New Adjuvant Strategies for the Management of Resectable Non-Small-Cell Lung Cancer*

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Continued development of adjuvant therapy strategies is required to improve chances of long-term survival in patients with resected non-small-cell lung cancer (NSCLC). Distant micrometastases comprise the bulk of failures in patients with resected stage I disease, although the risk of local failure increases in patients with stage II or IIIA disease, distant metastasis remains a critical problem. Optimum adjuvant treatment may require both radiotherapy and chemotherapy. Adjuvant radiotherapy has been shown to eliminate first failure in local sites in patients whose stage II or IIIA squamous cell carcinoma has been fully resected, without producing an overall improvement in survival. Adjuvant combination chemotherapy can delay time to recurrence significantly and improve failure-free survival, although once again, no statistically significant prolongation of survival has been observed. One trial combining sequential chemotherapy and radiotherapy reported a significant reduction in the incidence of distant metastases compared to treatment with radiation alone in patients with unresected stage III disease. Current and planned American trials have varied the timing, dose intensity, and scheduling of chemotherapy as well as the control arm employed. It is hoped that the results will demonstrate unequivocal benefit for adjuvant therapy in the management of patients with operable NSCLC.

Table 1—Comparison of Survival by TNM Subset and Histologic Cell Type*

<table>
<thead>
<tr>
<th>Classification</th>
<th>Squamous Cell Carcinoma</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Total Deaths†</td>
</tr>
<tr>
<td>Stage I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1N0</td>
<td>168</td>
<td>20</td>
</tr>
<tr>
<td>T1N1</td>
<td>152</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>8</td>
</tr>
<tr>
<td>Stage II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1N0</td>
<td>127</td>
<td>51</td>
</tr>
<tr>
<td>T1N1</td>
<td>20</td>
<td>10</td>
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<tr>
<td>T1N3</td>
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<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>549</td>
<td>161</td>
</tr>
</tbody>
</table>

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Approximately 25% of patients with non-small-cell lung cancer (NSCLC) present with stage I or II disease. The postresection outlook for such patients varies considerably. As shown in Table 1, individuals with T1N0 squamous cell disease have a nearly 85% failure-free survival expectation. In non-squamous cases of similar extent, the rate is below 70%. For stage II (N1) disease, overall 4-year survival drops further, reaching the bottom at 25% among the T2N1 non-squamous cell subgroup. Clearly these data, while favorable compared with results in stage IV disease, connote tens of thousands of deaths each year from fully resectable NSCLC. They indicate the importance of developing adjuvant therapy strategies to improve outcome for these individuals.

Available treatment modalities and treatment target(s) of interest must be assessed when adjuvant strategies are considered. In lung cancer, two adjuvant modalities, radiotherapy and chemotherapy, have been studied most intensively, both together and separately. Radiotherapy is locoregional treatment, potentially important if local failure is a concern. Chemotherapy has the potential to affect all sites of distant micrometastasis and possibly local disease as well. Optimum adjuvant treatment may conceivably require both approaches.

Patterns of failure in stage I NSCLC have been evaluated carefully by the Lung Cancer Study Group (LCSG). The database used for this retrospective review was derived from LCSG trial 771, a study of postoperative intrapleural bacille
Calmette Guérin vs observation as adjuvant therapy in patients with stage I NSCLC. Of 473 patients entered, 339 were evaluable. The group was divided almost equally into squamous vs nonsquamous cell histologies. Approximately one half were T1N0, 40% T2N0, and 10% T1N1 (currently stage II but at that time part of the stage I category). No survival differences were seen between the intrapleural therapy and observation arms.

Sites of failure among patients in trial 771 were overwhelmingly distant: 70% of first failures occurred outside the chest. Among individuals demonstrating local recurrence as the first failure site, a predominance of patients had squamous rather than nonsquamous cell histologies. Even among squamous cell patients, however, the majority of first failure sites were distant. Based on this database analysis, any rational adjuvant strategy for stage I disease should use predominantly systemic therapy for micrometastatic spread.

**Completed Adjuvant Trials: Selected LCSG Data**

Prior to the LCSG database review, there was a clear bias that intrathoracic failure was the overriding problem in resected squamous cell cancer. This was considered especially true in patients with more advanced but still resectable disease (currently stages II and IIIA). These impressions, widely held in the 1970s, led to a second LCSG study, trial 773. In this trial, patients with stage II or IIIA fully resected squamous cell carcinoma were randomized to adjuvant radiotherapy or observation. Pancoast tumors, T3N0 cases, and patients whose highest mediastinal node removed or biopsied at surgery contained tumor were excluded. Megavoltage radiotherapy to a total dose of 50 Gy was employed using a complex treatment plan. Follow-up was done every 3 months for 2 years and every 6 months thereafter.

Of 230 patients who entered the study, 210 eligible patients were included in all treatment comparisons using an intent-to-treat analysis format. There were no differences in overall recurrence or survival between the 2 treatment groups. Patterns of first failure, however, were radically altered by adjuvant radiotherapy. In the observation arm, 41% of first failure sites were intrathoracic. Among patients receiving adjuvant radiotherapy, only one patient (3% of first failures and less than 1% of radiated patients at risk) experienced local failure first.

These data confirm that although distant micrometastatic disease is of greatest concern after stage I through IIIA NSCLC has been resected, adjuvant radiotherapy, at least in the squamous cell subgroup (which is the highest-risk population for local and regional recurrence), can nearly eliminate local and regional disease as a site of first failure. If effective systemic therapy could be developed to eradicate distant micrometastatic disease, then the addition of adjuvant radiotherapy focused on the postoperative treatment bed — where delivery of chemotherapy may be compromised and the bulk of residual microscopic disease might be relatively large — could become a more important part of a multimodality approach to adjuvant treatment.

In 1979, with the long-term data from studies 771 and 773 still years away, the LCSG empirically initiated a multimodality adjuvant trial embodying this treatment strategy. Trial 791 compared postoperative split-course radiotherapy with the same radiotherapy plus chemotherapy with cyclophosphamide, doxorubicin, and cisplatin (CAP). The first 2 CAP cycles were given concurrently with split-course radiotherapy. Four additional CAP cycles were then administered. The patient population included both squamous and nonsquamous cell histologies with evidence of incomplete resection, defined as a microscopically positive bronchial margin or tumor in the highest node biopsied or removed at surgery.

The chemotherapy used in this trial, while state-of-the-art in the late 1970s, is not as active as that available today. Cisplatin and doxorubicin were each given at 40 mg/m²; the cyclophosphamide dose was 400 mg/m². All drugs were given intravenously (IV) on day 1 every 3 weeks. A substantial fraction of patients stopped chemotherapy early either because of treatment-related toxicities or unwillingness to continue. In other patients, doses were reduced. Overall dose intensity was low.

Despite these limitations, the trial demonstrated clear biologic activity for the CAP regimen. Among the 164 eligible patients, median time to recurrence was significantly delayed in patients treated with combined-modality therapy compared with adjuvant radiotherapy alone. The hazard rate for recurrence was significantly lower during the first year of follow-up in the combined-modality arm, but this difference disappeared in subsequent years. At more than 5 years of follow-up, a statistically significant difference in the failure-free survival curves favoring the bimodality adjuvant approach persisted (S. Piantadosi, M.D., Ph.D., personal communication, March 1992). However, at no time was an overall survival benefit demonstrable for the chemoradiotherapy strategy over radiotherapy alone.

What lessons were learned from these LCSG trials? There are many, but those this paper has focused on are the following: (1) adjuvant radiotherapy alone can improve local control but not survival; (2) distant micrometastatic disease is the target of major interest; (3) even modest-dose chemotherapy can have a measurable biologic impact; and (4) significant improvement in overall survival has not been demonstrated. Clearly, the data suggest that chemotherapy can delay recurrence and probably does so through its effect on distant metastatic disease.

**Can We Affect Distant Failure?**

Are there any data in the literature that clearly (statistically) demonstrate that chemotherapy decreases metastatic disease formation in NSCLC? A French trial of chemoradiotherapy in unresectable stage III disease provided such data. LeChevalier et al randomized stage IIIA or IIIB NSCLC patients (squamous or large cell histologies only) to either aggressive radiotherapy alone (65 Gy in once-daily fractions over 7 weeks) or to 3 cycles of initial chemotherapy (vinodesine, lomustine, cisplatin, and cyclophosphamide) followed by the full-dose radiotherapy program and 3 additional chemotherapy courses. The chemotherapy regimen had produced a 42% regression rate among stage III patients in a pilot study by the same investigators.

The randomized trial demonstrated a significant improvement in median survival for the combined-modality arm compared with the radiotherapy-alone arm (p = 0.02). In addition, a careful analysis of patterns of failure revealed a decreased actuarial metastasis rate for patients given the
combined modality. At 24 to 30 months' follow-up, the distant metastasis rate was 60% in the radiotherapy-only group vs 43% in the combined-modality arm (p<0.001). Longer follow-up was not associated with a further increase in the incidence of first distant metastases. This suggests that if a patient survives without distant failure for more than 2 to 2½ years, there is a reasonable chance of long-term distant failure-free survival.

Current Adjuvant Trials

These findings provide the impetus for continuing attempts at adjuvant therapy in patients with resected NSCLC. They also suggest a possible role for bimodality adjuvant therapy. If adjuvant systemic treatment can control distant micrometastases but is possibly less effective at the primary site due to compromised drug delivery postsurgically and/or a relatively large bulk of remaining microscopic disease, consolidative radiotherapy may add to overall curability. This rationale forms the basis for several current phase III adjuvant trials.

A Canadian consortium began a large-scale adjuvant trial in 1984. Both node-negative and node-positive patients were studied. The group without nodal involvement was randomized to either surgery alone or surgery followed by 6 months of adjuvant chemotherapy with vindesine and cisplatin. Node-positive patients were assigned to surgery followed either by adjuvant radiotherapy alone (thought by many to be standard therapy even though no prospective data support its use) or by 2 cycles of adjuvant vindesine and cisplatin, then radiotherapy, followed by 4 additional chemotherapy cycles. No meaningful survival data have yet been reported from this trial, which includes over 300 patients.

Three adjuvant trials in NSCLC are active (or will be soon) in the United States. One already rapidly accruing patients is an intergroup effort of the Eastern Cooperative Oncology Group (ECOG) and Radiation Therapy Oncology Group (RTOG) (D. Johnson, M.D., personal communication, March 1992). Eligible patients must have stage II or microscopic, fully resected stage IIIA (N2) disease. The type of lung resection is determined by the attending surgeon, but careful assessment of mediastinal nodes must be carried out during thoracotomy. Eligible patients are stratified by nodal stage (N1 vs N2), histology, and weight loss. The conventional treatment arm includes adjuvant radiotherapy to a total dose of 50.4 Gy postoperatively. In the investigational arm, 4 cycles of adjuvant cisplatin and etoposide, in moderate doses, are added: cisplatin, 60 mg/m² IV, on day 1 and etoposide, 120 mg/m² IV, on days 1 to 3. The initial chemotherapy cycle is given concurrently with postoperative radiotherapy.

Three concerns have been raised about the trial design. First, preoperative mediastinoscopic staging is not required for all patients. This may produce some heterogeneity among the stage IIIA patients included. Second, the chemotherapy doses may be lower than optimal. This same criticism has been raised about the Canadian adjuvant trial. There is, however, no compelling evidence to support use of dose-intensive chemotherapy against NSCLC. Third, the ECOG-RTOG investigators have chosen to use concurrent chemoradiotherapy despite the fact that all known disease will have been removed by surgery. Concurrent postoperative therapy may produce increased toxicity, diminish patient compliance, and decrease overall dose intensity of the adjuvant chemotherapy. Whether these concerns are realized and/or will affect the trial outcome remains to be seen.

A slightly different strategy is being pursued by the Cancer and Leukemia Group B (CALGB). To be eligible for this trial, all patients must have a negative surgical mediastinoscopy, a complete surgical resection with negative margins, and a complete mediastinal node dissection. Postoperative N1 or N2 disease patients will then be randomized to conventional adjuvant radiation (50 Gy in 5 weeks) or 4 cycles of intense combination chemotherapy followed by the consolidative 50-Gy radiation. The chemotherapy regimen, etoposide 200 mg/m² and cisplatin 33 mg/m² each given on days 1 through 3, will be repeated every 3 weeks for 4 cycles. Granulocyte colony-stimulation factor (5 µg/kg) will be given subcutaneously on days 4 through 11 to facilitate dose-intensive treatment.

The CALGB trial design acknowledges that systemic micrometastases are the major focus of treatment. Early aggressive use of chemotherapy should be the optimum strategy for achieving distant disease control. If the chemotherapy is effective, then consolidative radiation may add by sterilizing remaining intrathoracic disease. This trial design has been criticized for its delayed use of radiotherapy in the multimodality adjuvant arm. In response, CALGB investigators have pointed out that if chemotherapy cannot at least hold intrathoracic disease in check for 3 months, it is unlikely to be able to eradicate distant micrometastases; the timing of radiotherapy therefore may mean little to ultimate survival.

A substantially different strategy for patients with stages I through IIA mediastinoscopy-negative NSCLC is being pursued by the Southwest Oncology Group (SWOG). In the SWOG trial, patients with a negative surgical mediastinoscopy are randomized to standard thoracotomy resection alone or 2 cycles of etoposide and carboplatin chemotherapy initially followed by surgical resection (P. Bunn, M.D., personal communication, March 1992). Three additional cycles of the same chemotherapy are given postoperatively. In this trial, all patients are by definition operable at entry, and the surgery-only arm is intellectually sound. But the use of preoperative chemotherapy is controversial, since downstaging is not required to facilitate resection. Whether surgical morbidity will be increased by the induction chemotherapy cycles can be studied. However, the possibility that presurgical chemotherapy can diminish the shedding of “metastatogenic” tumor cells during surgical manipulation of tumor (an unproven but theoretical concern) cannot be assessed with this design, since the induction chemotherapy arm also includes postoperative chemotherapy.

Conclusions

Several current conclusions about adjuvant therapy of stages I through IIA NSCLC can be formulated as follows:

1. After complete resection of stage I disease, the majority of first failures are distant.
2. For stages II and IIIA disease, there is an increased risk of local failure, but distant metastases remain the primary problem.
3. For stages II and IIIA fully resected squamous cell carcinoma, adjuvant
radiotherapy can essentially eliminate local failure as a site of first failure. However, it provides no survival benefit. (4) LCSG trials with adjuvant chemotherapy demonstrated clear biologic activity for CAP treatment. Some studies show significant delay in time to recurrence with improved failure-free survival. However, no statistically significant prolongation of overall survival has been seen. (5) At least 1 large trial of chemotherapy added to radiotherapy for stage III NSCLC shows a significant decrease in distant metastases formation in the chemoradiotherapy arm. (6) Ongoing or upcoming American adjuvant trials differ in the timing, dose intensity, and scheduling of chemotherapy, as well as in the control arm employed. It is hoped that the results of 1 or more of these trials will demonstrate unequivocal benefit for adjuvant therapy and signal another step forward in the management of patients with operable NSCLC.

REFERENCES