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

Anna Płachcińska¹, Renata Mikolajczak², Józef Kozak³, Katarzyna Rzeszutek⁴, Jacek Kuśmierek⁵
¹Department of Nuclear Medicine, Medical University, Łódź, Poland
²Radioisotope Centre POLATOM, Otwock-Świerk, Poland
³Ward of Thoracic Surgery, Copernicus Hospital, Łódź, Poland
⁴Centre for Treatment of Pulmonary Diseases, Łódź, Poland

[Received 27 X 2004; Accepted 2 XI 2004]

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-
ground ratio without resolution recovery in malignant and benign nodules equaled 4.6 (sd 5.9) and 1.8 (sd 1.2), resp. (p = 7 × 10⁻⁴), while after resolution recovery coefficients — 7.8 (sd 7.2) and 2.7 (sd 2.8), resp. (p = 2 × 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: ⁹⁹mTc-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, ¹⁸FDG-PET study (if accessible) and receptor scintigraphy using ⁹⁹mTc-depotride are at disposal [4–6]. The results of our studies published recently also point out the usefulness of receptor scintigraphy using ⁹⁹mTc-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
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 x 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 ($C_B$):

$$C_M = C_R \times R_{CH} + C_B \times R_{Cc}$$  \hspace{1cm} (1)

where $R_{CH}$ denotes a hot spot recovery coefficient defined as a ratio of measured to real tracer concentration and $R_{Cc}$ — cold spot recovery coefficient.

After the transformation of formula (1) and taking into account that $R_{Cc} = 1 - R_{CH}$, 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 $C_B$:

$$C_R = C_M /R_{CH} - C_B (1/R_{CH} - 1)$$  \hspace{1cm} (2)

Optimal threshold value of the corrected tumour-to-background ratio ($C_M/C_B$) 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](https://example.com/figure2.png)

*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.*

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

<table>
<thead>
<tr>
<th></th>
<th>Lower lobe</th>
<th>Middle lobe</th>
<th>Upper lobe</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>P</td>
<td>L</td>
<td>M</td>
</tr>
<tr>
<td>FWHM [cm]</td>
<td>1.89</td>
<td>1.97</td>
<td>1.87</td>
<td>1.94</td>
</tr>
</tbody>
</table>

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).

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.
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 3. Tumour-to-background ratio without (A) and with (B) resolution recovery in malignant (M) and benign (B) nodules.](attachment:image1)

![Figure 4. Negative correlation between corrected tumour-to-background ratio and nodule size.](attachment:image2)

**Table 4. Results of semi-quantitative image analysis**

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Results of scintigraphy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

*27 out of 28 cases of primary lung cancer*
Figure 5. Example of a positive result of semi-quantitative analysis (nodule 1.2 cm in diameter). Histo-pathology: squamous cell lung cancer.

Tumour ROI  Background ROI  
(T/B)_{uncorr} = 2.4  
(T/B)_{corr} = 12.8

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

Tumour ROI  Background ROI  
(T/B)_{uncorr} = 1.5  
(T/B)_{corr} = 2.8
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 FGD 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 99mTc-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


Anna Płachcińska et al., 99mTc-EDDA/HYNIC-TOC scintigraphy in differentiation of solitary pulmonary nodules
