



# Medullary thyroid carcinoma — PET/CT imaging with <sup>68</sup>Ga-labelled gastrin and somatostatin analogues

Rak rdzeniasty tarczycy — badanie PET/CT ze znakowanymi <sup>68</sup>Ga analogami gastryny i somatostatyny

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## Abstract

Case presentation: a 75-year-old man with a 10-year history of nodular goitre was referred for clinical evaluation. The ultrasound scan revealed enlarged thyroid right lobe almost fully filled with a heterogeneous nodule with numerous calcifications. Fine-needle aspiration biopsy suggested medullary thyroid carcinoma (MTC). Before the surgery the patient was referred to the nuclear medicine department and somatostatin receptor imaging (SRS; <sup>68</sup>Ga-DOTATATE) with PET/CT was performed. The scan demonstrated an increased uptake within the right thyroid mass. Subsequent PET/CT with <sup>68</sup>Ga-gastrin analogue (MG48) revealed the same indications as the SRS: an increased alveolar uptake in the right thyroid mass without the signs of lymph node metastases. The patient underwent total thyroidectomy and central lymph nodes dissection. Histopathology examination confirmed the presence of MTC with vascular invasion, but without lymph node metastases (pT3NoMx according to the 7<sup>th</sup> edition of the AJCC Cancer Staging Manual). Immunohistochemical staining revealed positive reaction to calcitonin and CD56, whereas the reaction to thyroglobulin remained negative. The Ki-67 was 1%. Staining for SSTR2 and CCK2 showed high cytoplasmic expression in both cases.

Knowledge of the presence of CCK2 receptor in MTC patients may be an important indication for the choice of diagnostic and therapeutic procedures. The presence of both the receptor types, cholecystokinin-2/gastrin and somatostatin, is possibly an interesting combination as far as the therapeutic target is concerned. (*Endokrynol Pol* 2016; 67 (1): 68–71)

**Key words:** medullary thyroid carcinoma; CCK2 receptor; somatostatin receptor; <sup>68</sup>Ga; PET/CT

## Streszczenie

W pracy przedstawiono opis 75-letniego mężczyzny z dziesięcioletnią historią wola guzkowego skierowanego do Kliniki w celu badań kontrolnych. W badaniu USG stwierdzono powiększenie prawego płata tarczycy, wypełnionego prawie całkowicie niejednorodnym guzkiem z licznymi zwapnieniami. W biopsji aspiracyjnej cienkoigłowej wysunięto podejrzenie raka rdzeniastego tarczycy (MTC). Przed zabiegiem pacjenta skierowano do Zakładu Medycyny Nuklearnej w celu scyntygrafii receptorów somatostatynowych (SRS; <sup>68</sup>Ga-DOTATATE) wykonanej techniką PET/CT. W badaniu stwierdzono zwiększone gromadzenie znacznika w zmianie prawego płata tarczycy. Następnie wykonano badanie PET/CT z <sup>68</sup>Ga-analogiem gastryny (MG48), stwierdzając podobnie jak w SRS, zwiększone gromadzenie znacznika w guzku prawego płata tarczycy, nie stwierdzono przerzutów do węzłów chłonnych. Wykonano całkowite wycięcie tarczycy i centralnych węzłów chłonnych. Badanie histopatologiczne potwierdziło obecność MTC z cechami inwazji naczyniowej, ale bez przerzutów do węzłów chłonnych (pT3NoMx według 7. edycji AJCC stopnia złośliwości). Barwienie immunohistochemiczne ujawniło pozytywną reakcję na kalcytoninę i CD56, podczas gdy reakcja Tg była negatywna. Ki-67 wynosiło 1%. Barwienie na obecność receptorów SSTR2 oraz CCK2 wykazało wysokie poziomy ekspresji cytoplazmatycznej, w obu przypadkach.

Znajomość obecności receptora CCK2 u pacjentów z MTC może być ważna w trakcie wyboru procedur diagnostycznych i terapeutycznych. Obecność obu typów receptorów cholecystokininy-2/gastryny i somatostatyny potencjalnie może być wykorzystana w leczeniu celowanym. (*Endokrynol Pol* 2016; 67 (1): 68–71)

**Słowa kluczowe:** rak rdzeniasty tarczycy; CCK2 receptor; receptory somatostatynowe; <sup>68</sup>Ga; PET/CT

## Introduction

Medullary thyroid carcinoma (MTC) is a rare thyroid neoplasm originating from neuroendocrine parafol-

licular C-cells and secreting calcitonin, and in some cases also carcinoembryonic antigen (CEA). Most MTCs are sporadic (80%); however, they may also occur in hereditary form (MEN2, Multiple Endocrine



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Neoplasia type 2). Serum calcitonin level is the most sensitive and specific tumour marker in the preoperative diagnosis and the post-surgery follow-up [1]. The diagnostic imaging of MTC is still problematic. The sensitivity of scintigraphic imaging is strongly connected with serum calcitonin level [2, 3]. More than 75% of MTCs reveal overexpression of somatostatin receptors (SSTR). Cholecystokinin-2/gastrin receptor (CCK2R) is overexpressed in most tumours, such as MTC (>90%), astrocytomas (> 65%), and stromal ovarian cancers (100%). In such cases, gastrin receptor scintigraphy gives a higher tumour detection rate than SRS [4, 5]. Therefore, CCK2- scintigraphy parallel to SRS may improve the detection rate of MTC. The published data has been presenting the CCK2 scintigraphy using  $^{111}\text{In}$  or  $^{99\text{m}}\text{Tc}$ . The increased utilisation of PET/CT in oncology has led to the introduction of positron-emitting tracers labelled with gallium-68. Moreover, technical advantages (i.e. spatial resolution, attenuation correction, decreased examination time, and reduced radiation doses), in comparison to  $^{111}\text{In}$  or  $^{99\text{m}}\text{Tc}$ , make  $^{68}\text{Ga}$ -DOTA- peptides the new standard in oncological diagnosis.

To our knowledge, this is the first imaging of CCK2 receptors with PET/CT techniques in human.

## Case presentation

A 75-year-old man with a ten-year history of nodular goitre and hypertension was referred for a yearly clinical evaluation. The ultrasound scan (AIXPLORER system by Supersonic Imagine and 2–10 MHz linear transducer) revealed enlarged thyroid right lobe almost fully filled with a heterogeneous nodule with numerous calcifications. There were no signs of neck lymphadenopathy. Fine-needle aspiration biopsy (FNAB) of the right lobe nodule suggested medullary thyroid carcinoma. Biochemical evaluation revealed elevated calcitonin level 2000 pg/mL (normal 0–10), CEA 91.7 ng/mL (normal < 6.5), and chromogranin A 177.6 ng/mL (normal 19–100). The results of other tests such as TSH, thyroid hormones, parathormone, calcium, and phosphates were in the normal range. Diurnal excretion of metanephrines and normetanephrines was not increased. There was no family history of thyroid disorders. Abdominal ultrasound and contrast-enhanced computed tomography (CT) scan of the abdomen did not reveal any abnormalities within adrenal glands. Genetic study comprising routine screening within six RET proto-oncogene exons (exon: 10, 11, 13, 14, 15, 16) did not confirm any mutations. The patient underwent  $^{68}\text{Ga}$ -labelled gastrin and somatostatin analogues PET/CT for the preoperative staging.

Somatostatin receptor imaging ( $^{68}\text{Ga}$ -DOTATATE) with PET/CT demonstrated an increased uptake in the right thyroid mass (Fig. 1, A — PET MIP, C — fusion PET/CT).

Subsequent PET/CT with  $^{68}\text{Ga}$ -gastrin analogue (MG48) revealed the same indications as the somatostatin receptor — an increased alveolar uptake in the right thyroid mass (Fig. 1, B — PET MIP, E — fusion PET/CT) without the signs of lymph node metastases.

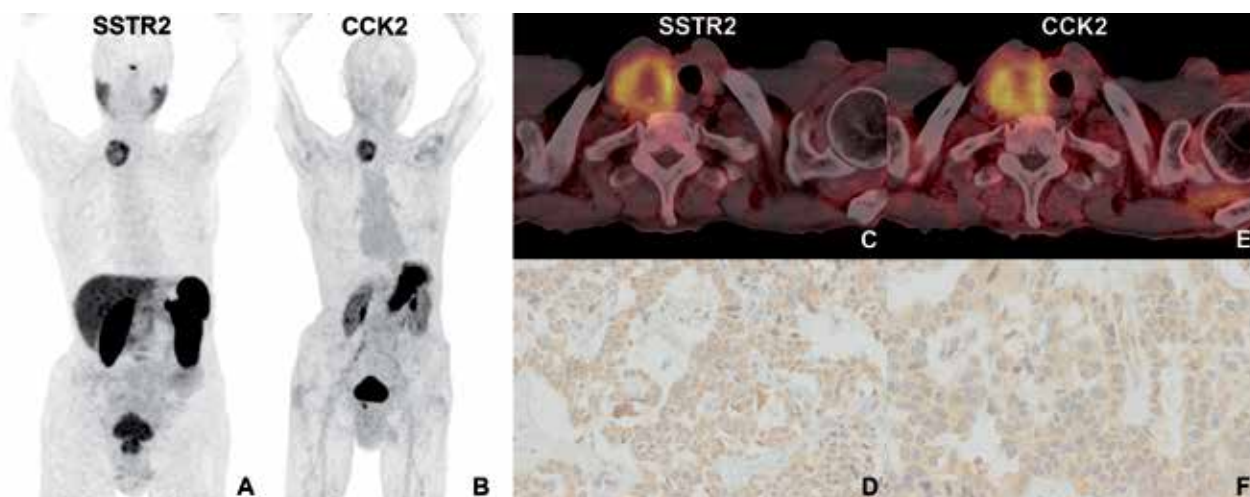
The patient underwent total thyroidectomy and central lymph nodes dissection. Histopathology examination confirmed the presence of medullary thyroid carcinoma with vascular invasion, but without lymph node metastases (pT3NoMx according to the 7<sup>th</sup> edition of the AJCC Cancer Staging Manual). Immunohistochemical staining revealed positive reaction to calcitonin and CD56, whereas the reaction to thyroglobulin remained negative. The Ki-67 was 1%. Staining for SSTR2 (Fig. 1D) and CCK2 (Fig. 1F) showed high cytoplasmic expression in both cases.

## Discussion

Early preoperative detection of primary lesions and metastases before the surgery in the case of medullary thyroid carcinoma is still a challenge. Many different imaging techniques, including CT scan, MRI, PET/CT, or scintigraphy, are used to define the staging of MTC, although the sensitivity of these techniques varies.

The aim of the paper is to report the detection of medullary thyroid carcinoma in the thyroid gland before the surgery, using two different imaging techniques: gastrin (CCK2) receptor and somatostatin receptor visualisation with PET/CT. The fact that some tumours express somatostatin receptors is used to localise primary lesion and metastases, and therefore it may also allow for the use of somatostatin receptor analogues in the treatment [6]. The sensitivity rate of SRS varies and may be as low as 37% and as high as 90% [7–9].

In ATA recommendations,  $^{18}\text{F}$ FDG-PET and SRS are not indicated in patients with MTC suspected or diagnosed before the surgery [10]. However, in patients with elevated calcitonin level (over 400 pg/mL) it is necessary to perform chest and neck CT with parallel liver CT or MRI. PET/CT and SRS are considered to have lower sensitivity and higher costs. Dahlberg et al. performed somatostatin receptor scintigraphy using ( $^{111}\text{In}$ )-octreotide in patients with MTC prior to the surgery. They found that SRS helped to visualise primary tumours in 84% of patients (among the 16 subjects that were examined). SRS detected metastases only in 53% of patients with advanced disease; therefore, they concluded that preoperative use of SRS is useful, but



**Figure 1.** PET/CT: **A.** <sup>68</sup>Ga-DOTATATE PET MIP (maximum intensity projection); **B.** <sup>68</sup>Ga-MG48-PET MIP; **C.** <sup>68</sup>Ga-DOTATATE fusion PET/CT; **D.** Staining for SSTR2; **E.** <sup>68</sup>Ga-MG48 fusion PET/CT; **F.** Staining for CCK2

**Rycina 1.** PET/CT: **A.** <sup>68</sup>Ga-DOTATATE PET MIP; **B.** <sup>68</sup>Ga-MG48-PET MIP; **C.** <sup>68</sup>Ga-DOTATATE badanie fuzyjne PET/CT; **D.** Barwienie SSTR2; **E.** <sup>68</sup>Ga-MG48 badanie fuzyjne PET/CT; **F.** Barwienie CCK2

there is no indication of using it before the surgery to state MTC advancement [11].

MTC as a neuroendocrine tumour may produce different peptides and express their receptors. As well as somatostatin receptors, MTC expresses also gastrin/cholecystikinin-2 (CCK-2), glucagon-like peptide 1 (GLP-1), or calcium-sensing receptors [12–14]. The presence of CCK-2 receptors was used for localising MTC and its metastases in different scintigraphic techniques. In some studies, gastrin receptor scintigraphy was used to enhance the sensitivity of SRS, especially in situations where the SRS scans were negative in the presence of advanced MTC or other neuroendocrine tumours [4, 5, 15]. Gastrin receptor scintigraphy seemed to have higher specificity and positive predictive value, but lower sensitivity than SRS. This could be related to peptide structure and purification [5].

In the last decade, PET/CT scan has become more popular for visualisation of MTC lesions. There are several publications reporting the application of <sup>18</sup>F-FDG or FDOPA or <sup>68</sup>Ga-DOTATATE PET/CT in the evaluation of neuroendocrine tumours [16, 17]. PET/CT with <sup>18</sup>F-DOPA seems to be the most useful imaging technique for the detection of recurrent MTC lesions, according to Treglia et al. [18]. Using PET/CT instead of conventional scintigraphy increased the sensitivity of this detection. Parallel <sup>68</sup>Ga-DOTATATE and <sup>68</sup>Ga-gastrin analogue PET/CT may also enhance the sensitivity of lesion detection, although we were not able to check whether local or distant metastases might be easily localised using this double technique. Until now, we could not find any information that such a study has been

conducted before. Visualisation using radiopeptides has an advantage over other imaging techniques because the presence of highly expressed receptors may serve as an additional therapeutic tool, as is the case with somatostatin receptors and somatostatin analogues.

## Conclusion

Knowledge of the presence of CCK2 receptor in MTC patients may be an important indication for the choice of diagnostic and therapeutic procedures. The presence of both the receptor types, cholecystikinin-2/gastrin and somatostatin, is possibly an interesting combination as far as the therapeutic target is concerned. Further studies are required to determine its value in patient management.

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