Consensus Conference: Multimodality Management of Early- and Intermediate-Stage Non-Small Cell Lung Cancer

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ABSTRACT
Surgery is the mainstay of treatment in early- and intermediate-stage non-small cell lung cancer (NSCLC), yet recurrences are frequent. Studies have documented the benefits of chemotherapy administered after resection, but a number of questions remain regarding how overall outcomes can be further improved. To provide the oncology community with direction on these issues, a consensus conference of leading experts in the NSCLC field was held at the Fifth Annual Atlanta Lung Cancer Symposium on October 25–27, 2007.

The available scientific literature is presented and when such literature is lacking, clinical experience is provided to support the following conclusions. Preoperative staging should be done in accordance with the National Comprehensive Cancer Network guidelines, but endoscopic fine needle aspiration of enlarged mediastinal nodes can be used, and if histology is positive for malignancy, mediastinoscopy can be avoided. Neoadjuvant systemic therapy is not generally recommended but can be considered to downstage an unresectable patient. There is currently no role for preoperative radiation or chemoradiation. Adjuvant systemic therapy is not recommended for stage IA and IB patients; however, adverse prognostic factors are acceptable reasons to consider adjuvant systemic therapy in the latter. Adjuvant systemic therapy is recommended for stage IIA, IIB, and IIIA patients, consistent with recent American Society of Clinical Oncology guidelines. A cisplatin-based regimen should be started within 60 days after surgery, but if relatively contraindicated, carboplatin is an acceptable alternative. Adjuvant radiation therapy is not recommended for N0 and N1 patients, but is used in N2 patients to decrease local recurrence. The Oncologist 2008;13:945–953
INTRODUCTION
This paper describes the proceedings of a mini-symposium held during the Fifth Annual Atlanta Lung Cancer Symposium on October 25–27, 2007. Since its inception in 2003, this accredited continuing medical education program has steadily expanded and gained recognition in the oncology community. Given that interaction between attendees and faculty has been a major emphasis of the symposium, holding a consensus conference on a controversial topic was a logical outgrowth of the program. Attendance at this 2007 meeting included 133 attendees. Panel members involved in the consensus conference were Rodolfo Bordoni (Georgia Cancer Specialists), Fadlo Khuri (Emory University), Edward Kim (MD Anderson Cancer Center), Thomas D’Amico (Duke University), Katherine Pisters (MD Anderson Cancer Center), Julie Brahmer (Johns Hopkins University), Maria Werner-Wasik (Thomas Jefferson University), and Eric Vallières (Swedish Medical Center).

BACKGROUND
Surgery is considered the mainstay of treatment in early- and intermediate-stage non-small cell lung cancer (NSCLC), yet recurrences remain frequent. In 2003, the first positive trial of the new era of adjuvant therapy was presented [1, 2]. Since then, two studies have been negative [3, 4], and a number of subsequent trials and meta-analyses have confirmed the benefit [5–8]. Nevertheless, numerous questions remain, including: (a) How can staging and surgical care be improved? (b) Is there a role for neoadjuvant therapy in inoperable stage patients? (c) Who should be treated with adjuvant therapy? and (d) What constitutes optimal adjuvant therapy?

STAGING
Thomas D’Amico discussed the importance of accurate staging and described how deficiencies add to the challenge of managing patients with solitary lung nodules. Because a cure is achieved in <60% of tumor–node–metastasis (TNM) stage I patients, as per clinical parameters, and in <70% of stage I patients pathologically staged, it is obvious that current staging modalities inaccurately predict which patients will recur. Pathological staging by the use of mediastinoscopy has been considered the standard of care. However, in a recent study of 40,000 surgical patients, preoperative mediastinoscopy was performed in only 27% of operated patients [9]. Among these operated patients, regional lymph node sampling was performed in only 47% of cases and intraoperative frozen sections were analyzed in only 35% of cases; positive margins were present in 8% of cases. Results of that study are in conflict with published guidelines and are a painful reminder of the suboptimal management of early-stage lung cancer in our country.

Since positron emission tomography (PET) scanning is widely available in the U.S. as a staging tool, its proper use and interpretation for the management of lung cancer are of critical importance. The National Comprehensive Cancer Network (NCCN) guidelines, the most widely used algorithm for the evaluation and management of cancer in this country, consider the use of PET scans in clinical stage I (peripheral T1N0, peripheral T2N0, central T1–2N0) and stage II (T1–2N1) NSCLC patients an evidence-based procedure, while mediastinoscopy is considered the gold standard for proper staging and management of mediastinal disease [10].

The basis for the guidelines’ conclusion is the literature on PET scanning for the detection of mediastinal disease, which initially showed promise but has proven to be less than optimal in most studies. Trials with sensitivity and specificity determinations are shown in Table 1. Another prospective study of 105 patients with NSCLC demonstrated a downstage rate of 12% and an upstage rate of 36% [11]. In 24% of the patients, otherwise undetected distant metastatic disease was found. The use of PET scans influenced management in 70 patients, or 67% of the total population. The NCCN guidelines recognize the use of PET scans as appropriate to detect disseminated disease that would make a thoracotomy futile in a patient otherwise incorrectly diagnosed as clinical early stage. Similar issues with stage II and stage III disease led to the conclusion that at least one third of patients in a typical practice are misstaged. Understaged patients do not receive the benefit of standard adjuvant or induction therapy, with the consequent detrimental effect on local disease control and survival. At the other side of the spectrum are overstaged patients, a group of patients with potentially curable disease who are banned from curative therapeutic approaches because of improper staging [12–15].

In addition to poor selection of staging techniques as the culprit for improper treatment of lung cancer, it has been clear for years that the current staging system, in use since 1997, has multiple prognostic inconsistencies that are translated into treatment generalizations and potentially into negative outcomes [16]. In recognition of this deficiency, a proposal for the revision of the TNM classification for lung cancer is being considered [17]. New definitions in the revision include:

- Division of T1 into T1a (<2 cm) and T1b (2–3 cm)
- Reclassification of tumors >7 cm from T2 to T3
- Reclassification of same lobe nodules from T4 to T3
- Reclassification of pleural dissemination from T4 to M1a
Reclassification of contralateral lung involvement from M1 to M1a
Reclassification of distant metastases from M1 to M1b
T2aN1M0 and T2bN0M0 would be stage IIA
T3N0M0 would be stage IIB and T3N1M0 would be stage IIIA

SURGICAL ISSUES
D’Amico continued by discussing the surgical issues in NSCLC. After appropriate preoperative staging, anatomic resection is preferred (sleeve lobectomy preferred over pneumonectomy and segmentectomy preferred over a wedge resection). At least three N2 lymph node stations should be sampled or dissected, with the latter being optimal. The safety and efficacy of thoracoscopic lobectomy for patients with early-stage lung cancer have been established. Although there are no prospective, randomized series that compare thoracoscopic lobectomy with conventional approaches, a sufficient number of series has been published, both single-institution and multi-institution experiences, to conclude that thoracoscopic lobectomy is a reasonable strategy for patients with clinical early-stage lung cancer.

The Cancer and Leukemia Group B (CALGB) reported on the results of a multi-institutional series of 97 patients who underwent thoracoscopic lobectomy [18]. In that series, the mortality rate was 2%, the operative time was 130 minutes, and the median length of stay was 3 days. Daniels and colleagues reported the results of thoracoscopic lobectomy in 170 consecutive patients [19]. The 30-day mortality rate was 2%, with no intraoperative deaths. The conversion rate was 1.8% and none were emergent. The median chest tube duration was 3 days and the median length of stay was 3 days. An expanded review of 500 patients from the same set of investigators demonstrated a mortality rate of 1% and chest tube duration of 2 days [20]. In that series, atrial fibrillation occurred in only 10% of patients postoperatively. Thoracoscopic lobectomy has recently been demonstrated to be effective in selective patients following induction therapy [21]. The use of thoracoscopic lobectomy may improve compliance with adjuvant chemotherapy, allowing a greater fraction of patients to undergo the combination of surgery and adjuvant therapy [22].

Many groups have demonstrated better outcomes among patients undergoing lobectomies and pneumonectomies in centers with a high volume of patients. Birkmeyer et al. [23] analyzed surgical mortality for patients undergoing both lobectomy and pneumonectomy. In hospitals performing fewer than nine procedures per year, the adjusted mortality rates were 5.7% and 16.1%, respectively, whereas in hospitals that performed more than 46 procedures per year, the adjusted mortality rates were 4% and 10.7%, respectively.

NEOADJUVANT/ADJUVANT CHEMOTHERAPY
Katherine Pisters described the evolution of systemic therapy in early- and intermediate-stage NSCLC, with surgery considered the standard of care in the treatment of early-stage NSCLC. However, it is notable that a significant number of patients relapse in the same area of the primary (local) or somewhere else (distant), compromising overall survival (Table 2) [24–27]. Perioperative systemic therapy was introduced in the 1980s to improve local, and mainly systemic, relapse and ultimately survival. Several small randomized trials of preoperative platinum-based chemotherapy were reported >10 years ago, with most of them demonstrating an improvement in survival (Table 3) [28–32].

### Table 1. Mediastinal staging with positron emission tomography scanning

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>Sensitivitya</th>
<th>Specificitya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pieterman et al. [12]</td>
<td>2000</td>
<td>102</td>
<td>91%</td>
<td>86%</td>
</tr>
<tr>
<td>Kernstin et al. [13]</td>
<td>2002</td>
<td>237</td>
<td>82%</td>
<td>82%</td>
</tr>
<tr>
<td>Gonzalez-Stawinsky et al. [14]</td>
<td>2003</td>
<td>203</td>
<td>64%</td>
<td>77%</td>
</tr>
<tr>
<td>Reed et al. [15] (ACOSOG Z0050)</td>
<td>2003</td>
<td>287</td>
<td>61%</td>
<td>84%</td>
</tr>
</tbody>
</table>

*aFor mediastinal node metastases.

### Table 2. Survival rates and pattern of failure in early-stage NSCLC, by stage [51]

<table>
<thead>
<tr>
<th>Surgical stage</th>
<th>Survival 5-yr (%)</th>
<th>Relapse rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Local</td>
</tr>
<tr>
<td>IA T1N0M0</td>
<td>67</td>
<td>10</td>
</tr>
<tr>
<td>IB T2N0M0 57</td>
<td>57</td>
<td>10</td>
</tr>
<tr>
<td>IIA T1N1M0</td>
<td>55</td>
<td>10</td>
</tr>
<tr>
<td>IIB T2N1M0</td>
<td>39</td>
<td>10</td>
</tr>
<tr>
<td>T3N0M0</td>
<td>38</td>
<td>12</td>
</tr>
<tr>
<td>IIIA T3N1M0</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>T1–3N2M0</td>
<td>23</td>
<td>15</td>
</tr>
</tbody>
</table>

Abbreviations: M, metastasis; N, node; NSCLC, non-small cell lung cancer; T, tumor.
The design of large trials in early-stage NSCLC has subsequently focused on the preoperative use of chemotherapy (Table 4), with the two largest clinical trials conducted in Europe [33] and in the U.S. (e.g., the S9900 trial) in the 1990s [34, 35]. More recent trials have been reported in preliminary [36] or final [37] fashion. Two meta-analyses on preoperative chemotherapy have been published to date. Berghmans and colleagues [38] evaluated six trials with 590 patients, while Burdett and colleagues [39] evaluated seven trials with 988 patients. An improvement in overall survival was found with preoperative chemotherapy in both analyses, with hazard ratios (HRs) of 0.66 (95% confidence interval [CI], 0.48–0.93) and 0.82 (95% CI, 0.69–0.97), respectively. Although these analyses of preoperative chemotherapy were not done on individual patient level data, they are important because of the improvement in outcome with a high level of statistical significance.

With regard to postoperative chemotherapy, the new era of successful adjuvant platinum-based chemotherapy in early-stage NSCLC began in 2004 (Table 5). Pisters remarked on the similarity of the survival curves from the International Adjuvant Lung Cancer Trial, which used a two-drug, cisplatin-containing regimen in stage IB, II, or IIIA disease patients, and the S9900 (neoadjuvant chemother-

<table>
<thead>
<tr>
<th>Table 3. Phase II trials of preoperative, platinum-based chemotherapy</th>
</tr>
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<tbody>
<tr>
<td><strong>Author</strong></td>
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<tr>
<td>Roth et al. [28]</td>
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<tr>
<td>Rosell et al. [29]</td>
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<tr>
<td>Nagai et al. [31]</td>
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<tr>
<td>Sorensen et al. [32]</td>
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</table>

*One of seven regimens (method of selection not stated).

Abbreviations: Cb, carboplatin; CEP, cyclophosphamide, etoposide, and cisplatin; EP, etoposide and cisplatin; MIP, mitomycin, ifosfamide, and cisplatin; NR, not reported, Pac, paclitaxel; VdP, vindesine and cisplatin.

<table>
<thead>
<tr>
<th>Table 4. Large, randomized trials of preoperative chemotherapy in stage IB–IIIA patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
</tr>
<tr>
<td>DePierre et al. [33]</td>
</tr>
<tr>
<td>Pisters et al. [34, 35] (S9900)</td>
</tr>
<tr>
<td>Zhou et al. [52]</td>
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<tr>
<td>Nicolson et al. [53]</td>
</tr>
</tbody>
</table>

*Trial terminated prior to accrual goal.

*Hazard ratio for overall survival 1.04 (95% confidence interval, 0.81–1.35).

*Data for 4-year survival, 95% confidence interval, 36–51 months and 28–42 months, respectively.

Abbreviations: C, cisplatin; Cb, carboplatin; Doc, docetaxel; G, gemcitabine; I, ifosfamide; M, mitomycin; NR, not reported; Pac, paclitaxel; V, vinorelbine; Vb, vinblastine.
apy) study [2, 35]. In 2005, a trial reported by the National Cancer Institute of Canada showed an impressive 30% lower risk for death in patients with stage IB and II disease when vinorelbine and cisplatin were used [8]. The same year, carboplatin and paclitaxel in the CALGB 9633 study produced an initial 17% lower risk for death at 4 years of follow-up [36]. However, 2 years later, these results were no longer statistically significant, except in a subset of patients with tumor size >4 cm, resulting in a controversy as to whether patients with stage IB disease and large tumors should be routinely offered adjuvant chemotherapy or not [37]. Finally, in 2006, the results of the Adjuvant Navelbine International Trialist Association (ANITA) trial, a European study using cisplatin and vinorelbine to treat patients with stage IB–III A disease, demonstrated positive results [5]. Interestingly, a retrospective analysis of the ANITA database suggested a positive impact on survival when adjuvant radiation therapy was used in sequence with chemotherapy, but only for patients with stage N2 disease [40]. Overall, 232 of 840 patients received postoperative radiation therapy (PORT) (33.3% in the observation arm and 21.6% in the chemotherapy arm). Patients with pN1 disease had a longer survival time with PORT in the observation arm (median, 25.9 months versus 50.2 months), whereas PORT had a detrimental effect in the chemotherapy group (median survival time, 93.6 months versus 46.6 months). In contrast, the median survival duration was longer in patients with pN2 disease who received PORT, both in the chemotherapy arm (23.8 months versus 47.4 months) and the observation arm (12.7 months versus 22.7 months).

The Lung Adjuvant Cisplatin Evaluation (LACE) pooled individual data from 4,584 patients in five adjuvant clinical trials using cisplatin-based chemotherapy to assess the impact of this approach by surgical substage (IA versus IB versus II versus III) [6]. The study suggested a possible detrimental effect of adjuvant, cisplatin-based chemotherapy in stage IA disease, when compared with surgery alone. Pisters concluded that there are currently not enough data to recommend the use of adjuvant chemotherapy in patients with IA disease. In stage IB disease, the HR trended in favor of chemotherapy, but it did not achieve statistical significance. For patients with stage II or III disease, the HRs did not overlap with one another, leading investigators to conclude that these results validate the use of adjuvant, cisplatin-based chemotherapy in these clinical scenarios. The most efficient cisplatin combination was with vinorelbine, followed by etoposide and other vinca alkaloids. However, this conclusion is weakened by the difference in dose intensity evidenced between trials. The LACE investigators updated their results at the 2007 American Society of Clinical Oncology (ASCO) Annual Meeting, including >8,100 patients and 30 randomized trials [7]. Cisplatin was administered in 15 of the trials. Overall, a highly significant 4% absolute benefit in the risk for death was reported, with an HR of 0.86 (95% CI, 0.81–0.93; p < .000001).

### Table 5. Results of “modern” adjuvant chemotherapy trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>n</th>
<th>Therapy</th>
<th>Results</th>
<th>PORT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IALT Collaborative Group [2]</td>
<td>I–III</td>
<td>1,867</td>
<td>Cisplatin based</td>
<td>HR, 0.86; p &lt; .03</td>
<td>27%</td>
</tr>
<tr>
<td>Winton et al. [8] (JBR.10)</td>
<td>IB–II</td>
<td>344</td>
<td>Cisplatin and vinorelbine</td>
<td>HR, 0.696; p = .012</td>
<td>No</td>
</tr>
<tr>
<td>Strauss et al. [36] (CALGB 9633, 4-yr follow-up)</td>
<td>IB</td>
<td>344</td>
<td>Carboplatin and paclitaxel</td>
<td>HR, 0.62; p = .028</td>
<td>No</td>
</tr>
<tr>
<td>Strauss et al. [37] (CALGB 9633, 6-yr follow-up)</td>
<td>IB</td>
<td>344</td>
<td>Carboplatin and paclitaxel</td>
<td>HR, 0.80; p = .10</td>
<td>No</td>
</tr>
<tr>
<td>Douillard et al. [5] (ANITA)</td>
<td>IB–IIIA</td>
<td>798</td>
<td>Cisplatin and vinorelbine</td>
<td>HR, 0.79; p = .013</td>
<td>28%</td>
</tr>
<tr>
<td>Scagliotti et al. [3] (ALPI)</td>
<td>I–IIIA</td>
<td>1,209</td>
<td>Cisplatin, mitomycin, and vindesine</td>
<td>HR, 0.96; p = .589</td>
<td>chemotherapy, 65%; control, 82%</td>
</tr>
<tr>
<td>Waller et al. [4] (BLT)</td>
<td>I–III</td>
<td>488</td>
<td>Cisplatin based</td>
<td>HR, 1.02; p = .90</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: ALPI, Adjuvant Lung Project Italy; ANITA, Adjuvant Navelbine International Trialist Association; BLT, Big Lung Trial; CALGB, Cancer and Leukemia Group B; HR, hazard ratio; IALT, International Adjuvant Lung Cancer Trial; PORT, postoperative radiation therapy.
61% of patients. After surgery, patients received an additional two cycles of the same chemotherapy. Overall, the median survival time for the resected group was 94 months, as compared with 33 months for the entire group.

Another potential indication for preoperative chemoradiation therapy is patients with stage IIIA, N2 disease. This group of patients is very heterogeneous, including those with N2 disease incidentally found at the time of surgery or mediastinoscopy, nonbulky N2 disease found on computed tomography scan and/or PET scan, and bulky N2 disease. Results of clinical trials using neoadjuvant combined chemoradiation therapy in N2 disease are inconclusive (Table 6) [42–46].

With the availability of newer chemotherapy agents and modern radiation techniques, the role of surgery following concurrent chemoradiation has been questioned. The Intergroup 0139 study evaluated definitive chemoradiotherapy versus induction chemoradiotherapy followed by surgery for stage IIIA N2 NSCLC [47].

The progression-free survival time was longer with the addition of surgery in this randomized trial (12.8 months versus 10.8 months; HR, 0.77; p = .017), but the 5-year overall survival rate was not greater (27.2% versus 20.3%; HR, 0.63; p = .10). In addition, the rate of pathologic complete response was 18% and the rate of nodal clearance (N0 status) was 46%. Subset outcome analysis by type of surgery (lobectomy versus pneumonectomy) and nodal downstaging at surgery (pN0 versus pN1–3) was unplanned and exploratory. Patients undergoing lobectomy versus pneumonectomy were matched by performance status, age, sex, and T stage, but not weight loss or single N2 versus multiple N2 nodal involvement. Independent favorable prognostic factors for overall survival for the entire trial population were: no weight loss (<5% versus ≥5%), female gender, and one N2 nodal station versus two or more N2 nodal stations.

PORT
Maria Werner-Wasik summarized the efficacy of radiation therapy after a complete (R0) resection, indicating that there have been numerous trials over the years but only a few have demonstrated a survival benefit. The PORT meta-analysis, which evaluated >2,000 patients enrolled in nine different trials, showed worse survival in patients who received postoperative radiation than in those receiving surgery alone (HR, 1.21; 95% CI, 1.08–1.34) [48]. Subset analysis indicated that postoperative radiotherapy was more detrimental among patients with stage I disease than among those with stage II disease. When stage III patients were considered alone, there was no clear evidence of a detriment. Although this study has been criticized for its inclusion of a wide variety of patient types and radiation techniques, it has been very influential in determining the standard of early lung cancer care in our country for the past decade.

More recently, a Surveillance, Epidemiology, and End Results database analysis of PORT versus observation and a meta-analysis of PORT versus PORT plus chemotherapy have become available [49, 50]. The former study ratified the findings of the original PORT study, showing worse survival in N0 and N1 patients who received PORT; however, better locoregional control and survival in N2 patients was seen (net benefit of 7% at 5 years). The latter meta-analysis evaluated studies from 1965 to 2003, including updated data from six of the seven studies in the 1998 meta-analysis and six newer trials. Adjuvant combined chemoradiotherapy produced superior overall survival and recurrence-free survival over adjuvant radiotherapy alone. Clearly, carefully designed phase III trials evaluating newer radiotherapy techniques with or without drug therapy are needed.

**CONCLUSION**
Rodolfo Bordoni and the panel members concluded the symposium by summarizing a consensus of the attendees, based upon the presented information, as follows:

- Neoadjuvant systemic therapy
  - Not recommended in general
- Perhaps can be considered during a multidisciplinary treatment planning process to attempt to make an inoperable patient operable
- Neoadjuvant radiation therapy
  - No evidence suggesting induction radiation therapy alone for stage IIIA patients
  - Neoadjuvant chemoradiation is associated with higher clearance of N2 nodes during surgery, although the long-term impact of this remains unclear
  - Evaluation by radiation oncologist prior to surgery and chemotherapy is advantageous
- Surgical management of early-stage NSCLC
  - Preoperative staging should be done in accordance with the NCCN guidelines
  - All patients need some form of mediastinal histological staging
    - Mediastinoscopy if nodes are normal size or smaller
    - Endobronchial ultrasound or endoscopic ultrasound fine needle aspiration for bigger nodes, although if negative, a mediastinoscopy is needed
  - A large proportion of lymph nodes in the nodal drainage area should be dissected, with dissection preferable over sampling
- Adjuvant systemic therapy
  - Not recommended for stage IA patients
  - Not recommended for stage IB patients, in general
  - Adverse prognostic factors such as tumors >4 cm in diameter are acceptable reasons to consider adjuvant systemic therapy
  - Recommended for stage IIA, IIB, and IIIA, consistent with recent ASCO guidelines
  - Cisplatin preferred, but if it is relatively contraindicated, carboplatin is an acceptable alternative
  - Should be started within 45–60 days, because patients who have not recovered from surgery by this time are usually not good chemotherapy candidates
- Adjuvant radiation therapy
  - Not recommended for N0 and N1 patients, but commonly used in N2 patients to decrease local recurrence

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