Peer Review File

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Reviewer A

Comment 1: I'm not familiar with how often these SPECT/CT scans are used clinically, my understanding was more VQ scans were used for pre-operative decision making. Is there a way to compare these predictions with VQ scans? Or are VQ scans just unable to be used to provide any sort of meaningful information this way?
Reply: As you mentioned, perfusion planar scan is the most common way to predict lung function after surgery. The utility of perfusion scan for lung reserve prediction used the anterior-posterior methods of region segmentation. It is well known that SPECT/CT helps to distinguish anatomical lesions, and its usefulness in predicting postoperative lung function is beginning to be recognized. In this study, we did not compared the VQ scan with SPECT/CT, because we have focused on the potential tool of ventilation SPECT/CT for prediction of lung function. In previous studies (reference 8-11), lung perfusion SPECT/CT were compared with planar images and both were useful for the prediction of posteroperative lung function. According to reference 8, SPECT/CT have more reproducibility compared with planar imaging.

Comment 2: Another question I have along these same lines, certainly it makes sense how you could obtain % uptake in the lobes to be resected using ventilation SPECT/CT, but how does this say compare to just CT lobar segmentation, without the ventilation component? Has this been done? In my mind, I'd imagine this could be as I imagine with paired inspiratory/expiratory scans you can get ventilation information like this. We get CT scans all the time pre-operatively, but I just don't know about SPECT/CT scans.
Reply: We did not compared perfusion/ventilation SPECT with CT lobar segmentation. CT scan was used only for attenuation correction and lobar segmentation of SPECT.

Comment 3: Also, I am wondering how pulmonary disease would affect these predictions? You started to mention it in the limitations section but I did note over 1/3 of the patients had emphysema. I suppose you could see if there are patterns in their results (upper/lower lobe ventilatory changes) etc or at least bring this up in the discussion. As an example, this information regarding ventilation/perfusion is particularly relevant for patients being considered for endobronchial (with valves) and surgical lung volume reduction for severe emphysema, where this regional information is important.
Reply: As you suggested, we wanted to see if there were differences between ventilation and perfusion SPECT by lung disease. However, as mentioned in limitation, this study have the limitation owing to its retrospective design and small

population of patients and lung disease included emphysema, old Tbc sequelae, inflammatory lung disease, etc. Among 13 patients with emphysema, the severity of emphysema varied, so SPECT comparison was limitation. Even when various lung disease were included, both SPECTs showed a good correlation of predictive postoperative lung function. We mentioned in limitation of Discussion section (page 15, line 258).

Comment 4: Figures: I noted here that FEV1 was predicted to be consistently lower using SPECT/CT (ventilation and perfusion), and not DLCO. Can the authors speculate why this may be the case?
Reply: The prediction of postoperative lung function can be influenced by several factors. Lung function recovery can be affected by the individual patient characteristic (e.g. age, comorbidities and preoperative health condition), extent of lung resection, the presence of postoperative complication (e.g. pneumonia, atelectasis), etc. In addition to these various factors, the respiratory system has compensatory mechanism after lung resection. In this study, SPECT/CT predicted lower FEV1. The remaining lung tissue may adapt and take on a greater functional role to compensate for the decreased lung function by lung resection. DLCO may be less affected by postoperative lung compensation than FEV1. Since our study is observational, unfortunately, we do not have any idea to speculate about this result. The relatively small sample size might have affected this. We would like to suggest further study would be needed regarding this issue.

Reviewer B

Comment 1: First, the content of the conclusion: Given the characteristics of lung cancer patients, who are often elderly and have underlying lung diseases, it is often more practical to perform perfusion SPECT/CT due to the difficulty in conducting ventilation SPECT/CT. Therefore, based on the research results, if perfusion SPECT/CT is found to be similar to ventilation SPECT/CT, there may be no need to perform the challenging ventilation SPECT/CT, making it difficult to understand the emphasis on ventilation SPECT/CT in the conclusion.
Reply: From the results of our study, ventilation SPECT/CT is as potent as perfusion SPECT/CT for predicting postoperative lung function. As mentioned in the manuscript, there is not much related research. Our study included patients with many lung disease. The prediction of postoperative lung function using lung ventilation SPECT/CT may be affect according to lung disease. Starting with this study, further research related to this should be conducted.

Comment 2: Second, statistical issues: The testing process to determine whether the underlying assumption of normal distribution for conducting correlation analysis is met is necessary.

Reply: We did the Shapiro-Wilk normality test of continuous variables was performed. All variables were normally distributed. This is added to Material and Method section (page 12, line 182).
Changes in the text: Shapiro-Wilk normality test of continuous variables was performed. All were normally distributed.

Comment 3: Third, patient enrollment: Why were sublobar resection patients excluded? and the conclusion should be revised to reflect that it pertains only to lung lobectomy patients according to the exclusion criteria.
Reply Thank you for your comments. Since there is no standard method to measure sublobar resection, we excluded patients who underwent sublobar resection. In the revised manuscript, we clarified our exclusion criteria and conclusion pertains only to lung lobectomy patients (see page 9, line 117 and page 16, line 282)
Changes in the text: Since there is no standard method to measure sublobar resection, we excluded patients who underwent sublobar resection (page 9). 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 (page 15).

Comment 4: Fourth, the timing of lung function measurement: Although it is mentioned that measurements were taken 3-6 months after surgery, it is important to provide evidence that this time frame aligns with the recovery of lung function and that the use of data over a 3-6 month period is appropriate. You should specify the precise timing for measuring lung function and describe the impact of measuring lung function at different time points on the results.
Reply: Thank you for the comments we did not acknowledge in the original manuscript. Regarding evidence that this time frame aligns with the recovery of lung function and the use of data over a 3-6 month period is appropriate, a previous study showed that lung function is relatively stable during this time period after lung resection (Figure 1 of following reference: Win et al. The effect of Lung Resection on Pulmonary Function and Exercise Capacity in Lung Cancer Patients. Respiratory Care 2007;52:720-6). Our protocol was to collect pulmonary function data 3 months after surgery. However, sometime the period was delayed due to patient's condition or order missing. Pulmonary function tests 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 two patients were performed over 6 month after surgery. We could not accurately evaluate the impact of measuring lung function at different time points on the results. We added the time of posteroperative pulmonary function tests of patients in Materials and Methods and this as a limitation of our study. The reference has been added to Reference (page 9, line 134; page 15, line 265; page 19, line 354).
Changes in the text: 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 two patients were performed over 6 month after surgery (page 9). The timing for lung function measurement ranged from 3 months 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 (page 15). 20. Win et al. The effect of Lung Resection on Pulmonary Function and Exercise Capacity in Lung Cancer Patients. Respiratory Care 2007;52:720-726 (page 19).

Comment 5: Fifth, the post-surgery condition is not reflected at all. Stage II or higher patients (13 individuals, 30%) are included, and an analysis should be conducted on the impact of adjuvant treatment on these patients. Additionally, there is no analysis of common complications such as pneumonia, atelectasis, or atrial fibrillation and their effect for the lung function.
Reply: We appreciate the reviewer's helpful suggestion. Of the 47 patients, 22 patients received chemotherapy after surgery, and 11 of them underwent postoperative pulmonary function tests during 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 treatment on these patients. We agree with the reviewer that post-operative complications may have affected our results. However, due to the retrospective nature of our study, we could not accurately evaluate post-operative complications. Future studies that comprehensively incorporate these factors are needed. We added this as a limitation to our study (see page 15, line 267) Changes in the text: 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 pulmonary function tests 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.

Comment 6: Lastly, please provide the X and Y values for each point on Figure 3's graph through supplementary data.
Reply: Unfortunately, providing each patient's data as supplementary materials was not permitted by the IRB. Although we performed anonymization, the IRB concerned about potential risk of identification since the number of subjects with lung cancer who underwent surgery during the study period was relatively small. We hope the reviewer understand our situation regarding this issue.

Reviewer C
Comment 1: I recommend using reformatted CT images in oblique projections for analysis, as this will give more accurate lobar quantitation. For reference 16, you should use "Accessed", not "Assessed".

Reply: Thank you for your comment. A typo was corrected.

Reviewer D

Comment 1: Minor comment when they said “scintigraphy” to explain that they mean planar imaging as compared to tomographic SPECT/CT imaging.
Reply: Thank you for your careful review. We modified ‘lung perfusion scintigraphy’ and ‘lung scintigraphy’ to ‘planar lung perfusion scintigraphy’ and ‘planar lung scintigraphy’, respectively (page 7, line 86)

Comment 2: Minor comment to explain what previous work has done in ventilation SPECT/CT as a predictor and what is actually missing in two publications they reference.
Reply: In two publication (reference 8 and 10), SPECT and CT images were obtained from different scanners and co-registered using a commercial software having automated registration algorithm. Since chest CT scan is generally obtained at the end of inspiration, misregistration between SPECT and CT may occur. 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. We added following sentence in Discussion section (page 14, line 245) Changes in the text: 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.

Comment 3: The first part of “Patient Characteristics” belongs to the Methods according to the reviewer.
Reply: Thank you for your careful review. The paragraph of ‘Patient Characteristics’ was moved to the Method section; Patients and clinical parameters (page 9, line 119)