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THE ROLE OF Tc-99m MIBI SPECT IN THE EVALUATION OF NON-SMALL CELL LUNG TUMORS

KÜÇÜK HÜCRELİ DIŞI AKCİĞER TÜMÖRLERİNİN DEĞERLENDİRİLMESİNDE Tc-99m MIBI SPECT'İN YERİ

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Abstract / Özet

Objective: In this study, it was aimed to investigate the role of Tc-99m MIBI scintigraphy in the diagnosis and evaluation of non-small cell lung cancers and also to evaluate the use of MIBI scintigraphy and MDP bone scintigraphy together in the detection of metastases. **Methods:** For this purpose, 30 patients with non-small cell lung cancer and 15 patients with benign lesions other than lung cancer (as a control group) were included in the study. By applying Tc-99m MIBI and Tc-99m MDP scintigraphy to whole patients with benign and malign lung lesions, anterior-posterior planar and SPECT MIBI images were obtained. Bone scintigraphy was performed as whole-body images. Scintigraphic findings were compared with the histopathological diagnosis of patients. Data were analyzed statistically. **Results:** According to the result of the findings, the sensitivity, specificity, positive, predictive value, negative predictive value, and accuracy rate of Tc-99m MIBI scintigraphy in the detection of non-small cell lung tumors were determined as 87%, 93.5%, 96%, 77.7%, and 88.8%, respectively. Scintigraphic findings were evaluated quantitatively and visually. While there was no statistically significant difference between the early uptake rates of non-small cell lung tumors and benign lesions in the quantitative evaluation using planar MIBI images, late Tc-99m MIBI uptake rates were significantly higher in lesions with non-small cell lung tumors than that of benign lesions. However, it was detected that both the early and late uptake ratios were significantly higher in malign lesions than in benign lesions in the quantitative evaluation of SPECT images. It was observed that MIBI washout in benign lesions was higher than in malignant lesions in visual washout analysis. Additionally, multiple bone metastases were observed in 14 patients on the visual evaluation of bone scan of the patients with non-small cell lung cancer. Tc-99m MDP uptake was not observed in the malignant lung lesion region or in the soft tissue except the lesion. **Conclusion:** In light of the findings, it was concluded that Tc-99m MIBI scintigraphy is a non-invasive method with high sensitivity and specificity that can be used to differentiate non-small cell lung tumors from benign lesions.

Key words: Non-small cell lung cancer, planar, SPECT, Tc-99m MIBI, Tc-99m MDP bone scintigraphy.

Amaç: Bu çalışmada, Tc-99m MIBI sintigrafisinin küçük hücreli dışı akciğer kanserlerinin tanısında ve değerlendirilmesindeki yerini araştırmak ve ayrıca metastazlarının tespitinde MIBI sintigrafisi ve MDP kemik sintigrafisinin birlikte kullanılabilirliğini değerlendirmek amaçlandı. **Materyal ve Metot:** Bu amaçla, 30 küçük hücreli dışı akciğer kanseri hastası ve 15 akciğer kanseri dışında benign lezyonu olan (kontrol grubu olarak) hasta çalışmaya dahil edildi. Benign ve malign akciğer lezyonu olan tüm hastalara Tc-99m MIBI ve Tc-99m MDP sintigrafisi uygulanarak ön-arka planar ve SPECT MIBI görüntüleri elde edildi. Kemik sintigrafisi tüm vücut görüntüleme şeklinde yapıldı. Sintigrafik bulgular hastaların histopatolojik tanıları ile karşılaştırıldı. Veriler istatistiksel olarak analiz edildi. **Bulgular:** Elde edilen bulgulara göre, Tc-99m MIBI sintigrafisinin küçük hücreli dışı akciğer tümörlerinin tespitindeki sensitivitesi %87, spesifisitesi %93,5, pozitif prediktif değeri %96, negatif prediktif değeri %77,7 ve doğruluk oranı %88,8 olarak belirlendi. Sintigrafik bulgular sayısal ve görsel olarak değerlendirildi. Planar MIBI görüntüleri kullanılarak yapılan sayısal değerlendirmede, küçük hücreli dışı akciğer tümörleri ile benign lezyonların erken tutulum oranları arasında istatistiksel olarak anlamlı bir fark bulunmazken, küçük hücreli dışı akciğer tümörlü lezyonlarda geç dönemdeTc-99m MIBI tutulum oranları iyi huylu lezyonlardan anlamlı derecede yüksekti. Bununla birlikte, SPECT görüntülerinin sayısal değerlendirmesinde hem erken hem de geç tutulum oranlarının malign lezyonlarda benign lezyonlara göre anlamlı derecede yüksek olduğu tespit edildi. Görsel washout analizlerinde ise, benign lezyonlardaki MIBI washoutunun malign lezyonlara göre yüksek düzeyde olduğu izlendi. Ayrıca, küçük hücreli dışı akciğer kanserli olan hastalarda kemik sintigrafileri görsel olarak değerlendirildiğinde; 14 hastada multipl kemik metastazı izlendi. Lezyon bölgesinde veya lezyon dışındaki yumuşak dokuda Tc-99m MDP tutulumu izlenmedi. **Sonuç:** Elde edilen bulguların ışığında, Tc-99m MIBI sintigrafisinin küçük hücreli dışı akciğer tümörlerinin benign lezyonlardan ayırımında kullanılabilecek, yüksek sensitivite ve spesifisiteye sahip non-invazif yöntem olduğu sonucuna varıldı. **Anahtar kelimeler:** Küçük hücreli dışı akciğer kanseri, planar, SPECT, Tc-99m MIBI, Tc-99m MDP kemik sintigrafisi.

1. INTRODUCTION

Lung cancer is the most common type of cancer globally; its incidence is increasing every year. Although environmental pollution and occupational conditions also play a certain role in the etiology, the main factor of the disease is smoking. Therefore, lung cancer is a largely preventable disease (Arseven, 2019, s. 156). Lung cancers are the most common type of cancer in men and women. However, it is 4-8 times more common in men than in women. This is due to the difference in smoking rates. Lung cancers have been seen more than prostate cancer in men, and breast cancer in women. Due to the increase in the smoking rate in women, lung cancer has surpassed breast cancer in some countries and has become the leading cause of death from cancer in women. It has most commonly seen between the ages of 50-70 (1,2).

Epidermoid cancer, adenocarcinoma, large cell cancer, and adenosquamous cancers except for small cell cancers, are called "non-small cell lung cancers" (1) and constitute approximately 75% of all lung cancers (3–5). Generally, resistant metastases have developed when the diagnosis was made, and the 5-year survey rate after surgical resection is less than 1%. They can be treated surgically highly if detected before metastasis (6,7). In this group of lung cancers, while the 5-year survey rate in the absence of nodal metastasis (Stage N0) is 46%, it is 33% in the presence of only hilar nodal metastasis (Stage Nl) and it is 8% in the presence of mediastinal nodal metastasis. The strongest prognostic factor in terms of the survey is whether there is a possibility of complete resection. If cancer can be detected before metastasis, there is potential for surgical treatment (8,9). Chest CT in patients with lung cancer is a standard examination in preoperative staging and diagnosis. In the detection of mediastinal lymph nodes, its sensitivity is reported as 46-91% and its specificity as 69-89% (5). It has been shown that scintigraphic imaging help to detect cancer in the early stage, to help in the differential diagnosis of active residual tumor or recurrent tumor after treatment in lung cancers (10). It has been found that 91% of patients with untreated non-small cell lung cancer have Tc-99m MIBI retention (high sensitivity) in recent studies (5,11,12).

1.1. Tc-99m MIBI scintigraphy

Technetium-99m 2-hexakis-methoxy-butyl-isonitrile (Tc-99m MIBI, MIBI, Tc-99m sestamibi) is a lipophilic monovalent cation primarily used in myocardial perfusion studies. The Tc-99m MIBI is preferred in all types of studies due to its superior physical properties (half-life of 6 hours, single gamma ray 140keV), easy, continuous, and cheap availability for use in imaging. But it is difficult to find pharmaceuticals that can be marked with Tc-99m for all types of applications. As a result of research, agents have been developed that can replace Tl-201, which is used to show myocardial perfusion. MIBI is one of them and is used as a myocardial perfusion agent in the basic sense. However, during clinical practice, it has been observed that Tc-99m MIBI is involved in some tumors and research has focused in this direction. Very precise information regarding the uptake mechanism of MIBI is not yet available. However, it was detected that it is perfusion-dependent and settled in mitochondria. Due to the negative and lipid structure of membrane potentials, it passes through the plasma membrane and mitochondrial membrane by passive diffusion and has a significant amount in the mitochondria in the cell. Therefore, it is more involved in tissues with good perfusion and a high number and activity of mitochondria in their cells. For this reason, it has been observed that many cancer tissues accumulate MIBI. Glioblastomas, head and neck tumors, lung cancers, breast cancers, and sarcomas are found among them (13–15).

The clinical contributions of MIBI imaging in this type of cancer are localization, metastasis, and post-treatment evaluation, however some studies in recent years have changed the way the work is done. For example, in the study conducted on breast cancers, it has been reported that the masses detected in the breast hold MIBI if they are malignant and not if they are benign and the sensitivity is over 90% (16). It has been also understood that uptake was altered according to the grade of the tumor tissue, with more MIBI uptake in more aggressive tumors (17). Another important improvement in MIBI studies is its association with MDR (Multiple Drug Resistancy). Another factor affecting the retention of MIBI in tumor cells is the multidrug resistance P glycoprotein (MDR l Pgp). According to some data, MDR receptors on the cancer cell surface are included in the localization mechanisms of MIBI. Thus, it is possible to determine whether there is MDR in cancer cases in vivo. This is undoubtedly an important development for oncology. In lesions with adequate perfusion and positive MDR1 Pgp function, as a result of active transport of Tc-99m-MIBI out of the cell by MDR1 Pgp, MIBI uptake may be undetectable or low or has a rapid washout. Similarly, in MDR l Pgp positive lesions, a decrease in retention in lipophilic and cationic cytotoxic drugs that have no chemical or functional similarity has been observed. However, with the administration of MDR inhibitors, washout of the agents in tumor cells is reduced and accumulation is observed. Thus, Tc-99mMIBI is one of the Tc-99m agents used in the in-vivo detection of MDR l Pgp function and inhibition. Tc-99m MIBI cannot be metabolized in-vivo and is excreted 27% urinary in 24 hours and 37% fecally excreted in 48 hours (18–20).

1.2. Tc-99m MIBI tumor scintigraphy indications

In nuclear oncology, Tc-99m MIBI is generally used for imaging primary and secondary tumors of the lungs, breasts, thyroids, parathyroids, brains, melanoma, lymphoma, bone, and soft tissues. In

tumors of the gastrointestinal tract and urogenital tract, radiopharmaceuticals are not widely used due to physiological involvement in the liver, biliary system, and splanchnic region (12,21,22).

Indications for Tc-99m MIBI tumor scintigraphy:

1. Differentiation of benign-malignant lesions
2. Staging of the disease
3. Distinguishing the necrotic and fibrotic tissue changes that occurred after treatment from recurrent or residual tumor tissue
4. Detection of early local recurrence or distant metastases
5. Evaluation of disease progression and lesions' response to chemotherapy, radiotherapy, or surgical treatment.
6. Determination of the presence, localization and viability of the tumor mass before biopsy or operation
7. Investigation of the primary tumor focus in cases with suspected tumors that cannot be detected despite being investigated by other examinations
8. Investigation of thyroid cancer metastases in patients with elevated serum thyroglobulin levels but having normal I-131 or I-123 whole-body scanning.
9. In the follow-up of cytologically high-risk thyroid nodules such as Hurtle Cell adenoma and follicular adenoma and hyperproliferative (fibrocystic) breast lesions
10. In functional thyroid cancer metastases, in the detection of suppressed thyroid tissue
11. It is used to evaluate the response of tumor tissue to chemotherapy.

As a result, MIBI applications have taken their clinical place, especially in breast and lung cancers. Even the name "sintimammography" for breast cancers has gained its terminological character. These tests can make significant contributions through whole-body scanning even in cancer cases where no primary is found, and it is of great importance for patients and physicians to include these tests, which can be easily performed in every nuclear medicine center (22–24).
In this study, we aimed to investigate the role of Tc-99mMIBI scintigraphy in the diagnosis of non-small cell lung tumors and the joint use of MIBI scintigraphy and MDP Bone scintigraphy in the detection of non-small cell lung cancers and their metastases.

2 MATERIALS AND METHODS

After receiving approval from the Clinical Research Ethics Committee of Atatürk University Faculty of Medicine, 30 patients with non-small cell lung cancer who applied to the Department of Radiation Oncology, Department of Chest Diseases, and Department of Internal Medicine-Oncology and 15 patients with lung disease other than lung cancer were included in our study. Informed consent was obtained from all patients included in the study.

2.1. Patient group

In the study, a total of 30 patients (mean: 60.9±10.88) with non-small cell lung cancer (27 men and 3 women aged between 42-83 years) and 15 patients (mean: 43.9±15.18) whit lung disease except lung cancer (11 men and 4 women aged between 25-72 years) were included (Table 1).

The patients included in the study were those diagnosed with non-small cell lung cancer by biopsies and/or sputum cytology. Control group patients who are shown to have lung disease other than lung cancer are; 6 were tuberculosis and 9 were pneumonia (Table 1).

2.2. Imaging method

Scintigraphic examinations of the patients were performed approximately 3-7 days before the start of chemotherapy and radiotherapy. 600 MBq (18 mCi) Tc 99m-MIBI was used for whole-body imaging and thorax-SPECT study. Fifteen control patients with lung disease except for lung cancer underwent whole-body imaging and thorax-SPECT studies with 600 MBq Tc 99m-MIBI.

MIBI whole body and SPECT images were taken 15 minutes after Tc 99m-MIBI injection (early) and 180 minutes later (late). In patients, anterior and posterior whole-body images, SPECT images of the thoracic region, as well as anterior and posterior planar thoracic images were taken. Tc 99m-MDP whole body bone scintigraphy images and thorax-SPECT images were obtained in the same patient group.

2.3. Evaluation of scintigraphic findings

Tc 99m-MIBI tumor screening and Tc 99m-MDP bone scintigraphy were evaluated visually and numerically.

2.3.1. Visual evaluation

The visual evaluation was performed by two different physicians. The degree of Tc 99m-MIBI retention of the lesions was evaluated in planar-anterior and posterior thorax images and thorax-SPECT images taken in early (15th min.) and late (180th min.) periods. The evaluation was made according to the degree of heart and ground retention of activity by comparing the images. The degree of retention was scored as follows:

0: Less than ground activity

1: At the ground activity level

2: More than ground activity, less than heart activity

3: Retention of activity at the heart level

4: Retention of activity in excess of the activity of the heart

In addition, the images of both isotopes taken at the 15th and 180th minutes were compared by viewing them on the same screen. The assessment was carried out by re-evaluating the degree of isotope involvement of the lesions without knowing whether they were early or late-period images.

Early and late images were compared with each other to examine whether there was a change in the retention of radiopharmaceuticals in tumor tissue or non-tumor pathologies over time. Changes in the form of increase or decrease in early and late images over time were examined in terms of malignant or benign pathologies.

The retention of Tc-99m-MIBI outside the primary lung tumor was investigated and the efficacy of MIBI in showing metastatic retention outside the primary focus was visually evaluated. Bone scintigraphy performed in patients with non-small cell lung cancer was visually evaluated and bone metastases in patients were investigated.

2.3.2. Numerical evaluation

When performing numerical evaluation; in each case, anterior, posterior planar thoracic images (static) and coronal sections obtained from thorax-SPECT images taken in early (15th min.) and late (180th min.) periods were used.

The numerical evaluation was performed in the lesions where radioactive material retention could be visualized most clearly in the early and late periods. Lesions in which substance retention was not seen in early images were evaluated together considering that they could be detected by decreasing ground activity in late-period images. In some lesions, the lesion that was observed in the early period could not be observed in the late period. While numerical evaluation was performed in the images where lesion involvement could not be detected in one of the early or late images, the localization compatible with the detected lesion in one of the images was selected. In lesions where substance retention was not observed in early or late images, numerical evaluation was not performed.

In the anterior, posterior planar thorax, and thorax SPECT images taken in the early and late period, mean counts per pixel were obtained by taking irregular areas of interest bordering the lesion site showing Tc 99m-MIBI at the pathological level. In the contralateral normal lung tissue, the dimensions of the irregular area of interest corresponding to the lesion site were arranged according to the normal lung tissue by means of a computer, without changing the number of pixels, and average counts per pixel were obtained. In one of the early or late periods, lesion involvement was observed and in the other, if the retention was at the ground activity level, the irregular interest area was drawn on normal ground activity. Average counts of the related areas that were drawn to the lesion site and normal lung tissue, were calculated.

2.3.3. Retention rates

In the differentiation of benign and malignant lesions, it is proposed to compare the ratio of lesions to normal tissues. In line with the times, the decrease in activity involvement in the normal lung tissue that constitutes the ground activity in the late-period images makes the difference in the lesion/ground activity rate evident. In the studies conducted, it has been observed that high rates were compatible with malignant and low rates were compatible with benign lesions. However, these ratios give an idea about the type of lesion but cannot lead to a definitive diagnosis.

In the anterior and posterior images taken in the early and late periods, the average counts obtained from the lesion site that fit the area of interest of each case were compared to the average counts in the area of normal lung tissue interest. Thus, lesion/normal lung tissue involvement rates were obtained. The lesion/normal lung tissue involvement rates of anterior and posterior images were averaged and thus the mean retention rate was calculated.

In addition, lesion/normal lung involvement rates obtained from SPECT images were calculated separately for early and late periods images.

The retention index, which is calculated by the early and late retention rates of the lesions, reflects the isotope retention in the lesions. In our study, the retention of Tc-99m sestamibi in tumor tissue and non-tumor lung lesions was calculated using the following formula:

RI = 100 x (Late rate - Early rate)/ Male Ratio

2.3.4. Statistical evaluation

The sensitivity and specificities of Tc-99mMIBI scintigraphy were calculated by comparing lung lesions evaluated as benign or malignant in scintigraphy with their histopathological results. Early and late involvement rates calculated for malignant and benign lung lesions on Tc-99m MIBI scintigraphy were compared using "The Mann-Whitney U test". The change between early and late involvement rates calculated at the 15th and 180th minutes in malignant and benign lesions was evaluated by the "Wilcoxon paired two sample test" method. The retention index values of the malignant and benign groups were compared by using the "Mann-Whitney U test". $p<0.05$ value was accepted as significant.

3. RESULTS

3.1. Findings of visual evaluation

In our study, by taking images at two different times (15th and 180th min), it was investigated whether early and late imaging contributed to the diagnosis in

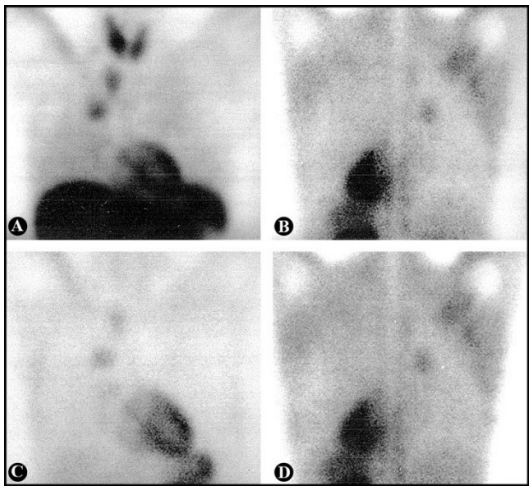
Table 1: .Demographic data and histopathological diagnosis of control group and non-small cell lung cancer cases

	Control	Non-Small Cell Lung Cancer
Number of patients	n=15	n=30
Age	43.9 ± 15.18	60.9 ± 10.88
Gender	Male=11 Female=4	Male=27 Female=3
Histopathological Diagnosis	Tuberculosis (n=6) Pneumonia (n=9)	Squamous cell (n=26) Bronchoalveolar (n=1) Adenocancer (n=1) Adenosquamous (n=2)

Table 2: Visual evaluation of Tc-99m MIBI involvement in malignant and benign lung lesions

	Tc-99m MIBI Retention			
	Malignant		Benign	
Patient No	15th Min.	180th min	15th Min.	180th min.
1.	2	2	1	1
2.	2	2	1	1
3.	2	2	1	1
4.	2	2	2	1
5.	1	2	1	1
6.	2	2	1	1
7.	1	1	2	1
8.	2	2	2	1
9.	2	2	2	1
10.	1	1	2	1
11.	2	2	1	1
12.	1	2	2	1
13.	2	2	2	2
14.	2	2	1	1
15.	2	2	2	1
16.	1	2		
17.	2	2		
18.	1	1		
19.	2	2		
20.	2	2		
21.	2	2		
22.	2	2		
23.	2	2		
24.	3	3		
25.	2	2		
26.	1	1		
27.	2	2		
28.	1	2		
29.	2	2		
30.	2	2		
Ort.±s.d	1.76±0.50	1.90±0.40	1.53±0.51	1.06±0.25

Figure 1: A. 15th minute anterior thoracic planar, B. 15th minute posterior thoracic planar, C. 180th minute anterior thoracic planar, and D. 180th minute posterior thoracic planar images of a patient with non-small cell lung cancer.



the differentiation of benign and malignant lung lesions (Figure 1).

Although there was no statistically significant difference between visually malignant and benign lung lesions (l.76±0.50, 1.53±0.516; >p.0.01) in early images of Tc-99m MIBI scintigraphy, there was a statistically significant difference in late images (l.90±0.40, 1.06±0.25; p<0.01) (Table 2). In our group of thirty patients with non-small cell lung cancer, early images showed 22 (73.5%) cases with pathological activity involvement and 8 (26.5%) cases that did not. Late imaging showed that 26 (87.5%) patients had pathological activity involvement and 4 (12.5%) patients did not. In the benign patient (control) group consisting of fifteen cases, it was observed that 7 (46.5%) cases did not show pathological activity involvement in early images, while 8 (53.5%) cases showed activity involvement. In the late images, it was seen that no involvement of pathological activity in 14 (93.5%) cases, and there was in 1 (6.5%) case.

When visual evaluations of the images of lung lesions taken in early and late periods are made, it is correct positive that a malignant lesion has scintigraphically malignancy criteria, and false negative if it is not; the presence of these criteria in a benign lesion as false positive and the absence as true negative with was evaluated.

When the visual evaluation results of the lesions are interpreted according to their histopathological diagnosis (Table 3); Tc-99m MIBI scintigraphy revealed that visual evaluations of early and late images were evaluated as true positive in 26 cases, true negative in 14 cases, false positive in 1 case and false negative in 4 cases.

The visual evaluation was performed using the diagnostic test criterion formulas given below:

Sensitivity	:	DP/(DP+YN)
Specificity	:	DN/(DN+YP)
Positive Predictive Value	:	DP/(DP+YP)
Negative Predictive Value	:	DN/(DN+YN)
Accuracy Rate	:	(DP+DN)/tüm olgular

As a result of these evaluations, the sensitivity of Tc-99m MIBI scintigraphy in the differentiation of benign-malignant lung lesions was determined as 87%, its specificity was 93.5%, its positive predictive value was 96%, its negative predictive value was 77.7%, and its accuracy rate was 88.8%.

When bone scintigraphy is visually evaluated in patients with non-small cell lung cancer; multiple bone metastases were observed in 14 patients. Tc-99m MDP involvement was not observed at the site of the lesion or in soft tissue outside the lesion (Figure 2).

Table 3: Interpretation of scintigraphic results according to histopathological diagnosis

Lesion	Malignancy criteria (Tc-99m MIBI retention)	Assessment
Malignant	+	True Positive (TP)
Malignant	-	False Negative (FN)
Benign	+	False Positive (FP)
Benign	-	True Negative (TN)

3.2. Numerical evaluation (retention rates) Findings

While there was no statistically significant difference between Tc-99m MIBI uptake rates for early images of malignant and benign lesions ($p>0.05$), late images showed that Tc-99m MIBI uptake rates were significantly higher in malignant lesions than in benign lesions ($p<0.05$) (Table 4).

In addition, when the change in the retention rates of malignant and benign lung lesions in early and late images over time was examined, it was found that the retention rates in both malignant lesions and benign lesions decreased in late images compared to early images. This decrease in the retention rates in malignant and benign lesions over time was statistically significant ($p<0.05$) (Table 5).

Table 4: Lesion/normal lung involvement rates in anterior and posterior planar images of Tc-99m MIBI scintigraphy in malignant and benign lung lesions.

	Lesion/normal lung Tc-99m MIBI involvement	
	15th Min.	180th min.
Malignant	1.569 ± 0.619	1.313 ± 0.155*
Benign	1.332 ± 0.242	1.167 ± 0.134*

*: $p<0.05$

Table 5: Lesion/normal lung involvement rates obtained from Tc-99m MIBI SPECT images taken in early and late periods in malignant and benign lung lesions

	Tc-99m MIBI SPECT lesion/normal lung involvement	
	15th Min.	180th min.
Malignant	1.639 ± 0.439*	1.823 ± 0.484*
Benign	1.388 ± 0.377*	1.424 ± 0.436*

*: $p<0.05$

Table 6: Retention index values of malignant and benign lesions

	Tc-99m MIBI retention	
	Malignant	Benign
Planar	-9.67 ± 20,58	-10.9 ± 12.3
SPECT	15.6 ± 30.8	3.8 ± 22.6

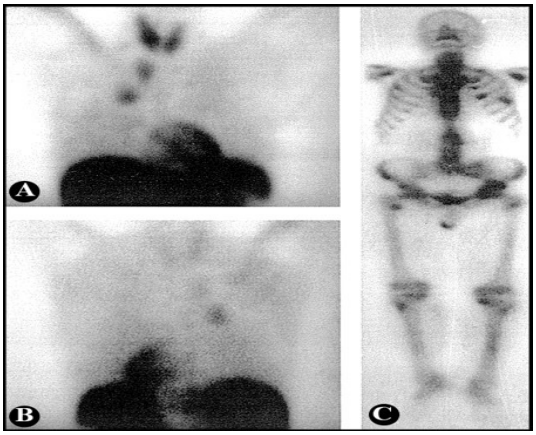
*: $p<0.05$

Early and late Tc-99m MIBI SPECT images of malignant lesions had significantly increased retention rates compared to benign lesions ($p<0.05$).

In addition, when the change in the involvement rates of benign and malignant lung lesions in early and late images over time was examined, it was observed that the involvement rates increased in both malignant lesions ($p<0.05$) and benign lesions ($p>0.05$) compared to early images in late images.

The retention index, which is calculated by the early and late retention rates of the lesions, reflects the isotope retention in the lesions. When the retention indices obtained from planar and SPECT images were compared in terms of malignant and benign lesions, there was no statistically significant difference ($p>0.05$) (Table 6)

Figure 2. A case with non-small cell lung cancer. 15 minSPECT, B. 180 min. SPECT, C. anterior whole body bone scan images (multiple metastatic foci are seen).



4. DISCUSSION

Although the diagnosis of malignant lung lesions is important, the diagnostic methods applied in the clinic are based on the principle that benign lesions can be diagnosed correctly and benign lesions are not considered malignant. The main purpose here is to reduce the number of thoracotomies performed in suspicious benign lesions or malignant lesions that do not require surgical treatment. In clinical trials, in the accumulation of knowledge formed by the use of two or more imaging methods; nuclear medicine methods allow us to visually and numerically evaluate the anatomical localization of the lesions and the functional activities of the tissues within these determined anatomical localization limits.

With the introduction of Thallium-201, which is used as a myocardial perfusion agent in Nuclear Medicine, to imaging benign or malignant lung lesions, much research has been carried out on the imaging of benign or malignant lung lesions (11). Thallium, a monovalence cationic radioisotope, is similar to potassium in terms of its biological properties. The involvement of thallium-201 in tumor tissue is mainly related to blood flow. Mechanism of intracellular involvement; is the exit of the sodium ion out of the cell and the potassium ion enters into the cell with the effect of the ATPase enzyme in the cell membrane. However, the intracellular involvement of potassium and thallium is not the same. Thallium binds to two places in the enzyme system, while potassium binds to one place. This may explain the clearance of thallium that lasts longer than the myocardium relative to potassium (25).

In the studies conducted to investigate the biological distribution of Thallium-201 in tumoral and inflammatory lesions by Müller et al. (26); it has been reported that activity decreased over time in inflammatory lesions with Tl-201 involvement, but following the delay of Tl-201 washout Tl-201 was mainly retained by living tumor tissue in malignant lesions. it has been reported that activity decreased over time in inflammatory lesions with Tl-201 involvement, but following the delay of Tl-201 washout Tl-201 was mainly retained by living tumor tissue in malignant lesions. In addition, it has been found that Tl-201 was kept to a lesser extent in connective tissue containing inflammatory cells and not in necrosis tissue. The absence of Tl-201 involvement in necrosis tissue is due to the nonfunctional ATPase activity in the cell membrane, hence the lack of active transport of Tl-201 to necrotic tumor cells.

In a study of 30 patients with suspected lung cancer, Tonami et al. (27), have reported that late tumor/ground activity rate and retention index may be parameters that can be used in the benign-malignant differentiation of tumors and in the evaluation of histological types. However, the same group later studied a group of 170 patients (147 malignant, 23 benign patients) to evaluate pulmonary nodules larger than 20 mm in diameter. And they found that the late tumor/ground activity ratio on Tl-201 SPECT images at the 15th to 180th minute did not differ in the differentiation of malignant histological groups and benign-malignant lesions except for adenocarcinoma and large cell lung cancer. These researchers found that the retention index of benign lesions was 6%±24% and that malignant lesions were 25%±24%, and suggested that this index could be used to distinguish between benign and malignant lung lesions, but was not useful in the histological typing of lung cancers (28).

Suga et al. (29), in the study conducted by taking images at early (15.dk.) and late (180th min.) periods in a group of patients with thoracic lesions larger than 20 mm in size (58 benign and 48 malignant), reported that tumor/ground activity rates could not help distinguish benign-malignant lesions, but retention index values were important. In the study of this group, retention index values have been found -4.3% ± 13.6% for benign lesions, and 23.3% ± 18.9% for malignant lesions. They have determined that benign lesions were not detected in late images or that their retention index was negative as benign criteria and reported the accuracy rate in identifying benign lesions as 81.1% and positive predictive value as 95.2%.

Sehweil et al. (30), in the study they conducted for diagnosing and staging lung cancer, breast cancer,

and malignant lymphomas in a group of 188 patients, visually evaluated the static images obtained 20 min later from the iv-injection of Tl-201. In addition, 10 patients with benign lung lesions were included in the study group. They reported that Tl-201 had a high sensitivity in detecting primary tumors (87.5% in lung cancer, 100% in breast cancer, 85% in lymphomas), but low sensitivity in the detection of mediastinal lymph nodes, and Tl-201 involvement in two cases of tuberculosis and one sarcoidosis from the benign lesion group. In conclusion, they reported that the specificity of Tl-201 was low (70%) in the differentiation of benign-malignant lung lesions. However, the fact that they did not take late period images of Tl-201 stands out as a deficiency of the study.

Duman et al. (31), in their SPECT study for benign-malignant differentiation of solitary lung lesions using Tl-201 and post-radiotherapy follow-up of primary lung cancer, in semiquantitative evaluation, have found that the sensitivity of Tl-201 in the differentiation of benign-malignant lesions was 56%, its specificity was 71%, and its accuracy value was 58%. Also, according to the results of quantitative analysis, they have detected the sensitivity as 88.8%, the specificity as 100%, and the accuracy value as 92%. They also reported a retention index of 2.9±1.3 for primary lung cancers, 2.78 ± 0.9 for benign lesions, and -2.3±1.5% for metastatic pulmonary lesions. However, they concluded that Tl-201 scintigraphy is a sensitive method for the differentiation of benign-malignant lung lesions, but has limited value in the differentiation of metastatic lesions and benign lesions and in the histological classification of primary lung cancers. They also observed compatibility between clinical follow-up of patients after radiotherapy and lesion involvement on Tl-201 scintigraphy.

In lung lesions, benign lesions (tuberculosis, silicosis, radiation pneumonia, atypical mycobacterial pneumonia, pneumonia, inflammatory pseudotumor, aspergilloma, granulomas, breast adenomas, sarcoidosis, abscess, sternotomy, atelectasis, cardioversion) with Tl-201 involvement have been reported without using late images or retention indices (32). However, there are few studies in which numerical evaluations are applied for these lesions.

As mentioned above, Tl-201, which is frequently used in tumor imaging, has a number of disadvantages such as its resolution not being good enough due to its low gamma energy (69-83 keV) and limiting the amount of activity applied due to its long half-life (73 h.). These disadvantages led researchers to investigate tumor imaging methods with radiopharmaceuticals with properties more suitable for Nuclear Medicine examinations.

The characteristics of an ideal radiopharmaceutical used in nuclear medicine methods should be as below (33):

It should be easily obtained in a hospital setting.

Its preparation should be simple and inexpensive.

Its effective half-life (the amount of radiation absorbed by the tissue) should not be longer than the time required to complete the study.

It should not emit gamma rays, should not form particle scatters (alpha or beta). The interest/ground activity ratio should not be high.

In in-vivo conditions, it should not be metabolized before its accumulation in the target organ.

Radiopharmaceuticals labeled with technetium-99m have almost all of the properties listed above. Therefore, approximately 80% of the radiopharmaceuticals used in nuclear medicine are radiopharmaceuticals labeled with Tc-99m. The superiority of Tc-99m in clinical use is due to its physical and radiation-related properties. Although the amount of activity applied to the patient is greater than Tl-201, the physical half-life is shorter (6.02 hours) and the fact that it emits fewer electrons causes the patient to receive fewer doses of radiation and the image quality to improve due to the increase in the number of counts obtained from the patient. In addition, gamma cameras have photon (140 keV) energy that is best suited for imaging, which doubles the image resolution. Tc-99m-labeled radiopharmaceuticals can be prepared by labeling commercially available kits with Tc-99m pertechnetate obtained from sterile, pyrogen-free, and carrier-free Mo-99-Tc-99m generators in radiopharmaceutical laboratories.

Because of these superior properties, Tc-99m-labeled radiopharmaceuticals are widely used today in the imaging of many soft tissue and bone tumors.

Lung malignancies are one of the most common uses of Tc-99m MIBI, and researchers have worked to develop many qualitative and quantitative methods for the differentiation of malignant and benign lung tumors (34).

Physiological changes such as plasma and mitochondrial membrane potentials, mitochondrion quantity, perfusion, and cell metabolism are reported to promote the involvement of Tc-99m MIBI by tumor tissue (5). Caner et al. (35) have reported in their studies with Tc-99m MIBI in benign-malignant bone lesions that isotope involvement of the lesions was related to blood flow, necrotic changes, metabolic function, and mitochondrial activity rather than the benign or malignant lesion. Furthermore, it has recently been reported that the involvement of Tc-99m MIBI in tumor tissue is related to the P-gp (P glycoprotein) levels of the tissues and that the

involvement of Tc-99m MIBI in tumor tissues with high P-gp levels is low.

Hassan et al. (36), in their study investigating the involvement and kinetics of Tc-99m MIBI in benign and malignant lung lesions, detected localized increased Tc-99m MIBI involvement in 10 patients with untreated malignant lung lesions; however, they were unable to detect Tc-99m MIBI involvement in an untreated undifferentiated epidermoid cancer, two lung cancers responding to radiation therapy, and four benign lung lesions. They have also observed a diffuse increase in lung involvement in two patients diagnosed with fibrosing alveolitis. In this first study for the imaging of lung lesions with Tc-99m MIBI, it has been reported that malignant lesions showed increased levels of Tc-99m MIBI involvement, unlike benign lesions.

In another study to evaluate the clinical significance of Tc-99m MIBI in the differential diagnosis of solitary-solid lung lesions; In a group of 54 patients, SPECT images have been taken 10 minutes after intravenous injection of Tc-99m MIBI. 75% (6/8) of benign lesions and 65% (30/46) of malignant lesions have been visualized and it has been detected that the sensitivity of Tc-99m MIBI in the differential diagnosis of solitary-solid lung lesions was 65%, specificity was 57%, and accuracy rate was70%. In this study, it has been reported that the use of Tc-99m MIBI scintigraphy in the differential diagnosis of lung lesions was limited.

Mueller et al. (23), comparing the SPECT study in bronchial cancers with Tc-99m MIBI and Tl-201 involvement, reported that both isotopes gave similar scintigraphic results and that the SPECT method was more sensitive in detecting lesions than static images.

In a study conducted by Aktolun et al. (37), they have compared Tc-99m MIBI and Tl-201 scintigraphy in various malignant tumors including lung cancers and reported the sensitivity of Tc-99m MIBI as 82.5% and the sensitivity of Tl-201 as 76.4%. They have also evaluated chest X-rays and computed tomography images of patients they included in their tumor imaging research programs with Tc-99m MIBI. And they have detected increased levels of Tc-99m MIBI involvement in pulmonary actinomycosis, which appeared to be a mass resembling a mediastinal tumor, and giant lymph node hyperplasia of the mediastinum (Castleman's disease), and also in seven cases of pulmonary sarcoidosis (38,39).

Lebouthillier et al. (40) have emphasized that Tc-99m MIBI is a sensitive agent in the evaluation of hilar and mediastinal lymph node involvement in the detection of primary lung cancer, and that SPECT or static scintigraphy with Tc-99m MIBI are noninvasive methods that can be applied before the operation.

In our study, we visually and numerically evaluated the Tc-99m MIBI images taken for the differentiation of malignant and benign lung lesions.

In the visual evaluation method, we apply to distinguish malignant pathologies (non-small cell lung cancers) from benign pathologies (control group patients); we interpreted the criteria such as no activity involvement of the lesion or decreasing of the activity of the lesion over time which initially showed activity involvement, in the direction of "benignity". We interpreted the increase or unchanged or slight decrease of the initial activity over time in favor of "malignancy".

In our study, scintigraphic findings were carrying malignant lesions in 26 out of 30 patients diagnosed with non-small cell lung cancer in their biopsies and/or sputum cytology. The lesion activity involvements of these lesions thought to be malignant were above-the-ground activity both in early images (score: 2, 3) and in late images. However, on scintigraphy with Tc-99m MIBI, we not observed monitor activity involvement in early and late images in 4 patients with non-small cell lung cancer. Histopathological diagnosis of these cases was: squamous cancer (7th, 10th, 18th, and 26th cases). These cases were evaluated as false negative results. In addition, Tc-99m MIBI scintigraphy revealed late involvement in 4 non-small cell lung cancer cases (score: 2), although no activity involvement was detected in the early period (score: 1). The histopathological diagnoses of these cases are; squamous cancer (cases 5, 16 and 28) and adenosquamous cancers (case 12).

We also obtained retention index values in our study. We calculated the retention index value in malignant lesions as -9.6 ±20.58 and the value in benign lesions as -10.9 ± 12.3 in anterior and posterior planar images. In SPECT images, we measured the retention index value in malignant lesions as 15.6 ±30.8 and the value in benign lesions as 3.8 ± 22.6.

While there was no statistically significant difference between the Tc-99m MIBI uptake rates of early planar images of benign and malignant lesions, we found that the late Tc-99m MIBI uptake rates of malignant lesions were significantly higher than benign lesions. In addition, on Tc-99m MIBI scintigraphy, we found that the retention rates in late images of malignant lung lesions remained the same or decreased slightly compared to early images, while in benign lesions they decreased significantly or the involvement disappeared completely. This situation has shown us that in order to make the correct distinction between malignant and benign lesions, it is absolutely necessary to take images in the late period.

In early and late Tc-99m MIBI SPECT images of malignant lesions, the retention rates significantly increased compared to benign lesions. In addition, when the change in the retention rates of benign and

malignant lung lesions in early and late images over time was examined, it was observed that the retention rates increased in both malignant lesions and late images in benign lesions compared to early images.

When we compared the retention indices obtained from planar and SPECT images in terms of malignant and benign lesions, we did not find a statistically significant difference.

Tc-99m MDP scintigraphy was also applied to all patients with non-small cell lung cancer. Tc-99m MDP scintigraphy revealed no involvement in lung tissue or soft tissues other than lung tissue in any case with non-small cell lung cancer. In addition, in the Tc-99m MDP whole-body scan scintigraphy from all patients, it was revealed metastatic bone pathologies in the thoracic, lumbar, and cervical vertebrae, ribs, pelvis, femoral head-acetabular regions in 14 cases.

5. CONCLUSION

In conclusion, we have shown that Tc-99m MIBI scintigraphy is an easy-to-apply, successfully used, reliable, noninvasive method with high sensitivity and specificity in the differentiation of non-small cell lung tumors from benign lesions. We also concluded that Tc-99m MDP scintigraphy, as mentioned above, is very successful, especially in terms of detecting the presence of metastases, and is useful in guiding the clinician.

In addition to the visual evaluation of scintigraphic results, we have seen that the use of numerical evaluation methods increases the superiority of these methods. We have shown that early and late involvement rates, which we consider numerical evaluation methods, can be used to distinguish between malignant and benign lesions. We found that in malignant lesions, while late-term involvement rates increased or remained the same, these rates decreased significantly in benign lesions. As a result of these findings, we have once again shown the importance of taking late images as well as early images in the differentiation of malignant and benign lesions.

If Tc-99m MIBI scintigraphy can be made widely available in the clinic to distinguish between malignant and benign lung lesions, we think it may be useful in reducing unnecessary invasive interventions, especially in benign lesions.

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