Utility of SPECT Lung Perfusion Scans in Assessing the Early Changes in Pulmonary Function after Radiotherapy for Patients with Lung Cancer

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OBJECTIVE Radiation-induced lung injury commonly follows radiotherapy (RT) for tumors within and near the thorax. Lung function is usually measured by pulmonary function tests (PFTs). But RT-induced regional changes of pulmonary function cannot be accurately evaluated by PFTs. Lung perfusion scintigraphy compared with other radiographic methods can assess well regional pulmonary physiological function, and a 3-dimensional conformal radiotherapy planning system can quantitatively calculate irradiation dosage. The purpose of this study is to assess, by lung perfusion scintigraphy, early changes in the pulmonary function of patients with lung cancer when receiving thoracic 3-dimensional conformal radiotherapy (3D-CRT).

METHODS Nineteen patients receiving thoracic 3D-CRT for lung cancer were studied. A single photon emission computed tomography (SPECT) lung perfusion scan, X-ray or CT scan before RT and after 40~50Gy radiation were performed. Pre-RT SPECT lung perfusion images were classified by comparing lung perfusion defects with radiological abnormalities before RT. Grade 0: There was no lung perfusion defect in the area of radiological abnormality. Grade 1: The size of the radiological abnormality was similar to the area of the lung perfusion defect. Grade 2: The area of the lung perfusion defect was bigger than the size of the radiological abnormality and extended to one lobe of the lung. Grade 3: The area of lung perfusion defect exceeded one lobe of the lung. The radiation field with more than 20 Gy was drawn as a region of interest (ROI). The proportion of radioactive dose within this ROI relative to total lung dose in one slice was calculated.

RESULTS All patients had lung perfusion defects, nine patients with grade 1, five patients with grade 2 and five patients with grade 3 damage, respectively. All tumors in the 19 patients were reduced in CT or X-ray images to various degrees after 40~50 Gy radiation. The mean proportion of ROI in 19 patients was 53. 7±29.8% before radiation as compared to 57.6±22.6% during RT. The difference between these two groups was not significant (P=0.280). The decreased relative lung perfusion post-RT was found in six patients, whereas the increased relative lung perfusion post-RT was observed in 13 patients.

CONCLUSION SPECT lung perfusion scaning is a simple, convenient and useful method for assessing regional lung function pre-RT and for monitoring the changes in regional lung function after irradiation.

KEYWORDS: tomography, emission-computed, single-photon(SPECT), radionuclide imaging, radiotherapy, conformal, lung neoplasms, radiation injury.

Radiotherapy (RT) of tumors located within or near the thoracic cavity inevitably results in partial irradiation of the surrounding normal lung tissue. Symptomatic radiation pneumonitis and lung fibrosis occur in approximately 5~20% of patients after RT. A large fraction of patients experience subclinical injury to the lung. [1,2] Compression of bronchi by tumors results in various degrees of atelectasis or pulmonary injury. Lung function can have partial improvement due to shrinkage of the tumor post-RT.[3]

Lung function is usually gauged by pulmonary function tests (PFTs) during the clinical course.[4,5] But PFTs can only assess whole lung function which usually reflects the summation of changes in regional function. RT-induced regional changes of pulmonary function cannot be accurately evaluated by PFTs. Lung perfusion scintigraphy compared with other radiographic methods can assess well the regional pulmonary physiological function, and 3-dimension conformal radiotherapy (3D-CRT) planning system can quantitatively calculate radiation dose distribution. Quantitative radionuclide perfusion lung scans coupled with 3D-CRT planning system can better evaluate the changes of regional lung function after irradiation.

The purpose of this study was to assess early changes, by lung perfusion scintigraphy in pulmonary regional function of patients with lung cancer when receiving thoracic 3D-CRT, and to evaluate the role of lung perfusion scintigraphy in surveillance of lung function before and after RT.

MATERIALS AND METHODS

Clinical materials

Between June 2003 and February 2004, 24 patients who underwent thoracic RT for carcinoma of the lung received planar and single photon emission computed tomography (SPECT) lung perfusion scans before RT and after 40~50 Gy radiation. Four patients received routine RT and 20 patients received thoracic 3-dimension conformal radiotherapy (3D-CRT) for carcinoma of the lung. One of the 20 patients had a pulmonary resection. Thus, 19 patients were entered into clinical study to assess the changes in regional lung function after thoracic 3D-CRT. The patients' median age was 56 years (range 38~78 years); 17 were males and two were females (seven small-cell lung carcinoma, eight squamous carcinoma, two undefined). All patients had CT-based 3D-dose computations performed in our treatment planning system. RT was administrated by 6 MV x-rays, coplanarity and isocenter. Patients received a total dose of 50~70 Gy (median dosage 55 Gy) and had mostly three irradiated fields fluctuating between two and four. Lung volume receiving more than a threshold dose of 20 Gy (V20) varied from 19% to 30%. Median volume was 24%. Patients underwent SPECT lung perfusion scans, chest X-ray or CT scan before and repeatedly after 40~50 Gy radiation. None had roentgenographic evidence of tumor progression at the time of pulmonary evaluation.

Methods

Radiopharmaceuticals

Technetium-99m-labeled macroaggregated albumin (^{99m}Tc-MAA) was provided by Peking Atomic Energy High-Tech Application Ltd Co. and Peking Senke Medicine Ltd Co.

Instrument and imaging methods

Lung perfusion scans were performed with a dual-head SPECT (GE Millennium™ VG V, Hawkeye) equipped with a low-energy high resolution collimator. All patients were placed in a supine position with both arms elevated above the head. Every attempt was made to have all of the scans and the radiation treatment delivered to the patients in a similar position. Planar perfusion images were obtained immediately following intravenous injection of ^{99m}Tc- MAA with an average dose of 5 mCi, including eight views (ANT, POST, LAO, LPO, RAO, RPO, LLAT, RLAT). We usually acquired 500 k counts in an antero-posterior scan and matrix of 128 × 128. Sixty projections were obtained over 360°. The acquisition time for a frame was 20 s, Zoom was 1.0. The SPECT scans were reconstructed using iterative algorithm obtaining transversal, coronal and sagittal images.

Visual analysis

The pre-RT CT or X-ray and SPECT images were visually reviewed to assess the presence of hypoperfusion. In order to estimate the relationship between size of the perfusion defect as seen by perfusion lung scan and size of the mass lesion as seen on the CT or chest X-ray film, each perfusion lung scan was classified as follows: Grade 0: There was no lung perfusion defect in the area of radiological abnormality. Grade 1: The size of the radiological abnormality was similar to the area of lung-perfusion defect. Grade 2: The area of lung perfusion defect was bigger than the size of the radiological abnormality and extended to one lobe of the lung. Grade 3: The area of lung perfusion defect exceeded one lobe of the lung (Figs.1~3).

Quantitative analysis

Each SPECT image set was registered with the pre-RT CT images; the 3D dose distribution was thus registered with the lung perfusion scan. In the central slice, the radiation field with more than 20 Gy was drawn as a region of interest (ROI) and a second ROI was drawn to include all of both lungs in the SPECT transversal images. The proportion of radioactive count within this ROI relative to total lung count in one slice was determined. Each post-RT SPECT scan was also compared with the pre-RT SPECT image to detect possible reperfusion of previously underperfused areas. Student's t test was used for statistical analyses.

RESULTS

Visual analysis

All patients had lung perfusion defects, nine patients with grade 1, five patients with grade 2 and five patients with grade 3 damage, respectively.

Quantitative analysis

The size of tumors in the 19 patients with lung cancer was reduced with various degrees after 40~50 Gy radiation in CT and chest X-ray images. For the group as a whole, the mean proportion of ROI was 53.67 ± 29.81% pre-RT as compared to 57.57 ± 22.56% during RT. The difference between pre- and post-RT wasn't significant (P=0.280). The decreased relative lung perfusion post-RT was found in six patients (32%). The mean proportion of ROI decreased from 72.22 ± 30.98% pre-RT to 58.18 ± 24.06% post-RT. The increased relative lung perfusion post-RT was observed in 13 patients (68%). The mean proportion of ROI increased from 45.11 ± 26.10% pre-RT to 57.28 ± 22.84% post-RT. There was no statistical significance pre-RT between the decreased and increased group (P=0.063).

In the decreased group, CT images showed fibrous strip or patchy opacity in the lung tissue in the 67% patients. But in the increased group, only 23% patients had such manifestations. A patient was reinvestigated two months after completion of RT. The relative percentage of ROI was 62%, which was significantly lower compared with 73% during-RT. CT images at the same time showed patchy opacity in the lung tissue, diagnosed as post-irradiation pulmonary fibrosis.

During the period of acquisition of the lung perfusion images, no patient had adverse effects.

DISCUSSION

The principle of radionuclide pulmonary perfusion imaging is that the radionuclide labeled macromolecule particles pass through the right heart and into the lung; because of their size, 90% of the particles are trapped in the pulmonary precapillary bed; the distribution of radioactivity corresponds to the regional blood flow. Thus lung perfusion scintigraphy can evaluate the condition of regional lung function on the basis of the regional blood flow. If a certain pulmonary artery is obstructed, a larger vascular defect could be correlated with segmental anatomy, and in some cases, the entire lobe or even the entire lung was involved. In patients with bronchogenic carcinoma, tumors often cause obstruction and encasement of

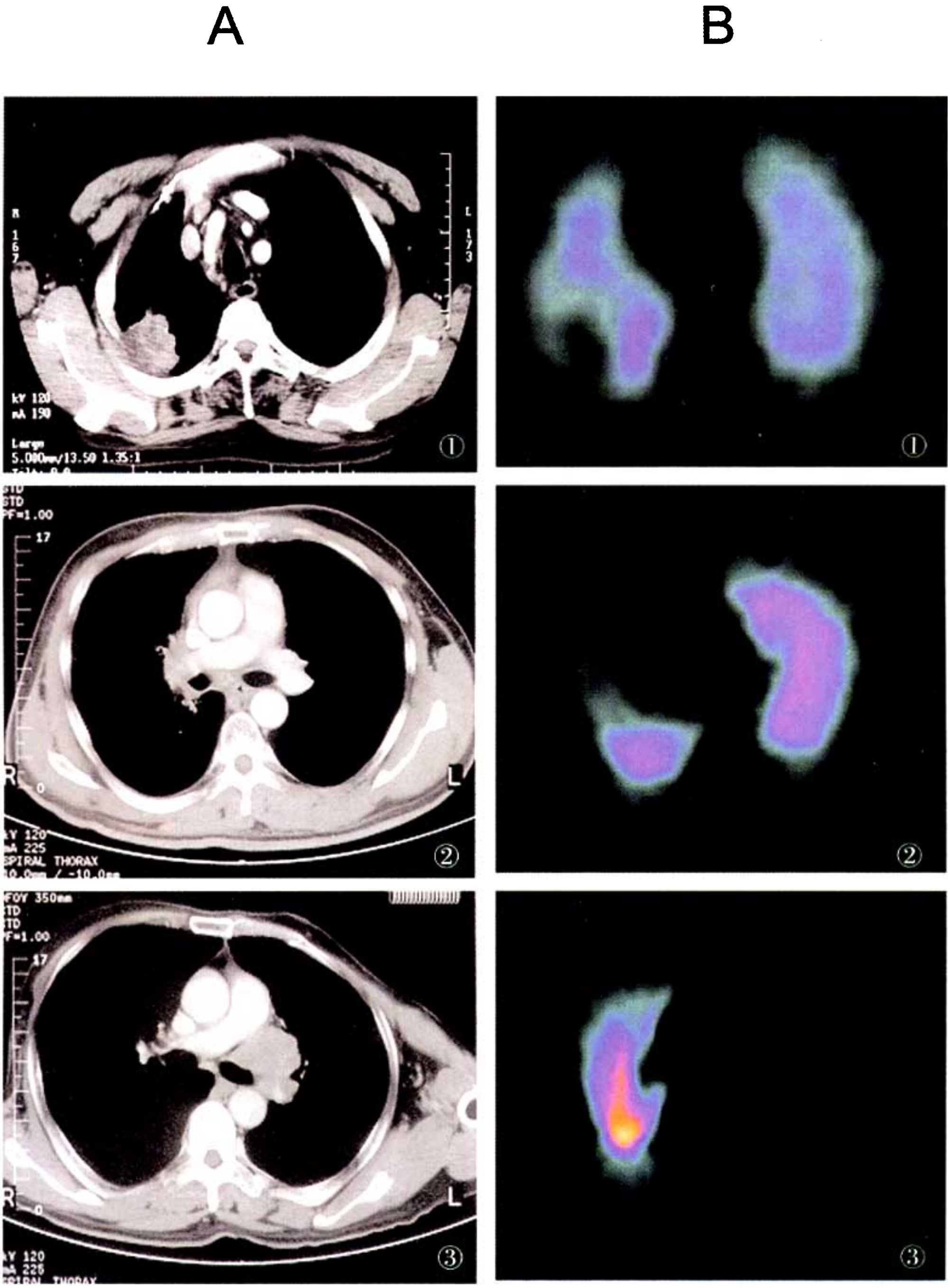

Fig.1. The size of the radiological abnormality is similar to the area of lung perfusion defect (Grade 1) before radiotherapy(RT).

Fig.2. The area of the lung perfusion defect is bigger than the size of the radiological abnormality and extends to 1 pulmonary lobe (Grade 2) before RT.

Fig.3. The area of the lung perfusion defect exceeds 1 pulmonary lobe (Grade 3) before RT.

A: CT; B: SPECT transversal image.

pulmonary vessels, thereby reducing the regional perfusion.

The presence of a pulmonary artery perfusion defect corresponds to the size, location and infiltrated degree of the mass lesion. These abnormalities of regional perfusion in carcinoma of the bronchus could not be confidently predicted on the basis of plain chest films or CT images. Macumber et al.[6] thought that possible explanation for a tumor affecting pulmonary artery perfusion includes the following: ① Direct compression of a branch of the pulmonary artery by the tumor or regional (hilar and/or mediastinal) lymph node resulting in vascular narrowing or an occlusion. ② The pulmonary arteries adjacent to the tumor were subject to a pathologic reaction and resulting in medial hypertrophy and intimal fibrosis. Such changes could also result in vascular narrowing and a decrease in perfusion. ③ The presence of bronchial obstruction resulting in regional hypoxia or atelectasis could lead to distal decrease in perfusion. Consequently some pulmonary artery perfusion defects associated with a tumor are the same as the mass lesion, others are larger than the mass lesion and even in the ipsilateral lung.

The perfusion defect of a central lung tumor is usually larger than a peripheral tumor, and the presence of a peripheral tumor with a larger vascular defect generally indicates hilar or mediastinal lymph node metastases. Ten patients in our study with central tumors or peripheral tumors accompanied with hilar adenopathy had larger perfusion defects than that shown in the corresponding radiographic densities (Grade 2 and 3). If pulmonary normal tissue exhibits pathologic changes but does not involve a chief artery, the regional pulmonary circulation is destroyed and shows a perfusion defect similar to the size of the pathologic tissue. In benign masses or peripheral neoplasms in stage Ⅰ, the size of the perfusion defect usually corresponds with the size of the densities seen on the roentgenograms. In our study, nine patients with peripheral tumors were grouped into grade 1.

Lung irradiation results in hyperemia and edema of interstitial tissue, exudation in the alveolar spaces, and a fibrotic reaction. These changes lead to injuries of the normal pulmonary parenchyma and some loss of lung function. Wennberg et al.[7] found that post-RT lung density changes on CT images were associated with total lung doses as low as 16~30 Gy. Thus we assessed changes in lung function when lungs were irradiated with 40~50 Gy. Similar to the data of Fan et al.,[8] we found lung perfusion function was significantly damaged when irradiated with doses of 20 Gy. Thus we drew ROI with more than 20 Gy in the SPECT images. Each post-treatment SPECT scan was also visually compared with the pre-RT SPECT image to detect reperfusion of previously underperfused areas. Our results revealed that the mean proportion of ROI pre-RT was not statistically significant between the decreased and the increased group (P=0.063). The decreased relative lung perfusion post-RT was found in six of 19 patients (32%). In the decreased group, CT images showed a fibrous strip or patchy opacity in the lung tissue in 67% of the patients. These data suggest that pulmonary fibrosis due to irradiation can decrease regional blood flow. A patient was reinvestigated two months after completion of RT. The relative percentage of ROI was 62%, significantly decreased compared with 73% during-RT. CT images at the same time showed patchy opacity in the lung tissue, revealing a progressive decrease in lung function. These findings are similar to those of Fazio et al.,[3] who reported that a slow but progressive deterioration of the indices of regional lung function was observed, which, in most patients, was associated with a progressive development of radiation fibrosis.

Currently, 3D-CRT is being applied in clinical treatment, the goal of which is to maximize the RT dose to the target volume while minimizing normal tissue effects. Therefore, two opposite effects can be induced by irradiation. On one hand, the radiation causes damage resulting in a decrease in perfusion and an increase of tissue density; on the other hand, shrinkage of the tumor with partial or total relief of infiltration or compression on airways or blood vessels, particularly pulmonary veins, may cause a "recovery" in perfusion and hence compensate for radiation-induced injury.[3,9] We saw a partial recovery in perfusion after treatment in 13 of the 19 analyzed patients. In a patient with a central tumor there was no perfusion in the whole left lung pre-RT, though radiologically the tumor in the left hilum was small. The patient was observed to have reperfusion in the left lower lobe due to tumor regression after irradiation. Fazio et al. [3] studied radionuclide perfusion and ventilation images in 45 patients with unresectable carcinoma of the bronchus before and after RT. Their conclusions included: ① Both ventilation and perfusion were always abnormal in the lung affected by the tumor; perfusion was usually more impaired than ventilation. These abnormalities were difficult to detect or to evaluate from standard chest radiographs. ② After radiotherapy, ventilation improved in 83% and perfusion in 86% of the patients. This improvement was associated with an amelioration of clinical symptoms.

Our studies did not consider changes in ventilation. We elected to focus on perfusion because of the available literature suggesting perfusion to be a more sensitive marker of assessing regional lung function and evaluating radiation-induced changes. [10-12]

SPECT lung perfusion scaning is a simple, convenient and useful method for assessing regional lung function pre-RT and for monitoring the changes in regional lung function after irradiation. However, additional studies involving a larger pool of patients and long-term follow-up are needed to better study correlations between the long-term effects of radiation and irradiated dose or time after RT.

REFERENCES

1 Marks LB. The pulmonary effects of thoracic irradiation. Oncology (Huntingt). 1994; 8: 89–106.

2 Marks LB, Fan M, Clough R, et al. Radiation–induced pulmonary injury: symptomatic versus subclinical endpoints. Int J Radiat Biol. 2000; 76: 469–475.

3 Fazio F, Pratt TA, McKenzie CG, et al. Improvement in regional ventilation and perfusion after radiotherapy for unresectable carcinoma of the bronchus. AJR Am J Roentgenol. 1979; 133: 191–200.

4 Rubenstein JH, Richter MP, Moldofsky PJ, et al. Prospective prediction of post –radiation therapy lung function using quantitative lung scans and pulmonary function testing. Int J Radiat Oncol Biol Phys. 1988; 15: 83–87.

5 Marks LB, Prosnitz LR. Estimation of normal tissue complication probabilities with three–dimensional technology. Int J Radiat Oncol Biol Phys. 1994; 28: 777–779.

6 Macumber HH, Calvin JW. Perfusion lung scan patterns in 100 patients with bronchogenic carcinoma. J Thorac Cardiovasc Surg. 1976; 72: 299–302.

7 Wennberg B, Gagliardi G, Sundbom L, et al. Early response of lung in breast cancer irradiation: radiologic density changes measured by CT and symptomatic radiation pneumonitis. Int J Radiat Oncol Biol Phys. 2002; 52: 1196–1206.

8 Fan M, Marks LB, Lind P, et al. Relating radiation–induced regional lung injury to changes in pulmonary function tests. Int J Radiat Oncol Biol Phys. 2001; 51: 311–317.

9 Seppenwoolde Y, Muller SH, Theuws JC, et al. Radiation dose –effect relations and local recovery in perfusion for patients with non–small–cell lung cancer. Int J Radiat Oncol Biol Phys. 2000; 47: 681–690.

10 Choi NC, Kanarek DJ. Toxicity of thoracic radiotherapy on pulmonary function in lung cancer. Lung Cancer. 1994; 10: S219–S230.

11 Prato FS, Kurdyak R, Saibil EA, et al. Physiological and radiographic assessment during the development of pulmonary radiation fibrosis. Radiology. 1977; 122: 389–397.

12 Marks LB, Spencer DP, Bentel GC, et al. The utility of SPECT lung perfusion scans in minimizing and assessing the physiologic consequences of thoracic irradiation. Int J Radiat Oncol Biol Phys. 1993; 26: 659–668.