Combined Modality Therapy for Stage III Non-Small Cell Lung Cancer

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Key Words. Non-small cell lung cancer • NSCLC • Combined modality therapy • Stage III Chemotherapy • Thoracic radiation • Review

Learning Objectives
After completing this course, the reader will be able to:
1. Discuss the evidence to date on the role of chemotherapy in the treatment of stage III non-small cell lung cancer (NSCLC).
2. Discuss the evidence to date on the role of radiotherapy in the treatment of stage III NSCLC.
3. Describe ongoing chemotherapy trials and radiotherapy trials in stage III NSCLC.

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Abstract
Lung cancer remains the leading cause of cancer death in the U.S. among both men and women. Approximately 45% of patients present with stage III disease. A proportion of these patients is amenable to surgical resection; however, the majority are “unresectable.” For patients with unresectable stage IIIA/B disease, thoracic radiotherapy (TRT) was considered the standard of care until the late 1980s despite a very poor 5-year survival rate. Several clinical trials demonstrated that the combination of chemotherapy and TRT was superior to TRT alone. Based on these data, combined modality therapy became the standard of care for patients with good performance status. Recent trials have shown that concurrent chemoradiotherapy offers a significant survival advantage over sequential chemoradiotherapy. Despite a substantial number of clinical trials, important questions on the optimal treatment paradigm remain. The most effective chemotherapy combination, the use of induction or consolidation chemotherapy in addition to the concurrent portion of therapy, and the optimal dose of chemotherapy with concurrent TRT have yet to be determined. The optimal total dose, fractionation, acceleration, treatment volume, and tumor targeting remain questions related to the TRT portion of therapy. Although significant progress has been made, the majority of patients experience locoregional or distant progression of their disease and die within 5 years of diagnosis. Thus, continued development and participation in clinical trials is crucial to further improvements in the treatment of patients with stage III disease. The Oncologist 2006;11:809–823
Lung cancer is the leading cause of cancer death in both men and women in the U.S. It is estimated that there will be 174,000 new diagnoses of lung cancer, resulting in 162,000 deaths in the U.S. in 2006 [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 80%–85% of all cases of lung cancer, and 45% of patients present with stage IIIA or stage IIIB disease [2]. The therapeutic strategies employed for stage III disease include surgical resection with adjuvant therapy, preoperative chemotherapy, preoperative chemoradiotherapy, chemoradiotherapy, and chemoradiotherapy followed by consolidation chemotherapy. The majority of patients with stage III NSCLC are “unresectable” and are treated with chemotherapy and radiation therapy, often referred to as combined modality therapy (CMT) or definitive chemoradiotherapy. For patients with good performance status and without significant comorbidities, CMT is a standard of care, and this patient population is the focus of this article [3].

Recent American Society of Clinical Oncology (ASCO) guidelines state that patients who are suitable candidates for CMT should receive two to four cycles of platinum-based chemotherapy and should receive no less than the biologic equivalent of 60 Gy of radiation in 1.8- to 2.0-Gy fractions [3]. Patients are generally required to have an Eastern Cooperative Oncology Group (ECOG) functional status score of 0 or 1, adequate pulmonary function (which is often defined as a forced expiratory ventilation in 1 second [FEV1] >800 cm3), and adequate renal, hematologic, and hepatic function. Patients with malignant pleural or pericardial effusions, supraclavicular lymphadenopathy, or weight loss >5% or 10% are frequently excluded from clinical trials.

Treatment paradigms involve systemic-dose chemotherapy to reduce the chances of distant metastases and concurrent chemoradiotherapy with either systemic-dose chemotherapy or lower dose chemotherapy designed to act as a “radiation sensitizer” to improve the efficacy of thoracic radiation therapy (TRT). Three frequently used treatment paradigms are: (a) initiating treatment with chemotherapy (referred to as induction chemotherapy) and then initiating concurrent chemoradiotherapy with either full-dose or weekly low-dose chemotherapy; (b) initiating treatment with systemic-dose chemotherapy concurrent with radiotherapy, potentially followed by additional systemic-dose chemotherapy (referred to as consolidation chemotherapy); and (c) initiating low-dose weekly chemoradiotherapy followed by consolidation chemotherapy. The optimal strategy as it relates to dose, timing of chemotherapy and radiation, and chemotherapy agents continues to be an area of investigation. Unfortunately, both local failure and distant failure are problematic, and therapeutic improvements will have to successfully address both issues.

**ROLE OF CHEMOTHERAPY IN THE TREATMENT OF STAGE III DISEASE**

**Chemotherapy and TRT Versus TRT Alone**

The use of induction chemotherapy has been developed through a series of clinical trials that have been ongoing since the mid-1980s (Table 1). The pivotal trial was the Cancer and Leukemia Group B (CALGB) 8433 trial, which randomized 155 patients to the sequential use of induction chemotherapy with cisplatin (Platinol®; Bristol-Meyers Squibb, Princeton, NJ) plus vinblastine (Velban®; Eli Lilly and Company, Indianapolis) followed by radiation therapy with 60 Gy beginning on day 50 versus radiation therapy alone to the same dose. That trial demonstrated significant improvements in the combined modality therapy group, with a longer median survival time (13.7 months vs. 9.6 months; \( p = .012 \)) and higher 5-year survival rate of 17% versus 6% or a 2.8-fold improvement [4]. A confirmatory three-arm trial was performed

### Table 1. Induction chemotherapy followed by radiotherapy versus radiotherapy alone

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Treatment</th>
<th>Median survival (mos)</th>
<th>5-year survival (%)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB [4]</td>
<td>155</td>
<td>Cis/Vlb → TRT 60 Gy vs. TRT alone</td>
<td>13.7</td>
<td>17%</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>RTOG [5]</td>
<td>458</td>
<td>Cis/Vlb → TRT 60 Gy</td>
<td>13.2</td>
<td>8%</td>
<td>.04a</td>
</tr>
<tr>
<td>Le Chevalier et al. [6]</td>
<td>353</td>
<td>PVCC → TRT</td>
<td>12</td>
<td>12%b</td>
<td>&lt;.02</td>
</tr>
</tbody>
</table>

*Comparison of chemotherapy plus TRT with TRT alone.

*Data reported as 3-year survival rate.

Abbreviations: CALGB, Cancer and Leukemia Group B; cis/Vlb, cisplatin plus vinblastine; Hfx, hyperfractionated; PVCC, cisplatin, vindesine, cyclophosphamide, and nitrosourea lomustine; RTOG, Radiation Therapy Oncology Group; TRT, thoracic radiation therapy.
by the Radiation Therapy Oncology Group (RTOG), Southwest Oncology Group (SWOG), and ECOG that randomized patients to radiation alone, the same chemotherapy used in the CALGB trial followed by radiation therapy to 60 Gy, or hyperfractionated radiation (1.2 Gy per fraction delivered twice daily [bid]) to a total dose of 69.6 Gy. The median survival time for patients receiving RT alone was 11.4 months; for the combined modality arm it was 13.2 months, and for CMT with hyperfractionated irradiation the median survival time was 12 months [5]. Overall survival was statistically superior for patients receiving CMT over radiation therapy alone (p = .04). A third trial, performed by Le Chevalier et al. [6] involving 353 patients, compared treatment with three cycles of induction chemotherapy followed by TRT with TRT alone. An analysis with a mean follow-up of 40 months revealed that the 2-year survival rate in the radiation alone arm was 14%, and in the CMT arm it was 21%, which approached statistical significance (p = .08). A second analysis was performed with a mean follow-up of 61 months, and the effect on overall survival became significant (p < .02) [7]. The metastasis rate was significantly lower in the CMT arm (p < .001).

In addition to these randomized controlled trials, there have been several meta-analyses that have investigated this issue [8–10]. These meta-analyses have revealed superior survival with the combination of cisplatin-based chemotherapy and TRT over TRT alone. A recent analysis of patients treated in CALGB trials for stage III disease found that the use of TRT alone versus CMT was associated with a poorer survival (hazard ratio [HR], 1.58; 95% confidence interval [CI], 1.22–2.05; p = .001) [11]. In summary, the combination of the data from the randomized controlled trials and from the meta-analyses performed on this subject support the use of a combination of chemotherapy and radiation therapy for stage III disease.

### Concurrent Chemoradiotherapy Versus Radiotherapy Alone

Several phase III trials have compared treatment with concurrent chemoradiotherapy with radiotherapy alone (Table 2). The first of these trials was performed by the European Organization for Research and Treatment of Cancer (EORTC). In that trial, 331 patients were randomized to three treatment programs: arm A, split-course radiation alone; arm B, radiation combined with daily cisplatin (6 mg/m²); or arm C, radiation combined with weekly cisplatin (30 mg/m²) [12]. The 3-year survival rate was significantly greater with the daily cisplatin than with the TRT alone (16% vs. 2%; p = .009). The survival benefit of weekly cisplatin was intermediate and not statistically different from either of the other two groups. The time to local recurrence was significantly longer in the groups given cisplatin (p = .015), especially the group given daily cisplatin (p = .003). There was no difference among the three groups in time to distant metastasis (p = .37).

The concurrent strategy was also investigated in two trials by Jeremic et al. [13, 14]. In one trial, 169 patients were randomized to receive either hyperfractionated TRT (group 1), hyperfractionated TRT plus carboplatin (Paraplatin®, Bristol-Meyers Squibb) and etoposide (Etopophos®, Vespid®; Bristol-Meyers Squibb) (group 2), or hyperfractionated TRT with a different schedule of carboplatin and etoposide (group 3). There was a statistically significant difference in the survival rate between groups 1 and 2 but not between groups 1 and 3 or groups 2 and 3. The relapse-free survival rate was better in group 2 than in group 1 patients (p = .0024) as a result of better local control. The same investigators performed a second trial comparing the hyperfractionated TRT treatment with the same TRT schedule plus carboplatin and etoposide on each day of radiation. The concurrent therapy group had a significantly longer median survival time.

### Table 2. Concurrent chemoradiotherapy versus radiotherapy alone

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Treatment</th>
<th>3-year survival (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC [12]</td>
<td>331</td>
<td>Daily cisplatin</td>
<td>16%</td>
<td>.009a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weekly cisplatin</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TRT</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Jeremic et al. [13]b</td>
<td>169</td>
<td>Hfx TRT</td>
<td>6.6%</td>
<td>.0024c</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hfx TRT with CB/etoposide</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hfx TRT with CB/etoposide</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Jeremic et al. [14]</td>
<td>131</td>
<td>Hfx TRT</td>
<td>9%b</td>
<td>.021</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hfx TRT with CB/etoposide</td>
<td>23%</td>
<td></td>
</tr>
</tbody>
</table>

aSurvival difference was statistically significant between the weekly cisplatin and TRT alone arms. There was no statistically significant difference between weekly cisplatin and TRT alone or daily cisplatin.

bData reported as 4-year survival rate.

cDifference in survival was statistically significant between groups 1 and 2 but not groups 1 and 3 or groups 2 and 3.

Abbreviations: CB, carboplatin; EORTC, European Organization for Research and Treatment of Cancer; Hfx, hyperfractionated; TRT, Thoracic radiotherapy.

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(22 months vs. 14 months) and a greater 4-year survival rate, 23% versus 9% \( (p = .021) \). The 4-year local recurrence-free survival rate was significantly greater in the concurrent therapy group (42% vs. 19%, respectively; \( p = .015 \)), but there was no significant difference in the rate of distant metastasis. These trials indicate that improvements in local control can be obtained with concurrent chemoradiotherapy, and that improvements in local control can result in longer survival. These trials used chemotherapy doses lower than those typically used to treat systemic disease.

### Systemic-Dose Concurrent Chemoradiotherapy Versus Sequential Chemotherapy and Radiotherapy

Several trials have compared systemic chemotherapy plus concurrent TRT with several cycles of systemic chemotherapy followed by TRT (the sequential approach). The West Japan Lung Cancer Group randomized 320 patients with stage IIIA/B NSCLC to concurrent or sequential chemotherapy. Patients in the first arm received chemotherapy with systemic doses of cisplatin, vindesine, and mitomycin \( \text{(Mutamycin}^\text{®}; \text{Bristol-Meyers Squibb)} \) with TRT starting on day 2 \( [15] \). The TRT given in that trial was split-course, where patients received 28 Gy for 14 treatment days followed by a 10-day rest, and then the treatment was repeated for a total TRT dose of 56 Gy. In the other arm, patients received the same chemotherapy but the TRT was initiated after completion of the chemotherapy and continued to 56 Gy. The median survival time was longer for patients receiving concurrent therapy (16.5 months vs. 13.3 months; \( p = .04 \)) (Table 3). The 5-year overall survival rate was 15.8% for concurrent therapy and 8.9% for sequential therapy. Myelosuppression was greater among the patients receiving concurrent therapy \( (p = .0001) \); however, the rate of esophageal toxicity was identical in both arms. The split-course TRT schedule may have contributed to the similar rates of esophagitis in the two treatment arms.

A similar three-arm trial was conducted by the RTOG involving 610 patients with stage II or stage III NSCLC \( [16] \). The concurrent chemotherapy with daily TRT arm had significant better survival than the sequential arm \( (p = .046) \). The rates of acute grade 3–4 nonhematologic toxicities were higher with the concurrent therapy; however, the late toxicity rates were similar. Zatloukal et al. \( [17] \) performed a phase II trial involving 102 patients with stage IIIA/B disease who were randomized to receive either concurrent or sequential chemoradiotherapy. The median survival time was longer in the concurrent arm (16.6 months vs. 12.9 months; \( p = .023 \)) and the time to progression was longer (11.9 months vs. 8.5 months; \( p = .024 \)). There was significantly greater World Health Organization (WHO) grade 3 or 4 leukopenia (53% vs. 19%; \( p = .009 \)) and nausea and vomiting (39% vs. 15%; \( p = .044 \)) in the concurrent chemoradiotherapy arm. There was no statistically significant difference in the rates of grade 3–4 neuropathy, febrile neutropenia, and esophagitis.

The French cooperative groups performed a phase III trial, consisting of 212 patients, that compared sequential treatment using two cycles of systemic-dose cisplatin and vinorelbine \( \text{(Navelbine}^\text{®}; \text{GlaxoSmithKline, Philadelphia)} \) followed by TRT to 66 Gy with concurrent cisplatin and etoposide using the same TRT followed by systemic doses of cisplatin and vinorelbine \( [18] \). The total dose of cisplatin was equivalent in both arms. The median overall survival time was 14.5 months for the sequential arm versus 16.3 months for the concurrent arm \( (p = .24) \). Patients in the sequential treatment arm experienced more grade 3 peripheral neuropathy (4% vs. 0%; \( p = .05 \)) and more grade 4 neutropenia (72% vs. 48%; \( p = .008 \)), while patients in the concurrent arm experienced more grade 3–4 esophagitis (3% vs. 32%; \( p < .0001 \)). Treatment was discontinued because of toxicity in 18% and 23% of patients in the sequential and concurrent arms, respectively.

Data from three of these four phase III trials support a benefit to the use of concurrent chemoradiotherapy with systemic doses of chemotherapy for survival, with longer median survival and long-term survival. The primary

### Table 3. Randomized trials comparing sequential with concurrent chemoradiotherapy strategies

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Chemotherapy</th>
<th>Radiotherapy (Gy)</th>
<th>Schedule</th>
<th>Median Survival (mos)</th>
<th>Actuarial Survival (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furuse et al. ( [15] )(320)</td>
<td>Mitomycin + cisplatin Vindesine</td>
<td>56</td>
<td>Sequential</td>
<td>13</td>
<td>9 (5-yr)</td>
<td>.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Concurrent</td>
<td>17</td>
<td>16 (5-yr)</td>
<td></td>
</tr>
<tr>
<td>Curran et al. ( [16] )(610)</td>
<td>Cisplatin Vinblastine</td>
<td>63</td>
<td>Sequential</td>
<td>14.6</td>
<td>18 (3-yr)</td>
<td>.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Concurrent</td>
<td>17.1</td>
<td>26 (3-yr)</td>
<td></td>
</tr>
<tr>
<td>Zatloukal et al. ( [17] )(102)</td>
<td>Cisplatin Vinorelbine</td>
<td>60</td>
<td>Concurrent</td>
<td>16.6</td>
<td>16 (5-yr)</td>
<td>.023</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sequential</td>
<td>12.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fournel et al. ( [18] )(212)</td>
<td>Cisplatin</td>
<td>66</td>
<td>Sequential</td>
<td>14.5</td>
<td>24 (2-yr)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Etoposide</td>
<td></td>
<td>Concurrent</td>
<td>16.3</td>
<td>35 (2-yr)</td>
<td></td>
</tr>
</tbody>
</table>
increased toxicity seen in these trials has been an increased rate of esophagitis. Future trials that modify the TRT dose or schedule or modify the intensity of the concurrent chemotherapy will most likely address acute esophagitis as the dose-limiting toxicity. It should be noted that the trials that have revealed a survival benefit to concurrent chemoradiotherapy have used systemic-dose chemotherapy and have been performed with agents that are not frequently used as systemic therapy for stage IV disease.

**Future Directions and Controversies in the Management of Stage III Disease**

**Consolidation Therapy**
In a recent phase II trial by SWOG (S9504), patients with stage IIIB disease were treated with systemic-dose cisplatin plus etoposide and concurrent TRT (total dose, 61 Gy) and additional consolidation chemotherapy with docetaxel (Taxotere®; Aventis Pharmaceuticals Inc, Bridgewater, NJ) at a dose of 75 mg/m² for three cycles [19]. The survival data, based on 83 patients, revealed an impressive median survival time of 26 months, and the 1-, 2-, and 3-year survival rates were 58%, 34%, and 17%, respectively. Sixty-five of the patients were able to proceed to the consolidation chemotherapy, and 49 patients were able to receive all three cycles of the docetaxel. The main toxicity seen in the consolidation chemotherapy portion of the treatment was myelosuppression, with a grade 4 neutropenia rate of 57% and a rate of febrile neutropenia of 9%. Three patients died of pulmonary complications, which consisted of probable radiation pneumonitis in two patients and aspiration pneumonia in one patient. A phase III trial by the Hoosier Oncology Group and U.S. Oncology is evaluating the role of consolidation chemotherapy with docetaxel as well. In that trial patients receive systemic chemotherapy with cisplatin and etoposide with concurrent TRT, and patients with stable disease and responding disease (partial response [PR] or complete response [CR]) are then randomized to consolidation docetaxel versus observation. The results of that trial will probably be available in approximately 1–2 years.

Based on the promising results of the phase II trial, the SWOG cooperative group initiated a phase III trial, S0023, that compared treatment with cisplatin plus etoposide and concurrent TRT followed by consolidation therapy with docetaxel and randomization to maintenance gefitinib (Iressa®; AstraZeneca, Inc; London) or observation. Five-hundred seventy-five patients were enrolled, and 412 received docetaxel consolidation therapy (Fig. 1) [20]. Patients were then randomized to gefitinib (250 or 500 mg daily until disease progression) or observation. The median survival time of all patients enrolled in the trial was 19 months. Among the patients randomized to gefitinib, the median overall survival was 19 months, versus 29 months with placebo (p = .09). Based on the survival results of an interim analysis, the data and safety monitoring board recommended closure of the trial because the hypothesized survival benefit of gefitinib therapy was “untenable.” Because of this trial, it is unlikely that maintenance gefitinib will have a significant role in stage III therapy in an unselected patient population. The placebo arm will provide additional survival and toxicity data on consolidation chemotherapy.

**Role of Induction Chemotherapy**
Induction chemotherapy followed by TRT has demonstrated survival benefit over TRT in three separate trials [4–6]; however, a recent CALGB trial compared induction chemotherapy followed by concurrent chemoradiotherapy with chemoradiation therapy alone [21]. In that trial, 366 patients were randomized to weekly carboplatin and paclitaxel (Taxol®; Bristol-Meyers Squibb) concurrent with TRT to 66 Gy or two cycles of carboplatin and paclitaxel and then the identical concurrent chemoradiotherapy treatment. The study was powered to have an 80% power to detect a 40% difference in

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**Figure 1.** Southwest Oncology Group -0023 phase III trial in patients with unresectable stage IIIA/B non-small cell lung cancer. Abbreviation: RT, radiotherapy.
median survival. The median survival time in the chemoradiotherapy arm alone was 11.4 months, versus 14 months for the induction chemotherapy arm (p = .154), and the 1-year survival estimates were 48% and 54%, respectively.

This study has raised questions about the commonly used practice of induction chemotherapy. The median survival times in both treatment arms were lower than recent experience for unclear reasons, possibly because of a selection bias by physicians as to who was enrolled in the trial. The lower survival may, in part, be a result of the fact a significant percentage of patients with weight loss, a known poor prognostic factor, was included in the trial. Of the 331 patients available for analysis, 18% had 5%–10% weight loss and 9% had >10% weight loss. However, if the survival curves are analyzed with the ineligible, cancelled, and >5% weight loss patients excluded, similar survival times were observed in the two arms; therefore, the proportion of patients with weight loss does not appear to explain the lack of benefit to induction chemotherapy seen in this trial. In light of the negative findings and the poorer outcome of patients enrolled in the trial, the role of induction therapy should be further evaluated in randomized trials.

Timing of Concurrent Chemoradiotherapy

The issue of the optimal timing of radiation with systemic therapy was addressed in a randomized phase II trial that compared three different treatment approaches (Table 4). This trial, known as the locally advanced multimodality protocol (LAMP), involved 276 patients in 49 centers [22]. The intent of this phase II trial was to select the best two treatment arms, and subsequently move to a phase III design. The trial randomized patients to induction chemotherapy followed by radiation, induction chemotherapy followed by concurrent chemoradiation, or chemoradiation followed by consolidation chemotherapy. Patients received systemic doses of carboplatin and paclitaxel as induction or consolidation therapy, and in the concurrent chemoradiotherapy arms they received weekly low doses of carboplatin and paclitaxel. All patients received TRT to 63 Gy. Unfortunately, slow accrual to the phase III portion of the trial led to the early closure of this trial.

The median survival time with a median follow-up of 39.6 months was longer with the concurrent/consolidation approach, with a median survival time of 16.3 months, while the median survival time for the sequential arm was 13 months and it was 12.7 months for the induction/concurrent arm. The randomized phase II trial design was not powered for direct comparisons among treatment arms. When comparisons were made with historical survival data from RTOG studies using induction chemotherapy followed by TRT, none of the three arms was different from historical controls.

The percentages of patients receiving the planned therapy were similar (70%, 69%, and 74%, respectively). Importantly, there was an imbalance of patients with weight loss among the arms, with a higher percentage of patients with 5%–10% weight loss in arm 2 (36%) compared with arm 1 (27%) and arm 3 (28%). The smaller sample size, because of early closure, the randomized phase II trial design, and the imbalance of patients with 5%–10% weight loss among the treatment arms, make it difficult to make any definitive conclusions about the superiority or inferiority of any of the three treatments in terms of efficacy. The numerical superiority of the concurrent chemoradiotherapy arm followed by consolidation chemotherapy is intriguing; however, phase III data using this approach are currently not available.

Integration of Novel Agents and Target Therapies

The recent ECOG Trial 4599, comparing the combination of carboplatin and paclitaxel with carboplatin, paclitaxel, and bevacizumab (15 mg/kg every 3 weeks) (Avastin®; Genentech, Inc; South San Francisco, CA) in patients with advanced NSCLC, revealed a higher response rate (10% vs. 27%, respectively; p < .0001) and longer median survival time (10.2 months vs. 12.5 months, respectively; p = .0075) with the addition of bevacizumab [23]. In the phase II trial of carboplatin, paclitaxel, and bevacizumab, patients with squamous histology, central lesions, and evidence of cavitation had a higher rate of fatal hemoptysis [24]. Therefore, patients with a history of significant bleeding or hemoptysis, coagulopathy, thrombosis, brain metastases, or squamous histology were excluded.

Table 4. Locally advanced multimodality trial [22]

<table>
<thead>
<tr>
<th>Treatment paradigm</th>
<th>Chemotherapy → TRT</th>
<th>Chemotherapy → Concurrent Chemoradiotherapy</th>
<th>Concurrent Chemoradiotherapy → Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>13.1 mos</td>
<td>12.7 mos</td>
<td>16.3 mos</td>
</tr>
<tr>
<td>1-year overall survival</td>
<td>59%</td>
<td>53%</td>
<td>64%</td>
</tr>
<tr>
<td>2-year overall survival</td>
<td>28%</td>
<td>24%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Abbreviation: TRT; thoracic radiotherapy.
These promising results in the stage IV setting indicate that bevacizumab may improve systemic therapy in the stage III setting. Bevacizumab may also play a role in the concurrent chemoradiotherapy portion of stage III treatment. Preclinical data indicate that the antiangiogenic therapy may increase the cytotoxicity of radiation therapy [25, 26], and a phase I trial of bevacizumab and radiation in rectal cancer is currently ongoing [27]. TRT with bevacizumab therapy may reduce the risk for pulmonary hemorrhage as well.

Two other new treatment agents that are being explored in the stage III setting are pemetrexed (Alimta®; Eli Lilly and Company), a multitargeted antifolate chemotherapy, and cetuximab (Erbitux®; Imclone Systems, Inc., New York), a monoclonal antibody against the epidermal growth factor receptor. A recent phase I trial indicated a favorable toxicity profile for the combination of carboplatin (area under the concentration–time curve [AUC] = 6) and pemetrexed (500 mg/m²) every 3 weeks for two cycles with concurrent chest radiotherapy (to 40–66 Gy) for patients with esophageal and lung cancer [28]. The main grade 3 toxicities seen were leukopenia, dehydration, and fatigue. Cetuximab has shown activity in the advanced disease setting in combination with chemotherapy or as a single agent in the second-line setting [29–31]. A recent phase III trial in patients with squamous cell cancer of the head and neck found superior survival with the treatment of cetuximab and radiation therapy over radiation therapy alone with minimally greater toxicity [32]. This synergy between radiation therapy and cetuximab has lead to interest in using this agent in the chemoradiotherapy portion of combined modality therapy in NSCLC.

Cetuximab is currently being explored in a phase II RTOG trial (Trial 0324) for unresectable stage IIIA/B patients (Fig. 2). Patients will be treated with concurrent chemoradiotherapy, with cetuximab in combination with weekly carboplatin and paclitaxel, and will then receive consolidation therapy with cetuximab and systemic doses of carboplatin and paclitaxel. The TRT dose will be 63 Gy over 7 weeks in 35 daily fractions. A randomized phase II trial, CALGB 30407, is exploring the use of carboplatin and pemetrexed with and without cetuximab concurrent with TRT (Fig. 2). After completion of the concurrent portion of the treatment, patients in both arms will receive four cycles of consolidation therapy with pemetrexed. Patients will receive TRT of 70 Gy over 7 weeks. This trial will be of interest, because it will use systemic-dose chemotherapy concurrent with TRT and will explore the tolerability of consolidation pemetrexed.

**Radiation Dose**

Treatment with TRT to 40–50 Gy has been shown to result in superior survival over best supportive care [33]. The RTOG has investigated a variety of doses for inoperable NSCLC, stages IA–IIIA (RTOG 73-01) and IIIB (RTOG 73-02). The results of these two trials were presented together by Perez et al. [34]. Five hundred fifty-one patients with medically or surgically inoperable NSCLC of the lung were treated with definitive TRT. No difference in survival was seen among the four different treatment regimens explored. Local control did show an advantage for higher radiation doses. Despite no difference in survival, the results of RTOG 73-01 indicated better local control with 60 Gy relative to lower doses and led to the adoption of 60 Gy as the standard dose for inoperable lung cancer. However, even the authors of that report suggested that higher doses of radiation would be necessary to control large masses in unresectable patients. Arriagada et al. [35] examined recurrence patterns among patients treated to 65 Gy with TRT alone or with chemotherapy given before and after TRT and found local control rates in the range of 15% in both groups. Given that local control is necessary for cure, enhanced local disease control has been the goal of numerous strategies, including examination of altered fractionation schemes, dose escalation, radiation sensitization, and better tumor targeting.

**Dose Escalation/Altered Fractionation**

Different fractionation schemes have been employed in an attempt to exploit the difference in repair capability between normal and tumor tissue and the accelerated tumor proliferation that occurs approximately 4 weeks into the treatment course. Pure hyperfractionation is a strategy in which two or more daily fractions are administered to the same total dose as with conventional fractionation in an attempt to reduce the late effects of radiation. However, this approach results in a radiobiologically lower total dose. Thus, in practice, hyperfractionation typically employs higher total doses than conventional fractionation and is used to achieve similar or better tumor control while maintaining a similar level of early radiation effects to that seen with conventional fractionation. This approach allows higher radiation doses while limiting normal tissue toxicity.

“ Accelerated fractionation” is designed to decrease overall treatment time in order to reduce the amount of tumor proliferation occurring during the course of therapy, in order to increase the probability of attaining local tumor control. Other strategies include continuous hyperfractionated accelerated radiation therapy (CHART), which includes aspects of both hyperfractionation and accelerated therapy. In this method, small fractions are given three
The overall treatment time can be shortened by employing concomitant boost therapy. This method starts with standard fractionation but uses an accelerated strategy during the last 2–3 weeks, allowing a shorter total treatment time. Several studies have employed altered fractionation and higher doses to improve local control. RTOG 81-08 established the feasibility of hyperfractionation in a multi-institutional setting, with doses up to 69.6 Gy in bid fractions of 1.2 Gy with acceptable toxicity [36]. From 1983 to 1987, patients with unresectable stage III NSCLC were enrolled in RTOG protocol 83-11 and randomized to one of three doses: 60 Gy, 64.8 Gy, or 69.6 Gy, delivered in two daily fractions of 1.2 Gy each [37]. The lowest of these doses was set based on the dose given using standard fractionation from the RTOG 73-01 trial. As the study accrued patients, the toxicity at these three levels was found to be acceptable, and two additional higher dose arms were opened (74.4 Gy and 79.2 Gy) and accrual to the two lowest dose arms was discontinued. In the total population of 848 patients, there was no association between radiation dose and overall survival. However, a subset analysis of 350 more favorable patients who met the criteria for CALGB Trial 8433 (stage III, Karnofsky performance score >70, and ≤5% weight loss) demonstrated longer overall survival for patients receiving 69.6 Gy compared with those receiving lower doses. There was no survival difference between the 69.6-Gy group and those with higher doses. Compared with patients treated on RTOG 83-21 (60 Gy in 30 fractions) patients receiving 69.6 Gy with hyperfractionated radiation had longer survival without greater toxicity to normal tissues.

More recently, attempts have been made to increase the overall dose with dose escalation using either altered fractionation schemes or standard fractionation schemes with or without chemotherapy. Maguire et al. [38] investigated the use of higher-dose radiotherapy using accelerated hyperfractionation in a study of 94 patients with unresectable NSCLC. The clinical target volume (CTV) was treated to 45 Gy in fractions of 1.25 Gy bid (6 hours apart).
The gross tumor volume (GTV) was treated at 1.6 Gy bid to a total dose of 73.6–80 Gy delivered over 4.5–5 weeks employing a concurrent boost technique. The median survival times were 13 months and 10 months for stage IIIA and IIIB patients, respectively.

Sim et al. [39] treated 152 patients with three-dimensional (3D) conformal TRT of 50–81 Gy either alone or following induction chemotherapy. The median survival time was significantly longer for those receiving combined chemotherapy and radiation (18.1 months) than for those receiving TRT alone (11.7 months) despite a higher median radiation dose among those treated with TRT alone (64.8 Gy vs. 70.2 Gy). The 2-year overall survival rate was significantly higher in the combined modality group than in the TRT alone group (30% vs. 25%; p = .001). Furthermore, no difference in toxicity was observed between the two treatment groups. That study supported the use of chemotherapy even among patients receiving higher than standard doses of TRT.

Hayman et al. [40] conducted a phase I dose-escalation trial in which 104 patients (69 stage III) received TRT of 63–84 Gy in 2.1-Gy fractions dependent on the irradiated normal lung volume [40]. Patients were segregated into five categories based on normal lung volume irradiated. The maximum-tolerated dose (MTD) of 65.1 Gy was reached for the group with the largest volume. MTDs were not reached for the remaining four groups; however, dose levels of 102.9, 102.9, 84, and 75.6 Gy were reached with acceptable toxicity. The median survival time for stage III and recurrent patients was 16 months, with overall survival rates at 1, 2, and 3 years of 61%, 36%, and 14%, respectively.

Graham et al. [41] reported on 163 inoperable NSCLC patients enrolled in the RTOG 9311 phase I/II 3D TRT dose-escalation trial. This was updated recently by Bradley et al. [42] for a total of 179 patients. Patients were grouped into different radiation treatment levels based on the percentage of total lung volume that received >20 Gy (V20). Radiation was delivered at 2.15 Gy per fraction. Patients with a V20 <25% (group 1) received dose escalation from 70.9 Gy to 90.3 Gy, those with a V20 of 25%–37% (group 2) were escalated from 70.9 Gy to 77.4 Gy, and those with a V20 >37% (group 3) failed to accrue in this study. Patients treated with neoadjuvant chemotherapy were allowed in the trial, but concurrent chemotherapy was not permitted. Acute grade 3 or higher toxicity in group 2 was seen in 1 of 21 patients at 70.9 Gy and 2 of 25 patients at 77.4 Gy. The rate of late lung toxicity in group 2 at 18 months was 15% for both dose levels. Both mean lung dose and V20 were predictive of late pneumonitis in a multivariate analysis. Grade 3 or worse esophageal toxicity was seen in 8% or less of the patients in both groups at all dose levels and was not associated with dose or lung volume. Locoregional control and overall survival were similar in all study arms within each group. Two-year locoregional control rates were in the range of 50%–78%, and locoregional failure was the sole site of failure in 18% and a component of failure in 38% of patients. The overall survival rate at 2 years was in the range of 42%–50% in group 1 and 20%–42% in group 2. However, nearly 50% of group 1 patients had stage I disease.

That study demonstrated that doses as high as 83.8 Gy can be delivered to patients with low-volume disease using 3D conformal techniques. However, among patients in this group treated to 90.3 Gy, two treatment-related deaths were observed. Patients with a somewhat higher V20 were treated with doses as high as 77.4 Gy without an unreasonable risk for treatment-related toxicity. Despite these relatively high radiation doses, locoregional failure continued to be a significant component of treatment failure. As such, trials were designed using radiation dose escalation with concurrent “radiation-sensitizing” doses of chemotherapy. The Carolina Conformal Therapy Consortium recently conducted a phase I dose-escalation trial of 39 evaluable patients with unresectable stage IIB–IIIA/B NSCLC to determine the MTD of accelerated hyperfractionated conformal TRT (1.6 Gy bid to GTV and 1.25 Gy bid to CTV) following induction chemotherapy with either carboplatin plus paclitaxel or carboplatin plus vinorelbine [43]. The primary grade 3 or higher toxicities seen in this trial were pulmonary and esophageal toxicities. The median survival time was 18 months and 2-year overall survival rate was 47%. The MTD for this chemoradiotherapy regimen was approximately 80 Gy based on the greater toxicity observed in the 86.4-Gy group.

The use of concurrent chemotherapy with dose-escalated radiation has also been performed in several studies with doses as high as 90 Gy. Rosenman et al. [44] were the first to complete a phase I/II dose-escalation trial (LCCC 9603) of 62 patients treated with induction and concurrent carboplatin plus paclitaxel chemotherapy with radiation doses from 60–74 Gy. The major toxicity was esophagitis, with five patients (8%) having grade 3 or 4. Esophagitis was directly related to the length of esophagus treated. The median survival time was 24 months and 1-, 3-, and 5-year overall survival rates were 71%, 39%, and 26%, respectively. Despite the aggressive locoregional therapy, at least 35% of patients had locoregional failure as a component of treatment failure. That study demonstrated that 74-Gy TRT could be delivered safely with concurrent chemotherapy. Similar studies have been performed with radiation-sensitizing chemotherapy [45].

Building upon the tolerance to 74-Gy TRT seen with LCCC 9603, a phase I dose-escalation trial of 25 unresectable stage IIIA/B NSCLC patients treated with doses of 78–90 Gy with induction carboplatin, irinotecan
aggressive regimen was acceptable. Investigators concluded that the greater toxicity with this very aggressive regimen than the one used in LCCC 9603 with escalation of TRT starting at 78 Gy and proceeding to 82, 86, and 90 Gy, or until MTD was achieved. The TRT dose was escalated from 78 to 90 Gy without any dose-limiting toxicity. However, late toxicity consisted of three grade 2 esophageal strictures, two cases of bronchial stenosis, and two cases of fatal hemoptysis. Despite these treatment-related deaths, early survival data appear quite good, with a median survival time of 24 months and a 1-year overall survival rate of 73%.

It is clear from these studies that the total dose of radiation can extend beyond the 60-Gy threshold set by the RTOG 73-01 clinical trial with concurrent low-dose sensitizing chemotherapy. The primary concern from these trials was related to pulmonary toxicity, specifically pneumonitis and subsequent fibrosis. When initially designed, there were limited parameters to assess for predictors of pulmonary toxicity. With standard beams and doses, the V20 and mean lung dose are predictive and have been validated. When multiple radiation beams are being used for many patients treated with 3D conformal therapy, this model may not be valid, and lower doses may be necessary. It has been suggested that a V13 of 50% and a mean lung dose of 20 Gy are good predictors of pneumonitis, with no grade 3 pneumonitis seen when the mean lung dose is <15 Gy [47]. However, more recently, there have been reports of pneumonitis in patients with mean lung doses <15 Gy [48].

A number of studies have employed CHART and CHART-like strategies in an attempt to improve the therapeutic ratio for radiation in unresectable locally advanced NSCLC. In a multi-institutional phase III trial in the United Kingdom, Saunders et al. [49] enrolled 563 patients with good performance status and inoperable NSCLC to receive either standard treatment (60 Gy in 30 fractions) or CHART (three daily fractions of 1.5 Gy given daily for 12 consecutive days, including weekends, to a total dose of 54 Gy). Approximately half of the patients had stage III disease, and 80% of the patients had squamous cell carcinoma. Patients randomized to the CHART arm had a significantly higher local control rate (23% vs. 15%) and 2-year overall survival rate (29% vs. 20%). In addition, a lower rate of distant disease was seen in the CHART arm, thus suggesting that better local control has a significant impact on the development of distant metastatic disease. The CHART treatment arm had a higher rate of grade 3 or higher esophagitis, pneumonitis, and late pulmonary toxicity. Nonetheless, the investigators concluded that the greater toxicity with this very aggressive regimen was acceptable.

Ball et al. [50] conducted a multicenter trial in Australia to examine both the effect of shortening the overall treatment time and the effect of administering carboplatin concurrently with radiotherapy. That study employed a 2 × 2 factorial design and enrolled 204 patients to one of four treatment arms. Patients were randomized to receive either standard TRT (60 Gy in 30 fractions over 6 weeks) or accelerated TRT (60 Gy in 30 fractions over 3 weeks), and were randomized to receive either concurrent carboplatin chemotherapy along with the radiotherapy or no chemotherapy. The median survival time for the entire study population was 15.7 months and the 2-year overall survival rate was 31%. No significant differences were seen among the different treatment arms.

The use of hyperfractionated radiation in the setting of combined-modality treatment was also tested by ECOG [51]. The study was closed secondary to slow accrual. One hundred forty-one of a planned 388 patients were enrolled, with initial induction treatment of two cycles of carboplatin and paclitaxel followed by either 64 Gy delivered in 2-Gy daily fractions or 57.6 Gy delivered in 1.5-Gy fractions three times per day over two and a half weeks. The median survival time and 3-year survival rate favored the accelerated hyperfractionation regimen, 20.3 months versus 14.9 months (p = .28) and 24% versus 14%, respectively [51]. Logistical issues of delivering treatment more than twice daily, the greater mucosal toxicity, and the interdigitation may create barriers to further exploring hyperfractionated regimens.

Normal Tissue Protection
Approaches to improving local control, including radiation dose escalation, altered TRT fractionation, and concurrent chemotherapy, typically result in greater toxicity to normal tissues. Several drugs are being developed and studied with the intent of decreasing radiation toxicity. Perhaps the most well studied and promising is amifostine (Ethylol®; MedImmune, Inc., Gaithersburg, MD). Amifostine is believed to protect cells by acting as a free radical scavenger for reactive oxygen species that would otherwise potentially damage DNA. Amifostine is thought to protect tissues because of the relatively greater uptake of the compound in normal tissue relative to tumor tissue. Thus the timing of the agent is very important. It must be given long enough prior to radiation to have high concentrations in normal tissue, but not so long that the passive diffusion of the drug into tumor tissue will combat the DNA-damaging effects of the radiation. Amifostine has been shown to protect a wide range of normal tissues not only from the effects of radiation, but also from cytotoxic drugs, including platinum agents and alkylators, anthracyclines, and taxanes [52]. Based on a phase III
trial conducted by Brizel et al. [53] in the late 1990s, amifostine has been used for radioprotection in head and neck cancer patients. Several randomized trials have examined the radioprotective effects of this drug in the setting of unresectable NSCLC. Antonadou et al. [54] performed a randomized phase III trial of radiation with or without amifostine for advanced-stage lung toxicity in order to assess the incidence of acute and late lung toxicity, as well as esophagitis. One-hundred forty-six patients were treated with TRT administered in 2-Gy fractions given 5 days per week to a total dose of 55–60 Gy either with or without amifostine (340 mg/m² given daily 15 minutes prior to radiation). Significantly lower rates of grade 2 or higher pneumonitis, lung damage, lung fibrosis at 6 months, and esophagitis were seen. No difference in response to the antitumor therapy was observed.

A randomized, double-blind study of combined-modality therapy with or without amifostine for unresectable stage III NSCLC was conducted by Leong et al. [55]. Sixty patients were initially treated with carboplatin plus paclitaxel induction chemotherapy for two cycles, then with combined TRT (64 Gy) with concurrent weekly paclitaxel. Patients were randomized to receive either amifostine (740 mg/m²) before each dose of chemotherapy or placebo. Grade 2–3 esophagitis was observed in 70% of patients receiving placebo and only 43% of those treated with amifostine. The difference was not statistically significant. Komaki et al. [52] conducted a randomized controlled trial to study the impact of amifostine on acute toxicity for patients with inoperable NSCLC treated with chemotherapy and radiotherapy. Sixty-two patients were randomly assigned to TRT (69.6 Gy in 58 fractions of 1.2 Gy bid 5 days per week) and concurrent etoposide plus cisplatin either with or without amifostine (500 mg 20–30 minutes prior to any treatment on the first 2 days of therapy each week). Significantly less severe esophageal toxicity, severe pneumonitis, and neutropenic fever were seen among patients treated with amifostine. No differences in survival were seen between the amifostine treatment arm and the control arm in either trial.

Because of the mixed results seen in numerous small randomized trials, the RTOG conducted a larger trial (RTOG 98-01) to examine the impact of amifostine on esophageal toxicity [56]. Two-hundred forty-three patients were treated with two cycles of induction carboplatin plus paclitaxel followed by TRT (69.6 Gy in 58 fractions of 1.2 Gy bid 5 days per week) and weekly concurrent paclitaxel and randomized to either amifostine (500 mg four times per week) or no amifostine. Patients receiving amifostine experienced higher rates of acute nausea, vomiting, cardiovascular toxicity, and infection/febrile neutropenia. Rates of grade 3 or higher esophagitis were not different between the arms (30% of patients treated with amifostine vs. 34% of patients not treated with amifostine). However, patient assessments of swallowing dysfunction and pain were better among those treated with amifostine. The median and overall survival rates did not differ between the two arms. The timing of administration of amifostine may have been problematic, because it was given between the two radiation doses. Nonetheless, one might expect that giving the drug 4 days per week would be at least equivalent to twice weekly, as in the Komaki et al. [52] trial, which showed a significant protective effect with amifostine. The discrepancies between the RTOG trial and the other trials have yet to be thoroughly sorted out; however, differences in the dose and schedule of amifostine may have been contributing factors.

Prophylactic Cranial Irradiation in the Treatment of Locally Advanced NSCLC

As many as one quarter to one half of the patients with locally advanced NSCLC develop brain metastases during the course of their illness [59–61]. The brain is the first site of failure for 15%–30% of patients, and the median survival time after the development of brain metastases is approximately 3–6 months [57–60, 62–65]. The development of brain metastases has a tremendous impact on quality of life, and a reduction in the incidence of brain metastases may have a clinically significant impact on patient quality of life without providing longer overall survival. The rate of brain metastases in NSCLC is similar to the rate seen for limited-stage small-cell lung cancer (SCLC), a disease for which prophylactic cranial irradiation (PCI) has become the standard of care.

Three prospective trials were conducted during the 1970s and 1980s to assess the impact of PCI on patients with localized NSCLC (Table 5) [66–68]. Those trials demonstrated a significantly lower risk for developing brain metastases with PCI, but no difference in survival. The trials used inferior locoregional and systemic therapy, compared with current standards. Advances in multimodality care and prolonged survival for NSCLC patients have led to an increase in central nervous system (CNS) as the sole site of failure. This holds true whether patients are treated with surgical resection [57, 60, 70, 71] or with combined chemo-radiotherapy in the absence of surgery [15, 72–74]. Despite promising results in the protection from brain metastases, PCI comes with a risk for neurocognitive deterioration. Toxicity data for PCI come largely from studies of patients with SCLC [75, 76]. The incidence appears to be related to fraction size (23 Gy) and the concurrent administration of systemic chemotherapy [77]. Randomized trials have been conducted in France and
Treatment of Stage III NSCLC

The United Kingdom to assess toxicity related to PCI in patients with limited-stage SCLC in complete remission following induction chemotherapy [78, 79]. Interestingly, a large proportion of patients (40% in the U.K. study) had cognitive dysfunction prior to randomization. Although deterioration in function was observed, neither study found significant differences in numerous measures of neurocognitive function between those treated with PCI and those not treated with PCI.

In an attempt to evaluate the role of PCI in locally advanced NSCLC, the RTOG initiated a large phase III randomized trial (RTOG 0214) [80]. Patients with stage IIIA or IIIB NSCLC who achieve a CR or PR, or have stable disease, following definitive local therapy will be randomized to receive either whole-brain radiotherapy (30 Gy in 15 fractions) or observation. Patients will be stratified according to stage (IIIA vs. IIIB), histology (nonsquamous cell vs. squamous cell), and therapy (no surgery vs. surgery). Quality of life data and neuropsychologic data will be collected for both groups. The primary end point is survival, and the secondary end points include neuropsychologic impact of PCI, impact on quality of life, and impact on incidence of CNS metastases.

Radiation Sensitizers

Attempts at using pure radiation or chemotherapy sensitizers have been made. The most recent attempt has been with the addition of hypoxic cell sensitizers. Etiproxiral (RSR13; Allos Therapeutics; Westminster, CO) reduces oxygen-binding affinity, thus facilitating oxygen release and increasing tissue pO2. In a phase II, multicenter trial, 51 patients were enrolled with treatment of induction chemotherapy of carboplatin (AUC = 6) and paclitaxel (225 mg/m^2) followed by 64 Gy of radiation with concurrent daily efaproxiral (50–100 mg/kg) [22]. Survival results were compared with those of the RTOG 94-10 trial. The median survival time was 20.6 months with a 2-year survival rate of 37%. These compared favorably with those of the RTOG study and warrant testing in a phase III study.

Future Directions

There are three basic components to attaining better locoregional control for inoperable NSCLC, as well as many other cancers. First, it is important to improve the therapeutic ratio and biological effectiveness of therapy through strategies including dose escalation, altered fractionation schemes, radioprotection of normal tissues, and concurrent chemotherapy and other radiation-sensitizing agents. Second, better means of identifying areas of tumor with such modalities as positron emission tomography [81] (thin cut computed tomography [CT], and respiratory-gated CT) will result in better targeting accuracy. Finally, dose delivery through the use of techniques including respiratory gating [82], tumor tracking [83], and 4D technology [84] will result in better precision. In addition to the need to deliver higher doses of radiation, it is clear that better tumor targeting is needed in order to have a significant impact on rates of local control.

Conclusions

The life expectancy of patients with stage III disease has steadily increased over the past several decades through a series of well-designed clinical trials. There are currently several different treatment paradigms being employed in the treatment of this patient population. All of these treatment paradigms include treatment with systemic-dose chemotherapy and radiation. Phase III trials have revealed a survival benefit of concurrent chemoradiotherapy over the sequential approach, when a concurrent systemic dose chemotherapy is employed with radiotherapy. However, patients treated with concurrent chemotherapy experience a higher rate of acute toxicity, particularly esophagitis. The late toxicity rate does not appear to be higher. The optimal chemotherapy agents, dose, and treatment schedule have yet to be definitively determined. Trials integrating newer chemotherapeutic agents, antiangiogenic agents, and biologic agents are ongoing. It is hoped that these agents may improve efficacy or reduce toxicity over the currently available therapies. There is interest in the development of radiation protectors and 3D treatment planning that may reduce...
the rate of radiation-related toxicity as well. Trials exploring different radiotherapy doses, schedules, fractionation, and radiation sensitizers may improve efficacy. The high rate of the development of brain metastases necessitates improvement in the treatment and prevention of brain metastases. Despite the improvements demonstrated in these trials, the majority of patients eventually progress and ultimately die from locoregional disease or distant progression of disease; therefore, the continued development of and participation in clinical trials is crucial.

**Disclosure of Potential Conflicts of Interest**

The authors indicate no potential conflicts of interest.

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Additional Reading

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Consolidation Therapy
In a recent phase II trial by SWOG (S9504), patients with stage IIIB disease were treated with systemic-dose cisplatin plus etoposide and concurrent TRT (total dose, 61 Gy) and additional consolidation chemotherapy with docetaxel (Taxotere®; Aventis Pharmaceuticals Inc, Bridgewater, NJ) at a dose of 75 mg/m² for the first cycle with dose escalation to 100 mg/m² for the second and third cycles in the absence of significant toxicity [19]. The survival data, based on 83 patients, revealed an impressive median survival time of 26 months, and the 1-, 2-, and 3-year survival rates were 76%, 54%, and 37%, respectively. This compared favorably to the previous SWOG trial (S9019) which had a median survival of 15 months, and the 1-, 2-, 3-year survival rates were 58%, 34%, and 17%, respectively. Sixty-five of the patients were able to proceed to the consolidation chemotherapy, and 49 patients were able to receive all three cycles of the docetaxel. The main toxicity seen in the consolidation chemotherapy portion of the treatment was myelosuppression, with a grade 4 neutropenia rate of 57% and a rate of febrile neutropenia of 9%. Three patients died of pulmonary complications, which consisted of probable radiation pneumonitis in two patients and aspiration pneumonia in one patient.

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