Comparative analysis of $^{99m}$Tc-depreotide and $^{99m}$Tc-EDDA/HYNIC-TOC thorax scintigrams acquired for the purpose of differential diagnosis of solitary pulmonary nodules

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Abstract

BACKGROUND: Aiming at comparison of diagnostic efficacy of 2 radiopharmaceuticals: $^{99m}$Tc-depreotide (Neospect, Amersham) and $^{99m}$Tc-EDDA/HYNIC-Tyr3-occtreotide (Tektrotyd, Polatom), in differentiation between malignant and benign etiology of solitary pulmonary nodules (SPNs), radionuclide studies with 2 radiotracers were performed in 18 patients.

MATERIAL AND METHODS: For both radiopharmaceuticals the same acquisition and processing protocols were applied. Studies were acquired with SPECT technique, after administration of 740 MBq of activity. Scintigrams were assessed visually, as: positive (+), equivocal (+/-) and negative (-). Additionally, uptake intensity of both radiotracers in nodules was assessed semiquantitatively, using a tumour-to-background ratio. Verification of scintigraphic results was based in 14 cases upon a pathological examination of tumour samples (histopathology) and in the remaining 4 — on clinical observation and bacteriological studies.

RESULTS: Normal scintigrams obtained with both radiopharmaceuticals differed significantly. $^{99m}$Tc-depreotide was markedly accumulated in spine, sternum, ribs and lungs (mean lung/heart ratio = 2.2). This accumulation was not observed on $^{99m}$Tc-EDDA/HYNIC-TOC scintigrams (mean lung/heart ratio = 0.7). In 6 patients a malignant etiology — lung cancer — was revealed (5 — adenocarcinoma, 1 — squamous cell) and the other 12 cases turned out to be benign (4 hamartomas, 3 tuberculous, a tuberculous infiltrate, an alien body with inflammatory reaction, a hyperplasia of lymphatic tissue and 2 cases of unknown etiology, from which one had a stable size and the other resolved during a 6 month observation period). In all 6 cases of lung cancer positive results were obtained with both tracers. Moreover, in 2 patients metastases in mediastinum could be observed on scintigrams obtained with both radiopharmaceuticals. From among 12 cases of benign etiology 6 $^{99m}$Tc-depreotide scintigrams were true negative, 1 — equivocal and 5 — false positive, whereas 6 $^{99m}$Tc-EDDA/HYNIC-TOC scintigrams were true negative, 4 — equivocal and 2 false positive. Moreover, $^{99m}$Tc-depreotide additionally revealed mediastinal and hilar lesions in 9 patients with benign lesions and $^{99m}$Tc-EDDA/HYNIC-TOC — in 8. A visual comparison of scintigrams revealed a higher quality of $^{99m}$Tc-Depreotide images in comparison with $^{99m}$Tc-EDDA/HYNIC-TOC ones. $^{99m}$Tc-Depreotide showed a higher than $^{99m}$Tc-EDDA/HYNIC-TOC accumulation

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in lung tumours compared with blood pool (heart) — 4.5 (s.d. 1.05) and 1.8 (s.d. 0.29), respectively (p < 0.05). However, mean values of tumour-to-lung-background ratio were equal for both radiotracers (2.2 in malignant and 1.4 in benign lesions, respectively). A statistically significantly higher non-uniformity of counts inside lung background regions was found on 99mTc-EDDA/HYNIC-TOC scintigrams than on 99mTc-depreotide ones (16.4% vs. 11.4%; p < 0.01).

CONCLUSIONS: Although both radiopharmaceuticals show similar diagnostic efficacy in differentiation of SPNs, a tendency toward a higher number of false positive results on 99mTc-depreotide scintigrams probably leads to a lower specificity. Better statistical quality of 99mTc-depreotide scintigrams facilitates their interpretation and a distinct outline of lungs simplify localization of lesions. A substantial number of false positive lesions in mediastinal and hilar regions in patients without a neoplastic process hamper the usefulness of both radiotracers for effective detection of lung cancer metastases to lymph nodes.

Key words: somatostatin receptor, receptor scintigraphy, solitary pulmonary nodule, lung cancer, octreotide

Introduction

Depreotide, a somatostatin analog, is a cyclic synthetic peptide that can be labelled with technetium-99m. It is known under the commercial names Neotec (Dia诊断, Berlex and Schering) and NeoSpect (Amerham). The radiopharmaceutical has been granted marketing authorization indicated for differential diagnosis of solitary pulmonary nodules (SPNs). According to available publications it provides a high diagnostic efficacy in differentiation between malignant and benign etiology of nodules. A multicenter trial performed in the United States in the year 2000 by Blum et al., in a group of 114 patients with SPNs and pulmonary masses smaller than 6 cm in diameter showed as high as 97% sensitivity of the method in detection of malignancies, with 73% specificity [1]. In a subsequent publication by Kahn et al., presenting results of a study made in a group of 157 patients, a lower specificity (51%) was revealed, with a sensitivity (94%) close to the one published earlier [2]. Results obtained recently by the European NeoSpect Trial Group examining the diagnostic usefulness of NeoSpect in a group of 118 patients with SPNs [3] showed sensitivity and specificity of 89% and 67%, respectively.

Another somatostatin analogue applied in this study, a Tyr3-octreotide (TOC) labelled with technetium-99m via HYNIC, has been developed by Maecke and Behe, who reported on its favourable characteristics when EDDA was used as a co-ligand [4]. It is introduced into the market in a dry kit formulation under the name Tektrotyd (POLATOM). Usefulness of this radiopharmaceutical in differential diagnosis of SPNs has been studied in the Department of Nuclear Medicine of the Medical University of Lodz since 2001. Preliminary results revealed a high efficacy of scintigraphy with this radiopharmaceutical [5-7]. Recent results in a group of 85 patients (40 with malignant and 45 with benign etiologies) confirmed its usefulness: in 37 cases (93%) true positive results were obtained (among them in 34/45 — 96% cases of primary lung cancer) and in 31 (69%) — true negative ones [8].

Comparison of diagnostic efficacies of studies with both radiotracers should be based on clinical trials made in large groups of patients. At present such results are not yet available. A comparative analysis of scintigrams acquired in the same patients might, however, reveal some additional data on image quality, typical distribution of both radiotracers, intensity of uptake in lung nodules and other details, potentially affecting diagnostic usefulness of studies with both radiopharmaceuticals.

Material and methods

While studying diagnostic efficacy of 99mTc-EDDA/HYNIC-Tyr3-octreotide in differential diagnosis of SPNs, additionally, in 18 patients, a 99mTc-Depreotide scintigraphy was performed. Prior to conducting the study, permission to make a comparative analysis in the same patients using two radiopharmaceuticals, was obtained from the Ethical Committee at the Medical University of Lodz.

The study group consisted of 10 females and 8 males with mean age of 57 years (ranging from 44 to 68), referred to the Department of Nuclear Medicine of the Medical University of Lodz after a SPN had been discovered on chest radiograph. Diameters of the nodules measured on CT scans ranged from 1.0 to 3.5 cm (mean 1.9 cm).
of both tracers and clarification of observed differences in quality of scintigrams. In order to compare tracer uptake in heart and lungs, circular regions of interest of radius equal to 6 pixels were drawn on transverse slices at sites corresponding to those organs. A comparison of tumour to lung background ratio was based on counts taken from circular regions of interest of diameters read from CT images extended by 4 pixels (in order to take into account the poorer resolution of scintigraphy) drawn on reconstructed transverse images at sites corresponding to nodule locations and in the other lung, contra-laterally (background).

Non-uniformity of counts inside background regions was measured with a coefficient of variance, i.e. a quotient of a standard deviation to a mean value.

Verification of studies in 14 cases was based upon pathology (histology) and in the remaining 4 — on clinical observation and bacteriological studies.

For comparisons of uptake of both radiopharmaceuticals a Wilcoxon matched pairs test was used.

### Results

Normal scintigrams obtained with both radiopharmaceuticals differed significantly. 99mTc-depreotide was markedly accumulated in spine, sternum, ribs and lungs (mean lung/heart ratio = 2.2). This accumulation was not observed on 99mTc-EDDA/HYNIC-TOC scintigrams (mean lung/heart ratio = 0.7) — see Figure 1.

In 6 patients a malignant etiology was revealed (6 cases of lung cancer: 5 — adenocarcinoma, 1 — squamous cell) and 12 cases turned out to be benign (4 hamartomas, 3 tuberculomas, a tuberculosis infiltrate, an alien body with inflammatory reaction, a hyperplasia of lymphatic tissue and 2 cases of unknown etiology, of which one had a stable size and the other resolved during a 6 month observation period). In all 6 cases of lung cancer positive results were obtained with both radiotracers. Moreover, in 2 patients metastases in mediastinum could be observed on scintigrams obtained with both radiopharmaceuticals.

A visual comparison of scintigrams revealed a higher quality of 99mTc-depreotide images in comparison with 99mTc-EDDA/HYNIC-TOC ones. With the aim of finding out reasons for this difference, a quantitative comparison of tracer uptake in lung nodules with blood pool (heart) and lung background was performed. 99mTc-depreotide showed a higher than 99mTc-EDDA/HYNIC-TOC accumulation in lung tumours compared with blood pool (heart) — 4.5 (s.d. 1.05) and 1.8 (s.d. 0.29), respectively (p < 0.05). However, mean values of tumour-to-lung-background ratio were equal for both radiotracers (2.2 in malignant and 1.4 in benign lesions, respectively).

Moreover, a statistically significantly higher non-uniformity of counts inside background regions was found on 99mTc-EDDA/HYNIC-TOC scintigrams than on 99mTc-depreotide ones (16.4% versus 11.4%; p < 0.01). An example of a false positive result obtained with 99mTc-depreotide and equivocal one with 99mTc-EDDA/HYNIC-TOC (the same patient) is presented in Figure 3.

### Table 1. Results of visual analysis of scintigrams obtained with two radiotracers, in malignant and benign nodules

<table>
<thead>
<tr>
<th>Result of scintigraphy</th>
<th>99mTc-depreotide</th>
<th>99mTc-EDDA/HYNIC-TOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Benign</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

| + — positive; +/- — equivocal; – — negative |

12 cases of benign etiology, 6 99mTc-depreotide scintigrams were true negative, 1 — equivocal and 5 — false positive, whereas 6 99mTc-EDDA/HYNIC-TOC scintigrams were true negative, 4 — equivocal and 2 false positive (Table 1). Moreover, 99mTc-depreotide was additionally accumulated in mediastinal and hilar lesions in 9 patients with benign lesions and 99mTc-EDDA/HYNIC-TOC — in 8. An example of scintigrams obtained with both radiotracers in a patient with lung cancer is presented in Figure 2.
Discussion

Depreotide was originally developed as a somatostatin analog binding to somatostatin receptors subtypes 2, 3 and 5 that could serve as an imaging agent for neuroendocrine tumours. Later on, its usefulness for detection of lung cancer was discovered and, as a consequence of clinical trials, depreotide was registered as a radiopharmaceutical suitable for radionuclide differentiation between malignant and benign etiologies of solitary lung nodules. Some authors [9,10] attribute its ability for visualization of lesions of non-small cell lung cancer to its affinity for somatostatin receptor subtype 3, for which octreotide derivatives, such as TOC (Tyr^3-octreotide), do not show significant affinity [11]. This opinion on a key role of somatostatin receptor subtype 3 in visualization of non-small cell lung cancer, however, cannot be supported with any reliable experimental evidence. Since the late 1980s experimental search for somatostatin receptors on cells of non-small cell lung cancer has been carried out. Initially, no traces of expression of those receptors could be found [12–15]. With the advancement of experimental methods, however, some evidence of presence of somatostatin receptors on cells of this tumour could be found, but mostly of subtypes 1, 2 and 4 [16–18]. Only one communication [19] reported on the presence of sstr3 in 6 cases of 25 malignant lung tumours, but additionally to sstr2 or sstr5. When somatostatin analog is used for radionuclide detection of malignant tumours, an affinity for a larger number of somatostatin receptor subtypes is certainly advantageous, but when a non small cell lung cancer is concerned, affinity of the radiopharmaceutical for a receptor subtype 3 should not be overestimated. High diagnostic efficacy of somatostatin receptor scintigraphy in the detection of lung cancer can be also explained by expression of somatostatin receptors in peri-tumoural vessels and on active lymphocytes [20–22].

Observed differences between distribution of both radiopharmaceuticals, and especially uptake of ⁹⁹mTc-depreotide in the skeleton and lungs, should not, however, be explained by different affinity for somatostatin receptor subtypes. Those differences probably result from the presence of microcolloid found by Burggasser et al. [23] in a product of kit labelling with technetium-99m. Although the share of colloid in their communication did not exceed 5%, it must grow with time, as colloid stays bound in the organs listed above and the labelled peptide is quickly eliminated from the organism. The microcolloid is probably also present in the liver, but it overlays on the labelled peptide and therefore cannot be observed separately.

Uptake of both radiopharmaceuticals in malignant lung tumours has been compared to blood pool because of a probably similarly fast plasma clearance of both tracers. There are communications on fast elimination of both radiopharmaceuticals, predominantly through the urinary tract [24, 25]. A significantly higher uptake of ⁹⁹mTc-depreotide in lung cancer in relation to blood pool, as compared with ⁹⁹mTc-EDDA/HYNIC-TOC, probably means a higher absolute accumulation of the former in lesions of this neoplasm. However, a higher lung background on ⁹⁹mTc-depreotide scintigrams probably equalizes tumour-to-lung-background ratio. Thus, a better quality of ⁹⁹mTc-depreotide scintigrams

Figure 2A. A lesion of adenocarcinoma (2 cm in diameter) visible on transverse and coronal slices of ⁹⁹mTc-depreotide study; B. ⁹⁹mTc-EDDA/HYNIC-TOC study.
There are communications on usefulness of 99mTc-depreotide scintigrams about 40% of patients with lung cancer diagnosed at SPN stage. Complementation of differential diagnosis of SPNs. According to Baldwin et al. [26], metastases to lymph nodes are observed in about 40% of patients with lung cancer diagnosed at SPN stage. There are communications on usefulness of 99mTc-depreotide scintigraphy in detection of metastases of non-small cell lung cancer to hilar and mediastinal lymph nodes [27, 28], although results of those studies are very divergent in the estimation of sensitivity (68% and 99%) and specificity (70% and 46%) of the method. Results presented in our work imply a low specificity of scintigraphy with both radiotracers, because of substantial numbers of false positive results in patients without a neoplastic process. Sensitivity of 99mTc-EDDA/HYNIC-TOC in staging of a non-small cell lung cancer is probably also low. It can be inferred from a communication on negative results of scintigraphy with the same aminocacid sequence (TOC) labelled with gallium-68 via DOTA in cases of metastatic lesions of this neoplasm [29]. Diagnostic usefulness of both radiotracers in staging of a non-small cell lung cancer needs further studies.

In summation, a comparative analysis showed similar diagnostic efficacy of scintigraphy with both radiopharmaceuticals in differential diagnosis of SPN. A better statistical quality (lower noise level) of 99mTc-depreotide images facilitates their interpretation and a distinct uptake in the lungs (probably of a colloidal fraction of the tracer) simplifies localization of lesions, although a tendency toward a higher number of false positive results on 99mTc-depreotide scintigrams probably leads to a lower specificity of studies with this tracer. A small number of malignant SPNs precludes detection of any differences in sensitivities of scintigraphy with both radiotracers. Significant numbers of false positive results in mediastinum and hilar regions of the lungs hampers the usefulness of both radiopharmaceuticals for effective detection of lung cancer metastases to lymph nodes.

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