The role of ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT in the follow-up of patients with medullary thyroid cancer

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Keywords: Medullary thyroid cancer - ^{68}Ga-DOTATATE - ^{18}F-FDG-PET/CT - Calcitonin

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Received:
8 December 2020
Accepted revised:
21 December 2020

Abstract

Objective: Medullary thyroid cancer (MTC) is an aggressive form of thyroid malignancy with local metastasis in 30%-50% of the cases and distant metastasis predominantly to lung, liver and skeleton in 13%-15% of patients. Identification of the lesion using imaging modalities is of crucial importance for disease management in the recurrent or metastatic MTC. In this study, we aimed to determine the efficacy of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and gallium-68 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid tyrosine-3-octreotate (^{68}Ga-DOTATATE) PET/CT imaging in patients with MTC and to evaluate the relationship between imaging findings and serum tumor markers. **Materials and Methods:** The records of MTC patients, who were treated and followed-up in our department between the years 2005 and 2018 were retrospectively analyzed. Seventy-three patients with MTC, who underwent either ^{68}Ga-DOTATATE PET/CT (n=61) and/or ^{18}F-FDG PET/CT (n=59) together with serum calcitonin (Ctn) and/or carcinoembryogenic antigen (CEA) measurement within 6 months period were included in the study. Gallium-68-DOTATATE PET/CT and ^{18}F-FDG PET/CT scans performed within 6 months on the same patient (n=38) were analyzed separately for comparison of the efficacy of both modalities. **Results:** The overall sensitivity of ^{18}F-FDG PET/CT and ^{68}Ga-DOTATATE PET/CT were 72.4% and 88.1%, respectively in detecting recurrent or metastatic disease. In the group of patients, who had both ^{18}F-FDG PET/CT and ^{68}Ga-DOTATATE PET/CT within 6 months interval (median: 1.14 months; range: 0.03-5.7 months), no significant difference was found in the overall sensitivity of both imaging modalities, however ^{68}Ga-DOTATATE PET/CT was found to be more sensitive in detection of bone lesions compared to ^{18}F-FDG PET/CT (P=0.005). **Conclusion:** Both ^{18}F-FDG PET/CT and ^{68}Ga-DOTATATE PET/CT are efficient imaging modalities in detection of recurrent or metastatic disease in MTC patients. Gallium-68-DOTATATE PET/CT could be more beneficial in detection of bone metastases with respect to ^{18}F-FDG PET/CT.

Hell J Nucl Med 2020; 23(3): 321-329 *Published online: 28 December 2020*

Introduction

Medullary thyroid cancer (MTC) originates from parafollicular C-cells of neural crest in thyroid parenchyma and makes up 3%-4% of all thyroid malignancies [1, 2]. It is generally more aggressive than differentiated thyroid cancers (DTC); regional metastases or distant organ metastases mainly to lung, liver and bones are observed in approximately 30%-50% and 13%-15% patients, respectively, at the time of diagnosis [3-5]. Serum calcitonin (Ctn) and carcinoembryonic antigen (CEA), which are secreted by parafollicular C-cells, are the most important tumor markers for MTC. Survival rates decrease significantly in the presence of distant metastasis; 10-year survival rates for stage I, II, III and IV disease were given as 100%, 92.6%, 70.9% and 20.7%, respectively [6]. Early diagnosis and appro-priate treatment increase survival rates of MTC [4, 6]. Primary treatment is surgery, which is also the most effective option for regional disease control and achievement of symptom-free survival if the patient is eligible for surgery [7]. Normalization of Ctn levels and long-term disease-free survival can be achieved in one third of the cases after surgery [8, 9]. Systemic therapy is spared for inoperable patients with progressive or symptomatic metastatic disease and tyrosine kinase inhibitors such as vandetanib is the most widely used systemic treatment option in such patients [10].

Detection of the lesion using imaging modalities is very important for disease management in the recurrent or metastatic MTC. Even though elevation of serum Ctn and CEA levels are indicators of recurrence, effective treatment strategy cannot be planned unless the recurrent or metastatic lesions are localized. Conventional imaging methods such as ultrasonography (US), magnetic resonance imaging (MRI) and computed tomography

(CT) are common tools for investigation of recurrent disease. However, these anatomic imaging modalities have limited sensitivity for detection of recurrent of metastatic foci [11-15]. Small-sized lesions and presence of post-operative scar tissue can limit the detection of recurrent lesions using anatomic imaging modalities [14, 15]. Lymph node detection rates vary between 28%-78% for US, 37%-70% for CT and 44%-74% for MRI [11-14]. In this respect, functional or metabolic imaging with PET/CT has gained importance in determination of obscure recurrent and metastatic foci. Fluorine-18-fluorodeoxyglucose (^{18}F-FDG), which demonstrates increased glucose utilization in neoplastic processes and gallium-68 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid tyrosine-3-octreotate (^{68}Ga-DOTATATE), which targets somatostatin receptors (SSTR) on neuroendocrine tumor cells are the most widespread used PET radiopharmaceuticals for the investigation of MTC recurrences and metastasis. Fluorine-18-fluoroDOPA (^{18}F-FDOPA) targeting upregulated amino acid decarboxylase enzyme (AADC) activity in neural crest originated tumors is another PET radiotracer used in the detection of recurrent or metastatic MTC lesions [16]. However, commercial product of FDOPA is not available in many countries and in-house production facility is limited.

In this study, we aimed to evaluate the contribution of ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT for the management of MTC patients during follow-up and to determine the relation of imaging findings with serum Ctn and CEA levels.

Materials and Methods

This retrospective study was approved by the Institutional Clinical Research Ethics Committee (19/06/18-10885).

Study Population

Seventy-three patients with a diagnosis of MTC and a history of thyroidectomy operation (with or without lymph node dissection), who had either ^{68}Ga-DOTATATE or ^{18}F-FDG PET/CT imaging done in our department together with serum Ctn and/or CEA measurement within 6 months between years 2005-2018 were included in this retrospective analysis. Inclusion and exclusion criteria are given in Table 1.

Fifteen patients had also concomitant DTC at the time of diagnosis, but no recurrence or metastasis of DTC was detected during the follow-up period. By using the details available in post-operative histopathological reports, the patients were initially staged according to TNM staging system as suggested on American Joint Committee on Cancer (AJCC) Version-8 based guide [17]. Patient characteristics were summarized in Table 2.

PET/CT imaging

Fluorine-18-FDG PET imaging was performed approximately 60 minutes after intravenous injection of ^{18}F-FDG (mean activity: 417.5±108.4MBq). The patients were required to fast for at least 4 hours before ^{18}F-FDG injection and blood glucose level of 180mg/dL was confirmed via strip test prior ^{18}F-FDG PET/CT scan.

Gallium-68 DOTATATE was synthesized in our radiopharmaceutical laboratory using a commercially available germanium-68 (^{68}Ge/^{68}Ga) generator (Eckert & Ziegler, Berlin, Germany) and a semi-automatic radiosynthesis device (Eckert & Ziegler Moduler Lab, Berlin, Germany) in compliance with national regulations and good radiopharmaceutical practices stated in European Association of Nuclear Medicine (EANM) guidelines as described by Mueller et al. (2012) previously [18]. The precursor peptide molecules and other consumables required for labeling procedure were obtained from the ABX company (ABX, Radeberg, Germany). Gallium-68 DOTATATE PET/CT imaging was done approximately 60 minutes following intravenous injection of the tracer (mean activity: 202.4± 121MBq).

Both sets of PET/CT imaging were acquired from vertex to mid-thigh in craniocaudal direction lasting for 2-3 minutes per bed position using either Siemens Biograph 6 (Siemens; Knoxville, Tennessee, USA) or GE Discovery 710 (GE Healthcare, Milwaukee, USA) PET/CT devices. Computed tomography parts of the study were done with low-dose tube current (120-130kVp, 48-76mAs) and essentially used for attenuation correction and anatomic localization of PET positive lesions. No intravenous contrast was used for CT scans.

Table 1. *Inclusion and exclusion criteria.*

Inclusion criteria

- Medullary thyroid cancer patients with total thyroidectomy operation
- Availability of either ^{18}F-FDG PET/CT or ^{68}Ga-DOTATATE PET/CT together with serum Ctn and/or CEA measurement within 6 months interval time
- Availability of either histopathological confirmation or clinical follow-up for at least two years including subsequent other imaging studies and serum calcitonin and carcinoembryonic antigen measurements

Exclusion Criteria

- Pediatric patients
- Presence of a secondary malignancy other than thyroid cancer

Image analysis

All PET images were evaluated using a dedicated workstation (Advantage Workstation, Version 4.6 and 4.7, GE Healthcare, Milwaukee, USA). Any increased focal uptake higher than mediastinal blood pool activity and other than normal physiological distribution of the tracer was accepted as positive lesion unless there was clear benign appearance on CT scans. For all PET positive metastatic lesions, both location (lymph nodes, bone, lung, liver) and their maximum standardized uptake value (SUVmax) were recorded. Further comparative patient and lesion-based analysis was performed in 38 of the 73 patients who had both ^{18}F-FDG and ^{68}Ga-DOTATATE PET done within 6 months interval (median=1.14 months, range=0.03-5.73 months). Among those 38 patients, 29 patients had time interval of less than 3 months and

only 9 patients had time interval of between 3-6 months. Those 9 patients did not have any significant difference among serum calcitonin levels between the two PET images, therefore they were accepted as in stable disease and included in the study.

Table 2. *Patient characteristics.*

Gender (Female; Male)	36 (49%): 37 (51%)
Mean age±SD (range)	47.7±13.8 years (26-85 years)
Median time from diagnosis to ^{18}F-FDG scan (range)	15 months (1-247 months)
Median time from diagnosis to ^{68}Ga-DOTATATE scan (range)	26 months (1-216 months)
Initial histopathological characteristics (available in 61 patients)	
Tumor size	3±1.6cm
Unilobar location	48 patients (78.7%)
Bilobar location	13 patients (21.3%)
Extrathyroidal invasion	33 patients (54.1%)
Positive surgical margins	21 patients (34.4%)
Lymph node metastasis	49 patients (80.3%)
Concomitant DTC	15 patients (20.5%); 11 T1a, 3 T1b, 1 T2
Initial TNM staging (according to AJCC Version-8 based guideline)	
Stage I	4 patients (6.6%)
Stage II	8 patients (13.1%)
Stage III	1 patient (1.6%)
Stage IV	48 patients (78.7%)
Follow-up time period (range)	79.9 months (25.9 - 361 months)
Death rate during follow-up	11/73 (15%)

SD: Standard deviation; DTC: Differentiated thyroid cancer

Standard of reference

Among positive PET scans, histopathological confirmation was available for only 37 of them. For the remaining PET scans, clinical follow-up for at least two years including subsequent other imaging studies and serum Ctn and CEA measurements were used as confirmatory tools. Normal values for Ctn and CEA were less than 10ng/L and less than 5 ng/ml, respectively.

Statistical analysis

Statistical tests were performed using IBM SPSS Statistics Version 25.0 program. Mean±standard deviation (SD) was provided for quantitative values with normal distribution, while median value and range were given for those without normal distribution or with small sample size. Serum calcitonin and CEA values were compared by Mann Whitney U test and P value smaller than 0.05 was accepted as significant. Sensitivity and positive predictive values of PET studies were calculated. Subgroup sensitivity analysis was performed for patients with Ctn >150ng/L and Ctn >500ng/L, which were the cut-off levels requiring additional imaging work-up [19]. Subgroup sensitivity analysis was performed for CEA levels higher than 20ng/mL, which was an arbitrary cut-off level at which we expected higher sensitivity. Efficacy of ^{18}F-FDG PET and ^{68}Ga-DOTATATE PET was compared using McNemar test and P value smaller than 0.05 was accepted as statistically significant. Number of lesions determined by both PET studies was compared using Wilcoxon test and P value smaller than 0.05 was accepted as statistically significant.

Results

Among 73 patients included in the study, 59 had ^{18}F-FDG PET study versus 61 with ^{68}Ga-DOTATATE PET. Thirty-eight patients had both ^{18}F-FDG and ^{68}Ga-DOTATATE PET performed within 6-months interval. Among 59 patients with ^{18}F-FDG PET study, 39 (66.1%) had positive findings, which were confirmed by either histopathology (n=19) or clinical follow-up and all of them were recorded as true-positive (TP). Twenty patients had negative ^{18}F-FDG PET imaging; 15 of them had proven recurrent or metastatic disease and were recorded as false-negative (FN) ^{18}F-FDG PET. Remaining five patients had suspicious neck US findings despite normal Ctn values and were recorded as true-negative (TN), since recurrent disease could not be confirmed during at least 2 years follow-up time.

Of the patients with ^{68}Ga-DOTATATE study, 52 (85.2%) had TP results confirmed by either histopathology (n=18) or clinical follow-up. Seven out of 9 patients with negative ^{68}Ga-DOTATATE PET had recurrent disease proven by subsequent imaging and/or elevated Ctn values, hence recorded as FN. Remaining 2 patients with negative ^{68}Ga-DOTATATE PET had normal Ctn values but suspicious neck US findings, which were resolved during follow-up and accepted as TN.

On patient-based analysis, overall sensitivity of ^{18}F-FDG PET and ^{68}Ga-DOTATATE PET were 72.4%, and 88.1% respec-

tively. The sensitivity values of both PET modalities tended to increase as tumor marker levels raised (Table 3, Figure 1).

Median Ctn and CEA values for PET positive and PET negative group were given in Table 4. Both Ctn and CEA values were significantly higher in PET positive group for both tracers (P=0.005, P=0.003 and P=0.003, P=0.006, respectively).

Distribution of PET identified recurrent or metastatic foci and related SUVmax values are summarized in Table 5.

Table 3. *The sensitivity values of ^{18}F-FDG PET and ^{68}Ga-DOTATATE PET.*

	^{18}F-FDG PET	^{68}Ga-DOTATATE
Sensitivity, overall	72.4%	88.1%
Sensitivity, subgroups		
Ctn >150ng/L	75.6%	90.4%
Ctn >500ng/L	78.4%	91.5%
CEA >5ng/mL	75.7%	89.7%
CEA >20ng/mL	82.6%	95.8%

Ctn: Calcitonin; CEA: carcinoembryonic antigen

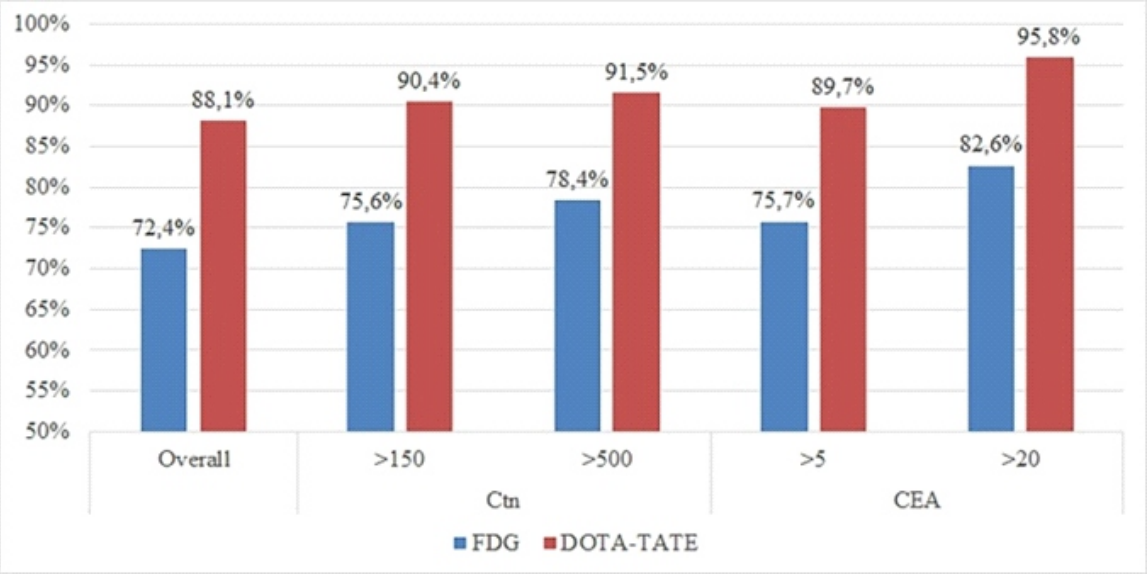

Figure 1. PET sensitivity variation for different calcitonin (Ctn) and carcinoembryonic antigen (CEA) threshold values.

Table 4. *Comparison of calcitonin and carcinoembryonic antigen (CEA) median values between PET negative and positive groups.*

	^{18}F-FDG positive	^{18}F-FDG negative	P	^{68}Ga-DOTATATE positive	^{68}Ga-DOTATATE negative	P
Calcitonin, median (range), ng/L (normal value <10)	1334.5 (50.4-29000.0)	205.5 (0.1-5422.1)	0.005	1582.2 (39.3-32700.0)	293.0 (0.1-1665.8)	0.003
CEA, median (range), ng/mL (normal value <5)	35.5 (1.7-937.3)	4.7 (0.7-552.6)	0.003	37.5 (1.8-1158.0)	5.6 (1.2-22.6)	0.006

Table 5. *Distribution of PET positive lesions and related median SUVmax values.*

Lesion sites	Lesion frequency		Median SUVmax (range)	
	^{18}F-FDG	^{68}Ga-DOTATATE	^{18}F-FDG	^{68}Ga-DOTATATE
Lymph Nodes	97.4% (n=38)	96.2% (n=50)	4.6 (2.4-18.1)	4.3 (1.4-24.7)
Central cervical	66.7% (n=25)	69.2% (n=36)		
Lateral cervical	48.7% (n=19)	50% (n=26)		
Mediastinal	39.5% (n=15)	38.5% (n=20)		
Supraclavicular	23.1% (n=9)	28.8% (n=15)		
Bone	30.8% (n=12)	38.5% (n=20)	5.8 (1.4-12.5)	9.5 (4-33.7)
Liver	5.1% (n=2)	5.8% (n=3)	7.9 (6.6-9.2)	14.5 (11.1-24.9)
Lung	7.7% (n=3)	5.8% (n=3)	1.7 (1.4-2)	4.1 (3.2-4.8)

n: Number of patients

Comparison of ^{18}F-FDG and ^{68}Ga-DOTATATE PET within the same patient group

Patient-based analysis

In the subgroup of 38 patients with both PET scans, sensitivity values of ^{18}F-FDG and ^{68}Ga-DOTATATE PET imaging were 66.7% and 77.8%, respectively and tended to rise as Ctn and CEA values increased. However, neither overall nor subgroup sensitivity values showed statistically significant difference, in spite of higher values for ^{68}Ga-DOTATATE (Table 6; Figure 2). Among 27 patients with lymph node metastases, 23 were positive with both ^{18}F-FDG and ^{68}Ga-DOTATATE PET, whereas 4 were positive only with ^{68}Ga-DOTATATE PET. Bone metastases were found in 13 patients; 10 were positive with both imaging modalities and remaining three were positive with ^{68}Ga-DOTATATE only. One patient had liver metastasis, which was ^{18}F-FDG positive and ^{68}Ga-DOTATATE negative. Two patients had ^{18}F-FDG positive lung metastases and only one of them showed ^{68}Ga-DOTATATE uptake.

Table 6. *The sensitivity values for ^{18}F-FDG PET and ^{68}Ga-DOTATATE PET on patient-based analysis in the subgroup of patients with both ^{18}F-FDG and ^{68}Ga-DOTATATE PET imaging.*

	^{18}F-FDG PET	^{68}Ga-DOTATATE	P
TP (n)	24	28	
FP (n)	0	0	
FN (n)	12	8	
TN (n)	2	2	
Sensitivity, Overall	66.7%	77.8%	0.219
Sensitivity, in subgroups			
Ctn >150ng/L	73.3%	80%	0.625
Ctn >500ng/L	82.6%	87%	1.0
CEA >5ng/mL	83.3%	87.5%	1.0
CEA >20ng/mL	86.7%	93.3%	1.0

TP: True positive; FP: False positive; FN: False negative; TN: True negative; n: Number of patients; Ctn: Calcitonin; CEA: Carcinoembryonic antigen

Figure 2. PET sensitivity variation for different calcitonin (Ctn) and carcinoembryonic antigen (CEA) threshold values in the subgroup of patients with both ^{18}F-FDG and ^{68}Ga-DOTATATE PET imaging.

Lesion-based analysis

On lesion-based analysis; total 182 lymph nodes, 169 bone lesions, 1 liver and 13 lung metastases were detected using both PET scans. ^{68}Ga-DOTATATE PET could identify 91.8% (n=167) of lymph nodes, 100% (n=169) of bone lesions and 92.3% (n=12) of lung metastases, whereas it failed to detect the ^{18}F-FDG positive liver lesion. On the other hand, ^{18}F-FDG PET could detect 72% (n=131) of lymph nodes, 40.2% (n=68) of bone lesions and 100% (n=13) of lung metastases as well as the liver metastasis. While no significant difference was found between the two imaging modalities in terms of detection of lymph node metastases (P=0.071) (Figure 3), the ability to detect bone metastasis was significantly higher for ^{68}Ga-DOTATATE PET (P=0.005, Figure 4).

Discussion

Detection of recurrent or metastatic lesions is of utmost importance for effective treatment in MTC patients, since surgery is the most effective treatment option for the patients eligible for surgery. Conventional imaging modalities like US, CT and MRI have limited sensitivity for detection of recurrent or metastatic foci. Most common nuclear medicine imaging modalities for investigation of recurrence or metastasis in MTC patients are ^{18}F-FDG and ^{18}F-FDOPA PET/CT. Literature findings report different sensitivities for ^{18}F-FDG PET imaging, with a range of 44%-80%, which increased to 86.7% for patients with Ctn ≥1000ng/mL [20-22]. A meta-analysis by Treglia et al. (2012) indicated a detection rate of 59%, which increased to 75% in Ctn values ≥1000ng/mL [23]. In our study, the overall sensitivity of ^{18}F-FDG was calculated as 72.4% and it increased to 78.4% and 82.6% in patients with Ctn values >500ng/L and CEA values >20ng/mL, respectively.

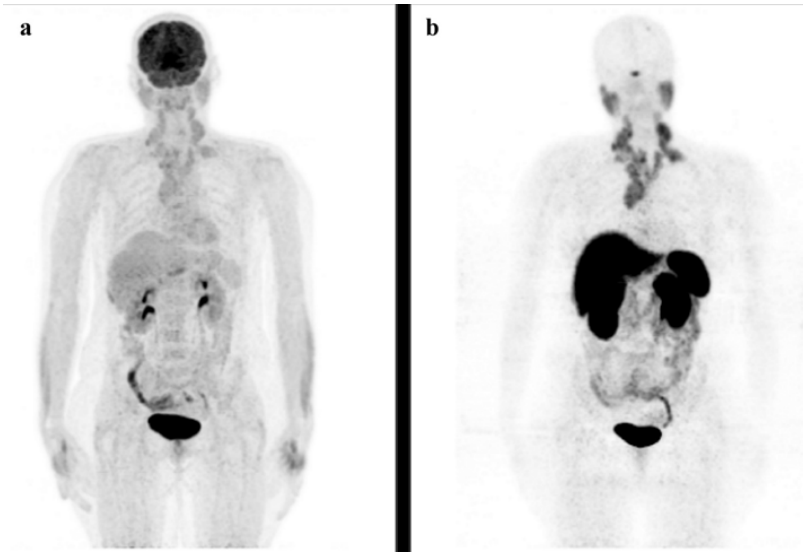

Figure 3. a-b. Fluorine-18 FDG (a) and ^{68}Ga-DOTATATE (b) PET maximum intensity projection (MIP) images of a 56-year-old female patient diagnosed for medullary thyroid carcinoma. Serum calcitonin and carcinoembryonic antigen levels were >2000ng/L and 55.14ng/mL. Both ^{18}F-FDG and ^{68}Ga-DOTATATE PET showed multiple cervical and mediastinal lymph node metastases.

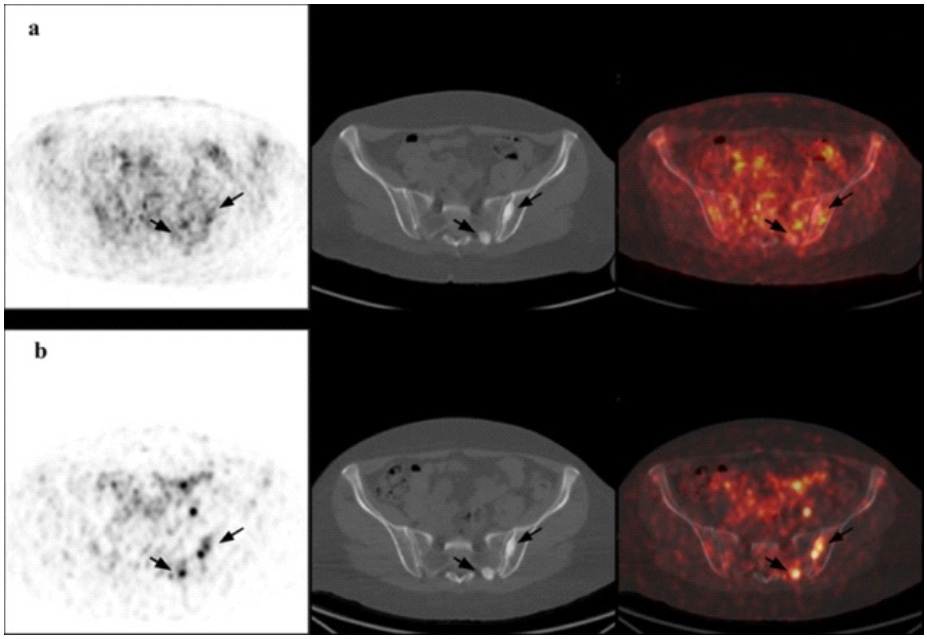

Figure 4. a-b. A 57-year-old female patient with medullary thyroid carcinoma had elevated serum calcitonin and carcinoembryonic antigen levels (3662.4ng/L and 5.6ng/mL, respectively). Axial ^{18}F-FDG PET and fused PET/CT images (a) fail to show metastases, whereas axial ^{68}Ga-DOTATATE PET and fused PET/CT (b) images showed increased uptake on left iliac bone and sacrum, which were in accordance with bone metastases (arrows).

Gallium-68 DOTATATE PET is a somatostatin receptor scintigraphy routinely used in neuroendocrine tumor imaging [24]. Studies regarding the role of ^{68}Ga-DOTATATE PET in MTC patients are limited with inadequate number of patients. According to the current literature, a wide range of sensitivity werea wide range of sensitivity was given for ^{68}Ga-DOTATATE PET in MTC patients, similar to ^{18}F-FDG PET studies [25-32]. A recent meta-analysis by Treglia et al. (2017) reported a detection rate of 63.5% (range: 25%-86.7%) for ^{68}Ga labeled somatostatin analogues, that increased to 83% in patients with Ctn values above 500ng/L [33]. Different sensitivity values are probably associated with heterogeneous structure and low number of patients in these studies. Sensitivity of ^{68}Ga-DOTATATE PET in our study was calculated as 88.1% and increased to 91.5% and 95.8% in the subgroup with Ctn value >500ng/L and CEA values >20ng/mL, respectively.

Approximately 45%, 35% and 45% of MTC organ metastases were reported to be located in bone, lung and liver, respectively [34, 35]. Fluorine-18-FDG PET was reported to detect 20% of lung or mediastinal lymph node metastases and 27% of liver metastases [35]. On the other hand, sensitivity of ^{68}Ga-DOTATATE PET for detection of lung, liver and bone metastases was reported as 63%, 9% and 100%, respectively [36]. One recent study has shown that conventional imaging outperformed ^{68}Ga-DOTATATE PET in detection of liver metastases [37]. In our study, lymph node, bone, lung and liver metastases were identified in 97.4%, 30.8%, 5.1% and 7.7% of ^{18}F-FDG PET positive images and in 96.2%, 38.5%, 5.8% and 5.8% of ^{68}Ga-DOTATATE PET positive images, respectively. In our cohort, despite the presence of elevated Ctn levels, the number of visceral organ metastasis was low in both imaging modalities, which could be related with the lower sensitivity of both imaging modalities in detection of visceral organ metastasis. Computed tomography component of PET/CT could be helpful to fill this gap for lung metastases; however, identification of small liver metastasis is still complicated with CT. In this respect, further evaluation of liver parenchyma with MRI is needed for MTC patients, who have elevated tumor markers despite negative PET or CT findings. Hybrid PET/MRI imaging also has the potential to compensate the insufficiency of PET in liver metastasis.

There are a few studies in the literature comparing ^{18}F-FDG PET and ^{68}Ga labeled somatostatin receptor PET imaging in the same cohort and all have limited number of patients. Among these studies, statistically significant difference was not found between sensitivities of these two imaging modalities, although ^{68}Ga labeled somatostatin receptor analogues showed higher sensitivity values (72.2% vs 77.8% and 63.4% vs 75.6%) [25, 28]. Fluorine-18-FDOPA PET on the other hand was reported to have higher sensitivity than both ^{68}Ga-DOTATATE and ^{18}F-FDG PET (72%, 33% and 17%, respectively) [27]. Another study reported a higher sensitivity for ^{68}Ga-DOTATATE PET compared to ^{18}F-FDG PET (68% and 44%, respectively) [29]. In our study, although we have detected a higher sensitivity for ^{68}Ga-DOTATATE PET compared to ^{18}F-FDG PET, (77.8% and 66.7%, respectively), this difference was not statistically significant, which was in accordance with the literature (Figure 2). Sensitivity rates increased to 82.6% and 86.7% for ^{18}F-FDG PET and to 87% and 93.3% for ^{68}Ga-DOTATATE PET in patients with Ctn values >500ng/L and CEA values >20ng/mL, respectively. On lesion based analysis, while no significant difference was found between the two imaging modalities in terms of detection of lymph node metastases, the ability to detect bone metastasis was significantly higher for ^{68}Ga-DOTATATE. This finding suggests that ^{68}Ga-DOTATATE PET could be a more effective imaging modality in detection of bone metastases in MTC patients.

Systemic treatment options are limited for MTC patients. Lutetium-177 (^{177}Lu) labelled somatostatin receptor analogues were proposed to be an alternative treatment option in patients with ^{68}Ga-DOTATATE positive metastases, although the number of conducted studies regarding their treatment efficacy is still limited [38]. Gallium-68 DOTATATE PET could be beneficial for both selection of patients for treatment with ^{177}Lu labelled somatostatin analogues, as well as for their therapy response assessment.

One of our main limitations is the retrospective nature of the study and the lack of histopathological confirmation for every lesion due to both technical difficulties and absence of clinical indication in a patient with multiple metastases. In this respect, both follow-up images and serum Ctn and CEA level measurements were used for confirmation. The majority of the patients had less than 3 months interval between two PET images; however, some patients had longer interval (3-6 months), but stable disease confirmed by serum biomarkers, which could be counted as a limitation of our study. Another limitation was the lack of liver MRI or thin-section thorax CT available for comparison of liver and lung lesions. Further prospective studies including PET/MRI and thin-section thorax CT could be helpful in this manner.

In conclusion, our study showed acceptable sensitivities for both ^{18}F-FDG and ^{68}Ga-DOTATATE PET. Neither overall nor subgroup sensitivity values showed statistically significant difference between two imaging modalities, in spite of the higher values for ^{68}Ga-DOTATATE PET. Although there was no statistically significant difference in overall sensitivities of both imaging modalities, ^{68}Ga-DOTATATE PET was more sensitive than ^{18}F-FDG PET in detection of bone metastasis. Both imaging modalities had low rate in detection of liver metastases, which may indicate lower sensitivity in liver parenchyma. In this respect, complementary liver MRI or hybrid PET/MRI imaging could increase their efficacy.

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