



The role of PET-CT scan with somatostatin analogue labelled with gallium-68 (^{68}Ga -DOTA-TATE PET-CT) in diagnosing patients with disseminated medullary thyroid carcinoma (MTC)

Rola badań PET-CT z analogiem somatostatyny znakowanym galem-68 (^{68}Ga -DOTA-TATE PET-CT) w diagnostyce rozsiewu rdzeniastego raka tarczycy (MTC)

Iwona Pałyga¹, Aldona Kowalska¹, Danuta Gąsior-Perczak¹, Małgorzata Tarnawska-Pierścińska², Janusz Słuszniaik³, Jacek Sygut⁴, Stanisław Góźdz⁵

¹Department of Endocrinology and Nuclear Medicine Holycross Cancer Centre (HCC), Kielce, Poland

²Department of Nuclear Medicine HCC, Kielce, Poland

³Department of Oncological Surgery HCC, Kielce, Poland

⁴Department of Pathology and Cancer Biology HCC, Kielce, Poland

⁵Department of Chemotherapy and Clinical Oncology HCC, Kielce, Poland

Abstract

Introduction: Calcitonin is a very sensitive marker of medullary thyroid carcinoma (MTC). High concentrations of basal or pentagastrin stimulated calcitonin in patients with MTC is a signal of recurrence or metastatic disease. Detection of metastatic foci remains a diagnostic and therapeutic challenge.

The aim of the study was to present examples of the use of ^{68}Ga -DOTA-TATE PET-CT examinations in the diagnosis of patients with MTC and concomitant elevated serum calcitonin concentrations.

Initially the study involved eight patients with MTC and elevated basal or stimulated calcitonin, in which earlier diagnostic imaging was negative for metastasis: neck ultrasound, chest and mediastinal CT scan, liver MRI, bone scintigraphy, and ^{18}F -FDG-PET. A total body scan was performed using ^{68}Ga -DOTA-TATE PET-CT. Two patients with positive diagnostic imaging tests were referred for surgery including resection of cervical lymph nodes with histopathological examination for assessment of metastases.

Conclusions: On the basis of the presented cases we conclude that PET-CT scan with somatostatin analogue labelled with gallium (^{68}Ga -DOTA-TATE PET-CT) may be useful in the diagnostic imaging of patients with disseminated MTC.

(*Pol J Endocrinol* 2010; 61 (5): 507–511)

Key words: medullary thyroid carcinoma, ^{68}Ga -DOTA-TATE, positron-emission tomography, calcitonin, neoplasm metastasis

Streszczenie

Wstęp: Kalcitonina jest bardzo czułym markerem rdzeniastego raka tarczycy (MTC, *medullary thyroid carcinoma*). Wysokie stężenie kalcitoniny podstawowej lub stymulowanej pentagastryną u pacjentów z MTC świadczy o wznowie lub obecności zmian przerzutowych. Poszukiwanie tych ognisk stanowi istotny problem diagnostyczno-kliniczny.

Celem pracy było przedstawienie możliwości wykorzystania badań ^{68}Ga -DOTA-TATE PET-CT w diagnostyce pacjentów z MTC i współistniejącym podwyższonym stężeniem kalcitoniny w surowicy.

Wyjściowo badaniem objęto 8 chorych z MTC i podwyższonym stężeniem kalcitoniny podstawowej lub stymulowanej, u których w dotychczasowych badaniach obrazowych (USG szyi, CT klatki piersiowej i śródpiersia, MRI wątroby, scyntygrafia kośćca oraz ^{18}F -FDG PET) nie uwidoczono ognisk przerzutowych.

U wszystkich chorych wykonano badanie całego ciała z zastosowaniem analogu somatostatyny znakowanego galem 68. Chorych z dodatnim wynikiem badania zakwalifikowano do leczenia operacyjnego. Oceniono wyniki badania histopatologicznego.

U 2 spośród 8 pacjentów z rozpoznaniem MTC oraz z podwyższonym stężeniem kalcitoniny stwierdzono dodatni wynik scyntygrafii ^{68}Ga -DOTA-TATE PET-CT. Chorych skierowano do leczenia operacyjnego obejmującego wycięcie węzłów chłonnych szyi.

Wyniki badania histopatologicznego potwierdziły obecność przerzutów w wyciętych węzłach chłonnych.

Wnioski: Prezentowane przypadki sugerują, że badanie PET z analogiem somatostatyny znakowanym galem 68 (^{68}Ga -DOTA-TATE PET-CT) jest przydatne w diagnostyce obrazowej chorych z MTC. Pozwoliło ono na lokalizację ognisk przerzutowych u 2 spośród 8 pacjentów.

(*Endokrynol Pol* 2010; 61 (5): 507–511)

Słowa kluczowe: rak rdzeniasty tarczycy, ^{68}Ga -DOTA-TATE, pozytronowa tomografia emisyjna, kalcitonina, przerzuty nowotworowe



Iwona Pałyga M.D., Department of Endocrinology and Nuclear Medicine Holycross Cancer Centre (HCC), 25-734 Kielce, Artwińskiego St. 3, tel.: +48 41 367 41 86, fax: +48 41 345 68 82, e-mail: iwonapa@o2.pl

Introduction

Medullary thyroid carcinoma (MTC) is a rare neoplasm which makes up from 5% to 10% of all thyroid cancers. It is characterized by an early metastasis to the cervical lymph nodes encompassing 50–75% of all cases. In initial diagnosis (preoperative), distant metastasis is confirmed in 10–15% of all patients. They are located most frequently in the mediastinum, lungs, liver, and bone, and less frequently in the brain and skin [1].

Calcitonin concentration in serum forms the most sensitive hormonal preoperative marker for MTC, monitoring effectiveness of treatment, and for detecting recurrence of disease [2].

Proper staging of primary MTC and early detection of recurrence or spread of neoplasm form the basis for the appropriate treatment scheme (decision on operation, scope of operation, and implementation of palliative care).

Due to the difficulty of imaging, various available diagnostic tests are employed. Among morphological imaging methods ultrasound and CT of the neck are used to search for lesions in the neck, chest CT to search for lung and mediastinal metastasis, and ultrasound and MRI of the liver to assess liver lesions [3]. Bone scintigraphy, used to evaluate the entire skeletal system, is also well established in the diagnostic algorithm of suspected MTC dissemination.

Other traditional nuclear medicine tests include planar imaging and SPECT using oncophilic radiopharmaceuticals (^{99m}Tc-(V)-DMSA, ¹³¹I-MIBG, ^{99m}Tc-SESTAMIBI, isotope-labelled anti-CEA and anti-calcitonin antibodies) and receptor imaging (somatostatin analogues labelled with technetium ^{99m}Tc or indium ¹¹¹In) [4, 5].

Nevertheless, classic nuclear medicine tests (both planar and SPECT) are characterized by low sensitivity due to low resolution and lack of reference to anatomical structures.

It was not until development of the PET scan and then the PET-CT that the resolution improved and resulted in better detection of neoplastic lesions. ¹⁸F-FDG — fluorodeoxyglucose is the most commonly used radiopharmaceutical used in PET scans, which serves to detect elevated glucose metabolism in neoplastic cells. ¹⁸F-DOPA is an amine precursor taken up by neuroendocrine cells. Radiopharmaceuticals for imaging of somatostatin receptors (i.e. ⁶⁸Ga-DOTA-TATE) constitute an alternative option.

Goal

The aim of the study was to present the usefulness of PET-CT examinations with somatostatin analogue labelled with gallium-68 (⁶⁸Ga-DOTA-TATE PET-CT) in

patients with MTC and elevated calcitonin concentrations, in whom previously performed imaging did not detect metastatic foci or local recurrence.

Material

The study initially compassed 8 patients with MTC (4 men and 4 women between 41 and 72 years of age, mean 55.6 years). The period of observation was from 1 to 7 years (mean: 3.6). In every patient an elevated basal and/or stimulated calcitonin concentration was evidence of persistent neoplastic disease. At the time of ⁶⁸Ga-DOTATATE PET-CT testing, the basal serum concentration of calcitonin in 5 patients was below 100 pg/ml, and in the others: 155 pg/ml, 500 pg/ml, 461pg/ml, and 720 pg/ml (mean 265pg/ml).

Before performing the ⁶⁸Ga-DOTA-TATE PET-CT examination no foci of metastasis were visualized in any patient with imaging done to that point: ultrasound of neck, CT of chest and mediastinum, MRI of liver, bone scintigraphy, and ¹⁸F-FDG PET.

The patient characteristics are shown in Table I. Calcitonin concentrations during observation are shown in Figure 1.

Method

A whole body scan using a gallium-labelled somatostatin analogue ⁶⁸Ga-DOTA-TATE PET-CT was performed. ⁶⁸Ga DOTA-TATE was prepared in the Nuclear Medicine Department of SOC. ⁶⁸Ga eluate was obtained from a generator of ⁶⁸Ge/⁶⁸Ga (manufactured by IDB Holland BV). DOTATATE was provided by IAE Radioisotope Centre POLATOM, Otwock-Swierk. PET-CT scans were performed using hybrid camera Biograph 64 Siemens, 60 minutes after intravenous administration of ⁶⁸Ga DOTA-TATE with an activity of 120–185 MBq. Acquisition time of PET was 3 min./bed. Examination range was from the top of the skull cap to 1/3 proximal femur. CT scan was performed with the aim of localizing changes and carrying out correction of attenuation (acquisition parameters: 120 kV, 35 mA, 4 s, slice thickness 2 mm).

Patients with a positive test were referred for surgical treatment.

Results

In 2 of 8 patients diagnosed with MTC and elevated calcitonin concentration, positive results of scintigraphy using ⁶⁸Ga-DOTA-TATE PET-CT were shown. These were: a woman G Z and a man W W with initial serum calcitonin concentrations of 720 pg/mL and 500 pg/mL, respectively. Both patients showed pathological radio-

Table 1. Clinical characteristics of examined patients

Tabela 1. Charakterystyka kliniczna badanych pacjentów

Patient	Gender	Age when examined (years)	Stage of advancement pTNM	Time since operation (years)	Initial calcitonin concentration at examination [pg/ml]
GS	M	72	pT3Nx	4	66
SB	K	56	pT1Nx (12 mm)	3	53
LB	K	41	pT3N1a	1	76
WW	M	61	pT3N2b	1	500
PE	K	45	pT2Nx	13	155
GZ	K	58	pT2No	7	720
ZZ	M	53	pTxN1	3	461
BP	M	59	pTxN1	3	89

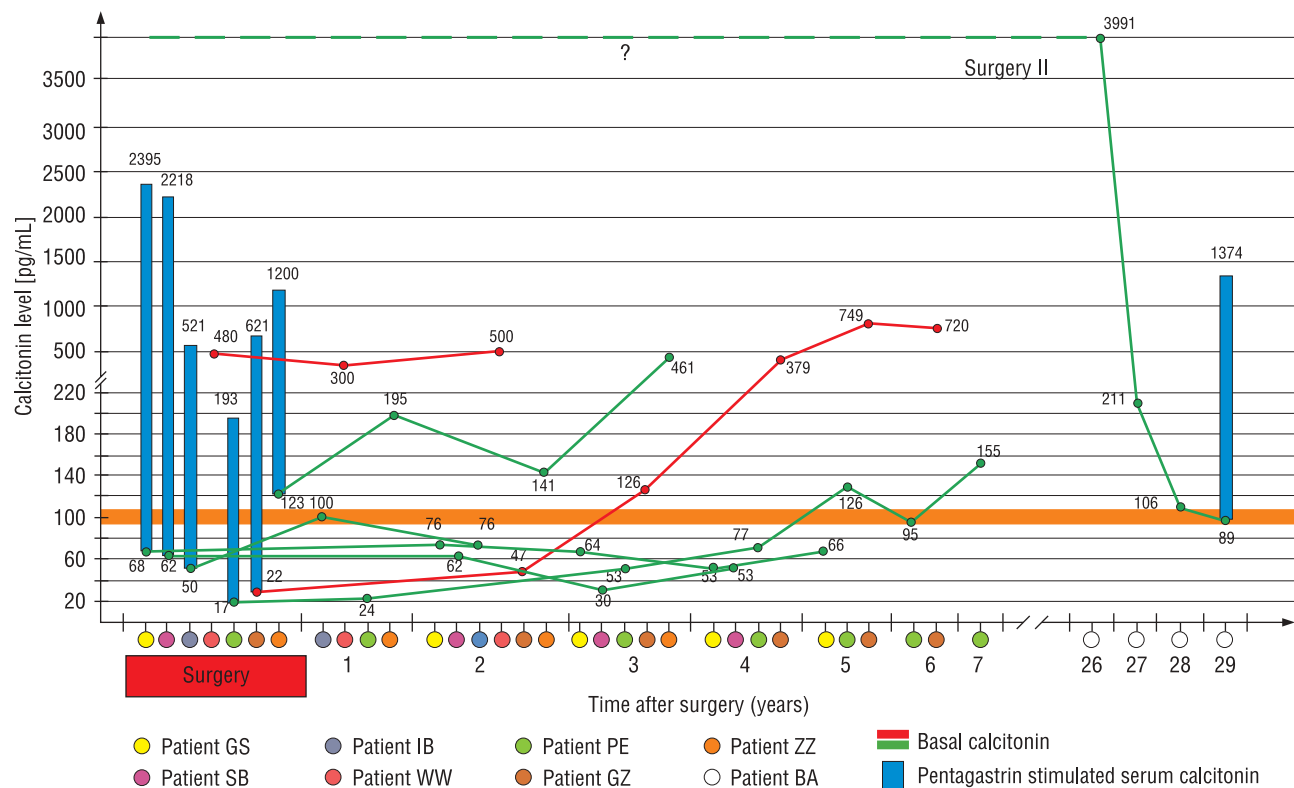


Figure 1. Primary and stimulated calcitonin concentrations in the patient study group

Rycina 1. Podstawowe i stymulowane stężenia kalcytoniny w badanej grupie

pharmaceutical accumulation in the neck lymph nodes. Patient W W showed foci of pathological accumulation in right upper paratracheal lymph node and anterior mediastinal lymph node, patient G Z within in the left upper cervical lymph node and the left supraclavicular lymph node. A noteworthy fact is that in the initial post-operative assessment, despite excision of 30 lymph

nodes (central compartment of the neck and right lateral side at the location of the tumour on the right side), no metastasis to the lymph nodes was discovered in the patient. Seven years later, lesions in lymph nodes were discovered on the left side.

Patients were referred for surgical treatment by modified dissection of lateral neck lymph nodes. His-

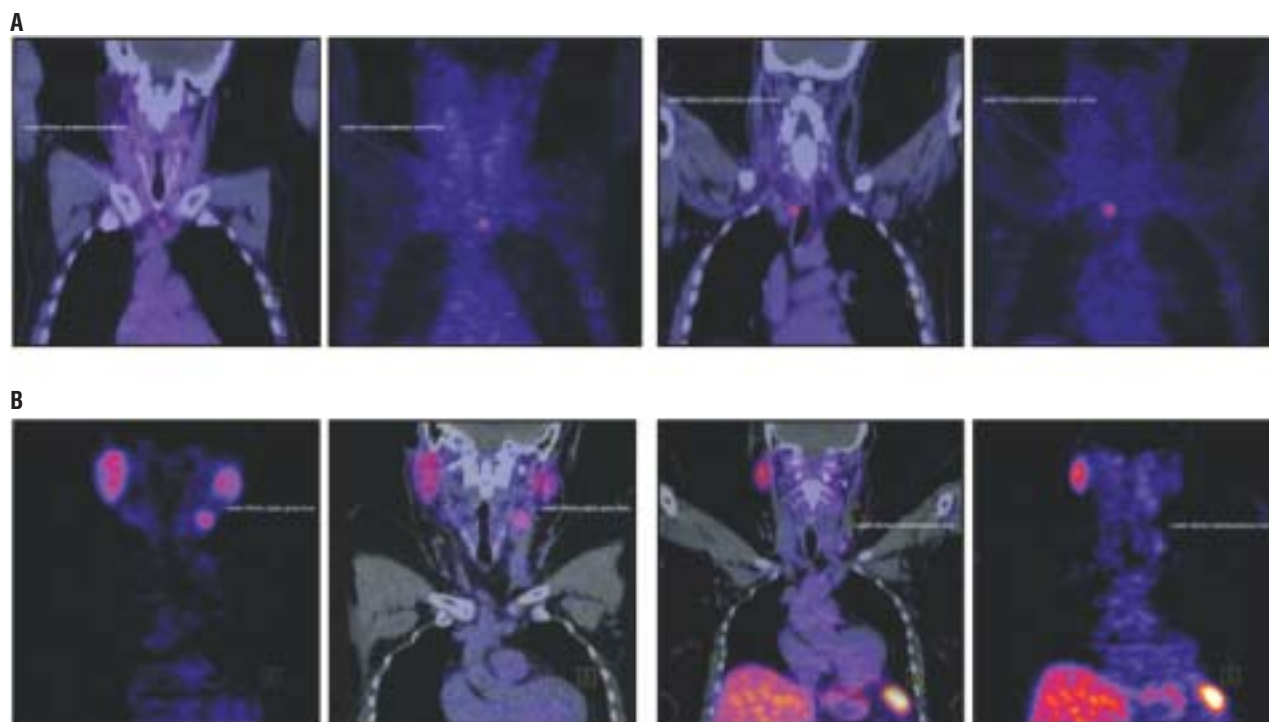


Figure 2 A. ⁶⁸Ga-DOTA-TATE PET-CT — patient WW; pathological accumulation in the right upper paratracheal lymph node and anterior mediastinal lymph node; **B.** ⁶⁸Ga-DOTA-TATE PET-CT — patient GZ; pathological accumulation in the left upper cervical lymph node and the left supraclavicular lymph node.

Rycina 2 A. ⁶⁸Ga-DOTA-TATE PET-CT — pacjent WW; ogniska patologicznego gromadzenia w węzłach chłonnych przytchawiczym po stronie prawej i w śródpiersiu przednim; **B.** ⁶⁸Ga-DOTA-TATE PET-CT — pacjent GZ; ogniska patologicznego gromadzenia w obrębie węzła chłonnego szyjnego górnego po stronie lewej i nadobojczykowego po stronie lewej

topathological examination confirmed the presence of metastatic medullary thyroid carcinoma (MTC) in the excised lymph nodes.

Discussion

The prognosis of MTC is intermediate between differentiated thyroid cancers and anaplastic cancer. Negative prognostic factors in MTC are: age, male gender, high preoperative calcitonin concentration, tumour size >4 cm, occupation of lymph nodes, vascular invasion, presence of “macroscopic disease”, and distant metastasis. Based on multivariate analysis, the most important survival prognostic factors are disease advancement and age of the patient at diagnosis [6–11].

In accordance with the recommendations of the American Thyroid Association (ATA), a calcitonin concentration of >150 pg/mL is believed to be “significantly elevated”, above which imaging is recommended with the aim of searching for metastasis. A similar procedure should follow if the increase of calcitonin concentration is 20–100% in subsequent control examinations [3, 12]. This was confirmed in our study as we were able to visualize cancer foci only in two patients with

the highest calcitonin level. Searching for foci of metastasis is an important diagnostic-clinical problem. The chance of cure is increased with early visualization of local recurrence or metastases and their effective surgical treatment. MTC as a neuroendocrine cancer may have somatostatin receptors on the surface of their cells. In-vitro studies on MTC cells with the help of RT-PCR identified two subtypes of somatostatin receptors: (SSTR)- type 2 (SSTR2) and type 5 (SSTR5). However, immunohistochemical examination showed a low density of these receptors on the cell surface of MTC cells [13]. Tumours that have SSTR on their surface can be diagnosed by using somatostatin analog radioisotopes labelled with indium (¹¹¹In) or technetium (^{99m}Tc) in SPECT tests or in PET scans using DOTA-TOC, DOTA-TATE, DOTA-NOC.

In our study we utilized a new radiopharmaceutical — ⁶⁸Ga-DOTA-TATE. This compound consists of somatostatin analog (DOTA-TATE) labelled with gallium 68, a PET generated isotope with a half life of 68 min. ⁶⁸Ga-DOTA-TATE shows an affinity to type 2 receptor. It is characterized by a good tumour/background ratio. The main limitation of using ⁶⁸Ga-DOTA-TATE is that only 40% of cells express somatostatin receptors on their

surface. The image of small metastases to the liver using ^{68}Ga -DOTA-TATE is usually negative. For this purpose ^{18}F -FDG is used but is effective only in large metastases [14].

Conclusions

On the basis of the presented cases we conclude that PET-CT scans with somatostatin analogue labelled with gallium (^{68}Ga -DOTA-TATE PET-CT) may be useful in the diagnostic imaging of patients with disseminated MTC.

References

- Schlumberger M, Pacini F. Chapter 18.8.3 medullary thyroid carcinoma — distant metastases. In: Schlumberger M, Pacini F (ed.). *Thyroid Tumors Second Edition*. Edition Nucleon, Paris 2003: 329.
- Elisei R, Bottici V, Luchetti F et al. Impact of routine measurement of serum calcitonin on the diagnosis and outcome of medullary thyroid cancer: experience in 10,864 patients with nodular thyroid disorders. *J Clin Endocrinol Metab* 2004; 89: 163–168.
- Kloos RT, Eng C, Evans DB et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid* 2009; 19: 565–612.
- Hoefnagel CA, Delprat CC, Zanin D et al. New radionuclide tracers for the diagnosis and therapy of medullary thyroid carcinoma *Clin Nucl Med* 1988; 13: 159–165.
- Sone T, Fukunaga M, Otsuka N et al. Metastatic medullary thyroid cancer: localization with iodine-131 metaiodobenzylguanidine *J Nucl Med* 1985; 26: 604–608.
- Modigliani E, Cohen R, Campos JM et al. Prognostic factors for survival and for biochemical cure in medullary thyroid carcinoma: results in 899 patients. The GETC Study Group. Groupe d'étude des tumeurs à calcitonine. *Clin Endocrinol (Oxf)* 1998; 48: 265–273.
- Scollo C, Baudin E, Travagli JP et al. Rationale for central and bilateral lymph node dissection in sporadic and hereditary medullary thyroid cancer *J Clin Endocrinol Metab* 2003; 88: 2070–2075.
- Kebebew E, Ituarte PH, Siperstein AE et al. Medullary thyroid carcinoma: clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. *Cancer* 2000; 88: 1139–1148.
- Schlumberger M, Pacini F. Chapter 18.7.2 medullary thyroid carcinoma — post-operative management. In: Schlumberger M, Pacini F (ed.). *Thyroid tumors second edition*. Edition Nucleon, Paris 2003: 325.
- Franc S, Niccoli-Sire P, Cohen R et al.; French Medullary Study Group (GETC). Complete surgical lymph node resection does not prevent authentic recurrences of medullary thyroid carcinoma. *Clin Endocrinol (Oxf)* 2001; 55: 403–409.
- Wells SA Jr, Baylin SB, Gann DS et al. Medullary thyroid carcinoma: relationship of method of diagnosis to pathologic staging. *Ann Surg* 1978; 188: 377–383.
- Giraudet LA, Ghulzan AA, Aupérin A et al. Progression of medullary thyroid carcinoma: assessment with calcitonin and carcinoembryonic antigen doubling times *Eur J Endocrinol* 2008; 158: 239–246.
- Papotti M, Kumar U, Volante M et al. Immunohistochemical detection of somatostatin receptor types 1–5 in medullary carcinoma of the thyroid *Clin Endocrinol (Oxf)* 2001; 54: 641–649.
- Conry BG., Papatianasiou ND, Prakash PV et al. Comparison of ^{68}Ga -DOTATATE and ^{18}F -fluorodeoxyglucose PET-CT in the detection of recurrent medullary thyroid carcinoma *Eur J Nucl Med Mol Imaging* 2010; 37: 49–57.