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Abstract: Tumor imaging with myocardial perfusion agents has been a focal point for researchers. A kinetic study with ^{99m}Technetium– methoxyisobutylisonitrile (^{99m}Tc–MIBI) was performed to evaluate the tumor uptake of this radiopharmaceutical in lung cancer. Thirty–five patients with lung cancer were studied. In 21 (60%) patients, there were regions of high uptake of ^{99m}Tc–MIBI in the lesions. Heart/tumor (H/T), heart/lung (H/L) and tumor/lung (T/L) ratios were obtained. H/T and H/L ratios were 1.66±0.22 and 2.10±0.28 in 2–3 min, and 1.69±0.25 and 2.14±0.27 in 29–30 min respectively. The T/L ratio was 1.28±0.10 in 2–3 min and 1.29±0.14 in 29–30 min. While the differences between H/T and H/L ratios were statistically significant, there were no significant differences between early and late uptake ratios. Seventy per cent (7/10) of small cell and 56% (14/25) of squamous cell cancers were detected visually. ^{99m}Tc–MIBI uptake in small cell tumors was higher than in squamous cell tumors. Tumor blood flow was seen in the systemic phase of the radiopharmaceutical as the blood supply of the tumor was the bronchial artery. The sensitivity of ^{99m}Tc–MIBI planar scintigraphy for lung cancer detection was inadequate, and the early and delayed ratios revealed that small cell cancer showed higher ^{99m}Tc–MIBI accumulation than squamous cell cancer.

Key Words: Lung cancer, Technetium –99 m methoxyisobutylisonitrile, planar scintigraphy

Introduction

Evaluation of patients with suspected or known lung cancer is a part of nuclear medicine practice. Bone scan for detection of metastatic involvement and tumor–directed tracers are gaining increasing use in the assessment of lung cancer. Myocardial perfusion agents, such as ^{201}Thallium (^{201}Tl) chloride and ^{99m}Technetium–methoxyisobutylisonitrile (^{99m}Tc–MIBI) have been under study for determination of their roles in the detection of tumors (1). ^{99m}Tc–MIBI is a more suitable agent than ^{201}Tl chloride because of its superior physical characteristics such as shorter half–life, better dosimetry and optimal photon energy peak (2). Another technetium–labeled myocardial perfusion agent, Tetrofosmin, has been investigated in tumor detection, but not enough data is available as greater numbers of patients are needed (3).

Technetium–99m–MIBI uptake in different tumors has been demonstrated by many investigators (4–7). One tumor that is known to accumulate ^{99m}Tc–MIBI is lung cancer. Lung cancer is the first leading cause of cancer death in men, and it consists of four major cell types, squamous carcinoma, small cell carcinoma, adenocarcinoma and large cell carcinoma. This study was designed to examine ^{99m}Tc–MIBI uptake and kinetics in various lung cancer cell types.

Materials and Methods

Thirty–five patients with lung cancer were studied. Primary lung cancer was proven by bronchoscopic biopsies in all of the patients. In all patients, CT and/or chest X–ray demonstrated a lesion or lesions bigger than 2.5 cm in the lung. Technetium–99m–MIBI study was performed on all patients before they received any therapy. A commercial MIBI preparation (Cardio–spect®) was obtained form FJC National Research Institute for Radiobiology and Radiohygiene, Budapest, Hungary. An

anterior throax dynamic acquisition was performed for 30 min after the i.v. bolus injection of 444–555 MBq of ^{99m}Tc–MIBI in the supine position, using a gamma camera with a low–energy all–purpose collimator with a 64x64 matrix, obtaining 2 sec images for 1 min and 1 min images for the following 29 minutes. The injection site and its volume were the same in all patients. Regions of interest (ROIs) were drawn over the lesions, the rest of the lung and the left ventricle in all patients (Fig 1). Time activity curves were generated. By assigning ROIs to the 2–3 min and 29–30 min added images of the patients, the mean counts per pixel were calculated and the uptake ratios of the heart to the tumor (H/T), the heart to the lung (H/L) and the tumor to the lung (T/L) were calculated. These ratios were presented as average ±S.D. The statistical significance between H/T and H/L was assessed by Mann–Whitney U test. A Wilcoxon test was used to determine the statistical significance between early and late uptake ratios.

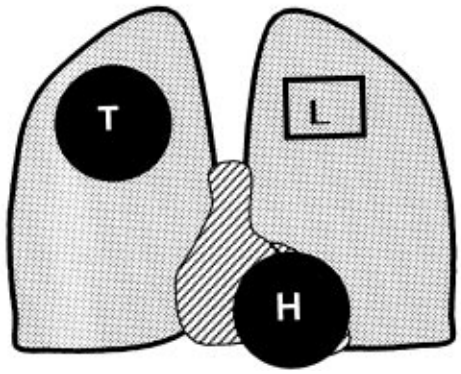


Figure 1. Schematic representation of regions of interest. (T: Tumor, L: Lung, H: Heart).

Results

Technetium–99m–MIBI uptake was demonstrated in 21/35 (60%) of the lung cancer patients qualitatively (Figures 2 and 3). It was shown that 25 of the patients had squamous cell cancer and 10 had small cell cancer. Sevently per cent (7/10) of the small cell and 56%

Table 1. Histological types and Tc–99m MIBI uptake ratios.

		EARLY			LATE		
NO	HIST.TYPE	H/T	H/L	T/L	H/T	H/T	T/L
1	Squa.Cell	1.61	2.33	1.45	1.66	2.41	1.45
2	"	1.78	2.27	1.28	1.68	2.10	1.25
3	"	1.60	2.18	1.36	1.74	2.30	1.32
4	"	1.59	1.83	1.15	1.57	1.99	1.27
5	"	1.80	2.41	1.34	2.08	2.35	1.13
6	"	1.92	2.86	1.49	1.98	2.90	1.46
7	"	1.98	2.26	1.14	2.22	2.74	1.23
8	"	1.90	2.21	1.16	1.81	2.08	1.15
9	"	1.79	2.15	1.20	1.81	2.18	1.20
10	"	1.74	1.96	1.13	1.68	2.01	1.20
11	"	1.84	2.29	1.24	1.71	2.18	1.27
12	"	1.97	2.05	1.04	1.92	2.03	1.06
13	"	1.58	1.73	1.09	1.57	1.86	1.18
14	"	1.80	1.93	1.07	1.74	2.00	1.15
Mean value ± S.D.		1.77±0.14		1.22±0.14	1.79±0.19		1.24±0.11
15	Small Cell	1.40	1.90	1.36	1.44	1.90	1.32
16	"	1.29	1.96	1.52	1.36	2.12	1.56
17	"	1.60	1.93	1.21	1.67	1.90	1.14
18	"	1.26	1.85	1.47	1.35	2.00	1.48
19	"	1.58	2.31	1.46	1.48	2.27	1.53
20	"	1.38	1.87	1.36	1.51	2.00	1.32
21	"	1.44	1.92	1.33	1.34	1.84	1.37
Mean value ± S.D.		1.42±0.13		1.39±0.10	1.45±0.11		1.39±0.15
Mean value±S.D.		1.66±0.22	2.10±0.28	1.28±0.10	1.69±0.250	2.14±0.27	1.29±0.14

A

B

Figure 2. Forty–nine–year–old man with small cell carcinoma of the lung. A- Chest X–ray reveals the lesion in the upper part of the left lung. B- ^{99m}Tc–MIBI scintigraphy reveals increased uptake at the tumor site.

(14/25) of the squamous cell cancers could be detected visually. Early and late T/L uptake ratios were 1.28±0.10 and 1.29±0.14 respectively. The difference was not significant (P>0.05). The early and late uptake ratios were 1.66±0.22 and 1.69±0.25 in tumors (H/T), and 2.10±0.28 and 2.14±0.27 in the rest of the lung (H/L), respectively. While the differences between tumor and lung uptake ratios were significant (P<0.01), no significant differences were found between early and late uptake ratios in tumors and lungs (Table 1). The early H/T ratio for squamous cell tumors was 1.77±0.14 and 1.42±0.13 for small cell tumors. The late H/T ratio for squamous cell tumors was 1.79±0.19 and 1.45±0.11 for small cell tumors. In small cell tumors, early and late ^{99m}Tc–MIBI uptake were higher than in squamous cell tumors, and the differences were significant (P<0.01). The differences between early and late ratios in each tumor type were not significant (P>0.05). There was no washout of ^{99m}Tc–MIBI in the tumor between 3 and 30 min of the study. Time activity curves showed that the peak activity was within the first minute. We also observed in patients that the blood flow of the lesion occured later than the flow of lung (Figure 4).

Discussion

The search to detect malignant tumors with radiopharmaceuticals has been continuous, but to date no

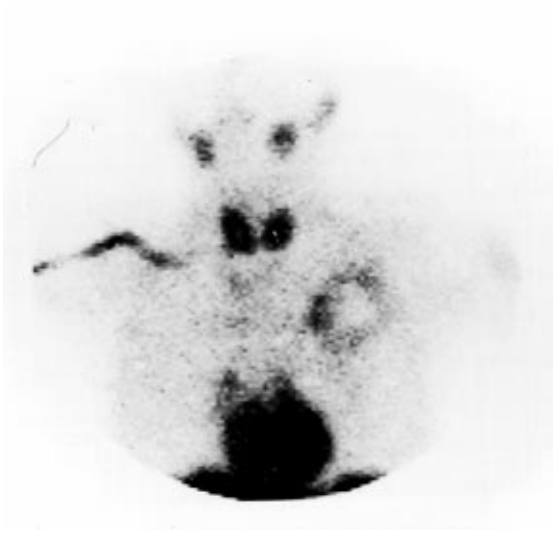


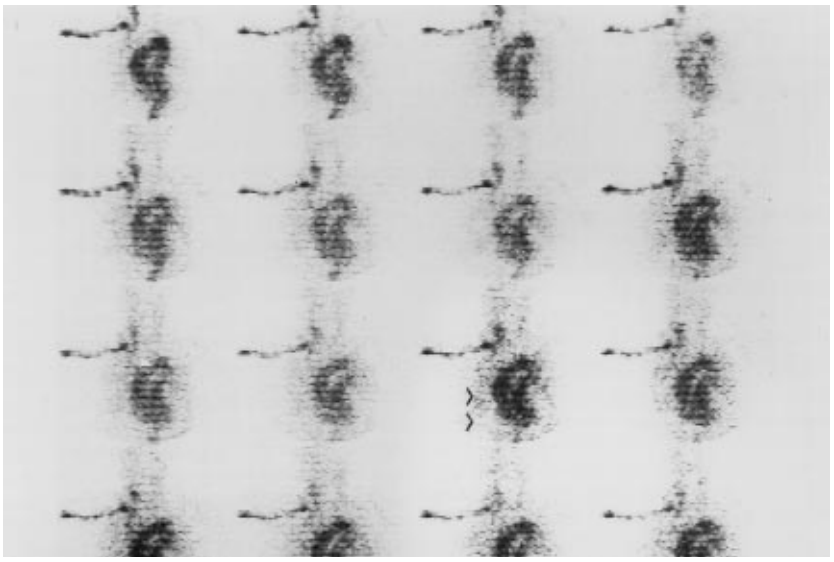
Figure 3. Fifty–five-year-old man with squamous cell carcinoma of the lung. ^{99m}Tc-MIBI scintigraphy reveals doughnut-like uptake in the upper part of the left lung due to necrosis in the center of the tumor.

effective compound has been available. Technetium–90m–MIBI has ben reported to accumulate in tumors. Although the tumor uptake mechanism is not clearly defined, possible factors that affect ^{99m}Tc–MIBI uptake by tumors are cell membrnae potential, mitochondrial content, increased tumor blood flow and capillary permeability (8, 9, 10). Piwnica–Worms et al. reported that P–glycoprotein (Pgp) activity plays a major role in ^{99m}Tc–MIBI accumulation in cells (11). Pgp is a transmembrane protein, encoded for by the multidrug resistance gene. This protein transports many chemotherapeutic agents, such as doxorubicin, out of cells. One of the mechanisims of the resistance of malignant tumors to chemotherapy is related to the level of pgp, increased levels of which are found in tumor biopsies from relapsing cancer patients. Accumulation of ^{99m}Tc–MIBI in cells is inversely proportional to the level of pgp. Functional imaging of tumors with ^{99m}Tc–MIBI may provide important information about the pgp status of tumors.

Hassan et al. demonstrated that the maximum ^{99m}Tc–MIBI accumulation in tumors occurs within one minute (4). The optimum time for imaging following injection of ^{99m}Tc–MIBI has been reported as being between 10 and 60 min (12). There have been reports in the literature on the use of ^{99m}Tc–MIBI for differentiating benign from malignant lung tomurs. In these studies, the sensitivity of ^{99m}Tc–MIBI for detecting primary lung cancer was within 65%–96% (13–15). The specificity was not high because of ^{99m}Tc–MIBI uptake in some benign lesions (12, 16). Some investigators have found a relationship between the accumulation of tumor researching tracers (^{67}Ga and ^{201}TI) in lung tumors and the histological type of the tumor, but others have shown no relationship (12).

In our patients, the results of the dynamic study showed an early peak (within one minute) in all tumor regions due to the increased blood flow. Factors that affect the height of this peak, such as the injection site and its volume, were the same in all patients. We also observed that the tumors presented different flow patterns in the first minute of the study. Tumor blood flow was not seen in the pulmonary phase, but it was seen in the systemic phase of the radiopharmaceutical. This is possibly due to the fact that lung tumors receive their blood supply from the bronchial arteries. We found no difference in tumor uptake ratios between 3 and 30 min. This finding showed that there was no significant tumor washout of ^{99m}Tc–MIBI. We detected lung cancer foci in 60% of our patients qualitatively, which were confirmed quantitatively. The degree of ^{99m}Tc–MIBI accumulation in the malignant lung tumors differed in each histological type. ^{99m}Tc–MIBI uptake in small cell was higher than in squamous cell tumors.

The sensitivity of ^{99m}Tc–MIBI for lung cancer detection was inadequate. Uptake of this radiopharmaceutical may vary according to the histological type of the lung cancer. Many studies have indicated that uptake of ^{99m}Tc–MIBI could permit the prediction of the response to the chemotherapy, when the decreased accumulation of ^{99m}Tc–MIBI implies the presence of pgp–associated drug resistance.



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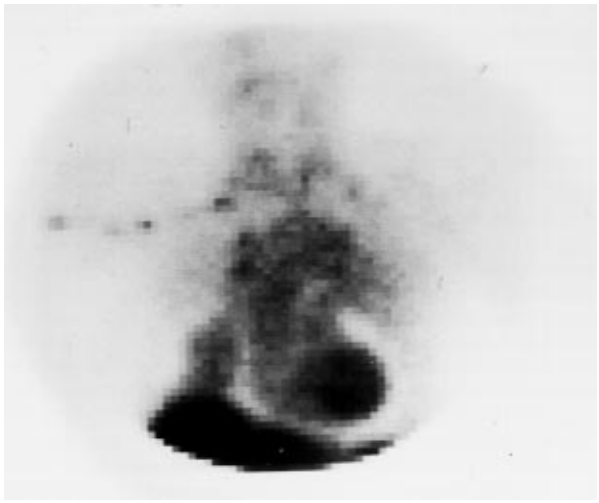

B

C

Figure 4. Forty–nine–year-old woman with small cell carcinoma of the lung. A- First phase of the dynamic study reveals that tumor perfusion is in the same phase as the systemic flow (between arrowheads). B- 2-3 min. added frame of the same study reveals increased ^{99m}Tc-MIBI uptake in the lower part of the right lung and pericardial hypoactivity due to pericardial effusion. C-CT scan of the patient demonstrates the tumor in the posterior region of the right lung with atelectasis in the anterior region.

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