

ORIGINAL ARTICLE

The clinical value of scintigraphy of neuroendocrine tumors using ^{99m}Tc -HYNIC-TOC

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Summary

Purpose: To assess the value of whole body scintigraphy using ^{99m}Tc -HYNIC-TOC (Tekrotyd) and with single photon emission computerized tomography (SPECT) in the detection of primary and metastatic neuroendocrine tumors (NETs).

Methods: Thirty patients with different neuroendocrine tumors, mainly gastroenteropancreatic (GEP), were investigated. Whole body scintigraphy was performed 2 h (if necessary 10 min and 24h) after i.v. administration of 740 Mbq ^{99m}Tc -Tekrotyd, Polatom. In cases of unclear findings obtained by whole body scintigraphy, investigation was followed by SPECT.

Results: From 12 patients with NETs of unknown origin, there were 10 true positive (TP), and 2 false negative (FN) findings. Diagnosis was made with SPECT in 6 patients.

From 8 patients with gut carcinoids, there were 4 TP, 2 true negative (TN), one FN, and one false positive (FP) finding. Diagnosis was made with SPECT in 2 patients. From 7 patients with neuroendocrine pancreatic carcinomas there were 4 TP and 3 TN findings. Diagnosis was made with SPECT in 2 patients. From 3 patients with gastrinomas there were 2 TP findings and one TN findings. Diagnosis was made with SPECT findings in 2 patients. Sensitivity of ^{99m}Tc -HYNIC-TOC was 87%, specificity 86%, positive predictive value 95%, negative predictive value 67% and accuracy 87%.

Conclusion: We concluded that scintigraphy with ^{99m}Tc -Tekrotyd is an useful method for diagnosis, staging and follow up of the patients with NETs.

Key words: neuroendocrine tumors, radionuclide imaging, ^{99m}Tc -HYNIC-TOC

Introduction

NETs are neoplasms originating from the neural crest, and consequently can be localized in different organs. These tumors are rare and slowly growing, making the diagnosis difficult, although many laboratory analyses and imaging modalities are currently being developed and employed. Radiological methods used are usually ultrasonography, computerized tomography (CT), magnetic resonance imaging (MRI) and angiography. According to Rufini et al. [1] the presence of neuroamine uptake mechanisms and/or peptide receptors on the cell membrane of these tumors is the basis of the clinical use of specific radiolabeled ligands, both for imaging and therapy. Radiolabeled metaiodobenzylguanidine (MIBG) was the first radiopharmaceutical used to

specifically depict and localize catecholamine-secreting tumors (pheochromocytomas, paragangliomas, and neuroblastomas) and is still considered as a first-choice imaging technique for the diagnosis and follow-up, as well as for the selection for ^{131}I -MIBG therapy. Technetium (^{99m}Tc) labeled pentavalent dimercaptosuccinic acid (DMSA-V), sestamibi (MIBI) or tetrofosmin are used only for the diagnosis of medullary thyroid cancer.

However, a fact that the majority of NETs express somatostatin receptors provided a possibility for development of various radiolabeled somatostatin analogues for their diagnosis and therapy. Somatostatin is a neurotransmitter in the central nervous system. It is also a hormone which binds to cells of neuroendocrine origin and inhibits the release of growth hormone, insulin, glucagon, and gastrin. These receptors also exist on the sur-

face of the human tumor cells, mainly with amine precursor uptake and decarboxylation (APUD) properties such as pituitary tumors, endocrine pancreatic tumors, carcinoids, paragangliomas, small cell lung cancers, medullary thyroid carcinomas and pheochromocytomas. Somatostatin receptors can also be found on the cells of non-neuroendocrine origin, such as activated lymphocytes, astrocytomas, and some breast carcinomas. Human somatostatin has a very short half-life in circulation (2-3 min) and is easily broken down by endogenous peptidases [2]; that's why various analogues were developed. They preserve its cyclic form and the 4 amino acids involved in the binding to the receptor. The most widely used is octreotide, which has been used as hormonal treatment in patients with carcinoid syndrome.

Thus, scintigraphy with ^{111}In - or $^{99\text{m}}\text{Tc}$ -labeled somatostatin analogues has become very frequent imaging method for the diagnosis of NETs, particularly those expressing a high density of somatostatin receptors, such as GEP tumors. The indications for application of this procedure include detection and localization of the primary tumor, evaluation of the disease extension, monitoring the effect of treatment and the selection of patients for peptide radionuclide receptor therapy (PRRT).

In order to overcome these disadvantages, ^{111}In -DTPA-D-Phe1-octreotide was developed [3]. It has a high affinity for somatostatin receptors, labeling is easy, and is mainly eliminated by the kidneys. Although ^{111}In pentetreotide is a reliable method for the detection of NETs, the potential clinical advantage of $^{99\text{m}}\text{Tc}$ labeling in comparison to labeling with ^{111}In , led to the development of $^{99\text{m}}\text{Tc}$ labeled somatostatin analogues, such as $^{99\text{m}}\text{Tc}$ -P829 [4], $^{99\text{m}}\text{Tc}$ HYNIC TOC, $^{99\text{m}}\text{Tc}$ HYNIC TATE, $^{99\text{m}}\text{Tc}$ demotate, $^{99\text{m}}\text{Tc}$ depreotide etc. $^{99\text{m}}\text{Tc}$ is not expensive and easily available on site. The physical characteristics of $^{99\text{m}}\text{Tc}$ are more suitable for imaging with gamma camera, leading to lower radiation burden to the patient and allowing for better image quality with lower radiation doses. Furthermore, patients can be imaged for only one day.

$^{99\text{m}}\text{Tc}$ -(EDDA)-HYNIC-TOC (Tektrotyd) is a radiopharmaceutical indicated for the diagnosis of tumors overexpressing somatostatin receptors (especially subtype 2, sstr_2), which can be imaged with this radiolabeled ligand. This radiopharmaceutical can image the following tumors: GEP, neuroendocrine tumors, including the most World Health Organization (WHO) type I and WHO type II tumors and a few WHO type III (previously called GEPNET tumors: carcinoid, APUDOMA, Kultchicky cells tumor, gastrinoma, insulinoma, VIP-oma, ACTH-oma, somatostatinoma etc). Also, other forms of mixed-form of GEP-NET and adenocarcinomas could be seen, including bronchial carcinoid, pheo-

chromocytoma (especially malignant), paraganglioma, neuroblastoma, ganglioneurinoma, medullary thyroid carcinoma, thymoma (malignant) etc. The examination can be potentially useful in case of other tumors indicating somatostatin receptor overexpression at various densities such as breast cancer, melanoma, gliomas, prostate cancer, non small cell lung carcinoma, sarcoma, ovarian cancer, meningioma and renal cell carcinoma.

With recently developed hybrid machines, it became possible to obtain simultaneously both anatomic (CT) and functional (SPECT or positron emission tomography - PET) information, thus improving the diagnostic accuracy. This field has been rapidly expanding, especially in the development of radiopharmaceuticals for PET studies that reflect the different metabolic pathways of NETs, such as glucose metabolism (^{18}F -fluorodeoxyglucose), the uptake of hormone precursors (^{11}C -5-hydroxytryptophan, ^{11}C - or ^{18}F -dihydroxyphenylalanine, ^{18}F -fluorodopamine, as well as the synthesis, storage, and release of hormones (^{11}C -hydroxyephedrine and others) and, the most widely used, ^{68}Ga -labeled somatostatin analogues. Furthermore, new somatostatin analogs with different receptor affinity as well as other peptides are under investigation, such as vasoactive intestinal polypeptide, cholecystokinin/gastrin and bombesin/gastrin. However, the ideal radiopharmaceutical for identification of all the primary sites and metastases of NETs has not been developed yet.

The aim of this study was to assess the value of whole body scintigraphy using $^{99\text{m}}\text{Tc}$ -HYNIC-TOC (Tektrotyd) and SPECT for the detection of primary and metastatic NETs.

Methods

A total of 30 patients (13 males and 17 females, age 53 ± 14 years) with different NETs, mainly GEP tumors, were investigated. Whole body scintigraphy was performed 2 h (if necessary 10 min and 24 h) after i.v. administration of 740 MBq $^{99\text{m}}\text{Tc}$ -Tektrotyd, Polatom. In cases of unclear findings obtained by whole body scintigraphy, investigation was followed by SPECT. It was performed using 360° orbit, step and shoot mode, at 30 sec per view. The acquired data were collected in a 128×128 computer matrix and reconstructed using iterative reconstruction. If necessary, the study was supplemented with liver/spleen radiocolloid and/or bone diphosphonate scintigraphy. Prior to the study, therapy with somatostatin analogues was withdrawn, mild laxatives were given, patients were fasting and were well hydrated. The study was performed with ECAM gamma camera and computer, using high resolution collimator and one photopack activity ($140\text{keV} \pm 20\%$). Other imaging techniques were also applied and analyzed in individual cases (ultrasonography, MRI, computed tomography, $^{99\text{m}}\text{Tc}$ (V)-DMSA, ^{131}I -MIBG, $^{99\text{m}}\text{Tc}$ -MDP, ^{111}In -DTPA-octreotide, $^{99\text{m}}\text{Tc}$ -Sn colloid) as well as laboratory analyses.

We assessed the number of true positive (TP), true negative (TN), false positive (FP) and false negative (FN) findings. Sensitiv-

Table 1. Distribution of findings in the groups of neuroendocrine tumors

<i>NET group</i>	<i>Patients, N</i>	<i>TP</i>	<i>TN</i>	<i>FP</i>	<i>FN</i>	<i>Planar</i>	<i>SPECT</i>
Unknown origin	12	10	0	0	2	4	6
Gut carcinoid	8	4	2	1	1	2	2
Pancreatic carcinoma	7	4	3	0	0	2	2
Gastrinoma	3	2	1	0	0	0	2

TP: true positive, TN: true negative, FP: false positive, FN: false negative, SPECT: single photon emission computerized tomography

ity was calculated according to formula $TP/(TP+FN)$, specificity $TN/(TN+FP)$, positive predictive value according to $TP/(TP+FP)$, negative predictive value according to $TN/(TN+FN)$ and accuracy according to $(TP+TN)/(TP+TN+FP+FN)$.

Results

Distribution of findings in the different groups of patients with NET is shown in Table 1 and Figures 1 and 2. Sensitivity of ^{99m}Tc -HYNIC-TOC (Tektrotyd) was 87%, specificity 86%, positive predictive value 95%, negative predictive value 67% and accuracy 87%.

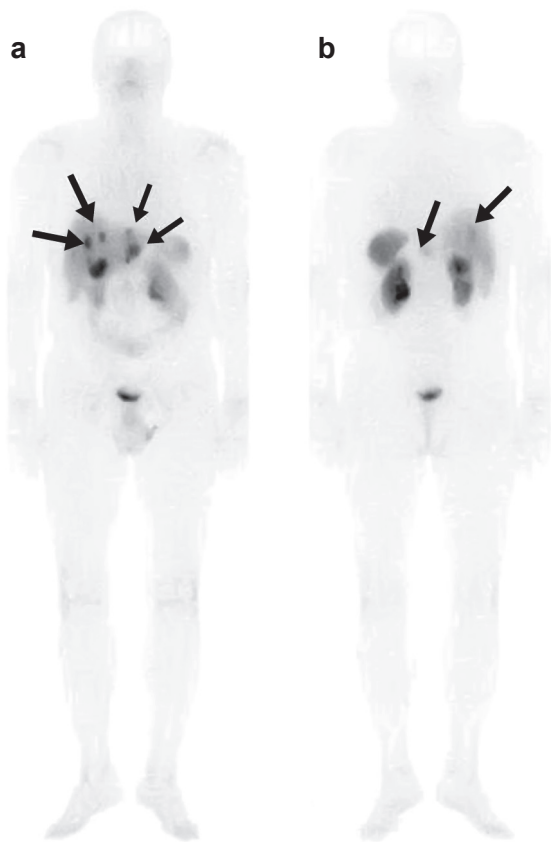


Figure 1. Anterior (a) and posterior (b) whole body scintigraphy with ^{99m}Tc -Tektrotyd in a patient with liver metastases of neuroendocrine carcinoma of unknown origin. Multiple “hot” spots in the liver - metastases (arrows).

From the group of patients NETs of unknown origin, TP findings were obtained in 4 cases with liver metastases, 3 with lung metastases, 2 with bone metastases and one with mediastinal lymph node metastases. FN findings were obtained in one patient with liver metastases of a poorly differentiated tumor, and in another one with small lung metastases (< 1 cm). In the group of patients with gut carcinoid, 3 of 4 with TP findings had liver metastases, 2 patients following surgery had TN findings, there was a FN finding in one patient with a small lung metastasis, and a FP finding in one patient, probably caused by physiological activity accumulated in the bowel. From the patients with neuroendocrine pancreatic carcinomas, TP findings were seen in 3 cases with liver metastases and one with metastases in the paraaortic lymph nodes, while TN findings included

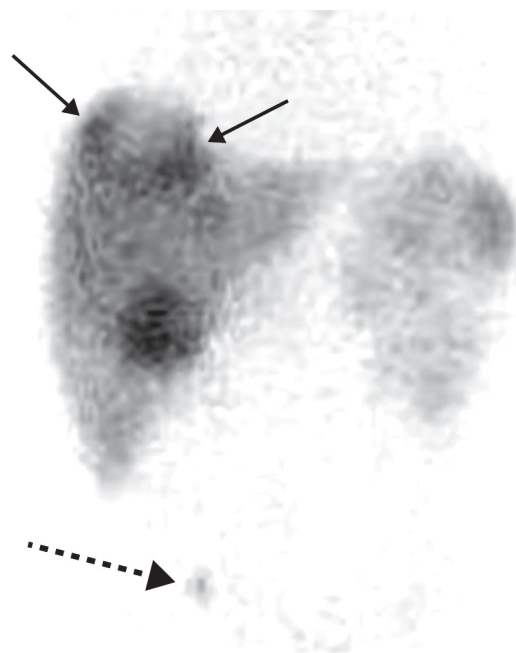


Figure 2. Anterior planar spot view of the abdomen with ^{99m}Tc -Tektrotyd in a patient with liver metastases from gut carcinoid. Small, round-shaped “hot” spot in the right part of abdomen indicates the primary tumor dotted (dotted arrow). Multiple “hot” spots in the liver - metastases (solid arrows). The patient was sent for scintigraphy with the diagnosis of liver metastases of carcinoma of unknown origin. After scintigraphy the diagnosis was changed to primary gut carcinoid.

one patient with somatostatinoma, one with insulinoma and one with carcinoid after surgery. As for the patients with gastrinomas, in 2 of them there were TP findings (jejunal, pancreatic), and in one TN findings (paraduodenal). Out of 30 patients studied, SPECT contributed to accurate diagnosis in 12 (40%), including 6 patients with NETs of unknown origin, 2 with gut carcinoid, 2 with neuroendocrine pancreatic carcinomas, and 2 with gastrinomas. Also, SPECT was useful for further management (i.e. to proceed or not to radionuclide therapy) in 13 (43%) patients, including 4 patients with NETs of unknown origin, 4 with gut carcinoid, 3 with neuroendocrine pancreatic carcinomas, and 2 with gastrinomas. Finally, radionuclide therapy with ^{90}Y -DOTA TATE was indicated in 10, and already performed in 5 patients.

Discussion

Many authors investigated the biophysical characteristics of $^{99\text{m}}\text{Tc}$ -HYNIC-TOC, mainly in experimental studies and recommended it for clinical application. González-Vázquez et al. [5] proved its high *in vitro* and *in vivo* stability, rapid background clearance and rapid detection of somatostatin receptor-positive tumors. Images showed an average tumor/blood (heart) ratio of 4.3 ± 0.7 in receptor-positive tumors at 1 h. Decristoforo et al. [6] and Guggenberg et al. [7] proved that the high specific tumor uptake, rapid blood clearance, and predominantly renal excretion, as well as improved image quality, lower radiation dose for the patient, and daily availability, make $^{99\text{m}}\text{Tc}$ -EDDA-HYNIC-TOC a promising candidate for an alternative to ^{111}In -DTPA-octreotide for NET imaging.

Widely performed clinical studies recommended further application of this radiopharmaceutical for the diagnosis of NETs. Thus, Gabriel et al. [8] evaluated the application of this radiopharmaceutical for staging and follow-up of GEP tumors in 88 patients, obtaining a sensitivity of 80%, specificity of 94.4% and accuracy of 82.9%, and recommended it as an accurate procedure in patients with neuroendocrine GEP tumors, especially with the use of SPECT and the early images. The same authors [9] revealed a higher sensitivity of this radiopharmaceutical compared with ^{111}In -octreotide in patients evaluated for the detection and localization of NETs, staging, determination of the SSTR status of tumor lesions, and follow-up. In order to avoid FP findings with $^{99\text{m}}\text{Tc}$ labeled radiopharmaceutical due to nonspecific tracer accumulation, additional scanning at 1-2 h after injection was recommended.

Recent investigations evaluated the potential of using this radiopharmaceutical for the imaging of a

wide range of primary and metastatic tumors such as hepatocellular carcinoma [10], pituitary adenomas, liposarcoma, carcinoids, breast carcinoma, and lung cancer, as well as metastases of malignant melanomas, pheochromocytoma, prostatic cancer, leiomyosarcoma, pancreatic carcinoma ectopically secreting adrenocorticotrophic hormone and carcinoid of the thymus [11,12].

Improvement of diagnostic methods, including fusion imaging and hybrid systems, additionally contributed to the accuracy and clinical validity of this method. Gabriel et al. [13] suggested the improvement of the method with fusion of SPECT and CT images. Image fusion reduces FP results and can detect additional lesions. Similarly, using SPECT/CT, Li et al. [14] using $^{99\text{m}}\text{Tc}$ -HYNIC-TOC in NETs, non-NETs and benign diseases, obtained sensitivity, specificity, and accuracy of 82.6%, 100%, and 87.5%, respectively, which makes this fusion method promising for the diagnosis and localization of somatostatin receptor-positive tumors.

Some other somatostatin analogues, very similar to $^{99\text{m}}\text{Tc}$ -HYNIC TOC, have been recently investigated and recommended for clinical use. In an experimental study Gandomkar et al. [15] concluded that $^{99\text{m}}\text{Tc}$ -EDDA-tricine-HYNIC-NATE is a specific radioligand for the somatostatin-receptor-positive tumors and is a suitable candidate for clinical studies. Hubalewska-Dydejczyk et al. [16] proved that scintigraphy with a new $^{99\text{m}}\text{Tc}$ marked somatostatin analogue –octreotate– allows a more sensitive detection of metastatic lesions in carcinoid tumors. Hubalewska-Dydejczyk et al. [17] aimed to assess the diagnostic efficiency of $^{99\text{m}}\text{Tc}$ -EDDA/HYNIC-octreotate scintigraphy in the detection and staging of carcinoid tumors, and for referring to ^{90}Y -DOTA-TATE therapy. The sensitivity of scintigraphy in comparison with CT was higher for primary lesions, liver and abdominal lymph node metastases. This radiopharmaceutical is proved to be an excellent alternative to ^{111}In -octreoscan for the staging of carcinoids, especially for the detection of the primary tumor in patients with metastases from an unknown primary tumor. Storch et al. [18] compared 3 somatostatin analogues designed for the labeling with $^{99\text{m}}\text{Tc}$ (HYNIC-OC, HYNIC-TOC and HYNIC-TATE) and ^{111}In (DTPA-OC and DOTA-TATE). These radiopeptides are specific radioligands for the somatostatin receptor subtype 2. The rate of internalization correlated with the uptake in the tumor and pancreas. The results indicated that ^{111}In -DOTA-TATE and $^{99\text{m}}\text{Tc}$ -EDDA-HYNIC-TATE are suitable candidates for clinical studies. Gabriel et al. [19] reported that $^{99\text{m}}\text{Tc}$ -demotate is a promising agent for somatostatin receptor scintigraphy, providing images of excellent quality as early as 1 h after injection. However, Lebtahi et al. [4] in their study with 43

patients with neuroendocrine tumors (with Zollinger-Ellison syndrome, carcinoid tumors, and other types of functioning or nonfunctioning endocrine tumors) concluded that the detection rate of ^{99m}Tc -P829 scintigraphy was lower than that of ^{111}In -pentetreotide scintigraphy, which appeared to be more sensitive, especially for liver metastases.

^{18}F -FDG PET and PET/CT, widely used as a powerful imaging technique in clinical oncology, are limited in the detection of carcinoid tumors due to their low proliferative activity. However, other positron emitting radionuclides are recommended, such as ^{11}C -5-hydroxytryptophan, ^{11}C - or ^{18}F -dihydroxyphenylalanine, ^{18}F -fluorodopamine, ^{11}C -hydroxyephedrine and others, and the most widely used, ^{68}Ga -labeled somatostatin analogues. Despite certain advantages regarding the receptor affinity and resolution, the price and availability of use of this pharmaceuticals still do not permit wide application [20,21]. A step forward was made with the potential use of radio-guided surgery in GEP-NETs [22,23]. Thus, ^{99m}Tc -EDDA-HYNIC-octreotate somatostatin receptor scintigraphy followed by radioimmunoguided surgery is a promising technique to improve the rate of detection and efficacy of treatment of GEP-NETs, especially in the presence of occult endocrine tumors, because of the imaging properties of ^{99m}Tc and the one-day imaging protocol.

Conclusion

Our preliminary results show that scintigraphy of NETs with ^{99m}Tc -Tektrotyd is a useful method for the diagnosis, staging and follow up of patients suspected to have NETs. SPECT had an important role in the diagnosis. It is also helpful for choosing the appropriate therapy and its monitoring, including the radionuclide therapy with radiolabeled somatostatin analogues. Special emphasis should be given to the application of fusion or hybrid imaging (SPECT/CT) as well as to the radioguided surgery.

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