ORIGINAL ARTICLE

Cisplatin-Based Adjuvant Chemotherapy in Patients with Completely Resected Non–Small-Cell Lung Cancer

The International Adjuvant Lung Cancer Trial Collaborative Group*

ABSTRACT

BACKGROUND

On the basis of a previous meta-analysis, the International Adjuvant Lung Cancer Trial was designed to evaluate the effect of cisplatin-based adjuvant chemotherapy on survival after complete resection of non–small-cell lung cancer.

METHODS

We randomly assigned patients either to three or four cycles of cisplatin-based chemotherapy or to observation. Before randomization, each center determined the pathological stages to include, its policy for chemotherapy (the dose of cisplatin and the drug to be combined with cisplatin), and its postoperative radiotherapy policy. The main end point was overall survival.

RESULTS

A total of 1867 patients underwent randomization; 36.5 percent had pathological stage I disease, 24.2 percent stage II, and 39.3 percent stage III. The drug allocated with cisplatin was etoposide in 56.5 percent of patients, vinorelbine in 26.8 percent, vinblastine in 11.0 percent, and vindesine in 5.8 percent. Of the 932 patients assigned to chemotherapy, 73.8 percent received at least 240 mg of cisplatin per square meter of body-surface area. The median duration of follow-up was 56 months. Patients assigned to chemotherapy had a significantly higher survival rate than those assigned to observation (44.5 percent vs. 40.4 percent at five years [469 deaths vs. 504]; hazard ratio for death, 0.86; 95 percent confidence interval, 0.76 to 0.98; P<0.03). Patients assigned to chemotherapy also had a significantly higher disease-free survival rate than those assigned to observation (39.4 percent vs. 34.3 percent at five years [518 events vs. 577]; hazard ratio, 0.83; 95 percent confidence interval, 0.74 to 0.94; P<0.003). There were no significant interactions with prespecified factors. Seven patients (0.8 percent) died of chemotherapy-induced toxic effects.

CONCLUSIONS

Cisplatin-based adjuvant chemotherapy improves survival among patients with completely resected non–small-cell lung cancer.

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WORLDWIDE, LUNG CANCER ACcounts for the largest number of new cases of cancer and of deaths from cancer annually.[1] Complete surgical resection, whenever feasible, is generally recognized as the most effective initial treatment for non–small-cell lung cancer. Despite several randomized trials, adjuvant treatment has not been shown to benefit patients who have undergone complete resection, and prolonged adjuvant treatment with alkylating agents[2] or with radiotherapy[3] in patients with early-stage disease has even had deleterious effects on long-term survival. A meta-analysis[2] suggested that cisplatin-based adjuvant chemotherapy could yield an absolute overall survival advantage of 5 percent at five years. Several cooperative groups launched prospective, randomized trials to test this hypothesis.

The main objective of the International Adjuvant Lung Cancer Trial (IALT) was to compare the effect on overall survival of adjuvant chemotherapy consisting of cisplatin plus a vinca alkaloid or etoposide with that of no adjuvant chemotherapy in patients with completely resected non–small-cell lung cancer.

METHODS

TRIAL DESIGN AND TREATMENT OPTIONS

Each participating center could determine the pathological stages of disease to include, the dose of cisplatin given per cycle, the drug that was combined with cisplatin, and the postoperative radiotherapy policy. Each center selected its options (Table 1) before the study began. Postoperative radiotherapy, when delivered, was given after the completion of chemotherapy in the chemotherapy group. This open-choice design was chosen to facilitate accrual, allow broad generalization of the results, and take into account the uncertainty regarding the best available chemotherapy regimen.

ELIGIBILITY CRITERIA

Eligible patients had pathologically documented non–small-cell lung cancer of stage I, II, or III (according to the 1986 classification of the American Joint Committee on Cancer[4]) and had undergone a complete surgical resection. Other inclusion criteria were an age between 18 and 75 years and the absence of previous chemotherapy or radiotherapy, contraindications to chemotherapy, and previous cancer other than nonmelanoma skin cancer or carcinoma in situ of the cervix. Local ethics committees approved the protocol according to the legal regulations in each participating country. When the study began in 1995, informed consent was obtained from each patient according to the regulations of the participating country; in 1999, all participants were required to give written informed consent.

RANDOMIZATION

Eligible patients were randomly assigned to the adjuvant-chemotherapy group or the control group by fax within 60 days after surgery through a centralized randomization system at the Institut Gustave-Roussy in Villejuif, France. Randomization was stratified according to the center, type of surgery (pneumonectomy vs. other surgical procedures), and pathological stage (I vs. II vs. III) with the use of a minimization procedure.[5] Patients from Sweden underwent randomization through the Uppsala Oncologic Center with stratification according to the same factors. In the chemotherapy group, the assigned treatment was to start within 60 days after surgery and within 14 days after randomization.

FOLLOW-UP

Six months after randomization, the data center collected a one-page treatment form describing the treatment administered and the occurrence of World Health Organization (WHO) toxic effects of grade 4 or grade 5 (lethal)[6] in each patient. Subsequently, the same one-page follow-up form was required annually. All patients had to be followed until death or the cut-off date of the analysis.

SITE VISITS AND TRIAL MONITORING

Site visits were performed at all centers that included 30 or more patients and at other, randomly selected centers. A steering committee composed of investigators from different countries met yearly to monitor the progress of the trial. An independent data-monitoring committee comprising two clinicians and two statisticians examined the progress of the study, adverse effects, and the interim analyses.

STATISTICAL ANALYSIS

The primary end point was overall survival after randomization. Secondary end points were disease-free survival, second primary cancers, and adverse effects. The events considered in disease-free survival were locoregional or distant recurrences and death without a recurrence. Median follow-up was estimated with the use of the inverse Kaplan–Meier method.[7]

Table 1. Treatment Options Offered to Each Participating Center.

Treatment Option	Timing of Treatment
Cisplatin	
80 mg/m² for 4 cycles	Days 1, 22, 43, 64
100 mg/m² for 3 cycles	Days 1, 29, 57
100 mg/m² for 4 cycles	Days 1, 29, 57, 85
120 mg/m² for 3 cycles	Days 1, 29, 71
Drug combined with cisplatin	
Vindesine, 3 mg/m² per day	Weekly from days 1 to 29*
	Then every 2 weeks after day 43 until last cisplatin administration
Vinblastine, 4 mg/m² per day	Weekly from days 1 to 29*
	Then every 2 weeks after day 43 until last cisplatin administration
Vinorelbine, 30 mg/m² per day	Weekly from day 1 to last cisplatin administration*
Etoposide, 100 mg/m² per day	Days 1 to 3 with each cisplatin administration
Postoperative radiotherapy†	
Never	
Pathological stage N2 only	After chemotherapy in the chemotherapy group, after randomization in the control group
Pathological stages N1 and N2	After chemotherapy in the chemotherapy group, after randomization in the control group

* The frequency of delivery was adapted according to the blood count.
† Postoperative radiotherapy consisted of 60 Gy or less, delivered to mediastinal lymph nodes, with conventional fractionation of the dose. N denotes node in the TNM (tumor–node–metastasis) staging system.

The trial was designed to demonstrate an absolute improvement in survival of 5 percent, from 50 percent to 55 percent, at five years with adjuvant chemotherapy, on the basis of the hypothesis generated by the meta-analysis.[2] A total of 3300 patients was required to provide the study with 90 percent power with a 5 percent type I one-sided error rate (with the use of a log-rank test). The trial was reformulated with a two-sided test on the recommendation by the data-monitoring committee, and this change provided the study with a power of 83 percent to detect a 5 percent difference in survival and a power of 90 percent to detect a 5.6 percent difference with the same sample size. Interim analyses were planned after 320 and 640 deaths. The data-monitoring committee was to consider stopping the trial if the results differed significantly between groups ($P<0.001$).[8]

All analyses were performed strictly according to the intention-to-treat principle and included all randomized patients, eligible or not. For the main analysis of overall survival, we used a Cox model[9] adjusted according to previously defined stratification factors (center, stage of disease, and type of surgery). For secondary analyses, we used Cox models to study variations in treatment effects according to major base-line characteristics (age, sex, performance status, type of surgery, stage of disease,

pathological nodal [N] stage, and histologic findings) and treatment options (the dose of cisplatin, the drug that was combined with cisplatin, and the radiotherapy policy). All reported P values are two-sided. Data were entered and checked with the use of PIGAS software[10] and analyzed with the use of SAS software, version 8.2.

RESULTS

ACCRUAL

Enrollment started in February 1995. Beginning in 1999, the rate of enrollment slowed, mainly because of rising interest in the preoperative use of chemotherapy. Because of this decrease, the steering committee, whose members were unaware of the results of any interim analyses, decided to discontinue recruitment as of December 31, 2000, with the approval of the data-monitoring committee. A total of 1867 patients underwent randomization. They were recruited by 148 centers in 33 countries. Fifty centers, each of which enrolled 10 or more patients, enrolled a total of 1468 patients. The cut-off date for the analysis of follow-up data was September 1, 2002. The median follow-up was 56 months in each group. The survival status of 1831 patients (98.1 percent) was known in 2002. The remaining 36 patients can be considered as lost to follow-up.

Table 2. Characteristics of the Patients.*		
Characteristic	Chemotherapy Group (N=932)	Control Group (N=935)
Age — yr		
Median	59	59
Range	27–77†	32–75
Sex — no. (%)		
Male	752 (80.7)	750 (80.2)
Female	180 (19.3)	185 (19.8)
Pathological TNM stage — no. (%)‡		
Stage I		
T1N0	96 (10.3)	87 (9.3)
T2N0	237 (25.4)	261 (27.9)
Stage II		
T1N1	40 (4.3)	40 (4.3)
T2N1	190 (20.4)	182 (19.5)
Stage III		
T3N0	84 (9.0)	73 (7.8)
T3N1	38 (4.1)	37 (4.0)
T1N2	33 (3.5)	24 (2.6)
T2N2	143 (15.3)	160 (17.1)
T3N2	60 (6.4)	54 (5.8)
T4N0	6 (0.6)	6 (0.6)
T4N1	3 (0.3)	8 (0.9)
T4N2	2 (0.2)	3 (0.3)
Type of surgery — no. (%)		
Pneumonectomy	324 (34.8)	324 (34.6)
Lobectomy	595 (63.8)	603 (64.5)
Segmentectomy	13 (1.4)	8 (0.9)
WHO performance status — no. (%)		
0	505 (54.2)	499 (53.4)
1	355 (38.1)	372 (39.8)
2	72 (7.7)	64 (6.8)
Histologic type — no. (%)		
Squamous-cell carcinoma	428 (45.9)	444 (47.5)
Adenocarcinoma	386 (41.4)	368 (39.4)
Large-cell carcinoma	60 (6.4)	62 (6.6)
Mixed	40 (4.3)	41 (4.4)
Other	18 (1.9)	20 (2.1)

* Because of rounding, percentages may not total 100. WHO denotes World Health Organization.

† Four patients were older than 75 years of age: two were 76 years old, and two were 77 years old.

‡ The 1986 classification of the American Joint Committee on Cancer was used to determine the tumor (T) and node (N) stage.[4]

STUDY POPULATION

Among the 1867 patients, 932 were randomly assigned to the chemotherapy group and 935 to the control group. Table 2 shows the base-line characteristics of the patients. Twenty-five patients were found to be ineligible: 17 in the chemotherapy group (10 underwent randomization between 61 and 122 days after surgery, 4 were older than 75 years of age, 1 had a previous lung cancer, 1 had a sarcomatoid carcinoma, and 1 had a history of nephropathy) and 8 in the control group (4 patients underwent randomization between 61 and 122 days after sur-

gery, 1 had a previous lung cancer, 1 had a previous bladder cancer, 1 had incomplete tumor resection, and 1 had a lung metastasis from a urothelial carcinoma).

THERAPY

Options

The chemotherapy options chosen are shown in Table 3. A regimen combining 100 mg of cisplatin per square meter of body-surface area for three or four cycles with etoposide was selected for 49.3 percent of the patients. Overall, postoperative radiotherapy was planned for 30.6 percent of patients (1.9 percent with pathological stage N0 disease, 33.7 percent with pathological stage N1, and 64.3 percent with pathological stage N2).

Compliance

In the chemotherapy group, 73.8 percent of patients received at least 240 mg of cisplatin per square meter and 7.8 percent never received chemotherapy, mainly because of the patient's or physician's refusal. The chief reasons for incomplete treatment were adverse effects (in 51.5 percent of patients), the patient's or physician's decision (24.3 percent), early death (8.1 percent), or disease progression (5.1 percent). The median delay between surgery and the start of chemotherapy was 40 days, and the delay exceeded 60 days in 6.6 percent of the patients. In the control group, 2.1 percent of the patients received chemotherapy.

Among the 572 patients (284 in the chemotherapy group and 288 in the control group) assigned to receive adjuvant thoracic radiotherapy, only 70.4 percent of those in the chemotherapy group and 84.2 percent of those in the control group actually received this treatment. This difference was mainly due to a longer delay between randomization and radiotherapy in the chemotherapy group; during this period certain events (e.g., early death or disease progression) prevented some patients from receiving radiotherapy. Among the 1295 patients who were not assigned to receive radiotherapy, 2.3 percent of those in the chemotherapy group actually received radiotherapy, as did 2.6 percent of those in the control group. The median total dose of postoperative radiotherapy was 50 Gy.

Acute Toxic Effects of Chemotherapy

In the chemotherapy group, 851 patients received chemotherapy. Seven patients (0.8 percent) died of toxic effects of chemotherapy: bone marrow aplasia

Table 3. Distribution of Patients as Stratified According to the Chemotherapy Options Chosen before Randomization.

Dose of Cisplatin	Drug Combined with Cisplatin				
	Vindesine	Vinblastine	Vinorelbine	Etoposide	Total
	number of patients				
80 mg/m² of body-surface area for 4 cycles	4	105	124	94	327
100 mg/m² for 3 cycles	103	43	185	484	815
100 mg/m² for 4 cycles	0	57	48	436	541
120 mg/m² for 3 cycles	1	0	143	40	184
Total	108	205	500	1054	1867

in five patients, renal failure in one, and hyponatremia in one. Two of these patients had received a cisplatin dose of 120 mg per square meter, four had received a dose of 100 mg per square meter, and one had received a dose of 80 mg per square meter. The rate of lethal toxic effects was 2.4 percent after a cisplatin dose of 120 mg per square meter, as compared with 0.6 percent after a dose of 100 mg per square meter or less (P=0.15). A total of 22.6 percent of the patients had at least one episode of a grade 4 toxic effect, mainly neutropenia (17.5 percent), thrombocytopenia (2.6 percent), and vomiting (3.3 percent). The rates of other grade 4 toxic effects did not exceed 1.0 percent.
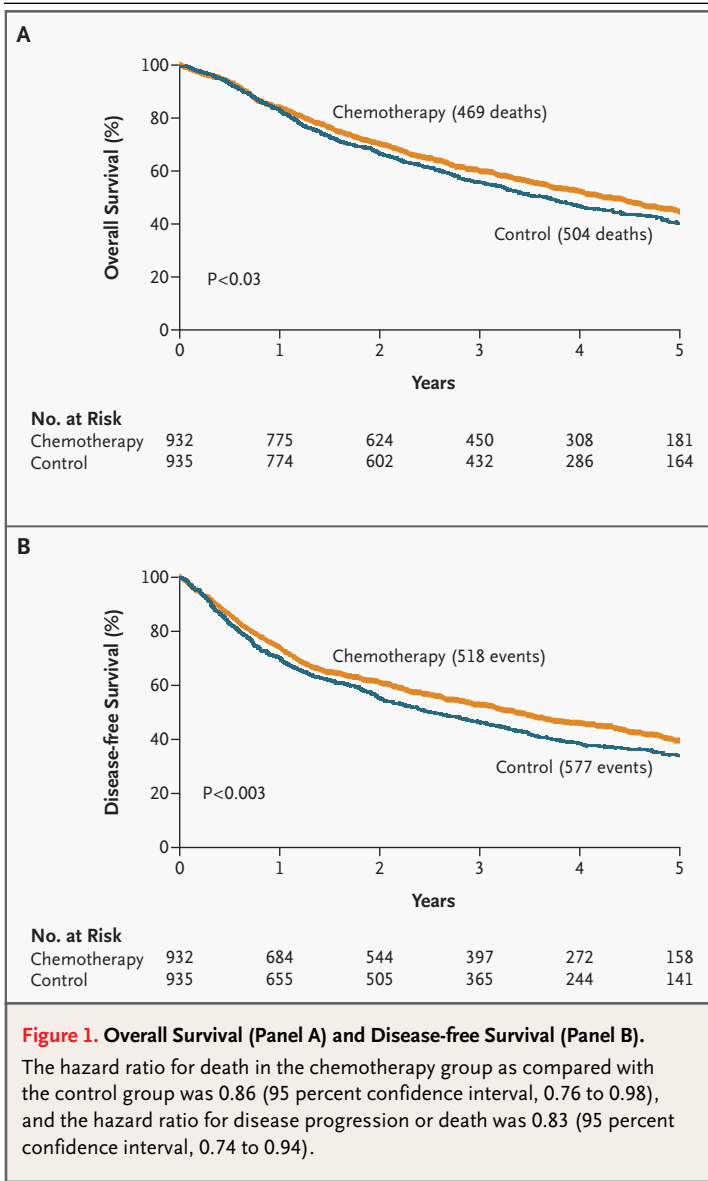
OVERALL SURVIVAL

Among the 1867 randomized patients, 973 died: 469 in the chemotherapy group and 504 in the control group. The survival rate was significantly higher in the chemotherapy group (P<0.03) (Fig. 1A). The hazard ratio for death was 0.86 (95 percent confidence interval, 0.76 to 0.98) in the chemotherapy group. The two-year survival rates were 70.3 percent in the chemotherapy group and 66.7 percent in the control group, and the five-year survival rates were 44.5 percent and 40.4 percent, respectively (Fig. 1A). Progression of disease caused the death of 361 patients in the chemotherapy group and of 405 patients in the control group. Hazard-ratio variations were studied according to predefined factors, including treatment options, demographic characteristics (age and sex), and clinical characteristics (stage of disease, type of surgery, histologic type, and WHO performance status). All P values for the interactions were 0.14 or higher (Fig. 2). The result of the test for heterogeneity of the treatment effect among center strata was not significant (P=0.11).

DISEASE-FREE SURVIVAL

There were 518 events (disease progression or death) in the chemotherapy group and 577 in the control group. The disease-free survival rate was significantly higher in the chemotherapy group (P< 0.003) (Fig. 1B). The hazard ratio for death or recurrence was 0.83 (95 percent confidence interval, 0.74 to 0.94) in the chemotherapy group. The two-year disease-free survival rates were 61.0 percent in the chemotherapy group and 55.5 percent in the control group, and the five-year disease-free survival rates were 39.4 percent and 34.3 percent, respectively (Fig. 1B). There were no significant interactions between treatment and the covariates, as defined for overall survival (all P values were above 0.15).

DISCUSSION

This large trial showed that cisplatin-based chemotherapy improves survival among patients who have undergone complete resection of non–small-cell lung cancer. The hypothesis we tested was based on the results of a meta-analysis of chemotherapy for non–small-cell lung cancer,[2] which showed a nonsignificant 5 percent absolute increase in the five-year survival rate with the use of adjuvant cisplatin-based chemotherapy (without postoperative radiotherapy). Our study was launched just after the publication of the meta-analysis.[2] An open-choice design was adopted. The optimal dose of cisplatin per cycle was controversial, so we settled on a range between 80 and 120 mg per square meter per cycle, for a total dose of 300 to 400 mg per square meter. The drugs that were combined with cisplatin were those available in most countries at the time the study was launched. In addition, when the study was planned, there was uncertainty about the stages

Figure 1. Overall Survival (Panel A) and Disease-free Survival (Panel B).
The hazard ratio for death in the chemotherapy group as compared with the control group was 0.86 (95 percent confidence interval, 0.76 to 0.98), and the hazard ratio for disease progression or death was 0.83 (95 percent confidence interval, 0.74 to 0.94).

of disease that were likely to benefit from adjuvant chemotherapy and about the indications for postoperative radiotherapy. Restricting the amount of information collected at randomization and during follow-up facilitated enrollment, as in previous trials.[11,12]

The absolute five-year benefit in overall survival was 4.1 percent, a value that is concordant with the estimation from the chemotherapy meta-analysis.[2] Survival according to the stage of disease in our study was similar to that in the meta-analysis. Our study also showed a benefit of chemotherapy with respect to disease-free survival (an absolute

difference of 5.1 percent at five years). There were no significant interactions between treatment effect and the patients' characteristics or the treatment options on overall or disease-free survival. One fourth of the patients received postoperative radiotherapy, with a moderate excess in the control group (27.7 percent vs. 22.9 percent). Radiotherapy might have increased the rate of death from causes other than cancer in the control group, thereby artificially increasing the benefit of adjuvant chemotherapy. However, this possibility appears to be highly unlikely because the deleterious effect of adjuvant radiotherapy in the Postoperative Radiotherapy (PORT) meta-analysis[3] was most apparent in patients with pathological stage N0 or N1 disease; patients with stage N0 or N1 who received radiotherapy accounted for only 9.9 percent of the patients in our study. There was, moreover, no significant interaction between the effect of chemotherapy and postoperative radiotherapy (P=0.66).

The size of the absolute benefit derived from adjuvant treatment in our study is meaningful,[1,13] given that worldwide, every year about 900,000 people below the age of 75 years receive the diagnosis of lung cancer.[1,13] Approximately 80 percent of these cancers are non–small-cell carcinomas, one third of those are resectable, and 75 percent of those are candidates for adjuvant chemotherapy. Thus, approximately 180,000 cases would be eligible for treatment annually. Our results indicate that roughly 7000 deaths from non–small-cell carcinoma would be averted annually with the use of adjuvant cisplatin-based chemotherapy.

Our study can be compared with three recent randomized trials of adjuvant chemotherapy.[14-16] The Adjuvant Lung Project Italy–European Organization for Research and Treatment of Cancer trial enrolled 1209 patients,[14] of whom 1088 were included in the analysis. The chemotherapy regimen combined mitomycin, vindesine, and cisplatin (100 mg per square meter) for three cycles. Forty-three percent of the patients received postoperative radiotherapy. The hazard ratio for death in the adjuvant-therapy group, as compared with the control group, was 0.96 (95 percent confidence interval, 0.81 to 1.13). It is noteworthy that in a randomized trial investigating preoperative chemotherapy,[17] mitomycin-based chemotherapy was also associated with an excess of early deaths. The second trial evaluated the use of uracil–tegafur as adjuvant chemotherapy in 979 patients with pathological stage T1N0 or T2N0 adenocarcinoma.[15] A significant survival benefit was ob-

Covariate	Chemotherapy Group	Control Group	P Value for Interaction	P Value for Trend	Hazard Ratio
	No. of deaths/No. of patients				
Age			0.46	0.26	
<55 yr	141/314	163/316			
55–64 yr	181/355	214/386			
>64 yr	147/263	127/233			
Sex			0.65	—	
Male	390/752	417/750			
Female	79/180	87/185			
WHO performance status			0.14	0.21	
0	240/505	259/499			
1	186/355	213/372			
2	43/72	32/64			
Type of surgery			0.98	—	
Pneumonectomy	182/324	193/324			
Lobectomy or segmentectomy	287/608	311/611			
Tumor stage			0.57	0.32	
1	67/169	59/151			
2	282/570	314/603			
3 or 4	120/193	131/181			
Nodal status			0.80	0.56	
0	164/423	174/427			
1	144/271	155/267			
2	161/238	175/241			
Stage			0.41	0.21	
I	115/333	122/348			
II	123/230	126/222			
III	231/369	256/365			
Histologic type			0.77	—	
Squamous cell	205/428	223/444			
Adenocarcinoma	199/386	208/368			
Other	65/118	73/123			
Dose of cisplatin per cycle			0.45	0.63	
80 mg/m^2	85/163	93/164			
100 mg/m^2	334/679	360/677			
120 mg/m^2	50/90	51/94			
Drug combined with cisplatin			0.77	—	
Vindesine	26/52	26/56			
Vinblastine	62/103	70/102			
Vinorelbine	113/248	128/252			
Etoposide	268/529	280/525			
Planned radiotherapy			0.66	—	
No	287/648	303/647			
Yes	182/284	201/288			
Total	469/932	504/935			

0.0 0.5 1.0 1.5 2.0 2.5

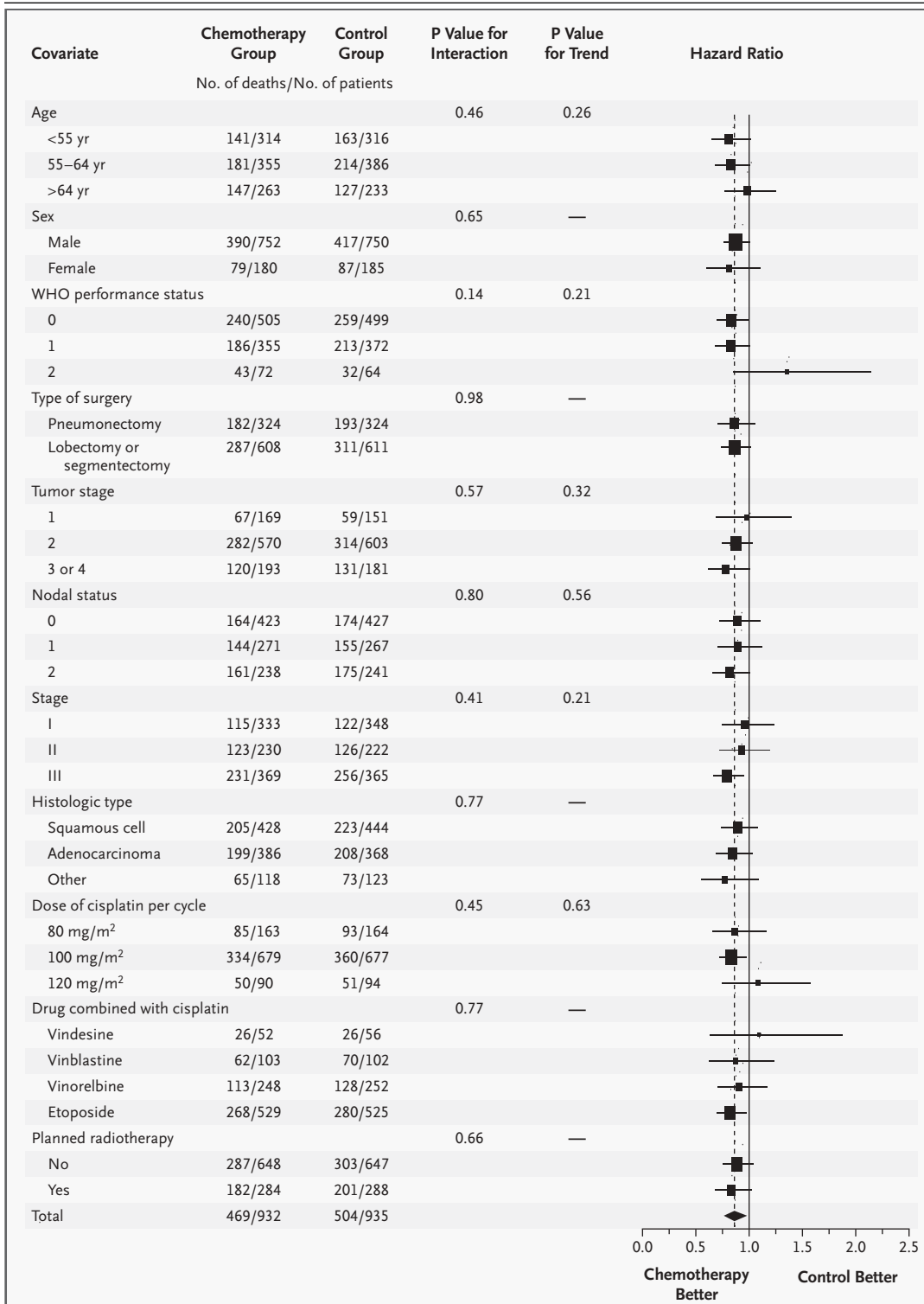Chemotherapy Better   Control Better

Figure 2. Hazard Ratios (with 95 Percent Confidence Intervals) for Death in Prespecified Subgroups of Patients in the Chemotherapy Group, as Compared with Patients in the Control Group.

WHO denotes World Health Organization.

served with adjuvant chemotherapy (P=0.04), but the benefit appeared to be limited to the subgroup with T2N0 disease. The results of these two trials and our trial are in the same range. A North American Intergroup trial[16] enrolled 488 patients and compared postoperative radiotherapy alone with radiotherapy plus concurrent treatment with etoposide and cisplatin. No significant difference was observed in overall survival (hazard ratio for death in the chemotherapy group, 1.08; 95 percent confidence interval, 0.85 to 1.35). The concomitant use of chemotherapy and radiotherapy may explain this negative result.

Other studies evaluating cisplatin-based chemotherapy have recently been completed. A joint analysis of the largest recent trials of adjuvant cisplatin-based chemotherapy (Lung Adjuvant Cisplatin Evaluation [LACE]) is under way. This analysis will include more than 4000 patients and will allow potential predictive factors for treatment effects to be investigated with more statistical power than in our study. The large number of patients evaluated in postoperative-chemotherapy trials contrasts with the total of less than 600 patients included in the reported randomized studies of preoperative chemotherapy; this approach remains investigational in early non–small-cell lung cancer.[18] Moreover, the use of new cytotoxic drugs should be evaluated in future trials.

The benefit of adjuvant treatment has been demonstrated in several other cancers in adults. Postoperative chemotherapy in patients with early breast cancer yields an absolute overall survival benefit of 3.2 percent at 5 years and 6.3 percent at 10 years.[19] Adjuvant tamoxifen in the same setting yields an overall benefit of 3.6 percent at 5 years and 6.2 percent at 10 years.[19] In patients with early ovarian cancer,[20] platinum-based chemotherapy affords a survival benefit of 8 percent at five years. In patients with colon cancer,[21] fluorouracil and folinic acid af-

ford a survival benefit of 5 percent at three years for Dukes' class B or C tumors. Both thoracic radiotherapy[22] and prophylactic brain irradiation[23] result in a survival benefit of 5.4 percent at three years in patients with small-cell lung cancer.

A large proportion of patients with cancer receive adjuvant treatment without any benefit, and some have only adverse effects. The proportion of deaths that are due to toxic effects of treatment is generally below 1.0 percent (0.8 percent in our study). Even if this proportion is low, the importance of treatment-induced toxicity should be considered in the indications for treatment and in the discussion of treatment with patients. We did not identify a group of patients who failed to benefit from adjuvant cisplatin-based chemotherapy. However, it might be possible to single out such a group in a larger population of patients, such as that included in the LACE project. In addition, the IALT study includes a program aimed at studying tissue specimens from about 1000 patients in order to identify potential markers that could better define candidates for chemotherapy.

In conclusion, our results strongly support the use of three or four cycles of cisplatin-based chemotherapy after complete surgical resection in patients with non–small-cell lung cancer. The benefit observed is in the same range as the improvement obtained with adjuvant chemotherapy in patients with other cancers, such as breast cancer, colon cancer, and ovarian cancer.

APPENDIX

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