Original
Copyright © 2016 Via Medica
ISSN 1506–9680
VIA MEDICA

Influence of PET/CT ^{68}Ga somatostatin receptor imaging on proceeding with patients, who were previously diagnosed with ^{99m}Tc-EDDA/HYNIC-TOC SPECT

Dorota Mądrzak[1], Renata Mikołajczak[2], Grzegorz Kamiński[3]
[1]Department of Nuclear Medicine, Voivodship Medical Specialty Center, Rzeszow, Poland
[2]Radioisotope Centre POLATOM, National Centre for Nuclear Research, Otwock, Poland
[3]Military Institute of Medicine, Warsaw, Poland

[Received 5 V 2016; Accepted 7 VII 2016]

Abstract

BACKGROUND: The aim of this study was the assessment of utility of somatostatin receptor scintigraphy (SRS) by SPECT imaging using ^{99m}Tc-EDDA/HYNIC-Tyr^3-octreotide (^{99m}Tc-EDDA/HYNIC-TOC) in patients with neuroendocrine neoplasm (NEN) or suspected NEN, referred to Nuclear Medicine Dept. of Voivodship Specialty Center in Rzeszow. The selected group of patients was referred also to ^{68}Ga PET/CT. The posed question was the ratio of patients for whom PET/CT with ^{68}Ga would change their management.

MATERIAL AND METHODS: The distribution of somatostatin receptors was imaged using ^{99m}Tc-EDDA/HYNIC-TOC in 61 planar and SPECT studies between 13/05/2010 and 04/02/2013 in Nuclear Medicine Dept. of Voivodship Specialty Center in Rzeszow. The patient age was within a range of 17–80, with the average age of 57.6. The average age of women (65% of patients overall) was 55.6 and the average age of men (35% of patients overall) was 61.4. In 46 participants (75% of the study group), that underwent SRS, NEN was documented using pathology tests. Selected patients were referred to PET/CT with ^{68}Ga labeled somatostatin analogs, DOTATATE or DOTANOC. This study group consisted of 14 female and 10 male participants with age range of 35–77 and average age of 55.5 years. Patients were classified into 3 groups, as follows: detection — referral due to clinical symptoms and/or biochemical markers (CgA-Chromogranin A, IAA-indoleacetic acid) with the aim of primary diagnosis, staging — referral with the aim of assessment of tumor spread, and follow-up — assessment of the therapy.

RESULTS: Out of 61 patients, 24 underwent both ^{99m}Tc-EDDA/HYNIC-Tyr^3-octreotide SPECT and ^{68}Ga PET/CT. The result of PET/CT was used as a basis for further evaluation. Therefore, the patients were divided into groups; true positive TP (confirmed presence of tissue somatostatin receptors with ^{68}Ga PET/CT) and TN (^{68}Ga PET/CT did not detect any changes and the results were comparable and had the same influence on treatment protocol). In case of SPECT, the results were assigned as follows: TP, TN (in cases where the results were confirmed by ^{68}Ga PET/CT), FP (patient's scintigraphy demonstrated focal change by SPECT but not PET/CT) and FN (^{99m}Tc-EDDA/HYNIC-Tyr^3-octreotide SPECT failed to demonstrate any abnormalities; however, the treatment protocol was changed after PET/CT).

CONCLUSIONS: The accuracy of SPECT diagnosis was found to be as high as 91.6%. Only in 8.4% of patients the additional PET/CT with ^{68}Ga-labeled somatostatin analog changed the treatment protocol.

KEY words: somatostatin receptor imaging, SRS, SPECT, PET, ^{68}Ga, ^{99m}Tc-EDDA/HYNIC-Tyr^3-octreotide

Nucl Med Rev 2016; 19, 2: 88–92

Correspondence to: lek. Dorota Mądrzak
Department of Nuclear Medicine,
Voividship Speciality Center in Rzeszow
e-mail: dmadrzak@gmail.com

Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous group of diseases which are of epithelial origin. They are characterized by neuroendocrine differentiation. The incidence of NENs is estimated to be 4–5 cases per 100,000, which is 0.5% of all tumors [1] and is increasing. NEN can originate in any organ but most commonly (70% of all NEN) they form in the gastro-intestinal tract, so-called GEP-NEN (GastroEnteroPancreatic-NEN). About 30% of NENs localize in the respiratory tract. Over 50% of GEP-NENs are carcinoid tumors which are most commonly discovered during small bowel surgery, appendectomy or during staging process, involving mainly liver metastases [2]. They grow slowly and the time needed for the development of symptoms is long, which is the reason why this illness is usually diagnosed at an advanced stage. Nevertheless, patients have a long lifespan on average. Overall, 5 year survival rate is 67.2% [3].

NENs are visualized using conventional radiological methods, MRI, USG (ultrasonography), endoscopy, EUS (endoscopic ultrasonography) and nuclear medicine techniques. These diagnostic procedures are obligatory in the assessment of the tumor origin as well as in staging and follow-up. Currently, the nuclear medicine relies on methods based on SPECT and PET, commonly involving CT, which allows more precise tumor localization and attenuation correction [4]. The great majority of tumors are characterized by overexpression of somatostatin receptors (SSTRs) [1, 4–6]. Targeting of these receptors with radiolabeled somatostatin analogs enabled the development of new imaging methods *in vivo* [7, 8]. ^{111}In-pentetreotide (Octreoscan) was the first approved radiopharmaceutical for neuroendocrine tumor functional studies. Introduction of multi-head gamma cameras and tomographic acquisition with SPECT allows for 3D imaging and increased sensitivity. Nevertheless, due to low resolution, any changes below 1 cm in diameter remain undiagnosed and also the long acquisition time required for ^{111}In-pentetreotide have both spurred the search for new and improved imaging methods. The limitations of SPECT with ^{111}In could be overcome with the development of ^{99m}Tc-labeled somatostatin analogs, which caused wider interest in the use of these tracers for NEN imaging diagnostics. Availability of ^{99m}Tc obtained from radionuclide generators over ^{111}In produced in cyclotrons improved the accessibility of this diagnostic tool. Imaging with ^{99m}Tc enables the use of low-energy collimators with high resolution. The initial research on the use of ^{99m}Tc-EDDA/HYNIC-TOC has already demonstrated its advantage over ^{111}In-pentetreotide for imaging of somatostatin receptor imaging [9]. Similar study was conducted also in Poland and showed the advantage of somatostatin receptor scintigraphy (SRS) with another ^{99m}Tc labeled somatostatin analog, ^{99m}Tc-HYNIC-TATE over Octreoscan for the detection of primary lesion in patients with NEN [10], which was also supported by other research [11, 12]. In the last years patients with NEN are usually referred for SPECT with ^{99m}Tc-EDDA/HYNIC-Tyr^3-octreotide (Tektrotyd), which was granted Marketing Authorization in Poland and in several other European countries for this indication. On the other hand, the better imaging properties of PET using ^{68}Ga in combination with somatostatin analogs are based on the higher spatial resolution of this technique [13] but also need an optimal acquisition protocol. PET is a technique that utilizes radioisotopes that emit positrons — antielectrons. Positron-emitting radionuclide, which is introduced into the body on a biologically active molecule, emits positrons that upon contact with electrons annihilate producing two gamma rays, which are then detected by the PET scanner.

NENs are usually well differentiated and are characterized by overexpression of somatostatin receptors that can be targeted by synthetic somatostatin analogs. It has been fifteen years since Hoffman et al. [14] demonstrated the advantage of PET with somatostatin analog labeled with ^{68}Ga (^{68}Ga-DOTATOC) over ^{111}In-pentetreotide for detection of abdominal metastases, using tomography as a reference.

According to study by Gabriel et al. [15] who compared receptor scintigraphy (^{111}In-DOTATOC and ^{99m}Tc-EDDA/HYNIC-TOC) with PET (^{68}Ga-DOTA-TOC) and CT in patients with NEN, PET showed diagnostic advantage over scintigraphy. In 38% cases there was a discrepancy between PET and scintigraphy, with PET showing greater accuracy, which resulted in a change of treatment in 14.3% of patients.

PET/CT diagnostics using somatostatin analogs with ^{68}Ga are currently unavailable in Podkarpackie region. Nevertheless, due to the accessibility of SPECT, patients with NEN are usually referred for SPECT with ^{99m}Tc-EDDA/HYNIC-TOC (Tektrotyd). This diagnostic procedure has been carried out in Nuclear Medicine Dept. of Voivodship Specialty Center in Rzeszow since 2010. At that time PET/CT using ^{68}Ga radiolabeled somatostatin analogs was only available in a very few centers in Poland.

The aim of this study was the comparative evaluation of the results of ^{99m}Tc-EDDA/HYNIC-TOC SPECT SRS, which was performed in our Center, with the externally carried out PET/CT with ^{68}Ga radiolabeled somatostatin analogs, and assessment of its influence on further diagnosis and treatment.

Material and methods

The distribution of somatostatin receptors was imaged using ^{99m}Tc-EDDA/HYNIC-TOC in 61 planar and SPECT studies between 13/05/2010 and 04/02/2013 in Nuclear Medicine Dept. of Voivodship Specialty Center in Rzeszow.

- study group age: 17–80;
- average age: 57.6 yrs.;
- female participants: 65%, average age 55.6 yrs.;
- male participants: 35%, average age 61.4 yrs.

In 46 participants (75% of the study group), that underwent SRS, NEN was documented using pathomorphology tests.

However, the group of patients was referred to PET/CT with ^{68}Ga labeled somatostatin analog. It was not advised to patients for whom any more precise diagnosis would change a treatment protocol. For example, patient with tumor dissemination, whose scintigraphy result is shown in Figure 1, was not referred to further diagnosis even in the event of other metastases. Also, some patients refused to travel outside of Podkarpackie region.

Among a group of patients who were referred for SPECT, 24 patients had the PET/CT scans carried out. The diagnostic results of the above-mentioned patients were carefully analyzed, since they undergone both imaging procedures. The PET/CT was done between 3–16 weeks after SPECT scan. The study group consisted of 14 female and 10 male participants with age range of 35–77 and average age of 55.5 years.

Patients were classified into 3 groups, as follows:

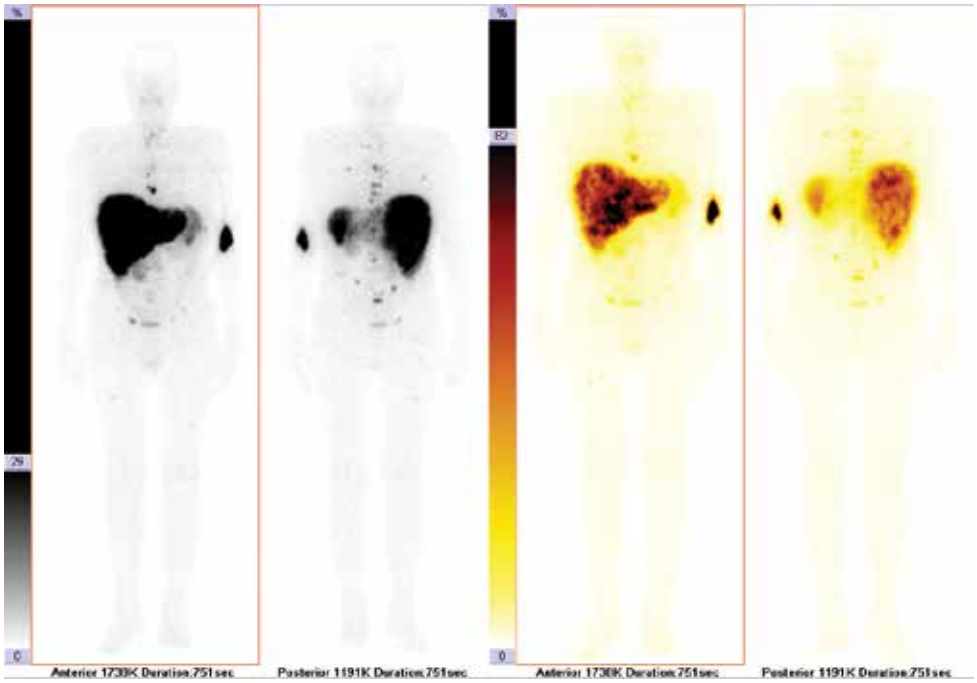

Figure 1. SRS imaging of a patient with disseminated NEN — an example

Table 1. The results of assessing the influence of SPECT and 68Ga PET/CT on further patient treatment

		SPECT				PET/CT			
GROUP	N	TP	TN	FP	FN	TP	TN	FP	FN
Detection	2	0	2	0	0	0	2	0	0
Staging	20	11	8	**1**	0	11	9	0	0
Follow-up	2	0	1	0	**1**	1	1	0	0
Total	24	11	11	**1**	**1**	12	12	0	0

1. detection — referral due to clinical symptoms and/or biochemical markers (CgA, IAA) with the aim of primary diagnostics — 2 patients;
2. staging — referral with the aim of assessment of tumor spread, patients were diagnosed with NEN based on histopathology and oligobiopsy tests — 20 patients;
3. follow-up — assessment of the therapy — 2 patients.

Imaging was carried out with: Dualhead Gamma Camera e-CAM, manufactured by Siemens in 2006, equipped with LEAP collimator. Imaging whole-type: 12 cm/s, Imaging SPECT-type: energy window 140 keV, width 10%, detector rotation 180°, 64 projections, 128 x 128 matrix, 30 s/projection. Data was reconstructed based on iterative reconstruction.

^{99m}Tc-EDDA/HYNIC-Tyr^{3}-octreotide (^{99m}Tc-Tektrotyd, National Centre for Nuclear Research, Polatom, Poland) was prepared according to manufacturer instructions and administered in the dose of average radioactivity of 690–760 MBq, while ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC were prepared in collaborating groups in Warsaw, Cracow and Gliwice according to the in-house developed protocols.

Results

Out of 61 patients, 24 underwent both SPECT and ^{68}Ga PET/CT. The result of PET/CT was used as a basis for further treatment. Therefore, the participants were divided into groups; true positive TP (confirmed presence of tissue somatostatin receptors with ^{68}Ga PET/CT) and TN (^{68}Ga PET/CT did not detect any changes and the results were comparable and had the same influence on treatment protocol).

In case of SPECT, the results were assigned as follows: TP, TN (in cases where the results were confirmed by ^{68}Ga PET/CT), FP (patient's scintigraphy demonstrated focal change by SPECT but not PET/CT) and FN (^{99m}Tc SPECT failed to demonstrate any abnormalities; however, the treatment protocol was changed after PET/CT). The results are presented in Table 1.

Based on data in Table 1, the accuracy of diagnosis using SPECT was calculated as follows:

ACCURACY = TP + TN / TP + TN + FP + FN = 11 + 11 / 11 + 11 + 1 + 1 = 22/24 = 0.916; 91.6%

100% – 91.6% = 8.4%

Hence, the accuracy of SPECT diagnosis is 91.6%. **Only in 8.4% of patients PET/CT with ^{68}Ga labeled somatostatin analogs changed the treatment protocol.**

The clinical data, pertaining to two patients, whose treatment protocol was changed after PET/CT, is shown in Table 2.

Patient 1 was a 54-year-old male, who underwent middle lung lobectomy due to NEN in 2010. His blood test showed increased CgA and SPECT study indicated abnormal focal tracer concen-

Table 2. Patients who benefited from PET/CT of somatostatin receptors imaging with ^{68}Ga

No	Sex	Age	Group	Clinical presentation	SPECT result	PET result	Change of treatment procedure after PET/CT
1	M	54	Staging	Post middle lobectomy due to NEN in 2010, increased level of CgA	Focal abnormality in left adrenal gland FP	Physiological concentration in adrenal gland TN	Planned surgery abandoned
2	K	67	Follow-up	Post right hemicolectomy due to NENG1; suprarenal gland tumor (CT)	Focal abnormality in left adrenal gland FN	Dissemination (metastasis to mesentery lymph nodes, liver, bone and suprarenal gland) TP	Planned surgery abandoned. Somatostatin analog therapy introduced

trating in left suprarenal gland. However, PET/CT scan confirmed a physiological character of that focal change and as a result patient did not undergo surgery.

Patient 2 was a 67-year-old female, who underwent right hemicolectomy due to NEN and also suffered from suprarenal tumor based on CT scan. SPECT scan indicated abnormal tracer concentration in the affected suprarenal gland. However, PET/CT detected dissemination to mesentery lymph nodes, liver, bone and suprarenal glands. As a result, patient did not undergo adrenalectomy but instead she was treated with somatostatin analogs.

Discussion

The aim of this prospective study was to assess the suitability of dual-head gamma camera for diagnosis, staging and therapy monitoring of NEN by SRS SPECT. This study was carried out in Nuclear Medicine Dept. of Voivodship Specialty Center in Rzeszow from 09.2010 to 02.2013 and was continued thereafter. In this voivodship, somatostatin receptor scintigraphy was performed only sporadically until 2010 and PET/CT is still unavailable.

This study compares suitability of PET and SPECT methods in diagnosis and treatment assessment of NEN. Similar studies were carried out previously by Gabriel et al. [15]. They assessed 84 patients, who were divided into groups: detection — 13 patients, staging — 36 patients and follow-up — 35 patients. They were diagnosed by PET using ^{68}Ga-DOTATOC and SPECT with both ^{111}In-DOTATOC and ^{99m}Tc-EDDA/HYNIC-TOC. According to this study, the discrepancy between SPECT and PET results was 38%, which influenced treatment protocol for 14.3% of patients [15]. The discrepancy between the outcomes of the aforementioned research and our study (14.3% vs 8.4%) can be explained by the fact that Gabriel et al. [15] in 40% of patients directed for somatostatin receptor scintigraphy used ^{111}In-pentetreotide and the use of 2 different compounds for SRS SPECT has been a limitation in that study while in our patients we used ^{99m}Tc-EDDA/HYNIC-TOC only. In our study the calculated accuracy of diagnosis using SPECT ^{99m}Tc-Tektrotyd is 91.6%, which is due to the high sensitivity and specificity of this tracer. It is well in agreement with earlier SRS investigations using ^{99m}Tc-EDDA/HYNIC-TOC in GEP NET patients by Gabriel et al. [16] who reported the specificity of 80.9% and sensitivity 94.4% in the group of 88 patients, Gomez et al. [17] with the sensitivity of 87% and 100% specificity in 32 patients and Artiko et al. [18] with the sensitivity of 87% and specificity of 86% in the group of 30 patients, respectively. The treatment procedure was altered only for 8.4% of patients (2 persons) after PET/CT with ^{68}Ga labeled somatostatin receptor agent. Hence, the reason for our results might be due to the use of ^{99m}Tc-Tektrotyd only.

Some patients, who underwent SPECT in Voivodship Specialty Centre, were not diagnosed with PET, since the detection of additional sites of disease by PET was not expected to influence the therapeutic approach [13, 19]. Theoretically, providing that other patients were included to the study, e.g. those who were diagnosed with NEN dissemination or those whose NEN was removed with safe margin, dissemination was negative in SRS and also the conventional imaging (US, CT, MRI) did not indicate pathology, the PET/CT findings might not affect the patient's clinical management. In such a case the calculated overall ratio of the patients who benefited from that test would be even lower. However, from this hypothetical calculation a group of patients should be excluded who did not agree for the diagnostic tests outside of voivodship or who could not be transported further away due to overall poor health condition or those who were not diagnosed with NEN in pathomorphological tests.

Nevertheless, due to the small size of this study it is not conclusive and the results should be confirmed in a larger number of participants. The study is ongoing.

Conclusions

This pilot study demonstrates high utility of somatostatin receptor scintigraphy using ^{99m}Tc SPECT. The great majority of patients, who underwent both SPECT and ^{68}Ga-PET/CT, were correctly diagnosed with SPECT only (91.6%). In the group under study, PET/CT changed the treatment protocol in only 8.4% of cases, out of 24 patients diagnosed with both techniques.

References

1. Rust E, Hubele F, Marzano E et al. Nuclear medicine imaging of gastro-entero-pancreatic neuroendocrine tumors. The key role of cellular differentiation and tumor grade: from theory to clinical practice. Cancer Imaging : The Official Publication of the International Cancer Imaging Society 2012; 12: 173–184.
2. Kos-Kudła B, Handkiewicz-Junak J, Kunikowska D, Krzakowski J, Nasierowska-Guttmejer M, Patkowski AW. Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumours) 2013; 64: 418–443.
3. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003; 97: 934–959.
4. De Herder WW. GEP-NETS update: functional localisation and scintigraphy in neuroendocrine tumours of the gastrointestinal tract and pancreas (GEP-NETs). Eur J Endocrinol 2014; 170: R173–183.
5. Koopmans KP, Neels ON, Kema IP et al. Molecular imaging in neuroendocrine tumors: molecular uptake mechanisms and clinical results. Crit Rev Oncol Hematol 2009; 71: 199–213.
6. Baum RP, Kulkarni HR. THERANOSTICS: From Molecular Imaging Using Ga-68 Labelled Tracers and PET/CT to Personalized Radionuclide Therapy — The Bad Berka Experience. Theranostics 2012; 2: 437–447.

7. Heppeler A, Froidevaux S, Eberle A et al. Receptor targeting for tumor localization and therapy with radiopeptides. Curr Med Chem 2000; 7: 971–994.
8. Ambrosini V, Fani M, Fanti S, Forrer F, Maecke HR. Radiopeptide Imaging and Therapy in Europe. J Nucl Med 2011; 52: 42S–55S.
9. Decristoforo C, Melendez-Alafort L, Sosabowski Jane K, Mather SJ. 99mTc-HYNIC-[Tyr3]-Octreotide for Imaging Somatostatin-Receptor-Positive Tumors: Preclinical Evaluation and Comparison with 111In-Octreotide. J Nucl Med. 2000; 41: 1114–1119.
10. Hubalewska-Dydejczyk A, Fröss-Baron K, Mikołajczak R et al. 99mTc-EDDA/ /HYNIC-octreotate scintigraphy, an efficient method for the detection and staging of carcinoid tumours: results of 3 years' experience. Eur J Nucl Med Mol Imaging 2006; 33: 1123–1133.
11. Táborská K. Somatostatin receptor scintigraphy — 99mTc-EDDA/HYNIC-TOC first clinical experience in the Czech Republic. Nukl Med 2012; 1: 7–12.
12. Kocyigit Deveci E, Ocak M, Bozkurt MF, Turker S, Kabasakal L, Ugur O. The diagnostic Efficiency of 99mTc-EDDA/HYNIC-Octreotate SPECT-CT in Comparison with 111In-Pentetrotide in the Detection of Neuroendocrine Tumours. Mol Imaging Radionucl Ther 2013; 22: 76–84.
13. Ambrosini V, Campana D, Bodei L et al. 68Ga-DOTANOC PET/CT clinical impact in patients with neuroendocrine tumors. J Nucl Med 2010; 51: 669–673.
14. Hofmann M, Maecke H, Börner R et al. Biokinetics and imaging with the somatostatin receptor PET radioligand (68)Ga-DOTATOC: preliminary data. Eur J Nucl Med 2001; 28: 1751–1757.
15. Gabriel M, Decristoforo C, Kendler D et al. 68Ga-DOTA-Tyr3-Octreotide PET in Neuroendocrine Tumors : Comparison with Somatostatin Receptor Scintigraphy and CT. J Nucl Med 2007; 48: 508–518.
16. Gabriel M, Muehllechner P, Decristoforo C et al. 99mTc-HYNIC-Tyr(3)-octreotide for staging and follow-up of patients with neuroendocrine gastro-entero-pancreatic tumours. Q J Nucl Med Mol Imaging 2005; 49: 237–244.
17. Gómez M, Ferrando R, Vilar J et al. 99mTc-octreotide in patients with neuroendocrine tumours from the GI tract. Acta Gastroenterol Latinoam 2010; 40: 332–338.
18. Artiko V, Sobic-Saranovic D, Pavlovic S et al. The clinical value of scintigraphy of neuroendocrine tumors using (99m)Tc-HYNIC-TOC. J BUON 2012; 17: 537–542.
19. Schillaci O. Somatostatin Receptor Imaging in Patients with Neuroendocrine Tumors: Not Only SPECT? J Nucl Med 2007; 48: 498–500.