

A RANDOMIZED TRIAL OF POSTOPERATIVE ADJUVANT THERAPY IN PATIENTS WITH COMPLETELY RESECTED STAGE II OR IIIA NON-SMALL-CELL LUNG CANCER

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ABSTRACT

Background We conducted a randomized trial to determine whether combination chemotherapy plus thoracic radiotherapy is superior to thoracic radiotherapy alone in prolonging survival and preventing local recurrence in patients with completely resected stage II or IIIa non-small-cell lung cancer.

Methods After surgical staging and resection of the tumor (usually by lobectomy or pneumonectomy), the patients were randomly assigned to receive either four 28-day cycles of cisplatin (60 mg per square meter of body-surface area intravenously on day 1) and etoposide (120 mg per square meter intravenously on days 1, 2, and 3) administered concurrently with radiotherapy (a total of 50.4 Gy, given in 28 daily fractions) or radiotherapy alone (a total of 50.4 Gy, given in 28 daily fractions).

Results Of the 488 patients who were enrolled in the study, 242 were assigned to receive radiotherapy alone and 246 were assigned to receive chemotherapy and radiotherapy. The median duration of follow-up was 44 months. Treatment-associated mortality was 1.2 percent in the group given radiotherapy alone and 1.6 percent in the group given chemotherapy and radiotherapy. The median survival was 39 months in the group given radiotherapy and 38 months in the group given chemotherapy and radiotherapy ($P=0.56$ by the log-rank test). The relative likelihood of survival among patients assigned to receive chemotherapy and radiotherapy, as compared with those assigned to receive radiotherapy alone, was 0.93 (95 percent confidence interval, 0.74 to 1.18). Intrathoracic disease recurred within the radiation field in 30 of 234 patients (13 percent) in the group given radiotherapy and in 28 of 236 patients (12 percent) in the group given chemotherapy and radiotherapy ($P=0.84$); data on recurrence were not available for 18 patients.

Conclusions As compared with radiotherapy alone, adjuvant radiotherapy and chemotherapy with cisplatin and etoposide does not decrease the risk of intrathoracic recurrence or prolong survival in patients with completely resected stage II or IIIa non-small-cell lung cancer. (N Engl J Med 2000;343:1217-22.)

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THE presence of metastatic tumor in the intrathoracic lymph nodes markedly worsens the prognosis of patients with resected non-small-cell lung cancer (which includes squamous-cell carcinoma, large-cell carcinoma, and adenocarcinoma). Despite the removal of all visible tumor, cancer recurs in most patients with metastases to intrapleural or extrapleural lymph nodes. The Lung Cancer Study Group investigated the value of postoperative therapy in such patients and found that radiotherapy, combination chemotherapy (with cyclophosphamide, doxorubicin, and cisplatin), or both improved local control and disease-free survival but not overall survival.¹⁻³

Regimens containing higher doses of cisplatin⁴ or etoposide plus cisplatin also showed promise,^{5,6} but many physicians questioned the efficacy of any type of postoperative chemotherapy and considered irradiation to be standard therapy in patients with intrathoracic lymph-node metastases. To investigate the possible benefits of adjuvant chemotherapy after the resection of stage II and stage IIIa non-small-cell lung cancer, we conducted a randomized trial comparing radiotherapy alone with chemotherapy and radiotherapy.

METHODS

Study Design

This trial was initiated by the Eastern Cooperative Oncology Group (ECOG) in April 1991, and enrollment was stopped in February 1997. The following groups also participated: the Radiation Therapy Oncology Group, the North Central Cancer Treatment Group, Cancer and Leukemia Group B, and the Southwest Oncology Group.

Randomization was performed over the telephone at a central site, and all patients underwent randomization within 42 days after surgery. The institutional review board or the ethics commit-

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tee at each site reviewed and approved the protocol. Written informed consent was obtained from all patients or their surrogates.

The patients were stratified according to histologic findings (squamous-cell carcinoma vs. other types), extent of weight loss during the six months preceding enrollment (<5 percent of body weight vs. \geq 5 percent of body weight), extent of nodal involvement according to the tumor–node–metastasis (TNM) staging system (N1 [metastasis to lymph nodes in the peribronchial region, ipsilateral hilar region, or both, including direct extension] vs. N2 [metastasis to ipsilateral mediastinal lymph nodes]), and the type of lymph-node dissection (systematic sampling vs. complete dissection).

Patients assigned to the control group (the group receiving radiotherapy alone) received a total of 50.4 Gy in 28 daily fractions of 1.8 Gy. The initial portion of the treatment was administered with anteroposterior and posteroanterior portals with a limit of 36 to 42 Gy. The remainder of the treatment involved the same target volume but used a lateral or oblique field arrangement that prevented any level of the spinal cord from receiving more than 45 Gy. An additional 10.8 Gy (six fractions of 1.8 Gy) was administered to nodal levels at which extracapsular extension of nodal metastases was documented. The combined-treatment group received the identical regimen of radiotherapy administered concomitantly with etoposide (120 mg per square meter of body-surface area intravenously on days 1, 2, and 3) and cisplatin (60 mg per square meter intravenously on day 1). Chemotherapy was initiated within 24 hours after radiotherapy was begun and repeated every 28 days for a total of four cycles.

Eligibility Criteria

Patients who had undergone complete resection of pathologically documented stage II (T1–2N1M0) or stage IIIa (T1–2N2M0 or T3N1–2M0) non–small-cell lung cancer were eligible for the study. Patients with multifocal bronchoalveolar tumors within the same lobe or different ipsilateral lobes were not eligible. We used a lung-cancer staging system that was current during the years 1986 to 1997.⁷ In this staging system, T1 indicates a primary tumor that is 3 cm or less in its greatest dimension, with no invasion of lobar bronchus or pleural involvement; T2 indicates a primary tumor that is larger than 3 cm or a primary tumor of any size that involves the visceral pleura or main bronchus or is associated with atelectasis or obstructive pneumonitis that extends to the hilar region; T3 indicates a primary tumor of any size that has invaded the chest wall, diaphragm, or mediastinal pleura or pericardium but does not involve the heart, great vessels, trachea, esophagus, or vertebral body or a tumor in the main bronchus that is within 2 cm of the carina but does not involve the carina; and M0 indicates the absence of distant metastasis. Lymph-node levels were defined according to the criteria of the American Thoracic Society.⁸ Peribronchial and hilar lymph nodes (levels 10 to 13 [hilar, interlobar, lobar, and segmental nodes, respectively]) were labeled N1, whereas ipsilateral mediastinal lymph nodes (levels 1 to 9 [highest mediastinal, upper paratracheal, pretracheal and retrotracheal, lower paratracheal, subaortic, para-aortic, subcarinal, paraesophageal, and pulmonary-ligament nodes, respectively]) were labeled N2.

All patients underwent either systematic sampling of lymph nodes or complete dissection of mediastinal lymph nodes at levels 4, 7, and 10 during a right-sided thoracotomy and at level 7 and level 5 or 6 or both during a left-sided thoracotomy. During systematic sampling, a representative lymph node was removed at the specified levels. During complete dissection all lymph nodes at the specified levels were removed. All operative notes and pathology reports were reviewed by a single investigator to ensure that the labeling and the staging of lymph nodes were uniform. A videotape illustrating the technique of the dissection of mediastinal lymph nodes was made available to all participating institutions.⁹

Cervical mediastinoscopy was required beginning in June 1993 if the preoperative computed tomographic scan demonstrated mediastinal lymph nodes that exceeded 1.5 cm in the short-axis diameter. Patients with multilevel lymph-node metastases, extranodal disease, or contralateral mediastinal disease at mediastinoscopy

were ineligible for the study. A lobectomy or pneumonectomy was required, though segmental or wedge resections were permitted during the first months of the study. Postoperatively, patients had to have a forced expiratory volume in one second that would allow them to tolerate the proposed radiotherapy, as well as an ECOG performance status of 0 or 1.

Statistical Analysis

Fisher's exact test was used to compare groups with respect to categorical end points (e.g., recurrence).¹⁰ A P value of less than 0.05 was considered to indicate statistical significance, and all resulting P values were two-tailed. Survival was calculated from the date of randomization to death. Data on patients who were alive were censored on the date on which they were last known to be alive. The time to recurrence was also computed from the date of randomization. Data on patients without recurrent disease were censored on the date on which they were last known to have stable disease. Data on patients who were alive and free of recurrent disease were censored at the time of the last follow-up visit.

Survival and time to recurrence were estimated with use of the Kaplan–Meier method,¹¹ and differences between groups were compared with the log-rank test.¹² A P value of less than 0.05 was considered to indicate statistical significance, and all resulting P values were two-tailed. An overall comparison of the two groups was made, and we also compared outcomes in subgroups defined according to specific variables: nodal status (N1 or N2), histologic findings (squamous-cell carcinoma or other types), extent of weight loss in the six months before enrollment (<5 percent of body weight or \geq 5 percent of body weight), type of lymph-node dissection (complete dissection or systematic sampling), age (<60 years or \geq 60 years), sex, race (white or other), ECOG performance status (0, denoting fully active, or 1, denoting ambulatory), and TNM stage (stage II or IIIa).

Multivariate analyses with the Cox proportional-hazards model were used to estimate the simultaneous effects of prognostic factors on survival.¹³ Stepwise selection was used to ensure more parsimonious models. Variables were retained in the model if the associated two-tailed P values were 0.10 or less. Factors considered for inclusion in the model were the stratification factors (nodal status, histologic findings, extent of weight loss, and type of lymph-node dissection) and selected base-line characteristics (age, sex, race, ECOG performance status, and TNM stage).

RESULTS

Characteristics of the Patients

We enrolled 488 patients from 121 institutions; 242 were randomly assigned to receive radiotherapy alone and 246 to receive radiotherapy and chemotherapy. Table 1 lists the base-line characteristics of the patients. There were no significant differences in stratification factors between the two groups. The operative procedures were performed by 267 surgeons, 192 of whom operated on only one patient. Thirteen surgeons (5 percent) operated on six or more patients (25 percent of the patients). Sixty-five percent of patients underwent lobectomy, and 32 percent underwent pneumonectomy. There was no significant difference between the two groups in the proportions of patients who underwent each type of surgery (P=0.57).

Fourteen patients who were assigned to receive chemotherapy and radiotherapy and 11 patients who were assigned to receive radiotherapy alone did not start the treatment (15 declined the treatment, 6 were found to be ineligible, 1 died, and other illnesses de-

TABLE 1. CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	RADIOTHERAPY ALONE (N=242)	CHEMOTHERAPY AND RADIOTHERAPY (N=246)
Age		
Median — yr	60	61
Range — yr	35–81	34–77
<60 yr — no. (%)	123 (51)	120 (49)
≥60 yr — no. (%)	119 (49)	126 (51)
Sex — no. (%)		
Male	147 (61)	138 (56)
Female	95 (39)	108 (44)
Race — no. (%)		
White	211 (87)	207 (84)
Black	26 (11)	27 (11)
Other	5 (2)	12 (5)
ECOG performance status — no. (%)*		
0 (Fully active)	97 (40)	93 (38)
1 (Ambulatory)	144 (60)	153 (62)
Tumor stage — no. (%)		
T1	62 (26)	50 (20)
T2	156 (64)	171 (70)
T3	24 (10)	25 (10)
TNM stage — no. (%)†		
II	101 (42)	101 (41)
IIa	140 (58)	145 (59)
Histologic findings — no. (%)		
Squamous-cell carcinoma	86 (36)	84 (34)
Adenocarcinoma	127 (52)	132 (54)
Large-cell carcinoma	17 (7)	19 (8)
Other	12 (5)	11 (4)
Stratification factors — no. (%)		
Nodal status		
N1	113 (47)	110 (45)
N2	129 (53)	136 (55)
Histologic findings		
Squamous-cell carcinoma	86 (36)	84 (34)
Other	156 (64)	162 (66)
Extent of weight loss during the 6 mo before enrollment		
<5% of body weight	191 (79)	193 (78)
≥5% of body weight	51 (21)	53 (22)
Type of lymph-node dissection		
Complete	120 (50)	105 (43)
Sampling	122 (50)	141 (57)

*Data were not available for one patient in the radiotherapy group. ECOG denotes Eastern Cooperative Oncology Group.

†One patient in the radiotherapy group had stage IIb non-small-cell lung cancer. TNM denotes tumor–node–metastasis.

veloped in 3). Sixty-nine percent of the 232 patients who began chemotherapy and radiotherapy received all or part of the four cycles of chemotherapy, 5 percent received three cycles, and 13 percent received two cycles of chemotherapy. The most common reasons for not completing the planned chemotherapy were the patient's refusal (in the case of 36), excessive toxicity (in the case of 18), and progressive disease (in the case of 8). Eighty-four percent of the 463 patients completed the required radiotherapy (86 percent in the group given radiotherapy alone and 82 percent in the group given chemotherapy and radiotherapy).

Table 2 lists commonly encountered adverse effects.

TABLE 2. TREATMENT-RELATED ADVERSE EFFECTS.*

ADVERSE EFFECT	RADIOTHERAPY ALONE (N=230)			CHEMOTHERAPY AND RADIOTHERAPY (N=232)		
	GRADE 3	GRADE 4	GRADE 5	GRADE 3	GRADE 4	GRADE 5
	percent					
Leukopenia	<1	—	—	41	38	—
Granulocytopenia	—	1	—	14	60	—
Thrombocytopenia	—	—	—	13	5	—
Anemia	—	<1	—	13	1	—
Sepsis	1	—	—	3	1	<2
Nausea	1	—	—	20	—	—
Vomiting	<1	—	—	10	5	—
Pneumonitis	2	—	1	3	<1	<1
Esophagitis	1	—	<1	14	3	<1

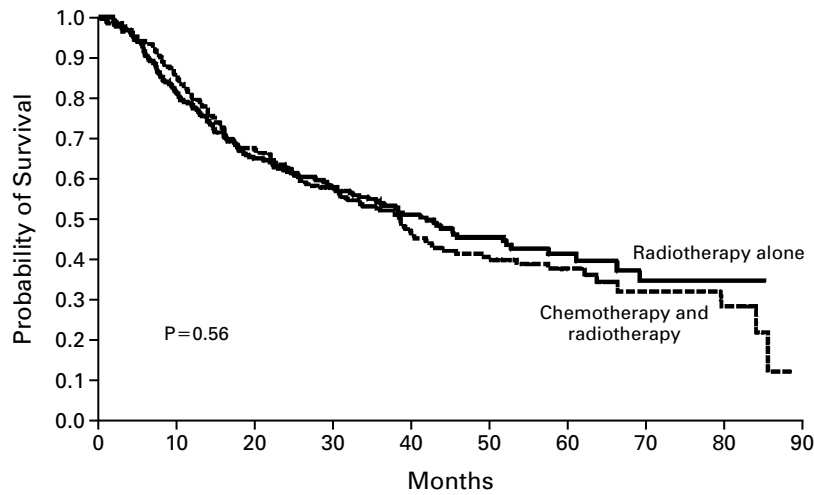
*The Common Toxicity Criteria of the National Cancer Institute were used, in which a grade of 3 indicates moderate adverse effects, a grade of 4 severe adverse effects, and a grade of 5 life-threatening adverse effects. Eleven patients in the group assigned to receive radiotherapy alone and 14 in the group assigned to receive chemotherapy and radiotherapy were excluded from the analysis because they never received the treatment. Data on adverse effects were not available for one additional patient in the radiotherapy-alone group.

Side effects of treatment were more common and more severe in the group given chemotherapy and radiotherapy. Sepsis caused two of the four deaths in this group; the other two patients died of pneumonitis and esophagitis, respectively. Two of the three deaths in the radiotherapy group were due to radiation-induced pneumonitis. The third was due to esophagitis.

Survival

The median duration of follow-up for all 488 patients was 44 months (range, 15 to 89). The median survival was 39 months (95 percent confidence interval, 30 to 52) in the group assigned to receive radiotherapy alone and 38 months (95 percent confidence interval, 31 to 42) in the group assigned to receive chemotherapy and radiotherapy (Fig. 1). The difference in survival was not significant (P=0.56 by the log-rank test). The relative likelihood of survival in the group assigned to chemotherapy and radiotherapy as compared with the group assigned to radiotherapy alone was 0.93 (95 percent confidence interval, 0.74 to 1.18).

When the two groups were compared in subgroups defined according to the four stratification factors, there was no significant difference in survival. There was also no significant difference in survival between the two groups when they were analyzed according to age (<60 years vs. ≥60 years), sex, race, TNM stage (II vs. IIIa), ECOG performance status (0 vs. 1), and



	No. OF PATIENTS	No. OF DEATHS	MEDIAN SURVIVAL (mo)
Radiotherapy	242	132	38.8
Chemotherapy and radiotherapy	246	146	37.9

Figure 1. Kaplan–Meier Estimates of Overall Survival among Patients with Stage II or IIIa Non–Small-Cell Lung Cancer, According to Whether They Received Postoperative Radiotherapy Alone or Radiotherapy and Chemotherapy.

The relative likelihood of survival in the group assigned to chemotherapy and radiotherapy as compared with the group assigned to radiotherapy alone was 0.93 (95 percent confidence interval, 0.74 to 1.18). There was no significant difference in survival between the groups ($P=0.56$ by the log-rank test). The three-year survival rate was 52 percent in the radiotherapy group and 50 percent in the chemotherapy-and-radiotherapy group. The estimated five-year survival rates were 39 percent and 33 percent, respectively.

the number of operations performed per surgeon (1 vs. ≥ 2). The factors that significantly influenced survival in the multivariate analysis are presented in Table 3.

Recurrence

Data concerning recurrence were available for 470 patients. Recurrence was documented in 53 percent of the patients in the group assigned to receive radiotherapy alone and 56 percent of the patients in the group assigned to receive chemotherapy and radiotherapy ($P=0.58$). Patterns of recurrence did not differ significantly between the two groups (Table 4). Relapse within the radiation field was documented in 30 patients (13 percent) in the group given radiotherapy alone and 28 patients (12 percent) in the group given chemotherapy and radiotherapy ($P=0.84$). The median time to recurrence was similar in the two groups ($P=0.88$ by the log-rank test): 30.4 months (95 percent confidence interval, 21.6 to 44.4) in the group given radiotherapy alone and 26.1 months (95 percent confidence interval, 18.4 to 38.5) in the group given chemotherapy and radiotherapy. The relative risk of recurrence in the group assigned

to chemotherapy and radiotherapy as compared with the group assigned to radiotherapy alone was 0.98 (95 percent confidence interval, 0.77 to 1.25).

Comparison of the two groups with respect to stratification factors revealed no significant difference in the time to recurrence. Results of the multivariate analysis are presented in Table 3.

Ineligible Patients

Of the 488 patients who were enrolled in the study, 103 (21 percent) had insufficient information for a definitive assessment of the pathological stage. Nevertheless, all patients had clear evidence of pathological involvement of either an N1 or an N2 lymph node. Twelve (2 percent) additional patients were deemed ineligible for a variety of nonsurgical reasons. The exclusion of the ineligible patients from the analysis had no effect on any of the major results.

DISCUSSION

This trial was designed with the patients assigned to radiotherapy alone as the control group, because it is widely used and apparently effective in decreasing the risk of local recurrence. The chemotherapy

TABLE 3. MULTIVARIATE ANALYSIS OF OVERALL SURVIVAL AND TIME TO RECURRENCE.*

VARIABLE	OVERALL SURVIVAL		TIME TO RECURRENCE	
	RISK RATIO (95% CI)	P VALUE	RISK RATIO (95% CI)	P VALUE
Extent of lymph-node involvement (multiple vs. single)	1.91 (1.50–2.42)	<0.001	1.82 (1.58–2.08)	<0.001
Type of lymph-node dissection (sampling vs. complete)	1.64 (1.28–2.10)	<0.001	1.32 (1.15–1.51)	<0.001
Histologic findings (other vs. squamous-cell carcinoma)	1.38 (1.06–1.81)	0.02	1.54 (1.34–2.08)	<0.001
Age (≥60 yr vs. <60 yr)	1.54 (1.21–1.96)	<0.001	Not included in model	
Sex (male vs. female)	1.26 (0.98–1.62)	0.08	Not included in model	

*CI denotes confidence interval.

TABLE 4. PATTERNS OF RECURRENCE.*

PATTERN OF RECURRENCE	RADIOTHERAPY ALONE (N=234)	CHEMOTHERAPY AND RADIOTHERAPY (N=236)	TOTAL (N=470)	P VALUE
	no. of patients (%)			
Intrathoracic	50 (21)	56 (24)	106 (23)	0.11
Distant, excluding central nervous system	54 (23)	45 (19)	99 (21)	0.09
Intrathoracic and distant, excluding central nervous system	16 (7)	12 (5)	28 (6)	0.16
Central nervous system	33 (14)	34 (14)	67 (14)	0.25

*Data on recurrence were not available for 18 patients. Some patients had recurrences at more than one site.

drugs, dosages, and number of cycles that we used were decided on by consensus and reflected what we considered to be a regimen active against non-small-cell lung cancer. Concurrent radiotherapy and chemotherapy was selected to decrease the duration of therapy, avoid a delay in the administration of either type of therapy, and exploit any radiosensitization provided by the chemotherapy.

We were unable to identify any advantage of chemotherapy and radiotherapy over radiotherapy alone in preventing local recurrence or increasing survival. Although the relative likelihood of survival was less than 1 in the group assigned to receive chemotherapy plus radiotherapy, suggesting that radiotherapy alone was superior to chemotherapy and radiotherapy, all the 95 percent confidence intervals included 1. There was therefore no evidence of the superiority of either treatment.

The simultaneous administration of chemotherapy and radiotherapy postoperatively caused a higher incidence of serious side effects than did the postoperative administration of radiotherapy alone. Though a sim-

ilar percentage of patients in each group were able to complete the full course of radiotherapy, 31 percent of patients were not able to receive all four cycles of chemotherapy. Despite the lack of a difference in treatment-related mortality between the two groups, the morbidity associated with combination therapy must be considered in the design of future trials.

The median survival of patients with stage II or IIIa non-small-cell lung cancer in our trial was longer than in previous reports. It is likely that accurate staging and the general improvement in the care of patients with recurrent cancer are responsible for this result, because no survival advantage has been associated with adjuvant radiotherapy.¹⁴

During the eight years between the initiation and the completion of this study, new chemotherapeutic agents with substantial activity against non-small-cell lung cancer were introduced. Some of these newer agents may be administered in the outpatient setting and are associated with fewer and less severe side effects than the combination of cisplatin and etoposide, but they appear to offer no survival advantage.¹⁵

Therefore, we believe that the introduction of these new drugs does not change our conclusions.

During the past two decades, the results of nine phase 3 trials of adjuvant therapy involving substantial numbers of patients with resected stage II or IIIa non-small-cell lung cancer have been published. Two studies compared radiotherapy with observation,^{2,16} two contrasted conventional chemotherapy administered at standard intervals with observation,^{1,17} and two compared chemotherapy and radiotherapy with radiotherapy alone.^{3,18} Though a significant increase in disease-free survival was observed in some of these trials, no significant increase in overall survival was documented.

Three other phase 3 trials used a novel approach in which observation was compared with a cisplatin-containing regimen followed by 6 to 12 months of a daily oral chemotherapeutic drug.¹⁹⁻²¹ All three studies demonstrated a statistically significant improvement in survival among patients who had been assigned to the treatment group. These results are of great interest but require validation before such an approach can be accepted as standard therapy.

The results of a meta-analysis of phase 3 trials of chemotherapy in patients with non-small-cell lung cancer that were conducted between 1965 and 1991 have been reported.²² Eight trials including a total of 1394 patients who were assigned either to receive cisplatin-containing chemotherapy or to undergo observation postoperatively were identified. With treatment, there was an absolute difference in two-year and five-year survival rates of 3 percent and 5 percent, respectively. However, these differences were not significant ($P=0.08$). Seven other trials compared adjuvant radiotherapy with chemotherapy and radiotherapy; six of them used cisplatin-containing regimens. The absolute increase of 2 percent in two-year and five-year survival among the 807 patients assigned to receive chemotherapy and radiotherapy was not significant ($P=0.46$). A similar meta-analysis of nine phase 3 studies in which radiotherapy was compared with observation revealed no significant difference in survival between the groups for patients with stage III disease and a possible adverse effect of radiotherapy for patients with stage II disease.¹⁴ In the light of these data, we believe that the use of adjuvant chemotherapy should be restricted to clinical trials.

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