Assessment of non-small cell lung cancer viability and necrosis with three radiopharmaceuticals

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Abstract

Assessment of tumor viability and necrosis of non-small cell lung cancer and detection of distant metastases are important for diagnosis, staging, monitoring the response to treatment and planning long-term management. *We performed* scintigraphy on patients with non-small cell lung cancer to determine the utility of three tumor targeting tracers for diagnosing primary lung cancer, for differentiating viable from necrotic tumor tissue and for detecting distant bone and soft tissue metastases. *Our patients* were divided into groups. Group A consisted of 27 patients, 25 male and 2 female, mean age 59 years, range from 35 to 72 years. These patients underwent radioimmunoscintigraphy (RIS) using monoclonal antibody against human milk fat globule labeled with technetium-99m (^{99m}Tc). Group B consisted of 23 patients, 21 male and 2 female, mean age 56 years, range: 37 to 70 years. Group C consisted of 24 patients, 20 male and 4 female, mean age 58 years, range: 35 to 74 years. Both Groups B and C underwent chest and whole-body scintigraphy with 555 MBq of ^{99m}Tc-sestamibi (^{99m}Tc-S) and 111 MBq of thallium-201 chloride (^{201}TlCl), respectively. Tumor to non-tumor ratio was calculated. *Our findings* show that RIS had 52% sensitivity in detecting primary non-small cell lung cancer. In contrast, the sensitivity of ^{99m}Tc-S and of ^{201}Tl scintigraphy was 87% and 88%, respectively. High uptake of all three radiopharmaceuticals was found in 6 patients with distant soft tissue and bone tissue metastases and in 1 patient with brain metastasis. Mean tumor to non-tumor ratios were similar: for RIS 1.7±0.4, for ^{99m}Tc-S 1.6±0.3 and for ^{201}Tl 1.6±0.2. *In conclusion*: ^{99m}Tc-S and ^{201}Tl scintigraphy are superior to RIS for detecting non-small primary lung cancers and potentially clinically useful methods for detecting primary lung cancer as above as well as bone and soft tissue metastases.

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Introduction

Comprehensive evaluation of patients with non-small cell lung cancer (NSCLC), accurate staging of the disease with detection of all distant metastases, and identification of the tumor cell type, are important for prospective treatment options and prognosis. Further assessment of tumor viability and necrosis is also essential for monitoring the response to treatment and planning long-term management.

Noninvasive techniques commonly used for assessing lung disease are chest X-rays, axial computed tomography (CT), magnetic resonance imaging (MRI), and various nuclear medicine procedures, including positron emission tomography (PET). Chest X-ray films are usually the first test in patients with suspected lung lesions, followed if necessary by CT and/or MRI. PET with fluorine-18-fluorodeoxyglucose (^{18}F-FDG) has also been used for diagnosis, staging, and for detecting recurrence of lung cancer. However, using PET is still an expensive and not widely available imaging modality in most nuclear medicine centers [1, 2]. Another disadvantage is that ^{18}F-FDG accumulates not only in malignant tumors but also in inflammatory tissues [3, 4]. Single photon emission tomography (SPET), with tumor directed radiopharmaceuticals, such as gallium-67 (^{67}Ga), thallium-201 (^{201}Tl), technetium-99m-sestamibi (^{99m}Tc-S), and tumor associated monoclonal antibodies, may determine the size of the primary tumor, its possible extent to mediastinum [5, 6] tumor viability and necrosis. Radio-immunoscintigraphy (RIS), using labeled antibodies or their fragments against tumor antigens, can detect the presence of primary and metastatic malignant tissue [7]. Antibodies against epithelial antigens, such as human milk fat globule (HMFG1) antigen, have been applied in studies of ovarian, colorectal, breast, and non-small cell lung cancers [8]. The suggested limitations of RIS include: the low absolute amount of antibodies targeting the tumor, the presence of high blood pool radioactivity, the nonspecific antibody localization in the tumors, and their accumulation in healthy tissue [9].

Several studies investigated and compared ^{201}Tl and ^{99m}Tc-S scintigraphy in evaluation of primary lung cancer [1, 10, 11]. However, comparative studies examining the diagnostic utility of these scintigraphic techniques against RIS in patients with NSCLC, are limited. The purpose of our study was not only to evaluate and compare the sensitivity of RIS with ^{99m}Tc-HMFG1-labeled monoclonal antibody (^{99m}Tc-HMFG1-MoAb), and of chest and whole-body ^{201}Tl and ^{99m}Tc-S scintigraphy for detecting primary NSCLC but also to differentiate tumor viability and necrosis, and detect distant bone and soft tissue metastases.

Subjects and methods

Subjects

We have investigated 74 patients with NCSLC. Bronchoscopy with biopsy and pathology verification of the typed lung cancer, served as a gold standard for diagnosing primary disease. All patients had either chest X-ray films or chest CT. None of the patients had received radiotherapy or chemotherapy before the study. Lung lesions were staged according to TNM classification. Patients were divided into three groups and prospectively allocated to RIS with ^{99m}Tc-HMFG1-MoAb, and chest and whole-body ^{201}Tl and ^{99m}Tc-S scintigraphy based on demographic and clinical data. Group A included 27 patients, mean age 59 years (from 35 to 72 years), with 15 squamous cell, 2 large cell and 10 adenocarcinomas. There were 25 men and two women. According to tumor stage, there were 4 patients in stage IIIA, 16 in IIIB and 7 in stage IV. All patients in this Group underwent RIS with ^{99m}Tc-HMFG1-MoAb. Group B consisted of 23 patients, mean age 56 years (37 to 70 years), with pathology proven NSCLC (14 squamous cell, 3 large cell and 6 adenocarcinomas), 21 men and two women. All patients in Group B underwent chest and whole-body scintigraphy with ^{99m}Tc-S. Distribution of Group B patients according to the tumor stage was: 3 in stage IIIA, 15 in IIIB and 5 in stage IV. Group C consisted of 24 patients with mean age 58 years (35 to 74 years), 20 men and 4 women. These patients underwent chest and whole-body scintigraphy with ^{201} Tl. In this group, 15 patients had pathology proven squamous cell, 2 large cell, and 7 adenocarcinomas. Tumor stage was as follows: 2 patients in IIIA, 15 in stage IIIB and 3 in stage IV. According to the chest CT the smallest tumor size was 2×2 cm and the largest 11×9cm.

Methods

CT imaging of the chest

All CT scans were performed by the helical CT protocol for detection/staging thoracic neoplasm with the intravenous (i.v.) infusion of 120 ml of contrast medium at a rate of 2 mL/s. The spiral CT scans were acquired from the apex of the lung to the suprarenal gland, including the liver. Using filtered back projection, transversal, coronal and sagital multiplanar reconstruction with 5 mm thickness was performed. Mediastinal lymph nodes >1cm in diameter were classified as metastases.

Radioimmunoscintigraphy for tumor targeting tracers and imaging

We used HMFG1-MoAb that naturally binds a mucin molecule in lactating breast but is also expressed by NSCLC, ovarian, breast, and colorectal cancer [12]. HMFG1-MoAb (0.5 mg) was labeled with 700 MBq of ^{99m}Tc using a standard protocol [13]. The thyroid gland was blocked with a single oral dose of 400 mg of potassium perchlorate 5 min before the i.v. administration of the radiolabeled antibody as suggested by Goldenberg and Larson (1992) [14]. Planar chest and whole-body scintigrams in anterior and posterior projections (matrix size 128 x 128) were obtained 10 min, 5 hours, and 24 hours after the administration of the antibody using large field of view single head gamma camera (Siemens, Orbiter ZLC, 3700, Germany) interfaced to a computer. Only 24-hour results are presented.

^{99m}Tc-S and ^{201}Tl scintigraphy

Commercially available sestamibi kit was labeled with ^{99m}Tc according to the instructions of the supplier. Radiochemical purity was higher than 95%. Planar chest and whole-body scintigrams were performed 10 min after the i.v. injection of 555 MBq of ^{99m}Tc-S using the same gamma camera. Planar chest and whole-body scintigrams were similarly performed with 111 MBq of ^{201}TlCl, 15 min after the tracer administration.

Image analysis

All scintigrams were evaluated by the same investigators and in the same manner, first visually and then semi-quantitatively. The goal of visual analysis was to delineate increased focal uptake of the tracer in the suspected tumor site and in distant metastases. When high uptake of the tracer was found indicating a positive finding, the pattern of uptake in the lesion was described. Homogenous increased uptake was considered as indicating viable tumor, while ring like uptake was considered as tumor with central necrosis. Semi-quantitative analysis followed, in which tumor to non-tumor (T/NT) ratio was calculated after drawing the region of interest (ROI) around the lesion and at the corresponding contralateral area. If the pattern of positive findings, was ring like uptake, then the ROI for calculating T/NT ratio included the high uptake of the radiopharmaceutical in the ring and not in the central necrosis area.

Statistical analysis

A standard statistical formula was used to calculate the sensitivity of each scintigraphic modality. The chi-square test was used to determine significant differences for sensitivity and the student's t-test for comparison of T/NT ratios between the groups. Data are presented as mean ± SD and $P \leq 0.05$ was considered significant.

Results

In Group A high uptake of ^{99m}Tc-HMFG1-MoAb was found in 14/27 patients on scans acquired 24 hours after the i.v. injection. Conversely, no uptake was seen in 13 patients.

Table 1. *Diagnostic utility of radioimmunoscintigraphy and ^{99m}Tc-sestamibi and ^{201}Tl chest scintigraphy for the detection of NSCLC.*

Method	Sens	T/NT
^{99m}Tc-HMFG1-MoAbs (n=27)	52%*	1.7 ± 0.4
^{99m}Tc-sestamibi (n=23)	87%	1.6 ± 0.3
^{201}Tl (n=24)	88%	1.6 ± 0.2
P value	<0.05	>0.05

Sens: Sensitivity; T/N: tumor to non-tumor ratio; n: number of patients; *significantly different (P<0.05).

Table 2. *Patterns of tumor uptake of ^{99m}Tc-HMFG1-MoAb, ^{99m}Tc-sestamibi, and ^{201}Tl.*

Radiopharmaceutical	Increased focal uptake	Ring-like uptake	No uptake
^{99m}Tc-HMFG1-MoAbs (n=27)	11	3	13
^{99m}Tc-sestamibi (n=23)	16	4	3
^{201}Tl (n=24)	16	5	3

Therefore, ^{99m}Tc-HMFG RIS had 52% sensitivity in detecting primary NSCLC (Table 1). ^{99m}Tc-HMFG1 RIS and CT findings in a representative case are presented in Figure 1. In the same group, high uptake of ^{99m}Tc-HMFG1-MoAb was found in 2/3 cases with bone metastases confirmed as bone osteolytic lesions on the X-ray films (Fig 2).

High tumor accumulation of ^{99m}Tc-S was found in 20/23 patients of Group B (Fig 3). Thus, the sensitivity of ^{99m}Tc-Se in the detection of NSCLC was 87% (Table 1). High uptake of ^{99m}Tc-S was seen in 2/3 patients with bone metastases and in 1 patient with brain metastases.

In Group C, high tumor uptake of ^{201}Tl was found in 21/24 patients with NSCLC. The sensitivity of ^{201}Tl in detecting primary NSCLC was 88%, (Table 1).Two patients showed high uptake of ^{201}Tl localized in bones (right femur and right tibia, respectively) and in the surrounding soft tissue.

Patterns of tumor uptake

Three general patterns of tumor uptake were seen, namely, increased focal uptake, ring-like uptake, and no apparent uptake (Table 2). Increased focal uptake was the most common positive finding indicating tumor viability. Ring-like uptake, a higher accumulation of radiopharmaceuticals at the perimeter with hypoactive central zone, was equally present in all groups (Fig. 4a and 4b). The latter pattern was considered as evidence of tumor necrosis.

Mean T/NT ratios were 1.7±0.4 for ^{99m}Tc-HMFG1, 1.6±0.3 for ^{99m}Tc-S, and 1.6±0.2 for ^{201}Tl (Table 1). The difference between T/NT ratios was not significant.

Discussion

The value of nuclear medicine imaging with tumor avid tracers for the initial evaluation and the follow-up of patients with lung cancer, has increasingly been recognized. Most commonly used tracers include ^{67}Ga, ^{201}Tl, ^{99m}Tc-S, and ^{99m}Tc-tetrofosmin [15]. Radiolabeled monoclonal antibodies directed against tumor-associated antigens have also been used for

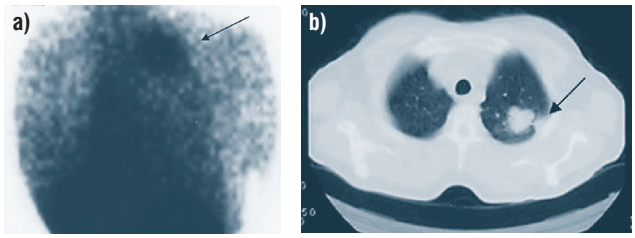

Figure 1. Findings in a patient with squamous cell carcinoma: a) increased uptake of ^{99m}Tc-HMFG1-MoAbs in the left upper lobe (black arrow); b) tumor mass on the CT image in the area of the left upper lobe (arrow).

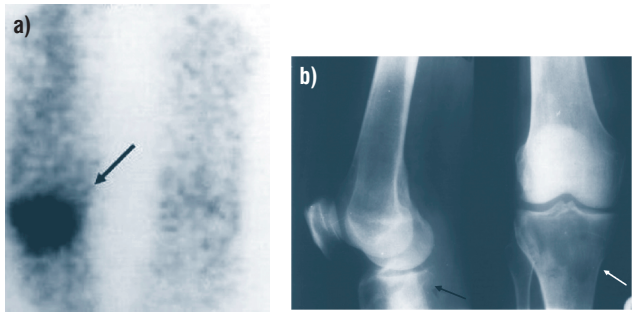

Figure 2. Radioimmunoscintigraphy in the patient with squamous cell carcinoma of the lung and a distant bone metastasis. a) increased uptake of ^{99m}Tc-HMFG1-MoAb in the right tibia and in the surrounding tissue; b) X-ray of right knee showed large osteolitic lesion in the right tibia (black and white arrows).

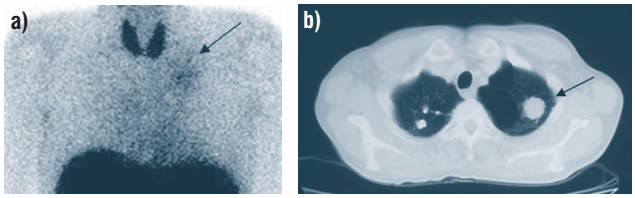

Figure 3. Findings in patient with adenocarcinoma of the lung: a) round tumor mass in the left upper lobe (arrow) and two small nodules in the right upper lobe on CT; b) increased uptake of of ^{99m}Tc-sestamibi in the left upper lobe (arrow); no uptake in the nodules in the right upper lobe.

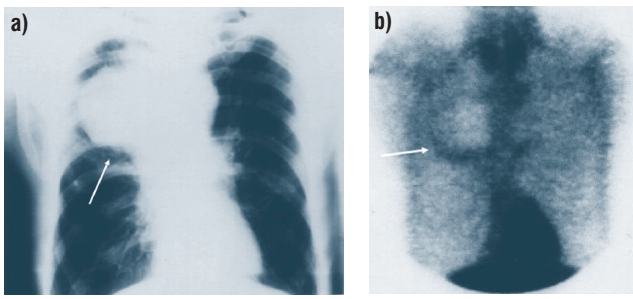

Figure 4. Findings in a patient with squamous cell carcinoma: a) round tumor mass (arrow) in the right upper lobe of the chest X-ray; b) ring-like uptake of ^{99m}Tc-sestamibi in the right upper lobe indicating tumor necrosis (arrow).

imaging lung cancer [16]. The present study adds information by examining the diagnostic utility of ^{201}Tl and ^{99m}Tc-S against RIS in patients with NSCLC.

Our findings indicate significantly higher sensitivity of the chest ^{99m}Tc-S and ^{201}Tl scintigraphy in comparison to RIS with ^{99m}Tc-HMFG1-MoAbs for the detection of NSCLC. Such results are at the high end of the previously reported 65% to 96% sensitivity range of ^{99m}Tc-S and ^{201}Tl scintigraphy for the detection of different types of lung cancer [17-20]. False negative findings in these groups of patients are probably due to the small size of tumors (2x2 cm and 2x1.8 cm, respectively). Few reports have recommended early (after 15 min) and delayed (after 3 hours) scans, mainly to differentiate malignant tumors from benign lesions and to increase the specificity of scinitgraphy [21, 22]. In our study all patients had NSCLC verified by pathology and therefore we performed early scans only as suggested by others and according to our previous results [23, 24]. In contrast to ^{99m}Tc-S and ^{201}Tl, RIS with ^{99m}Tc-HMFG1-MoAbs showed low sensitivity (52%). Localization of the lung tumors near the heart with rather high blood pool activity seen even on the 24-hour scans, may be one of the reasons for our false negative findings. In this group of patients, there was one large tumor (4x3.5 cm) without accumulation of the radiopharmaceutical. Therefore, low extraction of ^{99m}Tc-HMFG1-MoAb by the tumor could also be responsible for false negative results in our study. Previous reports suggest that labeling antibody fragments HMFG1 F(ab')2, rather than the whole antibodies as in our study, may increase sensitivity, probably due to a lower molecular size and better extraction by the tumor [16].

All three radiopharmaceuticals used in this study incorporate into a viable portion of tumors and not in the necrotic tissue. ^{201}Tl is a monovalent cationic radionuclide with biological properties similar to potassium. ^{201}Tl uptake by tumor or other cells may be influenced by blood flow, sodium-potassium pump and ATPase system, or by increased cell membrane permeability [25]. ^{99m}Tc-S is a lipophilic cation and its increased uptake in neoplastic cells is dependent on the negative potential of the cell and the mitochondrial membrane [26]. As a result, the pattern of radionuclide uptake of these three radiopharmaceuticals may help to distinguish viable tumor tissue from tumor necrosis. In the majority of our cases, we found a homogenous increase in focal uptake of the tracer indicating that tumors mainly comprised of viable tissue. Ring-like pattern noted in ~20%, likely indicates tumor necrosis [6, 27]. In general, possible cause of the central tumor necrosis could be either radiotherapy or relative ischemia due to the size of the tumor. In our study, patients did not receive any treatment before our investigation and tumor necrosis was probably due to relative ischemia because of the large size and fast growth of the tumor [27]. Distinguishing the pattern of uptake by ^{201}Tl, ^{99m}Tc-S or RIS imaging, could provide a means to differentiate viable tumor tissue from necrosis. This may be clinically useful for monitoring and predicting the response to treatment [26-28].

Distant blood-born metastases are common in patients with advanced NSCLC and may involve multiple organs. Higher physiological uptake of ^{99m}Tc-S, ^{201}Tl, and ^{99m}Tc-HMFG1-MoAb in the liver, spleen, and other splahnic areas limit their utility for tumor localization in these organs and in their neighboring areas [5, 6]. This explains why none of the three radiopharmaceuticals in our study has detected liver metastases evidently present in 15 of our patients. On the other hand, it is noteworthy that whole body imaging with ^{99m}Tc-S, ^{201}Tl, or ^{99m}Tc-HMFG1-MoAb revealed otherwise unsuspected bone and soft tissue metastases in 5 of our patients and had a direct impact on clinical management in 2 of these patients. We also found brain metastases with the ^{99m}Tc-S imaging, which is in agreement with a previous report [29]. These findings strongly suggest a potential, albeit still underutilized value of the whole-body scintigraphy in the evaluation of patients with advanced NSCLC who are at increased risk of developing widespread metastases.

It has been suggested that the T/NT ratio may be of value in monitoring patients' response to radio- and/or chemo-therapy [30-33]. In our study, however, T/NT ratios did not significantly differ between ^{99m}Tc-S, ^{201}Tl, and ^{99m}Tc-HMFG1-MoAb examinations, indicating the relatively similar uptake of these radiopharmaceuticals in tumors.

Our study has several limitations. First, we avoided exposing patients to higher radiation doses within a short period of time, and thus did not submit the same patients to all three examinations. This led in dividing the patients into three groups with reduced statistical power. Because groups' allocation was not random, there was a potential for the selection bias. To limit the influence of variability due to studying different patient populations, allocation to the respective scintigraphic group was based on clinical and demographic variables. In retrospect, the composition of these three groups appears well balanced in respect to age, gender, the presence of viable and necrotic primary NSCLC and distant soft tissue metastases. This provides confidence for comparison of these three scintigraphic methods. Another limitation is spatial resolution of the single head gamma camera. The full width at half-maximum of our camera is 0.7 cm, which reflects its intrinsic resolution. This practically means that lesions less than 2 cm in diameter might not be detected, possibly leading to false negative results, especially with planar imaging that we performed in our study. Better sensitivity in the detection of primary NSCLC could likely be attained with a double head system or with other diagnostic modalities.

In conclusion, RIS with ^{99m}Tc-HMFG1-MoAbs has lower sensitivity than the ^{201}Tl and ^{99m}Tc-S imaging for the detection of NSCLC and therefore, its clinical use cannot be recommended. All these radiopharmaceuticals can distinguish between viable and necrotic tumor tissue, which may have important implications for clinical management and follow-up of patients with NSCLC. Finally, whole-body imaging with ^{201}Tl and ^{99m}Tc-S is potentially useful for the detection of unsuspected distant metastases in patients with advanced NSCLC, such as in brain, bones and soft tissues.

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