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

Naoki Ozeki, Koji Kawaguchi, Toshiki Okasaka, Takayuki Fukui, Koichi Fukumoto, Shota Nakamura, Shuhei Hakiri and Kohei Yokoi

Department of Thoracic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

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 (FEV1) of 30–60% and/or a ppo-diffusing capacity of the lung for carbon monoxide (DLCO) 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, FEV1, DLCO, 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). 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. Current evidence suggests that a ppo-forced expiratory volume in the first second (FEV1) of < 30% and/or a ppo-diffusing capacity of the lung for carbon monoxide (DLCO) 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. In the American College of Chest Physicians (ACCP) guideline, patients with either a ppo-FEV1 or ppo-DLCO of
< 60% and in whom both values are ≥ 30%, are recommended to undergo further exercise tests as a preoperative assessment. 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. 

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.

**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. 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-FEV₁, % of predicted | (Mean ± SD)              | 63.0 ± 16.6             | 88.6 ± 17.0 | < 0.001 |
| ppo-DLCO, % 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; FEV₁, forced expiratory volume in the first second; DLCO, diffusing capacity of the lung for carbon monoxide; VATS, video-assisted thoracic surgery.
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-FEV1 and/or a ppo-DL CO of < 30%. In 6 patients with a ppo-FEV1 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-FEV1 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-FEV1 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-FEV1 and DL CO cut-off values of 30% and 60%, respectively, to evaluate surgical risks. These values are proposed in the ACCP guidelines. 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. 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...
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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. 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. Berry et al. reported that in patients with pathological stage I NSCLC OS after lobectomy was impacted not by ppo-FEV\textsubscript{1} but by lower ppo-DL\textsubscript{CO}. The two published studies did not include patients who underwent segmentectomy. In our study, ppo-DL\textsubscript{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.

**FUNDING**

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### 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 |       |         | 1.00 |       |         |
| ‘Marginal-risk’       | 2.07 | 1.09  | 3.83    | 1.18 | 1.00  | 1.40    |
| **ppo-FEV\textsubscript{1}** |      |       |         |      |       |         |
| (10% decrease)        | 1.18 |       |         | 1.16 |       |         |
| **ppo-DL\textsubscript{CO}** |      |       |         |      |       |         |
| (10% decrease)        | 1.45 | 0.98  | 2.19    | 1.59 | 1.07  | 2.43    |
| **Age**               |      |       |         |      |       |         |
| (10-year increase)    | 1.45 |       |         | 1.59 |       |         |
| **Sex**               |      |       |         |      |       |         |
| Female                | 2.03 | 1.00  | 4.55    | 1.99 | 0.97  | 4.52    |
| Male                  | 1.38 | 1.00  | 1.88    | 1.39 | 1.01  | 1.92    |
| **Nodule size**       |      |       |         |      |       |         |
| (1-cm increase)       | 1.38 |       |         | 1.39 |       |         |
| **Pathological N status** |      |       |         |      |       |         |
| N0                    | 2.35 | 1.10  | 4.63    | 2.13 | 1.01  | 4.17    |
| N1/2                  | 1.00 |       |         | 1.00 |       |         |

HR, hazard ratio; CI, confidence interval; ppo, predicted postoperative; FEV\textsubscript{1}, forced expiratory volume in the first second; DL\textsubscript{CO}, diffusing capacity of the lung for carbon monoxide.

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

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 |       |         | 1.00 |       |         |
| ‘Marginal-risk’       | 2.07 | 1.09  | 3.83    | 1.18 | 1.00  | 1.40    |
| **ppo-FEV\textsubscript{1}** |      |       |         |      |       |         |
| (10% decrease)        | 1.18 |       |         | 1.16 |       |         |
| **ppo-DL\textsubscript{CO}** |      |       |         |      |       |         |
| (10% decrease)        | 1.45 | 0.98  | 2.19    | 1.59 | 1.07  | 2.43    |
| **Age**               |      |       |         |      |       |         |
| (10-year increase)    | 1.45 |       |         | 1.59 |       |         |
| **Sex**               |      |       |         |      |       |         |
| Female                | 2.03 | 1.00  | 4.55    | 1.99 | 0.97  | 4.52    |
| Male                  | 1.38 | 1.00  | 1.88    | 1.39 | 1.01  | 1.92    |
| **Nodule size**       |      |       |         |      |       |         |
| (1-cm increase)       | 1.38 |       |         | 1.39 |       |         |
| **Pathological N status** |      |       |         |      |       |         |
| N0                    | 2.35 | 1.10  | 4.63    | 2.13 | 1.01  | 4.17    |
| N1/2                  | 1.00 |       |         | 1.00 |       |         |

HR, hazard ratio; CI, confidence interval; ppo, predicted postoperative; FEV\textsubscript{1}, forced expiratory volume in the first second; DL\textsubscript{CO}, diffusing capacity of the lung for carbon monoxide.
CONFLICT OF INTEREST

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

REFERENCES

1) Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest, 2013; 143 (5 Suppl): e278S–e313S.

2) Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest, 2013; 143 (5 Suppl): e166S–e190S.

3) Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier JP, Varela G, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). Eur Respir J, 2009; 34: 17–41.

4) Ferguson MK, Watson S, Johnson E, Vigneswaran WT. Predicted postoperative lung function is associated with all-cause long-term mortality after major lung resection for cancer. Eur J Cardiothorac Surg, 2014; 45: 660–664.

5) Berry MF, Jeffrey Yang CF, Hartwig MG, Tong BC, Harpole DH, D’Amico TA, et al. Impact of pulmonary function measurements on long-term survival after lobectomy for stage I non-small cell lung cancer. Ann Thorac Surg, 2015; 100: 271–276.

6) Sobin LHG, Wittekind C. International Union Against Cancer (UICC) TNM classification of malignant tumors. 7th ed. New York: Wiley-Liss; 2009.

7) Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: IARC Press, 2015.

8) Fernandez FG, Falcoz PE, Kozower BD, Salati M, Wright CD, Brunelli A. The Society of Thoracic Surgeons and the European Society of Thoracic Surgeons general thoracic surgery databases: joint standardization of variable definitions and terminology. Ann Thorac Surg, 2015; 99: 368–376.

9) Ozeki N, Iwano S, Taniguchi T, Kawaguchi K, Fukui T, Ishiguro F, et al. Therapeutic surgery without a definitive diagnosis can be an option in selected patients with suspected lung cancer. Interact Cardiovasc Thorac Surg, 2014; 19: 830–837.