

# The diagnostic role of $^{68}\text{Ga}$ -DOTATATE PET/CT in the detection of neuroendocrine tumours

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## Abstract

**BACKGROUND:** Positron emission tomography (PET) combined with computer tomography (CT) using  $^{68}\text{Ga}$ -DOTATATE is a promising method for the evaluation of patients with recognised or suspected neuroendocrine tumours (NET). The aim of this study was to assess the diagnostic value of  $^{68}\text{Ga}$ -DOTATATE PET/CT in the visualisation of the expression of somatostatin receptors (SSTR) and identification of new lesions.

**MATERIAL AND METHODS:** Between December 2009 and January 2011 ninety-seven patients with confirmed (88 cases) or suspected (9 cases) NET underwent  $^{68}\text{Ga}$  DOTATATE PET/CT. The primary, confirmed or suspected, NET localizations were: GEP tumours — 71 patients; medullary thyroid carcinoma — 4 patients; cancer of an unknown primary — 14 patients; and NET in other localisations — 8 patients. PET/CT acquisitions were performed using standard techniques,

45 to 60 minutes after the intravenous injection of 111–185 MBq  $^{68}\text{Ga}$ -DOTATATE.

**RESULTS:**  $^{68}\text{Ga}$ -DOTATATE PET/CT detected the presence of lesions demonstrating the somatostatin receptor affinity in 50 of the 97 patients (51.5%) and was negative in 47 patients (48.5%). Among 14 patients with metastatic unknown primary cancer, in 5 patients (45.5%) the primary tumour site was identified, and in 4 patients with medullary thyroid cancer distant metastases with SSTR expression were localized in only one patient.

**CONCLUSIONS:** Our findings confirm the diagnostic role of  $^{68}\text{Ga}$ -DOTATATE PET/CT as an accurate method of identifying primary tumours and distant metastases. It provides information on tumour cell receptors status, which has a significant bearing on planning target radionuclide therapy. Overall,  $^{68}\text{Ga}$ -DOTATATE PET/CT can be used in staging, re-staging, and in regular follow up of oncology patients.

**Key words:**  $^{68}\text{Ga}$ -DOTATATE; PET/CT; neuroendocrine tumours

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## Introduction

Neuroendocrine tumours (NETs) constitute a rare and heterogeneous group of neoplasms originating from the neural crest [1]. They are characterized by the presence of somatostatin receptors on their cell surface [2]. Somatostatin receptor scintigraphy (SRS) is regarded as one of the basic imaging procedures in NET patients. However, positron emission tomography (PET) combined with computer tomography (CT) has become a promising method for the evaluation of the cellular metabolism and expression of receptors in tumours. Recent studies have shown the superiority of PET using  $^{68}\text{Ga}$ -DOTA -TOC over somatostatin receptor scintigraphy (SRS) and diagnostic CT in NET detection [3, 4].

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<sup>68</sup>Ga-labelled somatostatin analogue peptides have proven to be increasingly useful in neuroendocrine tumour diagnostics due to several technical and biological advantages such as fast clearance, rapid tissue penetration, and low antigenicity [5]. Moreover, they are characterised by a shorter procedure and the possibility of imaging the whole body.

The aim of this study was to assess the diagnostic value of <sup>68</sup>Ga-DOTATATE PET/CT in the visualisation of the expression of somatostatin receptors (SSTR) in patients with recognised or suspected NET.

## Material and methods

We retrospectively reviewed ninety-seven patients (57 female, 40 male, aged 18–81 years, mean age 54 years, median 58 years) with confirmed (88 patients) or suspected (9 patients) NET, who underwent <sup>68</sup>Ga-DOTATATE PET/CT between December 2009 and January 2011 in our Institute. Fifty-one patients (52.6%) were previously examined using conventional imaging (CT, MRI, USG, SRS). Eighty-eight patients had histologically proven NET and 9 patients were suspected of neuroendocrine character of malignancy based on needle aspiration biopsy BAC or elevated tumour biomarkers levels.

The clinical indications for examination were: detection of localized primary (14 patients); efficacy assessment of surgical resection and follow-up after therapy carried out between two and six months after the procedure (47 patients); detection of suspected recurrence or metastasis (16 patients); identification of somatostatin receptor expression of lesions detected in other investigations (8 patients); and initial tumour staging (12 patients). Primary tumour localizations are shown in Table 1.

<sup>68</sup>Ga-DOTATATE was synthesized at the radiochemistry section of our department. DOTATATE (Dota-Phe<sup>1</sup>, Tyr<sup>3</sup>-octreotate) was obtained from IEA OR POLATOM. Gallium chloratum (<sup>68</sup>GaCl<sub>3</sub>) was obtained from a <sup>68</sup>Ge/<sup>68</sup>Ga generator eluted with 0.6 M hydrochloric acid. A final pH of 3.5–4% was assured by addition of 1.25 M sodium acetate solution (AcONa). Incubation was carried out at 100–110°C for 15 minutes. Effluent containing the <sup>68</sup>Ga fraction was passed through a cationic exchange column SepPak (C-18) to clean <sup>68</sup>Ga from any potential <sup>68</sup>Ge breakthrough and from others cations. Finally the product

was washed with ethanol and dissolved in 0.9% saline [6]. Quality control was performed with thin-layer chromatography (TLC) analysis using 0.1 M trisodium citrate/0.2 M HCL as a mobile phase [7]. Radiochemical purity was higher than 95% before being injected into the patient.

PET/CT acquisitions were performed using a dedicated combined PET-16 detector CT unit (Gemini 16TF, Philips). Images were obtained 45 to 60 minutes after the intravenous injection of 111–185 MBq <sup>68</sup>Ga-DOTATATE. Additionally, patients received intravenously furosemide for faster elimination of the tracer. While awaiting their examination, patients were given an oral contrast agent containing 15 ml of Gastrografin.

Whole-body examinations from brain to mid-thigh were performed with the patient lying supine. PET scan emission images were recorded for 2 minutes per bed position. Low-dose CT acquisition parameters were 120 kV, 50 mA, 0.5 tube rotation and 5 or 2 mm thickness. Image reconstruction was done with a 3D iterative ordered subsets expectation maximization (OSEM) algorithm with blob basis functions.

To calculate maximal standardized uptake values (SUVmax), manually defined regions of interest were drawn on the attenuation-corrected emission images throughout the axial planes in lesions identified as areas of focally increased uptake. The SUVmax values were calculated according to the formula:

$$SUV = \frac{\text{Tissue concentration (Bq/g)}}{\text{Injected dose (Bq) / Body weight (g)}}$$

## Results

<sup>68</sup>Ga-DOTATATE PET/CT detected the presence of lesions demonstrating the somatostatin receptor affinity in 50 of the 97 patients (51.5%) and was negative in the remaining 47 patients (48.5%).

From the group of 51 patients who underwent other conventional imaging before PET/CT scan, in 32 cases (63%) findings were concordant with previous studies, in 14 patients (27%) new lesions were found, and in 5 patients (10%) lesions detected in other investigations did not reveal SSRT expression. From those 5 patients, subsequent diagnostic did not confirm neuroendocrine character of the tumour in 4 patients (3 cases with liver metastases in CUP; 1 patient with suspected gastrinoma), and in the remaining case there was an absence of further data. Those 5 patients belong to the group of 9 patients with suspicion of NET. In the remaining 4 of the 9 patients in this group <sup>68</sup>Ga-DOTATATE revealed receptor expression in lesions that confirmed neuroendocrine character of neoplastic disease.

Only 5 of the 97 patients had previously undergone somatostatin receptor scintigraphy. In 3 of them our examination was discordant with SRS and revealed more information: 1 — new metastases in liver; 1 — new metastases in bones; and 1 — exclusion of recurrence in postoperative region.

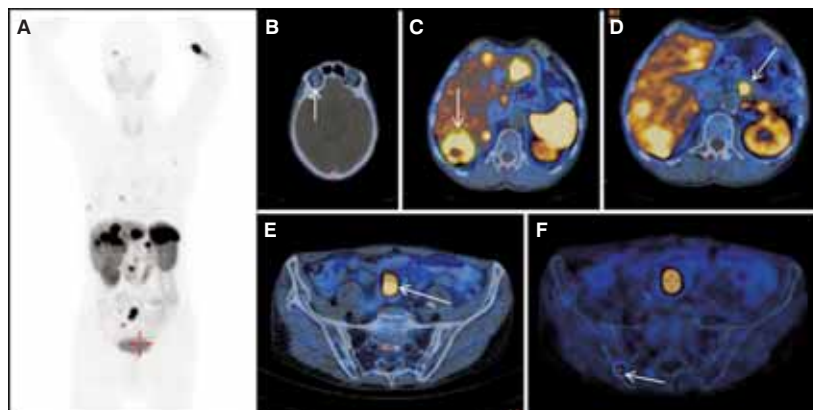
In 46 of the 97 patients no previous imaging examinations were performed. The main indication for PET investigation was efficacy assessment of surgical resection or follow-up after therapy. In this group in 33 patients (72%) no pathological lesions were detected. <sup>68</sup>Ga-DOTATATE was positive in the remaining 13 patients (28%).

**Table 1. Confirmed and suspected primary NET localization**

Localization	Number of patients	
	Confirmed	Suspected
GEP tumours (gastro-entero-pancreatic)	65	6
Stomach	9	2
Small intestine (appendix)	31 (21)	
Pancreas	10	3
Colon	15	1
Medullary thyroid carcinoma	4	
Cancer of unknown primary	11	3
NET in other localization	8	

**Table 2. SUVmax values in organs with physiological uptake**

Organ	Pituitary gland	Parotid gland	Thyroid	Liver	Spleen	Stomach	Adrenals	Kidneys
SUVmax average	4.65 ± 1.9	2.69 ± 1.2	2.52 ± 1.1	5.67 ± 1.8	16.93 ± 4.5	4.8 ± 2.1	9.11 ± 2.7	11.64 ± 3.9
SUVmax range	1.2–10.1	0.4–6	0.8–6	1.6–9.3	4–26	0.2–9.8	3.8–16.8	4.3–23.7

**Figure 1.** A 71-year-old man with colon carcinoid after surgery. The scan was carried out due to the suspicion of distant metastases.

**A.** MIP (maximum intensity projection) image shows multiple lesions with positive uptake of  $^{68}\text{Ga}$ -DOTATATE tracer. **B.** Small lesion behind right eyeball. **C.** Multiple hepatic metastases (in segment 7 with central necrosis). **D.** Lesion in pancreas. **E.** Soft tissue mass in peritoneum (probably lymph node). **F.** Lesion in right iliac bone.

Among 4 patients with medullary thyroid cancer after operation (indicative of rising level of calcitonin) distant metastases with SSTR expression (pancreas and retroperitoneal lymph nodes) were detected in only one patient.

$^{68}\text{Ga}$ -DOTATATE PET/CT performed in 14 of the 97 patients with metastatic unknown primary cancer (liver and lungs) was negative in 3 patients as the lesions did not take up the tracer and histopathological verification did not confirm preliminary diagnosis. In the remaining 11 patients with PET/CT-positive findings, in 6 patients (6/11 — 54.5%) no primary tumour site was detected, and in 5 patients (5/11 — 45.5%)  $^{68}\text{Ga}$ -DOTATATE PET/CT depicted the primary tumour (small intestine — 2; colon — 1; pancreas — 1; ovary — 1).

In order to improve the evaluation of the SST receptor expression in further practice, standardised uptake values (SUVmax) were measured using  $^{68}\text{Ga}$ -DOTATATE PET/CT results regarding normal biodistribution of the tracer in all patients included in the study. The average SUVmax values and their range shown in Table 2 are concordant with results obtained in other studies [8, 9].

## Discussion

In recent decades neuroendocrine tumour detection has significantly increased due to the development of imaging techniques and highly specific radiopharmaceuticals for PET studies [2].

Previously used conventional imaging (ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI)) allowed the detection of primary tumours and metastatic lesions in 40–60% of patients [10]. Neuroendocrine tumours, particularly those of the gastro-intestinal tract, frequently express high

levels of somatostatin receptors; therefore, radioisotope imaging techniques with somatostatin analogues labelled with  $^{111}\text{In}$  or  $^{99\text{m}}\text{Tc}$  proved to be considerably more sensitive (60–90% depending on the tumour type) in visualization of lesions [3, 11–14].

Our study has demonstrated that in 50 patients (51.5%)  $^{68}\text{Ga}$ -DOTATATE depicted lesions with an affinity to SSTR. In this group, SSTR expression presence confirmed neuroendocrine character of the neoplasm in 4 patients with previously suspected NET.

In 51 of the 97 patients who previously underwent conventional imaging procedures,  $^{68}\text{Ga}$ -DOTATATE confirmed the presence of lesions. Additionally, in 32 patients (63%) those lesions indicated SSRT expression. The obtained data affected the treatment plan, and most of all indicated possibilities for peptide receptor radionuclide therapy.

More recently, Ambrosini et al. [15] studied 90 patients with histological confirmation of NET, who underwent  $^{68}\text{Ga}$ -DOTANOC and CT scan. PET/CT findings were concordant with conventional imaging in 52.2% of cases and discordant in 46.7%, which resulted in stage modification in 28.6% of the patients from this group.

PET imaging offers great diagnostic value in different types of tumours. Its ability to combine high sensitivity with reasonable resolution and whole-body scans enables the detection of more lesions [16].

$^{68}\text{Ga}$ -DOTATATE PET/CT provides additional information and is more accurate than conventional imaging procedures in visualization of NET [17, 18]. Our study has also shown improvement in diagnostic performance of PET/CT imaging of NET. In 14 of the 51 patients (27%) more lesions were identified compared to previously carried out conventional imaging.

The usefulness of PET/CT in the localization of the primary site in patients with metastatic cancer of unknown origin has previously been reported in the literature [19, 20]. Routinely used in PET, fluorodeoxyglucose (FDG) reflects the expression of increased glucose metabolism in cancer cells. The FDG-PET scan demonstrates increased metabolic activity within the lesions. It can be applied especially in poorly differentiated neuroendocrine carcinomas, which lose their receptors. Most slow growing, well-differentiated neuroendocrine tumours can be characterized by low glucose utilization, which results in limited FDG usefulness [1, 21]. Radiolabelled peptides improve the detection of metastases, up to as much as 82% compared to 66% for FDG PET/CT [22].

In our study, among 14 patients who suffered metastatic cancer of unknown primary, in 3 cases <sup>68</sup>Ga-DOTATATE was negative (low tracer uptake) and final histopathological verification did not confirm neuroendocrine character of malignancy. In 5 of the 14 patients (45.5%) <sup>68</sup>Ga-PET/CT could localize the site of the primary tumour. In the remaining 6 patients the primary tumour site remained occult.

According to recent studies, FDG PET/CT depicted the primary tumour in 33% [23] and 39% [20] of cases whereas <sup>68</sup>Ga-DOTANOC could identify the site of the primary tumour in 59% of patients [19].

In patients with medullary thyroid carcinoma (MTC), with elevated levels of calcitonin and carcinoembryonic antigen, the detection of metastases proves to be highly difficult.

Widely used conventional radiological methods such as magnetic resonance imaging, computed tomography, or ultrasonography can be characterised by low sensitivity derived from their failure to localize the residual or recurrent disease [24].

Radioisotope methods have also proven to be insufficient in visualization of metastases. The sensitivity of <sup>131</sup>I-MIBG (meta-iodobenzyl-guanidine) for the detection of MTC is 29–30% [25], and the sensitivity of SRS ranges from 25 to 50% [5, 26].

Our findings also demonstrate the low efficacy of somatostatin receptor imaging. It was possible to visualize metastases in only 1 of the 4 patients with MTC.

In our study population, 46 of the 97 patients who underwent <sup>68</sup>Ga-DOTATATE PET/CT had not been subjected to any previous imaging. Based on those findings, it is difficult to assess the efficacy of <sup>68</sup>Ga-DOTATATE PET/CT as a diagnostic method. In those cases the main purpose of the investigation was the evaluation of surgical tumour resection and follow-up after therapy as the group consisted mainly of patients after surgery. Thirteen patients (28%) had positive <sup>68</sup>Ga-DOTATATE PET/CT, which was confirmed by further diagnostics or surgery. A group of 33 patients (78%) with negative <sup>68</sup>Ga-DOTATATE PET/CT remains under observation.

Our experience shows that lesion receptor expression evaluation in organs with physiological uptake of tracer (especially in the pancreas) and non-specific bowel uptake may mimic focal tumour disease, which impedes accurate diagnostic interpretation.

## Conclusions

Our findings indicate that <sup>68</sup>Ga-DOTATATE PET/CT is an accurate method for identifying primary tumours and distant metastases. It provides information on tumour cell receptor status,

which has a significant bearing on planning target radionuclide therapy. Moreover, it facilitates the evaluation of tumour recurrence and efficacy of therapeutic interventions. Overall, <sup>68</sup>Ga-DOTATATE PET/CT can be used in staging, re-staging, and in regular follow up of oncology patients.

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