

Thallium-201 Single Photon Emission Computed Tomography in the Evaluation of Suspected Lung Cancer

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Thallium-201 SPECT was performed in 30 patients with suspected lung cancer. Both early and delayed scans demonstrated abnormal accumulation in all of 23 malignant pulmonary lesions including 21 lung cancer and in two of seven benign conditions. There were significant differences in delayed ratio (uptake ratio of the lesion to the normal lung on delayed scan) and retention index (degree of retention in the lesion) between lung cancer and benign conditions, respectively ($p < 0.01$, $p < 0.05$). The delayed ratio and retention index revealed that adenocarcinoma showed higher ^{201}Tl accumulation than squamous cell carcinoma and small cell carcinoma ($p < 0.05$) and ^{201}Tl clearance in squamous cell carcinoma was faster than in the other two ($p < 0.05$). Mediastinal involvement was detected in five of seven patients on delayed scans. The smallest lesion depicted was 1.5 cm in diameter. Two false negatives had small metastases < 1.0 cm in diameter. This method seems to be useful to detect lung cancer, to differentiate malignant from benign lesions, and to evaluate mediastinal involvement from lung cancer.

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In the workup of a solitary pulmonary lesion there is a clinical demand for noninvasive techniques that precisely diagnose whether the lesion is benign or malignant and which can evaluate mediastinal involvement from lung cancer, thereby determining a rationale for treatment and reducing the number of unnecessary thoracotomies.

Thallium 201 chloride (^{201}Tl) has been described by Cox et al. (1), Salvatore et al. (2), Tonami et al. (3,4) as a positive indicator for lung neoplasms. A subsequent report by Hisada et al. (5) reported that sensitivity with ^{201}Tl in primary sites was fair but was not superior to that with gallium-67 (^{67}Ga). Since the distribution of ^{201}Tl in tumors is mainly determined in its initial passage, we have attempted scintigraphy after the administration of ^{201}Tl through the bronchial artery to enhance the uptake in the lung cancer (6). Good results were obtained in depicting both primary sites and met-

astatic lymph nodes in the hilus and the mediastinum. However, this technique is not suitable for routine clinical use because of its invasive nature. The development of improved rotational single photon emission computed tomography (SPECT) encouraged us to evaluate patients with suspected lung cancer by intravenous administration of a large dose of ^{201}Tl . This study was undertaken to evaluate whether ^{201}Tl SPECT is useful in the differentiation of a pulmonary lesion presenting as a nodular shadow on the chest radiograph and in the detection of mediastinal lymph node metastases from lung cancer.

MATERIALS AND METHODS

A total of 30 patients with suspected lung cancer were studied in our institution between July 1985 and October 1987. These consisted of 21 patients with histologically (20 patients) or cytologically (one patient) proven untreated primary lung cancer (squamous ten, adeno seven, small cell three, large cell one), one patient with pulmonary sarcoma, one with metastatic lung cancer, and seven patients with benign conditions (pulmonary tuberculosis three, broncho-

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TABLE 1
Summary of 23 patients with malignant pulmonary lesion

No.	Disease	Cell type	Stage	Size of pulmonary lesion (cm)	²⁰¹ Tl		Retention Index	Metastatic mediastinal Lymph nodes
					Early ratio	Delayed ratio		
1	Lung cancer	Squamous	T3N0M0(P)	7 × 5.5 × 8	1.29	1.56	21	-
2	Lung cancer	Squamous	T2N2M0(P)	4 × 4 × 3	2.12	2.20	4	+
3	Lung cancer	Squamous	T2N2M1(P)	4.5 × 6.5 × 5.6	1.28	1.57	23	+
4	Lung cancer	Squamous	T2N0M0(P)	3 × 2.8 × 2.8	2.01	2.51	25	-
5	Lung cancer	Squamous	T1N1M0(P)	1.5 × 1.5 × 2.3	1.43	1.59	11	-
6	Lung cancer	Squamous	T2N2M0(P)	7 × 6 × 8	1.50	1.89	26	+
7	Lung cancer	Squamous	T2N0M0(P)	2 × 1 × 2	1.49	1.52	2	-
8	Lung cancer	Squamous	T3N0M0(P)	8 × 4 × 5	2.24	2.05	-8	-
9	Lung cancer	Squamous	T2N2M1(P)	6.5 × 4 × 5	2.02	2.17	7	+
10	Lung cancer	Squamous	T2N2M1(C)	4.3 × 4.9 × 6.3	1.83	1.96	7	Not confirmed
11	Lung cancer	Adeno	T1N0M0(P)	2.8 × 2.8 × 2.9	1.41	1.69	20	-
12	Lung cancer	Adeno	T2N2M0(P)	3.5 × 3.0 × 2.8	1.49	2.03	36	+*
13	Lung cancer	Adeno	T2N0M0(P)	3.3 × 3.6 × 3.0	2.05	2.66	30	-
14	Lung cancer	Adeno	T3N0M0(P)	8.5 × 7 × 6	2.33	3.02	30	-
15	Lung cancer	Adeno	T1N0M0(P)	1.5 × 1.0 × 1.5	1.58	2.11	34	-
16	Lung cancer	Adeno	T3N2M1(P)	4.7 × 4.7 × 6	2.22	3.20	44	+
17	Lung cancer	Adeno	T3N2M0(P)	3 × 2 × 2 (Dissemination)	1.71	3.48	104	+*
18	Lung cancer	Small	T3N2MX(C)	Extensive	1.65	2.33	41	Not confirmed
19	Lung cancer	Small	T3N2MX(C)	Extensive	1.33	1.93	45	Not confirmed
20	Lung cancer	Small	T2N2M1(C)	3 × 3 × 4	1.15	1.72	50	Not confirmed
21	Lung cancer	Giant	T2N0M0(P)	8 × 5.5 × 5	1.99	2.24	13	-
22	Lung sarcoma	Leiomyosarcoma	T2N2M0(C)	5 × 5 × 6	1.45	1.83	26	Not confirmed
23	Metastatic lung cancer	Adeno (colon)	T2N2M1(C)	5 × 5 × 8	2.75	2.85	4	Not confirmed

* > 1cm in diameter.

pneumonia two, postpneumonia scar one, hemorrhagic infarction one). Thoracotomies were performed within a week after ²⁰¹Tl SPECT in 23 patients (primary lung cancer 17, benign conditions six). A dose of 8–10 mCi (296–370 MBq) ²⁰¹Tl chloride was injected intravenously. Tomographic scans were obtained 15 min (early scan) and 3 hr (delayed scan) after injection using a rotating gamma camera system with dual heads, equipped with high resolution collimators interfaced with a minicomputer. Sixty projections with an acquisition time of 30 sec each were stored on magnetic disk. Using a dual head gamma camera, the total actual acquisition time was 15 min. After preprocessing the data by nine-point weighted smoothing, the filtered back projection method was used for image reconstruction using the Shepp-Logan filter to suppress high frequency noise (7). Transverse, coronal and sagittal sections were reconstructed. Full width at half maximum of the system was 15 mm at the center of rotation with a rotation radius of 22 cm. Attenuation correction was not performed.

When the ²⁰¹Tl tomogram showed an abnormal uptake in a pulmonary lesion, regions of interest (ROIs) were set in the area with abnormal radioactivity and in the contralateral normal lung on the transverse sections of both early and delayed scans. Those transverse planes which demonstrated the lesion most clearly were carefully selected. The mean voxel counts for ROIs were measured and uptake ratios of the lesion to the contralateral normal lung were calculated on both scans.

Then, we obtained the Retention Index to evaluate quantitatively the degree of ²⁰¹Tl retention in the lesion as follows:

$$\frac{\text{Delayed ratio} - \text{early ratio}}{\text{Early ratio}} \times 100.$$

To test for differences between the mean values of early ratio, delayed ratio, and retention index among diseases, the Stu-

TABLE 2
Detection of Mediastinal Involvement

	²⁰¹ Tl		
	(+)	(-)	
Mediastinal Metastasis (+)	5	2	7
Mediastinal Metastasis (-)	2	8	10
	7	10	17
	Sensitivity		71.4%
	Specificity		80.0%
	Accuracy		76.5%

TABLE 3
Summary of Seven Patients with Benign Pulmonary Lesion

No.	Disease	Size of pulmonary lesion	²⁰¹ Tl accumulation	Early ratio	²⁰¹ Tl Delayed ratio	Retention Index
1	Pulmonary tuberculosis	2 × 1.5 × 2	+	1.70	1.36	-20
2	Pulmonary tuberculosis	1.2 × 1.4 × 1.0	-			
3	Pulmonary tuberculosis	1.5 × 1.2 × 1.2	-			
4	Bronchopneumonia	3.0 × 2.5	+	1.59	1.45	-9
5	Bronchopneumonia	1.5 × 1.0	-			
6	Postpneumonia scar	2.0 × 2.0	-			
7	Hemorrhagic infarction (by parasite)	2.0 × 1.8	-			

dent's t-test was used. Results were considered significant when $p < 0.05$.

In 17 patients who underwent thoracotomy for lung cancer, mediastinal involvement was determined as positive on ²⁰¹Tl scans when the mediastinal region showed an increased radioactivity except in the thoracic spine and the myocardium. Each abnormal uptake was evaluated in comparison with anatomy and pathology of mediastinal lymph nodes according to lymph node mapping of the Japan Lung Cancer Society (8). The evaluation of hilar involvement was not performed because of difficulty in locating the lesion. Pathologic TNM classification for lung cancer was made according to TNM clinical classification of The Japan Lung Cancer Society (8).

RESULTS

Tables 1, 2, and 3 present the results of the clinical findings and ²⁰¹Tl SPECT in all patients studied. Thallium-201 SPECT demonstrated a very high tracer uptake in all of the 23 malignant pulmonary lesions both on early and delayed scans. Out of seven benign conditions, one with bronchopneumonia and one with pulmonary tuberculosis showed abnormal ²⁰¹Tl accumulation on both scans. The smallest malignant pulmonary lesion in this study, a 1.5 × 1.0 × 1.5 cm adenocarcinoma, was clearly demonstrated on both scans.

The early ratio was 1.75 ± 0.41 (mean \pm 1 s.d.) in all malignant tumors, 1.72 ± 0.36 in lung cancer alone and 1.65 ± 0.08 in two patients with benign conditions. The ratios were 1.72 ± 0.36 in squamous cell carcinoma, 1.83 ± 0.37 in adenocarcinoma and 1.38 ± 0.2 in small cell carcinoma. There was no significant difference in early ratio between lung cancer and benign conditions, and among three different histologies of lung cancer. Delayed ratio was 2.16 ± 0.55 in all malignant tumors, 2.16 ± 0.55 in lung cancer alone and 1.41 ± 0.06 in benign conditions. There was a significant difference between lung cancer and benign conditions ($p < 0.01$).

The delayed ratio of adenocarcinoma (2.60 ± 0.67) was significantly higher than those of squamous cell carcinoma (1.90 ± 0.34) and of small cell carcinoma (1.99 ± 0.31) ($p < 0.05$) (Fig. 1). The retention indices were 26 ± 23 in malignant tumors, 27 ± 24 in lung cancer and -14 ± 8 in benign conditions. There was a significant difference between lung cancer and benign conditions ($p < 0.05$). Retention Indices of adenocarcinoma (42 ± 28) and of small cell carcinoma (45 ± 4) were significantly higher than that of squamous cell carcinoma (12 ± 12) ($p < 0.05$) (Fig. 2).

Mediastinal lymph node metastases were detected on the delayed scans and the degree of visualization of these lesions was better on the delayed scans than on

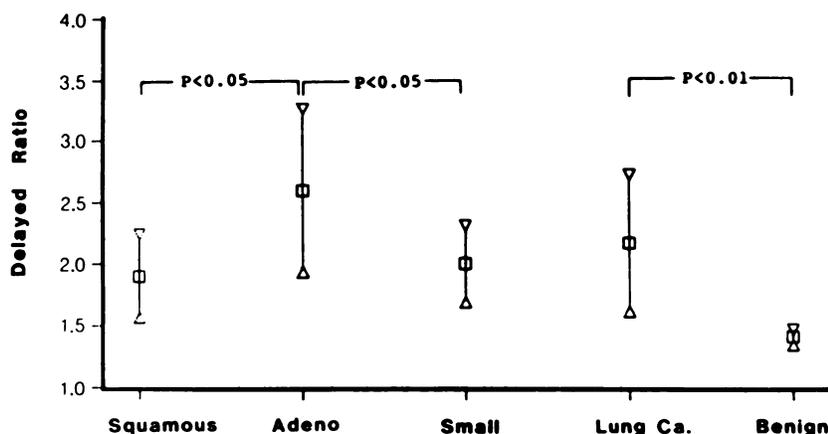


FIGURE 1
Delayed ratio in primary lung cancer and benign conditions.

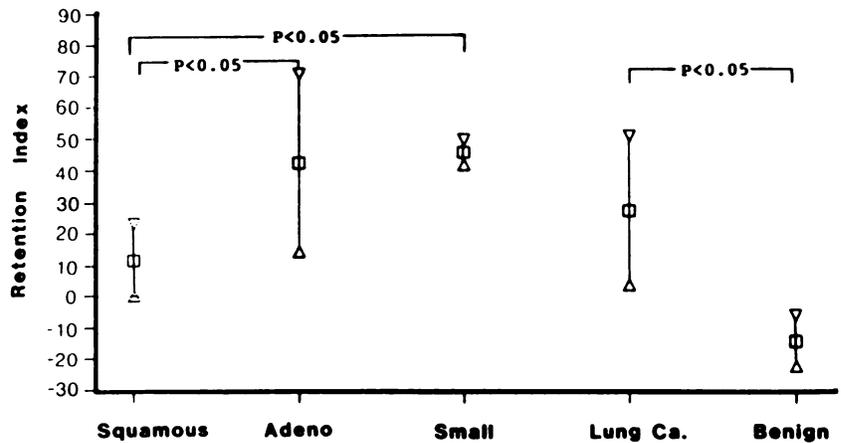


FIGURE 2
Retention index in primary lung cancer and benign conditions.

the early scans in five of seven patients with surgically proven mediastinal metastases (sensitivity 71.4%). The smallest mediastinal metastatic lesion depicted was 1.5 cm in diameter. Two patients with a false-negative

^{201}Tl study had small mediastinal metastases <1.0 cm in diameter. Two of ten patients without mediastinal metastasis showed a false-positive study (specificity 80.0%). Thus, the accuracy was 76.5%. There was a

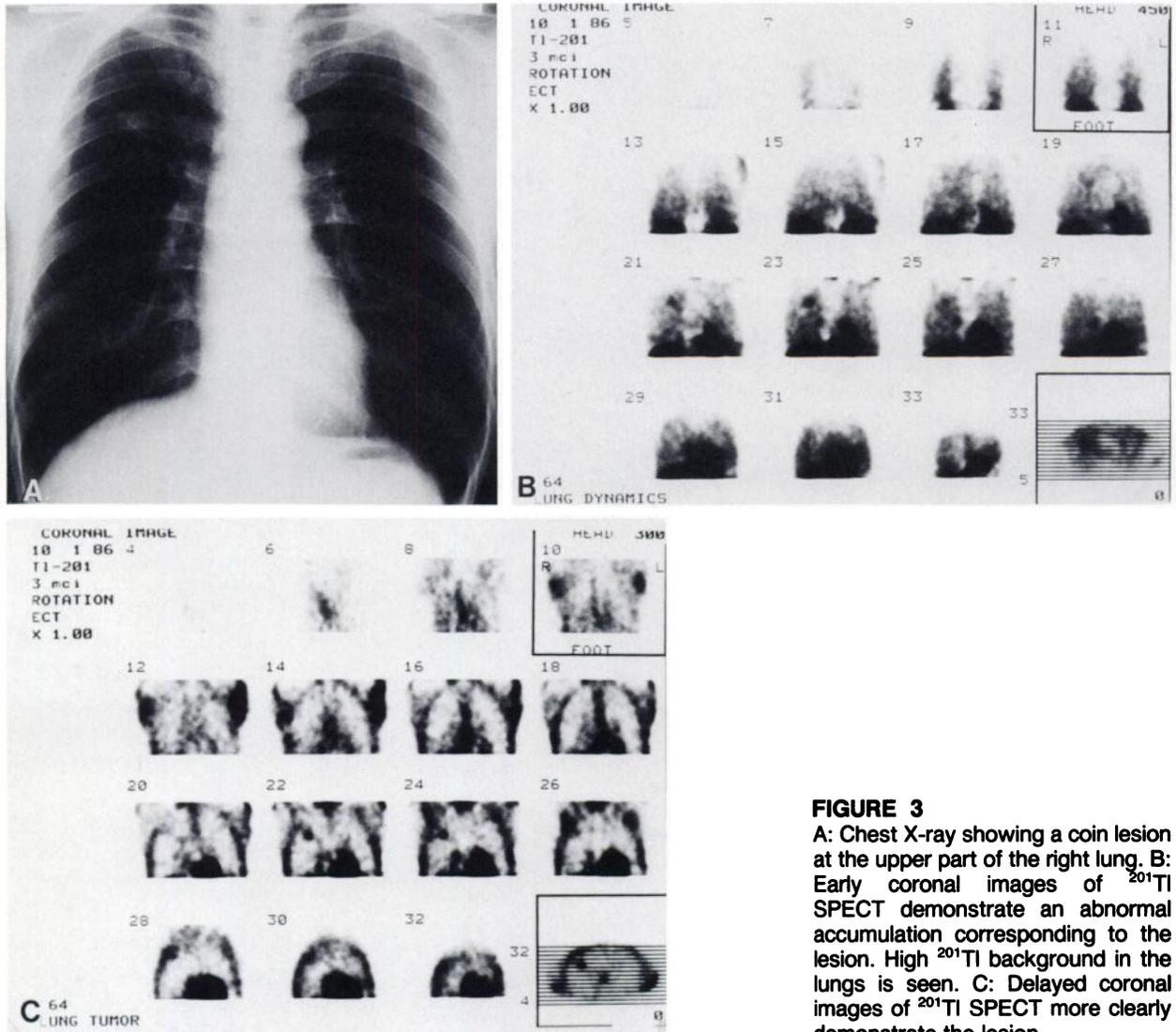


FIGURE 3
A: Chest X-ray showing a coin lesion at the upper part of the right lung. B: Early coronal images of ^{201}Tl SPECT demonstrate an abnormal accumulation corresponding to the lesion. High ^{201}Tl background in the lungs is seen. C: Delayed coronal images of ^{201}Tl SPECT more clearly demonstrate the lesion.

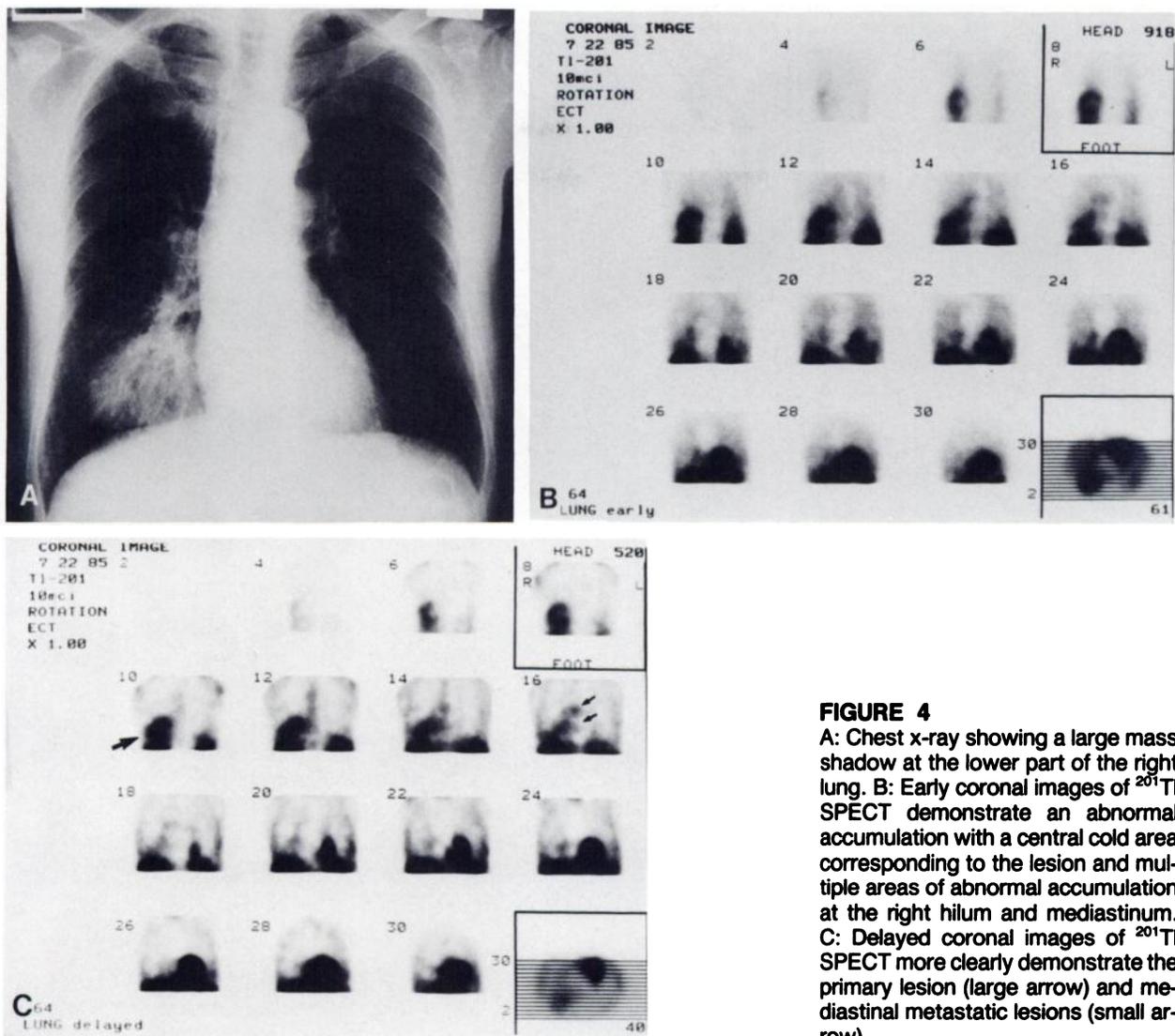


FIGURE 4

A: Chest x-ray showing a large mass shadow at the lower part of the right lung. B: Early coronal images of ²⁰¹Tl SPECT demonstrate an abnormal accumulation with a central cold area corresponding to the lesion and multiple areas of abnormal accumulation at the right hilum and mediastinum. C: Delayed coronal images of ²⁰¹Tl SPECT more clearly demonstrate the primary lesion (large arrow) and mediastinal metastatic lesions (small arrow).

positive correlation between delayed ratio and retention index ($r = 0.57$).

Representative Cases

Case 1 (Table 1 No. 15). A 47-yr-old man was admitted to our hospital to evaluate an abnormal shadow on the chest radiograph taken on the occasion of routine medical examination. A coin lesion of 1.0 cm \times 1.5 cm in diameter was noted at the upper part of the right lung (Fig. 3A). Thallium-201 SPECT demonstrated an abnormal accumulation corresponding to the pulmonary lesion on both early and delayed scans (Figs. 3B and C). No abnormal uptake was noted in the mediastinum. Delayed ratio and retention index were 2.11 and 34, respectively. Operative findings proved a 1.5 \times 1.0 \times 1.5 cm adenocarcinoma in S² of the right lung and the pathological stage was T1N0M0.

Case 2 (Table 1 No. 3). A 68-yr-old man who complained of a cough in the night for 2 mo. The chest radiograph showed a large abnormal shadow at the

lower part of the right lung (Fig. 4A). On physical examination, a lymphnode was palpable at the right neck. Thallium-201 SPECT demonstrated an abnormal accumulation with central cold area corresponding to the lesion and multiple areas of abnormal accumulation at the right hilum and the mediastinum (Figs. 4B and C). Delayed ratio and retention index were 1.57 and 23, respectively. Operative findings proved a 4.5 \times 6.5 \times 5.6 cm squamous cell carcinoma with central necrosis in S⁹ of the right lung and multiple lymph node metastases of the hilum, the mediastinum, and the right neck. The pathological stage was T2N2M1.

Case 3 (Table 1 No. 6). A 77-yr-old man complained of right chest pain. A large abnormal mass shadow associated with multiple cystic shadows was pointed out at the lower part of the right lung (Fig. 5A). Thallium-201 SPECT demonstrated an abnormal accumulation with a central cold area corresponding to the lesion on both early and delayed scans (Figs. 5B, C, and D). The delayed scan also showed an increased accumulation at

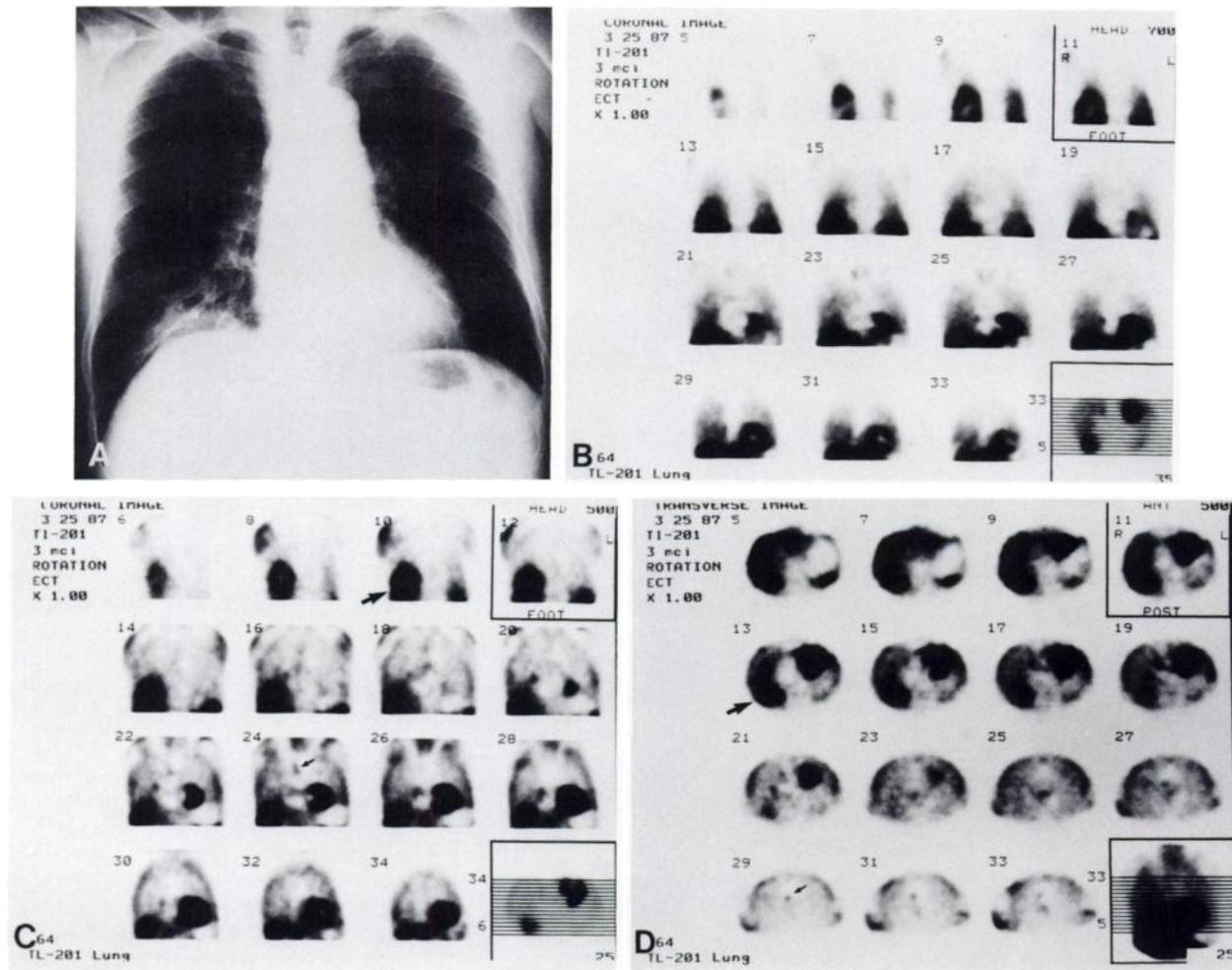


FIGURE 5

A: Chest x-ray showing a large mass shadow at the lower part of the right lung. B: Early coronal images of ^{201}Tl SPECT demonstrate a huge area with increased accumulation with a central cold area corresponding to the lesion. Faint but abnormal accumulation is seen at the mediastinum. C: Delayed coronal images of ^{201}Tl SPECT more clearly demonstrate the primary lesion (large arrow) and mediastinal metastatic lymph node (small arrow). D: Delayed transverse images of ^{201}Tl SPECT clearly demonstrate the primary lesion (large arrow) and mediastinal metastatic lymph node (small arrow).

the mediastinum (Fig. 5C and D). Delayed ratio and retention index were 1.89 and 26, respectively. A right middle and lower lobectomy with mediastinal lymph node dissection was performed. Histological findings proved a $7 \times 6 \times 8$ cm squamous cell carcinoma in S¹⁰ of the right lung and lymph node metastases of the mediastinum (a lesion of 1.5 cm, small lesions of <1.0 cm in diameter) and the right hilum. The pathologic stage was T2N2M0.

Case 4 (Table 3 No. 4). A 62-yr-old woman was admitted to our hospital because of a persistent cough and hemoptysis for 3 mo. The chest radiograph showed an 3.0×2.5 cm abnormal shadow in S⁹ of the left lung (Fig. 6A). Thallium-201 SPECT demonstrated an abnormal accumulation corresponding to the lesion on both early and delayed scans (Figs. 6B and C). However, the delayed scan showed fading radioactivity of the lesion compared to that of the early scan (Fig. 6D).

Delayed ratio and retention index were 1.45 and -9, respectively. At operation it was proven to be a bronchopneumonia in the process of fibrosis.

DISCUSSION

Our results demonstrate that [^{201}Tl]chloride accumulates well in lung cancer and that all primary lesions were clearly visualized by SPECT using a high dose of ^{201}Tl . It is noticeable that a lung cancer of $1.5 \times 1.0 \times 1.5$ cm was distinctly visualized. To the best of our knowledge, this is the first report that such a small lesion of lung cancer was visualized by radionuclide scanning. This method seems to have a potential power to visualize more smaller lesions of lung cancer. Two of seven benign conditions showed abnormal accumulation of ^{201}Tl . Since lesions of benign conditions

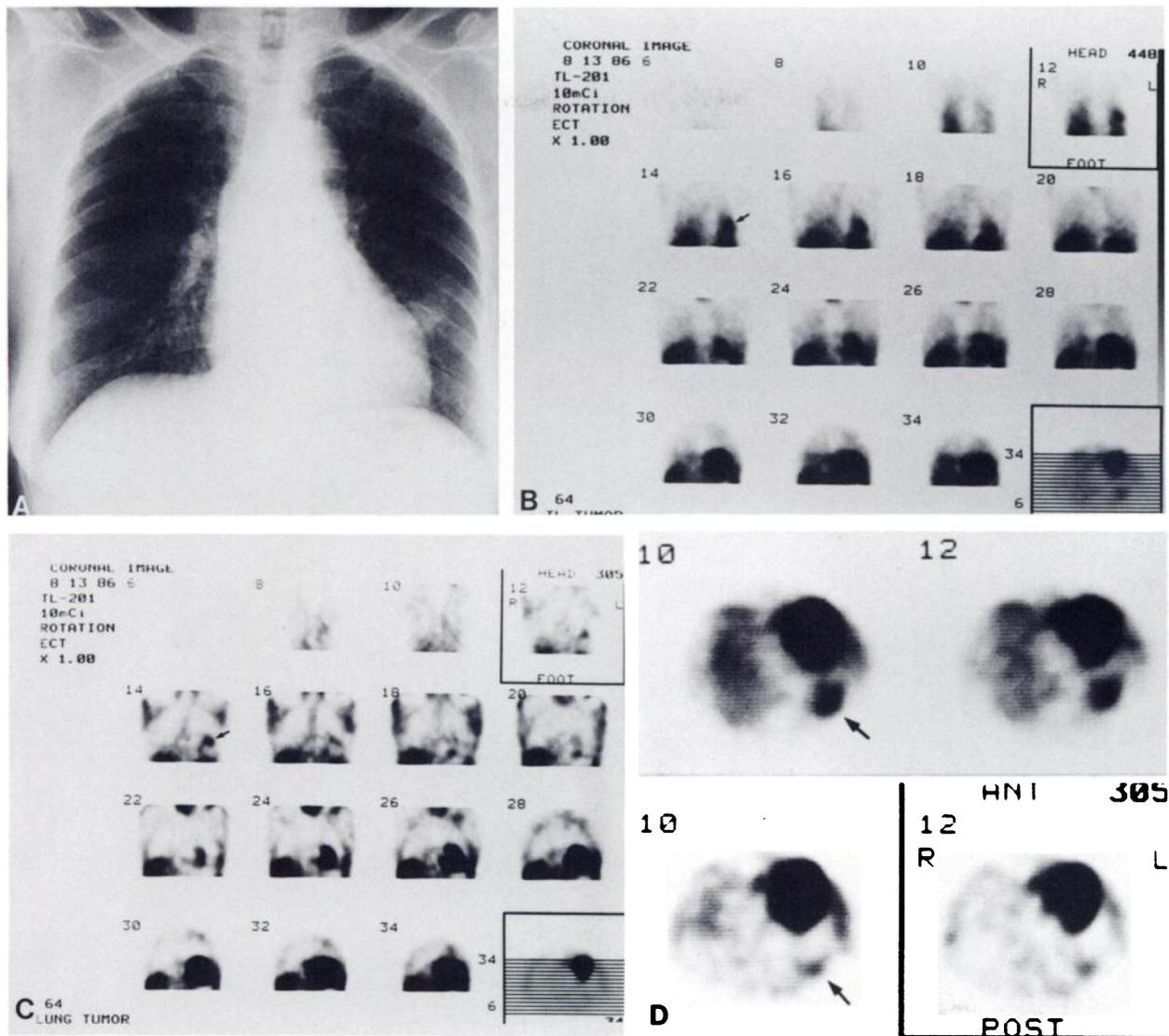


FIGURE 6

A: Chest x-ray showing an abnormal shadow at the lower part of the left lung. **B:** Early coronal images of ^{201}Tl SPECT demonstrate an abnormal accumulation corresponding to the lesion (arrow). **C:** Delayed coronal images of ^{201}Tl SPECT also demonstrate the accumulation at the same area (arrow). **D:** Abnormal accumulation of the lesion (arrow) is more prominent on ^{201}Tl early transverse images (upper row) than on delayed images (lower row).

smaller than 1.5 cm in diameter did not show any abnormal ^{201}Tl accumulation, it can be said that a lesion larger than 1.5 cm in diameter without abnormal ^{201}Tl accumulation may be benign. The delayed ratio of benign lesions with ^{201}Tl accumulation, was significantly lower than that of lung cancer and the fading appearance of radioactivity on delayed scan was noted in benign conditions. Therefore the delayed ratio and retention index might be useful in this differentiation.

In fact since we have experienced that several patients with benign conditions had a thoracotomy because lung cancer could not be ruled out; this method might be essential to the differential diagnosis of pulmonary lesions. Ando et al. (9) showed that in rats ^{201}Tl activity accumulating in inflammatory lesions decreased with

time but that ^{201}Tl washout from malignant tumors tended to be delayed. Ochi et al. (10) emphasized the usefulness of the delayed ^{201}Tl scan for the differentiation of malignant from benign tumors of the thyroid. In a clinical study of scintigraphy using ^{201}Tl chloride administered via the bronchial artery Shindo et al. (11) reported that ^{201}Tl activity in lung cancer showed a delayed washout compared to benign pulmonary lesions. However, since we have not had a chance to evaluate focal active inflammatory process, further study focussing on this point would be warranted. The accumulation of ^{201}Tl in the lesions is determined in the initial passage by the regional blood flow and the cell ability to pick up ^{201}Tl ; not much increase of accumulation in the lesions can be expected during

recirculation. Supposing that there is no significant difference in ^{201}Tl clearance from the normal lung in patients, the retention index is thought to reflect the difference in ^{201}Tl clearance from a lesion. It is likely that ^{201}Tl has a more prolonged retention in malignant pulmonary lesions than in benign lesions. With reference to histologic type in lung cancer Togawa et al. (12) reported that adenocarcinoma showed a higher accumulation than squamous cell carcinoma and small cell carcinoma on the planar images 30 min after i.v. injection of ^{201}Tl . It is interesting that there seems to be a difference in ^{201}Tl accumulation among histologic tumor types. From our results and published reports, it is apparent that the degree of ^{201}Tl accumulation to the malignant lesion and the clearance from the lesion differs in each histology. Thallium-201 clearance in squamous cell carcinoma was faster than those in adenocarcinoma and small cell carcinoma.

In the detection of mediastinal involvement from lung cancer, delayed scans were better than early scans because of a lower background of radioactivity. Considering the results that the smallest metastatic mediastinal lesion detected was 1.5 cm in diameter and two false-negative had small metastases <1.0 cm in diameter, it may be said that a sensitivity of 71.4%, a 80.0% specificity and a 76.5% accuracy on delayed scintigraphy are good results. The evaluation of hilar involvement is also important in considering surgical treatment. However, this was not performed because of difficulty in locating the lesions.

Comparing the information obtained from delayed ratio and retention index, the delayed ratio seems to be the better parameter in the differentiation of malignant and benign pulmonary lesions. The retention index may give additional information about the histological types of lung cancer. Therefore the combined use of these parameters is advocated for the histological differentiation of lung cancer. A large series of patients with surgical documentation is needed. A higher administered dose of ^{201}Tl should give rise to an increase of the count rates with an associated improvement of the signal to noise ratio for SPECT images. In addition, it would be greatly beneficial to minimize the examination time, since, in practice, the patients have to keep the arms up while the data are being acquired, accepting an increased radiation dose: kidney 11.7 rad/10 mCi, whole-body 2.1 rad/10 mCi (13).

We have tried smaller doses of 6 mCi with longer scanning time of 20 min in patients who do not complain about chest pain. It is concluded that SPECT

using a large dose of ^{201}Tl seems to be an excellent noninvasive method to detect malignant pulmonary lesions and to differentiate malignant lesions from benign conditions as well as to diagnose mediastinal metastases from lung cancer.

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