Original Article

Predicting postoperative lung function using ventilation SPECT/CT in patients with lung cancer

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Background: Single-photon emission computed tomography/computed tomography (SPECT/CT) has the advantage of assessing regional lung function. We aimed to investigate the potential of ventilation (SPECT/CT) for predicting postoperative lung function in patients with lung cancer.

Methods: This retrospective study included consecutive patients with lung cancer who underwent lobectomy, preoperative ventilation, and perfusion SPECT/CT between January 2020 and December 2021. The percentage of predicted postoperative forced expiratory volume in 1 s (ppoFEV_1%) and the percentage of predicted postoperative diffusion capacity of the lung for carbon monoxide (ppoDL_{CO}%) were calculated from the % counts of each scan based on anatomical segments for lobar function. Correlation tests were performed between the predicted lung function values and actual ppoFEV_1% and ppoDL_{CO}%.

Results: Among the 47 patients, 29 men and 18 women aged 67.5±9.6 years were included. Moreover, 46 ventilation and 41 perfusion SPECT/CT scans were obtained. The pulmonary function on ventilation SPECT/CT strongly correlated with perfusion SPECT/CT (correlation coefficient r=0.939 for ppoFEV_1%, P<0.001; r=0.938 for ppoDL_{CO}%, P<0.001). Both ppoFEV_1% and ppoDL_{CO}% values obtained from the ventilation and perfusion scans strongly correlated with postoperative FEV_1% and DL_{CO}% (correlation coefficient, r=0.774 and r=0.768 for ventilation; r=0.795 and r=0.751 for perfusion, each P<0.001).

Conclusions: Ventilation SPECT/CT was comparable to perfusion SPECT/CT in predicting postoperative lung function.

Keywords: Lung neoplasms; single-photon emission computed tomography (SPECT); ventilation; perfusion; forced expiratory volume

Submitted Oct 08, 2023. Accepted for publication Dec 21, 2023. Published online Feb 26, 2024.
doi: 10.21037/jtd-23-1563
View this article at: https://dx.doi.org/10.21037/jtd-23-1563

Introduction

The optimal treatment for early-stage lung cancer is complete surgical resection of the tumor involving the lung lobe(s) and regional lymph nodes (1). However, epidemiology shows that more than 70% of future lung cancer cases develop in older patients aged >65 years (2), and poor performance and lung function impairment are common (3,4). Predicting residual lung function after surgical resection is critical to avoid postoperative respiratory failure and other cardiopulmonary complications. Thus, a considerable proportion of patients with early-stage lung cancer are not expected to undergo surgical resection because of non-feasible physiological staging.

Of the pulmonary function measurements, predicted postoperative forced expiratory volume in 1 s ($ppoFEV_1$) and predicted postoperative diffusion capacity of the lung for carbon monoxide ($ppoDL_{CO}$) are the most significant parameters for determining the feasibility of surgical resection in patients with lung cancer (5,6). Among the various methods used to calculate these values, preoperative planar lung perfusion scintigraphy is widely used in real-world practice (5,7). However, planar lung scintigraphy has limitations in accurately calculating the individual lobes that reflect the patient's lung anatomy. Compared to the conventional method that calculates postoperative pulmonary function measurements based on regional lung anatomy involving lung cancer, single-photon emission computed tomography/computed tomography (SPECT/CT) has the advantage of reflecting regional lung function in tumor-containing lobe(s) (8-10).

Currently, two types of SPECT/CT—for ventilation and perfusion—are available for lung function measurements. However, previous studies have used perfusion scans to evaluate the role of preoperative SPECT/CT in estimating postoperative lung function in patients with lung cancer (9,11). SPECT/CT has an advantage in measuring the contribution of individual lobes of pulmonary ventilation; however, little information is available on whether ventilation SPECT/CT can be used as a preoperative test for the prediction of pulmonary function (8,10). Accordingly, our study aimed to compare the feasibility of ventilation SPECT/CT by comparing its performance with that of perfusion SPECT/CT in patients with lung cancer. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1563/rc).

Highlight box

Key findings

- Ventilation single-photon emission computed tomography/computed tomography (SPECT/CT) was comparable to perfusion SPECT/CT in predicting postoperative lung function. Ventilation SPECT/CT could be used for the prediction of postoperative lung function.

What is known and what is new?

- It is unclear how useful ventilation SPECT/CT is as a preoperative test for the prediction of pulmonary function.
- In this study, ventilation SPECT/CT predicted postoperative lung function in patients with lung cancer and showed a strong correlation with perfusion SPECT/CT in predicting postoperative lung function.

What is the implication, and what should change now?

- Ventilation SPECT/CT may be one of the tools that can predict postoperative lung function as well as perfusion SPECT/CT.

Methods

Patients and clinical parameters

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Institutional Review Board of Hanyang University Medical Center (IRB No. 2023-01-027). The requirement for written informed consent was waived by the Institutional Review Board because of the retrospective design of the study.

Patients who underwent lobectomy with preoperative lung SPECT/CT between January 2020 and December 2021 were included in this study. All patients underwent pulmonary function tests (PFTs) and lung SPECT/CT as part of the preoperative evaluation. The patients had biopsy-proven or suspected lung cancer. Patients with proven lung cancer were scheduled for surgery with curative intent based on the exclusion of distant metastatic disease using F-18 fluorodeoxyglucose positron emission tomography/CT. Patients with clinically suspected lung cancer were scheduled for an intraoperative frozen biopsy to confirm malignancy before treatment. All patients underwent curative surgical resection performed by two thoracic surgeons. Surgical type and pathology results were recorded. Patients with pathologies other than primary lung cancer, sublobar resection, or without postoperative PFT were excluded. Since there is no standard method to measure sublobar resection, we excluded patients who

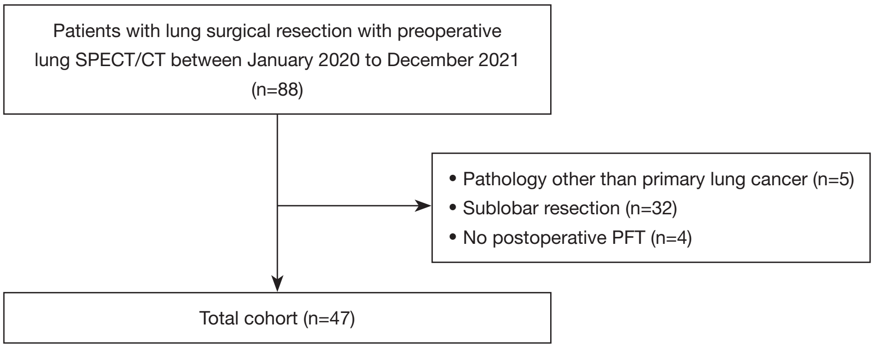

Figure 1 Enrollment flowchart of patients. SPECT/CT, single-photon emission computed tomography/computed tomography; PFT, pulmonary function test.

underwent sublobar resection. A total of 47 patients were enrolled (*Figure 1*).

A total of 47 patients (29 men and 18 women) were enrolled, and their clinical characteristics are summarized in *Table 1*. The mean age of the patients was 67.5±9.6 years (range, 45–88 years). Most patients had stage I lung cancer (68.1%). Lobectomy, bilobectomy, and pneumonectomy were performed in 89.4%, 8.5%, and 2.1% of the patients, respectively. FEV_1 was evaluated in all patients, and DL_{CO} was evaluated in 40 patients (85.1%). The mean interval between the preoperative PFT and lung SPECT/CT scan was 6.1±7.7 days. The mean interval between PFTs before and after surgery was 3.9±0.9 months.

PFTs

PFTs, including spirometry and single-breath DL_{CO} were measured using the MasterScreen Body Jaeger spirometer (CareFusion Ltd., Viasys Healthcare, Hoöchberg, Germany) for all patients in accordance with the American Thoracic Society guidelines (12,13). Preoperative PFTs were performed within an average of 7 days of the lung SPECT/CT scan. Absolute values of FEV_1 and DL_{CO} were obtained, and the percentage of predicted postoperative values for FEV_1 (ppoFEV_1%) and DL_{CO} (ppoDL_{CO}%) was calculated using a reference equation obtained from the analysis of a representative sample (14,15). Postoperative PFTs were performed between 3 and 6 months. PFTs were performed 3 months after surgery in most patients (40/47, 85.1%), 4 patients (8.5%) at 4 months, 1 patient (2.1%) at 5 months, and 2 patients (4.2%) at 6 months. Only 2 patients were performed over 6 months after surgery.

Lung SPECT/CT protocols

All imaging data were acquired using a SPECT/CT scanner (NM/CT 850; GE Healthcare, Milwaukee, USA). A ventilation SPECT scan was performed after inhalation of nano-sized technetium (Tc)-99m-labeled carbon particles, which were produced using a commercially available Technegas® generator (Cyclomedica Pty Ltd., Sydney, Australia). Tc-99m was concentrated to a volume of 0.1 mL and transferred to a Technegas® generator, where it was heated to produce nano-sized Tc-99m-labeled carbon (average size 30–60 nm) (16). The estimated inhalation activity was approximately 20 MBq.

Ventilation SPECT images were obtained using a dual-head camera equipped with a low-energy, high-resolution collimator. The patients were then imaged in the supine position, with the patient breathing freely. SPECT scans were obtained using parameters including an energy center of 140.5 keV with a window width of 20%, a total acquisition of 60 frames over 360°, 12 s per projection for the acquisition (10 s for perfusion scan), and a matrix size of 128×128. Images were reconstructed with CT-based attenuation correction using an iterative ordered-subset expectation-maximization algorithm. CT images were obtained using the following parameters: tube voltage (120 kV), tube current (10 mA), table speed (9.37 mm/rotation), pitch (0.938:1), collimation (10 mm), and matrix (512×512). CT images were reconstructed with a 1.25 mm slice thickness using an adaptive statistical iterative reconstruction algorithm (ASiR®, GE Healthcare). Perfusion SPECT scans were acquired after intravenous injection of Tc-99m macroaggregated albumin at a dose of

Table 1 Patient characteristics

Characteristics	Number (n=47)
Age (years, mean ± SD)	67.5±9.6
Gender, n (%)	
Men	29 (61.7)
Women	18 (38.3)
Histopathology of lung cancer, n (%)	
Adenocarcinoma	33 (70.2)
Squamous	12 (25.5)
Others	2 (4.3)
TNM stage, n (%)	
I	32 (68.1)
II	5 (10.6)
III	6 (12.8)
IV	3 (6.4)
Limited state	1 (2.1)
Surgery, n (%)	
Lobectomy	42 (89.4)
Bilobectomy	4 (8.5)
Pneumonectomy	1 (2.1)
PFT, n (%)	
FEV_1%	47 (100.0)
DL_{CO}%	40 (85.1)
PFT follow-up period (months, mean ± SD)	4.0±1.8
Lung SPECT/CT, n (%)	
Both ventilation and perfusion	40 (85.1)
Ventilation only	6 (12.8)
Perfusion only	1 (2.1)

SD, standard deviation; TNM, tumor-node-metastasis; PFT, pulmonary function test; FEV_1, forced expiratory volume in 1 s; DL_{CO}, diffusion capacity of the lung for carbon monoxide; SPECT/CT, single-photon emission computed tomography/computed tomography.

185 MBq, with the patient in a supine position. In patients who underwent both perfusion and ventilation SPECT, lung ventilation and perfusion scans were performed consecutively on the same day, and CT was performed only once. Perfusion SPECT was performed after ventilation using SPECT/CT.

Lobar segmentation and calculation of lung functions

Semi-quantitation of SPECT and CT images was performed using commercial software (Q. Lung, Xeleris 4.1; GE Healthcare). Each patient's ventilation and perfusion SPECT scan was fused with CT to calculate lobar function. The volume of interest (VOI) for each lobe was delineated along the lung fissures based on the bronchial tree on sagittal fused SPECT/CT images. All VOIs were reviewed and consensually confirmed by two nuclear medicine clinicians in consensus with 12 and 25 years of experience, respectively. The counts within the VOIs were assumed to be the lung function of that lung area and used in calculating the fraction of each lobe on SPECT. The lobar ratio based on the % uptake was assessed by dividing the count of each lobe by the total count of both lungs. In patients who underwent the perfusion SPECT following the ventilation SPECT, net lobar perfusion counts were obtained by subtracting the ventilation lobar counts from the perfusion lobar counts.

Postoperative lung function based on the % uptake of ventilation or perfusion SPECT was estimated using the following formula (8,17): $ppoFEV_1$ = preoperative FEV_1% × (1 − %uptake of resected lobe[s]/total lung %uptake). The $ppoDL_{CO}$% was calculated using the same method.

Statistical analysis

Data were analyzed using SPSS (version 22.0; IBM SPSS Statistics, IBM Corp., Armonk, NY, USA) and MedCalc Statistical Software (MedCalc version 20.211; Mariakerke, Belgium). Continuous data are presented as mean ± standard deviation. Shapiro-Wilk normality test of continuous variables was performed. All were normally distributed. The relationship between $ppoFEV_1$ values and actual postoperative FEV_1 was evaluated using Pearson's correlation analysis. Bland-Altman plots were constructed to visualize the agreement. Statistical significance was set at a P value of <0.05.

Results

Predicted postoperative lung function by lung SPECT/CT

The actual PFTs before and after surgery and the ppo-lung function for the enrolled patients are shown in *Table 2*. The mean values of $ppoFEV_1$% and $ppoDL_{CO}$% did not differ between ventilation and perfusion SPECT/CT. The mean $ppoFEV_1$% values were slightly underestimated

Table 2 Pulmonary function and predictive postoperative lung function of ventilation and perfusion SPECT/CT

Variables	FEV_1%	DL_{CO}%	ppoFEV_1%	ppoDL_{CO}%
PFT				
Preoperative values	87.0±18.3	68.4±14.5	–	–
Postoperative values	77.5±16.6	55.5±16.4	–	–
Ventilation SPECT/CT	–	–	70.5±16.3	55.4±12.7
Perfusion SPECT/CT	–	–	70.8±15.5	55.2±15.1

Data are presented as mean ± standard deviation. SPECT/CT, single-photon emission computed tomography/computed tomography; FEV_1, forced expiratory volume in 1 s; DL_{CO}, diffusion capacity of the lung for carbon monoxide; ppoFEV_1, predictive postoperative FEV_1; ppoDL_{CO}, predictive postoperative DL_{CO}; PFT, pulmonary function test.

than were actual postoperative FEV_1 values (pFEV_1% =77.5%±16.6%; ppoFEV_1% of ventilation =70.5%±16.3%; ppoFEV_1% of perfusion =70.8%±15.5%). No difference was observed between the mean values of postoperative DL_{CO}% (pDL_{CO}%) and ppoDL_{CO}% derived from ventilation and perfusion SPECT/CT (pDL_{CO}% =55.5%±16.4%; ppoDL_{CO}% of ventilation =55.4%±12.7%; ppoDL_{CO}% of perfusion =55.2%±15.1%).

Agreement of ppoFEV_1% and ppoDL_{CO}% between ventilation and perfusion SPECT/CT

A significant positive correlation was observed between predicted postoperative lung function obtained from ventilation and perfusion SPECT/CT. *Figure 2* shows the scatter plots and Bland-Altman plots obtained by ventilation and perfusion scans. The correlations between the two tools were high, with Pearson's correlation coefficients of 0.939 for ppoFEV_1% ($P<0.001$) and 0.938 for ppoDL_{CO}% ($P<0.001$). In the Bland-Altman method, the mean difference between ppoFEV_1% values was 0.3, with limits of agreement ranging from −10.9% to 11.6%. The mean difference between ppoDL_{CO}% was 0.1, with agreement limits ranging from −8.6% to 8.8%.

Agreement between actual postoperative lung function and predicted postoperative lung function

In *Figure 3*, the actual postoperative lung function, including, pFEV_1% and pDL_{CO}%, showed a strong correlation with lung function predicted by ventilation and perfusion, respectively ($P<0.001$ for all). The correlation coefficients were 0.751–0.795, with no difference between ventilation and perfusion. The Bland-Altman plot demonstrated agreement between pFEV_1 and predictive lung function [mean difference, 7.7; 95% confidence interval (CI): 4.48–11.0 for ventilation; mean difference, 6.9; 95% CI: 3.7–10.1 for perfusion]. Similar findings were obtained for the agreement between pDL_{CO}% and predictive lung function (mean difference, 1.50; 95% CI: −1.8 to 4.9 for ventilation; mean difference, 2.3; 95% CI: −1.12 to 5.8 for perfusion).

Discussion

Our study evaluated the feasibility of ventilation SPECT/CT in predicting pulmonary function in patients with lung cancer by comparing its performance with that of perfusion SPECT/CT. Our analyses showed that ventilation SPECT/CT strongly correlated with perfusion SPECT/CT in predicting postoperative lung function in patients with lung cancer. The predictive ability of residual lung function after surgical resection was comparable to that of perfusion SPECT/CT with actual postoperative lung function.

Ventilation and perfusion SPECT/CT principally measure different physiological quantities. However, this study of patients who underwent lobectomy showed a significant correlation between these two modalities. A lung perfusion scan reflects the blood flow by visualizing the pulmonary vasculature up to the capillary vessel level. In comparison, the ventilation scan showed that the tracer reached the periphery of the lungs and was mainly deposited in the bronchioles and alveoli, mostly by diffusion. The quality of the ventilation scan critically depends on the tracer type (17). Airway resistance is increased in chronic obstructive pulmonary disease; thus, tracers tend to deposit and create hotspots in the central airways. This is more pronounced in the micro-sized diethylenetriamine pentaacetate tracer than in the Tc-99m-labeled nano-sized particles, Technegas. We performed a ventilation scan using

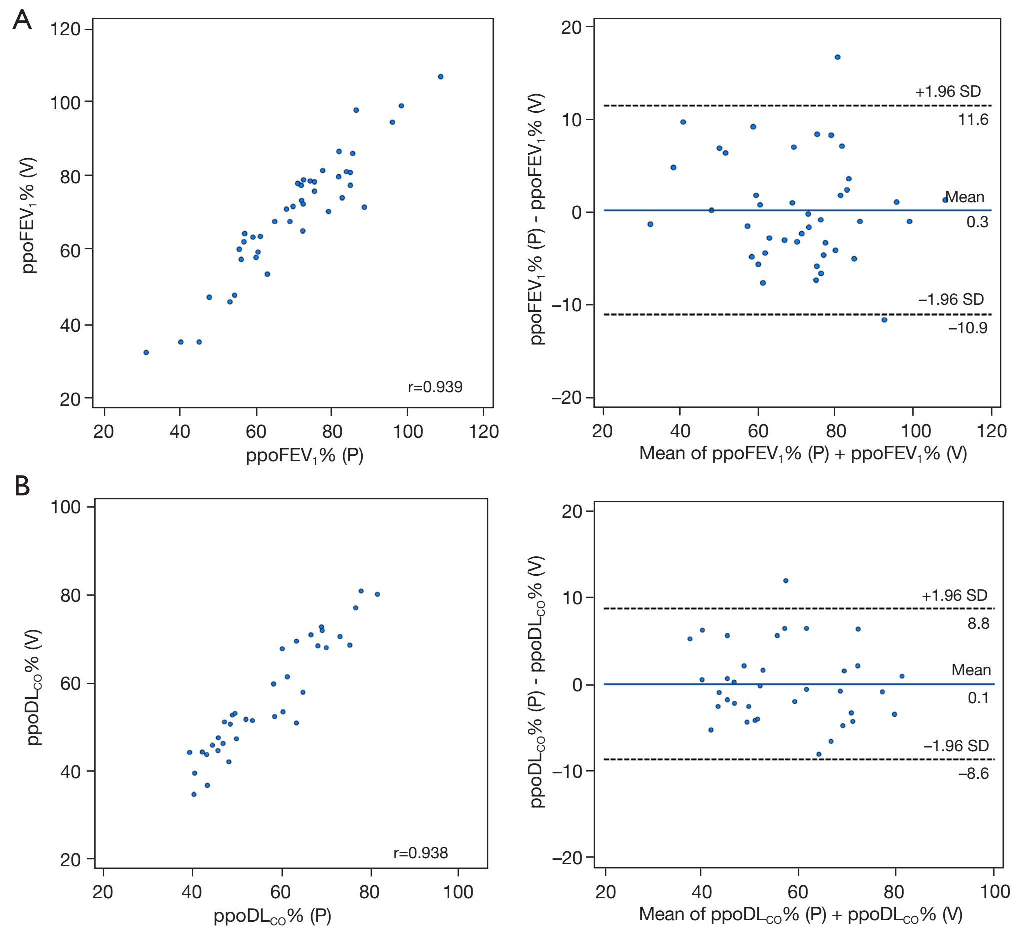

Figure 2 Scatter plots (left side) and Bland-Altman plots (right side) of predicted postoperative FEV$_1$% and DL$_{CO}$% by ventilation and perfusion SPECT/CT scan. (A) ppoFEV$_1$% and (B) ppoDL$_{CO}$%. Solid line: the mean difference between two methods; dotted line: limits of agreements as 95% confidence intervals. V, ventilation; P, perfusion; ppoFEV$_1$, predicted postoperative forced expiratory volume in 1 s; ppoDL$_{CO}$, predicted postoperative diffusion capacity of the lung for carbon monoxide; SD, standard deviation; SPECT/CT, single-photon emission computed tomography/computed tomography.

Technegas to avoid this effect in this study.

Ventilation SPECT/CT has an advantage in measuring the contribution of the individual lobes to pulmonary ventilation. Despite this advantage, ventilation SPECT/CT is not frequently used, whereas lung perfusion SPECT/CT is more widely used to evaluate the ppoFEV$_1$ in current medical practice (11,18,19). However, current medical practice is not supported by any evidence, and few studies have comprehensively compared the performance of these two scans, including postoperative lung function prediction (16). Ohno *et al.* reported that even though ventilation SPECT and perfusion SPECT were fused with a CT scan, which was not obtained simultaneously, it showed a more accurate ppo-lung function than SPECT and planar images (8). In this study, SPECT and CT images were performed sequentially in a hybrid SPECT-CT system and lung segmentation was performed using the installed software. It may reduce misalignment between two images and improve co-registration. This may help to analyze lobar function more accurately. Each ventilation and perfusion SPECT/CT showed good agreement with the actual postoperative lung function and FEV$_1$. Ventilation SPECT/CT had a mean difference of 5.7%, and the limits of agreement ranged from −5.1% to 16.5%. Perfusion SPECT/CT had a mean difference of 6.8%, and the limits of agreement ranged from −4.3% to 17.9%. In agreement with these results, our study showed a significant correlation between ventilation and perfusion SPECT/CT

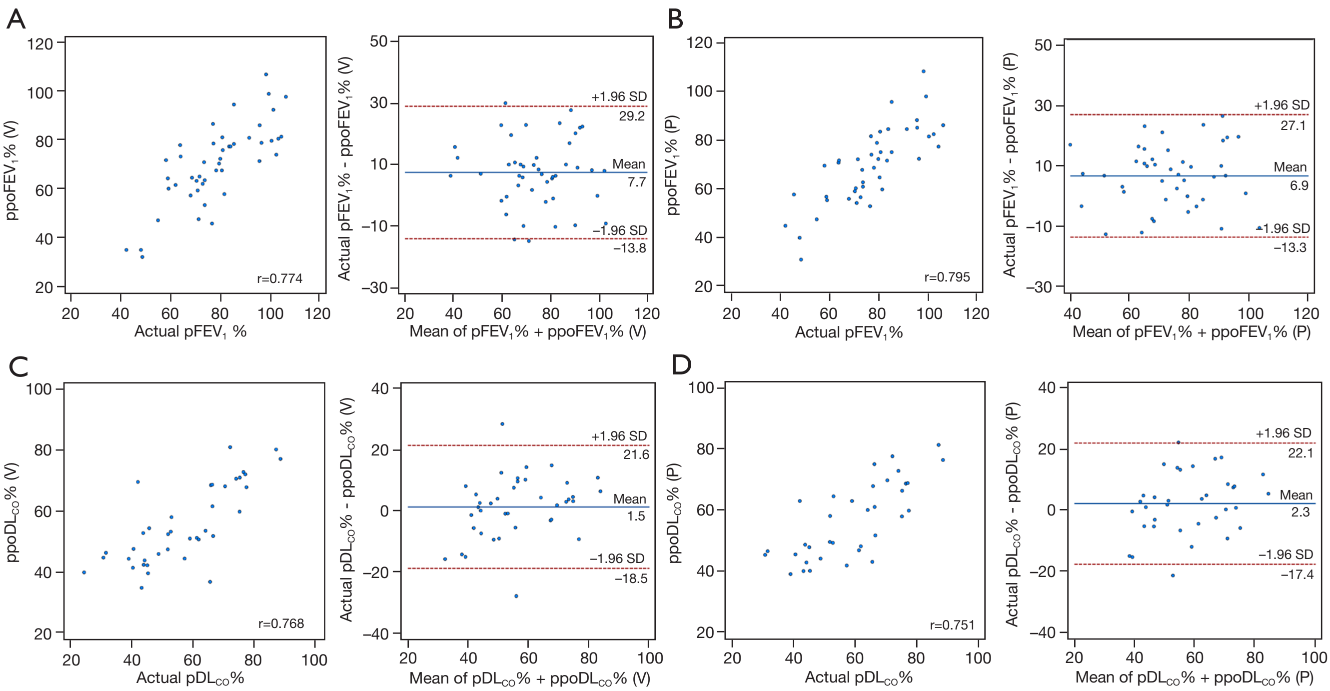

Figure 3 Scatter plots (left side) and Bland-Altman plots (right side) between actual postoperative lung function and predicted lung function by ventilation and perfusion SPECT/CT scan. (A) Actual $pFEV_1$% and $ppoFEV_1$% (V); (B) actual $pFEV_1$% and $ppoFEV_1$% (P); (C) actual pDL_{CO}% and $ppoDL_{CO}$% (V); and (D) actual pDL_{CO}% and $ppoDL_{CO}$% (P). Solid line: the mean difference between the two methods; dotted line: upper and lower limits. V, ventilation; P, perfusion; $pFEV_1$, postoperative forced expiratory volume in 1 s; pDL_{CO}, postoperative diffusion capacity of the lung for carbon monoxide; $ppoFEV_1$, predicted postoperative FEV_1; $ppoDL_{CO}$, predicted postoperative DL_{CO}; SD, standard deviation; SPECT/CT, single-photon emission computed tomography/computed tomography.

in predicting the ppo-lung function. However, compared to the previous study, our study showed a broader range of agreement limits (−13.8% to 29.2% for ventilation and, −13.3% to 27.1% for perfusion), which are considered differences in the patient populations.

Our study has several limitations owing to its retrospective design and small sample size from a single tertiary medical center. First, patients with various lung diseases were enrolled in the study. Among the enrolled patients, 12 (25.5%) had normal lungs, and 35 (74.5%) had lung disease based on CT (Table S1). Lung disease includes various diseases such as emphysema, old tuberculosis sequelae, inflammatory sequelae or inflammation, bronchiectasis, and radiation pneumonitis. The impact of lung disease could not be analyzed because of the small number of enrolled patients. Accordingly, we did not investigate the contribution of each lobe or the differences between ventilation and perfusion SPECT/CT. Second, the timing for lung function measurement ranged from 3 to 6 months. Although a previous study showed that lung function is relatively stable during this time period (20), different timing of lung function measurement might have affected our results. Third, post-operative complications and adjuvant chemotherapy may have affected our results. However, we could not accurately evaluate post-operative complications due to the nature of the retrospective design of our study. Of the 47 patients, 22 patients received chemotherapy after surgery, and 11 of them underwent postoperative PFTs during adjuvant chemotherapy (usually performed from 1–2 months after surgery for 3 months). Since their lung function measurement was performed during chemotherapy, we could not accurately evaluate the impact of adjuvant chemotherapy on these patients. Fourth, the clinical effects of ventilation and perfusion on the long-term prognostic outcomes were not compared. Finally, we could not evaluate the factors that were associated with a higher or lower performance of ventilation SPECT/CT over perfusion SPECT/CT. For example, central mass compression airway obstruction may decrease the performance of a ventilation scan by underestimating the lung function of the involved lobe. Further studies are required in this regard.

Conclusions

We evaluated how ventilation SPECT/CT predicted lung function after lobectomy in patients with lung cancer and found a strong correlation with perfusion SPECT/CT in predicting postoperative lung function. We considered that ventilation SPECT/CT could be used to predict lung function after lobectomy. Further studies are needed to determine in which cases the ventilation SPECT/CT more accurately predicts the postoperative lung function in patients with lung cancer.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1563/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1563/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1563/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1563/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 retrospective study was approved by the Institutional Review Board of Hanyang University Medical Center (IRB No. 2023-01-027). The requirement for written informed consent was waived by the Institutional Review Board because of the retrospective design of the study.

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Cite this article as: Jeong YH, Lee H, Jang HJ, Park DW, Choi YY, Lee SJ. Predicting postoperative lung function using ventilation SPECT/CT in patients with lung cancer. J Thorac Dis 2024;16(2):1054-1062. doi: 10.21037/jtd-23-1563

Supplementary

Table S1 Lung disease on preoperative computed tomography

Variables	n=47	Percent (%)
No disease	12	25.5
Lung disease	35	74.5
Emphysema	13	37.1
Old Tbc sequelae/NTM	7	20.0
Inflammatory sequelae or process	3	8.6
Bronchiectasis	3	8.6
Radiation pneumonitis	2	5.7
Pleuroparenchymal elastosis	1	2.9
Pulmonary edema	1	2.9
Giant bullae	1	2.9
Langerhans cell histiocytosis	1	2.9
Interstitial lung disease	1	2.9
Diffuse pulmonary meningotheliomatosis	1	2.9
Pneumoconiosis	1	2.9

Tbc, tuberculosis; NTM, nontuberculous mycobacteria.

https://dx.doi.org/10.21037/jtd-23-1563