those with a favorable risk profile and those with an unfavorable risk profile, received four to six cycles of ABVD. Among those assigned to subtotal nodal radiation therapy, patients who had a favorable risk profile received subtotal nodal radiation therapy alone and patients with an unfavorable risk profile received two cycles of ABVD plus subtotal nodal radiation therapy. The primary end point was 12-year overall survival.

RESULTS

The median length of follow-up was 11.3 years. At 12 years, the rate of overall survival was 94% among those receiving ABVD alone, as compared with 87% among those receiving subtotal nodal radiation therapy (hazard ratio for death with ABVD alone, 0.50; 95% confidence interval [CI], 0.25 to 0.99; $P=0.04$); the rates of freedom from disease progression were 87% and 92% in the two groups, respectively (hazard ratio for disease progression, 1.91; 95% CI, 0.99 to 3.69; $P=0.05$); and the rates of event-free survival were 85% and 80%, respectively (hazard ratio for event, 0.88; 95% CI, 0.54 to 1.43; $P=0.60$). Among the patients randomly assigned to ABVD alone, 6 patients died from Hodgkin's lymphoma or an early treatment complication and 6 died from another cause; among those receiving radiation therapy, 4 deaths were related to Hodgkin's lymphoma or early toxic effects from the treatment and 20 were related to another cause.

CONCLUSIONS

Among patients with Hodgkin's lymphoma, ABVD therapy alone, as compared with treatment that included subtotal nodal radiation therapy, was associated with a higher rate of overall survival owing to a lower rate of death from other causes. (Funded by the Canadian Cancer Society and the National Cancer Institute; HD.6 ClinicalTrials.gov number, NCT00002561.)

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TWENTY YEARS AGO, THE STANDARD strategy in the case of patients with stage IA or IIA nonbulky Hodgkin's lymphoma included staging by means of laparotomy and subtotal nodal radiation therapy.^{1,2} With this treatment, 70 to 80% of patients were cured, but they remained at risk for premature death from late radiation-induced adverse effects, including second cancers and cardiovascular disease.³⁻⁶ Subsequent clinical trials showed that combining radiation with chemotherapy eliminated the need for staging laparotomy, allowed for reduced doses and target volumes of radiation, and resulted in long-term control of the disease for 90% of the patients.⁷⁻¹¹ A current treatment standard for patients with low-risk stage IA or IIA nonbulky disease is the combination of two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) with 20 Gy of involved-field radiation therapy.¹¹ It is expected that long-term radiation-related risks will be reduced with this approach, but the magnitude of reduction is unclear.

Since ABVD alone is effective treatment for 65 to 70% of patients with stage III or IV Hodgkin's lymphoma^{12,13} and is not associated with the leukemogenic or gonadal toxic properties of the chemotherapy that was used previously, the role of ABVD therapy alone in treating patients with stage IA or IIA nonbulky Hodgkin's lymphoma is of interest. In 1994, we initiated the Hodgkin's Disease.6 (HD.6) trial to investigate whether ABVD therapy alone in these patients would lead to control of the disease similar to that achieved with radiation-based therapy but with fewer deaths due to late treatment effects and, therefore, improved long-term survival. We previously reported, after a median length of follow-up of 4.2 years, that the rate of freedom from disease progression was higher among patients assigned to radiation therapy than among those assigned to ABVD therapy alone; no difference in the rate of survival was detected.¹⁴ We now report the final analysis from this trial, which assessed the primary outcome — the rate of 12-year overall survival.

METHODS

STUDY OVERSIGHT

The HD.6 trial was a multicenter, nonblinded, randomized, controlled trial. Details of the evaluation of patients, the eligibility criteria, and the

design of the trial have been published previously¹⁴ and are also provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. The NCIC Clinical Trials Group designed and conducted the trial and analyzed the data. Patients were enrolled at centers of the NCIC Clinical Trials Group and at centers of the Eastern Cooperative Oncology Group. The process for randomization was concealed and was performed by means of a computer-generated random-number sequence that was held at the central office of the NCIC Clinical Trials Group in Kingston, Ontario. The study was approved by the research ethics board at each participating center, and written informed consent was obtained from all participants. The data were held and analyzed by the NCIC Clinical Trials Group. The independent data and safety monitoring committee of the NCIC Clinical Trials Group reviewed the details of the conduct of the trial at confidential meetings that were held every 6 months. The study chair (the first author) vouches for the integrity of the data, wrote the first draft of the manuscript, and prepared subsequent drafts with input from the coauthors. All the authors made the decision to submit the manuscript for publication. The study protocol, including a summary of amendments and the statistical analysis plan, is available at NEJM.org.

TREATMENT PROTOCOL

We randomly assigned patients with previously untreated stage IA or IIA nonbulky Hodgkin's lymphoma to receive treatment with ABVD alone or treatment that included subtotal nodal radiation therapy. Patients in the radiation-therapy group who had a favorable risk profile received subtotal nodal radiation therapy alone; patients with an unfavorable risk profile received two cycles of ABVD followed by subtotal nodal radiation therapy. The radiation target volumes included all supradiaphragmatic lymph-node regions (mantle field), the spleen, and paraaortic lymph nodes (see the Supplementary Appendix). Radiation therapy was administered by means of a linear accelerator to parallel opposed fields up to a midplane dose of 35 Gy in 20 daily fractions. Patients in the ABVD-only group, both those with a favorable risk profile and those with an unfavorable risk profile, received four cycles of ABVD, with restaging of the disease after two and four cycles of therapy. Restaging was performed by means

of computed tomographic scanning and optional gallium scanning. The treatment phase of the HD.6 trial preceded the use of positron-emission tomography (PET), and no patients underwent this type of scanning. Patients who had a complete remission or an unconfirmed complete remission¹⁵ after two treatment cycles received a total of four cycles of ABVD therapy; those who did not have a complete remission or an unconfirmed complete remission after their second cycle received six cycles. The ABVD regimen was administered according to standard dosing and scheduling.^{12,13} The treatment for progressive or recurrent Hodgkin's lymphoma was determined by each investigator and was not defined in the protocol. In the case of patients who had disease progression during treatment with ABVD alone, consideration of radiation therapy was recommended.

ASSESSMENT OF RESPONSE AND DEFINITION OF STUDY OUTCOMES

Responses to therapy were categorized according to the Cotswolds criteria.¹⁵ Patients underwent reevaluation 1 month after completing subtotal nodal radiation therapy (in the case of the radiation-therapy group) or ABVD (in the case of the ABVD-only group); 3 months, 6 months, and 12 months after that; and annually thereafter. The primary outcome, overall survival, was measured from the date of randomization until the date of death from any cause. In the assessment of the causes of death, deaths that occurred in patients with relapsed or progressive disease and deaths that were associated with an acute treatment-related toxic effect during the treatment period or as a result of subsequent therapy (e.g., stem-cell transplantation) were categorized as deaths due to Hodgkin's lymphoma. The attribution of the cause of death and the diagnoses of a second cancer or cardiac event were determined by the investigator, followed by a review, including a review of source data, by the central office of the NCIC Clinical Trials Group and resolution through query processes. Event-free survival was measured from the date of randomization until the date of disease progression or death from any cause; freedom from disease progression was measured from the date of randomization until the date of disease progression, with data from patients who died without evidence of progressive disease censored on the date of death.

STATISTICAL ANALYSIS

The life-table method of Kaplan and Meier¹⁶ was used to calculate the rates of freedom from disease progression, event-free survival, and overall survival, and between-group comparisons were performed with the use of the log-rank test,¹⁷ with stratification according to risk profile (favorable vs. unfavorable). All results are based on two-sided tests. We estimated that assuming a rate of 80% for 12-year survival in the radiation-therapy group, we would need to enroll 450 patients over the course of 7.5 years and follow the patients for an additional 7 years to observe 56 deaths; the study would then have 80% power to detect a 10% difference between the two groups, at a two-tailed alpha level of 0.05. We also estimated that if the rate of 12-year survival in the radiation-therapy group was 85%, the study would have 80% power to detect the same 10% improvement with the occurrence of 24 deaths. All primary analyses were performed on data from the modified intention-to-treat population, which excluded patients who were subsequently found to be ineligible on the basis of their prerandomization information. Secondary sensitivity analyses that included data from all the patients who underwent randomization were also performed. The analyses were performed with the use of SAS software, version 9.2 (SAS Institute).

PREMATURE CLOSURE OF THE TRIAL

The trial was initiated in January 1994 and was closed to enrollment in April 2002 after 405 patients had been enrolled. The premature closure was based on the availability of new data from a trial by the European Organization for Research and Treatment of Cancer, which showed excellent outcomes with combination therapy that included involved-field radiation therapy.⁸ On the basis of these data, we concluded that continuing the protocol therapy that included subtotal nodal radiation therapy would be inappropriate. In May 2003, the HD.6 trial committee requested permission to analyze the rates of freedom from disease progression, event-free survival, and overall survival with the assumption that these outcomes, assessed after a median follow-up period of almost 5 years, would inform treatment practices at that time. This request was reviewed by the executive body of the NCIC Clinical Trials Group, the clinical trials committee, and was approved. (Subsequently, it was the policy of the

Table 1. 12-Year Outcomes in Study Patients, According to Treatment Strategy.*

Cohort and 12-Yr Outcome	ABVD Alone	Radiation Therapy, with or without ABVD	Hazard Ratio with ABVD Alone (95% CI)	P Value
All patients				
Patients in cohort (no.)	196	203		
Rate of outcome (%)				
Overall survival	94	87	0.50 (0.25–0.99)	0.04
Freedom from disease progression	87	92	1.91 (0.99–3.69)	0.05
Event-free survival	85	80	0.88 (0.54–1.43)	0.60
Cohort with favorable risk profile				
Patients in cohort (no.)	59	64		
Rate of outcome (%)				
Overall survival	98	98	1.09 (0.07–17.40)	0.95
Freedom from disease progression	89	87	0.88 (0.31–2.55)	0.82
Event-free survival	89	86	0.78 (0.28–2.19)	0.64
Cohort with unfavorable risk profile				
Patients in cohort (no.)	137	139		
Rate of outcome (%)				
Overall survival	92	81	0.47 (0.23–0.97)	0.04
Freedom from disease progression	86	94	3.23 (1.28–8.13)	0.006
Event-free survival	83	78	0.91 (0.52–1.59)	0.74

* In the group that received treatment with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) alone, patients with a favorable risk profile and those with an unfavorable risk profile received four to six cycles of ABVD. In the group assigned to subtotal nodal radiation therapy, patients who had a favorable risk profile received subtotal nodal radiation therapy alone and patients with an unfavorable risk profile received two cycles of ABVD plus subtotal nodal radiation therapy. CI denotes confidence interval.

NCIC Clinical Trials Group that such requests be considered by the data and safety monitoring committee.) The results of these analyses were reported in December 2003¹⁸ and were published in 2005.¹⁴ The final analysis was not adjusted for these earlier analyses.

In March 2010, after 31 deaths had occurred, the trial committee determined that even with 5 additional years of follow-up, it was unlikely that 56 deaths would be observed. The committee therefore requested that the data and safety monitoring board consider permitting a final analysis with data on patient status as of December 31, 2010 (i.e., the clinical cutoff date). The estimated median duration of follow-up at that time would be 12 years. The data and safety monitoring board approved this request. The processes of data review and query resolution were completed, and the database was locked on July 15, 2011.

RESULTS

PATIENTS

A detailed description of the characteristics of the patients and of the treatments they received has been published previously¹⁴ and is also provided in the Supplementary Appendix. During the period from January 1994 through April 2002, we evaluated 405 patients; 6 patients (1%), 3 in each group, were subsequently considered to be ineligible on the basis of prerandomization data. A total of 180 of the 196 patients assigned to ABVD alone (92%) received the assigned therapy. Among the patients in the radiation-therapy group, 53 of the 64 patients in the cohort with a favorable risk profile (83%) and 125 of the 139 in the cohort with an unfavorable risk profile (90%) received the assigned therapy (see Fig. 2 in the Supplementary Appendix). The median duration of follow-up was 11.3 years. Included among the 399

eligible patients were 56 (14%) for whom the last date of follow-up preceded December 31, 2008; these patients were considered to have been lost to follow-up. There were no differences between the two groups in the distribution of follow-up time (see Table 3 in the Supplementary Appendix).

TREATMENT OUTCOMES

The treatment outcomes are shown in Table 1 and Figure 1. The rate of overall survival was higher among the patients in the ABVD-only group than among those in the radiation-therapy group (12-year estimates, 94% vs. 87%; hazard ratio for death with ABVD therapy, 0.50; 95% confidence interval [CI], 0.25 to 0.99; $P=0.04$). There was a lower rate of freedom from disease progression in the ABVD group than in the radiation-therapy group (12-year estimates, 87% vs. 92%; hazard ratio for disease progression, 1.91; 95% CI, 0.99 to 3.69; $P=0.05$); no significant differences were detected in the rate of event-free survival (12-year estimates, 85% vs. 80%; hazard ratio for event, 0.88; 95% CI, 0.54 to 1.43; $P=0.60$). Sensitivity analyses included an analysis of data from the true intention-to-treat population (i.e., all patients who underwent randomization) and an analysis that included data received between the clinical cutoff date and the date on which the database was locked; the results of both analyses were robust and yielded findings similar to those of the main analysis (see Tables 4 and 5 in the Supplementary Appendix).

Subset analyses were performed to evaluate the outcomes according to the risk profile (Table 1 and Fig. 2). Among patients with a favorable risk profile, no significant differences were detected, with respect to any outcome, between patients randomly assigned to subtotal nodal radiation therapy alone and those assigned to ABVD alone. In contrast, among patients with an unfavorable risk profile, the results were similar to those in the primary analysis. The rate of overall survival was higher among patients in the ABVD-only group than among the patients in the radiation-therapy group who received subtotal nodal radiation therapy plus ABVD (12-year estimates, 92% vs. 81%; hazard ratio for death with ABVD alone, 0.47; 95% CI, 0.23 to 0.97; $P=0.04$), whereas the rate of freedom from disease progression was lower in the ABVD-only group (12-year estimates, 86% vs. 94%; hazard ratio for disease

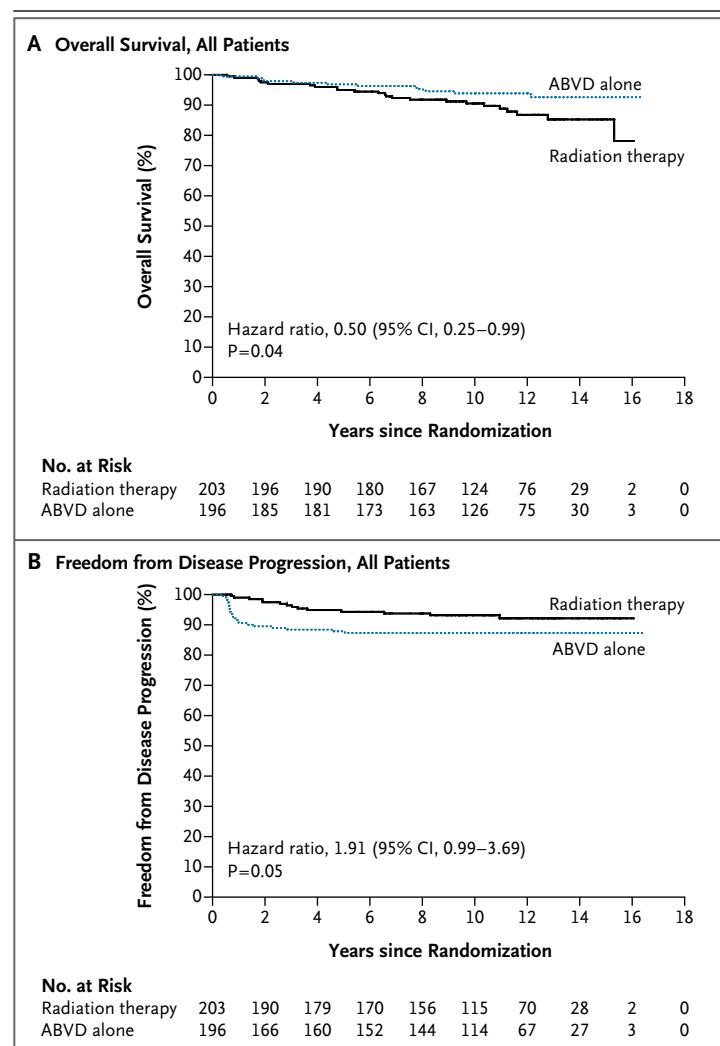


Figure 1. Kaplan-Meier Estimates of Overall Survival and Freedom from Disease Progression.

A total of 405 patients with stage IA or IIA nonbulky Hodgkin's lymphoma were randomly assigned to receive treatment with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) alone or to treatment that included subtotal nodal radiation therapy; 399 of the patients were included in the analyses. Among the 203 patients assigned to subtotal nodal radiation therapy, 64 had a favorable risk profile and received subtotal nodal radiation therapy alone and 139 had an unfavorable risk profile and received two cycles of ABVD plus subtotal nodal radiation therapy. At 12 years, the rate of overall survival (Panel A) was 94% among patients in the ABVD-only group and 87% among patients in the radiation-therapy group, and the rate of freedom from disease progression (Panel B) was 87% and 92% in the two groups, respectively.

progression, 3.23; 95% CI, 1.28 to 8.13; $P=0.006$); no significant between-group difference was seen in the rate of event-free survival (12-year estimates, 83% vs. 78%; hazard ratio for event, 0.91; 95% CI, 0.52 to 1.59; $P=0.74$).

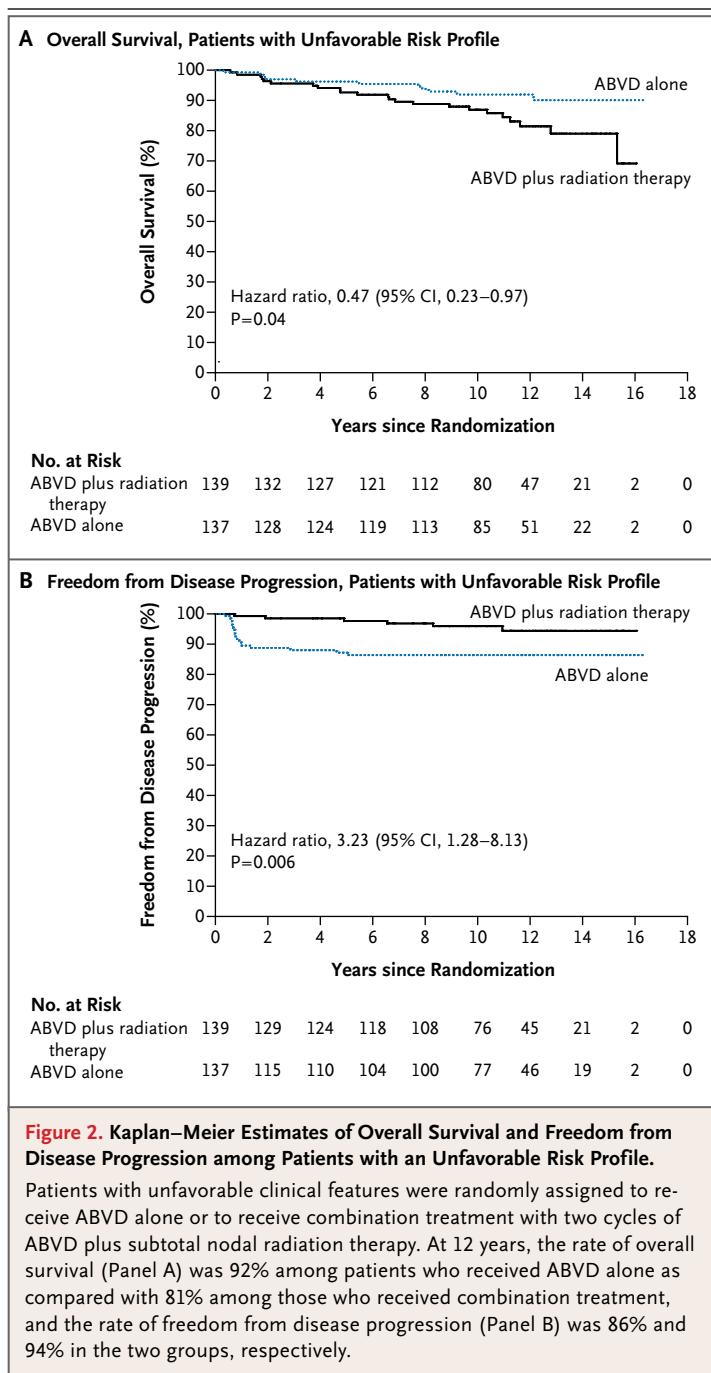


Figure 2. Kaplan-Meier Estimates of Overall Survival and Freedom from Disease Progression among Patients with an Unfavorable Risk Profile.

Patients with unfavorable clinical features were randomly assigned to receive ABVD alone or to receive combination treatment with two cycles of ABVD plus subtotal nodal radiation therapy. At 12 years, the rate of overall survival (Panel A) was 92% among patients who received ABVD alone as compared with 81% among those who received combination treatment, and the rate of freedom from disease progression (Panel B) was 86% and 94% in the two groups, respectively.

Subset analyses of the outcomes were performed with the patients within each group stratified according to risk profile. Among patients randomly assigned to ABVD alone, there was a nonsignificant trend toward a lower rate of overall survival among patients with an unfavorable risk profile than among those with a

favorable risk profile (12-year estimates, 92% vs. 98%; hazard ratio for death with an unfavorable risk profile, 4.96; 95% CI, 0.64 to 38.40; $P=0.09$), whereas no significant difference was seen in the rate of freedom from disease progression (12-year estimates, 86% vs. 89%; hazard ratio for disease progression, 1.28; 95% CI, 0.51 to 3.23; $P=0.60$). Among patients randomly assigned to the radiation-therapy group, the rate of freedom from disease progression was higher among patients with an unfavorable risk profile (i.e., patients who received subtotal nodal radiation therapy plus ABVD) than among patients with a favorable risk profile (i.e., patients who received subtotal nodal radiation therapy only) (12-year estimates, 94% vs. 87%; hazard ratio for disease progression with unfavorable risk profile, 0.35; 95% CI, 0.12 to 1.00; $P=0.04$); however, the rate of overall survival was lower in the group with an unfavorable risk profile (12-year estimates, 81% vs. 98%; hazard ratio for death, 11.54; 95% CI, 1.56 to 85.47; $P=0.002$).

Because the protocol requirements for patients assigned to ABVD alone included disease restaging after two treatment cycles, it was possible to evaluate the prognostic importance of complete remission or an unconfirmed complete remission at that time (see Fig. 5 in the Supplementary Appendix). Among the 196 eligible patients randomly assigned to ABVD alone, 19 (10%) could not be evaluated after two treatment cycles. The remaining 177 patients included 69 (39%) who had a complete remission or an unconfirmed complete remission after two treatment cycles and 108 (61%) who did not; the rate of freedom from disease progression was higher among those who had a complete remission or an unconfirmed complete remission after two cycles than among those who did not (12-year estimates, 94% vs. 81%; hazard ratio for disease progression, 0.28; 95% CI, 0.10 to 0.83; $P=0.02$), and there was also a trend toward a higher rate of overall survival (12-year estimates, 98% vs. 92%; hazard ratio for death, 0.17; 95% CI, 0.02 to 1.36; $P=0.06$).

CAUSES OF DEATH AND LATE TREATMENT EFFECTS

A total of 12 patients in the ABVD-only group died, as compared with 24 in the radiation-therapy group; the causes of death are shown in Table 2. In the radiation-therapy group as compared with the ABVD-only group, there were

Table 2. Causes of Death, According to Treatment Strategy and Risk Profile.

Cause of Death	ABVD Alone (N=196)			Radiation Therapy, with or without ABVD (N=203)		
	Total	Cohort with Favorable Risk Profile	Cohort with Unfavorable Risk Profile	Total	Cohort with Favorable Risk Profile	Cohort with Unfavorable Risk Profile
		number of patients				
Any	12	1	11	24	1	23
Hodgkin's lymphoma*	6	1	5	4	0	4
Second cancer	4	0	4	10	1	9
Cardiac event	2	0	2	2	0	2
Related to infection	0	0	0	3	0	3
Other†	0	0	0	5	0	5

* Deaths due to acute treatment-related protocol therapy or to therapy given for progressive Hodgkin's lymphoma were attributed to Hodgkin's lymphoma.

† Other causes of death included Alzheimer's disease, accidental drowning, suicide, and respiratory failure; the cause of one death was unknown.

more deaths due to second cancers (10 vs. 4) and more deaths from causes other than Hodgkin's lymphoma or second cancers (10 vs. 2). In addition, there were more patients in the radiation-therapy group than in the ABVD-only group who had second cancers (23 vs. 10) and who had cardiac events (26 vs. 16) (Table 3).

DISCUSSION

The strategy of treating patients who have stage IA or IIA nonbulky Hodgkin's lymphoma with chemotherapy alone is controversial.¹⁹⁻²¹ In four reports of randomized trials comparing ABVD or similar chemotherapy with combination therapy (chemotherapy plus radiation therapy), only the initial report of results from the HD.6 trial included a sample size that was large enough to detect a difference in control of the disease, and none of the reports showed a difference in the rate of survival.^{14,22-24} A recent meta-analysis that pooled the results of five trials in which chemotherapy regimens alone were compared with the same chemotherapy regimens (including the same number of treatment cycles) plus radiation therapy showed that the combination therapy was associated with both better disease control and a higher rate of survival.²⁵ However, in three of the trials, the chemotherapy that was used is considered to be inferior to ABVD, and the other two trials included patients with bulky or stage IIB or IIIA disease and thus were not confined to evaluating patients with stage IA or IIA nonbulky

disease. One published practice guideline recommends that ABVD alone is an option for patients with stage IA or IIA disease,²⁶ whereas another recommends against the use of ABVD alone for these patients.²⁷

Our results alter this debate. We found that the rate of long-term survival is higher with ABVD alone than with treatment that includes subtotal nodal radiation therapy, particularly when subtotal nodal radiation therapy is combined with two cycles of ABVD therapy. As postulated by the study hypothesis, the advantage that is seen with chemotherapy alone is due to the fact that there are fewer deaths from causes other than progressive Hodgkin's lymphoma or acute treatment-related toxic effects. Furthermore, we have addressed the question of whether chemotherapy alone has curative potential for these patients,¹⁹ since the rate of 12-year freedom from disease progression that we observed with ABVD alone was 87%. The major limitation associated with our results is that the subtotal nodal radiation therapy that was used in the radiation-therapy group is outdated, and the extent of radiation therapy is very likely to have contributed to the excess deaths. To place our results in the context of modern radiation-therapy practices, while recognizing the important risks of cross-trial comparisons, it is helpful to contrast our results with those in the groups with superior or noninferior outcomes in other randomized trials in which therapies for these patients were tested.^{10,11} We report 12-year outcomes af-

Table 3. Second Cancers and Cardiac Events, According to Treatment Strategy.

Event	ABVD Alone (N=196)	Radiation Therapy, with or without ABVD (N=203)
		number of patients
Second cancer*		
Any	10	23†
Bladder	0	2
Breast	1	1
Cervix	0	1
Colon	1	0
Leukemia or myelodysplastic syndrome	0	2
Esophagus	0	1
Head and neck	1	0
Lung	2	3
Lymphoma	3	3
Melanoma	0	4
Pancreas	1	0
Prostate	0	1
Rectum	1	2
Sarcoma	0	1
Unknown primary	0	2
Cardiac event		
Any	16	26‡
Death from cardiac causes	2	2
Coronary artery disease	12	15
Myocardial infarction	6	8
Coronary-artery bypass grafting	3	3
Coronary-artery stent insertion	3	2
Angina	0	2
Atrial fibrillation	1	3
Pericarditis or myocarditis	1	3
Valvular disease	0	1
Other	0	2§

* Basal-cell carcinomas were not included.

† A total of 19 second cancers occurred in patients who had an unfavorable risk profile and were assigned to combination therapy (radiation therapy plus ABVD); the 4 second cancers in the cohort with a favorable risk profile (who received radiation therapy only) included lymphoma (2), cervical cancer, and melanoma.

‡ A total of 25 cardiac events occurred in patients who had an unfavorable risk profile and were assigned to combination therapy (radiation therapy plus ABVD); 1 patient in the favorable risk cohort underwent coronary-artery bypass grafting.

§ Included are one case of peripheral vascular disease requiring bypass grafting and one case of new cardiomegaly.

later deaths among patients receiving radiation therapy are disproportionately associated with causes other than Hodgkin's lymphoma.

The enrollment period of the HD-6 trial overlapped with two practice-changing international trials. The H8-Favorable (H8F) trial (ClinicalTrials.gov number, NCT00379041) conducted by the European Organization for Research and Treatment of Cancer enrolled patients between 1993 and 1999 and established the strategy of combined chemotherapy–radiation therapy that included involved-field radiation therapy as a standard of care.⁸ These results were updated in 2007,¹⁰ and with a median follow-up period of 7.7 years, the projected 10-year results in the combination-therapy group show a rate of 97% for overall survival and a rate of 93% for event-free survival. Given the shorter duration of observed follow-up in that trial as compared with our trial, it is uncertain whether a full assessment of the rate of death from causes other than Hodgkin's lymphoma is possible.

The German Hodgkin Study Group¹¹ enrolled patients in the HD10 trial (NCT00265018) between 1998 and 2003 and, using a factorial design, compared two or four cycles of ABVD combined with 20 or 30 Gy of involved-field radiation therapy. Their results established two cycles of ABVD and 20 Gy of involved-field radiation therapy as a new standard of care, since this treatment was noninferior to the alternatives tested. With a median follow-up period of 7.5 years, the 8-year results associated with the group that received two cycles of ABVD and 20 Gy of involved-field radiation therapy showed that the rate of overall survival was 95% and the rate of both freedom from treatment failure and event-free survival was 86%; these results are virtually identical to the 12-year outcomes among patients in the ABVD-only group in our trial. Among 299 patients in the HD10 trial who were treated with two cycles of ABVD and 20 Gy of involved-field radiation therapy, there were 13 deaths, including 6 due to a second cancer or cardiovascular cause and 3 due to Hodgkin's lymphoma or an immediate complication of subsequent therapy. In addition, second cancers have developed in 14 patients, including 9 with solid tumors. These data suggest that an extended follow-up period is needed to better appreciate the risks that remain with less intensive radiation-therapy strategies. Since these results are not definitely superior to those we observed with ABVD therapy

ter a median follow-up of 11.3 years and speculate that longer follow-up data from all clinical trials evaluating patients with stage IA or IIA nonbulky Hodgkin's lymphoma will show that

alone, we conclude that treatment with ABVD therapy alone is a legitimate choice for patients with stage IA or IIA nonbulky Hodgkin's lymphoma. Furthermore, the excellent outcomes we observed in patients who had a complete remission or an unconfirmed complete remission after two cycles of ABVD gives credence to testing treatment strategies that are adapted on the basis of the initial response.²⁸ Potentially important predictive properties of PET scanning during the course of therapy have been seen in patients with stage III or IV Hodgkin's lymphoma²⁹ and are now being evaluated in patients with stage IA or IIA nonbulky disease.³⁰

The results of our trial have important implications for future clinical trials evaluating therapies for patients with stage IA or IIA nonbulky Hodgkin's lymphoma. Our results show that improving long-term survival is less dependent than previously assumed on further reducing deaths due to progressive Hodgkin's lymphoma and instead emphasize a need for treatments that will not lead to deaths from late treatment effects. Thus, trial end points should be redefined so that the importance of deaths from causes other than Hodgkin's lymphoma is captured. The end point of event-free survival, which considers events of disease progression as well as death, has similarities to a composite end point, and the use of this end point may dilute the importance of death and may breach a methodologic principle with respect to the use of composite end points, which requires that each component be of similar importance to patients³¹; the end point of freedom from disease progression does not account for death, which represents a far more important outcome, and our data show that it is no longer a reliable surrogate marker for

overall survival. Our trial also highlights the dilemma faced by investigators in evaluating overall survival as the primary end point in a clinical trial, since long-term follow-up is essential to understanding this outcome, and therapeutic advances will undoubtedly occur in the interim.

In summary, ABVD therapy alone, as compared with treatment that includes subtotal nodal radiation therapy, improves the rate of long-term overall survival in patients with stage IA or IIA nonbulky Hodgkin's lymphoma. Furthermore, the rates of 87% for 12-year freedom from disease progression and 94% for overall survival with ABVD alone suggest that this treatment can now more confidently be considered to be a therapeutic option for this population.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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