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ORIGINAL ARTICLE

^{68}Ga-DOTANOC and ^{18}F-FDG PET/CT in metastatic medullary thyroid carcinoma: novel correlations with tumoral biomarkers

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Abstract

Objective Metastatic disease is common in medullary thyroid carcinoma (MTC) and it is usually detected by raising calcitonin and carcinoembryonic antigen (CEA) levels. Nuclear medicine imaging has an important role in lesion identification/characterisation. We aim to compare ^{68}Ga-DOTANOC PET/CT and ^{18}F-FDG PET/CT performance and to explore the correlations between tumoral markers and functional imaging.

Methods This a retrospective cross-sectional study including 13 patients with MTC and high calcitonin/CEA levels that underwent both ^{68}Ga-DOTANOC PET/CT and ^{18}F-FDG PET/CT.

Results ^{68}Ga-DOTANOC PET/CT identified MTC metastases in 2twopatients that were ^{18}F-FDG-negative (sensitivity of 69.2% vs. 53.9%, respectively). ^{68}Ga-DOTANOC PET/CT also detected a higher number of lesions than ^{18}F-FDG PET/CT in seven patients, with only one patient showing the opposite pattern. Both differences lacked statistical significance ($p = 0.50$ and $p = 0.86$, respectively) but ^{68}Ga-DOTANOC PET/CT better performance allowed changes in patients' management. ^{68}Ga-positive/^{18}F-FDG-negative patients were the ones with the lowest calcitonin doubling time and presented a CEA doubling time >24 months, while the patient with more ^{18}F-FDG-positive lesions was the one with the highest CEA/calcitonin ratio. The number of lesions found in ^{68}Ga-DOTANOC PET/CT were correlated with calcitonin levels ($r = 0.73$; $p < 0.01$) but not with CEA ones ($r = 0.42$; $p = 0.15$). The number of ^{18}F-FDG hypermetabolic focus were correlated with CEA levels ($r = 0.60$; $p < 0.05$) but not with calcitonin ($r = 0.48$; $p = 0.09$).

Conclusions This is the first study to describe a positive correlation between ^{68}Ga-positive lesions and calcitonin levels and between ^{18}F-FDG-positivity and CEA levels. Tumoral markers pattern in metastatic MTC could help clinicians to decide which exam to perform first.

Keywords Thyroid cancer, medullary · PET-CT Scan · Calcitonin · Carcinoembryonic antigen

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Introduction

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumour that arises from the parafollicular C cells of the thyroid gland, accounting for 1 to 2% of all thyroid cancers [1]. Most of them are sporadic, but about 20–30% are inherited as part of multiple endocrine neoplasia type 2 syndrome (MEN 2) due to mutations in RET proto-oncogene [2]. This type of neoplasia has a worse prognosis than the much more frequent papillary thyroid carcinoma. The majority of patients already have local/distant metastases at diagnosis and 50% of them have persistent/recurrent disease after surgery [3, 4].

Both serum calcitonin and carcinoembryonic antigen (CEA) levels can be used as tumour markers in MTC and they should be measured at diagnosis and monitored after surgery to detect persistent/recurrent disease [5, 6].

Furthermore, post-operative calcitonin and CEA doubling times can be useful in evaluating tumour progression and aggressiveness of metastatic MTC [7]. Post-operative calcitonin levels above 150 pg/mL suggest distant metastases and patients should undergo additional imaging beyond neck ultrasound [1].

Integrated positron emission tomography and computed tomography (PET/CT) imaging has revealed itself increasingly useful in detecting MTC metastases that were not found or completely clarified in conventional imaging studies, potentially allowing timely curative surgery [8, 9]. ^{18}F-DOPA PET/CT is one of the most sensitive nuclear imaging studies to map MTC-associated lesions, but its limited availability and high cost when compared to other tracers preclude its regular use in some centres [9]. ^{18}F-FDG PET/CT is based in the increased glycolytic metabolism of many cancers while ^{68}Ga-somatostatin analogue PET/CT takes advantage of the somatostatin receptor (SSTR) profile in MTC (SSTR2, 3 and 5 subtypes preponderance), and both tracers have identified otherwise occult MTC metastases [10, 11]. In addition to diagnostic purposes, the evaluation of ^{68}Ga-somatostatin analogue uptake allows patient selection to peptide receptor radionuclide therapies (PRRNT), like ^{177}Lu-DOTA-TATE, the so-called theranostics [12]. ^{18}F-FDG uptake is usually associated with higher tumour aggressiveness and possible dedifferentiation. Therefore, lesions with high ^{18}F-FDG uptake are less likely to respond to this treatment modality [13].

As there are only few small studies comparing different nuclear imaging tracers in MTC, it is still difficult to choose the appropriate one in the clinical setting of a patient with biochemical evidence of persistent/recurrent MTC. While publications including patients that underwent ^{18}F-DOPA PET/CT and ^{18}F-FDG PET/CT are more frequent, those evaluating ^{68}Ga-somatostatin analogue PET/CT are relatively scarce [14]. American Thyroid Guidelines on MTC describe the role of PET/CT in investigating metastatic disease but they do not state a preferential tracer as robust evidence on this topic is still lacking [1]. Moreover, most research on this matter analyse the sensitivity of the different imaging exams but not their correlation with clinical/laboratorial parameters. To the best of our knowledge, there are no studies correlating ^{68}Ga-somatostatin analogue PET/CT and calcitonin/CEA levels or their doubling times.

The objective of this study is to compare ^{18}F-FDG PET/CT and ^{68}Ga-DOTANOC PET/CT performances in patients with persistent/recurrent MTC and to analyse their impact on patients' management. In addition, we aim to establish laboratorial-imagiological correlations that could help clinicians to individualise the choice of a diagnostic nuclear imaging method for each patient.

Methods

Study design and participants

This is a cross-sectional study conducted in 13 patients with MTC diagnosis with residual/recurrent disease. The following inclusion criteria were applied: previous thyroidectomy and prophylactic central compartment neck dissection, elevated calcitonin and/or CEA levels, two consecutive calcitonin and CEA measurements (one of them at the time of nuclear imaging acquisition), availability of both ^{18}F-FDG PET/CT and ^{68}Ga-DOTANOC PET/CT. Both nuclear imaging studies had to be performed <6 months apart to avoid evaluation in different stages of disease progression. No therapeutic interventions were carried out between the two exams. According to our laboratory reference values, calcitonin levels <11.5 pg/mL and CEA levels <4.5 ng/mL were considered as normal. Calcitonin and CEA doubling times (CTDT and CEADT, respectively) were calculated as follows: $DT \times \log 2/(\log B - \log A)$, where DT is the time between the first (A) and the second (B) measurements (expressed in months) [15]. Negative doubling times represent a decrease of calcitonin levels over time. Pathological tumour, node, metastasis (pTNM) staging was done according to the 7th Edition of the American Joint Committee on Cancer (AJCC) [16].

Imaging procedures

Both ^{18}F-FDG PET/CT and ^{68}Ga-DOTANOC PET/CT were performed at the same centre (Instituto Português de Oncologia do Porto, Porto, Portugal) from April/2010 to April/2018, with a median time interval between scans of 50 days [interquartile range (IQR) 95]. All exams were reviewed by two nuclear medicine physicians that discussed the non-consensual findings. In case of lack of agreement, a third element was involved in the discussion. Abnormal focus of ^{68}Ga and ^{18}F-FDG uptake likely to correspond to metastatic disease were counted. In some imaging studies, uncountable hyperfixation focus were found in certain anatomic locations and considered by the authors as >10 lesions (">10").

Patients were hydrated prior to intravenous injection of ^{68}Ga-DOTANOC (median activity 122.1 MBq, interquartile range [IQR] 46.53) or ^{18}F-FDG (median 347.8 MBq, IQR 98.05) and fasted for 6 h prior to the ^{18}F-FDG PET/CT exam. Two PET/CT systems were used for imaging: a Biograph 6 True Point and a Biograph 20 mCT Flow with added time-of-flight technology (Siemens Healthcare, Erlangen, Germany). Image acquisition was performed in supine position from mid-thigh to vertex, in median 76 (IQR 36.0) and 71 (IQR 35.5) minutes after injection of ^{68}Ga-DOTANOC or ^{18}F-FDG, respectively. CT was performed first, with no breathhold, a section width of 3 mm and standard window reconstruction. Exposure factors were modulated automatically, using 120 KeV and 30–60 mAs as reference. PET imaging was performed in three-dimensional mode for all scans. On the Biograph 6 system, "step-and-shoot" PET images were acquired (15 cm beds, 3 min/bed, 7–8 beds). On the Biograph 20 system, continuous table motion PET acquisition was performed (1.1–1.5 mm/s). Image reconstruction included attenuation and scatter correction, ordered subset expectation maximisation (OSEM) and Gaussian filter application. All 13 patients performed both scans in the same PET/CT system (ten patients on the Biograph 6 and three patients on the Biograph 20).

Radiopharmaceuticals

For ^{68}Ga-DOTANOC production a ^{68}Ge/^{68}Ga generator was eluted with 1 mL of 0.1 M HCL and an automated synthesiser was used (Modular Lab PharmTracer, Eckert and Ziegler, Berlin, Germany). Radiopharmaceutical precursor for the synthesis was obtained from ABX advanced biochemical compounds GmbH (Radeberg, Germany); reagents and cassettes from Eckert and Ziegler. The final injection solution of the ^{68}Ga-DOTANOC was particle-free, clear and colourless, with minimum radiochemical purity, accessed by high-performance liquid chromatography, of at least 95%. ^{18}F-Fluoride was produced via the ^{18}O (p,n) ^{18}F reaction by bombardment of enriched ^{18}O-water and ^{18}F-FDG was synthesised according to good manufacturing practices by Advanced Accelerator Applications (Saint Genis Pouilly, France).

Statistical analysis

Categorical variables were expressed as frequencies and percentages and were compared by chi-square test. Differences between the sensitivities of the used nuclear imaging methods were assessed by McNemar test. Continuous variables were presented as means and standard deviations, or medians and IQR for variables with skewed distributions, and were compared using Student's *t*-test and Mann–Whitney/Wilcoxon tests, respectively. Normal distribution was evaluated using Shapiro–Wilk test or skewness and kurtosis. Spearman's correlation coefficient was used to assess association between continuous variables. Reported *p*-values are two-tailed, and $p < 0.05$ was considered significant. Analyses were performed using SPSS Statistics 25®.

Results

Patients characteristics are described in Table 1. We included 13 patients (five males and eight females) with a mean age at diagnosis of 50.9 ± 12.7 years-old. RET mutation analysis was performed in all patients and it was positive in one of them [missense mutation p.(Val804Met), c.2410G>A]. On average, imagiological studies were performed 6.77 ± 6.70 years after the diagnosis.

Table 1 Characteristics of the enroled patients

Patient	Sex	Age at diagnosis	Age at imagiological evaluation	RET mutation	pTNM stage
1	M	47	66	No	T2N1a
2	F	42	63	No	T4aN1a
3	M	44	52	No	T3N1a
4	M	54	64	No	T2N0
5	M	64	66	No	T1N1b
6	F	56	64	No	T4aN1a
7	M	50	53	Yes	T1N1b
8	F	51	54	No	T2N1b
9	F	39	43	No	T2N1a
10	F	42	42	No	T3N1b
11	F	78	79	No	T2N0
12	F	65	66	No	T1bN1b
13	F	30	38	No	T3N1b

pTNM pathologic tumour, node, metastasis, *M* male, *F* female

Biochemical and nuclear imaging results are summed up in Table 2. Median calcitonin levels were of 828 (IQR 12,434) pg/mL, with 11 patients (84.6%) showing calcitonin levels above the 150 pg/mL threshold. Three patients (23.1%) presented with CTDT lower than 6 months (6M). CEA levels were increased in all but two individuals (median 19.31; IQR 71.63 ng/mL). Three patients (23.1%) presented with CEADT lower than 24 months (24M). There was no correlation between calcitonin and CEA levels ($r = 0.19$; $p = 0.53$). We found a non-significant trend to a positive association between the doubling time of both tumoral markers ($r = 0.39$; $p = 0.06$).

Patient-based analysis

As depicted in Table 2, at least one focus of abnormal uptake was seen on ^{68}Ga-DOTANOC PET/CT in nine patients (69.2% sensitivity; 95% CI 40.2–98.3%) – 1 of them with locoregional disease (11.1%) and eight with distant disease (89.1%). Seven patients exhibited at least one hypermetabolic focus in ^{18}F-FDG PET/CT (53.9% sensitivity; 95% CI 22.5–85.2%). There wasn't a statistically significant difference between the sensitivity of both imaging modalities ($p = 0.50$).

Two individuals presented a positive ^{68}Ga-DOTANOC PET/CT with negative ^{18}F-FDG PET/CT profile: patients 5 and 7. These two patients were the ones with the lowest

Table 2 Biochemical and patient-based analysis of nuclear medicine imaging results of the enroled patients

Patient	Calcitonin levels (pg/mL)	CEA levels (ng/mL)	CTDT (months)	CEADT (months)	Time between PETs (months)	Anatomic site	Number of lesions in ^{68}Ga-DOTANOC PET/CT	Number of lesions in ^{18}F-FDG PET/CT
1	25,058	7.47	6.50	17.5	1.67	Liver	3	3
						Bone	3	2
2	2427	12.0	15.5	38.6	0.10	Thyroid bed	3	1
						Neck and mediastinum nodes	4	2
3	231,696	2962	6.34	43.8	0.63	Neck and mediastinum nodes	>10	>10
						Lung	>10	>10
4	248	128	7.68	7.85	3.13	Thyroid bed	1	1
						Mediastinum nodes	3	4
						Lung	0	>10
						Bones	0	2
5	10,451	1.81	0.76	2680	5.67	Neck nodes	2	0
6	47.2	19.3	4.50	18.7	5.90	Lung	1	1
7	783	11.8	4.41	33.6	3.87	Mediastinum nodes	1	0
8	828	20.7	7.87	−128	5.47	Negative	0	0
9	2827	28.1	−29.5	389	0.03	Neck nodes	1	1
						Liver	3	2
10	509	30.8	−4.26	141	0.30	Negative	0	0
11	20.4	8.0	56.3	58.0	3.07	Negative	0	0
12	476	3.70	18.8	−9.14	0.27	Negative	0	0
13	15,140	391	67.1	54.6	0.90	Neck and mediastinum nodes	>10	3
						Liver	1	2
						Bone	1	0

CEA carcinoembryonic antigen, *CTDT* calcitonin doubling time, *CEADT* carcinoembryonic antigen doubling time, *PET* positron emission tomography, *CT* computed tomography

CTDT (0.76 and 4.41 months, respectively) among the analysed cohort, and both presented CEADT > 24 months. Patient 5 showed an abnormal ^{68}Ga-DOTANOC neck uptake focus. However, this patient had had a recent diagnosis of an aggressive glioblastoma multiforme, a neoplasia with a worse prognosis than MTC, that precluded neck node dissection or PRRNT therapy. In what concerns patient 7, ^{68}Ga-DOTANOC PET/CT identified a mediastinal lesion that was not noticed in ^{18}F-FDG PET/CT. The patient underwent surgical excision that confirmed a MTC metastasis and, 3 years later, there was no evidence of structural disease on ^{68}Ga-DOTANOC PET/CT (Fig. 1). It is also noteworthy that in the case of patient 13, the differential uptake pattern between ^{68}Ga-DOTANOC PET/CT and ^{18}F-FDG PET/CT (stronger expression of SSRT 2, 3 and 5 when compared to ^{18}F-FDG hypermetabolism) allowed the patient to recently perform PRRNT therapy (^{177}Lu-DOTATATE with a total activity of 22,200 MBq; divided in three cycles) (Fig. 2). The post-therapeutic scintigraphies after the second and third cycles revealed preliminary good results, showing no focus of ^{177}Lu uptake.

None of the patients had a positive ^{18}F-FDG PET/CT and negative ^{68}Ga-DOTANOC PET/CT. All patients with both negative studies presented with CTDT > 6 months and CEADT > 24 months.

Lesion-based analysis

A total of 71 abnormal uptake focus were identified in both nuclear imaging studies (Tables 2 and 3). ^{68}Ga-DOTANOC PET/CT identified 57 lesions (80.3%) and ^{18}F-FDG PET/CT 54 lesions (76.1%). There was no significant difference between both studies in the number of identified lesions per patient (4.38 ± 5.9 vs. 4.15 ± 6.67; $p = 0.86$).

Comparisons between the two studies revealed that, among patients with positive scans, only one of them (patient 6) had a concordant anatomic pattern of recurrent disease with both tracers. The ^{68}Ga-DOTANOC PET/CT scan identified more lesions than ^{18}F-FDG PET/CT scan in seven patients. Only in one patient (patient 4) ^{18}F-FDG PET/CT detected more abnormal uptake areas than ^{68}Ga-DOTANOC PET/CT, where it identified lung and bone lesions that were missed by ^{68}Ga-DOTANOC PET/CT. This individual was the one with the lowest calcitonin/CEA ratio among the group (1.94) and the one with the lowest CEADT (7.85 months).

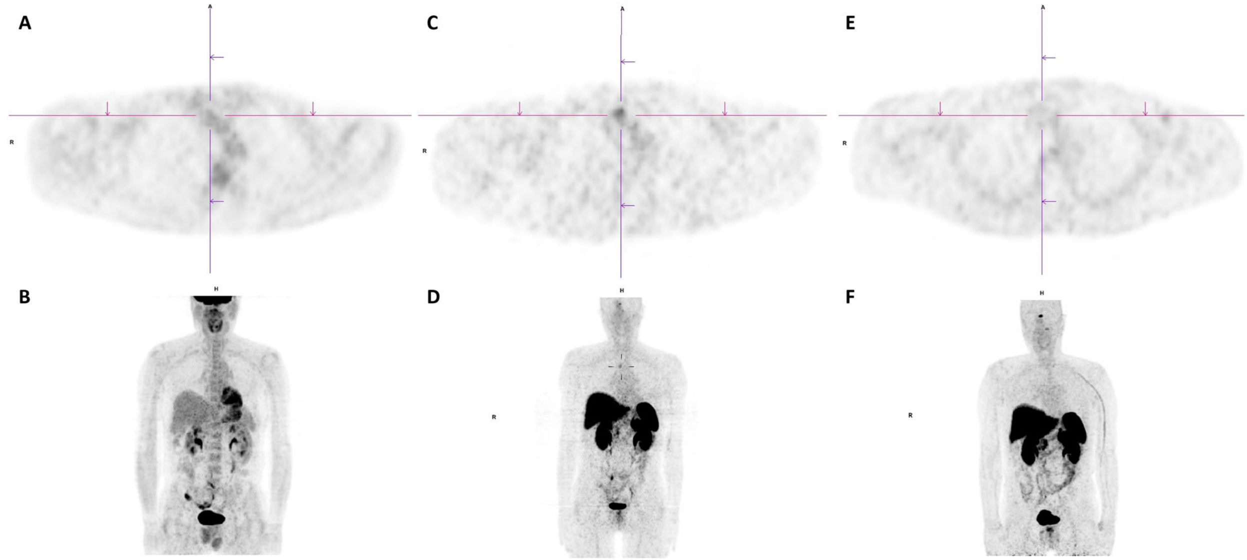

Fig. 1 Patient 7. Cross-sectional and maximum intensity projections (MIP) ^{18}F-FDG PET/CT **a** and **b** and ^{68}Ga-DOTANOC PET/CT **c** and **d** images showing a discordant lesion (^{68}Ga-positivity in a mediastinal lymph node that shows no ^{18}F-FDG avidity). ^{68}Ga-DOTANOC PET/CT imaging 3 years after mediastinal surgery **e** and **f** shows no evidence of residual structural disease (PET window 0–5 SUV). PET positron emission tomography, CT computed tomography

According to the involved site, there were 4 thyroid bed lesions, 32 lymph node lesions, 21 lung lesions, 8 liver lesions and 6 bone lesions. Despite ^{68}Ga-DOTANOC tracer has identified more lymph node positive focus than ^{18}F-FDG (31 vs. 20), and the opposite pattern has been observed in lung lesions (11 vs. 21), none of these associations was significant ($p = 0.17$ and $p = 0.42$, respectively). The number of lesions found in ^{68}Ga-DOTANOC PET/CT were significantly correlated with CT levels ($r = 0.73$; $p < 0.01$) but not with CEA levels ($r = 0.42$; $p = 0.15$). The number of hypermetabolic focus in ^{18}F-FDG PET/CT were correlated with CEA levels ($r = 0.60$; $p < 0.05$) but not with CT levels ($r = 0.48$; $p = 0.09$).

Discussion

In this study we report two main findings. First, ^{68}Ga-DOTANOC PET/CT identified MTC metastases in two additional patients when compared to ^{18}F-FDG PET/CT (sensitivity of 69.2% vs. 53.9%, respectively). ^{68}Ga-DOTANOC PET/CT also detected a higher number of abnormal uptake focus than ^{18}F-FDG PET/CT in seven patients, with only one patient showing the opposite pattern. Both differences lacked statistical significance, but they had impact on patients' therapeutic management. Secondly, we have found a correlation between MTC tumoral markers and functional nuclear medicine imaging. MTC metastases seem to be better detected by ^{68}Ga-DOTANOC PET/CT in those patients with higher calcitonin levels comparatively to patients with higher CEA levels. In contrast, ^{18}F-FDG PET/CT positivity appears to be correlated with the opposite pattern.

Few studies have compared these two nuclear medicine imaging methods. None of the publications on this matter showed significant differences between their sensitivity in both per-patient and per-lesion analysis [9, 17, 18]. The low number of included patients could have limited the ability to statistically find differences, both in our study and in the aforementioned ones. It is also noteworthy that the available literature report highly different ^{68}Ga-DOTANOC PET/CT sensitivities in metastatic MTC, with results ranging from 33% to 76% [9, 17, 18]. Considering that the patients included in those studies and in ours had relatively similar median calcitonin and CEA levels, the used somatostatin analogue in image acquisition could have partially accounted for these variations. While we use NOC somatostatin analogue, other centres have also used TOC and TATE, which have different profiles of SSTR affinity [19]. In addition, the sensitivity of this method in MTC is inferior to the sensitivity usually described for other neuroendocrine tumours [20]. This is probably due to the rich but heterogeneous SSRT expression found in immunohistochemical analysis of MTC [21], also explaining the mixed results of PRRNT in this type of cancer [22, 23]. Nevertheless, performing ^{68}Ga-DOTANOC PET/CT had a significant clinical influence in the management of some of our patients: (1) one of the patients had surgical resection of the metastasis that was uniquely found in ^{68}Ga-DOTANOC PET/CT and he is without evidence of structural disease 3 years

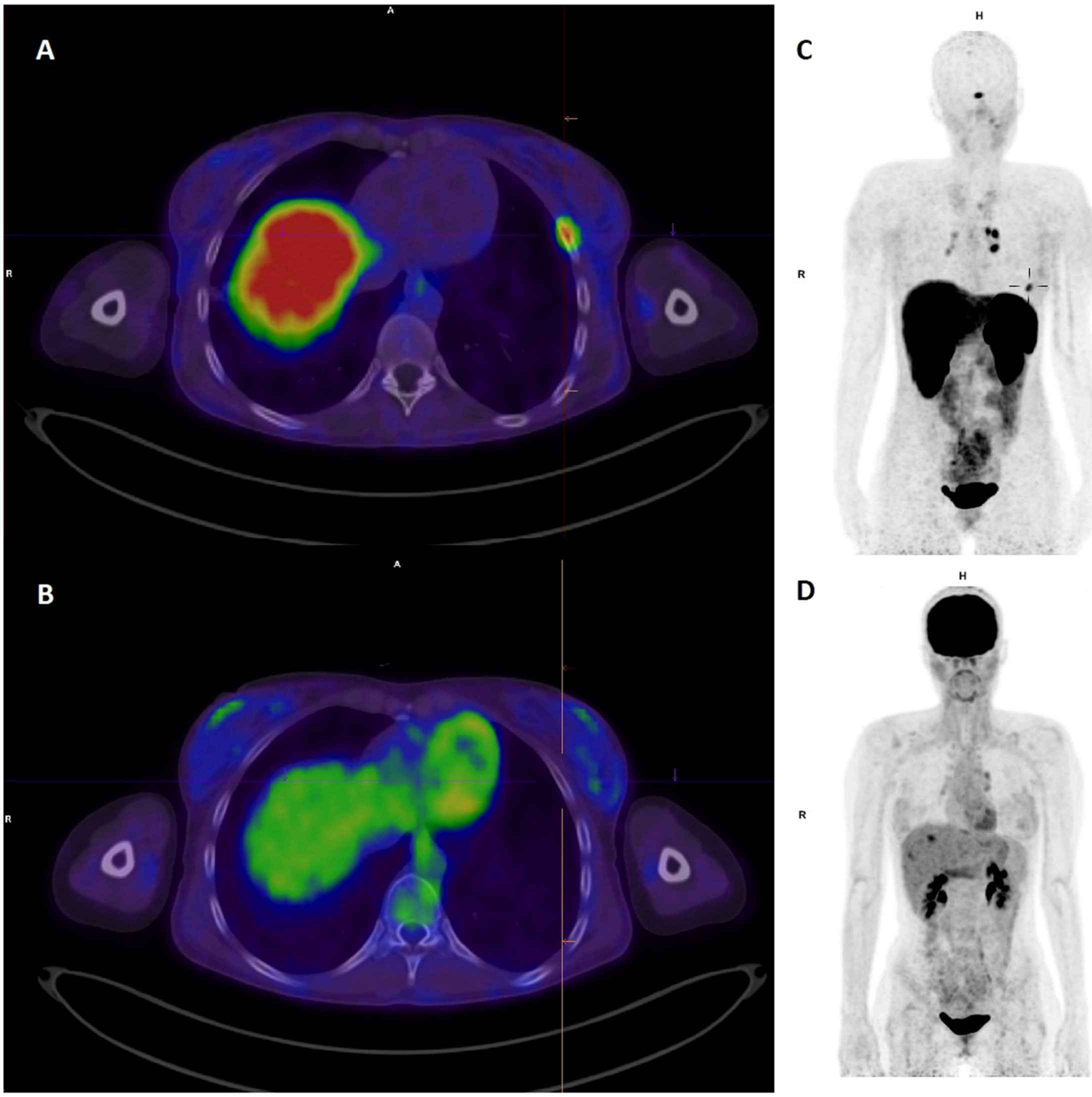

Fig. 2 Patient 13. Cross-sectional images showing a bone metastasis on ^{68}Ga-DOTANOC PET/CT **a** that that was not noticed in ^{18}F-FDG PET/CT **b** (PET window 0–5 SUV). ^{68}Ga-DOTANOC PET/CT **c** and ^{18}F-FDG PET/CT **d** maximum intensity projections (MIP) show a greater number and intensity of ^{68}Ga-positive lesions when compared to ^{18}F-FDG hypermetabolism. PET positron emission tomography, CT computed tomography

Table 3 PET/CT lesion-based analysis by anatomic site

Anatomic site	^{68}Ga-DOTANOC PET/CT	^{18}F-FDG PET/CT
Thyroid bed	4/4 (100%)	2/4 (50%)
Lymph nodes	31/32 (96.9%)	20/32 (62.5%)
Lung	11/21 (52.4%)	21/21 (100%)
Liver	7/8 (87.5%)	7/8 (87.5%)
Bone	4/6 (66.7%)	4/6 (66.7%)
Overall	57/71 (80.3%)	54/71 (76.1%)

PET positron emission tomography, *CT* computed tomography

later; (2) the relative higher ^{68}Ga uptake when compared to ^{18}F-FDG allowed a patient to perform PRNNT with preliminary good results; (3) in the case of the other patient with a ^{68}Ga-positive/^{18}F-FDG-negative pattern, surgery was not pursued because of the existence of a more aggressive cancer.

Several results in our study point to a parallelism between calcitonin levels and ^{68}Ga-DOTANOC PET/CT positivity and between CEA levels and ^{18}F-FDG hypermetabolism: (1) the two individuals with exclusively ^{68}Ga-DOTANOC PET/CT positivity where the ones with the lowest CTDT, and as so with a steeper rise in calcitonin production, and with CEADT superior to 24 months; (2) the three patients with the highest CEA secretion per unit of time (CEADT < 24M) were ^{18}F-FDG-positive; (3) the only patient of our cohort in whom ^{18}F-FDG PET/CT identified more lesions than ^{68}Ga-DOTANOC PET/CT was the one with the lowest CT/CEA ratio and with a lowest CEADT, suggesting a tumour with a higher CEA burden and dedifferentiation; (4) the number of lesions in ^{68}Ga-DOTANOC PET/CT correlated with calcitonin levels but not with CEA, and the opposite pattern was verified for ^{18}F-FDG PET/CT. Publications on other neuroendocrine tumours have associated ^{68}Ga-negative/^{18}F-FDG-positive PET/CT pattern with less differentiated tumours and a worse prognosis [24]. Similarly, studies have linked MTC with lower CEADT with poorer outcomes when compared with those with lower CTDT [25]. Some researchers have explored the association between ^{18}F-FDG hypermetabolism and CEA levels but with mixed results [26, 27]. However, to the best of our knowledge, this is the first study to come up with this laboratorial-functional imaging correlation in MTC as no other previous study has explored the relationship between ^{68}Ga-DOTANOC PET/CT and calcitonin/CEA levels or their doubling times. Considering our findings, we may hypothesise two profiles of metastatic MTC: a high calcitonin burden, well-differentiated, ^{68}Ga-positive disease with a better prognosis; and a more CEA preponderant, ^{18}F-FDG-positive disease, with a worse prognosis, characteristic of more dedifferentiated tumours. However, it is likely that many individuals will exhibit intermediate patterns given the heterogeneity of this type of cancer, as previously discussed.

The anatomic pattern of metastization in our patients was coincident with that described in the literature—most metastases occurred in lymph nodes, followed by the liver, lungs and bones [28]. Other studies have reported that ^{18}F-FDG PET/CT had greater sensitivity to identify liver metastases when compared to ^{68}Ga-DOTANOC PET/CT in lesion-based analysis [9, 10]. However, our results did not reveal significant differences between the two traces when abnormal uptake foci were stratified by anatomic site.

The retrospective cross-sectional design of this study precludes causal inference and that can be stated as a potential limitation. Moreover, the small sample of our cohort could have limited the power to find some statistically significant differences. Although, other publications on this topic have also included a similar number of patients owing to the rarity of MTC [9, 10, 29]. A prospective multicentre study design would benefit the validation of our results. Additionally, including ^{18}F-DOPA PET/CT imaging in the evaluation of these patients would also be of value, as it is a first line functional imaging to trace MTC lesions [8]. The superiority of this method when compared to ^{18}F-FDG PET/CT has been well-established throughout several publications [9, 26, 30]. However, only one study has compared ^{18}F-DOPA PET/CT performance with ^{68}Ga-somatostatin analogue PET/CT so far, reporting a higher sensitivity of the former (72.2% vs. 33.3%) [9]. However, Treglia et al. acknowledged that the use of two different somatostatin analogues (NOC and TOC) could have led to an underestimation of the ^{68}Ga-somatostatin analogue PET/CT performance. A meta-analysis on ^{68}Ga-somatostatin analogue PET/CT in recurrent MTC described higher detection rates (63.5%) that were further increased (83%) when only patients with calcitonin levels > 500 pg/mL were accounted. Combining these findings, we consider that prioritising ^{18}F-DOPA PET/CT over ^{68}Ga-DOTANOC PET/CT is not straightforward and this topic should be further investigated.

Conclusions

The authors believe that PET/CT studies have an important role in MTC, considering its good results in lesion detection. This publication highlights that tumoral biomarkers could help clinicians to choose the first PET/CT exam in the setting of a patient with biochemical evidence of metastatic MTC. In individuals with a higher calcitonin production ^{68}Ga-somatostatin analogue PET/CT could be a valuable imaging method, while ^{18}F-FDG PET/CT could be more tailored for those tumours with a relatively greater CEA secretion. Nevertheless, both exams should be seen as complementary techniques in selecting patients for PRRNT considering that they assess different aspects of the disease, as underlined by our results. Future larger multicentre studies designed to evaluate this association and its implications on prognostic outcomes are needed.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients gave their consent to be enroled in this study.

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