Role of Adjuvant Therapy in Resected Stage II/IIIA Non-Small-Cell Lung Cancer

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By Benjamin Movsas, MD [2]

The role of adjuvant therapy following complete resection of node-positive (stage II/IIIA) non-small-cell lung cancer remains controversial. Five-year survival rates in pathologic stage II disease range from 30% to 50% and in resected stage IIIA disease from 10% to 30%. The majority of recurrences following surgery are distant metastases.

The first part of this article began an exploration of adjuvant therapy for completely resected (margin-negative) stage II/IIIA (node-positive) non-small-cell lung cancer (NSCLC). Using an evidence-based approach, the review sorted though key studies on the role of adjuvant treatment, focusing primarily on randomized trials of postoperative radiotherapy and postoperative chemotherapy, as well as two large meta-analyses—the postoperative radiotherapy (PORT) meta-analysis and the NSCLC Cooperative Group meta-analysis. The second part of this article will describe several studies evaluating the role of adjuvant chemoradiation, and will address currently active phase III trials of adjuvant therapy in this setting. Part 2 will conclude with a discussion of future strategies for the adjuvant treatment of NSCLC.

**Adjuvant Chemoradiation**

Only a few studies have assessed the role of adjuvant chemoradiation in the phase III setting.

**Lung Cancer Study Group Trial**
The Lung Cancer Study Group (LCSG)-791 trial compared split-course radiotherapy (2,000 cGy in five fractions × 2 separated by 3 weeks) and concurrent CAP chemotherapy (cyclophosphamide, doxorubicin [Adriamycin], cisplatin) to radiotherapy alone.[1] This study focused on patients with an incomplete resection, defined as either tumor in the highest resected mediastinal node or the presence of a positive surgical margin. Most patients (N = 151) had stage III disease (119 had pN2 disease), 10 had stage II, and 3 had stage I. As in the previous LCSG study,[2] CAP was administered every 4 weeks for 6 months (with the first two cycles administered on day 1 of each radiotherapy course).

The chemoradiation group experienced a nonsignificant improvement in median survival (20 vs 13 months) but a significant improvement in median time to recurrence (14 vs 8 months, \( P = .004 \)).[3] Analysis of failure patterns showed a significant decrease in distant metastases in the chemotherapy arm (\( P = .01 \)). Subset analysis demonstrated a slight advantage for patients with pN2 disease who received both radiation and chemotherapy. However, with further follow-up, the survival curves converged at about 2.5 years.

**Memorial Sloan-Kettering Trial**
A study at Memorial Sloan-Kettering Cancer Center randomized 72 patients with pathologic T1-3, N2 (stage IIIA) NSCLC to postoperative radiotherapy vs radiotherapy and chemotherapy with vindesine and cisplatin.[4] No significant differences were found in overall survival (16.3 months for radiotherapy plus chemotherapy vs 19.1 months for radiotherapy alone, \( P = .42 \)) or time to progression (9.2 vs 9.0 months, respectively, \( P = .35 \)).

**French Trial**
In a trial from France,[5] 267 patients with resected NSCLC were randomized to postoperative radiotherapy alone (6,000 cGy in 6 weeks) vs three cycles of chemotherapy (cycles 1 and 3: doxorubicin, vincristine, cisplatin, lomustine; cycle 2: vincristine, cisplatin, cyclophosphamide) followed by radiotherapy. Most patients (N = 189) had stage III disease, 70 had stage II, and 8 had stage I.

There were no significant differences in overall survival or disease-free survival. Although the analysis was not stratified by stage, among the 137 patients who were pN2, a significant improvement in both survival and disease-free survival was observed in the chemoradiation group (\( P = .003 \) and \( P = .002 \), respectively), apparently due to a decreased incidence of metastases.
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(P = .003).[5] Inter group Trial 0115

Perhaps the biggest setback to the use of adjuvant chemoradiation came with the results of Intergroup Trial 0115 (E-3590). In this large randomized trial,[6] 488 patients who had undergone complete resection of stage II and IIIA NSCLC, as well as a thorough mediastinal lymph node sampling or dissection, were randomized to receive either four cycles of monthly cisplatin (60 mg/m² on day 1) and etoposide (120 mg/m² on days 1 to 3) administered concurrently with thoracic radiotherapy vs radiotherapy alone. Radiotherapy on both arms consisted of standard fractions (180 cGy) to a total dose of 5,040 cGy. An additional 1,080 cGy in six fractions was administered to nodal levels in which extracapsular extension was documented.

With a median follow-up of 44 months, the median survival was 39 months in the radiotherapy arm vs 38 months in the combined-modality arm (P = .56). An important finding on multivariate analysis was that survival was significantly influenced by extent of lymph node involvement (multiple vs single), type of lymph node dissection (sampling vs complete), age (60 or more vs < 60), and histology (other vs squamous). The authors concluded that postoperative chemoradiotherapy with cisplatin and etoposide does not prolong survival in patients with completely resected stage II/IIIA NSCLC compared to postoperative radiotherapy alone.

Potential caveats in interpreting this negative trial relate to the relatively high rate of ineligible patients (23%) and the relatively low rate of compliance with all the planned chemotherapy (69%). It is interesting to note that patients without evidence of K-ras mutations appeared to benefit from the addition of chemotherapy to radiotherapy (median survival: 42 vs 25 months), P = .066 on multivariate analysis.[7] This suggests that the underlying problem may not be the lack of effective adjuvant therapies, but rather the difficulty in properly selecting patients who truly benefit from these treatments.

German Trial

Yet another recent randomized trial further corroborates the lack of benefit of chemotherapy in addition to radiotherapy in the adjuvant setting.[8] In this study, patients with resected pN2 disease were randomized to either radiotherapy alone (50 Gy in 5 weeks) or chemotherapy with cisplatin, 75 mg/m² on day 1, plus ifosfamide (Ifex), 1.5 g/m² on days 1 to 4, for three cycles every 4 weeks followed by the same radiotherapy. An interim analysis showed a median overall survival of 34 months and a 3-year survival rate of 46%, with no differences between the groups (P = .7).

NSCLC Cooperative Group Meta-analysis

Seven trials (807 patients) included in an NSCLC Cooperative Group meta-analysis randomized patients with resected NSCLC to surgery plus radiotherapy vs surgery plus radiotherapy plus chemotherapy. Six of these trials used a cisplatin-based regimen.[9] The total planned doses of radiation therapy ranged from 4,000 cGy in 10 fractions to 6,500 cGy in 33 fractions. The meta-analysis demonstrated a hazard ratio of 0.94, or a 6% reduction in the risk of death, favoring the chemotherapy arm, which translated into a 2% absolute benefit at 5 years but was not statistically significant.

Summary of Evidence-Based Data

The role of adjuvant therapy following a complete resection for stage II/IIIA NSCLC remains controversial. To date, there is no convincing evidence that any therapy consistently improves survival in the adjuvant setting. Thus, observation remains a viable alternative for such patients. Postoperative radiotherapy has been associated with a significant improvement in local control, particularly in patients with pathologic N2 disease. Several studies suggest that the pN2 subset may also have an improvement in recurrence-free survival. Patients with pathologic N0 disease (with negative margins) have a low risk of locoregional recurrence and, therefore, should not be offered postoperative radiotherapy.

The benefit-risk ratio of adjuvant radiotherapy in the setting of pathologic N1 disease appears to be intermediate. Other factors may help in making treatment recommendations in this situation. For example, Yano et al[10] reported a 5-year survival of 40% for patients with hilar N1 disease, compared to 65% for those with lobar N1 disease (P = .014). As the survival for patients with lobar N1 disease approaches that of patients with pN0 disease, the benefit of postoperative radiotherapy is likely small in this group of patients. In the future, detection of lymph node micrometastases using immunohistochemical or molecular methods may be instrumental in further selecting which patients will benefit most from adjuvant therapies.[11]

If postoperative radiotherapy is administered, it should be done in the context of CT-based treatment planning with careful attention to the radiotherapy technique, including dose, fractionation, and volume. The most commonly used regimen in this country is 5,000 to 5,040 cGy in 25 to 28.
fractions. The use of posterior spinal cord shields must be avoided. Special care should be taken to limit the amount of normal lung radiation, particularly on the contralateral side. Thus, lateral radiation fields should not be utilized. Similarly, the dose and volume of heart radiation should be minimized.

Only patients with adequate performance status and pulmonary function (generally FEV1 > 1 liter) after surgery should be considered for postoperative radiotherapy. The role of adjuvant chemotherapy (with or without radiation therapy) is less clear. Chemotherapy, at this time, should be offered to patients in appropriate clinical trials.

**Current Phase III Trials**

Most of the phase III trials active at this time compare observation to various chemotherapy strategies. In its protocol BR10, the National Cancer Institute of Canada (NCIC) is randomizing patients with pathologic T2, N0 or T1-2, N1 disease to either observation or chemotherapy with four cycles of monthly cisplatin and weekly vinorelbine (Navelbine). The accrual goal is 600 patients. In a trial limited to stage IB patients, the Cancer and Leukemia Group B (CALGB) is comparing four cycles of adjuvant carboplatin (Paraplatin)/paclitaxel (Taxol) to observation. This study plans to accrue 504 patients.

Several large adjuvant trials are ongoing in Europe in patients with resected stage I-IIIA NSCLC. In European Union (EU) trial 94-043, 1,840 patients will be randomized to either observation or chemotherapy with mitomycin (Mutamycin), vindesine, and cisplatin. As in other EU trials, radiation is “optional” and may be administered “at the discretion of each institution.” If employed by the institution, it must be administered on both study arms. In study EU 96-010, 3,300 patients will be randomized to observation vs three cycles of chemotherapy consisting of cisplatin and either a vinca alkaloid or etoposide. Finally, in study EU 97-010, 750 patients will be randomized to receive three cycles of cisplatin and etoposide vs no further therapy.

**Future Strategies**

**Novel Chemotherapy**

Several studies have shown promising results with paclitaxel-based chemotherapy in patients with metastatic NSCLC.[12,13] Subsequent studies have indicated that chemoradiation with paclitaxel and carboplatin is active and well tolerated in patients with inoperable locally advanced NSCLC.[14-16] This approach was adapted to the adjuvant setting in patients who do not have bulky disease and where cure rates may be substantially enhanced.

At Fox Chase Cancer Center, a phase II study was aimed at determining the feasibility, toxicity, and efficacy of adjuvant paclitaxel and carboplatin plus radiotherapy for resected stage II/IIIA NSCLC.[17] Patients with pathologic N1 or N2 NSCLC receive four cycles (every 3 weeks) of IV paclitaxel (175 mg/m² over 3 hours on days 1 and 22; 225 mg/m² over 3 hours on days 43 and 64) and carboplatin (area under the concentration-time curve [AUC] of 5 on days 1 and 22; AUC 7.5 on days 43 and 64) plus radiotherapy (starting on day 1 of chemotherapy) to 5,040 cGy (6,120 cGy for extracapsular extension; 6,600 cGy for positive margins) in 180 cGy fractions.

All patients receive an iced sucralfate (1 g) slurry just before and after daily radiotherapy. Since April 1997, 30 patients (median age: 66 yr, range: 45-75 yr) have been enrolled, with the following American Joint Committee on Cancer (AJCC) disease stages (1992 classifications): 11 patients with stage II, 18 patients with stage IIIA, and 1 patient with stage IIIB (pT4). Six patients had a separate nodule in the resected lobe (pT4/ IIIB via AJCC 1997, published after study inception). The median radiotherapy dose was 5,040 cGy (range: 540-6,700 cGy). Twenty patients (67%) received all four cycles of chemotherapy, two patients had three cycles, six had two cycles, and one had one cycle. Four patients refused the iced sucralfate slurry.

With a median follow-up of 15.4 months (range: 2.2-26.2 months), the 12- and 18-month actuarial survival rates were 87%/87% and disease-free survival rates were 83%/72%, respectively. Of the eight failures, seven occurred distantly and one locally and distantly. Excluding the stage IIIB patients (by 1997 AJCC classifications) who had a 1-year disease-free survival of only 33%, the 18-month survival is 100%. The 12- and 18-month disease-free survival rates are 100% and 84%, respectively. The only significant predictor for disease-free survival was stage. Of the 25 patients who took the iced sucralfate slurry, none developed grade 3 esophagitis, compared with three of four patients (75%) who did not take it (P < .001).

Similar to the Fox Chase study, Radiation Therapy Oncology Group (RTOG) trial 97-05 employed adjuvant therapy with paclitaxel, carboplatin, and concurrent radiotherapy. This phase II study
completed accrual in June 1998 with a total of 93 patients. Other chemotherapy agents, such as gemcitabine (Gemzar), other taxanes, UFT, vinorelbine, and the camptothecins, that show promise in NSCLC will need to be carefully tested in the adjuvant setting. As systemic therapy improves, it is likely that the importance of radiation as a local treatment modality will only increase.

**Reducing Toxicity**

To enhance the therapeutic ratio for any treatment, one important strategy, often overlooked, is to reduce the toxicity to normal tissue. With thoracic radiotherapy, particularly with concurrent chemotherapy, the main toxicities are acute esophagitis and subacute/chronic radiation pneumonitis/fibrosis. While esophagitis is mostly reversible, it can negatively impact on quality of life.

A strategy that is actively being studied to reduce esophagitis is the use of the radioprotector amifostine (Ethyol).[18] This agent has been shown to significantly reduce xerostomia secondary to head and neck irradiation, without diminishing tumor control.[19] The attractiveness of amifostine lies in its ability to act as a radioprotector for a variety of normal tissues. Preliminary results of a randomized trial (N = 146) suggest that amifostine reduces esophagitis and pneumonitis in patients receiving chemoradiotherapy for lung cancer.[20] In a smaller randomized trial (N = 68), amifostine (300 mg/m²) administered before chemotherapy and daily radiotherapy reduced the incidence of acute esophagitis and grade 3 pneumonitis. There was no difference in the rate of complete and partial responses.[21]

Amifostine is being actively studied by RTOG in a larger randomized trial of 300 patients receiving intensive chemoradiation for locally advanced NSCLC (RTOG 98-01). Prospective quality-of-life data are being collected.[22]

Future studies will need to assess the role of more sophisticated radiation treatment planning, such as three-dimensional conformal radiotherapy, in reducing toxicity. The ability to analyze dose-volume histograms of critical structures (including the lungs, esophagus, and heart) can provide the radiation oncologist with crucial information in achieving this goal.

**Neoadjuvant Strategies**

Potential advantages of the neoadjuvant approach include the earlier use of systemic therapy, downstaging of disease to facilitate resection, prevention of tumor seeding at surgery, easier administration of therapy (compared with the postoperative setting), the ability to assess response to therapy, and treatment in a relatively more oxygenated setting. Potential disadvantages include delay in the curative therapy (surgery), increased risk of postoperative morbidity and mortality, and the overtreatment of patients who may not have required adjuvant therapy.

Neoadjuvant therapy (chemotherapy or chemoradiation) has shown promise in patients with potentially resectable stage III NSCLC. Two randomized trials comparing induction chemotherapy and surgery vs surgery alone in stage IIIA NSCLC have demonstrated a significant survival advantage to induction chemotherapy.[23,24] Similarly, preoperative chemoradiation in a phase II Southwest Oncology Group (SWOG) trial also showed promising results.[25]

Recently, investigators have begun to examine the role of induction chemotherapy in patients with early-stage NSCLC. The Bimodality Lung Oncology Team (BLOT) phase II trial examined the role of induction paclitaxel and carboplatin followed by surgery in patients with clinical stage IB, II, and selected IIIA (T3, N1) NSCLC.[26] Study patients received paclitaxel (225 mg/m², 3-hour infusion) and carboplatin (AUC of 6) every 21 days for two cycles before and three cycles after surgery. Of 94 patients treated in this protocol, major responses were seen in 54% following induction chemotherapy; 82% of patients underwent a complete surgical resection, with 4% achieving a complete response. The investigators reported one death during induction chemotherapy and two postsurgery. Interestingly, 97% of the patients received the two cycles of induction chemotherapy, but only 38% received the full planned three cycles of postoperative chemotherapy. This important observation of the BLOT study sheds light on the challenges involved in delivering chemotherapy in the adjuvant setting. Based on this phase II study, an Intergroup phase III trial (S9900) is currently comparing three cycles of induction chemotherapy with paclitaxel and carboplatin followed by surgery vs surgery alone (BLOT vs NOT). Eligible patients are those with clinical stage T2, N0; T1-2, N1; and T3, N0-1.

The preliminary results of a randomized trial from France of induction chemotherapy vs surgery alone in early-stage NSCLC (stages IB/II/IIIA) have recently been reported.[27] In this multi-institutional trial, 373 patients were randomized to surgery vs two cycles of preoperative chemotherapy with MIP (mitomycin, 6 mg/m² on day 1; ifosfamide, 1.5 g/m² on days 1 to 3; and cisplatin, 30 mg/m² on days 1 to 3) with a 3-week interval. Patients who had an objective response received two additional cycles postoperatively. In both arms, patients with pT3 or pN2 disease were
administered postoperative radiotherapy.

Of the 355 eligible patients, 188 had stage I or II disease and 167 had stage IIIA disease. Radiotherapy was delivered to 72 patients treated with surgery only vs 41 patients in the combined-modality arm. The results showed that the median survival favored the chemotherapy arm (36 vs 26 months, \( P = .11 \)). Disease-free survival was significantly longer in the perioperative chemotherapy arm (\( P = .02 \)), particularly in the N0/N1 patients (\( P = .002 \)).

In Italy, a large randomized study called the Chemotherapy for Early Stages Trial (ChEST) is comparing surgery alone vs preoperative chemotherapy (gemcitabine, 1,250 mg/m² on days 1 and 8; cisplatin, 75 mg/m² on day 2 every 3 weeks \( \times 3 \)) and surgery in patients with T2-3, N0; T1-2, N1; or T3, N1 NSCLC. Another neoadjuvant strategy that may merit future study is the use of induction chemoradiation in early-stage patients with NSCLC. Recently, the results of an Intergroup study applying this approach in more locally advanced disease (T3/T4 Pancoast tumors) using preoperative cisplatin/etoposide and concurrent radiotherapy (to 4,500 cGy) showed promising results with both pathologic complete response and 3-year survival rates of approximately 50%. [28]

**Biologic Therapies**

Perhaps the greatest promise for the adjuvant treatment of NSCLC stems from the abundance of new, relatively nontoxic, biologic therapies, ranging from angiogenesis inhibitors, matrix metalloproteinase inhibitors (MMPIs), signal transduction inhibitors, and immunotherapy approaches to gene therapy strategies. [29] Emerging data suggest that such biologic agents, which appear to affect the tumor milieu (eg, its vasculature), may play an important role in NSCLC therapy. **Angiogenesis Inhibitors** \[30\] Volm et al found that expression of vascular endothelial growth factor (VEGF), a pivotal mediator of tumor angiogenesis, was an independent prognostic factor for patients with lung cancer. Recently, DeVore et al reported the results of a promising randomized phase II trial of recombinant humanized monoclonal anti-VEGF in 99 patients with advanced NSCLC. [31] In the high-dose anti-VEGF plus chemotherapy arm, time to progression was 7.4 months, compared with 4.2 months in patients receiving chemotherapy alone. Of note, six patients who received anti-VEGF experienced sudden and life-threatening hemoptysis, which was fatal in four.

Some of these biologic agents may not be as "benign" as initially presumed, and their potential toxicities must be carefully studied. A phase III Eastern Cooperative Oncology Group (ECOG) trial is planned to compare the addition of anti-VEGF to standard chemotherapy in patients with advanced lung cancer.

Antiangiogenic approaches targeting VEGF include the development of monoclonal antibodies to VEGF, specific inhibitors of the VEGF receptor (ie, the KDR receptor), as well as more generalized tyrosine kinase receptor antagonists. One of these agents, cetuximab (IMC-C225), a monoclonal antibody directed at the EGF receptor, is believed to be a potent radiosensitizer and enhances the antitumor activity of several chemotherapeutic agents, such as cisplatin, doxorubicin, and paclitaxel. [32] Similarly, a recent study suggests that endostatin, an antiangiogenic factor, enhances the antitumor effects of ionizing radiation in human and murine tumors. [33] Testing such agents in the adjuvant setting may ultimately enhance the efficacy of more conventional therapies.

Recent studies suggest that a reduction in vascularization can induce a state of tumor dormancy. [34] The optimal management of early malignancies may ultimately hinge on the ability to induce a dormant state. This theory further supports the use of antiangiogenic therapies as a strategy to achieve a greater proportion of long-term remissions. [35] Such biologic therapies may ultimately play a role in the chemoprevention of second primary cancers.

**MMPIs and COX-2 Inhibitors** [36] Metalloproteinases are a family of enzymes that degrade the components of the extracellular matrix. MMP-2 (gelatinase A) and MMP-9 (gelatinase B), in particular, have been found to be expressed in human NSCLC lines and to correlate with pathologic invasiveness. [36] Anderson et al reported that MMP inhibition in combination with chemotherapy was significantly more effective than either single agent in delaying local tumor growth and reducing the number and size of pulmonary metastases in a murine Lewis lung carcinoma. [37] Cyclooxygenase-2 (COX-2), which catalyzes the synthesis of prostaglandins from arachidonic acid, has also been found to play a role in lung cancer. Hida et al reported that a selective COX-2 inhibitor, nimesulide, can inhibit proliferation of NSCLC cell lines in vitro in a dose-dependent manner. [38] **Anti-idiotypic Antibodies** [39] RTOG plans to explore an adjuvant approach to radiotherapy involving the addition of active immunotherapy with vaccines directed against tumor-associated antigens. Anti-idiotypic antibodies can be used as vaccines to mimic tumor-associated antigens and generate an active immunity against them. Because these agents are seen as self-antigens by the immune system, the patient is typically immunologically tolerant to them. Two such anti-idiotypic antibodies will be utilized: 3H1 (CeaVac), which mimics carcinoembryonic
antigen, and 11D10 (TriAb), which mimics the human milk fat globule antigen. Expression of both the carcinoembryonic antigen and the human milk fat globule antigen was demonstrated in 19 of 20 patients sampled. This supports the strategic concept of a bivalent vaccine. The study will measure the immune (ie, humoral and T-cell) response to the anti-idiotype vaccines in combination with radiotherapy and determine survival, disease-free survival, and toxicity associated with this regimen. **Ultimate Goals** Investigational agents are usually tested first in patients with stage IV disease. Promising agents are then moved into the stage III arena with combined-modality strategies and ultimately, as we are currently witnessing with chemotherapy, into patients with early-stage disease. A similar process is beginning to take place for the biologic therapies. In light of the "dormancy" hypothesis, however, perhaps these therapies should be moved more rapidly into earlier-stage disease. Ultimately, the goal will be to apply "molecular fingerprinting" technology, to individually tailor biologic therapies based on unique molecular targets.

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