

## Randomized Study of Adjuvant Chemotherapy for Completely Resected Stage I, II, or IIIA Non-Small-Cell Lung Cancer

Giorgio V. Scagliotti, Roldano Fossati, Valter Torri, Lucio Crinò, Giuseppe Giaccone, Giovanni Silvano, Massimo Martelli, Maurizia Clerici, Francesco Cognetti, Maurizio Tonato

For the Adjuvant Lung Project Italy/European Organisation for Research and Treatment of Cancer–Lung Cancer Cooperative Group Investigators

**Background:** Surgery is the primary treatment for patients with stage I, II, or IIIA non-small-cell lung cancer (NSCLC). However, long-term survival of NSCLC patients after surgery alone is largely unsatisfactory, and the role of adjuvant chemotherapy in patient survival has not yet been established. **Methods:** Between January 1994 and January 1999, 1209 patients with stage I, II, or IIIA NSCLC were randomly assigned to receive mitomycin C (8 mg/m<sup>2</sup> on day 1), vindesine (3 mg/m<sup>2</sup> on days 1 and 8), and cisplatin (100 mg/m<sup>2</sup> on day 1) every 3 weeks for three cycles (MVP group; n = 606) or no treatment (control group; n = 603) after complete resection. Randomization was stratified by investigational center, tumor size, lymph-node involvement, and the intention to perform radiotherapy. The primary endpoint was overall survival and secondary endpoints were progression-free survival and toxicity associated with adjuvant treatment. Survival curves were analyzed using the log-rank test. All statistical tests were two-sided. **Results:** After a median follow-up time of 64.5 months, there was no statistically significant difference between the two patient groups in overall survival (hazard ratio = 0.96, 95% confidence interval = 0.81 to 1.13; *P* = .589) or progression-free survival (hazard ratio = 0.89, 95% confidence interval = 0.76 to 1.03; *P* = .128). Only 69% of patients received the three planned cycles of MVP. Grades 3 and 4 neutropenia occurred in 16% and 12%, respectively, of patients in the MVP arm. Radiotherapy was completed by 65% of patients in the MVP arm and by 82% of patients in the control group. In the multivariable analysis, only disease stage and sex were associated with survival. **Conclusion:** This randomized trial failed to prospectively confirm a statistically significant role for adjuvant chemotherapy in completely resected NSCLC. Given the poor compliance with the MVP regimen used in this study, future studies should explore more effective treatments. [J Natl Cancer Inst 2003;95:1453–61]

Although radical surgery is the primary treatment for early non-small-cell lung cancer (NSCLC), the long-term survival of patients who undergo surgery alone is largely disappointing, with estimated 5-year survival rates ranging from 67% for those with pathologic stage IA disease to 39% for those with pathologic

stage IIB disease (1). Among patients who undergo surgery alone, relapses occur more commonly at distant sites (2–5), and the efficacy of adjuvant treatments remains unproven [reviewed in (6)].

In 1995, a meta-analysis reviewed eight cisplatin-based adjuvant chemotherapy trials that enrolled 1394 NSCLC patients and reported that such therapy was associated with a 13% reduction of the risk of death. However, that risk reduction was of borderline statistical significance (7). In the early 1990s, results of a randomized clinical trial in patients with advanced NSCLC demonstrated that two different chemotherapy triplet combinations—mitomycin C, ifosfamide, and cisplatin and mitomycin C, vindesine, and cisplatin (MVP)—were superior to the doublet combination of cisplatin and etoposide in terms of overall response rate and survival (8). Of the three chemotherapies examined, MVP yielded the best median survival time, an incidence of grades 3 and 4 toxicities comparable to that associated with the doublet combination of cisplatin and etoposide, and a better therapeutic ratio than mitomycin C, ifosfamide, and cisplatin (8). To investigate the potential benefits of adjuvant chemotherapy for survival, we designed Adjuvant Lung Project Italy (ALPI), a randomized trial to test the MVP regimen in patients with radically resected stages I–II and IIIA NSCLC.

*Affiliations of authors:* G. V. Scagliotti, University of Torino, Department of Clinical and Biological Sciences, S. Luigi Hospital, Thoracic Oncology Unit, Orbassano (Torino), Italy; R. Fossati, V. Torri, Laboratory of Clinical Cancer Research, Mario Negri Institute, Milan, Italy; L. Crinò, Division of Medical Oncology, Bellaria Hospital, Bologna, Italy; G. Giaccone, Division of Medical Oncology, Free University Medical Center, Amsterdam, The Netherlands; G. Silvano, Department of Radiation Oncology, Moscati Hospital, Taranto, Italy; M. Martelli, Division of Thoracic Surgery, S. Camillo-Forlanini Hospital, Rome, Italy; M. Clerici, Division of Medical Oncology, S. Giuseppe Hospital, Milan, Italy; F. Cognetti, Division of Medical Oncology A, Regina Elena Cancer Institute, Rome; M. Tonato, Division of Medical Oncology, Policlinico Hospital, Perugia, Italy.

*Correspondence to:* Giorgio V. Scagliotti, MD, PhD, University of Torino, Department of Clinical and Biological Sciences, S. Luigi Hospital, Regione Gonzole 10, 10043 Orbassano (Torino), Italy (e-mail: giorgio.scagliotti@unito.it).

See "Appendix" for a list of contributors to this study.

See "Notes" following "References."

DOI: 10.1093/jnci/djg059

Journal of the National Cancer Institute, Vol. 95, No. 19, © Oxford University Press 2003, all rights reserved.

## PATIENTS AND METHODS

### Study Design and Treatment Schedules

From January 1994 through January 1999, 66 Italian centers participated in this study; beginning in April 1995, five European centers located outside Italy that were affiliated with the European Organisation for Research and Treatment of Cancer (EORTC)–Lung Cancer Cooperative Group (LCCG) joined the study. Data monitoring and quality-control procedures were set in place to ensure the quality of the information collected by the participating centers. These procedures included random site visits and source validation procedures. An independent data monitoring committee was set up to check the progress of the trial. One interim analysis was planned and performed on data collected as of June 1998 and submitted to the independent data monitoring committee of the study. It was then decided to continue the follow-up of the patients until reaching the planned number of events.

After surgery, patients who fulfilled the eligibility criteria were randomly assigned to receive the MVP regimen (mitomycin C at 8 mg/m<sup>2</sup> on day 1, vindesine at 3 mg/m<sup>2</sup> on days 1 and 8, and cisplatin at 100 mg/m<sup>2</sup> on day 1 every 3 weeks for three cycles) or no chemotherapy. Randomization was performed centrally by the Laboratory of Clinical Cancer Research at the Mario Negri Institute (Milan, Italy) and by the EORTC Data Center (Brussels, Belgium). Stratification included tumor size and lymph-node involvement, which were defined according to the tumor–node–metastasis staging system (9), investigational center, and intended radiotherapy. All patients were randomly assigned to a treatment group within 42 days after surgery. Written informed consent was obtained from each patient before study entry. The study was approved by the local ethical review boards and the protocol review committee of the EORTC; we also followed the recommendations of the Declaration of Helsinki for biomedical research involving human subjects.

Dose adjustments within a treatment cycle were based on patients' absolute neutrophil and platelet counts, which were measured on day 8 of each cycle of therapy, and on the assessment of non-hematologic toxicities. Patients who experienced progressive disease (defined as recurrence or relapse of radiologically or clinically detectable neoplastic disease) or unacceptable toxicity (defined as grade 4 hematological toxicity persisting at day 1 of the subsequent courses of chemotherapy or any grade 4 nonhematological toxicity occurring at any time during the chemotherapy treatment), or who did not receive chemotherapy for 6 weeks from the time of the last treatment, were discontinued from the study. The second and the third cycles of chemotherapy were administered every 3 weeks only to patients who had fully recovered from toxicities associated with the previous cycle of therapy; otherwise, chemotherapy was delayed for 1 week and, for patients with any persisting grade 2 toxicity, a 25% dose reduction was planned on day 28. For patients with any higher grade toxicities, the chemotherapy cycle was further delayed by 1 week. Toxicity was graded according to World Health Organization criteria (10).

Patients received adjuvant radiotherapy according to the policy of the individual participating center. The treatment policy for adjuvant radiotherapy was decided before the first patient from each center was enrolled into the study and was applied, according to each stage of the disease, in all patients from that specific center; for patients in the MVP arm, radio-

therapy was initiated 3–5 weeks after the last MVP treatment and for patients in the control arm, radiotherapy was initiated 4–6 weeks after radical surgery. In both study arms, the total radiotherapy dose was 50–54 Gy (2 Gy/day, 5 days/week) over 5–6 weeks. Radiotherapy was administered to the clinical target volume through two or three antero-posterior, postero-anterior, lateral, or oblique fields. In cases of documented extracapsular invasion of any lymph node, an additional dose of 6 Gy was specifically delivered to those involved areas. Acute toxicities and late toxicity associated with radiotherapy were graded according to Radiation Therapy Oncology Group criteria (11).

After patients were off the protocol therapy (chemotherapy and/or radiotherapy), we assessed their disease status by monitoring them every 3 months for the first 2 years, then every 6 months during the third year, and annually thereafter. Monitoring consisted of a clinical examination. Each patient received a chest x-ray every 6 months for the first 2 years after completion of chemotherapy and/or radiotherapy, and then once a year thereafter. In 2002, patients who were still alive were flagged with the National Death Registry to ensure the collection of long-term mortality data. Median follow-up time was 64.5 months.

### Eligibility and Exclusion Criteria

Patients who had undergone complete resection of pathologically documented stage I, II, or IIIA NSCLC by either lobectomy or pneumonectomy were eligible for this study. Patients who had more limited, albeit pathologically complete, resections were also eligible for our study. We used the International Union Against Cancer (UICC) and American Joint Committee on Cancer staging system (9) for lung cancer as a guide to stage patients. Lymph-node involvement was defined according to the criteria of the American Thoracic Society (12). Surgical procedures used for staging and treatment of mediastinal lymphatics included complete dissection of mediastinal lymph nodes at levels 4, 7, and 10 during right-sided thoracotomy and at levels 5 and/or 6 and 7 during left-sided thoracotomy or, alternatively, a systematic sampling of representative lymph nodes at the specified levels.

Additional eligibility criteria included adequate bone marrow reserves (i.e., white blood cell count,  $\geq 3.5 \times 10^9$  cells/L; platelets,  $\geq 120 \times 10^9$  cells/L; hemoglobin,  $\geq 10$  g/L; and hematocrit,  $\geq 30\%$ ), adequate liver and renal function (i.e., creatinine level  $< 1.5$  times the upper normal limit), and a postoperative forced expiratory volume of greater than 1.2 L in 1 second.

### Prospective Evaluation of Molecular Markers

In selected participating centers, tumor tissue samples were centrally collected and evaluated for the degree of positivity to p53 and Ki67 immunostaining and for the presence or absence of K-ras mutations at codon 12, the commonest site in lung cancer. Formalin-fixed, paraffin-embedded specimens from surgically removed tumors were incubated with antibodies to p53 (Ab-2; Oncogene Sciences, Manhasset, NY) or to Ki67 (MIB-1; DAKO, Glostrup, Denmark), and immunoreactivity was visualized as previously described (13,14). We categorized tumors into four grades according to the proportion of labeled neoplastic cells they contained, as detailed in a previous study (14): grade 0 = 0%–5% Ki67-positive cells or 0% p53-positive cells; grade 1 = 6%–10% Ki67-positive cells and 1%–10% p53-positive cells; grade 2 =  $> 10\%$ –25% Ki67-positive or p53-positive cells;

grade 3 = >25% Ki67-positive or p53-positive cells. These cutoff points were selected *a priori* and were based on previously reported data (13,14).

Sections were cut from paraffin-embedded tumor samples and collected in an Eppendorf tube. The DNA in the sections was heat-denatured by using a rapid lysis technique (15) and was used for amplification *in vitro*. Conditions for the polymerase chain reaction (PCR) and the detection of point mutations for codon 12 in exon 1 of K-ras using mutation-specific oligonucleotides followed previously published procedures, and results were categorized for the presence or absence of point mutations at codon 12 (16).

### Statistical Analysis

The primary endpoint was overall survival, which was defined as the time from randomization to death from any cause. Secondary endpoints were progression-free survival (defined as the time from randomization to the earliest occurrence of relapse or death from any cause) and toxicity associated with chemotherapy. The trial was designed to have an 80% power to detect a 20% relative reduction in mortality (i.e., increasing 5-year survival rate from 50% to 57%, corresponding to a hazard ratio [HR] of 0.8) with a two-sided  $\alpha$  of .05. We anticipated that 1300 patients would have to be recruited to the trial over 5 years to provide the 535 events necessary to meet these specifications. The study was closed prematurely after having enrolled 93% of the planned sample size, because the accrual rate was low during the last 6 months of the trial. However, we extended the follow-up time to reach the originally planned number of events.

The data for all randomly assigned patients (including those with protocol violations) were analyzed for overall survival on an intent-to-treat basis using the log-rank test without adjustment for prognostic factors. Additional analyses used a Cox proportional hazards model adjusted for baseline characteristics after the verification that proportional hazards assumptions were met. We used the Kaplan–Meier estimate of overall or progression-free survival in the control group at specific time points and the hazard ratio to calculate absolute benefits at those time points according to the formula: absolute benefit =  $e^{[HR - \log(\text{control survival})] - \text{control survival}}$ , where  $e$  is the base of natural logarithms. Although this approach implicitly assumes proportional hazards, it is preferable to comparing differences between Kaplan–Meier curves at individual time points. Differences in median progression-free and overall survival times were calculated in a similar way, except that we used the formula: difference in medians = (control group median/hazard ratio) – control group median. This approach assumes approximately exponentially distributed survival curves. We also developed a Cox proportional hazards model to assess the effect of the molecular prognostic factors investigated. Provisions for subgroup analyses were not included in the original study design. We conducted a *post hoc* per-protocol analysis to explore the relationship between progression-free and overall survival and the amount of chemotherapy delivered.

## RESULTS

### Patient Characteristics

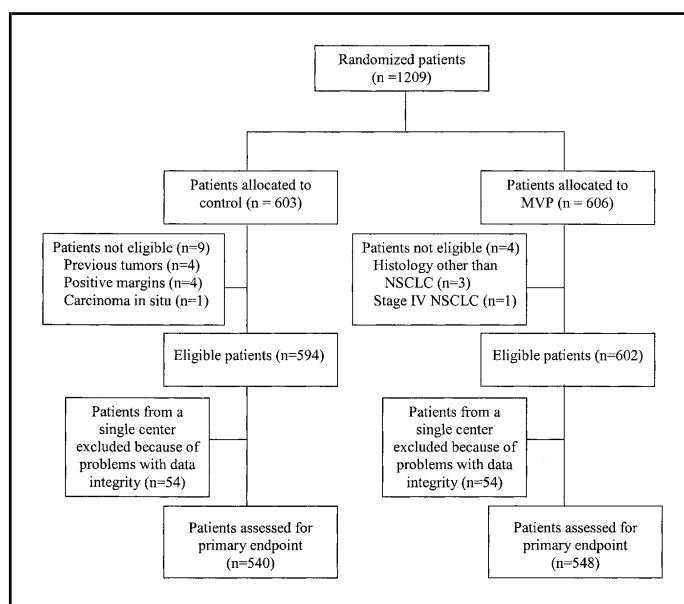
From January 1994 through January 1999, 1209 patients (1086 from the Italian centers and 123 from EORTC–LCCG centers) were enrolled in this study. We randomly assigned 606 patients to the MVP arm and 603 patients to the control arm

(Fig. 1). Thirteen patients were excluded from the analysis because of eligibility criteria violations (four in the MVP arm and nine in the control arm; reasons for ineligibility are listed in Fig. 1). We excluded all 108 patients from one center (54 patients in the MVP arm and 54 patients in the control arm) from the final analysis because of serious concerns about data integrity. Thus, this study reports on 548 patients in the MVP arm and 540 patients in the control arm (Fig. 1). However, we performed all analyses of efficacy outcomes with and without the inclusion of the 108 patients from that one center and found that the two sets of results were not statistically significantly different.

Patient characteristics are reported in Table 1. Among the 470 patients who were scheduled to receive radiotherapy, 11 patients (5%) in the MVP arm and nine patients (4%) in the control arm had stage I NSCLC, 107 patients (45%) in the MVP arm and 112 patients (48%) in the control arm had stage II NSCLC, and 120 patients (50%) in the MVP arm and 111 patients (48%) in the control arm had stage IIIA NSCLC.

### Treatment Compliance

We collected full details about the MVP treatment received by 508 patients (93% of those randomly assigned to the MVP arm) and summaries of the MVP treatment received by the remaining patients. Of the 350 patients (69%) who completed the MVP treatment, 177 did so with some dose adjustment or with omission of part of the planned regimen (mainly the elimination of vindesine administration on day 8). One hundred ten patients (22%) stopped MVP treatment early because of toxicity (66 patients; 60%) or personal choice (44 patients; 40%). Forty-eight patients (9%) never began MVP treatment, primarily because they withdrew their consent to participate. The median doses of cisplatin, mitomycin C, and vindesine actually delivered to patients were 96 mg/m<sup>2</sup>/cycle, 7.6 mg/m<sup>2</sup>/cycle, and 2.8 mg/m<sup>2</sup>/cycle, respectively, corresponding to 96%, 95%, and 93%, respectively, of the planned doses.



**Fig. 1.** Trial flow diagram for Adjuvant Lung Project Italy (ALPI), a randomized trial to test the MVP regimen in patients with radically resected stages I–II and IIIA non–small-cell lung cancer (NSCLC). MVP = mitomycin C (8 mg/m<sup>2</sup> on day 1), vindesine (3 mg/m<sup>2</sup> on days 1 and 8), and cisplatin (100 mg/m<sup>2</sup> on day 1) every 3 weeks for three cycles.

**Table 1.** Selected patient, disease, and treatment characteristics\*

Characteristic	MVP group (N = 548)	Control group (N = 540)
Male, n (%)	472 (86)	465 (86)
Median age, y (range)	61 (33–76)	61 (37–76)
TNM pathologic stage, n (%)†		
I	216 (39)	207 (38)
II	172 (31)	183 (34)
IIIA	160 (29)	150 (28)
T1	118 (22)	100 (19)
T2	345 (63)	360 (67)
T3	85 (16)	80 (15)
N0	257 (47)	254 (47)
N1	154 (28)	151 (28)
N2	137 (25)	135 (25)
Tumor histology, n (%)		
Squamous cell carcinoma	278 (51)	262 (49)
Adenocarcinoma	196 (36)	206 (38)
Large-cell carcinoma	27 (5)	31 (6)
Bronchoalveolar carcinoma	23 (4)	20 (4)
Others‡	24 (4)	21 (4)
Underwent pneumonectomy, n (%)	134 (24)	140 (26)
Complete lymph node dissection, n (%)	313 (57)	290 (54)
Underwent planned radiotherapy, n (%)	238 (43)	232 (43)

\*MVP = mitomycin C (8 mg/m<sup>2</sup> on day 1), vindesine (3 mg/m<sup>2</sup> on days 1 and 8), and cisplatin (100 mg/m<sup>2</sup> on day 1) every 3 weeks for three cycles; TNM = tumor–node–metastasis.

†Reference (9).

‡Non–small-cell lung cancer without additional specifications.

We collected full details from selected centers about the radiotherapy received by 331 patients (70% of those patients scheduled to receive radiotherapy). Radiotherapy was completed by 117 (65%) of the 179 evaluable patients in the MVP arm and by 124 (82%) of the 152 evaluable patients in the control arm. Forty-seven patients (26%) in the MVP arm and 16 patients (11%) in the control arm did not complete the planned course of radiotherapy because it was interrupted at an early stage.

### Toxicity

In the MVP arm, grades 3 and 4 neutropenia occurred among 16% and 12% of the patients, respectively. Thrombocytopenia was rarely reported (i.e., only 5% of patients had grade 3 or 4 thrombocytopenia); 20% of the patients had grade 2 anemia, but only 2% of the patients had grade 3 anemia. In the MVP arm, the incidence of nausea and vomiting was relatively low (grade 3 nausea and vomiting was reported for 13% of the patients; grade 4 nausea and vomiting was reported for 4% of the patients). Other serious non-hematologic toxicities were infrequent (e.g., grade 3 neurotoxicity was reported for 3% of the patients; grade 2 ototoxicity was reported for 4% of the patients).

During sequential radiotherapy, the incidence of grade 3 or 4 hematologic toxicity was low (2% in the MVP arm, 3% in the control arm), whereas grades 2 and 3 esophagitis were the most commonly reported side effect (16% in the MVP arm and 15% in the control arm). One patient in the control arm experienced grade 4 esophagitis during radiotherapy. Grades 2 and 3 acute pneumonitis were recorded for 10 patients (6%) in the MVP arm and 13 patients (9%) in the control arm; grade 4 acute pneumonitis was seen in two patients (1%) in the control arm.

Early deaths (i.e., deaths within 12 months after randomization) were documented for 90 patients in the MVP arm and 69 patients in the control arm. The excess of early deaths among patients in the MVP arm was attributable to cancer progression

(11 deaths) and to cardiopulmonary events (seven deaths). There were 10 treatment-related deaths during the study (three in the MVP arm and seven in the control arm); all except one (in the control arm) occurred during the first year after randomization.

Among the patients who received radiotherapy, two patients developed acute cardiac failure (one in the MVP arm and one in the control arm), one patient in the MVP arm had radiation pneumonitis, and seven patients developed respiratory failure (one in the MVP arm and six in the control arm). No late toxicity (i.e., at 3–6 months after the end of radiotherapy) was reported, and no potential harmful interaction between previous administration of mitomycin C and radiotherapy was documented.

### Recurrence and Survival

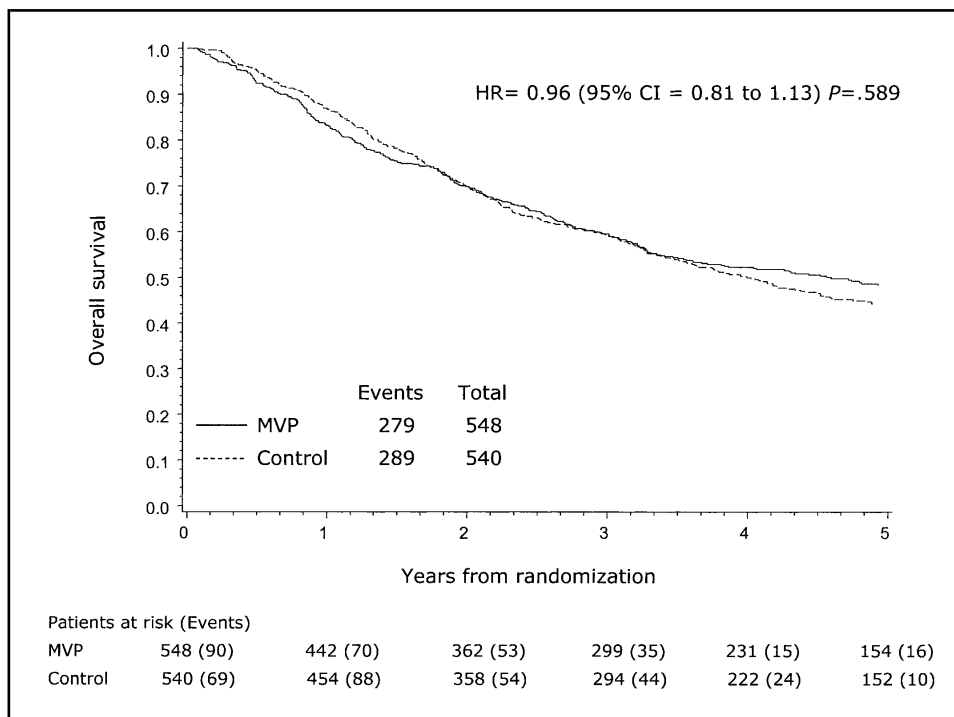
The median duration of follow-up for all 1088 patients analyzed was 64.5 months (interquartile range = 52.1–79.6 months). By May 2002, the number of observed deaths was 568 (52%; 279 in the MVP arm and 289 in the control arm). The most common cause of death was progression of cancer, which accounted for 71% of the deaths. Sixteen percent of deaths were due to non-neoplastic causes, and 9% of deaths were from unknown causes. Deaths due to a second primary cancer and treatment-related deaths were documented in 11 patients (five patients in the MVP arm and six patients in the control arm) and 10 patients (three patients in the MVP arm and seven patients in the control arm), respectively. As of May 2002, 456 patients (42%) were still alive without evidence of disease, while the remaining 64 (6%) were alive with recurrent disease.

By May 2002, 437 patients had disease progression (199 patients in the MVP arm and 238 patients in the control arm). The pattern of relapse was available for 419 patients; a large proportion of patients in both arms relapsed in the central nervous system, either as a single metastatic site (16% of relapsed patients in the MVP arm and 16% of relapsed patients in the control arm) or as part of more widespread disease (28% of relapsed patients in the MVP arm and 31% of relapsed patients in the control arm). Locoregional relapse was documented for 23% of patients in the MVP arm and for 22% of patients in the control arm.

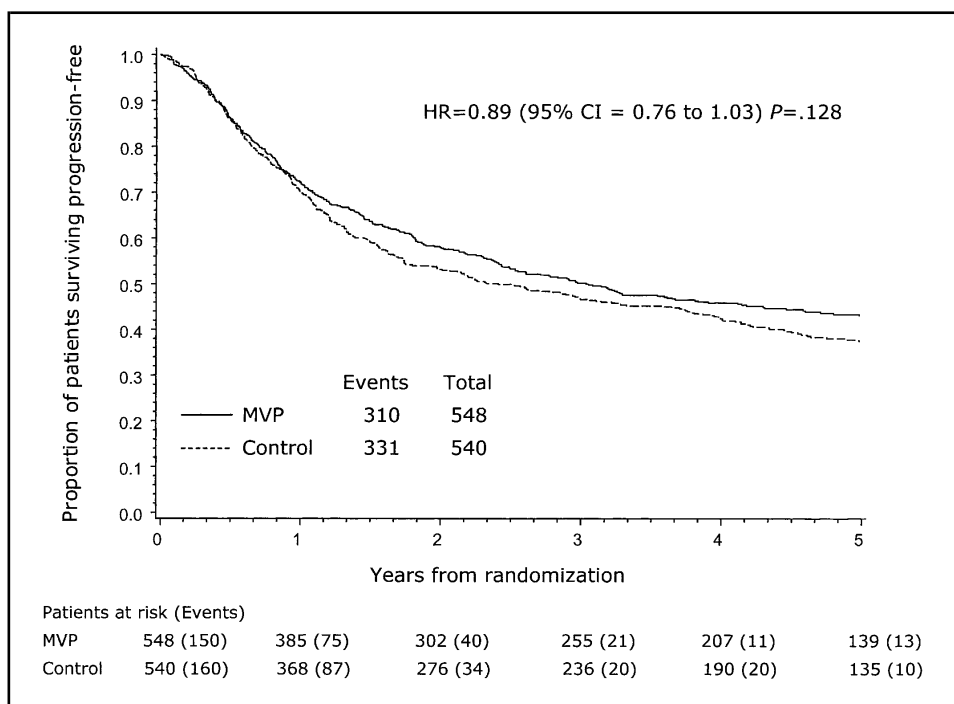
The primary outcome measure, overall survival, was observed in 279 patients in the MVP arm and 289 patients in the control arm. Comparison of the Kaplan–Meier curves for overall survival gave a hazard ratio of 0.96 (95% confidence interval [CI] = 0.81 to 1.13; *P* = .589) (Fig. 2), which translates into absolute increases in 2- and 5-year overall survival of 1% (95% CI = –3% to 5%) and 1% (95% CI = –4% to 7%), respectively. Median overall survival was 48 months for patients in the control arm and 55.2 months for patients in the MVP arm, but the increase of 7.2 months (95% CI = –6.6 to 21.1 months) in overall survival for the MVP arm derived by the Kaplan–Meier curves estimate decreased to 2 months (95% CI = –5.5 to 11 months) when we calculated it using the hazard ratio and the median survival in the control arm.

The secondary outcome measure, progression-free survival, was observed in 310 patients in the MVP arm and 331 patients in the control arm. Comparison of the Kaplan–Meier curves for progression-free survival gave a hazard ratio of 0.89 (95% CI = 0.76 to 1.03; *P* = .128) in favor of the MVP arm (Fig. 3). This hazard ratio represents absolute increases in 2- and 5-year progression-free survival of 4% (95% CI = –1% to 9%) and 4%

**Fig. 2.** Kaplan–Meier curves for overall survival time from randomization by allocated treatment. MVP = mitomycin C (8 mg/m<sup>2</sup> on day 1), vindesine (3 mg/m<sup>2</sup> on days 1 and 8), and cisplatin (100 mg/m<sup>2</sup> on day 1) every 3 weeks for three cycles.



**Fig. 3.** Kaplan–Meier curves for progression-free survival time from randomization by allocated treatment. MVP = mitomycin C (8 mg/m<sup>2</sup> on day 1), vindesine (3 mg/m<sup>2</sup> on days 1 and 8), and cisplatin (100 mg/m<sup>2</sup> on day 1) every 3 weeks for three cycles.

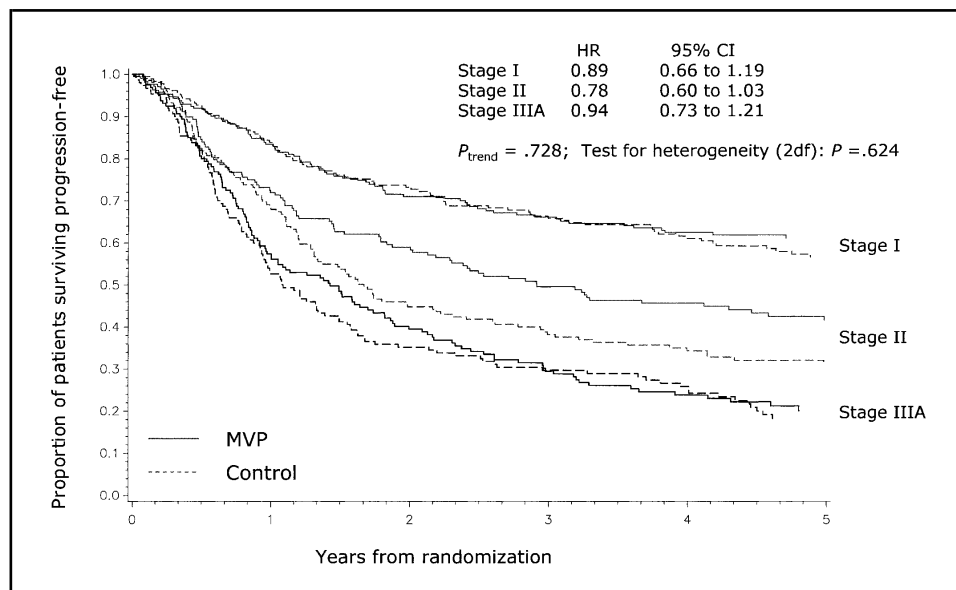


(95% CI = -1% to 10%), respectively, for patients receiving the MVP treatment. These Kaplan–Meier estimates of median progression-free survival times were 28.9 months for patients in the control arm and 36.5 months for patients in the MVP arm (absolute difference = 7.6 months [95% CI = -1.5 to 16.6 months]; difference derived from hazard ratio and median progression-free survival in the control arm = 3.6 months, 95% CI = -0.8 to 9.1 months).

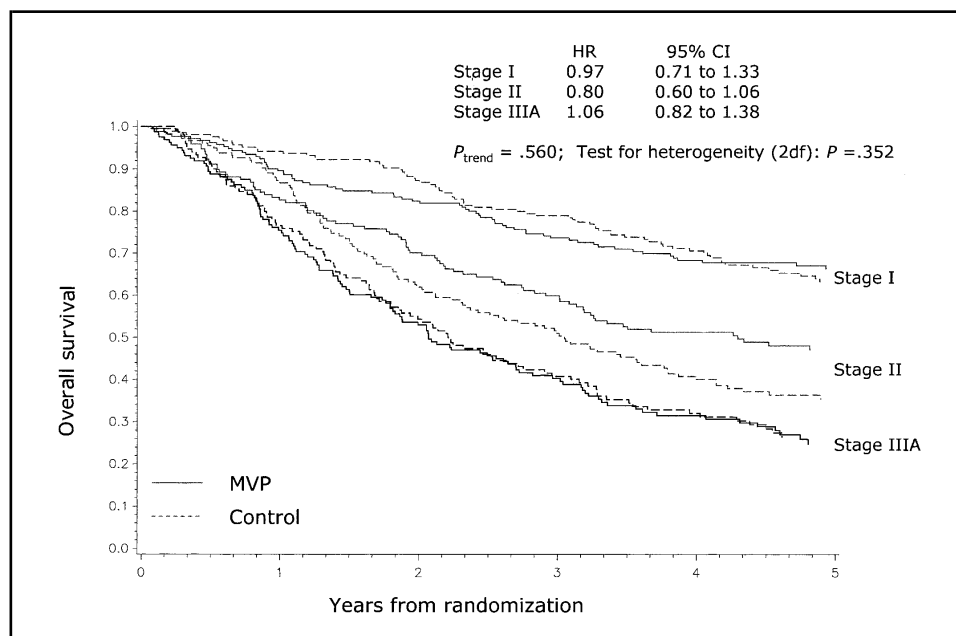
Figs. 4 and 5 depict the Kaplan–Meier curves for progression-free survival and overall survival, respectively, by disease stage; no clear interaction between treatment and stage of dis-

ease emerged for either outcome measure. In the multivariable analysis for selected baseline and treatment characteristics, stage of disease and sex were statistically significantly associated with overall survival ( $P < .001$  for stage II or III versus stage I and  $P = .034$  for male versus female, respectively), whereas only stage of disease was statistically significantly associated with progression-free survival ( $P < .001$  for stage II or III versus stage I) (Table 2). We also performed a per-protocol analysis to compare overall survival among patients who received all three planned cycles of chemotherapy with that of patients who underwent no adjuvant therapy and found no statistically signifi-

**Fig. 4.** Kaplan–Meier curves for progression-free survival from randomization by allocated treatment and stage of disease. MVP = mitomycin C (8 mg/m<sup>2</sup> on day 1), vindesine (3 mg/m<sup>2</sup> on days 1 and 8), and cisplatin (100 mg/m<sup>2</sup> on day 1) every 3 weeks for three cycles; HR = hazard ratio; CI = confidence interval.



**Fig. 5.** Kaplan–Meier curves for overall survival time from randomization by allocated treatment and stage of disease. MVP = mitomycin C (8 mg/m<sup>2</sup> on day 1), vindesine (3 mg/m<sup>2</sup> on days 1 and 8), and cisplatin (100 mg/m<sup>2</sup> on day 1) every 3 weeks for three cycles; HR = hazard ratio; CI = confidence interval.



cant difference in overall survival between those two groups of patients (HR = 0.86, 95% CI = 0.71 to 1.04).

#### Association Between Tumor Tissue Markers and Outcome

In NSCLC, the influence of other prognostic variables in addition to tumor–node–metastasis stage and performance status could explain the survival heterogeneity that has been observed among patients with the same stage of the disease (17). Many molecular and biologic features of NSCLC, including Ki67 and p53 expression and K-ras mutation status, have been investigated for their potential prognostic value (17). We analyzed 38% of the primary tumors for levels of p53 and Ki67 expression. Fifty percent of the tumor specimens expressed p53, and 62% of the tumor specimens expressed Ki67 in more than 25% of tumor cells examined (data not shown). We found no statistically significant associations between disease stage or tumor histology and tumor expression of p57 or Ki67, even when we considered 5%, 10%, and 25% cut points for positive cells (data not shown).

We also performed an analysis of the association between K-ras mutation status and survival only among tumor specimens that were histologically identified as adenocarcinoma or large-cell carcinoma, because a preliminary analysis revealed that the K-ras point mutation in exon 1 was present in only one (2%) of the first 50 samples of squamous cell carcinoma we examined. K-ras mutation status was examined by PCR amplification of DNA extracted from tumor samples. We found point mutations in exon 1 of the K-ras gene of 22% of the 117 tumor samples that were successfully amplified by PCR (23 samples were not successfully amplified). In a multivariable analysis that was adjusted for stage of disease, we found no association between any of these three tumor tissue markers and overall survival or progression-free survival (Table 2).

#### DISCUSSION

The efficacy of adjuvant chemotherapy in completely resected NSCLC is controversial, even though the results of more

**Table 2.** Multivariable Cox proportional hazards analysis for overall and progression-free survival\*

Variable	Overall survival		Progression-free survival	
	HR (95% CI)	P value†	HR (95% CI)	P value†
Age, 5-y intervals	1.06 (1.00 to 1.12)	.062	1.04 (0.99 to 1.10)	.149
TNM pathologic stage‡				
II versus I	2.01 (1.62 to 2.49)		1.88 (1.54 to 2.30)	
III versus I	3.19 (2.59 to 3.93)	<.001	2.94 (2.39 to 3.53)	<.001
Tumor histology (squamous versus other)	0.87 (0.73 to 1.03)	.112	0.84 (0.72 to 0.99)	.037
Sex (male versus female)	1.33 (1.02 to 1.72)	.034	1.19 (0.94 to 1.51)	.150
Type of lymph node dissection (sampling versus complete)	0.88 (0.75 to 1.04)	.135	0.86 (0.74 to 1.01)	.068
MVP versus control	0.95 (0.81 to 1.12)	.559	0.88 (0.76 to 1.03)	.115
Tumor tissue markers§				
p53 (n = 387)	1.03 (0.98 to 1.08)	.30	1.02 (0.97 to 1.06)	.49
Ki67 (n = 395)	1.42 (0.82 to 2.47)	.63	1.04 (0.98 to 1.11)	.16
K-ras gene mutation (n = 108)	1.02 (0.95 to 1.08)	.20	1.25 (0.73 to 2.14)	.41

\*The values in this table are adjusted for the other covariates reported in the table. HR = hazard ratio; CI = confidence interval; TNM = tumor–node–metastasis; MVP = mitomycin C (8 mg/m<sup>2</sup> on day 1), vindesine (3 mg/m<sup>2</sup> on days 1 and 8), and cisplatin (100 mg/m<sup>2</sup> on day 1) every 3 weeks for three cycles.

†Wald test (two-sided) was used to estimate P values.

‡Reference (9).

§Data regarding tumor tissue markers were adjusted only by TNM pathologic stage and analyzed as continuous variables (Ki67 and p53) or as positive versus negative (K-ras mutation).

than 20 randomized clinical trials of chemotherapy alone versus no chemotherapy are currently available [reviewed in (18)]. Results of the 1995 meta-analysis of NSCLC, which considered 17 trials of adjuvant chemotherapy versus best control, suggested that only patients with completely resected NSCLC who received cisplatin-based chemotherapy (eight trials) had a 5% improvement in 5-year survival rate compared with those treated with surgery alone (7). However, these findings failed to influence clinical practice, not because the absolute gain was too small, but because of the imprecision of the survival benefit estimate, which ranged from a 1% detriment to a 10% benefit. By contrast, clinical practice has been influenced by the results of a meta-analysis of randomized clinical trials of adjuvant chemotherapy in breast cancer involving approximately 75 000 patients, 31 000 recurrences, and 24 000 deaths that suggested a 6% benefit in 10-year survival rate for women who received adjuvant chemotherapy compared with those who did not (19).

Even more controversial is the efficacy of adjuvant radiotherapy after radical surgery for NSCLC. For example, results of a meta-analysis of trials involving patients with resected NSCLC suggested that adjuvant radiotherapy was associated with a 7% reduction in overall survival at 2 years; results of the subset analyses suggested that this adverse effect was greatest for patients with stage I or II disease, whereas no clear evidence was found for an adverse effect in patients with stage III disease (20).

Over the last decade, several randomized clinical trials of platinum-based chemotherapy (with and without thoracic radiotherapy) in completely resected stage I, II, and IIIA NSCLC have been initiated and concluded. In one such trial, by the Eastern Cooperative Oncology Group, patients with clinical stage II or IIIA NSCLC received radiotherapy alone or concurrent chemotherapy and radiotherapy after complete resection (21). Although overall toxicity was higher in the chemotherapy-plus-radiotherapy group than in the radiotherapy-alone group, there were no statistically significant differences in the efficacy outcomes between the two groups (21). However, the results of this study were limited by the lack of a surgery-alone arm and by the modest sample size.

The ALPI trial was the first large, prospective adjuvant study

designed to detect reasonably small differences in survival that were in the range of those detected by the NSCLC meta-analysis (7). The ALPI trial was also the first large trial to successfully enroll the number of patients very close to that originally planned. This trial, however, failed to show any clinically significant survival benefit for patients who received MVP treatment after surgery. One possible reason for this result was the low compliance with chemotherapy. Inadequate dose delivery is often reported in most trials testing postoperative chemotherapy [for review see (22)], with an average of 50% of patients receiving the full course of treatment. However, even when we performed a per-protocol exploratory analysis that compared outcomes among patients receiving all three planned cycles of chemotherapy with those of patients undergoing no adjuvant therapy, we found that MVP chemotherapy conferred only a marginal, and still statistically nonsignificant, overall survival advantage.

The health of patients who have undergone a major thoracic surgical procedure is very often compromised by the procedure itself, and these patients usually require a long time to fully recover. Evidence supporting this observation is reflected in the percentage of patients who never started adjuvant treatment (9% in the ALPI trial and up to 24% of patients in previous studies) (23). By contrast, compared with NSCLC patients, breast and colon cancer patients undergo less debilitating surgeries and receive less toxic adjuvant therapies, thereby allowing more effective delivery of those therapies.

When the ALPI trial was being planned, the choice of chemotherapy regimen was greatly influenced by the positive data reported from a trial comparing three chemotherapy regimens in patients with advanced NSCLC (8) and by a report of the efficacy of the MVP regimen in the neoadjuvant setting (24). Although tumor shrinkage is one of the main aims of neoadjuvant therapies, triplet combinations allow a higher objective response rate than doublet combinations. In patients with stage IIIA NSCLC, triplet combinations were used as induction regimens in two small randomized phase III clinical studies (25,26) that showed a clinically meaningful superiority of the combined approach over surgery alone.

The amounts of grades 3 and 4 hematologic and non-hematologic toxicities related to chemotherapy did not differ quantitatively and qualitatively from those commonly observed in advanced NSCLC; nonetheless, the marginal reduction in survival observed in the MVP arm in the first year after randomization could reflect a potential toxicity effect. This observation is also indirectly confirmed by the lower percentage of patients in the MVP arm than in the control arm that completed subsequent thoracic radiotherapy (65% versus 82%). However, the treatment-related deaths occurring in the first year after randomization did not differ between the two treatment arms.

In the majority of the patients who have undergone complete resection for NSCLC, death is cancer-related and follows systemic recurrence. In our trial, this pattern was confirmed and, more relevantly, in both arms, more than 40% of patients had brain metastases as the first site of relapse. This issue not only raises the question of how to prevent these brain metastases but also suggests that prophylactic cranial irradiation should potentially be investigated in these patients in future trials.

During the last decade, several new chemotherapeutic agents, including gemcitabine, taxanes, and vinorelbine, became available and have been extensively investigated in advanced NSCLC. When combined with cisplatin or carboplatin and compared with older regimens, these new regimens resulted in a 13% improvement in response rate and reduced toxicity but only in a marginal increase in overall survival rate (27). Therefore, it is unlikely that the use of these new regimens as adjuvant treatment in early stages of NSCLC will greatly change the efficacy outcomes.

In conclusion, the ALPI trial failed to confirm the effectiveness of adjuvant MVP chemotherapy for patients with NSCLC. Future trials of adjuvant therapy should be planned only when the full results of all ongoing or completed randomized trials of adjuvant therapy in NSCLC and of a new meta-analysis including at least 4000 patients are available.

## APPENDIX

Data management and statistical analysis: ALPI office Mario Negri Institute, Milan, Italy: M. Flann, A. Cattaneo, I. Floriani, R. Fossati, S. Marsoni, A. Tinazzi, V. Torri. EORTC office, Brussels, Belgium: A. Kirkpatrick, A. Dehoorne.

The following investigators, listed according to accrual rate, contributed patients to the trial (all are located in Italy unless otherwise noted): G. Liguori, G. Nittolo, M. Vasta, C. Curcio, Ascalesi Hospital, Naples; P. Borasio, L. Dogliotti, G. V. Scagliotti, San Luigi Hospital, Orbassano, Turin; C. A. Angeletti, P. F. Conte, M. Laddaga, A. Rebecchini, S. Spagnesi, Santa Chiara Hospital, Pisa; T. Lewinski, Maria Sklodowska-Curie Cancer Center, Warsaw, Poland; F. Salvati, F. De Marinis, A. Altieri, F. Giordano, G. Puglisi, San Camillo-Forlanini Hospital, Rome; A. Cipriani, A. Favaretto, M. Fiorentino, G. Giampaglia, L. Loreggian, R. Zuin, Civilian Hospital, Padova; J. Jassem, Department of Oncology and Radiotherapy, Medical Academy, Gdansk, Poland; R. Ukmar, A. Buffoni, C. Puricelli, G. Talmassons, A. Morelli, Santa Maria Misericordia Civilian Hospital, Udine; A. Boidi Trotti, S. Bretti, G. Maggi, A. Mussa, G. L. Sannazzari, S. Baldi, U. Ricardi, E. Ruffini, San Giovanni Hospital, Turin; G. Bruni, C. Gridelli, National Institute of Cancer, Naples; F. Checaglini, Santa Maria Hospital, Terni; P. Latini, E. Maranzano, T. Todisco, M. Tonato, Monteluce General Hospital, Perugia; A. Santo Antonio, A. Terzi, Verona Hospital, Verona; G. Pavia, A. Sartirana, Civilian Hospital, Rho, Milan; D. Ottoni, Civilian Hospital, Brescia; M. Fontanili, C. Sturani, "C. Poma" Hospital, Mantova; L. M. Aiello, S. Barbera, Santa Mariano

Hospital, Cosenza; F. Baracco, A. Cinquegrana, R. Felletti, T. Scolaro, J. Serrano, Santa Martino Hospital, Genoa; U. Felci, Riuniti Hospital, Bergamo; P. Manente, Civilian Hospital, Castelfranco Veneto, Treviso; P. Drings, Thorax Klinik Rohrbach, Heidelberg, Germany; P. Zannini, E. Villa, San Raffaele Hospital, Milan; N. Bordone, M. Tordiglione, M. Bandera, M. Fioretti, Circolo Hospital and Filippo del Ponte Hospital, Varese; G. Roviario, San Giuseppe Hospital, Milan; A. R. Bianco, G. Ferrante, A. Rossi, A. Sodano, Federico II General Hospital, Naples; C. Boni, L. Covacev, V. Lodini, Santa Maria Nuova Hospital, Reggio Emilia; P. Espana, Oncologia Medica, Clinica Puerta de Hierro, Madrid, Spain; P. A. Belloni, E. Soresi, U. Borghini, G. Cimino, M. Leoni, M. Ravini, Riguarda Ca' Grande Hospital, Milan; G. Luporini, G. Todeschini, San Carlo Hospital, Milan; N. Campioni, F. Cognetti, F. Facciolo, Regina Elena Institute, Rome; V. Clini, E. Tisi, Santa Gerardo Tintori Hospital, Monza, Milan; G. Bolzicco, M. Gulsano, R. Negrin, M. Vidali, Civilian Hospital, Vicenza; M. Musi, F. Ozzello, L. Sblendorio, Regional Hospital, Aosta; G. Buccheri, D. Ferrigno, G. Marchetti, M. Quaranta, Santa Croce e Carle Hospital, Cuneo; F. Virginio, P. Elena, Luigi Sacco Hospital, Milan; G. Arcangeli, G. Baiano, F. Cardillo, M. D'Aprile, Santa Maria Goretti Hospital, Latina; G. Bragherio, A. De Stefano, V. Lanzetti, Legnano Hospital, Magenta, Milan; L. Armaroli, Santa Maria Nuova Hospital, Regio Emilia; G. Barbera, C. Lanfranco, M. Morelli, P. Rotta, F. Testore, Civilian Hospital, Asti; A. Bordin, G. Degli Angeli, Provincial General Hospital, Belluno; G. Biasco, University of Bologna, Seragnoli Institute of Hematology and Oncology, Bologna; A. Desogus, Businco Oncology Hospital, Cagliari, Sardegna; L. Gandola, Maggiore Hospital, Crema, Cremona; L. Landa, R. Mattioli, S. Croce General Hospital, Fano; F. Di Costanzo, S. Gasperoni, A. Lopes Pegna, Careggi Hospital, Florence Careggi; G. W. P. Kramer, Arnhem, The Netherlands; P. Foa, A. Mantovani, S. Paolo Hospital, Milan; P. Astorre, R. Maritati, M. Nardi, Celio Military General Hospital, Rome; F. Bassi, T. Tommaseo-Ponzet, G. Di Falco, G. Marazzato, G. Nicolai, G. Santelli, Ca' Fondello Hospital, Treviso; F. Gozzelino, G. Moro, Hospital for Invalids, Biella; G. Ghiotti, B. Rho, Salvini Hospital, Garbagnate, Milan; M. Marcellini, Civilian Hospital, Senigaglia, Ancona; F. Bassan, Boldrini Regional General Hospital, Tione, Vicenza; G. Fornari, Valdese Evangelist Hospital, Torino; F. Artioli, Ramazzini Hospital, Carpi, Modena; C. Zambianchi, L. Amaducci, Hospital for Invalids, Faenza, Ravenna; G. Airoidi, Santa Giovanni Battista Hospital, Gattinara, Vercelli; G. Cruciani, Umberto I Hospital, Lugo di Romagna, Ravenna; S. Di Prima, Civilian Hospital, Moncalieri, Torino; M. Spatafora Mario, Cervello Hospital, Palermo; G. Cacciani, Parma Hospital, Parma; C. Ricci, E. Cortesi, A. Dagianti, V. Donato, E. A. Rendina, F. Romeo, F. Venuta, Umberto I General Hospital, University La Sapienza, Rome; E. Longhini, Sesto S. Giovanni Hospital, Sesto S. Giovanni, Milan; P. Fasullo, Santa Luca Hospital, Vallo della Lucania, Salerno; S. Gans, Harderwijk, The Netherlands; H. Karnicka, Department of Oncology, University Hospital, Gdansk, Poland; S. Barni, Piazzave Hospital, Treviglio.

Biological Prognostic Factors Subcommittee: A. Marchetti, Department of Pathology, University of Chieti, Chieti, Italy; Eugenio Leonardo, Paolo De Giuli, Susanna Cappia, Department of Pathology, Santa Luigi Hospital, Orbassano (Torino), Italy.

Data Monitoring Committee: G. J. McVie, Cancer Intelligence, London, United Kingdom; U. Pastorino, National Cancer Institute, Milan, Italy; P. van Houtte, Institute Jules Bordet, Brussels, Belgium; M. G. Valsecchi, University of Milano-Bicocca, Dipartimento di Medicina Clinica, Prevenzione e Biotecnologie Sanitarie, Milan, Italy.

## REFERENCES

- (1) Mountain CF. Revisions in the international system for staging lung cancer. *Chest* 1997;111:1710-7.
- (2) Martini N, Flehinger B, Zaman M, Beattie EJ Jr. Prospective study of 445 lung carcinomas with mediastinal lymph node metastases. *J Thorac Cardiovasc Surg* 1980;80:390-9.



- (3) Feld R, Rubenstein I, Weisenberger T. Sites of recurrence in resected stage I non-small cell lung cancer: a guide for future studies. *J Clin Oncol* 1984; 2:1352–8.
- (4) Pairolo P, Williams D, Bergstrahl M, Pehler JM, Bernatz PE, Payne WS, et al. Post-surgical stage I bronchogenic carcinoma. Morbid implications of recurrent disease. *Ann Thorac Surg* 1984;38:331–8.
- (5) Thomas P, Rubinstein L. Cancer recurrence after resection: T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg* 1990; 49:242–6.
- (6) Ruckdeschel JC, Robinson LA. Non-small cell lung cancer: surgery and post-operative adjuvant chemotherapy. In: Pass HJ, Mitchell JB, Johnson DH, Turrisi AT, editors. *Lung cancer. Principles and practice*. Philadelphia (PA): Lippincott-Raven Publishers; 1996. p. 839–49.
- (7) Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. *BMJ* 1995;311:899–909.
- (8) Crinò L, Clerici M, Figoli F, Barduagni M, Carlini P, Ceci G, et al. Chemotherapy of advanced non-small cell lung cancer: a comparison of three active regimens. A randomized trial of the Italian Oncology Group for Clinical Research (GOIRC). *Ann Oncol* 1995;6:347–53.
- (9) Mountain CF. A new international staging system for lung cancer. *Chest* 1986;89(4 Suppl):225S–233S.
- (10) World Health Organization. Handbook for reporting results of cancer treatment. Publication 48. Geneva (Switzerland): World Health Organization; 1979.
- (11) Byhardt RW, Martin L, Pajak TF, Shin KH, Emami B, Cox JD. The influence of field size and other treatment factors on pulmonary toxicity following hyperfractionated irradiation for inoperable non-small cell lung cancer (NSCLC)—analysis of a Radiation Therapy Oncology Group (RTOG) protocol. *Int J Radiat Oncol Biol Phys* 1993;27:537–44.
- (12) American Thoracic Society. Medical section of the American Lung Association. Clinical staging of primary lung cancer. *Am Rev Respir Dis* 1983; 127:659–64.
- (13) Marchetti A, Buttitta F, Merlo G, Diella F, Pellegrini S, Pepe S, et al. p53 alterations in non-small cell lung cancers correlate with metastatic involvement of hilar and mediastinal lymph nodes. *Cancer Res* 1993;53:2846–51.
- (14) Scagliotti GV, Micela M, Gubetta L, Leonardo E, Cappia S, Borasio P, et al. Prognostic significance of Ki67 labelling in resected non-small cell lung cancer. *Eur J Cancer* 1993;29A:363–5.
- (15) Higuchi H. Rapid, efficient DNA extraction for PCR from cells or blood. *Perkin Elmer Cetus Amplifications* 1990;2:1–3.
- (16) Verlaan-de Vries M, Bogaard ME, van den Elst H, van Boom JH, van der Eb AJ, Bos JL. A dot-blot screening procedure for mutated ras oncogenes using synthetic oligonucleotides. *Gene* 1986;50:313–20.
- (17) Kanters SD, Lammers JW, Voest EE. Molecular and biological factors in the prognosis of non-small cell lung cancer. *Eur Respir J* 1995;8:1389–97.
- (18) Pisters KM. Stage I/II non-small cell lung cancer: is there a role for combined-modality therapy? *American Society of Clinical Oncology (educational book)* 2002; p. 465–70.
- (19) Systemic treatment of early breast cancer by hormonal, cytotoxic and immune therapy. 133 randomized trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 1992;339:71–85.
- (20) Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group. *Lancet* 1998;352: 257–62.
- (21) Keller SM, Adak S, Wagner H, Herskovic A, Komaki R, Brooks BJ, et al. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung cancer. Eastern Cooperative Oncology Group. *N Engl J Med* 2000;343:1217–22.
- (22) George S, Schell MJ, Detterbeck FC, Socinski M. Adjuvant chemotherapy for resected non-small cell carcinoma of the lung: why we still don't know. *Oncologist* 1998;3:35–44.
- (23) Holmes EC, Gail M. Surgical adjuvant therapy for stage II and stage III adenocarcinoma and large-cell undifferentiated carcinoma. *J Clin Oncol* 1986;4:710–5.
- (24) Martini N, Kris MG, Flehinger BJ, Gralla RJ, Bains MS, Burt ME, et al. Preoperative chemotherapy for stage IIIa (N2) lung cancer: the Sloan-Kettering experience with 136 patients. *Ann Thorac Surg* 1993;55: 1365–74.
- (25) Rosell R, Gomez-Codina J, Camps C, Maestre J, Padille J, Canto A, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med* 1994;330:153–8.
- (26) Roth JA, Fossella F, Komaki R, Ryan MB, Putnam JB Jr, Lee JS, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *J Natl Cancer Inst* 1994;86:673–80.
- (27) Socinski MA, Morris DE, Masters GA, Lilenbaum R; American College of Chest Physicians. Chemotherapeutic management of stage IV non-small cell lung cancer. *Chest* 2003;123(1 Suppl):226S–243S.

## NOTES

Partially supported by grants from the National Research Council and the Italian Association for Cancer Research to the Laboratory of Clinical Cancer Research, Mario Negri Institute, Milano, and to the University of Turin, Department of Clinical and Biological Sciences, S. Luigi Hospital, Orbassano (Torino). Preliminary results of this study were presented at the 38<sup>th</sup> Annual Meeting of the American Society of Clinical Oncology (Orlando, FL), May 18–21, 2002. Manuscript received March 18, 2003; revised July 23, 2003; accepted July 30, 2003.