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The Usefulness of Combined Diagnostic CT and ^{99m}Tc-Octreotide Somatostatin Receptor SPECT/CT Imaging on Pulmonary Nodule Characterization in Patients

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Abstract

The objective of this study was to evaluate the clinical value of combination of diagnostic computed tomography (CT) and somatostatin receptor imaging with ^{99m}Tc-octreotide acetate SPECT/CT in differentiation of benign pulmonary nodules from cancers.

Methods: This was a retrospective study, 29 patients with suspected pulmonary neoplasm underwent diagnostic CT and ^{99m}Tc-octreotide SPECT/CT scans, and the tumor-to-normal tissue tracer value (T/N) for ^{99m}Tc-octreotide was measured. Diagnosis was confirmed by histological analysis.

Results: Eighteen of the 29 patients included in this study had lung cancer: 2 with small cell lung cancer and 16 with nonsmall cell lung cancer. The other 11 patients had benign lung lesions: 5 with tuberculosis, 4 with nontuberculosis infection, 1 with hematoma, and 1 with fibroma. ^{99m}Tc-octreotide uptake (expressed as mean T/N ± SD) was significantly higher in lung cancers (2.58 ± 0.91) than benign lesions (1.38 ± 0.79) ($p = 0.002$). Specificity for pulmonary malignant nodule diagnosis was 63.6% for diagnostic CT, 72.7% for somatostatin receptor SPECT/CT imaging, and 81.8% for the combined use of diagnostic CT and somatostatin receptor SPECT/CT imaging.

Conclusion: Somatostatin receptor imaging with ^{99m}Tc-octreotide SPECT/CT is useful for the differentiation of benign pulmonary nodules from lung cancers, the combination of diagnostic CT and ^{99m}Tc-octreotide SPECT/CT further increases the specificity of malignant pulmonary nodule detection.

Key words: computed tomography, lung cancer, pulmonary nodules, somatostatin receptor, SPECT/CT

Introduction

Lung cancer is the leading cause of cancer death worldwide. It is estimated that 226,160 patients will be diagnosed with, and 160,340 patients will die of cancer of the lung and bronchus in US in 2012, the overall 5-year relative survival was 15.9%.[1] A solitary pulmonary nodule is defined as "a round opacity, at least moderately well-marginated and no greater than 3 cm in maximum diameter."[2] The 5-year survival rate of patients after surgical removal of earlier stage primary lung cancer, without regional lymph nodes spreading and distal metastases, was reported more than 50%, however, more than 50% resected pulmonary nodules were benign.[3,4] Therefore, early detection and differentiation of malignant solitary pulmonary nodule is important for lung cancer therapy, which may avoid unnecessary surgical procedure for patients with benign nodules.

Noninvasive diagnostic modalities currently used in evaluating lung tumors such as chest X-ray, computed tomography (CT), and sputum cytology, have a high percentage of indeterminate diagnosis.[5,6] Although CT plays a critical role on the differentiating diagnosis of pulmonary

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nodules, it provides only morphologic information and reflects little biology of pulmonary nodules. ^{18}F-FDG PET/CT have been widely used in the detection of lung cancers for diagnosis and anticancer management after staging,[7–12] however, infection and inflammation lung diseases have been reported ^{18}F-FDG uptake, ^{18}F-FDG PET/CT may also result indeterminate diagnosis of lung nodules.[13,14]

The affinity of receptor analogs such as somatostatin has been demonstrated overexpressing in some malignant lung tumors.[15–20] It has been reported that somatostatin receptor imaging has a high value in differentiating the property of pulmonary nodules with equal sensitivity and specificity to ^{18}F-FDG PET.[19–21] Somatostatin receptor imaging is beneficial to both small cell lung cancer and nonsmall cell lung cancer; this is a specific receptor imaging and has considerable diagnostic values in the group of patients with suspected lung cancers by diagnostic CT.[22] The objective of this study was to test the hypothesis that, the combination of somatostatin receptor imaging with ^{99m}Tc-octreotide acetate and diagnostic CT is able to further improve lung cancer diagnosis noninvasively.

Materials and Methods

Patients

The Institutional Review Board of the Nanjing Medical University and the local ethics committee approved this investigation. Written consent was obtained from all patients with indeterminate pulmonary nodules. This is a retrospective study, 29 consecutive cases of pulmonary nodules (19 men, 10 women; 63 ± 10 years [mean ± SD]) were enrolled. Diagnostic CT and somatostatin receptor imaging with ^{99m}Tc-octreotide acetate performed within a week in patients with solitary nodules were included. The final diagnosis was confirmed by surgically removed tissue or transthoracic needle biopsy histopathology.

Diagnostic CT study

A Siemens sensation 16-slice CT scanner (Germany) was used with fixed scanning protocol (collimation 16 × 0.75 mm, 120 kV, 180 mA). Omnipaque was used for enhanced imaging; the contrast agent (1.5 mL/kg body weight) was injected at 3 mL/s through the elbow vein.

^{99m}Tc-octreotide SPECT/CT study

Octreotide (10 mg, sandostatin; Novartis Pharma Schweiz AG) was labeled with ^{99m}Tc-pertechnetate. Radiochemical purity was great than 95% for each study. As described previously,[20] ^{99m}Tc-octreotide [1110 MBq (30mCi)] was injected intravenously to each patient without fasting. The imaging apparatus was a dual-head detector SPECT/CT (Millennium VG, Hawkeye; GE Healthcare) equipped with low-energy and high-resolution collimation, the peak energy is 140 keV, window width was set as 20%. Planar images were collected at 1 and 4 hours, SPECT/CT images of the chest were obtained followed 4 hours planar scan. SPECT data were acquired in a 128 × 128 matrix through a 360° rotation with 64 projections. The acquisition time for each projection was 40 seconds. Transverse slices were reconstructed with ordered subset expectation maximization iterative algorithm and formatted as a 128 × 128 matrix. SPECT image attenuation correction was performed. Regions of interest were drawn over lung lesions and the contralateral normal lung tissue based on CT imaging of SPECT/CT; tumor uptake of ^{99m}Tc-octreotide activity was expressed as tumor-to-normal tissue activity ratios (T/N).

Imaging analysis

Diagnostic CT images were read by 2 radiologists who were blinded to pathologic diagnosis. The diagnosis was made according as internal and margin characteristics of lesions. Somatostatin receptor ^{99m}Tc-octreotide SPECT/CT imaging was evaluated by two nuclear medicine physicians blinded to pathologic findings. In case of disagreement, a third radiologist/nuclear medicine physician made a diagnostic conclusion.

Statistical analysis

Data were presented as the mean ± SD. The sensitivity, specificity, positive predictive value, and negative predictive value were estimated and compared between these two modalities using SPSS software (version 15.0). The Student's *t*-test was used to assess statistical difference. A *p*-value less than 0.05 was considered statistically significant.

Results

The patients' information is summarized in Table 1, of 29 lung nodules, 18 were identified as lung cancers by histological findings: nonsmall cell lung cancer in 16 and small cell lung cancer in 2. Eleven lung nodules were benign: 5 tuberculosis, 4 inflammatory pseudotumors, 1 hematoma, and 1 fibroma.

Four hours after injection of ^{99m}Tc-octreotide, the maximal radioactivity accumulation in lung nodules was observed; SPECT/CT scans were performed at 4-hour time point. Lung cancer had a higher ^{99m}Tc-octreotide accumulation, a representative SPECT/CT imaging showed intense ^{99m}Tc-octreotide uptake in lung cancer of a 76-year-old male (Fig. 1). Lung nodules with pathological confirmations of infection or inflammation generally had low ^{99m}Tc-octreotide accumulation, Figure 2 showed low ^{99m}Tc-octreotide uptake in a tuberculosis lesion. Benign tumors included in this study had very low ^{99m}Tc-octreotide accumulation, ^{99m}Tc-octreotide SPECT/CT imaging of a patient with hamartoma is presented in Figure 3. ^{99m}Tc-octreotide uptake was significantly higher in malignant lung nodules (2.58 ± 0.91) than benign lesions (1.38 ± 0.79) ($p = 0.002$) (Table 2).

The specificity for pulmonary malignant nodule diagnosis was 63.6% for diagnostic CT, 72.7% for somatostatin receptor imaging, and 81.8% for combined use of diagnostic CT and somatostatin receptor imaging.

Discussion

Overexpressing somatostatin receptor in many malignant tumors is the fundamental of somatostatin receptor nuclear imaging for differentiating malignant tissues from benign diseases.[23] Studies have confirmed the presence of somatostatin receptors in nonsmall cell lung cancer and their cell lines.[16,24] It has demonstrated the usefulness of somatostatin analog scintigraphy on detection of solitary pulmonary nodules (discussed in ref. Wang et al.[20]). In this study, overexpression of somatostatin receptor, we have observed

Table 1. Clinical and Histological Information of Patients Included in the Study

Patient no.	*Sex*	*Age (years)*	*Location*	*Size in diameter (cm)*	*Histology*
1	F	74	Right upper	3.0	Squamous cell carcinoma
2	M	72	Left lower	3.9	Squamous cell carcinoma
3	M	47	Left upper	3.5	Squamous cell carcinoma
4	M	70	Left lower	3.4	Squamous cell carcinoma
5	F	60	Right upper	2.7	Squamous cell carcinoma
6	M	71	Left upper	2.9	Squamous cell carcinoma
7	F	70	Left upper	4.0	Squamous cell carcinoma
8	M	42	Right upper	2.3	Squamous cell carcinoma
9	M	63	Right upper	0.8	Squamous cell carcinoma
10	F	63	Left upper	2.0	Adenocarcinoma
11	M	76	Left upper	3.2	Adenocarcinoma
12	M	73	Left lower	3.1	Adenocarcinoma
13	F	71	Right lower	3.6	Adenocarcinoma
14	F	64	Right upper	1.7	Adenocarcinoma
15	M	51	Right lower	2.0	Adenocarcinoma
16	M	68	Right lower	1.9	Small cell lung carcinoma
17	F	79	Right upper	3.8	Small cell lung carcinoma
18	F	35	Right lower	4.0	Adenocarcinoma
19	M	68	Right lower	3.2	Tuberculosis
20	M	47	Left upper	4.0	Tuberculosis
21	M	55	Right upper	2.1	Tuberculosis
22	M	70	Right upper	2.6	Tuberculosis
23	F	62	Left lower	2.2	Tuberculosis
24	M	71	Right upper	2.6	Granuloma
25	M	62	Left upper	1.0	Granuloma
26	M	65	Right lower	2.2	Granuloma
27	F	69	Right lower	2.8	Granuloma
28	M	62	Left upper	1.6	Hamartoma
29	M	70	Right upper	2.1	Fibroma

that ^{99m}Tc-octreotide uptake in malignancy is significantly higher than benign tumors and infectious diseases (Figs. 1–3 and Table 2); therefore, somatostatin receptor imaging has advantages than diagnostic CT on pulmonary solitary nodule characterization.

Although ^{18}F-FDG PET/CT has been widely used for lung cancer diagnosis, staging and following up of cancer management, high ^{18}F-FDG uptake in infection and inflammation lung diseases have been reported, ^{18}F-FDG PET/CT may also result in indeterminate diagnosis of lung nodules.[13,14]

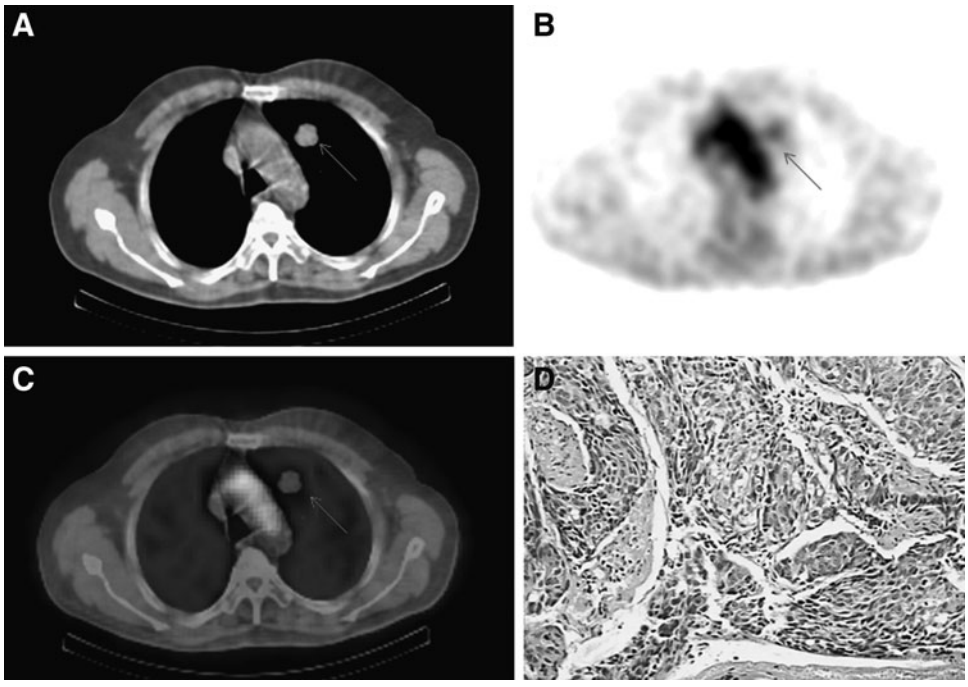

FIG. 1. A 76-year-old male patient with adenocarcinoma lung cancer in left upper lobe. **(A)** CT scans showed abnormality in left upper lobe; **(B)** ^{99m}Tc-octreotide images showed intense uptake in the lung lesion (arrow); **(C)** the overlay of **(A)** and **(B)**; **(D)** adenocarcinoma was verified on histology. CT, computed tomography.

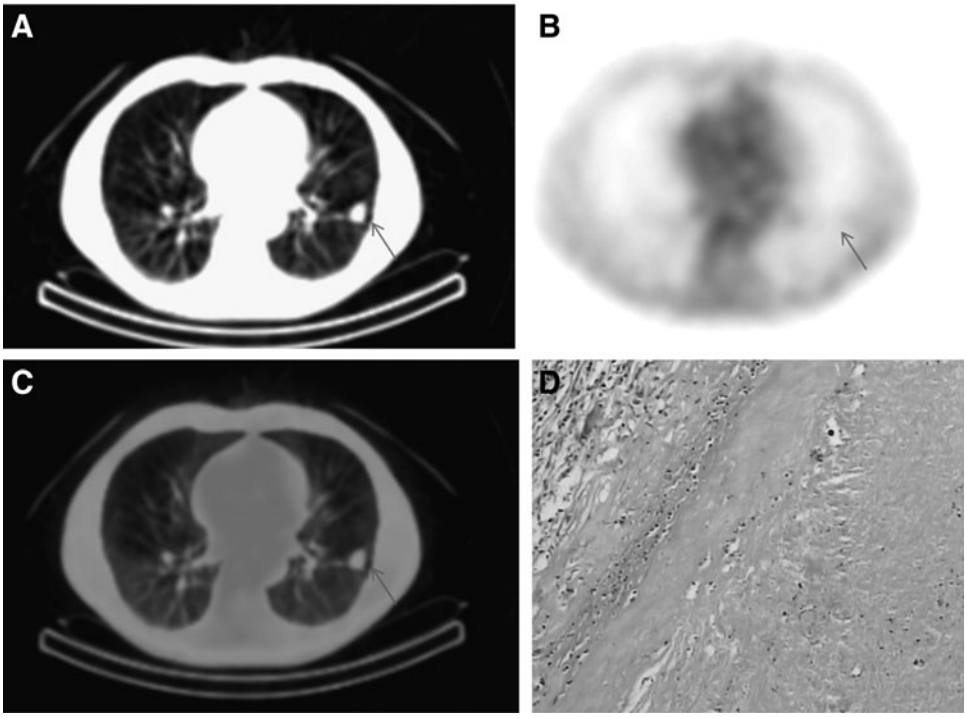

FIG. 2. A 63-year-old male patient with tuberculosis, **(A)** CT scans showed abnormality in the right lower lobe. **(B)** ^{99m}Tc-octreotide images were negative in the lung lesion (arrow). **(C)** Overlay of **(A)** and **(B)**; **(D)** tuberculosis was verified on histology.

On the other hand, low ^{18}F-FDG uptake in malignancy has also reported.[20] We have recently found in animal models that ^{18}F-FDG uptake in lung cancer as well as colon cancer is hypoxia dependent, oxic cancer cells associate with low ^{18}F-FDG accumulation,[25–28] accordingly, we reasonably assume that oxic cancer lesions may result in ^{18}F-FDG PET/CT negative imaging. Higher ^{99m}Tc-octreotide uptake in malignancy than benign neoplasm and infection lesions could be the advantage of somatostatin receptor imaging than ^{18}F-FDG PET/CT for lung malignancy characterization. Considering the pilot nature of this study, we had not compared ^{99m}Tc-octreotide SPECT/CT with ^{18}F-FDG PET/CT in the same patients in this study.

In this study, we used ^{99m}Tc-octreotide instead of ^{111}In-Octreotide; ^{99m}Tc is much convenient for daily use, ^{99m}Tc has a much shorter half-life than ^{111}In, which may decrease irradiation to patients and public population, and Octreotide reaches maximal accumulation 4 hours after injection,

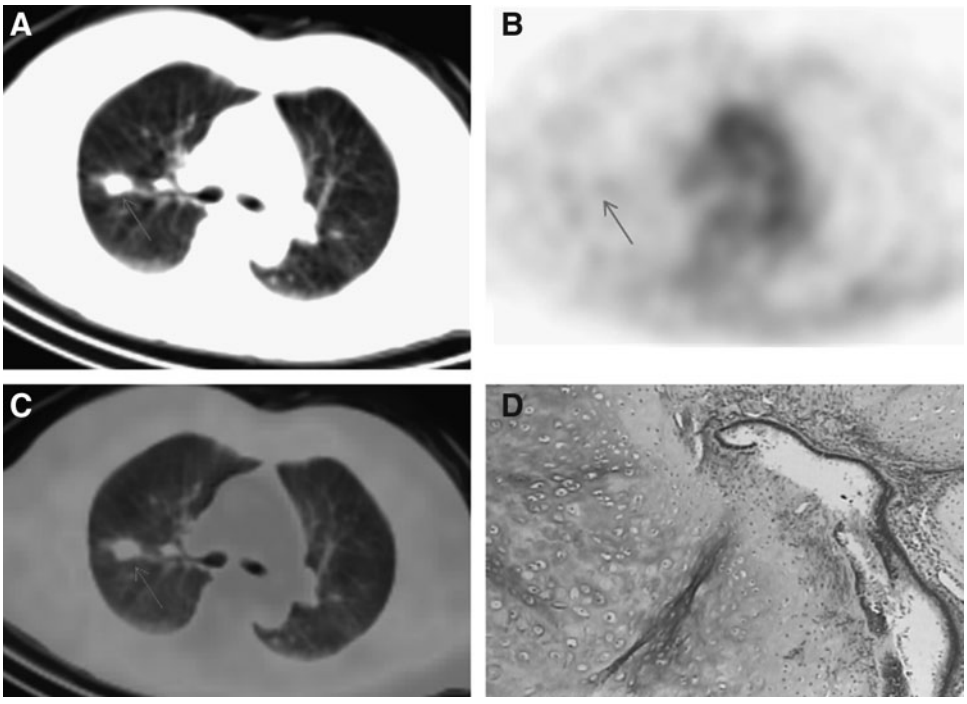

FIG. 3. A 62-year-old female patient with hamartoma. **(A)** CT scans showed neoplasm of the upper lobe of the right lung. **(B)** ^{99m}Tc-octreotide images had little uptake in the lesion. **(C)** Overlay of **(A)** and **(B)**. **(D)** Hamartoma was verified on histology.

Table 2. ^{99m}Tc-octreotide Uptake in Benign and Malignant Pulmonary Nodules

Parameter	*Malignant*	*Benign*	p-*Value*
Age (years)	63.83 ± 12.37	63.72 ± 7.38	0.98
Diameter (cm)	2.88 ± 0.92	2.40 ± 0.79	0.17
T/N	2.58 ± 0.91	1.38 ± 0.79	0.0002

T/N, tumor-to-normal tissue tracer value.

prolonging scan with a longer half-life ^{111}In-Octreotide seems unnecessary.

The objective of this study was to evaluate the clinical value of the combination of diagnostic CT and somatostatin receptor ^{99m}Tc-octreotide acetate SPECT/CT imaging in differentiation of benign pulmonary nodules from cancers. We found that the specificity for pulmonary malignant nodule diagnosis was 63.6% for diagnostic CT, 72.7% for somatostatin receptor imaging, and 81.8% for the combined use of diagnostic CT and somatostatin receptor imaging. Therefore, the combination of diagnostic CT and somatostatin receptor ^{99m}Tc-octreotide acetate SPECT/CT in characterization of malignancy from benign pulmonary nodules is superior to ^{99m}Tc-octreotide acetate SPECT/CT and, much superior than diagnostic CT.

Conclusions

Somatostatin receptor imaging with ^{99m}Tc-octreotide SPECT/CT is useful for the differentiation of benign pulmonary nodules from lung cancers, the combination of diagnostic CT and ^{99m}Tc-octreotide SPECT/CT further increases the specificity of malignant pulmonary nodule detection.

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Disclosure Statement

There are no existing financial conflicts.

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