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*Induction chemotherapy
(with or without radiation)
offers the potential to both
control occult metastases
and improve resectability.*

The Role of Induction Therapy in the Management of Resectable Non-Small Cell Lung Cancer

Thomas A. Hensing, MD, Frank Detterbeck, MD, and Mark A. Socinski, MD

Background: *Combined-modality therapy has become standard for many patients with non-small cell lung cancer. Although surgical resection offers the best chance for long-term survival, the limited number of resectable patients and the presence of occult micrometastatic disease has limited the effectiveness of this modality alone.*

Methods: *The authors reviewed several trials involving the use of induction chemotherapy in managing resectable non-small cell lung cancer.*

Results: *Extensive phase II experience in patients with stage III disease has confirmed the feasibility of this approach. Unfortunately, heterogeneous patient populations and treatment regimens limit the ability to draw firm conclusions from these trials alone. While the phase III experience has been limited, long-term follow-up is now available suggesting that induction therapy may have a beneficial impact on survival, especially for those patients who can be sufficiently downstaged. Recent phase II trials have included stage III patients who have traditionally been considered inoperable. Although encouraging, the role of surgery after chemoradiotherapy for this population of patients remains undefined.*

Conclusions: *Results from ongoing randomized trials studying the impact of induction therapy on well-defined patient populations will be necessary before the optimal regimen and patient population can be identified.*

From the Multidisciplinary Thoracic Oncology Program and Divisions of Hematology/Oncology and Thoracic Surgery at the University of North Carolina, Chapel Hill, NC.

Address reprint requests to Thomas A. Hensing, MD, Multidisciplinary Thoracic Oncology Program, University of North Carolina, 3009 Old Clinic Building, CB 7305, Chapel Hill, NC 27519.

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Introduction

Lung cancer remains a leading cause of cancer-related mortality. In 1999, an estimated 171,000 new cases of lung cancer will be diagnosed in the United States and 158,000 people will die of this disease.¹ Of these cases, 75% to 80% will be non-small cell histology. Complete surgical resection continues to offer the best chance for long-term survival for this population

of patients; however, only 20% to 30% of patients will ultimately have resectable disease.² In addition, the five-year survival from the time of surgery for patients with pathologically staged IB to IIIA disease is only 23% to 57% (Table 1). While both local and distant disease recurrence limits the curative ability of surgery alone, the majority of resected patients will fail outside of the chest, suggesting that the predominant factor affecting survival is the presence of occult micrometastatic disease. Given this, effective systemic therapy is needed to control occult disease to improve survival.

Clinical trials studying the impact of adjuvant chemotherapy with or without radiation have not yet shown a clear survival benefit. In a meta-analysis completed by the Non-small Cell Lung Cancer Collaborative Group,³ the use of cisplatin-based combination chemotherapy regimens after surgery compared to surgery alone was associated with an absolute benefit of 3% at two years and 5% at five years. Similarly, the combination of surgery, radiotherapy, and chemotherapy (cisplatin-based) was associated with a 2% absolute benefit at both two and five years when compared to surgery and radiation without chemotherapy. However, both results were not statistically significant. In a more recent analysis of randomized trials,⁴ adjuvant cisplatin-based chemotherapy was evaluated based on the predominant nodal status of the patients enrolled onto the trials. The use of adjuvant cisplatin-based chemotherapy regimens for node-negative patients was associated with a composite five-year survival rate of 61% compared with 55% for the control groups ($P=0.06$). When node-positive trials were analyzed, the composite two-year survival rate for the adjuvant arms was 48% compared with 40% for the controls ($P=0.06$). Unfortunately, many of the randomized trials to date have included relatively small and variable patient populations, thus limiting the ability to draw firm conclusions regarding the true effectiveness of this approach. In addition, compliance to adjuvant cisplatin-based chemotherapy regimens after thoracotomy has been relatively poor.⁴

Induction (neoadjuvant) chemotherapy with or without radiation offers many of the same theoretical benefits as adjuvant treatment. In general, the effect of chemotherapy is greater when the tumor burden is low. This is likely related to several factors, including a lower likelihood for tumor-resistant clones, lower kinetic resistance, and an increased likelihood for efficient drug delivery to the tumor.^{5,6} Therefore, the use of chemotherapy earlier in the disease process may increase the potential for a significant tumor response. In the induction setting, this would be useful in downstaging tumors in order to improve resectability rates. Furthermore, earlier exposure of micrometastases to

Table 1. — Five-Year Survival From Time of Surgery*

Stage	Clinical (%)	Pathologic (%)
IA (T1 N0 M0)		61 67
IB (T2 N0 M0)		38 57
IIA (T1 N1 M0)		34 55
IIB (T2 N1 M0, T3 N0 M0)	22 - 24	38 - 39
IIIA (T3 N1 M0, T1-3 N2 M0)	9 - 13	23 - 25
IIIB (T4 N0-2 M0, T1-4 N3 M0)	3 - 7	NR

* Outcomes represent five-year survival from time of surgery for clinically and pathologically staged patients. From Mountain CF. Revisions in the international system for staging lung cancer. *Chest.* 1997;111:1710-1717. Adapted with permission.

systemic therapy may increase the potential for cure. Finally, it is also likely that compliance to induction therapy will be greater than compliance to classical adjuvant therapy.

Several investigators have confirmed the feasibility of induction therapy in the management of patients with non-small cell lung cancer. The majority of the experience thus far has involved patients with operable stage IIIA tumors. Recently, induction therapy has also been studied on more advanced stage III patients and patients with earlier-stage disease. Survival in the phase II setting has been promising when compared to the historical outcomes of patients with locally advanced tumors. In a review of 15 phase II induction trials,⁷ response to preoperative therapy was seen in greater than 50% of patients, with complete resection rates in the range of 60% to 70% of those patients treated. Overall survival rates (2- to 3-year) of 25% to 30% were generally reported, and treatment-related morbidity did not appear to be excessive.

While the experience in the randomized setting has been somewhat limited, recent data suggests that a survival benefit may be achieved with this approach. However, several questions remain, including the optimal induction regimen and the patient population most likely to benefit from preoperative therapy. Furthermore, the role of surgery after combined chemoradiotherapy for patients with bulky stage IIIA or IIIB disease is not yet known, especially for those patients whose disease cannot be sufficiently downstaged with induction. This article reviews current strategies of induction therapy and updates current and ongoing phase III trials in an effort to better define the role of induction therapy in the management of patients with non-small cell lung cancer.

Surgery

Surgery remains the standard treatment for patients with clinical stage I and II disease. This includes patients with T1-2 N0-1 tumors as well as T3 N0 tumors.⁸ Resectability rates are generally highest in this population of patients. However, while surgical resection offers the best chance for cure, five-year survival rates after surgery leave much room for improvement (Table 1). Locoregional recurrence rates range between 5% to 30% after surgical resection, and they vary depending on the extent of surgery and stage.⁹⁻¹¹ Ultimately, the majority of recurrences for those patients who have undergone resection will occur at distant sites, demonstrating that systemic dissemination often occurs even in the early stages of this disease.¹¹⁻¹³

Surgery has a much more limited role in the management of stage III patients. In general, surgical resection is reserved for a select group of patients with stage IIIA tumors. With the reclassification of T3 N0 tumors as stage IIB, stage IIIA now consists predominantly of patients with N2 disease.⁸ Only a minority of stage III patients are considered candidates for surgical resection.¹⁴ Two distinctly different prognostic groups of patients with N2 disease have been identified. In a series reported by Pearson and colleagues,¹⁵ those patients with pathologic N2 disease identified prior to surgery had a 9% five-year postoperative survival compared with 24% for those patients with occult N2 disease found at thoracotomy despite a negative mediastinoscopy. Similarly, in a series reported by Martini and Flehinger,¹⁴ the five-year survival from the time of surgery for those patients with clinically evident vs clinically occult N2 disease was 9% and 34%, respectively ($P=0.0002$). Therefore, those patients who are proven to have pathologic N2 involvement during their

initial staging are generally not considered candidates for surgery alone.

Induction Chemotherapy

Table 2 represents selected phase II trials of induction chemotherapy. The response rates to induction therapy in these trials ranged from 60% to 88%, with complete resection rates between 31% and 65% and an overall three-year survival of 23% to 28%.¹⁶⁻¹⁹ The variable outcomes in these trials reflect some of the difficulty in interpreting the phase II experience. Although all of the induction regimens were cisplatin-based, the different combinations used and the inconsistent use of postoperative adjuvant chemotherapy with or without radiation contribute somewhat to this difficulty. In addition, both the Cancer and Leukemia Group B (CALGB)¹⁶ and Toronto¹⁹ series included only patients with surgically staged IIIA N2 disease that was confirmed by mediastinoscopy. In contrast, both the Memorial Sloan-Kettering (IIIA N2)¹⁷ and Roswell Park (IIIA N0-2, IIIB)¹⁸ series included patients who were not consistently surgically staged prior to initiating induction chemotherapy. Therefore, the potential inclusion of patients with different long-term prognosis limits the ability to generalize these results to a specific patient population.

Many of these same concerns also apply when interpreting the randomized experience with preoperative chemotherapy. In two randomized phase II trials,^{20,21} improvements in either tumor downstaging or survival were not seen. In a Lung Cancer Study Group (LCSG) trial reported by Wagner and colleagues,²⁰ induction chemotherapy (mitomycin, vinblastine, and cisplatin) was compared to preoperative radiation in 67 patients with surgically staged unresectable N2 or

Table 2. — Selected Phase II Trials of Induction Chemotherapy in Stage III Non-Small Cell Lung Cancer

Trial	Number of Patients	Substage	Induction	Response Rate	Complete Resection*	Treatment Mortality	Overall Survival
CALGB 8935 ¹⁶	74	p T1-3N2 (100%)	Cisplatin, vinblastine	88%	31%	5.4%	23% (3 yr)
Memorial Sloan-Kettering ¹⁷	136	c T1-3N2 (100%)	MVP	77%	65%	5%	28% (3 yr)
Roswell Park ¹⁸	41	c, p T3N0 (7%) c, p T1-3N2 (27%) c, p T4 or N3 (66%)	PACCO	60%	42%	2%	NR
Toronto ¹⁹	39	p N2 (100%)	MVP	64%	46%	15%	25% (3 yr)

* Percent of all evaluable patients.
 RR = response rate to induction chemotherapy
 PACCO = cisplatin, doxorubicin, cyclophosphamide, CCNU, vincristine
 MVP = mitomycin, vinblastine, cisplatin
 c = clinical stage
 p = pathologic stage
 NR = not reported

T4 tumors. Toxicity was excessive in both arms, with an overall perioperative death rate of 18%. There was no clear difference in radiographic or pathologic response. In the second trial reported by Dautzenberg and colleagues,²¹ studying preoperative PCV (cisplatin, cyclophosphamide, and vinblastine), enrollment was stopped after only 26 patients were randomized due to a high rate (36%) of disease progression during chemotherapy. Although no benefit was seen, small numbers limit its impact.

There are currently five reported randomized phase III trials designed to evaluate the effect of induction chemotherapy on survival for patients with stage III disease (Table 3).²²⁻²⁸ In a trial reported by Rosell et al,^{23,24} 60 stage IIIA patients were randomized either to induction mitomycin (6 mg/m²), ifosfamide (3 g/m²), and cisplatin (50 mg/m²) followed by surgery vs surgery alone. Both arms received postoperative mediastinal radiation (50 Gy). Of note, this was not a pure N2 study population as T3 N0 (22%) and T3 N1 (5%) patients were included. Mediastinoscopy was used in 73% of the patients, and all patients classified as N2 had clinically enlarged nodes as well as pathologic confirmation by node biopsy. The radiographic response rate

to induction was 60%. Enrollment was stopped after 24 months due to a significant difference in both disease-free survival (DFS) and overall survival (OS) favoring the induction arm (median DFS: 20 months vs 5 months, $P<0.001$; median OS: 22 months vs 10 months, $P<0.005$). This study has been criticized because of an imbalance of K-ras mutations (15% chemotherapy arm vs 42% surgery arm, $P=0.05$) and aneuploid tumors (29% in the chemotherapy arm vs 70% surgery arm, $P=0.02$) between the two groups. This may be reflected in the median survival for the surgery-alone arm, which was much lower than would be expected for resected stage IIIA disease, especially given that 30% of the patients on this arm had T3 N0 tumors.

In another randomized trial completed at M.D. Anderson Cancer Center,²⁵ enrollment was also terminated early due to a significant survival benefit for those patients receiving induction therapy. The trial was designed for patients with stage IIIA disease. A total of 85% of the patients were staged by mediastinoscopy or the Chamberlain procedure, and all patients classified as N2 had clinically enlarged N2 nodes as well as pathologic confirmation of malignant involvement. However, both T3 N0 (23%) and T3 N1 (3%) tumors were also

Table 3. — Randomized Phase III Trials of Preoperative Chemotherapy in Stage III Non-Small Cell Lung Cancer

Study	Number of Patients	Substage	Induction Treatment	Median Survival (mos)	Overall Survival
Spain ^{23,24}	60	p T1-3 N2 (63%) c T3 N0 (30%)	Arm 1: none	10	0% (5 yr)
		p T1-3 N2 (83%) c T3 N0 (13%)	Arm 2: cisplatin, mitomycin, ifosfamide	22 $P=0.005$	17% (5 yr)
M.D. Anderson ^{25,28}	60	p T1-3 N2 (69%) c, p T3 N0 (25%)	Arm 1: none	14	15% (5 yr)
		p T1-3 N2 (71%) c, p T3 N0 (21%)	Arm 2: cisplatin, etoposide, cyclophosphamide	21 $P=0.048$	36% (5 yr)
NCI ²²	27	p T1-3 N2 (100%)	Arm 1: none	16	12% (3 yr)
			Arm 2: cisplatin, etoposide	29 $P=0.095$	42% (3 yr)
CALGB ²⁶	57	p T1-3 N2 (100%)	Arm 1: thoracic radiotherapy (40 Gy)	23	NR
			Arm 2: cisplatin, etoposide	19 $P=0.64$	NR
NCI-Canada ²⁷	31	p T1-3 N2 (100%)	Arm 1: thoracic radiotherapy alone (60 Gy)*	16	NR
			Arm 2: cisplatin, vinblastine	19 $P=ns$	NR

* The control arm was radiation alone.
 NCI = National Cancer Institute
 CALGB = Cancer and Leukemia Group B
 c = clinical stage
 p = pathologic stage
 NR = not reported
 ns = not significant

included. Sixty patients were randomized to induction therapy that included cyclophosphamide (500 mg/m²), etoposide (100 mg/m² daily × 3), and cisplatin (100 mg/m²) followed by surgery, vs surgery alone. Responding and completely resected patients in the induction arm received additional chemotherapy after surgery. Postoperative radiation was reserved for those patients who had unresectable or incompletely resected tumors. Investigators reported a major response rate (complete response plus partial response) of 35% to induction chemotherapy. Long-term follow-up data have recently been reported.²⁸ The median survival for the perioperative chemotherapy arm was 21 months compared to 14 months for surgery alone ($P=0.056$ by log rank test; $P=0.048$ by Wilcoxon test), with a five-year survival of 36% vs 15%, respectively. This trial has been criticized because of a postoperative stage imbalance with 40% stage IIIB and IV patients in the surgery-alone arm compared with 11% in the chemotherapy arm. However, given that both arms were well balanced with preoperative staging, this may be more reflective of downstaging due to induction therapy. Therefore, its impact on the survival difference between the two arms is unclear.

Three of the randomized trials have focused specifically on patients with surgically staged N2 disease. National Cancer Institute (NCI) investigators randomized patients with N2 disease that was documented by mediastinotomy, mediastinoscopy, or Wang needle biopsy to immediate surgery with postoperative radiation (54 to 60 Gy) or two cycles of induction cisplatin (80 mg/m² on day 1) and etoposide (120 mg/m² on days 1-3) prior to surgery.²⁶ Responding patients in the induction arm received four additional cycles of chemotherapy postoperatively. This trial was reported after the accrual of only 27 patients. The radiographic response rate to the induction regimen was 60%. There was a trend toward improved survival for patients who received induction chemotherapy, but this was not statistically significant (28.7 months vs 15.6 months, $P=0.095$).²²

In a CALGB trial,²⁶ patients with surgically staged N2 disease were randomized to preoperative radiation (40 Gy) vs two cycles of preoperative cisplatin (35 mg/m² on days 1-3) and etoposide (200 mg/m² on days 1-3) with granulocyte colony-stimulating factor support. Patients in the induction chemotherapy arm received two additional cycles of chemotherapy postoperatively, and both arms were treated with radiotherapy (total dose = 54 to 60 Gy). Like the NCI trial, accrual was slower than anticipated, and the trial was terminated short of the enrollment goal after the accrual of 57 patients. An improved response rate was reported for those patients who received chemotherapy (47% vs 38%), although this did not translate into a survival ben-

efit (median survival = 19 months with induction chemotherapy vs 23 months with radiotherapy and surgery, $P=0.64$).

Finally, in a trial conducted by the National Cancer Institute of Canada,²⁷ patients with biopsy-proven N2 disease were randomized to a control arm that consisted of radiation alone or to preoperative chemotherapy followed by resection. The induction regimen consisted of cisplatin (120 mg/m² days 1 and 29) and vinblastine (6 mg/m² days 1, 15, 22, 29, and 43). After results from the Radiation Therapy Oncology Group study (RTOG) 88-08²⁹ were published showing a survival benefit with chemoradiotherapy over radiation alone in inoperable patients, this trial was stopped early due to a concern over the use of a radiation-alone control arm for this population of patients. The radiographic response rate did not differ significantly in either arm (50% with induction chemotherapy vs 53% with radiotherapy). The median survival was 18.7 months and 16.2 months for the induction chemotherapy/surgery and radiation-alone arms, respectively, but this was also not statistically significant.²⁷

Much like the phase II experience, heterogeneity in patient populations and treatment regimens make drawing firm conclusions from these trials somewhat difficult. All five are limited by small sample size. The results from the trials by Rosell et al^{23,24} and Roth et al²⁵ are encouraging, and both trials were stopped appropriately after an interim analysis identified a significant survival benefit. However, the positive results in both trials may be partially explained by an imbalance in stage or other poor prognostic factors. Furthermore, both trials included patients with T3 N0 tumors. Therefore, any attempt to generalize these results to all patients with stage IIIA disease, especially those with confirmed N2 involvement prior to surgery, is not possible. The latter three trials were well done in that all patients were surgically staged and a specific N2 population was studied. However, a significant survival benefit was not seen in any of these trials.

Induction Chemotherapy for Early-Stage Disease

Recent investigators have attempted to study the role of induction chemotherapy in patients with early-stage (IB-III A) non-small cell lung cancer because of the substantial proportion of these patients who develop recurrent disease following resection (Table 4). A phase II trial known as the Bimodality Lung Oncology Trial (BLOT),³⁰ presented in abstract form, included 94 patients with T2 N0, T1-2 N1, and T3 N0-1 tumors (stage IB, IIA, and IIB). Patients were treated with two cycles

Table 4. — Ongoing and Planned Phase III Trials of Induction Chemotherapy in Resectable Early-Stage Non-Small Cell Lung Cancer

Trial	Patients	Treatment Arms
Bimodality Lung Oncology Trial ³⁰	Resectable stage IB, IIA, IIB and selected IIIA (T3 N1)	Arm 1: surgery alone Arm 2: induction carboplatin/paclitaxel × 3 cycles
Medical Research Council LU-22 ³¹	Resectable stage I, II, IIIA	Arm 1: surgery alone Arm 2: group 1 - induction MVC × 3 cycles group 2 - induction MIC × 3 cycles
French Thoracic Cooperative Group ³²	Resectable stage I, II, IIIA	Arm 1: surgery alone Arm 2: induction MIC × 2 cycles

MIC = mitomycin, ifosfamide, and cisplatin
MVC = mitomycin, vinblastine, and cisplatin

of induction paclitaxel (225 mg/m²) and carboplatin (AUC 6) prior to surgery, followed by three additional cycles postoperatively for completely resected patients. The major response rate to the induction chemotherapy was 54%. Survival data have not yet been reported. British investigators have presented similar results in a pilot randomized phase II study of induction mitomycin, vinblastine, and cisplatin in 22 patients with early-stage disease.³¹ Toxicity was not excessive in either of these trials.

The French Thoracic Cooperative Group has presented preliminary phase III data of induction therapy in this population.³² A total of 373 patients with clinical stage IB-IIIa disease (including N2 mediastinal nodes) were randomized to immediate surgery vs induction mitomycin (6 mg/m²), ifosfamide (1.5 g/m² daily × 3), and cisplatin (30 mg/m²) followed by surgery. Responding patients received additional chemotherapy postoperatively. Patients with T3 or N2 tumors were treated with postoperative radiation (60 Gy) as well. The response rate to induction therapy was 64% (11% pathologic complete response). Median survival appeared to favor those patients treated with chemotherapy, although this was not statistically significant at the time of the analysis (36 vs 26 months, *P*=0.11). The three-year overall survival rate was 49% and 41%, respectively. Unlike the BLOT and British trials, there was a trend towards increased perioperative toxicity in the induction arm that was related predominantly to the development of bronchopleural fistula. The hazard ratio for death was nonproportional, and a delayed survival benefit was seen when survival was analyzed beginning five months from surgery (relative risk = 0.71, *P*=0.03). This benefit was largely restricted to N0-1 patients (*P*=0.02). Additional follow-up is needed before definitive conclusions can be drawn. An ongoing phase III study by the Medical Research Council (MRC LU-22), as well as a planned randomized trial comparing the BLOT regimen to surgery alone, will also be helpful in defining the role of induction therapy in patients with early-stage disease.³¹

Induction Chemotherapy and Radiation

Combined-modality treatment with chemotherapy and radiation has become the standard approach for patients with stage III disease who have not been resected. Dillman and colleagues³³ reported a survival benefit with sequential cisplatin and vinblastine followed by radiation compared with radiation alone for patients with stage IIIa and IIb disease. These results are consistent with those from other randomized studies.^{29,34} Thus, the benefit of chemotherapy and radiation compared to radiation alone for selected stage IIIa and IIb patients who are not resected is well established. Whether preoperative therapy in these stage III patients should involve chemotherapy and radiation or chemotherapy alone has not been well studied. In the phase II induction trial of chemotherapy alone conducted by the CALGB,³⁵ the major site of disease progression during chemotherapy occurred locally, suggesting a potential role for the addition of radiotherapy to maximize local control and tumor downstaging prior to surgery. However, in the overview of the phase II experience with induction therapy reported by Shepherd,⁷ there did not appear to be a clear benefit for combining both modalities preoperatively. There have not been enough patients studied in the phase III setting to accurately answer this question, although in a small randomized trial comparing induction chemoradiotherapy to surgery alone reported by Yoneda and colleagues,³⁶ a survival benefit was not reported.

The majority of early trials that suggested a beneficial impact on survival for combined chemoradiotherapy in inoperable patients utilized a sequential schedule.^{29,33,34} However, this may not represent the optimal scheduling of these modalities for several theoretical reasons, including the potential for increased tumor cell repopulation during radiation, the selection of drug-resistant cells, and the stimulation of metastases.³⁷ These theoretical concerns are believed to be less likely with concurrent scheduling of chemotherapy and

radiation, although the potential for overlapping toxicity may be greater.³⁷ There has been some suggestion in sequential combined-modality trials that, while distant metastases are decreased, local control remains relatively poor.³⁸ Concurrent chemotherapy plus radiation and hyperfractionated radiotherapy (hfRT) schedules are two strategies that have been associated with improved local control and survival in randomized trials of patients with inoperable stage III tumors.^{39,41} In a recently updated trial⁴² comparing sequential and concurrent scheduling of chemoradiotherapy for unresected stage III patients, there was a survival benefit associated with the concurrent administration of both modalities.

Table 5 represents selected phase II trials that incorporate both of these strategies into induction regimens. Importantly, in all four trials, patients were surgically staged prior to starting therapy. Furthermore, unlike the phase II trials presented previously, three of these trials included patients with stage IIIB tumors (either T4 or N3).^{43,45} In addition, although the Massachusetts General Hospital series⁴⁶ focused on a pure N2 study population, 67% of the patients had clinically evident nodal disease as defined by lymph nodes greater than 1 cm on computed tomography (CT). Despite the advanced stage of these patients, the complete resection rate and overall survival was comparable to the phase II trials of induction chemotherapy alone. Local tumor control was generally good, and the majority of relapses appeared to occur at distant sites. In the Southwest Oncology Group (SWOG) 8805 trial,^{43,47} the initial relapse sites were locoregional in only 11%, dis-

tant in only 61%, and combined in 28%, with 40% ultimately relapsing in the central nervous system.

To date, only one randomized trial⁴⁸ has compared induction concurrent chemoradiotherapy to chemotherapy alone. In this trial, 69 stage IIIA (N2) and IIIB (T4) patients were randomized either to preoperative concurrent cisplatin (100 mg/m² on day 1 and day 29), 5-fluorouracil (continuous infusion on days 1 to 4 and days 29 to 32), and radiation (30 Gy in 15 fractions) or to induction cisplatin (100 mg/m² on days 1, 29, and 71), mitomycin (8 mg/m² on days 1, 29, and 71), and vinblastine (4.5 mg/m² every 2 weeks for 6 doses) alone. The radiographic response rate (67% vs 44%, *P*=0.02), resectability rate (52% vs 31%, *P*=0.03), and freedom from progression (40% vs 21%, *P*=0.04) all favored the concurrent arm. However, overall survival data were not reported. German investigators have recently presented toxicity data from an ongoing randomized trial⁴⁹ comparing induction chemotherapy followed by concurrent hfRT and chemotherapy vs induction chemotherapy alone for patients with surgically staged IIIA and IIIB disease. When completed, this trial should help further define the impact on downstaging, resectability, and survival associated with an aggressive induction chemoradiotherapy approach.

An unanswered question concerns the role of surgery after chemoradiotherapy in patients with histologically confirmed stage IIIA (bulky) N2 or stage IIIB disease. These patients are generally considered inoperable and have usually been included in nonsurgical combined-modality trials. Although this population of

Table 5. — Selected Phase II Trials of Induction Chemoradiotherapy in Non-Small Cell Lung Cancer

Trial	Number of Patients	Substage	Induction	RR	Complete Resection*	Treatment Mortality	Overall Survival
SWOG 8805 ⁴³	126	p T1-3 N2 (60%) p T4 or N3 (40%)	Cisplatin, etoposide, concurrent XRT 40 Gy	59%	71% (overall)	10%	27% (3 yr) IIIA 24% (3 yr) IIIB
German ⁴⁵	54	p T1-3 N2 (46%) p T4 or N3 (54%)	Ifosfamide, carboplatin, etoposide × 2, then concurrent hfRT 45 Gy, carboplatin, etoposide	69%	63%	9%	30% (3 yr)
MGH ⁴⁶	42	p T1-3 N2 (100%)	Cisplatin, vinblastine, 5FU, concurrent hfRT 42 Gy	74%	81%	7%	37% (5 yr)
WGCC ⁴⁴	94	p T3 N0 (6%) p T1-3 N2 (49%) p T4 or N3 (45%)	Cisplatin, etoposide × 3, then concurrent hfRT 45 Gy	64%	53%	6%	31% (4 yr) IIIA 26% (4 yr) IIIB

* Percent of all evaluable patients.
 RR = response rate to induction chemotherapy
 SWOG = Southwest Oncology Group
 MGH = Massachusetts General Hospital
 WGCC = West German Cancer Center
 hfRT = hyperfractionated radiotherapy
 c = clinical stage
 p = pathologic stage

Table 6. — Ongoing Phase III Trials of Induction Therapy in Locally Advanced Non-Small Cell Lung Cancer

Trial	Patients	Treatment Arms
Intergroup 0139 ⁴⁹	Stage IIIA (T1-3 N2)	Arm 1: concurrent cisplatin, etoposide and radiation followed by surgery Arm 2: concurrent cisplatin, etoposide and radiation
EORTC-08941	Stage IIIA (T1-3 N2) responding to induction chemotherapy	Arm 1: surgery Arm 2: radiation
MRC-LU20	Stage IIIA (T3 N1 or T1-3 N2), unresectable	Arm 1: radiation Arm 2: induction MVP or MIC followed by surgery or radiation

MVP = mitomycin, vinblastine, cisplatin
MIC = mitomycin, ifosfamide, cisplatin

patients has been included in recent phase II induction trials, there has not yet been a randomized study that has shown a survival benefit associated with the resection of locoregional disease after combined-modality therapy. An ongoing Intergroup trial⁵⁰ is attempting to define the role of surgery in this setting. This study focuses on patients with confirmed N2 disease and randomizes them to surgery or additional radiation after induction with concurrent chemoradiotherapy. Table 6 outlines this trial as well as other ongoing phase III trials that are attempting to define the optimal combination of modalities for this population of patients.

Tumor Downstaging

In phase II trials, tumor downstaging has consistently been associated with improved long-term survival. In CALGB 8935, tumor downstaging occurred in 22% of the patients (to N1 in 9% and to N0 in 13%).¹⁶ This compares to 39% in the Memorial Sloan-Kettering (MSK) series¹⁷ and 67% in the Massachusetts General Hospital (MGH) series.⁴⁶ The five-year survival from the start of therapy for those patients treated in the MGH trial for postoperative pathologic stage 0 and I, stage II, and stage III was 79%, 42%, and 18%, respectively ($P=0.04$). In the MSK trial,⁵¹ a complete pathologic response (stage 0) resulted in an estimated five-year survival from the start of therapy of 54%. In SWOG 8805,⁴³ the best predictor for long-term survival in univariate analysis was the presence of negative mediastinal nodes in the postoperative specimen. The three-year survival rate was 44% for this population compared with 18% for those patients with persistent nodal disease. For the subset of completely resected patients who had documented nodal involvement prior to treatment, the three-year survival for the postoperative node-negative and node-positive groups was 41% and 11%, respectively.

In light of the poor long-term survival associated with the inability to downstage disease, the development of a strategy to assess the mediastinum prior to

definitive local therapy would be useful as both a prognostic tool as well as a guide for further treatment. In this regard, noninvasive testing would serve to avoid the additional morbidity associated with a second mediastinoscopy. Investigators from the Leuven Lung Cancer Group have reported pilot data investigating the role of PET scanning after induction therapy in nine patients.⁵² In this trial, PET scanning was performed prior to and after platinum-based induction chemotherapy. For patients who subsequently underwent surgery, the use of this modality was 100% accurate in defining the extent of mediastinal downstaging compared with 67% for CT scan alone. Confirmatory trials are clearly needed. However, data obtained from PET scanning may ultimately prove useful in guiding the optimal locoregional therapy for patients who have been treated with induction therapy.

Toxicity

In phase II trials, the morbidity and mortality associated with induction therapy have largely depended on the particular treatment regimen. Hematologic, gastrointestinal, and pulmonary toxicities are the most commonly described. Myelosuppression is typically transient and well tolerated, although serious infectious complications, including occasional treatment-related deaths, have been reported. In the CALGB 8935 trial,¹⁶ 6% of the patients experienced a serious (grade III) infection. Using similar cisplatin-based combination chemotherapy plus mitomycin, investigators at MSK¹⁷ and the University of Toronto¹⁹ reported rates of febrile neutropenia requiring hospitalization of 15% and 10%, respectively. The incidence of significant esophagitis and pneumonitis is usually higher when radiation is added to the induction therapy, especially in those series studying the impact of accelerated or concurrent radiation schedules. In the SWOG 8805 study,⁴³ serious (>grade III) esophagitis was seen in 11% of patients. This compares to 14% (grade IV) in the MGH series,⁴⁶ 8% (>grade III) in the German series,⁴⁵ and 43% (>grade III) in the West German Cancer Center (WGCC)

series.⁴⁴ Also of particular concern for those regimens utilizing preoperative radiation has been the incidence of bronchial-stump insufficiency. In both the WGCC trial⁴⁴ and the German trial,⁴⁵ this occurred in 5% and 10% of the patients, respectively. In both series, right-sided resections were more commonly associated with this complication, and the incidence decreased after protection of the bronchial stump by an intercostal muscle flap.

With this background, some investigators have raised concerns regarding the impact of induction therapy on perioperative complications. In a retrospective analysis, Vanderbilt investigators⁵³ reported a statistically significant increase in the incidence of life-threatening complications (defined as pneumonia, intubation, or transfer to the intensive care unit, $P=0.054$) in a cohort of patients treated with preoperative chemotherapy compared to a similar cohort of patients taken immediately to surgery. It should be noted, however, that the two patient populations differed in stage (median stage = 1.5 vs 2.5) and no multivariate analysis of potential etiologies for this observation was performed. In the BLOT trial, postoperative complications have been minimal, and there does not appear to be a striking increase in toxicity (K. W. Pisters, MD, personal communication, 1999).

In randomized trials, induction chemotherapy has generally been well tolerated without a consistent adverse effect on postoperative morbidity or mortality. While raising concerns about a potential detrimental effect on bronchial healing and postoperative pulmonary morbidity, the increase in bronchopleural fistula seen in the French trial³² may reflect the impact of mitomycin rather than an impact of induction chemotherapy in general. In contrast to this experience, the NCI, MD Anderson, and Spanish investigators²²⁻²⁵ did not report a significant increase in postoperative complications or mortality after induction chemotherapy. Whether the addition of radiotherapy or other newer chemotherapy agents will contribute to an increase in postoperative complications has not yet been established.

Conclusions

Given the propensity for local and distant relapse, the combined-modality approach is considered by many to be the standard of care for the majority of patients with non-small cell lung cancer. Over the last decade, several randomized trials have confirmed a survival benefit associated with the combination of chemotherapy and radiation over radiation alone for patients with unresectable stage IIIA or IIIB disease.

Although there are fewer randomized trials available for analysis involving patients with resectable stage III disease, overall these trials suggest that induction chemotherapy (with or without radiation) improves survival, particularly in those patients who undergo significant downstaging. Heterogeneous study populations limit the ability to define the optimal patient population who would most benefit from this approach. However, in randomized trials reported thus far, patients with N0-1 or minimal N2 disease appear to benefit the most. Although the phase II experience with patients who have bulky N2 or stage IIIB disease is encouraging, the added benefit of surgery for this traditionally unresectable patient population remains unknown.

Despite the suggestion of survival benefit associated with induction chemotherapy (with or without radiation), distant relapse remains a dominant factor limiting survival, especially for completely resected patients. This reflects the inability of current chemotherapy regimens to adequately control occult micrometastatic disease. Newer chemotherapy agents that may be more effective in this regard are now being studied in an effort to decrease distant relapse and improve survival. Given the problems with local control seen in sequential chemotherapy and standard radiation trials, hFRT and concurrent chemoradiotherapy schedules have been incorporated into combined-modality therapy without surgery for stage IIIA and IIIB patients. Although the phase II experience with these strategies in induction regimens has been extensive, a clear survival benefit over induction chemotherapy alone has not yet been seen. Toxicity concerns remain, and data from ongoing phase III trials will be necessary to define the optimal management strategy in the curative approach to resectable NSCLC.

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