Management of Early-Stage Lung Cancer: Past, Present, and Future Adjuvant Trials

By Gary M. Strauss, MD, MPH

The standard of care with regard to adjuvant chemotherapy of lung cancer has changed remarkably over the past 3 years. Until the initial report of the International Adjuvant Lung Trial in 2003, there was no real evidence from any individual randomized clinical trial (RCT) that adjuvant chemotherapy improves survival in resectable non-small-cell lung cancer. However, five RCTs that have now been reported indicate that adjuvant chemotherapy is effective, at least in certain subgroups of resectable patients. Moreover, numerous meta-analyses have also reported a positive effect from adjuvant treatment. Nonetheless, because of methodologic issues and conflicting results, the question of who should be treated and what constitutes optimal adjuvant therapy remains controversial. This article reviews the recent randomized trials that have contributed to a change in the state of the art, as well as some of the methodologic problems that may have confounded their proper interpretation. It also considers newer approaches to adjuvant therapy, with a particular focus on strategies that incorporate our growing knowledge of molecular medicine and predictive factors to the field of adjuvant chemotherapy of lung cancer.

Lung cancer remains the most frequent cause of cancer death both in the United States and worldwide.[1,2] The American Cancer Society (ACS) estimates that lung cancer is the third most common cancer in the US, ranking behind prostate cancer and breast cancer (Table 1). However, in terms of cancer mortality, it is in a league of its own.

Indeed, the ACS estimates that lung cancer will be responsible for 162,460 cancer deaths in the US in 2006.[2] By way of comparison, an estimated 156,250 deaths were expected from colorectal cancer, breast cancer, pancreatic cancer, and prostate cancer combined. These diseases represent...
the second through fifth leading causes of cancer mortality, respectively (Table 1). It is estimated that lung cancer will be responsible for 28.8% of all cancer deaths in the US in 2006, despite the fact that it represents only 12.5% of all new cancers.[2] Overall, 5-year survival in the US is currently estimated to be approximately 15%.

On a worldwide basis, lung cancer is both the most common cancer and most common cause of cancer mortality. In the year 2002, there were an estimated 1,350,000 new cases of lung cancer, and an estimated 1,179,000 lung cancer deaths. Globally, lung cancer represents 12.4% of all new cancers, and 17.6% of all cancer deaths. Overall, 5-year survival is estimated to be 10% in Europe and 9% in developing countries.[1]

Among patients with early-stage non-small-cell lung cancer (NSCLC), the most powerful predictor of long-term survival is the ability to achieve complete surgical resection. Nonetheless, patients remain at substantial risk for recurrence and death despite an apparent complete surgical excision. For example, data reported by Mountain in 1986 that were used to establish the International Staging System for lung cancer included 5-year survival rates of 64% and 45% for patients with pathologic stage I or II disease, respectively (Table 2).[3] High recurrence rates among those with resected lung cancer underscore the potential role of adjuvant chemotherapy in this setting.

### Table 2

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-yr Survival</th>
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<tbody>
<tr>
<td>IA</td>
<td>70%–85%</td>
</tr>
<tr>
<td>IB</td>
<td>45%–65%</td>
</tr>
<tr>
<td>IIA</td>
<td>40%–55%</td>
</tr>
<tr>
<td>II B</td>
<td>30%–45%</td>
</tr>
<tr>
<td>IIIA (N2)</td>
<td>5%–25%</td>
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NSCLC = non–small-cell lung cancer.

While a considerable risk of recurrence and death following resection has long provided a powerful rationale for adjuvant treatment, research in the area of adjuvant chemotherapy has never received the same priority in NSCLC as it has in other common cancers, particularly breast and colorectal cancer.[4] Nonetheless, several influential randomized clinical trials on adjuvant chemotherapy in lung cancer and an important meta-analysis of trials did appear in the literature prior to 2003, when the first positive report from a large randomized trial was published, helping to change the standard of care.

I will briefly review the most influential of these older randomized trials along with the meta-analysis. Subsequently, I will address recent randomized trials that have led to a change in clinical practice in resectable NSCLC. In the discussion section, I will attempt to define the current state of the art in adjuvant therapy and to articulate major unanswered questions. Finally, I will consider newer approaches to adjuvant therapy in lung cancer.

### Randomized Trials and Meta-Analysis Published Prior to 2003

Three cisplatin-based adjuvant randomized trials sponsored by the Lung Cancer Study Group (LCSG) are among the best known older studies in the area of adjuvant chemotherapy of lung cancer. Each trial utilized an adjuvant chemotherapy regimen consisting of the CAP (cyclophosphamide, doxorubicin [Adriamycin], and cisplatin [Platinol]) regimen in various stages of NSCLC. LCSG-772 randomized 141 patients with resected stage II or III adenocarcinoma or large-cell carcinoma of the lung to six cycles of CAP chemotherapy or to a control group that received no chemotherapy.[5] (It should be noted that control participants did receive an immunotherapy...
regimen, consisting of intrapleural bacillus Calmette-Guérin (BCG) and levamisole, for which there is no other evidence for efficacy.) While early results indicated a 15% survival advantage at 1 year (77% vs 62%), continued follow-up failed to reveal any significant long-term survival advantage. LCSG-791 randomized 172 patients with incompletely resected NSCLC, as defined either by the presence of tumor in the highest resected mediastinal node, or by a positive margin.[6] Patients were randomized to either adjuvant CAP chemotherapy with postoperative radiation (40 Gy) or to postoperative radiation therapy alone. This study also showed significantly better survival at 1 year in the CAP arm (68% vs 54%), although with longer follow-up the significant survival advantage disappeared.

LCSG-801 randomized 283 patients with T2, N0 or T1, N1 NSCLC to either four cycles of CAP or no adjuvant therapy.[7] Overall, 85% of participants had T2, N0 and 15% had T1, N1 tumors. Five-year survival was 55% in both groups. While compliance and delivery of the intended therapy was problematic, the results of this trial were clearly negative.

In contrast, however, a smaller study conducted at Helsinki University Central Hospital in Finland, with a very similar design to LCSG-801, was the only individual randomized trial to report a significant survival advantage.[8] In this trial, 110 patients with T1-3, N0 NSCLC were randomized to surgery followed by six cycles of CAP chemotherapy or to surgery alone. Stage distribution included 31% with T1, N0 disease, 62% with T2, N0 disease, and 7% with T3, N0 NSCLC. The investigators found a statistically significant 5-year survival advantage favoring the adjuvant chemotherapy arm (67% vs 56%; P = .050).[8] However, problems with randomization appear to have confounded interpretation of this trial: Those randomized to surgery alone included almost twice as many patients who required pneumonectomy as was true in the adjuvant chemotherapy arm (39% vs 20%; P = .038). As would be expected, pneumonectomy patients had a significantly worse survival than those requiring lobectomy (P = .002).

Two randomized trials conducted in predominantly stage II and III NSCLC failed to demonstrate a survival benefit for adjuvant chemotherapy and radiation compared to adjuvant radiation alone. In a French trial conducted by the Groupe D'etude et de Traitement des Cancer Bronchiques (GETCB), 267 patients were randomized to either adjuvant chemotherapy with COPAC (cyclophosphamide, vincristine [Oncovin], cisplatin, doxorubicin, lomustine [CeeNU]), followed by 60 Gy of postoperative radiation therapy (PORT) over 6 weeks or to PORT alone.[9] Stage distribution included 70% with stage III, 26% with stage II, and 3% with stage I disease. With a minimum follow-up of 6 years, survival was similar in the two groups (P = .68).

Finally, the Eastern Cooperative Oncology Group (ECOG) conducted a randomized trial comparing adjuvant chemoradiation vs PORT alone in completely resected stage II or IIIA NSCLC.[10] In this study, 488 patients were randomized to receive four cycles of adjuvant chemotherapy with cisplatin and etoposide and concurrent radiation (50.4 Gy) or to a similar PORT regimen. Survival was virtually identical within the two groups (hazard ratio [HR] = 0.93; 95% confidence interval [CI] = 0.74-1.18). While none of these or other older randomized trials demonstrated a clear and unequivocal survival advantage associated with randomization to adjuvant chemotherapy, a meta-analysis of chemotherapy in NSCLC published in 1995 did suggest a survival benefit for those randomized to cisplatin-based adjuvant chemotherapy regimens.[11] Eight trials utilizing a cisplatin-based adjuvant chemotherapy regimen showed an overall 13% proportional reduction in the risk of death among those receiving adjuvant chemotherapy. This translated into an absolute 5% improvement in the probability of long-term survival among those receiving adjuvant treatment. However, the difference favoring cisplatin-based adjuvant chemotherapy was not statistically significant (HR = 0.87; 95% CI = 0.74-1.02; P = .08).

Nonetheless, the 5% survival advantage observed in the 1995 meta-analysis with cisplatin-based chemotherapy provided an incentive for conducting additional randomized trials in this area. Several of these studies have now been reported and have dramatically changed the practice of medicine as it relates to adjuvant chemotherapy for NSCLC. On the other hand, numerous important questions remain. The next several sections review key recent trials that have begun to answer these questions.

Large Simple Randomized Trials

International Adjuvant Lung Trial

The International Adjuvant Lung Trial (IALT) was presented at the American Society of Clinical Oncology (ASCO) meeting in 2003 and published in early 2004. It represents the first investigation to show an improvement in overall survival.[12,13] IALT is the largest randomized trial of adjuvant chemotherapy for lung cancer, with 1,867 patients randomized. All patients with resectable NSCLC were eligible to participate, and stage distribution included 10% stage IA, 27% stage IB, 24% stage II,
38% stage IIIA, and 1% stage IIIB. It should be noted that T3, N0 patients were considered as having stage IIIA disease in this analysis.

Participants were randomized to either an experimental group treated with three or four cycles of a cisplatin-based doublet or an untreated control group. Patients randomized to adjuvant therapy received either etoposide or a vinca alkaloid (vinblastine, vinorelbine [Navelbine], or vindesine) in combination with cisplatin. Each IALT-participating institution was responsible for the decision regarding the particular chemotherapy doublet, the dose of cisplatin, the question of whether three or four cycles were delivered, and whether or not PORT was administered.

Overall results indicated a modest but statistically significant improvement in overall survival for those randomized to adjuvant chemotherapy (HR = 0.83, 95% CI = 0.76-0.98, $P < .03$). In absolute terms, the investigators found a 4.1% improvement in 5-year survival (44.5% vs 40.5%).

The trial also revealed a significant advantage in disease-free survival in the experimental group (HR = 0.86, 95% CI = 0.74-0.94, $P < .003$).

The IALT study employed a design known as a large simple randomized trial (LSRT), which seeks to determine whether an advantage exists for all eligible participants.[14-16] LSRTs usually differ from more typical RCTs in that they utilize simple and relatively broad inclusion criteria to facilitate large sample size. Moreover, they often permit a choice of therapeutic options, as was the case in IALT. Because the primary objective of the trial was realized with an overall significant advantage in survival, results of IALT have been interpreted as supporting the conclusion that adjuvant chemotherapy should be administered to all stages of resectable NSCLC. The question is whether this truly is what the data show.

Indeed, subgroup analysis reveals that a significant survival benefit was only observed among patients with stage III NSCLC. Table 3 shows a subgroup analysis stratified by stage, and suggests that the effect of adjuvant chemotherapy is not uniform. As shown, adjuvant chemotherapy produced no significant survival benefit in patients with stage I or II disease, whereas those with stage III disease showed a significant improvement in survival. Nonetheless, the authors concluded that there was no significant effect based on stage, because an interaction term between stage of disease and treatment group was not significant.

### Table 3

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number of Deaths/Number of Patients</th>
<th>Chemotherapy</th>
<th>Control</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>115/333 (34.5%)</td>
<td>122/348 (35.1%)</td>
<td>0.95</td>
<td>0.74-0.93</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>123/230 (53.3%)</td>
<td>126/222 (56.8%)</td>
<td>0.93</td>
<td>0.72-1.20</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>231/369 (62.6%)</td>
<td>256/365 (70.1%)</td>
<td>0.79</td>
<td>0.66-0.95</td>
<td></td>
</tr>
<tr>
<td>Overall results</td>
<td>469/932 (50.3%)</td>
<td>504/935 (53.9%)</td>
<td>0.86</td>
<td>0.76-0.98</td>
<td></td>
</tr>
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</table>

*The test of interaction ($P = .41$) and the test for trend ($P = .21$) were not significant; analyses stratified by center and adjusted for stage and type of surgery.

CI = confidence interval; HR = hazard ratio.

While interaction terms were not significant in IALT, it is well known that such terms (which are used to assess heterogeneity of effect) have limited statistical power, even in the setting of a large study[17,18]. In the context of LSRTs, the trials are powered to seek an overall effect rather than an effect on a specific subset. For this reason, the value of interaction terms has been controversial. Specifically, a negative interaction term does not exclude clinically important effect modification. Notwithstanding, one cannot conclude from IALT that adjuvant chemotherapy is only effective in stage III NSCLC, because it was not designed for this purpose. Instead, it was designed to test the effectiveness of adjuvant cisplatin-based chemotherapy in all cases of resectable NSCLC. In this regard, if adjuvant chemotherapy were only effective in stage III NSCLC, the LSRT would not have
provided an appropriate study design. Nonetheless, if considered in the context of an overall effect, IALT results could be interpreted as transforming the state of the art of adjuvant chemotherapy in NSCLC from unproven in any stage to standard care in all stages. Interestingly, this overall survival advantage in IALT has not been confirmed in two other LSRTs conducted over the past several years. These other LSRTs also tested the effectiveness of cisplatin-based chemotherapy in all resectable stages of NSCLC.

Adjuvant Lung Project Italy

The Adjuvant Lung Project Italy (ALPI) study was the second largest randomized trial of adjuvant chemotherapy for lung cancer, including 1,209 participants. As with IALT, patients with stages IA to III NSCLC were eligible. Stage distribution included 39% with stage I NSCLC, 33% with stage II, and 28% with stage IIIA. Among those with stage I NSCLC, proportions of stage IA and stage IB patients were not reported.

Participants were randomized to three cycles of MVP (mitomycin, vinblastine, cisplatin) or to no chemotherapy.[19] As in IALT, the use of PORT was determined at the institutional level. The results of ALPI failed to demonstrate an advantage in overall survival for adjuvant chemotherapy (HR = 0.96, 95% CI = 0.81-1.13, P = .59). Indeed, during the first year and a half, survival in the control group was slightly superior to that in the adjuvant group. Thereafter, survival was slightly superior in the chemotherapy group, and by 5 years there was a 2.7% survival advantage in the treated group (49.2% vs 46.5%). Similarly, the investigators saw no significant difference in disease-free survival (HR = 0.89, 95% CI = 0.76-1.03, P = .13).

Subgroup analysis in ALPI showed that adjuvant chemotherapy appeared to be most effective among patients with stage II NSCLC (HR = 0.80; 95% CI = 0.60-1.06). In stage I NSCLC, adjuvant chemotherapy had no effect (HR = 0.97; 95% CI = 0.71-1.33). In stage III disease, the hazard ratio was consistent with a possible slight detrimental effect of adjuvant chemotherapy. (HR = 1.06; 95% CI = 0.82-1.38). As in IALT, the interaction term was not significant, providing no statistical evidence for effect modification.

Big Lung Trial

The third LSRT was the Big Lung Trial (BLT), which was broader in scope than either IALT or ALPI. Its primary objective was to explore the role of short-term cisplatin-based chemotherapy for all patients with NSCLC.[20] Accordingly, all NSCLC patients were eligible to participate, and in this regard, primary treatment could consist of resection, radiation therapy, or best supportive care. In addition to primary treatment, participants were randomized to three cycles of one of four cisplatin-based chemotherapy regimens or to no chemotherapy. Chemotherapy could consist of cisplatin-based doublets or triplets. The two doublets comprised either cisplatin and vindesine, or cisplatin and vinorelbine, while the triplets consisted of cisplatin, mitomycin, and vinblastine, or cisplatin, mitomycin, and ifosfamide. The choice of the chemotherapy could be made on an individual basis, although it had to be specified prior to randomization. Overall, 1,394 patients were randomized to primary therapy with or without cisplatin-based chemotherapy.

BLT involved a total of 381 patients whose primary treatment consisted of surgical resection.[21] Accordingly, despite it name, the adjuvant component of BLT was a rather small trial. Stage distribution consisted of 27% with stage I, 38% with stage II, and 34% with stage III NSCLC. The results of BLT provided no suggestion of an overall survival advantage for those randomized to adjuvant chemotherapy (HR = 1.02; 95% CI = 0.77-1.35; P = .90). Similarly, there was no improvement in disease-free survival (HR = 0.97; 95% CI = 0.74-1.26; P = .81). Subgroup analysis was not reported in BLT.

Overview of IALT and Other LSRTs

Accordingly, neither ALPI nor BLT confirmed the major positive findings of IALT. There are several potential explanations for this discrepancy. Certainly, smaller sample size in ALPI and BLT might have contributed to the negative results, particularly in BLT. There were also potentially important differences in the adjuvant regimens used.

However, it should also be pointed out that while the well-designed and properly implemented randomized clinical trial has long represented the "gold standard" investigative strategy for medical therapy,[22] little empiric evidence suggests that the LSRT is capable of providing clinically relevant answers to important therapeutic questions.[4,23,24]

In the example of adjuvant chemotherapy of lung cancer, each LSRT asked the broad question of whether adjuvant cisplatin-based chemotherapy is effective in resectable lung cancer. If the real effect of adjuvant chemotherapy varies among prognostic subgroups, the overall point estimate observed in an LSRT would not provide an accurate measure of the effect of treatment. If this were the case, then randomized trials designed to test adjuvant chemotherapy in well-defined prognostic
groupings would be the preferred method to define the true effectiveness of therapy and to determine who should be treated.

Japanese Trials of Adjuvant UFT in Stage I NSCLC
For a number of years, investigators from Japan have studied the value of a mild form of adjuvant chemotherapy in resectable NSCLC. The chemotherapy, an oral fluorouracil (5-FU) derivative, consists of uracil/tegafur, more commonly known as UFT. Tegafur is a precursor of 5-FU that is well absorbed orally and converted into 5-FU in vivo. Uracil inhibits degradation of 5-FU, resulting in sustained tissue levels of the active drug. UFT is not commercially available in the United States.[25]

JLCRG Study
Several small randomized trials compared surgery plus UFT to surgery alone in various stages of disease and in various histologies.[26-28] Earlier studies suggested that the benefits of adjuvant UFT were primarily observed in patients with stage I adenocarcinoma. Such results provided the rationale for a much larger randomized clinical trial conducted by the Japan Lung Cancer Research Group (JLCRG). This trial was specifically designed to test the effectiveness of adjuvant UFT in stage I adenocarcinoma of the lung.[29]

When reported in 2004, the results of the JLCRG trial represented the second positive trial on adjuvant chemotherapy of lung cancer. A total of 979 stage I patients were randomized to receive either 2 years of adjuvant UFT or no postoperative treatment.[29] The overall results of the study showed a statistically significant survival advantage for those randomized to adjuvant UFT (HR = 0.71; 95% CI = 0.52-0.98; P = .04). Five-year survival rates were 88% and 85% in chemotherapy and control groups, respectively.

However, subgroup analysis demonstrated a striking heterogeneity of effect. Overall, 73% of participants had stage IA adenocarcinoma, and this subgroup showed no evidence of benefit (HR = 0.97; 95% CI = 0.64-1.46; P = .87). Indeed, 5-year survival was 89% in the UFT group and 90% in the control group among stage IA patients.

In dramatic contrast, a highly significant survival advantage was seen among the 27% of participants with stage IB disease (HR = 0.48; 95% CI = 0.29-0.81; P = .005). Among stage IB patients, 5-year survival was 85% vs 74% in the treated and control groups, respectively. The fact that hazard ratios for each subgroup fall outside the 95% confidence interval of the other group underscores the heterogeneity of effect of adjuvant UFT in stage I adenocarcinoma. Indeed, there was a significant interaction between both tumor size and substage on survival in the JLCRG study.

WJSG Study
To add to the existing uncertainty regarding which subgroups require adjuvant therapy with UFT, a more recently published randomized trial presented findings that contradicted the results of the JLCRG trial in stage I adenocarcinoma. In this later study, conducted by the West Japan Study Group (WJSG), 332 patients with both adenocarcinoma or squamous cell carcinoma of the lung were randomized to surgery followed by 1 year of oral UFT or to surgery alone.[30]

Overall results failed to reveal a statistically significant survival difference between chemotherapy and control groups, although this may well reflect a relatively small sample size and limited statistical power. WJSG investigators did not report hazard ratios, but 5-year survival rates were 82% and 76% for the chemotherapy and control groups, respectively (P = .11).

However, what is most surprising is that subset analysis in the WJSG study appears to directly contradict the results from the JLCRG trial. In this trial, a significant survival benefit was seen for patients with T1, N0, stage IA NSCLC (5-year survival: 84% vs 78%; P = .036). In contrast, there was no benefit for those with T2, N0, stage IB NSCLC (5-year survival: 76% in both groups; P = .81).

In the WJSG trial, UFT was more effective in adenocarcinoma than in squamous cell carcinoma. Indeed, for the subset of patients with T1, N0, stage IA adenocarcinoma, adjuvant UFT was associated with a highly significant survival advantage (5-year survival: 89% vs 80%; P = .011).[30]

Adjuvant Trials of Vinorelbine and Cisplatin
Two adjuvant trials with similar study designs employed vinorelbine and cisplatin for the adjuvant regimen. One of these trials was conducted in North America and the other in Europe.

NCIC JBR-10 Study
The North American trial was carried out by the National Cancer Institute of Canada (NCIC), and is known as the JBR-10 trial.[31,32] Patients were eligible for this trial if they had stage IB or II NSCLC (although patients with T3, N0 disease were excluded). PORT was not permitted in the context of this trial.

A total of 459 patients with completely resected stage IB (T2, N0), or stage II (T1, N1 or T2, N1) NSCLC were randomized to surgery followed by four cycles of vinorelbine (25 mg/m² weekly for 16 weeks) plus cisplatin (50 mg/m² on days 1 and 8, every 4 weeks) or to surgery alone. The dose of
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Overall results from NCIC JBR-10 demonstrated an advantage in survival favoring the adjuvant chemotherapy arm (HR = 0.69; 95% CI = 0.52-0.91, P = .009). Median survival was significantly longer in the experimental group (94 vs 73 months), and there was a 15% absolute survival advantage at 5 years (69% vs 54%). A significant advantage in disease-free survival was also found (HR = 0.60; 95% CI = 0.45-0.79; P < .001). A very recent retrospective subset analysis suggested that elderly patients did achieve significant benefit from adjuvant chemotherapy in JBR-10.\[33\] Approximately one-third of participants were over age 65 years. In the elderly subset, adjuvant chemotherapy was associated with a significant improvement in survival compared to surgery alone (HR = 0.61, CI = 0.38-0.98, P = .04). This was true despite the fact that elderly patients received fewer cycles of chemotherapy and a lower dose intensity compared to younger patients. Because relatively few patients over 75 were included in the trial, it was not clear from this recent analysis whether the very elderly subset also benefit.

While the significant overall survival advantage in JBR-10 led the authors to conclude that adjuvant vinorelbine and cisplatin "prolongs disease-free and overall survival among patients with completely resected early-stage NSCLC,"\[34\] this conclusion did not appear to apply to each treated subset. Among the 45% of participants with stage IB NSCLC, there was no difference in survival (P = .79; HR = not reported). In contrast, among the 55% of patients with stage II disease, there was a highly significant survival advantage among those randomized to adjuvant treatment (HR = 0.59; 95% CI = 0.42-0.85; P = .004). Median survival was almost twice as long in those randomized to adjuvant therapy in this group (80 vs 41 months).

Despite these differences, JBR-10 investigators cautioned that differences as a function of stage must be interpreted with caution. This was because the interaction term was not statistically significant (P = .13), which provided no statistical evidence for effect modification.

ANITA Study

The European trial testing the effect of this same combination was the Adjuvant Navelbine International Trialist Association (ANITA) study. The design of ANITA was very similar to that of JBR-10.\[35,36\] As in the JBR-10 study, the adjuvant regimen consisted of vinorelbine and cisplatin, and stage IB and II patients were both eligible.

The major differences between these trials are that stage IIIA patients were also eligible to participate in ANITA, whereas this group was not eligible for JBR-10. Moreover, the schedule of adjuvant chemotherapy was different, in that experimental patients were randomized to four cycles of vinorelbine (30 mg/m\(^2\) per week for 16 weeks) and cisplatin (100 mg/m\(^2\) on day 1 every 4 weeks).

A total of 840 patients were randomized to four cycles of adjuvant vinorelbine/cisplatin or to observation. The use of PORT was optional and determined by each center's policy. Overall, 24% of patients randomized to adjuvant chemotherapy received PORT, compared to 33% of those in the control group. Stage distribution in ANITA included 36% with stage IB, 24% with stage II, and 39% with stage IIIB NSCLC.

At a median potential follow-up of 76 months, a significant overall survival advantage favored the group randomized to adjuvant chemotherapy (HR = 0.80; 95% CI = 0.66-0.96, P = .017). Median survival was also significantly longer in the chemotherapy group (66 vs 44 months). The absolute overall survival benefit with adjuvant chemotherapy was 8.7% at 5 years and 5.5% at 7 years. The ANITA trial also showed a corresponding advantage in disease-free survival favoring the adjuvant chemotherapy group (HR = 0.76; 95% CI = 0.64-0.91; P = .002).

As with other studies discussed, however, there appears to have been clinically relevant heterogeneity of effect as a function of disease stage. No significant advantage was seen for chemotherapy among those with stage IB NSCLC (HR = 1.10; 95% CI = 0.76-1.57). Five-year survival rates were 62% and 64%, while median survivals were 96 and 100 months in the experimental and control groups, respectively.

In contrast, the investigators found advantages for adjuvant chemotherapy among patients with stages II and IIIA NSCLC. Those with stage II disease had a 29% reduction in the risk of death, although the 95% confidence interval did cross 1 (HR = 0.71; 95% CI = 0.49-1.03). In this subgroup, 5-year survivals were 52% and 31%, while median survivals were 66 vs 31 months in the experimental and control groups, respectively. Similarly, among patients with stage IIIA disease, there was a significant 31% reduction in the risk of death (HR = 0.69; 95% CI = 0.53-0.90). Among stage IIIA patients, 5-year survival was 42% and 25%, and median survival was 33 vs 20 months in experimental and control groups, respectively. That said, the authors felt that their subset analysis did not permit any definitive conclusions. This was because the interaction term on survival between
tumor stage and chemotherapy did not reach statistical significance ($P = .07$).
In both the JBR-10 and ANITA trials, toxicity was significant but manageable. In JBR-10,
chemotherapy-related neutropenia occurred in 88% of patients receiving adjuvant treatment, and
there were two chemotherapy-related toxic deaths. Similarly, in the ANITA chemotherapy group,
85% of patients developed grade 3 or 4 neutropenia, and four patients died from septic shock.
Compliance with chemotherapy due to toxicity was a significant problem in both studies. In both
JBR-10 and ANITA, only about half of patients completed all four cycles of adjuvant
chemotherapy.[36,37]

CALGB 9633: Paclitaxel and Carboplatin in Stage IB NSCLC
Cancer and Leukemia Group B (CALGB) 9633 is the only adjuvant chemotherapy trial in NSCLC that
employed a carboplatin- rather than cisplatin-based combination. It is also the only trial designed for
a single disease stage.[38] In this trial, 344 patients with completely resected stage IB NSCLC were
randomized to an experimental group that was treated with four cycles of adjuvant paclitaxel (200
mg/m$^2$ over 3 hours every 3 weeks) and carboplatin (area under the concentration-time curve [AUC]
of 6 mg/mL/min every 3 weeks), or to a control group that received no adjuvant treatment.
In a preliminary report of this study presented at ASCO in 2004, treatment with adjuvant
chemotherapy was associated with significant improvements in overall and disease-free survival.[38]
At the time, adjuvant chemotherapy was associated with a 38% reduction in the risk of death (HR =
0.62; 95% CI = 0.41-0.95, $P = .028$). With a median follow-up of 34 months, this difference
translated into an absolute 12% improvement in 4-year survival (71% vs 59%). Indeed, the study
was stopped early by the Data Safety Monitoring Board after a planned interim analysis
demonstrated a $P$ value for overall survival that was lower than the prespecified stopping boundary.
Treatment was well-tolerated, and the most common side effect was grade 3 or 4 neutropenia, which
occurred in 36% of patients. No chemotherapy-related toxic deaths occurred in this study.
An updated analysis of CALGB 9633 was presented at ASCO in 2006, which was clearly different from
the results presented 2 years earlier.[39] Most importantly, the updated results no longer showed a
significant improvement in overall survival (HR = 0.80; CI = 0.60-1.07; $P = .10$). Although not
statistically significant, median survival was substantially longer in the adjuvant chemotherapy group
(95 vs 78 months).
Because overall survival was the primary endpoint, CALGB 9633 should now be interpreted as a
negative trial. Nonetheless, several findings continue to indicate that adjuvant chemotherapy had a
beneficial effect. For example, statistically significant advantages were seen in 2- and 3-year
survival. Moreover, disease-free survival in the chemotherapy arm was statistically significantly
greater than that in the observation arm (HR = 0.74; CI = 0.57-0.96; $P = .030$). Median disease-free
survival was also longer in the experimental group (89 vs 52 months).[39]
Although overall survival was not significantly improved, exploratory analysis demonstrated
improved survival among those with larger tumors. Among patients with tumors greater than or
equal to 4 cm in diameter, there were significant advantages in both overall survival and
disease-free survival. On the other hand, among patients with tumors less than 4 cm in size, there
was no evidence for benefit of adjuvant chemotherapy. While this unplanned subgroup analysis is
only exploratory, it does suggest that patients with large tumors may derive meaningful benefit from
adjuvant chemotherapy.
Because the updated analysis no longer shows a significant advantage in overall survival, the results
of CALGB 9633 clearly do not mandate adjuvant chemotherapy as the standard of care in stage IB
NSCLC. Nonetheless, the authors of CALGB concluded that the updated results of the study support
continued consideration of adjuvant paclitaxel and carboplatin in stage IB disease, particularly
among patients with tumors greater than 4 cm in diameter.

Discussion
A remarkable shift in the state of the art of adjuvant chemotherapy for NSCLC has taken place over the past 3 years. Until the report of a significant survival advantage from IALT, there was no convincing evidence that adjuvant chemotherapy was effective among any patients with NSCLC. However, five individual randomized clinical trials have reported statistically significant survival advantages associated with adjuvant chemotherapy in this setting. These positive studies, as well as other recently reported trials, are summarized in Table 4 and in Figure 1.
While the results of these trials provide powerful evidence that adjuvant chemotherapy is beneficial in early-stage lung cancer, there remain numerous unanswered questions. One major problem is that existing trials support inconsistent conclusions regarding which patients should be treated with adjuvant chemotherapy. For example, while the results of IALT demonstrated a modest but statistically significant improvement in survival for all patients randomized to adjuvant cisplatin-based chemotherapy in resectable NSCLC,[13] subgroup analysis demonstrated that only stage III patients derived benefit. However, two other LSRTs—ALPI and BLT—failed to confirm this finding.[19,21]

The results of NCIC JBR-10 and ANITA both demonstrated statistically significant overall survival advantages in favor of adjuvant cisplatin and vinorelbine in the adjuvant setting.[32,36] Both also showed a beneficial effect for patients with stage II NSCLC. Moreover, in ANITA, stage IIIA patients achieved a magnitude of benefit that was very similar to that achieved in stage II patients. (Stage IIIA patients were not eligible to participate in JBR-10.) In contrast to this benefit, there was no evidence for a positive effect in patients with stage IB disease in either JBR-10 or ANITA.

On the other hand, results of CALGB 9633 do provide evidence that adjuvant chemotherapy has some effect on stage IB NSCLC. The preliminary results in this study, as presented in 2004, showed a large and significant effect in overall and disease-free survival. Indeed, the hazard ratio of 0.62 that was reported in 2004 represented the largest proportional reduction in the risk of death observed in any individual randomized trial.[38] While this highly encouraging result has not held up over time, the hazard ratio of 0.80 reported in the 2006 analysis is much closer to that observed in most other
individual randomized trials. Unfortunately, most likely because of the relatively small sample size, the updated analysis no longer shows an overall survival difference that is statistically significant. Accordingly, while the recent results of CALGB 9633 have failed to confirm earlier findings, they do support that adjuvant treatment has a positive effect on outcome of stage IB disease. This conclusion is further supported by the results of the JLCRG trial on adjuvant UFT in stage I adenocarcinoma of the lung. The JLCRG study showed a positive overall effect for all stage I patients considered together, although subgroup analysis demonstrated that the benefit was limited to patients with stage IB disease. On the other hand, the much smaller WJSG study for stage I NSCLC failed to show a significant overall survival advantage. In contrast, the results from the JLCRG trial subgroup analysis showed a significant advantage for patients with stage IA but not for those with stage IB disease.

The results of all these individual randomized trials suggest that adjuvant chemotherapy is effective in early-stage NSCLC. However, they leave considerable uncertainty regarding who should be treated and what regimens are most efficacious.

Role of Meta-Analysis

In addition to the individual randomized trials presented above, numerous systemic reviews or meta-analyses, which have incorporated results from some of the recent trials, have also appeared over the past several years. Each meta-analysis reported a positive overall effect of adjuvant chemotherapy in resectable NSCLC. Accordingly, these meta-analyses support the conclusion that adjuvant chemotherapy is effective in resectable NSCLC. Published meta-analyses have used a variety of techniques. Several were literature-based meta-analyses of published studies. One was a meta-analysis based upon individual patient data (IPD). IPD meta-analyses are generally considered preferable to literature-based meta-analyses, since they are less likely to yield biased conclusions. Moreover, IPD meta-analysis may be particularly useful for conducting subgroup analysis in order to identify those most likely to benefit from treatment. It should also be understood that the term meta-analysis is sometimes distinguished from a pooled analysis. A pooled analysis is generally not exhaustive, but includes more data per trial so as to be able to evaluate the effects of therapy in greater detail than is possible with even an IPD meta-analysis.

Indeed, the Lung Adjuvant Cisplatin Evaluation (LACE) is a pooled analysis, which included 4,584 patients from five recent cisplatin based randomized trials. It revealed an overall significant 11% reduction in the risk of death from adjuvant cisplatin-based chemotherapy (HR = 0.89; 95% CI = 0.82-0.96). Moreover, LACE reported stage-specific data and confirmed a significant benefit among patients with stage II or III NSCLC (HR = 0.83; 95% CI = 0.73-0.95). On the other hand, LACE showed no benefit for patients with stage I NSCLC. Indeed, among the relatively small proportion of stage IA patients included, adjuvant cisplatin-based chemotherapy appeared to be detrimental (HR = 1.43; 95% CI = 0.96-2.09). Among stage IB patients, there was an insignificant trend favoring adjuvant chemotherapy (HR = 0.93; 95% CI = 0.78-1.10).

Notwithstanding, the meta-analytic approach is a statistical technique that does not adequately address the problem of inconsistent results between individual trials, and can provide only limited insight as to why heterogeneity of results may have been observed. While meta-analysis was developed as a solution to the problem of insufficient statistical power, the technique is increasingly being used in an attempt to reconcile divergent and often directly conflicting results from well-powered individual trials.

Certain statistical models do account for heterogeneity in calculating a single-point estimate. While the fixed-effects model assumes that a common point estimate exists across studies, the random-effects model assumes that different studies are not measuring an identical effect. Because it takes heterogeneity between studies into account, it is more conservative. However, the important and fundamental question is whether meta-analysis is useful when the effect of an intervention varies across treated subpopulations. In this regard, it is important to appreciate that even conservative statistical models are unable to provide useful insights as to why different trials may support seemingly inconsistent conclusions.

From a statistical perspective, each randomized clinical trial presented herein was designed and powered to provide a single-point estimate regarding the effect of adjuvant chemotherapy among all subsets eligible to participate in the trial. Figure 2 indicates the overall survival results observed among recent individual randomized trials on adjuvant chemotherapy.
The problem, however, is that from a biologic perspective, these trials cannot provide an accurate answer to the question of adjuvant chemotherapy, if a single "correct" answer does not exist. Accordingly, a single-point estimate for all patients, or even stage-specific estimates (as reported in LACE), cannot provide definitive evidence regarding the effect of adjuvant chemotherapy in the context of biologic heterogeneity.

In the context of real biologic heterogeneity, it might be most valid to focus on subgroups that are most likely to benefit. Figure 3 illustrates the results of these recent randomized trials, using a subset analysis based on stage of disease, and provides a more useful guide than that suggested in Figure 2.

Role of Molecular and Predictive Markers

Abundant evidence is beginning to mount that decisions regarding the adjuvant treatment of cancer will evolve from a standard in which risk assessment and therapeutic benefit within a population are based exclusively on clinical and pathologic determinants, to a new standard that routinely incorporates biologic determinants of prognosis. The objective is to identify individuals who are most likely to benefit from adjuvant therapy.

The best existing example of the utility of such an approach in the adjuvant setting comes from recently published randomized trials focusing on breast cancer that compared adjuvant chemotherapy with or without trastuzumab (Herceptin) in women with HER2-positive disease.\[54,55\]
By limiting eligibility exclusively to women who were likely to respond to trastuzumab, these randomized trials were able to demonstrate a large and rather dramatic improvement in outcome. Indeed, traditional prognostic markers have been useful for defining risk in populations of patients. However, individual risk assessment has not been possible. Numerous molecular markers appear to be able to provide information about the likelihood of relapse beyond that obtained from traditional clinical and pathologic determinants.

- **Gene-Expression Profiling**—Gene-expression profiling appears to have the potential to dramatically affect decisions regarding who is likely to benefit from adjuvant therapy,[56-58] permitting risk assessment for the individual. Many reports on gene-expression profiling in a variety of human cancers (including NSCLC) have demonstrated that cancers with similar histologies can behave in a biologically heterogeneous manner. Indeed, two large randomized trials designed to validate assays based on gene-expression profiling in breast cancer have begun, including a trial that utilizes the Oncotype DX assay in North America (TAILORx, or Trial Assigning Individualized Options for Treatment) and the other in the European Union (known as the MINDACCT trial).[59] A recent report from Duke demonstrated the potential role of gene-expression profiling in lung cancer.[60] The investigators initially categorized outcomes using their gene-expression model, which they called the Lung Metagene Predictor Model, in a series of 89 patients with NSCLC from their own institution. Subsequently, they validated their initial results from two independent cohorts participating in multicenter cooperative group trials. The authors found that the metagene model was a significantly more accurate predictor of outcome than the traditional clinical model based on age, gender, stage, size of tumor, histologic subtype, and smoking history. The metagene model also was applied to a group of 68 patients with stage IA disease.[60] Among 47 patients with a low predicted risk of relapse, the 5-year survival rate was approximately 90%. In dramatic contrast, among 21 patients in whom the metagene model predicted a high risk of recurrence, 5-year survival was < 10%. The results of the metagene analysis is the basis for a proposed randomized trial designed to evaluate the role of adjuvant chemotherapy in high-risk stage IA NSCLC.

- **ERCC1**—Another very recent report indicates that excision repair cross-complementation group 1 (ERCC1) protein serves as both a predictive and prognostic marker in early-stage NSCLC. ERCC1 is a highly conserved excision nuclease within the nucleotide excision repair pathway. It is essential for efficient repair of DNA-adducts induced by alkylating agents. Olaussen evaluated the importance of ERCC1 expression in 783 resected tumor tissues from patients enrolled in the IALT trial.[61] What was most interesting is that patients with ERCC1-negative tumors who were randomized to adjuvant cisplatin-based chemotherapy had significantly longer survival compared to those with ERCC1-negative tumors randomized to observation (HR = 0.67; 95%CI = 0.51-0.89). On the other hand, there was no survival advantage for adjuvant chemotherapy among ERCC1-positive patients (HR = 1.18; 95% CI = 0.87-1.61). When one considers only patients randomized to observation, those with ERCC1-positive tumors had superior survival compared to those with ERCC1-negative tumors (HR = 0.65; 95% CI = 0.48-0.89). The authors concluded that patients with resected NSCLC and ERCC1-negative tumors derived benefit from adjuvant chemotherapy, while patients with ERCC1-positive tumors did not.[61]

These and other reports of molecular markers provide the opportunity for exciting new avenues of investigation within the area of adjuvant chemotherapy. Moreover, an understanding of the biologic differences between tumors is likely to provide important insights into the heterogeneity observed in existing randomized trials on adjuvant chemotherapy of lung cancer.

PORT in the Adjuvant Setting

While none of the recent randomized trials were designed to assess the efficacy of PORT in the adjuvant setting, IALT, ANITA, ALPI, and BLT all permitted this modality, based on policies determined at each participating institution. What do we know about the role of PORT in the adjuvant setting? In fact, older systematic reviews had supported the conclusion that PORT is detrimental in resected NSCLC, particularly in those with stage I or stage II disease.[62-64] The efficacy of PORT in resected stage III NSCLC has been less clear from these studies. Recently, Lally reported on the results of an analysis of patients with early-stage NSCLC, based on the Surveillance, Epidemiology, and End Results (SEER) database.[65] This analysis utilized a cohort of 7,465 patients. The results demonstrated a significant survival advantage among those with N2 disease (HR = 0.86; 95% CI = 0.76-0.96; P = .008). In patients with stage I or stage II disease, PORT was associated with a significant detrimental effect on survival.
Neoadjuvant vs Adjuvant Chemotherapy in Early Lung Cancer

What can be stated about the role of neoadjuvant rather than adjuvant chemotherapy in early-stage NSCLC? There is a powerful rationale that neoadjuvant chemotherapy may be more effective than adjuvant treatment.[66]

The Bimodality Lung Oncology Team (BLOT) trial was a phase II trial of neoadjuvant chemotherapy with paclitaxel and carboplatin in clinical stages IB-IIIA NSCLC.[67] The results of this trial established the feasibility of this approach, and also reported encouraging survival results. These results provided the impetus for an intergroup randomized trial (known as Southwest Oncology Group [SWOG] 9900) designed to confirm these encouraging preliminary findings.

SWOG 9900 tested whether neoadjuvant chemotherapy with paclitaxel and carboplatin followed by surgery was superior to surgery alone in patients with clinical stages IB, II, and IIIA (T3, N1) NSCLC.[68] The planned sample size was 600 patients, but the study closed early because of positive results from recently reported adjuvant studies. At the time of study closure, 354 patients (or 59% of the accrual target) had been entered on the trial. With a median follow-up of 28 months, the results of SWOG 9900 showed a trend toward increased survival favoring the neoadjuvant chemotherapy group. However, these differences were not statistically significant (HR = 0.88; 95% CI = 0.63-1.23; P = .47).

Two trials comparing neoadjuvant to adjuvant chemotherapy are currently ongoing. One of these is the Neoadjuvant-Adjuvant Taxol Carboplatin Hope (NATCH) trial, which is being conducted in Spain.[69] NATCH is designed to test the relative effectiveness of three cycles of paclitaxel and carboplatin given either preoperatively or postoperatively compared to surgery alone in stages IB, II, and IIIA (T3, N1) NSCLC. A study of similar design comparing neoadjuvant to adjuvant cisplatin and docetaxel in patients with stages I, II, and IIIA is also ongoing.[66] No results from either of these trials is currently available. While neoadjuvant chemotherapy represents a promising strategy in early stage NSCLC, the relative paucity of data, at least compared to that available for adjuvant therapy, currently limits its applicability in this area.

Conclusions

Existing evidence strongly supports that adjuvant chemotherapy is effective in stages II and IIIA NSCLC. Among patients with stage IB disease, greater uncertainty exists. The updated results of CALGB 9633, particularly when considered in conjunction with the results of NCIC JBR-10 and ANITA, raise questions about the value of adjuvant chemotherapy in stage IB NSCLC. Nonetheless, adjuvant chemotherapy remains a reasonable option, particularly among patients with large tumors.

Furthermore, the JLCRG UFT trial indicates that adjuvant therapy is effective in stage IB disease. The carboplatin vs cisplatin debate remains unresolved. Recent meta-analyses in advanced NSCLC suggest a modest advantage for cisplatin-based combinations compared to carboplatin-based regimens.[70,71] There is no question that cisplatin-based combinations have been far more extensively utilized in the adjuvant setting that carboplatin-based regimens. Moreover, the recent LACE pooled analysis demonstrated that cisplatin and vinorelbine was an effective adjuvant regimen in early lung cancer [45].

On the other hand, carboplatin-combinations, particularly carboplatin and paclitaxel, remains the most widely used regimen in NSCLC in the United States. A large randomized trial (ECOG 1594) indicated that carboplatin/paclitaxel was equivalent to three cisplatin-based combinations in advanced NSCLC.[72] Moreover, the hazard ratio of 0.80 observed in stage IB in the updated results of CALGB 9633 compares favorably to a hazard ratio of 0.93 associated with cisplatin-based regimens in the LACE analysis.[44]

The design of the next large intergroup trial on adjuvant chemotherapy in resectable NSCLC supports the fact that adjuvant chemotherapy is now standard in patients with early-stage NSCLC. This study (ECOG 1505) is being designed to address the incremental effectiveness of bevacizumab (Avastin) in combination with a cisplatin-based doublet, in stages IB, II, and IIIA NSCLC. Based upon updated results of CALGB 9633, stage IB patients will only be eligible if they have tumors greater than 4 cm in diameter.[73]

Clearly, future adjuvant trials need to be designed to account for biologic heterogeneity, as well as standard clinicopathologic parameters. Indeed, our growing knowledge of molecular biology and factors that predict responsiveness to specific anticancer agents may have the effect of rendering traditional large randomized clinical trials somewhat obsolete in the relatively near future. There is no question that future randomized trials must be designed to incorporate our growing knowledge of tumor biology, as is being done with trials now being planned. Indeed, it is not unlikely that imbalances in unmeasured and/or unknown factors that determine differences in clinical behavior of tumors of similar stage and histology have contributed greatly to many of the conflicting results.
observed in prior large unselected randomized trials.

Disclosures:
The author has no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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