doi:10.4149/neo_2010_01_068

The utility of ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy for assessment of lung lesions in patients with neuroendocrine tumors

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Received March 26, 2009

Our aim was to assess clinical utility of ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy for evaluation of lung lesions in patients with neuroendocrine tumors (NETs). Single photon emission computed tomography (SPECT) of the thorax and whole body scintigraphy were performed in 34 patients using ^{99m}Tc-EDDA/HYNIC-TOC. Visual assessment was complemented by semiquantitative evaluation based on tumor to non-tumor (T/NT) ratio. Clinical, laboratory, and histological findings served as the standard for comparison. Enhanced tracer uptake was observed on both SPECT and whole body scintigraphy in 29 of 34 patients (88% sensitivity). T/NT ratios were significantly higher on SPECT than whole body images (2.96±1.07 vs.1.70±0.43, $p<0.01$) and did not correlate with NET proliferation index Ki-67 ($r= - 0.36$, $p=0.27$). Conclusion: ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy is useful for evaluation of NET tissue in the lungs. SPECT provides better visualization of lung lesions than whole body scintigraphy. The intensity of tracer uptake, however, does not relate to the proliferation rate of NETs. ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy may be helpful for selecting and monitoring treatment options, particularly when radiolabeled somatostatin analogue therapy becomes available.

Key words: ^{99m}Tc-EDDA/Hynic-TOC, lung involvement of NETs, T/NT ratio

Expression of somatostatin receptors (SSTRs) has been documented in neuroendocrine tumors (NET) and in small cell (SCLC) and some non-small cell lung cancers (NSCLC) [1, 2]. These receptors constitute molecular basis for clinical application of somatostatin analogues, particularly for *in-vivo* localization of lung tumors.

Somatostatin analogues, such as the ^{123}Iodine-labeled octreotide [3], have been used in attempt to improve early detection of NETs and various cancers in the lungs. Since this compound has several drawbacks (e.g., high gastrointestinal activity due to liver excretion, short half-life), recent efforts have been focused on labeling octreotide with ^{111}Indium (^{111}In) using the chelate dietilene triamine penta-acetic acid, which resulted in ^{111}In-pentetreotide [4, 5]. ^{111}In-pentetreotide proved sensitivity for detecting NETs and bronchogenic carcinoma, although differentiating SCLC from NSCLC was not possible [6]. The use of ^{111}In-pentetreotide, however, has also substantial drawbacks (high cost, suboptimal physical characteristics).

More recently, somatostatin analogue depreotide has been labeled with ^{99m}Technetium (^{99m}Tc) and the resulting compound (NeoSpect) has been approved by the U.S. Food and Drug Administration for evaluation of solitary pulmonary nodules [7]. However, high uptake in the liver and bone marrow has been reported [2, 7]. Mecke and Behe introduced hydrasinonicotinamide (HYNIC) as a bifunctional chelator for ^{99m}Tc labeling of octreotide and Tyr^3-octreotide (TOC) with high efficiency [8]. Decristoforo and co-workers reported favorable clinical characteristics of HYNIC when ethylene diamine diacetic acid (EDDA) was used as a co-ligand, thereby introducing ^{99m}Tc-EDDA/HYNIC-TOC somatostatin analogue to clinical practice [9]. Recent investigations indicated a potential value of ^{99m}Tc-EDDA/HYNIC-TOC for evaluating malignant tumors that express SSTRs, especially subtype 2, but indicated the need for further investigations [10, 11].

The main purpose of this study was to assess the clinical utility of ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy (single

photon emission computed tomography-SPECT) and whole body imaging for evaluation of lung lesions in patients with NETs . Our specific aims were to 1) determine sensitivity of ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy for detecting NETs in the lungs, 2) compare tumor to non tumor (T/NT) ratio of ^{99m}Tc-EDDA/HYNIC-TOC on SPECT and whole body scintigraphy in lung lesions, and 3) relate the uptake of ^{99m}Tc-EDDA/HYNIC-TOC by NETs to the tumor proliferation index Ki-67.

Patients and methods

Patients were recruited from a sample referred by the Institute for Endocrinology for clinical staging or follow-up. Thirty-four consecutive patients (18 men, 16 women, mean age 52 years, range 23-74) with a known or suspected NET and lung lesions on chest X-ray or computed tomography-CT were included in the study. The diagnosis of NET was based on clinical symptoms, increased urinary excretion of serotonin metabolite 5-hydroxyindolacetic acid (5HIAA), chromogranin A, and biopsy or postoperative histology.

Twenty-one patients underwent surgery after ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy (mean interval 14±6 days). For 13 of 21 patients, Ki-67 labeling index was derived after immunostaining tumor material with MIB-1 antibody. The same 13 patients underwent a follow-up ^{99m}Tc-EDDA/HYNIC-TOC SPECT and whole body scintigraphy between 6 months and one year after surgery. 3 patients received radionuclide therapy with radiolabeled somatostatin analogues while the remaining 10 of 34 patients continued with a long-acting somatostatin analogue treatment. All patients provided written consent prior to the study.

Imaging protocol. Long-acting cold somatostatin analogue treatment was stopped one month before imaging. Patients were on laxatives and liquid diet for 2 days before the examination. ^{99m}Tc-EDDA/HYNIC-TOC (740 MBq) was injected intravenously. Imaging started 2 hours post-injection. A whole body scan was first performed followed by SPECT of the thorax. Data were acquired using dual-head Mediso or one-head e-cam Siemens gamma camera. A general purpose collimator and an image matrix of 512x1024 pixels were used for whole body scans. SPECT was acquired in 64 projections (each lasting 30 sec) with a matrix size of 128x128 pixels.

Image reconstruction and analysis. Reconstruction of tomographic images was performed by the iterative method (MOSEM). Whole body and SPECT images were first evaluated visually by two experienced nuclear medicine physicians. Visual appearance of an increased focal uptake of the tracer in the suspected tumor site was considered a positive finding, which served for determining sensitivity of ^{99m}Tc-EDDA/HYNIC-TOC SPECT and whole body imaging (aim 1). Subsequent semi-quantitative analysis was limited to cases with positive findings to compare the tumor uptake of ^{99m}Tc-EDDA/HYNIC-TOC to non tumor tissue in NETs on SPECT and whole body imaging (aim 2). For that purpose, tumor to non-tumor (T/NT) ratio was calculated after drawing the region of interest around the lesion and at the corresponding contralateral area on both whole body and SPECT images. T/NT ratio was also used to relate the uptake of ^{99m}Tc-EDDA/HYNIC-TOC by NETs to the tumor proliferation index Ki-67 (aim 3).

Statistical analysis. Statistical program SPSS for Windows was used for analysis. Standard statistical formula was used for calculating sensitivity of scintigraphy (aim 1). Student's t-test was used to test differences between T/NT ratios derived from whole body and SPECT images (aim 2). Pearson's correlation coefficient was calculated to relate T/NT ratio to Ki-67 index (aim 3). Data are presented as mean ± SD. P value of less than 0.05 was considered significant.

Results

Overall, there were 34 primary or metastatic NETs in the lungs (see Table 1 for primary tumor locations). Mean lesion size on CT was 2.9±1.2 cm (range 1.4-4.1 cm).

Table 1. Primary locations of neuroendocrine tumors (n=34).

Tumor site	Number of patients (n)
Lungs	17
Esophagus	2
Appendix	1
Endocrine pancreas	2
Pituitary gland	2
Thyroid	2
Unknown	8

Sensitivity of ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy. On visual examination, both SPECT and whole body scintigraphy identically identified patients with and without increased ^{99m}Tc-EDDA/HYNIC-TOC uptake. Increased focal uptake in NETs was found in 29 of 34 patients (true positive findings-TP), including 14 primary lung NETs (Fig. 1) and 15 lung metastases from NETs of different or unknown origin. Five false negative (FN) results included two cases with low-differentiated primary lung NETs, a case with lung metastases from a low-differentiated aggressive NET in the esophagus, and two cases with NETs of unknown origin. The tumor size for 5 FN cases is given in Table 2. None of 13 patients who underwent surgery showed evidence of increased tracer uptake in the lungs on the follow-up SPECT or whole body imaging (true negative-TN) (Fig 2). Accordingly, the results indicate 88% sensitivity of both ^{99m}Tc-EDDA/HYNIC-TOC SPECT and whole body scintigraphy for detecting lung lesions in patients with NETs.

T/NT ratio and correlation with Ki-67 proliferation index. The mean T/NT ratio for TP cases (n=29) was significantly ($p<0.01$) higher on SPECT (2.96±1.07) than whole body images (1.70±0.43).

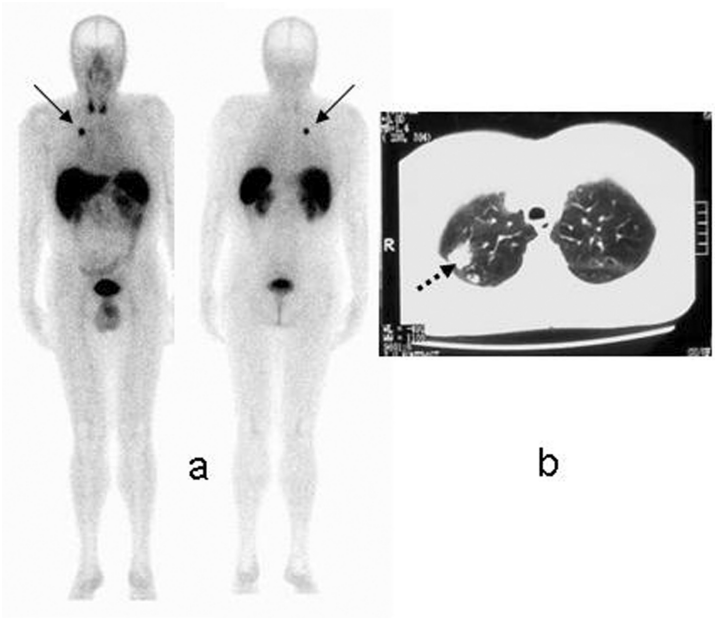

Figure 1 a) Enhanced uptake of ^{99m}Tc-EDDA/HYNIC-TOC on whole body scintigraphy in a patient with NET in the right upper lobe (arrows); Ki-67 = 37% b) Solitary pulmonary nodule with soft tissue density in the right upper lobe on CT, di ameter 2.8cm (dash arrow)

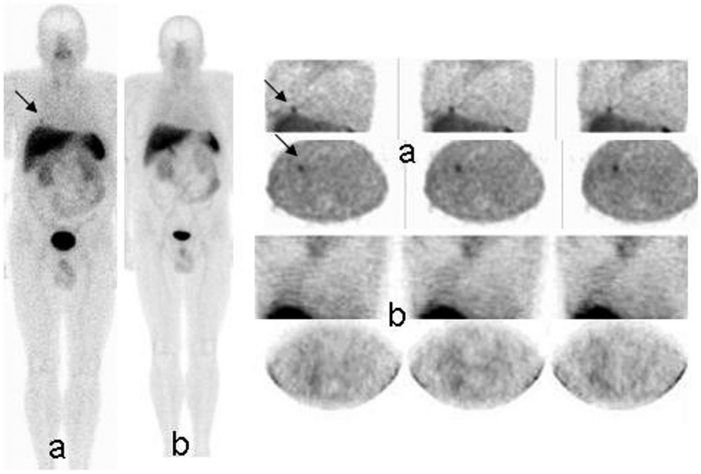

Figure 2 a) Enhanced uptake of ^{99m}Tc-EDDA/HYNIC-TOC on whole body scintigraphy and SPECT in a patient with NET in the right lower lobe, diameter 2.2cm (arrow). b) No uptake after surgery. Ki-67= 0%.

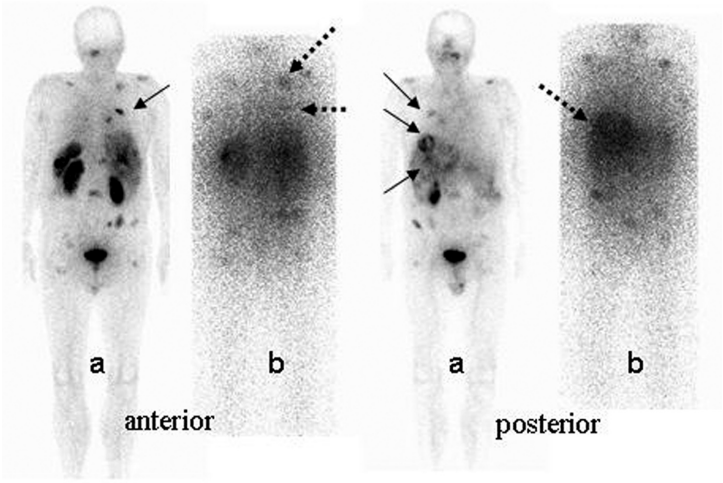

Figure 3 a) Whole body scan with 99mTc-EDDA/HYNIC-TOC shows multifocal lung, bone and liver lesions in a patient with low differentiated NET of unknown origin (black arrows). b) High uptake in the same metastatic sites 96 hours after application of the therapeutical dose (3.5 GBq) of ^{90}Y-DOTA TATE ("bremsstrahlung images")(dash arrows).

Table 2. Tumor size for 5 false negative cases on ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy

Lung lesion	Size (cm)
Low-differentiated primary lung NET	1.4
Low-differentiated primary lung NET	3.5
Lung metastases from a low-differentiated NET in the esophagus	1.7
Lung lesion from NET of unknown origin	1.9
Lung lesion from NET of unknown origin	4.2

NET- neuroendocrine tumor

Ki-67 index was 18±7% (range 0-78%) for 13 patients who had tumor material immunostained with MIB-1 antibody after surgical removal. Ki-67 index was low (0-20%) for 10 patients who had positive findings on scintigraphy (TP). Two of the remaining 3 patients had high Ki-67 index and negative SPECT and whole body findings (FN). The correlation between T/NT ratio and Ki-67 index was negative and not statistically significant (r= -0.36, p=0.27, n=11).

Preliminary results of peptide receptor radionuclide therapy. Because of high uptake of ^{99m}Tc-EDDA/HYNIC-TOC in the tumor tissue, and after using all available treatment options (surgery, somatostatin analogues, α-interferons), three patients with metastatic NETs underwent a peptide receptor radionuclide therapy with ^{90}Yttrium tetraazacyclododecane tetra acetic acid (metal chelator-DOTA) Tyr3-octreotate (TATE)-^{90}Y DOTA TATE (Fig. 3). At the clinical follow-up 6 to 12 months later, one patient was in a partial remission, one was in a stable condition, and one was presented with signs of disease progression.

Discussion

This study has 3 main findings. First, it demonstrates high sensitivity of ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy for detecting tumor tissue within lungs in patients with NETs. Secondly, T/NT ratio of ^{99m}Tc-EDDA/HYNIC-TOC is expectedly higher on SPECT than whole body scintigraphy. Finally, the intensity of tracer uptake does not correlate with the rate of NET proliferation (Ki-67 index).

The diagnosis of lung tumors remains a challenge. Conventional radiologic imaging techniques are of limited value for detecting malignant solitary lung lesions because of 20-50% error rate [12]. That is not surprising since radiologic assessment is mainly based on a lesion size or detection of calcifications [12]. High diagnostic accuracy of contrast-enhanced CT is promising but requires further validation [13]. Bronchoscopy is only useful when lesion is accessible for a bronchoscope. The receptor scintigraphy widens the spectrum of available methods, particularly in uncertain cases [11].

The reported 88% sensitivity of both ^{99m}Tc-EDDA/HYNIC-TOC SPECT and whole body scintigraphy for detecting primary lung NETs or lung metastases is in agreement with previous reports [14, 15]. Several factors may be responsible for our FN findings, such as an insufficient expression of SSTR2 for *in-vivo* detection by ^{99m}Tc-EDDA/HYNIC-TOC or a comparably higher expression of other SSTR subtypes (SSTR3, SSTR4 or SSTR5) in our cases with low-differentiated tumors. Additional reasons may be a limited spatial resolution of SPECT imaging system along with relatively small size of lung lesions in 3 patients (1.4 cm, 1.7 cm and 1.9 cm, respectively). Finally, a non-specific uptake of radiolabeled somatostatin analogues, such as in arteries supplying tumor tissue or in epithelial cells of lung granulomatosis, also needs to be considered when interpreting the accumulation of ^{99m}Tc-EDDA/HYNIC-TOC. This factors may influence the specificity of the method [16, 17, 7].

Semiquantitative results in our study confirm previously reported higher T/NT ratios on SPECT than whole body images [9, 15]. As expected, therefore, SPECT should be preferred over whole body scintigraphy as it can more precisely detect and localize focal lung lesions. The previous study using ^{99m}Tc-EDDA/Hynic-octreotate (^{99m}Tc-EDDA/HYNIC-TATE) revealed higher tumor/lung ratios (8.3) than reported here (2.96,) and concluded that this analogue is an excellent alternative to ^{111}In-Octreoscan for staging of carcinoids [15]. The reason for a higher uptake of ^{99m}Tc-EDDA/HYNIC-TATE is its comparably higher potential to bind and internalize in tumor cells expressing SSTR2 than ^{99m}Tc-EDDA/HYNIC-TOC [18].

The final finding of our study is that intensity of tracer uptake (T/NT ratio) in NETs is not closely associated with the rate of tumor proliferation (Ki-67 index). This result, however, has to be taken with caution considering a small sample size (n=11) available for correlation analysis. It is reassuring, however, that the relationship between ^{99m}Tc-EDDA/HYNIC-TOC uptake and tumor proliferation rate was negative. The negative correlation is expected because somatostatin receptors responsible for tracer uptake are more expressed in slowly growing, highly differentiated NETs compared to aggressive low-differentiated NETs [2, 5]. Therefore, a smaller uptake of ^{99m}Tc-EDDA/HYNIC-TOC is expected in NETs with a high proliferation rate. This is further supported by the finding that two patients with low-differentiated NETs of high proliferation rate were false negative on scintigraphy, as found in the previous report [19]. Positron emission tomography (PET) with ^{18}Fluor (^{18}F) fluorothymidine (^{18}F-FLT), which is a marker of tumor cell proliferation, similarly yields no correlation between ^{18}F-FLT uptake and Ki-67 [20]. PET imaging with ^{18}F- fluoro-deoxy-glucose (^{18}F-FDG) is highly accurate in differentiating malignant from benign solitary lung lesions [13] and for detecting NETs in the lungs due to different FDG metabolism in malignant and benign cells [21]. More recently, PET using specific ^{68}Gallium (^{68}Ga) labeled somatostatin analogue DOTA-D-Phe^{1}-Tyr^{3}-(DOTATOC) was found superior to ^{18}F-FDG for detecting NETs [22]. However, PET is expensive and not easily accessible. On the other hand, because of its higher spatial resolution compared to SPECT, PET may be

helpful for detecting small NETs with low density of SSTRs for which the classic, conventional scintigraphy seems insufficient [23].

Three patients with NETs received radionuclide therapy with radiolabeled somatostatin analogue ^{90}Yttrium (^{90}Y) DOTA TATE because of its high potential to bind and internalize in tumor cells expressing SSTR2 [18]. Despite our mixed results, radionuclide therapy with radiolabeled somatostatin analogues warrants further investigations in a larger sample. Such an approach may become the therapy of choice for patients with metastatic or inoperable NET [24].

This study has several limitations. ^{99m}Tc-EDDA/HYNIC-TOC is indicated for diagnosis of tumors that express mainly SSTR2, thus of limited value for tumors expressing other receptor types. Another limitation is that we did not evaluate *in-vitro* somatostatin receptor status, which is planned in our future investigations. In this series, however, SSTR2 was evidently expressed in lung lesions in patients with NETs, resulting in high sensitivity of ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy. The limited spatial resolution of SPECT is also of concern in detection of small lesions. A newly introduced hybrid SPECT/CT system provides precise anatomical localization with overall better visualization of lung lesions and increases sensitivity and specificity of scintigraphic findings [25].

In conclusion, our results demonstrate the clinical utility of SPECT and whole body scintigraphy with ^{99m}Tc-EDDA/HYNIC-TOC for diagnosing NET tissue within the lungs. Although the two methods yield identical sensitivity, SPECT is preferred over whole body scintigraphy as it provides better visualization of lung lesions. The intensity of tracer uptake, however, does not closely relate to the proliferation rate of NETs. Overall, ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy may be helpful for selecting and monitoring treatment options, particularly when radiolabeled somatostatin analogue therapy becomes widely available.

Acknowledgements: This work was supported by grant No145033 Ministry of Science Republic of Serbia. We thank Stokic S. Dobrivoje, M.D., D.Sc., Senior Scientist at Center for Neuroscience and Neurological Recovery, Administrative director for research and Chair of Research Council of Methodist Rehabilitation Center, Jackson, Mississippi, USA for his kind assistance and suggestions and in particular for English revision.

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