Long-term results and predictors of survival after surgical resection of patients with lung cancer and interstitial lung diseases

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Objectives: Patients with interstitial lung diseases have a poor prognosis and are at increased risk of developing lung cancer. We evaluated the survival and predictors of survival after surgical resection in lung cancers in patients with interstitial lung diseases.

Methods: We retrospectively analyzed data from 1763 patients with non-small cell lung cancer with a clinical diagnosis of interstitial lung disease who underwent pulmonary resection between 2000 and 2009 at 61 Japanese institutions.

Results: Male patients (90.4%) and smokers (93.8%) were in the majority. The overall 5-year survival was 40%. The 5-year survivals were 59%, 42%, 43%, 29%, 25%, 17%, and 16% for patients with stage Ia, Ib, IIa, IIb, IIIa, IIIb, and IV, respectively. Patients with stage IA had a 5-year survival of 33.2%, 61.0%, and 68.4% in the wedge resection, segmentectomy, and lobectomy groups, respectively (log-rank test, $P = .0038$). The leading cause of death was cancer recurrence (50.2%), followed by respiratory failure (26.8%). Wedge resection reduced mortality due to respiratory failure when compared with that of lobectomy ($P = .022$). Multivariable analysis revealed that the type of surgical procedure, predicted percent vital capacity, and tumor locations were independent predictors for survival. The 5-year survival was 20% for patients with stage Ia with a predicted percent vital capacity of 80% or less, and 64.3% for patients with a predicted percent vital capacity greater than 80% (log-rank test, $P < .0001$).

Conclusions: In these patients, there are competing risks of death. Wedge resection reduced death caused by respiratory failure but resulted in poorer long-term prognosis than lobectomy. For patients with poor predictors of survival, such as predicted percent vital capacity of 80% or less, surgical resection should be limited. (J Thorac Cardiovasc Surg 2015;149:64-70)

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Interstitial lung diseases (ILDs) are associated with an increased risk of lung cancer,^{1,2} and the prevalence of lung cancer ranges from 6% to 17% during the course of ILDs. In these patients, Ozawa and colleagues³ reported that the cumulative incidence rate of lung cancer was approximately 3.3%, 15.4%, and 54.7% at 1, 5, and 10 years, respectively.³ However, the contribution of anticancer therapies is unclear because these therapies may trigger fatal complications, such as acute exacerbation (AE), and are confounded by the progressive nature and poor prognoses of ILDs. Although the survival of this group of patients was considered to be poorer than that of other

Abbreviations and Acronyms

AE	= acute exacerbation
CI	= confidence interval
CT	= computed tomography
DLCO	= carbon monoxide diffusing capacity
FEV1	= forced expiratory volume in 1 second
FVC	= forced vital capacity
ILD	= interstitial lung disease
IPF	= idiopathic pulmonary fibrosis
OR	= odds ratio
UIP	= usual interstitial pneumonia
%VC	= percent vital capacity

patient cohorts with ILDs, no reliable figures based on a large study have been reported to address this problem.

In our previous report using data from 61 institutes in Japan on 1763 patients with lung cancer who had ILDs, we studied the morbidity and mortality rate of patients with pulmonary resection and identified 7 risk factors for postoperative AE of pulmonary fibrosis.⁴ By using the same cohort, we have analyzed their long-term survival and the probable factors influencing their survival.

PATIENTS AND METHODS

The patients' basic backgrounds are shown in Table 1. The patient cohort was identical to that used in our previous study. Briefly, the majority of patients were men (90.4%) and ex- or current smokers (93.8%). Usual interstitial pneumonia (UIP) diagnoses were made in 73.7% of the patients by computed tomography (CT) scan. Squamous cell carcinoma was the most common type of lung cancer (46.9%), followed by adenocarcinoma (41.4%). Most of the patients had stage I disease (1028 cases). Lobectomy was the most common surgical procedure (1236 cases, 70.4%), followed by wedge resection (275 cases, 15.7%), segmentectomy (150 cases, 8.6%), bilobectomy (61 cases, 3.4%), and pneumonectomy (33 cases, 1.9%). TNM stages were based on the classification of the malignant tumors by the Union for International Cancer Control (6th edition).⁵

Inclusion criteria for the patients have been described.⁴ Patients with ILDs and non-small-cell lung cancer who had undergone pulmonary resection other than surgical biopsy for diagnostic purpose were included. ILDs were confirmed on the basis of a radiologic finding on the chest CT scan according to the clinical criteria proposed by the Japanese Respiratory Society, and these criteria are consistent with the 2011 guidelines of the American Thoracic Society.⁶ The cases were categorized into 2 groups according to their radiologic appearance on CT scan: (1) UIP pattern: This group is characterized by the presence of basal-dominant reticular opacities and predominantly basal and subpleural distribution of honeycomb lesions with multiple equal-sized cystic lesions of 2 to 10 mm in diameter with a thick wall; and (2) non-UIP pattern: This group is characterized by the presence of basal-predominant ground glass opacities and infiltrative shadows inconsistent with UIP patterns. The patient data were retrospectively accumulated between January 2000 and December 2009, which is more than the 3 consecutive years at 61 hospitals throughout Japan. The number of patients at each institute varied from 4 to 133; the institutes with a small number patients were the result of more than 3 consecutive years of observation. We were unable to set or investigate the selection criteria for the surgical procedures in each institute.

The study protocol was approved by the institutional review boards of all participating hospitals, including that of the Ethics Committee, Kyoto University Graduate School and Faculty of Medicine (Approval Number: E-982).

The primary end point was overall survival time, defined as the time from surgical procedure to death from any cause. Postoperative patient information, including cancer recurrence site, exacerbation of IP, and cause of death, was also collected until March 2011, the end of data collection.

Statistical Analyses

Survival curves were estimated using the Kaplan–Meier method. The variables in Table E1 were analyzed for multivariate Cox regression analysis to identify probable predictors of survival. Klebs von Lungen-6, carcinoembryonic antigen, partial pressure of carbon dioxide, partial pressure of oxygen, carbon monoxide diffusing capacity (DLCO), and percent predicted DLCO were not included in the analysis because of missing data more than 5%. Forced expiratory volume in 1 second (liters) was eliminated because it is correlated with predicted percent vital capacity (%VC) (Pearson's correlation coefficient = 0.621). Cox proportional hazards regression analysis was used to estimate the hazard ratio and the 95% confidence interval (CI) of each factor. Multivariate Cox regression analysis with backward elimination was performed to select significant prognostic factors. To examine the relationship between surgical procedures and cause of death, multivariate logistic regression analysis that was adjusted for the significant prognostic factors was used. All reported *P* values were 2-sided, and a value less than .05 was used for variable selection. Data management and statistical analyses were conducted in the Department of Clinical Trial Design and Management, Translational Research Center, Kyoto University Hospital. All statistical analyses were performed using SAS version 9.3 and JMP version 8.1 (SAS Institute, Inc, Cary, NC).

RESULTS

Cause of Death

Death due to cancer was the main cause of mortality (378/753, 50.2%), and death due to respiratory failure (202/753, 26.8%) was the second most common cause of death. Details of the respiratory failure death were as follows; 72 patients (35.6%) died of AE of interstitial pneumonia within 30 days from the operation, and 117 patients died of AE during the following period (Table 2).

Identification of Prognostic Factors

Cox regression analysis identified that age, sex, pTNM stages, %VC, type of surgical procedure, and tumor location were independent predictors for survival (Table 3). As for surgical procedures, the hazard ratios of the segmentectomy and lobectomy groups versus the wedge resection group were 0.957 (95% CI, 0.698-1.313; *P* = .786) and 0.704 (95% CI, 0.565-0.878; *P* = .002), respectively (Table 3).

Survival

The 5-year survivals were 59%, 42%, 43%, 29%, 25%, 17%, and 17% for pTNM stages Ia, Ib, IIa, IIb, IIIa, IIIb, and IV, respectively (Figure 1, A). The 5-year survivals in patients with pathologic stage Ia were estimated to be 33.2% for the wedge resection group, 61% for the segmentectomy group, and 68.4% for the lobectomy group

TABLE 1. Patients' characteristics

Categories	Cases (%)	Median (range)
Age (y)	1763	71 (36-88)
Sex (male/female)	1593 (90.4)/170 (9.6)	
Smoking history		
Never smoker	109 (6.2)	
Ex/current smoker	1006/632	
Brinkman index*	1742	1000 (0-5760)
Radiologic diagnosis		
UIP/non-UIP pattern	1300 (73.7)/463 (26.3)	
Pathology		
Squamous cell carcinoma	816 (46.9)	
Adenocarcinoma	721 (41.4)	
Large cell carcinoma	64 (3.7)	
Pathologic stage†		
1/2/3/4	1028/311/358/34	
Surgical procedures		
Wedge resection	275 (15.7)	
Segmentectomy	150 (8.6)	
Lobectomy	1236 (70.4)	
Bilobectomy	61 (3.4)	
Pneumonectomy	33 (1.9)	

UIP, Usual interstitial pneumonia. *Brinkman Index: The numbers of cigarettes smoked per day times years. †TNM stages based on the classification of the malignant tumors by the Union for International Cancer Control, 6th edition.⁵

(Figure 1, B). Survival of patients with pTNM stage Ia who had wedge resection was poorer than that of the lobectomy group ($P < .0008$) but not significantly different from that of the segmentectomy group ($P < .365$) (Figure 1, B).

For all patients, the 5-year survivals of those with lower %VC ($\leq 80\%$) and normal %VC ($>80\%$) were estimated as 20.8% and 43.8%, respectively (log-rank test, $P < .0001$). For patients with stage IA, the 5-year survivals of those with lower %VC ($\leq 80\%$) and normal %VC ($>80\%$) were estimated as 20% and 64.3%, respectively (log-rank test, $P < .0001$) (Figure 1, C and D).

Surgical Procedures and Cause of Death in Patients With Stage IA

Patients with stage IA were selected to evaluate the influence of the types of surgical procedure on the cause of death, using logistic regression analyses that adjusted for age, sex, and %VC. In cases involving death due to cancer, wedge resection and segmentectomy were associated

TABLE 2. Cause of death and details of respiratory failure deaths

Categories	Cases (%)
Cause of death	
Lung cancer	378 (50.2)
Respiratory failure	202 (26.8)
Other	173 (23.0)
Death due to respiratory failure	
Postoperative AE*	72 (35.6)
Chronic exacerbation†	117 (57.9)
Other	13 (6.4)

AE, Acute exacerbation. *Interstitial pneumonia within 30 days after surgery.

†Exacerbation of interstitial pneumonia occurring ≥ 31 days after the operation.

TABLE 3. Cox proportional hazards regression analysis for survival

Categories	Cases	Hazard ratio	95% CI	P value
Age (y)	1656	1.017	1.005-1.028	.004
Sex				
Male	1497	1.000	—	—
Female	159	0.711	0.535-0.945	.019
Pathologic stage				
Ia	528	1.000	—	—
Ib	469	1.728	1.381-2.163	<.001
IIa	65	2.009	1.352-2.984	<.001
IIb	226	2.497	1.933-3.225	<.001
IIIa	233	3.708	2.884-4.767	<.001
IIIb	102	3.204	2.354-4.361	<.001
IV	33	3.774	2.438-5.841	<.001
%VC	1656	0.980	0.975-0.984	<.001
Procedures				
Wedge resection	250	1.000	—	—
Segmentectomy	137	0.957	0.698-1.313	.786
Lobectomy	1209	0.704	0.565-0.878	.002
Bilobectomy/ pneumonectomy	60	0.745	0.494-1.123	.159
Tumor location				
Upper lobe	649	1.000	—	—
Middle lobe	74	1.421	0.977-2.065	.066
Lower lobe	928	1.409	1.202-1.652	<.001
Multiple	5	0.000	N/A	N/A

CI, Confidence interval; N/A, not available; %VC, percent vital capacity.

with poor outcome; the odds ratio (OR) of wedge resection versus lobectomy was 2.98 (95% CI, 1.56-5.68; $P = .001$), and the OR of segmentectomy versus lobectomy was 2.56 (95% CI, 1.15-5.67; $P = .021$). In cases involving respiratory failure, the OR of wedge resection versus lobectomy was 0.35 (95% CI, 0.15-0.82; $P = .015$), and the OR of segmentectomy versus lobectomy was 0.80 (95% CI, 0.32-2.01; $P = .641$).

DISCUSSION

Determining the surgical indication for patients with lung cancer with ILDs is difficult. In addition to their impaired pulmonary reserve, it is not clear whether pulmonary resection is beneficial or harmful for each individual. The median survival of the patients with idiopathic pulmonary fibrosis (IPF) reportedly ranges from 2 to 4.2 years from the date of diagnosis.⁶⁻⁸ Although there is a general understanding that the prognosis of patients with lung cancer with ILDs is poor, existing evidence to support these conclusions was based on a few studies with a comparatively small number of patients (14-56).⁹⁻¹⁶ Saito and colleagues⁹ reported that the 5-year survival of patients with stage IA lung cancer with IPF was 54.2%, and the propensity-matched analysis confirmed that IPF was the only significant prognostic factor. Watanabe and colleagues¹⁰ reported a 5-year survival of 61.6% after pulmonary resection for patients with stage Ia and stage Ib. Our study elucidated the 5-year survival of this group

FIGURE 1. A, Overall survival of patients with ILDs who underwent pulmonary resection. B, Survival of the wedge resection, segmentectomy, and lobectomy groups in patients with stage 1A; 5-year survival of each group was 29.2%, 60.0%, and 68.6%, respectively. No significant difference was found between the wedge resection and segmentectomy groups (log-rank $P = .365$). C, For all stages, 5-year survival of patients with lower %VC ($\leq 80\%$) and normal %VC ($>80\%$) was 43.8% and 20.8%, respectively (log-rank test, $P < .0001$). D, For patients with stage 1A, 5-year survival of patients with lower %VC ($\leq 80\%$) and normal %VC ($>80\%$) was 64.3% and 20.0%, respectively (log-rank test, $P < .0001$). %VC, Percent vital capacity.

of patients for the various cancer stages and found that the survival was substantially poorer than the recent figures reported by the Japanese Joint Committee for Lung Cancer Registration for overall patients (86.8%, 73.9%, 61.6%, 49.8%, 40.9%, 27.8%, and 27.9% for pathologic stage Ia, Ib, IIa, IIb, IIIa, IIIb, and IV, respectively).¹⁷ This poorer

survival is likely due to the high incidence of cancer recurrence, combined with the poor survival of ILD itself. Watanabe and colleagues⁹ and Okamoto and colleagues¹⁶ reported an increased cancer recurrence in patients with IPF, but the recurrence rate has not been reported. We determined that recurrence was the main cause of death

TABLE 4. Logistic regression analysis in patients with stage 1A, adjusted for age, sex, and predicted percent of vital capacity

Cause of death	Procedures	Cases (%)	OR	95% CI	P value
Cancer	Lobectomy	20/312 (6.4)	1	—	—
	Segmentectomy	12/71 (16.9)	2.56	1.15-5.67	.021
	Wedge resection	26/159 (16.4)	2.98	1.56-5.68	.001
Respiratory failure	Lobectomy	31/312 (9.9)	1	—	—
	Segmentectomy	7/71 (9.9)	0.80	0.32-2.01	.641
	Wedge resection	10/159 (6.3)	0.35	0.15-0.82	.015

CI, Confidence interval; OR, odds ratio.

and was approximately twice as high as that of respiratory failure, indicating the importance of oncologic control for survival.

As for predictors of the patients' survival, multivariable analysis revealed that low %VC was an independent and strong predictor together with the age, sex, pTNM, type of surgical procedure, and tumor location. It is rather appalling that the 5-year survival of the patients with stage 1A whose %VC was less than 80% was as poor as 20%. For this group of patients, the decision to perform pulmonary resection should be considered carefully. The natural course of patients with ILDs varies in their disease progression: Some are stable for years, whereas others exhibit more rapid deterioration.⁶ Nishiyama and colleagues¹⁸ claimed the median survival of patients with a modified Medical Research Council score of 0 (not troubled with breathlessness except with strenuous exercise) and 1 (troubled by shortness of breath when hurrying on the level or walking up a slight hill) was estimated at 66.7%.¹⁹ Because we showed that cancer was the primary cause of death, lobectomy should be the first choice for those with preserved %VC and good physical status.

Although DLCO is a well-known survival predictor for patients with ILDs, we did not include this in the analysis because of too many missing values, which indicates that DLCO measurement in clinical practice is costly and not common. Impaired right heart function and pulmonary hypertension are known to be associated with the poor prognosis of patients with pulmonary fibrosis.²⁰ However, preliminary research showed that few patients had the preoperative assessment; thus, we did not include these variables in the study questionnaires.

Patients with lung cancer and ILDs have a high incidence of morbidity and mortality in the perioperative period and a poor long-term prognosis due to both cancer recurrence and deterioration of interstitial pneumonia. To achieve better survival in this group of patients, we propose 2 strategies; one is to decrease the incidence of perioperative fatal complications, namely, AE of IP, and the other is to decrease cancer recurrence. Since Kutlu and colleagues²¹ pointed out the high incidence of morbidity and mortality of patients with ILDs in the perioperative periods, AE has begun to be a concern of surgeons.^{1,22} Among the

problems regarding morbidity, AE is an important issue because it has serious consequences once it occurs. We reported that the incidence of operation-induced AE in this patient group is up to 9.3% and the mortality rate is as high as 43.9%.⁴ No effective prophylactics or measures for AE prevention are available so far; only wedge resection may reduce the risk of AE. We reported that segmentectomy and lobectomy increase the risk of AE compared with wedge resection (OR, 3.83; 95% CI, 1.941-7.567; $P = .0005$).⁴ However, as we have shown in the present study, long-term survival of patients with stage 1a disease who underwent wedge resections was poorer than that of patients who underwent lobectomy (Figure 1, B). The estimated survival curve of the wedge resection group crossed that of the lobectomy group 1 year after the surgery, and the survival of the wedge resection group was significantly poorer than that of the lobectomy group (log-rank test, $P = .0008$). These observations can be explained by the fact that the wedge resection group was less likely to develop AE but had a higher cancer recurrence rate than the lobectomy group. Of note, the curves of the wedge resection group and segmentectomy groups did cross 30 months after the operation, and the survival of both groups showed no significant difference (log-rank test, $P = .365$). Furthermore, multivariate logistic regression analysis on the cause of death (Table 4) showed that the wedge resection and segmentectomy groups had less favorable oncologic outcomes when compared with the lobectomy group. In terms of death caused by respiratory failure, the wedge resection showed a favorable effect when compared with the lobectomy group ($P = .022$), but the segmentectomy group showed no significant effect ($P = .580$). These results implied that segmentectomy seemed to not be beneficial in controlling cancer or reducing respiratory failure. On the other hand, wedge resection may reduce the risk of respiratory failure but resulted in more cancer deaths than in the lobectomy group. Cancer control was shown as the key to achieve better survival; therefore, we believe that lobectomy should be selected except in patients with a high risk of AE. Our former study showed that the patients with a combination of a history of AE of ILDs, preoperative steroid use, UIP pattern on CT, and male gender proved to be at high risk for AE.⁴

Study Limitations

There are study limitations that should be considered in the interpretation of the results. First, this was a retrospective cohort study, which may not necessarily reflect the characteristics of the entire population with this disease. Second, the primary inclusion criterion was the appearance of ILDs on CT. Although radiologic diagnoses were made by each individual institute following criteria based on widely used guidelines, the diagnosis of interstitial pneumonia may vary among institutes. We could not include the assessment of patients' physical status, such as the Borg Scale, 6-minute walk test, and modified Medical Research Council score, which reportedly correlate well with patient survival.^{5,17,23}

CONCLUSIONS

In this study, we have investigated the cause of death and the long-term survival of patients with lung cancer concomitant with ILDs who underwent pulmonary resection. We showed that cancer was the primary cause of death, and to achieve better surgical outcomes for this group of patients, lobectomy should be the first choice for those with preserved %VC.

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Discussion

Dr Chukwumere Nwogu (Buffalo, NY). Dr Date, I congratulate you and your colleagues for conducting such a large multi-institutional study. This study provides us with some guidance for decision-making in this difficult group of patients. We typically approach these patients with trepidation as we evaluate them for possible surgical resection. I appreciate the provision of the article and slides before your presentation.

I have 3 questions for you. Before the identification of some risk factors in this study, what specific selection criteria did the surgeons in your consortium use to select the surgical procedures that were offered to your patients, for instance, segmentectomy versus lobectomy? How were those decisions made?

Dr Date. Regarding the selection criteria during this period, this decision was entirely up to the individual institution. This is a retrospective multicenter trial.

Dr Nwogu. In your institution, how did you make that decision?

Dr Date. First, we discussed with the medical oncologists and radiologists whether the patient should be taken to the operating room or not, and then if we decided to perform surgery, we looked at the pulmonary function, quality of life, and so on, and then we decided, but this was probably more of a subjective assessment at that time.

Dr Nwogu. You chose a %VC of 80% as a threshold to decide who should undergo surgery or as a cutoff to decide who would be a favorable candidate, but it seems you did not take into consideration the volume of lung to be resected. Did you look into other parameters, such as the predicted postoperative percent forced vital capacity (FVC) or the predicted postoperative percent DLCO. It seems to me that the risk would be less in a patient in whom you would be able to perform a complete resection with

segmentectomy versus a bilobectomy, for instance. Did you take into consideration the volume of lung to be resected?

Dr Date. That is a great suggestion. We have not looked at our data in that way yet. We will, after your suggestion. I assume that when the postoperative %VC is low, the result is going to be very bad, but we have not done that analysis yet.

Dr Nwogu. Now that you have this information, how has it affected your practice? How do you balance the tradeoff between higher AE of ILD in the larger resections versus the markedly improved long-term survival in those patients? How do you make that decision now?

Dr Date. Regarding the current practice, the decision is still made on a patient-by-patient basis. However, now that we know the 7 risk factors for AE and 5 independent predictors of survival, we can select the optimal surgical procedure for each patient more objectively than before. Regarding bilobectomy or pneumonectomy, a bigger operation, we looked at the rate of AE, and it was 5 to 7 times more than lobectomy and the long-term survival was disappointing. Therefore, for patients requiring a bigger operation (eg, bilobectomy or pneumonectomy), the surgical option should be limited.

Dr Thomas Egan (*Chapel Hill, NC*). You chose 80% FVC. With such a large number, were you able to look at different thresholds and come up with a suggestion that 80% was an important threshold or was it just chosen as one item to look at?

Dr Date. Honestly, 80% was chosen because 80% is usually used for restrictive disease, and we found that there was a significant difference. That is why we chose that number.

Dr Egan. The reason I ask is because it seems to me that there is probably an FVC threshold where the stage I cases would be better served by another modality, like stereotactic radiosurgery.

Dr Date. That is a good suggestion.

Dr Daniel Miller (*Marietta, Ga*). Were you able to look at the perioperative events that occurred, especially bronchopleural fistula, prolonged air leak, and empyema? We all know that when we operate on patients with ILD, they have a more complicated course. Did that play a major role in the acute respiratory failure during that early recovery period and did that make a difference?

Dr Date. We collected those data and found that the postoperative events, such as prolonged air leak, infection, and so on, can trigger the AE as well, but we wanted to know the preoperative factors that could predict the outcome. Those kind of events occurred after the surgery, and the decision-making is difficult before the surgery.

Dr Miller. Was there a difference between the approach, either video-assisted thoracoscopic surgery or a thoracotomy? Sometimes with these patients, as you know, they are difficult from the standpoint that you have to do a lot of these open.

Dr Date. Approximately 45% of the patients received this operation by video-assisted thoracoscopic surgery and 55% by open thoracotomy. There was no difference between the 2 groups in terms of AE and no difference in survival.

Dr Robert Cerfolio (*Birmingham, Ala*). I have 2 quick questions and a comment. I am surprised you didn't mention pulmonary artery hypertension or assessment of that by echocardiography. Maybe it's different in the United States, but we don't operate in most of these patients because of pulmonary artery hypertension. Did you look at that?

Dr Date. No, we did not look at that because these are the patients who were found to have ILD during the workup phase of lung cancer itself. We believe these are in the very early phase of fibrosis.

Dr Cerfolio. The second question is technical tricks to take the fissure. These fissures are nightmares. They are big and thick. Just quickly tell us some tricks on how you took the thick fissure, especially if you are doing a right upper lobe, the fissure between the upper and the middle.

Dr Date. That is probably a question to my personal experience.

We try not to go into the fissure at first. We try to divide the vessels.

Dr Cerfolio. We understand that you do the fissures last.

Dr Date. Yes.

Dr Cerfolio. How do you take them?

Dr Date. We usually use a stapler.

Dr Cerfolio. Which stapler? They are very thick.

Dr Murthy. You're thinking of a different animal. These are patients who have been described on CT scan as having some evidence of ILD.

Dr Cerfolio. So you don't think that they are the real bad ones that we're talking about.

Dr Murthy. Well, you have an FVC greater than 80% predicted in 80% of their study population. The entrance criteria is purely radiographic for this study and appears to be independent of positron emission tomography or functional criteria.

Dr Cerfolio. So they didn't clinically have thick fissures.

Dr Murthy. I doubt it. It's not the type of case you're thinking about of more end-stage disease.

Dr Cerfolio. That's important for us to know in the audience, because those patients don't do well with surgery. The third thing is that I would invite you to look at stereotactic body radiation therapy versus this for the T1As if they really do have significant pulmonary fibrosis.

Dr Sudish Murthy (*Cleveland, Ohio*). Another difference I think the audience has to understand is that when you are looking at percent predicted forced expiratory volume in 1 second (FEV1) and you have a homogeneous population from whom you are getting your norms and you are comparing it with a homogeneous population, it's easy to translate, but in the United States, if you take a standard FEV1 of 80% as being something that is grossly abnormal, it depends on the ethnicity of the person who is getting the spirometry checked. A small East Indian male will have a predicted FVC of 65% or 70%, but he may have totally normal spirometry if he would have had his spirometries done in India. I wouldn't get hung up on the 80% FVC. That is another misleading piece of information.

Dr Ara Vaporciyan (*Houston, Tex*). The decision on the surgical approach was not set in advance because this was a retrospective study, so could a reason for the wedge resection in the patients with high FEV1 be that those patients had a higher disease stage and were being forced into a wedge resection because of concern about their interstitial disease. Likewise, in the lower than 80% group, could those patients have received a wedge resection because they had horrific FEV1, very low, and so the differences in the survival patterns of the wedge resections are due to the bias introduced by the surgeon's decision and differences in stage and FEV1?

Dr Date. That is true, but we did a multivariate analysis that still showed a difference between the 2 groups. I think there is a bias, but that can be overcome by an analysis in a multivariate way.

Dr Vaporciyan. I would warn you that when 2 factors in a multivariate analysis track parallel one another, you can get fooled.

Dr Date. Yes. You may need a randomized prospective trial to prove that.

TABLE E1. Univariate analysis for patients' survival

Factors	Categories	Cases	Hazard ratio	95% CI	P value	P value of global association
Age		1763	1.013	1.003-1.024	.009	
Sex	Male	1593	1	—	—	
	Female	170	0.659	0.504-0.861	.002	
BMI		1746	0.973	0.951-0.996	.022	
Smoking history	Never smoked	109	1	—	—	.006
	Ex-smoker	1006	1.649	1.170-2.326	.004	
	Current smoker	632	1.428	1.004-2.032	.048	
Brinkman index		1742	1.000	1.000-1.000	.302	
Comorbidities						
Asthma	—	1742	1	—	—	
	+	33	0.838	0.484-1.450	.527	
Emphysema	—	1167	1	—	—	
	+	589	1.084	0.933-1.259	.294	
Collagen disease	—	1654	1	—	—	
	+	102	1.123	0.849-1.485	.416	
KL6* (U/mL)		1043	1.000	1.000-1.000	.002	
	<1000	834	1	—	—	
	>1000	209	1.431	1.157-1.769	<.001	
CEA (ng/mL)		1664	1.001	1.000-1.002	.005	
PAO ₂ (torr)		1552	0.998	0.991-1.004	.493	
PACO ₂ (torr)		1547	0.979	0.961-0.998	.030	
%VC		1741	0.977	0.973-0.982	<.001	
	<80	263	1	—	—	
	>80	1478	0.516	0.431-0.617	<.001	
FEV1 (L)		1748	0.739	0.645-0.847	<.001	
FEV1.0%		1749	1.006	1.001-1.012	.024	
	<70	460	1	—	—	
	>70	1289	1.301	1.100-1.539	.002	
%FEV1.0		1742	0.997	0.994-1.001	.122	
DLCO (mL/min/torr)		1121	0.960	0.943-0.978	<.001	
%DLCO		1128	0.993	0.989-0.997	<.001	
Radiologic findings	UIP pattern	1300	1	—	—	
	Non-UIP pattern	463	0.836	0.706-0.988	.036	
Histology	Adenocarcinoma	721	1	—	—	<.001
	Squamous cell	816	1.172	1.005-1.366	.042	
	Large cell	64	1.071	0.722-1.587	.734	
	Others	139	1.440	1.107-1.874	.007	
Pathologic stage	Ia	547	1	—	—	
	Ib	481	1.548	1.255-1.909	<.001	
	IIa	70	1.723	1.178-2.521	.005	
	IIb	241	2.203	1.741-2.787	<.001	
	IIIa	244	3.020	2.405-3.791	<.001	
	IIIb	114	3.264	2.464-4.324	<.001	
	IV	34	4.036	2.663-6.116	<.001	
Surgical procedures	Wedge resection	275	1	—	—	<.001
	Segmentectomy/lobectomy	1386	0.840	0.694-1.018	.076	
	Bilobectomy/pneumonectomy	94	1.440	1.056-1.965	.021	
Tumor location	Upper lobe	670	1	—	—	.028
	Middle lobe	77	1.372	0.963-1.953	.080	
	Lower lobe	958	1.249	1.072-1.456	.004	
	Multiple	5	0	N/A	N/A	
VATS	—	964	1	—	—	
	+	798	0.952	0.825-1.099	.500	

(Continued)

TABLE E1. Continued

Factors	Categories	Cases	Hazard ratio	95% CI	P value	P value of global association
Node dissection	0	311	1	—	—	.680
	1	339	0.919	0.723-1.167	.487	
	2	1104	0.921	0.762-1.113	.394	

BMI, Body mass index; *CEA*, carcinoembryonic antigen; *CI*, confidence interval; *DLCO*, carbon monoxide diffusing capacity; *FEV1*, forced expiratory volume in 1 second; *KL-6*, Klebs von Lungen-6; *N/A*, not available; *Paco₂*, arterial carbon dioxide tension; *PaO₂*, arterial oxygen tension; *UIP*, usual interstitial pneumonia; *VATS*, video-assisted thoracoscopic surgery; %*VC*, percent vital capacity. *Serum biomarker for pulmonary fibrosis.