ASSESSMENT OF PREOPERATIVE ACCELERATED RADIOTHERAPY AND CHEMOTHERAPY IN STAGE IIIA (N2) NON-SMALL-CELL LUNG CANCER

Forty patients with N2 non-small-cell lung cancer (stage IIIA), as determined by mediastinoscopy, were entered into a preoperative neoadjuvant study of chemotherapy (platinum, 5-fluorouracil, vinblastine) and accelerated radiotherapy (150 cGy twice per day for 7 days) for two cycles. Surgical resection was then performed and followed up with an additional cycle of chemotherapy and radiotherapy. All patients completed preoperative therapy. A major clinical response was seen in 87% of patients. Thirty-five patients underwent resection (one preoperative death, one refused operation, one had deterioration of pulmonary function, and two had pleural metastases). Operative mortality rate was 5.7% (2/35). Sixty percent of patients had no complications. Major complications included pulmonary emboli (three), pneumonia (two), and myocardial infarction (one). Downstaging was seen in 46% of patients, with two patients (5.7%) having no evidence of tumor in the specimen, five patients having sterilization of all lymph nodes, and nine patients having sterilization of mediastinal nodes but positive N1 nodes. Median survival of 40 patients was 28 months, with a projected 5-year survival of 43%. Patients with downstaged disease had statistically significant improved survival compared with patients whose disease was not downstaged. (J THORAC CARDIOVASC SURG 1996;111:123-33)

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The incidence of lung cancer continues to increase, especially among women. The number of new cases in 1995 is estimated to be 96,000 among men and 73,000 among women.[1] Lung cancer is the leading cause of cancer deaths among both men and women, accounting for an estimated 95,400 deaths among men and 62,000 among women.

Despite the enormity of the problem and the attention it has generated, little progress has been made in improving overall. The most recent edition of *Cancer Statistics* for 1995 reveals that the overall survival for lung cancer is still only 14% among whites and 11% among blacks, compared with 8% and 5%, respectively, in 1960. Although this is a statistically significant

increase, innovative treatment strategies are needed to improve even further the overall survival of this devastating cancer. It is estimated that about 43% of patients are initially seen with localized (15%) or regional (28%) disease, making this group the most likely target for further investigation.

Recent years have seen great improvements in surgical techniques to allow sleeve lobectomy, carinal resections, and other radical operations to be performed. These improvements have benefited a small number of patients. Progress in postoperative care and lung-sparing techniques have expanded the possibilities for high-risk patients and contributed to decreased postoperative morbidity and mortality rates. Unfortunately, these advancements are suitable only for a small percentage of the patients with lung cancer. Operation is accepted as the best therapy for stage I and II lung cancer, achieving cure rates between 40% and 80%. The results for more advanced local regional lung cancer have not been as good with operation alone. The current staging system for lung cancer has identified a subgroup of patients with a potentially more favorable prognosis. These patients have disease classified as stage IIIA,

which includes lung cancer invading the chest wall, superior sulcus tumors, and certain cases of affected ipsilateral mediastinal lymph nodes.

The group of patients with affected ipsilateral mediastinal lymph nodes represents a challenge and a possibility to improve the overall results. It is estimated that approximately 25% to 30% of patients with potentially operable lung cancer have affected mediastinal lymph nodes.[2, 3] A small subset of patients has been identified as having potentially favorable outcome—those with single tracheobronchial, intranodal metastases. This unfortunately situation represents only about 10% of the group with affected mediastinal nodes. If these nodes are found before operation by mediastinoscopy and treated with surgical resection and postoperative irradiation, the 5-year survival is approximately 10%.[2] If these nodes are found at the time of thoracotomy, after negative results of mediastinoscopy, and treated with resection and postoperative irradiation, the 5-year survival is about 30%.[2, 3] Even in this most favorable group, long-term survival is lower than desired, and the remaining 90% of patients with affected mediastinal nodes not in this favorable subset have an expected survival less than 10%. Because of the large number of patients, the poor results, and the possibility of affecting the overall prognosis of lung cancer, it is important to develop effective treatment strategies to deal with this group of patients.

Multimodality therapy of lung cancer has many theoretic advantages. Certain chemotherapeutic agents and radiotherapy have synergistic effects. The ability of certain chemotherapeutic agents to act as radiosensitizers may enhance the local control of tumors. If the chemotherapeutic agents are active against the neoplasms, they may be able to control micrometastatic disease that may be undectable at the time of presentation. There are also theoretic disadvantages, but in light of the poor outlook of this group of patients, the potential advantages seem to outweigh any negatives.

There is a growing body of data regarding the multimodality neoadjuvant approach to stage IIIA lung cancer.[4-10] To date, the optimal regimen has yet to be defined. Questions remain regarding whether chemotherapy is better alone or in combination with radiotherapy. Concern has been raised regarding the increased morbidity of preoperative radiotherapy in conjunction with chemotherapy. In an attempt to add to the body of knowledge regarding neoadjuvant therapy for stage IIIA lung cancer, as defined by mediastinoscopy-proven affected medias-

tinal nodes, we entered patients prospectively into a phase II preoperative trial of accelerated radiotherapy and chemotherapy.

Patients and methods

Eligibility. A consecutive group of patients with mediastinoscopy-proven affected ipsilateral mediastinal lymph nodes were eligible for the protocol (T1 to T3 N2). All patients had histologically proven non-small-cell lung cancer (NSCLC) (bronchoalveolar carcinoma was excluded). All patients were judged to have adequate lung function to undergo surgical resection, with predicted postoperative forced expiratory volume in 1 second (FEV$_1$) greater than 800 ml. All patients had negative results of bone scans, brain scans, and liver scans and were found to have normal adrenal glands by computed tomography. Patients were excluded if previous malignancy existed. Patients were required to have a granulocyte count greater than 1800 cells/μl, platelet count greater than 100,000 cells/μl, hemoglobin level greater than 10 gm/dl, blood urea nitrogen less than one fifth of normal values, bilirubin level less than 1.5 mg/dl, creatinine level less than 1.5 mg/dl, or creatinine clearance greater than 60 ml/min. Informed consent was obtained from all patients.

Treatment plan

Accelerated radiotherapy. A preoperative dose of 4200 cGy was delivered in two separate sessions by an accelerated schedule. The first session delivered 2100 cGy in 150 cGy fractions, twice daily with an intertreatment interval of 5 to 7 hours, 5 days a week for 1 week, starting on day 1. The second session delivered an additional dose of 2100 cGy in the same way, starting day 19 after a resting period of 10 days after the first session to avoid excessive dysphagia from anticipated esophagitis.

Chemotherapy. All patients received chemotherapy with 5-fluorouracil, vinblastine, and cisplatin, of which two cycles were given beginning on days 1 and 29. Doses were as follows: 5-fluorouracil at 30 mg · kg^{-1} · day^{-1} by 72-hour continuous infusion beginning day 1 of each cycle, cisplatin at 100 mg/m^2 given 2 to 6 hours after initiation 5-fluorouracil and administered over a 30-minute period, and intravenous vinblastine as a 4 mg · m^{-2} · day^{-1} bolus given on day 1. From 1 to 2 hours before cisplatin was given, 1 L of 5% dextrose in water and 0.5N saline solution with 8 meq magnesium sulfate was given. Immediately before cisplatin, 2.5 gm of mannitol was given intravenously over 10 minutes. Once cisplatin was given, 500 ml of 5% dextrose in water and 0.5N saline solution with 10 meq potassium chloride, 8 meq magnesium sulfate, and 12.5 gm of mannitol was given over a 2-hour period with replacement of urine output with an equal volume of 5% dextrose in water and 0.5N saline solution over a 24-hour period.

Operation. All patients underwent restaging of disease before surgical resection. Surgical resection, designed to take place on day 57, encompassed all known tumor at the time of operation and included mediastinal lymph node dissection in all patients. Because of the potential for bronchial stump complications, special precautions were taken to cover the bronchial stump with pedicled tissue flaps (intercostal muscle, pericardial fat pad, or even omentum in some cases). Each patient was given prophy-

laxis against deep venous thrombosis consisting of 5000 units of subcutaneous heparin before operation and twice daily after operation until that patient was fully ambulatory. Compression boots were placed before operation and continued after operation until the patient was fully ambulatory.

Additional therapy. After thoracotomy on day 85, all patients were to receive an additional 1800 cGy in 150 cGy fractions, twice daily with an intertreatment interval of 5 to 7 hours, 5 days a week for 6 treatment days. A third cycle of chemotherapy as previously described was also given on day 85.

All patients were monitored for toxic effects from chemotherapy and radiation therapy. Adjustments in doses and treatment intervals were made accordingly. Patients were monitored for tolerance to treatments, complications, ability to complete all treatments, surgical results, and survival. Response to treatment was categorized as complete disappearance of all measurable disease, as determined by radiographic examination. Partial response was determined when a reduction of greater than 50% compared with pretreatment measurements in the sum of the perpendicular diameters of measurable disease was observed. Regression was determined by a decrease in measurements agreed on by two independent investigators. Stable disease was determined by observation of a reduction of less than 50% or up to a 25% increase in measurements compared with pretreatment measurements.

Any patient with rapid progression of disease during treatment was removed from the protocol. If at any time the constraints of this protocol were determined to be detrimental to a patient's health, that patient was removed from the protocol.

Statistics. The survival curves were calculated by the Kaplan-Meier method.[11] The log-rank test was used to compare survival among subgroups. Follow-up data were obtained from direct patient contact, office records, or referring doctor's offices.

Results

Patient demographics. From January 1988 to December 1994, 40 patients were entered into the protocol. There were 26 male and 14 female patients. The mean age of the men was 56.4 years; mean age was 61 years for the women. The performance status of all patients was judged to be 0 or 1 (Karnovsky). The average FEV_1 of the 40 patients was 2.56 L (1.3 to 4.1 L). All patients had histologic proof by mediastinoscopy of NSCLC metastatic to mediastinal nodes. All but one patient had either ipsilateral paratracheal, tracheobronchial, or subcarinal nodes found to be affected by metastatic carcinoma (stage IIIA). The one patient entered into the study whose disease was technically IIIB was entered on the basis of an affected left tracheobronchial node and a primary lung cancer involving the carina. It was considered reasonable to include this patient because the left tracheobronchial node was in proximity to the

Table I. *TNM status before and after operation*

Status	No. of patients
Before operation	
T1N2	10
T2N2	24
T3N2	5
T4N3	1
After operation, downstaged	
T0N0	2
T1N0	5
T1N1	6
T2N1	3
After operation, unchanged	
T1N2	
T2N2	
T3N2	

primary lesion and would be removed en bloc fashion with the carinal pneumonectomy.

All patients completed preoperative radiotherapy. No patients were removed from the protocol because of toxic effects. One patient died at home after completion of chemoradiotherapy. One patient sustained an asystolic arrest at surgical exploration, was subsequently judged to have insufficient pulmonary reserve to withstand a bilobectomy, and underwent consolidative radiotherapy. Two patients were found to have pleural metastases before surgical resection and therefore did not undergo resection. The remaining 35 patients underwent surgical resection with curative intent. Of the 35 patients undergoing surgical resection, 32 received a third cycle of chemotherapy. Thirty-four of the 35 patients undergoing surgical resection received postoperative irradiation.

Histology. According to the final pathologic specimen, adenocarcinoma was the diagnosis in 25 patients and squamous cell carcinoma was the diagnosis in 15 patients. Adenocarcinoma was present in 15 men and squamous carcinoma was present in the remaining 11. Adenocarcinoma was present in 10 women and squamous carcinoma was present in the remaining four.

Nodal status. Single nodes only were affected in 27 patients (right paratracheal in nine, left tracheobronchial in seven, subaortic in six, subcarinal in four, and right tracheobronchial in one). Thirteen patients were found to have multiple positive nodes at the time of mediastinoscopy (right paratracheal and subcarinal in nine, right tracheobronchial and right paratracheal in three, and left tracheobronchial and subcarinal in one). The preoperative TNM statuses are shown in Table I.

Table II. *Operations performed on 35 patients*

Procedure	No. of patients
Right upper lobectomy	7
Sleeve right upper lobectomy	6
Right pneumonectomy	3
Right carinal pneumonectomy	2
Right upper and middle lobectomy	2
Right upper lobe and chest wall	1
Right lower and middle lobectomy	1
Left upper lobectomy	6
Left pneumonectomy	3
Left upper lobe and chest wall	1
Left lower lobectomy	1

Response to treatment. Treatment toxic effects were manageable in all patients. Moderate dysphagia and leukopenia were noted in 50% of patients. There were no deaths directly related to preoperative treatment. The single death before surgical resection was from a presumed pulmonary embolus after completion of preoperative treatments. This patient died at home and no post mortem examination was done. All patients had pathologic evidence of response to treatment, either by downstaging of disease or the presence of necrosis in the final specimen submitted for pathologic examination. Major clinical response (>50% reduction in tumor volume) was obtained in 87.5% of patients (35/40).

Operations. Thirty-five patients underwent resection of the primary tumor and mediastinal node dissection. All patients were judged to have complete resection at the time of operation on basis of the surgeon's judgment and results of intraoperative frozen-section examination. The operations are listed in Table II. This group is notable for the six sleeve right upper lobectomies and two carinal resections. The bronchial stump was covered with a viable pedicle of tissue in all patients. The pericardial fat pad was used in 15, a pedicled intercostal muscle was used in 14, omentum was used in four patients early in the experience, and pleura alone was used in two patients.

Resectability. As stated previously, 35 of the 40 patients underwent surgical resection (87.5%). All 35 patients who underwent resection (100%) were considered to have complete resections on the basis of the surgeon's judgment and results of intraoperative frozen-section examination. On final review, however, four patients had a change in interpretation, with affected margins being found on review of frozen sections in two cases and unsampled margins being called positive in two cases (88.5% complete

resections among those undergoing resection [31/35] and 77.5% among the entire protocol cohort [31/40]).

Mortality. There were three treatment-related deaths (7.5%). One 63-year-old woman who had completed her preoperative therapy died before operation. She died at home of a presumed pulmonary embolus. No post mortem examination was performed. There were two postoperative deaths (5.7%). One patient died of pneumonia 1 month after operation. This patient had a preoperative FEV_1 of 2.43 and had undergone a left upper lobectomy and chest wall resection. The second patient died of an arrhythmia and pulmonary embolus after a right upper lobectomy and chest wall resection. Preoperative FEV_1 was 2.02. Both patients who died after operation had dramatic responses to therapy, with no viable tumor anywhere in one patient and 90% radiation effect and negative lymph nodes in the other patient.

Morbidity. Twenty-one patients of the 35 undergoing resection had no postoperative complications (60%). A prolonged air leak (>7 days) and atrial fibrillation each occurred in five patients. There were three documented pulmonary emboli, one of which was fatal. Two patients had documented pneumonia, one case of which was fatal. There was a single instance each of gastrointestinal bleeding and myocardial infarction. One patient sustained an intraoperative asystolic arrest as a result of a contralateral tension pneumothorax at the institution of one-lung ventilation. This patient was successfully resuscitated but never was operated on because of diminished pulmonary reserve. One patient was found to have a completely atelectatic lung after postoperative radiation therapy was completed. This patient had previously undergone a sleeve right upper lobectomy and omental wrap. A delayed separation of the bronchus was diagnosed, necessitating completion pneumonectomy. The patient made an uneventful recovery from this operation.

Postoperative pathologic findings. Two of 35 patients (6%) were judged to have no evidence of tumor in their specimens. Five additional patients had no evidence of tumor in any examined lymph nodes but did have evidence of residual tumor in the primary site. Nine patients had residual tumor in the primary site with only N1 nodes having evidence of tumor. Sixteen patients overall had sterilization of previously affected mediastinal lymph nodes (46%). Twenty percent (7/35) had all nodes sterilized. The overall incidence of downstaging was 46% among
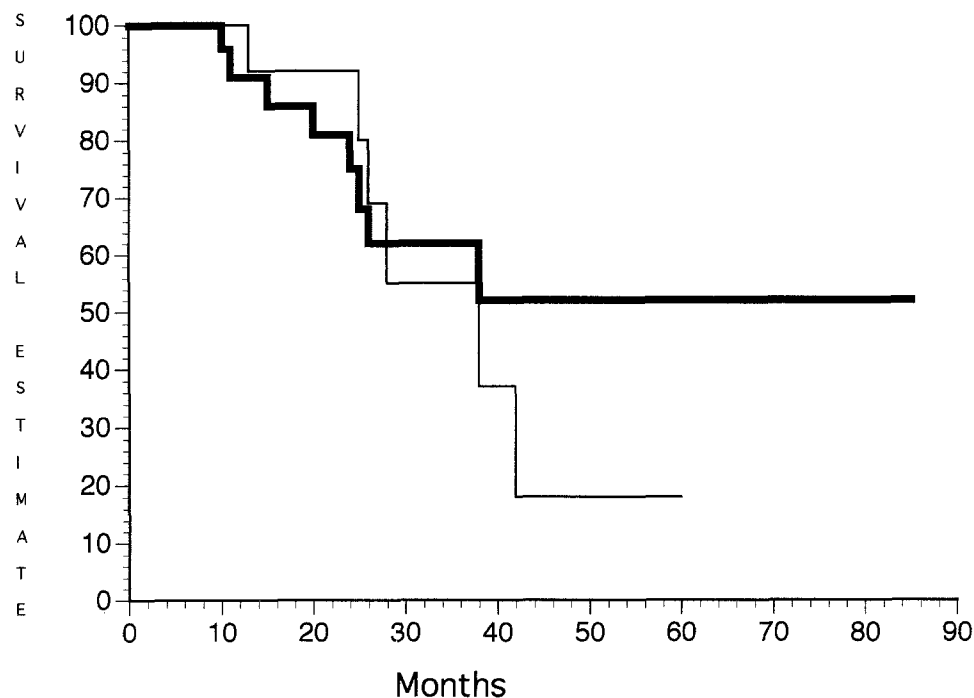
Fig. 1. Overall survival ($n = 40$).

patients who underwent resection (Table I). Fifty-four percent of all patients who underwent resection still had microscopic evidence of disease in mediastinal lymph nodes or showed essentially no change in overall stage of disease. The one patient judged to have stage IIIB disease on the basis of carinal involvement and a positive left tracheobronchial node was judged after operation to have T1 N0 status, with no tumor seen in lymph nodes and only a 4 mm residual tumor in the right main bronchus.

Survival. Follow-up has ranged from 4 months to 83 months. The median overall survival of the 40 patients was 28 ± 1.98 months (Fig. 1). The median overall survival of the 35 patients undergoing resection was 37 ± 1.74 months. The median survival of the patients whose disease was downstaged by preoperative chemotherapy and radiotherapy has not yet been reached, with 11 of 16 patients still alive. The median survival of those with disease that was not downstaged was 26 ± 1.1 months. Eight of 19 patients whose disease was not downstaged remain alive. The survival of the patients with downstaged disease was greater than that of those patients whose disease was not downstaged, and this represents a significant statistical difference ($p = 0.04$; Fig. 2). Analysis of the survival for patients with single node involvement compared with those with

multiple node involvement showed no statistical difference between the two groups, but a trend toward better long-term survival among patients with only single node involvement ws apparent (Fig. 3). Local-regional tumor control has been judged to be effective in 85% of patients (34/40).

Discussion

The goals of this phase II study were to determine the feasibility of this multimodal approach to the treatment of patients with histologically proven stage IIIA disease, toxic effects of therapy, response to therapy, resectability rate, postoperative morbidity and mortality rates, and survival. The study results were judged to be favorable on all accounts.

All patients who were entered into the protocol completed the preoperative phase of the study. Although moderate dysphagia or leukopenia occurred in 50% of patients, there were no deaths directly related to the treatment. Noncompliance was a factor in only one patient, who chose to delay operation because of fatigue. By the time this patient agreed to operation (4-month delay), metastatic disease was evident. A major clinical response (>50% reduction) was noted in 87.5% of patients.

Two patients were found to have pleural metastases (one before operation and one at exploration)
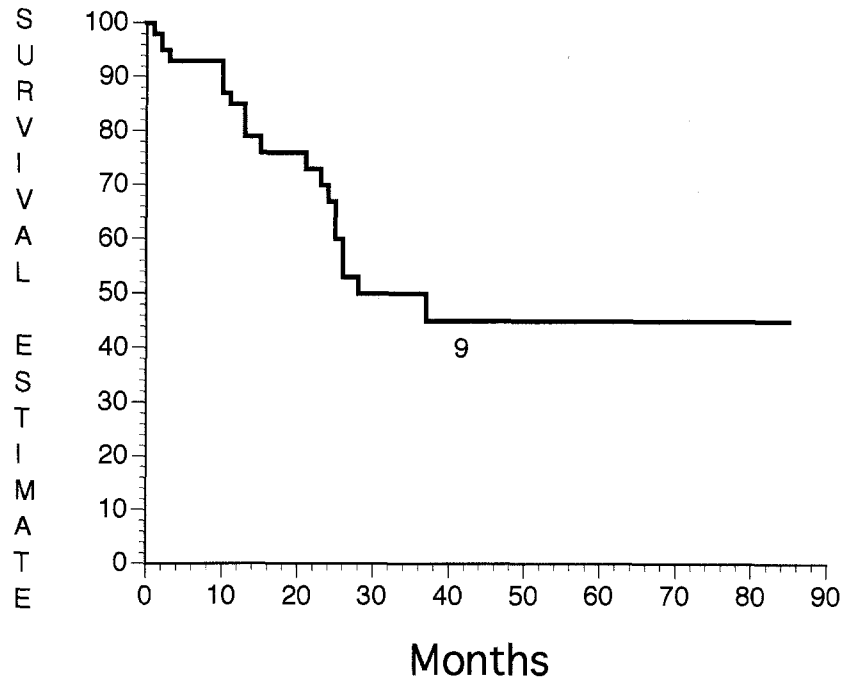
Fig. 2. Survival: patients with downstaged disease versus those with unresponsive disease.
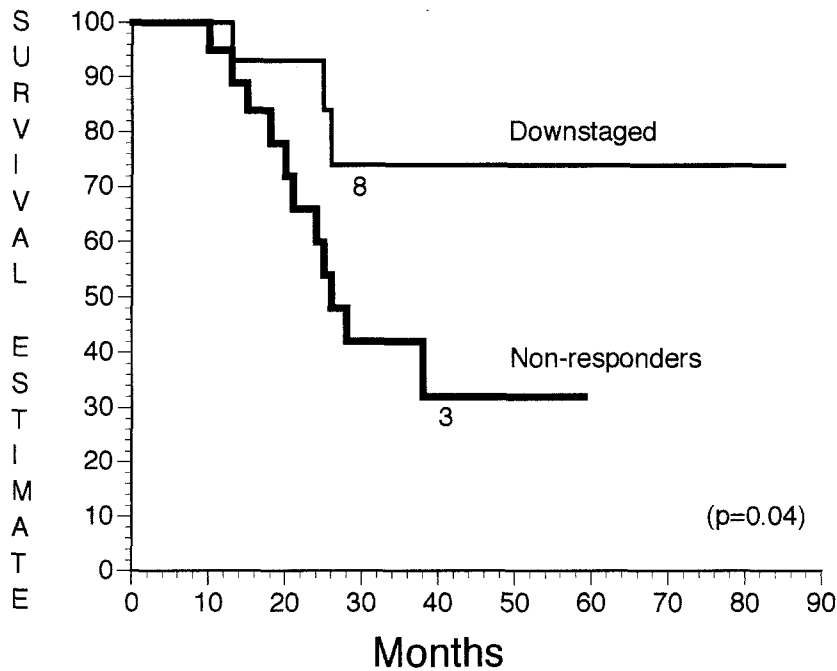

Fig. 3. Survival of patients with single *(bold line)* versus multiple *(narrow line)* affected nodes.

and did not undergo resection of the primary tumor. Thoracoscopy at the time of initial presentation might have detected this problem in these two patients and should be considered in the future to accurately assess patients with advanced stage disease before their entry into neoadjuvant protocols.

The ability of preoperative regimens to downstage disease has been demonstrated by others.[4-10] Of the

35 evaluable patients, only two patients had no evidence of disease in the entire specimen (6%), which is lower than the 20% figure others have reported (Table III).[6] Our previous experience with standard, daily radiotherapy and similar chemotherapy achieved a 16% rate of no evidence of disease in the resected specimen.[8] Downstaging by result of sterilization of mediastinal nodes in this study was achieved in 46% of the 35 patients who underwent resection, with complete sterilization of all lymph nodes in 20% of patients (7/35). The ability of neoadjuvant therapy to sterilize the mediastinum is an important aspect of this form of therapy and possibly has even greater implications in some patients with stage IIIB disease.[9]

The resectability rate in this group of patients has been excellent (Table IV). Of the 40 patients entered into this study, 35 underwent what was thought to be a curative resection (87.5%). Of the five patients who did not undergo resection, two might have been eliminated from the protocol in the beginning had thoracoscopy been done and detected their pleural metastases. One patient had a resectable lesion, but intraoperative anesthetic airway complications developed and the operation had to be stopped. One patient with a potentially resectable lesion delayed operation for 4 months and was then found to have metastatic disease. All 35 patients underwent resection presumed to be curative on the basis of intraoperative frozen sections and the surgeon's judgment. Four patients were classified in the final pathology report as having positive resection margins. Therefore, 31 of 35 resections (88.6%) were complete, and 31 of the original group of 40 patients (77.5%) had complete resections. This resectability rate is as good or better than that seen in most other series[4-10] and is better than our previous experience with another preoperative regimen[8] (Table IV).

The overall morbidity and mortality rates were quite acceptable. There were three deaths among the 40 patients entered into the protocol (one before and two after operation). The operative mortality rate of 5.7% is comparable to the other reports in the literature.[4-10] Both postoperative deaths appeared to be unrelated to the preoperative therapy. Morbidity was a concern because of the preoperative therapy and the planned postoperative therapy. Most surgeons elected to cover the bronchial stump with pedicled viable tissue to reduce the risk of postoperative bronchopleural fistula. There were no bronchopleural fistulas despite the use of

Table III. *Response rates to various neoadjuvant programs*

Study	No. of patients	NED (%)	% Downstaged
MSKCC	136	17	21
CALGB 8935	74	—	22 (10/46)
RUSH	128	22 (22/94)	—
MGH*	40	6 (2/35)	46 (16/35)

MSKCC, Memorial Sloan Kettering Cancer Center; *CALGB 8935*, Cancer and Leukemia Group B; *RUSH*, Rush–Presbyterian–St. Luke's; *MGH*, Massachusetts General Hospital; *NED*, no evidence of disease.
*This study.

preoperative and postoperative radiation and bronchoplastic procedures in eight patients. The single patient requiring a completion pneumonectomy had undergone a sleeve right upper lobectomy wrapped with pedicled omentum. After completion of the planned postoperative radiotherapy, the patient was found to have a totally atelectatic lung occluded by omentum. The two ends of the bronchial anastomosis were found to have separated, and completion pneumonectomy was required. Whether the problem was a technical problem or caused by the radiotherapy is unclear, but it is clear that the omentum prevented a catastrophic complication. Twenty-one of the 35 patients who underwent resection had no postoperative complications. None of the postoperative complications were considered directly related to the preoperative therapy.

There is a spectrum of disease that is classified as N2. The most favorable outcomes occur among patients with a single node containing intranodal microscopic deposits of tumor, preferably in a low tracheobronchial angle node. Multiple affected nodal sites have been found to carry a worse prognosis than a single affected nodal site, reducing survival by about 50%.[12] Matted nodes with extranodal involvement have generally not been suitable for resection and represent yet another group in this category. In a randomized prospective study, all of these factors would obviously need to be taken into account and reflected by proper stratification.

In our study, all patients with positive ipsilateral mediastinal nodes were entered into this study. In most patients (27/40), only a single nodal station was affected. It was difficult to determine retrospectively which of these patients would have been classified as in the favorable subset of patients with N2 nodes. To the best of our knowledge, roughly 75% would have been in the unfavorable category and therefore not subjected to operation. A preponderance of patients with favorable, single node involvement would ob-

Table IV. *Comparison of various resectability rates with various neoadjuvant regimens*

Study	Regimen	Entered (N)	Explored N	Explored %	Resection N	Resection %	Complete N	Complete %
MSKCC	MVP	136	114	84			89	65
CALGB 8935	P, Vbl; post XRT + P, Vbl	74	63	88	46	62	23	31
RUSH	Chemotherapy	128 (78%)	102	77	99	77	99	77
MGH*	Accelerated XRT; P, 5FU, Vbl	40	35	88	35	88	31	78

MSKCC, Memorial Sloan Kettering Cancer Center; *MVP,* mitomycin, vinblastine, platinum; *P,* platinum; *Vbl,* vinblastine; *XRT,* radiation therapy; *CALGB 8935,* Cancer and Leukemia Group B; *RUSH,* Rush–Presbyterian–St. Luke's; *MGH,* Massachusetts General Hospital; *5FU,* 5-fluorouracil.
*This study.

Table V. *Survival comparisons of different neoadjuvant regimens*

Study	Median (mo)	3-year (%)	5-year (%)
MSKCC	19	—	17
CALGB 8935	—	23	—
RUSH	22	—	34
MGH*	28	—	43

MSKCC, Memorial Sloan Kettering Cancer Center; *CALGB 8935,* the Cancer and Leukemia Group B (CALGB 8935); *RUSH,* Rush–Presbyterian–St. Luke's; *MGH,* Massachusetts General Hospital.
*This study.

viously skew the results of any study of neoadjuvant therapy. We could not identify better survival among patients with single node involvement, but we did see a trend toward improved survival after 30 months.

We had previous experience with neoadjuvant therapy for stage III disease and chose to change only one parameter.[8] We previously had used the same chemotherapy regimen with concurrent standard daily radiotherapy. We chose to use accelerated radiotherapy because of favorable experience treating other neoplasms and the theoretic advantages. This therapy has been shown to enhance tumor kill in rapidly dividing tumors. It has been shown to improve local control and possibly improve survival among patients with oropharyngeal cancer.[13] It also reduces the number of visits to the hospital in general, improving patient compliance. It has been reported to increase the incidence of esophagitis, but in our experience this side effect was only moderate. The overall impact of the accelerated radiotherapy seemed to be an increased resectability rate and improved survival compared with our earlier experience and the reports of others who used different preoperative regimens.[6-10]

We could find no correlation between radiographic and pathologic responses. All patients un-

derwent exploration regardless of radiographic findings. A complete pathologic response was found in only two of 35 resected specimens (5.7%). This is somewhat lower than in other reports (Table III). Memorial Sloan Kettering reported a 17% complete pathologic response rate with only chemotherapy before operation, and Rush–Presbyterian–St. Luke's reported a 22% complete pathologic response with preoperative chemotherapy and concurrent radiotherapy.[4, 10] Of greater importance, however, was the number of patients in our study whose disease was downstaged on the basis of negative mediastinal nodes (46%). The ability of this regimen to sterilize the mediastinal nodes certainly enhances our resectability rate and may translate into improved survival. The Memorial Sloan Kettering downstaging percentage was only 21% and the Cancer and Leukemia Group B (CALGB 8935) reported a downstaging figure of 22% among patients who underwent resection.[4, 10]

The ultimate test of any neoadjuvant therapy rests on the survival rate. Our study is too small with only intermediate follow-up available to allow us to make definitive conclusions. It does at least seem to be in line with other reports for treating patients with N2 disease (Table V). The projected overall survival of 43% and median survival of 28 months is comparable to those seen in other studies that used preoperative chemotherapy and radiotherapy[6] and somewhat better than those seen in studies that used chemotherapy alone.[4, 10] There was also a trend toward improved survival among patients with evidence of pathologic downstaging, as others have reported.[4, 6, 10]

Roth and colleagues[7] and Rosell and colleagues[5] have both conducted randomized prospective studies for stage IIIA NSCLC. Both groups used preoperative chemotherapy plus operation versus operation alone. Both trials treated patients with stage

IIIA disease, including some with T3N0 or T3N1 disease. Both trials showed a statistically significant improvement in survival for the chemotherapy-treated groups. These two studies lend credence to the concept of neoadjuvant therapy for stage IIIA NSCLC.

The body of work that exists regarding neoadjuvant therapy for stage IIIA NSCLC serves as an impetus for further randomized prospective studies. Large numbers of patients will be required so that proper stratification can be done to help determine which patients with advanced disease are best treated in this fashion. As mentioned previously, N2 disease is a spectrum, and it is important to define which subgroups benefit from this aggressive approach. Because of the magnitude of the undertaking of such a randomized trial, the cost, and the importance of the project, it is important that all of the pilot data be examined carefully to identify which regimen seems to offer the best chance for achieving the optimal result before committing all of the resources needed. There will continue to be a need for single-institution phase II trials to look for even more promising regimens.

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Discussion

Dr. Joseph LoCicero *(Boston, Mass.).* I appreciate the invitation to discuss this paper.

Congratulations to Dr. Mathisen and his colleagues on a carefully constructed study and, as usual, a skillful presentation. The manuscript that you kindly provided is most thoughtful. Since I received it early, our thoracic oncology program had an opportunity to review it, and some of these comments are collective.

Patients with stage III disease are complex, and, as Dr. Shields tried to teach me during my training, N2 disease is bad, but we make incremental progress with trials such as this one. It emphasizes the point that patients with local or regional disease should not be managed in the community but should be investigated at tertiary centers dedicated to improving survivorship through multimodal, multidisciplinary approaches.

To underscore the depth of this problem, I performed a MEDLINE search and found 17,000 articles on lung cancer since 1966. One hundred eighty-eight articles specifically dealt with N2 disease, and 114 of these have been published since 1991.

We obviously cannot address all of these issues today, but I would like to ask you a few questions. Everybody has slightly different criteria for performing mediastinoscopy. We at the Deaconess Hospital now perform mediastinoscopy on virtually all patients and use the CT scan only to guide our primary nodal targets. What are your specific criteria for mediastinoscopy, and do you think you have captured all of the patients with radiologically occult N2 nodes?

Many investigators, most of them members of this Association, have studied and published on patients with N2 disease. Martini and colleagues noted a negative

correlation between tumor size and survival. Do you have sufficient data from your 40 patients to confirm or refute this observation?

Pearson, Patterson, and Watanabe, all in different publications, have noted increased survival among patients with single-level versus multilevel N2 involvement. You have a number of single-station disease patients. Do you think that this group has a better survival?

Faber and colleagues have noted difficulty in completing rigorous postsurgical radiotherapy after a debilitating thoracotomy. Did all of your patients complete postsurgical therapy, and have you found any long-term debility in those patients who did?

Many radiation therapists do not favor split-course therapy, with some adjuvant therapy before operation and some after. For this reason, we use a preoperative neoadjuvant approach similar to the Southwest Oncology Group protocol reported by Rusch and associates. We give 56 Gy of standard radiation along with two concomitant cycles of cisplatin and etoposide, followed by resection on day 56. Isolated studies with this heavy-dose neoadjuvant therapy have predicted a 5-year survival between 28% and 50% in patients with completely resected disease. On the basis of your work, do you believe that we can now go back to the radiation therapists and say that there is justification for split-course therapy?

Finally, an international trial is being mounted to evaluate adjuvant therapy after primary resection. This proposed study plans to include patients with stage IIIA disease. On the basis of our collective experience from this Association and previous reports, as well as your report today, is this a backward step?

Dr. Mathisen. Regarding mediastinoscopy, it is our policy, as is yours, to perform mediastinoscopy on virtually everybody. It has been our experience that we have picked up nodal involvement in people who by CT scan would have been thought to have negative nodes somewhere on the order of 12% to 15%. It is a policy that we institute uniformly almost all the time. There is a possibility that an occasional patient with occult nodal disease could have been missed by mediastinoscopy, but it is doubtful.

In terms of tumor size, it is a small study and difficult to separate that out. Most of the patients were in the T2, T3 category. Any conclusion about tumor size is difficult because of the size of the study.

We have looked at the issue of single-level nodes versus multiple-level nodes. Dr. LoCicero received the manuscript on the fly, as it were, being pieced together at least to a point where he could read it, and one of the things I think that was left out from at least the version he had was this evaluation, looking at just that question of single versus multiple nodes in terms of survival. There was no statistically significant difference in survival, but there is a trend toward improved survival for patients who have only a single-node station involved.

With respect to the issue of therapy after operation, it certainly is a challenge, I think, in this group of patients who have undergone a lot with preoperative chemotherapy and radiotherapy and then surgery. If we looked at those patients who were available for therapy—in other words, if we eliminate those who had died, those who were found to have metastases—there were 34 patients. All of these patients received postoperative radiotherapy. About 25% to 30% of them had a reduction in the total amount, but all received a total dose of between 5100 cGy and 6000 cGy total between preoperative and postoperative therapy. In terms of chemotherapy, there were three patients that had their chemotherapy held and another half dozen or so who had reductions in the total amount of chemotherapy given afterward. By and large, however, the group got the planned postoperative therapy.

It is difficult, I think, to sort out long-term disability from the effects of operation versus the total effect of chemotherapy, radiotherapy, and operation. It is my impression that this group of patients, although somewhat wilted by the experience, have recovered well, and, at least in this interim analysis of the data, we do not see any long-term disability directly attributable to their neoadjuvant therapy.

With respect to the issue of split-course therapy, certainly our experience suggests that it is very well tolerated. It is associated with low morbidity. There is evidence that these twice-a-day treatments have some experimental and clinical benefit in terms of the overall tumor kill and local control, and I think our results are at least comparable to what others have seen with either higher doses or more conventional standard therapy. I think it does have a benefit for the patient in that it cuts down the amount of time spent going back and forth to the hospital. It is my impression in talking to the radiotherapists that the patients have a very positive feeling about that.

Regarding the trial that you have mentioned, I am not totally familiar with it. I believe that the door is still open for us to explore any number of different ideas. I do not think that it is necessarily true that preoperative therapy is better than postoperative therapy; it has never been subjected to any kind of analysis. Obviously patients with stage I and II disease have undergone operation, so I think therapy after resection for stage I and stage II disease is a viable field for investigation. Concerning patients who have identifiable stage IIIA disease, this option may have to be looked at. Certainly some people who have dealt with superior sulcus tumors feel strongly that resection followed by radiotherapy might be better than the conventional preoperative treatment. Again, I think it is something we need to keep an open mind about. I do not think that the evidence that we have so far is so conclusive that it eliminates any approaches from consideration at this point.

Dr. Willard A. Fry *(Evanston, Ill.).* I think that when a report comes out like this from a famous institution, people in the community may take this as standard of care, whereas this is just another well-presented phase II trial. I urge this audience to pay attention to some of the comments that Valerie Rusch has made. We have five major cooperative groups, and at least four of those have agreed that they will not have competing protocols. I think that if you feel strongly that you have a hot idea, you should present it to the group and work it out so that we can get some significant numbers. I am afraid that some doctors are going to make some great conclusions on the basis of 40 patients in a phase II trial, and I urge the assembly here to give serious consideration to supporting

the four clinical trial groups that have agreed to have no competing protocols.

Dr. Mathisen. I think your comments are absolutely appropriate. I think that it is important that the situation be carefully looked at when investing the time, effort, energy, and resources in a study such as you referred to in a multiinstitutional, multicooperative group so that the best regimen available is examined. I therefore agree with what you say about the need for that type of study. Because of the length of time it will take for that study to be completed, however, I think the door remains open for single-institution phase II studies to look for even more effective therapies, so that this hiatus from the inception of a randomized prospective trial is not a void of activity. This is a very challenging and difficult problem, and I'm certain that there are going to be even better solutions than what we currently have now, and I think those will come to light by single-institution Phase II trials.

Dr. Jack A. Roth *(Houston, Texas).* I think this is an interesting study and a well-presented series of patients.

A year ago two groups, our group and a group from Barcelona, presented what I believe are the only randomized studies looking at perioperative chemotherapy in NSCLC. These studies showed that the addition of three cycles of chemotherapy before and three after operation improved survival for patients with resectable stage IIIA disease. I think this study provides further evidence of that and emphasizes that surgery alone is no longer standard treatment for patients with clinically evident resectable stage IIIA lung cancer. In fact, long-term survival in your study is virtually identical to that of the patients in our study who received chemotherapy alone.

The total dose of chemotherapy in your study seems low, and I wonder if you had any explanation for the rather surprising systemic efficacy for this dose. Second, your treatment-related morbidity and mortality rates are high compared with those in other studies. You had a 10% treatment-related mortality rate. Perhaps the preoperative radiation therapy is actually contributing to this. Why not give a continuous course of radiation after operation only to patients with histologically positive margins?

Dr. Mathisen. With respect to the chemotherapy, we decided to change only one variable. We had previously looked at chemotherapy and radiotherapy, and we decided to continue with the same chemotherapy regimen and change only the radiotherapy. That was the reason for the selection of the chemotherapy doses.

Regarding the treatment-related morbidity and mortality rates, the 10% treatment-related death rate that you referred to was one patient who died before operation and two patients who died after operation (7.5%). I think these figures are not too dissimilar from those others have reported. It was difficult for me to identify any factors related to the treatment that caused these patients' death. Of the two who died after operation, one had pneumonia after a chest wall resection and the other had an arrhythmia and probably a pulmonary embolus, also after a chest wall resection. I therefore cannot specifically say that these deaths were directly related to the treatment.

Dr. William H. Warren *(Chicago, Ill.).* I wonder if you can comment on how you would now choose to cover your right main stem bronchial stump. We have had some difficulty with the supports that you have suggested here. We have started to use serratus anterior muscle to cover the stump as a broad muscle flap. Have you had an experience with that?

Dr. Mathisen. We have not, except in highly selected cases. It is my feeling, one shared by at least the majority of people who work at Massachusetts General, that with preoperative radiotherapy at least posing the potential for an increased incidence of bronchial stump problems operation we prefer to cover it with a pedicled intercostal muscle. As you saw, about half of the patients had that done. The pericardial fat pad was used about 40% of the time. I think that the important message is that it is important to cover the stump with something. We sew all of our stumps and then cover them, preferably with either fat pads or intercostal muscles. We have had good success, with no fistulas of which I am aware in nearly 75 patients in the two studies looking at preoperative chemotherapy and radiotherapy followed by surgery. I think how the closure is done and providing coverage with viable tissue is important to avoid such complications.