# Quantitative study of lung perfusion SPECT scanning and pulmonary function testing for early radiation-induced lung injury in patients with locally advanced non-small cell lung cancer

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**Abstract.** Radiation lung injury is a common side-effect of pulmonary radiotherapy. The aim of this study was to quantitatively assess early changes in lung perfusion single photon emission computed tomography (SPECT) scanning and pulmonary function testing (PFT) prior to and after intensity modulated radiotherapy (IMRT) for patients suffering from locally advanced non-small cell lung cancer (LANSCLC). Twenty patients with LANSCLC received lung perfusion SPECT scanning and PFT prior to IMRT and immediately after IMRT. Lung perfusion index (LPI) was calculated after the quantification of perfusion SPECT images. The LPI of the two groups was analyzed by matched t-test. The radioactive count of each layer of single lung was added to obtain the sum of the irradiated area. The percentage of the irradiated area of single lung was calculated. Linear correlation analysis was carried out between the percentage of the irradiated area and LPI in order to verify the validity of LPI. In this study, LPI and the percentage of the irradiated area of single lung exhibited an excellent correlation either prior to or after IMRT (r=0.820 and r=0.823, respectively; p<0.001). There was no statistically significant difference between pre-IMRT LPI and post-IMRT LPI (p=0.135). LPI in the group receiving a radical dose had no statistically significant difference (p=0.993), however, it showed a statistically significant difference in the group receiving a non-radical dose (p=0.025). In the non-radical dose group, the post-IMRT LPI was larger compared to pre-IMRT. None of the parameters of PFT exhibited a statistically significant difference prior to and after IMRT (p>0.05). The quantitative method of lung perfusion SPECT scanning can be used to evaluate changes in perfusion early in patients receiving a non-radical dose (BED ≤126,500 cGy) IMRT. Evaluating early changes in global lung function using the current method of PFT is difficult, since time can be a contributing factor for radiation-induced lung injury.

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## Introduction

Radiotherapy is one of the main treatments for locally advanced non-small cell lung cancer (LANSCLC). During radiotherapy, normal lung tissue is inevitably irradiated, which causes radiation injury to a greater or leser extent. It was reported that 5-50% of patients irradiated for lung cancer suffer from clinically significant symptomatic radiation pneumonitis (RP) (1,2). Intensity modulated radiotherapy (IMRT) reduces the dose at which normal tissues are irradiated and reduces the risk of RP (3). However, several studies revealed that 8-10% of patients with NSCLC still develop RP after IMRT (4,5). The pulmonary function of patients with LANSCLC is poorer than that of patients with stage I or II NSCLC, thus RP occurs more easily. Acute lung injury appears 1-3 months after radiotherapy, while chronic lung damage (radiation fibrosis) evolves over 6-24 months after radiotherapy (6).

At present, chest CT and X-ray are the main clinical diagnostic methods for RP. However, they barely detect early changes in pulmonary ventilation and blood flow. Thus, it is necessary to evaluate early radioactive injury effectively. Pulmonary function testing (PFT) is the main method to reflect the ventilation function of the global lung, while lung perfusion single photon emission computed tomography (SPECT) scanning is the method to evaluate variation in blood flow.

In the present study, we aimed to develop a quantitative method in order to reflect early change in perfusion and to evaluate the change in ventilation function by PFT. At the same time, we tried to explore the factors that caused these changes.

## Patients and methods

*Patients*. Twenty patients with LANSCLC were treated with IMRT from July 2009 to August 2011 in Fujian Provincial Cancer Hospital. Totally, there were 16 male patients and 4 female patients. The age of patients was 38-68 years. The average age was 51.85±2.065 years. Of them, 13 patients had a history of smoking and 7 patients never smoked; 14 cases were central type lung cancer, while 6 cases were peripheral type; 12 patients had been operated for lung cancer and the others had no history of surgery. According to the patients' condition, 7 patients received 1-2 cycles of concurrent chemoradiotherapy based on platinum-containing drugs, and 13 patients received radiotherapy only. All of the patients underwent lung perfusion SPECT scanning and PFT prior to and after treatment.

*Patient grouping*. All of the patients were divided into two groups according to the biological effective dose (BED). Grouping was based on the NCCN Clinical Practice Guidelines in Oncology (v.3.2011). The recommended dose of NCCN for NSCLC was 60-70 Gy; 60 Gy was approximately equal to our grouping criteria (BED=126,500 cGy).

*Lung perfusion SPECT scanning and quantification*. Lung perfusion SPECT images were obtained based on a dual-head γ camera (Infinia VC Hawkeye 4) equipped with a low-energy and high-resolution collimator and a 4-slice spiral CT. The instrument was produced by General Electric Company of America. The imaging agents were 99mTc macroaggregated albumin (99mTc-MAA) that was produced by the Guangdong Xi'ai Nucleus Pharmaceutical Center, China.

Lung perfusion SPECT scanning included three aspects: i) Sectional images of perfusion were taken. 99mTc-MAA (185-370 kBq/5 ml) was administered by intravenous injection for the patients in the supine position. The collimator was kept close to the patients' chest and both lungs were in the vision of the camera. Each camera acquired thirty projection images over 180˚ during 20 sec per projection as 128x128 matrices. The magnification was 1.0. Patients were told to breathe calmly in order to reduce interference of respiratory movement. ii) CT images were acquired. Patients kept still in a supine position and breathed calmly. The condition of scanning included voltage (140 kV), electric current (2.5 mA), layer thickness (5 mm) and layer thickness of reconstruction (4 mm). iii) Image fusion was performed. Original images were processed by GE Xeleris image fusion software (version 2.0). The fused image of the cross-section, sagittal section and coronal section was acquired (Fig. 1).

The outline of the irradiated side lung was delineated layer after layer from the apex to the base of the lung. The radioactive count of each layer was counted as X (Fig. 1). The total radioactive count of the irradiated lung was counted as $T_1$ ($T_1 = X_1+X_2+X_3+\ldots X_n$). The mean of the irradiated side lung was counted as M ($M=T_1/n$). The top layer $X_i$ and bottom layer $X_r$ of the irradiated area were confirmed according to the IMRT plan. The total radioactive count of the irradiated area was counted as $T_2$ ($T_2 = X_i+X_{i+1}+X_{i+2}+\ldots X_r$). According to the calculation above, lung perfusion index (LPI) was calculated ($LPI = T_2/M$).

*Pulmonary function testing (PFT)*. PFT was performed on a lung function instrument (Jaeger, version 4.6; Germany). Parameters of PFT included vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in 1 sec ($FEV_1$) and the percentage ($FEV_1/FVC$), maximum midexpiratory flow ($MMEF_{25-75}$) and carbon monoxide diffusing capacity (DLCO). Patients received PFT before and after IMRT. The detection conditions were kept consistent.

*Statistical analysis*. All of the parameters for PFT and LPI were analyzed with matched t-test and all the results were represented as the means ± standard deviation. Statistical significance was indicated by p-values <0.05. The LPI of the radical dose (BED >126,500 cGy) group and the non-radical dose (BED ≤126,500 cGy) group was analyzed by matched t-test. Statistical significance was indicated also by p-values <0.05.

Linear correlation between the percentage of irradiated area and LPI was performed to evaluate their relationship. Correlation coefficient (r) and p-values were obtained. The statistical software used was PASWStatistics18.

## Results

*Statistics of ungrouped data*. The statistics of ungrouped data of lung perfusion and PFT are shown in Table I.

*Statistics of grouped data*. After grouping by BED, the radical dose (BED >126,500 cGy) group consisted of 10 patients, and the non-radical dose (BED ≤126,500 cGy) group consisted of 10 patients. According to the WHO criteria, the therapeutical effects of all the patients were evaluated. In the radical dose group, 1 case was evaluated as complete response (CR), 8 cases as partial response (PR) and 1 case as no change (NC). In the non-radical dose group, 4 cases were evaluated as CR, 3 cases as PR and 3 cases as NC. The two groups were analyzed with matched t-test. The results are shown in Table II.

*Linear correlation*. As previously described, the total radioactive count of the irradiated single lung was counted as $T_1$. The total radioactive count of the irradiated area was counted as $T_2$. Therefore, the percentage of the irradiated area was described as P ($P=T_2/T_1$). The percentage of the irradiated area and LPI were analyzed with linear correlation. The result exhibited an excellent correlation between the percentage and LPI, no matter whether this value was prior to or after treatment (r=0.820 and r=0.823, respectively; p<0.001) (Fig. 2).

## Discussion

The main complications caused by radiotherapy for lung cancer are acute radiation injury of the lung and radiation pulmonary fibrosis. At present, the diagnosis of radiation-induced lung injury mainly depends on symptomatology and image detection. However, chest CT and X-ray barely detect early radiation injury. Changes in ventilation and blood flow are usually discovered before radiation injury develops into RP. Therefore, investigation of these two aspects may have great significance for the early evaluation of radiation injury.

PFT includes several parameters. VC and FVC reflect the lung volume and total ventilatory function. $FEV_1$ is a measure

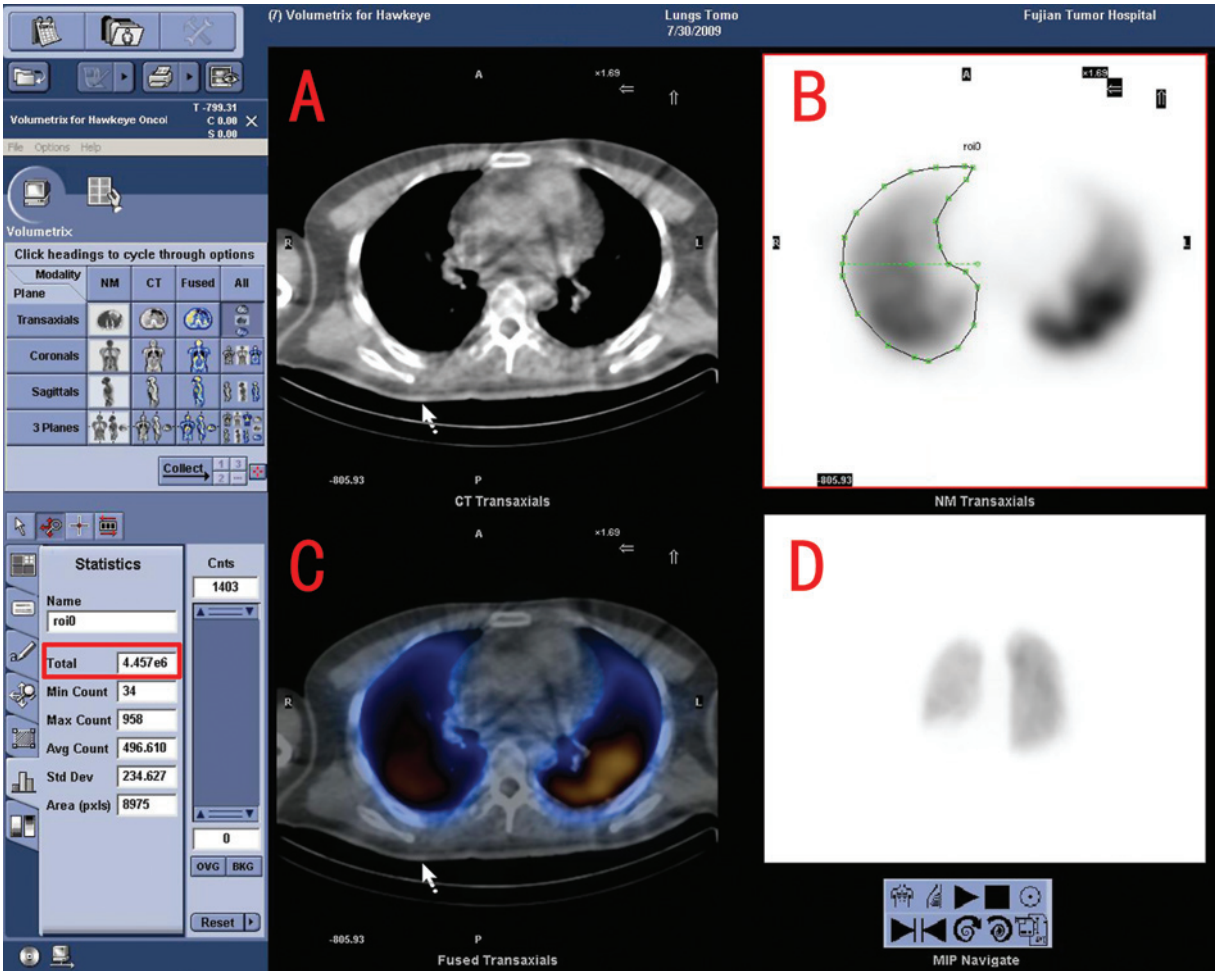


Figure 1. Image of lung perfusion SPECT scanning. (A) Computed tomography (CT) image; (B) SPECT image; (C) fusion image; (D) coronal section image. The count at the left marked in red is the radioactive count of the area outlined in B.

Table I. Statistics of ungrouped data.

| Parameters | Mean ± SD | | p-value |
|---|---|---|---|
| | Pre-IMRT | Post-IMRT | |
| VC | 2.99±0.18 | 2.97±0.17 | 0.760 |
| FVC | 2.92±0.18 | 2.94±0.18 | 0.663 |
| $FEV_1$ | 2.29±0.14 | 2.34±0.60 | 0.477 |
| $FEV_1$/FVC (%) | 78.89±1.44 | 80.32±1.72 | 0.311 |
| MMEF | 1.87±0.18 | 1.93±0.17 | 0.624 |
| DLCO | 5.94±0.32 | 5.82±0.34 | 0.576 |
| LPI | 31.76±3.20 | 32.87±3.02 | 0.135 |

IMRT, intensity modulated radiotherapy; VC, vital capacity; FVC, forced vital capacity; $FEV_1$, forced expiratory volume in 1 sec; MMEF, maximum midexpiratory flow; DLCO, carbon monoxide diffusing capacity; LPI, lung perfusion index.

Table II. Statistics of LPI in the radical dose and non-radical dose groups.

| | LPI (mean ± SD) | | p-value |
|---|---|---|---|
| | Pre-IMRT | Post-IMRT | |
| Non-radical dose group | 27.32±3.14 | 29.54±3.13 | 0.025 |
| Radical dose group | 36.20±5.39 | 36.19±5.14 | 0.993 |

LPI, lung perfusion index; IMRT, intensity modulated radiotherapy.

of large- and medium-size airways, which is always analyzed together with the percentage ($FEV_1$/FVC). Decreased $FEV_1$ with a normal $FEV_1$/FVC often indicates a restrictive process, such as fibrosis (7), or reflects an acute exudative process in the alveolar space (8). $MMEF_{25-75}$ stands for the average expiratory flow over the middle half of the FVC and is considered to be a more sensitive measure of small airway (bronchioles) narrowing than $FEV_1$. DLCO reflects the diffusing capacity through the alveolar-capillary barrier. Since the function influenced first by the radiation injury is blood gas exchange, DLCO is regarded as a sensitive parameter for radiation injury. PFT is a test reflecting the ventilation function of global lungs. In this study, none of the parameters of PFT exhibited significant difference, as shown in Table I, which may be due to the fact that PFT was performed immediately after IMRT and some local injury may not have yet appeared; it often takes several months for parameters of PFT to manifest obvious changes. In

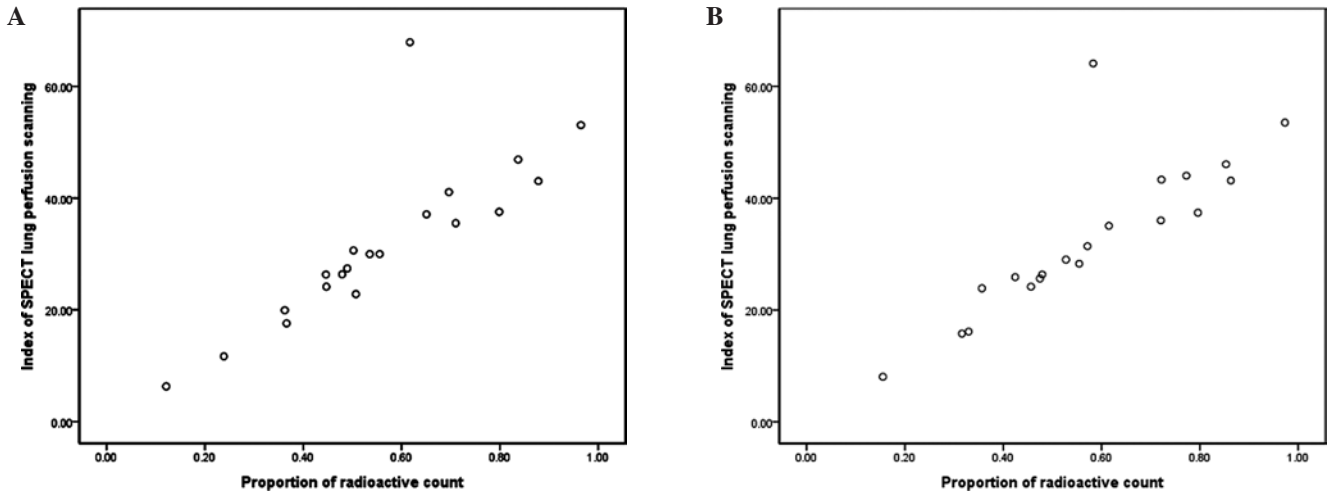


Figure 2. Linear correlation analysis between LPI and percentage of radioactive count. (A) Pre-IMRT scatter plots; (B) post-IMRT scatter plots.

studies that have evaluated radiation injury by PFT, the follow-up period was 3-38 months. DLCO was found to be reduced by 5.7-14% and $FEV_1$ was diminished by 1-7% (9-11). In a study by Miller *et al*, parameters of PFT were continuously reduced during 2-8 years after radiotherapy (11). Although there was no significant difference in parameters of PFT in this study, the results indicate that an early change in lung radiation injury mainly reflects local injury. Lung perfusion SPECT scanning may be more effective for the early diagnosis of radiation injury than PFT.

Lung perfusion SPECT scanning is a functional imaging modality. It reflects changes in local blood flow. It is more sensitive to detect radiation-induced lung injury than CT and X-ray (7). Theuws *et al* reported that it was more common to note change caused by radiotherapy in perfusion scanning than in CT (12). At present, lung perfusion SPECT scanning is reported mainly according to the visual inspection of the physician. This method is inevitably influenced by the doctor's subjective judgement, therefore it is difficult to measure early subtle variations in perfusion.

Several studies have attempted to quantify SPECT images by radioactive count. These studies indicate that the radioactive count is an available quantitative method for SPECT images (13-15). As described above, this study calculated LPI through radioactive count. LPI related the blood flow of the irradiated area and global single lung. After linear correlation analysis, LPI and the percentage of the irradiated area exhibited an excellent correlation (Fig. 2). Thus, we hypothesized that LPI reflects the distribution of blood within and outside the irradiated area. In order to explore the reason for these changes, we evaluated the therapeutic effect using WHO criteria.

In the non-radical dose group, 4 cases were evaluated as CR, 3 cases as PR and 3 cases as NC. The tumor size of 7 cases markedly decreased. Reduction in tumor size releases compression to normal lung tissue, which may allow a portion of the perfusion defect region restored blood flow. Munley *et al* hypothesized that the area with poor perfusion caused by tumor compression could recover after therapy (16). Non-radical dose group receives lower dose radiotherapy than the radical dose group. The technique of IMRT guarantees the dose of the target while protecting normal lung tissue (3). Therefore, radiotherapy has little influence on the non-irradiated area. In the tumor mass, the percentage of the irradiated area throughout the global single lung becomes larger after IMRT. This explained the increase in LPI in this study. Of course, it must be pointed out that the increase in LPI is just an increase in proportion, but not an increase in global lung perfusion. The total radioactive count decreases. In the radical dose group, large-dose radiation damages both the blood flow of the irradiated area and that of the non-irradiated area. Although tumor size in most cases is reduced markedly, the recovery of blood flow is insignificant against the damage of large-dose radiation. In the mass, post-IMRT LPI did not exhibit significant difference with pre-IMRT LPI.

Many studies have confirmed that radiotherapy causes a defect in blood flow (12,17,18). However, few studies have focused on the change in percentage of the irradiated area's perfusion in global perfusion. This study indicates that the percentage may predict the recovery of blood flow in lung tissue around the tumor, which will provide a basis for the prevention of lung function after radiotherapy. By comparison of the two groups in this study, the factor of dose significantly affected the radiation-induced pulmonary toxicity. Radical dose radiotherapy also damaged the normal lung tissue, while it inhibited cancer growth and invasion. Miller *et al* observed bronchial stenosis following high-dose external-beam RT (74-86 Gy) (19). Several studies have probed the relationship between dose and radiation injury through dose response curves (DRC), and these studies indicate that reduction in local blood flow is proportional to the increase in dose (20-22). Another two studies previously reported that dose-dependent reductions in perfusion were noted as early as 1.5 months after radiotherapy and peaked by approximately 6 months (23,24). In this study, the perfusion scanning was performed immediately after IMRT. Therefore, the result only displayed the difference between radical dose and non-radical dose, whereas it did not display any correlation between dose and reduction in perfusion.

Lung perfusion SPECT scanning is a method to evaluate local pulmonary function, while PFT is a method for global function. The combination of the two methods may be helpful for diagnosing radiation-induced lung injury earlier.

Marks *et al* found that SPECT was useful in models for predicting radiation-induced changes in PFT (25). Fan *et al* found a significant correlation between local perfusion and global pulmonary function (26). However, current PFT is unable to determine early radiation injury.

In conclusion, the quantitative method of lung perfusion SPECT scanning evaluates changes in perfusion early in LANSCLC patients receiving a non-radical dose (BED ≤126,500 cGy) IMRT. The current method of PFT is not able to evaluate the early change in global lung function, since time is a contributing factor for radiation-induced lung injury. Methodology of PFT should be investigated to improve sensitivity. In addition, a larger sample and longer-term studies are required to provide a basis for the early diagnosis of radiation injury.

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