A META-ANALYSIS OF THORACIC RADIOTHERAPY FOR SMALL-CELL LUNG CANCER

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Abstract *Background.* In spite of 16 randomized trials conducted during the past 15 years, the effect of thoracic radiotherapy on the survival of patients with limited small-cell lung cancer remains controversial. The majority of these trials did not have enough statistical power to detect a difference in survival of 5 to 10 percent at five years. This meta-analysis was designed to evaluate the hypothesis that thoracic radiotherapy contributes to a moderate increase in overall survival in limited small-cell lung cancer.

Methods. We collected individual data on all patients enrolled before December 1988 in randomized trials comparing chemotherapy alone with chemotherapy combined with thoracic radiotherapy. Trials that included only patients with extensive disease were excluded.

Results. The meta-analysis included 13 trials and 2140 patients with limited disease. A total of 433 patients with extensive disease were excluded. Overall, 1862 of 2103 patients who could be evaluated died; the median follow-up period for the surviving patients was 43 months. The relative risk of death in the combined-therapy group as compared with the chemotherapy group was 0.86 (95 percent confidence interval, 0.78 to 0.94; $P = 0.001$), corresponding to a 14 percent reduction in the mortality rate. The benefit in terms of overall survival at three years (±SD) was 5.4±1.4 percent. Indirect comparison of early with late radiotherapy and of sequential with nonsequential radiotherapy did not reveal any optimal time for treatment. There was a trend toward a larger reduction in mortality among younger patients: the relative risk of death in the combined-therapy as compared with the chemotherapy group ranged from 0.72 for patients less than 55 years old (95 percent confidence interval, 0.56 to 0.93) to 1.07 (0.70 to 1.64) for patients over 70.

Conclusions. Thoracic radiotherapy moderately improves survival in patients with limited small-cell lung cancer who are treated with combination chemotherapy. Identification of the optimal combination of chemotherapy and radiotherapy will require further trials. (N Engl J Med 1992; 327:1618-24.)

THE role of thoracic radiotherapy in the management of limited small-cell lung cancer remains controversial. Most investigators agree that it decreases the risk of thoracic recurrence significantly, but no agreement has been reached concerning its possible effect on survival.[1] Sixteen randomized trials have been conducted in the past 15 years, with inconsistent results (Appendix 2); thus, the controversy persists. If the heterogeneity of the patients studied is assumed not to be too great, there are three main possible explanations for the inconsistency: (1) that technical factors such as the radiation dose, tissue volume treated, drug administered, and timing of radiotherapy and chemotherapy are so critical that differences in them may modify the effect of treatment[2]; (2) that thoracic radiotherapy has no effect at all on survival, and the differences in results are simply the effect of statistical variations around the mean zero effect; or (3) that thoracic radiotherapy has a moderate effect on survival, but the trials did not have sufficient statistical power to test the hypothesis. The latter two explanations could be ruled out by a study that included a large number of patients. As has been demonstrated in breast cancer,[3] the meta-analysis of randomized trials is a useful tool to evaluate adjuvant treatments that produce a moderate increase in overall survival — i.e., an increase of 5 to 10 percent at five years. Such a small benefit would be of value to patients with limited small-cell lung cancer, among whom survival at five years is only about 10 percent.[4]

The hypothesis that we tested in our meta-analysis was that thoracic radiotherapy produces a moderate improvement in the overall survival of patients with limited small-cell lung cancer. To detect a survival benefit of 6 percent — for example, an increase from 10 to 16 percent — more than 1000 patients would be needed, assuming that the Type I and II errors were equal to 0.05 (by two-sided test). The meta-analysis included 2140 patients with limited small-cell lung cancer studied in 13 randomized trials (Appendix 2). Such a meta-analysis should be a reliable test of the effect of treatment, but it may not provide definitive information about details of treatment, such as the dose and timing of radiation.

METHODS

Data Collection

The collection of data started in September 1989.

Inclusion Criteria

All randomized trials that included patients with small-cell lung cancer and compared chemotherapy alone with chemotherapy plus thoracic radiotherapy were studied. Trials limited to patients with extensive disease were excluded, as were patients with extensive disease in trials addressing both limited and extensive disease. Tri-

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als with enrollment that had not ended before December 31, 1988, were also excluded.

Identification of Trials

Multiple sources of information were used to identify trials. The first step involved discussion with the investigators and scrutiny of review articles; this was supplemented by a MEDLINE literature search and examination of proceedings of oncology meetings. The list of identified trials was sent to all trial members participating in the meta-analysis. The comparison of our list with the list of randomized trials of treatments of lung cancer compiled by Nicolucci et al.[5] revealed no additional trials. Appendix 2 lists the included and excluded trials and the reasons for exclusion.

Data from Individual Trials

We sought data on each patient ever enrolled in the trials studied. All trial members provided such data on either a standard paper questionnaire or a magnetic tape. The collected data included identifying information, the extent of disease as defined in each trial, the treatment assigned, the dates of randomization and of the last follow-up evaluation, vital status at the last evaluation, and three covariates — sex, age, and performance status. Because the coding of performance status varied among trials, it could only be summarized in two ways: as a performance status of 0 or 1 as defined by the World Health Organization (WHO) or a Karnofsky index above 60 percent, and as a WHO performance status of 2 to 4 or a Karnofsky index of 60 percent or less. Data on the assigned treatment and on follow-up were available for 98.2 percent of the patients. Table 1 shows the number of patients in each trial and the number excluded from the published analyses and the present meta-analysis. Information on sex, age, and performance status was obtained for 98.2 percent, 97.9 percent, and 95.6 percent of patients, respectively. It was impossible to obtain data from three small trials; one had 35 patients (only 12 with limited disease), another had 32, and the third had 18.

Data Checking

Data on patients who were entered in trials but excluded from analyses were systematically sought to avoid the potential bias of postrandomization exclusion. In cases of imbalance in the sizes of the treatment groups, we checked for improper exclusion or undocumented changes in treatment assignment. The treatment groups were also checked for imbalances in sex, age, performance status, and the proportion of patients lost to follow-up. A patient was considered lost to follow-up if no information was available after September 1, 1988, one year before the beginning of data collection for the meta-analysis. Of the 190 patients lost to follow-up, 43 (22.6 percent) were lost after three years of follow-up.

Statistical Analysis

All comparisons were performed according to the treatment assigned by randomization (intention-to-treat analysis).

The statistical method used has been described elsewhere.[3] For each trial, the number of deaths observed (O) among patients assigned to combined therapy (chemotherapy combined with radiotherapy) was compared with the number of deaths expected (E) under the assumption that the probability of death was unrelated to treatment. The variance (V) of the observed number minus the expected number (O − E) was also computed. The values for O − E and V were then summed over the whole set of trials to produce a grand total (GT) and a total variance (V_T). The ratio $GT/\sqrt{V_T}$, or z, tests treatment effect for significance.

For each trial, the relative risk of death was estimated as $\exp[(O - E)/V]$. The pooled relative risk was estimated as $\exp(GT/V_T)$, with a 95 percent confidence interval estimated as $\exp(GT/V_T \pm 1.96/\sqrt{V_T})$. The percent reduction in the relative risk of death (r) was estimated as $100 - 100 \exp(GT/V_T)$ and expressed with its approximate standard deviation, $-r/z$.

Tests of heterogeneity among different trials[3] were performed, but such tests are of limited value because of their low power. Furthermore, substantial heterogeneity does not invalidate the results of a meta-analysis. An interaction test[3] was used for indirect comparisons of trial subgroups according to the timing of radiotherapy and chemotherapy. This test was also used for subgroup analyses according to sex, age, and performance status. All P values are two-tailed. The standard deviations for the reduction in the relative risk and the difference between survival rates are given.

Table 1. Enrollment of Patients with Limited Disease and Exclusions from Analysis in Randomized Trials of Thoracic Radiotherapy for Small-Cell Lung Cancer Treated with Chemotherapy.

Trial*	Radiotherapy	Patients Enrolled	Patients Excluded from Analysis	
			In Trial	In Meta-Analysis
		no. of patients		
Copenhagen, 1976 (Østerlind)	No	76	0	0
	Yes	72	3	3
Sydney, 1977 (Rosenthal)	No	49	1	0
	Yes	46	3	1
NCI, 1977 (Bunn)	No	49	0	0
	Yes	48	0	0
SECSG I, 1978 (Birch)	No	155	13	13
	Yes	161	12	8
London, 1979 (Souhami)	No	75	2	0
	Yes	64	7	1
SWOG, 1980 (Kies)	No	56	3	0
	Yes	47	7	0
SAKK, 1980 (Joss)	No	34	3	0
	Yes	36	5	0
Uppsala, 1980 (Nõu)	No	31	0	0
	Yes	26	1	0
CALGB, 1981 (Perry)	No	134	5	0
	Yes (day 1)†	138	13	0
	Yes (day 64)†	154	9	0
ECOG, 1981 (Creech)	No	133	14	0
	Yes	131	18	0
Okayama, 1981 (Ohnoshi)	No	28	1	0
	Yes	28	3	0
SECSG II, 1982 (Birch)	No	170	9	2
	Yes	163	16	9
GETCB, 1986 (Lebeau)	No	17	0	0
	Yes	19	0	0
Total	No	1007	51	15
	Yes	1133	97	22

*Each trial is shown with the year in which enrollment started; the name in parentheses is the first author of the reference given in Appendix 2 (i.e., the first 13 trials listed).

†Radiotherapy was begun in one group on the same day as chemotherapy began, and in another group 64 days after the start of chemotherapy.

Results

Description of the Included Trials

This meta-analysis was based on 13 randomized trials that included 2573 patients (range per trial, 54 to 426). Table 2 shows the heterogeneity of these trials with respect to the timing of radiotherapy and chemotherapy, doses and fractionation of radiation, drug regimens, and study design. Five trials included both patients with limited disease and patients with extensive disease (Table 2). A total of 433 patients with extensive disease were excluded from the meta-analysis. Among the 2140 patients with limited disease, there were enough data on 2103 to permit them

Table 2. Design of Randomized Trials Evaluating the Role of Thoracic Radiotherapy in the Treatment of Limited Small-Cell Lung Cancer with Chemotherapy.*

Trial and Period of Enrollment	Selection Criteria			Sequence of CT and RT	CT Regimen†	Randomization Just before RT	Starting Day of RT	RT — Gy/Fraction	PCI
	Stage	Age	PS						
Copenhagen, 1976–79 (Østerlind)	Lim.	<71	None‡	Con.	CYC, VCR, MTX, CCNU	No	Day 43	40/10, split	No
Sydney, 1977–79 (Rosenthal)	Any	None	None§	Seq.	CYC, ADR, VCR	Yes	Day 63	40/20	No
NCI, 1977–86 (Bunn)	Lim.	None	None	Con.	CYC, MTX, CCNU alt. VCR, ADR, PCB	Yes	Days 1–3	40/15	Yes
SECSG I, 1978–82 (Birch)	Lim.	<76	>30% (Ka)	Alt.	CYC, ADR, VCR	No	Day 29¶	40/14, split	Yes
London, 1979–82 (Souhami)	Any	<76	None	Seq.	VCR, ADR alt. CYC, MTX	No	Day 85	40/20	No
SWOG, 1980–83 (Kies)	Lim.	None	None‖	Seq.	VCR, MTX, VP-16 alt. CYC, ADR, VCR	Yes	Day 85	48/22, split	Yes
SAKK, 1980–84 (Joss)**	Any	<71	<4 (WHO)	Seq.	ADR, VP-16, CDDP or CYC, ADR, VP-16 or CYC, VCR, MTX alt. ADR, VP-16, CDDP	Yes	Day 127	45/25, split	Yes
Uppsala, 1980–1984 (Nõu)	Any	None	None	Seq.	CYC, ADR, VCR, MTX alt. CYC, VCR, MTX, CCNU	Yes	Day 77	40/20	No
CALGB, 1981–84 (Perry)	Lim.	None	<4	Con.	CYC, VCR, VP-16 alt. CYC, ADR, VCR	Yes No	Day 1 or day 64††	50/24	Yes
ECOG, 1981–85 (Creech)‡‡	Lim.	<71	<3 (WHO)	Seq.	CYC, CCNU, MTX	Yes	Day 43	50/25	Yes
Okayama, 1981–86 (Ohnoshi)	Lim.	<80	<4 (WHO)	Seq.	CYC, VCR, MTX, PCB alt. VP-16, ADR, NIM	No	Day 30	40/20	§§
SECSG II, 1982–85 (Birch)	Lim.	<76	>30% (Ka)	Con.	CYC, ADR, VCR¶¶	Yes	Day 1	45/15, split	Yes
GETCB, 1986–88 (Lebeau)‖‖	Any	None	None	Seq.	CYC, ADR, VP-16, CCNU or CYC ADR CCNU alt. VP-16, CDDP, VDS	Yes	Day 224	32/8	Yes

*The names in parentheses are those of the first 13 studies listed in Appendix 2. CT denotes chemotherapy, RT chest radiotherapy, PCI prophylactic cranial irradiation, and PS performance status. The starting day of radiotherapy is shown in relation to the starting day of chemotherapy (day 1). Lim. denotes limited disease, and Any denotes limited or extensive disease. Ka denotes Karnofsky performance status, and WHO denotes WHO performance status. Con. denotes concurrent chest radiotherapy and chemotherapy; Seq. sequential; and Alt. alternating.

†CYC denotes cyclophosphamide, VCR vincristine, MTX methotrexate, CCNU lomustine, ADR doxorubicin, alt. alternating chemotherapy, PCB procarbazine, VP-16 etoposide, CDDP cisplatin, NIM nimustine, and VDS vindesine.

‡Eleven patients treated with chemotherapy alone and three treated with chemotherapy plus radiotherapy underwent complete tumor resection before they were included in the trial.

§Only patients with a complete or partial response to chemotherapy were randomized; the second randomization was carried out on day 1, to either intrathecal or intravenous methotrexate.

¶In the group assigned to chemotherapy plus radiotherapy, only patients without tumor progression at evaluation after three to five weeks received radiotherapy.

‖Only patients with a complete response to chemotherapy were randomized.

**Only patients with a complete or partial response to induction chemotherapy were included in the second randomization (chemotherapy vs. chemotherapy plus radiotherapy). The alternating chemotherapy regimen was given to the two treatment groups after the second randomization. Patients were randomly assigned to one of the three induction-chemotherapy regimens listed.

††One treatment group received chemotherapy, and two groups received chemotherapy plus radiotherapy (early or late radiotherapy).

‡‡Patients with a complete or partial response to induction chemotherapy received cyclophosphamide plus methotrexate plus lomustine alternating with doxorubicin plus etoposide; patients with no response received doxorubicin plus etoposide. Only patients responding to induction chemotherapy received prophylactic cranial irradiation.

§§A second randomization was carried out in patients with a complete response to chemotherapy; they were assigned to either prophylactic cranial irradiation plus chemotherapy (the same chemotherapy given initially) or to chemotherapy alone.

¶¶A second randomization was performed in patients with a complete or partial response; they received either intensification chemotherapy (etoposide plus cisplatin) or no chemotherapy. Randomization to chemotherapy or chemotherapy plus radiotherapy was stopped in May 1985 when an interim analysis showed significantly greater toxicity in the group given chemotherapy plus radiotherapy. After May 1985, 61 patients systematically treated with chemotherapy alone were included only in the second part of the trial.

‖‖Only patients with a complete response were randomized to radiotherapy. For induction chemotherapy, a two-by-two factorial randomization was used to assign 434 patients to the two chemotherapy groups and to subcutaneous heparin or not. Only patients with a complete response to induction chemotherapy received prophylactic cranial irradiation.

to be included in the study. Of these 2103 patients, 1862 died; the median follow-up period for the surviving patients was 43 months. One hundred eleven patients who had not been included in the analyses of individual trials were included in the meta-analysis (Table 1).

Meta-Analysis

Among the 2103 patients with limited disease, there were 890 deaths among the 992 patients assigned to chemotherapy and 972 among the 1111 patients assigned to chemotherapy combined with radiotherapy. Figure 1 shows the results of the meta-analysis for patients with limited disease. The overall relative risk of death in the combined-therapy group as compared with the chemotherapy group was 0.86 (95 percent confidence interval, 0.78 to 0.94; P = 0.001). This result corresponded to a 14 percent reduction in the risk of death, in favor of combined therapy. The increase in terms of overall survival at three years was 5.4±1.4 percent (Fig. 2).

Sensitivity Analysis

Analysis without the Copenhagen Trial

The results of 1 of the 13 trials, the Copenhagen trial, showed borderline significance in favor of chemotherapy alone (Fig. 1). Since these results might be partially explained by the difference between the two treatment groups in the number of patients with complete tumor resection (11 of 76 patients in the chemotherapy group vs. 3 of 72 in the combined-therapy group; P = 0.047 by Fisher's exact test) and in age distribution (mean ±SD, 58.5±6.9 vs. 60.8±6.2 years, respectively; P = 0.04 by t-test), a second anal-

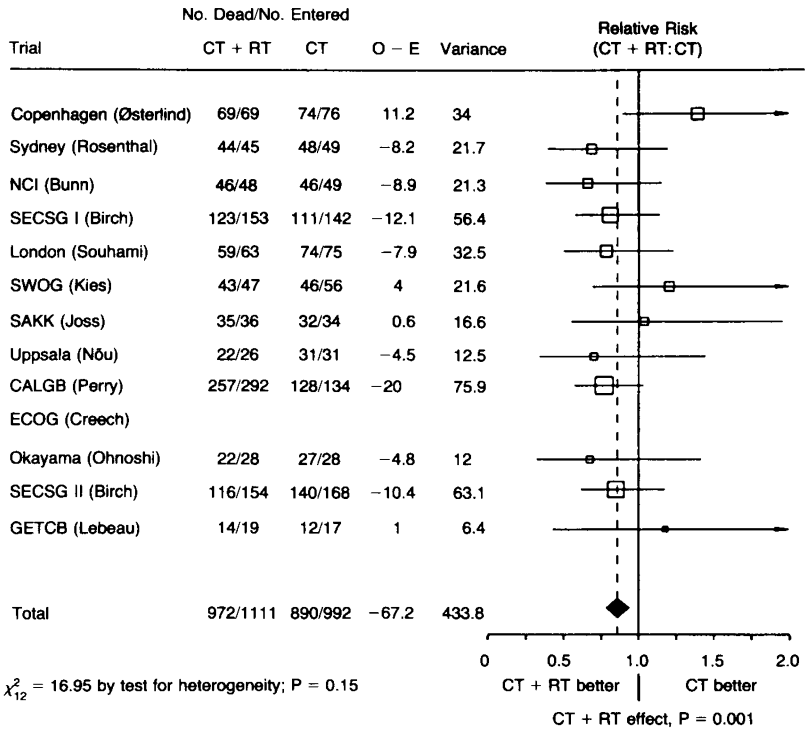

Figure 1. Relative Risk of Death among Patients Receiving Both Chemotherapy and Radiotherapy (CT + RT) as Compared with Patients Receiving Chemotherapy Alone (CT).

Each open square represents the relative risk for the trial, and each horizontal line its 99 percent confidence interval; the area of each square is proportional to the amount of information from the corresponding trial. The broken line and the solid diamond represent the pooled relative risk and its 95 percent confidence interval (see the Statistical Analysis section for details). The percentage reduction in the pooled relative risk (±SD) was 14±4 percent. The names in parentheses are those of the first authors of the first 13 studies listed in Appendix 2. For an explanation of the abbreviations, see Appendix 2.

The patients in two combined-therapy groups of the CALGB trial (early chemotherapy plus radiotherapy, and late chemotherapy plus radiotherapy) were added together for this analysis. The relative risk for the ECOG trial is not shown because the results of this trial have not been published, but it contributed to the overall relative risk, and the ECOG patients are included in the totals.

ysis was performed without this trial. The pooled relative risk derived from this analysis was 0.82 (95 percent confidence interval, 0.75 to 0.91; P<0.001), corresponding to an 18 percent reduction in the risk of death. When the Copenhagen trial was excluded, the test of heterogeneity produced a P value of 0.76 instead of 0.15. This trial was a major source of heterogeneity among the trials included in the meta-analysis, as shown in Figure 1. In the few instances in which the tests of heterogeneity showed significance or some trend, they did not show it after this trial was excluded.

Analysis without the GETCB Trial

All the trials had ended enrollment by 1986 except the trial by the Groupe d'Etude et de Traitement des Cancers Bronchiques (GETCB), which enrolled patients from 1986 to 1988. Failure to include other unpublished and concurrent trials could have resulted in a bias. When the GETCB trial was excluded, the pooled relative risk remained virtually unchanged, at 0.85 (95 percent confidence interval, 0.78 to 0.94).

Analysis with Censoring of Follow-up at Three Years

To avoid the possible bias resulting from better follow-up of the combined-therapy group than of the chemotherapy group, the analysis was repeated after censoring of the follow-up data available at three years. The resulting analysis yielded a very similar result, with a pooled relative risk of 0.83 (95 percent confidence interval, 0.76 to 0.92; P<0.001).

Analysis Including Patients with Extensive Disease

To avoid bias related to the exclusion of patients in the five trials that studied both limited and extensive disease, the 433 patients with extensive disease were included in the meta-analysis. Of the 2536 patients, 2293 died, leading to a very similar relative risk, 0.86 (95 percent confidence interval, 0.79 to 0.94; P<0.001).

Indirect Comparisons

Trials with Early and Late Radiotherapy

The analysis limited to the trials with early radiotherapy — defined as radiation given within 60 days after the beginning of treatment — yielded a pooled relative risk of 0.88 (95 percent confidence interval, 0.78 to 0.98); when the Copenhagen trial was excluded from this analysis, the pooled relative risk was 0.83 (95 percent confidence interval, 0.73 to 0.93). The analysis limited to trials with late radiotherapy yielded a pooled relative risk of 0.81 (95 percent confidence interval, 0.69 to 0.94). The relative risks generated in these analyses of early and late radiotherapy were not significantly different.

Trials with or without Sequential Radiotherapy

The analysis limited to the trials with sequential radiotherapy yielded a pooled relative risk of 0.86 (95 percent confidence interval, 0.75 to 1.00). The analysis limited to the trials with nonsequential (alternating or concurrent) radiotherapy yielded a pooled relative risk of 0.85 (95 percent confidence interval, 0.75 to 0.96), with significant heterogeneity (P = 0.03). When the Copenhagen trial was excluded from the analysis of trials with nonsequential radiotherapy, the pooled

relative risk was 0.79 (95 percent confidence interval, 0.69 to 0.90) (heterogeneity test, P = 0.78). The relative risks in the analyses of sequential and nonsequential radiotherapy were not significantly different.

Subgroup Analysis

Treatment Effect According to Age

Figure 3 shows a significant trend (P = 0.01) toward a larger proportional effect on mortality among younger patients than among older patients in favor of the combined-therapy group: the relative risk of death in the combined-therapy group as compared with the chemotherapy group ranged from 0.72 (95 percent confidence interval, 0.56 to 0.93) among patients less than 55 years old to 1.07 (0.70 to 1.64) among patients more than 70 years old; the reductions in the risk of death were 28±8 percent and −7±17 percent, respectively. The exclusion of the Copenhagen trial did not modify this result. Among patients less than 55 years old, the three-year survival rates estimated with the Kaplan–Meier method were 9.2±1.9 percent in the chemotherapy group and 17.4±2.2 percent in the combined-therapy group; among patients more than 70 years old, the rates were 10.2±3.4 percent and 8.7±2.7 percent, respectively.

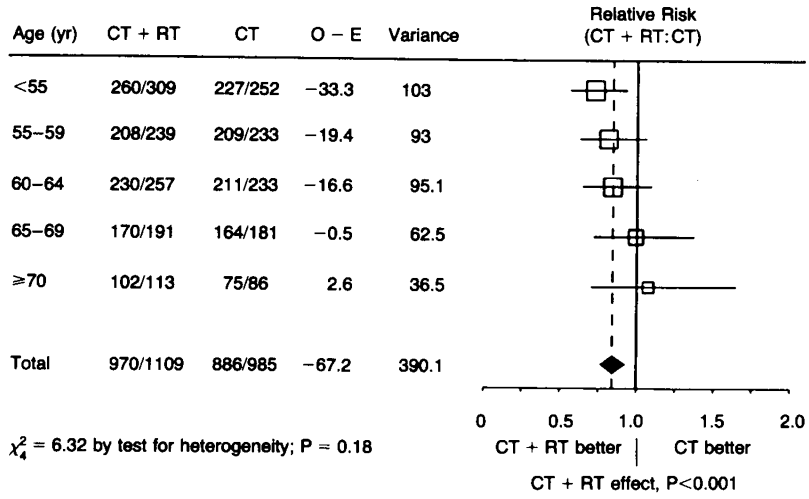

Figure 3. Relative Risk of Death in the Combined-Therapy Group (CT + RT) as Compared with the Chemotherapy Group (CT), According to Age.
The test for trend was significant (P = 0.01). The percentage reduction in the pooled relative risk (±SD) was 16±5 percent. See the legend to Figure 1 for an explanation of the symbols.

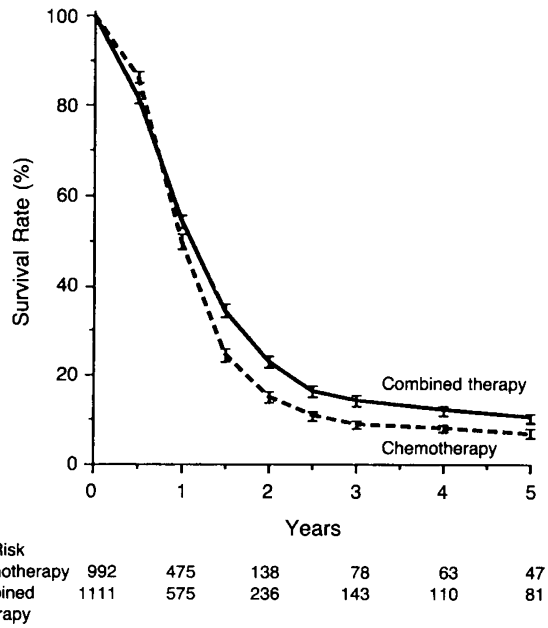

Figure 2. Survival Curves for the Combined-Therapy Group and the Chemotherapy Group.
The three-year survival rates were 14.3±1.1 percent in the combined-therapy group and 8.9±0.9 percent in the chemotherapy group (for a difference of 5.4±1.4 percent; P = 0.001 by stratified log-rank test). Each I bar denotes the standard deviation.

Treatment Effect According to Sex

The pooled relative risk for the 667 women was 0.79 (95 percent confidence interval, 0.66 to 0.94), and that for the 1434 men was 0.88 (0.78 to 0.98). These two relative risks were not significantly different. The three-year survival rates were 13.8 percent for women and 10.8 percent for men.

Treatment Effect According to Performance Status

The pooled relative risk for the 1808 patients with a WHO performance status of 0 or 1 was 0.86 (95 percent confidence interval, 0.77 to 0.95), and that for the 237 patients with a performance status of 2 to 4 was 0.76 (0.57 to 1.01). These two relative risks were not significantly different. The three-year survival rates were 12.1 percent for the patients with a status of 0 or 1 and 10.4 percent for those with a status of 2 to 4.

Discussion

Among the 16 published trials comparing chemotherapy alone with chemotherapy combined with radiotherapy for limited small-cell lung cancer, including 5 trials reported as abstracts, 5 showed that combined therapy had a significant benefit as compared with chemotherapy (the trials by Bunn et al., Birch et al., Perry et al., and Creech et al. and the excluded trial by Schütte et al., all listed in Appendix 2); among the 5 largest trials, 3 showed a significant benefit (the trials by Birch et al., Perry et al., and Creech et al.). The meta-analysis of the 13 largest

trials showed that the administration of thoracic radiotherapy led to a 14 percent reduction in the mortality rate ($P = 0.001$), corresponding to a 5 percent increase in the three-year survival rate. If the three smallest trials excluded because of a lack of individual data had been included in the meta-analysis, the results would not have been significantly different, because the patients in these three trials represented 2.8 percent of those included in trials potentially suitable for the meta-analysis. Because of the lack of heterogeneity among the trials, particularly when the Copenhagen trial was excluded, statistical methods taking this heterogeneity into account, such as the DerSimonian and Laird method,[6] would have led to similar conclusions.

We found that the benefit from radiotherapy was greatest in patients under 55 years of age. The smaller effect of treatment in the older patients could be explained by increased toxicity, but it is not possible to examine this hypothesis with the available data. However, the lack of a clearly significant reduction in mortality among patients over the age of 64 is not good evidence that the effect of treatment on survival is negligible among such patients, because of the difficulty of proving a negative result and the large confidence intervals. Therefore, this subgroup analysis should be interpreted with caution.

Nicolucci et al.[5] concluded after reviewing randomized trials of the treatment of lung cancer that a meta-analysis of existing trials would not be constructive; however, their review was based only on trials published as full papers before 1987. Our meta-analysis was based on data on individual patients submitted by each trial group, and we did not exclude unpublished data.[7] This method allowed us to avoid the exclusion of trials with insufficient published information on survival, to check for imbalances between treatment groups, to recover data on patients who had been excluded from analyses in published studies, to update follow-up information, and to take into account the whole follow-up period when comparing treatments. As a result, our analysis is more powerful and less subject to bias.

The present meta-analysis did not allow a good estimation of the survival rates after three years, because of the large proportion of patients lost to follow-up thereafter (16 percent); further follow-up will be needed. However, since approximately 90 percent of the patients included in these trials died, the results of the meta-analysis would not have been changed significantly if information about patients lost to follow-up had been included.

We were unable to evaluate the nonlethal toxicity of treatment.[1] Complication rates varied, and information about toxicity was heterogeneous.

Intention-to-treat analysis serves as an unbiased test of whether treatment has a real effect, but it may underestimate the size of the effect — i.e., the difference between the two treatment groups if all patients comply fully with their regimen. Furthermore, results may improve as more modern regimens are formulated. The results obtained in the patients receiving chemotherapy combined with radiotherapy probably do not give a true picture of what combined treatment might offer today. It is likely that there would be a major benefit if treatment variables such as the radiation dose, tissue volume, drugs administered, and timing of radiotherapy and chemotherapy were optimized.

The selection of an optimal schedule of chemotherapy combined with radiotherapy that would lead to a major increase in survival with minimal toxicity is the principal challenge raised by our study. There are theoretical reasons to favor early radiotherapy and concurrent or alternating chemotherapeutic regimens.[8] We hope that the results of future trials will settle this question.

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Appendix 1

The following trial groups and investigators (listed in alphabetical order) collaborated in the meta-analysis (detailed citations appear in Appendix 2): Cancer and Leukemia Group B (CALGB): R. Comis, W.B. Eaton, M. Green, M.C. Perry, and K.J. Propert; Finsen Institute (Copenhagen, Denmark): H.H. Hansen and K. Østerlind; Eastern Cooperative Oncology Group (ECOG): R. Creech, D. Finkelstein, M. Richter, and H. Wagner; Groupe d'Etude et de Traitement des Cancers Bronchiques (GETCB): C. Chastang and B. Lebeau; Cancer Research Campaign (London): C.M. Ash, P. Harper, R. Souhami, and S. Spiro; National Cancer Institute (Bethesda, Md.): P.A. Bunn, D.C. Ihde, and A.S. Lichter; Okayama University (Okayama, Japan): S. Hiraki, I. Kimura, T. Onoshi, and H. Ueoka; Southeastern Cancer Study Group (SECSG): A. Bartolucci, R. Birch, L.H. Einhorn, F.A. Greco, D.H. Johnson, G. Omura, and C. Perez; Southwest Oncology Group (SWOG): J. Crowley, M.S. Kies, and J. Mira; Swiss Group for Clinical Cancer Research (SAKK): E.A. Bleher, R.A. Joss, and E. Schatzmann; Ludwig Institute (Sydney, Australia): G.N. Brodie, R.M. Fox, M.A. Rosenthal, M.H.N. Tattersall, and R.L. Woods; Uppsala University (Uppsala, Sweden): O. Brodin and E. Nõu.

Coordinators: R. Arriagada and J.-P. Pignon; Writing Committee: D.C. Ihde, D.H. Johnson, M.C. Perry, and R.L. Souhami.

Appendix 2

The following trials were included in the meta-analysis of limited small-cell lung cancer treated by chemotherapy alone or chemotherapy combined with radiotherapy:

Østerlind K, Hansen HH, Hansen HS, Dombernowsky P, Hansen M, Rørth M. Chemotherapy *versus* chemotherapy plus irradiation in limited small cell lung cancer: results of a controlled trial with 5 years follow-up. Br J Cancer 1986;54:7-17. (Copenhagen trial.)

Rosenthal MA, Tattersall MHN, Fox RM, Woods RL, Brodie GN. Adjuvant thoracic radiotherapy in small cell lung cancer: ten-year follow-up of a randomized study. Lung Cancer 1991;7:235-41. (Sydney trial.)

Bunn PA Jr, Lichter AS, Makuch RW, et al. Chemotherapy alone or chemotherapy with chest radiation therapy in limited stage small cell lung cancer: a prospective randomized trial. Ann Intern Med 1987;106:655-62. (NCI [National Cancer Institute] trial.)

Birch R, Omura GA, Greco FA, Perez CA. Patterns of failure

in combined chemotherapy and radiotherapy for limited small cell lung cancer: Southeastern Cancer Study Group experience. In: Wittes RE, Coleman CN, eds. Conference on the interaction of radiation therapy and chemotherapy. NCI monographs. No. 6. Washington, D.C.: Government Printing Office, 1986:265-70. (SECSG I and II trials.)

Souhami RL, Geddes DM, Spiro SG, et al. Radiotherapy in small cell cancer of the lung treated with combination chemotherapy: a controlled trial. BMJ 1984;288:1643-6. (London trial.)

Kies MS, Mira JG, Crowley JJ, et al. Multimodal therapy for limited small-cell lung cancer: a randomized study of induction combination chemotherapy with or without thoracic radiation in complete responders; and with wide-field versus reduced-field radiation in partial responders: a Southwest Oncology Group study. J Clin Oncol 1987;5:592-600. (SWOG trial.)

Joss R, Alberto P, Bleher E, Kapanci Y, Cavalli F. Combined modality treatment of small cell lung cancer (SCCL): randomized comparison of three induction chemotherapies (CT) followed by maintenance chemotherapy with or without radiotherapy (RT) to the chest. In: Proceedings of the Fourth World Conference on Lung Cancer, Toronto, August 25–30, 1985. Toronto: International Association for Study of Lung Cancer, 1985:141. abstract. (SAKK [Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung] trial.)

Nõu E, Brodin O, Bergh J. A randomized study of radiation treatment in small cell bronchial carcinoma treated with two types of four-drug chemotherapy regimens. Cancer 1988;62:1079-90. (Uppsala trial.)

Perry MC, Eaton WL, Propert KJ, et al. Chemotherapy with or without radiation therapy in limited small-cell carcinoma of the lung. N Engl J Med 1987;316:912-8. (CALGB [Cancer and Leukemia Group B] trial.)

Creech R, Richter M, Finkelstein D. Combination chemotherapy with or without consolidation radiation therapy (RT) for regional small cell carcinoma of the lung. Proc Am Soc Clin Oncol 1988; 7:196. abstract. (ECOG [Eastern Cooperative Oncology Group] trial.)

Ohnoshi T, Hiraki S, Kimura I. Randomized trial of chemotherapy alone or with chest irradiation in limited stage small cell lung cancer. In: Kimura K, Ota K, Herberman RB, Takita H, eds. Cancer chemotherapy: challenges for the future. Vol. 2. Proceedings of the Second Nagoya International Symposium on Cancer Treatment, Nagoya, Japan, October 16–18, 1986. Amsterdam: Excerpta Medica, 1987:186-91. (Okayama trial.)

Lebeau B, Chastang C, Bréchot JM. Small cell lung cancer (SCLC): negative results of a randomized clinical trial on delayed thoracic radiotherapy administered to complete responders (CR) patients. Lung Cancer 1991;7:Suppl:94. abstract. (GETCB [Groupe d'Etude et de Traitement des Cancers Bronchiques] trial.)

Although the following trials apparently satisfied our inclusion criteria, they were excluded from the meta-analysis because individual data could not be collected and the data could not be checked:

Stevens E, Einhorn L, Rohn R. Treatment of limited small cell lung cancer. Proc Am Assoc Cancer Res Proc Am Soc Clin Oncol 1979;20:435. abstract.

Schütte J, Niederle N, Eberhardt W, et al. Sequentielle Induktionschemotherapie und Strahlenbehandlung inoperabler kleinzelliger Bronchialkarzinome: Ergebnisse einer prospektiven randomisierten Studie. Klin Wochenschr 1989;67:1182-93.

Donavan M, Baxter D, Sponzo R, Cunningham T, Horton J. The rationale for combined modality management in small cell cancer of the lung. Proc Am Assoc Cancer Res 1976;17:100. abstract.

The following trial was excluded because of confounded comparisons (randomization to thoracic radiotherapy alone [not radiotherapy combined with chemotherapy] or chemotherapy):

Carlson RW, Sikic BI, Gandara DR, et al. Late consolidative radiation therapy in the treatment of limited-stage small cell lung cancer. Cancer 1991;68:948-58.

The following trial was excluded because the radiotherapy was not limited to the thorax:

Brincker H, Hindberg J, Hansen PV. Cyclic alternating polychemotherapy with or without upper and lower half-body irradiation in small cell anaplastic lung cancer: a randomized study. Eur J Cancer Clin Oncol 1987;23:205-11.

The following trials were excluded because they studied only patients with extensive disease:

Wilson HE, Stanley K, Vincent RG, et al. Comparison of chemotherapy alone versus chemotherapy and radiation therapy of extensive small cell carcinoma of the lung. J Surg Oncol 1983;23:181-4.

Williams C, Alexander M, Glatstein EJ, Daniels JR. Role of radiation therapy in combination with chemotherapy in extensive oat cell cancer of the lung: a randomized study. Cancer Treat Rep 1977;61:1427-31.

Eagan RT, Frytak S, Lee RE, Therneau TM, Richardson RL, Creagan ET. No routine role for vincristine, adriamycin, and cyclophosphamide (VAC) or thoracic radiation therapy in extensive stage small cell lung cancer. Am J Clin Oncol 1987;10:141-5.

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3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Treatment of early breast cancer. Vol. 1. Worldwide evidence 1985–1990: a systematic overview of all available randomized trials of adjuvant endocrine and cytotoxic therapy. Oxford, England: Oxford University Press, 1990.
4. Morstyn G, Ihde DC, Lichter AS, et al. Small cell lung cancer 1973–1983: early progress and recent obstacles. Int J Radiat Oncol Biol Phys 1984;10: 515-39.
5. Nicolucci A, Grilli R, Alexanian AA, Apolone G, Torri V, Liberati A. Quality, evolution, and clinical implications of randomized, controlled trials on the treatment of lung cancer: a lost opportunity for meta-analysis. JAMA 1989;262:2101-7.
6. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clin Trials 1986;7:177-88.
7. Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited stage small cell carcinoma of the lung — a meta-analysis. Int J Radiat Oncol Biol Phys 1991;19:Suppl 1:146. abstract.
8. Arriagada R, Pignon JP, Le Chevalier T. Thoracic radiotherapy in small cell lung cancer: rationale for timing and fractionation. Lung Cancer 1989;5:237-47.