Influence of More Extensive Radiotherapy and Adjuvant Chemotherapy on Long-Term Outcome of Early-Stage Hodgkin's Disease: A Meta-Analysis of 23 Randomized Trials Involving 3,888 Patients

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Purpose: **To assess the effect of more extensive radiotherapy and of adjuvant combination chemotherapy on long-term outcome of early-stage Hodgkin's disease.**

Methods: **In a collaborative worldwide systematic overview, individual patient data were centrally reviewed on 1,974 patients in eight randomized trials of more versus less extensive radiotherapy and on 1,688 patients in 13 trials of radiotherapy plus chemotherapy versus radiotherapy alone. Crude mortality data on 226 patients in two other trials of chemotherapy were also reviewed.**

Results: **More extensive radiotherapy reduced the risk of treatment failure (resistant or recurrent disease) at 10 years by more than one third (31.3% *v* 43.4% failures; $P < .00001$), but there was no apparent improvement in overall 10-year survival (77.1% *v* 77.0% alive). The addition of chemotherapy to radiotherapy halved the 10-year risk of failure (15.8% *v* 32.7%; $P < .00001$), with a small, nonsignificant improvement in survival (79.4% *v* 76.5% alive). This involved a reduction of borderline significance for deaths from Hodgkin's disease (12.3% *v* 15.4% dead at 10 years; $P = .07$), which was partly counterbalanced by a nonsignificant excess of deaths from other causes (12.4% *v* 10.0% 10-year risk).**

Conclusion: **More extensive radiotherapy fields or the addition of chemotherapy to radiotherapy in the initial treatment of early-stage Hodgkin's disease had a large effect on disease control, but only a small effect on overall survival. Recurrences could be prevented by more extensive radiotherapy or by additional chemotherapy. However, if chemotherapy had not been given initially, recurrences were generally salvageable by re-treatment with chemotherapy. Hence, less intensive primary treatment—particularly a reduction in radiotherapy fields—appears to achieve similar survival rates as more intensive treatment, although more randomized evidence is needed to confirm this.**

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HODGKIN'S DISEASE is highly sensitive both to radiotherapy and to combination chemotherapy, and most patients with early-stage disease are cured whether treated initially with either or with both treatment modalities. Traditionally, early-stage disease has been treated with radiotherapy, and as radiotherapy techniques have improved, treatment fields have become more extensive. Several randomized trials have compared more versus less extensive radiotherapy[1-10]—in the absence and presence of chemotherapy—and some reported significantly fewer recurrences with more extensive treatment fields. Still, a substantial proportion of patients with early-stage Hodgkin's disease will recur, despite an apparently complete response to radiotherapy.

With the advent of effective modern multiagent chemotherapy, adjuvant chemotherapy has also been tested. Several of the randomized trials of radiotherapy plus adjuvant chemotherapy versus radiotherapy alone[11-22] reported significantly fewer recurrences with adjuvant combination chemotherapy, although none has reported better survival.

Because of the success of salvage chemotherapy for recurrence after radiotherapy, any reduction in mortality that may be produced by more extensive radiotherapy or by adjuvant chemotherapy is likely to be far less extreme, and hence more difficult to assess reliably, than the reduction in the risk of recurrence. However, even a moderate improvement in survival would be important, especially since many of the patients with Hodgkin's disease are young. On the other hand, both treatment modalities carry risks of serious long-term side effects.

To assess reliably any effects on cause-specific or overall survival, a much larger number of patients is needed than has hitherto been entered onto any single trial. We therefore undertook a systematic overview (meta-analysis) of individual patient data from all randomized trials worldwide of

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more versus less extensive radiotherapy, and of radiotherapy plus adjuvant chemotherapy versus radiotherapy alone.

Meta-analyses are particularly helpful in two main respects. First, since far more patients are involved in a meta-analysis than in a single trial, random errors are smaller. Second, if many trials address related questions, then by chance alone some are likely to appear misleadingly promising, while others appear misleadingly unpromising. Emphasis on just the more promising (or just the less promising) results could be substantially misleading, especially since not all trials are published and those that are may tend to be those with more striking results. By seeking all relevant trials, published or unpublished, meta-analyses can give a more accurate and balanced view of the randomized evidence.

METHODS

Collaboration was sought between the coordinators of all randomized trials of the treatment of early-stage Hodgkin's disease in which more extensive radiotherapy was compared with less extensive radiotherapy or in which combination chemotherapy plus radiotherapy was compared with radiotherapy alone. All of the more versus less radiotherapy trials were unconfounded in that the two arms differed only with regard to the size of the radiation fields, with any additional chemotherapy being the same in both arms. However, some of the trials of chemotherapy plus radiotherapy versus radiotherapy alone were confounded, in the sense that more extensive radiotherapy was given to patients who did not receive adjuvant chemotherapy than to patients who did.

Most trials included only stage I and/or stage II patients, but a few stage III patients were randomized into some studies, and these, as well as any randomized patients who were eventually reclassified as having been ineligible, are included in the present overview. Trials were identified from computer searches of medical literature data bases and the National Cancer Institute (NCI) CLINPROT trial protocol data base; from lists prepared by the Union International Contre le Cancer (UICC); the United States NCI; and the United Kingdom Coordinating Committee on Cancer Research (UKCCCR); as well as from abstracts presented at meetings; from the reference lists of published trials and review articles; and from discussions with investigators. We included only trials from Western Europe and North America, as we were unable to contact the investigators of the only two apparently relevant trials identified from elsewhere (Obminsk[22] and Moscow[23]). Trials were included only if they were believed to have been randomized in a manner that precluded prior knowledge of the next treatment assigned. All patients were evaluated according to the treatment assigned to them at randomization (ie, intention-to-treat analysis).

We originally requested only tabular data on overall mortality from each study. However, it became apparent that proper interpretation of the meta-analysis would require individual patient data, rather than tabular data, and information not just on overall mortality, but also on cause-specific mortality and recurrence. These extra data have now been obtained for most studies. Trialists were asked to provide information on the age, stage, date of entry, treatment allocation, date of recurrence, and date and cause of death, or date last seen, for each patient randomized in the trial. There was no consistent record of bulk of disease across trials, so this was not requested. Each study is given a unique trial number (eg, 69C, 77B) with the first two digits indicating the year patient entry began. Trials are split into distinct parts whenever the treatment comparison differed. For example, $70C_1$ and $70C_2$ have different randomizations for different risk groups and the intergroup $75B_1$ and $75B_2$ study had two different randomization options. Data sets were compared with published figures and were checked for completeness, for internal consistency, for balance of group sizes overall and of prognostic subgroups, and for other indications of possible errors in the conduct of the trial or the submission of data. Errors and omissions were rectified by correspondence with the relevant investigators. For the few eligible trials that did not provide individual patient data for this report, crude mortality data from the investigators or from published data have been used wherever possible. As a final check, the manuscript of this report has been circulated to those whose trial results it contains and revised in the light of their comments.

Statistical Methods

Statistical methods have been described in detail by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG).[24-26] Briefly, log-rank analyses are used to estimate the effects of treatment on the annual odds of failure and death, with failure defined as death without remission or recurrence after remission. Patients who died of causes other than Hodgkin's disease with no reported recurrence are censored at that point in analyses of failure. All other deaths are described as Hodgkin's disease deaths. In analyses of Hodgkin's disease deaths, the statistical conventions used to avoid bias are as in the EBCTCG overview of radiotherapy trials,[26] and involve log-rank subtraction. This method of analysis of cause-specific mortality is necessary to avoid bias, but does somewhat dilute any real effect on Hodgkin's disease mortality by including some deaths from other causes after recurrence in this category.

For each trial, the total number of deaths (or failures) observed (O) among patients assigned to treatment was compared with the number expected (E) to occur in each year of follow-up if, in that year, the probability of death (or of failure) was unrelated to treatment. The log-rank difference (observed minus expected [O − E]) is negative if the treatment group fared better than the control group. The variance (V) of O − E is calculated according to standard methods and summated for each year to estimate the effect of treatment on the annual odds of failure or death.[24] Where separate data for each year of follow-up were not available, O − E and V were calculated from the crude total number of deaths in each group.

From this log-rank (O − E) and its variance can be calculated the odds ratio for that trial and its 99% confidence interval.[24,25] Information from different trials is then combined by summing the separate O − E values, one per trial. (The variance of this grand total is simply the sum of the separate variances.) Use of this grand total ensures that patients within one trial are directly compared only with other patients in that same trial, and not with those in other trials. Finally, the grand total and its variance are used not only to calculate a statistical significance test, but also to calculate an overall odds ratio and its 95% confidence interval and to help calculate descriptive survival curves.[24,25]

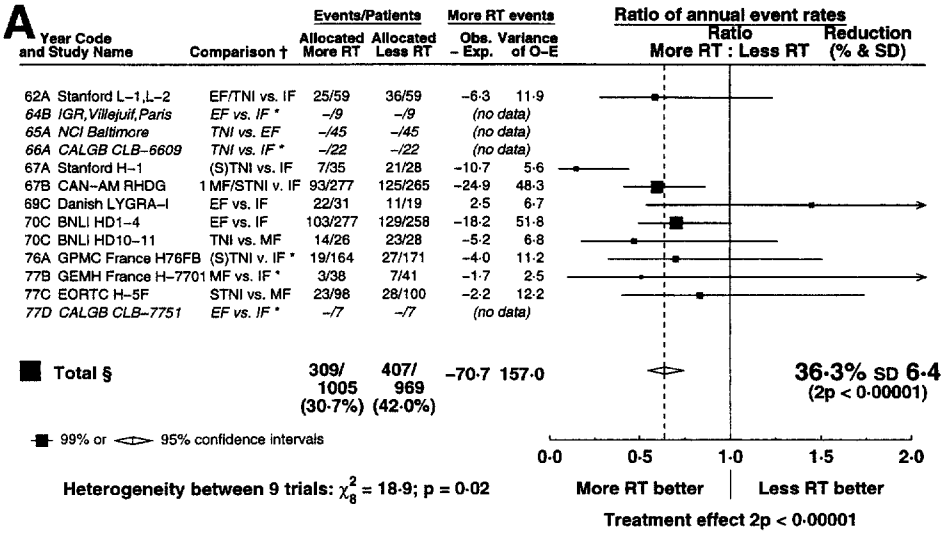
RESULTS

Trials of More Versus Less Extensive Radiotherapy

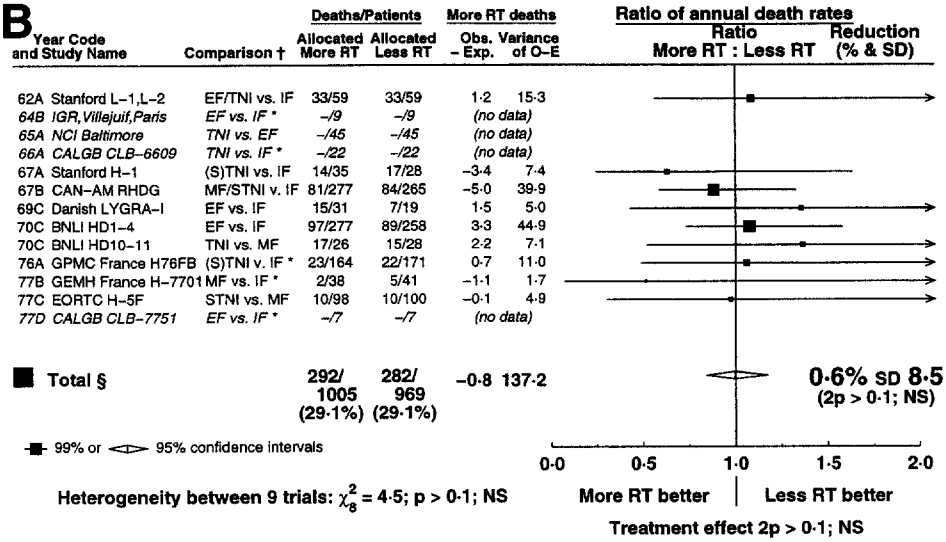
Full individual patient data, on almost 2,000 patients, are available from eight of the 12 trials of more versus less extensive radiotherapy (Appendix 2A). The four remaining trials randomized in total fewer than 200 patients, and so

recently updated individual patient data are available on some 90% of all patients ever randomized into such trials.

Time to failure. Figure 1A shows treatment comparisons and results of analyses of time to failure (ie, recurrence or death from refractory disease) for each of these eight trials (one of which, 70C, is in two parts) along with the overall estimate of the effect of more extensive radiotherapy in all eight trials combined. In seven of the eight trials, the black square is to the left of the solid line, indicating a reduction in the risk of failure in the more extensive radiotherapy arm. In two of the trials (67A and 67B), the confidence limits for the odds reduction do not overlap the solid vertical line, ie, there is a statistically significant ($P < .01$) improvement in risk of recurrence in the more extensive radiotherapy arm, but in the other trials, the results are less definite ($P > .01$). However, the combined result of all eight trials shows an overall reduction in the risk of failure of approximately one third (36.3% ± 6.4% [SD]), which is highly significant ($P < .00001$). The confidence limits for the reduction in the risk of recurrence in the more extensive radiotherapy arm range from 25% to 45%. Figure 2A shows life-table estimates of the risk of failure for these patients. Most

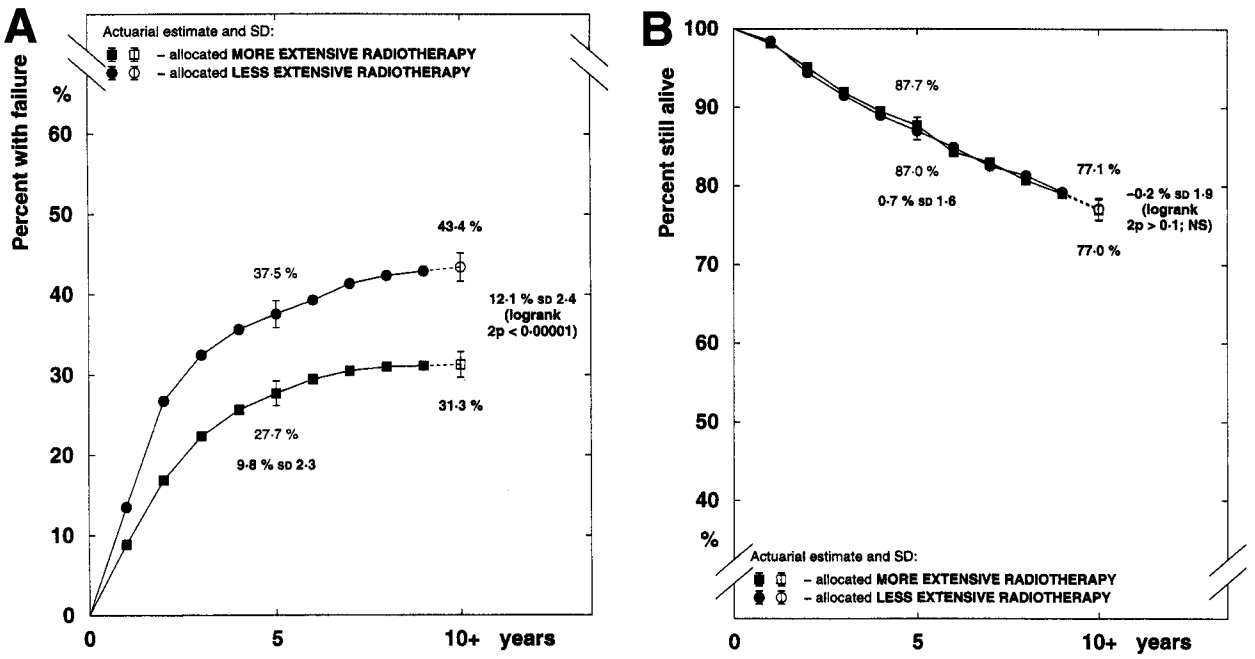


§ 4 trials with no data do not contribute to the total (allocated more RT: 83; allocated less RT: 83)
* Same chemotherapy to both arms
† Radiotherapy abbreviations: IF = involved field; EF = extended field; MF = mantle field; STNI = sub–total nodal irradiation; TNI = total nodal; (S)TNI = sub–total or total nodal; HDRT = higher–dose radiotherapy.



§ 4 trials with no data do not contribute to the total (allocated more RT: 83; allocated less RT: 83)
* Same chemotherapy to both arms
† Radiotherapy abbreviations: see Figure 1A

Fig 1. Time to (A) failure and (B) survival analyses in 8 trials of more extensive versus less extensive radiotherapy (RT) in early Hodgkin's disease. Black squares with horizontal lines: odds reductions and 99% confidence intervals of individual trials. Diamond shape: odds reduction and 95% confidence interval of meta-analysis.



Annual failure rates

	Years 0 – 4	Years 5 – 9	Years 10+
More RT	6·97 % SD 0·42	1·15 % SD 0·21	0·30 % SD 0·11
Less RT	10·14 % SD 0·55	2·03 % SD 0·31	1·00 % SD 0·24
Events / person-years			
More RT	271 / 3887	31 / 2689	7 / 2325
Less RT	346 / 3411	44 / 2172	17 / 1694

Annual death rates

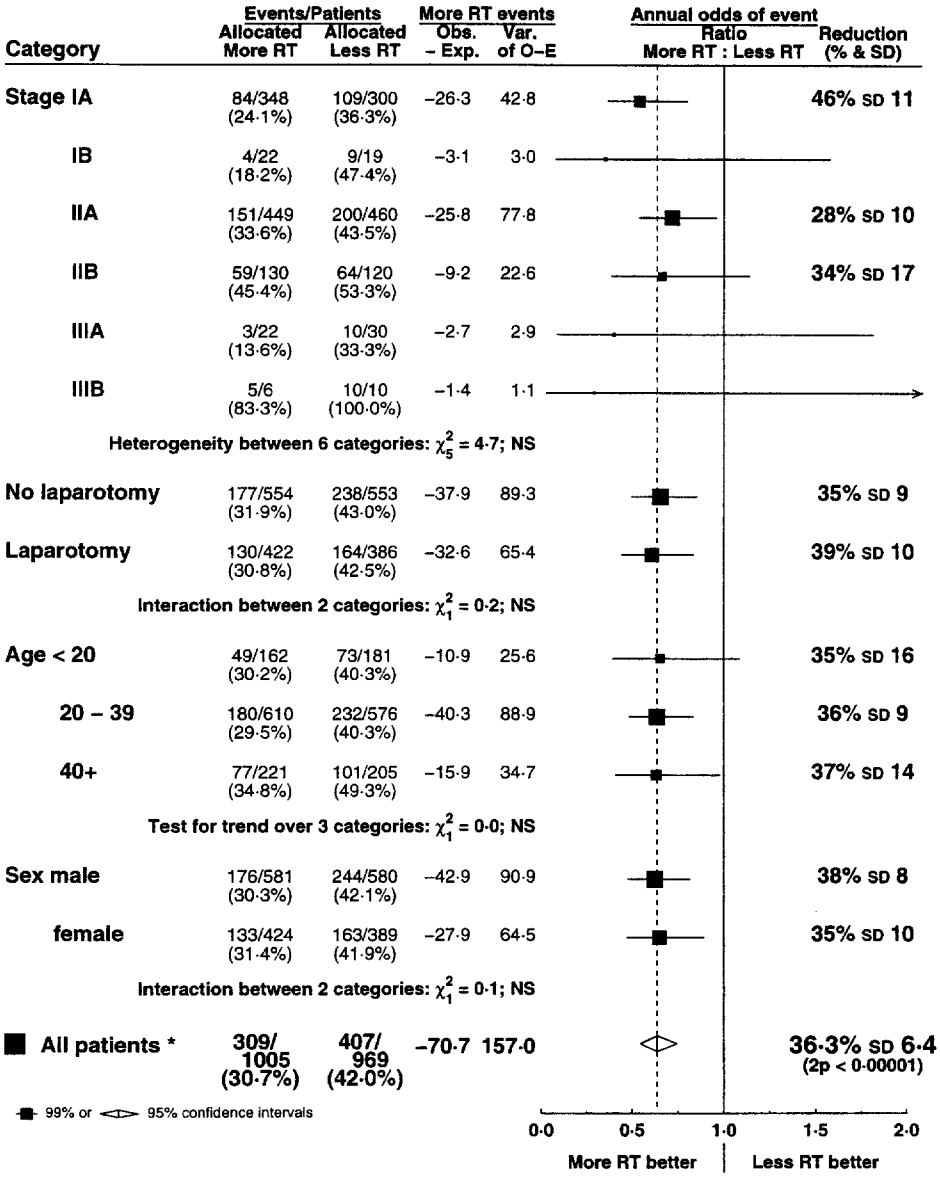
	Years 0 – 4	Years 5 – 9	Years 10+
More RT	2·61 % SD 0·24	2·58 % SD 0·27	2·65 % SD 0·29
Less RT	2·81 % SD 0·26	2·34 % SD 0·27	2·85 % SD 0·31
Deaths / person-years			
More RT	118 / 4526	90 / 3492	84 / 3164
Less RT	121 / 4300	77 / 3289	84 / 2948

Fig 2. Risk of (A) failure and (B) survival by treatment in 8 trials of more extensive versus less extensive RT.

failures occurred in the first few years after randomization, and so most of the absolute benefit from more extensive radiotherapy was also seen in years 0 to 4 after randomization. However, there were also statistically significantly fewer failures in years 5 to 9, and in years 10 onwards. This sustained reduction in the risk of failure led to an absolute difference in the 10-year risk of failure of 12% (31% *v* 43% failed).

Heterogeneity of effects on risk of failure. The designs of the trials of more versus less radiotherapy varied, with some using chemotherapy in both arms and with different radiation doses and radiation fields used (Appendix 2A). It is possible, therefore, that there is some real heterogeneity between the nine treatment comparisons. However, a formal test for heterogeneity in Fig 1A yields only a marginally significant result (χ^2, 8 df = 18.9; P = .02). This is chiefly due to the atypically large benefit seen in the Stanford H-1 study and the apparently adverse effect in the small LYGRA I study. However, examination of treatment effect in various subcategories of trials (eg, trials in the presence [34% ± 22%] and absence [36% ± 7%] of chemotherapy, trials where less extensive radiotherapy was to the involved field only [37% ± 7%], or was mantle-field [32% ± 19%]) failed to produce any significant evidence of selective benefit in particular subgroups of trials. Similarly, comparisons of the size of the reduction in the risk of failure seen in different stages of disease, for stage B patients (with symptoms) and stage A (without symptoms), in patients staged with laparotomy (39% ± 10%) or without laparotomy (35% ± 9%), in patients of different ages, and in patients of different sex (Fig 3) suggest that the proportional reduction in the risk of failure is of broadly similar size in all of these categories of patients. In particular, even among the few stage III patients or patients with B symptoms, the reduction in risk of failure was statistically significant (64% ± 31%, P = .04; and 40% ± 15%, P = .008; respectively).

Overall mortality. Although additional radiotherapy prevents a substantial proportion of recurrences, it does not significantly affect overall mortality. Figure 1B shows the effect of more extensive radiotherapy on mortality for each of the eight individual trials. In none of the trials was there a conventionally significant difference in survival between treatment arms. Overall, the reduction in the odds of death is approximately zero (0.6% ± 8.5%). But, even with 2,000 patients randomized, the confidence limits are wide, ranging from approximately 15% fewer to approximately 15% more deaths with more extensive radiotherapy. Figure 2B shows survival curves for the 2,000 patients with full data avail-



*Not additive, as patients with missing data are not shown.

Fig 3. Effect of more extensive RT fields on the risk of treatment failure by stage, laparotomy, age, and sex. In each subgroup, the area of the black square is proportional to the amount of "information" that it provides.

able. There is no suggestion of divergence between the curves at any point.

Cause-specific mortality. Information on the cause of death was sought on all patients who had died without recorded recurrence of Hodgkin's disease. The cause was known for 89% of the 160 such deaths. The cause of the 18 other deaths without recurrence could not be ascertained. Most of these deaths occurred late—half after 10 years—and it seems likely that the majority were from causes other than Hodgkin's disease. A breakdown of these deaths from other causes is shown in the first two columns of Table 1. Although the difference in the total numbers of deaths (100 *v* 60) appears striking, it is not statistically significant once proper allowance is made for the lower recurrence rate, and hence longer exposure to risk of death without recurrence, in the more extensive radiotherapy arm (8,441 person-years at risk *v* 6,770). Overall, in the more extensive radiotherapy arm, there was a nonsignificant 28% ± 18% increase in the odds of death from causes other than Hodgkin's disease (1.18%/yr *v* 0.89%/yr). Although there are some imbalances, most notably for iatrogenic death (10 *v* 2) and for death from solid tumors (28 *v* 13), no statistically significant difference between the two treatment groups remains for these or for any other particular causes of death once appropriate

Table 1. Causes of Death for the 360 Patients Who Died Without Recurrence of Causes Other Than Hodgkin's Disease in the Trials of More Extensive Versus Less Extensive Radiotherapy and of Adjuvant Chemotherapy

Cause of Death	More RT (n = 1,005)	Less RT (n = 969)	Unconfounded Trials: CT + RT (n = 236)	Unconfounded Trials: Same RT (n = 240)	Confounded Trials: CT + Less RT (n = 603)	Confounded Trials: More RT (n = 616)
Solid tumors	28	13	15	13	14	9
Leukemia	0	1	2	0	7	4
Non-Hodgkin's lymphoma	5	2	0	0	3	0
Pulmonary/iatrogenic	10	2	1	3	3	3
Cardiovascular	29	25	12	11	19	23
Infection	7	5	5	3	8	3
Not Hodgkin's disease	4	4	0	0	2	3
Other known cause	4	3	3	2	2	3
Unknown cause	13	5	0	0	14	10
Total deaths/person-years	100/8,441	60/6,770	38/2,810	32/2,220	72/5,273	58/4,793
Annual death rate (%)	1.18	0.89	1.35	1.44	1.37	1.21

NOTE. In each of these comparisons, allowance must be made for the first group having a considerably lower risk of recurrence and hence a longer exposure to risk of death without recurrence from non-Hodgkin's disease causes.

Abbreviations: RT, radiation; CT, chemotherapy.

allowance has been made for the greater time at risk in the more extensive radiotherapy group.

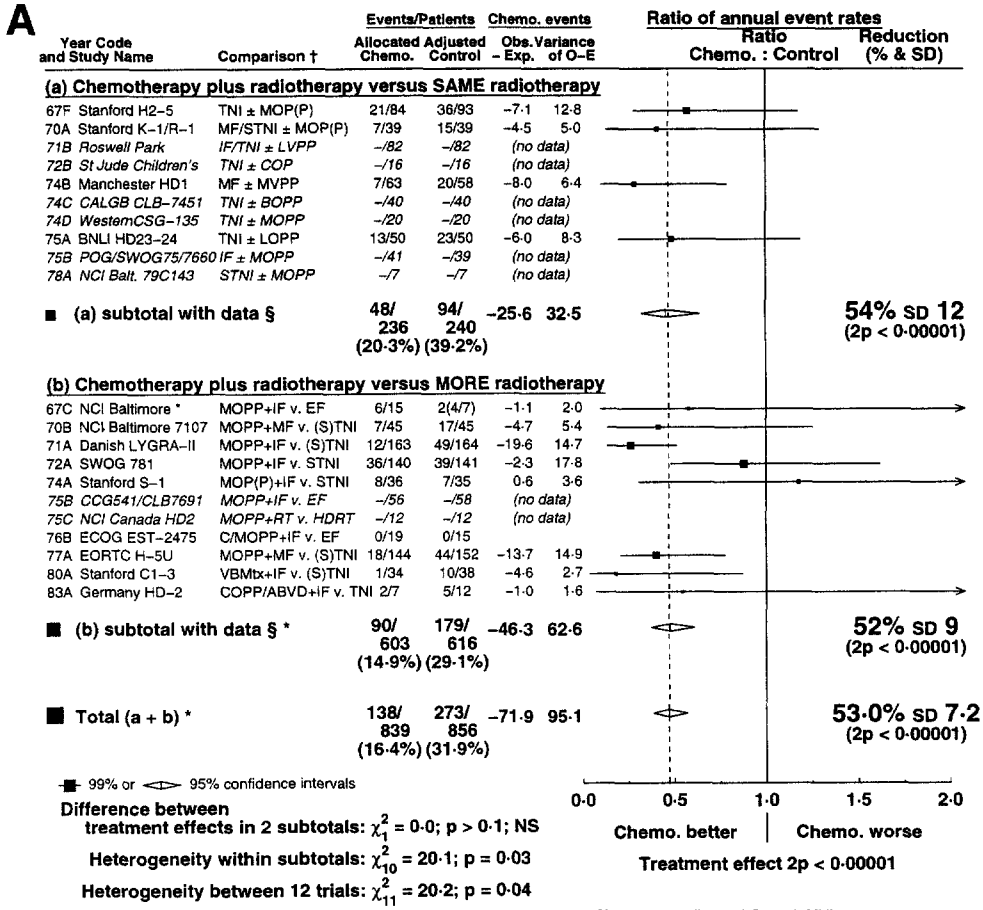
Analyses were undertaken of the remaining Hodgkin's disease deaths (ie, excluding deaths without recurrence from causes other than Hodgkin's disease or from unknown causes). Overall, the reduction in the odds of death from Hodgkin's disease with more extensive radiotherapy is approximately 10% (9.5% ± 9.5%), with confidence limits that range from 26% fewer to 10% more deaths. So, although there is a trend toward fewer Hodgkin's disease deaths in the more extensive radiotherapy arm, the difference was not statistically significant. Moreover, as described earlier, it was approximately balanced by a slightly higher (although again not significantly so) risk of dying from causes other than Hodgkin's disease with more extensive radiotherapy.

Trials of Chemotherapy Plus Radiotherapy Versus Radiotherapy Alone

Full individual patient data were supplied from only 12 of the 20 identified trials of chemotherapy plus radiotherapy versus radiotherapy alone, but these 12 trials included 1,666 patients, which is about three quarters of the total numbers ever randomized (Appendix 2B). Tabular data on overall mortality only were supplied on 226 children in two pediatric trials (72B and 75B); and individual data on 22 patients were extractable from the publication for one other trial (67C).[11] No data are available from five trials that included a total of about 300 patients. In all five of these trials, the data had been lost. Thus, for the addition of chemotherapy trials, detailed information is available on some 75% of all patients ever randomized and basic mortality data on a further 10%.

Time to failure. Figure 4A shows results of analyses of time to failure for each of the 13 trials with individual patient data. The trials are grouped by trials in which the same radiotherapy was given in each arm (unconfounded trials, upper part of figure) and by trials in which more extensive radiotherapy was given to patients who did not receive chemotherapy (confounded trials, lower part of figure). In all but one of the trials with available data, there were fewer failures in the chemotherapy arm, and in four trials (74B, 71A, 77A, and 80A), there was a statistically significant reduction in the risk of failure in the chemotherapy arm ($P < .01$). The combined result of all 13 trials shows that the recurrence rate was approximately halved (odds reduction, 53% ± 7%; $P < .00001$). Figure 5A shows the risk of failure by treatment for the 1,688 patients randomized with individual patient data available. Adjuvant combination chemotherapy resulted in a highly significant halving in the risk of failure at 10 years from approximately one third to approximately one sixth. As with radiotherapy, most of the absolute benefit appeared in years 0 to 4, but there were again significantly fewer recurrences in years 5 to 9, with few recurrences thereafter.

Heterogeneity of effects. Most chemotherapy regimens tested were either mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) or variants of MOPP. The meta-analysis provides no good evidence that any of the various chemotherapy regimens tested were any more or less effective in delaying recurrence. A formal statistical comparison between the apparent sizes of the effects of chemotherapy in each of the 12 separate trials with some data (there were no failures in 76B) shows marginally significant heterogeneity (χ^2, 11 df = 20.2; P = .04). As noted, some of the trials were confounded with regard to the radiotherapy-



§ 7 trials with no data do not contribute to subtotals or to the overall total (allocated Chemo.: 274; allocated Control: 274)

* For balance, control patients in 3–way trials or trial strata count half or twice in subtotal(s) and in final total of events/patients.

† Radiotherapy abbreviations: see Figure 1A

Chemotherapy abbreviations: MOPP = mechlorethamine, vincristine, procarbazine, prednisone; LOPP = chlorambucil, vincristine, procarbazine, prednisone; BOPP = carmustine, vincristine, procarbazine, prednisone; LVPP = chlorambucil, vinblastine, procarbazine, prednisone; MOP(P) = MOPP with optional use of prednisone; COP = cyclophosphamide, vincristine, procarbazine; ABVD = adriamycin, bleomycin, vinblastine, DTIC; VBMtx = vinblastine, bleomycin, methotrexate.

Fig 4. Time to failure analyses in 13 trials (A) and survival analyses in 15 trials (B) of RT plus multiple-agent chemotherapy versus RT alone. See legend to Fig 1.

given in the two treatment arms. About two thirds of the patients were in these trials, and benefit from the more extensive radiotherapy given to patients not receiving chemotherapy might be expected to reduce the size of the apparent benefit from adjuvant chemotherapy. However, an estimate of the effects of chemotherapy in the unconfounded and the confounded trials separately—subtotals (a) and (b), shown as open diamonds—provides no indication of any difference in the size of the effect of chemotherapy seen in trials with the same radiotherapy in each arm (reduction in odds of failure, 54% ± 12%) and in trials with more extensive radiotherapy in the no chemotherapy group (reduction in odds of failure, 52% ± 9%).

The reduction in the risk of failure was similar in the trials that compared chemotherapy plus involved-field radiotherapy versus more extensive radiotherapy (48% ± 11%) and the trials of mantle-field radiotherapy plus chemotherapy versus more extensive radiotherapy (60% ± 15%). Similarly, comparisons of the reduction in the risk of failure seen in different stages of disease, in patients staged with laparotomy (54% ± 8%) or without laparotomy (59% ± 17%), in patients of different ages and in patients of different sex (Fig 6) showed remarkably similar size reductions, significant at $P < .05$ in each subgroup, in all of these different categories of patients.

Overall mortality. However, as was the case with the radiotherapy trials, any effect on mortality rates was much smaller than the effect on recurrence rates. Figure 4B shows overall survival analyses (ie, deaths from any cause) for the 13 trials with individual patient data and for the two trials with data from the publication or tabular data only (one of these trials, 75B, is in two parts), along with an estimate of

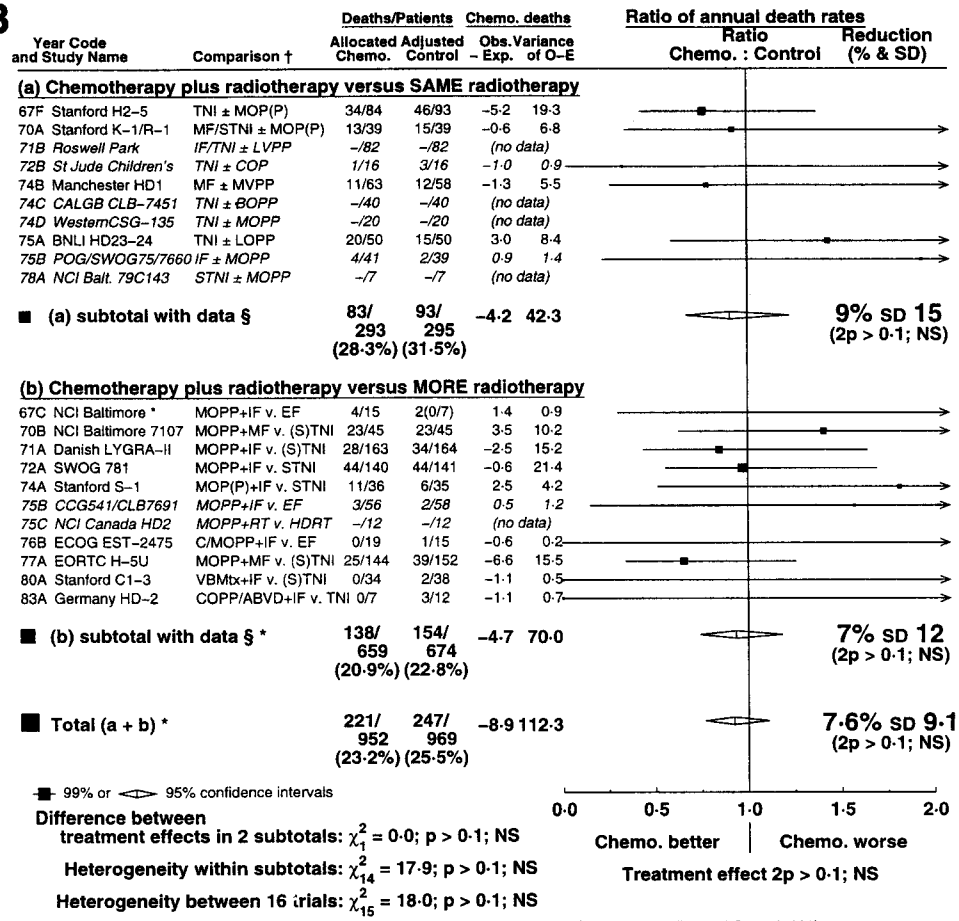
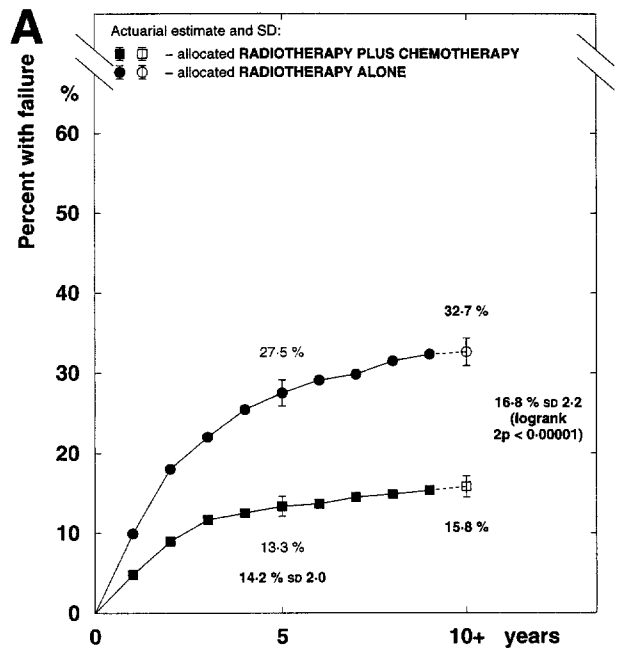


Fig 4. (cont'd)

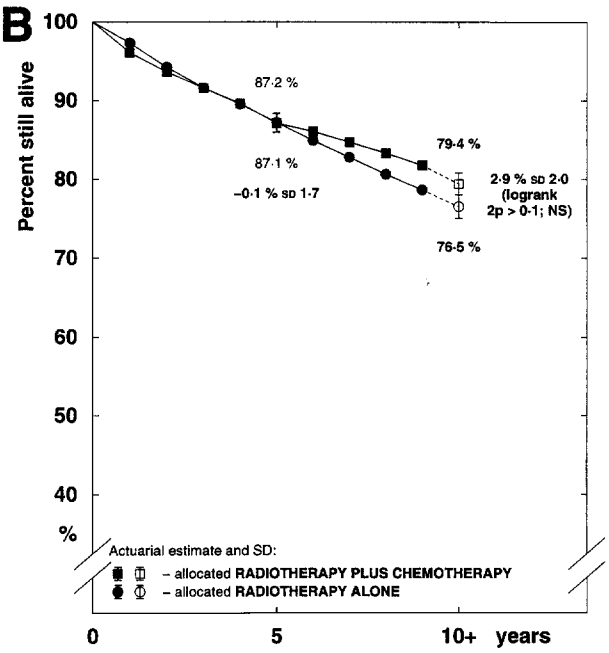
the effect of chemotherapy plus radiotherapy versus radiotherapy alone in all of the trials combined. There is considerable variability in the apparent effects of treatment in the individual trials, but the wide confidence intervals reflect the unreliability of these separate estimates. In none of the individual trials was there a conventionally significant difference in survival between treatment arms, and although overall there were somewhat fewer deaths with chemotherapy (23.2% *v* 25.5% dead), this result was not significant. As would be expected if the extent of radiotherapy itself has little effect on overall survival, the effect of chemotherapy appeared to be about the same in the trials with the same radiotherapy in each arm (reduction in odds of death, 9% ± 15%) and in trials with more radiotherapy in the no chemotherapy group (7% ± 12%). For survival, the overall finding was an odds reduction of 7.6% ± 9.1%. This reduction is not conventionally statistically significant (two-tailed $P > .1$), despite almost 2,000 patients having been randomized in these trials. The 95% confidence interval in Fig 4B shows that the overall results are compatible with the addition of chemotherapy producing up to 25% fewer deaths or 10% more deaths. Figure 5B shows the survival curves for the 1,666 patients with full data available. There is some suggestion of divergence of the survival curves between years 5 and 10, but this is based on only 46 versus 78 deaths and the 10-year survival is not significantly better with chemotherapy. After year 10 there were, if anything, slightly more deaths (62 *v* 55) in those who had received chemotherapy.

Cause-specific mortality. The causes of deaths without recurrence are listed in Table 1 for the 476 patients in the four unconfounded trials and the 1,219 patients in the nine confounded trials for which individual patient data, including that on causes of death, were available. Again, although



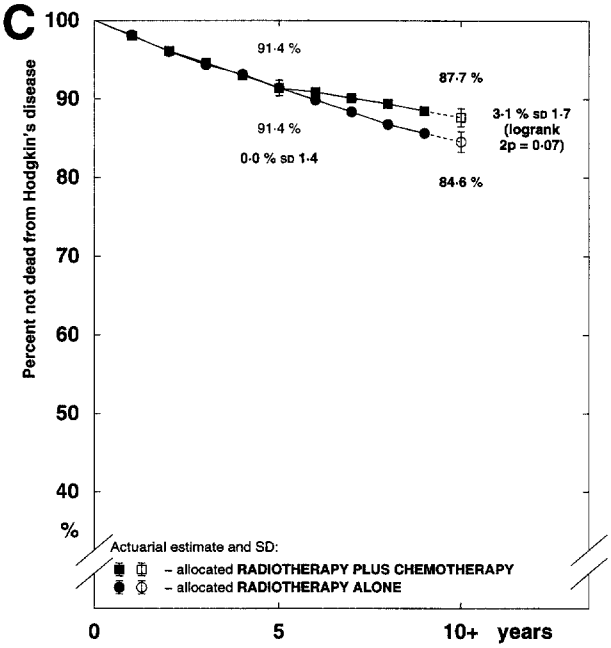
Annual failure rates

	Years 0 – 4	Years 5 – 9	Years 10+
Chemo.	3·04 % SD 0·29	0·66 % SD 0·16	0·54 % SD 0·17
Control	6·81 % SD 0·45	1·68 % SD 0·28	0·31 % SD 0·14
Events / person–years			
Chemo.	110 / 3618	18 / 2721	10 / 1838
Control	227 / 3332	37 / 2199	5 / 1620



Annual death rates

	Years 0 – 4	Years 5 – 9	Years 10+
Chemo.	2·76 % SD 0·27	1·58 % SD 0·23	3·08 % SD 0·39
Control	2·76 % SD 0·27	2·73 % SD 0·31	2·66 % SD 0·36
Deaths / person–years			
Chemo.	105 / 3804	46 / 2909	62 / 2012
Control	107 / 3871	78 / 2859	55 / 2067



Annual "Hodgkin's disease" death rates

	Years 0 – 4	Years 5 – 9	Years 10+
Chemo.	1·76 % SD 0·22	0·62 % SD 0·15	0·89 % SD 0·21
Control	1·86 % SD 0·22	1·75 % SD 0·25	1·35 % SD 0·26
Deaths / person–years			
Chemo.	67 / 3804	18 / 2909	18 / 2012
Control	72 / 3871	50 / 2859	28 / 2067

Fig 5. Risk of (A) failure, (B) survival, and (C) death from Hodgkin's disease in 13 trials of RT plus multiple-agent chemotherapy versus RT alone. Death from Hodgkin's disease excludes deaths without recurrence from causes other than Hodgkin's disease (see text).

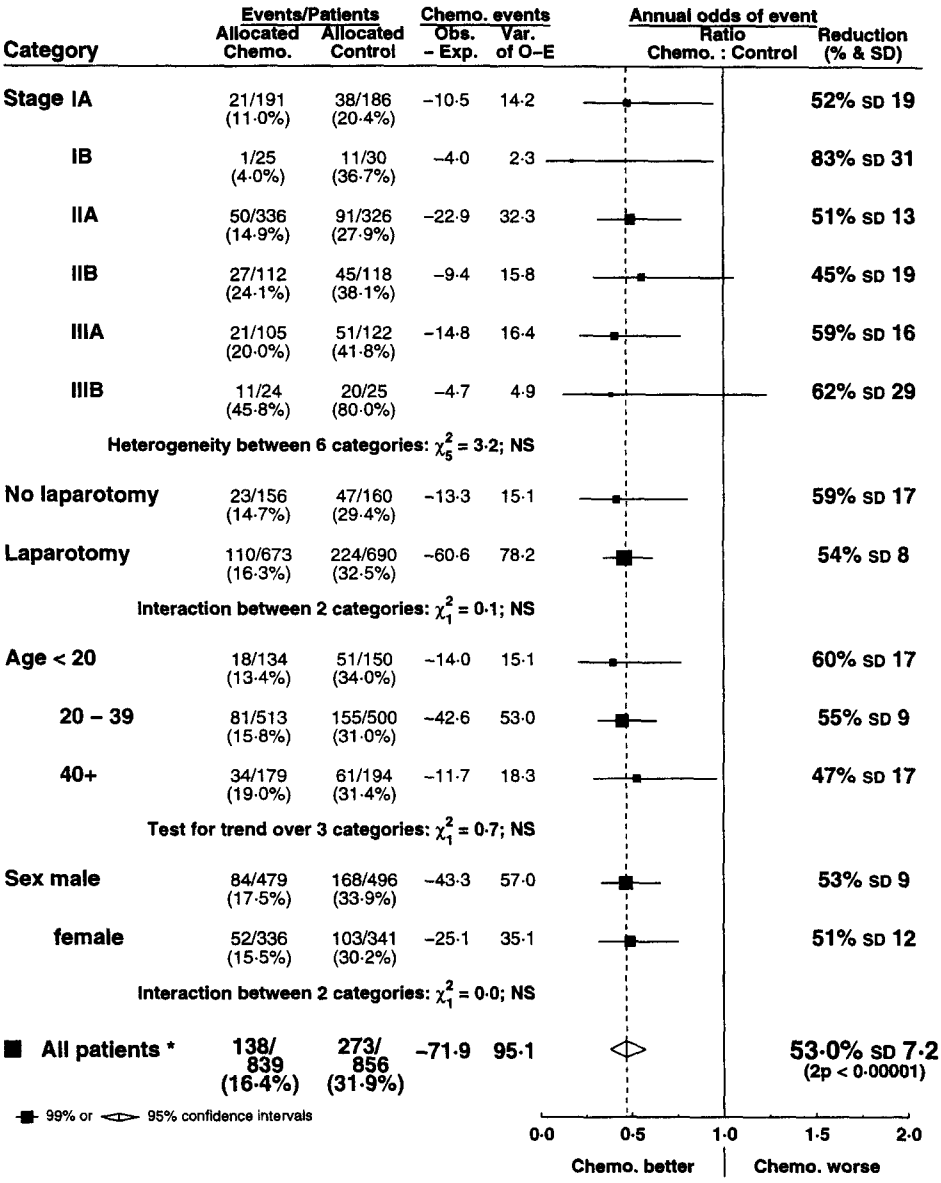


Fig 6. Effect of adding chemotherapy to RT on the risk of treatment failure by stage, laparotomy, age, and sex. See legend to Fig 3.

*Not additive, as patients with missing data are not shown.

some imbalances in the numbers of such deaths exist, no significant difference between the two treatment groups exists overall, or for any specific cause of death, after taking into account the differences in follow-up duration. Taking the confounded and unconfounded studies together, there was a 9% ± 16% increase in the odds of death from known causes other than Hodgkin's disease without recurrence in the chemotherapy group, 11% ± 15% if unknown causes are included with the deaths from other causes.

Figure 5C shows Hodgkin's disease-specific survival curves (ie, excluding deaths from causes other than Hodgkin's disease without recurrence) for the 1,688 patients in the 13 trials with individual patient data available. Although none of the trials showed a conventionally significant difference in mortality from Hodgkin's disease between treatment arms, overall, the reduction in the annual odds of death from Hodgkin's disease in the adjuvant chemotherapy arms was 21% ± 11% (P = .07), with wide confidence limits ranging from approximately 40% lower to about the same risk of death. The effect of chemotherapy on death from Hodgkin's disease appeared slightly smaller in the unconfounded trials (14% ± 19%) than in the confounded trials (25% ± 14%), but this difference is not statistically significant. So, although the analyses of mortality from Hodgkin's disease do appear to suggest an advantage for adjuvant chemotherapy, the difference is of only borderline statistical significance

and is partly counterbalanced by the nonsignificant excess of deaths from other causes.

DISCUSSION

This worldwide collaboration has brought together updated information on recurrence, survival, and causes of death from most of the randomized patients in trials that have assessed more extensive radiotherapy or adjuvant combination chemotherapy in early-stage Hodgkin's disease. As such, it involves the largest amount of properly randomized evidence on Hodgkin's disease treatment that has ever been available. Unfortunately, although the first randomized trials to address these two questions were started more than 30 years ago, only a few thousand patients have been randomized in total, and so some important conclusions remain uncertain.

The trials of more versus less extensive radiotherapy indicate a definite and substantial reduction in the risk of failure of first-line treatment if more extensive radiotherapy is used, which confirms results seen in some of the individual trials. However, the use of salvage chemotherapy for patients who recur after radiotherapy alone often achieves good results, and there is no indication from this meta-analysis that the reduced risk of failure with more extensive radiotherapy translates into any overall survival benefit or any reduction in deaths from Hodgkin's disease.

The trials of the addition of chemotherapy to radiotherapy show that chemotherapy has an even larger effect than extending radiotherapy fields on avoidance of recurrence, which again confirms the results of several individual trials. However, salvage chemotherapy for patients who recur following a combination of radiotherapy and chemotherapy is less successful than after radiotherapy alone and, as a result, the apparent improvement in survival for patients treated with adjuvant chemotherapy is only small and is not statistically significant. However, this slight trend towards better survival with chemotherapy does reach borderline statistical significance for mortality from Hodgkin's disease, particularly from about year 5 onwards. But, this is partly offset by a small, nonsignificant excess of deaths from other causes. As the use of more extensive radiotherapy fields has little or no apparent effect on survival, the confounding by more radiotherapy in the no-chemotherapy arm in some studies is likely not to have produced any material reduction in the estimated effects of chemotherapy.

At present, the usual practice is to offer radiotherapy alone just to patients with favorable prognostic factors. A risk of relapse of 20% to 25% or more is considered by many to be unacceptably high and such patients are treated with a combination of involved-field irradiation and six cycles of chemotherapy. However, clinical staging can be unreliable and the question of whether the apparent absence of adverse prognostic factors should be confirmed by laparotomy or not was addressed in the European Organization for Research and Treatment of Cancer (EORTC) H6F trial, which compared adaptive therapy based on staging laparotomy with irradiation alone for clinically staged patients.[27] There was a nonsignificant trend toward better progression-free survival with adaptive therapy, but survival was, if anything, worse, partly because of laparotomy-related deaths.

Chemotherapy alone as front-line treatment has been proposed to obviate the need for staging laparotomy and to avoid potential complications from radiotherapy, which may be particularly relevant for pediatric patients. However, chemotherapy alone has not been adequately tested in early-stage Hodgkin's disease. Two small trials have compared radiotherapy alone with chemotherapy alone; one[13] showed essentially no difference in overall survival in 106 randomized patients, while the other[28] reported superior overall survival for radiotherapy in just 89 randomized patients. A third trial[29] compared possibly suboptimal chemotherapy alone with the same chemotherapy plus radiotherapy in 277 patients with early-stage Hodgkin's disease. No difference in overall survival was reported in patients with good prognostic characteristics, but somewhat better survival was seen with combined modality treatment for patients with poor prognostic characteristics; however, such subgroup analyses are potentially misleading and no firm conclusions can be made.

With increasing awareness of the long-term sequelae of both radiotherapy and chemotherapy,[30,31] the tendency now is to try to minimize initial treatment, at least for subgroups of patients with early-stage Hodgkin's disease with favorable prognostic characteristics. Reductions in radiation treatment fields are being introduced and tested in several centers worldwide, as recently reviewed by Jones and Mauch.[32] This approach must be pursued cautiously, but the present results do provide welcome reassurance that reduction of radiation treatment fields—even down to involved field only—may have little, if any, adverse effect on the patient's chance of survival. Indeed, there was a nonsignificant excess of deaths from solid tumors with more extensive radiotherapy in this meta-analysis, and if the long-term sequelae are substantially increased, then less extensive radiotherapy may actually result in better long-term survival. This would have to be balanced against the extra costs of re-treatment and the psychologic distress suffered by patients who relapse.

Strategies are also currently being explored to improve efficacy and decrease toxicity of chemotherapy. These include the use of novel chemotherapy regimens, seven- or eight-drug combinations with consequent reductions in the total dose of each drug delivered, and a lower number of cycles of chemotherapy. There is accumulating evidence that

there are more effective and less toxic forms of chemotherapy than the MOPP regimens—or variants thereof—used in most of the trials in this meta-analysis. These data have recently been reviewed by Cosset et al.[33]

The chemotherapy results are problematic to interpret, as the marginally significant reduction in deaths from Hodgkin's disease, particularly beyond year 5, makes it quite possible that a moderate but important survival benefit from adding chemotherapy to radiotherapy may have been missed. Preliminary results of the EORTC H7F trial, which started too recently to be eligible for this meta-analysis, show no apparent survival benefit from combined modality treatment compared with irradiation alone, but the follow-up duration in this study is still short.[34] A survival benefit from adding chemotherapy to radiotherapy is, therefore, still possible, particularly if more effective and less toxic chemotherapy regimens can be developed. However, a strategy of radiation therapy followed by salvage chemotherapy in those who relapse does result in a much smaller fraction of patients who receive both chemotherapy and radiotherapy than one of primary combined modality therapy. This may, in time, result in fewer deaths from secondary cancers, which could swing the balance in favor of less early treatment. Longer follow-up evaluation of these studies will help clarify the extra risks and benefits from the addition of chemotherapy to radiotherapy but, ultimately, larger scale randomized evidence will be needed to resolve this question.[35]

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We acknowledge the thousands of patients who took part in these trials and so helped determine how best to treat Hodgkin's disease, and the medical, statistical, and administrative trial investigators who carefully checked any queries and provided details on trials.

APPENDIX 1. International Hodgkin's Disease Collaborative Group

The trial groups and trialists that collaborated in the meta-analysis were as follows, in alphabetical order: Baltimore Cancer Research Program—Dutcher JP, Wiernik PH; *British National Lymphoma Investigation Group*—Vaughan Hudson G; *Cancer and Leukemia Group B*—Anderson JR, Canellos GP, Propert KJ, Schiffer C; *Children's Cancer Study Group*—Hammond D; *Eastern Cooperative Oncology Group*—Cassileth PA, McFadden E; *European Organization for Research and Treatment of Cancer*—Henry-Amar M, Meerwaldt JH, Noordijk EM; *German Hodgkin Study Group*—Diehl V, Hasenclever D, Löffler M; *Groupe d'Etudes sur la Maladie de Hodgkin*—Andrieu J-M, Teillet F; *Groupe Pierre et Marie Curie*—Najman A, Eghbali H, Bonichon F; *LYGRA Danish National Hodgkin Study*—Nissen NI, Specht L; *Manchester Lymphoma Group*—Crowther D, Deakin D, Swindell R; *National Cancer Institute of Canada*—Bergsagel D, Gospodarowicz M, Pater JL; *United States National Cancer Institute*—Longo DL; *Northern California Oncology Group*—Hoppe RT; *Oxford, Imperial Research Cancer Fund/Medical Research Council Clinical Trial Service Unit (Secretariat)*—Clarke MJ, Godwin J, Gray RG, Greaves E, Harwood C, Peto R, Wheatley K; *Pediatric Oncology Group*—Sullivan MP, Fuller LM, Gehan E; *Radiotherapy Hodgkin's Disease Group*—Hutchison GB; *Roswell Park Memorial Institute*—Henderson ES; *St Jude Children's Research Hospital*—Thompson EI; *Southwest Oncology Group*—Coltman CA, Dahlberg S; *Stanford*—Rosenberg S, Hoppe RT; *and Western Cancer Study Group*—Chlebowski R.

APPENDIX 2A. Randomized Trials Comparing More Versus Less Extensive Radiotherapy

Trial Group	Study Start Year, Code, and Name	Period of Entry	Eligible Stages	Laparotomy	Randomized Comparison	No. Died/ Randomized
British National Lymphoma Investigation Group (BNLI)	70C1—BNLI HD 01-02[1]	70-79	IA/IIA	+	EF v IF	88/326
	—BNLI HD 03-04[1]	70-79	IA/IIA	−	EF v IF	98/209
	70C2—BNLI HD 10[1]	70-79	IB/IIB	+	TNI v MF	24/42
	—BNLI HD 11[1]	70-79	IB/IIB	−	TNI v MF	8/12
Cancer and Leukemia Group B (CALGB)	66A—CLB—6609[2]	66-71	III	+/−	VM + TNI v VM + IF	−/44
	77D—CLB—7751	77-79	I/II	+	CVPP + EF v CVPP + IF	−/14
European Organization for Research and Treatment of Cancer (EORTC)	77C—EORTC H-5F[3]	77-82	I/II	+	STNI v MF	20/198
Groupe d'Etudes sur la Maladie de Hodgkin	77B—H-7701[4]	77-80	IA/II_2A	−	MOPP + MF v MOPP + IF	7/79
Groupe Pierre et Marie Curie	76A—H76[5]	76-81	I/II/III	−	MOPP + (S)TNI v MOPP + IF	45/335
Institut Gustave-Roussy	64B—IGR Paris[6]	64-?	III	−	V + EF v V + IF	−/17+
Danish National Hodgkin Study (LYGRA)	69C—LYGRA I[7]	69-71	I/II	−	EF v IF	22/50
National Cancer Institute, United States	65A—NCI Baltimore[8]	65-69	I/II	+/−	TNI v EF	−/90
Radiotherapy Hodgkin's Disease Group	67B—CAN-AM RHDG[9]	67-73	I/II	+/−	MF or STNI v IF	165/542
Stanford University	62A1—L-1[10]	62-68	I/II	−	EF v IF	48/96
	62A2—L-2[10]	62-65	III	−	TNI v IF	18/22
	67A—H-1[10]	67-70	IA/IIA	+/−	(S)TNI v IF	31/63

Abbreviations: See footnote to Appendix 2B.

APPENDIX 2B. Randomized Trials Comparing Radiotherapy Plus Adjuvant Chemotherapy Versus Radiotherapy Alone

Trial Group	Study Start Year, Code, and Name	Period of Entry	Eligible Stages	Laparotomy	Randomized Comparison	No. Randomized	No. Died
Baltimore Cancer Research Program/ National Cancer Institute	67C—NCI Baltimore[11]	67-69	I/II	−	IF + MOPP v MOPP + IF v EF	22	
	70B—BCRP-7107[12]	70-74	IA/IIA/IIIA	+	MF (+IF) + MOPP v (S)TNI	90	46
	78A—NCI 79C 143/BCRP-7824[13]	78-80	I/II/IIIA	+	STNI + MOPP v STNI	14	No data
British National Lymphoma Investigation Group (BNLI)	75A—BNLI HD 23-24[1]	75-80	IIIA	+	TNI + LOPP v TNI	100	35
Cancer and Leukemia Group B (CALGB)	74C—CLB-7451[14]	74-81	III	−	BOPP + TNI v TNI + BOPP v TNI	80	No data
Danish National Hodgkin Study (LYGRA)	71A—Danish LYGRA II[15]	71-82	I/II	+	MF + MOPP v (S)TNI	327	62
Eastern Cooperative Oncology Group (ECOG)	76B1—EST-2475A	76-77	IA/IIA	+	IF + COPP/MOPP v EF	17	1
	76B2—EST-2475B	76-77	I/II	+	EF + COPP/MOPP v TNI	17	0
European Organization for Research and Treatment of Cancer (EORTC)	77A—EORTC H-5U[3]	77-82	I/II	−/+	MOPP + MF v (S)TNI	296	64
German Hodgkin Study Group (GHOST)	83A—Germany HD 2[16]	83-86	IIA	+	COPP/ABVD + IF v TNI	19	3
Intergroup Trial: Pediatric Oncology Group/South West Oncology Group/Children's Cancer Study Group/Cancer and Leukemia Group B	75B1—POG/SWOG-7560/ 7660[17]	77-81	I/II	+	IF + MOPP v IF	80*	6
	75B2—CCG-541/CALGB-7691[17]	77-81	I/II	+	IF + MOPP v EF	114*	5
Manchester Lymphoma Group	74B—Manchester HD 1[18]	74-81	I/II	+	MF + MVPP v MF	121	23
National Cancer Institute of Canada	75C—HD 2	75-	II		RT + MOPP v HDRT	24	No data
Northern California Oncology Group	86A—NCOG—8H851	86-	I/II/IIIA		IF + VBMtx v (S)TNI	15†	No data
Roswell Park Memorial Institute	71B—Roswell Park[19]	71-79	I/II/III	+/−	IF or TNI + LVPP v IF or TNI	164	No data
St Jude Children's Research Hospital	72B—St Jude Children's[20]	72-75	IIA/IIIA	+	TNI + COP v TNI	32*	4
Southwest Oncology Group (SWOG)	72A—SWOG 7821[21]	72-78	I/II	+	IF + MOPP v STNI	281	88
Stanford University Hospital	67F1-4—H2 to H-5[10]	67-74	IB/IIB/III	+	TNI + MOP(P) v TNI	177	80
	70A1—R-1[10]	70-74	IA/IIA	+	MF + MOP(P) v MF	20	7
	70A2—K-1[10]	70-74	IA/IIA	+	STNI + MOP(P) v STNI	58	21
	74A—S-1[10]	74-80	IA/IIA	+	IF + MOP(P) v STNI	71	17
	80A1-2—C1 & C2[10]	80-88	I/II	+	IF + VBMtx v STNI	58	0
	80A3—C3[10]	81-88	IIIA	+	IF + VBMtx v TNI	14	2
Western Cancer Study Group	74D—WCSG 135	74-78	II/III		TNI + MOPP v TNI	40	No data

Abbreviations: IF, involved field radiotherapy; EF, extended-field radiotherapy; TNI, total-nodal irradiation; STNI, subtotal-nodal irradiation; MF, mantle-field irradiation; RT, radiotherapy (unspecified); HDRT, higher-dose RT; MOPP, mechlorethamine, vincristine, procarbazine, and prednisone; LOPP, chlorambucil, vincristine, procarbazine, and prednisone; BOPP, carmustine, vincristine, procarbazine, and prednisone; COPP, cyclophosphamide, vincristine, procarbazine, and prednisone; MVPP, mechlorethamine, vinblastine, procarbazine, and prednisone; LVPP, chlorambucil, vinblastine, procarbazine, and prednisone; MOP(P), MOPP with optional use of prednisone; COP, cyclophosphamide, vincristine, and procarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; VBMtx, vinblastine, bleomycin, and methotrexate; VM, vinblastine and mechlorethamine; V, vinblastine alone; CVPP, lomustine, vinblastine, procarbazine, and prednisone.

*Only tabular data available.

†These patients are included with Stanford C1-3 data.

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