



Prospective study on the clinical relevance of ^{18}F -DOPA positron emission tomography/computed tomography in patients with medullary thyroid carcinoma

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Abstract

Purpose ^{18}F -DOPA Positron Emission Tomography/Computed Tomography (^{18}F -DOPA PET/CT) is a sensitive functional imaging method (65–75%) for detecting disease localization in medullary thyroid cancer (MTC). We aimed: (i) to assess the clinical usefulness of ^{18}F -DOPA PET/CT in patients with MTC and elevated calcitonin (Ctn) and CEA levels and, (ii) to evaluate changes in disease management secondary to the findings encountered with this methodology.

Methods Thirty-six patients with MTC and Ctn levels ≥ 150 pg/ml were prospectively included. Neck ultrasound, chest contrast-enhanced CT, liver magnetic resonance imaging/abdominal three-phase contrast-enhanced CT and bone scintigraphy were carried out up to 6 months before the ^{18}F DOPA PET/CT.

Results Seventy eight percent of patients were female and 27% had hereditary MTC. Median Ctn level was 1450 pg/ml [150–56620], median CEA level 413 ng/ml [2.9–7436]. Median Ctn DT was 37.5 months [5.7–240]; median CEA DT was 31.8 [4.9–180]. ^{18}F -DOPA PET/CT was positive in 33 patients (91.6%); in 18 (56%) uptake was observed in lymph nodes in the neck or mediastinum, in seven cases (22%) distant metastases were diagnosed, and in eight additional patients (24%) both locoregional and distant sites of disease were found. Ctn and CEA levels were higher in patients with ≥ 3 foci of distant metastases. In 14 patients (38.8%), findings on ^{18}F -DOPA PET/CT led to changes in management; surgery for locoregional lymph nodes was the most frequent procedure in 8 patients (22%).

Conclusion ^{18}F -DOPA PET/CT was useful for the detection of recurrent disease in MTC, providing incremental value over conventional imaging procedures that led to modification in treatment strategies in nearly 40% of patients.

Keywords Medullary thyroid cancer · PET/CT · Positron Emission Tomography · ^{18}F -DOPA

Introduction

Medullary thyroid carcinoma (MTC) accounts for <2% of all thyroid cancers. It arises from the parafollicular cells, and it usually secretes calcitonin (Ctn) and

carcinoembryonic antigen (CEA), which are useful tumor markers. Although it generally presents as a sporadic tumor, nearly 25% of MTC are found to be hereditary [1].

Localization of recurrent or persistent disease after initial treatment of MTC is often challenging. MTC usually disseminates to lymph nodes in the central neck, with further spread to cervical and mediastinal lymph nodes. Distant metastases occur at the time of the diagnosis of MTC in 10–12% of cases, and they are most frequently located in the liver, bone, and lungs [2, 3].

A combination of neck ultrasound (US), chest contrast-enhanced computed tomography (CT), abdominal magnetic resonance imaging (MRI) or three-phase contrast-enhanced abdominal CT, and axial MRI combined with bone scintigraphy is usually recommended for radiological surveillance of patients with elevated tumor markers [1, 4, 5]. Nevertheless, in up to 20% of cases, these procedures may

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fail to identify the sites of metastatic disease, underscoring an unmet need for more accurate diagnostic procedures [6].

Performance results of ^{18}F -Fluorodeoxyglucose (FDG) PET/CT for assessing the extent of disease in patients with MTC vary widely. ^{18}F -FDG PET/CT is recognized as a useful staging method in patients with markedly elevated Ctn levels (above 1000 pg/ml), short Ctn doubling time, or in patients in whom aggressive disease is suspected. Nevertheless, in the majority of the cases, MTC is a slow-growing tumor, and consequently, low FDG uptake is expected [7–9].

^{18}F Dihydroxyphenylalanine (^{18}F -DOPA) is a label amino acid that is also used as a radiotracer for PET/CT. The uptake of DOPA is elevated in neuroendocrine cells because this molecule is incorporated into the cytoplasm by using an amino acid transporter called LATs (L- type amino acid transporter) and then converted to ^{18}F -dopamine by cytosolic aromatic amino acid decarboxylase (AADC) which plays a special role in neuroendocrine cells. The combination of both mechanisms allows for increased ^{18}F -DOPA uptake in MTC lesions [10].

^{18}F DOPA PET/CT is a functional imaging method that was shown to be highly sensitive (65–75%) for detecting disease localization in MTC [10]. However, its role in the follow-up of this population of patients remains uncertain. We aimed to assess the clinical usefulness of ^{18}F -DOPA PET/CT in patients with MTC and elevated serum tumor markers, evaluating changes in disease management secondary to the findings observed with this methodology, in addition to the information provided by standard imaging procedures.

Material and methods

Patient population

From August 2016 to November 2019, we included thirty-six consecutive adult patients with proven histologic diagnosis of MTC and Ctn level ≥ 150 pg/ml after initial treatment were prospectively included in this study. None of the patients had previously received any systemic treatment.

In each case, the standard combination of American Thyroid Association (ATA) guidelines-recommended procedures was carried out up to 6 months before the ^{18}F -DOPA PET/CT [1].

Neck US was performed to assess the presence of cervical lymph nodes and/or thyroid bed recurrence. Metastatic lymph nodes were diagnosed when the following features were present: round shape, increased size, and loss of fatty hilum, irregular margins, heterogeneous echotexture, calcifications and increased vascularity throughout the lymph node on Doppler evaluation. Hypoechoic nodules in the

thyroid bed with calcification and imprecise margins were diagnosed as local recurrence. When cytological confirmation of diagnosis was needed, fine needle aspiration of suspicious lymph nodes or of those lesions in the thyroid bed was performed, as well as CT measurement in aspiration needle washout fluid.

On chest CT scan, multiple micronodular lesions or larger, round nodules were considered as lung metastases.

Liver metastases were diagnosed on three-phase contrast-enhanced CT when lesions were hyperdense in arterial phase and hypo or isodense during the portal vein phase. If liver MRI was performed, hepatic metastases were diagnosed when masses were iso or hypointense in T1-WI and iso to hyperintense in T2-WI and similar enhanced findings similar to those on CT. Histologic or cytologic confirmation of metastases was obtained when each investigator deemed it necessary, however, it was not considered mandatory.

^{18}F -DOPA PET/CT

All patients underwent whole body ^{18}F -DOPA PET/CT for assessment of the extent of disease at CEMIC University Hospital.

Patients were fasted for at least 4 h before injection of the radiotracer. All ^{18}F -DOPA PET/CT scans were acquired using a GEMINI 64 TOF PHILIPS Healthcare, Cleveland. Early imaging (30 min) of neck and superior mediastinal were acquired in all the patients and then whole body scanning 60 min after injection of 2.59 MBq/Kg ^{18}F -DOPA. Transaxial, coronal and sagittal PET images were analyzed for visual and semiquantitative analysis calculating mean and maximum standardized uptake value (SUV max) of the data were corrected for dead time, decay and photon attenuation and reconstructed in a 128×128 matrix. PET data were reconstructed with CT-based attenuation correction. All images were analyzed by consensus of two experienced nuclear medicine and two radiologist physicians.

Laboratory measurements

Ctn levels were assessed by electrochemiluminescence[®] (Elecsys Roche, Cobas e411), and CEA levels were measured by autoanalyzer. Ctn and CEA doubling times (DT) were calculated using the ATA online calculator (<https://www.thyroid.org/professionals/calculators/>). At least 4 measurements over 2 years were required. Patients undergoing any therapeutic intervention during this lapse were excluded.

All procedures were performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments; informed written consent was obtained from all patients.

Table 1 General characteristics of 36 patients with MTC and Ctn ≥ 150 pg/ml

T	
X	5 (13.9%)
1	9 (25%)
2	7 (19.4%)
3	11 (30.5%)
4	4 (11.1%)
N	
X	3 (8.3%)
0	7 (19.4%)
1a	6 (16.6%)
1b	20 (55.5%)
M	
0	32 (88.9%)
1	4 (11.1%)
S	
X	3 (8.3%)
1	1 (2.8%)
2	5 (13.9%)
3	5 (13.9%)
4	22 (61.1%)
Ctn (pg/ml), median [range]	1450 [150–56620]
Ctn DT (months), median[range] $n = 25$	37.5 [5.7–240]
CEA (ng/ml), median [range]	413 [2.9–7436]
CEA DT (months), median [range] $n = 29$	31.8 [4.9–180]
Time from initial surgery to ^{18}F -DOPA	96 [0–420]

T Tumor, N Node, M metastases, S Stage, Ctn calcitonin, CEA carcinoembryonic antigen, DT Doubling time

Statistical analysis

Continuous variables were expressed as means \pm SD or median (interquartile range), according to their distribution; and categorical data were expressed in percentages. Continuous variables were compared using Mann–Whitney U and Kruskal–Wallis tests; χ^2 test was used to compare categorical variables. A p value < 0.05 was considered significant. Statistical analyses were performed using SPSS (Version 21: SPSS Inc, Chicago, IL).

Results

Thirty-six patients were enrolled from August 2016 to November 2019. Baseline patient and tumor characteristics can be observed in Table 1. Most patients were women (77.7%), mean age at diagnosis was 53.5 years, and hereditary disease was found in 27% of cases.

^{18}F -DOPA PET/CT was positive in 33 patients (91.6%). In 18 (56.25%) of positive ^{18}F -DOPA PET/CT scans,

uptake was observed in lymph nodes in the neck or mediastinum, in 7 (21.8%) distant metastatic disease was diagnosed. In 8 (24.2%) patients there was involvement of both locoregional and distant sites. (Table 2; Figs. 1, 2) 1,2,3).

Systemic metastatic disease was more frequently found in the liver ($n = 9$, 27.2%), followed by bone/s ($n = 7$, 21.8%) and lungs ($n = 2$, 6%). In two patients with adrenal gland uptake, surgical resection was performed and pathology report confirmed pheochromocytoma in both cases (Fig. 3). No statistical differences in SUV max, time from initial surgery, Ctn/CEA levels or DT of Ctn/CEA were found when comparing patients with locoregional and distant disease (Table 2). However, when results were analyzed according to the extension of the disease, those patients with more than 3 foci of distant metastases had significantly higher levels of Ctn and CEA when compared with patients with more limited disease (Table 3).

In 14 patients (38.8%), findings on ^{18}F -DOPA PET/CT led to changes in management. Eight patients (22%) underwent surgery for locoregional lymph nodes, three started treatment with a multikinase inhibitor (MKI), one was submitted to cervical external beam radiotherapy, and one received chemoembolization of liver metastases. In a case of a patient with a renal lesion, negative uptake on ^{18}F -DOPA PET/CT led to the suspicion of renal carcinoma and a nephrectomy was performed. As shown on Table 4, surgery was chosen instead of control or active surveillance in three patients due to the discovery of a larger number of suspicious lymph nodes or lymph nodes located in areas not readily assessed by neck US (such as the paraesophageal or upper mediastinal region). In four cases, surgical strategy was modified due to the detection of previously unrecognized metastatic lymph nodes. In one patient, ^{18}F -DOPA PET/CT ruled out clinically significant distant disease, thus leading to the decision of performing an extensive cervicomediastinal lymphadenectomy. As for the three patients in which MKI was prescribed, this was determined by the detection of several additional foci of metastatic disease or the finding of in ^{18}F -DOPA uptake in lesions considered nonspecific in CT scan.

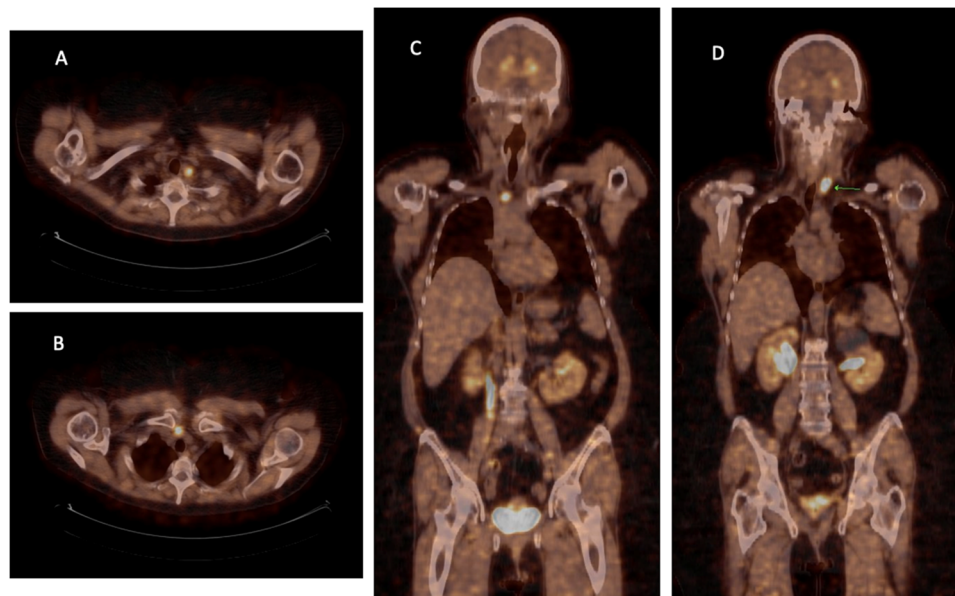
No patient achieved undetectable levels of Ctn as result of the treatment implemented. However, a decrease $\geq 50\%$ was observed in 7 (50%) of them. When assessed by RECIST 1.1 criteria, a complete response was observed in 2 patients (14%), partial response in 4 (28%), and stable disease in 6 (42%); data was missing in two patients. Median progression free survival was 47 months (range: 16–54 months). One of these patients died of causes related to MTC (11 months after ^{18}F -DOPA PET/CT was performed). Median overall survival was 50.5 months (range 11–63 months).

Table 2 Findings on ^{18}F -DOPA PET/CT according to clinical features, disease extension and tumoral markers

	No uptake <i>N</i> = 3	Locoregional disease <i>N</i> = 18	Distant metastases <i>N</i> = 7	Locoregional and distant disease <i>N</i> = 8	<i>p</i>
Age at diagnosis (years)	58.8 ± 18.8	52.3 ± 18.5	58.6 ± 12.2	45.1 ± 13.7	0.23
Months from diagnosis	24.0 ± 19.6	120.0 ± 97.0	97.7 ± 42.4	149.1 ± 146.6	0.23
Ctn (pg/ml)	2177 ± 2773	4872 ± 12376	5798 ± 6890	15836 ± 19196	0.23
Ctn DT (months)	76.3 ± 50.1	58.9 ± 66.1	24.7 ± 21.0	98.6 ± 91.0	0.4
CEA ng/ml	74.0 ± 115.2	116.8 ± 240.6	237.5 ± 307.7	1301 ± 2724	0.17
CEA DT (months)	62.9 ± 22.7	58.4 ± 53.9	31.2 ± 24.8	52.1 ± 44.0	0.66
SUVm	NA	6.9 ± 3.4	9.0 ± 3.3	8.5 ± 4.0	0.31

Ctn calcitonin, *CEA* carcinoembryonic antigen, *DT* Doubling time

Fig. 1 Sixty-five year-old female, with a stage III sporadic medullary thyroid cancer. Calcitonin: 1136 pg/ml. (Doubling time 39.9 months), CEA: 31 ng/ml (Doubling time: 49.4 months). **A** and **B** Axial; **C** and **D** coronal ^{18}F -DOPA PET/CT images showing two avid cervical foci of uptake. **A/ D** Left paratracheal region (SUV max 14.8) and (**B/C**) peritracheal (SUV max 12)



Discussion

Synthesis and use of ^{18}F -DOPA were developed more than three decades ago, and were described by Barrio et al. [11]. Though originally designed for Parkinson's disease, this radiotracer has demonstrated enzyme activity in neuroendocrine tumors, thus showing its potential as a new radiotracer for all diseases with presence/increased activity of aromatic AADC [12]. In one of the first reports, it was suggested that ^{18}F -DOPA PET/CT was a useful supplement to morphological diagnostic imaging, improving lymph node staging and enabling a more specific diagnosis of primary tumors and local recurrence [13]. However, the current ATA guidelines for the management of MTC, published in 2015, do not endorse the diagnostic use of ^{18}F -DOPA PET/CT in the follow-up of these patients [1], since the use of ^{18}F -DOPA was approved in the USA in 2019 (<https://www.fda.gov/drugs/drug-approvals-and-data>

bases/drug-trials-snapshots-fluorodopa-f-18). Therefore, on a worldwide level, there is a lack of consensus regarding recommendations under which setting ^{18}F -DOPA PET/CT should be carried out. While European Society of Medical Oncology Guidelines acknowledge ^{18}F -DOPA PET/CT usefulness in detecting unidentified or small metastases, they also admit that high cost and low availability may make this method unsuitable [5]. The National Comprehensive Cancer Network guidelines do not recommend performing ^{18}F -DOPA PET/CT, but ^{68}Ga DOTAs [14]. Finally, the European Association of Nuclear Medicine guidelines state that ^{18}F -DOPA PET/CT should be considered a first line procedure when compared with other PETs [10].

In recent years, there was an increasing body of publications on the advantages of ^{18}F -DOPA PET/CT in MTC, where it was found to be a sensitive imaging tool for detecting foci of disease, both regional and distant [10]. In

Fig. 2 Thirty-six year-old female, with a stage II hereditary medullary thyroid cancer. Calcitonin: 11,270 pg/ml (Doubling time 15 months). CEA: 413 ng/ml. (Doubling time 23 months). Multiple foci of ¹⁸F DOPA uptake (cervical, liver and vertebrae). Of note, a larger number of ¹⁸F-DOPA-avid metastatic foci on the liver can be seen when compared with CT images

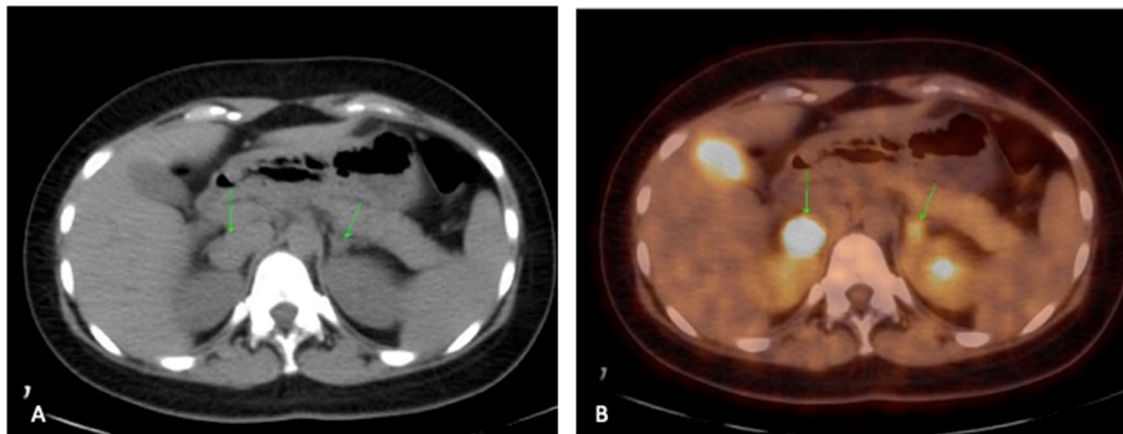
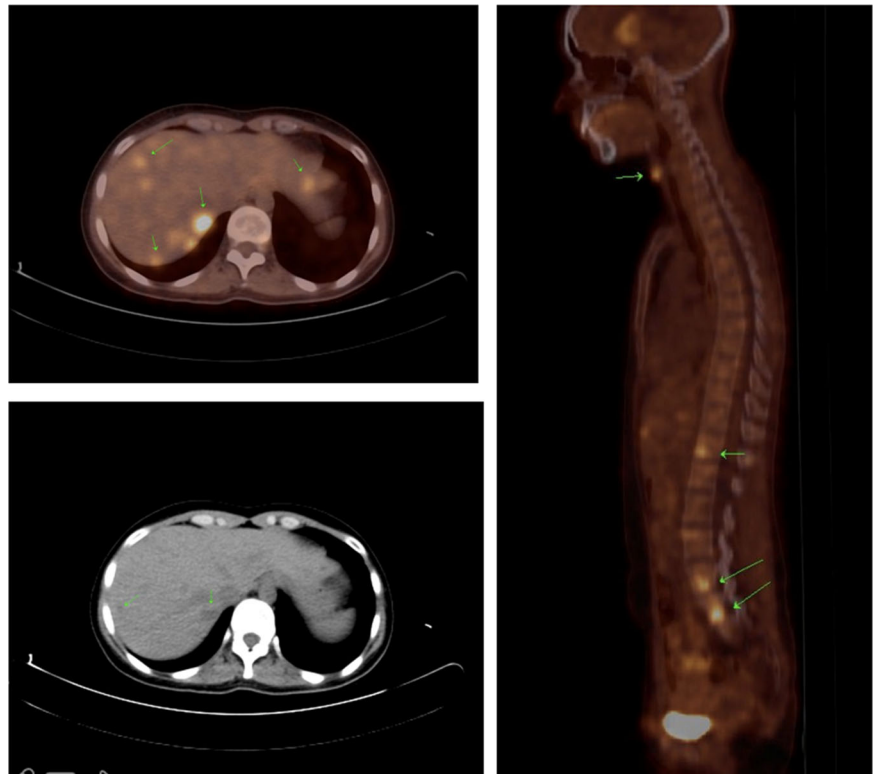


Fig. 3 Bilateral pheochromocytoma. **A** Axial CT images show a nodule in the right adrenal gland and a nonspecific increase in size of the left adrenal gland. **B** Both lesions show avid uptake of ¹⁸F-DOPA

Table 3 Comparison of tumoral markers according to the number of foci of distant disease

	0	<3	≥3	<i>p</i>
Ctn (pg/ml)	748 (304; 1800)	2000 (526; 11,849)	12,746 (6987; 29,155)	0.006
Ctn DT (months)	40.8 (26.5; 58.4)	34.6 (9.6; 85.9)	15.0 (6.7;)	0.67
CEA (ng/ml)	16.3 (6.7; 86.7)	57.0 (12.7; 573)	329.0 (170; 2266)	0.027
CEA DT (months)	46.8 (21.0; 86.1)	31.4 (17.9; 46.6)	44.6 (10.6; 116)	0.53

Ctn calcitonin, *CEA* carcinoembryonic antigen, *DT* Doubling time

patients with indolent MTC (eg. prolonged Ctn/CEA DT), it was shown to be superior to other imaging procedures, both traditional and functional scans.

Rates of detection of disease with ¹⁸F-DOPA PET/CT range between 45 and 78% [4, 15, 16]. We found an even larger rate in our population of 36 patients with MTC and

Table 4 Findings on imaging procedures in 14 patients in which ^{18}F -DOPA PET/CT led to changes in management

	Neck US	Chest CT	Liver MRI/ Abdominal CT	Bone scan	^{18}F -DOPA PET/CT	Change in management (vs. previous approach)
Pt 1	Non-specific bilateral lymph nodes FNAB: only positive for MTC in one left lymph node	Negative	MRI: negative	Negative	Positive on left lateral neck and right retro-sternocleidomastoid muscle	Bilateral neck lymphadenectomy (vs. unilateral)
Pt 2	Right lymph nodes. FNAB positive for MTC	Negative	MRI: negative	Negative	Right lymph nodes and lower paratracheal lymph nodes	Lateral and central lymphadenectomy (vs. lateral lymphadenectomy)
Pt 3	Paratracheal right nodule	Negative	MRI: negative	Negative	Paratracheal nodule and right laterocervical lymph node	Resection of central and lateral lesions (vs. resection of central lesion)
Pt 4	Paratracheal left nodule	Negative	MRI: negative	Negative	Paratracheal right and left nodules, right retrosternomastoid-muscle lymph node	Central neck exploration and right lateral lymphadenectomy (Vs. central neck exploration)
Pt 5	Negative	Negative	MRI: negative	Negative	Lower paratracheal lymph node	Surgery (vs. control)
Pt 6	Nonspecific lateral lymph nodes	Negative	MRI: negative	Negative	Para-esophageal lymph node	Surgery (vs. control)
Pt 7	Positive lateral neck	Negative	MRI: negative	Negative	Central and lateral cervical lymph nodes	Surgery (vs. active surveillance)
Pt 8	Positive left and right lymph nodes	Mediastinal lymph nodes	MRI: small non-conclusive lesion	Non-specific T12 uptake (normal MRI)	Cervical and mediastinal lymph nodes, no uptake on bones and small liver metastases	Cervicomedial lymphadenectomy (vs. MKI)
Pt 9	Positive lateral neck	Lung metastases and mediastinal lymph nodes	CT: nonspecific findings	Negative	More than 5 foci of disease: liver, lung, mediastinal	MKI (vs. active surveillance)
Pt 10	Positive lateral neck	Lung metastases	MRI: Liver metastases	Negative	Multiple liver (and lung) metastases	MKI (vs. active surveillance)
Pt 11	Negative	Negative	MRI: liver metastases	Small foci on dorsal vertebra	Liver metastases, several bone metastases and deep cervical lymph node	MKI (vs. liver chemoembolization)
Pt 12	Negative	Negative	MRI: negative	Negative	Positive on retropharyngeal and lower paratracheal space	EBRT (vs. control)
Pt 13	Negative	Negative	CT: nonspecific findings on liver	Negative	Liver metastases, small foci of bone metastases	Liver chemoembolization (vs. control)
Pt 14	Negative	Negative	MRI: Negative for liver metastases Renal mass	Negative	Negative	Nephrectomy (as treatment for clear cell renal carcinoma)

US ultrasound, CT Computed tomography, MRI magnetic resonance imaging, MKI multi-kinase inhibitor, EBRT external beam radiotherapy, FNAB fine needle aspiration biopsy, MTC medullary thyroid cancer

Ctn levels ≥ 150 pg/ml after initial treatment, where abnormal findings in ^{18}F -DOPA PET/CT were found in over 90% of cases. This underscores the sensitivity of the ^{18}F -DOPA PET/CT in restaging patients.

In the present series, most of the foci of disease were found in locoregional lymph nodes ($n = 26$), in agreement with previous findings [6].

^{18}F -DOPA PET/CT was also useful for detection of distant metastases, which were found in 44% of patients. In nearly half of them, distant metastases coexisted with locoregional involvement. As expected, the most frequent distant metastatic localization was the liver in over half of the patients. No differences were found in findings of ^{18}F -DOPA PET/CT according to Ctn/CEA levels. It is relevant to mention that in two of 10 patients with diagnosis of multiple endocrine neoplasia type 2 A, ^{18}F -DOPA PET/CT was also useful to detect associated pheochromocytoma [17].

Of note, every patient in the present series had undergone conventional imaging procedures recommended for MTC with elevated biochemical markers after initial treatment, including neck US, chest contrast-enhanced CT, liver MRI or abdominal three-phase contrast-enhanced CT and bone scintigraphy. However, ^{18}F -DOPA PET/CT led to changes in management in nearly 40% of the cases. This highlights the clinical impact of the accurate disease characterization achieved by the additional information obtained by ^{18}F -DOPA PET/CT. The most frequent changes in management based on ^{18}F -DOPA PET/CT results were the decision to perform surgical procedures on locoregional lymph nodes and/or to modify previously planned surgical approach in patients without distant metastases. According to the ATA guidelines [1], neck US is considered the first method for locating cervical disease in MTC. However, in the pre-operative setting of MTC patients, some studies found that ^{18}F -DOPA PET/CT was more sensitive than US for the detection of both central and lateral lymph nodes [18, 19]. Coincidentally, Terroir et al. found that, in MTC patients with elevated tumoral markers, ^{18}F -DOPA PET/CT was more sensitive than US, CT and MRI to detect foci of disease in the neck and mediastinum [20]. ^{18}F -DOPA PET/CT has the advantage of detecting recurrences in cervical areas not easily assessed by US (such as retropharyngeal space or upper mediastinal area), providing better evaluation of small or nonspecific findings on CT/MRI in patients with post-surgical changes in the normal anatomy of the neck. Based on data from two meta-analysis [21, 22] Castinetti et al. recommend that ^{18}F -DOPA PET/CT should be the first-choice radiopharmaceutical study for staging at the setting of pre-operative neck surgery and it could also be useful for the accurate assessment of small foci of disease which may be

submitted to active surveillance [23]. Accordingly, our findings suggest that ^{18}F -DOPA PET/CT may be more useful when it is performed in patients with suspected low tumor burden (i.e., patients with biochemical recurrence and tumoral markers suggesting limited extent of disease), or in cases with isolated cervical and/or mediastinal lymph nodes. In these cases, an accurate evaluation of the areas involved is critical to plan the extension of the surgical procedure. Moreover, excluding distant metastases is relevant to define whether a surgical intervention might be beneficial. Further studies are needed to elucidate this.

From a practical standpoint, ^{18}F -DOPA PET/CT also has the advantage of allowing whole-body assessment for clinically relevant foci of disease in a single procedure, as opposed to the many practices currently recommended by guidelines. A simplified follow-up protocol is less demanding on patients, and therefore may lead to improved compliance with scheduled studies. Specificity of uptake of ^{18}F -DOPA is also helpful in the rare instances in which more than one oncologic diagnostic is suspected, as was the case in one patient in this series.

The present study has several limitations, such as the limited number of patients included, due to the low incidence of MTC. Ctn and CEA DT were not available in every case, which was due to changes over time in methodologies of measurement of Ctn and/or CEA in some patients. Histological confirmation of ^{18}F -DOPA PET/CT-positive lesions was not systematically obtained. However, it is important to stress that in the setting of elevated tumoral markers, a lesion with uptake on ^{18}F -DOPA PET/CT, is highly specific for metastatic disease, due to the low incidence of non-oncological causes of false positive uptake [24].

Conclusion

^{18}F -DOPA PET/CT was useful for the detection of recurrent disease in MTC, regardless of serum Ctn/CEA levels and their DT, and provided helpful information for patient management, in addition to conventional imaging procedures, which led to management changes in nearly 40% of the population.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional research

committee and with the principles of the 1964 Declaration of Helsinki and its later amendments.

Informed consent Written informed consent was obtained from every participant patient.

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