Lung tumors: early and delayed ratio of ^{99m}Tc-methoxy-2-isobutylisonitrile accumulation

Tumori pluća: rana i odložena akumulacija ^{99m}Tc-metoksi-2-izobutilizonitrila

Katarina Nikoletić*, Jasna Mihailović*, Dolores Srbovan*, Violeta Kolarov[†],
Radmila Žeravica[‡]

*Department of Nuclear Medicine, Institute of Oncology of Vojvodina, Sremska
Kamenica, Serbia; [†]Department of General Pulmology, Institute of Pulmonary Diseases,
Sremska Kamenica, Serbia; [‡]Department of Nuclear Medicine, Clinical Center of
Vojvodina, Novi Sad, Serbia

Abstract

Background/Aim. Currently used radiopharmaceuticals are nonspecific and most of them are accumulated by benign tumors as well as inflammatory lesions, abscess or granulomatous lesions. Some factors such as the choice of radiopharmaceutical applied, histopathologic type of tumor, its size, location or previous tumor treatment could influence tumor imaging sensitivity. The aim of this study was to investigate accumulation of ^{99m}Tc-methoxy-2-isobutylisonitrile (^{99m}Tc-MIBI) by counting early/delayed uptake and release of this radiopharmaceutical inside lung tumors and evaluating possible factors which could be involved in its accumulation. **Methods.** Two-phase ^{99m}Tc-methoxy-2-isobutylisonitrile single photon emission computed tomography scan (early and delayed scan) was performed in 60 patients with lung tumors (the group 1 – 30 benign, and the group 2 – 30 malignant tumors). We calculated the uptake ratio on early (early ratio – ER), delayed images (delayed ratio – DR) and retention index (RI). Individual influence of etiology, diameter, localization, and histological type on uptake/release values was evaluated with regression analysis. **Results.** The values of ER and DR were significantly different in both groups ($p < 0.01$), showing lower values in benign *vs* malignant lung tumors (ER 1.36 ± 0.094 and DR 1.25 ± 0.089 *vs* ER = 1.93 ± 0.106 and DR = 1.7 ± 0.095 respectively). Tumor size showed a significant influence on the change of ER and DR values ($p < 0.01$), with greater uptake in tumors > 3 cm. RI values showed no significance between the two groups ($p > 0.05$). **Conclusion.** The uptake ratio of ^{99m}Tc-methoxy-2-isobutylisonitrile could be a useful index in differentiating lung tumors, while RI has no influence on this. Among the evaluated factors, ER and DR values are significantly influenced only by the diameter of lung tumor, while localization or different histological types between the groups has no influence on this.

Key words:
radiopharmaceuticals; tomography, emission-computed; lung neoplasms; diagnosis, differential; pathology; sensitivity and specificity.

Apstrakt

Uvod/Cilj. Novi radiofarmaceutici su nespecifični i većina njih se akumuliše u benignim tumorima, ali i u zapaljenskim lezijama, apscesima ili granulomatoznim lezijama. Na senzitivnost snimaka tumora utiču razni faktori kao što su izbor radiofarmaceutika, patohistološki tip tumora, veličina, lokalizacija ili način lečenja. Cilj ove studije bio je da se proceni nakupljanje ^{99m}Tc-metoksi-2-izobutilizonitrila (^{99m}Tc-MIBI) unutar tumora pluća određivanjem rane/odložene akumulacije, odnosno eliminacije ^{99m}Tc-MIBI, kao i da se utvrde mogući faktori koji bi mogli uticati na akumulaciju ovog radiofarmaceutika. **Metode.** Dvofazna ^{99m}Tc-metoksi-2-izobutilizonitril jednofotonska emisiona kompjuterizovana tomografija (rana i kasna) urađena je kod 60 bolesnika sa tumorom pluća (grupa 1 – 30 benignih i grupa 2 – 30 malignih tumora). Izračunavali smo odnos nakupljanja na ranim (*early ratio* – ER) i odloženim snimcima (*delayed ratio* – DR), kao i indeks retencije (*retention index* – RI). Regresiona analiza korišćena je u cilju utvrđivanja pojedinačnog uticaja etiologije, veličine, lokalizacije i patohistološkog tipa tumora na vrednosti akumulacije/eliminacije radiofarmaka. **Rezultati.** Vrednosti ER i DR bile su statistički značajno različite u obe ispitivane grupe ($p < 0,01$), sa manjim izmerenim vrednostima kod benignih u poređenju sa malignim tumorima (ER 1,36 ± 0,094 i DR 1,25 ± 0,089 *vs* ER = 1,93 ± 0,106 i DR = 1,7 ± 0,095, respektivno). Utvrđeno je da veličina tumora pluća značajno utiče na promene vrednosti ER i DR ($p < 0,01$), sa intenzivnijom akumulacijom unutar tumora dimenzija preko 3 cm. **Zaključak.** Rana i odložena akumulacija ^{99m}Tc-metoksi-2-izobutilizonitrila u tumorima pluća je koristan parametar za njihovu diferencijaciju, dok vrednost indeksa retencije nema uticaja na diferenciranje benignih i malignih tumora pluća. Veličina tumora pluća statistički značajno utiče na vrednosti ER i DR. Ostali ispitivani faktori, kao što su lokalizacija ili patohistološki tip unutar grupe 1 ili grupe 2, ne utiču na vrednosti ER i DR.

Ključne reči:
radiofarmaci; tomografija, kompjuterizovana, emisiona; pluća, neoplazme; dijagnoza, diferencijalna; patologija; osetljivost i specifičnost.

Correspondence to: Katarina Nikoletić, Department of Nuclear Medicine, Institute of Oncology of Vojvodina, 21 204 Sremska Kamenica, Srbija. Phone: +381 63 520 085, +381 21 4805 458. E-mail: ketins@yahoo.com

Introduction

Tumor imaging with various radiopharmaceuticals has been a focal point for nuclear medicine researchers. Currently used radiopharmaceuticals are nonspecific and most of them are also accumulated by benign tumors and infectious lesions, such as inflammatory lesions, abscess or granulomatous lesions. Some factors such as the choice of radiopharmaceutical applied, histopathologic type of tumor, its size, location or previous tumor treatment could influence sensitivity of tumor imaging.

Commonly used radiopharmaceuticals in lung cancer imaging are ^{201}Tl-chloride (talium-201 chloride) and ^{99m}Tc-MIBI (technetium-99m labelled hexakis-2-methoxyisobutylisonitrile) [1–3]. New studies introduce simultaneous double-tracer single photon emission tomography (SPECT) with 99m-Tc-technetril and 67-Ga-citrate for follow-up of patients with non-small cell lung cancer [4]. Studies *in vitro* in cultured tumor cells found out that the uptake of ^{201}Tl is almost 3-fold greater than ^{99m}Tc-MIBI, while the cellular release or the washout rate is almost identical for both radiopharmaceuticals [5]. Kinetics of some radiopharmaceuticals can be changed by adding certain drugs such as actinomycin D resulting in increased cellular release of ^{201}Tl while it has no change in washout rate of ^{99m}Tc-MIBI [6]. Slower washout of ^{201}Tl in high growth cells enables this tracer to act as an indicator of tumor malignancy. Some papers have reported the benefit of ^{201}Tl-chloride in detecting tumor malignancies which is determined by the grade of washout rate to normal tissue especially in lung cancer lesions and mediastinal lymph node metastases [6]. Among these two radiopharmaceuticals, ^{99m}Tc-MIBI has been emphasized because of its superior physical characteristics such as shorter half-life, better dosimetry, and optimal photon energy peak. Moreover, it is continuously available for use, permits freedom in scheduling patients and the injected concentration is higher.

^{99m}Tc-MIBI which is used in everyday practice for myocardial perfusion imaging, also gains its roll in evaluating various malignant tumors such as breast carcinoma, thyroid cancer, central nervous system malignancies and lung cancer [7–9]. Recently, many papers have reported accumulation of this radiopharmaceutical within tumor lesion considering its role in differentiating benign from malignant lesions [10–12] but only few have evaluated factors related to kinetics, uptake and washout of radiopharmaceuticals [13–15]. One of the earliest studies considering the uptake and kinetics of ^{99m}Tc-MIBI in malignant lung lesions was reported by Hassan et al [13].

This study is designed to investigate kinetics of ^{99m}Tc-MIBI by investigating its early and delayed uptake, release of ^{99m}Tc-MIBI in benign and malignant lung lesions and evaluating possible factors which could be involved in the kinetics of this radiopharmaceutical.

Methods

A total of 60 patients with lung lesions (LLs) was evaluated from 2006 to 2009 (45 males and 15 females, age 37–76 years, mean age ± SD: 56.70 ± 9.527 years). All the patients were divided into 2 groups: the group 1 included 30 patients with benign LLs, and the group 2 included 30 patients with malignant solitary pulmonary nodule (SPN). This study included only the patients who had been evaluated by chest computed tomography (CT) (reporting diameter and localization of LLs) prior to ^{99m}Tc-MIBI scanning and with the final diagnosis. The diagnosis was made by pathohistology findings after surgery (49/60 or 81.7%), cytological findings of sputum or by positive TBC culture (4/60 or 6.7%) or by clinical course of the disease (7/60 or 11.6%).

Two-phase (early and delayed) ^{99m}Tc-MIBI SPECT imaging was performed prior to definitive diagnosis. Early ^{99m}Tc-MIBI imaging was performed 10 minutes after the intravenous injection of 740 MBq ^{99m}Tc-MIBI with dual-headed gamma-camera equipped with low-energy, high resolution collimator. Delayed imaging was done 60–120 minutes after the intravenous injection of the radiopharmaceutical. ^{99m}Tc-MIBI was prepared according to the instructions of the manufacturer. The images were acquired every 20 seconds, at the angle of 3º, in a circular orbit of 180º per detector array, and stored in 64 × 64 matrix. The equipment was calibrated for a photopeak of 140 keV with a symmetric 20% window. The images were reconstructed in the coronal, transversal and sagital sections and both early and delayed images were evaluated qualitatively considering positive findings if there was an increased accumulation of the radiopharmaceutical in the lung area corresponding to the location of the LLs. Quantification of the images included evaluation of the uptake ratio on early (ER = early ratio) and delayed images (DR = delayed ratio) calculated on transverse slices placing region of interest (ROI) around abnormal uptake of ^{99m}Tc-MIBI (T = tumor) and in an area of contralateral normal (N = normal) lung tissue (ER or DR = T/N). The ROIs of the early images were copied and set on LLs on delayed images. For semiquantitative evaluation of the degree of retention in LLs the retention index (RI) was calculated as:

$$RI = [(\text{delayed ratio} - \text{early ratio}) / \text{early ratio}] \times 100.$$

To test the differences between ER, DR and RI in benign (group 1) and malignant (group 2) LLs, Student's *t*-test was used. The results were considered significant when the *p* value was less than 0.05. Mutual and individual influence of diameter, localization, and histological type of LLs on uptake values (ER, DR, RI) and on ^{99m}Tc-MIBI accumulation was analyzed with regression analysis.

Results

Visual evaluation of ^{99m}Tc-MIBI accumulation included positive and negative findings assessment on early and delayed images in both groups of patients. In the group 1, 23 (76.7 %) of the patients were negative on both early and delayed images: 8 inflammatory pseudonodules, 7 cases of tuberculosis, 6 hamarthoma, 1 primary neuroendocrine cyst and 1 fibrotic nodule. The majority of false positive results in the group 1 (7/30 or 23.3%) occurred in inflammatory pseudonodule and only one was the case of botryomycosis (Figure 1).

Most of lung lesions from the group 2 were positive on both early and delayed images (27/30 or 90%): 9 adenocarcinoma, 13 squamous-cell carcinoma, 3 large-cell carcinoma and 2 small-cell carcinoma (Figure 2).
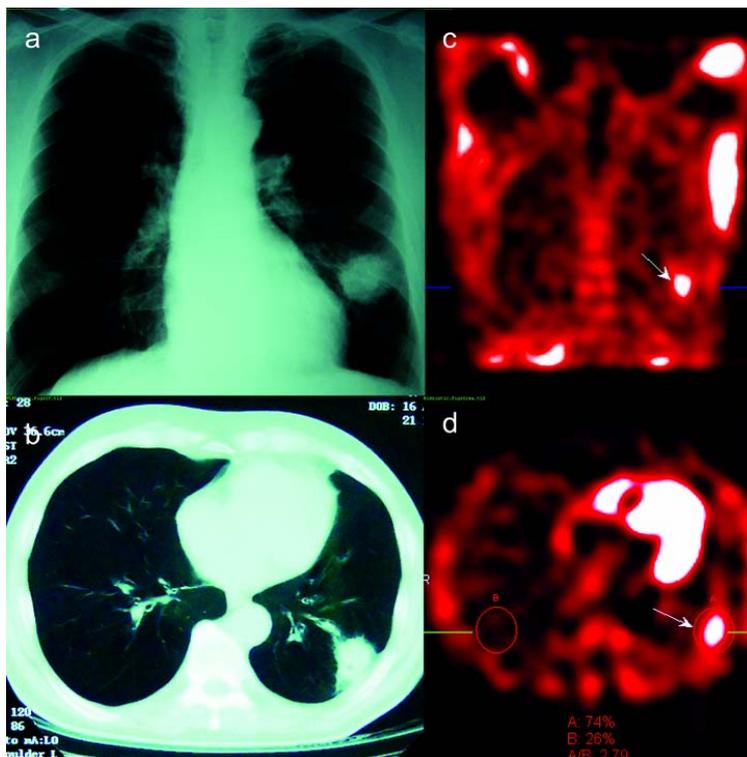
Fig. 1 – A 70-year-old patient with a lung lesion located in the left lower lobe identified on X-ray and computed tomography (CT) scan (a, b). ^{99m}Tc-metoxy-2-isobutylisonitrile single photon emission computed tomography (^{99m}Tc-MIBI SPECT) scan in the same patient shows intense accumulation of ^{99m}Tc-MIBI in the lung region corresponding to the location of the nodule (c, d); the tumor/nodule (T/N) ratio was 2,79 on early scan. Percutaneous transthoracic fine needle aspiration cytology identified lesion as chronic pneumonia – a false positive result.
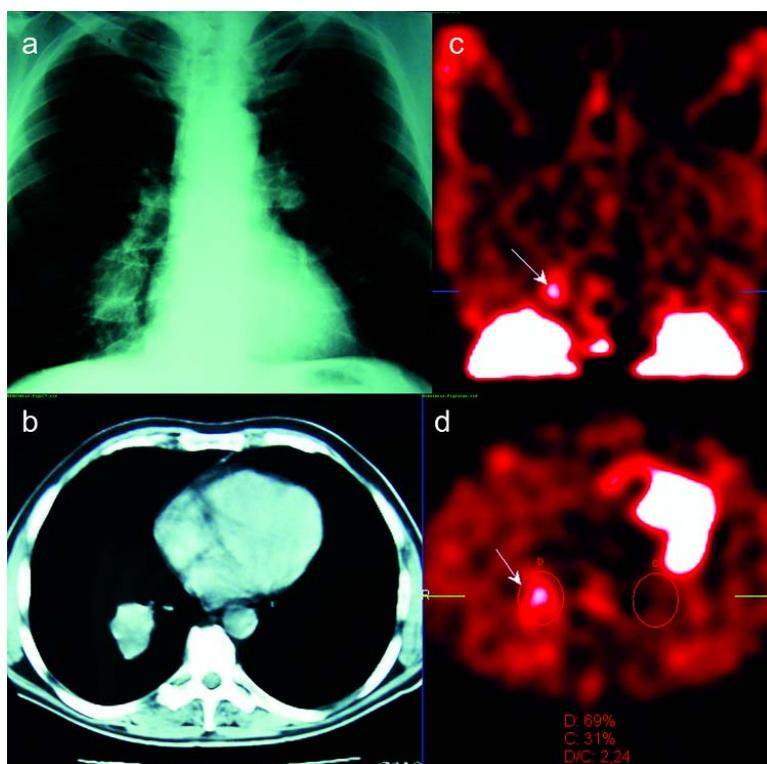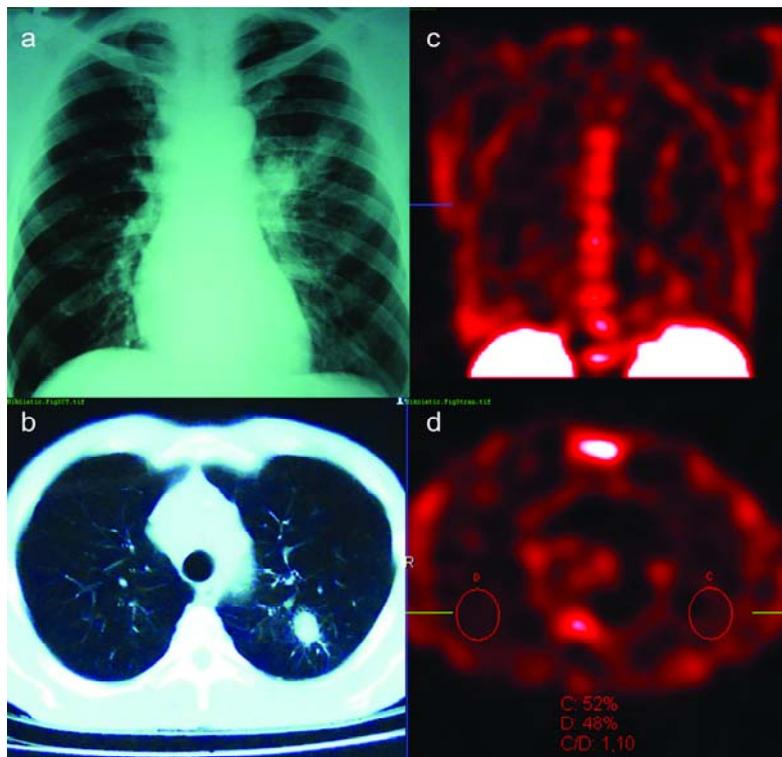

Fig. 2 – A 53-year-old patient with a lung lesion located in the right lung identified on radiography and computed tomography (CT) scan (a, b). ^{99m}Tc-metoxy-2-isobutylisonitrile single photon emission computed tomography (^{99m}Tc-MIBI SPECT) scan in the same patient shows high accumulation of ^{99m}Tc-MIBI in the lung region corresponding to the location of the nodule (c, d); the tumor/nodule (T/N) ratio was 2.24 on early scan. After lobectomy, the lesion was identified as squamous-cell carcinoma – a true positive result.

Only 3 lesions from this group did not accumulate the radiopharmaceutical (false negative): 1 adenocarcinoma (Figure 3), 1 undifferentiated squamous-cell carcinoma and 1 small-cell carcinoma.

The difference in ER values between groups was statistically significant ($t = 3.982$, $p < 0.05$).

Also, the difference in DR values between groups was statistically significant ($t = 3.448$, $p < 0.05$).

Fig. 3 – A 51-year-old patient with a lung lesion located in the left upper lobe identified on radiography and computed tomography (CT) scan (a, b). ^{99m}Tc-metoxy-2-isobutylisonitrile single photon emission computed tomography (^{99m}Tc-MIBI SPECT) scan in the same patient shows no accumulation of ^{99m}Tc-MIBI in the lung region corresponding to the location of the nodule (c, d); the tumor/nodule (T/N) ratio was 1.10 on early scan. Percutaneous transthoracic fine needle aspiration cytology and sputum cytology identified lesion as adenocarcinoma – a false negative result.

In both groups, the values of ER, DR and RI were evaluated. The mean ER and DR values ± SD are shown in Figures 4 and 5.
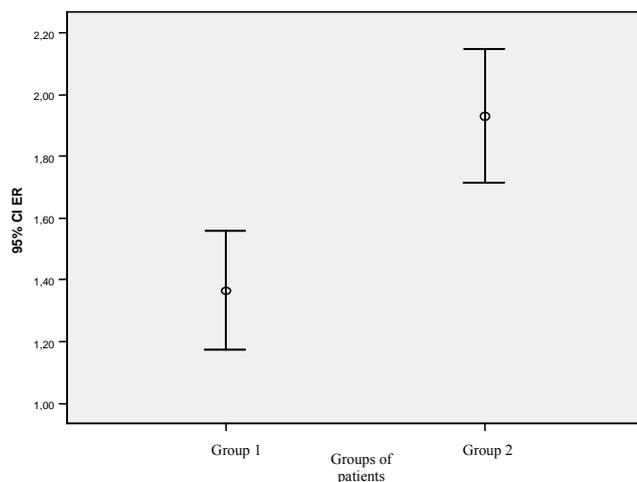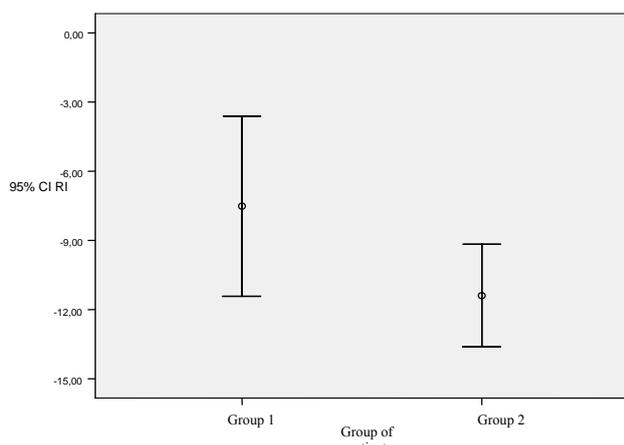

Fig. 4 – Early ratio (ER) values in the patients with benign (the group 1) and malignant (the group 2) lung lesions.
95% CI – 95% confidence interval.
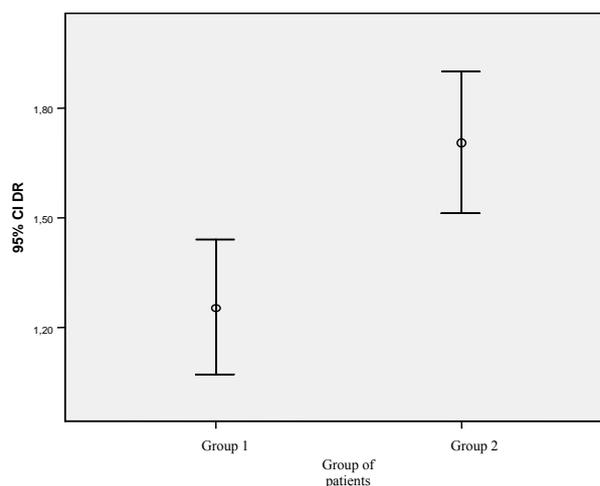
Fig. 5 – Delayed ratio (DR) values in the patients with benign (the group 1) and malignant (the group 2) lung lesion.
95% CI – 95% confidence interval.

There was no significant difference between the RI values in benign and malignant SPN (-7.512 ± 10.44 and -11.394 ± 5.945, respectively) (Figure 6).

Fig. 6 – Retention index (RI) values in the patients with benign (the group 1) and malignant (the group 2) lung lesion.
95% CI – 95% confidence interval.

Among the false positive results in the group 1 (7 patients with a benign lung lesions), 5 cases of inflammatory

ER = 2.2 ± 0.4 and DR = 2.0 ± 0.5. Among the two different histopathological types of benign lung lesions leading to false positive findings, there was no significant difference in ER, DR and RI values. In the group 2, the lowest ER and DR values were found in large-cell carcinoma (1.7 ± 0.2 and 1.5 ± 0.2, respectively) followed by small-cell and squamous-cell carcinoma with almost identical results (Table 1).

Adenocarcinoma had the highest ER and DR values of all histopathological types (2.2 ± 0.7 and 1.9 ± 0.7, respectively). Among the 4 different histopathological types of lung carcinoma, there was no significant difference in ER, DR and RI values.

Considering the size, malignant lung lesions were divided into 3 groups (small: 0–1.9 cm; medium: 2.0–3.9 cm and large lesions: over 4 cm). The results showed that the values of both early and delayed ratio increased with the larger size (ER: small 1.5; medium: 1.9; large: 2.1 and DR: small 1.3; medium 1.7, and large 1.8). There was a significant difference in ER and DR values between smallest and medium or large lung lesions ($p < 0.05$). There was no significant difference in retention index values compared to size of lung lesion (Table 2).

Table 1

Values of early (ER), delayed ratio (DR) and retention index (RI)
according to histopathology (HP) type of lung lesion

HP type	mean ER ± SD	mean DR ± SD	mean RI ± SD
Adenocarcinoma	2.2 ± 0.7	1.9 ± 0.7	-10.1 ± 4.7
Squamous-cell carcinoma	1.8 ± 0.5	1.6 ± 0.4	-12.1 ± 6.8
Large-cell carcinoma	1.7 ± 0.2	1.5 ± 0.2	-12.9 ± 3.9
Small-cell carcinoma	1.8 ± 0.6	1.6 ± 0.4	-10.8 ± 4.7
Benign lung lesions (false positive)	2.2 ± 0.4	2.0 ± 0.5	-8.5 ± 21.3

Table 2

Values of early (ER), delayed ratio (DR) and retention index (RI)
according to the size of malignant lung lesion

Size (mm)	mean ER ± SD	mean DR ± SD	mean RI ± SD
0–19	1.5 ± 0.3	1.3 ± 0.3	-12.1 ± 4.6
20–39	1.9 ± 0.6	1.7 ± 0.5	-9.6 ± 5.6
> 40	2.1 ± 0.6	1.8 ± 0.5	-13.9 ± 6.7

pseudonodule showed washout of the tracer on delayed images. No washout of the tracer was noticed in 2 cases of benign lung lesions (1 botryomycosis and 1 inflammatory pseudonodule) with high values of RI (24.6 and 10.8, respectively).

All the true positive malignant lung lesions (27/30) showed washout of the tracer on delayed images. A highest difference between early and delayed ratio was noticed among adenocarcinomas and smallest difference among small-cell carcinomas. Two cases of adenocarcinoma had the highest values of ER in the group 2 (ER = 2.9 and ER = 3.0), but there was no significant difference in the ER values among the different histopathological types in the group ($p < 0.05$).

In the group 1, according to histopathological type, false positive findings were registered in 7 cases of benign LLs (6 pneumonia and 1 botryomycosis) with high values of

The values of ER, DR and RI were analyzed for lung lesions in both groups considering its localization in the right or the left lung and its lobes. In the group 1, 17 lesions were found in the left (10 were located in the lower lobe, 7 in the upper lobe) and 13 in the right lung (7 in the lower lobe, 5 in the upper lobe and 1 in the middle lobe). Among the lung lesions in the group 2, 16 were located in the right (6 in the upper, 5 in the middle and 5 in the lower lobe), and 14 in the left lung (8 in the upper and 6 in the lower lobe). No significant difference was found in ER, DR and RI values between the group 1 and the group 2 considering localization of lung lesions.

Regression analysis was used to evaluate how size, localization, histopathological report, ER and DR values influence ^{99m}Tc-MIBI accumulation (dependent variable – ^{99m}Tc-MIBI accumulation). There was a significant influence of mutual factor such as size, localization, histopathological report, ER and DR values on ^{99m}Tc-MIBI accumulation ($p <$

0.05). ^{99m}Tc-MIBI accumulation findings were explained with 75.4% ($R^2 = 0.754$) change of LLs size, localization, histopathological report, ER and DR values meaning that 75.4% of all ^{99m}Tc-MIBI findings were dependent on these factors.

The values of ER and DR were evaluated by mutual influence of the factors such as size, localization and histopathological report of lung lesions showing a significant influence of these factors on ER and DR values ($p < 0.05$). ER value was explained with 29.5% ($R^2 = 0.295$) change of these factors meaning that 29.5% ER values were dependant on these factors. At the same time, values of ER and DR were evaluated by individual influence of above factors, and the results showed that the size of lung lesions and histopathological report had significant influence on ER and DR values ($p < 0.05$; $R^2 = 0.185$ and $R^2 = 0.137$, respectively), while localization had no influence on ER or DR values (Figure 7).
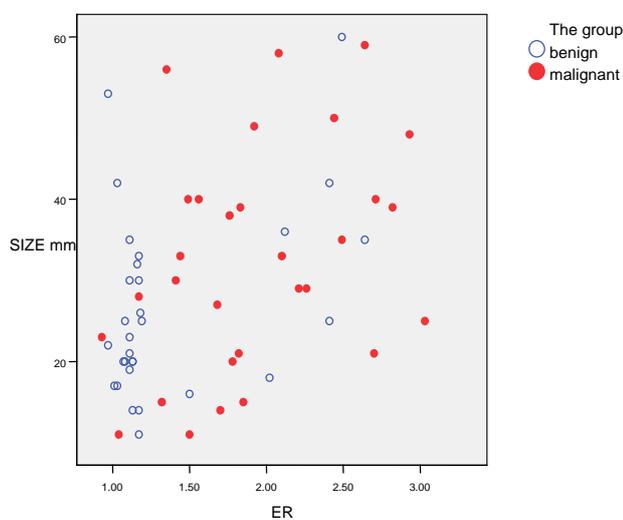
Fig. 7 – Early ratio (ER) values and size of lung lesion in the patients with benign (the group 1) and malignant (the group 2) lung lesion.

Discussion

The uptake mechanism of ^{99m}Tc-MIBI by tumor cells is not yet known but there are some possible factors influencing the uptake such as the amount of mitochondria in the cell, cell membrane potential, increased tumor blood flow and capillary permeability.[16] It is known that accumulation of ^{99m}Tc-MIBI in the tumor cell is reversely proportional to the level of P-glycoprotein (Pgp), the protein responsible for the transport of many chemotherapeutic drugs, thus increased Pgp level in the tumor is related to the resistance of malignant tumor to chemiotherapy [17]. Increased levels of Pgp were 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 [18].

Our study on 60 patients with lung lesions resulted in a significant difference between ER and DR values of ^{99m}Tc-MIBI accumulation in benign and malignant lesions showing increased values in carcinomas which could be explained with differences in mitochondrial cell amount between malignant and healthy cells, as it was reported that passive ^{99m}Tc-MIBI uptake is dependent on negative potential of the cytoplasmatic and mitochondrial membrane of neoplastic cells, showing increased accumulation in cells with higher number of mitochondria [19].

We found no significant difference in retention index values between the group 1 and the group 2. Therefore, the result suggests that the ^{99m}Tc-MIBI uptake ratio is more useful as a parameter for either benign or malignant lung lesion than values of RI. Our results are confirmed with previously reported *in vitro* studies with Hela cells where washout rate of ^{99m}Tc-MIBI from cultured cells was not related to their malignant potential [5]. Nishiyama et al. [20] agree with the conclusion that there is no significant tumor washout of ^{99m}Tc-MIBI from the tumor mass according to RI values. Concurrently, some papers report no significant difference in ER and DR values or RI of ^{99m}Tc-MIBI between benign and malignant lung lesions [21].

In our study, ER and DR values were greater in malignant than in benign lesions of the lung (1.4-fold greater and 1.36-fold greater, respectively) which is the case in numerous studies [13, 22, 23]. Hassan et al. [13] investigated accumulation of ^{99m}Tc-MIBI in 19 patients on planar images, and reported even higher DR values: 1.58-fold greater in tumor tissue than in normal lung tissue at 30 minutes. Compared to these results, our lower DR values could be explained with the methodology of our study, calculating DR on images after 60 to 120 minutes.

Our study came up with the result that the size of lung lesion significantly affects ER and DR values tending to increase values of ER and DR in larger lesions which is in concordance with the results of other papers [20, 22]. Nishiyama et al. [20] investigated 45 patients with malignant lung lesions divided by size (≤ 3 cm, ≤ 6 and ≥ 6 cm) and reported higher ER and DR values of ^{99m}Tc-MIBI (ranged from 2.1–3.3 and 1.9–3.0, respectively) than in our study but with the same growing tendency as the size of lung lesion increases. Minai et al. [11] reported a correlation of quantitative uptake of ^{99m}Tc-MIBI with the diameter of the nodule with a correlation coefficient of 0.61 ($p = 0.02$). However, several studies reported no influence of sex, age, size of tumor and histological type on ^{99m}Tc-MIBI accumulation results [22–24].

In benign group of patients (the group 1) false positive results occurred in 7 out of 30 benign lesions, 6 in inflammatory pseudonodule and 1 in botryomycosis. It is well-known that chronic inflammation and active pulmonary tuberculosis could lead to high ^{99m}Tc-MIBI uptake due to tissue factors such as high degree of tissue vascularization and capillary permeability. Alterations in cell metabolism that affect membrane potential, as might be the case in inflammatory lung lesions, could influence accumulation of ^{99m}Tc-MIBI. Furthermore, a rich mitochondrial content of epitheloid cells in granulomas might be a key point for ^{99m}Tc-MIBI uptake in tuberculosis [25]. Onsel et al. [26] investigated ^{99m}Tc-MIBI accumulation in extensive pulmonary dis-

ease with bilateral infiltrates and gained ^{99m}Tc-MIBI scan positive results in 92% cases. These results show that chronic inflammatory diseases, inflammatory pseudonodules and active tuberculosis limit the value of ^{99m}Tc-MIBI in differentiation benign from malignant lung lesions and have similar limitations as are known for [18]FDG-PET/CT [27].

In our series of malignant lung lesions, there was no significant difference in ER, DR and RI values among four different histopathological types. Of the 3 malignant lung lesions with ER values less than 1.20, one was adenocarcinoma (ER = 1.04), one was squamous-cell carcinoma (ER = 0.93) and one small-cell carcinoma (ER 1.17). Nishiyama et al. [20] report that squamous-cell carcinoma has lower ER and DR values compared to adenocarcinoma (concordant to our results) and small-cell carcinoma (discrepant to our results). Hassan et al. [13] found that adenocarcinoma and small-cell carcinoma have higher T/N values than squamous-cell carcinoma, but the results of our study show equal accumulation of ^{99m}Tc-MIBI in both squamous-cell and small-cell carcinoma. These authors also highlight that undifferentiated squamous-cell carcinoma can show no accumulation of ^{99m}Tc-MIBI, a finding that was confirmed in our study by the one case of this pathohistological cancer type which was negative on ^{99m}Tc-MIBI scan. In our study the finding that small-cell carcinoma has similar ER values as squamous-cell is in discrepancy with the Sahin et al. [28] results showing lower uptake of ^{99m}Tc-MIBI in squamous-cell than small-cell carcinoma (1.22 ± 0.14 and 1.39 ± 0.1, respectively) with a significant difference in ER and DR values between these two histopathological types of lung cancer.

There are certain limitations of our patients population preventing us to give final conclusion about the correlation between histological type and ^{99m}Tc-MIBI scan results. Firstly, in our study on 30 patients with malignant lung lesions, there were only 2 cases of small-cell carcinoma with respect to 27.2% of cases reported by Hassan et al. [13]. Secondly, the majority of malignant lung lesions in our patients were squamous-cell carcinoma, with a low prevalence of large-cell carcinoma.

Conclusion

This study suggests that the uptake ratio of ^{99m}Tc-MIBI (early and delayed ratio) could be a useful index in evaluating benign and malignant lung lesions, while retention index has no influence on this. Considering the factors related to uptake and release of the radiopharmaceutical, there was a significant difference in ER and DR values between smallest and medium or large lung lesions, while there was no significant difference in retention index values. Other investigated factors, such as localization of the lesion or different pathohistological types among benign or malignant lesions, showed no influence on the values of ER, DR or RI.

Declaration of interest

There was no financial support received for the work and the authors had no financial involvement, or affiliation nowith any organization whose financial interests may be affected by the material in the manuscript, or which might potentially bias it.

R E F E R E N C E S

1. *Yamamoto Y, Nishiyama Y, Fukunaga K, Kobayashi T, Satoh K, Fujita J,* et al. Evaluation of histopathological differentiation in lung adenocarcinoma patients using 201Tl-chloride and 99Tcm-MIBI SPET. Nucl Med Commun 2001; 22(5): 539−45.

2. *Kashitani N, Makihara S, Maeda T, Eda R, Takeyama H, Hiraki Y.* Thallium-201-chloride and technetium-99m-MIBI SPECT of primary and metastatic lung carcinoma. Oncol Rep 1999; 6(1): 127−33.

3. *Yamamoto Y, Kawasaki Y, Nishiyama Y, Fukunaga K, Satoh K, Takashima H,* et al. Comparative evaluation of 99mTc-MIBI (hexakis2-methoxy isobutyl isonitrile) and 201Tl-chloride in primary lung cancer. Kaku Igaku 1996; 33(5): 501−11.

4. *Kanaev SV, Novikov SN, Beĭnusov DS, Girtovich MM, Levchenko EV, Barchuk AS,* et al. Use of simultaneous double-tracer SPECT with 99m-Tc-technetril and 67-Ga-citrate for follow-up of patients with non-small cell lung cancer. Vopr Onkol 2012; 58(3): 346−51.

5. *Komori T, Matsui R, Adachi I, Shimizu T, Sueyoshi K, Narabayashi I.* In vitro uptake and release of 201Tl and 99mTc-MIBI in HeLa cell. Kaku Igaku 1995; 32(7): 651−8.

6. *Matsui R, Komori T, Namba R, Shimizu T, Sueyoshi K, Sano K,* et al. In vitro uptake and release of TI-201 and Tc-99m MIBI in cultured tumor cells and effect of anticancer drug. Radiat Med 1998; 16(3): 187−94.

7. *Sergieva S, Hadjieva T, Doldurova M, Stefanova S, Dudov A.* Nuclear medicine approaches in the monitoring of thyroid cancer patients. J BUON 2006; 11(4): 511−8.

8. *Nagai H, Yamasaki T, Yamamoto Y, Takada D, Miyazaki T, Sugimoto K,* et al. Evaluation of brain tumors by simultaneous dual isotope SPECT with 201Tl-chloride and 99mTc-MIBI. No Shinkei Geka 2004; 32(10): 1029−37.

9. *Yildiz A, Garipağaoğlu M, Güngör F, Boz A, Dalmaz G.* The role of technetium-99m methoxyisobutyl isonitrile scintigraphy in suspected recurrent breast cancer. Cancer Biother Radiopharm 2001; 16(2): 163−9.

10. *Nikoletic K, Lucic S, Peter A, Kolarov V, Zeravica R, Srbovan D.* Lung 99mTc-MIBI scintigraphy: impact on diagnosis of solitary pulmonary nodule. Bosn J Basic Med Sci 2011; 11(3): 174−9.

11. *Minai OA, Raja S, Mehta AC, Sullivan EJ, Khan SU, Dasgupta A,* et al. Role of Tc-99m MIBI in the evaluation of single pulmonary nodules: a preliminary report. Thorax 2000; 55(1): 60−2.

12. *Komori T, Narabayashi I, Matsui R, Sueyoshi K, Aratani T, Utsunomiya K.* Technetium-99m MIBI single photon emission computed tomography as an indicator of prognosis for patients with lung cancer-preliminaly report. Ann Nucl Med 2000; 14(6): 415−20.

13. *Hassan IM, Sahweil A, Constantinides C, Mahmoud A, Nair M, Omar YT,* et al. Uptake and kinetics of Tc-99m hexakis 2-methoxy isobutyl isonitrile in benign and malignant lesions in the lungs. Clin Nucl Med 1989; 14(5): 333−40.

14. *Shirakawa T, Mori Y, Moriya E, Dohi M, Kawakami K, Akiba T,* et al. Uptake of Tc-99m hexakis 2-methoxy isobutyl isonitrile in lung or mediastinal lesions by SPECT. Nihon Igaku Hoshasen Gakkai Zasshi 1995; 55(8): 587−92. (Japanese)

15. *Komori T, Narabayashi I, Matsui R, Tatsu Y, Sueyoshi K, Adachi I,* et al. Evaluation of uptake and release of technetium-99m MIBI SPECT of pulmonary and mediastinal lesions. Ann Nucl Med 1997; 11(3): 227−32.

16. *Chiu ML, Herman LW, Kronauge JF, Piwnica-Worms D.* Comparative effects of neutral dipolar compounds and lipophilic anions on technetium 99m-hexakis (2-methoxyisobutyl isonitrile) accumulation in cultured chick ventricular myocytes. Invest Radiol 1992; 27(12): 1052−8.

17. *Del Vecchio S, Ciarmiello A, Salvatore M.* Scintigraphic detection of multidrug resistance in cancer. Cancer Biother Radiopharm 2000; 15(4): 327−37.

18. *Mohan HK, Miles KA.* Cost-effectiveness of 99mTc-sestamibi in predicting response to chemotherapy in patients with lung cancer: systematic review and meta-analysis. J Nucl Med 2009; 50(3): 376−81.

19. *Scopinaro F, De VG, Pani R, Pellegrini R, Banci M, Casu C,* et al. 99Tcm-MIBI uptake in green plants. Nucl Med Commun 1994; 15(11): 905−15.

20. *Nishiyama Y, Kawasaki Y, Yamamoto Y, Fukunaga K, Satoh K, Takashima H,* et al. Technetium-99m-MIBI and thallium-201 scintigraphy of primary lung cancer. J Nucl Med 1997; 38(9): 1358−61.

21. *Yamamoto Y, Nishiyama Y, Fukuda Y, Satoh K, Ohkawa M, Tanabe M.* Differentiation of small solitary pulmonary nodules using Tc-99m MIBI and Tl-201 SPECT. Clin Nucl Med 1999; 24(10): 751−5.

22. *Santini M, Fiorello A, Mansi L, Rambaldi PF, Vicidomini G, Busiello L,* et al. The role of technetium-99m hexakis-2-methoxyisobutyl isonitrile in the detection of neoplastic lung lesions. Eur J Cardiothorac Surg 2009; 35(2): 325−31.

23. *Nosotti M, Santambrogio L, Gasparini M, Baisi A, Bellaviti N, Rosso L.* Role of (99m)tc-hexakis-2-methoxy-isobutylisonitrile in the diagnosis and staging of lung cancer. Chest 2002; 122(4): 1361−4.

24. *Oskoei SD, Mahmoudian B.* A comparative study of lung masses with 99mTechnetium Sestamibi and pathology results. Pak J Biol Sci 2007; 10(2): 225−9.

25. *Robbins SL, Kumar V.* Basic pathology. Philadelphia: W.B. Saunders; 1987.

26. *Onsel C, Sönmezoglu K, Camsari G, Atay S, Cetin S, Erdil YT,* et al. Technetium-99m-MIBI scintigraphy in pulmonary tuberculosis. J Nucl Med 1996; 37(2): 233−8.

27. *Chun EJ, Lee HJ, Kang WJ, Kim KG, Goo JM, Park CM,* et al. Differentiation between malignancy and inflammation in pulmonary ground-glass nodules: The feasibility of integrated (18)F-FDG PET/CT. Lung Cancer 2009; 65(2): 180−6.

28. *Sahin M, Ozcan A, Bernay I, Basoglu T, Demircali T, Uzun O,* et al. Radioisotopic Evaluation of Malignant Lung Tumors: A Technetium-99m-Methoxy-Isobutilisonitrile Study. Tr J Med Sci 1999; 29: 135−40.