Survival of patients with clinical stage IIIA non–small cell lung cancer after induction therapy: Age, mediastinal downstaging, and extent of pulmonary resection as independent predictors

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Background: In clinical stage IIIA non–small cell lung cancer, the role of surgical resection, particularly pneumonectomy, after induction therapy remains controversial. Our objective was to determine factors predictive of survival after postinduction surgical resection.

Methods: We retrospectively reviewed a prospectively collected database of 136 patients who underwent surgical resection after induction chemotherapy (n = 119) or chemoradiation (n = 17) from June 1990 to January 2010.

Results: One hundred five lobectomies or bilobectomies and 31 pneumonectomies were performed. There was 1 perioperative death (pneumonectomy). Seventy-one patients had downstaging to N0 or N1 nodal status (52%). There were 2 complete pathologic responses. Median follow-up was 42 months (range, 0.69–136 months). Overall 5-year survival for entire cohort was 33% (36% lobectomy, 22% pneumonectomy, $P = .001$). Patients with pathologic downstaging to pN0 or pN1 had improved 5-year survival (45% vs 20%, $P = .003$). For patients with pN0 or pN1 disease, survival after lobectomy was better than after pneumonectomy (48% vs 27%, $P = .011$). In patients with residual N2 disease, there was no statistically significant survival difference between lobectomy and pneumonectomy (5-year survival, 21% vs 19%; $P = .136$). Multivariate analysis showed as independent predictors of survival age (hazard ratio, 1.05; $P = .002$), extent of resection (hazard ratio, 2.01; $P = .026$), and presence of residual pN2 (hazard ratio, 1.60; $P = .047$).

Conclusions: After induction therapy for patients with clinical stage IIIA disease, both pneumonectomy and lobectomy can be safely performed. Although survival after lobectomy is better, long-term survival can be accomplished after pneumonectomy for appropriately selected patients. Nodal downstaging is important determinant of survival, particularly after lobectomy. (*J Thorac Cardiovasc Surg* 2011;141:48-58)

Patients with clinical stage IIIA non–small cell lung cancer (NSCLC) show a broad spectrum of disease.¹⁻¹⁶ Although the disease at this stage is defined mainly by the presence of ipsilateral mediastinal nodal metastases, there is significant variability in both the extent and bulk of nodal involvement, as well as the size and extent of the primary tumor. Accordingly, resectability rates after preoperative therapy vary between 30% and 83%.¹⁻¹⁹ Because of the heterogeneity in disease presentation, there is reasonable controversy regarding the optimal treatment approach for these patients. Many have disputed the role of surgical

resection and consider that the best available evidence supports concurrent chemoradiation alone as the standard of care.^{7,11,14,20-25} In contrast, 2 small randomized trials and several large retrospective series have suggested that surgical resection after preoperative therapy may be a better option for at least a subset of patients.^{1,3,4,6,8-10,12,15,26} The precise role of surgical resection is not well defined, however, especially for patients with residual mediastinal nodal disease and those in whom a pneumonectomy may be necessary.^{4,5,13,27} For the purposes of this report, we retrospectively reviewed our results in a selected subset of patients with clinically staged N2 disease deemed resectable at presentation and treated by induction therapy before surgical resection. Our results reaffirm that sterilization of the mediastinal nodes is a dominant determinant of survival. The data also suggest that in this *selected* group of patients, surgical resection may be a useful modality in the presence of persistent nodal disease and that pneumonectomy is associated with a significant reduction in long-term survival, regardless of mediastinal nodal downstaging.

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Abbreviations and Acronyms

CI	= confidence interval
CT	= computed tomography
NSCLC	= non-small cell lung cancer
PET	= positron emission tomography

MATERIALS AND METHODS**Study Design and Patient Selection**

We conducted a retrospective review of a prospective lung cancer database to select patients with clinical stage IIIA NSCLC treated by neoadjuvant therapy followed by surgical resection. Patients were selected for review if they had mediastinal nodal metastases confirmed by either mediastinoscopy or radiographic criteria (positron emission tomography [PET] positive nodes at least 1.5 cm in size). Only patients with clearly resectable disease were considered for induction therapy. Patients with multistation mediastinal nodal disease were treated with preoperative intent only if a complete surgical resection was deemed probable before induction therapy. We excluded patients with contralateral nodal metastases (N3), extra-nodal extension at mediastinoscopy, clinical T4 disease, or severe cardiopulmonary impairment precluding surgical resection. Patients with multistation mediastinal nodal disease deemed technically unresectable before preoperative therapy were also excluded. This study was approved by the institutional review board of the New York Presbyterian Hospital–Weill Cornell Medical Center. Informed consent was waived.

Clinical Staging

All patients underwent preoperative evaluation with a complete history and physical examination, computed tomography (CT) of the chest and upper abdomen, a brain imaging study, and (since 2000) a fludeoxyglucose F 18 PET scan. A staging cervical mediastinoscopy was performed in 114 cases (84%). The remaining 22 patients were referred after neoadjuvant therapy was started on the basis of clinical N2 disease determined from nodal size on CT scan and nodal fludeoxyglucose F 18 uptake.

Neoadjuvant Therapy

One hundred nineteen patients received 2 to 3 cycles of induction chemotherapy (platinum/taxane doublets, $n = 104$) given every 3 weeks. The remainder ($n = 17$) received weekly chemotherapy with concurrent radiation, with the radiation dose varying between 40 and 54 Gy.

Clinical Response

Clinical response was determined by restaging CT and PET scans done 2 to 4 weeks after the last preoperative treatment. Clinical response (complete response, partial response, minimal response, stable disease, or disease progression) was determined by World Health Organization criteria before 2000 and subsequently by Response Evaluation Criteria In Solid Tumors (RECIST) criteria.²⁸ Major clinical responses included complete and partial responses, whereas patients with minimal response or stable disease were considered to have a minimal response. Restaging of the mediastinum by remediastinoscopy, endobronchial ultrasonography, or video-assisted thoracoscopy was not performed.

Surgical Resection

All patients underwent resection through an open thoracotomy. After the planned anatomic resection was completed, all patients underwent a complete mediastinal lymph node dissection, including nodal stations 2, 4, 7, 8, and 9 for right-sided tumors and 4, 5, 6, 7, 8, and 9 for left-sided tumors. A complete resection (R0) was defined as no residual gross

or microscopic disease detected at the bronchial or vascular margins and no residual disease in the mediastinum after nodal dissection. Incomplete resections (R1 and R2) were defined as the presence of microscopic residual tumor at the resected bronchial or vascular margins or residual unresectable nodal disease.

Data Collection and Statistical Considerations

Hospital and office records were reviewed for each patient for demographic and clinical data including age, sex, pretreatment clinical staging, induction therapy, surgical pathology, and adjuvant therapy. Data were expressed as medians or percentages. Bilobectomies and sleeve lobectomies were grouped with lobectomies for statistical analysis. To assess the association between categorical and outcome variables, χ^2 analyses were used. The nonparametric Mann–Whitney U test was used to assess the association between categorical variables and continuous outcomes. Median follow-up time was calculated on the basis of surviving patients. Overall survival and disease-free survival were estimated with the Kaplan–Meier method from the date of surgery because the date of initiation of preoperative therapy was not consistently available. Overall survival was estimated from the date of surgical resection until death from any cause or the date of last follow-up. Disease-free survival was estimated from the date of surgical resection until tumor recurrence or death from any cause. Comparisons of survival distributions between clinical factors were conducted with the log-rank test. All P values were 2-sided. Cox proportional hazards regression analysis was used to identify univariate predictors factors of survival that were thought to be of clinical significance a priori. All univariate predictors with a P value of .2 or less were entered into the multivariate model. The variables considered in the model included the following: age, sex, histologic type, clinical and pathologic T size, clinical N size, clinical response to therapy, residual pathologic nodal status, and extent of resection. Because there were 80 events (deaths) and 56 nonevents (live patients), the multivariate input was limited to no more than 6 factors. The statistical package used was SPSS statistical software version 17.0 (SPSS Inc, an IBM Company, Chicago, Ill).

RESULTS**Patient Characteristics**

One hundred thirty-six patients underwent surgical resection after induction therapy for clinical stage IIIA NSCLC between June 1990 and January 2010. Their median age was 64.0 years (range, 37–84 years), and most were women ($n = 79$). Patient demographic data, clinical staging information, and cell types are shown in Table 1.

Pretreatment Staging

Mediastinoscopy was performed in 114 patients (84%), 95 of whom (83%) had single-station mediastinal disease. The median number of sampled nodal stations at mediastinoscopy was 3 (range, 2–4). Patients in whom N2 disease was radiographically diagnosed without mediastinoscopy had significantly larger median primary tumor size than those with N2 disease detected by mediastinoscopy (5.20 cm vs 3.40 cm, $P = .002$) and significantly larger median mediastinal nodal size (2.15 cm vs 1.5 cm, $P < .001$) but comparable survival (data not shown).

Clinical Response

Sixty-one patients (45%) had a major clinical response (4 complete responses, 57 partial responses). Seventy-five

TABLE 1. Patient characteristics (n = 136)

Age (y, median and range)	64.0 (37–84)
Sex (no. female)	79 (58%)
Comorbidities (no.)	
Chronic obstructive pulmonary disease	50 (37%)
Coronary artery disease	11 (8%)
Hypertension	50 (37%)
Diabetes mellitus	14 (10%)
Smoking history	110 (81%)
Radiologic characteristics	
Clinical T size (cm, median, n = 123)	3.6
Clinical N size (cm, median, n = 116)	1.7
Positron emission tomography with or without computed tomography (no. since 2000)	102 (75%)
Mediastinoscopy (no.)	114 (84%)
Single station	95 (70%)
Multiple station	12 (9%)
Unknown	7 (5%)
Not performed	22 (16%)
cT status (no.)	
cT1	38 (28%)
cT2	85 (62%)
cT3	13 (10%)
Induction therapy (no.)	
Chemotherapy	119 (88%)
Chemoradiation	17 (12%)
Clinical response (no.)	
Complete	4 (3%)
Partial	57 (42%)
Minimal	21 (15%)
Stable disease	54 (40%)
Cell type (no.)	
Squamous	26 (19%)
Adenocarcinoma or bronchoalveolar carcinoma	89 (65%)
Other	21 (15%)

patients (55%) had either stable disease or a minimal response (Table 1).

Surgical Treatment

Lobectomy was performed in 93 patients, bilobectomy in 11 patients, and sleeve lobectomy in 1 patient. Thirty-one patients underwent pneumonectomy (23%). R0 resection was achieved in most cases (n = 131, 96.3%; Table 2). There were no in-hospital deaths among the lobectomy, bilobectomy, and sleeve lobectomy patients. There was 1 in-hospital death in the pneumonectomy group (3.2%); death was due to adult respiratory distress syndrome after a right pneumonectomy.

Postsurgical Pathology

Postsurgical staging is shown in Table 3. The median number of resected lymph nodes was 17, and the median number of positive nodes was 2 (range, 1–22). A complete pathologic response was observed in 2 patients (1.4%). Re-

TABLE 2. Surgical characteristics (n = 136)

Characteristic	No.	%
Procedure		
Lobectomy	93	68%
Sleeve resection (right upper lobe)	1	1%
Bilobectomy	11	8%
Pneumonectomy	31	23%
Right	13	
Left	18	
Completeness of resection		
R0	131	96.3%
R1 or R2	5	3.6%
In-hospital mortality	1	0.7%

sidual N2 disease was present in 65 patients (48%), whereas 71 patients (52%) had downstaging to N0 or N1 disease. Multilevel residual N2 disease was present in 16 patients (12%; Table 3). Although patients with a major clinical response were significantly more likely to have downstaging of disease in the mediastinum (42/61, 69%), 39% of patients with stable disease or minimal response also had sterilization of the mediastinal nodes (29/75, $P = .001$). There was a nonstatistically significant trend toward a higher probability of mediastinal nodal downstaging in patients treated by lobectomy than in those treated by pneumonectomy (lobectomy 56%, 59/105, pneumonectomy 39%, 12/31, $P = .104$). Median pathologic tumor size was significantly larger in patients undergoing pneumonectomy than in those undergoing lobectomy (4.3 cm vs. 2.5 cm, $P < .001$).

Adjuvant Therapy

Half of the patients received no adjuvant therapy (n = 68, 50%). The remainder received either chemotherapy (n = 11, 8%), radiation (n = 26, 19%), or both (n = 14, 10%). Radiation or chemoradiation were typically given

TABLE 3. Postsurgical pathology (n = 136)

Pathologic response	
Complete response	2 (1.4%)
Total nodes examined per patient (median and range)	17 (1–42)
Positive nodes pN2 per patient (median and range)	2 (1–22)
Residual pN2 disease	65 (48%)
Multilevel residual pN2 disease	16 (12%)
Pathologic stage*	
0	2 (1.4%)
IA	17 (12.5%)
IB	14 (10.3%)
IIA	14 (10.3%)
IIB	16 (11.8%)
IIIA	63 (46.3%)
IIIB	10 (7.4%)

Data represent numbers and percentages of patients except as noted. *Per Greene FL, Page DL, Fleming ID, Fritz A, Balch CM, Haller DG, et al. AJCC cancer staging manual. 6th ed. New York: Springer; 2002.

in cases of residual mediastinal nodal disease at the discretion of the medical oncologist. The adjuvant therapies for 17 patients (13%) are unknown.

Survival Analysis

Overall and disease-free survivals. Median follow-up for surviving patients was 42 months (range, 0.69–136 months). Median and 5-year overall survivals for the entire cohort were 31.8 months (95% confidence interval [CI], 25.6–38.0 months) and 33.4% (95% CI, 33.3%–33.5%), respectively. Median and 5-year disease-free survivals were 19.6 months (95% CI, 15.6–23.8 months) and 27.8% (95% CI, 19.0%–36.6%), respectively.

Survival and response. Five-year overall survival was better among patients with a major clinical response (complete response or partial response) than among all others (minimal response or stable disease, 43.8% vs 25.2%; $P = .024$). Patients with pathologic downstaging of disease to ypN0 or ypN1 had a significant improvement in 5-year overall survival relative to those with ypN2 disease (45% vs 20%, $P = .003$; Figure 1). Among patients with downstaging to ypN0 or ypN1, there was no significant difference in survival noted between those with ypN0 disease and those with ypN1 (47% vs 42%, $P = .450$). In the subset of patients with residual N2 disease, the level of ypN2 disease (multilevel vs single level) was not a significant predic-

tor of survival (hazard ratio, 1.12; 95% CI, 0.550–2.275; $P = .756$). Similarly, there was no difference in survival according to the level of cN2 disease determined at mediastinoscopy (38% vs 32%, $P = .500$).

Extent of resection and survival. Survival was significantly higher among patients treated by lobectomy than among those treated by pneumonectomy (36% vs 22%, $P = .001$; Figure 2). As shown in Figure 3, A, patients with downstaging to ypN0 or ypN1 had a 5-year survival of 48% after lobectomy and a 5-year survival of 27% after pneumonectomy ($P = .01$). There was no significant difference in 5-year survival between patients with residual N2 disease treated by lobectomy and those treated by pneumonectomy (21% vs 19%, $P = .136$; Figure 3, B).

Recurrence and Death

Disease recurred in 75 patients (55%): 56 patients after lobectomy (53%) and 19 patients after pneumonectomy (62%). Information about the site of first recurrence was available in 64 cases. The first site of recurrence was systemic in 50 patients (78%): 94% (16/17) after pneumonectomy and 72% (34/47) after lobectomy. For the whole cohort of 135 patients who survived hospitalization, local recurrence alone was the site of first recurrence in 13 patients (12%) after lobectomy and in 1 patient (10%) after

FIGURE 1. Overall survival, downstaged disease (ypN0 or ypN1) versus disease not downstaged (ypN2).

FIGURE 2. Overall survival, pneumonectomy versus lobectomy.

FIGURE 3. A, Overall survival, pneumonectomy versus lobectomy in patients with downstaged disease (ypN0 or ypN1). B, Overall survival, pneumonectomy versus lobectomy in patients with disease not downstaged (ypN2).

pneumonectomy. Deaths were predominantly cancer related in both the lobectomy and pneumonectomy groups (44.8% and 54.8%, respectively). Non-cancer related deaths were 11% in the lobectomy group and 16% in the pneumonectomy group ($P = .122$). Median times to disease recurrence were 8.00 months (95% CI, 7.96–14.24 months) after pneumonectomy and 23.20 months (95% CI, 15.40–30.96 months) after lobectomy ($P = .001$; Figure 4).

Univariate Analysis

The effects of several factors, including age, sex, clinical response, histologic type, clinical T and N size, pathologic T size, residual pN2 status, and extent of resection, on overall survival were tested with Cox regression analysis (Table 4). Five univariate predictors of survival were identified: age, clinical response, pathologic T size, the presence of residual N2 disease, and extent of resection (Table 4).

Multivariate Analysis

Univariate predictors with P values of at least .2 were entered into a multivariate model. This model identified extent of resection ($P = .026$) as an independent predictor of poor survival, along with age ($P = .002$) and the presence of residual pN2 disease ($P = .047$) (Table 5). A multivariate analysis examining the impact of the same factors on

disease-free survival yielded the same results (data not shown).

DISCUSSION

This series provides supportive evidence that sterilization of the mediastinum is an important predictor of good outcome. The data also suggest that although survival is undoubtedly best in patients with downstaged disease, the presence of persistent N2 disease should not preclude consideration of surgical resection in patients for whom a lobectomy is planned and an R0 resection is anticipated. In such circumstances, the expected 5-year survival is approximately 20%. The overall survival reported here for patients with ypN2 disease is generally similar to values previously reported by several randomized and phase II trials, as well as single-institution case series.^{1,5-7,9,10,12,14,15,17-19} In a phase II study, the Swiss Group for Clinical Cancer Research reported a 5-year survival of 16% for patients with persistent N2 disease after 3 cycles of docetaxel and cisplatin.^{6,19} Similarly, patients with residual ypN1 to ypN3 disease after induction chemoradiation in the surgical arm of the Intergroup trial 0139 and those with ypN1 to ypN3 disease after induction chemotherapy in the phase II Spanish Lung Cancer Group 9001 trials had 5-year survivals of 24% and 18%, respectively.^{7,12} Several

Patients at Risk

Survival (months)	0	12	24	36	48	60
Lobectomy	105	74	42	29	21	15
Pneumonectomy	31	10	6	5	4	3

FIGURE 4. Disease-free survival, pneumonectomy versus lobectomy.

retrospective institutional series have also reported 5-year survivals of 20% to 27% among patients with persistent N2 disease after induction therapy.^{4,8,10,13,17} Whether similar results in patients with ypN2 disease could be achievable by chemoradiation is in our view debatable.²⁰⁻²² A randomized trial by Dillman and colleagues comparing sequential chemoradiation to radiation alone in patients with clinical IIIA disease reported a 5-year survival of 17% in the chemoradiation arm of the trial.^{21,22} Although

these results are sometimes compared with surgical results, only 50% of patients in that trial were surgically staged. Furthermore, the reported 17% 5-year survival after chemoradiation reflects the aggregate survival of patients with and without mediastinal nodal downstaging. We therefore believe that the case against surgical resection in the face of persistent nodal metastases is not conclusive and requires further evaluation. In the meantime, the decision to proceed with surgical resection should be an individual determination that is based on age, performance status, comorbidities, the likelihood of achieving an R0 resection (especially if by lobectomy), and in no small measure, the availability of viable treatment alternatives.

Regardless, the larger question is whether surgical resection is ever appropriate for patients with cN2 disease. Two large randomized trials have suggested that postinduction surgical resection (specifically resection after chemoradiation) adds little or no benefit beyond that achieved by chemoradiation alone.^{7,15} Even in these trials, however, either patient selection criteria or insufficient accrual may limit generalization of the results to *all* patients with N2 disease. For example, the randomized European Organization for Research and Treatment of Cancer (EORTC) trial reported by van Meerbeeck and associates¹⁵ included patients with “unresectable” disease, and the reported resectability rate in the surgical arm of that trial was accordingly only 50%.¹⁵ This differs from our report in that we only considered patients with clearly resectable disease for treatment with preoperative intent. The intergroup randomized trial reported by Albain and colleagues⁷ showed no difference in the primary end point of overall survival between patients treated by chemoradiotherapy followed by surgery and those treated by chemoradiation alone. The study was prematurely closed because of poor accrual, however, having failed to accrue the sample size required to demonstrate the 10% survival benefit after surgical resection postulated by the investigators.

TABLE 4. Univariate predictors of survival

Variable	Subgroup	B	Hazard ratio	95% Confidence interval	P value
Age		0.028	1.03	1.01–1.05	.021
Sex	Male		1.00		
	Female	0.02	1.02	0.82–1.27	.859
Clinical response	Stable or minimal		1.00		
	Complete or partial	–0.520	0.59	0.38–0.94	.026
Histologic type	Nonsquamous		1.00		
	Squamous	0.382	1.47	0.87–2.48	.155
cT size		0.042	1.04	0.92–1.18	.499
cN size		0.085	1.09	0.70–1.70	.709
pT size		0.113	1.12	1.03–1.22	.007
pN status	pN0 or pN1		1.00		
	pN2	0.651	1.93	1.24–3.01	.004
Extent of resection	Lobectomy		1.00		
	Pneumonectomy	0.783	2.19	1.35–3.56	.002

TABLE 5. Multivariate predictors of survival

Variable	Subgroup	B	Hazard ratio	95% Confidence interval	P value
Age		0.047	1.05	1.02–1.08	.002
Clinical response	Stable or minimal		1.000		
	Complete or partial	−0.468	0.63	0.37–1.06	.082
Histologic type	Nonsquamous		1.00		
	Squamous	0.439	1.55	0.80–3.00	.193
pT size		0.033	1.034	0.94–1.14	.488
pN status	pN0 or pN1		1.00		
	pN2	0.469	1.60	1.01–2.54	.047
Extent of resection	Lobectomy		1.00		
	Pneumonectomy	0.699	2.01	1.09–3.71	.026

Furthermore, the 26% mortality after pneumonectomy, which was performed in nearly a third of those patients, may have negated any potential benefit from surgical resection. It is now generally accepted that such a high perioperative mortality after postinduction pneumonectomy may not reflect operative outcomes in specialized surgical centers.^{18,29} The question of surgical restaging the mediastinum by remediastinoscopy, video-assisted thoracoscopy, or endobronchial ultrasonography cannot be answered by our data. Advocates of such measures consider that resection in the face of persistent nodal disease in the mediastinum is not warranted, a view to which we do not subscribe in the absence of more definitive evidence.

A second controversial aspect in surgical treatment is the extent of parenchymal resection. Several studies have reported that in-hospital mortality after pneumonectomy is quite high, and it may be prohibitive after right pneumonectomy.¹³ Martin and coworkers¹³ reported on 97 patients treated by pneumonectomy after preoperative chemotherapy. Whereas in-hospital mortality was 11% overall, it was a much higher 24% after right pneumonectomy. Similarly, and as noted previously, in-hospital mortality after pneumonectomy was 26% in the surgical arm of the Intergroup 0139 trial.⁷ The same study showed no benefit in survival if patients were treated by chemotherapy or radiotherapy followed by pneumonectomy relative to a matched group of patients in the nonsurgical arm of the study. It is certainly possible that a perioperative mortality of 26% may have disguised any possible therapeutic benefit after resection, and some have advocated that sleeve lobectomy should be strongly considered as an alternative surgical option whenever possible. Some have also suggested that pneumonectomy is a disease entity unto itself, with a profound impact on cardiorespiratory physiology leading to decreased overall survival.³⁰ In our data set, despite a low in-hospital mortality, pneumonectomy was associated with both worse overall survival and worse disease-free survival relative to lobectomy, regardless of mediastinal downstaging. This finding suggests that the notion that survival after pneumonectomy may be improved if in-hospital mortality is reduced to acceptable levels may be incorrect. The poor

outcomes after pneumonectomy are also not likely to be averted if a sleeve lobectomy is done instead. In this study, patients undergoing pneumonectomy had a higher tumor burden, as shown by larger primary tumor size and bulkier nodal disease, factors that may have precluded lung-sparing resections.

Finally, our study does not attempt to answer the question regarding the optimal preoperative therapy. We can, however, make several observations that in the aggregate may argue against adding radiation to the preoperative regimen, at least for the patient population described in this work. First, the 52% rate of sterilization of the mediastinum in our study compares favorably with that reported after preoperative chemoradiotherapy in the Intergroup trial.⁷ Second, 12% of patients after lobectomy and 10% of patients after pneumonectomy had isolated local recurrence as the first site of relapse, whereas most recurrences (78%) were systemic in nature. This probably argues that the addition of another modality of local therapy may simply increase morbidity without translating into a major survival benefit. A recent randomized trial by the German Lung Cancer Cooperative Group showed that in comparison to preoperative chemotherapy alone, preoperative chemotherapy and radiation led to a higher complete pathologic response rate, but at the expense of higher morbidity and without an ultimate improvement in survival.¹⁴

Despite the prospective acquisition of the data, this study is limited by its retrospective nature. Therefore, hidden selection biases cannot be reasonably excluded. The study also extended through at least 2 decades, raising some concern regarding differences in treatment strategies and outcomes with time. Nonetheless, the surgical strategy of anatomic parenchymal resection and radical mediastinal nodal dissection and the chemotherapeutic strategy of a platinum-based doublet regimen have remained relatively stable through time within our group, thus diminishing the impact of that concern. Finally, some of our findings have to be considered with caution because of our small sample size. For example, the lack of a significant difference in survival between patients with single-level versus multilevel nodal disease is likely a reflection of our inability to detect

such a difference because of the limitations imposed on statistical analysis by the small sample size.

In conclusion, this retrospective analysis of surgical resection after induction therapy for clinical stage IIIA NSCLC demonstrates that surgical resection can be performed safely with long-term survival for appropriate patients. Our study suggests that the ideal patient who would benefit maximally from surgical resection after induction therapy for clinical IIIA disease is young, requires only lobectomy for complete resection, and has evidence of mediastinal downstaging. Our analysis, however, has insufficient data to suggest that patients with residual N2 disease after induction therapy should be excluded from surgical resection. Five-year survival even for nonideal patients, such as patients who undergo pneumonectomy with residual N2 disease, is approximately 20%, which may be acceptable for appropriate patients as long as operative mortality can be kept low.

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Discussion

Dr Gail E. Darling (Toronto, Ontario, Canada). Dr Paul, I thank you and your coauthors for providing me with the manuscript and your presentation in advance of the meeting. I compliment you for tackling this topic and also for your very commendable operative mortality, which is particularly outstanding for this group of patients.

During the study interval, you found 136 patients with N2 disease who underwent surgical resection after induction. How many patients with N2 disease were evaluated in your center, and how did you select patients for surgery?

Dr Paul. During that interval, probably around 450 patients had positive results of mediastinoscopy; however, those included patients who had likely stage III disease and some patients who probably underwent a mediastinoscopy for diagnosis as well. Because we are a referral center, we also get patients sent to us who have had positive results of mediastinoscopy at an outside institution and are coming in after induction therapy to undergo resection. So it's a fairly low number of patients who actually finally made it to surgery. In our series, it was probably around 20% to 25%. Our selection criteria are basically that patients must have good functional status and the cardiopulmonary ability to tolerate resection and also must have at least stable disease in response to induction therapy.

Dr Darling. Thank you. I noticed that 11% of patients had multiple-station N2 disease.

Dr Paul. Correct.

Dr Darling. So you did not exclude those patients from consideration for surgery?

Dr Paul. We did not.

Dr Darling. Among patients who did not have confirmation of N2 disease before induction, was there any evidence of tumor regression on final pathologic examination? We know that 40% of enlarged nodes on CT scan are actually benign, and 20% to 25% of hot nodes on PET scan are actually benign. So how can you be sure that those 22 who didn't actually undergo invasive staging before induction really did have N2 disease?

Dr Paul. Of those 22 patients, 11 patients had either N1 or N2 disease in the final pathologic specimen, so about 50%. Specifically, 7 of those 22 patients had N2 disease pathologically in the specimen. As well, we compared the survival of patients who underwent mediastinoscopy and patients who had disease diagnosed by radiographic criteria, and survival did not statistically differ between these groups.

Dr Darling. Did you consider analyzing the whole group without those patients?

Dr Paul. Sure. We also did the analysis excluding all 22 patients who had diagnoses based solely on radiographic criteria, and essentially we came up with the same conclusions. Our multivariate analysis showed age, extent of resection, and residual N2 as factors; however, the *P* value for one of them changed to be greater than .05. So it was a trend as opposed to being significant.

Dr Darling. In light of the importance of the mediastinal downstaging, do you have any recommendations for us in terms of whether we should be restaging the mediastinum? Would you not offer surgery to patients who have persistent N2 disease?

Dr Paul. Our policy has been not to restage the mediastinum, because we do offer resection to patients who have persistent N2 disease. We believe that a 20% 5-year survival is better than nothing.

Dr Robert J. Cerfolio (*Birmingham, Ala*). But you just showed that they did poorly. Are you going to change your recommendations from your own data?

Dr Paul. It depends on what the alternative is. If they have no viable alternative therapy that they can receive, we're not going to change.

Dr Mark J. Krasna (*Towson, Md*). Congratulations, Dr Paul, on an excellent presentation, and congratulations to you and your group for amazing mortality statistics.

I have a comment and a question. I think what you have done is help us to refine further who are the patients we should operate on after induction therapy. My personal bias, and that of Drs Cerfolio, Weder, and Venuta, 3 other people in the room who presented in the past year on either pneumonectomy or lobectomy, is that chemotherapy and radiation together might give you a better pathologic response and might give you better long-term survival, but I don't think that's the issue. You have done a very good job, though, in showing us exactly what Dr Cerfolio pointed out. That is, if you can determine up front that you have patients with persistent positive nodes, don't operate on them. If you find out up front that there are patients who have other predictors for poor long-term outcome, don't operate on them. We should only be operating on those patients for whom we can document downstaging and who had a good response. So I think the question of chemoradiotherapy versus chemotherapy would be interesting, but the same issue comes up. You should really be tackling those.

My question relates to, and I guess Dr Meyers needs to help us statistically, I'm sure there is statistical error. You had only 1 death. How could one death out of 27 pneumonectomies in the overall pneumonectomies and lobectomies still have survived both univariate and multivariate analysis to be an independent prognosticator? I think there has got to be some other explanation.

Dr Paul. The numbers are small, and we ran the numbers in various different ways, and I think it's a statistical thing that happens when numbers are that small.

Dr Krasna. I would suggest that the last conclusion may not in fact be upheld by that 1 death. I think there are enough confounders, although I can't explain them. The conclusion that pneumonectomy in fact is a poor independent prognosticator, I don't know whether that is upheld by that 1 death.

Dr Altorki. The issue of operating on patients with residual N2 disease is obviously controversial. In reality, however, although 20% survival in such patients is not great, I don't know that there are many other options out there to treat patients who have persistent N2 disease that is not responsive to chemotherapy. So I think at the very least, we can all agree that the question is open for discussion. If there were a clinical trial in which those patients could be realistically enrolled, I think that would be ideal, but there isn't, and until there is you would have to decide whether a lobectomy that can achieve an R0 resection with a 1% or 2% mortality is a reasonable option. I would contend that it is.

Dr Cerfolio. Dr Altorki, if it was more than 1 station and required a pneumonectomy, do you agree that you wouldn't do it?

Dr Altorki. Well, I think that the issue of multistation disease is interesting, because it's sometimes difficult to make that determination except intraoperatively.

Jean Deslauriers just told that he thought pneumonectomy is not a great operation. I agree with that. But regardless of its physiologic impact on the patient, it is a marker of higher tumor burden. At least in this study, the tumor bulk precluded treatment with a sleeve lobectomy. So the idea that we're going to somehow improve survival for these patients by avoiding pneumonectomy and doing sleeve lobectomy instead is an erroneous concept.

Dr Marcin Zielinski (*Zakopane, Poland*). You showed very nicely that some patients who do not have downstaging still have some chance for 5-year survival. Twenty percent is quite a good number of patients who can be long-term survivors. But the problem is determining which patients without downstaging have a chance for 5-year survival. In my institution, our policy is to restage these patients who are candidates for an operation with transcervical extended mediastinal lymphadenectomy, and the patients in whom we are able to completely resect the nodes and the number of the metastatic nodes is not so large are the ones for whom we propose resection. I think this is the group we choose with the best prognosis.

Of the patients without downstaging, with persistent N2 nodes, who are the best candidates for an operation, and who can expect 5-year survival? What is your policy?

Dr Paul. Well, first of all, I don't think our study is powered enough to answer that question. Our policy has been to offer resection to patients who are young and have good performance status, as long as we think, at least preoperatively looking at the scans, that we can do an adequate R0 resection, take out most of the nodal stations through a thoracotomy. I think it's a similar answer to what you're alluding to, that you can give them a good cleanout of the mediastinum by looking at the preoperative scans.

Dr Zielinski. But can you predict who will be the long-term survivors?

Dr Paul. We don't have the data to predict that.

Dr Frank C. Detterbeck (*New Haven, Conn*). Dr Paul, very nice study. I think this was very helpful. On the other hand, there are a couple pieces of data that are missing that I think would be helpful. One is just to elucidate very carefully what your philosophy was during this relatively long period. You have kind of said you didn't restage, anybody that looked reasonable you took to the operating room, but it would be nice to know a little bit more precisely what the philosophy was, so that we can interpret a little bit better what that means. Another piece of data that would be very interesting would be how many patients you ended up giving preoperative therapy to and then did not take to the operating room, just like Rob [Dr Cerfolio] had told us about 2 years ago, I think it was. I think that would help us kind of gauge how selective or nonselective you were. And the third piece of data that I would love to have would be, about those patients on whom you decided not to operate and who didn't have brain metastases or progressive disease, how did they do? If your 20% is better than 5%, then that's very convincing. If those patients actually also had 20%, then, of course, it's different.

Dr Paul. Dr Detterbeck, those are excellent questions, and actually when we originally approached this project, that was one of our aims, to see what happens to all those patients who had mediastinoscopy, got induction therapy, and never made it to surgery. Unfortunately, we get patients referred to us from all over the city who come from outside oncologists, and often they go back to those outside oncologists, and it's very difficult for us to assess actually what happened to them, what their survival was. That is an excellent question, and we are exploring ways of trying to answer it.

Dr Altorki. I think that's an important question, and I think the judgment regarding resectability is made at time zero. If the patient is deemed to have a resectable tumor, then he or she gets 3 or 4 cy-

cles of chemotherapy. I personally have not seen many patients progress from resectability to unresectability within that period.

Dr Paul DeLeyn (*Leuven, Belgium*). Thank you very much for this presentation. I think that many centers indeed have patients with persistent N2 disease who have a survival of 20% or 25%, but I would like to stress that mostly this is among selected patients, patients who had all aims of restaging, patients who had a good response on PET or CT. So probably there is some selection.

I have a few questions. Your complete resectability rate is very high when you compare it to the literature. Can you give us your definition of complete resectability? The highest lymph node, was it positive, negative?

Dr Paul. The highest lymph node being negative, as well as the bronchial margin being negative.

Dr DeLeyn. But this is very high.

Dr Paul. It's a high R0 rate. I recognize that.

Dr DeLeyn. Patients with persistent N2, did they get adjuvant radiotherapy?

Dr Paul. Patients with persistent N2, if they could tolerate adjuvant radiotherapy, did get it.

Dr DeLeyn. How many patients?

Dr Paul. I don't remember off the top of my head. It's in the article. It's probably on the order of about 60%.

Dr DeLeyn. And now that we have endobronchial ultrasonography or endoscopic ultrasonography for primary staging, is your current practice still to do mediastinoscopy?

Dr Paul. Our current policy is that we do not restage these patients if they—

Dr DeLeyn. I know, but do you still do mediastinoscopy?

Dr Paul. We still do mediastinoscopy on patients who have suspected N2 disease.

Dr Cerfolio. He wants to know whether you're saving the mediastinoscopy until after the neoadjuvant. So you're starting off with endobronchial ultrasonography and endoscopic ultrasonography and doing the mediastinoscopy second?

Dr Paul. We have not started doing that quite yet.

Dr Joe B. Putnam (*Nashville, Tenn*). I enjoyed your presentation and was intrigued by the number of patients who underwent an operation versus the denominator of about 450 patients who were treated. These procedures represent the ultimate in personalized surgical care, in that these patients were highly selected by the individual surgeon as capable of tolerating the operation, with a high likelihood of R0 resection, which you so clearly demonstrated. As you mentioned, these operations were done by accomplished surgeons, in an excellent center, supported by an experienced multidisciplinary team before the operation and a talented multispecialty team during the operation as well. So I think these findings reflect to some extent the advantages that come from a focused expertise in this area within a single hospital and may not be generalizable to hospitals broadly across the United States or internationally. Recognizing this personal approach, many patients have undergone chemotherapy and radiation in varying amounts and in various intervals between cessation of radiation and the time they appear in my outpatient clinic ready to have their tumor removed! Could you comment on the number of patients who had therapy outside your institution who were then operated on and on the interval between the induction chemoradiotherapy being concluded and the time the operation was performed?

Dr Paul. There were approximately 12 patients basically had their staging done at an outside institution and received chemotherapy. As for the interval, I'm not sure. Our general policy has been to wait about 3 to 4 weeks after the last dose of chemotherapy before operating.

Dr L. Penfield Faber (*Chicago, Ill*). I compliment you on an outstanding series that corresponds to our approach to clinically advanced lung cancer at the Rush University Medical Center.

I noted that you only had 2 complete pathologic responses. In other words, only 2 were sterilized, yet you had 49% downstaged. This is a very nice result of downstaging. On the other hand, we know that series that use "chemo-beamo," or chemoradiation, have 18% to 22% complete pathologic responses. These patients have long-term survival of 50%. So, I suggest your results might improve with chemoradiation rather than chemotherapy alone.

Dr Paul. We have a few thoughts on that. One is that our rate of nodal downstaging is similar to that which was published in the intergroup trial, which is roughly around 52%. In terms of recur-

rences, in most cases the site of first recurrence was distant. About 78% to 80% of the patients had distant disease as the site of first recurrence. In terms of local recurrence, rates were about 10% in the pneumonectomy group and 12% in the lobectomy group. Our thoughts are that we don't see how adding preoperative radiation is going to improve on those results. I think that's a controversial topic, however, and that's just our take on it.

Dr Faber. Different strokes for different folks. I have one historical comment. If you look very carefully at the picture of the pneumonectomy specimen removed by Evarts Graham, you will note that there were N2 nodes present. So it began on day 1. Resect those N2 nodes.

Dr Dominique H. Grunenwald (*Paris, France*). Excellent presentation. There is a question raised regarding the role of postoperative radiotherapy in N2 disease, and there is a place for a large clinical trial addressing this issue. That is what we are trying to do in Europe actually at this time, but with very great difficulties regarding inclusion of the patients, because N2 disease that is operated on and completely resected is rare.