


Diagnostic utility of PET/CT with ^{18}F -DOPA and ^{18}F -FDG in persistent or recurrent medullary thyroid carcinoma: the importance of calcitonin and carcinoembryonic antigen cutoff

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Abstract

Purpose This study sought to evaluate and compare the utility of 18-F-fluorodihydroxyphenylalanine (^{18}F -DOPA) and 18-F-fluorodeoxyglucose (^{18}F -FDG) positron emission tomography/computed tomography (PET/CT) for identification of lesions in patients with recurrent medullary thyroid carcinoma (MTC). In addition, we analyzed the correlation between the calcitonin (Ct), carcinoembryonic antigen (CEA) levels, each doubling time (DT), and PET positivity. We evaluated the reliability of the 150 pg/mL Ct cutoff set by the American Thyroid Association guidelines for further imaging (including ^{18}F -DOPA PET/CT).

Methods We prospectively recruited 18 patients with recurrent MTC, identified by elevation of Ct or CEA. Each patient underwent a ^{18}F -FDG PET/CT and a ^{18}F -DOPA PET/CT.

Results Abnormal uptakes were detected with ^{18}F -DOPA (n=12) and ^{18}F -FDG (n=9), (sensitivity of 66.7% vs. 50%; $p<0.01$). Twenty-eight lesions were detected with ^{18}F -DOPA vs. 16 lesions with ^{18}F -FDG (1.56 ± 1.5 vs. 0.89 ± 1.18 lesions per patient; $p=0.01$). None of our patients showed additional lesions with ^{18}F -FDG in comparison to ^{18}F -DOPA. Patient-based detection rate increased significantly with Ct levels ≥ 150 pg/mL vs. Ct < 150 pg/mL for both ^{18}F -DOPA (sensitivity 90.9% vs. 28.6%; $p=0.013$) and ^{18}F -FDG PET/CT

(sensitivity 72.7% vs. 14.3%; $p=0.025$). Using a CEA cutoff of ≥ 5 ng/mL, detection rates of ^{18}F -DOPA and ^{18}F -FDG PET/CT were 81.1% and 72.7%, respectively. No correlation between Ct-DT or CEA-DT and PET positivity was found. Histological confirmation was obtained in eight patients.

Conclusions ^{18}F -DOPA PET/CT appears to be superior to ^{18}F -FDG PET/CT in detecting and locating lesions in patients with recurrent MTC. This technique tends to be especially useful in patients with negative results in other imaging modalities and Ct ≥ 150 pg/mL or CEA ≥ 5 ng/mL.

Keywords Medullary thyroid carcinoma · ^{18}F -DOPA · ^{18}F -FDG · PET/CT · recurrence

Introduction

Medullary thyroid carcinoma (MTC) is an uncommon neuroendocrine tumor, accounting for 1–2% of all thyroid malignancies in the United States [1]. From a clinical perspective, these tumors have a more aggressive behavior than differentiated thyroid neoplasms, and the presence of residual disease or tumor recurrence after initial surgery is a usual finding, especially when lymph node metastases are present at diagnosis [2]. Given that surgery is the only curative treatment modality at present, localization of the disease is essential in cases where persistence or recurrence is suspected by elevated levels of calcitonin (Ct) or carcinoembryonic antigen (CEA).

18-F-Fluorodihydroxyphenylalanine (^{18}F -DOPA) is an amino acid analog used for positron emission tomography (PET). Typically, this tracer uptake is high in neuroendocrine cells because ^{18}F -DOPA is incorporated into the cell cytoplasm through an amino acid transporter called LAT 1 (L-

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type amino acid transporter 1) and then decarboxylated by amino acid decarboxylase (AADC) [3, 4].

Since 2001, several studies have evaluated the sensitivity of ^{18}F -DOPA PET in the detection of persistent or recurrent MTC compared with the morphological and functional techniques available up to date [5–14]. These studies generally agree on the superiority of ^{18}F -DOPA PET over other diagnostic methods. In 2012, Treglia et al published a meta-analysis including the eight most relevant studies to assess the diagnostic accuracy of PET or PET/CT (computed tomography) with ^{18}F -DOPA in recurrent MTC. This study comprised a total number of 146 patients and concluded that the detection rate per patient and per lesion was 66% and 71%, respectively. They also found an increased detection rate in patients with higher calcitonin levels and lower calcitonin doubling times (Ct-DT) [15]. However, there is a significant heterogeneity among published studies and the number of patients, ranging between 11 and 39, is quite short. Most studies suggest the superiority of PET/CT with ^{18}F -DOPA regarding PET isolated on the location of lesions [9]. Therefore, it would be more appropriate to design studies where PET/CT with ^{18}F -DOPA is compared to other techniques, mainly to ^{18}F -FDG (^{18}F -Fluorodeoxyglucose) PET/CT, as this is the reference tracer used in most hospitals and has differential characteristics. Only five papers have compared these two techniques so far [8–12].

The American Thyroid Association (ATA) guidelines for the management of MTC, first published in 2009 and updated in 2015 [1, 16], recommend that additional imaging procedures beyond cervical ultrasound should be done in patients with a serum calcitonin value above 150 pg/mL after the initial surgery, looking for lymphatic or distant metastases. In current literature, only two studies have tried to validate this cutoff, offering no consistent results [9, 14].

The aim of our study was to evaluate and compare the usefulness of ^{18}F -DOPA and ^{18}F -FDG PET/CT in the detection of persistent or recurrent MTC, as well as to analyze the correlation between their positivity and Ct, CEA, Ct-DT, and CEA-DT (CEA doubling time) values. As a secondary objective, we evaluated whether the 150 pg/mL Ct cutoff set by the ATA guidelines to perform additional imaging is appropriate.

Material and methods

Patients

This observational, prospective study was conducted between November 2011 and January 2014. All patients with suspected persistent or recurrent MTC referred from endocrinology to nuclear medicine department to perform a PET/CT, underwent a ^{18}F -FDG and a ^{18}F -DOPA PET/CT.

Inclusion criteria for this study were:

- Previous total thyroidectomy associated or not to lymph node dissection, with histological result of MTC.
- Suspected recurrent or persistent disease after initial surgery by elevated calcitonin levels above the laboratory range (> 11.5 pg/mL in women and > 18 pg/mL in men).
- Confirmation by cytology, histological exam or other imaging tests during follow-up (at least 12 months after the PET/CT study).

Patients were referred from different endocrinology departments in Andalusia and in all cases, both PET/CT scans were performed in Virgen del Rocío University Hospital (Seville), as this is the reference center.

Biochemical analysis

The serum Ct levels were measured by chemiluminescence immunoassay (Immulite 2000, Siemens). Normal values in our laboratory are set at 5–11.5 pg/mL for women and 8.4–18 pg/mL for men. Serum CEA levels were measured by electrochemiluminescence immunoassay (Cobas 8000, Roche), normal range considered as 0–3 ng/mL. Ct-DT and CEA-DT were calculated using the web calculator provided by the ATA (<http://www.thyroid.org/thyroid-physicians-professionals/calculators/thyroid-cancer-carcinoma/>). We only calculated doubling times in those cases in which at least four Ct and CEA determinations over a minimum period of 2 years were available. Ct-DT and CEA-DT > 24 months were considered associated with a better long-term prognosis than those < 24 months [16].

PET/CT with ^{18}F -FDG and ^{18}F -DOPA

In first instance, each patient underwent a PET/CT with ^{18}F -FDG. ^{18}F -DOPA scan was performed at a second stage. Time between both scans ranged from 5 to 80 days (median 21.5 days, interquartile range 13–31). A blood sample to measure Ct and CEA levels was extracted before administration of the radiopharmaceutical. The study was conducted prior fasting, after appropriate hydration and furosemide administration. Women were tested for pregnancy. Both radiopharmaceuticals were administered intravenous. The activity range was 174–288 MBq for ^{18}F -DOPA and 164–444 MBq for ^{18}F -FDG.

Body PET/CT scan (without contrast) was performed according to the European Association of Nuclear Medicine guidelines (EANM) [17]. The images were obtained using a PET/CT hybrid tomograph model Biograph-16 (Siemens) 60 min after administration of the radiopharmaceutical, with a rate of 3 min/bed. The scan included sections from the cranial vertex up to the middle third of the femoral diaphysis. PET emission images were acquired in 3D and then

normalized performing an attenuation correction with CT image (parameters 120 kV and 50 mA). Reconstructions in coronal, sagittal and transverse planes were performed through the application of five successive iterations and three subsets. Interpretation of the results was carried out by two different nuclear medicine specialists (J.I.C and J.L.T) with large expertise (more than six years) in PET/CT imaging. These nuclear medicine physicians were blinded to each other, but they could access to electronic health record and check out tumor markers levels and radiological tests done before ^{18}F -FDG and ^{18}F -DOPA PET/CT. As all the patients had elevated Ct levels, a negative result in the PET/CT scan was considered as a false negative (FN). To rule out false positive (FP), imaging results were compared with cytology, histological exams or follow-up examinations.

PET images were analyzed visually and semiquantitatively by calculating maximum standardized uptake value (SUVmax) in the region of interest (ROI). Any focal accumulation of ^{18}F -DOPA exceeding normal regional tracer uptake was interpreted as a pathological finding. In addition, focally increased ^{18}F -FDG that did not correspond to normal structures was recorded as positive. ROIs were placed around the regions of increased tracer uptake for SUVmax determination.

Other imaging studies

Once the study was completed, we compared ^{18}F -FDG and ^{18}F -DOPA PET/CT results with other previously acquired imaging studies (cervical ultrasound, CT with iodinated contrast). These morphological techniques were performed before PET/CT and reported by experienced radiologists.

Follow-up

Follow-up was carried out according to recommendations of clinical practice guidelines in-force at the time of the study [1, 16, 18–20], with a minimum follow-up period of 12 months after PET/CT. We identified those patients in whom the therapeutic approach was changed as a result of the PET/CT study. In patients with a positive PET/CT, findings were confirmed during follow-up using cytological analysis (with fine needle aspiration biopsy, FNAB), histological analysis (when final clinical decision was surgery), or with other imaging tests.

Those patients with an initial negative ^{18}F -DOPA PET/CT who underwent a second PET scan because of increasing Ct and CEA level were also studied.

Statistical analysis

Data were collected using the computer system of the hospital (electronic health record). The statistical tests were performed using the SPSS Statistics software, version 21.0 (IBM). Quantitative variables were defined as mean \pm standard

deviation (SD) if the sample followed a normal distribution or as median [IQR, interquartile range] if not. To compare proportions between groups, Fisher's exact test was used. Means between two groups were compared using Student's T-test (Mann-Whitney U-test was employed for non-normal distributions). The Wilcoxon test was used to test whether there were differences between the number of lesions detected by ^{18}F -DOPA and ^{18}F -FDG for specific locations or not. A *p* value <0.05 was considered significant.

Results

Eighteen patients (13 women, five men) were included (demographics are listed in Table 1). Of the patients, 55.5% had a sporadic MTC, and the remaining 45.5% had a MEN 2A Syndrome (multiple endocrine neoplasia type 2A). The age of the patients at the time of the study was 48 ± 11.7 years, with an average disease duration of 7.3 ± 6.2 years.

Laboratory and imaging data for each patient are shown in Table 2. PET/CT was used for tumor restaging purposes. Although tumor markers were elevated in all cases, in 14 out of 18 patients the previous imaging tests were negative or ambiguous. The remaining four cases had other positive imaging tests before PET/CT, so it was performed to find out if there were any additional lesion. Nine out of 18 patients enrolled had undergone a cervical ultrasound (thyroid bed and lymph nodes) and a CT with iodinated contrast (neck, chest, and/or abdomen) 12 months before being referred to PET/CT. Among the remaining nine patients, five had only a CT study available and four had a cervical ultrasound.

The average level of Ct and CEA was 311.1 ± 342.6 pg/mL and 11.6 ± 9.9 ng/mL, respectively. The average Ct-DT was 62.2 ± 76 months ($n = 12$), while the average CEA-DT was 92.3 ± 78.3 months ($n = 10$). The range of follow-up time after the PET/CT study was 18 to 43 months.

Patient-based analysis

In six patients (33.3%) both ^{18}F -DOPA and ^{18}F -FDG PET/CTs were negative. ^{18}F -DOPA PET/CT was positive in 12 patients (sensitivity 66.7%, 95%CI 45-88.4), while ^{18}F -FDG PET/CT detected nine tumor-positive patients (sensitivity 50%, 95%CI 26.9-73.1; $p < 0.01$). In three patients with a negative ^{18}F -FDG PET/CT result, ^{18}F -DOPA was able to detect lesions. Moreover, ^{18}F -FDG PET/CT did not show any pathological findings in ^{18}F -DOPA-negative patients.

Cytohystological confirmation was obtained in eight patients. In the remaining four ^{18}F -DOPA PET/CT-positive patients, confirmation was obtained using other imaging tests and monitoring disease progression during the follow-up. The positive predictive value (PPV) of both examinations was 100% (see Table 2).

Table 1 Patient characteristics at baseline

No. of patient	Gender	Age at diagnosis (years)	Type of MTC	No. of surgical procedures	Type of surgery	Stage	Time of disease duration (months)
1	F	19	MEN 2A	1	TT + CND + BND	IV a	202
2	F	58	Sporadic	2	TT + CND + BND	IV a	44
3	M	27	MEN 2A	1	TT	IV a	194
4	F	37	MEN 2A	1	TT	II	85
5	F	23	MEN 2A	2	TT + CND	I	219
6	F	41	Sporadic	3	TT + CND + LND	IV a	72
7	F	55	Sporadic	2	TT + CND + LND	IV a	64
8	F	35	Sporadic	1	TT + CND + LND	IV a	5
9	M	49	Sporadic	3	TT + CND + RND	IV a	64
10	F	18	MEN 2A	1	TT	II	106
11	M	57	Sporadic	1	TT + CND + LND	IV a	4
12	F	43	MEN 2A	2	TT + CND + BND	IV a	26
13	F	27	Sporadic	2	TT + CND + BND	NA	15
14	M	56	Sporadic	3	TT + CND + LND	IV a	23
15	M	61	Sporadic	1	TT+ LND	IV a	13
16	F	55	Sporadic	3	TT + CND + BND	IV a	122
17	F	29	MEN 2A	1	TT	I	214
18	F	34	MEN 2A	1	TT + CND	III	94

MTC, Medullary Thyroid Carcinoma ; F, female; M, male; MEN 2 A, Multiple Endocrine Neoplasia type 2A; TT, Total Thyroidectomy; CND, Central Neck Dissection; BND, Bilateral Neck Dissection; RND, Right Neck Dissection; LND, Left Neck Dissection; NA, Not available

Ct, CEA, Ct-DT and CEA-DT were similar among patients with sporadic MTC and MEN 2A. No statistical differences were found in the results of PET/CT with ^{18}F -DOPA or ^{18}F -FDG between patients with MEN 2A and sporadic MTC, but the sensitivity of both PET/CT tended to be greater in cases with sporadic carcinoma. ^{18}F -FDG PET/CT had a sensitivity of 60% (95%CI 29.6-90) in patients with sporadic MTC vs. 37.5% (95%CI 4-71) in MEN 2A ($p=0.32$). The sensitivity of ^{18}F -DOPA PET/CT was 80% (95%CI 55.2-100) in patients with sporadic MTC vs. 50% (95%CI 15.4-84.6) in inherit MTC ($p=0.2$).

Lesion-based analysis

A total of 28 lesions were detected with ^{18}F -DOPA compared with 16 lesions with ^{18}F -FDG (1.56 ± 1.5 lesions per patient, lpp, with ^{18}F -DOPA PET/CT vs. 0.89 ± 1.18 lpp with ^{18}F -FDG PET/CT; $p=0.01$). Of the nine patients with a positive result in both PET/CT with ^{18}F -DOPA and ^{18}F -FDG, ^{18}F -DOPA identified more lesions in 44.4% (4/9) of cases (2.56 ± 1.33 lpp with ^{18}F -DOPA PET/CT vs. 1.78 ± 1.09 lpp with ^{18}F -FDG PET/CT; $p=0.065$). ^{18}F -FDG PET/TC did not detect more lesions than ^{18}F -DOPA in any patient (Fig. 1).

With regard to region-based analysis, both types of PET/CT detected 19 cervical and mediastinum lymph nodes, six local recurrences, two bone metastases, and

one liver lesion. ^{18}F -DOPA PET/CT identified all these lesions while ^{18}F -FDG PET/CT was only able to detect 52.6% of lymph node metastases (1.5 [0-2.8] lpp with ^{18}F -DOPA vs. 0.5 [0-1] lpp with ^{18}F -FDG; $p=0.04$), 83.3% of local recurrences and 50% of bone lesions. ^{18}F -FDG PET/CT failed to detect the liver metastasis. There were no statistically significant differences when comparing the number of lesions with both methods in these last three locations ($p=0.32$).

No statistically significant differences were found in the maximum SUV between lesions detected with ^{18}F -FDG and ^{18}F -DOPA (4.2 ± 2.5 vs. 4.1 ± 2.7 , respectively; $p=0.9$).

Calcitonin, CEA, Ct-DT, and CEA-DT values and PET/CT positivity

A) ^{18}F -DOPA PET/CT:

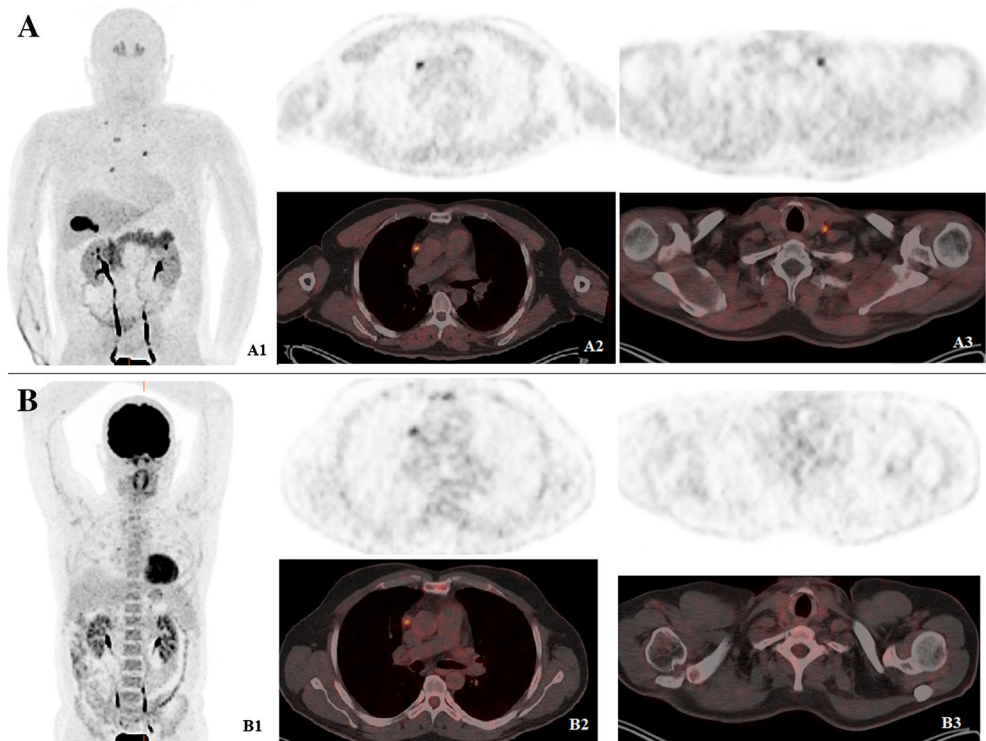
Median values of Ct, CEA, Ct-DT, and CEA-DT of ^{18}F -DOPA PET/CT-negative and positive patients are shown in Table 3. Ct and CEA levels were significantly higher in ^{18}F -DOPA PET/CT-positive patients than in negatives ones (Fig. 2). No statistically significant differences between medians values of Ct-DT and CEA-DT in patients with positive and negative ^{18}F -DOPA PET/CT were found, despite being the DT shorter in patients with a positive test (see Table 3).

Table 2 Biochemical markers and imaging tests

No. of Patient	Calcitonin (pg/mL)	CEA (ng/mL)	Ct-DT (months)	CEA-DT (months)	Previous Image Studies		DOPA Result	No. of lesions and location	FDG Result	No. of lesions and location	Confirmation	Change in management
					Type	Result						
1	200	4.2	>24	>24	N, US	-	-		-			No (Surveillance)
2	164	6.6	<24	<24	N-T, CT	-						Yes (Surgery)
3	785	24.1	>24	>24	N, US	2 equivocal lesions (Local and LN)	+	2 (Local: 1; LN:1)	+	2 (Local: 1; LN:1)	Histology	Yes (Surgery)
4	100	1.3	<24	>24	N-T, CT	Non-specific LN	+	4 (LN)	+	1 (LN)	Histology	Yes (Surgery)
5	1368	50.2	>24	>24	N, US	-	-		-			No (Surveillance)
6	739	15.3	<24	>24	N-T, CT	Non-specific Cervical LN	+	3 (LN: 2; Liver: M. 1)	+	1 (LN)	Histology	Yes (Surgery)
7	154	4.6	>24	>24	N, US	Non-specific Cervical LN	+	2 (LN)	-	2 (LN)	Histology	Yes (Surgery)
8	262	10	NA	NA	N-T-A, CT	Local Tumor + LN Metastases + Non-specific Lung Nodules	+	5 (Local: 1; LN: 4)	+	4 (Local: 1; LN: 3)	Follow-up	Yes (RT, Vandetanib)
9	546	9	NA	NA	N, US	Non-specific LN LN Metastasis	+	1 (LN)	+	1 (LN)	FNAB	Yes (RT, Sorafenib – progressive disease)
10	178	5.9	>24	>24	N, US	Equivocal lesion in Thyroid bed	+	1 (Local)	+	1 (Local)	Histology	Yes (Surgery)
11	272	9	NA	NA	N-T-A, CT	LN Metastases + Non-specific Lung Nodules	+	2 (Local)	+	2 (Local)	Follow-up	Yes (RT, Vandetanib)
12	148	5.4	>24	NA	N, US	-	-		-			No (Surveillance)
13	93	3.1	NA	NA	N-T, CT	-	-		-			No (Surveillance)
14	277	14.6	>24	>24	N, US	Local Tumor	+	2 (Bone Metastases)	+	1 (Bone Metastases)	Follow-up	Yes (Vandetanib)
15	97	7.2	>24	>24	N, US	Non-specific LN	-		-			No (Surveillance)
16	49	1.9	<24	NA	N-T, CT	LN Metastases	+	3 (LN)	+	3 (LN)	Histology	Yes (Surgery, RT)
17	66	4.1	>24	>24	N, US	-	-		-			No (Surveillance)
18	102	2.1	>24	>24	N-T, CT	Local tumor of 4 mm Non-specific LN	+	1 (Local - 6 mm)	-		Follow-up	No (Surveillance. Very small lesion)

CEA, Carcinoembryonic Antigen; Ct-DT, Calcitonin- Doubling Time; CEA-DT, CEA- Doubling Time; NA, Not available; N, Neck; T, Thorax; A, Abdomen; US, Ultrasound; CT, Computed Tomography; LN, Lymph Node; FNAB, Fine Needle Aspiration Biopsy; RT, Radiotherapy; -, negative; +, positive

Fig. 1 A 44-year-old man (patient 3) with MEN 2A syndrome. He had a persistent MTC after the first surgery, with high levels of calcitonin (785 pg/mL) and CEA (24.1 ng/mL). **A.** ¹⁸F-DOPA PET/CT images. **B.** ¹⁸F-FDG PET/CT images. **A1.** ¹⁸F-DOPA PET/CT shows multiple areas of abnormal uptake in the neck and mediastinum. **B1-B2.** ¹⁸F-FDG PET/CT only demonstrated one perivascular mediastinum lymph node (right) also seen with ¹⁸F-DOPA PET/CT (**A2**). **A3.** One of the metastatic lymph nodes detected with ¹⁸F-DOPA PET/CT located in the left cervical region (this lesion was not detected with ¹⁸F-FDG PET/CT. **B3**)



Using a Ct threshold of 150 pg/mL, as indicated by ATA guidelines [1], 10 out of 11 patients with serum Ct levels equal to or greater than this value had positive ¹⁸F-DOPA PET scans. However, only two out of seven patients with Ct levels below 150 pg/mL were ¹⁸F-DOPA PET/CT-positive (sensitivity of 90.9% vs. 28.6%, respectively; $p=0.013$). The detection rate of the technique was higher in patients with CEA levels over 5 ng/mL, compared to those with serum CEA below 5 ng/mL, but no significant differences were found (sensitivity of 81.1% vs. 42.9%, respectively; $p=0.11$). This CEA value cutoff was set arbitrarily. No statistical differences were found when comparing ¹⁸F-DOPA PET/CT results in patients with different Ct-DTs and CEA-DTs, using a DT threshold of 24 months, perhaps due to the small number of patients (sensitivity 75% with Ct-DT \leq 24

months vs. 62.5% with Ct-DT > 24 months, $p= 0.59$; sensitivity 100% with CEA-DT \leq 24 months vs. 66.6% with CEA-DT > 24 months, $p= 0.7$). **B)** ¹⁸F-FDG PET/CT:

Table 4 summarizes the median values of Ct, CEA and the doubling times based on the result obtained in ¹⁸F-FDG PET scan. Ct and CEA levels were significantly higher in ¹⁸F-FDG PET/CT-positive patients compared with negative ones. No differences were found in Ct and CEA-DTs regarding PET positivity.

Eight out of 11 patients with serum Ct levels over 150 pg/mL had positive ¹⁸F-FDG PET scans, but only one out of seven patients with Ct levels below 150 pg/mL were ¹⁸F-FDG PET/CT-positive (sensitivity of 72.7% vs. 14.3%, respectively; $p=0.025$). Similarly, a significant increase in the detection rate of PET/CT with ¹⁸F-FDG was observed using a CEA threshold of 5 ng/mL (sensitivity of 72.7% with CEA \geq 5 ng/mL vs. 14.3% with CEA < 5 ng/mL; $p= 0.025$).

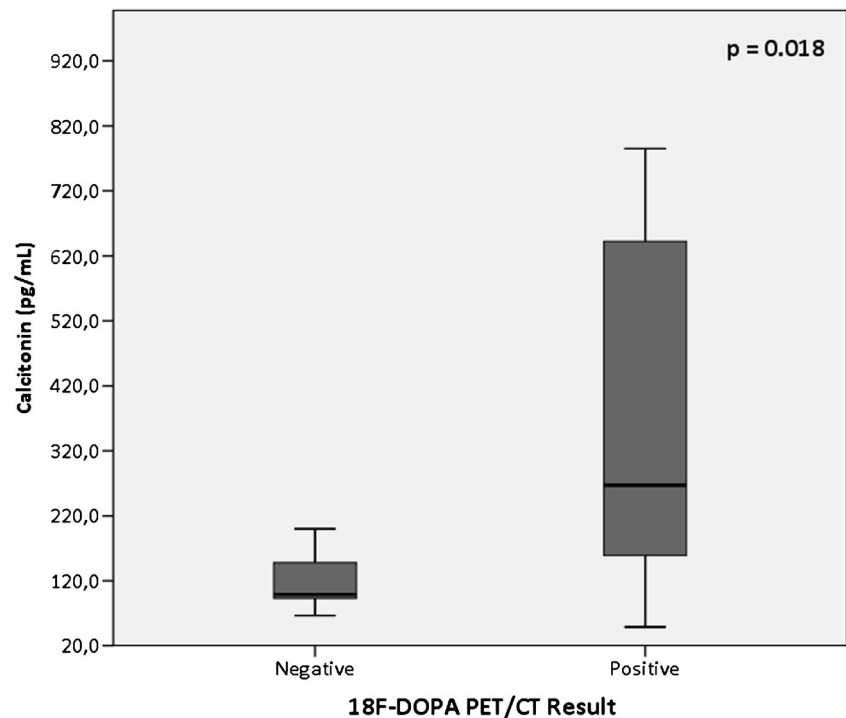
In our study, as it happened with ¹⁸F-DOPA PET/CT, the detection rate of ¹⁸F-FDG PET/CT was higher in patients with Ct and CEA-DTs less than 24 months, but no statistical differences were found (sensitivity of 50% with Ct-DT \leq 24 months vs. 37.5% with Ct-DT > 24 months, $p=0.57$; sensitivity of 100% with CEA-DT \leq 24 months vs. 44.4% with CEA-DT > 24 months, $p= 0.5$).

Table 3 Tumor markers, duplication times, and ¹⁸F-DOPA PET/CT result

	¹⁸ F-DOPA +	¹⁸ F-DOPA -	<i>p</i>
Calcitonin (pg/ml)	267 [156.5-690.8]	98.7 [86.2-161]	0.018
CEA (ng/ml)	9 [4.9-15.1]	4.15 [2.7-5.9]	0.041
Ct-DT (months)	32.7 [17.4-146.3]	35.7 [25.7-50.3]	ns (0.81)
CEA-DT (months)	29.5 [24.2-222.8]	105.1 [45.2-113]	ns (0.67)

Variables expressed as median [interquartile range]. CEA, Carcinoembryonic Antigen; Ct-DT, Calcitonin-Doubling Time; CEA-DT, CEA-Doubling Time; ns, non-significant

Fig. 2 ^{18}F -DOPA PET/CT results and calcitonin level. Box and whisker plot representing the median and interquartile range of calcitonin in patients with positive and negative ^{18}F -DOPA PET/CT results



Comparative results with other imaging techniques

All imaging tests performed before to PET/CT and the corresponding findings are detailed in Table 2. Cervical ultrasound imaging was available in 13 patients. Seven out of these 13 patients had a negative result, and in six patients findings were nonspecific or ambiguous (not clearly pathological cervical lymph nodes). ^{18}F -DOPA and ^{18}F -FDG PET/CT were able to identify cervical lymph nodes metastases in two out of the seven patients with a negative cervical ultrasound. In the six patients with ambiguous sonographic findings, ^{18}F -DOPA PET/CT was positive for lymph node metastasis or local tumor in five cases, while the study ^{18}F -FDG PET/CT confirmed the lesions in four patients.

CT scans of neck, chest or abdomen were available in 14 patients. In four of them, CT failed to identify disease foci; in another five, the results were inconclusive, and in the

remaining five there was evidence of disease. ^{18}F -FDG PET/CT detected metastatic disease in two patients with a previous nonspecific CT result, and in four out of five patients with an apparently positive CT. ^{18}F -DOPA PET/CT seems to be superior to ^{18}F -FDG PET/CT or CT, allowing disease detection in two patients with a previous negative CT, in three patients with previous equivocal findings and in four out of five patients with a positive CT scan.

Follow-up

In all patients except one a change in clinical management was possible (see Table 2, case number 18, in which a wait-and-see attitude was decided by a multidisciplinary team, because of the small size of the detected lesion). Seven patients were surgically treated; four patients received external beam radiotherapy; and in four patients, treatment with tyrosine kinase inhibitors (TKI) was started.

^{18}F -DOPA PET/CT was repeated throughout the clinical follow-up in two out of the six patients with an initial negative result in both PET/CT with ^{18}F -FDG and ^{18}F -DOPA, due to the progressive rise of tumor markers (patients number 12 and 13 of Table 2). In the case number 12 a new ^{18}F -DOPA PET/CT was performed 26 months after the first one, with a Ct value of 307 pg/mL (previous level of 148 pg/mL), obtaining a second negative result. In the patient number 13, which had a Ct value of 93 pg/mL at the beginning of the study, ^{18}F -DOPA PET/CT was repeated 20 months later, when Ct levels had risen to 427 pg/mL. The second PET/CT with ^{18}F -DOPA showed a paratracheal lesion suggestive of local tumor. The

Table 4 Tumor markers, duplication times, and ^{18}F -FDG PET/CT result

	^{18}F -FDG +	^{18}F -FDG -	<i>p</i>
Calcitonin (pg/ml)	272 [171-665.5]	102 [95.2-177]	0.04
CEA (ng/ml)	9 [6.3-19.4]	4.2 [2.6-6.3]	0.031
Ct-DT (months)	27.1 [16.4-109.3]	40 [23.8-53.8]	ns (0.43)
CEA-DT (months)	106.6 [25.9-223.9]	45.2 [26.5-109.2]	ns (0.55)

Variables expressed as median [interquartile range]. CEA, Carcinoembryonic Antigen; Ct-DT, Calcitonin-Doubling Time; CEA-DT, CEA-Doubling Time; ns, non-significant

patient was operated, proving the findings on histological examination of the removed node.

Discussion

Our study shows the increased diagnostic sensitivity of ^{18}F -DOPA compared to ^{18}F -FDG PET/CT in the residual or recurrent MTC, in both the analysis per patient and per lesion. These results are in consonance with those of other researches published to date [8–12]. In our study, ^{18}F -DOPA PET/CT had a sensitivity of 66.7% in the patient-based analysis, while the sensitivity of ^{18}F -FDG PET/CT was 50%. In addition, ^{18}F -FDG PET/CT detected only 57.2% of the lesions identified by ^{18}F -DOPA. These data are similar to those from other studies, because integrating all published so far, the overall sensitivity of ^{18}F -DOPA PET or PET/CT is 70%, while for ^{18}F -FDG PET or PET/CT is 44% per patient and 42% per lesion [3, 21, 22]. We have not found statistical differences when comparing sensitivity of PET/CT with ^{18}F -FDG or ^{18}F -DOPA between patients with sporadic and familial MTC. However, according to our results, the sensitivity of both scans may be higher in patients with sporadic MTC than in MEN 2A cases. No data have been reported in this respect, so additional research is required.

Regarding region-based analysis, ^{18}F -DOPA PET/CT was more suitable to identify metastatic lymph nodes, even those small in size (6 mm). These data are consistent with those published by Hoegerle, Treglia, and Archier previously [5, 12, 22]. In particular, in our study, ^{18}F -FDOPA detected local tumor or metastatic lymph nodes in 53.8% of patients with a negative or inconclusive cervical ultrasound (7/13). Moreover, PET/CT with ^{18}F -DOPA has also proven to be a sensitive technique to identify metastases of MTC in unusual locations; for example, two cases have been recently published in which peritoneal carcinomatosis and orbital metastasis were diagnosed using this method [23, 24]. In our series, ^{18}F -DOPA PET/CT identified a liver metastasis not detected by ^{18}F -FDG.

^{18}F -DOPA PET/CT is a powerful tool that allows changes in patient management, and thus has an important clinical weight. In our series, eight out of 12 patients with a positive ^{18}F -DOPA PET/CT underwent surgery with a curative intent. In the remaining three patients with pathological findings on this exam, TKIs were offered (progressive disease with distant metastases).

Although the ATA guidelines recommend expanding the morphological or functional study in addition to cervical ultrasound in patients with MTC and calcitonin levels above 150 pg/mL [1, 16], there is only one study so far that supports this recommendation [9]. Luster et al. in a retrospective study that included 28 patients found a 100% sensitivity and specificity of ^{18}F -DOPA PET/CT with calcitonin levels over this

cutoff [9]. However, these outcomes were not confirmed in subsequent studies [14, 22]. Sesti et al. tried to validate the calcitonin cutoff of 150 pg/mL, finding a lower sensitivity and specificity of the technique (79% and 80%, respectively) than Luster et al [14]. In a recent paper published by Archier et al. including 86 patients with MTC, ^{18}F -DOPA PET/CT sensitivity was not affected by serum calcitonin values when using calcitonin as a continuous variable or in a percentile group analysis [22]. In the meta-analysis from Treglia et al., the sensitivity of ^{18}F -DOPA PET or PET/CT was 73% if calcitonin values were above 150 pg/mL, but reached 86% when the Ct value rose over 1000 pg/mL or Ct-DT was below 24 months [15]. In our series we found that only one out of all the patients with Ct \geq 150 pg/mL had a negative result with ^{18}F -DOPA PET/CT, being the sensitivity of this test of 90.9% using this cutoff value. We achieved a sensitivity of 100% with Ct or CEA above 200 pg/mL and 7.2 ng/mL, respectively.

Concerning CEA values, Treglia et al. in their meta-analysis also found higher detection rates of ^{18}F -DOPA PET or PET/CT when setting the cutoff of CEA at 5 ng/mL (detection rate of 64% with CEA > 5 ng/mL vs 48% with CEA \leq 5 ng/mL) [15]. In this study, it seems that from this threshold of CEA, the diagnostic accuracy of ^{18}F -DOPA and ^{18}F -FDG PET/CT increase significantly (sensitivity of 81.1% and 72.7%, respectively, with CEA \geq 5 ng/mL vs. 42.9% and 14.3% CEA < 5 ng/mL). Nevertheless, more studies to evaluate this cutoff value are needed.

Although we have not found a significant association between Ct or CEA doubling times and PET/CT positivity, we have seen a tendency to positivity with lower values of Ct-DT. Other studies have proven that the utility of ^{18}F -FDG PET is higher when Ct-DT is less than 24 months, or CEA levels are rapidly rising [11, 13, 25], providing a prognostic value to ^{18}F -FDG PET, with decreased survival or faster disease progression in patients showing uptakes. In our study, only one out of 11 patients with a negative ^{18}F -FDG PET/CT result (patient number 6 of Table 2) developed a progressive disease with distant metastases during the follow-up. The rest of the ^{18}F -FDG-negative cases had a persistent disease with stable or decreasing tumor markers. Four out of nine patients with pathological findings on ^{18}F -FDG PET/CT had progressive disease (cases No. 3, 9, 11, and 16 in Table 2), one patient has died (No. 8), and the other remained stable or improved after surgery. Despite the limited number of patients in our study, it also seems that those with a positive ^{18}F -FDG PET/CT result had a worse outcome.

Gallium-68-labeled somatostatin analogues represent a promising tool for evaluation of the expression of somatostatin receptors in neuroendocrine tumors [26]. The experience with ^{68}Ga -labelled DOTA peptides in MTC is very limited [12, 27–29]. Conry et al. compared ^{68}Ga -DOTATATE PET/CT and ^{18}F -FDG PET/CT in 18 patients with recurrent MTC

and found that the sensitivity of both tracers was similar (72% vs 78%, respectively) [27]. Ozkan et al. retrospectively evaluated the role of ^{68}Ga -DOTATATE and ^{18}F -FDG PET-CT in 22 patients with residual MTC [28]. They found a better performance of ^{68}Ga -DOTATATE PET/CT than ^{18}F -FDG PET/CT (sensitivity of 68.2% vs 44.4%, respectively) and conclude, as in other papers, that ^{68}Ga -DOTATATE PET-CT is an efficient imaging modality in MTC patients with very increased calcitonin and CEA levels (especially >500–1000 pg/mL and 50 ng/mL, respectively) [28, 29]. However, the only study comparing ^{18}F -FDG, ^{18}F -DOPA and ^{68}Ga -somatostatin analogues PET/CT imaging in patients with residual MTC (n=18) showed, as in our series, that ^{18}F -DOPA PET/CT was the most useful imaging method for detecting recurrent MTC lesions (sensitivity of 72% for ^{18}F -DOPA, 33% for ^{68}Ga -somatostatin analogue and 17% for ^{18}F -FDG PET/CT) [12]. The above-mentioned studies showed that ^{68}Ga -somatostatin analogue PET/CT missed all the liver lesions detected by the other tracers, a finding that may be explained by the low lesion-to-background ratio due the low hepatic expression of somatostatin receptors and the physiological uptake of this tracer in the liver [12, 27]. Finally, ^{68}Ga -DOTATATE PET/CT could be a useful complementary imaging method that could identify patients suitable for targeted radionuclide somatostatin analogue therapy (^{177}Lu tetium or ^{90}Y ttrium-labelled DOTATATE) [26].

Our study has several limitations. In first instance, the number of patients recruited for the study is small. Medullary thyroid cancer is a very rare neuroendocrine tumor and it is difficult to gather long series of cases. Second, it has not been possible to compare the results between PET/CT with ^{18}F -DOPA and ^{18}F -FDG and other imaging modalities in all patients. This is because this objective was retrospectively included and only some of the patients had cervical ultrasound and CT before PET/CT. Finally, the doubling times of calcitonin and CEA were not available in all cases. This fact justifies that when comparing the results of ^{18}F -FDG and ^{18}F -DOPA PET/CT depending on calcitonin and CEA doubling times no statistically significant differences were obtained.

In this and other studies [7–10], the ^{18}F -DOPA PET/CT sensitivity to locate the disease seems to be superior to other morphological studies (CT). Taking into account these data, it would be reasonable to position ^{18}F -DOPA PET/CT in the second step of diagnosis (after cervical ultrasound) when trying to locate the disease in patients with recurrent or persistent MTC.

In conclusion, ^{18}F -DOPA PET/CT seems to be superior to ^{18}F -FDG PET/CT in demonstrating recurrent or persistent MTC. The highest diagnostic performance of the technique would be obtained in patients with Ct levels ≥ 150 pg/mL and negative or ambiguous morphological exams. The sensitivity of ^{18}F -FDG and ^{18}F -DOPA PET/CT may be increased with a CEA cutoff of ≥ 5 ng/mL.

Compliance with ethical standards

Conflicts of Interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. Revised american thyroid association guidelines for the management of medullary thyroid carcinoma. *Thyroid*. 2015;25(6):567–610. doi:10.1089/thy.2014.0335.
2. Hu MI, Ying AK, Jimenez C. Update on medullary thyroid cancer. *Endocrinol Metab Clin North Am*. 2014;43(2):423–42. doi:10.1016/j.ecl.2014.02.004.
3. Balogova S, Talbot JN, Nataf V, Michaud L, Huchet V, Kerrou K, et al. 18F-fluorodihydroxyphenylalanine vs other radiopharmaceuticals for imaging neuroendocrine tumours according to their type. *Eur J Nucl Med Mol Imaging*. 2013;40(6):943–66. doi:10.1007/s00259-013-2342-x.
4. Minn H, Kauhanen S, Seppänen M, Nuutila P. 18F-FDOPA: a multiple-target molecule. *J Nucl Med*. 2009;50(12):1915–8. doi:10.2967/jnumed.109.065664.
5. Hoegerle S, Altehofer C, Ghanem N, Brink I, Moser E, Nitzsche E. 18F-DOPA positron emission tomography for tumour detection in patients with medullary thyroid carcinoma and elevated calcitonin levels. *Eur J Nucl Med*. 2001;28:64–71.
6. Beuthien-Baumann B, Strumpf A, Zessin J, Bredow J, Kotzerke J. Diagnostic impact of PET with 18F-FDG, 18F-DOPA and 3-Omethyl-6-[18F]fluoro-DOPA in recurrent or metastatic medullary thyroid carcinoma. *Eur J Nucl Med Mol Imaging*. 2007;34(10):1604–9.
7. Koopmans KP, de Groot JWB, Plukke JTM, de Vries EG, Kema IP, Sluiter WJ, et al. 18F-dihydroxyphenylalanine PET in patients with biochemical evidence of medullary thyroid cancer: relation to tumor differentiation. *J Nucl Med*. 2008;49:524–31. doi:10.2967/jnumed.107.047720.
8. Beheshti M, Pöcher S, Vali R, Waldenberger P, Broinger G, Nader M, et al. The value of 18F-DOPA PET-CT in patients with medullary thyroid carcinoma: comparison with 18F-FDG PETCT. *Eur Radiol*. 2009;19:1425–34. doi:10.1007/s00330-008-1280-7.
9. Luster M, Karges W, Zeich K, Pauls S, Verburg FA, Dralle H, et al. Clinical value of 18-fluorine-fluorodihydroxyphenylalanine positron emission tomography/computed tomography in the follow-up of medullary thyroid carcinoma. *Thyroid*. 2010;20(5):527–33. doi:10.1089/thy.2009.0342.
10. Marzola MC, Pelizzo MR, Ferdeghini M, Toniato A, Massaro A, Ambrosini V, et al. Dual PET/CT with (18F)-DOPA and (18F)FDG in metastatic medullary thyroid carcinoma and rapidly increasing calcitonin levels: comparison with conventional imaging. *Eur J Surg Oncol*. 2010;36(4):414–21. doi:10.1016/j.ejso.2010.01.001.
11. Kauhanen S, Schalin-Jääntti C, Seppänen M, Kajander S, Virtanen S, Schildt J, et al. Complementary roles of 18F-DOPA PET/CT and 18F-FDG PET/CT in medullary thyroid cancer. *J Nucl Med*. 2011;52(12):1855–63. doi:10.2967/jnumed.111.094771.

12. Treglia G, Castaldi P, Villani MF, Perotti G, deWaure C, Filice A, et al. Comparison of 18F-DOPA, 18F-FDG and 68Ga somatostatin analogue PET/CT in patients with recurrent medullary thyroid carcinoma. *Eur J Nucl Med Mol Imaging*. 2012;39(4):569–80. doi:10.1007/s00259-011-2031-6.
13. Verbeek HH, Plukker JT, Koopmans KP, de Groot JW, Hofstra RM, Muller Kobold AC, et al. Clinical relevance of 18F-FDG PET and 18F-DOPA PET in recurrent medullary thyroid carcinoma. *J Nucl Med*. 2012;53(12):1863–71. doi:10.2967/jnumed.112.105940.
14. Sesti A, Mayerhoefer M, Weber M, Anner P, Wadsak W, Dudeczak R, et al. Relevance of calcitonin cut-off in the follow-up of medullary thyroid carcinoma for conventional imaging and 18-fluorine-fluorodihydroxyphenylalanine PET. *Anticancer Res*. 2014;34(11):6647–54.
15. Treglia G, Cocciolillo F, Di Nardo F, Poscia A, de Waure C, Giordano A, et al. Detection rate of recurrent medullary thyroid carcinoma using fluorine-18 dihydroxyphenylalanine positron emission tomography: a meta-analysis. *Acad Radiol*. 2012;19(10):1290–9. doi:10.1016/j.acra.2012.05.008.
16. Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid*. 2009;19(6):565–612. doi:10.1089/thy.2008.0403.
17. Boellaard R, O'Doherty MJ, Weber WA, Mottaghy FM, Lonsdale MN, Stroobants SG, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. *Eur J Nucl Med Mol Imaging*. 2010;37(1):181–200. doi:10.1007/s00259-009-1297-4.
18. Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, et al. Guidelines for the management of thyroid cancer. *Clin Endocrinol (Oxf)*. 2014;81(Suppl 1):1–122. doi:10.1111/cen.12515.
19. Schlumberger M, Bastholt L, Dralle H, Jarzab B, Pacini F, Smit JW, et al. European thyroid association guidelines for metastatic medullary thyroid cancer. *Eur Thyroid J*. 2012;1(1):5–14. doi:10.1159/000336977.
20. Leenhardt L, Erdogan MF, Hegedus L, Mandel SJ, Paschke R, Rago T, et al. 2013 European thyroid association guidelines for cervical ultrasound scan and ultrasound-guided techniques in the postoperative management of patients with thyroid cancer. *Eur Thyroid J*. 2013;2(3):147–59. doi:10.1159/000354537.
21. Minn H, Kemppainen J, Kauhanen S, Forsback S, Seppänen M. 18F-fluorodihydroxyphenylalanine in the diagnosis of neuroendocrine tumors. *PET Clin*. 2014;9(1):27–36. doi:10.1016/j.cpet.2013.08.013.
22. Archier A, Heimburger C, Guerin C, Morange I, Palazzo FF, Henry JF, et al. 18F-DOPA PET/CT in the diagnosis and localization of persistent medullary thyroid carcinoma. *Eur J Nucl Med Mol Imaging*. 2016;43(6):1027–33. doi:10.1007/s00259-015-3227-y.
23. Aziz AL, Dierickx L, Courbon F, Taïeb D, Zerdoud S. (18F)Fluorine-18-l-dihydroxyphenylalanine ((18F)-DOPA) positive isolated peritoneal carcinomatosis from a MENII-related medullary thyroid carcinoma. About an atypical metastatic site and utility of (18F)-FDOPA. *Clin Case Rep*. 2015;3(2):81–3. doi:10.1002/ccr3.159.
24. Ruiz JB, Orré M, Cazeau AL, Henriques de Figueiredo B, Godbert Y. 18F-DOPA PET/CT in Orbital Metastasis From Medullary Thyroid Carcinoma. *Clin Nucl Med*. 2016;41(6):e296–7. doi:10.1097/RLU.0000000000001216.
25. Treglia G, Rufini V, Salvatori M, Giordano A, Giovannella L. PET Imaging in Recurrent Medullary Thyroid Carcinoma. *Int J Mol Imaging*. 2012;2012:324686. doi:10.1155/2012/324686.
26. Skoura E. Despicing medullary thyroid cancer recurrence: the past and the future of nuclear medicine imaging. *Int J Endocrinol Metab*. 2013;11(4):e8156. doi:10.5812/ijem.8156.
27. Conry BG, Papanthasiou ND, Prakash V, Kayani I, Caplin M, Mahmood S, et al. Comparison of (68)Ga-DOTATATE and (18F)-fluorodeoxyglucose PET/CT in the detection of recurrent medullary thyroid carcinoma. *Eur J Nucl Med Mol Imaging*. 2010;37:49–57. doi:10.1007/s00259-009-1204-z.
28. Ozkan ZG, Kuyumcu S, Uzum AK, Gecer MF, Ozel S, Aral F, et al. Comparison of ⁶⁸Ga-DOTATATE PET-CT, ¹⁸F-FDG PET-CT and ^{99m}Tc-(V)DMSA scintigraphy in the detection of recurrent or metastatic medullary thyroid carcinoma. *Nucl Med Commun*. 2015;36(3):242–50. doi:10.1097/MNM.0000000000000240.
29. Tran K, Khan S, Taghizadehasl M, Palazzo F, Frilling A, Todd JF, et al. Gallium-68 Dotatate PET/CT is superior to other imaging modalities in the detection of medullary carcinoma of the thyroid in the presence of high serum calcitonin. *Hell J Nucl Med*. 2015;18(1):19–24. doi:10.1967/s002449910163.