ORIGINAL ARTICLE

Results of a Trial of PET-Directed Therapy for Early-Stage Hodgkin's Lymphoma

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ABSTRACT

BACKGROUND

It is unclear whether patients with early-stage Hodgkin's lymphoma and negative findings on positron-emission tomography (PET) after three cycles of chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) require radiotherapy.

METHODS

Patients with newly diagnosed stage IA or stage IIA Hodgkin's lymphoma received three cycles of ABVD and then underwent PET scanning. Patients with negative PET findings were randomly assigned to receive involved-field radiotherapy or no further treatment; patients with positive PET findings received a fourth cycle of ABVD and radiotherapy. This trial assessing the noninferiority of no further treatment was designed to exclude a difference in the 3-year progression-free survival rate of 7 or more percentage points from the assumed 95% progression-free survival rate in the radiotherapy group.

RESULTS

A total of 602 patients (53.3% male; median age, 34 years) were recruited, and 571 patients underwent PET scanning. The PET findings were negative in 426 of these patients (74.6%), 420 of whom were randomly assigned to a study group (209 to the radiotherapy group and 211 to no further therapy). At a median of 60 months of follow-up, there had been 8 instances of disease progression in the radiotherapy group, and 8 patients had died (3 with disease progression, 1 of whom died from Hodgkin's lymphoma); there had been 20 instances of disease progression in the group with no further therapy, and 4 patients had died (2 with disease progression and none from Hodgkin's lymphoma). In the radiotherapy group, 5 of the deaths occurred in patients who received no radiotherapy. The 3-year progression-free survival rate was 94.6% (95% confidence interval [CI], 91.5 to 97.7) in the radiotherapy group and 90.8% (95% CI, 86.9 to 94.8) in the group that received no further therapy, with an absolute risk difference of –3.8 percentage points (95% CI, –8.8 to 1.3).

CONCLUSIONS

The results of this study did not show the noninferiority of the strategy of no further treatment after chemotherapy with regard to progression-free survival. Nevertheless, patients in this study with early-stage Hodgkin's lymphoma and negative PET findings after three cycles of ABVD had a very good prognosis either with or without consolidation radiotherapy. (Funded by Leukaemia and Lymphoma Research and others; RAPID ClinicalTrials.gov number, NCT00943423.)

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Long-term survival in early-stage Hodgkin's lymphoma was first made possible by the introduction of the mantle[1] and inverted Y[2] fields of radiotherapy in the 1960s. The addition of adjuvant mechlorethamine, vincristine, procarbazine, and prednisone (MOPP)–like chemotherapies improved progression-free survival rates,[3] but these chemotherapies were associated with severe emesis,[4] gonadal dysfunction,[5,6] and in rare cases, secondary leukemia.[7] Evidence of late toxic effects of mantle-field radiotherapy, such as hypothyroidism,[8] second cancers (especially of the breast[9] and lung[10]), and cardiovascular disease,[11,12] also emerged. Thus, it was increasingly apparent that cure was bought at a high price and that less damaging therapies were required. Studies were therefore performed to evaluate fewer cycles of less toxic chemotherapy combined with smaller fields or doses of radiotherapy[13,14]; as a result, for the treatment of patients with favorable prognostic features,[14,15] two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)[16,17] followed by 20 Gy of involved-field radiotherapy is now commonly used.[15]

In moving toward the goal of maximizing cure while minimizing toxic effects, greater individualization of therapy is appealing. Positron-emission tomography (PET) can be used to predict the prognosis in Hodgkin's lymphoma, with a high negative predictive value associated with early metabolic response.[18-20] Therefore, this technique might be useful in guiding a response-adapted approach in early-stage Hodgkin's lymphoma, whereby patients who have positive PET findings after chemotherapy receive radiotherapy but patients with negative PET findings undergo no further treatment. The late toxic effects of radiotherapy are avoided in patients cured by chemotherapy, and overall survival may be improved. Clearly, however, a response-adapted strategy leading to treatment de-escalation for some patients requires careful evaluation. Here, we report the results of a phase 3 trial to evaluate response-adapted therapy using PET in patients with early-stage Hodgkin's lymphoma (Randomised Phase III Trial to Determine the Role of FDG–PET Imaging in Clinical Stages IA/IIA Hodgkin's Disease [RAPID]). Our aim was to determine whether patients with clinical stage IA or stage IIA Hodgkin's lymphoma (i.e., one nodal site [stage IA] or two or more nodal sites on the same side of the diaphragm [stage IIA], with no night sweats, unexplained fever [temperature, ≥38°C], or weight loss of ≥10%[21]) and negative PET findings after three cycles of ABVD chemotherapy require consolidation radiotherapy to areas of previous involvement to delay or prevent disease progression.

Methods

Eligibility

Previously untreated male or female patients 16 to 75 years of age with histologically confirmed classic Hodgkin's lymphoma of clinical stage IA or IIA, as determined by means of clinical history and examination and computed tomographic (CT) scan of the thorax, abdomen, and pelvis, were eligible for trial entry. A baseline PET scan was not mandated and in most cases was not performed. Patients with mediastinal bulk (maximal mediastinal diameter ≥33% of the internal thoracic diameter at T5–T6) were not eligible. Written informed consent was obtained from all patients before trial entry.

Study Design

This is an ongoing randomized, controlled, noninferiority trial to determine whether there is an unacceptable increase in the relapse rate among patients with negative PET findings who are assigned to no further treatment, as compared with patients assigned to receive involved-field radiotherapy. After baseline staging, eligible and consenting patients received three cycles of standard ABVD chemotherapy.[17] A PET scan was then performed during the 2 weeks after day 15 of ABVD cycle 3, and images were transmitted to the core laboratory at St. Thomas' Hospital, King's College, London, for central review. Patients with negative PET findings were randomly assigned, in a 1:1 ratio, to receive 30 Gy of involved-field radiotherapy or no further treatment. Block randomization was performed at the Cancer Research UK and University College London Cancer Trials Centre; no stratification factors were used. Patients with positive PET findings received a fourth cycle of ABVD and involved-field radiotherapy. After completion of the assigned treatment, patients underwent routine clinical evaluation every 3 months in year 1, every 4 months in year 2, every 6 months in year 3, and annually thereafter. A CT scan was obtained at 6, 12, and 24 months, but beyond that there were no protocol-mandated CT scans.

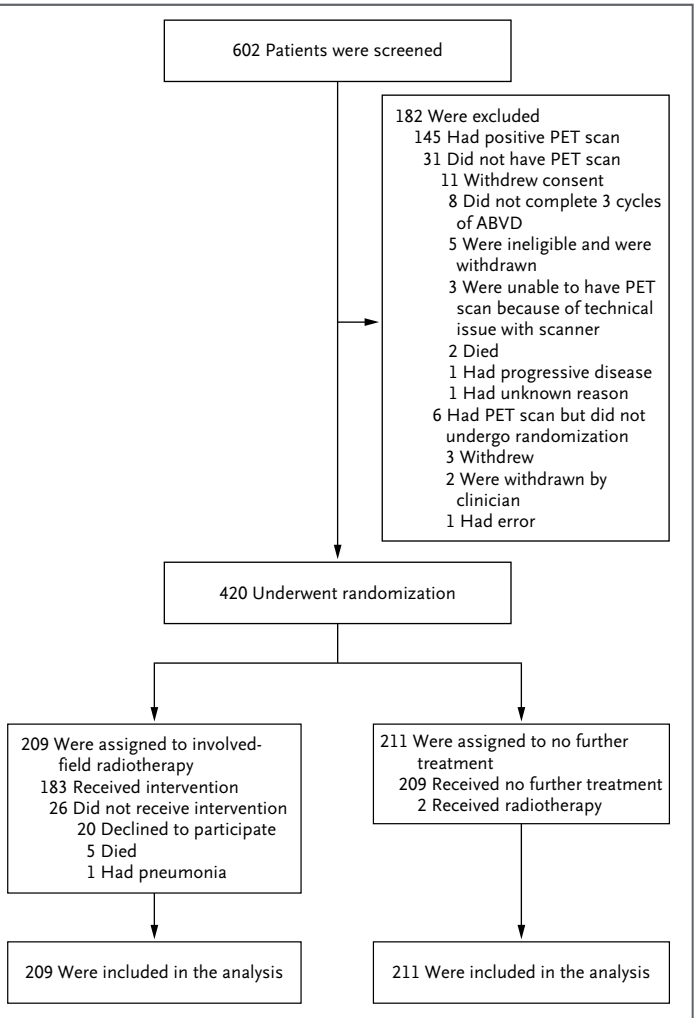


Figure 1. Screening and Randomization.

STUDY OVERSIGHT

The authors designed the study, and they vouch for the accuracy of the data and fidelity to the protocol, which is available with the full text of this article at NEJM.org. No commercial support was provided. No one who is not an author contributed to the writing of the manuscript.

PET SCANNING

PET scanning was performed on full-ring PET or PET–CT cameras at centers within the United Kingdom National Cancer Research Institute PET Research Network. As reported elsewhere,[22] centers complied with commonly agreed-on methods for quality control to ensure that the performance of imaging equipment, data transfer, and image quality were within an acceptable range that was prespecified by the core laboratory. Physicists from the core laboratory visited each PET center and scanned a standard plastic structure ("phantom") to check image quality and quantitative accuracy before starting the study.

Before undergoing scanning, patients fasted for 6 hours, after which 350 to 400 MBq of ^{18}F-fluorodeoxyglucose (FDG) was administered intravenously. Scans were acquired 60 minutes later from the skull vertex or base of the brain to the upper thighs. Images were deidentified and transferred to the core laboratory for reporting. Two experienced reporters independently scored the scans with the use of a 5-point scale to evaluate the degree of FDG uptake, if present, as well as the likelihood of residual disease. Any differences in opinion were resolved by consensus. Results were faxed to the trials unit, with a score of 1 or 2 regarded as indicating negative findings and a score of 3, 4, or 5 regarded as indicating positive findings. A conservative threshold was chosen to define negative PET findings, with uptake equivalent to or lower than uptake in the normal mediastinal blood pool regarded as indicating negative findings.[23]

STATISTICAL ANALYSIS

When this noninferiority trial was initiated in 2003, it was designed to have a 10-percentage-point noninferiority margin — that is, to exclude a difference in progression-free survival in the group receiving no further treatment of 10 or more percentage points from the assumed 3-year progression-free survival rate of 95% in the radiotherapy group. However, after a delegate survey at the 7th International Symposium on Hodgkin Lymphoma in 2007, the noninferiority margin was reduced to 7 percentage points. We calculated that 46 events of progression or death in total would be required for the study to have 90% power to exclude the 7-percentage-point difference, at a 5% significance level, and we estimated that 400 of 600 registered patients would have to undergo randomization for 46 events to occur. Because few events were seen in recent follow-up years, the independent data monitoring committee agreed that the trial could be reported before the target of 46 events was reached; initial results were reported at the American Society of Hematology meeting in December 2012 (database frozen in March 2012), and additional results are being re-

Table 1. Pretreatment Characteristics of the Patients.

Characteristic	Negative PET Findings		Positive PET Findings (N=145)
	Radiotherapy (N=209)	No Further Treatment (N=211)	
Age — yr			
Median	34	34	36
Range	16–74	16–75	18–75
Sex — no. (%)			
Male	103 (49.3)	107 (50.7)	96 (66.2)
Female	106 (50.7)	104 (49.3)	49 (33.8)
Ann Arbor stage — no. (%)*			
IA	69 (33.0)	70 (33.2)	48 (33.1)
IIA	140 (67.0)	141 (66.8)	97 (66.9)
Favorable pretreatment features — no./total no. (%)†			
EORTC criteria[14]	118/184 (64.1)	122/185 (65.9)	85/158 (53.8)
GHSG criteria[15,24]	114/175 (65.1)	136/184 (73.9)	97/153 (63.4)
No. of nodal sites — no./total no. (%)			
1	77/208 (37.0)	71/210 (33.8)	51/145 (35.2)
2	67/208 (32.2)	78/210 (37.1)	44/145 (30.3)
≥3	64/208 (30.8)	61/210 (29.0)	50/145 (34.5)
Nonmediastinal bulk present — no. (%)	2 (1.0)	1 (0.5)	3 (2.1)

* The Ann Arbor stages indicate one nodal site (stage IA) or two or more nodal sites on the same side of the diaphragm (stage IIA) with no B symptoms (i.e., night sweats, unexplained fever [temperature, ≥38°C], or weight loss of ≥10%).[21]

† Complete data for the calculation of prognostic scores were unavailable in some cases. Favorable features as defined with European Organisation for Research and Treatment of Cancer (EORTC) criteria include stage I or stage II disease with none of the following risk factors: large mediastinal mass, age ≥50 years, elevated erythrocyte sedimentation rate (ESR) (ESR ≥50 mm per hour in the absence of B symptoms or ≥30 mm per hour in the presence of B symptoms), and four or more involved nodal sites. Favorable features as defined with German Hodgkin Study Group (GHSG) criteria include stage I or stage II disease with none of the following risk factors: large mediastinal mass, extranodal disease, elevated ESR (ESR ≥50 mm per hour in the absence of B symptoms or ≥30 mm per hour in the presence of B symptoms), and three or more involved nodal sites.

ported here (database frozen in February 2014). Any additional events will occur after the 3-year time point and will not materially change the main result.

The Cox proportional-hazards model was used to calculate hazard ratios (hereafter referred to as rate ratios) and 95% confidence intervals. Survival curves were estimated with the use of the Kaplan–Meier method. Analysis of the primary end point (defined as the time from the date of randomization to first progression, relapse, or death, whichever occurred first) was performed on an intention-to-treat and per-protocol basis with the use of SAS software, version 9.3 (SAS Institute). Secondary end points include the incidence of PET scan positivity or negativity after three cycles of ABVD, overall survival time and cause of death, and incidence and type of second cancers.

RESULTS

PATIENTS

From October 2003 through August 2010, a total of 602 patients were enrolled in the trial at 94 centers in the United Kingdom. The median age was 34 years (range, 16 to 75), 321 patients (53.3%) were male, and 200 patients (33.2%) had stage IA disease.

PET SCANS

After three cycles of ABVD, 571 patients underwent PET scanning (Fig. 1). Central review of the

Table 2. Events of Disease Progression or Death.

Event	Negative PET Findings		Positive PET Findings (N=145)
	Radiotherapy (N=209)	No Further Treatment (N=211)	
	number of patients (percent)		
Alive without disease progression	193 (92.3)	187 (88.6)	127 (87.6)
Disease progression only	8 (3.8)	20 (9.5)	10 (6.9)
Died with disease progression	3 (1.4)	2 (0.9)	5 (3.4)
Died without disease progression	5 (2.4)	2 (0.9)	3 (2.1)

locally acquired images showed a PET score of 1 in 301 patients (52.7%), a score of 2 in 125 patients (21.9%), a score of 3 in 90 patients (15.8%), a score of 4 in 32 patients (5.6%), and a score of 5 in 23 patients (4.0%). Overall, 426 patients (74.6%) had negative PET findings (a score of 1 or 2), and 145 patients (25.4%) had positive PET findings (a score of 3, 4, or 5). Pretreatment characteristics of the patients with negative findings and those with positive findings are summarized in Table 1.

RANDOMIZATION OF PATIENTS WITH NEGATIVE PET FINDINGS

A total of 420 (98.6%) of the 426 patients with negative PET findings underwent randomization, with 209 patients randomly assigned to the radiotherapy group and 211 randomly assigned to the group with no further therapy. A total of 6 patients did not undergo randomization, because of patient choice in 3 cases, physician choice in 2 cases, and an error in 1 case. Of the 209 patients assigned to the radiotherapy group, 26 did not receive this treatment: 20 declined after having been told the outcome of randomization, 5 had died, and 1 had pneumonia.

OUTCOMES IN THE GROUP WITH NEGATIVE PET FINDINGS

At a median of 60 months of follow-up after randomization and more than 36 months after the last patient underwent randomization, 40 events (disease progression or death) had occurred. Overall, 380 patients (90.5%) among the 420 who underwent randomization were alive without disease progression (193 of 209 patients [92.3%] in the radiotherapy group and 187 of 211 patients [88.6%] in the group with no further therapy). There had been 28 episodes of disease progression (8 of 209 [3.8%] in the radiotherapy group and 20 of 211 [9.5%] in the group with no further therapy), 5 deaths after disease progression (3 of 209 [1.4%] in the radiotherapy group and 2 of 211 [0.9%] in the group with no further therapy), and 7 deaths without disease progression (5 of 209 [2.4%] in the radiotherapy group and 2 of 211 [0.9%] in the group with no further therapy). The distributions of events and causes of death are summarized in Tables 2 and 3; 1 patient in the radiotherapy group died from Hodgkin's lymphoma.

We performed an intention-to-treat analysis that included the 420 patients who underwent randomization (Fig. 2A). The 3-year progression-free survival rate was 94.6% (95% confidence interval [CI], 91.5 to 97.7) in the radiotherapy group and 90.8% (95% CI, 86.9 to 94.8) in the group with no further therapy. The rate ratio for progression-free survival was 1.57 (95% CI, 0.84 to 2.97) in favor of radiotherapy (P=0.16); the 3-year absolute risk difference was −3.8 percentage points (95% CI, −8.8 to 1.3). The 3-year overall survival rate was 97.1% (95% CI, 94.8 to 99.4) in the radiotherapy group and 99.0% (95% CI, 97.6 to 100) in the group with no further therapy, with a nonsignificant rate ratio of 0.51 (95% CI, 0.15 to 1.68) in favor of no further therapy (P=0.27) (Fig. 3).

Subsequently, a per-protocol analysis involving 392 patients was performed (Fig. 2B). This analysis did not include 28 patients from the intention-to-treat analysis — 26 from the radiotherapy group who had not received radiotherapy (20 patients had declined this treatment, 5 had died, and 1 had pneumonia) and 2 from the

Table 3. Causes of Death.

PET Status, Sex, and Age at Registration	Time from End of Therapy to Death	Cause of Death
Negative PET findings, radiotherapy group		
Male, 71 yr*	3 wk	Pneumonia
Male, 70 yr*†	4 wk	Pneumonitis
Male, 62 yr*	7 wk	Cerebral hemorrhage
Female, 73 yr*†	9 wk	Pneumonitis
Male, 61 yr*‡	4 mo	Angioimmunoblastic T-cell lymphoma
Male, 28 yr§	20 mo	Myocardial fibrosis and heart failure
Female, 74 yr	54 mo	Hodgkin's lymphoma
Male, 67 yr	60 mo	Mycosis fungoides
Negative PET findings, group with no further treatment		
Female, 75 yr	3 wk	Bronchopneumonia
Female, 64 yr	31 mo	Small-cell carcinoma of lung
Male, 64 yr	60 mo	Diffuse large-B-cell lymphoma
Male, 51 yr	69 mo	Mantle-cell lymphoma
Positive PET findings		
Female, 60 yr	4 wk	Pneumonia
Male, 57 yr	10 mo	Pneumonia
Male, 55 yr	14 mo	Hodgkin's lymphoma
Male, 59 yr	19 mo	Hodgkin's lymphoma
Male, 46 yr	24 mo	Hodgkin's lymphoma
Male, 27 yr	25 mo	Diffuse large-B-cell lymphoma
Male, 74 yr	28 mo	Hodgkin's lymphoma
Male, 32 yr	64 mo	Meningitis

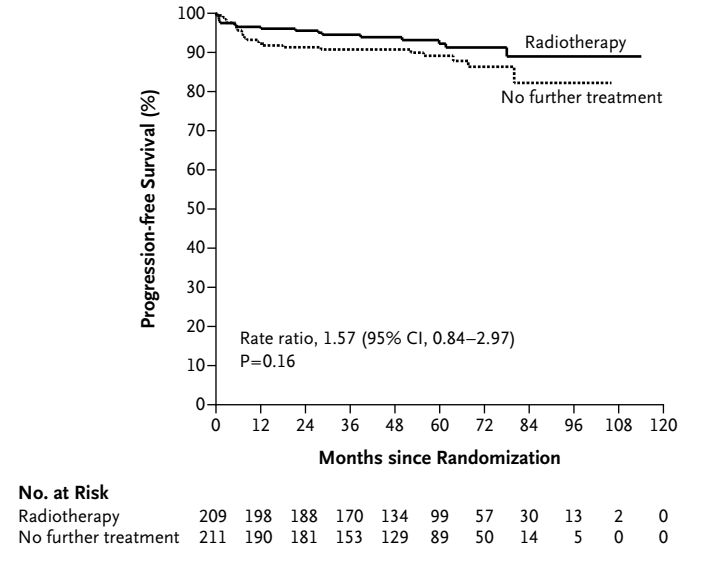
* Although randomly assigned to the radiotherapy group, this patient did not receive radiotherapy.
† The pneumonitis in this patient was probably caused by the bleomycin component of ABVD.
‡ After re-review of the histologic data at the time of recurrence, this patient was determined to have had angioimmunoblastic T-cell lymphoma at trial entry.
§ This patient had received a field of radiotherapy incorporating the heart.

group with no further therapy who had received radiotherapy. On a per-protocol basis, the 3-year progression-free survival rate was 97.1% (95% CI, 94.7 to 99.6) in the radiotherapy group and 90.8% (95% CI, 86.8 to 94.7) in the group with no further therapy, with a rate ratio of 2.36 (95% CI, 1.13 to 4.95) in favor of radiotherapy ($P=0.02$).

Second-line treatment is summarized in Table S1 in the Supplementary Appendix, available at NEJM.org. Among patients in the group with negative PET findings who received second-line treatment for recurrent Hodgkin's lymphoma, 5 of 10 (50.0%) in the radiotherapy group and 7 of 22 (31.8%) in the group with no further therapy received high-dose chemotherapy and subsequently underwent autologous stem-cell transplantation.

OUTCOMES IN THE GROUP WITH POSITIVE PET FINDINGS

At a median of 62 months of follow-up after enrollment among all patients who underwent randomization and all patients with positive PET findings (565 patients in total), 127 of the 145 patients (87.6%) in the group with positive PET findings were alive without disease progression (Fig. S1 in the Supplementary Appendix). There had been 18 events in this group; 10 events of



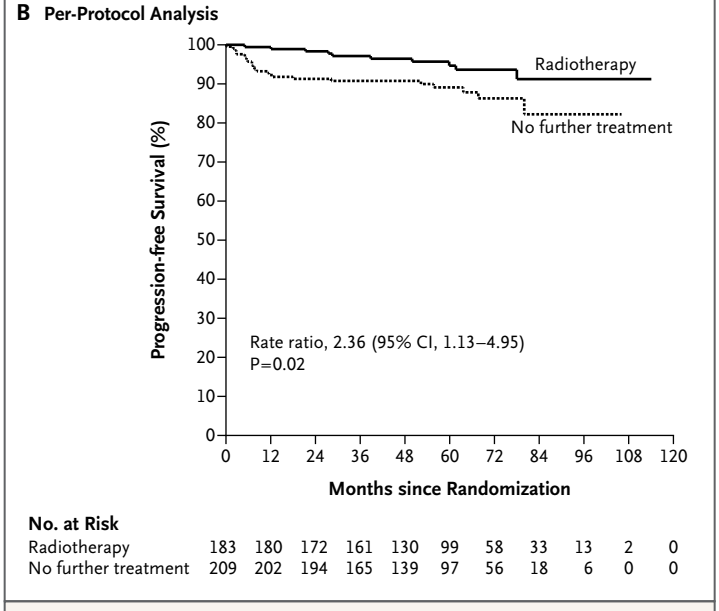


Figure 2. Kaplan–Meier Plots of Progression-free Survival.

Included are data from patients with negative positron-emission tomography (PET) findings who underwent randomization. The intention-to-treat analysis included 420 patients, and the per-protocol analysis included 392 patients.

disease progression (6.9% of the patients), 5 deaths with disease progression (3.4% of the patients), and 3 deaths without disease progression (2.1% of the patients) (Table 2). A total of 8 of the 14 patients (57.1%) in this group who received second-line treatment underwent transplantation (7 patients underwent autologous transplantation, and 1 underwent allogeneic transplantation) (Table S1 in the Supplementary Appendix).

DISCUSSION

RAPID was designed to determine whether patients with clinical stage IA or stage IIA Hodgkin's lymphoma and negative PET findings after three cycles of ABVD require consolidation radiotherapy. If not, the number of patients receiving radiotherapy could be reduced, and the late toxic effects of this therapy could be avoided for patients cured by chemotherapy alone. Chemotherapy alone has previously been compared with combined chemotherapy and radiotherapy in a trial conducted by the National Cancer Institute of Canada Clinical Trials Group and Eastern Cooperative Oncology Group. Initial disease control was superior in the group receiving combination therapy,[25] but after longer follow-up, survival was better among patients treated with chemotherapy alone.[26] That study has been criticized for using wide-field radiotherapy, but it highlighted the importance of analyzing survival after an appropriate follow-up period in studies of curable cancers in which the treatment itself may have a negative effect on this end point.[26,27]

In the study-design phase of RAPID, it was acknowledged that progression-free survival in the group with no further therapy was likely to be lower than that in the radiotherapy group because the negative predictive value of PET, although high, is less than 100%.[28] This was judged to be acceptable, as long as the reduction in disease control was not excessive, because of the likely benefits in overall survival that would result from a lower incidence of second cancers and cardiovascular disease in association with exposing fewer patients to radiation. Whether –7 percentage points is an appropriate margin of noninferiority is a value judgment, but it represents an attempt to balance the effects of treatment on disease control and late toxic effects.

Our results show that when quality-assured PET-image acquisition and central review are used, patients with nonbulky stage IA or stage IIA Hodgkin's lymphoma and negative PET findings after three cycles of ABVD have an excellent prognosis without further treatment (3-year progression-free and overall survival rates of 90.8% and 99.0%, respectively). Patients in the radiotherapy group had 3-year progression-free and overall survival rates

of 94.6% and 97.1%, respectively, with nonsignificant rate ratios for the radiotherapy group as compared with the group receiving no further therapy of 1.57 (95% CI, 0.84 to 2.97; P=0.16) and 0.51 (95% CI, 0.15 to 1.68; P=0.27), respectively. It is important to note that the lower limit of the 95% confidence interval for the absolute risk difference (–3.8 percentage points; 95% CI, –8.8 to 1.3) exceeds the designated noninferiority margin of –7 percentage points, with only 40 of the required 46 events observed despite the fact that it has been 3 years since the last patient underwent randomization.

Of the eight deaths in the radiotherapy group, three (due to Hodgkin's lymphoma, heart failure, and second cancer) occurred in patients who had actually received radiotherapy. The other five deaths in the radiotherapy group occurred in patients who had been assigned to the radiotherapy group but had not received radiotherapy. This included one death from T-cell lymphoma in which re-review of the patient's diagnostic biopsy results revealed that this condition rather than Hodgkin's lymphoma was present at trial entry (i.e., the patient was enrolled in error). The remaining four deaths were due to pneumonitis (two), pneumonia (one), and cerebral hemorrhage (one), and it seems likely that chemotherapy was implicated in at least three of these cases. No deaths from Hodgkin's lymphoma have so far been observed in the group with negative PET findings who were randomly assigned to no further therapy.

The per-protocol analysis showed virtually no difference from the intention-to-treat analysis in terms of the 3-year progression-free survival rate in the group with no further therapy (90.8%; 95% CI, 86.8 to 94.7), because only 2 patients randomly assigned to no further therapy received radiotherapy. However, the per-protocol analysis showed a greater 3-year progression-free survival rate than the intention-to-treat analysis in the radiotherapy group — 97.1% (95% CI, 94.7 to 99.6), with a rate ratio of 2.36 (95% CI, 1.13 to 4.95; P=0.02) — because 26 patients did not receive the assigned radiotherapy and 6 events occurred among those patients.

These results, 3 years after the last patient with negative PET findings underwent randomization, show that a modest improvement in the 3-year progression-free survival rate (3.8 percentage points in the intention-to-treat analysis and 6.3 percentage points in the per-protocol analysis) can be obtained with the addition of radiotherapy. However, this effect is bought at the expense of exposing all patients to radiation, most of whom will not benefit and some of whom will be harmed. In fact, for patients cured with chemotherapy, the addition of radiotherapy can only contribute additional toxic effects. Among the 46 patients requiring second-line therapy, 32% of those in the group with no further therapy, 50% in the radiotherapy group, and 57% in the group with positive PET findings underwent transplantation; this provides reassurance that recurrence of Hodgkin's lymphoma in the group with no further therapy was not associated with excessive use of intensive treatment approaches.

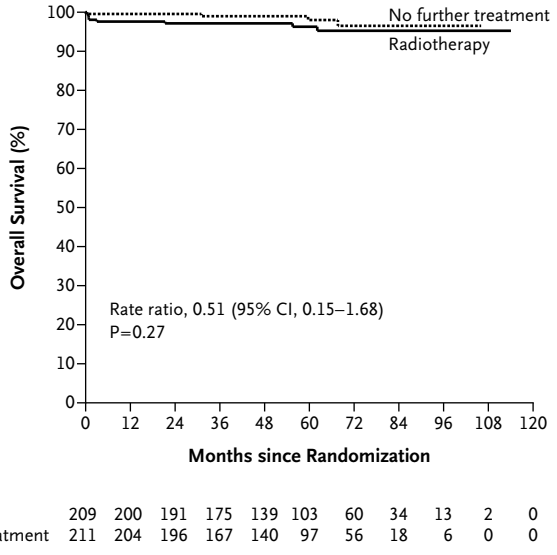


Figure 3. Kaplan–Meier Plot of Overall Survival.
Included are data from patients with negative PET findings who underwent randomization and were included in the intention-to-treat analysis (420 patients).

On the basis of a maximum allowable difference of 7 percentage points, this study did not show noninferiority of the strategy of no further treatment; although the measured difference was 3.8 percentage points, the 95% confidence interval included a possible difference of up to 8.8 percentage points. Nevertheless, the results of RAPID suggest a rationale for taking a more individualized approach to the treatment of early-stage Hodgkin's lymphoma.

The European Organisation for Research and Treatment of Cancer (EORTC) and Lymphoma

Study Association (LYSA) H10 trial[29] has also investigated a PET-based response-adapted approach in stage IA and stage IIA Hodgkin's lymphoma. Patients with favorable or unfavorable pretreatment characteristics (the favorable subgroup and unfavorable subgroup, respectively) were randomly assigned to receive either standard treatment (ABVD plus involved-node radiotherapy) or treatment based on PET findings after two cycles of ABVD. In the PET-directed group, patients with negative PET findings after two cycles of ABVD received an additional two (favorable subgroup) or four (unfavorable subgroup) cycles, and the patients with positive PET findings after the initial two cycles of ABVD received escalated therapy with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP)[30,31] plus radiotherapy. An interim analysis performed after a median of 1.1 years of follow-up showed that in the favorable subgroup with negative PET findings, the 1-year progression-free survival rate was 100.0% in the ABVD plus radiotherapy group and 94.9% in the ABVD-only group (hazard ratio for progression-free survival, 9.36; P=0.026). In the unfavorable subgroup, the corresponding 1-year progression-free survival rates were 97.3% and 94.7% (hazard ratio, 2.42; P=0.026). On the basis of the statistical design, the authors determined that the chemotherapy-only treatment for patients with negative PET findings should be halted early for futility. It can be argued, however, that the H10 and RAPID trials show similar results: radiotherapy after initial chemotherapy marginally improves the progression-free survival rate, as compared with chemotherapy alone, but at the expense of exposing to radiation all patients with negative PET findings, most of whom are already cured.

In stage IA and stage IIA Hodgkin's lymphoma with no mediastinal bulk, patients with negative PET findings after three cycles of ABVD have a very good prognosis either with or without consolidation radiotherapy. Although the noninferiority margin was exceeded in this study, the results suggest that radiotherapy can be avoided for patients with negative PET findings. A longer follow-up period is required to determine whether the response-adapted approach used in RAPID leads to fewer second cancers, less cardiovascular disease, and improved overall survival, as compared with a strategy incorporating radiotherapy for all patients.

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