

Neoadjuvant Chemotherapy in Stage III NSCLC

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Key Words

Neoadjuvant chemotherapy, non-small cell lung cancer, review

Abstract

Non-small cell lung cancer (NSCLC) continues to be the leading cause of cancer-related mortality in the United States. Current standard care for treating NSCLC is surgical resection, when feasible, followed by adjuvant chemotherapy in stages II and III. Neoadjuvant or induction chemotherapy may have several potential advantages compared with adjuvant chemotherapy and has been evaluated in randomized and nonrandomized clinical trials in NSCLC. This article reviews the data for neoadjuvant chemotherapy in NSCLC with a particular focus on regionally advanced disease (stage III) that is still amenable to surgical resection. (*JNCCN* 2008;6:285–293)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- List the potential benefits of neoadjuvant chemotherapy for non-small cell lung cancer (NSCLC)
- Identify the efficacy of neoadjuvant chemotherapy in trials of patients with stage III NSCLC
- Describe the safety of neoadjuvant chemotherapy for patients with stage III NSCLC
- Specify factors that may predict a higher rate of response to neoadjuvant chemotherapy among patients with NSCLC

Lung cancer continues to be the leading cause of cancer-related mortality in the United States, accounting for more deaths than the next 3 leading causes combined (colorectal, breast, and prostate). More than 213,000 cases of newly diagnosed lung cancer and more than 160,000 deaths were estimated to occur in the United States in 2007.¹ Lung cancer is largely a preventable disease; cigarette smoking contributes to nearly 90% of cases. Although screening trials have not yet shown conclusive evidence of a decrease in mortality, trials aimed at reducing cigarette consumption have found a corresponding decrease in the risk for future lung cancer.² Among lung cancer cases, 85% are non-small cell (NSCLC), which includes adenocarcinoma,

squamous cell carcinoma, and large cell carcinoma. Although surgery is considered the mainstay of therapy for early-stage NSCLC, most patients present with either metastatic or locally advanced disease not amenable to surgical resection. Furthermore, most patients with early-stage disease will ultimately experience relapse and die of lung cancer. Currently, the estimated overall 5-year survival for patients with NSCLC is 16%, a sobering reminder of the immense public health problem that lung cancer poses.

Stage III NSCLC represents a heterogeneous group of cases. Tumors that have penetrated through the pleural envelope with any lymph node involvement (T3–4 N1–2), involvement of lymph nodes beyond the pleural reflection (T1–4 N2–3), and tumors which have invaded critical structures or have a malignant pleural effusion with or without lymph node involvement (T4 N0–3) are all considered stage III. However, estimated 5-year survival with T3 N1 disease (stage IIIA) may be as high as 20% to 25%, whereas it is only 3% to 5% with T4 N3 disease (stage IIIB). Proposed revisions in the AJCC staging system were announced at the 12th Annual World Conference on Lung Cancer in September 2007 that will address some of these inequities. Patients with stage III disease are frequently evaluated for resection potential and enrolled in separate clinical trials of multimodality therapy. However, this categorization of individual patients is not uniform and is subject to the biases of the evaluating surgeon.

For patients with unresectable disease, the NCCN guidelines currently recommend definitive chemoradiotherapy (except for those with malignant pleural effusions, who should be treated with palliative intent; see NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer, page 228). This article focuses on patients who are potentially resectable and on trials involving neoadjuvant chemotherapy followed by surgical resection as opposed to trimodality approaches involving the concurrent or sequential addition of radiotherapy.

Despite the success of surgery as single-modality therapy in early-stage lung cancer, surgery alone in patients with stage III disease has had limited success, largely because of the high rate of occult micrometastatic disease at presentation. Several authors have shown that patients with clinical evidence of ipsilateral mediastinal lymph node involvement (N2) have a 5-year survival of only 3% to 8% with surgery alone.^{3,4} A meta-analysis of chemotherapy benefit in NSCLC published

in 1995 showed an absolute improvement in 5-year survival of 5% favoring postoperative (adjuvant) platinum-based chemotherapy, although with a nonsignificant *P* value (*P* = .08).⁵ Based on this finding, several large prospective trials were initiated to evaluate adjuvant therapy in NSCLC.^{6–10} Many of these trials have shown a survival advantage with adjuvant chemotherapy and are summarized elsewhere in this issue.

Neoadjuvant (preoperative) chemotherapy may have several potential advantages over adjuvant chemotherapy, particularly in stage III disease, which has a high risk of distant failure. Neoadjuvant chemotherapy attacks micrometastases earlier in the course of treatment. Additionally, the ability to deliver full doses of planned chemotherapy in NSCLC is often compromised postoperatively. Treating patients with neoadjuvant chemotherapy increases the likelihood of being able to deliver adequate systemic doses of chemotherapy, and does so while the tumor vasculature is still intact. It also provides an opportunity to assess the *in vivo* chemosensitivity of the primary lesion and nodal metastases, allowing unparalleled opportunities for translational research. For patients who respond to neoadjuvant therapy, “downstaging” may increase the likelihood of complete resection, organ preservation, and long-term survival. Lastly, patients with progressive disease on neoadjuvant chemotherapy may be spared the morbidity of a thoracotomy, which would have proven futile.

Nonrandomized Trials of Neoadjuvant Chemotherapy

Numerous phase II studies have evaluated neoadjuvant chemotherapy in stage III NSCLC. Table 1 shows selected trials. Early experiences with combination chemotherapy regimens such as MVP (mitomycin, vindesine, and cisplatin) and the modified MVP400 (increased dose intensity of cisplatin) established the feasibility of neoadjuvant chemotherapy in NSCLC. Response rates were as high as 77% and operability was not impaired. Of patients who experienced a complete pathologic response to induction MVP, 5-year survival was 56%, far exceeding expected survival.^{11,12}

Newer trials using third-generation chemotherapy agents have documented their activity and safety. The Bimodality Lung Oncology Team (BLOT) phase II trial of induction chemotherapy with 2 cycles of paclitaxel

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Table 1 Selected Nonrandomized Trials of Neoadjuvant Chemotherapy

Trial	Number of Patients (Stage III)	Chemotherapy	Response Rate	pCR	Complete Resection	PFS	OS (Median)	5-Y Survival
Martini et al. ¹¹	136 (136)	MVP	77%	14%	65%*	NR	19 mo	17%
Ng et al. ¹²	37 (37)	MVP400	65%	5%	67% [†]	NR	17 mo	NR
Pisters et al. ¹³	94 (7)	Carboplatin Paclitaxel [‡]	56%	6%	92%	NR	NR	NR
Lorent et al. ¹⁴	131 (131)	VIP	54%	9%	89%	NR	24 mo	21%
Betticher et al. ¹⁵	90 (90)	Cisplatin Docetaxel	66%	16%	48%	11.7 mo (EFS)	27.6 mo	NR
Van Zandwijk et al. ¹⁸	47 (47)	Gemcitabine Cisplatin	70.2%	NR	71% [§]	NR	18.9 mo	NR
Migliorino et al. ¹⁹	70 (70)	Gemcitabine Cisplatin	57.1%	3%	97% [¶]	12.6 mo (TTF)	14.5 mo	NR
De Marinis et al. ²⁰	49 (49)	Gemcitabine Paclitaxel Cisplatin	73.5%	16%	55%**	17.8 mo (TTP)	23 mo	NR

Abbreviations: EFS, event-free survival; MVP, mitomycin-C, vindesine, platinum; MVP400, dose-intense cisplatin with mitomycin and vinblastine; NR, not recorded; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; TTF, time to treatment failure; TTP, time to treatment progression; VIP, vindesine, ifosfamide, platinum.

*Complete resection rate in patients with major response to chemotherapy was 78%.

[†]Complete resection rate was 80% (20/25) in patients with stage IIIA NSCLC.

[‡]Two cycles of carboplatin/paclitaxel were given preoperatively and an additional 3 cycles postoperatively for patients experiencing response.

[§]Only 17 patients were randomized to surgery based on response to induction chemotherapy.

[¶]Complete resection rate was 93% (27/29) in patients undergoing thoracotomy.

**Only 27 patients underwent resection.

and carboplatin in patients with early-stage NSCLC (7/94 patients were stage IIIA) showed that nearly all patients could complete both cycles of induction therapy and 92% (81/88) who underwent surgical exploration could undergo complete resection (R0). This trial included planned postoperative chemotherapy, but only 42 of 66 (64%) patients were able to complete postoperative therapy. Treatment-related mortality occurred in 3 patients, 1 during induction chemotherapy and 2 postoperatively.¹³ A follow-up randomized phase III trial was subsequently completed and is discussed later.

The Leuven Lung Cancer Group published their experience with 3 cycles of preoperative VIP (vindesine, ifosfamide, and cisplatin) followed by local therapy based on response to chemotherapy (surgery vs. radiotherapy). Responses were seen in 54% of patients, and 34 of 70 patients who underwent complete resections were downstaged to pN0 or pN1 with chemotherapy. Patients who responded to therapy had an overall median survival of 38 months and a 5-year survival of 30%.¹⁴ A similar phenomenon was seen with induction docetaxel and cis-

platin in patients with biopsy-proven N2 disease. Downstaging to N0 or N1 was prognostic and significantly prolonged event-free and overall survival ($P = .0001$ for overall survival). Three-year survival for patients with mediastinal downstaging was 61% compared with 11.3% for those with residual mediastinal disease.¹⁵ CALGB conducted a phase II trial of induction cisplatin plus vinblastine followed by surgery, adjuvant cisplatin plus vinblastine, and thoracic irradiation (CALGB 8935), which similarly showed that patients without residual N2 disease had a median failure-free interval of 47.8 months compared with 8.2 months for patients with residual N2 disease ($P = .01$).¹⁶ A separate retrospective review of 103 patients with pathologic N2 disease who underwent either induction chemotherapy or chemoradiotherapy found that for 29 patients who were downstaged to N0 (18 underwent induction platinum-based chemotherapy, 8 radiotherapy, and 3 chemoradiotherapy), 5-year survival was 35.8% compared with only 9% for those with persistent nodal involvement (25 patients had N1 and 49 had N2 residual disease; $P = .023$).¹⁷

Other trials incorporating gemcitabine and cisplatin, with or without paclitaxel, showed this approach to be safe and effective. An every-4-week schedule of gemcitabine and cisplatin produced mediastinal downstaging in 53% of patients who ultimately underwent surgical resection.¹⁸ Gemcitabine and cisplatin given every 3 weeks was equally safe and produced a response rate of 68.1% in patients with stage IIIA disease. Nearly all patients undergoing surgery were able to undergo a complete resection (R0).¹⁹ The addition of paclitaxel to induction cisplatin and gemcitabine in patients with stage IIIA disease (pN2) produced a response rate of 73.5%, with an additional 4 patients having stable disease with mediastinal clearance. Nonhematologic grade 4 toxicity was only seen in 4% of patients (diarrhea), and the complete resection rate was 93% (27/29). Mediastinal lymph nodes were clear in 35% of patients and 8 pathologic

complete responses (16%) were seen. At publication, median survival was 23 months.²⁰

Randomized Trials of Neoadjuvant Therapy

Based on early encouraging results in the phase II setting, many randomized trials were initiated to evaluate neoadjuvant therapy in stage III NSCLC (see Table 2). Much enthusiasm was generated by early randomized trials by Roth et al.²¹ and Rosell et al.,²² both found a survival advantage favoring neoadjuvant chemotherapy. Roth et al.²¹ initially published in 1994. Patients underwent 6 cycles of perioperative cisplatin, cyclophosphamide, and etoposide (3 cycles prior to and 3 cycles after surgery only in patients who experienced tumor regression from their preoperative chemotherapy). Sixty patients were enrolled, but the trial was stopped after

Table 2 Selected Randomized Trials of Neoadjuvant Chemotherapy

Trial (Reference)	Number of Patients (Stage III)	Chemotherapy	Response Rate	pCR	Complete Resection	PFS	OS	5-Y Survival
Rosell et al. ^{22,24}	60 (60)	Mitomycin Ifosfamide Cisplatin	60%	4%	85%	12 vs. 5 mo (DFS; <i>P</i> = .006)	22 vs. 10 mo (<i>P</i> = .005)	16% vs. 0%
Roth et al. ^{22,23}	60 (60)	Cyclophosphamide Etoposide Cisplatin	35%	NR	39% vs. 31%	Not reached vs. 9 mo (<i>P</i> = .006)	64 vs. 11 mo (<i>P</i> = .008)	56% vs. 15%*
Pass et al. ³⁴	27 (27)	Etoposide Cisplatin	62%	8%	85% vs. 86%	12.7 vs. 5.8 mo (<i>P</i> = .083)	28.7 vs. 15.6 mo (<i>P</i> = .095)	NR
Nagai et al. ²⁸	62 (62)	Cisplatin Vindesine	28%	0%	65% vs. 77%	NR	17 vs. 16 mo (<i>P</i> = .5274)	10% vs. 22%
Gilligan et al. ²⁶	519 (80)	Platinum-based [†]	49%	4%	82% vs. 80%	NR	54 vs. 55 mo (<i>P</i> = .86)	44% vs. 45%
Depierre et al. ²⁵	355 (167)	Mitomycin Ifosfamide Cisplatin	64%	11%	92% vs. 86%	26.7 vs. 12.9 mo (<i>P</i> = .033)	37 vs. 26 mo (<i>P</i> = .15)	43.9% vs. 35.3% [‡]
Pisters et al. ²⁹	354 (113 [§])	Carboplatin Paclitaxel	41%	NR	94% vs. 89%	33 vs. 21 mo (<i>P</i> = .07)	75 vs. 46 mo (<i>P</i> = .19)	50% vs. 43%
Sorensen et al. ³⁰	90 (NR)	Paclitaxel Carboplatin	46%	0%	79% vs. 70%	NR	34.4 vs. 22.5 mo (NS)	36% vs. 24% (NS)
Mattson et al. ³⁵	274 (274)	Docetaxel	28%	NR	77% vs. 76% [¶]	9 vs. 7.6 mo (NS)	14.8 vs. 12.6 mo (NS)	NR

Abbreviations: DFS, disease-free survival; NR, not recorded; NS, not significant; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival.

*3-year survival.

[†]Options included MVP (mitomycin-C, vindesine, platinum), MIC (mitomycin, ifosfamide, and cisplatin), NP (cisplatin and vinorelbine), PacCarbo (paclitaxel and carboplatin), GemCis (cisplatin and gemcitabine), and DocCarbo (docetaxel and carboplatin).

[‡]4-year survival.

[§]113 patients were reported as stage IIB or IIIA (32%).

[¶]22 and 29 patients had resectable disease in the chemotherapy and control arms, respectively.

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an unplanned interim analysis found a statistically significant improvement in survival favoring the chemotherapy arm. Median survival of patients who underwent chemotherapy was reported to be 64 months, compared with 11 months for patients who underwent surgery alone ($P < .008$, log-rank test).²¹

In 1998, they published a long-term follow-up after a median of 82 months.²³ The survival advantage persisted, but narrowed to 21 versus 14 months ($P = .056$, log-rank test). Overall 3- and 5-year survivals were 43% and 36% for the neoadjuvant arm compared with 19% and 15% for the surgery-alone arm, respectively. For patients who underwent resection, median survival for the perioperative group had not been reached; it was 18.8 months for the surgery-alone group. For patients with unresectable NSCLC, median survival was 12 months for the perioperative group versus 7 for the surgery-alone arm.²³ Some have criticized this trial, however, because the surgery-alone arm had a disproportionate number of patients with stage IIIB disease compared with the chemotherapy arm and the outcome of the surgery-alone arm was somewhat lower than expected.

Rosell et al.²² randomized 60 patients with stage IIIA NSCLC (T1–3 N0–2) to surgery alone or 3 courses of chemotherapy (mitomycin, ifosfamide, and cisplatin) followed by surgery. Patients in both treatment groups also underwent mediastinal radiation (50 Gy) approximately 4 weeks after surgery. Median survival of patients treated with chemotherapy plus surgery was 26 months compared with 8 months for surgery alone ($P < .001$). Recurrence was reduced from 74% in the surgery-alone arm to 56% in the chemotherapy-plus-surgery arm, despite a higher number of patients with N2 disease in the chemotherapy-plus-surgery arm (25/30 vs. 19/30).²² Updated results published in 1999 continued to show a survival advantage favoring preoperative chemotherapy, although the margin was a more modest 22 versus 10 months ($P = .005$, log-rank test).²⁴ In patients who underwent a postchemotherapy mediastinoscopy, 32% had evidence of tumor downstaging. Overall 3- and 5-year survival rates were 20% and 17% compared with 5% and 0% in the surgery arm. The chemotherapy arm had 5 long-term survivors, 4 of whom had been downstaged with preoperative chemotherapy.²⁴

In one of the largest neoadjuvant trials, 353 patients with stage I (except T1 N0), II, or IIIA NSCLC

(167 with stage IIIA) were randomized to receive 2 cycles of preoperative chemotherapy (mitomycin, ifosfamide, and cisplatin) versus primary surgery alone.³⁵ Patients who responded underwent an additional 2 cycles of postoperative chemotherapy, and all patients with pT3 or pN2 disease also underwent postoperative thoracic irradiation. Median survival was 37 months in the preoperative chemotherapy arm compared with 26 months for primary surgery ($P = .15$). However, 2 preoperative toxic deaths occurred, and treatment-related mortality was 6.7% in the chemotherapy arm. Among those who underwent chemotherapy, responses were seen in 64% (complete response, 11%; partial response, 53%). Distant recurrences were significantly reduced in the chemotherapy arm (relative risk, 0.54; 95% CI, 0.33–0.88; $P = .01$), whereas the risk for locoregional failure was similar in both arms.²⁵

The recently published results of the MRC LU22/NVALT 2/EORTC 08012 randomized trial of preoperative chemotherapy in patients with stage I, II, or IIIA NSCLC also did not find a statistically significant advantage for neoadjuvant chemotherapy.²⁶ A total of 519 patients were randomized to 3 cycles of chemotherapy followed by surgery or surgery alone. Although several different chemotherapy regimens were allowed, all were platinum-based, and some included third-generation chemotherapy agents. At surgery, 47 patients were found to have pathologic IIIA disease and 33 had pathologic IIIB disease. No evidence was seen of a benefit in overall survival (hazard ratio [HR], 1.02; 95% CI, 0.80–1.31; $P = .86$), but when the authors added the results of this trial to previous trials of neoadjuvant therapy^{23–25,27–31} in a systematic review, a relative benefit of 12% was seen that corresponded to an absolute 5% improvement in 5-year survival, not unlike the results found by the 1995 meta-analysis of chemotherapy and the International Adjuvant Lung Cancer Trial.^{5,6} Additionally, the authors postulated that the treatment effect may have been underestimated because the surgery-alone arm performed better than expected, and that further follow-up may provide a better statistical representation because the current CIs are wide due to the low number of events.

The subsequent phase III randomized trial that followed the BLOT phase II design evaluated 354 patients with early-stage lung cancer (S9900), including stage IIIA (30% were IIB or IIIA). The results of this trial have not been finalized, but a recent update showed that

progression-free and overall survival favored induction chemotherapy; median progression-free survival was 33 vs. 21 months (HR 0.79 [0.60–1.04], $P = .098$) and overall survival was 50 vs. 47 months (HR 0.83 [0.61–1.14], $P = .24$) after 52 months of median follow-up.²⁹

Two recent meta-analyses of neoadjuvant chemotherapy in patients with resectable NSCLC have been published.^{32,33} Based on the 6 trials^{23–25,27,28,34} that were included in the meta-analysis by Berghmans et al.,³² and looking specifically at patients with stage III disease, a trend favoring neoadjuvant chemotherapy was observed but did not reach statistical significance (HR, 0.65; 95% CI, 0.41–1.04). Across all stages, however, a significant improvement in overall survival was seen with neoadjuvant therapy (HR, 0.69; 95% CI, 0.57–0.84). Burdett et al.³³ used a slightly different collection of trials^{23–25,27,28,30,31} and found an absolute survival benefit of 6%, increasing overall 5-year survival from 14% to 20% (HR, 0.82; 95% CI, 0.69–0.97; $P = .02$). These analyses mirror the positive effect seen in the pooled analysis performed by Gilligan et al.,²⁶ which incorporates the more recent results from MRC LU22/NVALT2/EORTC 08012.

Two other early trials of neoadjuvant chemotherapy by Dautzenberg et al.²⁷ and Pass et al.³⁴ were very limited in accrual, and definitive conclusions are not possible. Similarly, a phase III trial from Scandinavia was recently reported that randomized patients with early-stage NSCLC (including T3 N0–1) to 3 cycles of induction carboplatin and paclitaxel followed by surgery or to surgery alone. Unfortunately, this trial was designed to accrue 280 patients but was closed early because of slow accrual after only 44 patients. Patients who underwent chemotherapy plus surgery had a 12% improvement in 5-year survival and a 12-month improvement in median survival, but this did not reach statistical significance.³⁰

Single-agent induction chemotherapy with docetaxel has also been evaluated in a phase III trial.³⁵ Locoregional therapy in this trial was more likely to consist of radiotherapy rather than surgery, and the overall median survival was only 14.8 months with docetaxel and 12.6 months without ($P =$ nonsignificant). The Japanese Clinical Oncology Group trial also failed to find an advantage to neoadjuvant chemotherapy (JCOG 9209). Patients with potentially resectable stage IIIA (N2) disease were randomized to induction chemotherapy with 3 cycles of cisplatin and vindesine followed by surgery or to surgery alone. A total of 62 patients were accrued and

evenly split between the arms. The trial failed to show a survival difference between the groups, but the response rate to induction chemotherapy was only 28% with no pathologic complete responses and only 71% of patients completed their planned chemotherapy. Median survival was 17 months in the induction arm compared with 16 months in the surgery-alone arm ($P = .527$).²⁸

Discussion

Neoadjuvant chemotherapy has several potential advantages to adjuvant chemotherapy. In NSCLC, where the ability to deliver full doses of planned chemotherapy is often limited, it seems logical to deliver systemic therapy before surgery. Randomized and non-randomized trials have shown efficacy in stage III NSCLC, but many have been compromised by heterogeneity in patient eligibility, nonuniform use of radiotherapy, and differences in the proportion of patients treated with surgery. Even in trials strictly involving stage III disease, standardization of inclusion criteria has been lacking, causing prognostically disparate subgroups of patients to be studied simultaneously.

Nonetheless, the findings of the Lung Adjuvant Cisplatin Evaluation (LACE)³⁶ and those of Bria et al.³⁷ clearly suggest that patients with stage III NSCLC can benefit from chemotherapy. Neoadjuvant chemotherapy has been shown to be safe, improves the odds of delivering full doses of planned chemotherapy, and does not compromise operability.³⁸ The meta-analyses by Berghmans et al.³² and Burdett et al.³³ and the systematic review by Gilligan et al.²⁶ all found a survival advantage favoring neoadjuvant therapy. Importantly, however, the total number of patients enrolled on randomized neoadjuvant chemotherapy trials is fewer than the number entered on the largest randomized adjuvant trial, the International Adjuvant Lung Cancer Trial (IALT)⁶ and the 2 largest randomized neoadjuvant trials^{25,26} did not find statistically significant improvements in overall survival, at least with current follow-up.

Though third generation chemotherapy agents have improved response rates in the neoadjuvant setting, there may still be significant biological heterogeneity within NSCLC. Molecular signatures may ultimately prove useful in tailoring the choice of chemotherapy regimen to the individual patient. One such example was seen in a recent study involving 67 patients with resected stage IIB, IIIA, or IIIB NSCLC who were treated with neoadjuvant gemcitabine and

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cisplatin. Low expression of ribonucleotide reductase subunit 1 (RRM1) was associated with a significant benefit from neoadjuvant therapy.³⁹ In patients with advanced NSCLC treated with docetaxel and cisplatin, a single nucleotide polymorphism (SNP) at base pair 188 in the excision repair cross-complementing 1 (ERCC1) gene was found to be associated with improved survival.⁴⁰ Although low ERCC1 expression in tumors may independently select for patients with a greater likelihood of benefit from cisplatin, the combination of low ERCC1 and RRM1 expression may predict for prolonged survival.⁴¹ These gene signatures may some day allow for a priori selection of chemotherapy agents that are most likely to produce a response in a given tumor. This approach is being incorporated into the design of new adjuvant trials.

However, even if the optimal chemotherapy regimen could be chosen, selecting patients most likely to benefit from surgery after neoadjuvant chemotherapy remains clinically challenging. Several authors have shown that mediastinal lymph node clearance portends improved overall survival after neoadjuvant chemotherapy.^{14,16,17} Unfortunately, standard radiographic techniques such as CT and even PET-CT may be limited in their ability to accurately predict lymph node clearance preoperatively.⁴² Repeat mediastinoscopy may be able to accurately predict patients who should undergo definitive surgery.⁴³⁻⁴⁵ However, a prospective comparison of PET-CT with repeat mediastinoscopy found that PET-CT outperformed repeat mediastinoscopy, although repeat mediastinoscopy was limited by adhesions and fibrosis in several patients in this particular trial.⁴⁶ Endoscopic ultrasound with fine needle aspiration (EUS-FNA) has also been evaluated and found to be effective, although its availability may be limited to large academic medical centers.⁴⁷ Thus, the ability to detect patients who are most likely to benefit from surgical resection may be limited without definitive surgical pathologic evaluation.

It is, therefore, difficult to draw definitive conclusions about neoadjuvant chemotherapy in stage III NSCLC, except that it appears to be safe and does not impair surgical resection. Existing data suggest that patients who are downstaged with neoadjuvant chemotherapy may have a survival advantage compared with those with residual mediastinal disease, and more molecular signatures may some day allow for the individualization of chemotherapy to increase the likelihood of mediastinal downstaging. Currently, however,

neoadjuvant chemotherapy cannot be considered the standard approach until randomized comparisons with adjuvant chemotherapy establish its superiority or, at a minimum, noninferiority. Such a trial may not be feasible, as a recent attempt to randomize patients to neoadjuvant versus adjuvant chemotherapy with 3 cycles of cisplatin plus docetaxel failed to meet accrual goals (Chandra Belani, Personal communication). One also must not lose sight of the importance of smoking cessation programs and early detection techniques to decrease mortality from this largely preventable disease.

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Neoadjuvant Chemotherapy in Stage III NSCLC

Neoadjuvant Chemotherapy for NSCLC

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- Which of the following is *not* a potential advantage of neoadjuvant chemotherapy for non-small cell lung cancer (NSCLC)?
 - The ability to provide full doses of chemotherapy unlimited by postoperative complications
 - Treatment with chemotherapy with the tumor vasculature intact
 - The opportunity to record in vivo tumor sensitivity to chemotherapy
 - The chance to use urgent thoracotomy for patients with progressive disease on chemotherapy
- Which of the following statements summarizing the efficacy of neoadjuvant chemotherapy in randomized trials of the treatment of stage III NSCLC is *most* accurate?
 - There are consistent improvements in statistically significant progression-free and overall survival associated with neoadjuvant chemotherapy
 - Neoadjuvant chemotherapy has consistently improved only overall survival
 - Neoadjuvant chemotherapy has significantly improved survival rates only in some studies
 - Neoadjuvant chemotherapy has not been shown to improve survival
- Which of the following statements in regard to the tolerability and safety of neoadjuvant chemotherapy for patients with stage III NSCLC is *most* accurate?
 - Neoadjuvant chemotherapy does not appear safe enough to use routinely
 - Neoadjuvant chemotherapy compromises the operability of the patient
 - Neoadjuvant chemotherapy at full doses is unsafe before surgery
 - Neoadjuvant chemotherapy appears safe and does not adversely affect the operability of the patient
- Which of the following combinations of factors predicts an improved rate of response of NSCLC to neoadjuvant chemotherapy?
 - Low levels of both ribonucleotide reductase subunit 1 (RRM1) and excision repair cross-complementing 1 (ERCC1)
 - High levels of RRM1 and low levels of ERCC1
 - Low levels of RRM1 and high levels of ERCC1
 - High levels of both RRM1 and ERCC1

Activity Evaluation

1. The activity supported the learning objectives.

Strongly Disagree			Strongly Agree		
1	2	3	4	5	

2. The material was organized clearly for learning to occur.

Strongly Disagree			Strongly Agree		
1	2	3	4	5	

3. The content learned from this activity will impact my practice.

Strongly Disagree			Strongly Agree		
1	2	3	4	5	

4. The activity was presented objectively and free of commercial bias.

Strongly Disagree			Strongly Agree		
1	2	3	4	5	