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Thallium-201 SPECT with triple-headed gamma camera for differential diagnosis of small pulmonary nodular lesion 20 mm in diameter or smaller

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[Aim] Although thallium-201 (^{201}Tl) has been used for the diagnosis of lung cancer, its detectability of small pulmonary nodules is not known. The aim of this study was to evaluate the ability of ^{201}Tl SPECT for the differential diagnosis for the pulmonary nodules 20 mm in diameter or smaller. *[Methods]* ^{201}Tl SPECT was performed in 31 patients suspected of having primary lung cancer. The final diagnosis was established by histology, and tumor size was 10 to 20 mm in diameter. Twenty of 31 patients had malignant tumors, including squamous cell lung cancer (n = 5), adenocarcinoma (n = 14) and small cell lung cancer (n = 1), but in none of them was there mediastinal lymphnode involvement. *[Results]* Ten of 20 malignant tumors and 1 of 11 benign lesions demonstrated significant ^{201}Tl uptake, so that the positive predictive value, negative predictive value, sensitivity and specificity for the diagnosis of lung cancer were 90.9% (10/11), 50.0% (10/20), 50.0% (10/20) and 90.9% (10/11), respectively. *[Conclusion]* These data suggest that sensitivity for detecting lung cancer 20 mm or less in diameter may be insufficient, but even in patients with small pulmonary nodules, a positive ^{201}Tl result is highly predictive of lung cancer.

Key words: thallium-201, single photon emission computed tomography (SPECT), small pulmonary nodule, lung cancer

INTRODUCTION

THE DETECTABILITY of small pulmonary lesion has recently been dramatically improved by the development of X-ray computed tomography (CT), but the qualitative diagnosis of lung nodules is not always easy. It is important to diagnose small pulmonary nodular lesions in order plan treatment. For this purpose, various imaging methods have been developed and used. In nuclear medicine, the clinical usefulness of positron emission tomography (PET) has been examined for the detection of small lung cancers with L-[metyl^{11}C]-metionine (MET) and ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG).[1,2] In single photon emission computed tomography (SPECT), technetium-99m labeled agents for tumor imaging have recently been reported,[3–5] but the conventional tumor imaging agent ^{201}TlCl is widely used in Japan for detecting primary lung cancer because of its high diagnostic efficiency.

We previously reported the efficiency of ^{201}Tl SPECT for detecting pulmonary lesions, but the lesion sizes were rather large in most cases.[6] In a subsequent study, we reported that ^{201}Tl SPECT was able to visualize all tumors greater than 20 mm in diameter,[7] but few studies have been reported on the ability of ^{201}Tl SPECT to detect small lung cancers.

The aim of this study was to evaluate the abilitiy of ^{201}Tl SPECT differentiate primary lung cancer from benign lesions in the small pulmonary nodules 20 mm in diameter or smaller.

MATERIALS AND METHODS

Patients

A total of 31 patients (18 men and 13 women) with suspected primary lung cancer were studied. They had not received any therapy before the operation. Patient age ranged from 39 yr. to 78 yr. with a mean of 62.5 yr. Final diagnosis was established by histology (thoracotomy), and tumor size was 10 to 20 mm in diameter. There were 14 adenocarcinomas, 5 squamous cell carcinomas, 1

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Table 1 Patients charactrisitics and ^{201}Tl imaging results

Case No.	Sex	Age	Diagnosis	Histology	Max. diameter (mm)	Visual analysis	ER	DR	RI
1	M	78	malignant	small cell	10	–			
2	F	60	malignant	adenocarcinoma (mod. dif.)	10	–			
3	F	57	malignant	squamous cell (poorly dif.)	10	–			
4	F	53	benign	fibrosis	10	–			
5	M	48	benign	tuberculosis	10	–			
6	M	42	benign	intra-pulmonary lymph nodes	10	–			
7	M	45	malignant	adenocarcinoma (well dif.)	12	+	1.10	1.26	14.79
8	M	75	benign	epidermoid	12	–			
9	F	70	malignant	adenocarcinoma (well dif.)	12	–			
10	F	41	malignant	adenocarcinoma (mod. dif.)	13	–			
11	F	39	benign	teratoma	14	–			
12	F	71	malignant	adenocarcinoma (well dif.)	15	+	1.34	1.48	10.25
13	M	68	malignant	adenocarcinoma (mod. dif.)	15	+	1.82	2.24	23.49
14	M	74	malignant	adenocarcinoma (poorly. dif.)	15	+	1.57	2.52	60.63
15	M	70	malignant	squamous cell (poorly dif.)	15	+	3.34	3.00	−10.12
16	M	74	benign	epidermoid	15	–			
17	M	71	malignant	adenocarcinoma (mod. dif.)	15	–			
18	F	58	malignant	adenocarcinoma (mod. dif.)	15	–			
19	M	64	malignant	squamous cell (mod. dif.)	15	–			
20	M	65	benign	tuberculosis	15	–			
21	F	71	benign	granuloma	15	–			
22	F	72	benign	adenomatous hyperplasia	15	–			
23	F	51	benign	hamartoma	18	+	2.32	2.20	−5.23
24	F	70	malignant	adenocarcinoma (well dif.)	18	–			
25	M	49	benign	tuberculosis	18	–			
26	F	72	malignant	squamous cell (mod. dif.)	20	+	3.25	2.41	−25.90
27	M	75	malignant	squamous cell (mod. dif.)	20	+	2.77	3.06	10.27
28	M	74	malignant	adenocarcinoma (well dif.)	20	+	1.13	2.07	82.80
29	M	56	malignant	adenocarcinoma (well dif.)	20	+	1.24	1.02	−18.03
30	M	69	malignant	adenocarcinoma (well dif.)	20	+	2.63	4.77	81.54
31	M	56	malignant	adenocarcinoma (mod. dif.)	20	–			

small cell carcinoma, 3 tuberculomas, 2 epidermoids, 1 teratoma, 1 fibrosis, 1 intra-pulmonary lymph nodes, 1 hamartoma, 1 granuloma and 1 adenomatous hyperplasia. In none of the malignant tumors was there mediastinal lymph node metastasis.

Thallium imaging

After intravenous injection of 111 MBq (3 mCi) of ^{201}TlCl, SPECT imaging was performed 20 min (early scan) and 180 min (delayed scan) later with a triple-headed rotating gamma camera (GCA 9300A, TOSHIBA), equipped with low energy high resolution parallel hole collimators. Data were acquired from 60 projection for 50 sec each over 360° with a 128 × 128 matrix (pixel size was 3.2 × 3.2 mm). Transverse, coronal and sagittal sections were reconstructed with Butterworth filter (order 8, cut off frequency 0.10) and Ramp filter. After reconstruction, 4 slices of each tomographic image were added and displayed on transparent film (slice thickness was 12.8 mm). No attenuation correction was performed.

Visual analysis

Without clinical information, including chest radiograph and chest CT, ^{201}Tl tomographic images were independently interpreted by two nuclear medicine specialists for the presence or absence of abnormal accumulation. If the interpretations were different, another specialist participated in the film interpretation and consensus was obtained among 3 specialists. The images were classified as positive when any obvious foci of increased ^{201}Tl uptake over background were detected by both observers.

Quantitative analysis

For quantitative analysis, regions of interest (ROIs) were placed over the obvious foci of increased ^{201}Tl uptake on a transverse image by the isocount method with a 60% cut off of peak count. On the contralateral normal lung in the same slice, ROIs were set symmetrically. The same ROIs were set on both early and delayed images. The mean pixel counts for ROIs were measured and uptake ratios of the lesion to the contralateral normal lung were calculated on both early and delayed scans. We then obtained the retention index (RI) to quantitatively evaluate the degree

of ^{201}Tl retention in the lesion as follows[6]:

$$RI = \frac{\text{delayed uptake ratio} - \text{early uptake ratio}}{\text{early uptake ratio}} \times 100$$

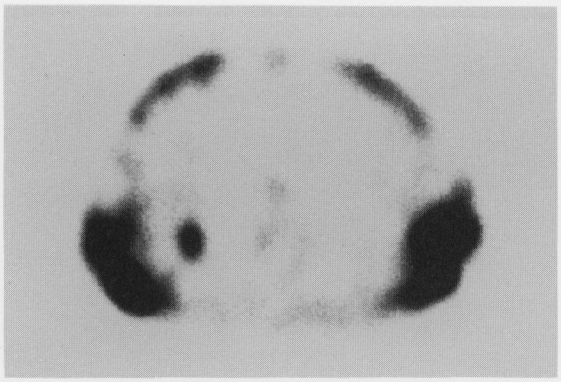
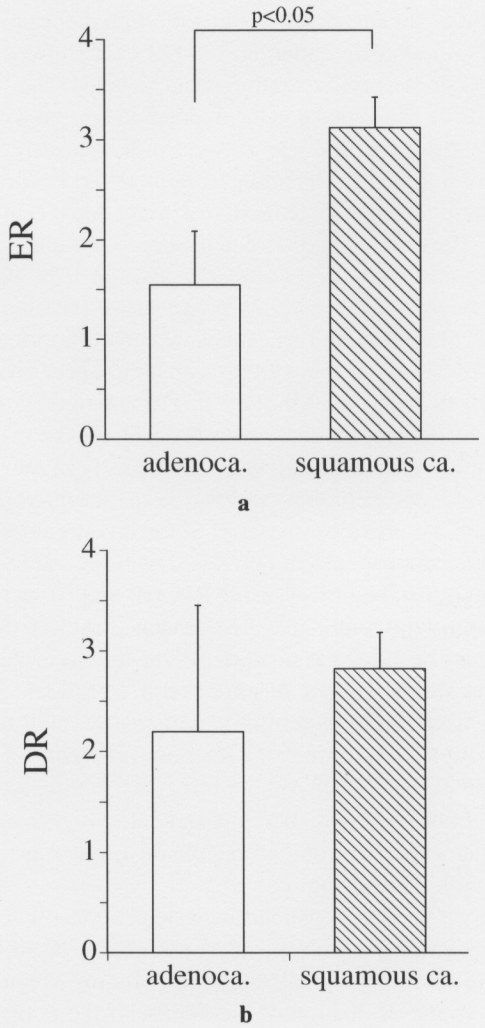


Fig. 1 A 68-year-old male with primary lung cancer (moderately differentiated adenocarcinoma). Tumor size was 15 mm in diameter. Delayed image demonstrated apparent ^{201}Tl uptake in the lesion. The delayed ratio was 2.25 and the retention index was 23.5%.



Statistical analysis

Comparison of differences between adenocarcinoma and squamous cell carcinoma in quantitative indices was done by means of unpaired t-test. Probability values of less than 0.05 were considered to be statistically significant.

RESULTS

Table 1 summarizes the results of ^{201}Tl SPECT and pathological findings for 31 patients.

Visual analysis

In this study, 10 of 20 malignant tumors and 1 of 11 benign lesions demonstrated significant ^{201}Tl uptake, so that, for the diagnosis of lung cancer, the positive predictive value (PPV) was 90.9% (10/11), the negative predictive value (NPV) was 50.0% (10/20), sensitivity was 50.0% (10/20) and specificity was 90.9% (10/11). For tumors 15 mm in diameter or smaller, PPV, NPV, sensitivity and specificity were 100% (5/5), 52.9% (9/17), 38.5% (5/13) and 100% (9/9), respectively.

A representative case is shown in Figure 1.

Quantitative analysis

The mean early uptake ratio (ER) for all ^{201}Tl positive lesions (n = 11) was 2.05 ± 0.84, the delayed uptake ratio (DR) was 2.37 ± 1.03 and RI was 20.4 ± 38.3%. No indices correlated with tumor size. The ER of squamous cell carcinoma (n = 3) was significantly higher than that of

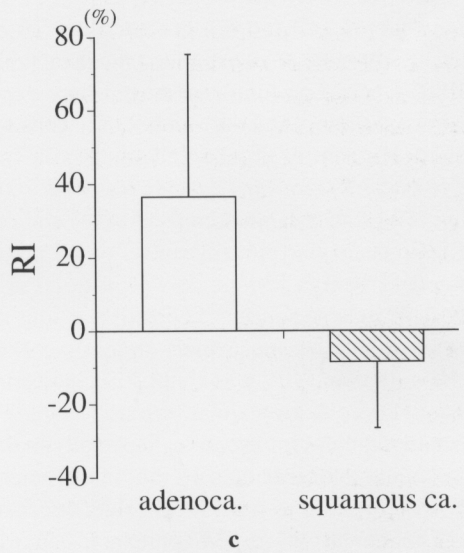


Fig. 2 (a) Early uptake ratio (ER) between adenocarcinoma and squamous cell carcinoma. (b) Delayed uptake ratio (DR) between adenocarcinoma and squamous cell carcinoma. (c) Retention index (RI) between adenocarcinoma and squamous cell carcinoma.

The ER differed significantly between adenocarcinoma and squamous cell carcinoma.

adenocarcinoma (n = 7) (3.12 ± 0.30 vs. 1.55 ± 0.54, $p < 0.05$). No significant difference in other indices was seen among pathohistological types (Fig. 2). The difference among the differentiations of adenocarcinoma was not examined because of the small number of these cases.

DISCUSSION

There have been many attempts to use nuclear medical procedures to overcome the limitation of morphological imagings such as CT for the diagnosis of lung cancer. Recently FDG PET, MET PET, technetium-99m-hexakis-2-methoxy-2-isobutylisonitrile (^{99m}Tc-MIBI) SPECT and ^{99m}Tc-tetrofosmin SPECT have been studied for lung cancer.[1–5]

Higashi et al. reported that FDG PET provided high sensitivity in the detection of lung cancer less than 20 mm in diameter,[2] but PET is too expensive and complicated to perform at ordinary hospitals.

Although ^{201}Tl SPECT has achieved widespread acceptance in clinical use for various tumor imagings, ^{99m}Tc labeled agents were expected to improve detectability because of their superior physical characteristics to those of ^{201}TlCl. But ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin SPECT are not superior to ^{201}Tl SPECT in detecting lung cancer.[3–5]

We previously reported that ^{201}Tl SPECT had a positive predictive value (PPV) of 92% (23/25), a negative predictive value (NPV) of 100% (5/5), a sensitivity of 100% (23/23), and a specificity of 71.4% (5/7) in various sizes,[6] and that it could depict a lung cancer as small as 15 mm in diameter.[6,8] We also reported that ^{201}Tl SPECT visualized all of 147 tumors greater than 20 mm in diameter.[7] Nishiyama et al. examined the detectability of ^{201}Tl SPECT based on tumor size;[3] but they examined only malignant tumors and the number of lesions was not mentioned. Higashi et al. showed sensitivity of ^{201}Tl SPECT to be 57.1% for lung cancers less than 20 mm in diameter.[2] But they examined only 7 cases and omitted benign lesions. In our current study, of 20 malignant tumors and 11 benign lesions, PPV was good in visual analysis. This indicates that ^{201}Tl positive lesions 20 mm in diameter or smaller are strongly suggestive of malignancy. Nevertheless, NPV was about 50%, indicating that ^{201}Tl negative results for nodular lesions 20 mm in diameter or smaller are not informative. Especially in the case of lesions equal to or less than 10 mm in diameter, ^{201}Tl SPECT is considered to have little value, because all 6 lesions (3 benign lesions and 3 malignant lesions) 10 mm in diameter showed no sign of ^{201}Tl uptake. When the prevalence of lung cancer is considered, ^{201}Tl SPECT may be more effective in hospitals with a high prevalence of lung cancer than in hospitals with a low prevalence because PPV was high.

The mechanisms of ^{201}Tl accumulation in tumors have not been clearly defined. Waxman summarized the possible factors influencing ^{201}Tl uptake by tumor cells, i.e.: blood flow, viability, tumor type, Na^+-K^+ ATPase system, cotransport system, Ca^{2+} channel, vascular immaturity due to leakage, and increased cell membrane permeability.[9] In these factors, blood flow is supposed to be the most important factor for ^{201}Tl uptake in tumors, but it should always be taken into account that other factor such as viability of tumor cells, metabolic activity, and areas of tumor necrosis play a considerable role.[10–12]

Thallium is a potassium analogue and has five times the affinity for the Na^+-K^+ ATPase existing in the cell membrane as potassium.[13] Thallium is therefore transported into cells rather than potassium. In *in vitro* studies, the correlation between ^{201}Tl uptake and Na^+-K^+ ATPase activity was demonstrated in thyroid tumor (papillary and follicular carcinoma and follicular adenoma) specimens and squamous lung carcinoma cells SK-MES.[10,13] Takekawa et al. reported that the delayed ratio of ^{201}Tl uptake was related to degree of Na^+-K^+ ATPase expression.[14] These findings suggested that ^{201}Tl uptake in malignant tumors might be regulated by Na^+-K^+ ATPase.

In malignant tumors, the grade of accumulation of ^{201}Tl on the delayed scan is associated with the malignant potential including the metastatic potential and proliferative ability. In adenocarcinoma with high metastatic potential or poor differentiation, ^{201}Tl SPECT showed slow washout or increased retention on the delayed scan.[15] The intensity of ^{201}Tl uptake in the nodules correlated with the proliferating cell nuclear antigen index (proliferative activity marker) in thyroid carcinoma[13] and 5-bromodeoxyuridine index (proliferative activity marker) in gliomas.[16] The correlation between the accumulation of ^{201}Tl and the malignant potential suggests that ^{201}Tl uptake might be associated with the prognosis of patients with malignant tumors. In fact, Takekawa et al. reported that the low ^{201}Tl uptake ratio group with lung cancer survived significantly longer than the high ^{201}Tl uptake ratio group.[17]

In our present study, the early ^{201}Tl uptake ratio of squamous cell carcinoma was significantly higher than that of adenocarcinoma, and this is different from the results of our previous studies.[6,7] Some investigators have reported that tumor size is correlated with ER and DR.[3] In the present study, however, the ER, DR and RI were not correlated with tumor size. The reasons for these differences may be due to the small size of the lesions evaluated, and the small number of cases with significant ^{201}Tl uptake assessed by quantitative indices. A small tumor needs high uptake of ^{201}Tl for positive visualization because of the partial volume effect. ^{201}Tl positive in a small tumor itself may therefore indicate a higher uptake ratio than expected from the calculated uptake ratio compared with a larger tumor.

A larger number of patients with small tumors will have to be examined in order to reveal the meaning of ^{201}Tl positive findings in small tumors, including diagnostic ability in the evaluation of the degree of the malignant

potential and the prognostic implications.

CONCLUSION

In small lung nodular lesions, ^{201}Tl SPECT provides less additional information for differential diagnosis when no abnormal uptake is observed, but ^{201}Tl positive small pulmonary nodules are highly predictive of lung cancer. ^{201}Tl SPECT should therefore be considered in the diagnosis of small lung nodules when diagnosis by anatomical methods is questionable.

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