Original Article
Mol Imaging Radionucl Ther 2023;32:1-7 DOI:10.4274/mirt.galenos.2022.81904

The Role of ^{18}F-FDOPA PET/CT in Recurrent Medullary Thyroid Cancer Patients with Elevated Serum Calcitonin Levels

Serum Kalsitonin Yüksekliği Bulunan Rekürren Medüller Tiroid Kanseri Hastalarında ^{18}F-FDOPA PET/BT'nin Rolü

Mine Araz[1], Çiğdem Soydal[1], Özgür Demir[2], Mustafa Kürşat Gökcan[3], Nuriye Özlem Küçük[1]

[1]*Ankara University Faculty of Medicine, Department of Nuclear Medicine, Ankara, Turkey*
[2]*Ankara University Faculty of Medicine, Department of Endocrinology and Metabolism, Ankara, Turkey*
[3]*Ankara University Faculty of Medicine, Department of Otorhinolaryngology and Head and Neck Surgery, Ankara, Turkey*

Abstract

Objectives: To evaluate the diagnostic performance of ^{18}F-dihydroxyphenylalanine (FDOPA) positron emission tomography/computed tomography (PET/CT) in the detection of medullary thyroid carcinoma (MTC) recurrence in patients with elevated calcitonin levels.

Methods: The patients who had undergone ^{18}F-FDOPA PET/CT imaging for elevated calcitonin levels after primary surgery of MTC were included in the study. addition, if available ^{18}F-fluorodeoxyglucose (FDG) PET/CT and Gallium-68 (^{68}Ga)- DOTATATE PET/CT images of the patients were evaluated retrospectively. The sensitivity and diagnostic performance of ^{18}F-DOPA PET/CT were investigated.

Results: A total of 14 patients (9 F and 5 M; median age: 45) were included in the analysis. Three patients had MEN IIA syndrome and 1 patient had MEN IIB syndrome, 10 patients had a diagnosis of sporadic MTC. Median calcitonin levels of the patients were calculated as 757.5 (min-max: 28.5-7911) pg/mL. Nine patients and 5 patients had undergone ultrasound and contrast-enhanced computed tomography (ceCT) of the neck, respectively, before ^{18}F-FDOPA PET/CT imaging. ^{18}F-FDOPA PET/CT revealed pathological uptake in the thyroid bed, lymph nodes, and distant organs in three, five and two patients, respectively. Median maximum standardized uptake value for the recurrent or metastatic lesions were calculated as 6.4 (min-max: 1.9-18.4). The sensitivity of ^{18}F-FDOPA PET/CT in the detection of recurrent disease was calculated as 64%. Eight patients had ^{68}Ga-DOTATATE PET/CT and 7 of them had ^{18}F-FDG PET/CT within 3 months period before ^{18}F-FDOPA PET/CT. ^{18}F-FDOPA PET/CT revealed recurrent disease in 4 of 5 and 2 of the 5 patients who had negative ^{18}F-FDG PET/CT and negative ^{68}Ga- DOTATATE PET/CT, respectively.

Conclusion: ^{18}F-FDOPA PET/CT can detect recurrence in about two- thirds of patients with elevated calcitonin levels after primary surgery for MTC. Due to variable differentiation degree, different receptor status, and clinical behavior of MTC, all three radiopharmaceuticals can be beneficial and are complementary to each other in patient management.

Keywords: Medullary thyroid cancer, PET/CT, ^{18}F-FDOPA, calcitonin

Öz

Amaç: Serum kalsitonin yüksekliği bulunan medüller tiroid kanseri (MTK) tanılı hastalarda rekürrensin saptanmasında ^{18}F-dihidroksifenilalanin (FDOPA) pozitron emisyon tomografisi/bilgisayarlı tomografinin (PET/BT) performansının değerlendirilmesidir.

Yöntem: Primer MTK cerrahisi sonrasında yüksek kalsitonin düzeyi olan ve ^{18}F-FDOPA PET/BT uygulanmış olan hastalar çalışmaya dahil edildi. Ek olarak, eğer varsa ^{18}F-florodeoksiglukoz (FDG) PET/BT ve Galyum-68 (^{68}Ga)-DOTATATE PET/BT bulguları da retrospektif olarak değerlendirildi.^{18}F-FDOPA PET/BT'nin duyarlılığı ve tanısal performansı araştırıldı.

Address for Correspondence: Mine Araz MD, Ankara University Faculty of Medicine, Department of Nuclear Medicine, Ankara, Turkey
Phone: +90 532 666 73 13 **E-mail:** minesoylu@yahoo.com ORCID ID: orcid.org/0000-0001-6467-618X
Received: 11.02.2022 **Accepted:** 17.07.2022

Bulgular: Toplam 14 hasta (9 K, 5 E, medyan yaş: 45) analize dahil edildi. Üç hastada MEN IIA, 1 hastada MEN IB sendromu, 10 hastada sporadik MTK mevcuttu. Hastaların medyan kalsitonin seviyeleri 757,5 (min-maks: 28.5-7911) pg/mL bulundu. ^{18}F-FDOPA PET/BT görüntülemesinden önce 9 hastaya boyun ultrasonu, 5 hastaya kontrastlı boyun BT uygulanmıştı. ^{18}F-FDOPA PET/BT'de 3 hastada tiroid yatağında nüks, 5 hastada lenf nodu metastazı ve 2 hastada uzak metastaz saptandı. Rekürren veya metastatik lezyonlarda medyan maksimum standartlaştırılmış alım değeri: 6,4 (min-maks: 1,9-18,4) olarak hesaplandı. Rekürren hastalığın saptanmasında ^{18}F-FDOPA PET/BT'nin duyarlılığı %64 bulundu. ^{18}F-FDOPA PET/BT'den önceki 3 ay içerisinde 8 hastanın ^{68}Ga-DOTATATE, 7 hastanın ^{18}F-FDG PET/BT görüntülemeleri mevcuttu. ^{18}F-FDOPA PET/BT, negatif ^{18}F-FDG PET/BT'si olan 5 hastanın 4'ünde ve negatif ^{68}Ga-DOTATATE PET/BT'si olan 5 hastanın 2'sinde rekürren hastalığı gösterdi.

Sonuç: ^{18}F-FDOPA PET/BT, MTK için primer cerrahi sonrası yüksek kalsitonin düzeyi bulunan hastaların yaklaşık 2/3'ünde rekürrens saptayabilir. Tiroid medüller karsinomunun değişken diferansiyasyon derecesi, farklı reseptör durumu ve klinik davranışına bağlı olarak, her üç radyofarmasötik de hasta yönetiminde faydalı olabilir ve birbirine tamamlayıcıdır.

Anahtar kelimeler: Medüller tiroid kanseri, PET/BT, ^{18}F-FDOPA, kalsitonin

Introduction

Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor of the thyroid gland, originating from parafollicular C-cells with a frequency of 5% among all thyroid cancers. Sporadic (75%) and familial (25%) forms have been defined (1). The only curative therapy for medullary thyroid cancer is total resection of the primary tumor and metastatic lesions, and the prognosis is strongly related to the performance of surgery (2). However, despite all aggressive and effective surgeries performed, persistent or recurrent disease is commonly seen during medullary thyroid cancer. Serum calcitonin and carcinoembryonic antigen (CEA) are the tumor markers that are used in the follow-up. CEA has also been reported to be as a marker of dedifferentiation (1,3).

Biochemical recurrence necessitates accurate detection of the recurrent or the metastatic focus. In patients with increased serum calcitonin and/or CEA levels in the follow-up, a thorough examination and imaging of the whole body is crucial because early detection of recurrent disease enables clinicians and surgeons to perform effective surgeries, local or systemic therapies of the limited disease. With ultrasonography of the neck, computed tomography (CT) of the thorax, abdomen, and pelvis are usually performed for the detection of recurrence. When the levels of serum calcitonin exceeded 150 pg/mL, radionuclide whole-body imaging methods are also indicated because distant metastasis is likely (1,3,4).

Positron emission tomography (PET)/CT with ^{18}F-fluorodeoxyglucose (FDG) is the most common radionuclide imaging tool in oncology. However, it has been reported that the performance of ^{18}F-FDG PET/CT is highly related to serum calcitonin levels and is recommended for cases with serum calcitonin >500-1000 (5). Alternative tracers using different uptake pathways have been tested. Somatostatin receptor imaging with (Gallium-68) ^{68}Ga labeled somatostatin analogs (DOTATATE, DOTATOC or DOTANOC) and ^{18}F-dihydroxyphenylalanine (FDOPA) have been proposed for restaging in case of biochemical recurrence. Being a cyclotrone-produced radiopharmaceutical, which can be highly expensive, ^{18}F-FDOPA is not easily maintained throughout the world and the literature is still a lack of data about the role of ^{18}F-FDOPA PET/CT in medullary thyroid cancer, a relatively rare tumor type of thyroid.

In this study, we evaluated the role of ^{18}F-FDOPA PET/CT in the detection of recurrence in medullary thyroid cancer patients with elevated serum calcitonin levels.

Materials and Methods

Patients

This retrospective study was approved by the Ankara University Review Board (approval no: İ7-522-21, date: 06.09.2021). Medullary thyroid cancer patients who were referred to the nuclear medicine department for ^{18}F-FDOPA PET/CT between January 2018 and January 2021 were included in the study. Inclusion criteria were i) >18 years old male or females with histopathologically confirmed medullary thyroid cancer diagnosis after thyroidectomy, ii) elevated levels of serum calcitonin in the follow-up after surgery for primary tumor, iii) clinical follow-up results of at least 2 years for confirmation of recurrence. Exclusion criteria were, i) age <18 years, ii) history of secondary malignancy, iii) lack of clinical follow-up.

^{18}F-FDOPA PET/CT Protocol and Image Interpretation

Premedication with carbidopa was not performed. Following a minimum of 4 h fasting, 2 to 4 MBq/kg of ^{18}F-FDOPA was intravenously administered by slow injection. Whole-body PET/CT images from the vertex to the upper thigh were obtained 60 min after radiopharmaceutical injection by using a hybrid PET/CT scanner (GE Discovery 710, General Electric Company, USA). PET images were acquired for 2 min per bed position. PET images were reconstructed with non-contrast low-dose CT images. CT images were obtained with a standardized protocol of 140 kV, 70 mA,

tube rotation time of 0.5 s per rotation, a pitch of 6 and a slice thickness of 5 mm. Patients were allowed to breathe normally during the procedure. Attenuation-corrected PET/CT fusion images were reviewed in three planes (transaxial, coronal and sagittal) on Advanced Workstation Volumeshare 5 (GE Medical Systems).

All PET/CT images were reevaluated by two nuclear medicine specialists with consensus. Any area of focal uptake higher than the adjacent background activity outside the areas of physiological distribution of the radiotracer with a corresponding nodular lesion on CT were considered as pathological. Maximum standardized uptake value (SUV_{max}) was measured for all lesions for semiquantitative analysis.

Statistical Analysis

In this retrospective analysis, with demographics, serum calcitonin levels, results of any radiological or functional imaging studies, including neck US, CT of the thorax, abdomen or pelvis, Tc-99m methylenediphosphanate whole body bone scan, ^{18}F-FDG PET/CT, or ^{68}Ga- DOTATATE PET/CT were recorded. Clinical follow-up or histopathological examination results in patients who underwent surgeries after ^{18}F-FDOPA PET/CT were used for confirmation of results. Patient-based sensitivity, specificity, and accuracy were calculated for ^{18}F-FDOPA PET/CT in the detection of disease recurrence.

Results

A total of 14 patients (9 F and 5 M; median age: 45) were included in the analysis. Three patients had MEN IIA syndrome and 1 patient MEN IIB syndrome, 10 patients had a diagnosis of sporadic MTC. Median calcitonin levels of patients were calculated as 757.5 (min-max: 28.5-7911) pg/mL. Nine patients and 5 patients had undergone ultrasound and contrast-enhanced computed tomography (ceCT) of the neck, respectively, before PET/CT imaging. Eight patients had ^{68}Ga- DOTATATE and 7 patients had ^{18}F-FDG PET/CT within 3 months period before ^{18}F-DOPA PET/CT. Results were confirmed histopathologically in 7 patients. Clinical follow-up results were used for confirmation in 7 patients. Four of these patients showed no sign of recurrence, and in 3 patients, progression was recorded on radiological examinations [CT and/or magnetic resonance imaging (MRI)] in the follow-up. Patient characteristics, details of PET/CT and follow-up results are given in Table 1.

^{18}F-FDG PET/CT Findings

^{18}F-FDG PET/CT was normal in 5 patients. In 1 patient, ^{18}F-FDG PET/CT revealed cervical metastatic lymph node, and in 1 patient ^{18}F-FDG was positive in both cervical and mediastinal lymph nodes. In these 2 patients, ^{18}F-FDOPA PET/CT was negative for lymph node metastasis and ^{68}Ga PET/CT was not available.

^{68}Ga-DOTATATE PET/CT Findings

^{68}Ga-DOTATATE was negative in 5 patients. In patients with a positive ^{68}Ga-DOTATATE PET/CT, cervical lymph nodes were detected in all 3 of them, mediastinal lymph nodes in one patient, and pathological uptake was recorded in the thyroid bed in 1 patient. In 1 patient with cervical lymph node metastasis, ^{18}F-FDOPA PET/CT was negative and ^{18}F-FDG PET/CT was not performed.

^{18}F-FDOPA PET/CT Findings

^{18}F-FDOPA PET/CT was normal in 5 patients. ^{18}F-FDOPA PET/CT revealed pathological uptake on the thyroid bed, lymph nodes and distant organs in 3, 5, and 2 patients, respectively. Median SUV_{max} for the recurrent lesions were calculated as 6.4 (min-max: 1.9-18.4). Although not statistically significant, serum calcitonin levels in ^{18}F-FDOPA PET/CT-positive patients were higher than ^{18}F-FDOPA PET/CT-negative patients (800 pg/mL min: 47, max: 7911 vs. 98.2 pg/mL, min: 28.5, max: 800, respectively, p=0.30).

^{18}F-FDOPA PET/CT detected recurrent disease in 4 of 5 and 2 of the 5 patients who had negative ^{18}F-FDG PET/CT and negative ^{68}Ga-DOTATATE PET/CT, respectively. In 5 patients with negative ^{18}F-FDG PET/CT, ^{18}F-FDOPA was positive in the thyroid bed in 2 patients, in regional lymph nodes in 2 patients, and in lung metastasis in 1 patient. In 2 patients with a negative ^{68}Ga-DOTA PET/CT scan, ^{18}F-FDOPA was positive in the thyroid bed (Figure 1). The sensitivity of ^{18}F-FDOPA PET/CT in the detection of recurrent disease was calculated as 64%.

Discussion

Medullary thyroid cancer is a relatively rare malignancy of the thyroid. Disease progression is usually slow, and overall survival rates are acceptable if an effective surgical resection at the time of diagnosis could be achieved. However, calcitonin recurrence or persistence is observed in up to 80% of the patients. Detection and accurate localization of structural diseases in patients with biochemical recurrence is important for further therapies (6). Reoperation aims to total resection of recurrent or persistent malignant tissues and to achieve undetectable calcitonin levels. Even with experienced operators and excellent surgeries, complete remission could be maintained in only 30% of patients (7). Thus, imaging studies are expected to detect insignificant-volume diseases with high accuracy for differentiating candidates of surgery/local therapies or systemic therapy (8).

Table 1. Patient characteristics, PET/CT findings and Follow-up results

Patient number	Gender	Age	^{18}F-FDOPA PET/CT		^{18}F-FDG PET/CT		^{68}Ga-DOTATATE PET/CT		CEA	Calcitonin	Syndrome	Follow-up results
			Location	SUV_{max}	Location	SUV_{max}	Location	SUV_{max}				
1	M	47	Cervical LN	3.5	(-)	NA	Cervical LN	4.4	2.48	800	Sporadic	Right central lymph node dissection revealed metastasis
2	M	36	Thyroid bed	5.8	(-)	NA	Thyroid bed, cervical LN	17.4	5.16	48.4	MEN IIA	Left central revision lymph node dissection revealed lymph node metastasis and thyroid bed recurrence
3	F	68	Bone, mediastinal LN, liver, adrenal gland	13.3	(-)	NA	(-)	NA	4079.6	800	MEN IIA	Progression on CT and MR in the follow-up
4	M	53	Normal	NA	(-)	NA	Normal	0	920	457	Sporadic	No recurrence in clinical follow-up
5	F	45	Thyroid bed	2.2	Normal	0	Normal	0	NA	1372	MEN IIA	Biopsy revealed local recurrence
6	F	54	Normal	NA	Cervical LN	5	(-)	NA	1.31	43.4	Sporadic	Cervical lymph node biopsy revealed metastasis
7	F	78	Normal	NA	(-)	NA	Normal	0	NA	28.5	Sporadic	No recurrence in clinical follow-up
8	F	45	Cervical LN	2.2	(-)	NA	(-)	NA	1.74	47	Sporadic	Left cervical lymph node dissection revealed lymph node metastasis
9	F	34	Lung	1.9	Cervical LN, mediastinal LN	3.5	(-)	NA	7.27	1800	Sporadic	Progression in lung nodule and lymph node dimensions on CT
10	M	30	Normal	NA	Normal	NA	Normal	0	7.75	800	MEN IIB	No recurrence in clinical follow-up
11	F	19	Cervical LN	2.8	Normal	NA	(-)	NA	3.48	138.1	Sporadic	Right cervical lymph node dissection revealed metastasis
12	M	71	Thyroid bed	18.4	Normal	NA	Normal	NA	7.4	715	Sporadic	Biopsy revealed local recurrence
13	F	44	Cervical lymph node, mediastinal lymph node	6.4	Normal	NA	Cervical LN, mediastinal LN	2.8	174	7911	Sporadic	Progression in cervical and mediastinal lymph node dimensions on CT
14	F	46	Normal	NA	(-)	NA	(-)	NA	2.28	98.2	Sporadic	No recurrence in clinical Follow-up

M: Male, F: Female, LN: Lymph node, PET/CT: Positron emission tomography/computed tomography, FDOPA: ^{18}F-dihydroxyphenylalanine, ^{68}Ga: Gallium-68, FDG: Fluorodeoxyglucose, SUV_{max}: Maximum standardized uptake value, CEA: Carcinoembryonic antigen, MR: Magnetic resonance

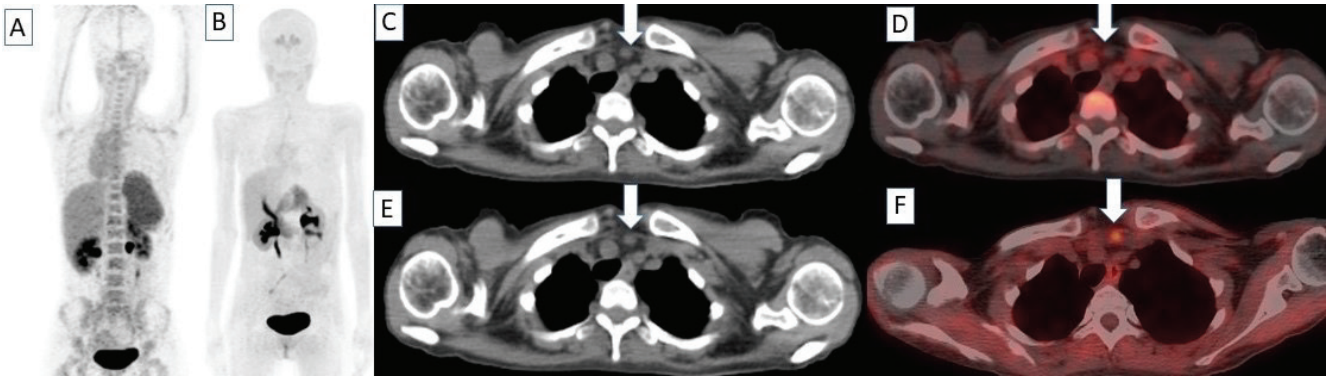

Figure 1. ^{68}Ga- DOTATATE and ^{18}F-FDOPA PET/CT images of patient number 5. Forty-five years old female diagnosed with MEN IIA syndrome (medullary thyroid carcinoma and adrenal paraganglioma) was referred with elevated serum calcitonin levels (1372 pg/mL) following total thyroidectomy. On maximum intensity projection (A, B), axial CT, and fusion images of ^{68}Ga-DOTATATE (C, D) and ^{18}F-FDOPA (E, F) PET/CT studies, focal pathological ^{18}F-FDOPA uptake was detected on a nodular lesion located in the thyroid bed (SUV_{max}: 2.2), which was ^{68}Ga-DOTATATE negative (arrows). A biopsy revealed local recurrence in the thyroid bed

^{68}Ga: Gallium-68, FDOPA: ^{18}F-dihydroxyphenylalanine, PET/CT: Positron emission tomography/computed tomography, SUV_{max}: Maximum standardized uptake value

^{18}F-FDOPA has gained importance in medullary thyroid cancer recently. In a meta-analysis, the patient-based and lesion- based detection rates of ^{18}F-FDOPA in patients with increased tumor markers were calculated as 66% and 71% respectively. The performance of ^{18}F-FDOPA PET/CT was related to serum calcitonin levels. The detection rate of ^{18}F-FDOPA was found 86% in patients with serum calcitonin levels >1000 pg/mL (9). In another study comparing the diagnostic utility of ^{18}F-FDOPA and ^{18}F-FDG PET/CT, the sensitivity of ^{18}F-FDOPA was significantly higher in patients with serum calcitonin levels >150 pg/mL compared to <150 pg/mL (90.9% vs. 28.6%; p=0.013) (10). In our study, compatible with the literature, patient-based sensitivity of ^{18}F-FDOPA PET/CT in medullary thyroid cancer patients with elevated serum calcitonin levels was found to be 64%. Serum calcitonin levels were relatively higher in ^{18}F-FDOPA PET/CT-positive patients compared to others (800 pg/mL vs. 98.2), but this difference could not be proved statistically due to the very small number of patients in the subgroups.

In comparative studies with ^{18}F-FDG PET/CT and ^{68}Ga-DOTATATE PET/CT, ^{18}F-FDOPA PET/CT was reported to be superior (11,12,13). This is why the European Association of Nuclear Medicine recommends ^{18}F-FDOPA PET/CT in the first line in medullary thyroid cancer patients with elevated serum calcitonin levels after initial treatment (14). In this study, because not all patients had ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT, no direct comparison of patient or lesion-based sensitivity or detection rates of these three modalities could be possible. In regional analysis, it is shown that ^{18}F-FDOPA was positive in lymph nodes in 2 patients and in the thyroid bed in 2 patients with negative ^{18}F-FDG PET/CT and in the thyroid bed in 2 patients with negative ^{68}Ga-DOTATATE PET/CT. However, there were 2 patients (patients 6 and 9) with ^{18}F-FDG positive but ^{18}F-FDOPA negative lymph node metastasis and 1 patient (patient 2) with ^{68}Ga-DOTATATE-positive but ^{18}F-FDOPA negative lymph nodes. According to the literature, ^{18}F-FDOPA has a higher performance in the neck compared to both ^{18}F-FDG and ^{68}Ga-DOTATATE. This is probably due to a higher ratio of tumor/background counts compared to the other two radiopharmaceuticals. Another thing is that the uptake mechanisms of these three radiopharmaceuticals are different, and ^{18}F-FDOPA is rather positive in relatively differentiated medullary thyroid cancer. While ^{18}F-FDG uptake is related to dedifferentiation, ^{68}Ga-DOTATATE uptake is a measure of somatostatin receptor expression of the tumor cells (11,12,15,16). Our results partly confirm previous reported data, as there are patients with locoregional disease either ^{18}F-FDG or ^{68}Ga-DOTATATE positive but ^{18}F-FDOPA negative.

Regarding distant metastasis, only ^{18}F-FDOPA was positive in a single patient with lung metastasis, which was also reported on ceCT (patient 9). Because ^{68}Ga-DOTATE PET/CT was not performed in this patient, a comparison between ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDOPA PET/CT could not be made but, this lung nodule was ^{18}F-FDG negative. No other patients had lung metastasis detectable by any radiological or functional imaging modality. In lung metastasis, as it is the case in our study, ceCT seems adequate enough to detect lung lesions. No significant superiority of ^{18}F-FDOPA PET/CT was reported over other imaging modalities. However, ^{18}F-FDG PET/CT is sometimes insufficient in the evaluation of lesions with low metabolic rate or small nodules (<1cm) (17).

^{18}F-FDOPA was found superior to ^{68}Ga-DOTATATE PET/CT in the detection of liver metastasis (11). There was only one patient in our study (patient 3) who had liver metastasis shown by ^{18}F-FDOPA PET/CT. Although no comparison with ^{18}F-FDG or ^{68}Ga-DOTATATE could be possible in our study, in the follow-up liver lesions showed progression on both CT and MRI and accuracy of ^{18}F-FDOPA PET/CT was confirmed. This result was compatible with previous data in the literature (11).

Study Limitations

The major limitation of this study is that few patients were enrolled. Further statistical analysis would be possible including subgroup analysis if a larger patient population could be achieved. Another limitation is that the study was designed retrospectively. Thus, head-to-head comparison of ^{18}F-FDOPA with ^{18}F-FDG and ^{68}Ga-DOTATATE was not possible for all patients. Although patients involved in this study were scanned at 60 min, as recommended in the guideline, in recent studies, higher detection rates with the earlier acquisition for ^{18}F-FDOPA PET/CT in medullary thyroid cancer was reported (14,18). Calculated sensitivity could have been higher if dual time point imaging could be performed. Despite these limitations, in our opinion, clinical results of a relatively specific and hard- to- reach radiopharmaceutical in a rare patient group are still valuable and would contribute to the literature.

Conclusion

^{18}F-FDOPA PET/CT can detect recurrence in about two-thirds of the patients with elevated calcitonin levels after primary surgery for MTC. Due to variable differentiation degree, different receptor status, and clinical behavior of MTC, all three radiopharmaceuticals can be beneficial and are complementary to each other in patient management.

Ethics

Ethics Committee Approval: Ankara University Ethics Committee approval was received for this study (decision no: İ7-522-21, date: 06.09.2021).

Informed Consent: The patient consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.K.G., Concept: Ç.S., N.Ö.K., Ö.D., Design: Ç.S., M.A., Data Collection or Processing: Ç.S., M.A., Analysis or Interpretation: Ç.S., M.A., Literature Search: M.A., Writing: M.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Pitt SC, Moley JF. Medullary, anaplastic, and metastatic cancers of the thyroid. Semin Oncol 2010;37:567-579.
2. Machens A, Dralle H. Surgical treatment of medullary thyroid cancer. Recent Results Cancer Res 2015;204:187-205.
3. Pacini F, Castagna MG, Brilli L, Pentheroudakis G; ESMO Guidelines Working Group. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23(Suppl 7):vii110-vii119.
4. American Thyroid Association Guidelines Task Force; Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, Moley JF, Pacini F, Ringel MD, Schlumberger M, Wells SA Jr. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009;19:565-612. Erratum in: Thyroid 2009;19:1295.
5. Ong SC, Schöder H, Patel SG, Tabangay-Lim IM, Doddamane I, Gönen M, Shaha AR, Tuttle RM, Shah JP, Larson SM. Diagnostic accuracy of 18F-FDG PET in restaging patients with medullary thyroid carcinoma and elevated calcitonin levels. J Nucl Med 2007;48:501-507.
6. Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, Lee N, Machens A, Moley JF, Pacini F, Raue F, Frank-Raue K, Robinson B, Rosenthal MS, Santoro M, Schlumberger M, Shah M, Waguespack SG; American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 2015;25:567-610.
7. Fialkowski E, DeBenedetti M, Moley J. Long-term outcome of reoperations for medullary thyroid carcinoma. World J Surg 2008;32:754-765.
8. Klain M, Hadoux J, Nappi C, Finessi M, Ambrosio R, Schlumberger M, Cuocolo A, Deandreis D, Salvatore D. Imaging medullary thyroid cancer patients with detectable serum markers: state of the art and future perspectives. Endocrine 2022;75:330-337.
9. Treglia G, Cocciolillo F, Di Nardo F, Poscia A, de Waure C, Giordano A, Rufini V. Detection rate of recurrent medullary thyroid carcinoma using fluorine-18 dihydroxyphenylalanine positron emission tomography: a meta-analysis. Acad Radiol 2012;19:1290-1299.
10. Romero-Lluch AR, Cuenca-Cuenca JI, Guerrero-Vázquez R, Martínez-Ortega AJ, Tirado-Hospital JL, Borrego-Dorado I, Navarro-González E. Diagnostic utility of PET/CT with 18F-DOPA and 18F-FDG in persistent or recurrent medullary thyroid carcinoma: the importance of calcitonin and carcinoembryonic antigen cutoff. Eur J Nucl Med Mol Imaging 2017;44:2004-2013.
11. Treglia G, Castaldi P, Villani MF, Perotti G, de Waure C, Filice A, Ambrosini V, Cremonini N, Santimaria M, Versari A, Fanti S, Giordano A, Rufini V. 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;39:569-580.
12. Treglia G, Rufini V, Salvatori M, Giordano A, Giovanella L. PET imaging in recurrent medullary thyroid carcinoma. Int J Mol Imaging 2012;2012:324686.
13. Slavikova K, Montravers F, Treglia G, Kunikowska J, Kaliska L, Vereb M, Talbot JN, Balogova S. What is currently the best radiopharmaceutical for the hybrid PET/CT detection of recurrent medullary thyroid carcinoma? Curr Radiopharm 2013;6:96-105.
14. Bozkurt MF, Virgolini I, Balogova S, Beheshti M, Rubello D, Decristoforo C, Ambrosini V, Kjaer A, Delgado-Bolton R, Kunikowska J, Oyen WJG, Chiti A, Giammarile F, Sundin A, Fanti S. Guideline for PET/CT imaging of neuroendocrine neoplasms with 68Ga-DOTA-conjugated somatostatin receptor targeting peptides and 18F-DOPA. Eur J Nucl Med Mol Imaging 2017;44:1588-1601. Erratum in: Eur J Nucl Med Mol Imaging 2017.

15. Chondrogiannis S, Marzola MC, Al-Nahhas A, Venkatanarayana TD, Mazza A, Opocher G, Rubello D. Normal biodistribution pattern and physiologic variants of 18F-DOPA PET imaging. Nucl Med Commun 2013;34:1141-1149.
16. S. Hoegerle, C. Altehoefer, N. Ghanem, I. Brink, E. Moser, and E. Nitzsche, "18F-DOPA positron emission tomography for tumour detection in patients with medullary thyroid carcinoma and elevated calcitonin levels," European Journal of Nuclear Medicine, 2001;28:64-71.
17. Tan BB, Flaherty KR, Kazerooni EA, Iannettoni MD; American College of Chest Physicians. The solitary pulmonary nodule. Chest. 2003;123(Suppl 1):89S-96S.
18. Soussan M, Nataf V, Kerrou K, Grahek D, Pascal O, Talbot JN, Montravers F. Added value of early 18F-FDOPA PET/CT acquisition time in medullary thyroid cancer. Nucl Med Commun 2012;33:775-779.