Completely resected N1 non–small cell lung cancer: Factors affecting recurrence and long-term survival

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Objective: N1 disease in non–small cell lung cancer represents a heterogeneous patient subgroup with a 5-year survival of approximately 40%. Few reports have evaluated the correlation between N1 disease and tumor recurrence or which subgroup of patients would most benefit from adjuvant chemotherapy.

Methods: From 1997 through 2002, all patients with pathologic T1-4 N1 M0 non–small cell lung cancer who had a complete resection with systematic mediastinal lymphadenectomy were retrospectively analyzed and evaluated for factors associated with recurrence and long-term survival.

Results: One hundred eighty patients with N1 disease were evaluated. Sixty-six (37%) patients had either locoregional recurrence (n = 39 [22%]), distant metastasis (n = 41 [23%]), or both during follow-up. Univariate analysis demonstrated that visceral pleural invasion and age were associated with locoregional recurrence, whereas visceral pleural invasion, distinct N1 metastasis (as opposed to direct N1 invasion by the primary tumor), and multistation lymph node involvement were associated with distant metastasis ($P < .05$). Multivariable analysis demonstrated that visceral pleural invasion, multistation N1 involvement, and distinct N1 metastasis were the only independent predisposing factors for locoregional recurrence and distant metastasis. Overall 5-year survival was 42.5%. Survival was significantly decreased by advanced pathologic T classification ($P = .015$), visceral pleural invasion ($P < .0001$), and higher tumor grade ($P = .014$).

Conclusions: In patients with N1-positive non–small cell lung cancer, visceral pleural invasion, multistation N1 disease, and distinct N1 metastasis are independent predictors of subsequent locoregional recurrence and distant metastasis. Advanced T classification, visceral pleural invasion, and higher tumor grade were predictors of poor survival. These patients represent a subgroup of patients with N1 disease who might benefit from additional therapy, including adjuvant chemotherapy.

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Metastasis to the N1 lymph nodes in non–small cell lung cancer (NSCLC) portends an unfavorable prognosis, with a 5-year survival of only approximately 40%.[1] N1 disease might be difficult to diagnosis preoperatively, despite the combined use of computed tomography and positron emission tomography, and is often first discovered at the time of pulmonary resection.[2,3] Surgical resection remains the recommended initial treatment of choice. A recent randomized trial has shown a modest survival benefit with the addition of adjuvant chemotherapy in patients with N1 disease.[4] Although various factors, such as T classification, number and location of N1 involvement, mode of lymph node involvement (direct invasion vs distinct metastasis), tumor histology, and genetic abnormalities, have been shown to affect survival, few studies have demonstrated any correlation between these factors and tumor recurrence.[5-11] Factors affecting tumor recurrence and long-term survival might provide insight into which subgroup

Abbreviations and Acronyms
CI = confidence interval
NSCLC = non–small cell lung cancer

of patients would most likely benefit from adjuvant treatment. Thus the purpose of this study was to retrospectively review our experience with patients having completely resected N1 disease and to assess factors affecting the rate and pattern of tumor recurrence and long-term survival.

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Patients and Methods

Between January 1997 and December 2002, 2224 patients underwent an anatomic complete resection (lobectomy, sleeve lobectomy, bilobectomy, or pneumonectomy) for primary NSCLC at the Mayo Clinic in Rochester, Minnesota. Excluded from consideration were patients with a malignant pleural effusion or pleural dissemination, limited resection (wedge resection or segmentectomy), or induction therapy (chemotherapy, radiation therapy, or both). One hundred ninety-six patients underwent complete resection for pathologic T1-4 N1 M0 primary NSCLC with mediastinal lymph node dissection, including removal of the paratracheal (stations 2 and 4), subcarinal (station 7), paraesophageal (station 8), inferior pulmonary ligament (station 9), hilar (station 10), and interlobar (stations 11 and higher) lymph nodes. Sixteen patients did not consent at the time of the operation to research participation. The remaining 180 patients were analyzed and form the basis for this study.

The primary tumor histology was classified according to the World Health Organization classification,[12] and TNM classification was based on the revised international system for staging lung cancer.[1] The location of lymph node metastasis was defined according to the regional lymph node classification for lung cancer staging[13] as hilar (station 10), interlobar (station 11), or intrapulmonary (stations 12, 13, and 14). Lymph node involvement was also analyzed with regard to the number of metastatic lymph nodes (single vs multiple) and the mode of involvement (direct primary tumor invasion vs distinct metastasis).

Tumor recurrence was classified as either locoregional or distant. Tumor recurrence was considered locoregional if the cell type was the same as the original and was located within the ipsilateral hemithorax, mediastinum, or supraclavicular lymph node chain. All other sites of recurrence were considered to be distant metastases. For the purposes of analysis, 3 end points were identified: locoregional recurrence, distant metastasis, and any recurrence (locoregional or distant). We categorized patients in the distant metastasis group if both locoregional recurrence and distant metastasis were discovered synchronously. The interval to recurrence was defined as the interval between the time of the operation and the discovery of the recurrence by means of either imaging or cytopathologic examination.

Clinical data are reported as means ± standard deviation or median (range). Cumulative survival was estimated with a Kaplan-Meier model and calculated by using the time of the operation as the starting point.[14] The comparisons of survival and survival free of recurrence between subgroups were investigated univariately by using a Kaplan-Meier model and a Cox multivariable regression model.[15] Univariate predictors significant at the .10 level of significance were considered for the multivariable models. Variables were then eliminated from these multivariable models until all components were significant at the .05 level. All tests were 2-tailed and performed with commercial statistical software, SAS version 8.0 (SAS Inc, Cary, NC).

This study was reviewed and approved by the Mayo Foundation Institutional Review Board.

TABLE 1. Patient characteristics

	No. of patients
Age, y (mean ± SD)	65 ± 10
Sex	
Male	122 (68%)
Female	58 (32%)
Histology	
Squamous cell carcinoma	98 (54%)
Adenocarcinoma	72 (40%)
Large cell carcinoma	5 (3%)
Adenosquamous carcinoma	3 (2%)
Other	2 (1%)
Pathologic T status	
T1	53 (29%)
T2	89 (49%)
T3	22 (12%)
T4	16 (9%)
Tumor location	
Upper lobe	105 (58%)
Middle lobe	9 (5%)
Lower lobe	66 (37%)
Side	
Right	94 (52%)
Left	86 (48%)
Operative procedure	
Lobectomy	121 (67%)
Bilobectomy	13 (7%)
Pneumonectomy	46 (26%)
Tumor grade	
2	10 (6%)
3	104 (58%)
4	66 (37%)
Total	180 (100%)

SD, Standard deviation.

Results

There were 180 patients (122 men and 58 women) with a median age of 67 years (range, 37-89 years). Preoperative staging comprised a history and physical examination, conventional chest roentgenography, and chest and abdominal computed tomography. N2 disease was excluded either before thoracotomy by means of mediastinoscopy or at the time of thoracotomy by means of systematic mediastinal lymphadenectomy. Clinical characteristics of these 180 patients are summarized in Table 1. There were no intraoper-

ative deaths, but 2 deaths occurred within 30 days of the operation (operative mortality, 1.1%). Both occurred in patients who had undergone a pneumonectomy.

Mean follow-up was 33 months (range, 0.1-92.4 months). Tumor recurrence developed in 66 (37%) patients. The recurrences were locoregional in 25 (38%) patients, distant in 27 (41%) patients, and both in 14 (21%) patients. The overall mean interval to recurrence after the operation was 17 ± 14 months (range, 1-72 months), 20 ± 15 months (range, 0.3-72 months) in the locoregional group and 15 ± 15 months (range, 2-72 months) in the distant metastasis group. The site of distant metastasis was the brain in 15 patients, bone in 14, the liver in 12, the contralateral lung in 6, the adrenal gland in 4, the kidney in 2, and the pancreas in 1. The 3-year survival free of recurrence was 60%, with a 95% confidence interval (CI) of 52.8% to 69.0%. Overall cumulative 3- and 5-year survival was 52.6% (95% CI, 45.5%-60.9%) and 42.5% (95% CI, 35.0%-51.5%), respectively. Median survival was 38 months.

Univariate analysis demonstrated that visceral pleural invasion and age were associated with locoregional recurrence, whereas visceral pleural invasion, distinct N1 metastasis, and multistation lymph node involvement were associated with distant metastasis ($P < .05$, Tables 2-4). Multivariable analysis demonstrated that visceral pleural invasion, multistation N1 disease, and distinct metastatic N1 involvement were the only independent predisposing factors for locoregional recurrence and distant metastasis (Table 5).

Table 6 demonstrates the influence of multiple variables on overall survival. A significant influence was observed with regard to T classification ($P = .015$, Figure 1), visceral pleural invasion by the primary tumor ($P < .0001$, Figure 2), tumor size ($P = .0117$), and tumor grade ($P = .014$, Figure 3). A weak association was observed between survival and the extent of pulmonary resection (lobectomy or bilobectomy vs pneumonectomy, $P = .093$), but it did not reach statistical significance. No association with survival was observed with age, sex, cell type, location of tumor, involvement of a hilar lymph node (station 10), number of lymph node stations involved, or mode of nodal involvement.

TABLE 2. Univariate analysis for tumor recurrence: Any recurrence

	3-y survival, %	95% Confidence interval, %	Log-rank test, *P* value
Age			
<65 y (n = 75)	57.4	46.4-71.0	.6139
≥65 y (n = 105)	62.8	53.0-74.4	
Sex			
Male (n = 122)	58.7	49.7-69.3	.3272
Female (n = 58)	63.8	51.1-79.7	
Histology			
Squamous (n = 98)	65.9	56.3-77.2	.3935
Nonsquamous (n = 82)	53.6	42.5-67.5	
T factor, pathologic			
T1 (n = 53)	67.5	55.1-82.8	.1608
T2 (n = 89)	61.4	51.1-73.8	
T3 (n = 22)	49.8	29.1-85.3	
T4 (n = 16)	40.1	20.5-78.1	
Laterality			
Right (n = 94)	65.0	54.8-77.1	.0952
Left (n = 86)	55.2	44.7-68.2	
Primary lobe			
Upper lobe (n = 105)	60.8	51.2-72.1	.2810
Middle lobe (n = 9)	85.7	63.3-100.0	
Lower lobe (n = 66)	57.2	45.2-72.4	
Pleural invasion			
With invasion (n = 43)	39.7	25.7-61.4	.0003
Without invasion (n = 137)	66.2	57.9-75.6	
Station of nodal metastasis			
Hilar (n = 18)	46.2	24.7-86.4	.3910
Others (n = 162)	61.6	53.7-70.5	
No. of nodal stations involved			
Single (n = 98)	69.9	60.6-80.7	.0099
Multiple (n = 82)	48.0	36.9-62.3	
Mode of nodal involvement			
Direct invasion (n = 31)	85.0	72.4-99.7	.0077
Distinct metastasis (n = 149)	55.1	46.8-65.0	
Tumor grade			
2 + 3 (n = 114)	61.1	51.9-72.0	.1444
4 (n = 66)	59.9	48.0-74.7	
Tumor size			
<3 cm (n = 65)	65.6	53.9-79.7	.1333
≥3 cm (n = 115)	57.1	47.7-68.4	
Operative procedure			
Lobectomy, bilobectomy (n = 134)	62.0	53.4-72.0	.6563
Pneumonectomy (n = 46)	54.8	40.6-73.8	

Discussion

Stage I and II NSCLC has been traditionally managed with surgical intervention alone. However, a recent randomized trial by the International Adjuvant Lung Cancer Trial Collaborative group demonstrated that cisplatin-based adjuvant chemotherapy provided a modest survival advantage in patients with stages IB, II, and IIIA completely resected NSCLC.[4] Their patient population was heterogeneous, with 29% of patients having N1 disease. The overall 5-year survival benefit for the entire group was only 4.1%, and the benefit for the N1 subgroup was even smaller. Considering that the morbidity of adjuvant therapy could well outweigh the benefit for this group as a whole, it would be important to identify subgroups that are more predisposed to tumor recurrence and reduced long-term survival for adjuvant treatment. In our study the most significant finding was that visceral pleural invasion by the primary tumor was associ-

TABLE 3. Univariate analysis for tumor recurrence: Local recurrence

	3-y survival, %	95% Confidence interval, %	Log-rank test, *P* value
Age			
<65 y (n = 75)	72.6	61.4-85.9	.0320
≥65 y (n = 105)	85.9	77.1-95.8	
Sex			
Male (n = 122)	79.0	70.4-88.8	.4862
Female (n = 58)	81.8	69.3-96.5	
Histology			
Squamous (n = 98)	85.7	77.2-95.0	.1817
Nonsquamous (n = 82)	72.7	60.8-86.8	
T factor, pathologic			
T1 (n = 53)	85.8	74.9-98.4	.4104
T2 (n = 89)	79.2	69.1-90.8	
T3 (n = 22)	74.7	52.2-100.0	
T4 (n = 16)	68.4	43.1-100.0	
Laterality			
Right (n = 94)	81.2	71.6-92.2	.4941
Left (n = 86)	78.2	67.6-90.6	
Primary lobe			
Upper lobe (n = 105)	76.3	66.7-87.2	.7795
Middle lobe (n = 9)	85.7	63.3-100.0	
Lower lobe (n = 66)	86.4	75.6-98.7	
Pleural invasion			
With invasion (n = 43)	65.5	48.7-88.2	.0024
Without invasion (n = 137)	83.8	76.2-92.1	
Station of nodal metastasis			
Hilar (n = 18)	60.0	34.7-100.0	.1186
Others (n = 162)	81.6	74.2-89.7	
No. of nodal stations involved			
Single (n = 98)	85.6	77.5-94.6	.1941
Multiple (n = 82)	70.8	58.1-86.3	
Mode of nodal involvement			
Direct invasion (n = 31)	95.7	87.7-100.0	.1036
Distinct metastasis (n = 149)	76.0	67.3-85.7	
Tumor grade			
2 + 3 (n = 114)	79.5	70.5-89.7	.5733
4 (n = 66)	81.3	70.0-94.4	
Tumor size			
<3 cm (n = 65)	83.1	72.2-95.7	.4466
≥3 cm (n = 115)	77.7	68.2-88.4	
Operative procedure			
Lobectomy, bilobectomy (n = 134)	81.0	72.8-90.1	.5636
Pneumonectomy (n = 46)	76.1	61.4-94.3	

TABLE 4. Univariate analysis for tumor recurrence: Distant metastasis

	3-y survival, %	95% Confidence interval, %	Log-rank test, *P* value
Age			
<65 y (n = 75)	79.1	69.5-90.0	.2995
≥65 y (n = 105)	73.1	64.1-83.3	
Sex			
Male (n = 122)	74.3	65.9-83.7	.4845
Female (n = 58)	78.0	67.3-90.5	
Histology			
Squamous (n = 98)	76.9	68.3-86.7	.9681
Nonsquamous (n = 82)	73.8	63.7-85.5	
T factor, pathologic			
T1 (n = 53)	78.7	67.7-91.5	.4698
T2 (n = 89)	77.6	68.6-87.7	
T3 (n = 22)	66.7	44.7-99.5	
T4 (n = 16)	58.6	36.2-95.0	
Laterality			
Right (n = 94)	80.0	71.3-89.7	.1135
Left (n = 86)	70.6	60.6-82.2	
Primary lobe			
Upper lobe (n = 105)	79.7	71.6-88.7	.0616
Middle lobe (n = 9)	100.0	. . .	
Lower lobe (n = 66)	66.2	54.5-80.4	
Pleural invasion			
With invasion (n = 43)	60.6	44.2-83.3	.0231
Without invasion (n = 137)	79.0	72.0-86.7	
Station of nodal metastasis			
Hilar (n = 18)	76.9	56.6-100.0	.9012
Others (n = 162)	75.4	68.4-83.2	
No. of nodal stations involved			
Single (n = 98)	81.7	73.6-90.6	.0240
Multiple (n = 82)	67.8	57.1-80.5	
Mode of nodal involvement			
Direct invasion (n = 31)	88.9	77.7-100.0	.0350
Distinct metastasis (n = 149)	72.6	64.9-81.2	
Tumor grade			
2 + 3 (n = 114)	76.8	68.7-85.9	.1583
4 (n = 66)	73.6	62.5-86.7	
Tumor size			
<3 cm (n = 65)	78.9	68.9-90.3	.1900
≥3 cm (n = 115)	73.5	64.9-83.4	
Operative procedure			
Lobectomy, bilobectomy (n = 134)	76.6	69.0-85.0	.9098
Pneumonectomy (n = 46)	72.0	58.5-88.6	

ated with both tumor recurrence and shortened long-term survival. In addition, pleural invasion was a predisposing factor for both locoregional recurrence and distant metastasis. Anatomically, the visceral pleura contains abundant lymphatic capillaries that form a network draining into the pulmonary lymphatic system. It is possible that this network provides a pathway for systemic micrometastasis after invasion by the primary cancer. If so, dissemination in such cases might already have occurred by the time of pulmonary resection.

TABLE 5. Multivariable Cox models for recurrence analysis

Recurrence end point	Variable	Odds ratio (95% CI)	*P* value
Any recurrence (local, distant, or both)	Visceral pleural invasion	2.4 (1.4-4.0)	.0012
	Multistation N1 involvement	1.8 (1.1-2.9)	.0220
	Distinct metastatic N1 involvement	2.9 (1.1-7.2)	.0241
Locoregional recurrence only	Visceral pleural invasion	3.4 (1.5-7.7)	.0041
Distant metastasis (with or without locoregional recurrence)	Visceral pleural invasion	2.0 (1.0-4.0)	.0404
	Multistation N1 involvement	1.9 (1.0-3.6)	.0378

CI, Confidence interval.

TABLE 6. Analysis of factors affecting survival

	5-y survival, %	95% Confidence interval, %	Log-rank test, *P* value
Age			
65 y (n = 75)	44.9	33.7-60.0	.3347
≥65 y (n = 105)	40.5	31.2-52.4	
Sex			
Male (n = 122)	39.2	30.6-50.2	.1638
Female (n = 58)	50.0	37.3-67.2	
Histology			
Squamous (n = 98)	43.2	33.4-55.9	.4335
Nonsquamous (n = 82)	41.4	31.0-55.5	
T factor, pathologic			
T1 (n = 53)	54.7	42.1-70.9	.0152
T2 (n = 89)	42.7	32.1-56.6	
T3 (n = 22)	23.5	9.4-58.5	
T4 (n = 16)	20.3	6.3-64.9	
Laterality			
Right (n = 94)	44.8	34.8-57.8	.3037
Left (n = 86)	40.0	29.9-53.5	
Primary lobe			
Upper lobe (n = 105)	43.3	33.9-55.3	.5194
Middle lobe (n = 9)	64.8	39.3-100.0	
Lower lobe (n = 66)	37.9	26.3-54.5	
Pleural invasion			
With invasion (n = 43)	19.7	9.6-40.2	<.0001
Without invasion (n = 137)	49.1	40.6-59.5	
Station of nodal metastasis			
Hilar (n = 18)	28.6	11.6-70.6	.3348
Others (n = 162)	43.7	35.9-53.2	
No. of nodal stations involved			
Single (n = 98)	46.4	36.7-58.7	.2282
Multiple (n = 82)	38.0	27.6-52.2	
Mode of nodal involvement			
Direct invasion (n = 31)	51.2	35.4-74.0	.3369
Distinct metastasis (n = 149)	40.6	32.5-50.7	
Tumor grade			
2 + 3 (n = 114)	46.6	37.2-58.4	.0141
4 (n = 66)	35.3	24.5-50.9	
Tumor size			
<3 cm (n = 65)	53.5	41.4-69.1	.0117
≥3 cm (n = 115)	36.3	27.6-47.7	
Operative procedure			
Lobectomy, bilobectomy (n = 134)	45.2	36.4-56.0	.0931
Pneumonectomy (n = 46)	34.5	22.4-53.1	

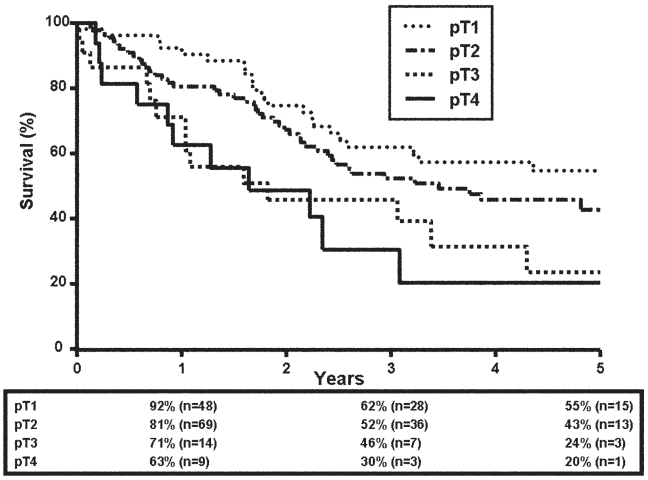
The grade of tumor differentiation was another indicator of poor prognosis in our study. Although it did not reach statistical significance ($P = .57$ in local recurrence and $P = .16$ in distant metastasis), patients with tumor recurrence had tumors with a seemingly more aggressive grade. A higher tumor grade was associated with poorer long-term survival. These observations are consistent with a report by Ichinose and colleagues.[16]

Martini and associates[17] have observed a difference in 5-year survival between single (45%) and multiple (31%) lymph nodes with N1 disease. In our study a similar trend toward better survival in patients with single N1 disease was found (5-year survival, 46% vs 38%), although this difference did not attain statistical significance ($P = .23$).

A number of authors have reported that direct invasion of the primary tumor to N1 lymph nodes predicted a better prognosis compared with distinct metastatic involvement.[6,18] Our study shows that distinct metastatic N1 disease, compared with direct invasion of N1 lymph nodes, portends a worse prognosis with regard to locoregional control and distant metastatic dissemination. The survival rate of the direct tumor invasion group was also higher, but this too did not reach statistical significance. Nonetheless, patients with N1 disease by direct tumor extension might represent a true limited disease state, which might be cured with complete surgical resection alone.

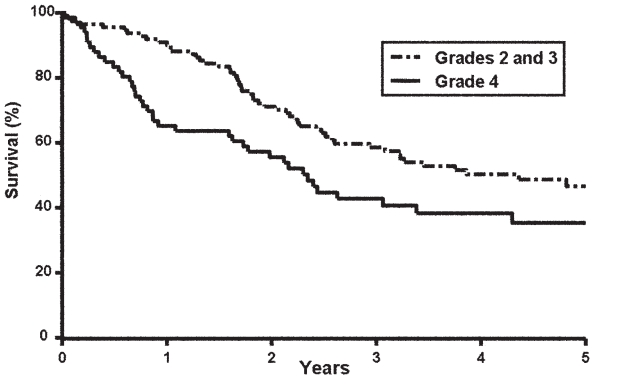
Marra and coworkers[18] demonstrated that patients with hilar lymph node (station 10) metastasis had a 5-year survival of 30%. Our data show a similar 5-year survival of 28.6%; however, this difference did not reach statistical significance when compared with that seen in N1 disease at the other stations. It has been suggested that hilar N1 disease can be regarded as an early form of N2 disease because the poor survival rate seen in this group is closely comparable with that seen in patients with single-station N2 disease.[19]

Several studies have suggested that with N1 disease, pneumonectomy offers a better locoregional control than lobectomy.[20,21] It is difficult to compare survival in terms of operative procedures because several patients undergoing pneumonectomy in our series had a more advanced stage (higher T classification), and the mortality for the procedure



pT1	92% (n=48)	62% (n=28)	55% (n=15)
pT2	81% (n=69)	52% (n=36)	43% (n=13)
pT3	71% (n=14)	46% (n=7)	24% (n=3)
pT4	63% (n=9)	30% (n=3)	20% (n=1)

Figure 1. Survival (death from any cause) by pathologic T classification *(pT)*. Zero time on the abscissa represents the date of the operation ($P = .015$).

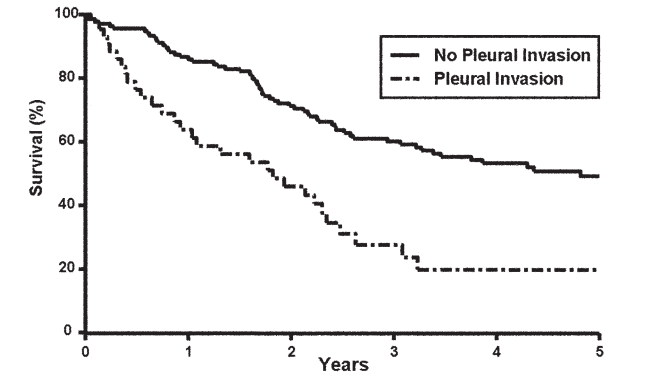


Grade 2 and 3	91% (n=98)	59% (n=53)	47% (n=20)
Grade 4	65% (n=42)	43% (n=21)	35% (n=12)

Figure 3. Survival (death from any cause) by tumor grade. Zero time on abscissa represents the date of the operation ($P = .014$).

is clearly known to be higher than that for a lobectomy (3.2% for pneumonectomy vs 1.2% for lobectomy).[22] It is more reasonable to compare the locoregional recurrence rate, which in our study showed no statistical difference between patients undergoing pneumonectomy and those undergoing either bilobectomy or lobectomy. In our opinion lobectomy is the procedure of choice for N1 disease, as long as complete resection can be performed. Lobectomy is associated with a lesser operative mortality[21] and does not appear to increase the local recurrence rate.

It would seem that N1 disease includes 2 subgroups: limited N1 disease with only local tumor spread that potentially can be cured with complete surgical resection and advanced N1 disease with distant occult micrometastases at the time of pulmonary resection. The inclusion of the latter group explains the poor survival rate of the entire N1 disease group. Our data demonstrate that visceral pleural invasion, multistation N1 disease, and distinct metastatic N1 involvement (as opposed to direct tumor extension to the N1 lymph node) were the predisposing factors for locoregional recurrence and distant metastasis. T classification, visceral pleural invasion, and tumor grade predicted poor long-term survival in patients with N1-positive NSCLC. Patients with the above risk factors might be more likely to benefit from adjuvant systemic therapy. By defining this higher-risk group of patients with N1 disease, we might be better able to tailor administration of adjuvant therapy. Overall results of adjuvant therapy might be improved by providing treatment for this select higher-risk group and avoiding treatment-related injury in the completely resected N1 group that does not have these risk factors.



No Pleural Invasion	87% (n=115)	60% (n=66)	49% (n=30)
Pleural Invasion	64% (n=25)	28% (n=8)	20% (n=2)

Figure 2. Survival (death from any cause) by visceral pleural invasion by the primary tumor. Zero time on the abscissa represents the date of the operation ($P < .0001$).

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Discussion

Dr Eric Vallières (*Seattle, Wash*). There has been growing evidence that adjuvant chemotherapy improves the survival of our patients after complete resection. The IALT study referred to in today's presentation was published in January of last year and demonstrated a 4.1% improvement in survival for patients receiving platinum-based doublet chemotherapy after complete resection of stages I, II, and IIIA non-small cell lung cancer. If you turn those results around, it meant that you had to treat 23 patients after surgery to save one life. While statistically significant, this improvement was judged by many to be not enough to justify giving postop chemo, possibly toxic chemo, to all of our patients. In an effort to better define a subpopulation at risk for recurrence and thus a population that should and could benefit the most from adjuvant chemotherapy, Dr. Cassivi and colleagues retrospectively studied the patterns of recurrence and survival in a subgroup of 180 patients with completely resected N1 disease. In a multivariate analysis, three descriptors were found to predict either local, regional, or systemic recurrence: parietal pleura involvement and distinct and/or multistation N1 nodal involvement. Survival was affected by pleural invasion, the higher T descriptors, the grade of the tumor, and the size of the tumor. As a result, they recommend considering a more selective use of adjuvant chemotherapy targeting these populations at higher risks and possibly avoiding potentially toxic adjuvant treatment in the others.

Stephen, I applaud your efforts to try to better define the population that we should consider for additional treatments after surgery. This is an interesting series that confirms many of the previously suggested bad player descriptors.

Twenty-one percent of your study patients, however, had T3 and T4 disease, and in my opinion it may have been more appropriate to try to be a little more homogeneous and to study such patients in possibly a separate review.

I was surprised to see that the percentages of locoregional and systemic failures were almost identical in this Mayo series. This contrasts with the notion that in patients with nodal disease, systemic failures usually predominate. Locoregional failures were particularly an issue when the parietal pleura was involved. Using a model of a selective approach to adjuvant therapy as you are proposing, should we reconsider selectively studying the role of adjuvant radiation therapy in patients with parietal pleural involvement where locoregional failures were so high?

Dr Cassivi. First of all, I think one of the things to clarify was that the pleural involvement we described was the visceral pleura. If that was unclear in the manuscript, I apologize.

I think you are right; we too were surprised when we identified that locoregional recurrence was as high as distant recurrence. As you mentioned, our notion is that if patients fail, they fail distantly or systemically. It does raise the question of whether better local treatment is possible or is advisable. However, I don't think we have the data necessary to advocate sending these patients to radiation therapy at this point.

Dr Vallières. Along the same lines, you have demonstrated that 15 of the 41 patients who failed systemically did so at the brain level. We know that chemotherapy has very little impact on disease across the blood-brain barrier. Should we consider some of these patients for adjuvant prophylactic cranial radiation?

Dr Cassivi. We did indeed find that brain metastases show up at a relatively high rate. My only comment on this subject is that this demonstrates once more why lung cancer remains the most lethal cancer. Early-stage disease in lung cancer, even when so-called complete resection is performed, still has a way of humbling us. I don't think that the data in our research presented today has the strength, however, to advocate for prophylactic cranial radiation. It doesn't really define in which group we could expect this to occur.

Dr Vallières. The premise for this review was that a 4.1% improvement in survival at five years is not a home run and that

maybe we need to be selective in offering these treatments. Yesterday, the New England Journal of Medicine published results of the NCI Canada Br.10 randomized trial, which showed a 15% improvement in five-year survival with the use of adjuvant platinum vinorelbine chemotherapy after complete resection of stages IB, IIA and IIB non-small cell lung cancer. In this trial you needed to treat 7 patients in the adjuvant setting to save one life. The overall survival was improved by nearly 2 years in the chemotherapy arm, and if one allows a subset analysis of patients with N1 disease only, which made up 55% of the patients on that trial, their survival was improved by 39 months with chemotherapy. Such results in my opinion strongly support a less restrictive use of adjuvant chemotherapy after complete resection in good performance-status patients. Now, 4.1% I can understand some resistance; 15%, things are changing a little. I'd like you to comment.

Dr Cassivi. I would agree. It is a very timely question, because the article has just been published while we are here in Victoria, British Columbia. Dr. Winton and his multicenter collaborative group showed very encouraging results. Fifteen percent is not 4%. How this applies to the research I've just presented remains to be seen. I do believe, though, that this is just another example of how we need to better identify our patients who will benefit from adjuvant therapy, either by using clinical parameters such as we've used in this research or by using other types of labels-either molecular or other biologic markers. I think better identifying those patients who will improve with adjuvant therapy is still a vital task we have to perform.

Dr Vallières. I couldn't agree more, and just reading my notes here, I agree that there may be some benefits in the future of better identifying those who should or, probably more importantly, who do not need to receive adjuvant chemotherapy after surgery. I also agree completely that the selection, however, will likely be based more on molecular biological descriptors of behavior than on crude prognostic TNM factors as we have been using for too long. I thank you for this presentation. It was very well done.

Dr Cassivi. Thanks for your kind remarks.

Dr Ross Bremner (*Phoenix, Ariz*). Thanks very much. I thought it was a fantastic paper and greatly presented. I was very interested in the percentage of squamous cell carcinomas that you had. I wonder if you had noticed any change in that. Our regional distribution in Southern California now is that about 80% of the resected cancers are adenocarcinomas, and along the lines of that, were you able to do any subset analysis to see whether there was a difference in the behavior of the squamous cell carcinomas and adenocarcinomas in terms of both local as well as distant failure?

Dr Cassivi. We had 54% of our patients with squamous cell carcinoma in this series. When we analyzed by tumor histology, we found no association with either locoregional, distant, or any recurrence and indeed neither with survival. Tumor histology did not really factor in for those outcomes. It is, however, an interesting issue that again speaks to molecular markers and tumor-specific markers that may be of more use.

Dr. Bremner. Secondly, I just wondered if you had the opportunity of looking at the degree of visceral pleural invasion as the Japanese have done and whether you have been able to see if there are any prognostic factors from that.

Dr Cassivi. Unfortunately, the retrospective nature of this study doesn't allow us to go back to study this. We haven't tabulated or prospectively gathered data on the degree of visceral pleural invasion. Nevertheless, a review of those classifications of visceral pleural invasion may be of use.