Original Article

Preoperative respiratory assessment predicts post-operative survival in stage IA non-small cell lung cancer

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Background: Respiratory impairment can lead to pulmonary complications after surgery; therefore, it should be considered when determining the choice of surgical procedure. Several studies have examined the relationship between preoperative respiratory function and postoperative mortality and morbidity after lung resection; however, there are no indicators for limited surgical procedure selection. The aim of this study was to examine the association between preoperative respiratory function and postoperative early and late complications, recurrence-free survival (RFS), and overall survival (OS) in patients undergoing pulmonary resection for stage I lung cancer.

Methods: We performed a retrospective analysis of data from 192 patients undergoing pulmonary resection for primary pathological stage IA non-small cell lung cancer (NSCLC) at the Iwakuni Clinical Center in Japan between 2012 and 2015. We reviewed clinicopathological characteristics including preoperative pulmonary function and elucidated the relationship between them and postoperative survival.

Results: Obstructive ventilatory impairment was present in 55 patients (28.6%), and restrictive ventilatory impairment was present in 31 patients (16.1%). Seven patients (3.6%) had both ventilatory impairment. Obstructive ventilatory impairment did not affect the 5-year RFS (P=0.08) or OS (P=0.21). However, restrictive ventilatory impairment reduced the 5-year RFS (P=0.002) and OS (P=0.009). The rates of early and late complications were not significantly different based on the preoperative respiratory function.

Conclusions: In patients with preoperative restrictive ventilatory impairment in whom lobectomy or segmentectomy cannot be performed, careful consideration is needed for surgical indications.

Keywords: Ventilatory impairment; stage IA non-small cell lung cancer (stage IA NSCLC); postoperative prognosis

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Introduction

Chronic obstructive pulmonary disease, interstitial pneumonia, inhalation lung diseases such as asbestosis, and aging are believed to develop respiratory failure and increase the risk of lung cancer (1-3).

Although several studies have examined the relationship between preoperative respiratory function and postoperative mortality and morbidity after lung resection, there are no indicators for limited surgical procedure selection in these patients (4,5). The 5-year survival rate of patients with stage IA lung cancer [the Union for International Cancer Control (UICC) tumor, node, metastasis (TNM) classification 7th edition] after standard surgery is 83.9%, and the local recurrence rate and prognosis of stage I lung cancer patients who undergo sublobar resection consisting of either segmentectomy or wedge resection because of low lung function are similar to those of patients treated with lobectomy (6,7). Therefore, we conducted a retrospective study examining the association between preoperative respiratory function and postoperative early and late complications, recurrence-free survival (RFS), and overall survival (OS) to consider whether the surgery is acceptable or not for patients with respiratory impairment. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-22/rc).

Methods

Patient selection

Patients who underwent pulmonary resection for primary lung cancer at the Iwakuni Clinical Center in Japan were prospectively added to a database. A total of 436 patients from the database who underwent pulmonary resection between January 1, 2012 and December 31, 2015, were eligible for this study. We included only patients with postoperative pathological stage IA (UICC TNM classification 7th edition) non-small cell lung cancer (NSCLC) because of the expectation of good prognosis. In addition, stage IB and above were not included because it is difficult to consider a limited surgery and postoperative adjuvant chemotherapy is recommended (8,9). Small cell carcinoma and pleomorphic carcinoma were also excluded because they often have a poorer prognosis than NSCLC (10,11). We excluded patients with a history of lung cancer at the beginning of the study because of the possibility of recurrence.

We defined respiratory dysfunction as follows: restrictive impairment was defined as an actual vital capacity (VC) <80% of the VC expected based on age and height and obstructive impairment was defined as <70% forced expiratory volume in one second/forced VC ratio. Postoperative early and late complications were defined as complications occurring within and after 30 days of surgery, respectively. Complications were evaluated using the Clavien-Dindo classification.

During the study, the standard surgical procedure for patients with clinical stage I lung cancer was lobectomy. However, we sometimes performed wedge resection or segmentectomy for patients with small peripheral nodules including patients with tumors <2 cm, a consolidation-to-tumor ratio <0.5, a concomitant disease, or poor performance status.

Patients were followed up for at least 5 years, with blood examination including tumor markers every 3 or 6 months and computed tomography scans at least every 6 months during the first 2 years and at least 12 months for the duration of the follow-up.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Iwakuni Clinical Center (approval No. 0462). Informed consent was obtained using the opt-out option on the hospital's website, based on the Ethical Guidelines for Medical and Biological Research Involving Human Subjects, implemented in Japan.

Data collection

Medical charts were reviewed to collect information about age at surgery, sex, smoking status, respiratory function,

Highlight box

Key findings

- In patients with preoperative restrictive ventilatory impairment in whom lobectomy or segmentectomy cannot be performed, careful consideration is needed for surgical indications.

What is known and what is new?

- Limited surgery is often selected for patients with low respiratory function, but there are no specific criteria.
- Patients with restrictive ventilatory impairment and partial resection were performed had significantly higher recurrence and lower survival rates.

What is the implication, and what should change now?

- In cases of restrictive ventilation disorders, the indication for surgery should be carefully examined.

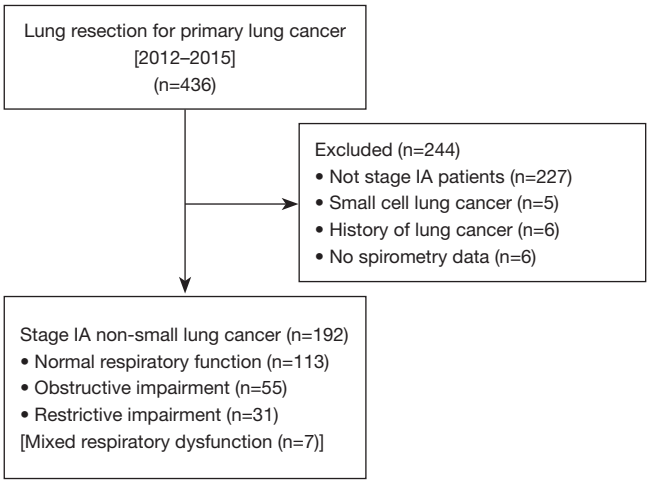

Figure 1 Study flow diagram of the selection process.

and TNM classification, 7th edition. We also collected information on the surgical approach (thoracoscopy and thoracotomy), length of hospital stay, and the occurrence of postoperative complications.

Statistical analysis

All statistical analyses were performed using EZR software version 1.60 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R software (R Foundation for Statistical Computing, Vienna, Austria) (12). Comparisons of patient characteristics and univariate analysis of postoperative outcomes were performed using Student's *t*-test or the Mann-Whitney *U* test. RFS and OS were calculated using the Kaplan-Meier method, and differences between groups by respiratory function and surgical procedure were assessed using the log-rank test. A conventional P value <0.05 was used to determine the level of statistical significance.

Results

A flow diagram of the study selection process is shown in *Figure 1*, and the patient backgrounds are shown in *Table 1*. Patient background by respiratory function is shown in Table S1. We included 192 patients with pathological stage IA NSCLC, all of whom also had clinical stage IA disease and underwent radical resection during the observation period. One hundred patients (52.1%) were former or current smokers at their first visit to our hospital. Obstructive ventilatory impairment was present in 55 patients (28.6%), and restrictive ventilatory impairment was present in 31 patients (16.1%). Of these, only 7 patients (3.6%) had both ventilatory impairment. Surgery was mainly performed thoracoscopically, and 185 patients (96.4%) underwent thoracoscopic lung

Table 1 Patient characteristics (n=192)

Characteristics	Value
Age, years, median [range]	72 [31–92]
Sex, n (%)	
Male	102 (53.1)
Female	90 (46.9)
Body mass index, kg/m^2, median [range]	22.8 [14.5–35.5]
Smoking status, n (%)	
Never	92 (47.9)
Former/current	100 (52.1)
Brinkman index, median [range]	850 [8–3,120]
Performance status, n (%)	
0	151 (78.6)
1	30 (15.6)
2	7 (3.6)
3	4 (2.1)
Respiratory impairment, n (%)	
Obstructive	55 (28.6)
Restrictive	31 (16.1)
Surgical approach, n (%)	
Thoracotomy	7 (3.6)
VATS	185 (96.4)
Extent of resection, n (%)	
Lobectomy	80 (41.7)
Segmentectomy	61 (31.8)
Wedge	51 (26.6)
Histology, n (%)	
Ad	155 (80.7)
Sq	27 (14.1)
Other	10 (5.2)

VATS, video-assisted thoracic surgery; Ad, adenocarcinoma; Sq, squamous cell carcinoma.

Table 2 Early postoperative complications

Respiratory function	No complications, n (%)	Any complications, n (%)
Normal	99 (87.6)	14 (12.4)
Obstructive ventilatory impairment	51 (92.7)	4 (7.3)
Restrictive ventilatory impairment	27 (87.1)	4 (12.9)

resection. Lobectomy was performed in 80 patients (41.7%), segmentectomy in 61 patients (31.8%), and wedge resection in 51 patients (26.6%).

Table 2 shows the early complication rates based on preoperative respiratory function. A total of 22 early postoperative complications were observed. The details are shown in Table S2. The most frequent complication was prolonged air leakage. Although there were seven patients with prolonged air leakage, six had normal preoperative respiratory function. The difference in complication rates due to ventilatory impairment was not clear.

Regarding the hospitalization period, the normal respiratory function group was hospitalized for an average of 8.2 days; the obstructive ventilatory impairment group, for an average of 8.0 days; and the restrictive ventilatory impairment group, for an average of 11.7 days. Patients with preoperative restrictive ventilatory impairment were significantly more likely to require postoperative hospitalization (P=0.007).

There were 40 cases of late postoperative complications (Table S3). The most common complication was pneumonia, which occurred in 14 patients. Patients with respiratory impairment tended to develop pneumonia and arrhythmia. These patients needed hospitalization for treatment, and some required transfer to a convalescent hospital.

Four patients (16.7%) with restrictive dysfunction required home oxygen therapy (HOT) at the discharge hospital, two of whom died within 90 days; one patient developed pneumonia, and the other experienced sudden cardiopulmonary arrest. In the obstructive ventilatory impairment group, six patients (12.5%) required HOT and two patients died within 90 days. However, one patient died from unexpected perforation of the intestinal tract, and the other developed pyothorax after surgery. Among patients with normal respiratory function, only one died within 90 days after surgery, and the patient developed heart impairment.

Obstructive ventilatory impairment did not affect the 5-year RFS (no obstructive ventilatory impairment, 81.5% *vs.* obstructive ventilatory impairment, 74.4%; P=0.08) or the 5-year OS (no obstructive ventilatory impairment, 82.3% *vs.* obstructive ventilatory impairment, 78.4%; P=0.21). However, patients with restrictive ventilatory impairment had significantly higher recurrence and lower survival rates. Restrictive ventilatory impairment reduced the 5-year RFS (no restrictive ventilatory impairment, 83.6% *vs.* restrictive ventilatory impairment, 57.4%; P=0.002) and the 5-year OS (no restrictive ventilatory impairment, 84.9% *vs.* restrictive ventilatory impairment, 61.8%; P=0.009) (*Figure 2*).

Although neither RFS nor OS was affected by the surgical technique in the entire cohort, we performed further subgroup analysis based on the surgical technique. Patients with obstructive ventilatory impairment had similar RFS and OS rates regardless of the type of surgery. However, partial resection tended to cause early recurrence in patients with restrictive ventilatory impairment, although this was not significant (*Figure 3*).

Discussion

The prognosis of stage I lung cancer patients who undergo sublobar resection due to low lung function is similar to that of patients treated with standard therapy (6,7,13-15). In this study, we investigated the prognostic value of preoperative ventilatory function in patients with stage IA NSCLC who underwent pulmonary resection and found that patients with restrictive ventilatory impairment had significantly more recurrence and shorter survival times compared to patients without restrictive ventilatory impairment. In particular, patients who underwent only partial resection owing to restrictive ventilatory impairment showed a tendency to develop recurrence, although the difference was not statistically significant (*Figure 3C*, P=0.10).

Limited surgery is often considered in patients with preoperative ventilatory impairment because of concerns regarding postoperative respiratory complications (5,16,17). We observed no significant difference in early postoperative complications between patients with and without preoperative ventilatory impairment. However, the postoperative hospitalization period was longer in the restrictive ventilatory impairment group; the average hospitalization stay in the normal respiratory function and obstructive ventilatory impairment groups was

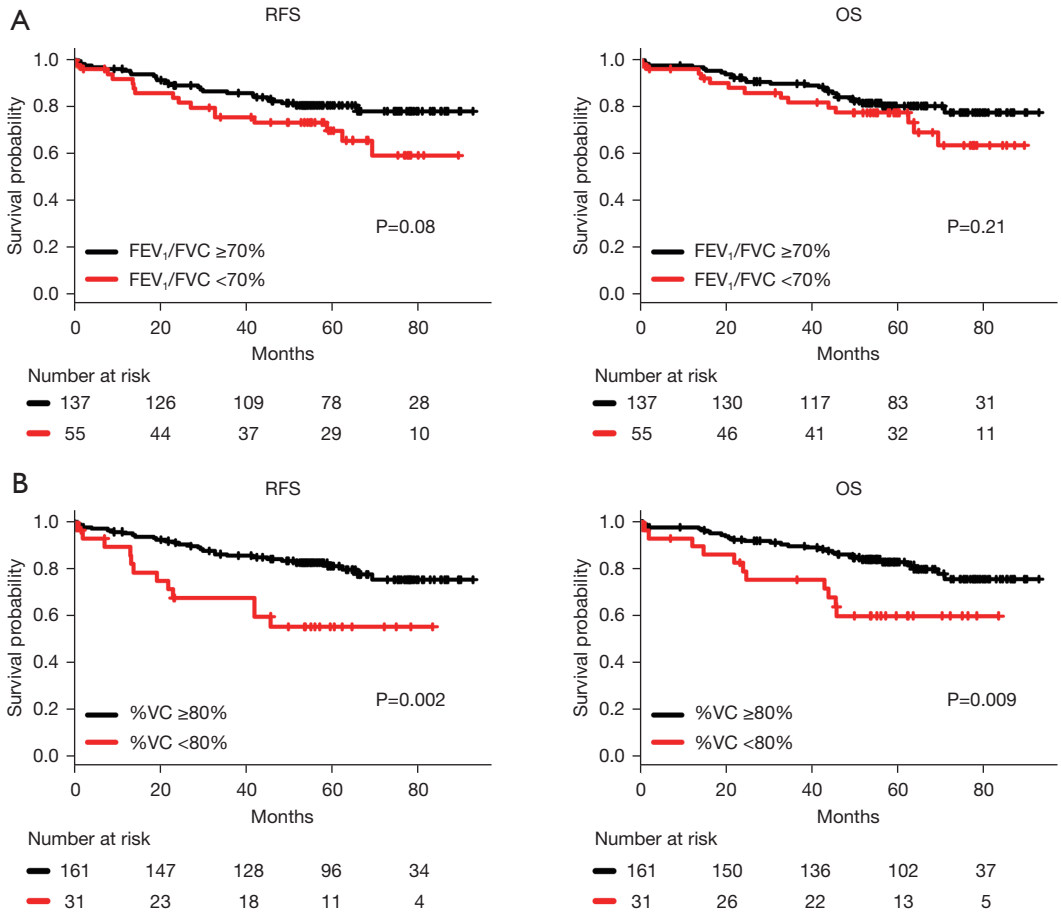

Figure 2 Kaplan-Meier survival curves for RFS and OS based on preoperative (A) obstructive ventilatory impairment and (B) restrictive ventilatory impairment among patients with pathological stage I lung cancer who underwent pulmonary resection. RFS, recurrence-free survival; OS, overall survival; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; VC, vital capacity.

approximately 8 days, whereas that in the restrictive ventilatory impairment group was 11.7 days (Table S1). Even though perioperative complications occurred in only 4 of the 31 patients in the restrictive ventilatory impairment group, they needed rehabilitation to return home with or without minimal oxygen therapy. Five of the 192 patients died within 90 days. Respiratory failure may relate to be a contributing cause of death in only two patients and they had preoperative restricted ventilation problems. These results seem to indicate that postoperative respiratory dysfunction may lead to mortality in patients with preoperative restrictive ventilatory impairment. Therefore, respiratory impairment may be a factor for poor prognosis, and postoperative respiratory dysfunction should be considered a risk factor.

The surgical technique did not affect survival in patients with obstructive ventilatory impairment in this study; however, partial resection tended to cause early recurrence in patients with restrictive ventilatory impairment. Among 31 patients with restrictive ventilatory impairment, 5 developed recurrence, of whom 4 underwent partial resection. Three of these patients had pulmonary metastases, and 2 had marginal recurrences. The margin distance was shorter than the maximum tumor diameter in 4 of the 5 patients with recurrence. When performing pulmonary resection, the distance to the resection edge should be greater than the maximum tumor diameter, as previously reported (18,19). Additionally, partial resection without secure resection margins may lead to spread through air spaces (20). Focusing on the cases in which partial resection was performed, all but one case with normal respiratory function were well-differentiated

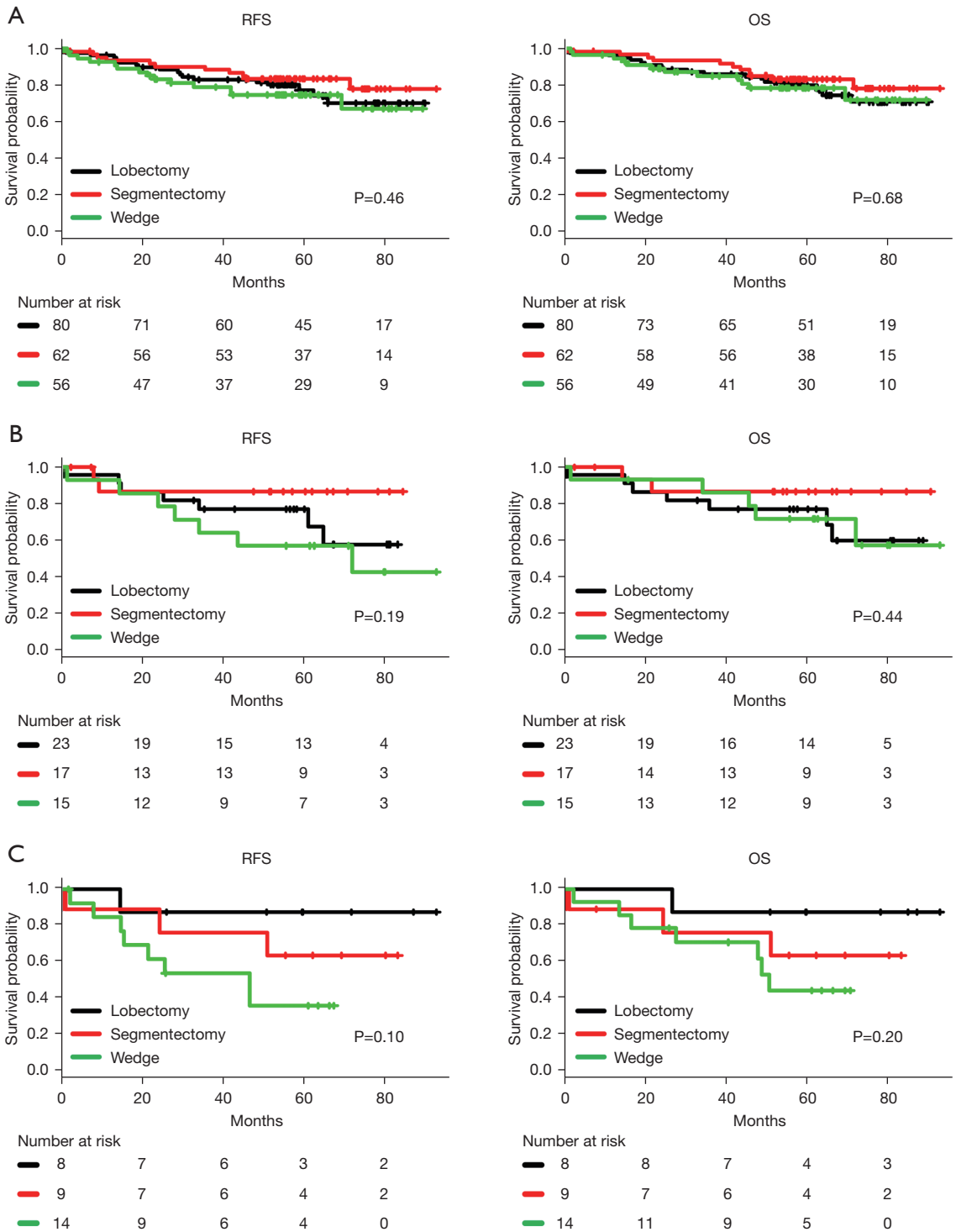

Figure 3 Kaplan-Meier survival curves for RFS and OS based on the surgical procedure among (A) all patients, (B) patients with preoperative obstructive ventilatory impairment, and (C) patients with preoperative restrictive ventilatory impairment. RFS, recurrence-free survival; OS, overall survival.

Table 3 %VC in patients with restrictive ventilatory impairment

Extent of resection	Median [range], %
Lobectomy	68.9 [63.9–76.6]
Segmentectomy	67.9 [57.2–78.4]
Wedge	63.0 [35.3–73.7]

%VC, preoperative actual vital capacity/expected vital capacity.

adenocarcinomas, and in 25 out of 29 cases we were able to secure a resection margin that was larger than the tumor diameter. In 11 of 15 cases of obstructive ventilation disorder, the surgical margin was enough, but in contrast, in all but 4 of 14 cases of restrictive ventilation disorder, the surgical margin was insufficient (Tables S4-S6). Of the 10 cases with insufficient results, 5 cases were squamous cell carcinoma and the other case was large cell neuroendocrine carcinoma. Reviewing the surgical records, it appears that the lung parenchyma was too stiff to facilitate an adequate resection distance in our patients, despite no diagnosis of interstitial pneumonia. The resection margins were well secured for patients with obstructive ventilatory impairment who underwent partial resection, which may explain the differences between the two groups in the effect of partial resection on recurrence. This may also explain the difference in OS between patients with obstructive and restrictive ventilatory impairment. Additionally, in the eight patients in the restrictive ventilatory impairment group in whom lobectomy was possible, the 5-year survival rate was similar to that of patients with normal respiratory function. Therefore, surgical indications for lobectomy or segmentectomy should be carefully considered for patients in whom wedge resection cannot be achieved with sufficient surgical margins. Furthermore, the efficacy of stereotactic body radiotherapy for small lung cancer has been already reported (21,22). Thus, it might be a good idea to choose radiotherapy for cases that cannot be perform lobectomy or segmentectomy.

In addition to the five recurrent cases in the restrictive ventilatory impairment group, there were five deaths from other causes, including those in three patients who underwent partial resection. The causes of death were pneumonia in two cases, interstitial pneumonia in one case, asphyxia due to sputum in one case, and pathogenic colitis in one case. Although interstitial pneumonia was the most common cause of restrictive ventilatory impairment in two patients and the cause of death in one patient, it did not appear that patients in the restrictive ventilatory impairment group with interstitial pneumonia had a worse prognosis.

Patients with preoperative restrictive ventilatory impairment had a poorer postoperative course than those with obstructive ventilatory impairment. Although not significantly different, patients who underwent segmentectomy had a worse prognosis than those who underwent lobectomy, and patients who underwent wedge resection had the worst prognosis (*Figure 3*). Focusing on the preoperative actual VC/expected VC rate (%VC), there was a trend toward a low median %VC in the lobectomy group (68.9%), segmentectomy group (67.9%), and wedge resection group (63.0%) (*Table 3*). Because no clear criteria were established, it was thought that limited surgery was selected according to worse respiratory function at the discretion of the attending physician. In addition, 15 of the 31 patients with restrictive ventilatory impairment had unexpected hospitalizations after surviving the perioperative period. The reasons varied (Table S2). Therefore, these patients should be carefully monitored during the long-term postoperative course. In other words, choosing limited surgery easily for those with preoperative restricted ventilatory impairment may not lead to good outcome, as a result of surgical treatment performed in practices in city hospitals. Pezzuto *et al.* have described the usefulness of the chronic obstructive pulmonary disease assessment test as a way to anticipate postoperative respiratory failure (23). Because it is a simple and noninvasive for patients, it is one of the best methods to consider the indication of surgical treatment. Based on the results of our study, we have focused our attention on the 6-minute walk test. The 6-minute walk test is also simple to perform, and it can confirm exercise tolerance (24). Recently, we have been checking this test in patients with preoperative ventilation problems. If the results are poor, we suggest non-surgical treatments such as radiotherapy.

Our study had several limitations. This was a retrospective study in a single-institution setting, and only a small number of patients with pathological stage IA lung cancer were included. Most importantly, there may be selection bias of surgical procedures in our cohort because our institution did not clearly show the surgical indications. We did not perform a respiratory function test during our postoperative routine, which was inadequate for postoperative evaluation. Prospective or larger retrospective and multicenter studies are required.

Conclusions

Preoperative restrictive ventilatory impairment might be a poor prognostic factor in patients with pathological stage I lung cancer undergoing pulmonary resection. In cases where lobectomy or segmentectomy cannot be performed, careful consideration should be given to whether surgery is indicated.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-22/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-22/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-22/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Iwakuni Clinical Center (approval No. 0462). Informed consent was obtained using the opt-out option on the hospital's website, based on the Ethical Guidelines for Medical and Biological Research Involving Human Subjects, implemented in Japan.

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Supplementary

Table S1 Patient characteristics (n=192)

Characteristics	Normal (n=113)	Obstructive (n=55)	Restrictive (n=31)	Mixed (n=7)
Age, y, median [range]	69 [31-92]	74 [56-88]	75 [60-88]	71 [62-82]
Sex				
Male	46	39	16	4
Female	67	16	15	3
Body mass index, kg/m^2, median [range]	22.6 [16.3-31.2]	22.8 [16.5-29.7]	23.0 [14.5-29.7]	22.8 [18.4-29.7]
Smoking status				
Never	67	18	13	3
Former/current	46	37	18	4
Brinkman index				
Median [range]	750 [20-3120]	1040 [12-2880]	900 [8-2640]	1350 [700-1560]
Performance status				
0	98	38	20	3
1	11	14	7	3
2	3	2	2	0
3	1	1	2	1
Surgical approach				
Thoracotomy	4	1	3	0
VATS	109	54	28	7
Extent of resection				
Lobectomy	78	13	8	2
Segmentectomy	31	17	9	2
Wedge	4	15	14	3
Histology				
Ad	102	41	18	6
Sq	9	9	10	1
Other	2	5	3	0
Hospitalization period, days				
Average [range]	8.2 [2-30]	8.0 [3-21]	11.7 [3-73]	10.0 [6-15]

Data are presented as n unless otherwise indicated. VATS, video-assisted thoracic surgery; Ad, adenocarcinoma; Sq, squamous cell carcinoma.

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Table S2 Details of early postoperative complications

Respiratory dysfunction	Normal	Obstructive ventilatory impairment	Restrictive ventilatory impairment
Prolonged air leak	6		1
Pneumonia			1
Surgical site infection	2	2	
Arrythmia	3		1
Chylothorax	1	1	
Pulmonary embolism	1		
Others	1	1	1

Table S3 Details of postoperative late complications

Respiratory dysfunction	Normal	Obstructive ventilatory impairment	Restrictive ventilatory impairment	Mixed ventilatory impairment
Pneumonia	5	4	4	1
Organizing pneumonia	1			
Internal pneumonia	3		1	
Pneumothorax	2		1	
Pyothorax		2		
Pulmonary embolism	2			
Heart failure	3		1	
Arrythmia	3	3	2	1
Angina	4	1	1	
Acute myocardial infarction	2	1		
Valvular disease			1	
Aortic dissection	1	1		
Cerebral infarction	1			
Cerebral hemorrhage	1		1	
Renal failure	2			
Pyelonephritis	1	1		
Cholecystitis	1			
Surgical wound dehiscence	1			
Bone fracture	4	3	2	1
Others	1	2	1	1

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Table S4 Details of tumor size, surgical margin and follow-up outcomes in patients with wedge resection—normal respiratory function

No.	Tumor size (mm)	Surgical margin (mm)	Recurrence	Follow-up outcomes
1	16	15	No	Alive at 81-month
2	15	22	No	Alive at 72-month
3	5	10	No	Alive at 60-month
4	8	10	No	Alive at 43-month
5	15	16	No	Alive at 52-month
6	8	10	No	Lost to follow-up
7	8	10	No	Alive at 91-month
8	8	15	No	Alive at 90-month
9	8	12	No	Alive at 97-month
10	5	20	No	Alive at 61-month
11	6	15	No	Lost to follow-up
12	8	15	No	Alive at 62-month
13	5	10	No	Alive at 31-month
14	4	16	No	Alive at 72-month
15	6	20	No	Alive at 75-month
16	12	10	Yes	Alive at 24-month
17	8	14	No	Alive at 93-month
18	5	7	No	Alive at 61-month
19	6	23	No	Alive at 48-month
20	10	11	No	Alive at 62-month
21	7	15	No	Alive at 60-month
22	11	10	No	Alive at 57-month
23	5	10	No	Alive at 84-month
24	9	12	Yes	Died, lung cancer
25	7	20	No	Alive at 67-month
26	14	17	No	Lost to follow-up
27	13	5	No	Alive at 62-month
28	10	10	No	Alive at 24-month
29	4	10	No	Alive at 66-month

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Table S5 Details of tumor size, surgical margin and follow-up outcomes in patients with wedge resection—obstructive ventilatory impairment

No.	Tumor size (mm)	Surgical margin (mm)	Recurrence	Follow-up outcomes
1	11	15	Yes	Alive at 17-month
2	13	20	No	Alive at 66-month
3	8	20	No	Alive at 86-month
4	6	15	No	Alive at 67-month
5	13	10	Yes	Alive at 70-month
6	23	5	Yes	Died, lung cancer
7	10	12	No	Died, aortic dissection
8	11	13	No	Died, another lung cancer
9	11	10	No	Died, empyema
10	20	19	No	Alive at 60-month
11	8	13	No	Alive at 68-month
12	8	20	No	Alive at 79-month
13	4	6	Yes	Alive at 87-month
14	11	12	No	Died, colon cancer
15	15	19	No	Alive at 101-month

Table S6 Details of tumor size, surgical margin and follow-up outcomes in patients with wedge resection—restrictive ventilatory impairment

No.	Tumor size (mm)	Surgical margin (mm)	Recurrence	Follow-up outcomes
1	30	4	Yes	Died, lung cancer
2	18	10	Yes	Died, pneumonia
3	9	15	No	Alive at 7-month
4	23	20	No	Alive at 15-month
5	27	30	Yes	Alive at 9-month
6	8	15	No	Alive at 71-month
7	9	5	Yes	Alive at 27-month
8	13	15	No	Alive at 67-month
9	19	12	Yes	Died, lung cancer
10	21	1	No	Died, *E. coli* O-157 enteritis
11	18	15	Yes	Died, lung cancer
12	23	5	Yes	Died, lung cancer
13	11	8	No	Died, another lung cancer
14	19	8	No	Alive at 26-month

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