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A visual and semi-quantitative assessment of ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy in differentiation of solitary pulmonary nodules

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Abstract

BACKGROUND: The aim of the study was the assessment of the clinical usefulness of scintigraphy with ^{99m}Tc-EDDA/HYNIC-TOC for purposes of a differential diagnosis of SPNs by means of a visual inspection and semi-quantitative assessment of uptake intensity of the radiopharmaceutical (RPh).

MATERIAL AND METHODS: In 53 patients (32 males and 21 females at the ages between 38 and 78 years, mean value 57) with SPN on chest radiographs or CT scans, of diameters from 1 to 5.5 (mean 2.3) cm a SPECT acquisition was performed, 2–4 h after administration of 740 MBq of RPh. Additionally, aiming at the implementation of a correction of a partial volume effect resulting from finite resolution of this technique, the measurement of the resolution of this technique was performed on an thorax phantom. Scintigraphic studies were inspected visually and semi-quantitatively, restoring real concentration of the RPh in nodules in comparison with the peritumoral background (tumour-to-backgroud ratio) by the application of resolution recovery coefficients for the respective nodule diameters. The threshold values of tumour-to-background ratio providing optimal differentiation between malignant and benign nodules of sizes smaller and larger than 2 cm in diameter were determined. Verification of scintigraphic results was based on pathological examinations of tumour samples (histopathology or cytology) and in some cases on bacteriological studies. The additional criterion of tumour benignity was accepted, based on its stable size in a time interval no shorter than 3 years.

RESULTS: In 32 patients the following malignant tumours were diagnosed: 12 adenocarcinomas, 6 squamous cell carcinomas, 6 non-small cell lung cancers of unspecified more detailed morphology, 2 large cell carcinomas, 2 small cell lung cancers, 2 carcinoids and 2 metastatic lesions (malignant melanoma and leiomyosarcoma). In 21 patients benign etiologies were found: 6 tuberculomas, 2 other granuloma, 4 hamartomas, 2 non-specific inflammatory infiltrate, 1 alien body with inflammatory reaction and 1 suppurating inflammatory lesion, 1 abscesses, 1 peripheral carcinoid of morphological features of a benign tumour, 2 tumours of unspecified etiology with sizes stable over 3 and 5 years, and 1 ectopic lesion of thyroid tissue. A visual inspection of scintigrams revealed enhanced uptake of RPh at 29 of 32 sites corresponding to locations of malignant nodules, in 2 cases (1 adenocarcinoma and 1 metastatic lesion of malignant melanoma) results were negative and in 1 (metastatic leiomyosarcoma) equivocal; in 13 of 21 benign nodules true negative results were obtained, in 4 — positive (foreign body with inflammatory reaction, abscess, suppurating inflammatory lesion and tuberculoma), in the next 4 — equivocal (2 tuberculomas, 1 hamartoma, 1 tumour of unspecified aetiology, but with a stable size over 3 years). The mean values of tumour-to-back-

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ground ratio without resolution recovery in malignant and benign nodules equalled 4.6 (sd 5.9) and 1.8 (sd 1.2), resp. ($p = 7 \times 10^{-4}$), while after resolution recovery coefficients — 7.8 (sd 7.2) and 2.7 (sd 2.8), resp. ($p = 2 \times 10^{-4}$). The semi-quantitative method resulted in true positive results in 29/32 malignant cases and true negative in 15/21 benign cases.

CONCLUSIONS: ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy is a very promising method for the differentiation of SPNs. The semi-quantitative method using resolution recovered tumour-to-background ratio enables the differentiation of malignant and benign SPNs based on the intensity of RPh uptake and facilitates the making of a decision as to the positive or negative scintigraphic character of the equivocal lesions.

Key words: lung cancer, solitary pulmonary module, receptor scintigraphy, somatostatin analogue, partial volume effect

Introduction

Lung cancer is the most commonly diagnosed malignant neoplasm worldwide. This is also true for countries of European Union, where about 190,000 new cases are diagnosed every year and about 180,000 deaths are noted due to this tumour [1]. The first identifiable manifestation of pulmonary carcinoma in a sizeable proportion of cases is a solitary pulmonary nodule (SPN), visible on a chest radiograph. SPNs are well defined, intra-parenchymal lung lesions of a diameter not exceeding 3 or 4 cm [2–4]. According to U.S. sources, the incidence of SPNs on routine chest radiographs amounts to about 1 per 500 images [5]. SPNs are caused by malignant tumours, such as primary pulmonary carcinoma or other neoplasms of the lung and metastatic tumours, but also benign lesions such as granuloma, inflammatory infiltrate, benign neoplasm and other causes. Optimal diagnostic management should reveal the character of the lesion as soon as possible and enable surgical removal of malignant ones. At the same time surgical intervention could be avoided in the majority of benign cases.

In case of difficulties being met during differential diagnosis of solitary pulmonary nodules (SPNs), when routine diagnostic methods such as CT, transthoracic fine needle biopsy, or in some cases bronchoscopy are inconclusive, ^{18}FDG PET study (if accessible) and receptor scintigraphy using ^{99m}Tc-depreotide are at disposal [4–6]. The results of our studies published recently also point out the usefulness of receptor scintigraphy using ^{99m}Tc-EDDA/HYNIC-Tyr3-octreotide (TOC) under these circumstances [7, 8]. Because of difficulties encountered while assessing visually receptor scintigrams, the idea of semi-quantification of radiopharmaceutical uptake in SPNs appeared, which would support a visual image analysis. This method would use a tumour-to-background-ratio as a measure of the radiopharmaceutical uptake. The use of such a method, however, necessitates the correction of the effects resulting from poor resolution of the SPECT technique, such as the "partial volume effect" (the displacement of a part of the gamma rays originating at the tumour site outside its image) and the "spill over effect" (the registration at the tumour site of some counts originating in the background). Because of small size of SPNs, these effects dramatically change the values of the tumour-to-background ratio calculated directly from the image — Figure 1. A Kessler and et al. [9] model of the correction of the effects of finite resolution on counts in small hot foci in the radioactive background, further developed and verified by Zito et al [10] was used.

Material and methods

Studies of 53 patients (32 men and 21 women at the age of 34 to 78 years, mean value 57) were analyzed, referred to Department of Nuclear Medicine of Medical University in Lodz after a SPN on a pulmonary radiograph had been found. Computer tomography studies were made not earlier than 1.5 months before scintigraphy. Diameters of the nodules measured on CT images ranged between 1.0 and 5.5 cm (mean 2.3 cm); in 33 cases

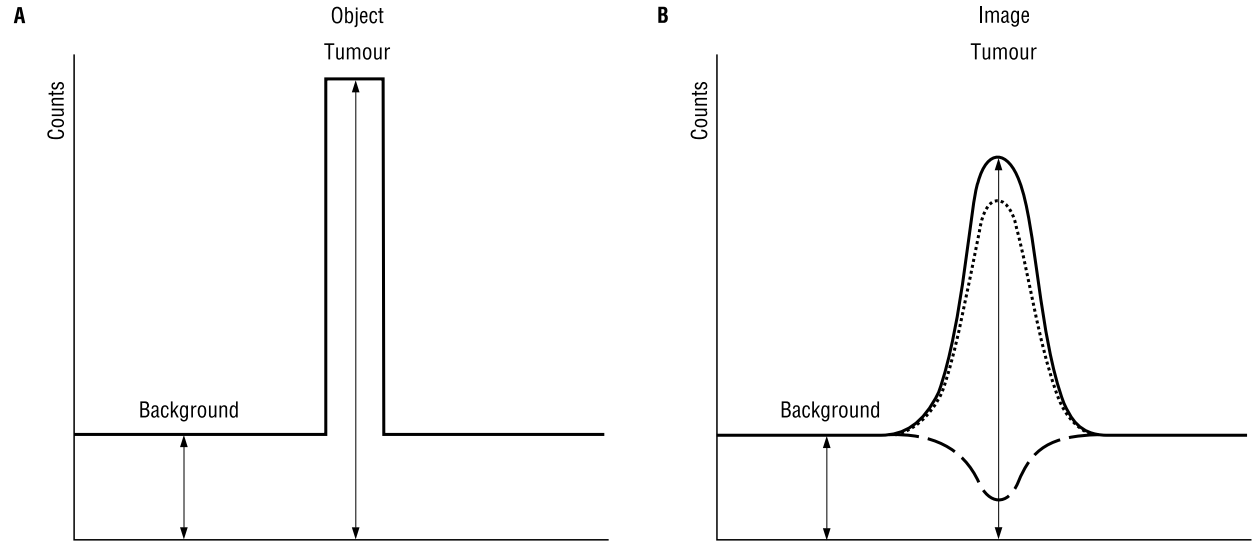

Figure 1 AB. Effect of resolution on imaging of a hot spot object in radioactive background. Dotted line — count profile of hot object, dashed line — background, continuous line — effective profile.

(77%) did not exceed 3 cm. Scintigraphic studies were performed with SPECT technique after administration of 740 to 925 MBq of ^{99m}Tc-EDDA/HYNIC-TOC (OBRI, Otwock, Poland). Details of radiopharmaceutical preparation were published earlier [7].

Study acquisition and reconstruction

The imaging started 2 hours post injection. The SPECT acquisition was made using a dual head VariCam gamma camera (Elscint, Haifa, Israel). High resolution collimators, the matrix size of 128 × 128 pixels and body contouring were applied. 120 projections were acquired, each of 25 s duration. For the reconstruction of tomographic images a Metz filter of power 3 and FWHM of 1 cm was used.

Interpretation of scintigrams

Images were evaluated visually and semi-quantitatively.

Visual analysis was made by two specialists in nuclear medicine, not aware of the tumour aetiology and results were achieved by consensus. Scintigrams were classified as positive, negative or equivocal.

Semi-quantitative analysis was based on the calculation of the tumour-to-background-ratio. A correction of the effects resulting from the poor resolution of the SPECT technique was applied.

The following formulae were used, presenting relationship between the tracer concentration on the image of a small spherical object (C_M) and its real value (C_R), image resolution and radioactive background (C_B):

$$C_M = C_R \times RC_H + C_B \times RC_c \quad (1)$$

where RC_H denotes a hot spot recovery coefficient defined as a ratio of measured to real tracer concentration and RC_C — cold spot recovery coefficient.

After the transformation of formula (1) and taking into account that $RC_C = 1–RC_H$, Zito et al [10] obtained the following formula enabling the recovery of real tracer concentration in a small spherical object, based on measured values C_M and C_B:

$$C_R = C_M/RC_H - C_B(1/RC_H - 1) \quad (2)$$

The application of formula (2) is possible when the real diameter of spherical object and values of RC_H as a function of object size are known. Diameters of SPNs were measured on CT images; in cases when their shape was not strictly spherical, the mean values of diameters along 3 axes were applied. Values of RC_H for various nodule diameters related to a SPECT study resolution were read from a plot presented in a publication by Zito et al [10], obtained as a result of an experimental examination of the effect of hot spot sizes, in a range comparable with gamma camera resolution, on the tracer concentration read directly from image. The resolution of the SPECT technique was measured on a thorax phantom (Rando Man, Alderson), with the application of the acquisition and reconstruction parameters as in the clinical studies. Values of C_M and C_B were obtained directly from a transverse slice with maximal cross-section of the nodule. Tracer concentration C_M in a nodule was measured from a small centrally located 5 pixels ROI. Background tracer concentration was determined from a circular, 6 pixels in diameter ROI located contralaterally in the other lung. After a real tracer concentration (C_R) in a nodule had been obtained, its value was related to the background concentration (C_B), thus giving a corrected tumour-to-background-ratio (C_R/C_B). In case when at a site corresponding to the nodule location no enhanced tracer uptake was found, a tumour-to-background ratio without correction was used.

Optimal threshold value of the corrected tumour-to-background ratio (C_R/C_B) was chosen providing the most effective differentiation of malignant from benign SPNs.

No attenuation correction was applied.

Phantom studies

Phantom studies were performed in order to obtain resolution measures as in the clinical studies. In a thorax phantom Rando Man (Alderson), in 3 pulmonary lobes (upper, middle and lower), parallel to camera axis of rotation, capillaries filled with ^{99m}Tc of specific activity of 740 MBq/ml were placed — Figure 2. In order to examine variability of resolution inside lower and middle pulmonary lobes, 4 capillaries at the 4 utmost locations (posterior, anterior, lateral and mediastinal) were placed. The acquisition protocol was the same as in the clinical studies, except for a short-

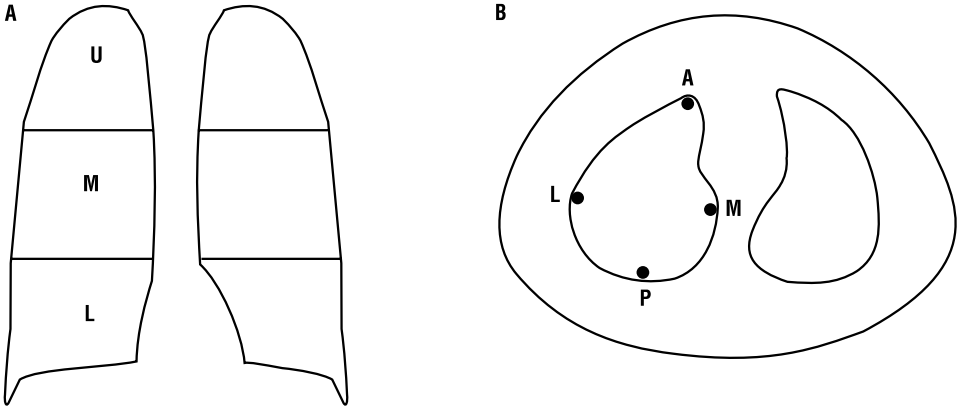

Figure 2 AB. Resolution measurement of clinical studies. Lung phantom with ^{99m}Tc-filled capillaries. U, M, L — upper, middle and lower lobes; A, P, L, M — anterior, posterior, lateral, and mediastinal locations.

Table 1. Results of resolution measurements in 3 lung lobes (U — upper, M — middle, L — lower) and 4 (A — anterior, P — posterior, L — latteral and M — mediastinal) locations

	Lower lobe				Middle lobe				Upper lobe	Mean
	A	P	L	M	A	P	L	M		
FWHM [cm]	1.89	1.97	1.87	1.94	1.93	1.99	1.92	1.89	2.03	**1.94**

ened time per image (10 s). Tomographic reconstructions were performed using the same filter as in the clinical studies. Profiles along X and Y axes on transverse slices were generated and by the use of STATISTICA package Gaussian functions were fitted. Standard deviations of those functions were transformed to resolution measures (as FWHM), by substituting real measures (in cm) of pixels for their numbers. The mean values of the resolutions along X and Y were used as actual resolutions.

Results

Phantom studies

The resolution measures in specific locations of three pulmonary lobes, are presented in Table 1. The resolution is relatively stable, inside as well as among pulmonary lobes. For this reason, a uniform resolution measure equal to 1.9 cm was accepted for further calculations.

Patient studies

Diagnosed aetiologies of SPNs are presented in Table 2. The diameters of malignant tumours fell in the range of 1.0 to 5.5 cm (mean 2.9 cm), whereas the diameters of benign lesions ranged from 1.0 to 4.5 cm (mean 1.7 cm).

Table 2. Diagnosed etiologies of SPNs

Malignant tumours	No. of cases
Adenocarcinoma	12
Squamous cell carcinoma	6
Large cell carcinoma	2
NSCLC	6
SCLC	2
Typical carcinoid	2
Metastatic tumours	2
Total	**32**
Benign tumours	
Tuberculoma	6
Other granuloma	2
Hamartoma	4
Non-specific inflammatory infiltrate	2
Foreign body with inflammatory reaction	1
Suppurating inflammatory lesion	1
Abscess	1
Peripheral carcinoid of morphological features of a benign tumour	1
Tumours of unspecified etiology with sizes stable over 3 and 5 years	2
Ectopic lesion of thyroid tissue	1
Total	**21**

SCLC — small cell lung cancer; NSCLC — non-small cell lung cancer

Table 3. Results of visual image analysis

	Results of scintigraphy			Total
	+	–	±	
Malignant tumours	29*	2	1	32
Benign tumours	4	13	4	21

*27 out of 28 cases of primary lung cancer

Visual analysis: positive scintigraphic results were found in 29 out of 32 (91%) patients with malignant SPNs (Table 3); among those 27 out of 28 (96%) in patients with primary lung carcinoma. Among two remaining cases, one was negative (metastatic malignant melanoma) and one equivocal (metastatic leiomyosarcoma).

Out of 21 benign tumours, in 13 cases (62%) negative results were obtained, in 4 — positive (foreign body with inflammatory reaction, abscess, suppurating inflammatory lesion and tuberculoma), in the next 4 — equivocal (2 tuberculomas, 1 hamartoma, 1 tumour of unspecified aetiology, but with a stable size for over 3 years).

Semi-quantitative analysis: in Figure 3 mean values and standard deviations of the tumour-to-background ratio, without and with resolution recovery, in patients with benign and malignant nodules are presented. As can be seen, the introduction of resolution recovery coefficients improved the separation between results in both groups. The statistical significance between mean values increased from 7×10^{-4} to 2×10^{-4}. Moreover, in malignant nodules taking up the tracer a statistically significant negative correlation between nodule size and intensity of the tracer uptake was found (Figure 4). For this reason, before a semi-quantitative criterion for differentiation between malignant and benign nodules was introduced, nodules were divided into 2 groups according to their size: smaller or equal to 2 cm in diameter and larger. As can be inferred from Figure 4, the tumour-to-background ratio in no nodule smaller or equal 2 cm was lower than 5, whereas among nodules larger than 2 cm in diameter — 3. These values were accepted as threshold criteria, differentiating semi-quantitatively tracer uptake in malignant and benign SPNs. The application of those semi-quantitative diagnostic criteria enabled a correction of suboptimal specificity of visual analysis of scintigrams to be carried out (Table 4). Out of 4 equivocal results in cases of benign nodules, 2 were semi-quantitatively negative, improving specificity of the study to 71%, and the remaining 2 were positive. The equivocal result of visual analysis in cases of metastatic leiomyosarcoma turned out negative according to the semi-quantitative analysis.

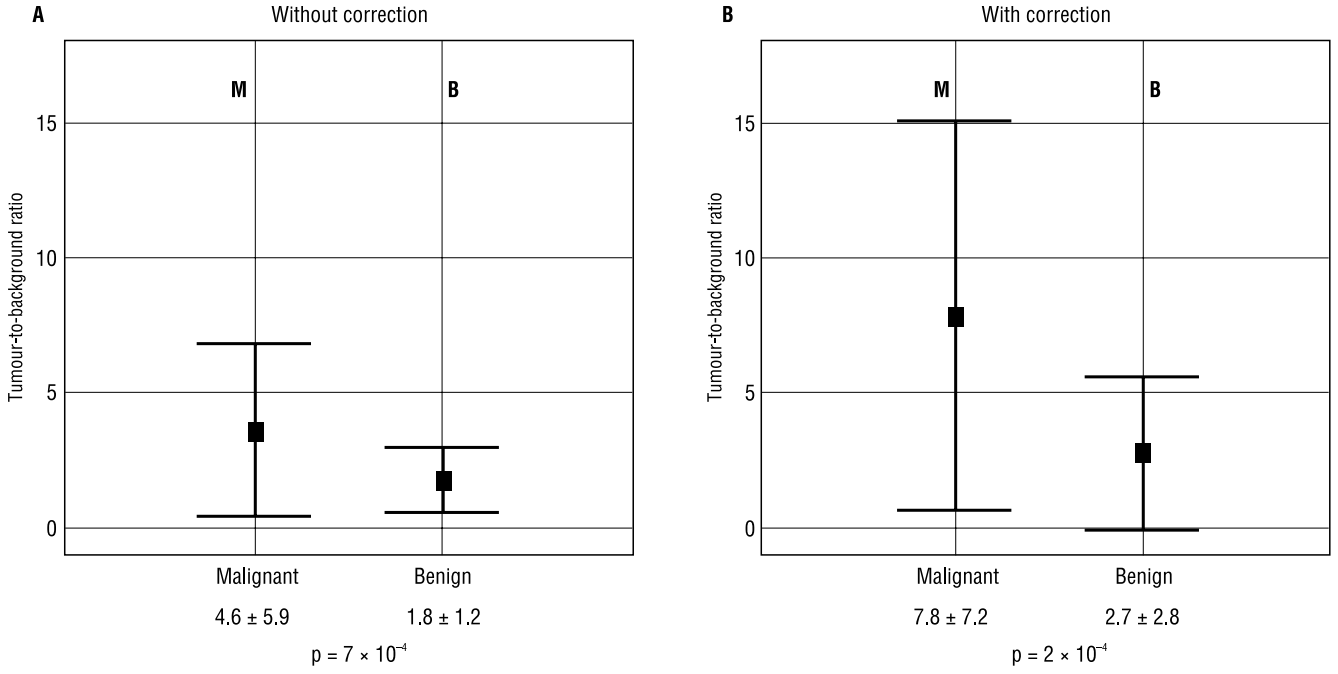

Figure 3. Tumour-to-background ratio without (**A**) and with (**B**) resolution recovery in malignant (M) and benign (B) nodules.

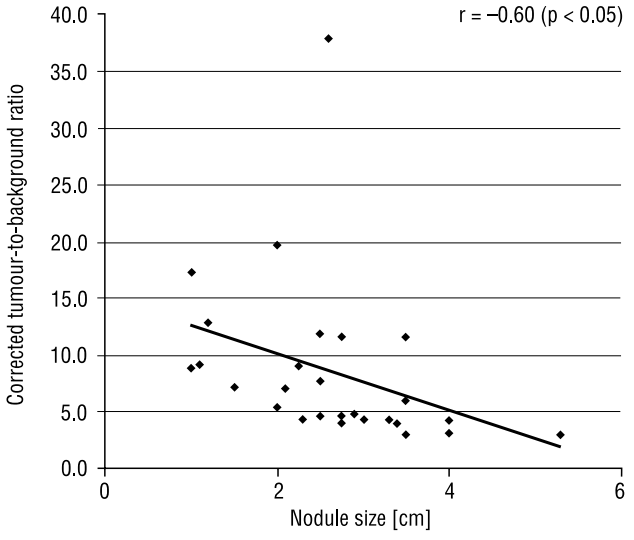

Figure 4. Negative correlation between corrected tumour-to-backgroud ratio and nodule size.

Table 4. Results of semi-quantitative image analysis

	Results of scintigraphy		Total
	+	–	
Malignant tumours	29*	3	32
Benign tumours	6	15	21

*27 out of 28 cases of primary lung cancer

Examples of lung scintigrams obtained using ^{99m}Tc-EDDA/HYNIC-TOC as a tracer, along with the results of a semi-quantitative analysis, are presented in Figures 5 and 6. Figure 5 presents the effect of the application of the semiquantitative method on a case of a small tumour (12 mm in diameter) and Figure 6, on a case visually assessed as equivocal.

Discussion

A need for a semiquantitative assessment of the radiopharmaceutical uptake in SPNs resulted from difficulties met while assessing images after the administration of ^{99m}Tc-EDDA/HYNIC-TOC, when a slight uptake in a tumour surrounded by a non-homogenous distribution of a tracer does not necessarily seem to justify a positive result of scintigraphy. This situation was retrospectively recognized mostly in cases of benign nodules, thus justifying expectations for the improvement in the specificity of the method resulting from the introduction of the semiquantitative assessment of scintigrams.

However, the introduction of the semiquantitative method for the assessment of SPECT images as a means for differentiating between malignant and benign SPNs is a challenge for this imaging modality because of small tumour sizes, comparable with the resolution of the technique. These effects play an important role because of a strong impact of tumour sizes on values of tumour-to-background ratio obtained directly from scintigraphic images. Thus, before using values of tumour-to-background ratio for differentiation purposes, the strong impact of tumour sizes should be eliminated. This problem has also been noticed while using an FDG PET study for the purposes of the differentiation of SPNs. In

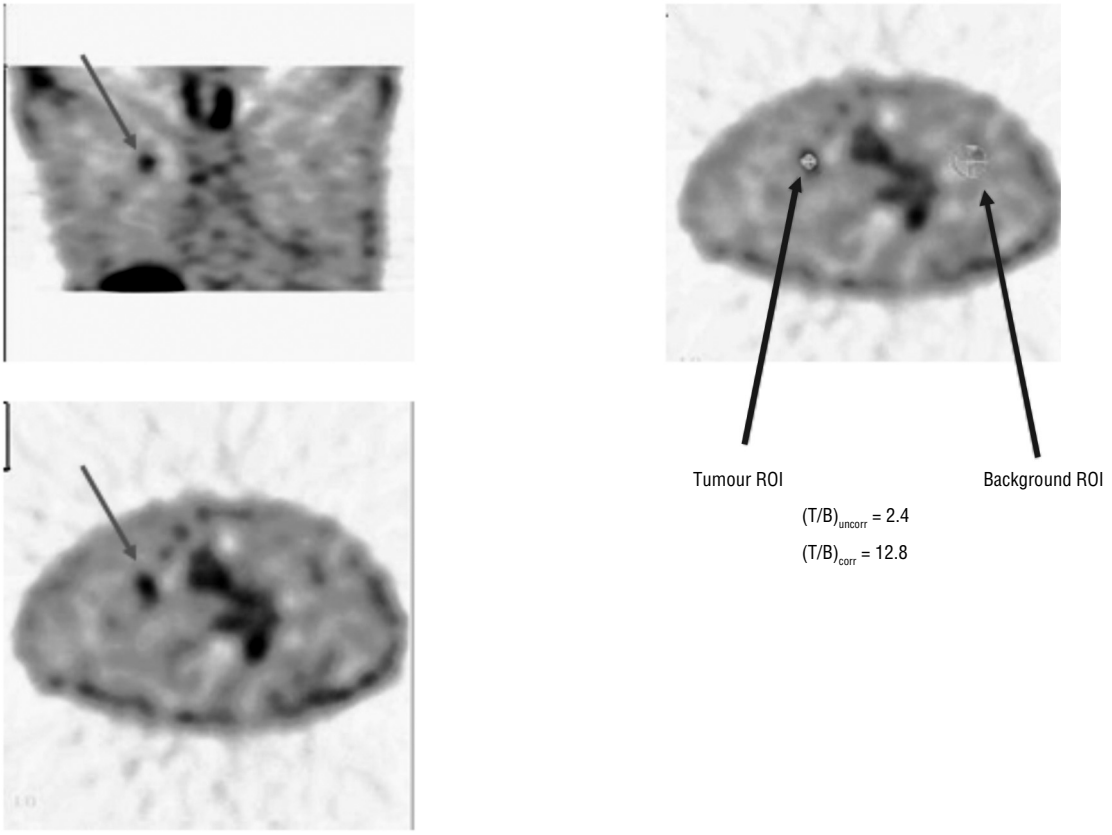

Figure 5. Example of a positive result of semi-quantitative analysis (nodule 1.2 cm in diameter). Histo-pathology: squamous cell lung cancer.

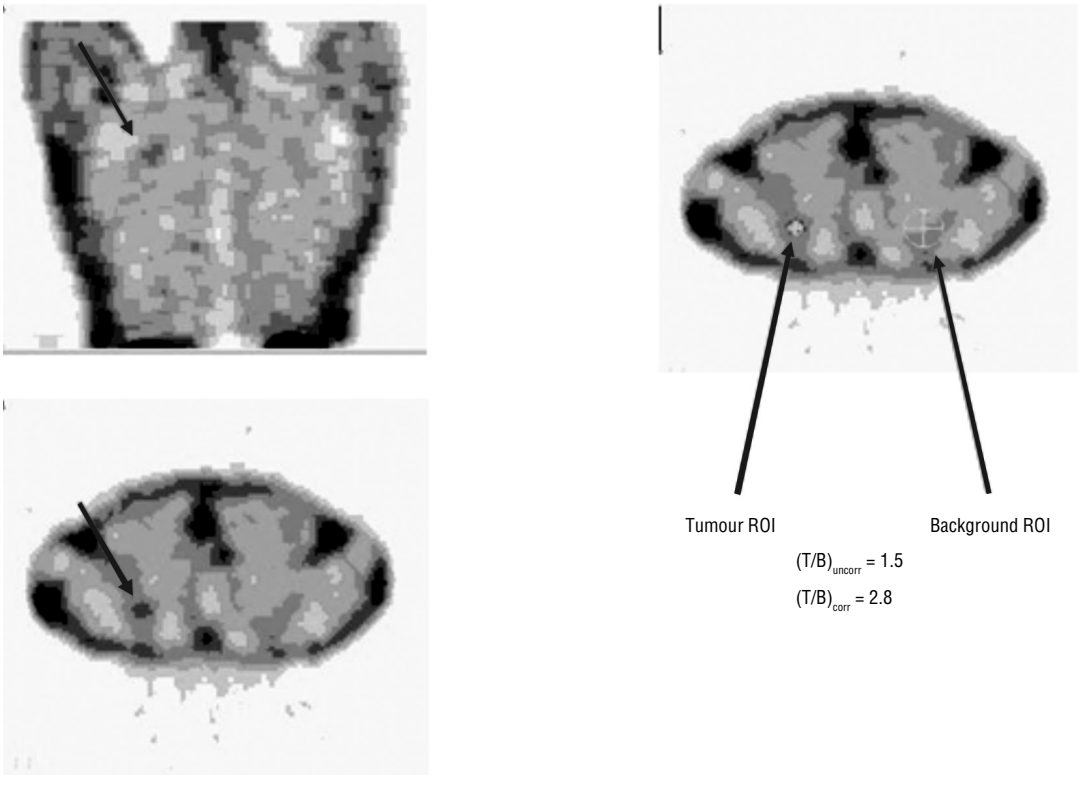

Figure 6. Example of a negative result of a semi-quantitative analysis (nodule 2 cm in diameter). Final diagnosis — tuberculoma.

cases of nodules smaller than 2 cm in diameter standardized uptake values (SUV) do not provide an effective means for differentiation between malignant and benign ones. Introduction of a correction for partial volume effect to standardized uptake values of FGD in a PET study improved its efficacy [11].

Theoretically, the most appropriate method for the correction of a radiopharmaceutical uptake in a tumour should take into account all counts originating at the tumour, spread in adjacent tomographic slices, after the subtraction of adequate background values originating in adjacent structures and, after normalization to background value in a contralateral lung and actual tumour volume. Such a method, however, would be very time consuming and susceptible to random errors. Moreover, a need for using a region of interest much bigger than actual tumour size, resulting from poor resolution of this imaging modality would preclude a proper separations of counts originating at a tumour from that at other structures. A model of correction for partial volume and spill over effects applied in this work has been verified by Zito et al [10] on a phantom with hot spots of various sizes, filled with uniform background. It uses only a small sample of counts taken from the central part of the tumour, thus minimizing problems resulting from the overlapping of other structures expressing somatostatin receptors on tumour margin. The application of this model to tumours located in the thorax results in a considerable disadvantage because the patient's respiratory movements cannot be taken into account. These movements further compromise the resolution of the study. The range of respiratory movements is particularly pronounced in the proximity of the diaphragm [12] and therefore results of a semiquantitative assessment of tumours localized in this region should be treated with caution.

This method, however, enables the elimination of effects resulting from different tumour sizes. Respiratory movements should additionally lower maximum counts, especially in cases of small tumours, and thus hamper their detection. This is why a negative, statistically significant correlation between tumour size and radiopharmaceutical uptake intensity found in our work cannot be easily explained. The presence of somatostatin receptors in peritumoral vessels [13] causing additional, surface uptake of the tracer resulting in a higher effective uptake in small tumours, or a more likely presence of necrosis in bigger tumour lesions than in smaller ones, resulting in lower tracer concentration might provide some explanations for this phenomenon. All in all, it probably improves the sensitivity of the method in the detection of small lesions such as SPN and, at least partly, compensates for the poor resolution of SPECT imaging.

As mentioned earlier, the specificity of somatostatin receptor scintigraphy used in the differential diagnosis of SPNs is relatively low, but the same is true for the FDG PET study. In our material, 3 benign lesions (1 abscess and 2 suppurating inflammatory lesions) were definitely positive on scintigrams, and another 4 (3 granulomas and 1 hamartoma) were assessed as equivocal. From among the latter, the semiquantitative method evaluated 2 as positive and the remaining 2 as negative, thus improving the specificity of the receptor scintigraphy using 99mTc-HYNIC/ /EDDA-TOC as a tracer from 62 to 71%. The low specificity of the study can be attributed to the structure of the material — a relatively high percentage of active inflammatory lesions among benign nodules. From among malignant nodules only one case (a metastatic leiomyosarcoma) was visually evaluated as equivocal. A semiquantitative analysis, using a value of 3 as a threshold criterion, assessed this case as negative. Although acceptance of a threshold criterion of 2 was also possible without worsening specificity of the method, this low threshold would have probably caused acceptance of all lesions of only a slight tracer accumulation as positive results, thus compromising the differentiation capabilities of the semiquantitative method. Taking into account the fact, that the other case of metastatic lesion (melanoma) also turned out negative, a probable low efficacy of somatostatin receptor scintigraphy in visualisation of metastatic lesions in the lung should be rather accepted, which is in agreement with the opinions presented in the literature [14].

In summation, the supplementary role of the proposed semiquantitative method for the assessment of ^{99m}Tc-EDDA/HYNIC-TOC uptake in SPNs in relation to the visual evaluation should be emphasized. The application of coefficients correcting the effects of a finite resolution of SPECT modality followed by the optimal cut-off threshold value facilitates the making of a decision as to the positive or negative scintigraphic character of the equivocal lesion.

References

1. Cancer incidence, mortality and prevalence in the European Union. www-dep.iarc.fr/eucan/eucan.htm.
2. Dewan NA, Shehan CJ, Reeb SD, Gobar LS, Walter JS, Ryschon K. Likelihood of malignancy in solitary pulmonary nodule. Comparison of Bayesian analysis and results of FDG-PET scan. Chest 1997; 112: 416.
3. Gambhir SS, Shepherd JE, Shah BD, Hart E, Hah CK, Valk PE, Emi T, Phelps ME. Analytical decision model for the cost-effective management of solitary pulmonary nodules. J Clin Oncol 1998; 16: 2113.
4. Lowe VJ, Hoffman JMM, De Jong DM, Patz EF, Coleman RE. Semiquantitative and visual analysis of FDG-PET images in pulmonary abnormalities. J Nucl Med. 1994; 35: 1771.
5. Blum J, Handmaker H, Lister-James J. A multicenter trial with a somatostatin analogue 99mTc Depreotide in the evaluation of solitary pulmonary nodules. Chest 2000; 117: 1232.
6. Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. JAMA 2001; 285: 914.
7. Płachcińska A, Mikołajczak R, Maecke HR, Michalski A, Rzeszutek K, Kozak J, Kuśmierek J. Eur J Nucl Med. Mol Imaging ^{99m}Tc-EDDA/HYNIC TOC scintigraphy in differential diagnosis of solitary pulmonary nodules. 2004; 31: 1005–1010.
8. Płachcińska A, Mikołajczak R, Maecke HR, Kozak J, Michalski A, Rzeszutek K, Kuśmierek J. Efficacy of ^{99m}Tc-EDDA/HYNIC TOC scintigraphy in differential diagnosis of solitary pulmonary nodules. Cancer Biother Radiopharm 2004; 19: 613–620.
9. Kessler RM, Ellis JR, Eden M. Analysis of emission tomographic scan data: limitations imposed by resolution and background. J Comput Assist Tomogr 1984; 8: 514–522.
10. Zito F, Gillardi MC, Magnani P, Fazio F. Single-photon emission tomographic quantification in spherical objects: effects of object size and background. Eur J Nucl Med 1996: 23: 263–271.
11. Hickeson M, Yun M, Matthies A, Zhuang H, Adam LE, Lacorte L, Alavi A. Use of a corrected standardized uptake value based on the lesion size on CT permits accurate characterization of lung nodules on FDG-PET. Eur J Nucl Med Mol Imaging 2002; 29: 1639–1647.

12. Erdi YE, Nehmeh SA, Pan T, Pevsner A, Rosenzweig KE, Mageras G, Yorke ED, Schoder H, Hsiao W, Squire OD, vernon P, Ashman JB, Mostafari H, Larson SM, Humm JL. The CT motion quantitation of lung lesions and its impact on PET-measured SUVs. J Nucl Med 2004; 45: 1287–1292.
13. Denzler B, Reubi JC. Expression of somatostatin receptors in peritumoral veins of human tumors. Cancer 1999; 85: 188–198.
14. Chiti A, Schreiner FAG, Crippa F, Pauwels EKJ, Bombardieri E. Nuclear medicine procedures in lung cancer. Eur J Nucl Med Mol Imaging 1999; 26: 533–555.