

# Treatment of Locally Advanced Non-small Cell Lung Cancer

Mary Jo Fidler, MD, Anthony W. Kim, MD, Thomas Zusag, MD, Philip Bonomi, MD

Dr. Fidler is Assistant Professor, Section of Medical Oncology; Dr. Kim is Assistant Professor, Thoracic Surgery in the Department of Cardiothoracic Surgery; Dr. Zusag is Assistant Professor of Radiation Oncology; and Dr. Bonomi is Alice Pirie Wirtz Professor of Medical Oncology and Director, Division of Hematology-Oncology at Rush University Medical Center in Chicago, IL.

Address correspondence to:  
Mary Jo Fidler, MD  
Assistant Professor  
Section of Medical Oncology  
Rush University Medical Center  
1725 W. Harrison  
Professional Building, Suite 855  
Chicago, IL 60612  
Phone: (312) 942-5904  
Fax: (312) 942-3192  
E-mail: Mary\_Fidler@rush.edu

## Keywords

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**Abstract:** Approximately one third of non-small cell lung cancer (NSCLC) patients will present with locally advanced, stage III disease. With the use of pretreatment positron emission testing and mediastinal lymph node sampling, classifying stage III NSCLC has become more involved and treatment strategies have shifted from single modality thoracic radiation to combined chemoradiotherapy. This article reviews evidence-based strategies in the treatment of locally advanced NSCLC and presents new efforts for improving the poor prognosis of this disease by incorporating novel chemotherapy and biologic based regimens.

## Introduction

Lung cancer is responsible for the largest number of cancer-related deaths in the United States with approximately 219,440 new cases of lung cancer in 2009.<sup>1</sup> Approximately 85% of these patients have non-small cell lung cancer (NSCLC) and one third of them have locally advanced NSCLC. Exceeding the combined number of ovarian and pancreatic cancer cases expected for 2008, locally advanced NSCLC represents a major healthcare problem in the United States.

Prior to the area of combined modality therapy, locally advanced NSCLC patients were treated with thoracic radiation alone and this resulted in long-term survival for approximately 5% of patients. Approximately 20 years ago, several studies showed that 2 or 3 courses of cisplatin-containing chemotherapy given prior to thoracic radiation resulted in significantly longer survival than radiation therapy alone, with an increase in the 5-year survival rate from approximately 5% to 10%.<sup>2,3</sup> These initial observations led to a significant amount of activity in testing combined modality therapy in patients with locally advanced NSCLC. This review includes discussion of staging guidelines for locally advanced NSCLC patients, practical aspects of selecting patients for combined modality therapy, and a review of treatment strategies that have been tested in this group of patients.

## Staging

Patients with clinical stage IIIA/IIIB NSCLC are potential candidates for combined modality treatment. Many of these patients present with symptoms related to thoracic disease including onset of cough, change in cough, hemoptysis, dyspnea, and chest pain. In addition, locally advanced patients are found inadvertently while being evaluated for an unrelated condition. At the time of referral to a cancer specialist, a computed tomography (CT) chest scan has been performed in the majority of locally advanced lung cancer patients. Current guidelines recommend that CT scans include both adrenal glands and the entire liver. A whole body positron emission tomography (PET) scan is recommended for NSCLC patients whose CT scans show no evidence of distant metastasis. If the PET scan shows equivocal results of osseous lesions, or if the patient has pain and no evidence of bone metastasis on PET scan, then a nuclide bone scan is recommended to evaluate suspicious areas. Magnetic resonance imaging (MRI) or CT scans frequently provide useful information in evaluating potential bone metastasis. In contrast to recommendations for stage IV NSCLC patients, MRI or CT brain scan with or without infusion is recommended prior to initiating potentially curative therapy in stage III NSCLC patients, even in the absence of symptoms suggestive of brain metastasis.

### *Mediastinal Lymph Node Staging*

Current recommendations suggest that mediastinoscopy or other invasive procedures including endoscopic ultrasound-guided biopsy and transbronchial biopsy be done to evaluate mediastinal lymph nodes that are greater than 1 cm in the shortest diameter or which show increased uptake of fluorodeoxyglucose F 18 on PET scan. A number of studies of PET have evaluated the accuracy of identifying mediastinal nodal involvement compared with cervical and anterior mediastinoscopy; the sensitivity of PET ranges from 61–95% and specificity ranges from 84–96%.<sup>4–6</sup> In fact, a systematic review of the accuracy of PET scans as a means to noninvasively stage the mediastinum, published by the American College of Chest Physicians (ACCP), estimated that the sensitivity and specificity was 74% and 85%, respectively.<sup>7</sup> When focusing on patients with enlarged mediastinal lymph nodes on CT scan, the PET scan sensitivity and specificity has been reported to be even higher at 100% and 78%, respectively.<sup>8</sup> It is believed, but yet to be definitively established, that noninvasive mediastinal staging is improved if both CT and PET are used in an integrated format. Though PET has higher accuracy over CT alone, the incidence of false positive and false negative results suggests that PET may not obviate the need for histologic confirmation provided by biopsy.

Routine use of PET in conjunction with selective surgical mediastinal evaluation has been shown to reduce the rate of surgical procedures by 35%, while maintaining a similar rate of pN2 disease detection.<sup>9</sup> In addition to detecting nodal disease, PET is able to identify metastatic disease missed by other staging techniques.<sup>5,10</sup> Accurate detection of metastatic disease prior to surgery can spare a patient the morbidity of an aggressive surgical procedure. The ideal practice that incorporates both PET and invasive surgical procedures in a complementary fashion has yet to be elucidated.

Endobronchial ultrasound (EBUS) guided needle aspiration is an emerging invasive staging tool that is being employed with greater frequency. The ACCP evidence-based clinical practice guidelines recently reported that the sensitivity and specificity of this technique were 90% and 100%, respectively.<sup>11</sup> When focusing on PET scan-positive lymph nodes, a more recent multi-institutional experience with EBUS showed similar results with a sensitivity and specificity of 91% and 100%, respectively, and an accuracy of 92%.<sup>12</sup> In this series, EBUS staging precluded the need for other surgical staging in 71% of the cases.

Endoscopic ultrasound (EUS) guided needle aspiration has been used with greater frequency than EBUS, but like EBUS, has yet to be established as the primary technique for invasive mediastinal staging. Based on a pooled analysis, the overall sensitivities and specificities of this tool have been estimated to be 84% and 99.5%, respectively, in identifying malignant mediastinal lymph node involvement. For determining mediastinal extension of primary tumors, the sensitivity and specificity are 88% and 98%, respectively.<sup>11</sup> More recently, it has been shown that the use of PET scan-directed EUS yields a higher sensitivity and specificity of 95% and 100%, respectively, with an overall accuracy of 97%.<sup>13</sup> In a more recent and smaller study, EUS guided biopsy was found to be more sensitive in detecting malignant mediastinal node involvement (93%) than surgical staging (73%), suggesting that surgical staging could be reduced in patients with suspected mediastinal disease. The specificities of both techniques were the same at 100%, which mirrors the experience of several other investigations.<sup>14</sup> A disadvantage of this technique is that the number of nodal stations accessible by EUS is limited.

It remains to be seen where exactly in the sequence of NSCLC staging EBUS/EUS will be placed, but given its current success, it is possible that EBUS/EUS may supplant cervical mediastinoscopy as the invasive tests of choice prior to neoadjuvant therapy for suspected stage III NSCLC. Cervical mediastinoscopy may, therefore, be reserved for evaluating post treatment mediastinal lymph nodes for persistent disease prior to recommending surgical resection in select patients.

**Table 1.** Positive Randomized Trials Comparing Radiation to Sequential Chemoradiation

Investigators	Treatment	Patients	Survival (months)	P value	2-year survival
Dillman et al <sup>16</sup>	Radiation (60 Gy)	77	9.7	.012	13%
	Vinblastine/cisplatin/radiation (60 Gy)	78	13.8		26%
LeChevalier et al <sup>3,79</sup>	Radiation (65 Gy)	176	10	.08	14%
	Vindesine/lomustine/cyclophosphamide/radiation (65 Gy)	176	12		21%
Sause et al <sup>17</sup>	Radiation once (daily 60 Gy)	149	11.4	NS	19%
	Radiation twice daily (69 Gy)	152	12		24%
	Vinblastine/cisplatin/radiation (60 Gy)	151	13.2		.04

Revisions to the current AJCC staging system for NSCLC have been proposed and are likely to be implemented in September 2009. The proposed staging revisions have relatively little implications for the treatment of stage III disease because nodal staging definitions will not change. One recommended change that may impact decision making in stage III patients is the reclassification of tumors with additional nodules in the same lobe from T4 to T3. If the satellite nodules can be included in a radiation portal, it is possible that these patients will be considered for definitive combined modality treatment. However, these nodules incorporated into the new staging system were more often discovered at the time of resection rather than being apparent at the time of clinical imaging.<sup>15</sup> Therefore, the new guidelines may not influence combined modality treatment, which is usually based on clinical staging.

**Treatment Strategies for Locally Advanced Cancer**

Definitive thoracic radiation has been the primary treatment for fit patients with locally advanced NSCLC. Although radiation provides palliation for many of these patients, 5-year survival rates are only 3–5%. A variety of strategies have been tested to improve long-term survival including induction chemotherapy followed by radiation alone, low dose chemotherapy and simultaneous radiation, full dose concurrent chemotherapy and radiation, and a variety of permutations of these approaches. Consolidation therapy consisting of the same or different treatment regimens following completion of chemotherapy has also been tested. Most recently, novel noncytotoxic agents

(cetuximab [Erbix, ImClone/Bristol-Myers Squibb], gefitinib [Iressa, AstraZeneca], and bevacizumab [Avastin, Genentech]) and pemetrexed (Alimta, Eli Lilly)—a relatively new cytotoxic drug—have been evaluated in chemoradiotherapy regimens.

**Induction Chemotherapy Followed by Radiation**

Based on the high rate of distant metastases, early combined modality trials tested the use of induction chemotherapy followed by definitive doses of thoracic radiation. Three positive phase III trials (Table 1) comparing radiation to sequential chemoradiation had a number of common features. Two or 3 courses of a chemotherapy regimen, which included cisplatin and a vinca alkaloid, were followed by thoracic radiation given at a dose of 60–65 Gy. Results were also quite similar. Median survival durations of 9.7–11.4 months for radiation alone compared with 12–13.8 months for chemotherapy followed by radiation. The 5-year survival rates were 17% and 6%, respectively, in the smallest study. There were smaller variances in long-term survival rates in the larger trials with the differences being 6% versus 3% and 8% versus 5%.<sup>3,16,17</sup> A meta-analysis of studies comparing cisplatin-containing induction therapy versus radiation alone showed a trend for longer survival for combination therapy, but the differences at 3 and 5 years were not significant.<sup>18</sup>

**Simultaneous Low-dose Chemotherapy and Radiation Versus Radiation Alone**

Low-dose chemotherapy has been added to thoracic radiotherapy in an attempt to enhance sensitivity to radiation and improve local control. Initial efforts studied low-dose cisplatin given on daily and weekly schedules.

**Table 2.** Radiation versus Radiation Plus Low-dose Cisplatin

Investigators	No. Patients Randomized	Radiation	Cisplatin	2-year survival	P value (OS)
Schaake-Koning <sup>19</sup>	331	54 Gy split course	6 mg/m <sup>2</sup> /day	26%	.009
			30 mg/m <sup>2</sup> /wk	19%	.36
			none	13%	
Trovo et al <sup>20</sup>	167	45 Gy over 3 weeks	6 mg/m <sup>2</sup> /day	Approx 15%	NS
			None	Approx 15%	

OS=overall survival

Conflicting results were observed in 2 randomized trials that tested identical daily cisplatin schedules (6 mg/m<sup>2</sup>/day).<sup>19,20</sup> Ironically, the investigators who studied a less intense radiation regimen (54 Gy given over 7 weeks on a split course schedule) observed a modest improvement in survival and better local control in patients who received daily cisplatin, whereas simultaneous daily cisplatin with a more intense radiation regimen (45 Gy over 3 weeks) was not associated with longer survival. Similarly, survival was not improved with weekly cisplatin and concurrent radiation (Table 2).

#### **Induction Chemotherapy Followed by Radiation and Low Dose Simultaneous Chemotherapy**

Radiation and simultaneous low-dose single<sup>21,22</sup> or doublet<sup>23,24</sup> chemotherapy following induction chemotherapy have been evaluated in randomized trials. In the earliest study by Clamon and colleagues, the Cancer and Leukemia Group B (CALGB) and the Eastern Cooperative Oncology Group (ECOG) attempted to improve upon induction cisplatin and vinblastine followed by thoracic radiation (60 Gy) with radiation sensitizing doses of carboplatin in a large phase III trial, which included 283 patients. Concurrent carboplatin at 100 mg/m<sup>2</sup> failed to have an impact on disease control or survival.<sup>21</sup> A phase III trial of 303 patients using weekly paclitaxel at 60 mg/m<sup>2</sup> concurrently with radiation after 2 cycles of paclitaxel 200 mg/m<sup>2</sup> and carboplatin area under the curve (AUC)=6 showed improved progression-free survival (PFS) and a trend toward improved overall survival (OS;  $P < .001$ ,  $P = .091$ , respectively).<sup>22</sup> The benefit was seen in patients who either did not progress or became eligible for surgical resection after the induction regimen. Preliminary results from a larger randomized trial comparing radiation alone to weekly carboplatin and radiation following 2 cycles of induction cisplatin and vinblastine have been reported.<sup>24</sup> There were no differences in the rates of local control or distant metastases. A higher

rate of death, which appeared to be treatment related, occurred in patients who received carboplatin concurrently with radiation.

Weekly paclitaxel/carboplatin and concurrent thoracic radiation after induction with 2 courses of full dose paclitaxel/carboplatin have been studied in 2 randomized trials by Vokes and associates and Belani and coauthors.<sup>23,24</sup> In the Locally Advanced Multimodality Protocol (LAMP) trial by Belani and coauthors, there was an additional arm studying weekly paclitaxel/carboplatin and concurrent radiation followed by 2 cycles of full dose paclitaxel/carboplatin.

The dose and schedule for the induction regimens were identical, and the total radiation dose (63 and 66 Gy) and the weekly concurrent chemotherapy regimens (paclitaxel/carboplatin) were virtually the same. In the larger trial by Vokes and associates, the experimental variable was induction chemotherapy.<sup>24</sup> In the smaller randomized LAMP study, determining the effect of a simultaneous weekly chemotherapy doublet and radiation was the primary objective.<sup>23</sup> The trial by Vokes and associates revealed relatively disappointing survival results for both regimens with no significant difference in survival between arms. The authors suggested that the continued study of weekly paclitaxel/carboplatin should be re-examined. In the LAMP trial, disappointing survival durations were also seen, with a trend for shorter survival with concurrent chemoradiation after induction chemotherapy. The third arm of the LAMP trial used concurrent chemoradiation followed by full dose paclitaxel/carboplatin and also did not seem better than historical controls of chemoradiation alone. These results lend credence to the suggestion made by Vokes and associates that alternative chemotherapy regimens to be given concurrently with radiation should be sought. Survival data from both of these studies are summarized in Table 3.

Although the doses of weekly paclitaxel and carboplatin given simultaneously with chest radiation are relatively

**Table 3.** Carboplatin (AUC 6)/Paclitaxel (200 mg/m<sup>2</sup>) and Concurrent Weekly Carboplatin/Paclitaxel Plus Radiation

Investigators	Concurrent Regimen	Full-dose chemotherapy	RT dose	Pts	Survival (months)	3-year survival
Vokes et al <sup>24</sup>	Paclitaxel (50 mg/m <sup>2</sup> )/ carboplatin (AUC=2) weekly plus daily radiation	Induction	66 Gy	170	14	23%
		None	66 Gy	161	12	19%
Belani et al <sup>23</sup>	Paclitaxel (45 mg/m <sup>2</sup> )/ carboplatin (AUC=2) weekly plus daily radiation	Induction	63 Gy	74	12.7	15%
	Paclitaxel (45 mg/m <sup>2</sup> )/ carboplatin (AUC=2) weekly plus daily radiation	Post chemoradiation	63 Gy	94	16.3	17%
	No chemotherapy	Induction	63 Gy	91	13.0	17%

small, the incidence of esophagitis following induction paclitaxel/carboplatin is significant. Grade 3/4 esophagitis was seen in 19–36% of patients who received this concurrent paclitaxel/carboplatin combination.<sup>23,26</sup> Similar patients treated with radiation alone after induction chemotherapy have a 3% rate of grade 3/4 esophagitis. The incidence of grade 3/4 pulmonary toxicity (4–10%) in patients treated with concurrent paclitaxel/carboplatin was similar to that seen in patients receiving radiation alone (7%) following induction chemotherapy.

**Radiation with Concurrent, Full-dose Chemotherapy Versus Sequential Chemoradiation**

Two phase III trials addressing the timing of chemotherapy and radiation favor concurrent administration. A large Radiation Therapy Oncology Group (RTOG) trial involving 610 patients compared induction versus concurrent cisplatin (100 mg/m<sup>2</sup>) and vinblastine (5 mg/m<sup>2</sup>).<sup>27</sup> A third arm involved hyperfractionated radiation (69.6 Gy) with concurrent cisplatin and oral etoposide. The concurrent chemoradiation arms were superior to the sequential chemotherapy-radiation arm (median survival 17.0 vs 14.6 months; *P*=.038). A phase III trial from Japan in unresectable stage III NSCLC patients also compared identical chemotherapy regimens given sequentially versus concurrently with 56 Gy of thoracic radiation.<sup>28</sup> The chemotherapy was cisplatin 80 mg/m<sup>2</sup>, vindesine 3 mg/m<sup>2</sup>, and mitomycin 8 mg/m<sup>2</sup>, with the radiation given on a split course schedule only in the concurrent chemotherapy arm. Median survival was superior in the concurrent chemoradiotherapy arm (16.6 vs 13.3 months, *P*<.04) and approximately 80% of the patients in both arms received the planned treatment. Of note, the Japanese regimen of cisplatin, vindesine, and mitomycin was tested against the third generation

regimen of cisplatin and docetaxel (40 mg/m<sup>2</sup> weekly for both) with concurrent no split radiation in a recent phase III trial. Overall survival was superior in the cisplatin/docetaxel regimen, though PFS was the same in each arm, possibly suggesting increased late toxicity in the older regimen.<sup>29</sup> Currently there are ongoing trials with the newer chemotherapy agent pemetrexed combined with cisplatin at full doses with concurrent daily radiation (Table 4).

**Consolidation Chemotherapy After Concurrent Chemoradiation**

Two SWOG single-arm phase II trials suggested that consolidation chemotherapy after radiation and simultaneous full dose chemotherapy might prolong survival. In the earlier study, SWOG 9019, patients were treated with concurrent cisplatin, etoposide, and radiation with a median survival of 15 months and a 3-year survival rate of 17%.<sup>30</sup> In the subsequent SWOG 9504 trial, patients were treated with the identical SWOG 9019 regimen followed by 3 courses of docetaxel. The observed median survival in this trial was 27 months, and the 3-year survival rate was 37%.<sup>31</sup>

Unfortunately, the initial observations, which suggested that consolidation docetaxel improved survival, were not confirmed in a randomized trial conducted by the Hoosier Oncology Group. These investigators compared treatment with cisplatin/etoposide/radiation (SWOG 9019 regimen) with or without 3 courses of consolidation docetaxel. There were no significant differences in survival (median survival 21.6 months for consolidation docetaxel vs 24.2 months for observation). In addition, 28.8% of patients were hospitalized during treatment with docetaxel versus 8.1% on the observation arm. Apparent treatment-related mortality was observed in 5.5% of docetaxel-treated patients.<sup>32,33</sup>

**Table 4.** Sequential Versus Concurrent Chemoradiation

Investigators	No. patients	Chemotherapy	Radiation	Median Survival (months)	P value
Curran et al <sup>27</sup>	610	Cisplatin/vinblastine	Sequential 60 Gy	14.6	.046
		Cisplatin/vinblastine	Concurrent 60 Gy	17	
		Cisplatin/etoposide	Concurrent 69.6 Gy	15.2	
Furuse et al <sup>28</sup>	320	Cisplatin/vindesine/mitomycin	Sequential 56 Gy	13.3	.040
			Concurrent 56 Gy split course	16.6	
Kiura et al <sup>29</sup>	200	Cisplatin/vindesine/mitomycin	Concurrent 60 Gy	23.7	.018*
		Cisplatin/docetaxel	Concurrent 60 Gy	26.8	

\*2 year survival statistically significant.

Consolidation chemotherapy has also been evaluated after treatment with radiation and simultaneous low-dose chemotherapy. Weekly paclitaxel/carboplatin (45 mg/m<sup>2</sup>; AUC=6) followed by 2 cycles of consolidation paclitaxel/carboplatin (200 mg/m<sup>2</sup>; AUC=6) was compared to a historical control arm, which consisted of 2 courses of vinblastine/cisplatin followed by radiation alone.<sup>17,23</sup> Although median survival in the paclitaxel/carboplatin consolidation arm was numerically superior to the historical control regimen (16 vs 14 months), the 2-year survival rates were virtually identical (31% vs 32%). Comparison of toxicity revealed higher rates of grade 3/4 esophagitis (28% with concurrent chemoradiation and consolidation chemotherapy versus 3% in the historical control sequential chemoradiation). Similarly, grade 3/4 lung toxicity was reported in 16% of patients treated with the experimental regimen versus 7% on the historical control arm, and granulocytopenia was more frequent on the experimental versus the control arm (26% vs 0%; Table 5).

#### **Chemoradiation Incorporating Novel Agents**

Multiple phase II and III clinical trials are underway studying platinum combined with pemetrexed and concurrent radiation. Pemetrexed is a folate analog with radiation sensitizing properties currently approved with cisplatin as first-line therapy and as a single agent for second line therapy in the treatment of advanced non-squamous NSCLC. Existing data suggest that the toxicity is feasible and, notably, unlike any other third generation platinum doublet, platinum and pemetrexed can be given at full doses with concurrent radiation.<sup>34</sup> Full doses of

pemetrexed, cisplatin, and simultaneous definitive thoracic radiation are being compared to etoposide, cisplatin, and thoracic radiation in an ongoing phase III trial in stage III nonsquamous NSCLC.

Recently, the addition of cetuximab to a chemotherapy doublet was shown to be associated with a modest improvement in survival in previously untreated stage IV NSCLC patients.<sup>35</sup> Preclinical data in squamous cell cancer of the head and neck show that inhibiting the endothelial growth factor receptor (EGFR) pathway induces radiation sensitivity.<sup>36</sup> Based on observations that adding cetuximab improved OS when added to both chemotherapy and definitive radiation in other solid tumors, the CALGB conducted a randomized phase II trial of pemetrexed (500 mg/m<sup>2</sup>) and carboplatin (AUC=5) and concurrent, daily thoracic radiation (70 Gy) with or without concurrent cetuximab in locally advanced NSCLC patients.<sup>37,38</sup> Patients received 4 cycles of pemetrexed/carboplatin with 4 additional planned cycles of pemetrexed alone. Those randomized to cetuximab began with a loading dose of 400 mg/m<sup>2</sup> followed by weekly cetuximab for an additional 6 weeks. The investigators found that the toxicity of the chemoradiation portion was feasible, but that only approximately 50% of patients received the planned 4 additional cycles of pemetrexed. The median survival in both arms was 22 months. The RTOG also added cetuximab to radiation for locally advanced NSCLC, but with weekly carboplatin/paclitaxel. This was a small phase II trial with a median survival of 22.7 months and a 2-year OS of 49%.<sup>39</sup> There were 5 events (grade 5) that appeared to be associated with larger lung treatment volumes.

**Table 5.** Survival Results and Grade 3/4 Toxicities for Regimens of Concurrent Chemotherapy and Radiation with and without Consolidation

Investigators	Regimen	Consolidation	Patients	Survival (months)	Esophageal	Lung
Albain et al <sup>30</sup>	Cisplatin/etoposide/radiation	None	50	15	20%	0%
Gandara et al <sup>31</sup>	Cisplatin/etoposide/radiation plus consolidation	Docetaxel at 75 mg/m <sup>2</sup> x 3 cycles	83	26	19%	5%
Hanna et al <sup>32</sup>	Cisplatin/etoposide/radiation	None	74	24.2	17.2%	1.4%
	Cisplatin/etoposide/radiation	Docetaxel x 3 cycles	73	21.6	17.2%	8.2%
Belani et al <sup>23</sup>	Weekly carboplatin/paclitaxel/radiation	None	91	13.0	3%	7%
	Weekly carboplatin/paclitaxel/radiation	Carboplatin (AUC=6)/paclitaxel 200 mg/m <sup>2</sup> x 2 cycles	92	16.3	28%	16%

Data also suggest that the EGFR tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib (Tarceva, Genentech/OSI Pharmaceuticals) can be safely added to radiation therapy without prohibitive toxicity, and EGFR TKIs have been incorporated into combined modality regimens.<sup>40-43</sup> Gefitinib was tested as consolidation therapy in unresectable stage III NSCLC patients. All patients received cisplatin/etoposide and concurrent radiation (SWOG 9019 regimen) followed by 3 courses of docetaxel. Patients whose disease had regressed or remained stable on this treatment were randomized to gefitinib or to placebo. OS and PFS were shorter in gefitinib treated patients, although there is no obvious explanation for this outcome. Attempts to provide an explanation indicate that increased toxicity from gefitinib does not appear to be the reason.<sup>44</sup>

The antiangiogenic agent bevacizumab has been shown to improve survival in advanced NSCLC patients receiving carboplatin and paclitaxel as first-line therapy.<sup>45</sup> Significant preclinical synergy with radiation has been seen with several inhibitors of vascular endothelial growth factor (VEGF) signaling including antibodies to VEGFR2, VEGFR/platelet derived growth factor (PDGFR) inhibitors, dual VEGFR/EGFR inhibitors, and VEGF trap.<sup>46-53</sup> Despite the theoretical concern for decreased oxygen delivery and subsequent decreased efficacy of radiation, anti-angiogenic therapies during radiation have been shown to increase tumor oxygenation due to blood vessel reorganization.<sup>51,54</sup>

Anti-angiogenic agents are currently being combined with radiation for NSCLC in clinical trials. How-

ever, initial reporting noted 2 tracheal-esophageal fistulas and cases of life threatening hemoptysis in trials that added bevacizumab to concurrent chemoradiation for small cell lung cancer. Socinski and coworkers<sup>55</sup> recently published preliminary data on a regimen combining bevacizumab and erlotinib with induction and concurrent chemotherapy with 75 Gy of radiation. With 20 patients enrolled, 2 patients developed pulmonary hemorrhage (grades 3 and 5); the regimen was considered safe enough to continue enrolling patients (Table 6).

Definitive chemotherapy/radiation trials have also begun to investigate escalating the radiation dose and adding additional chemotherapy drugs to the standard, platinum 2-drug regimen. Phase I and II trials suggest that the maximum tolerated dose is about 74 Gy. Furthermore, CALGB demonstrated that 74 Gy could safely be given with induction, full dose carboplatin and paclitaxel, and concurrent weekly carboplatin/paclitaxel dosing. One recent trial investigating the addition of irinotecan to carboplatin and paclitaxel required de-escalation of drugs due to neutropenia. The clinical benefit, however, was comparable to current commonly used regimens.<sup>56-58</sup> Clinical trials in NSCLC with full dose pemetrexed and cisplatin and daily radiation are also ongoing and the findings by Vokes and associates have already shown the feasibility of concurrent carboplatin/pemetrexed and radiation.<sup>34</sup>

**Combined Modality Treatment for Poor Risk Locally Advanced Patients**

Several groups of investigators have conducted phase II studies of combined modality in poor risk locally advanced

**Table 6.** Novel Chemoradiation Regimens

Investigators	Regimen	Radiation	Number patients
Siewart et al <sup>34</sup>	Carboplatin/pemetrexed	66 Gy	30
Govindan et al <sup>37</sup>	Carboplatin/pemetrexed/cetuximab	70 Gy	52 in cetuximab arm
Blumenschein et al <sup>39</sup>	Carboplatin/paclitaxel/cetuximab	63 Gy	93
Socinski et al <sup>55</sup>	Carboplatin/paclitaxel/bevacizumab/erlotinib	74 Gy	20

lung cancer patients. Two studies were conducted by SWOG investigators who classified patients who were not candidates for cisplatin therapy as poor risk individuals.<sup>59,60</sup> Some of the characteristics that resulted in a patient being classified as poor risk were related to cisplatin toxicity. These parameters included reduced kidney function, impaired hearing, reduced cardiac function, and the presence of peripheral neuropathy. Other criteria for classifying a patient as poor risk included impaired functional status (SWOG performance status of 2), poor nutritional status (recent weight loss >10% of usual body weight and/or serum albumin <.85 of the lower limit of normal), and reduced pulmonary function ( $1 \leq \text{FEV1} < 2.0$  liters with a predicted FEV1 of 0.8 liters in the contralateral lung). In the first trial, thoracic radiation was combined with simultaneous carboplatin and etoposide. The investigators found that this regimen was relatively well tolerated by poor risk locally advanced NSCLC patients.<sup>59</sup> The more recent SWOG trial utilized the same carboplatin, etoposide, and thoracic radiation regimen followed by 3 courses of docetaxel. Investigators found that there was unacceptable toxicity in poor risk locally advanced lung cancer patients during treatment with consolidation docetaxel.<sup>60</sup>

The RTOG conducted a randomized phase III trial of full dose thoracic radiation alone compared to the same radiation regimen and simultaneous beta interferon on poor risk locally advanced lung cancer patients.<sup>61</sup> The criteria for defining a patient as poor risk included Karnofsky performance status of greater than 50 and less than or equal to 70, or weight loss of 5% in the last 3 months. They observed increased toxicity and no survival advantage in patients who received radiation and interferon.

Recent randomized trials testing for combined modality therapy in locally advanced NSCLC excluded patients with an ECOG performance status of 2 or greater for patients with reduced pulmonary function, though variable cutoff levels of FEV1 (0.8 vs 2.0 L/sec) were being used to exclude patients. One of the studies excluded patients based on recent weight loss.<sup>23</sup> Currently, it appears that ambulatory performance status (ECOG 0–1) and adequate pulmonary function (FEV1  $\geq 0.8$  liters

per second) constitute the basis for selecting patients for combined modality treatment greater than 10% of their usual body weight, whereas nutritional status was not used as a selection criteria in other studies.

The prognostic implication of age, with elderly being defined as greater than 70 years of age, has been evaluated by a number of investigators.<sup>62–65</sup> Results of analyses utilizing recursive partitioning in locally advanced NSCLC patients treated in RTOG studies revealed 5 prognostic groups.<sup>63</sup> Age of greater than 70 years was included as a negative prognostic characteristic in 2 of the worse groups. Subsequently, several groups of investigators have evaluated performance status and comorbidities in multivariate analyses, and none of the investigators found that age alone was a significant negative prognostic factor.<sup>64,65</sup>

In stage IV NSCLC there is evidence that treatment with chemotherapy is tolerated relatively well in fit elderly patients.<sup>66</sup> However, it should be noted that the median age for lung cancer is 68 years and the median age for patients included in combined modality studies is 61–64 years, therefore suggesting that physician and/or patient bias may result in exclusion of older patients.<sup>23,24</sup> Recent population-based studies appear to support this possibility. Just under half of new lung cancer cases in the national Surveillance, Epidemiology and End Results (SEER) data base from 1998–2003 occurred in patients over the age of 70, with a 5-year OS rate of 5.1% for stage III patients over the age of 80.<sup>67</sup> A recent study by Edelman and colleagues suggested that older patients are less likely to receive combined modality treatment even when comorbidities and performance status are factored in.<sup>68</sup> They analyzed over 6,000 patients in the SEER database that were linked with Medicare claims for stage III NSCLC patients. Approximately 2/3 of total patients over the age of 65 received treatment and only 45% of those received both chemotherapy and radiation.

Currently it appears that ambulatory performance status (ECOG 0–1) and adequate pulmonary function (FEV1  $\geq 0.8$  liters per second) are the major criteria for selecting patients for combined modality treatment. Age alone, or comorbidities in patients with acceptable

performance status, should not exclude consideration of combined modality treatment.

### ***Potentially Resectable Locally Advanced NSCLC***

Survival of resectable stage IIIA patients was shown to be improved with neoadjuvant chemotherapy. A randomized trial using cyclophosphamide, cisplatin, and etoposide plus surgery versus surgery alone was stopped early due to the dramatic improvement in survival in the neoadjuvant chemotherapy arm (64 vs. 11 months,  $P < .008$ ).<sup>69</sup> Rosell and associates also showed the benefit of neoadjuvant mitomycin, cisplatin, and ifosfamide with surgery versus surgery alone with a median survival of 26 versus 8 months ( $P < .0001$ ).<sup>70</sup>

RTOG 8901 was the first large randomized trial to address the benefit of surgery in stage IIIA disease.<sup>71</sup> This trial randomized patients to sequential chemotherapy and radiation versus chemotherapy followed by surgical resection in mediastinoscopy-proven stage IIIA NSCLC patients. When phase II data from the SWOG suggested the feasibility of adding concurrent radiation to preoperative chemotherapy, RTOG 8901 was prematurely closed in order to improve accrual to the Intergroup 0139 trial that randomized patients to chemoradiation versus chemoradiation followed by surgical resection.<sup>72,73</sup> Results from the 73 evaluable patients in RTOG 8901 showed no benefit in the surgical arm. Van Meerbeeck and coauthors conducted a slightly different trial randomizing responders to induction chemotherapy to receive radiation versus surgical resection. In the trial, 321 patients were randomized and there was no survival benefit in the surgically resected group.<sup>74</sup>

In the Intergroup 0139 trial in resectable stage IIIA NSCLC, all patients received 2 cycles of cisplatin and etoposide with concurrent radiation up to 45 Gy and were then reassessed. Those without radiographic progression were randomized to receive either additional chemoradiotherapy or surgery. Both groups were consolidated with 2 additional cycles of chemotherapy. Surgery yielded an improvement in median PFS over definitive chemoradiotherapy (12.8 months vs 10.5 months,  $P = .017$ ) and a trend toward improved 5-year OS that did not reach statistical significance. Significant toxicity and perioperative mortality were associated with pneumonectomy (all surgical deaths but one), especially of the right lung. An unplanned subset analysis showed that patients receiving lobectomy had nearly double the 5-year OS as compared to matched patients in the definitive chemoradiotherapy arm (36% vs 18%,  $P = .002$ ). These results suggest consideration of surgery in IIIA disease if an anatomic lobectomy can be performed. Based on the Intergroup trial findings, caution is advised in performing pneumonectomies in patients with poor preoperative pulmonary function or right-disease.<sup>73</sup>

Since the Intergroup 0139 trial, smaller single-institution studies have produced favorable results also suggesting that the role of chemoradiation therapy followed by surgery may be beneficial. A retrospective review of stage III patients treated at the University of Toronto using a protocol similar to the Intergroup 0139 trial also found a high mortality rate with pneumonectomies. However, the deaths in this series were restricted to pneumonectomies defined as complex (ie, those requiring intrapericardial dissection secondary to bulky central disease).<sup>75</sup> Work from the University of Maryland showed that chemotherapy and hyperfractionated radiation therapy followed by surgery in patients with stage IIIA and IIIB disease, of which 22 of 29 patients who underwent resection were in the former stage, resulted in a median survival of 55.8 months when their lymph nodes were sterilized.<sup>76</sup> In this study, hyperfractionation of the radiation therapy allowed the investigators to increase the total dosage of radiation while maintaining a relatively safe morbidity profile with their trimodality approach.

A more definitive role for surgery, however, is with superior sulcus or Pancoast tumors. These tumors often invade nearby structures, including the chest wall, brachial plexus, subclavian vessels, vertebral bodies, and the stellate ganglion. Patients with superior sulcus tumors often present with symptoms including shoulder pain, brachial plexopathy, and Horner's syndrome (ipsilateral ptosis, meiosis, and anhidrosis). The involvement of important structures complicates surgical management. The currently accepted treatment paradigm for patients with this diagnosis was established by Intergroup 0160.<sup>77</sup> In this phase II trial, patients received cisplatin and etoposide with concurrent radiotherapy up to 45 Gy. Patients without disease progression then underwent surgical resection followed by consolidation chemotherapy. The overall 5-year survival was 54% for patients undergoing complete resection and 44% for patients with an incomplete resection. After the results of the Intergroup 0160 trial were published, the Japan Clinical Oncology Group (JCOG) published the results of their very similar trial. Although the JCOG utilized a different chemotherapy regimen of cisplatin, mitomycin, and vindesine, and a modified split course radiation therapy regimen with the same total dosage of 45 Gy, they were also able to demonstrate that the use of trimodality therapy benefited their patients with an overall 5-year survival of 56% (Table 7).<sup>78</sup>

Both of these landmark superior sulcus or Pancoast tumor studies included patients who fulfilled specific eligibility criteria including: 1) T3 or T4 disease involving the superior sulcus, 2) no evidence of N2 mediastinal disease either before or after neoadjuvant chemoradiation therapy, 3) absence of distant metastasis, and 4) good performance status. In both studies, induction therapy resulted in 76% of the patients ultimately proceeding to

**Table 7.** Pancoast/Superior Sulcus Tumor Regimens

Investigators	Chemotherapy	Radiation	Number patients	5-year OS
Rusch et al <sup>77</sup>	Cisplatin/etoposide	Concurrent 45 Gy	110	54% *
Kunitoh et al <sup>78</sup>	Cisplatin/mitomycin/vindesine	Split course concurrent 45 Gy	76	56%

\* 54% 5-year overall survival in patients with complete resection with 44% survival in those unable to have complete resection.

OS=overall survival

resection. The Intergroup 0160 study obtained complete surgical resection in 94% of T3 lesions and 96% of T4 lesions. The JCOG group had a lower incidence of complete resection, with 78% of T3 lesions and 40% of T4 lesions. The JCOG study differed in that patients with ipsilateral supraclavicular involvement, N3 disease, without mediastinal lymph node involvement still went on to resection.

Due to the substantial success associated with these trials, the eligibility criteria have generally been extrapolated to become the current guidelines for resectability. Currently, there is no consensus opinion regarding the role of surgery in patients with superior sulcus tumors and positive mediastinal lymph nodes, and thus this may have to be readdressed in the near future.

## Conclusion

The backbone of the treatment of stage III NSCLC is radiation with concurrent full-dose chemotherapy, though median survivals remain low. Low-dose weekly chemoradiation and consolidation chemotherapy offer no proven benefit to a strategy of radiation with concurrent full-dose chemotherapy. An ongoing study in nonsquamous stage III NSCLC patients is comparing the novel full-dose regimen of pemetrexed/cisplatin with etoposide/cisplatin, both with concurrent thoracic radiation. When given simultaneously with radiation, anti-EGFR compounds appear safe, and the efficacy of this strategy awaits results of randomized clinical trials to detect a survival benefit. Anti-angiogenic agents such as bevacizumab and sorafenib should not be tested outside of a carefully constructed clinical trial. The role of surgical resection following concurrent chemotherapy and radiation has yet to be resolved though post-treatment lobectomies, and select pneumonectomies by experienced surgeons may be considered.

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