Evaluation of radiotherapeutic response in non-small cell lung cancer patients by technetium-99m MIBT and thallium-201 chloride SPET

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Abstract. The purpose of this study was to investigate the relationship between technetium-99m hexakis-2-methoxyisobutylisonitrile (^{99m}Tc-MIBI) accumulation in tumours and response to radiotherapy in non-small cell lung cancer patients in comparison with the findings obtained using thallium-201 chloride (^{201}Tl). Simultaneous dual single-photon emission tomography (SPET) imaging with 600 MBq ^{99m}Tc-MIBI and 111 MBq ^{201}Tl was performed in 31 patients with biopsy- or sputum cytology-proven lung cancer. SPET images were acquired 15 min (early) and 2 h (delayed) after injection, and the early ratio, delayed ratio and retention index were measured. The tumours were classified into two groups on the basis of follow-up computed tomography (CT): responders (at least 50% reduction in tumour size) and non-responders (little or no change in tumour size). The mean (± SD) values of early ratio, delayed ratio and retention index using ^{99m}Tc-MIBI SPET were 3.0±1.1, 2.7±1.0 and –9.5±12.7, respectively, in responders and 2.4±0.7, 2.0±0.5 and –18.4±9.0, respectively, in non-responders. The corresponding values using ^{201}Tl chloride SPET were 3.7±1.0, 4.7±1.5 and 24.2±22.1 in responders and 3.3±1.2, 4.0±1.3 and 20.4±20.5 in non-responders. Using ^{99m}Tc-MIBI, the delayed ratio and retention index in responders were significantly higher than those in non-responders (P<0.01 and P<0.05, respectively). The results of this study indicate that patients with higher delayed ratio and retention index values using ^{99m}Tc-MIBI SPET are likely to respond better to radiotherapy than those with lower values. ^{99m}Tc-MIBI SPET may give an indication of the short-term response to radiotherapy in patients with non-small cell lung cancer.

Key words: Non-small cell lung cancer – Dual single-photon emission tomography – Technetium-99m hexakis-2-methoxyisobutylisonitrile – Thallium-201 chloride – Radiotherapy

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Introduction

In non-small-cell lung cancer, surgery offers the greatest chance of obtaining complete remission if performed very early in the course of the disease (UICC stages I and II) [1, 2]. Unfortunately, less than 30% of patients are eligible for curative resection. Radiotherapy and chemotherapy can be used as palliative treatment in patients with advanced disease (UICC stages III and IV) [1, 2]. However, major obstacles to successful therapy are the failure of cancer to respond to treatment and the development of resistance.

Morphological imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) have problems in the evaluation of treatment response and in establishing whether a residual mass is due to residual tumour or local recurrence. Nuclear medicine imaging techniques may be applicable to the evaluation of therapeutic efficacy and the prediction of therapeutic response in cancer.

During the past decade, thallium-201 chloride (^{201}Tl) single-photon emission tomography (SPET) has attracted attention as a means of detecting lung cancer [3, 4]. Non-cardiac uses of technetium-99m hexakis-2-methoxyisobutylisonitrile (^{99m}Tc-MIBI), such as visualization of lung cancer, have also been investigated [5, 6, 7, 8]. However, there have been no reports on the correlation between ^{99m}Tc-MIBI scintigraphy and radiotherapeutic response. In this study, we evaluated the relationship between ^{99m}Tc-MIBI accumulation in tumours and response to radiotherapy in non-small cell lung cancer patients in comparison with the findings obtained using ^{201}Tl.

Materials and methods

Patients. Thirty-one patients (30 males and 1 female, age range 31–83 years) with non-small cell lung cancer were investigated before radiotherapy between April 1995 and October 1999. None of the patients had received chemotherapy before the dual-isotope study. There were 24 patients with squamous cell carcinomas, five with adenocarcinomas and two with large cell carcinomas. The patients were divided into two groups according to tumour size: small tumour group (<5 cm) and large tumour group (≥5 cm). Diagnosis was made by cytological or histopathological analysis of sputum, CT-guided needle biopsy specimens or endoscopic samples. All patients received conventional 10-MV X-ray radiotherapy with a linear accelerator. A radiation dose ranging from 50 to 70.8 Gy was given depending on the tumour size and location and the patient's physical condition. All patients underwent simultaneous dual-isotope SPET of the chest with ^{99m}Tc-MIBI and ^{201}Tl. After the purpose of the study had been explained, each patient gave their informed consent.

On the basis of a follow-up CT examination performed within 4 weeks after radiotherapy, patients were classified into two groups: responders and non-responders. In responders, tumours either disappeared or showed a reduction in mass of at least 50% (complete response or partial response). In non-responders, tumours showed little or no change in mass or progression.

Simultaneous dual-isotope imaging. Dual-isotope imaging was carried out with a large field of view gamma camera equipped with a high-resolution parallel-hole collimator (Picker Prism 2000). This camera was interfaced to a dedicated computer (Odyssey). Doses of 600 MBq of ^{99m}Tc-MIBI and 111 MBq of ^{201}Tl were injected intravenously. Early SPET acquisition was performed 15 min after the injection of each radioisotope, while delayed SPET images were acquired 2 h after injection. For SPET images of the chest, 72 projections were obtained using a 64× 64 matrix at 45 s per view. Three energy analysers were used for acquisition. These were set at: 71 keV with a 15% window for ^{201}Tl images, 90 keV with a 10% window for scatter images, and 140 keV with a 15% window for ^{99m}Tc images. The projection data were processed with a two-dimensional low-pass filter, and then corrected for the contamination scatter. Image reconstruction was done using filtered backprojection with a ramp filter. Transverse, coronal and sagittal sections were reconstructed.

Contamination scatter correction for each radionuclide. As this study involved simultaneous dual-isotope imaging, the raw data at the 71-keV window were contaminated by ^{99m}Tc Compton scatter, and the raw data at the 140-keV window included the 167-keV γ-ray count of ^{201}Tl. To eliminate such contamination scatter, the raw ^{99m}Tc and ^{201}Tl data were corrected according to the equations in each pixel. Simultaneous dual-isotope studies were performed using the original size and shape of the phantom [9]. Measurements of scatter and cross-talk coefficients were carried out according to our previously reported method [9]. Briefly, the scatter correction coefficient, α, was measured to be 1.07, whereas the cross-talk correction coefficient, β, was measured to be 0.14. The corrected counts in the 71-keV window for ^{201}Tl images, *a*, and in the 140-keV window for ^{99m}Tc images, *b*, were calculated as follows: $a=A-\alpha C$; $b=B-\beta a$, where *A*, *B* and *C* stand for the raw counts in the 71-, 140- and 90-keV windows, respectively.

Data analysis. SPET images were compared with chest CT and accumulation in lung tumours was evaluated by two nuclear medicine physicians (Y.N. and Y.Y.). Quantitative analysis of the abnormal uptake of the two radiopharmaceuticals was performed by drawing identical regions of interest (ROIs) over the tumour uptake (T) and contralateral normal lung areas (N) on one transverse section which demonstrated the lesion most clearly and which was carefully selected on both early and delayed images. The mean ROI values (total counts/total pixels) were measured and the ratios of tumour to contralateral uptake (T/N ratios) were obtained. Below we refer to the T/N ratio of the early image as the "early ratio" and to the T/N ratio of the delayed image as the "delayed ratio". To quantitatively evaluate the degree of retention in the lesion, the retention index was calculated using the following formula: [(delayed ratio – early ratio)/early ratio]×100. Furthermore, we attempted to calculate the ^{201}Tl/^{99m}Tc-MIBI ratio in order to ascertain the differences in tumour accumulation between ^{201}Tl and ^{99m}Tc-MIBI. The values of the T/N ratio, the retention index and the ^{201}Tl/^{99m}Tc-MIBI ratio were expressed as mean±SD. To test for differences between these parameters, Student's *t* test was used. Results were considered significant when the *P* value was below 0.05.

Table 1. The mean values of ER, DR and RI in the responder and non-responder groups of patients for ^{99m}Tc-MIBI SPET

Follow-up group	No.	Tumour size (cm)	^{99m}Tc-MIBI SPET		
			ER	DR	RI
Responder	13	4.2±1.4	3.0±1.1	2.7±1.0*	–9.5±12.7**
Non-responder	18	5.0±1.9	2.4±0.7	2.0±0.5	–18.4±9.0

ER, Early ratio; DR, delayed ratio; RI, retention index
*P<0.01 and **P<0.05 compared with the corresponding non-responder group (Student's *t* test)

Table 2. The mean values of ER, DR and RI in the responder and non-responder groups of patients for ^{201}Tl SPET

Follow-up group	No.	Tumour size (cm)	^{201}Tl SPET		
			ER	DR	RI
Responder	13	4.2±1.4	3.7±1.0	4.7±1.5	24.2±22.1
Non-responder	18	5.0±1.9	3.3±1.2	4.0±1.3	20.4±20.5

ER, Early ratio; DR, delayed ratio; RI, retention index

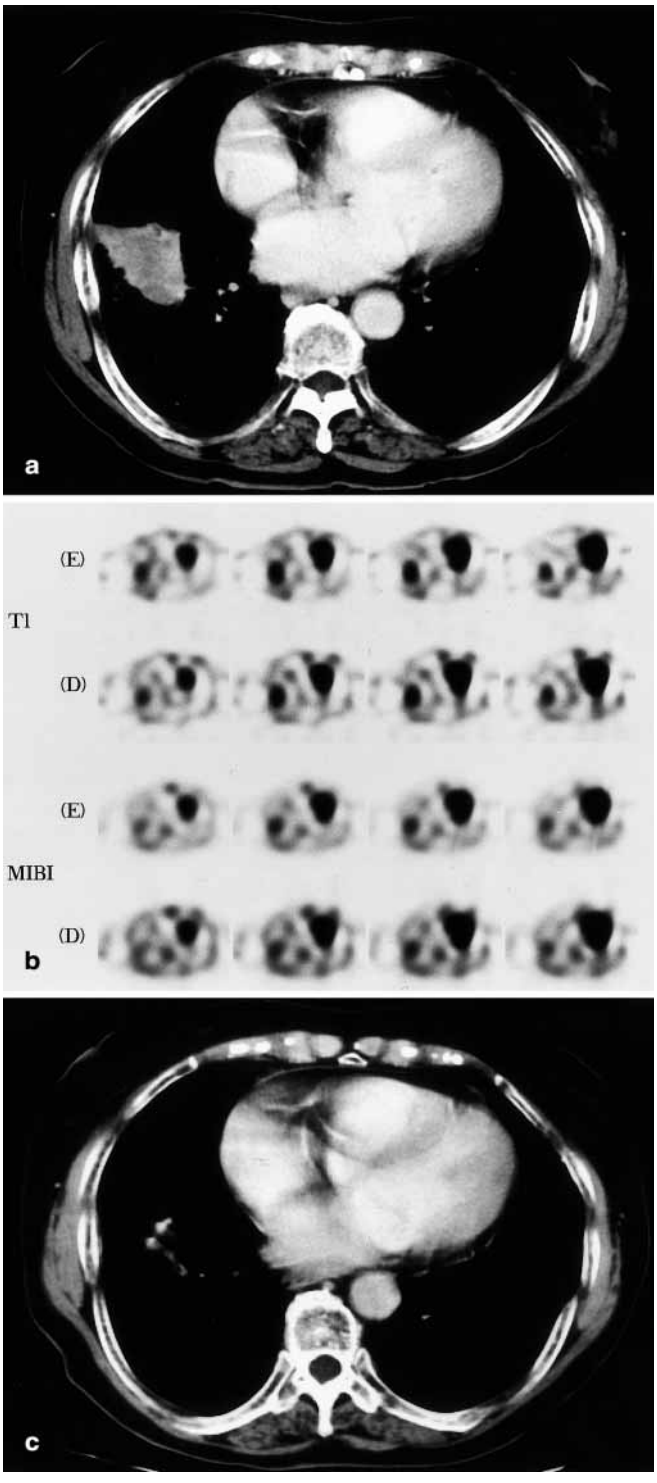

Fig. 1a–c. Typical case in the responder group: an 80-year-old female with squamous cell carcinoma. **a** Chest CT before radiotherapy shows a mass at the right middle lobe. **b** Transverse ^{201}Tl and ^{99m}Tc-MIBI SPET images both demonstrate an area of abnormal accumulation corresponding to the lesion. With ^{201}Tl the early ratio was 4.3, the delayed ratio 4.9 and the retention index 14.0. With ^{99m}Tc-MIBI, the early ratio was 2.7, the delayed ratio 2.9 and the retention index 7.4. **c** After radiotherapy (total dose 65.8 Gy), the patient was classified as a responder. *E*, Early image; *D*, delayed image

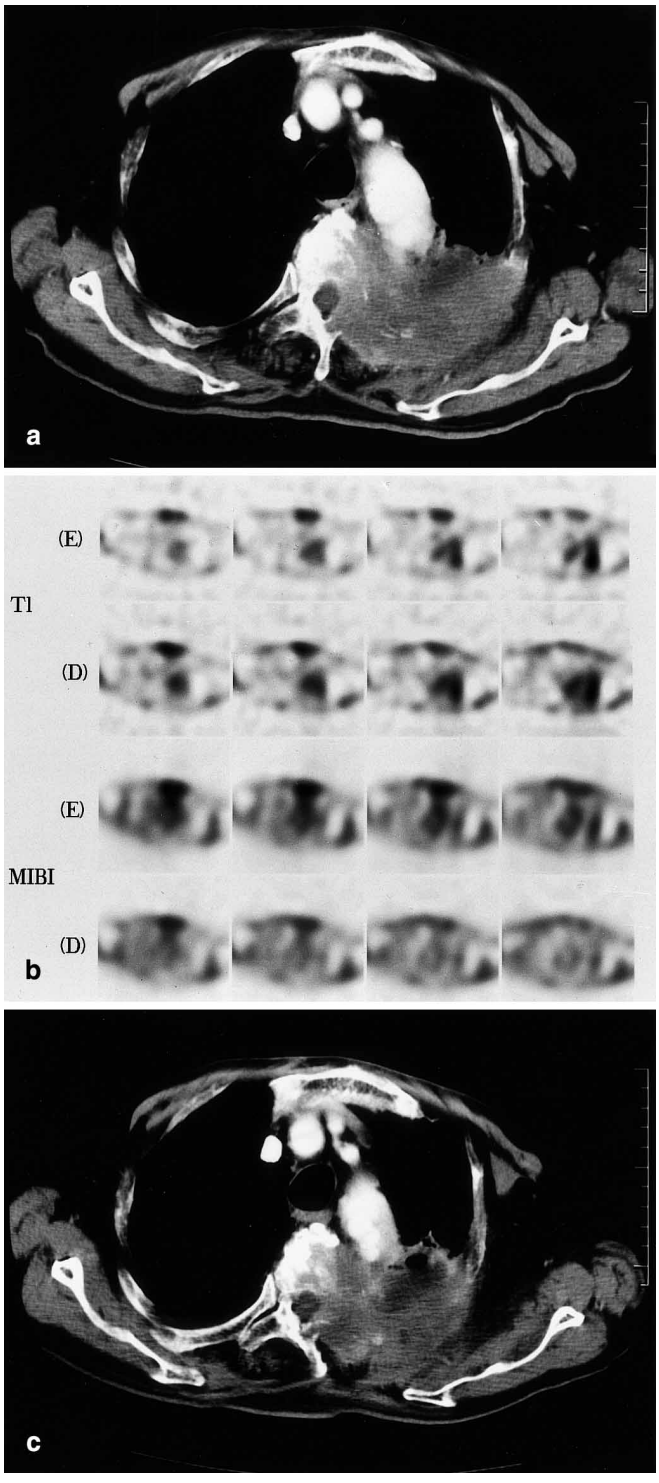

Fig. 2a–c. Typical case in the non-responder group: a 75-year-old male with squamous cell carcinoma. **a** Chest CT before radiotherapy shows a mass at the upper lobe of the left lung, invading the chest wall. **b** Early and delayed SPET images acquired with ^{201}Tl and ^{99m}Tc-MIBI demonstrate an area of abnormal accumulation corresponding to the lesion. With ^{201}Tl the early ratio was 3.7, the delayed ratio 4.2 and the retention index 13.5. With ^{99m}Tc-MIBI, the early ratio was 2.5, the delayed ratio 1.9 and the retention index –24.0. **c** After radiotherapy (total dose 50 Gy), the patient was classified as a non-responder. *E*, early image; *D*, delayed image

Table 3. The mean values of ER, DR and RI in the responder and non-responder groups of patients for ^{99m}Tc-MIBI SPET according to tumour size

Follow-up group	Small tumour group (<5 cm)			Large tumour group (≥5 cm)		
	ER	DR	RI	ER	DR	RI
Responder	2.4±0.6	2.2±0.7	–6.1±16.5	3.8±1.1**	3.3±0.9*	–13.3±4.9**
Non-responder	2.0±0.4	1.7±0.4	–12.4±7.0	2.8±0.8	2.2±0.5	–20.8±7.3

ER, Early ratio; DR, delayed ratio; RI, retention index
*P<0.01 and **P<0.05 as compared with the corresponding non-responder group (Student's t test)

Table 4. The mean values of ER, DR and RI in the responder and non-responder groups of patients for ^{201}Tl SPET according to tumour size

Follow-up group	Small tumour group (<5 cm)			Large tumour group (≥5 cm)		
	ER	DR	RI	ER	DR	RI
Responder	3.4±1.1	4.2±1.5	22.3±25.2	4.1±0.7	5.2±1.4	26.4±19.8
Non-responder	2.5±0.6	3.0±1.1	18.6±21.1	4.0±1.1	4.7±1.1	20.7±22.0

ER, Early ratio; DR, delayed ratio; RI, retention index

Results

There were 13 patients in the responder group and 18 in the non-responder group. The maximum tumour diameter on CT ranged from 1.5 to 6.0 cm for the responder group and from 1.2 to 9.0 cm for the non-responder group. There was no significant difference in tumour size between the two groups.

The mean values of the early ratio, delayed ratio and retention index are shown in Tables 1 and 2 for ^{99m}Tc-MIBI SPET and ^{201}Tl SPET, respectively. The delayed ratio using ^{99m}Tc-MIBI SPET in the responder group (Fig. 1) was significantly higher (P<0.01) than that in the non-responder group (Fig. 2, Table 1). There was also a significant difference in the retention index using ^{99m}Tc-MIBI SPET between the responder and non-responder groups (P<0.05) (Table 1). There were no significant differences in either ratio or the retention index between the two groups using ^{201}Tl SPET images (Table 2).

The mean values of the early ratio, delayed ratio and retention index in the responder and non-responder groups according to tumour size using ^{99m}Tc-MIBI and ^{201}Tl are shown in Tables 3 and 4, respectively. In the large tumour group, using ^{99m}Tc-MIBI all three parameters were significantly higher in the responder group than in the non-responder group (P<0.01–0.05) (Table 3). On the other hand, in the small tumour group there were no significant differences in either ratio or in the retention index between the responder and non-responder groups (Table 3). Using ^{201}Tl there were no significant differences in either ratio or the retention index between the responder and non-responder groups according to tumour size (Table 4).

There was no significant correlation between T/N ratio and histological type of tumour in either the ^{99m}Tc-MIBI or the ^{201}Tl images.

The mean (±SD) values of the ^{201}Tl/^{99m}Tc-MIBI ratio for early and delayed images were 1.3±0.3 and 1.8±0.6, respectively, in the responder group. The corresponding values in the non-responder group were 1.4±0.5 and 2.0±0.7, respectively. The ^{201}Tl/^{99m}Tc-MIBI ratio did not differ significantly between the two groups, but there was a tendency for the ^{201}Tl/^{99m}Tc-MIBI ratio of the responder group to be lower than that of the non-responder group.

Discussion

When lung cancer is suspected, investigations are aimed at the establishment of a diagnosis, the determination of operability and assessment of the patient's fitness for surgery. Radionuclide imaging with gallium-67, ^{201}Tl and positron-emitting radiopharmaceuticals is utilized in lung cancer for staging (by establishing the presence or absence of hilar and mediastinal disease and distant metastasis), follow-up (by showing recurrence or residual disease) and monitoring the response to therapy. Higashi et al. reported the significance of ^{67}Ga scintigraphy in estimation of the radiosensitivity of primary lung cancer [10]. Nishigauchi described the utility of ^{201}Tl scintigraphy in assessing the radiotherapeutic effect on rabbit VX-2 tumours [11]. The usefulness of ^{201}Tl SPET in the evaluation of treatment effect (radiotherapy alone or combination of chemotherapy and radiotherapy) in lung cancer patients was reported by Yamaji [12]. He concluded that the retention index after treatment was useful in evaluation of the therapeutic effect for primary lung cancer [12]. Ichiya and co-workers showed that in patients with bronchogenic carcinoma, lesions with a higher fluorodeoxyglucose uptake on positron emission tomography responded better to radiotherapy than did

those with a lower uptake [13]. Positron emission tomography, however, has its limitations due to high cost and poor availability.

^{99m}Tc-MIBI is a lipophilic cation primarily used for myocardial perfusion imaging. Since the late 1980s, an increasing number of reports have appeared describing ^{99m}Tc-MIBI uptake in several carcinomas, including lung tumours [7, 8, 9, 10, 11, 12]. Moretti et al. reported that ^{99m}Tc-MIBI scintigraphy may be used to monitor acquired drug resistance induced by chemotherapy [14]. P-glycoprotein (Pgp) overexpression has been associated with clinical evidence of drug resistance.

To our knowledge, this is the first study to compare the clinical utility of ^{99m}Tc-MIBI and ^{201}Tl SPET images in the prediction of radiotherapeutic response in non-small cell lung cancer. In this study, no significant difference was observed between responder and non-responder groups when using ^{201}Tl SPET. Although, as shown in our previous study, ^{201}Tl SPET is more useful than ^{99m}Tc-MIBI SPET for scintigraphic visualization of the lesions [5], results of the former technique were not predictive of the response to subsequent radiotherapy. On the other hand, when using ^{99m}Tc-MIBI SPET the delayed ratio and retention index values in the responder group were significantly higher than those in the non-responder group. Thus a single pre-radiotherapy study with ^{99m}Tc-MIBI may be adequate for predicting therapeutic results, whereas using ^{201}Tl studies both pre- and post-radiotherapy studies are required to determine the effect of treatment.

Hypoxia in a tumour is thought to be an important factor in resistance to radiation therapy and chemotherapy. Thus, recognition of the hypoxic tumour fraction can have implications for therapy. There has been much interest in the detection of tumour hypoxia by radionuclide imaging techniques based on selective retention of the radionuclide in regions of hypoxia. The major radiolabelled compounds used for this purpose are fluorine-18 misonidazole and ^{99m}Tc-HL91 [15, 16]. In contrast, tumour-seeking agents such as ^{99m}Tc-MIBI and ^{201}Tl seem to represent the tumour vascularity. In the present study, although the differences were not significant, there was a tendency for the early ratio of ^{99m}Tc-MIBI and both the early and delayed ratios of ^{201}Tl to be higher in the responder group than in the non-responder group. These results may indicate that patients responding to radiotherapy had a better blood supply, membrane transport and metabolism and were thus more oxygenated – hence the better response.

Mote et al. reported that multidrug-resistant HL60 cells which express Pgp have increased radiation resistance and so more closely reflect the type of extended drug and radiation resistance encountered in the treatment of cancer [17]. Radiotherapy can lead to overexpression of transmembrane Pgp [18, 19, 20]. It has been demonstrated that treatment of a tumour by radiotherapy can give rise to tumour resistance to methotrexate, 5-fluorouracil and doxorubicin [21]. An increase in intracellular glutathione concentrations provides an explanation for tumour resistance to both chemotherapy and radiotherapy [21]. The aforementioned observations show that resistance induced in tumours by chemotherapy and radiotherapy may be an interactive phenomenon. Pauwels et al. reported that chemoresistant bladder cell lines may also be radioresistant [18].

Resistance can be intrinsic or acquired [22]. In the present study, the lower ^{99m}Tc-MIBI ratio before radiotherapy in the non-responder group may have been related to intrinsic resistance, because none of these patients had received chemotherapy or radiotherapy before the SPET study. On the other hand, Pgp may play a major role in acquired resistance [22] although it has been postulated that overexpression of Pgp is not related to intrinsic resistance.

There are several mechanisms whereby cells may become resistant to radiation and drugs, such as increased DNA repair, binding of free radicals by glutathione, increased glutathione-*S*-transferase and increased expression of bcl-2 leading to decreased ability to undergo apoptosis. Furthermore, p53 plays a significant role in chemo- and radioresistance [23, 24]. However, the lack of sensitization by radiation immediately after treatment confirms that it is not simply a direct effect. We could not study the correlation between immuno-histochemical analysis and the grade of differentiation of the tumour because of the small size of the biopsy specimens.

The present study indicates that ^{99m}Tc-MIBI SPET may be of value for the prediction of radiotherapeutic efficacy, which is currently difficult by means of morphological imaging techniques such as CT and MRI. Vecchio et al. reported that determination of the fractional retention of ^{99m}Tc-MIBI may be used as a functional test for Pgp expression in breast cancer [25]. The results of the present study indicate that patients with higher delayed ratio and retention index values using ^{99m}Tc-MIBI SPET are likely to respond better to radiotherapy than those with lower values.

We conclude that ^{99m}Tc-MIBI SPET may give an indication of the short-term response to radiotherapy in patients with non-small cell lung cancer. Further evaluation in a larger population is needed to assess the relation between ^{99m}Tc-MIBI results and the effectiveness of radiotherapy.

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