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# $^{99m}$tc-Depreotide And $^{99m}$tc-EDDA/HYNIC-Tyr3-Octreotide Somatostatin Receptor Scintigraphy in Evaluation of Radiologically Indeterminate Solitary Pulmonary Nodules

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## Abstract

The aim of our study was to assess somatostatin receptor scintigraphy (SRS) in evaluation of solitary pulmonary nodules (SPNs). 93 patients with SPNs underwent SRS single photon emission tomography (SPECT) performed with use of one of two somatostatin analogues: $^{99m}$Tc-depreotide (49 patients) and $^{99m}$Tc-EDDA/HYNIC-Tyr$^3$-octreotide (44 patients). $^{99m}$Tc-depreotide uptake was true positive (TP) in 37/38 malignant SPNs, and true negative (TN) in 10/11 patients, one false-negative (FN) result and one false-positive (FP) result; the sensitivity, specificity and diagnostic accuracy was 97%, 91% and 96% respectively. In $^{99m}$Tc-EDDA/HYNIC-Tyr$^3$-octreotide SRS there were 12 of 20 TP results, 21 of 24 TN results, 8 of 20 were FN and 3 of 24 was FP, resulting in a sensitivity, specificity and diagnostic accuracy of 60%, 88% and 75% respectively.

**Conclusions**: $^{99m}$Tc-depreotide SRS in evaluation of SPNs can be recommended as alternative method of diagnosis, while $^{99m}$Tc-EDDA/HYNIC-Tyr$^3$-octreotide SRS is less effective.

**Keywords:** Solitary pulmonary nodule; $^{99m}$Tc-depreotide; $^{99m}$Tc-TOC; Somatostatin receptor scintigraphy

## Introduction

Solitary pulmonary nodules (SPNs) are relatively common radiological findings (1/500 routine chest radiographs) [1,2], which may be defined as a round lesion ≤3 cm, surrounded by normal pulmonary parenchyma, without other abnormalities [3]. The need for diagnosis of such nodules remains still very high because of possible neoplastic origin [2,4,5] and difficulties with obtaining material for histopathology in possibly harmless way. Noninvasive diagnosis of SPN with somatostatin receptor scintigraphy (SRS) may be provided by a number of somatostatin analogues, with different affinity to various subtypes of somatostatin receptors (SSTRs). The majority of pulmonary tumors including small cell lung cancer (SCLC) express SSTRs in high density, but the expression of subtypes of SSTRs varies in different tumor types [6-8]. Although *in vitro* studies have not demonstrated somatostatin receptors in non-small cell lung cancer (NSCLC), the ability of somatostatin analogues to detect NSCLC *in vivo* is well known [4]. Among variety somatostatin analogues $^{99m}$Tc-depreotide and $^{99m}$Tc-EDDA/HYNIC-Tyr$^3$-octreotide ($^{99m}$Tc-TOC) are widely used in Poland. The aim of our study was to assess and compare $^{99m}$Tc-depreotide and $^{99m}$Tc-TOC somatostatin receptor scintigraphy in evaluation of radiologically indeterminate SPNs.

## Material and Methods

### Study design

Somatostatin receptor scintigraphy (SRS) was performed in 93 patients to verify radiologically indeterminate SPN. This prospective study encompassed 27 men and 66 women, aged 30-76 years, mean 57 years (Table 1). All patients were asymptomatic and enrolled in the study after accidental detection of SPN with the use of chest x-ray or computed tomography (CT). Examined group did not include patients with characteristic patterns of calcification within nodules on CT scans, considered as markers of benignity. Patients with the history of cancer, tumors larger than 3 cm. multiple lesions in lungs or tumors accompanied by regional lymphadenopathy were excluded from the study. The study population was subdivided into two groups according to the type of radiolabelled somatostatin analogues used in the project. The selection of radiopharmaceuticals was dependent on blind test. $^{99m}$Tc-depreotide-study cohort consisted of 49 patients (34 male, 15 female); $^{99m}$Tc-TOC-study group comprised 44 patients (32 male, 12 female (Table 2).

### Imaging procedures

Radiotracers were administered i.v., mean activity for both of them was 740 MBq; $^{99m}$Tc-depreotide (NeoSPECT Cisbio, France) contained 50 μg depreotide peptide whereas $^{99m}$Tc-TOC ($^{99m}$Tc-Tektrotyd, POLATOM, Swierk, Poland) 20 μg HYNIC-TOC peptide. The scintigraphies were performed using double-headed gamma camera (Varicam, Elscint, Haifa, Israel) with low-energy, high-resolution collimators. All patients had whole-body scan and single photon emission tomography (SPECT) of the thorax obtained 2-4 hours after

| | | |
|---|---|---|
| Gender | Female | 27 |
| | Male | 66 |
| Age, years | 57±11.3 (30-76) | |
| Smoking history | Never smoked | 20 |
| | Ex-smokers | 48 |
| | Current smokers | 25 |

**Table 1:** Demographic characteristic of 93 patients included to the study.

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| Histology | $^{99m}$Tc- depreotide | $^{99m}$Tc-TOC |
|---|---|---|
| Small cell lung cancer | 1 | 1 |
| Adenocarcioma | 9 | 10 |
| Squamos cell carcioma | 23 | 6 |
| Large cell carcinoma | 3 | - |
| Typical carcionoid | 2 | 3 |
| **All malignant lesions** | **38** | **20** |
| Tuberculoma | 2 | 3 |
| Hamartoma | 4 | 4 |
| Fibrosis | 2 | 4 |
| Non-specific inflammations | 3 | 6 |
| Granulomas | - | 3 |
| Mycosis | - | 3 |
| Vascular malformation | - | 1 |
| **All benign lesions** | **11** | **24** |

**Table 2:** Etiology of SPNs.

injection. SPECT data were acquired on 128x128 matrix, through 360° rotation with 120 projections (25 seconds/projection). Tomographic reconstruction was performed using filtered back projection (Butterworth filter, cut off frequency 0.3, order 5). The attenuation correction was not performed.

Radiopharmaceutical accumulation in the lesions was evaluated visually and semi-quantitatively. For semi-quantitative evaluation of SPECT images, coronal slices were used. Semi-quantitative analysis was based on the calculation of radioactivity measurement of a tumor–to–background ratio (T/B). Ratios were expressed as the quotient of activity in the regions of interest (ROIs): mean counts per pixel in the tumor and mean counts in the background (determined symmetrically on both sides of the same slice), as describe previously [9] (Figure 1). In all cancer patients, besides primary lesion we analyzed hilar lymph nodes uptake of both radiotracers. SRS results were assessed by two independent nuclear medicine specialists.

## Surgery procedures

Surgery procedures were performed in all patients with high accumulation of radiotracer within the SPN. In patients with no lesion uptake of radioactive somatostatin analogue, biopsies under CT control were performed and further procedures were dependent on cytological diagnosis and the surgery risk factors. Some patients with no radiotracer uptake, whose lesions were insufficient for biopsy, underwent thoracic surgery procedures. In the whole study cohort 65 patients underwent surgery. The wedge resection (segmentectomy) was performed in 20 cases, lobectomy in 43 patients and pulmonectomy (because of lesion localization) in 2 patients. Surgery was not performed in 28 patients with benign, histologically proved SPNs. All these patients stay under close observation in the outpatient manner. In each case intra-operative pathomorphological tests were carried out as well as mediastinum lymph nodes sampling. On the basis on performed histopathology studies 51 patients were diagnosed with NSCLC, 2 with SCLC and 5 with typical carcinoids. Clinical staging of NSLC was established as IA in 14 patients, IB in 25 patients and stage II in 12 patients. Two cases of SCCL were diagnosed as local disease.

Each of the patients signed an informed consent for the study. The study protocol and informed consent form was approved by the ethics committee of The Bioethical Council, Medical University of Lublin, Poland. The tests were well tolerated by all the patients.

## Statistical analysis

All measures were expressed as mean values ± standard deviation. Statistical significance was defined as $p \leq 0.05$. Statistical analysis was performed using the software STATISTICA 6.0 (StatSoft, Poland)

# Results

## $^{99m}$Tc-depreotide-study group

$^{99m}$Tc-depreotide scan concerning primary lesion was true-positive (TP) in 37 cases (1 SCLC, 35 NSCLC, 2 typical carcinoids) of 38 malignant SPNs. In 1 case of NSCLC (adenocarcinoma, diameter 7 mm) accumulation of the tracer was not detected (Figure 2), what resulted in one false negative (FN) result. In one case a benign lesion (tuberculoma) (Figure 3), presented accumulation of radiotracer which was marked as false-positive (FP) result whereas true-negative (TN) results were confirmed in 10 of 11 patients with benign lesions. Based on these results, the values of sensitivity, specificity and diagnostic accuracy for depreotide-study group were 97%, 91% and 96% respectively.

Besides the primary lesions, we also analyzed radiotracer uptake in regional lymph nodes of 36 lung cancers patients who were operated on. In 18 patients regional lymph nodes did not accumulate somatostatin analogue. Ipsilateral to SPN, hilar uptake of $^{99m}$Tc-depreotide was seen in 10 patients. In 6 of these cases histological examination of the hilar lymph nodes revealed metastases. These 6 patients were diagnosed with NSCLC (1 large cell carcinoma, 3 squamous cell carcinomas and 2 adenocarcinomas. Bilateral uptake of $^{99m}$Tc-depreotide in the hilar nodes was noticed in 8 cases, which was interpreted as reactive. Apart from the patients with lung cancer, regional lymphnode involvement was observed in scintigraphy and confirmed histologically in one patient with carcinoid tumor.

## $^{99m}$Tc-TOC-study group

The uptake of $^{99m}$Tc-TOC was detected in 15 of 44 patients but only 12 of 20 were TP. Histopathological evaluation revealed 8 adenocarcinomas, 2 carcinoids and 2 squamous cell carcinomas. In this

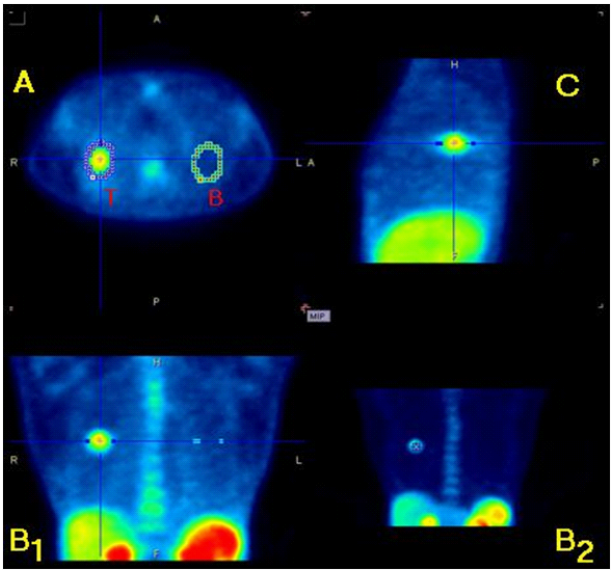


**Figure 1:** A. Example of regions of interest (ROIs): T- Tumor ROI and B-Background ROI, choosing in transverse SPECT slice. This is true positive result; T/B ratio 5.92; high $^{99m}$Tc-depreotide uptake in the SPNs within right lung (histopathology revealed adenocarcinoma; diameter on CT = 2.9 mm), B. coronal SPECT slice C. sagittal SPECT slice.

group we observed 3 of 24 FP results. One was vascular malformation, one tuberculoma and one hamartoma. Other malignant SPNs did not present relevant $^{99m}$Tc-TOC uptake and after histological evaluation 8 of 20 were flagged as FN results, including two adenocarcinomas, one carcinoid, four squamous cell carcinomas and one SCLC. Consecutive 21 of 24 benign lesions were TN and did not accumulate $^{99m}$Tc-HYNIC-TOC. The sensitivity, specificity and diagnostic accuracy in this study group were 60%, 88% and 75% respectively.

Slightly increased hilar uptake was seen ipsilaterally to SPN in 10 cases: 5 adenocarcinomas, 2 squamous cell carcinomas and 3 benign lesions (non-specific inflammatory infiltration and mycosis). In the rest of the subgroup there was no relevant tracer uptake within mediastinum or hilar regions. Table 3 presents results of visual analysis of $^{99m}$Tc-depreotide and $^{99m}$Tc-TOC SPECT in our group.

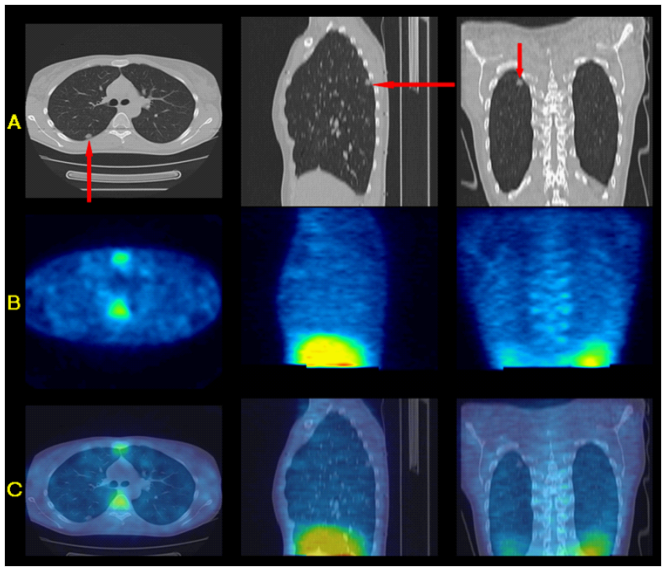


**Figure 2:** False negative result.A. SPN was detected on CT (diameter 7 mm). B. No uptake of $^{99m}$Tc-depreotide in SPN in SPECT (transverse, sagittal, coronal) slices (histopathology revealed adenocarcinoma). C. CT/SRS fusion image.

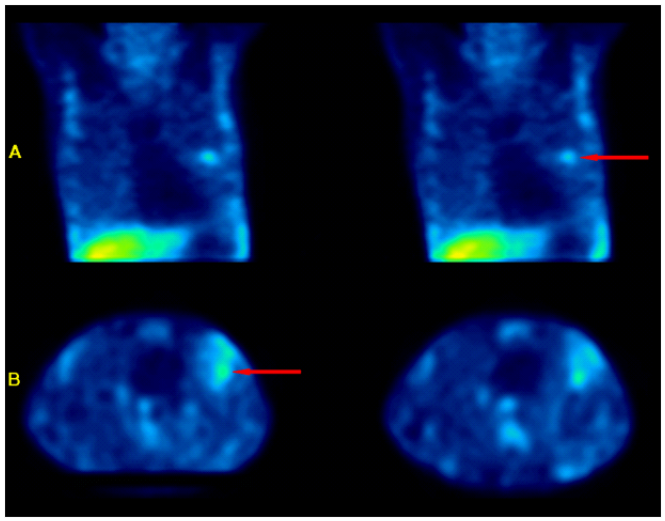


**Figure 3:** False positive result. T/B ratio 1.53. A. Accumulation of $^{99m}$Tc-depreotide was depicted in tuberculoma on coronal and B. transverse SPECT slice.

| SPN | Radiopharmaceuticals | | | |
|---|---|---|---|---|
| | $^{99m}$Tc-depreotide | | $^{99m}$Tc-TOC | |
| | uptake | no uptake | uptake | no uptake |
| Lung cancer (SCLC+NSCLC) | 35 | 1 | 10 | 7 |
| Carcinoid | 2 | 0 | 2 | 1 |
| Benign lesions | 1 | 10 | 3 | 21 |

**Table 3:** Radiopharmaceuticals ($^{99m}$Tc- depreotide/$^{99m}$Tc-TOC) uptake in SPNs.

| Character of lesions | Groups | | | |
|---|---|---|---|---|
| | $^{99m}$Tc-depreotide | | $^{99m}$Tc-TOC | |
| | N | T/B | N | T/B |
| All malignant lesions | 38 | 2.51±2.00 | 20 | 1.05±0.34 |
| Lung cancers | 36 | 2.98±2.18 | 17 | 1.05±0.34 |
| Benign lesions | 11 | 0.25±0.6 | 24 | 0.97±0.22 |

**Table 4:** The values of a tumor–to–background ratio (T/B) in the presented groups.

## Semi-quantitative evaluation of SPECT images

The values of the tumor–to–background ratio (T/B) are presented in Table 4. Significant differences in depreotide group were ascertained between the values of T/B in benign lesions (0.25±0.6) and in lung cancer tissue (2.98±2.18). In $^{99m}$Tc-TOC group there were no significant differences in T/B ratio between malignant and benign lesions. Nevertheless, a significant difference in this ratio between both analogues was noted.

## Discussion

Lung cancer is currently the leading cause of cancer death among both men and women [10,11]. The over-expression of SSTRs in SCLC and intense accumulation of the tracer in NSCLC are the basis for SRS SPECT in lung cancer where conventional imaging techniques have limited accuracy to diagnose malignancy in SPNs [12-14]. In our material 62% of patients (n=58) were diagnosed with malignant disease. In this number there were 53 cases of lung cancer (56%). In $^{99m}$Tc-depreotide study, sensitivity, specificity and diagnostic accuracy were 97% , 91% and 96% respectively. This stays in accordance to data presented by Blum et al. [14] (96.6% sensitivity and 73.1 % specificity), where 114 patients with SPNs were diagnosed with the use of the same radiotracer. In $^{99m}$Tc-TOC group sensitivity, specificity and diagnostic accuracy were lower than in $^{99m}$Tc-depreotide study and ranked 60%, 88% and 75% respectively. Similar accuracy (83%) was presented by Płachcińska et al. on cohort consisted of 59 patients [15]. These authors also applied semi-quantitative methods with T/B ratio and they concluded that 2.0 is the cut-off value for optimal differentiation between malignant and benign SPNs. In our $^{99m}$Tc-TOC study group the values of this ratio for malignant SPN were lower 1.05±0.34, whereas for $^{99m}$Tc-depreotide group was higher and reached 2.51±2.00.

Only in $^{99m}$Tc-depreotide-study group the semi-quantitative analysis, based on the calculation of a T/B ratio revealed significant differences between the value of T/B in benign lesions and lung cancer tissue. Based on $^{99m}$Tc-TOC SRS Płachcińska et al. [15] concluded that the combination of visual analysis and semi-quantitative assessment provided higher accuracy (88%) in comparison to visual analysis alone (84%). In our study among 20 malignant lesions only 12 presented

SSR overexpression. Moreover, 3 benign lesion showed accumulation of $^{99m}$Tc-TOC. These results are not satisfactory, and need further evaluation on a bigger cohort of patients.

Halley et al. [16] presented a comparison between $^{99m}$Tc-depreotide SPECT and $^{18}$FFDG PET in 28 patients. Both methods were found to be equally sensitive (92,3%) for large tumors and equally specific (85,7%) for small (<1.5 cm) SPNs. Higher sensitivity of $^{18}$F FDG in comparison with $^{99m}$Tc-depreotide SPECT in small SPNs (100% vs. 80 %) is partly due to great differences in spatial resolution between PET and SPECT. A potential advantage of SRS SPECT over of $^{18}$F FDG PET might be higher accuracy in detecting carcinoid tumors. In our study 2 cases of carcinoid tumours were visulalised with $^{99m}$Tc-depreotide. In $^{99m}$Tc-TOC-study cohort the accuracy wasn't so high because we had 1 FN result, which is too few to jump to any conclusions. A higher number of carcinoid tumors must be diagnosed with both methods (SRS SPECT and F-FDG PET) to achieve reliable results. In lung cancer tissue the accumulation of $^{99m}$Tc-depreotide was seen in 35 of 36 patients whereas in $^{99m}$Tc- TOC in 10 of 17 cases.

The identification of potential malignancy of lesions smaller than 1 cm stays main diagnostic problem in the evaluation of SPNs. In $^{99m}$Tc-depreotide group only one FN case – adenocarcinoma - had 0.7 cm diameter, which was below spatial resolutions of our gamma camera, whereas three FN cases in $^{99m}$Tc-TOC study had diameter larger than1 cm.

Danielsson et al. [17] suggested that the absence of $^{99m}$Tc-depreotide uptake excludes with high degree of probability, regional lymph node involvement in the patients with lung cancer (negative predictive value-98,0%). The specificity of the radiotracer accumulation in the regional lymph nodes is low and for that reason sampling of mediastinal lymph nodes during surgery was performed in all operated patients despite scintigraphy findings. A thorough research of this important problem of staging and monitoring of lung cancer will be continued in the nearest future by our team.

## Conclusion

The diagnostic accuracy, sensitivity and specificity of $^{99m}$Tc-depreotide scintigraphy, in evaluation of SPNs of indeterminate origin is high and can be recommended as alternative method of diagnosis of patients with lung lesions, before qualification for surgical resection. $^{99m}$Tc-TOC is less effective in the assessment of SPNs, therefore cannot be recommended.

The prediction of malignancy in hilar and mediastinal lymph nodes requires further investigation.

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