Combined-Modality Treatment of Locally Advanced Non-small Cell Lung Cancer*

Incorporation of Novel Chemotherapeutic Agents

Chandra P. Belani, MD; and Ramesh K. Ramanathan, MD

The role of multimodality management in locally advanced non-small cell lung cancer (NSCLC) continues to evolve and is a subject of ongoing clinical research. Induction chemotherapy followed by surgical resection with or without thoracic radiotherapy has proved superior to surgical resection alone in patients with ipsilateral mediastinal (N2) disease. Whether surgery alone still plays a role in these patients is the subject of an ongoing intergroup study. As no definitive, optimal effective chemotherapeutic regimen currently exists for NSCLC, future studies will attempt to incorporate novel and active agents like the taxanes, irinotecan, vinorelbine, and gemcitabine into combined-modality therapy for locally advanced NSCLC. Thoracic radiation therapy by itself provides local control and effective palliation of tumor-related symptoms but has minimal impact on the survival of patients with locally advanced disease. Novel schemes such as hyperfractionated radiotherapy and continuous hyperfractionated accelerated radiotherapy are currently being investigated and appear promising but need to be tested in combination with chemotherapeutic agents. Randomized studies have demonstrated the benefit of concurrent or sequential chemoradiation in selected patients with a good performance status and minimal weight loss. The exact sequence of combined-modality therapy has yet to be determined. The combination of paclitaxel and platinum compounds has shown impressive activity in advanced NSCLC in both phase II and III randomized studies. We have incorporated weekly low-dose paclitaxel and carboplatin with concurrent thoracic radiation in treating patients with locally advanced, inoperable NSCLC, and long-term follow-up has shown remarkable survival rates. Confirmation of these phase II combined-modality studies is needed. Combination sequential chemotheraphy followed by concurrent chemoradiation in patients with advanced NSCLC has the potential to improve overall survival by increasing both local and distant control. (CHEST 1998; 113:535-60S)

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Lung cancer is a major public health problem of epidemic proportions in the United States. It comprises 14% of new cancer cases in men and 13% in women and is the most frequent cause of cancer death. In 1996, an estimated 177,000 new cases were diagnosed and 158,700 deaths were attributed to lung cancer. The incidence of lung cancer appears to have reached a plateau in men but continues to increase in women. Non-small cell lung cancer (NSCLC) comprises 75 to 80% of all lung cancers. The histologic subtypes are adenocarcinoma (40 to 50% of cases), squamous cell carcinoma (40 to 45%), and large cell carcinoma (10%). Overall 5-year survival for NSCLC is approximately 13%, and most cures occur with surgery. Fewer than 15% of all NSCLC patients are candidates for surgical resection, however.

Approximately 25 to 35% of NSCLC patients present with stage III disease, which is defined as locally advanced tumor confined to the chest without distant metastasis. Extrathoracic disease recurrence makes the possibility of surgical cure unlikely in this group. The International Staging System, devised in 1986, subdivides these patients into stages III A and IIIB, based on resectability. Stage III A patients undergoing resection have a 5-year survival of 15 to 20%. Five-year survival for the relatively favorable subset of stage III A patients with T3N0 or T3N1 disease is 33 to 39%. In this particular subset, no role for adjuvant therapy exists outside the study setting. Stage III A patients with N2 (T1-3N2) disease are candidates for multimodality therapy. Stage IIIB disease with contralateral mediastinal lymphadenopathy or supraclavicular adenopathy (N3) is categorically unresectable, and the presence of pleural effusion (T4) worsens the overall prognosis.

The traditional treatment for stage III patients who are not surgical candidates has been thoracic radiotherapy (TRT). However, the impact of TRT alone in locally advanced lung cancer has been minimal, with published studies showing median survival of <1 year and 5-year survival of 5 to 7%. In a three-arm randomized study published by Johnson et al., patients received radiotherapy (RT) to a total dose of 60 Gy, single-agent vindesine, or RT and vindesine. Results showed no survival differences among the three arms, and median survival ranged from 8.6 to 10.1 months.

Novel RT fractionation regimens have been an area of continued investigation. The Radiation Therapy Oncology Group (RTOG) published a five-arm randomized trial of hyperfractionated RT (HRT) in patients with advanced unresectable NSCLC. HRT was given at a dose of 1.2 Gy in two fractions per day, to total doses of 60.0, 64.8, 69.6, 74.4, and 79.2 Gy. Results showed no survival differences among the three highest total dose arms. Patients who received a total dose of 69.6 Gy had a median survival of 13.0 months, and the 2-year survival rate was 29%. These findings were significantly superior to results obtained with lower doses of HRT in this study.

Continuous hyperfractionated accelerated RT (CHART) is another novel regimen in which multiple fractions per day are given in a short period of time. Saunders et al. administered CHART to a total dose of 54 Gy in 36 fractions over 12 continuous days to patients with NSCLC, most of
whom had stage III disease. They reported a 40% complete radiologic response rate and 2-year survival of 29%. These encouraging results led to a large multicenter trial of CEP (cyclophosphamide/etoposide/cisplatin; chemotherapy) vs conventional RT involving 563 patients.\textsuperscript{11} Interim analysis showed the 2-year survival for CHART patients (30%) to be significantly higher than in patients who received conventional RT (20%) (p=0.0006).

New treatment modalities are needed in the management of locally advanced lung cancer. Combined-modality therapy employing systemic (chemotherapy) and local (RT with or without surgery) approaches has shown favorable results in patients with stage III disease.\textsuperscript{12-14} Randomized studies in stage IIIA potentially resectable disease show a significant survival advantage for patients receiving combined-modality treatment.\textsuperscript{12-14} This also holds true for patients with stage III inoperable disease, although the advantage is less clear, with published studies showing mixed results.\textsuperscript{15-18}

**INDUCTION OR NEoadjuvant Therapy for Locally ADVANCED NSCLC**

Although NSCLC continues to be a surgical disease, the role of surgery alone as the standard of care for patients with stage IIIA (N2) disease remains controversial. A review of 706 patients with N2 disease by Martini and Flesinger\textsuperscript{19} showed that only 151 (21%) had completely resectable disease. Of the 151 patients with resections, 119 had been suspected to have only N0 or N1 disease preoperatively by radiography or bronchoscopy, but microscopic N2 disease was seen in the resected specimens. The 5-year survival of those who had microscopic N2 disease (34%) was higher compared with the group that had clinically evident N2 disease (9%). Thus, surgery alone in the latter subgroup does not appear to affect overall survival.

Induction or neoadjuvant therapy can be defined as cytoreductive therapy administered before definitive locoregional therapy. Cytoreductive therapy consists of either chemotherapy or RT or combined RT and chemotherapy. The intent of cytoreductive therapy is to downstage primary tumors and hence, increase the resectability rate. Earlier administration of chemotherapy may eradicate micrometastasis, improve overall survival, and allow accurate pathologic assessment of response to induction therapy.\textsuperscript{20} The latter concept was tested in phase II trials, with encouraging results.\textsuperscript{21-25} In general, the response rate to induction therapy in these studies was approximately 50%, with pathologic complete responses (CRs) seen in about 10% of patients. At the end of therapy, complete surgical resection was possible in about 60% of patients, and 2- to 3-year survival was approximately 30%.\textsuperscript{21-27} These studies showed that neoadjuvant or induction therapy can be administered safely with tolerable toxic reactions. Disease considered marginally resectable can be made potentially resectable, and patients who achieve a histologic CR have prolonged long-term survival.\textsuperscript{21-27}

These phase II studies have been sufficiently encouraging to form the basis for phase III trials. Three such trials have been published, and these have generated much enthusiasm for neoadjuvant therapy for locally advanced stage IIIA NSCLC (Table 1).\textsuperscript{12,14} In 1992, Pass et al\textsuperscript{14} published a small randomized study of 27 patients with NSCLC and histologically confirmed N2 disease. Patients randomized to the neoadjuvant arm received chemotherapy with etoposide, 120 mg/m\textsuperscript{2}, on three consecutive days with cisplatin, 80 mg/m\textsuperscript{2}, on the first day, repeated every 21 days. Patients received two cycles of chemotherapy and then underwent surgery. Patients whose response to chemotherapy was demonstrated at surgery received another four cycles of the same regimen. Patients who were randomized to immediate surgery received postoperative split-dose RT to the mediastinum, to a total dose of 54 to 60 Gy. The resectability rate was about 85% in both groups, with no operative mortality. The response rate after two cycles of chemotherapy was 62%, with one histologically confirmed CR. Median survival and disease-free interval for the neoadjuvant chemotherapy group were 28.7 months and 12.7 months, respectively, vs 15.6 months and 5.8 months for the control arm; the differences between treatment groups, however, were not statistically significant. The original study design called for 148 patients to be accrued to detect a 20% improvement in 5-year survival due to chemotherapy. As a result of slower-than-anticipated accrual, the trial was closed with only 27 patients, thus reducing the power of the study to

### Table 1—Randomized Trials of Induction Therapy in Advanced NSCLC\textsuperscript{*}

<table>
<thead>
<tr>
<th>Investigators</th>
<th>No. of Patients</th>
<th>Regimen</th>
<th>Response Rate, %</th>
<th>Resection Rate, %</th>
<th>Median Survival, mo</th>
<th>Disease-Free Survival, mo</th>
<th>Survival, %</th>
<th>2 yr</th>
<th>3 yr</th>
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<tr>
<td>Rosell et al\textsuperscript{12}</td>
<td>30</td>
<td>MIP ( q 3 w k \times 3 ) cycles ( \rightarrow ) Surgery ( \rightarrow ) RT (50 Gy)</td>
<td>60</td>
<td>85</td>
<td>26</td>
<td>20</td>
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<td>(p&lt;0.001)</td>
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<tr>
<td>Roth et al\textsuperscript{13}</td>
<td>30</td>
<td>Surgery ( \rightarrow ) RT (50 Gy)</td>
<td>—</td>
<td>90</td>
<td>8</td>
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<td></td>
<td>28</td>
<td>CEP ( q 3 w k \times 3 ) cycles ( \rightarrow ) Surgery ( \rightarrow ) CEP ( \times 3 ) cycles</td>
<td>35</td>
<td>61</td>
<td>64</td>
<td>NR</td>
<td>60</td>
<td>56</td>
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<td>32</td>
<td>Surgery ( \rightarrow ) CEP ( \times 3 ) cycles</td>
<td>—</td>
<td>66</td>
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<td>9</td>
<td>25</td>
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<tr>
<td>Pass et al\textsuperscript{14}</td>
<td>13</td>
<td>PE ( q 2 d l \times 2 ) cycles ( \rightarrow ) Surgery ( \rightarrow ) PE ( \times 4 ) cycles</td>
<td>62</td>
<td>85</td>
<td>28.7</td>
<td>12.7</td>
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<td>14</td>
<td>Surgery ( \rightarrow ) RT (54-60 Gy)</td>
<td>—</td>
<td>86</td>
<td>15.6</td>
<td>5.8</td>
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\*MIP=mitomycin/ifosfamide/cisplatin; CEP=cyclophosphamide/etoposide/cisplatin; NR=not reached; PE=cisplatin/etoposide.
detect a meaningful difference. Although neoadjuvant therapy in this trial did not result in a statistically significant survival advantage, it demonstrated the feasibility of this approach.

A randomized phase III trial published by Rosell et al. in 1994 randomly assigned 60 patients with histologically confirmed stage IIIA NSCLC to either surgery or chemotherapy followed by surgery. All patients received postoperative RT to the mediastinum to a total dose of 50 Gy. Patients in the neoadjuvant arm received three courses of chemotherapy consisting of mitomycin, 6 mg/m², ifosfamide, 3 g/m², and cisplatin, 50 mg/m² every 3 weeks. The response rate to chemotherapy was 60%; resectability rates were 85% in the chemotherapy arm and 90% in the surgery-only arm. Highly significant differences in disease-free and overall survival were seen favoring the chemotherapy arm. Disease-free survival in the surgery-only arm was 5 months vs 20 months in the chemotherapy arm. Similarly, median survival, which was 8 months in the surgery-only arm, was prolonged to 26 months in the chemotherapy arm. This trial was terminated early due to the highly significant differences in survival seen at interim analysis. The low survival in the surgery-alone arm may be explained by the higher incidence of K-ras oncogene point mutation in this arm (42%) vs the neoadjuvant chemotherapy arm (15%). It has been recognized that K-ras oncogene mutation may portend a poor prognosis in NSCLC. The authors argued, however, that the difference in ploidy patterns may have been due to chemotherapy reversing the pattern of ploidy by selecting tumor subclones in which the DNA content is close to the diploid value and destroying those with a larger number of DNA alterations.

The second study to show a highly significant survival advantage for neoadjuvant chemotherapy was also terminated early at interim analysis. In this study, by Roth et al., 60 patients were randomized to either surgery or preoperative chemotherapy followed by surgery. Chemotherapy was given every 28 days for three cycles and consisted of cyclophosphamide, 500 mg/m², etoposide, 100 mg/m² for 3 days, and cisplatin, 100 mg/m². After surgery, patients who had a major or minor response to chemotherapy received another three cycles of similar chemotherapy. The response rate to chemotherapy was 35% with one CR. Sixty-one percent of patients in the chemotherapy arm and 66% in the control arm had surgically resectable disease. Estimated median survival in the chemotherapy arm was 64 months vs 11 months in the surgery-only arm. Event-free survival, which was 9 months in the surgery-only arm, had not been reached in the chemotherapy arm at the time of publication.

Based on the results of the above studies, it is probably safe to say that chemotherapy plays an important role, adding to the survival of patients with stage III (N2) NSCLC. Whether surgery is of benefit in these patients continues to be a point of debate among lung cancer oncologists. An ongoing intergroup study is comparing chemoradiation with or without surgical resection in patients with well-documented stage IIIA (N2) NSCLC in an attempt to define the role of surgical resection in NSCLC. New agents with activity in advanced/metastatic NSCLC, such as paclitaxel, gemcitabine, docetaxel, irinotecan, and vinorelbine, and combination regimens like paclitaxel/carboplatin, paclitaxel/cisplatin, and vinorelbine/cisplatin need to be incorporated into neoadjuvant regimens for stage III disease in future studies.

**Combined-Modality Therapy for Inoperable Stage III NSCLC**

The effect of combined-modality therapy in patients with inoperable stage III NSCLC is an area of continued clinical research. Many studies have reported varying results, probably due to the different criteria for patient inclusion and performance status employed by each. The exact sequence of chemotherapy and RT has yet to be determined. In general, chemotherapy is given either sequentially followed by RT or concurrently with RT. Concurrent chemoradiotherapy protocols have used chemotherapeutic agents as radiosensitizers given weekly or daily during the period of RT or in standard doses every 3 to 4 weeks. Chemotherapy after RT has not found favor, as overall responses in previously radiated lesions are generally low.

**Sequential Chemotherapy and RT**

Randomized studies on the role of sequential chemoradiation in patients with inoperable NSCLC have had mixed results. In these studies, chemotherapy consisted of a combination regimen given in standard doses prior to RT (Table 2). A large study published by Le Chevalier et al. randomized 353 patients with locally advanced unresectable NSCLC to either RT alone (65 Gy over 45 days) or combination chemotherapy followed by RT. Patients randomized to chemotherapy received three monthly cycles of vindesine, 1.5 mg/m² (days 1 and 2), lomustine, 50 mg/m² (day 2) and 25 mg/m² (day 3), cisplatin, 100 mg/m² (day 2), and cyclophosphamide, 200 mg/m² (days 2 to 4). Three additional cycles of chemotherapy were given after completion of RT to patients whose disease had not progressed after chemotherapy. The distant metastasis rate in the combined-modality arm was significantly lower than in the group that received RT alone. At first analysis, the combined-modality arm had a 2-year survival of 21% compared with 14% in the RT-alone group, a finding that was not statistically significant (p=0.08). At 3 years, however, survival rates between treatment arms were statistically significant (12% and 4%, respectively; p<0.02). This study demonstrated the impact of chemotherapy not only on survival but also on systemic control.

Dillman et al. published a study of 155 evaluable patients who were randomized to RT alone (60 Gy over 6 weeks) or combination chemotherapy followed by RT. Chemotherapy consisted of cisplatin, 100 mg/m² (days 1 and 29) and vinblastine, 5 mg/m² (days 1, 8, 15, 22, and 29), followed by RT on day 50. Response rates were similar in both groups (35% and 46% in the RT-alone and combined-modality arms, respectively). Vomiting and neutropenic infections were higher in the combined-modality group. The median survival of 13.7 months in the combined-modality arm was significantly better than the
Concurrent Chemoradiation

Administering radiosensitizing chemotheraphy concurrently with RT may improve locoregional control. Many agents have been used as radiosensitizers with RT over the last 40 years. Three published randomized studies of concurrent RT with single-agent bleomycin,39 hydroxyurea,30 and levamisole49 did not show a survival advantage for chemoradiotherapy. However, these studies did demonstrate the feasibility of this approach and the need for further investigation with more active agents.

Cisplatin has demonstrated radiosensitizing properties in preclinical models.31,32 When used as a radiosensitizer, cisplatin has been given daily, weekly, or every 3 weeks to patients with advanced NSCLC. Preliminary studies showed that cisplatin could be given at a daily dose of 6 mg/m²,84,44 or a weekly dose of 30 mg/m²,45 with tolerable toxic reactions in combination with split-dose RT. These studies formed the basis for Phase III trials using various cisplatin regimens in patients with advanced NSCLC.

A number of randomized studies have combined radiosensitizing doses of cisplatin with concurrent RT (Table 3).15-18,46-48 The largest of these, a three-arm study published by Schaake-Koning et al.,46 used split-course RT in 330 patients with inoperable NSCLC. The first group received 30 Gy over 2 weeks followed by a 3-week rest period and an additional 25 Gy over 2 weeks; the second group received the same RT with cisplatin, 30 mg/m² on the first day of each treatment week, and the third group received the same RT and cisplatin, 6 mg/m² daily before each RT fraction. The 3-year survival in the radiotherapy arm was 2% compared with 13% in the RT and weekly cisplatin group. The daily cisplatin and RT arm demonstrated significantly improved survival compared with the RT-alone arm (p=0.009). The addition of chemotherapy to RT did not increase the incidence of esophagitis in this study; however, nausea and vomiting were a significant

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9.6 months observed in the RT-only arm (p=0.01). This study was closed after accrual of 180 patients, as interim analysis showed a significant difference in treatment outcome. In the first 15 weeks, 14 deaths occurred in the RT-alone group compared with only 4 in the combined-modality arm. It is unclear whether premature closure of this study and the high early death rate in the RT-alone arm contributed to the significant differences in survival between groups.

The RTOG and the Eastern Cooperative Oncology Group set out to confirm the findings of the Dillman er al.33,34 study and added a third arm of HRT, based on the encouraging results of an earlier RTOG study.9 In their three-arm study, 452 patients were randomized to RT (60 Gy), HRT (60.6 Gy), or chemotherapy followed by RT.39 Results showed 1-year and median survivals in the combined-modality (60% and 13.8 months, respectively) were significantly improved compared with the HRT-alone arm (51 months, 12.3 months) and the standard RT arm (46%, 11.4 months) (p=0.03). The difference in 1-year survival for standard RT and HRT was not significant. Toxic reactions in all three arms were manageable.

In contrast to these positive results, a study published in 1988 by Mattson et al.37 in which 238 patients were randomized to either RT or RT in combination with CAP (cyclophosphamide/doxorubicin/platinum), failed to show an advantage in local control or survival for combined-modality treatment. However, the doses of chemotherapeutic agents were inadequate, based on present standards, and probably accounted for the absence of benefit. Similarly, a study by the North Central Cancer Treatment Group,31 in which patients were randomized to combination chemotherapy with MACC (methotrexate/doxorubicin/cyclophosphamide/lomustine) followed by TRT, or to TRT alone, failed to show a benefit in overall survival. This study, however, was criticized for not using an effective chemotherapeutic regimen for patients with NSCLC.

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Table 2—Randomized Trials of Sequential Chemotherapy and RT in Locally Advanced Inoperable NSCLC*  

<table>
<thead>
<tr>
<th>Investigators</th>
<th>No. of Patients</th>
<th>Therapy</th>
<th>Response Rate, %</th>
<th>Median Survival, mo</th>
<th>Survival, %</th>
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<tr>
<td>LeChevalier et al32</td>
<td>176</td>
<td>VCPC × 3 cycles → RT (60 Gy) → VCPC × 3 cycles</td>
<td>31</td>
<td>NS</td>
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<td>177</td>
<td>RT (60 Gy)</td>
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<td>NS</td>
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<td>5 yr</td>
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<tr>
<td>Sause et al35</td>
<td>77</td>
<td>P (days 1, 29) → VB (days 1, 8, 15, 22, 29) → (day 50) → RT (60 Gy)</td>
<td>46</td>
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<td>(p=0.01)</td>
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<tr>
<td>Mattson et al37</td>
<td>149</td>
<td>RT (60 Gy)</td>
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<td>Mattson et al37</td>
<td>152</td>
<td>HRT (60 Gy)</td>
<td>44</td>
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<td>(p=0.69)</td>
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<tr>
<td>Morton et al31</td>
<td>119</td>
<td>CAP × 3 cycles → RT (55 Gy)</td>
<td>49</td>
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<td>RT (55 Gy)</td>
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<td>56</td>
<td>MACC × 2 cycles → RT (60 Gy)</td>
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<td>(p=0.03)</td>
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<td>58</td>
<td>RT (60 Gy)</td>
<td>64</td>
<td>10.3</td>
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</table>

*VCPC=vindesine/cyclophosphamide/cisplatin/lomustine; NS=not stated; P=cisplatin; VB=vinblastine; CAP=cyclophosphamide/doxorubicin/cisplatin; MACC=mitomycin/doxorubicin/cyclophosphamide/lomustine.
problem in almost 70% of patients who received chemo-radiotherapy compared with only 24% of those who received RT alone.

Concurrent chemotherapy and HRT were evaluated by Jeremic et al.\textsuperscript{16,18} in two randomized studies in an effort to further refine combined-modality treatment of locally advanced NSCLC. In the first study,\textsuperscript{16} patients received HRT, 64.8 Gy, either alone, with weekly carboplatin (100 mg on days 1 and 2) and etoposide (100 mg on days 1 to 3), or with carboplatin (200 mg on days 1 and 2) and etoposide (100 mg on days 1 to 5) given in the first, third, and fifth weeks of therapy. The incidence of acute and delayed toxic reactions was highest in the groups that received concurrent chemoradiation. Median and 3-year survivals were highest in the group that received HRT with weekly carboplatin and etoposide (18 months and 23%, respectively). The 3-year survival in this group approached statistical significance compared with the group that received HRT alone (6.6%) (p=0.017). These results showed that HRT and continuous administration of carboplatin and etoposide improved the survival of patients with locally advanced NSCLC.

In their second study, Jeremic et al.\textsuperscript{18} increased the total dose of HRT to 69.6 Gy and modified the chemotherapy regimen to be given on a daily basis. Patients with stage III NSCLC received HRT, 1.2 Gy twice a day to a total dose of 69.6 Gy either alone or with concurrent chemotherapy consisting of carboplatin and etoposide both given at doses of 50 mg IV prior to each RT fraction. Median and 4-year survivals were 22 months and 23%, respectively, in the combined-modality arm vs 14 months and 9% in the HRT-only arm (p=0.021 for differences in 4-year survival). The two groups showed similar rates of acute and late high-grade toxic reactions. This study showed that concurrent chemotherapy enhanced the effect of TRT and significantly improved local control compared with the HRT-alone group (4-year local recurrence-free survival, 42% vs 19%, respectively, p=0.015). Distant metastasis-free survival was not significantly altered with chemotherapy (33% vs 39% for patients receiving HRT plus chemotherapy and HRT alone, respectively, p=0.33).

**Concurrent Chemotherapy and RT Using Carboplatin/Paclitaxel**

Although RT and chemotherapy with cisplatin either alone or in combination with other agents can achieve a survival benefit in patients with locally advanced NSCLC, it also is associated with significant side effects.\textsuperscript{16-18,46} In an attempt to decrease the toxicity of cisplatin-based chemoradiation, the University of Maryland Cancer Center (UMCC) conducted a pilot study using weekly carbopla-

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<th>Investigators</th>
<th>No. of Patients</th>
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<th>Median Survival, mo</th>
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<tbody>
<tr>
<td>Belani et al\textsuperscript{46}</td>
<td>35</td>
<td>Weekly C (100 mg/m\textsuperscript{2}) + RT (60 Gy)</td>
<td>34</td>
<td>13</td>
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<tr>
<td>Belani et al\textsuperscript{43}</td>
<td>32</td>
<td>Weekly C (100 mg/m\textsuperscript{2}) and P (45 mg/m\textsuperscript{2}) + RT (60-65 Gy)</td>
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\textsuperscript{4}C=carboplatin; P=paclitaxel.
tin, the less toxic analogue of cisplatin, and TRT in patients with locally advanced NSCLC (Table 4). Like cisplatin, carboplatin appears to have radiosensitizing properties, and when given concurrently with RT, has been associated with dose-limiting myelosuppression. The carboplatin/TRT regimen was evaluated in patients with head and neck cancer and appeared to be active and well tolerated. In the UMCC study, 35 previously untreated patients with stage III NSCLC were given weekly carboplatin, 100 mg/m² with concurrent TRT (total dose, 60 Gy). The response rate was 34%, and median survival was 15 months. The treatment was well tolerated, with only three patients requiring treatment prolongations of >1 week. This regimen demonstrated activity with a mild toxicity profile and appeared suitable for combination with other chemotherapeutic agents.

Paclitaxel is a novel agent with a wide spectrum of activity. In combination with platinum agents, paclitaxel has demonstrated cytotoxic activity in a wide variety of tumor types. Paclitaxel has proven activity in NSCLC, achieving impressive results both as a single agent and in combination with carboplatin in patients with advanced and metastatic disease.

The radiosensitizing effects of paclitaxel have also been well documented. Preclinical and clinical studies have shown that small concentrations of paclitaxel (10 to 100 nmol/L) enhance the cytotoxic effect of RT. A phase I study by Choy et al established that the maximum tolerated dose of paclitaxel in patients with locally advanced NSCLC was 60 mg/m² in combination with 60 Gy of concurrent TRT. The antimitotuble effects of paclitaxel lead cells to accumulate in the G2/M phase, the most radiosensitive phase of the cell cycle. Recent evidence indicates that p53 mutations herald a poor prognosis for NSCLC patients treated with chemotherapy. However, another recent report suggests that p53 mutations do not predict response to concurrent RT and paclitaxel therapy in locally advanced NSCLC and that this combination may be effective in treating locally advanced tumors with high rates of p53 mutations.

Based on these findings, we added small doses of paclitaxel to our UMCC pilot regimen of concurrent carboplatin and TRT in patients with stage III NSCLC. Patients were given paclitaxel, 45 mg/m² IV over 3 h with standard predemedication following by carboplatin, 100 mg/m² over 30 min. Concurrent TRT was given to a total dose of 60 to 65 Gy over 6 or 7 weeks. Thirty-two patients have been treated with this combined-modality program. Toxic reactions have been manageable; no grade 4 toxicity has been observed. Nine patients had to have one or more weekly doses of chemotherapy interrupted for >1 week due to grade 3 neutropenia. Only two patients had grade 3 mucositis and esophagitis requiring hospitalization. The three early deaths observed in this study were due to rapidly progressive disease and not to dose-limiting toxic reactions. This regimen has shown a high degree of activity in patients with stage III NSCLC. Actuarial survival at 1, 2, and 3 years is 63%, 54%, and 54%, respectively; median survival has not yet been reached (Table 4).

**CONCLUSIONS**

The results of these randomized studies highlight a role for chemoradiation therapy in locally advanced NSCLC. At present, the combined-modality approach has become the standard of care for patients who have a good performance status and <5% loss in body weight. The relatively high rate of local and systemic relapse, however, suggests the need for further improvements in this approach. The results from our phase II study of weekly paclitaxel and carboplatin with concurrent TRT are intriguing. These results need to be confirmed in future randomized studies. Based on patterns of failure following concurrent combined-modality approaches, it may be necessary to administer full doses of the same chemotherapy as induction therapy prior to or as consolidation therapy after simultaneous combined-modality treatment with radiosensitizing doses. Future strategies should also incorporate newer ways to administer RT (eg, conformal three-dimensional RT, HRT, or CHART in combination with chemotherapy). In addition, we should continue to identify intermediate events or prognostic markers that can better predict survival and identify patients who will likely benefit from specific combined-modality approaches.

**REFERENCES**

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