Technetium-99m-tetrofosmin imaging of lung cancer: Relationship with histopathology

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Tc-99m-tetrofosmin is an agent to delineate cancer. To elucidate the usefulness of Tc-99m-tetrofosmin scintigraphy, we analyzed the relationship between the uptake of Tc-99m-tetrofosmin and histopathology in patients with lung cancer. SPECT studies were conducted twice: 15 minutes (early scan), and 60 minutes (delayed scan), after intravenous injection of 740 MBq Tc-99m-tetrofosmin. We calculated the retention index in order to evaluate the degree of Tc-99m-tetrofosmin retention in the primary tumor. The retention indices were significantly lower in squamous cell carcinoma than those of small cell carcinoma or adenocarcinoma. As the retention indices of Tc-99m-tetrofosmin were different in each histopathology, the index might play a part as a tumor marker of lung cancer.

Key words: technetium-99m-tetrofosmin, lung cancer, histopathology

INTRODUCTION

Technetium (Tc)-99m-1,2-bis(bis(2-ethoxyethyl)phosphino)ethane (tetrofosmin) has been introduced as a myocardial imaging agent.[1] This radiopharmaceutical is now widely used in myocardial imaging and is commercially available (Myoview™, Amersham, London, United Kingdom). Tc-99m-tetrofosmin has several advantages over thallium (Tl)-201 chloride which is known as a tumor imaging agent.[1,2] Its uptake was reported to be recognized in patients with breast cancer[3,4] and thyroid cancer.[5–7] We reported previously that Tc-99m-tetrofosmin is as highly effective as thallium-201 as an agent to delineate lung cancer.[8] But Kao reported that only 61% of lung cancers were detected by Tc-99m-tetrofosmin SPECT of the chest.[9] Its sensitivity for lung malignancies is now controversial.

Tc-99m-methoxyisobutylisonitrile (MIBI) is also a use-ful tracer for lung cancer,[10] but tetrofosmin is easily labeled with Tc-99m at room temperature and therefore does not require the heating process which MIBI labeling procedure requires.[11]

In our preliminary study, the degree of retention of Tc-99m-tetrofosmin in lung carcinoma was associated with its histopathology. The uptake of Tc-99m-tetrofosmin decreased in delayed scans of squamous cell carcinoma. Adenocarcinoma and small cell carcinoma showed prolonged retention of Tc-99m-tetrofosmin on the delayed scan.[8] In the treatment of lung cancer, histopathology provides useful information for choosing the therapy and prognosis.[12–14] In the current study, we investigated the relationship between the uptake ratio of Tc-99m-tetrofosmin and histopathology in patients with lung cancer.

MATERIALS AND METHODS

Patients
Eighty-five unselected adult patients with primary lung cancer who underwent Tc-99m-tetrofosmin scanning between June, 1994 and August, 1997 at our hospital were

Table 1 Characteristics of patients with lung cancer

	Small cell carcinoma (n = 9)	Adenocarcinoma (n = 40)	Squamous cell carcinoma (n = 25)
Age (mean ± s.d. years)	9.8 ± 10.7	66.2 ± 12.1	68.1 ± 8.5
Sex			
No. of males	8	29	23
No. of females	1	11	2
Tumor size (mean ± s.d. cm)	5.0 ± 2.1	3.8 ± 2.0	4.5 ± 1.7
Tc-99m-tetrofosmin			
early ratio (mean ± s.d.)	2.08 ± 0.35	2.18 ± 0.67	2.52 ± 0.52
delayed ratio (mean ± s.d.)	2.15 ± 0.46	2.21 ± 0.74	2.29 ± 0.54
retention index (mean ± s.d.)	0.03 ± 0.07	0.03 ± 0.17	−0.09 ± 0.12

s.d.: standard deviation
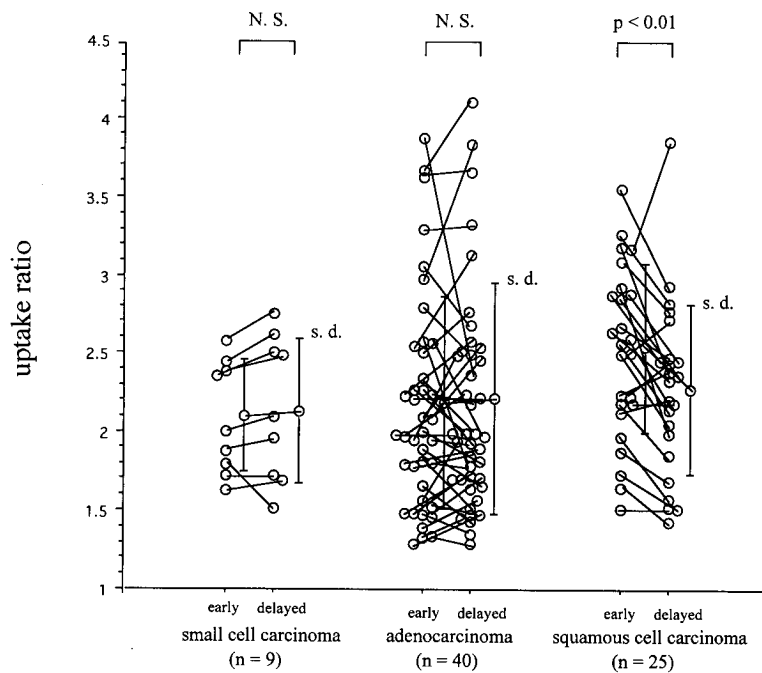
Fig. 1 Relationship between the histological type of lung cancer and the uptake ratio of Tc-99m-tetrofosmin imaging on the early scan and the delayed scan.

initially considered for this study. Lung cancer was diagnosed by cytology of endoscopic samples (catheter biopsy and bronchoalveolar lavage), and/or the histopathology of endoscopic forceps biopsy, lobectomy and pneumonectomy. Tc-99m-tetrofosmin scanning was done before cancer treatments (chemotherapy, radiation and surgery). Three patients, two with large cell carcinoma and one with carcinoid tumor, were excluded because of the limited number for statistics. Eight patients were excluded because of the lack of Tc-99m-tetrofosmin uptake. The subjects of this study therefore consisted of the remaining 74 patients (60 men and 14 women, mean ± SD ages being 67.2 ± 10.6 years). Each patient had given informed consent. Ethical committee approval was obtained for the study.

Methods

Tc-99m-tetrofosmin scans were obtained twice, at 15 minutes (early scan) and 60 minutes (delayed scan) after an intravenous injection of 740 MBq of Tc-99m-tetrofosmin. A gamma camera (SNC-510R, Shimadzu Co.) equipped with a high resolution collimator was interfaced with a dedicated computer (SCINTIPAC 7000, Shimadzu Co.). The detector aimed on the chest was rotated six degrees at a time for a total of 360 degrees. Image data were collected for 30 seconds at each stop. Transaxial images were reconstructed with a Shepp & Logan filter. Coronal and sagittal section images were assembled from transaxial images.[15] Full width at half maximum of the system was 14 mm in the central field of view. Transaxial, sagittal, and coronal images were constructed with a slice thickness of 6.4 mm.

Geographic localization of a focal uptake of Tc-99m-tetrofosmin by the tumor was visually estimated by two nuclear medicine specialists without prior knowledge of the cytological or pathological findings. The location was determined by taking into account the tumor activity with reference to findings on both the chest radiograph and CT scan. The region of interest (ROI) was determined from this information. A circular ROI was drawn inside the border of the lesion on the coronal image that showed most activity. An identical ROI was drawn over the opposite lung field, presumed to be normal.

The mean voxel counts for the ROIs were measured and the uptake ratios of the lesion to the contralateral normal lung were calculated for both the early and delayed scans.[16] We calculated the retention index[16-19] in order to quantitatively evaluate the degree of Tc-99m-tetrofosmin retention in the nodule, as follows:

$$\text{Retention index} = \frac{\text{Delayed ratio} - \text{Early ratio}}{\text{Early ratio}}$$

The histopathological classification of the tumors was based on the World Health Organization criteria.[20] We measured both the largest diameter and the smallest one of a tumor on the plain chest radiograph and then calculated the mean diameter as the tumor size.

Statistics

The comparisons between groups were done with Wilcoxon signed rank test and Mann-Whitney U test. Differences were considered significant when the P value was less than 0.05.

RESULTS

Table 1 shows the clinical findings in 9 patients with small cell carcinoma, 40 patients with adenocarcinoma and 25 patients with squamous cell carcinoma. There was no statistically significant difference between the tumor diameters and the histopathologies. Some squamous carcinomas had cavities or obstructive pneumonia. In these cases we determined ROI on the tumor itself. The uptake ratios of squamous cell carcinoma decreased on the delayed scans in comparison to the early scan ($p < 0.01$ Wilcoxon signed rank test). Those of small cell carcinomas and adenocarcinomas did not show significant change on the delayed scans in comparison to the early scan (Fig. 1). The retention indices were significantly lower in squamous cell carcinoma than those of small cell carcinoma and adenocarcinoma (retention index, mean ± SD being −0.09 ± 0.12 in squamous cell carcinoma, 0.03 ±
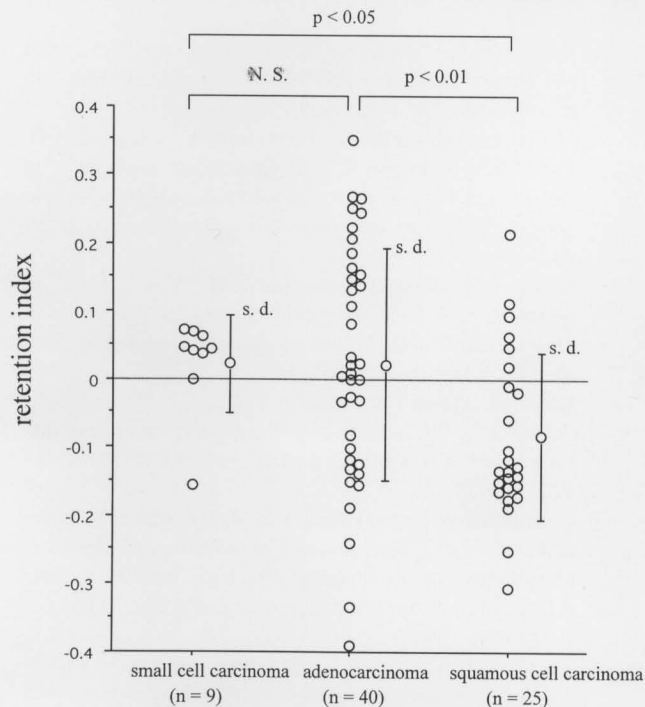

Fig. 2 Relationship between the histological type of lung cancer and the retention index of Tc-99m-tetrofosmin imaging.
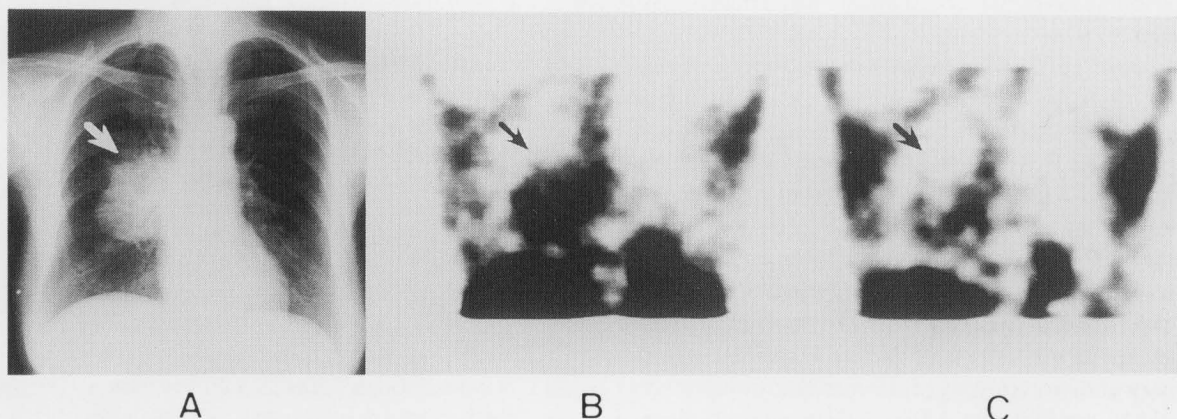

Fig. 3 Images in a 72-year-old female with squamous cell carcinoma. Plain chest radiograph showed a pulmonary nodule (arrow) (A). Tc-99m-tetrofosmin SPECT images on the early scan (B) and on the delayed scan (C) showed an abnormal accumulation (arrow) corresponding to the pulmonary lesion.

0.07 in small cell carcinoma, and 0.03 ± 0.17 in adenocarcinoma) (Fig. 2). The retention indices did not significantly correlate with the grade of differentiation in the squamous cell carcinoma.

Representative case (Fig. 3)
A 72-year-old female was admitted for evaluation of an abnormal shadow on a chest radiograph. The chest radiograph revealed a 7.5 × 6.2 cm tumor shadow in the right lower lobe (A). Tc-99m-tetrofosmin images on the early scan (B) and on the delayed scan (C) demonstrated an abnormal accumulation corresponding to a pulmonary lesion. The uptake ratios on the early scan, on the delayed scan and retention index of Tc-99m-tetorofosmin were 3.18, 2.38 and −0.252 respectively. Pathological examination proved squamous cell carcinoma and the clinical stage was T2N1M1 (Stage IV).

DISCUSSION

The current study demonstrated that squamous cell carcinoma showed a tendency to washout of Tc-99m-tetrofosmin compared to those of small cell carcinoma and adenocarcinoma. The biological characteristics of lung cancer vary according to the individual and histopathology is one of the important factors in determining the nature of the tumor.[21-23] In particular, squamous cell carcinoma has a lower metastatic potential than other types.[14,24] The histopathology should be taken into account when choosing the method of treatment.[12-14] The retention index of Tc-99m-tetrofosmin might be a useful clinical marker because of its higher washout tendency in squamous cell carcinoma.

According to the results of a previous experiment, Tc-99m-tetrofosmin is excreted from malignant cells by P-glycoprotein, an energy-dependent efflux pump.[25] Scagiotti et al. reported that in the immunoreactivity of P-glycoprotein, high grade expression (more than 10% positive cells) was recognized in 23 out of 43 squamous cell carcinomas of the lung, a greater percentage than the 7 out of 26 adenocarcinomas of the lung.[26] The enhanced washout of Tc-99m-tetrofosmin in squamous cell carcinoma might be associated with such a higher grade expression of P-glycoprotein.

In addition, P-glycoprotein is encoded by the multidrug resistance (MDR) gene and is related to resistance to a variety of chemotherapeutic agents.[25] This finding does indicate the potential usefulness of the retention index of Tc-99m-tetrofosmin in evaluating the presence of P-glycoprotein and thus multidrug resistance in the tumor which in turn may help to predict the response to chemotherapy and selecting its regimens, but further studies should be conducted to define the clinical usefulness of Tc-99m-tetrofosmin scintigraphy.

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