



Comparative Analysis of Lung Perfusion Scan and SPECT/CT for the Evaluation of Functional Lung Capacity

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Received: 9 July 2019 / Revised: 24 September 2019 / Accepted: 11 October 2019 / Published online: 11 November 2019
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Abstract

Purpose This study aimed to compare lung perfusion scan with single photon emission computed tomography/computed tomography (SPECT/CT) for the evaluation of lung function and to elucidate the most appropriate modality for the prediction of postoperative lung function in patients with lung cancer.

Methods A total of 181 patients underwent Tc-99m macroaggregated albumin lung perfusion scan and SPECT/CT to examine the ratio of diseased lung and diseased lobe. Forty-one patients with lung cancer underwent both preoperative and postoperative pulmonary function tests within 1 month to predict postoperative pulmonary function. Predicted postoperative forced expiratory volume in 1 s (ppoFEV₁) was calculated by the % radioactivity of lung perfusion scan and SPECT, and the % volume of the residual lung, assessed on CT.

Results The ratios of diseased lung as seen on lung perfusion scan and SPECT showed significant correlation, but neither modality correlated with CT. The ratios of the diseased lung and diseased lobe based on CT were higher than the ratios based on either perfusion scan or SPECT, because CT overestimated the function of the diseased area. The lobar ratio of both upper lobes was lower based on the perfusion scan than on SPECT but was higher for both lower lobes. Actual postoperative FEV₁ showed significant correlation with ppoFEV₁ based on lung perfusion SPECT and perfusion scan.

Conclusions We suggest SPECT/CT as the primary modality of choice for the assessment of the ratio of diseased lung area. Both perfusion scan and SPECT/CT can be used for the prediction of postoperative lung function.

Keywords Lung perfusion scan · Lung perfusion SPECT/CT · SPECT/CT · Lung function test · Lung cancer

Introduction

Lung cancer is the most commonly diagnosed cancer and is the leading cause of cancer-related death in both genders [1]. Although radiotherapy and chemotherapy have shown technical advancement, surgical resection remains the primary treatment option for lung cancer patients. The accurate prediction

of postoperative lung function is essential for identifying patients with the acceptable risks of surgery [2]. To predict postoperative lung function, ventilation indices including forced expiratory volume in 1 s (FEV₁) have been suggested to be useful predictors of postoperative morbidity and mortality in lung cancer patients [3]. The extent of functional loss after surgical resection depends on the extent of surgery, the relative functionality of the removed tissue to that of the remaining tissue, and basal lung disease [4].

The Tc-99m macroaggregated albumin (MAA) lung perfusion scan is the most widely used modality for the prediction of postoperative functional loss. However, the poor spatial resolution of lung perfusion scan may cause large prediction errors [5]. Lung perfusion single photon emission computed tomography/computed tomography (SPECT/CT) has been suggested as a more effective modality than the lung perfusion scan as it avoids spatial overlapping [6, 7]. Other approaches for the prediction of postoperative lung function include

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quantitative evaluation based on lung attenuation of CT [4, 8] and semi-quantitative evaluation by perfusion MRI [9]. Although various modalities for the prediction of postoperative lung function have been suggested, consensus lacks on a standardized modality for lung quantitation.

Using percentage (%) uptake on the Tc-99m MAA lung perfusion scan and SPECT as well as % volume on CT from SPECT/CT, we evaluated the ratios of diseased lung and diseased lobe. We also obtained the predicted postoperative lung function based on each modality and compared these with the actual postoperative lung function. The purpose of the study was to compare the lung perfusion scan with SPECT/CT for the evaluation of functional lung capacity and to suggest the most appropriate preoperative assessment modality for lung cancer patients.

Materials and Methods

Subjects

This retrospective study included patients who underwent Tc-99m MAA lung perfusion scan and lung perfusion SPECT/CT between March 2017 and December 2018. Lung perfusion scan and lung perfusion SPECT/CT images and clinical data including age, sex, treatment method, pathology, and lung function tests were obtained. Lung function tests were performed according to the American Thoracic Society standards [10]. All preoperative lung function tests were performed within 1 month (20.1 ± 9.9 days) before the surgery. All postoperative lung function tests were performed within 1.5 months (37.3 ± 39.7 days) after the surgery. Our institutional review board approved this study, and the need for informed consent was waived (IRB No. 2019-0270-0001).

Tc-99m MAA Lung Perfusion Scan and Lung Perfusion SPECT/CT

The lung perfusion scans were acquired 3–5 min after the administration of Tc-99m MAA at a dose of 8 mCi (296 MBq) with the patient in a supine position. Planar and SPECT images were obtained with a dual-head camera (NM/CT670; GE Healthcare) equipped with low-energy high-resolution collimator with the patient breathing freely. The patient underwent lung perfusion scan and SPECT/CT maintaining a supine position. Planar images from anterior, posterior, both lateral, and both posterior oblique views were acquired at 150,000 counts per view. SPECT/CT images were obtained immediately after the lung perfusion scan. CT images were obtained using parameters which included a tube voltage of 120 kV, a tube current of 10 mA, a 0.5-s rotation time, a table speed of 55 mm/s, a pitch of 1.375:1, a collimation of 20 mm, and a matrix size of 512×512 . CT images

were reconstructed with 1.25 mm slice thickness using an adaptive statistical iterative reconstruction algorithm (ASiR, GE Healthcare). SPECT images were acquired immediately after the CT images. The SPECT parameters included a 20% energy window centered at 140.5 keV, a total acquisition of 60 frames over 360° , 15 s per projection for the acquisition, and a matrix size of 128×128 . SPECT images were reconstructed using an iterative ordered subset expectation maximization (OSEM) algorithm with CT-based attenuation correction. Applying a zoom factor of 1.5, the SPECT images were reconstructed into a 128×128 matrix with a thickness of 1.0 mm. All processes were conducted using a vendor-provided workstation (Xeleris 4.0; GE Healthcare).

Image Segmentation and Parameter Acquisition

For the lung perfusion scan, counts of each ipsilateral lung were obtained from the geometric mean of counts on the anterior and posterior scans and the right and left ratios were acquired. The region of interest (ROI) for each lobe was manually drawn on both posterior oblique scans. To calculate % uptake, the counts of each lobe were divided by the counts of the ipsilateral lung and multiplied by the relative ratio of the ipsilateral lung to both lungs on anterior and posterior scans [2].

For the lung perfusion SPECT, ROIs were manually drawn based on the sagittal CT images and were integrated to generate the volume of interest (VOI) for each lobe. The counts within VOIs were used in the calculation of the fraction of each lobe on SPECT. The lobar ratio based on the % uptake was assessed by dividing the count of each lobe divided by the total count of both lungs. Similarly, manually drawn ROIs were used to derive the VOI which is volume for each lobe on CT. The lobar ratio based on the % volume was defined as the volume of each lobe divided by the total volume of both lungs. Quantitation of SPECT and CT was performed with commercial software (Q. Lung, Xeleris 4.0; GE Healthcare).

Postoperative lung function based on % uptake of lung perfusion scan and SPECT was estimated with the following formula [11]:

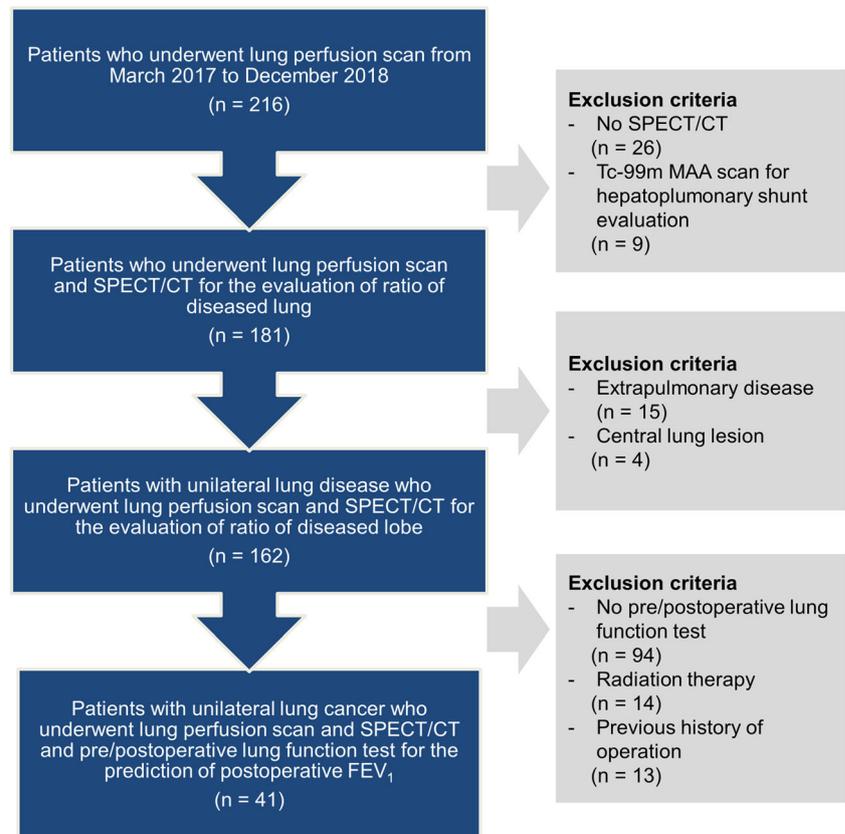
Predicted postoperative FEV_1 (ppo FEV_1) = Preoperative $FEV_1 \times (1 - \text{radioactivity of resected area}/\text{total lung radioactivity})$

Postoperative lung function based on % volume of CT from SPECT/CT was estimated by applying the following formula:

Predicted postoperative FEV_1 (ppo FEV_1) = Preoperative $FEV_1 \times (1 - \text{volume of resected area}/\text{total lung volume})$

Two experienced nuclear medicine physicians (H.Y.S. and S. K.) independently analyzed and verified the data for concurrence.

Fig. 1 Scheme of patient selection



Statistical Analysis

Statistical analysis was performed using MedCalc Statistical Software (MedCalc version 19.0.4; Mariakerke, Belgium). The values were expressed as mean \pm standard deviation. The paired *t* test was performed to test whether the ratios of diseased lung and diseased lobe were significantly different among the three different modalities. The relationships between predicted postoperative FEV₁ and actual postoperative FEV₁ were evaluated using Spearman correlation analysis. Correlation coefficients were compared using the Fisher transformation. A *p* value of less than 0.05 was considered statistically significant.

Results

Patient Characteristics

We evaluated 181 patients who underwent Tc-99m MAA lung perfusion scan and lung perfusion SPECT/CT between March 2017 and December 2018 (male/female = 139:42, age = 68.5 \pm 9.1 years; Fig. 1; Table 1). The exclusion criteria for the 181 patients who underwent a lung perfusion scan and a SPECT/CT for the evaluation of functional lung capacity were (1) patients without SPECT/CT (*n* = 26) and (2) patients

who underwent a Tc-99m MAA scan for the evaluation of hepatopulmonary shunt (*n* = 9). Further exclusion criteria for

Table 1 Characteristics of total patients (*n* = 181)

Characteristics	Value
Age (years, range)	68.5 \pm 9.1 (38–88)
Sex (male/female)	139 : 42
Primary disease	
Lung cancer	157
Squamous cell carcinoma	79 (48.4 %)
Adenocarcinoma	73 (45.2 %)
Small cell lung cancer	3 (6.4 %)
Other cancers	18
Not reported ^a	6
Location of disease	
Right lung	94
Right upper lobe	36 (37.9 %)
Right middle lobe	16 (16.8 %)
Right lower lobe	41 (43.6 %)
Right central	1 (1.1 %)
Left lung	72
Left upper lobe	44 (61.1 %)
Left lower lobe	25 (26.3 %)
Left central	3 (4.2 %)
Others ^b	15

^a Not reported include three cases with suspicious primary lung cancer but pathologically unknown due to patients' follow up loss, and three cases without any medical information about primary lesion

^b Others include diseases in extrapulmonary space such as pleura

Table 2 Characteristics of subgroup patients ($n = 41$)

Characteristics	Value	
Age (years, range)	68.9 ± 8.9 (48–84)	
Sex (male/female)	36:5	
Histologic subtype	Squamous cell carcinoma	28 (68.3 %)
	Adenocarcinoma	11 (26.8 %)
	Others	2 (0.5 %)
Operation	Pneumonectomy	3 (0.7 %)
	Bilobectomy	7 (17.1 %)
	Lobectomy	26 (63.4 %)
	Segmentectomy	1 (0.2 %)
	Wedge resection	4 (1.0 %)
TNM Stage	I	11 (26.8 %)
	II	14 (34.1 %)
	III	15 (36.6 %)
	IV	1 (0.2 %)
Underlying lung disease ($n = 14$)	Asthma	1 (7.1 %)
	COPD	7 (50.0 %)
	Pulmonary tuberculosis	6 (42.9 %)

COPD chronic obstructive pulmonary disease

162 patients who had unilateral lung disease and thus suitable for the evaluation of the ratio of diseased lung were (1) patients with extrapulmonary disease ($n = 15$) and (2) patients with a central lung lesion ($n = 4$). Finally, 41 patients who had initially been diagnosed with unilateral lung cancer and underwent preoperative and postoperative lung function tests were included for the prediction of postoperative lung function (male/female = 36:5, age = 68.9 ± 8.9 years, Table 2).

Comparison of Image Parameters in Three Different Modalities

To evaluate the relative ratio of the diseased lung, the % uptake on lung perfusion scan and SPECT and the % volume on CT during SPECT/CT were examined in 181 patients. The % uptake on lung perfusion scan and SPECT showed a linear correlation ($r = 0.9967$, $p < 0.0001$; Fig. 2a); the % uptake on SPECT and % volume on CT also showed linear correlation while the distribution was widespread ($r = 0.8317$, $p < 0.0001$;

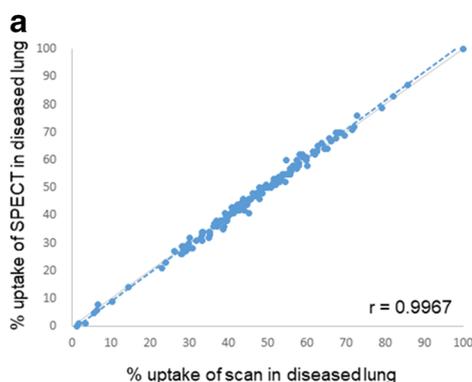


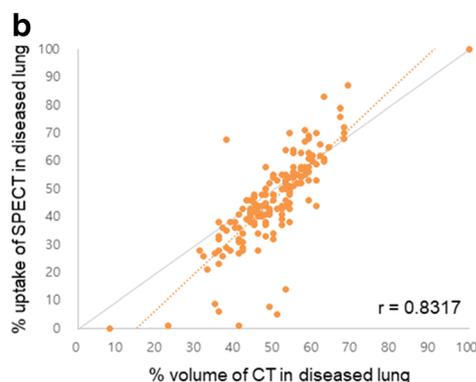
Fig. 2 Scatter plot of the ratios of the diseased lung measured by three modalities. **a** Comparison of the % uptake on lung perfusion scan and SPECT in the diseased lung. **b** Comparison of the % volume on CT and the % uptake on SPECT in the diseased lung. The gray solid line and

Fig. 2b). The difference between the % uptake on SPECT and the % volume on CT was significant ($p < 0.0001$, paired t test).

In addition, the lobar ratios measured by each modality were compared in 162 patients who were divided into five groups according to position of the diseased lobe: right upper lobe (RUL), right middle lobe (RML), right lower lobe (RLL), left upper lobe (LUL), and left lower lobe (LLL). Patients with disease in the RUL or LUL showed higher % uptake on SPECT than on lung perfusion scan. Moreover, % volume on CT was higher than % uptake on SPECT in patients with disease in the RUL or LUL ($r = 0.8877$, $p < 0.0001$ for scan vs. SPECT; $r = 0.7283$, $p < 0.0001$ for SPECT vs. CT in RUL, Fig. 3a; $r = 0.9165$, $p < 0.0001$ for scan vs. SPECT; $r = 0.7904$, $p < 0.0001$ for SPECT vs. CT in LUL, Fig. 3d). When the disease was localized in the RML, there was no significant difference in lobar ratio among the three modalities ($r = 0.8472$, $p < 0.0001$ for scan vs. SPECT; $r = 0.9341$, $p < 0.0001$ for SPECT vs. CT, Fig. 3b). Patients with disease in the RLL or LLL had a lower % uptake on SPECT than on lung perfusion scan and the % volume on CT showed larger range than the % uptake on SPECT ($r = 0.9036$, $p < 0.0001$ for scan vs. SPECT; $r = 0.8033$, $p < 0.0001$ for SPECT vs. CT in RLL, Fig. 3c; $r = 0.9124$, $p < 0.0001$ for scan vs. SPECT; $r = 0.8520$, $p < 0.0001$ for SPECT vs. CT in LLL, Fig. 3e). There were significant differences between the % uptake on lung perfusion scan and that on SPECT in all lobes except the RML ($p = 0.0592$ for RML, $p < 0.05$ for other lobes, paired t test). In addition, significant differences were found between the % uptake on SPECT and the % volume on CT in all lobes except the RLL ($p = 0.1025$ for RLL, $p < 0.001$ for other lobes, paired t test).

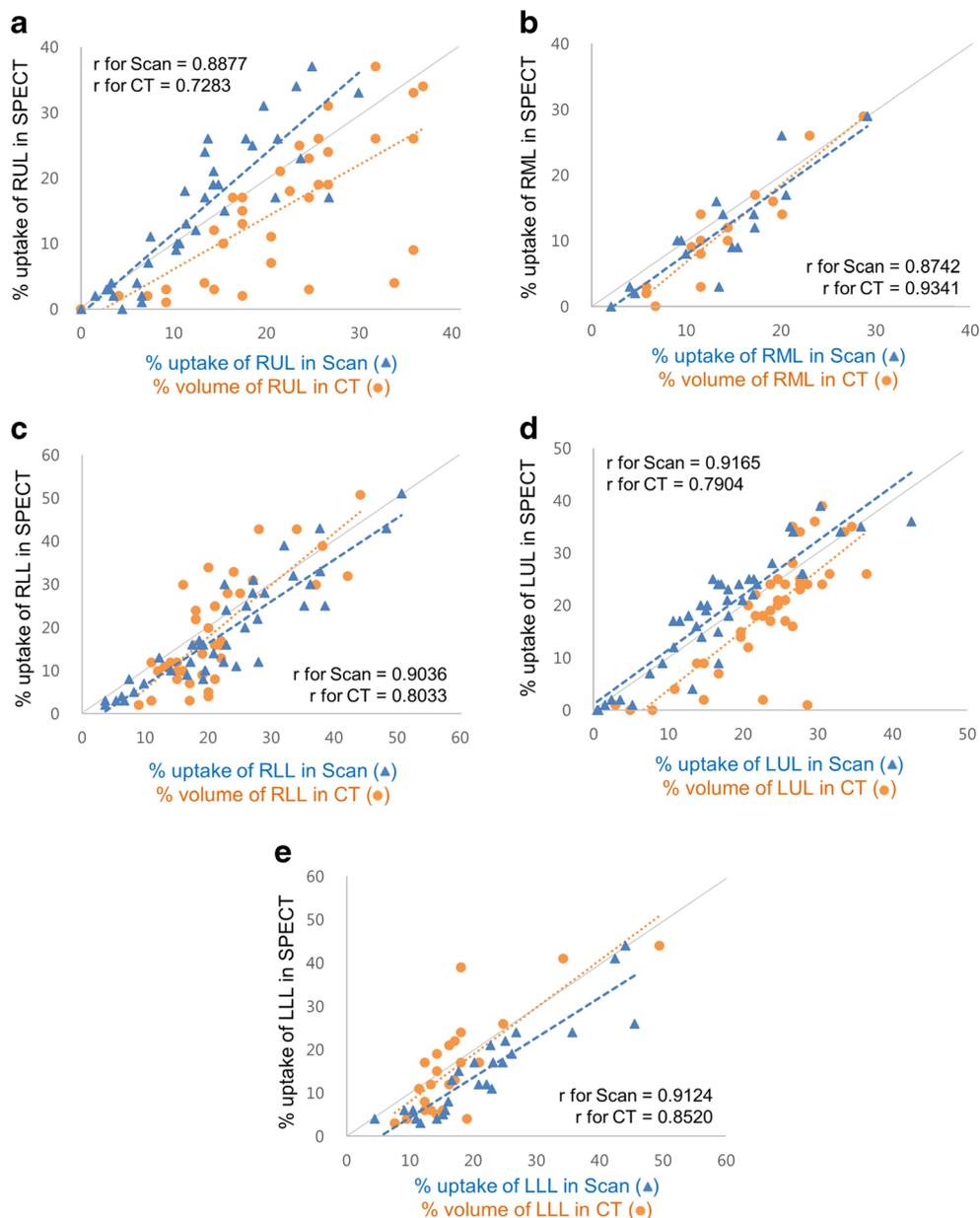
Correlation Between the Predicted and Actual Postoperative Lung Function

In 41 patients who were initially diagnosed with lung cancer, the predicted postoperative FEV₁ (ppoFEV₁) was acquired using three modalities and compared with the actual



color (blue, orange) dotted line represent the line of equality and the linear regression equation, respectively. SPECT, single photon emission computed tomography

Fig. 3 Scatter plot of the ratios of the diseased lobe as measured by three modalities. The ratio of the diseased lobe measured by the % uptake on lung perfusion scan and SPECT, and the % volume on CT when the disease is presented in each lobe: right upper lobe (a), right middle lobe (b), right lower lobe (c), left upper lobe (d), and left lower lobe (e). The gray solid line and color (blue, orange) dotted line represent the line of equality and the linear regression equation, respectively. RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; SPECT, single-photon emission computed tomography



postoperative FEV₁ (Fig. 4; Table 3). A significant decrease was found in the actual postoperative FEV₁ than preoperative FEV₁ values ($p < 0.0001$, paired t test). A significant correlation was found between the actual postoperative FEV₁ and ppoFEV₁ using lung perfusion SPECT ($r = 0.6716$, $p < 0.0001$; Fig. 4a). The actual postoperative FEV₁ was significantly lower than ppoFEV₁ analyzed by lung perfusion SPECT ($p = 0.0005$, paired t test). Similarly, the actual postoperative showed significant correlation with the ppoFEV₁ on lung perfusion scan ($r = 0.6652$, $p < 0.0001$; Fig. 4b) and CT ($r = 0.7288$, $p < 0.0001$). There was no significant difference in the degree of correlation between the actual postoperative FEV₁ and ppoFEV₁ based on lung perfusion scan and SPECT ($z = 0.05043$, $p = 0.9598$).

Linear regression analysis of lung perfusion SPECT using the actual postoperative FEV₁ as a dependent variable and ppoFEV₁ as an explanatory variable generated the following equation:

$$\text{Actual postoperative FEV}_1 = (0.596 \times \text{predicted postoperative FEV}_1) + 0.552$$

Discussion

The current study aimed to compare the ratios of diseased lung and diseased lobe using lung perfusion scan and SPECT/CT and evaluate the correlation between the predicted and actual postoperative lung function.

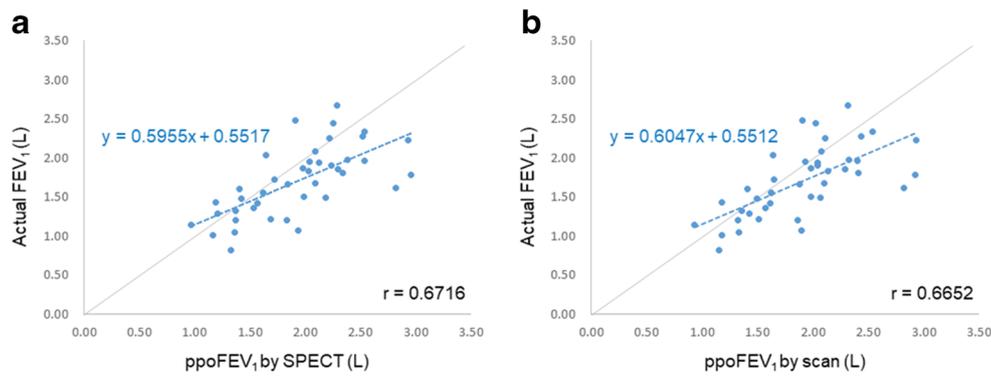


Fig. 4 Scatter plot of actual postoperative FEV₁ and predicted postoperative FEV₁. Comparison of actual postoperative FEV₁ and predicted postoperative FEV₁ using lung perfusion SPECT (a) and scan (b). The gray solid line and blue dotted line represent the line of equality

The present study showed that the ratio of diseased lung was variable when measured by % volume on CT, while the ratios of diseased lung based on % uptake on lung perfusion scan and SPECT were closely correlated (Fig. 2). In patients with a lower ratio of the diseased lung based on % uptake of SPECT than the ratio of the diseased lung based on % volume on CT, the disease was either centrally located, or the underlying lung had cavitary or consolidative changes. The decrease in perfusion of the diseased lung shown which was shown on SPECT was caused by bronchogenic obstruction of the diseased lung or by a decrease in the lung capacity due to a non-functioning portion. In contrast, patients with a higher ratio of the diseased lung based on % uptake on SPECT than that based on % volume on CT had a previous history of operation or old inflammatory sequelae in the contralateral lung. This high % uptake on SPECT may have resulted from a decrease in the total lung capacity which causes a relative increase in the proportion of the diseased lung. Thus, the % volume on CT overestimates the volume of the diseased lung as if it is functioning. In patients who are planning for pneumonectomy, the weakness of volumetric assessment based on CT should be considered,

Table 3 FEV₁ values of each modality ($n = 41$)

	Modality	Value (range)
Actual preoperative FEV ₁ (L)		2.23 ± 0.53 (1.15–3.70)
Actual postoperative FEV ₁ (L)		1.70 ± 0.44 (0.82–2.67)
ppoFEV ₁ (L)	Scan	1.90 ± 0.49 (0.93–2.93)
	SPECT	1.93 ± 0.50 (0.97–2.96)
	CT	1.79 ± 0.52 (0.94–2.93)

FEV₁ forced expiratory volume in 1 s, ppoFEV₁ predicted postoperative FEV₁, SPECT single-photon emission computed tomography, CT computed tomography

and the linear regression equation, respectively. FEV₁, forced expiratory volume in 1 s; ppoFEV₁, predicted postoperative FEV₁; SPECT, single-photon emission computed tomography.

and a modality that accurately represents the functional capacity of the diseased lungs should be chosen.

We evaluated the ratio of the diseased lobe as calculated by % uptake on lung perfusion scan, SPECT, and % volume on CT, and we found different correlation patterns between each modality according to the location of the disease (Fig. 3). To date, there is no standardized method for the segmentation of the lung perfusion scan. In practice, the posterior oblique method and anterior/posterior method are used for segmentation and quantification of the lung perfusion scan [12, 13]. In this study, we used the posterior oblique method for the analysis of the lung perfusion scan. The correlation coefficient between % uptake on lung perfusion scan and SPECT in the diseased lung was close to 1, whereas the correlation coefficients between % uptake on lung perfusion scan and SPECT varied between diseased lobes. Comparing the lung perfusion scan and SPECT, the % uptake of SPECT in either the RUL or LUL was higher than that of the lung perfusion scan. In both upper lobes, the % uptake may be underestimated, because the upper lobes constitute a small portion of the scan [12]. The % uptake of either the RLL or LLL on the lung perfusion scan was higher than that on SPECT. This overestimation of % uptake in the lower lobe on the lung perfusion scan could have been the result of the posterior oblique method, as the lower lobe constitutes a larger portion of the scan using this view. In addition, a change in the patient's position from supine to upright before the Tc-99m MAA reaches the peripheral vein can lead to the accumulation of tracers in the lower lobes. The % volume on CT was higher than the % uptake on SPECT in patients with a disease in either both upper lobes or both lower lobes. In these patients, the decrease in the functional capacity of the lung may result from the large size, or from the central localization of the disease. Compared to the upper areas of the lung, air spaces of dependent areas of the lung are less expanded and constitute a lower volume [14]. This phenomenon is mainly caused by a pleural pressure gradient, as there is more negative pressure in the pleural space of nondependent

area [15]. Although the previous study demonstrated that lung perfusion SPECT is preferable than lung perfusion scan when examining the RML (which anatomically located adjacent to the mediastinum) [16], there was no significant difference in lobar ratios between the two modalities. A small number of enrolled patients with disease of the RML may not have shown this difference in lobar ratios clearly.

We have found that the calculation of ppoFEV₁ by lung perfusion SPECT and lung perfusion scan showed a significant positive correlation with the actual postoperative FEV₁, immediately after the operation (Fig. 4). The critical role of prediction of postoperative lung function in the selection of operable patients has been emphasized in the guidelines from the American College of Chest Physicians (ACCP) [17]. Moreover, the ppoFEV₁ has been reported to be related to postoperative morbidity and mortality [18, 19]. Our results showed that the actual postoperative FEV₁ was smaller than the ppoFEV₁. Considering that our study collected postoperative lung function within 1.5 months of surgery, patients' lung function could be restricted due to pain and restriction of the chest wall [20]. There were no significant differences in the degree of correlations between the actual postoperative FEV₁ and the ppoFEV₁ based on % uptake on lung perfusion SPECT and scan. Although the predictive abilities of postoperative lung function between SPECT and scan showed no significant difference, SPECT has advantages over scan in the estimation of the functional volume of diseased lung area: (1) the % uptake on SPECT was obtained without overlapping, and (2) SPECT provided more geographical information including underlying lung lesion than scan. Furthermore, we presented an equation derived using a linear regression model for an actual postoperative FEV₁ prediction derived from the ppoFEV₁ based on % uptake on SPECT. Using this equation, we expect that clinicians can estimate patients' postoperative lung function depending on the location of the disease.

There are several limitations to this study. Firstly, clinical data from enrolled patients were heterogeneous, and analysis of predicted postoperative lung function was conducted in a small subgroup of lung cancer patients, particularly in patients with RML lung cancer. Thus, further studies with a larger population of homogeneous patients are warranted to circumvent this limitation. Another limitation was the technical error derived from interpersonal differences in the drawing of the ROI and VOI. Anatomical distortion caused by underlying lung disease could lead to error not only in the drawing of the ROI and VOI, but also in the estimation of lung function. However, we made an effort to minimize this possible error by verification of the extracted data for concurrence. Lastly, any misregistration between SPECT and CT images might influence data obtained using lung perfusion SPECT/CT. The discrepancy between free-breathing lung perfusion SPECT and CT could lead to errors in CT-based attenuation correction. Therefore, a study regarding respiratory-gated lung perfusion SPECT/CT with proper registration is needed.

Conclusion

The three modalities of measuring the % uptake on lung perfusion scan and SPECT and the % volume on CT were compared for the evaluation of lung function. A close correlation was found between the lung perfusion scan and SPECT in terms of the evaluation of the ratios of the diseased lung, although the lung perfusion scan was limited in its assessment of the lobar ratio. The immediate postoperative actual FEV₁ was significantly correlated with the ppoFEV₁ calculated by lung perfusion SPECT and scan. Therefore, we recommend the use of lung perfusion SPECT/CT for the assessment of the ratios of the diseased lung and diseased lobe, and that either lung perfusion scan or SPECT/CT may be used for the prediction of postoperative FEV₁.

Acknowledgements The authors would like to thank the members of the Department of Nuclear Medicine, National Cancer Center for their technical assistance and support.

Funding information This work was supported by a grant from the National Cancer Center (NCC-1810201).

Compliance with Ethical Standards

Conflict of Interest Hoon Young Suh, Sohyun Park, Hyun Gee Ryoo, Ji-Young Kim, Tae Sung Kim, Jong Mog Lee, Moon Soo Kim, Hee Chul Yang, and Seok-Ki Kim declare that they have no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent The institutional review board of our institute approved this retrospective study (IRB No. 2019-0270-0001), and the requirement to obtain informed consent was waived.

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