Original
Nuclear Medicine Review 2006
Vol. 9, No. 1, pp. 24–29

ISSN 1506–9680

VIA MEDICA

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

Anna Płachcińska[1], Renata Mikołajczak[2], Józef Kozak[3], Katarzyna Rzeszutek[4], Jacek Kuśmierek[1]

[1]Department of Nuclear Medicine, Medical University, Lodz, Poland
[2]Radioisotope Centre POLATOM, Otwock-Świerk, Poland
[3]Ward of Thoracic Surgery, Copernicus Hospital, Lodz, Poland
[4]Centre for Treatment of Pulmonary Diseases, Lodz, Poland

[Received 8 III 2006; Accepted 9 III 2006]

Abstract

BACKGROUND: Aiming at comparison of diagnostic efficacy of 2 radiopharmaceuticals: ^{99m}Tc-depreotide (Neospect, Amersham) and ^{99m}Tc-EDDA/HYNIC-Tyr^3-octreotide (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 tuberculomas, 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

Correspondence to: Anna Płachcińska
Department of Nuclear Medicine, Medical University of Lodz
ul. Czechosłowacka 8/10, 92–216 Łódź, Poland
Tel: (+48) 42 678 36 84
e-mail: anna@csk.umed.lodz.pl

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 ^{99m}Tc-EDDA/HYNIC-TOC scintigrams than on ^{99m}Tc-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 ^{99m}Tc-depreotide scintigrams probably leads to a lower specificity. Better statistical quality of ^{99m}Tc-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 Neotect (Diatide, Berlex and Schering) and NeoSpect (Amersham). 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 Tyr^3-octreotide (TOC) labelled with technetium-99m via HYNIC, has been developed by Maecke and Béhé, 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 Medical University in Łódź 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 ^{99m}Tc-EDDA/HYNIC-Tyr^3-octreotide in differential diagnosis of SPNs, additionally, in 18 patients, a ^{99m}Tc-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 Łódź.

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 Łódź 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).

Labelling protocols

Depreotide: The instant kit containing 47 mg of the peptide (Amersham) was used for all examinations. This kit was reconstituted with 1 GBq 99mTc-pertechnetate in a final volume of 3 ml. The product was incubated in a boiling water bath for 10 min and kept at room temperature for 15 min.

HYNIC-TOC: The HYNIC-Tyr^3-octreotide kit (Radioisotope Centre POLATOM containing 20 μg of the peptide, stannous chloride, tricine and EDDA was labelled with the activity of about 1 GBq of ^{99m}Tc-pertechnetate in a volume of 1–2 ml. The product was incubated at 80^{o}C for 20 min.

Imaging protocol

The patients received 740 MBq of each radiopharmaceutical. A delay between the two studies ranged from 1 to 7 days, a sequence of the use of both tracers was random.

Studies with both radiopharmaceuticals applied the same acquisition and reconstruction protocols. The imaging started 2 hours post injection. SPECT acquisition was performed using a dual head VariCam gamma camera (Elscint). High resolution collimators and a matrix of 128 × 128 pixels were applied. One hundred and twenty projections were acquired, each of 25 sec duration. For reconstruction of tomographic images a filtered back-projection was used, with Metz filter of power 3 and FWHM of 1 cm.

Scintigram analysis was made visually by two specialists in nuclear medicine, unaware of tumour etiology, and results were achieved by consensus. Three series of tomograms (transversal, coronal and sagittal) were inspected simultaneously, in a "triangulation mode". A lesion of enhanced radiopharmaceutical uptake was looked for at a site corresponding to the location of a SPN on CT. Scintigrams were classified as positive, equivocal or negative. Moreover, enhanced radiotracer uptake in other parts of lungs and in mediastinum was searched for.

Additionally, tracer uptake was analyzed quantitatively, aiming at objective confirmation of visible differences in the uptake

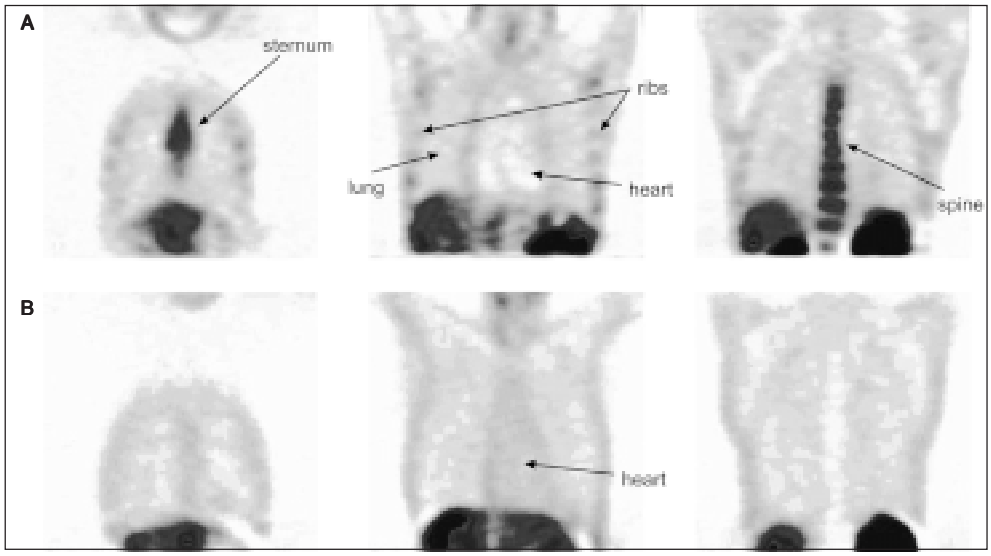

Figure 1A. Normal coronal tomograms of thorax study with ^{99m}Tc-depreotide; **B.** The study with ^{99m}Tc-EDDA/HYNIC-TOC.

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. ^{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) — 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 tuberculous 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. From

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

Result of scintigraphy	+	+/–	–	Total
^{99m}Tc-depreotide				
Malignant	6	0	0	6
Benign	5	1	6	12
^{99m}Tc-EDDA/HYNIC-TOC				
Malignant	6	0	0	6
Benign	2	4	6	12

+ — possitive; +/– — equivocal; – — negative

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 (Table 1). Moreover, ^{99m}Tc--depreotide was additionally accumulated in mediastinal and hilar lesions in 9 patients with benign lesions and ^{99m}Tc-EDDA/ /HYNIC-TOC — in 8. An example of scintigrams obtained with both radiotracers in a patient with lung cancer is presented in Figure 2.

A visual comparison of scintigrams revealed a higher quality of ^{99m}Tc-depreotide images in comparison with ^{99m}Tc-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. ^{99m}Tc--depreotide showed a higher than ^{99m}Tc-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 ^{99m}Tc-EDDA/ /HYNIC-TOC scintigrams than on ^{99m}Tc-depreotide ones (16.4% versus 11.4%; $p < 0.01$). An example of a false positive result obtained with ^{99m}Tc-depreotide and equivocal one with ^{99m}Tc--EDDA/HYNIC-TOC (the same patient) is presented in Figure 3.

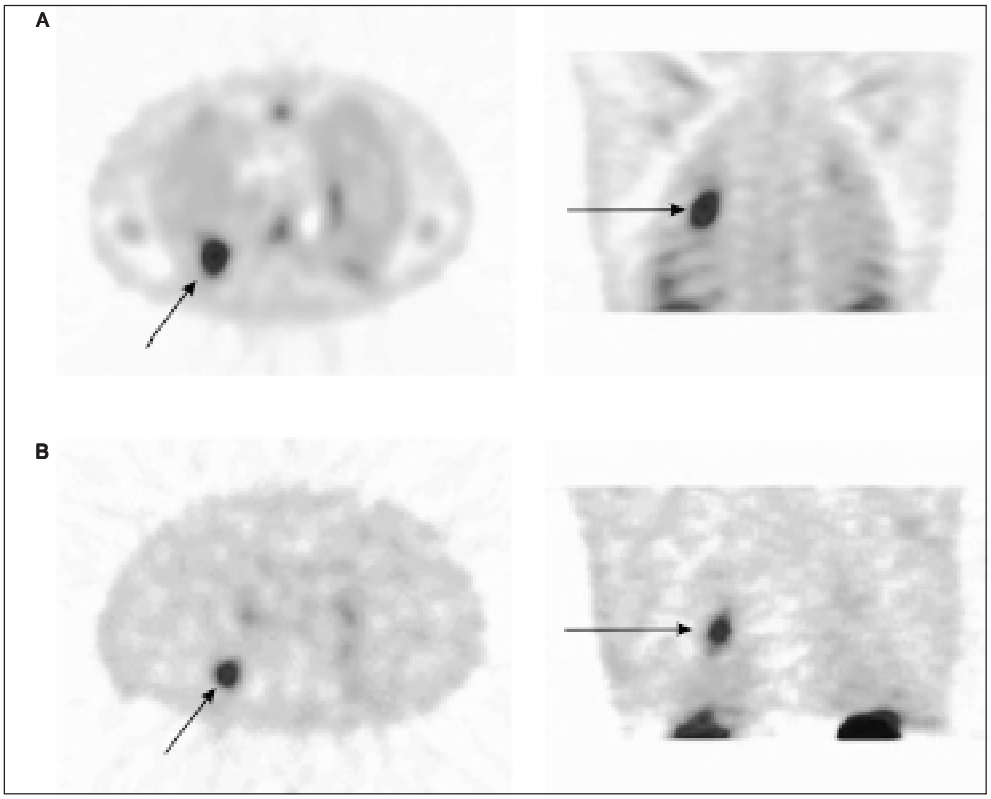

Figure 2A. A lesion of adenocarcinoma (2 cm in diameter) visible on transverse and coronal slices of ^{99m}Tc-depreotide study; **B.** ^{99m}Tc-EDDA/HYNIC-TOC study.

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 ^{99m}Tc-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 ^{99m}Tc-depreotide in lung cancer in relation to blood pool, as compared with ^{99m}Tc-EDDA/HYNIC-TOC, probably means a higher absolute accumulation of the former in lesions of this neoplasm. However, a higher lung background on ^{99m}Tc-depreotide scintigrams probably equalizes tumour-to-lung-background ratio. Thus, a better quality of ^{99m}Tc-depreotide scintigrams

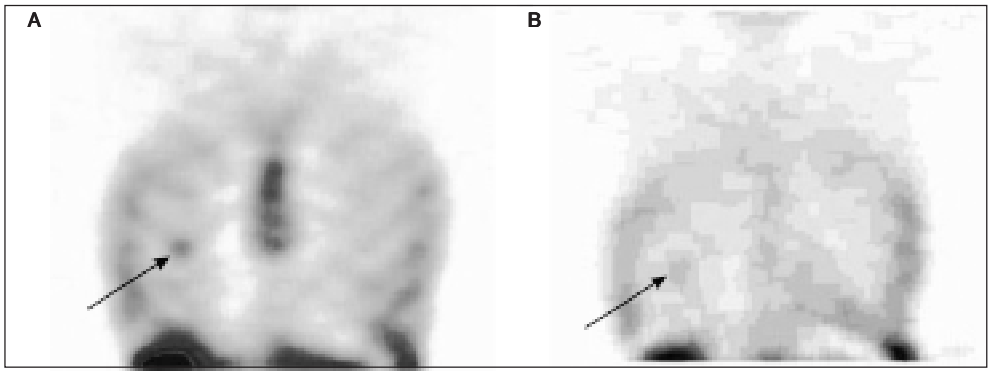

Figure 3A. An example of positive ^{99m}Tc-depreotide scintigram of a benign nodule of unknown etiology (it resolved during a 6 month observation period); **B.** Equivocal ^{99m}Tc-EDDA/HYNIC-TOC scintigram.

results from a larger number of collected counts and not from a higher tumour-to-lung-background ratio. A higher non-uniformity following lower counts in lung background on ^{99m}Tc-EDDA/ /HYNIC-TOC scintigrams additionally confirms statistical differences between images obtained with the two radiopharmaceuticals. This higher level of statistical noise in ^{99m}Tc-EDDA/HYNIC-TOC scintigrams probably reduces confidence in results of visual analysis. A higher quality of ^{99m}Tc-depreotide images causes a stronger tendency to recognize them as positive (Table 1), thus reducing specificity of the method in detection of malignant etiology of SPNs. On the other hand, lower counts in ^{99m}Tc-EDDA/HYNIC-TOC scintigrams may reduce the sensitivity of the method in detection of small lesions of enhanced uptake (small malignancies), but at present no experimental evidence confirms this theoretical possibility.

Detection of metastases to lymph nodes in cases when a nodule turns out to be a primary pulmonary carcinoma is a valuable 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 ^{99m}Tc-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 ^{99m}Tc-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 aminoacid 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 ^{99m}Tc-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 ^{99m}Tc-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.

References

1. 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.
2. Kahn D, Menda Y, Kernstine K et al. The utility of 99mTc depreotide compared with F-18 fluorodeoxyglucose positron emission tomography and surgical staging in patients with suspected non-small cell lung cancer. Chest 2004; 125: 494–501.
3. Naalsund A, Maublant J. The solitary pulmonary nodule — Is it malignant or benign? Diagnostic performance of ^{99m}Tc-depreotide SPECT. Respiration 2006. To be published.
4. Maecke HR, Béhé M. New octreotide derivatives labelled with technetium-99m [abstract]. J Nucl Med 1996; 37: 1144.
5. Płachcińska A, Mikołajczak R, Maecke HR et al. ^{99m}Tc-EDDA/HYNIC TOC scintigraphy in differential diagnosis of solitary pulmonary nodules. Eur J Nucl Med Mol Imaging 2004; 31: 1005–1010.
6. Płachcińska A, Mikołajczak R, Maecke HR et al. Efficacy of ^{99m}Tc-EDDA/ /HYNIC TOC scintigraphy in differential diagnosis of solitary pulmonary nodules. Cancer Biother Radiopharm 2004; 19: 613–620.
7. Płachcińska A, Mikołajczak R, Kozak J, Rzeszutek K, Kuśmierek J. Semi-quantitative assessment of ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy in differentiation of solitary pulmonary nodules — a complementary role to visual analysis. Cancer Biother Radiopharm 2006; 21: 61–67.
8. Płachcińska A, Mikołajczak R, Kozak J, Rzeszutek K, Kuśmierek J. Differential diagnosis of solitary pulmonary nodules based on ^{99m}Tc- -EDDA/HYNIC-TOC scintigraphy — the effect of tumour size on optimal method of image assessment. Eur J Nucl Med Mol Imag 2006. Accepted for publication.
9. Freeman LM, Blaufox MD. Letter from the Editors. Semin Nucl Med 2002; 32: 77.
10. Goldsmith SJ. Guest Editorial. Semin Nucl Med 2002; 32: 78.
11. Reubi JC, Waser B, Schaer JC, Laissue JA. Somatostatin receptor sst1-sst5 expression in normal and neoplastic human tissues using receptor autoradiography with subtype-selective ligands. Eur J Nucl Med 2001; 28: 836–846.

12. Reubi JC, Waser B, Sheppard M, Macaulay V. Somatostatin receptors are present in small-cell but not in non-small-cell primary lung carcinomas: relationship to EGF-receptors. Int J Cancer 1990; 45: 269–274.
13. Bogden AE, Taylor JE, Moreau J-P, Coy DH, LePage DJ. Response of of human lung tumour xenografts to treatment with a somatostatin analogue (somatuline). Cancer Res 1990; 50: 4360–4365.
14. Krenning EP, Kwekkeboom DJ, Bakker WH et al. Somatostatin receptor scintigraphy with [111In-DTPA-D-Phe1]- and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. Eur J Nucl Med 1993; 20: 716–731.
15. Kwekkeboom DJ, Kho GS, Lamberts SWJ, Reubi CJ, Laissue JA, Krenning EP. The value of octrotide scintigraphy in patients with lung cancer. Eur J Nucl Med 1994; 21: 1106–1113.
16. Fujita T, Yamaji Y, Sato M, Murao K, takahara J. Gene expression of somatostatin receptor subtypes, sst1 and sst2, in human lung cancer cell lines. Life Sci 1994; 55: 1797–1806.
17. Taylor JE, Theveniau MA, Bashirzadeh R, Reisine T, Eden PA. Detection of somatostatin receptor subtype 2 (sstr2) in established tumors and tumor cell lines: evidence for sstr2 heterogeneity. Peptides 1994; 15: 1229–1236.
18. Traub T, Petkov V, Ofluoglu S et al. 111In-DOTA-lanreotide scintigraphy in patients with tumors of the lung. J Nucl Med 2001; 42: 1309–1315.
19. Papotti M, Croce S, Bello M et al. Expression of somatostatin receptor types 2, 3 and 5 in biopsies and surgical specimens of human lung tumours. Virchows Archiv 2001; 439: 787–797.
20. Kwekkeboom DJ, Krenning EP. Somatostatin receptor imaging. Sem Nucl Med 2002; 32: 84–91.
21. Reubi JC, Horisberger U, Laissue J. High density of somatostatin receptors in veins surrounding human cancer tissue: role in tumor-host interaction? Int J Cancer 1994; 56: 681–688.
22. Reubi JC, Schaer JC, Laissue JA, Waser B. Somatostatin receptors and their subtypes in human tumors and in peritumoral vessels. Metabolism 1996; 45 (8 suppl 1): 39–41.
23. Burggasser G, Hurtl I, Hauff W et al. Orbital scintigraphy with the somatostatin receptor tracer ^{99m}Tc-P829 in patients with Graves' disease. J Nucl Med 2003; 44: 1547–1555.
24. Decristoforo C, Mather SJ, Cholewinski W, Donnemiller E, Riccabona G, Moncayo R. ^{99m}Tc-EDDA/HYNIC-TOC: a new ^{99m}Tc-labelled radiopharmaceutical for imaging of somatostatin receptor-positive tumours: first clinical results and intra-patient comparison with 111In-labelled octreotide derivatives. Eur J Nucl Med. 2000; 27: 1318–1325.
25. Van den Bosche B, D'haeninck E, Bacher K et al. Biodistribution and dosimetry of 99mTc-depreotide (P829) in patients suffering from breast carcinoma. Cancer Biother Radiopharm 2004; 19: 776–783.
26. Baldwin DR, Eaton T, Kolbe J et al. Management of solitary pulmonary nodules: how do thoracic computed tomography and guided fine needle biopsy influence clinical decision? Thorax 2002; 57: 817–822.
27. Kahn D, Menda Y, Kernstine K et al. The utility of ^{99m}Tc depreotide compared with F-18 fluorodeoxyglucose positron emission tomography and surgical staging in patients with suspected non-small cell lung cancer. Chest 2004; 125: 494–501.
28. Danielsson R, Baath M, Svennson L, Forslov U, Kolbeck HG. Imaging of regional lymph node metastases with ^{99m}Tc-depreotide in patients with lung cancer. Eur J Nucl Med Mol Imaging 2005; 32: 925–931.
29. Dimitrakopoulou-Strauss A, Georgoulias V, Schuhmacher J et al. Quantitative expression of SSTR2 in patients with non-small-cell-lung — cancer using ^{68}Ga-DOTA-TOC PET and comparison to F-18-FDG. Eur J Nucl Med Mol Imaging 2006. To be published.