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Marginal pulmonary function is associated with poor short- and long-term outcomes in lung cancer surgery

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ABSTRACT

We sought to determine the short- and long-term prognoses among 'marginal-risk' non-small cell lung cancer patients who have a predicted postoperative- (ppo) forced expiratory volume in the first second (FEV_1) of 30–60% and/or a ppo-diffusing capacity of the lung for carbon monoxide (DL_{CO}) of 30–60%. The present study included 73 'marginal-risk' and 318 'normal-risk' patients who underwent anatomical resection for clinical stage I lung cancer between 2008 and 2012. The rates of postoperative morbidity, prolonged hospital stay, and overall survival were assessed. Postoperative morbidity occurred in 35 (48%) 'marginal-risk' patients and 66 (21%) 'normal-risk' patients, and 17 (23%) 'marginal-risk' patients and 20 (6%) 'normal-risk' patients required a prolonged hospital stay. The three- and five-year survival rates were 79% and 64% in the 'marginal-risk' patients and 93% and 87% in the 'normal-risk' patients, respectively. A 'marginal-risk' status was a significant factor in the prediction of postoperative morbidity (odds ratio [OR] 2.97, $p < 0.001$), the rate of prolonged hospital stay (OR 3.83, $p < 0.001$), and overall survival (hazard ratio 2.07, $p = 0.028$). In conclusion, 'Marginal-risk' patients, who are assessed based on ppo-values, comprise a subgroup of patients with poorer short- and long-term postoperative outcomes.

Key Words: lung cancer, FEV_1, DL_{CO}, surgery, survival

INTRODUCTION

Lobectomy with systematic mediastinal lymph node dissection has played the most important role in the treatment of patients with stage I non-small cell lung cancer (NSCLC).[1] With regard to pulmonary function, the predicted postoperative (ppo) pulmonary function values have been reported to be more strongly related to operative morbidity, mortality, and survival than the preoperative values.[2-5] Current evidence suggests that a ppo-forced expiratory volume in the first second (FEV_1) of < 30% and/or a ppo-diffusing capacity of the lung for carbon monoxide (DL_{CO}) of < 30% are high-risk factors (and contraindications) for major anatomical lung resection for lung cancer from the point of view of postoperative morbidity and mortality.[2,3] In the American College of Chest Physicians (ACCP) guideline, patients with either a ppo-FEV_1 or ppo-DL_{CO} of

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< 60% and in whom both values are ≥ 30%, are recommended to undergo further exercise tests as a preoperative assessment.[2] Historically, however, 'marginal-risk' patients with a ppo-FEV_1 and/or a ppo-DL_{CO} of 30–60% have not received much attention. Moreover, only a few studies have reported the long-term prognostic significance of the ppo-pulmonary function values.[4,5]

Based on the circumstances indicated above, we hypothesized that 'marginal-risk' patients with a ppo-FEV_1 and/or a ppo-DL_{CO} of 30–60% are a subgroup of patients with poor short- and long-term postoperative outcomes. The present study was designed to elucidate the significance of the 'marginal-risk' status in those outcomes of a cohort of patients with suspected clinical stage I NSCLC and, consequently, to help establish better management procedures for patients with suspected lung nodules.

METHODS

The study was conducted with the approval of the Institutional Review Board of Nagoya University Hospital. We reviewed the medical records of 426 consecutive patients who underwent anatomical complete resection for clinical stage I NSCLC at Nagoya University Hospital between April 2008 and December 2012. Patients with concomitant cancer resection of the lung and other organs (n = 2), concomitant cardiovascular surgery (n = 2), or incomplete pulmonary function test data (n = 6) were excluded from the analysis. Twenty-five patients with nonsolid nodules were also excluded. After applying the exclusion criteria, 391 patients were included in the study population. Seventy-three patients were classified as 'marginal-risk' (ppo-FEV_1: 30–60% and/or ppo-DL_{CO}: 30–60%); 318 patients were classified as 'normal-risk' (ppo-FEV_1 ≥ 60% and ppo-DL_{CO} ≥ 60%).

Ppo-FEV_1 and ppo-DL_{CO} were defined as follows:
ppo-FEV_1 (%) = measured FEV_1 (%) × (1 – the number of segments resected / the number of functional segments).
ppo-DL_{CO} (%) = measured DL_{CO} (%) × (1 – the number of segments resected / the number of functional segments).

Segmentectomy was performed instead of lobectomy in selected patients who had previously undergone pulmonary resection and patients with another major comorbidity, peripheral nodules ≤ 2 cm in diameter, limited pulmonary function, or lower exercise tolerance. The 7th edition of the tumor-node-metastasis classification was applied in this cohort, and the pathological diagnosis of the tumor was made based on the World Health Organization classification.[6,7]

STATISTICAL ANALYSIS

The chi-square and Wilcoxon tests were used for the comparisons of proportions and continuous values, respectively. Postoperative morbidity was defined as the occurrence of at least one postoperative event based on The Society of Thoracic Surgeons and the European Society of Thoracic Surgeons general thoracic surgery databases.[8] Prolonged hospital stay was defined as hospitalization for more than 14 days after surgery. Overall survival (OS) was defined as the time from surgery to death due to any cause. A multivariate logistic regression analysis was performed to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for postoperative morbidity and a prolonged hospital stay. The Kaplan–Meier method was used to estimate OS, and

the log-rank test was used to compare the survival curves. A multivariate Cox regression analysis was performed to estimate the hazard ratios (HRs) and 95% CIs for OS. Statistical significance was defined as $p < 0.05$. All analyses were conducted using the JMP software program (version 11.0.0, SAS institute Inc., Cary, NC).

RESULTS

In the preoperative setting, 283 ('marginal-risk' [84%]; 'normal-risk' [70%]) patients underwent a lung biopsy, which led to a definitive diagnosis in 194 patients ('marginal-risk' [63%]; 'normal-risk' [47%]). Table 1 shows the clinicopathological characteristics of 73 'marginal-risk' patients and 318 'normal-risk' patients. The 'marginal-risk' patient subgroup was characterized by a greater proportion of males, a higher number of current or former smokers, a greater proportion of pathological N1/2 disease, and a higher rate of thoracotomy.

Postoperative morbidity occurred in 35 (48%) 'marginal-risk' patients and 66 (21%) 'normal-risk' patients. Pulmonary complications occurred in 25 (34%) 'marginal-risk' patients and 35 (11%) 'normal-risk' patients. Prolonged hospital stay was required in 17 (23%) 'marginal-risk' patients and 20 (6%) 'normal-risk' patients. There were no cases of 30-day postoperative mortality. After adjusting age, sex, smoking status, nodule size, surgical procedure, surgical approach,

Table 1 The characteristics of patients stratified by the predicted postoperative pulmonary function values

		'Marginal-risk' (n = 73)	'Normal-risk' (n = 318)	P value
ppo-FEV_1, % of predicted	(Mean ± SD)	63.0 ± 16.6	88.6 ± 17.0	< 0.001
ppo-DL_{CO}, % of predicted	(Mean ± SD)	67.2 ± 22.3	95.2 ± 20.3	< 0.001
Age, years	(Mean ± SD)	69.7 ± 5.8	68.1 ± 8.6	0.143
Sex	Female	12	127	< 0.001
	Male	61	191	
Smoking status	Never	10	117	< 0.001
	Current or former	63	201	
Nodule size, cm	(mean ± SD)	2.71 ± 0.82	2.55 ± 0.96	0.090
Pathological N status	N0	59	286	0.039
	N1/2	14	32	
Surgical procedure	Segmentectomy	6	48	0.105
	Lobectomy	67	270	
Surgical approach	Thoracotomy	72	290	0.010
	VATS	1	28	
Lymph node dissection	Sampling	8	34	0.947
	Systematic	65	284	
Postoperative morbidity	No	38	252	< 0.001
	Yes	35	66	
Prolonged hospital stay	No	56	298	< 0.001
	Yes	17	20	
Cause of death	Lung cancer	12	17	0.428
	Pulmonary event	3	4	
	Others	2	8	
	Total	17	29	

SD, standard deviation; ppo, predicted postoperative; FEV_1, forced expiratory volume in the first second; DL_{CO}, diffusing capacity of the lung for carbon monoxide; VATS, video-assisted thoracic surgery.

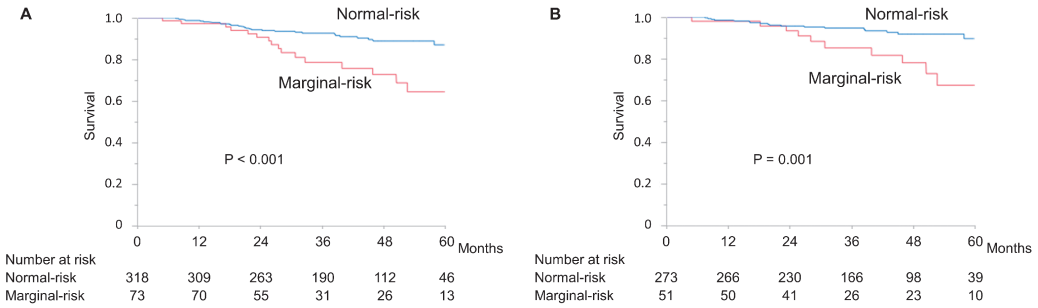

Fig. 1 (A) The overall survival curves in 391 patients with clinical stage I lung cancer according to the predicted postoperative pulmonary function values.

Fig. 1 (B) The overall survival curves in 324 patients with pathological stage I non-small lung cancer according to the predicted postoperative pulmonary function values.

lymph node dissection, the 'marginal-risk' status was a significant predictor of both postoperative morbidity (OR: 2.97; 95%CI: 1.71–5.18; $p < 0.001$) and a prolonged hospital stay (OR: 3.83; 95%CI: 1.81–8.07; $p < 0.001$).

There were no patients with a ppo-FEV_1 and/or a ppo-DL_{CO} of < 30%. In 6 patients with a ppo-FEV_1 and/or a ppo-DL_{CO} of < 40%, postoperative morbidity occurred in 5 (83%), pulmonary complications occurred in 5 (83%), prolonged hospital stay was required in 1 (17%). In 27 patients with a ppo-FEV_1 and/or a ppo-DL_{CO} of < 50%, postoperative morbidity occurred in 12 (44%), pulmonary complications occurred in 9 (33%), prolonged hospital stay was required in 6 (22%).

The median follow-up period was 38 months. The OS of 'marginal-risk' patients was significantly shorter than that of 'normal-risk' patients (three-year OS: 79% vs. 93%; the five-year OS: 64% vs. 87%; $p < 0.001$) (Figure 1A). Similarly, in 324 patients with pathological stage I NSCLC, the OS of 'marginal-risk' patients was also shorter in comparison to 'normal-risk' patients ($p = 0.001$) (Figure 1B).

In the multivariate Cox regression analysis, 'marginal-risk' had a prognostic value for OS (Table 2, analysis 1). The results of a multivariate Cox regression analysis in which the ppo-FEV_1 and ppo-DL_{CO} were used as continuous variables instead of the 'marginal-risk' and 'normal-risk' groups are shown in Table 2, analysis 2. The ppo-DL_{CO} was a statistically significant prognostic factor for OS.

Forty-six patients died during the study period. There were no significant differences in the causes of death between the two groups (Table 1). The cancer-specific survival of 'marginal-risk' patients was also shorter in comparison to 'normal-risk' patients ($p < 0.001$).

DISCUSSION

We used ppo-FEV_1 and DL_{CO} cut-off values of 30% and 60%, respectively, to evaluate surgical risks. These values are proposed in the ACCP guidelines.[2] Historically, the lower threshold of those values for curative lung resection has been the main focus of discussion. Several recent studies have demonstrated acceptable postoperative outcome in patients with a ppo-pulmonary function of > 30% with an evaluation of ppo-oxygen consumption and a low technology exercise test.[2,3] The upper threshold of a ppo value of 60% has not received much attention. In our study of patients with clinical stage I lung cancer, 'marginal-risk' patients (defined by ppo-values of

Table 2 The results of the multivariate Cox regression analysis for overall survival

		Analysis 1				Analysis 2			
		HR	95%CI		P value	HR	95%CI		P value
Group	'Normal-risk'	1.00							
	'Marginal-risk'	2.07	1.09	3.83	0.028				
ppo-FEV_1	(10% decrease)					1.18	1.00	1.40	0.050
ppo-DL_{CO}	(10% decrease)					1.16	1.02	1.33	0.027
Age	(10-year increase)	1.45	0.98	2.19	0.065	1.59	1.07	2.43	0.023
Sex	Female	1.00				1.00			
	Male	2.03	1.00	4.55	0.050	1.99	0.97	4.52	0.062
Nodule size	(1-cm increase)	1.38	1.00	1.88	0.047	1.39	1.01	1.92	0.045
Pathological N status	N0	1.00				1.00			
	N1/2	2.35	1.10	4.63	0.028	2.13	1.01	4.17	0.047

HR, hazard ratio; CI, confidence interval; ppo, predicted postoperative; FEV_1, forced expiratory volume in the first second; DL_{CO}, diffusing capacity of the lung for carbon monoxide.

30–60%) had significantly poorer short-and long-term postoperative outcomes.

As we previously reported, we agree that 'normal-risk' patients in whom an unverified highly suspected lung nodule is identified by diagnostic imaging can be surgically diagnosed.[9] However, in 'marginal-risk' patients with an unverified suspected nodule, it is preferable that a non-surgical definitive diagnosis be obtained before surgery. As for pulmonary function, only a few studies have reported the prognostic significance of ppo-pulmonary function values for predicting OS. In one retrospective study, which included patients with all-stage NSCLC, Ferguson *et al*. reported that postoperative pulmonary function was a better predictor of long-term survival after lung cancer surgery than preoperative pulmonary function.[4] Berry *et al*. reported that in patients with pathological stage I NSCLC OS after lobectomy was impacted not by ppo-FEV_1 but by lower ppo-DL_{CO}.[5] The two published studies did not include patients who underwent segmentectomy. In our study, ppo-DL_{CO} (as continuous variables) was an independent prognostic factor for OS after surgical resection (Table 2, analysis 2).

The cancer specific survival of 'marginal-risk' patients was shorter in comparison to 'normal-risk' patients. The differences in the OS may also come from the difference in the aggressiveness of the cancer.

The present study is associated with some limitations; specifically, the study population was relatively small and the follow-up period was relatively short. Moreover, because the selection criteria of segmentectomy were highly dependent on the decisions of individual surgeons, we could not establish new valid criteria to determine the appropriate extent of surgical resection in patients with marginal ppo-pulmonary function values from this retrospective study.

In conclusion, patients who are classified as 'marginal-risk' based on ppo-pulmonary function values are a subgroup of patients with poor short-and long-term outcomes after surgery for clinical stage I NSCLC. Surgeons should take into account not only morbidity and local recurrence, but also long-term mortality.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest in association with the present study.

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