Induction Chemotherapy for Resectable Non–Small-Cell Lung Cancer

Published on Physicians Practice (http://www.physicianspractice.com)

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Lung cancer remains the leading cause of cancer death in American men and women. Non–small-cell lung cancer (NSCLC) accounts for 85% of these cases. Although surgery is the best curative approach for resectable NSCLC, long-term survival for patients with operable disease remains poor. More than half of patients who initially present with stage I to IIIA disease experience relapse of metastatic disease. Postoperative adjuvant therapy has been evaluated in several randomized trials, and provides a survival benefit. It appears reasonable to look to induction chemotherapy, or preoperative chemotherapy, to provide a similar improvement in survival with early treatment of micrometastatic disease. Multiple trials of induction therapy have been carried out with encouraging results. The use of various induction regimens with chemotherapy alone or chemotherapy combined with radiotherapy for stage IIIA NSCLC is under investigation. Randomized trials are under way to better define the role of induction therapy in the multimodality treatment of NSCLC.

An estimated 173,000 men and women in the United States will develop lung cancer in 2004, of whom 160,000 will die. Non–small-cell lung cancer (NSCLC) accounts for approximately 85% of these cases. Despite advances in therapy and attempts at prevention through smoking cessation programs, limited advertising, and restricted public smoking, lung cancer continues to be the leading cause of cancer death in the United States. Unfortunately, the majority of patients with NSCLC will present with advanced, incurable disease. At presentation, approximately 30% of patients will have stage I or II disease that is potentially curable by surgery, and an additional 25% to 30% of patients will have locally advanced disease (stage III) that is generally treated with combined-modality therapy. Treatment Background

Standard Surgical Treatment

For patients with early-stage NSCLC (clinical stage I/II), lobectomy or pneumonectomy with mediastinal sampling or lymphadenectomy is the optimal treatment modality for the potential cure of patients and may result in a 5-year survival ranging from 67% in patients with pathologic T1, N0 disease to 38% in patients with pathologic T3, N0 disease. Clinical staging often understages NSCLC, particularly if newer modalities such as positron-emission tomography (PET) scanning are not utilized. As a result, patients with disease at a given clinical stage fare much worse than those at the corresponding pathologic stages. The majority of patients with stage III NSCLC evaluated for resection have a disease extent that precludes immediate curative surgery. However, even in patients who are immediately resectable, those with pathologic T1-3, N2 disease (stage IIIA) have a 5-year survival of only 23%. Moreover, when bulky mediastinal involvement is noted on chest radiography, 3-year survival is dismal-less than 10%. Although in all of these patients disease is confined to the chest at onset and can be removed surgically, the vast majority suffer from recurrent NSCLC and ultimately die of metastatic disease.
Adjuvant Approaches

In order to improve on the disappointing results of surgery alone, investigators have focused on chemotherapy and radiotherapy in addition to surgery. The majority of historical clinical trials examining adjuvant (ie, postoperative) therapy have not found unequivocal, reproducible evidence of efficacy for adjuvant chemotherapy.\[5-7\] However, a meta-analysis of 14 trials including over 4,000 patients and comparing postoperative chemotherapy with no further therapy demonstrated a survival advantage for chemotherapy regimens containing cisplatin.\[8\] More recently, a large randomized study showed that cisplatin-based adjuvant chemotherapy improves survival by 4% at 5 years.\[9\] More recently, two trials in early-stage homogeneous populations demonstrated significant survival benefits in patients treated with platin-based adjuvant chemotherapy.\[10, 11\]

Induction Therapy

Given this uncertainty, chemotherapy prior to surgery, or induction therapy, has been the subject of ongoing investigations. Induction therapy has been attractive to clinicians because regression of the primary tumor to chemotherapy serves as a surrogate marker for the control of clinically undetectable metastases. In fact, consistently higher response rates and better tolerability have been noted in locally advanced disease than in metastatic NSCLC.\[12-14\] Notably, a complete pathologic response rate of 13% has been reported in early clinical studies of induction chemotherapy.\[15\] Thus, chemotherapy given before surgery has the potential to allow for assessment of tumor response to chemotherapy, to treat micrometastatic disease early, to facilitate the complete eradication of lesions, and to provide better dose delivery with fewer treatment interruptions. Additionally, decreasing tumor size may improve resectability and decrease the morbidity of resection.

Resectable NSCLC

Patients with stage I/II NSCLC can generally undergo immediate surgery with curative intent. Although patients with stage III disease have no evidence of distant metastases and are viewed as potentially curable, their prognosis is generally poor, and the overwhelming majority die of their disease. Stage IIIA encompasses patients for whom extended surgery can remove all known sites of disease. Patients with stage IIIB disease are frequently considered unresectable, because of contralateral mediastinal lymph node involvement (N3) or extensive tumor invasion (T4) that requires specialized surgical techniques to accomplish complete resections. A carefully selected subset of patients with T4 disease may be suitable for surgical resection. The basic division between stage IIIA and IIIB NSCLC was established in the 1980s.\[3\] However, in the 1997 revision of the International Staging System, patients with T3, N0 disease were reclassified as having stage IIIB because their survival was almost identical to patients with T2, N1 tumors. This grouping complicates interpretation of stage III trials before 1997, because treatment groups with T3, N0 patients have improved outcomes. Furthermore, within stage IIIA disease there is significant variability that can have an impact on prognosis. Larger tumors and multiple involved
lymph node stations result in worse survival.[16-19] **Staging NSCLC Computed Tomography**

Patients with potentially resectable NSCLC, especially those with stage III disease, benefit from rigorous staging evaluation prior to therapy. Computed tomography (CT) scanning is critical in evaluating the location and extent of the primary tumor. CT scans, however, may underestimate mediastinal lymph node involvement. Normal-sized lymph nodes (generally considered to be < 1 cm in the short axis) can contain tumor cells, and enlarged lymph nodes do not always contain metastatic tumor. Lymph node metastases become more likely with increasing nodal size.[20] In one meta-analysis of 29 studies involving 2,226 patients utilizing CT scans for the detection of mediastinal nodal metastases, the mean sensitivity and specificity were 60% and 77%, with a positive predictive value of 50% and a negative predictive value of 85%. An enlarged mediastinal lymph node detected by CT scanning, therefore, only contains cancer 50% of the time, and 15% of normal-sized (< 1 cm) lymph nodes contain tumor cells.[21] **Positron-Emission Tomography**

PET with 18F-fluorodeoxyglucose is a newer staging technique that uses the relatively increased metabolic activity of cancer cells to differentiate them from normal cells. In the aforementioned meta-analysis, data from 14 studies involving 514 patients were examined, and the authors found that the mean sensitivity and specificity for PET were 79% and 91%, respectively, with a positive predictive value of 90% and a negative predictive value of 93%.[21] Pieterman et al reported their experience in 102 patients with resectable NSCLC with preoperative PET scanning and found sensitivity and specificity of 91% and 86%, respectively.[22] However, in this group of patients, the positive predictive value of PET was 74%. Therefore, 26% of patients with increased uptake on PET have no evidence of nodal disease on histopathology. Furthermore, even lymph nodes that are positive by CT and PET require histopathologic proof of involvement. The negative predictive value of both a negative PET and CT scan of 97% was excellent in this series, and many surgeons feel that PET scans can reliably rule out N2 disease but that surgical staging is necessary to confirm its presence. **Mediastinoscopy**

In many centers, mediastinoscopy is routinely performed to stage patients with lung cancer who are candidates for surgical resection. Mediastinoscopy is used to detect N3 disease for which surgical therapy would not be advised and to detect N2 disease for which induction therapy prior to definitive surgery would be warranted. Because not all lymph nodes can be sampled, cervical mediastinoscopy provides sensitivity between 72% and 89%.[23-25] Cervical mediastinoscopy allows access to the right and left paratracheal lymph nodes and subcarinal lymph nodes. The aortopulmonary window and subaortic lymph nodes are not accessible via cervical mediastinoscopy and require anterior mediastinotomy. **Combined Modalities**

Appropriate staging procedures for patients with resectable NSCLC, therefore, include a CT scan not only to assess the primary tumor and mediastinum but also to evaluate for evidence of metastatic disease within the lung, liver, and adrenal glands. All patients with mediastinal lymph nodes that are greater than 1 cm by CT imaging or are positive by PET scan should have mediastinal disease confirmed histopathologically. In patients with normal mediastinal lymph nodes by CT scan, a negative PET scan may obviate the need for mediastinoscopy. Mediastinoscopy, however, may identify patients with micrometastatic lymph node involvement not apparent on imaging modalities who may benefit from induction therapy. **Detecting Brain Metastases**

The incidence of brain metastases in the initial staging of patients with primary lung cancer has been reported to between 12% and 18%.[26,27] Asymptomatic brain metastases occur more frequently in patients with more advanced stages of disease, with rates as high as 30% at 2 years in stage II/III patients. Higher stage and nonsquamous histology have been identified as risk factors for brain metastases.[28,29] In asymptomatic patients, gadolinium-enhanced magnetic resonance imaging (MRI) of the brain is superior for the detection of occult brain metastases. A recent study randomized 332 patients with potentially operable NSCLC, but without neurologic symptoms, to brain CT or MRI in order to detect occult brain metastases before lung surgery.[30] MRI showed a trend toward a higher preoperative detection rate than CT ($P = .069$), with an overall detection rate of approximately 7% from pretreatment to 12 months after surgery. In patients with stage I/II disease, the detection rate was 4% (8 of 200), whereas for individuals with stage III disease, the rate was 11.4% (15 of 132). Whether the improved detection rate of brain metastases by MRI translates into improved outcome remains unknown. Brain imaging is currently recommended as a part of the initial evaluation for all patients with potentially curable locally advanced NSCLC. Finally, reevaluation of disease after induction chemotherapy and prior to thoracotomy is recommended to exclude disease progression. The ability of noninvasive tests to predict pathologic response has thus far been suboptimal. **Induction Chemotherapy Trials Initial Observations**
Several clinical trials have tested combination chemotherapy prior to surgery to improve the outcome of patients with resectable NSCLC. Initial studies using older chemotherapy regimens suggested that preoperative chemotherapy may be beneficial.[31,32] Martini demonstrated that otherwise resectable patients with ipsilateral mediastinal lymphadenopathy as their sole site of distant spread can have 3-year survivals of 43%, and 5-year survivals of 24%, if both the primary tumor and ipsilateral mediastinal nodes were completely resected and followed by mediastinal irradiation.[33,34] These same studies revealed that individuals with bulky ipsilateral mediastinal lymphadenopathy had only an 8% 3-year survival. Based on these observations, a preoperative combination chemotherapy program with MVP (mitomycin [Mutamycin], vinca alkaloids, and highdose cisplatin [Platinol] at 120 mg/m2) was developed at Memorial Sloan-Kettering Cancer Center for use in stage IIIA patients with clinical N2 disease.[15] In a group of 136 patients, the objective major response rate to MVP was 77%, with a 10% complete response rate. Overall, 65% of patients underwent complete resections; 14% had achieved a pathologic complete response at surgery. The median survival was 19 months for all patients. The 3-year survival for completely resected patients was 41%-a significant improvement over the prior surgery-only experience, where the 3-year survival for this group was 8% (P = .001).[15] Particularly noteworthy was that a pathologic complete response was observed in approximately 12% of advanced NSCLC patients who received preoperative MVP chemotherapy, with survival estimates in this population of 54% at 5 years.[35] The Cancer and Leukemia Group B (CALGB) conducted a second similarly designed trial. A total of 74 patients with surgically staged IIIA (N2) NSCLC were treated with two cycles of preoperative cisplatin and vinblastine.[36] Patients who underwent resection were then treated with two cycles of adjuvant cisplatin and vinblastine followed by thoracic radiation. Approximately 64% of patients achieved a radiographic response or stable disease, and 62% underwent a complete resection. Operative mortality was 3% (2 deaths). Median survival was 15 months. Elias and investigators at the Dana-Farber Cancer Institute treated 34 patients with pathologically confirmed N2 disease, using infusional cisplatin, fluorouracil (5-FU), and leucovorin plus postoperative radiotherapy to 54-60 Gy.[37] The radiographic response rate to this regimen was 65%. Thoracotomy was performed in 82% of patients. No operative mortality was noted, and 18% of patients achieved a pathologic complete response. Median survival was 18 months. The authors noted that few local recurrences occurred and that 15% of first relapses were solely in the brain.

**Randomized Studies**

Following these initial observations that suggested promising results with induction therapy, a number of randomized studies aimed at establishing the role of induction therapy were conducted.

- **Spanish Study**-The first randomized trial that compared cisplatin-based chemotherapy plus surgery with surgery alone was conducted by Rosell et al in patients with stage IIIA disease.[38] Pathologic confirmation of N2 was not mandatory, and approximately 27% of patients had clinical T3, N0/1 disease. Chemotherapy consisted of the MIP regimen (mitomycin, ifosfamide [Ifex], cisplatin) given at 3-week intervals before surgery for three cycles. All patients received mediastinal irradiation (50 Gy) after surgery. A total of 60 patients were randomized, 30 in each arm. After 2 years, the trial was prematurely terminated because of the significant benefits seen in the chemotherapy arm. No toxic deaths occurred during preoperative therapy. The partial response rate was 53%, with a 7% clinical complete response rate. Postoperative mortality was similar in both groups (two deaths each). Overall median survival was 26 months in the chemotherapy arm vs 8 months in the surgery arm (P < .001). Survival rates at 2 years were 27% and 0%. Survival in the control arm of surgery alone was much lower than expected from historic controls. An analysis performed 7 years later confirmed the survival advantage in favor of preoperative chemotherapy, with median survival of 22 months in the chemotherapy arm vs 10 months in the surgery-alone arm (P = .005).[39] The survival rate at 5 years was 17% and 0%, respectively.

- **M. D. Anderson Study**-Roth and investigators at M. D. Anderson Cancer Center conducted another randomized study of preoperative chemotherapy in stage IIIA NSCLC.[40] Chemotherapy consisted of three cycles of cyclophosphamide (Cytoxan, Neosar), etoposide, and cisplatin. Patients who responded to preoperative chemotherapy were given an additional three cycles of adjuvant therapy after complete resection. Patients who were found to have unresectable disease with incomplete resection could undergo postoperative radiation therapy. A total of 28 patients were randomized to receive preoperative chemotherapy, and 32 were randomized to receive primary surgery. Almost one-quarter of patients had T3, N0/1 disease. The overall response rate was 35%, including one pathologic...
complete response. Disease progression developed in four patients during chemotherapy; however, the resectability rate and the rate of complete responses were the same in both arms. An interim analysis showed a statistically significant survival advantage for the preoperative chemotherapy arm ($P < .008$). The trial was therefore halted after 60 patients were enrolled. The estimated 2-year survival rate in the preoperative arm was 60% and in the surgery arm was 25%. An analysis 4 years later revealed that median survival in the chemotherapy arm was 21 months and in the surgery arm was 14 months ($P = .056$).[41]

- **NCI Study** - A third randomized trial in histologically confirmed N2 NSCLC was conducted by Pass et al at the National Cancer Institute (NCI).[42] Chemotherapy consisted of cisplatin and etoposide. At interim analysis, 27 patients had been randomized. The response rate was 61%. Preliminary results suggested a trend toward increased survival for the preoperative chemotherapy arm (median survival = 29 vs 16 months, $P = .095$).

- **Japanese Study** - A fourth randomized study, conducted in Japan, compared induction chemotherapy with cisplatin and vindesine (Eldisine) vs surgery alone in patients with stage IIIA (N2) NSCLC. After 62 patients were enrolled, this study was terminated due to slow accrual. There were no statistically significant differences in survival in this trial (median overall survival was 17 months for patients receiving surgery and 16 months for patients undergoing surgery alone).[43]

**Early-Stage Disease**

Taken together, the four small, randomized studies described above demonstrated a potential benefit with the addition of induction chemotherapy in stage IIIA NSCLC. Studies have since been designed to evaluate the role of induction chemotherapy before surgery in even earlier-stage NSCLC.

- **French Study** - The French Cooperative Oncology Group conducted a large randomized study in stage I (except T1, N0), II, and IIIA resectable NSCLC.[44,45] The 355 eligible patients were randomized to induction therapy with two cycles of mitomycin, ifosfamide, and cisplatin or to primary surgery. Patients who responded to chemotherapy received an additional two cycles postoperatively. In both arms, patients with pT3 or pN2 disease or incomplete surgery received radiotherapy after either surgery or completion of chemotherapy. This regimen yielded a response rate of 64% with a pathologic complete response rate of 11%. The complete resection rate was similar between the two arms: 92% with induction vs 86% with surgery alone. A 10-month improvement in median survival in the chemotherapy arm was documented (26 vs 36 months), although this was not statistically significant ($P = .11$). Operative mortality was similar in both arms, but there was a trend toward increased postoperative mortality (7% vs 4.5%) and increased postoperative complications in the chemotherapy arm. Although a statistically significant improvement in survival could not be demonstrated, subset analysis showed that patients with stage N0/1 disease derived a survival benefit from induction chemotherapy (hazard ratio = 0.68, 95% CI = 0.49-0.96, $P = .027$). This survival benefit was not observed in patients with N2 disease (hazard ratio = 1.04, 95% CI = 0.68-1.60, $P = .85$). The study by Depierre et al is the largest trial of induction chemotherapy conducted to date. However, it remains nonconclusive as it included a heterogeneous group of patients with various stages of disease and its implications for the treatment of patients with stage IIIA NSCLC are only based upon subset analysis.

- **US Studies** - The role of induction chemotherapy for early-stage NSCLC has also been under investigation in the United States. Pisters et al reported promising results from the multicenter phase II study, the Bimodality Lung Oncology Team (BLOT) trial.[46] Patients with stage IB-IIIA (T3, N1, M0) NSCLC received induction therapy with two cycles of carboplatin (Paraplatin) and paclitaxel followed by three additional cycles postoperatively. Evaluable patients included 94 evaluated for survival and toxicity and 90 for response. The response rate was 56%, the pathologic complete response rate was 6%, and 3% of patients had disease progression during induction. The 1-year survival rate was 85%. Results from a second group of patients who received three rather than two cycles of induction chemotherapy with carboplatin and paclitaxel have also been reported.[47] In a total of 124 patients, the response rate was 51% and 3-year survival was 61%, which was superior to historical controls. The surgical mortality rate was only 1%. The North Central Cancer Treatment Group (NCCTG) conducted a similar phase II study with induction carboplatin and paclitaxel in patients with stage T1-3, N0/1, M0 disease.[48] Of 52 patients, 3 died postoperatively. The 2-year survival rate was 73%. An ongoing phase III randomized study
(S9900) is randomizing patients to three cycles of induction carboplatin and paclitaxel followed by two additional cycles of postoperative carboplatin and paclitaxel or surgery alone. Over 325 patients have thus far been entered into this trial, which has an accrual goal of 600.

**Newer Chemotherapy Regimens**
Despite the often impressive results with induction chemotherapy, one-quarter or more of patients do not respond to current primary chemotherapy regimens. Also, the majority of patients who initially respond and have complete surgical resections eventually relapse. Two-thirds of the relapses are systemic. It appears unreasonable to look to further advances in surgery or radiation to substantially improve survival. The ability of a locoregional therapy modality such as radiotherapy to control systemic relapse is inherently limited. Based on the accumulated results and relapse patterns, improvements in primary chemotherapy regimens are most likely to result in improvements in overall outcome. However, while response rates to chemotherapy are high in stage III patients, clinical and pathologic complete response rates are generally less than 20%. Because individuals with complete pathologic responses have the highest resection and survival rates, the complete pathologic response rate can serve as a surrogate for patient outcome in the development of novel induction regimens.

- **Novel Agents**-Platinum-based combinations with newer agents, such as gemcitabine (Gemzar) and docetaxel have attracted the interest of investigators. The European Organization for Research and Treatment of Cancer (EORTC) group conducted a phase II trial of cisplatin and gemcitabine (Gemzar) in 47 patients with stage IIIA NSCLC and showed a 70% response rate with mediastinal node clearing in 53% of cases. The estimated 1-year survival was 69%.[49]

Another phase II study, by Betticher et al, investigated the efficacy and toxicity of induction docetaxel (Taxotere) and cisplatin in stage IIIA NSCLC.[50] A total of 90 patients were treated in this trial. The response rate in this trial was 66%, and 75 patients were able to undergo resection. Pathologic complete responses occurred in 19% of patients who underwent resection, and mediastinal node clearing was strongly predictive of long-term survival ($P = .0003$). Another multi-institutional study randomized 274 patients with stage IIIA/IIIB NSCLC to receive up to three cycles of single-agent docetaxel (100 mg/m²) prior to definitive surgery or radiation.[51] Overall survival in the docetaxel group was 14.8 months and in the control
group was 12.6 months. Although not statistically significant, there was a trend toward longer survival in the docetaxel arm.

- **Triplet Regimens**- Triplet combinations have also been investigated. In a phase I study conducted at Memorial Sloan-Kettering Cancer Center, the combination of gemcitabine, cisplatin, and docetaxel was evaluated before surgery.[52] The recommended dose for phase II studies was gemcitabine at 1,000 mg/m² on days 1, 8, and 15; docetaxel at 100 mg/m² on day 1; and cisplatin, 100 mg/m² on day 15. The response rate in the phase I trial was 44%, and the phase II trial has not yet been reported. The Spanish Lung Cancer Group reported a similar triplet combination. In this trial, 120 patients with stage IIIA, N2 and T4, N0/1 NSCLC were treated with gemcitabine, cisplatin, and docetaxel. All patients received three cycles of therapy prior to surgery. Nodal clearing occurred at resection in 37% of patients with N2 disease at diagnosis. When reported, the median survival for 84 evaluable patients was 14.6 months.[53] A third study from Italy treated 49 patients with pathologically proven stage IIIA (N2) disease with gemcitabine, paclitaxel, and cisplatin prior to surgery or definitive radiotherapy.[54] Approximately 74% of patients achieved an objective response, and 60% of patients underwent thoracotomy. Mediastinal nodes were free of tumor in 35% of all cases, and eight pathologic complete responses (16%) were reported. Median survival was 23 months. Multiple ongoing phase III randomized studies are evaluating the role of induction chemotherapy based upon newer chemotherapy regimens in early-stage NSCLC (Table 2.)

**Induction Chemoradiotherapy** It is postulated that chemotherapy decreases the distant failure rate of surgery by eradication of micrometastatic disease, whereas radiation can reduce the bulk of the primary tumor and nodal disease, thereby increasing the rate of complete pathologic response—arguably the most important predictor of long-term survival. Therefore, investigators have attempted to integrate chemotherapy and radiation therapy into induction therapy for resectable disease. **Phase II Trials**

- **CALGB Study**- The Cancer and Leukemia Group B reported a phase II study of two cycles of induction cisplatin, vinblastine, and infusional 5-FU with concomitant radiation to 30 Gy, surgery, then an additional cycle of chemotherapy and an additional 30 Gy radiation postoperatively in patients with stage IIIA NSCLC.[55] A total of 41 patients were studied (80% with N2 disease). The response rate to induction therapy was 51%. Of the 31 patients who went to surgery, only 25 were resected. The pathologic complete response rate was 16%. Toxicity was substantial, with six (15%) treatment-related deaths. The 1-year survival was 58%, with a median survival of 15.5 months.

- **SWOG 8805**- A Southwest Oncology Group phase II trial (SWOG 8805) examining trimodality therapy included patients with stage IIIA and IIIB disease.[56] The 75 patients with stage IIIA disease and 51 patients with stage IIIB disease were treated with two cycles of cisplatin and etoposide plus 45 Gy irradiation over 5 weeks. Resectable disease was confirmed in 85% of stage IIIA patients and 80% of stage IIIB patients. Patients who were not resectable received an additional two cycles of chemotherapy and a 14.4-Gy radiation boost. The pathologic complete response in this trial was 21%. Treatment-related mortality was 10%. The 6-year survival was 20% for patients with stage IIIA disease and 22% for patients with stage IIIB disease. Subset analysis revealed that patients with T4, N0/1 disease had a particularly high long-term survival rate of 49%, whereas patients with N3 disease based on contralateral mediastinal lymphadenopathy had a dismal 2-year survival rate of 0%.[57]

- **Hyperfractionated Radiotherapy Trials**- A number of phase II studies that used hyperfractionated radiotherapy schedules along with concurrent chemotherapy as induction have been reported. Choi et al studied preoperative twice-daily radiation therapy with two cycles of concurrent cisplatin, vinblastine, and 5-FU in stage IIIA (N2) and IIIB patients.[58] They reported an 84% complete resection rate, and a 5-year survival rate of 37%. Eberhardt et al conducted a study in which 94 stage IIIA/IIIB patients received four cycles of preoperative cisplatin and etoposide, three before radiation therapy, and the fourth combined with twice-daily radiation (45 Gy, 1.5 Gy per fraction, twice daily for 3 weeks).[59] A complete resection was performed in 53% of patients (60% in stage IIIA and 45% in stage IIIB groups). The median survival and 4-year survival rates were 20 months and 31% for stage IIIA patients, and 18 months and 26% for stage IIIB patients. Thomas et al examined preoperative chemotherapy (two cycles of ifosfamide, carboplatin, and etoposide) with
subsequent chemoradiotherapy (carboplatin and vindesine plus concurrent 45 Gy irradiation) and then surgery in patients with stage IIIA/IIIB disease. Median survival (25 months in patients with stage IIIA disease and 17 months in those with stage IIIB disease) compared favorably with other studies.

**Phase III Trial**
Based on the promising results of the SWOG phase II trial, a phase III, randomized trial of the North American Intergroup (0139) was initiated. The goal of the study was to evaluate the need for surgical resection after chemoradiotherapy. Patients with stage IIIA pathologically proven N2 NSCLC were randomized to fullcourse chemotherapy with cisplatin and etoposide plus radiotherapy to 61 Gy, or to induction chemoradiation with the same regimen to 45 Gy followed by surgical resection. Due to slow accrual, the study was closed after 429 patients (411 of whom were eligible) were enrolled. In a preliminary analysis of 392 patients after a median follow-up of 69 months, progression-free survival was significantly improved in the surgical vs the nonsurgical arm (29% vs 19%, \( P = .02 \)), but overall survival was similar between the two arms (38% vs 34%). Although more early noncancer deaths occurred in the surgical arm—primarily postoperatively (12 of 14 deaths occurred in patients undergoing pneumonectomy)—the survival curves crossed at the median of 22 months and showed an absolute benefit of approximately 5% for surgery at 3 years. Importantly, patients who achieved a pathologic complete response in the mediastinal lymph nodes achieved 50% 3-year overall survival. The results of this study challenge the role of surgery in traditionally resectable stage IIIA NSCLC. Concurrent chemoradiotherapy alone may be sufficient therapy for resectable stage IIIA NSCLC. It is likely that the impact of postoperative mortality observed in the surgical arm obscured a potential survival advantage resulting from surgical resection. Final results of this Intergroup study are awaited. Other Small Trials
The addition of radiotherapy to preoperative programs deserves further evaluation. Two small studies presented in abstract form only have compared induction chemotherapy to chemoradiotherapy in potentially resectable stage III NSCLC. A study from Brazil demonstrated a significant improvement in resection rates, freedom from progression, and 2-year survival in patients receiving induction chemoradiotherapy vs chemotherapy alone before surgery. The long-term results of this study have not been published; it therefore remains to be seen whether these data will hold up over time. A study from France in 92 patients with stage IIIA/IIIB NSCLC evaluated induction MVP chemotherapy alone vs induction MVP followed by 5-FU and cisplatin plus split-course radiation to 40 Gy. Higher resection rates were noted in the induction chemoradiotherapy arm, but this did not translate into improved survival over induction chemotherapy alone. Surgical complications were increased in the chemoradiotherapy arm. The use of both induction chemotherapy with carboplatin and gemcitabine followed by concurrent chemoradiotherapy and then surgery in patients with stage III NSCLC has also been investigated. This study enrolled 39 patients, 19 of whom ultimately underwent surgical resection (16 with stage IIIA disease and 3 with selected T4 tumors). The pathologic complete response rate was 16% (42% in the mediastinal lymph nodes), and the 3-year overall survival rate in surgically treated patients was 51%. Further investigation of this approach is warranted. Importance of Patient Selection
A potential advantage of induction chemoradiotherapy may be that a higher proportion of pathologic complete responses is achieved compared to the use of induction chemotherapy alone. However, postoperative morbidity and mortality appears to be somewhat higher with induction chemoradiotherapy compared to induction chemotherapy. Thus, if surgery is to be performed after chemoradiotherapy, careful patient selection is paramount. Patients with compromised performance status or borderline cardiopulmonary reserve are unsuitable for this approach. Future trials need to address whether the addition of radiotherapy to induction chemotherapy translates to a survival advantage in patients with resectable NSCLC. Surgical Considerations After Induction Therapy
Although multiple studies have demonstrated the safety of surgical resection after induction therapy, several issues make interpretation of the data difficult. First, many studies involve heterogeneous populations that include patients with both stage IIIA tumors with nodal involvement and stage IIIB tumors that are locally advanced. Resection of peripheral tumors with nodal disease is associated with significantly lower complication rates than extended resections for locally advanced disease. Additionally, patients who ultimately undergo surgical resection are a selected group often without comparable controls. They are fit enough for surgical resection and have tumors with demonstrated sensitivity to induction chemotherapy. These patients have better nutritional status, immunocompetency, and overall function, and therefore, an overall better prognosis than those unable to tolerate chemotherapy or who may not be candidates for multimodality therapy. Finally,
many studies are retrospective, involve few subjects, and include variable induction regimens such as chemotherapy alone and induction chemoradiotherapy. Despite the limitations of the available data, some conclusions about the risks and benefits of surgical resection after induction therapy can be made. **Tumor and Host Responses**

Induction therapy causes tumor and host responses that have both advantages and disadvantages in terms of surgical resection. Large, bulky tumors may be downsized, permitting easier intraoperative visualization and manipulation. Induction therapy may also result in tumor shrinkage away from vital structures making significantly more radical resection unnecessary. However, the inflammatory response and fibrosis resulting from induction therapy can make resection more difficult. This is particularly true when trying to determine whether "close" margins are clear of tumor. Because intraoperative frozen sections show fibrosis around treated tumor, the true extent of the original tumor cannot be established. Resection of all fibrosis may require a substantially more radical operation, but incomplete resection risks leaving microscopic deposits of tumor. This issue is not trivial, as patients with incompletely resected tumor invariably have poor prognoses. Tumor fibrosis also obscures the normal anatomic planes, making dissection around vessels, airways, and the esophagus more difficult. Repeat mediastinoscopy after previous mediastinoscopy and induction therapy is generally considered a risky procedure and is frequently inadequate.[65] Physical conditioning and immune function are weakened by induction therapy such that patient tolerance of perioperative complications may be reduced. Induction therapy likely impairs lymphatic drainage of the lung and pleural space and causes parenchymal changes that alter lung elastic recoil and healing. These factors may contribute to postoperative air leaks and pleural space problems. Most studies have focused only on major complication rates and mortality. Important although less significant difficulties with postoperative recovery after induction therapy may be underreported.

**Surgical Mortality and Complications**

Surgical mortality for most resections appears comparable to that for resections without induction therapy. However, pneumonectomy, particularly right-sided, is associated with increased risk of mortality. A report from Memorial Sloan-Kettering Cancer Center by Martin et al examined 470 patients with stage I-IV NSCLC receiving a variety of regimens, but primarily MVP. These investigators showed a high rate of surgical mortality after right pneumonectomy (24%) compared to an overall rate of surgical mortality of 4% after induction chemotherapy.[66] Preoperative chemotherapy was otherwise not found to be a risk factor for morbidity or mortality in multivariate analysis. Most studies report complication rates of 15% to 40% in patients undergoing postinduction therapy resections. With the previously mentioned caveats, authors report rates equal to[66-70] or above[71-73] those for standard resections. Most complications are pulmonary, such as bronchopleural fistula, pneumonia, postresectional pulmonary edema, adult respiratory distress syndrome (ARDS), and atelectasis. A retrospective analysis from Vanderbilt University reported an increase in morbidity and mortality after induction chemotherapy.[74] This single-institution experience from 1997 to 1999 included 34 patients with early-stage disease (IB-IIIA) receiving carboplatin and paclitaxel for three cycles compared with 67 patients undergoing resection without prior systemic therapy. They observed significant increases in life-threatening complications (27% vs 3%), major complications (47% vs 19%), and reintubation (18% vs 3%) in patients receiving chemotherapy. No hospital mortality was observed. A Spanish case-control study examined postoperative morbidity and mortality in 42 patients receiving induction chemotherapy (74% clinical stage III or IV) compared with 42 matched controls (all clinical stage I) undergoing surgery alone.[67] No postoperative mortality was recorded. Although the authors concluded that there was no significant influence of chemotherapy on postoperative complication rates (26% in the chemotherapy arm vs 43% in controls), the complication rate in the controls was unusually high. Depierre et al reported a trend toward increased mortality and morbidity when surgery followed a cisplatin-based induction regimen, compared to a surgery-alone arm.[45] In a large multicenter study, Albain et al observed a surgical mortality rate of 5% in patients who underwent thoracotomy postchemoradiotherapy.[61] Most deaths were due to pulmonary complications in patients undergoing pneumonectomy. In multicenter phase II studies with induction carboplatin and paclitaxel in early-stage NSCLC, postoperative mortality has been acceptable, ie, 1% to 6%.[46,48] Extended resections that include bronchoplastic or tracheoplastic reconstructions probably have higher complication rates in the setting of induction therapy. This is most likely to be the case when radiotherapy is involved. Macchiarini and colleagues compared two groups of patients with T4 disease.[71] Induction chemotherapy alone was administered to 11 patients, and 12 patients received combined chemoradiotherapy with 40 Gy to the lesion, mediastinum, and ipsilateral supraclavicular fossa. Major complication rates were 42% in the chemoradiation group vs 9% in the
chemotherapy-alone group. Similarly, bronchial stump breakdown may be more common in the setting of radiotherapy.[75] In conclusion, it appears that induction therapy, especially chemoradiotherapy, may slightly increase surgical complications, with a minimal, perhaps negligible, increase in surgical mortality. This potential detrimental effect is likely to be outweighed by the potential survival benefit from the use of induction therapy. A number of ongoing randomized comparisons with a surgical control arm is expected to provide additional data on the safety of contemporary induction chemotherapy regimens (Table 2). Incorporation of Novel Agents Recent years in lung cancer research have been an exciting time, with the identification of targeted agents such as gefitinib (Iressa) and erlotinib (Tarceva), which inhibit the epithelial growth factor receptor (EGFR) tyrosine kinase, and bevacizumab (Avastin), a monoclonal antibody against the vascular endothelial growth factor (VEGF). Some of these drugs, eg, gefitinib and erlotinib, have been combined with cytotoxic chemotherapy in the advanced disease setting without significantly improving outcome. Investigators, however, are looking at the induction setting in an effort to understand why a fraction of patients does benefit from these agents. For example, the Memorial Sloan-Kettering Cancer Center group is currently conducting one such trial of gemcitabine and cisplatin plus intermittent erlotinib as induction therapy in patients with locally advanced disease. In these studies, the availability of posttreatment tissue may help further elucidate mechanisms of action of novel agents. Another trial, reported by Altorki et al, included patients with stage IB to IIIA NSCLC.[76] A total of 29 patients were treated with the combination of paclitaxel, carboplatin, and celecoxib (Celebrex). The addition of celecoxib to chemotherapy normalized levels of PGE₂ found in NSCLC patients after treatment with chemotherapy. The authors felt that the addition of celecoxib enhanced the response to preoperative therapy. The Optimal Therapy There are no validated criteria available that can be used to determine whether a patient with potentially resectable, locally advanced NSCLC should be treated with induction chemotherapy followed by surgical resection, chemoradiotherapy alone, or chemoradiotherapy followed by surgery. In general, patients with nonbulky, mobile lymphadenopathy tend to be offered induction chemotherapy, and patients with more extensive mediastinal disease are treated with chemoradiotherapy, possibly followed by surgery. When chemotherapy is combined with concurrent radiotherapy, usually only suboptimal systemic doses of chemotherapy can be delivered due to increased toxicity. It is possible that giving full-dose systemic therapy treats micrometastatic disease immediately before it has the opportunity to progress or become resistant to the lower doses of chemotherapy that are typically given with radiation. Ichinose et al attempted to identify risk factors for recurrence and survival in 406 patients with resected N2 NSCLC that might allow selection of patients who should have adjuvant therapy.[6] In the multivariate analysis, survival was worse in patients with multiple N2 stations, pathologic T2, T3, or N1 disease, and age older than 65. Local recurrence was increased with multiple N2 lymph nodes and clinical N1 or N2 disease. Patients with multiple involved mediastinal lymph nodes had a 5-year survival rate of 17% and a freedom from local recurrence rate of 48%, compared with 43% and 75%, respectively, for patients with an isolated mediastinal lymph node. Ichinose et al surmised that the number of mediastinal lymph nodes involved is an important prognostic factor. It is necessary to better select patients who would benefit from each treatment approach, and it could well be that patients with bulkier disease fare worse regardless of the addition of radiation to induction therapy. Similarly, Andre et al evaluated prognostic factors in 702 patients who underwent surgical resection for stage IIIA disease.[14] Negative prognostic indicators were clinical N2 disease, multiple lymph node involvement of the mediastinum, pathologic T3 or T4 disease, and no preoperative chemotherapy. The role of surgery in the multimodality therapy of resectable stage III NSCLC has been questioned by some clinical studies. In fact, three small phase III trials with nonsurgical arms failed to show benefit for surgery over radiation.[77-79] More recently, as discussed previously, the results of Intergroup trial 0139 seem to fuel the debate. Many have questioned the role of radiotherapy in the therapy regimen. It may be that the early noncancer deaths may have been a function of the radiation, not the chemotherapy. Emerging data on adjuvant therapy for NSCLC has certainly changed the practice of oncology. The International Adjuvant Lung Cancer Trial (IALT) Collaborative Group concluded that cisplatin-based adjuvant therapy improved survival in patients with completely resected NSCLC.[9] In this study of 1,867 patients who were randomly assigned to adjuvant therapy or to observation, overall survival was significantly higher in the adjuvant chemotherapy group (P < .03), with an absolute increase of 4% in the 5-year survival rate. Similarly, both the National Cancer Institute of Canada trial JBR.10[10] and the Cancer and Leukemia Group B (CALGB)[11] study 9633 presented at the American Society of Clinical Oncology meeting in 2004 conducted in early-stage homogeneous populations demonstrate absolute survival benefits of 15% at 5 years (P = .0022) and 12% at 4 years (P = .028) respectively. No randomized
study has yet reported results of a comparison between induction and adjuvant chemotherapy for resectable NSCLC, but most believe that at least a comparable survival benefit will be demonstrated with the use of induction therapy. The ongoing study enrolling patients with stage IB to IIIA NSCLC, orchestrated by Rosell et al, is comparing induction chemotherapy, adjuvant chemotherapy, and surgery alone. Patients in both chemotherapy arms receive carboplatin and paclitaxel. **Conclusions**

Despite what appears to be complete resection of NSCLC, the majority of patients with non-small-cell lung cancer die from recurrent, metastatic disease. Therapy aimed at eradicating micrometastatic disease has been the goal of induction chemotherapy. It is hoped that improvements in systemic chemotherapy with the advent of targeted agents will translate into a survival benefit for patients with resectable NSCLC. Induction treatment represents an important paradigm for clinical research in NSCLC, allowing in vivo chemosensitivity assessment and offering a testing field for new, targeted agents. Furthermore, the delivery of induction chemotherapy seems more effective than the same therapy in the adjuvant setting. For patients with stage I and II NSCLC, the use of induction has been shown to be feasible but is not recommended outside of a clinical trial. For patients with resectable stage III disease, induction chemotherapy-with or without radiotherapy—appears to definitively answer lingering questions is by the timely accrual of patients to well designed clinical trials. be the best approach. The only way to definitively answer lingering questions is by the timely accrual of patients to well designed clinical trials.

**Disclosures:** The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

**References:**


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