Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Prospective Study on the Performance of ^{18}F-DOPA Positron Emission Tomography/Computed Tomography in Patients with Medullary Thyroid Carcinoma

Inés Califano (ines.m.califano@gmail.com)
Instituto de Oncologia Angel H Roffo https://orcid.org/0000-0002-7450-5832
Fabian Pitoia
Hospital de Clínicas José de San Martín: Hospital de Clinicas Jose de San Martin
Roxana Chirico
Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno: Centro de Educacion Medica e Investigaciones Clinicas Norberto Quirno
Alejandra de Salazar
Instituto Universitario CEMIC Escuela de Medicina: Centro de Educacion Medica e Investigaciones Clinicas Norberto Quirno
Maria Bastianello
CEMIC: Centro de Educacion Medica e Investigaciones Clinicas Norberto Quirno

Research Article

Keywords: medullary thyroid cancer, PET/CT, Positron Emission Tomography, 18F-DOPA

Posted Date: January 14th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1251733/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

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 3-phase contrast-enhanced CT and bone scintigraphy were carried out up to 6 months before the ^{18}F DOPA PET/CT.

Results

77.7% 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 7 cases (22%) distant metastases were diagnosed, and in 8 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 and provided helpful information for patient management.

Introduction

Medullary thyroid carcinoma (MTC) accounts for less than 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 moment 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 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 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 patients with MTC and elevated serum tumoral markers remains uncertain. We aimed to assess the clinical usefulness of ^{18}F-DOPA PET/CT in patients with MTC and elevated Ctn and CEA, by comparing its performance with the standard imaging procedures routinely carried out in these patients and evaluating changes in disease management secondary to the findings found with this methodology.

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 six 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 hours 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 minutes) of neck and superior mediastinal were acquired in all the patients and then whole body scanning 60 minutes 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 x 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 electrochemiluminescense ® (Elecsys Roche, Cobas e411), and CEA levels were measured by autoanalyzer. Ctn and CEA doubling times (DT) were calculated using the ATA online calculator [11]. At

least 4 measurements over two 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.

Statistical Analysis

Continuous variables were expressed as means ± 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; $\chi 2$ 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.

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

T	**5**
X	**9 (25%)**
1	**7 (19.4%)**
2	**11 (30.5%)**
3	**4 (11.1%)**
4	
N	3
X	7 (19.4%)
0	6 (16.6%)
1a	20 (55.5%)
1b	
M	32 (88.9%)
0	4 (11.1%)
1	
S	3
X	1 (2.8%)
1	5 (13.9%)
2	5 (13.9%)
3	22 (61.1%)
4	
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: carcinoembrionary antigen: DT: Doubling time	

^{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; figures 1,2,3) 1,2,3)

Table 2

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

	No uptake N=3	Locoregional disease N=18	Distant metastases N=7	Locoregional and distant disease N=8	p
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: carcinoembrionary antigen: DT: Doubling time					

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 2 patients with adrenal gland uptake, surgical resection was performed and pathology report confirmed unilateral pheochromocytoma in both cases. 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)

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

	0	<3	≥3	p
Ctn (pg/ml)	748 (304; 1800)	2000 (526; 11849)	12746 (6987; 29155)	**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: carcinoembrionary antigen: DT: Doubling time				

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, two started treatment with a multikinase inhibitor, one was submitted to cervical external beam radiotherapy, and one received chemoembolization of liver metastases (Figure 4).

Discussion

Synthesis and use of ^{18}F-DOPA were developed more than three decades ago, and were described by Barrio et al [12]. 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 amino acid decarboxylase (AADC) [13]. 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 [14]. 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 [15]. 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 [16]. 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 patients with indolent MTC (eg prolonged Ctn/CEA DT), it was shown to be superior to other imaging procedures, both traditional scans and functional.

Rates of detection of disease with ^{18} F-DOPA PET/CT range between 45-78% [4, 17, 18]. We found an even larger rate in our population of 36 patients with MTC and 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, half of the foci of disease were found in locoregional lymph nodes (n=18), in agreement with previous findings [6]and they were slightly more frequent in the mediastinum (n=10) than in the neck (n=8).

^{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 [19].

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/ abdominal 3 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 change in management based on ^{18} F-DOPA PET/CT results was the decision to perform surgical procedures on locoregional lymph nodes 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 preoperative 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 [20, 21]. Coincidently, 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 [22]. ^{18}F-DOPA PET/CT has the advantage of detecting recurrences in cervical areas not easily assessed by US (such as retropharyngeal space), providing better assessment 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 [23, 24] Castinetti recommends that ^{18} F-DOPA PET/CT should be the first-choice radiopharmaceutical study for staging at the setting of preoperative neck surgery and it could also be useful for the accurate assessment of small foci of disease which may be submitted to active surveillance [25].

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, among

whom ruling out distant metastases is crucial to define whether a surgical intervention might be beneficial. Further studies are needed to elucidate this.

The present study has several limitations, such as the reduced 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 [26].

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.

Declarations

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. Written informed consent was obtained from every participant patient.

Funding: The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Conflict of interest: The authors declare that they have no conflict of interest

Acknowledgements

We thank Drs. Eduardo Faure and Graciela Berlingieri for the referral of patients

References

1. S. Wells, Revised American Thyroid Association Guidelines for the management of medullary thyroid carcinoma. Thyroid **25**(6), 567–590 (2015). https://doi.org/ 10.1089/thy.2014.0335
2. M.R. Pelizzo. Natural history, diagnosis, treatment and outcome of medullary thyroid cancer: 37 years experience on 157 patients. Eur. J. Surg. Oncol., 33 (4), 493–497 (2007) https://doi.org/ 10.1016/j.ejso.2006.10.021
3. L. Louhibi, Demographic, clinical, and genetic characteristics of patients with medullary thyroid cancer in the past 16 years in Castilla-La Mancha. Endocrinol Nutr **61**(8), 398–403 (2014). https://doi.org/ 10.1016/j.endonu.2014.02.006

4. K.S. Slavikova, What is currently the best radiopharmaceutical for the hybrid PET/CT detection of recurrent medullary thyroid carcinoma? Curr Radiopharm **6**(2), 96–105 (2013). https://doi.org/10.2174/1874471011306020006
5. S. Filetti, Thyroid Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. Ann. Oncol. **30**(12), 1856–1883 (2019). https://doi.org/ 10.1093/annonc/mdz400
6. A. Giraudet, Imaging medullary thyroid carcinoma with persistently elevated calcitonin levels. J Clin Endocrinol Metab **92**(11), 4185–4190 (2007). https://doi.org/ 10.1210/jc.2007-1211
7. G. Treglia, Detection rate of recurrent medullary thyroid carcinoma using fluorine-18 fluorodeoxyglucose positron emission tomography: a meta-analysis. Endocrine **42**, 535–545 (2012). https://doi.org/10.1007/s12020-012-9671-6
8. J. Yang, The combined use of calcitonin doubling time and 18F-FDG PET/CT improves prognostic values in medullary thyroid carcinoma: the clinical utility of 18F-FDG PET/CT. Endocr Pract **23**(8), 942–948 (2017). https://doi.org/10.4158/EP171806.OR
9. Y. Ito, Calcitonin doubling time in medullary thyroid carcinoma after the detection of distant metastases keenly predicts patients' carcinoma death. Endocr. J. **63**(7), 663–667 (2016). https://doi.org/ 10.1507/endocrj.EJ16-0140
10. L. Giovanella, EAMN practice guideline for PET TC imaging in medullary thyroid carcinoma. Eur J Nucl Med Mol **47**(1), 61–77 (2020). https://doi.org/10.1007/s00259-019-04458-6
11. https://www.thyroid.org/professionals/calculators/
12. W. Melega, L-6-e8F]Fluoro-DOPA Metabolism in monkeys and humans: biochemical parameters for the formulation of tracer kinetic models with positron emission tomography. J. Cereb. Blood Flow Metab. **11**, 890–897 (1991). https://doi.org/10.1038/jcbfm.1991.154
13. M. Bergström, In vivo demostration of enzyme actity in endocrime pancreatric tumors: decarboxylation of carbon 11 DOPA to carbon 11 dopamine. J Nucl Med **37**, 32–37 (1996)
14. S. Hoegerle, 18F-DOPA positron emission tomography for tumour detection in patients with medullary thyroid carcinoma and elevated calcitonin levels. Eur. J. Nucl. Med. **28**(1), 64–71 (2001). https://doi.org/10.1007/s002590000404
15. https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-fluorodopa-f-18.
16. R. Haddad. NCCN Guidelines version 2.2021. Thyroid carcinoma. https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed 10/15/2021
17. A. Archier, (18)F-DOPA PET/CT in the diagnosis and localization of persistent medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging **43**(6), 1027–1033 (2016). https://doi.org/10.1007/s00259-015-3227-y
18. F. Caobelli, Predictive and prognostic value of 18F-DOPA PET/CT in patients affected by recurrent medullary carcinoma of the thyroid. Ann Nucl Med **1**(32), 7–15 (2018). https://doi.org/10.1007/s12149-017-1213-0

19. W. Noordzij, Adrenal tracer uptake by 18F-FDOPA PET/CT in patients with pheochromocytoma and controls. Eur J Nucl Med Mol Imaging **46**, 1560–1566 (2019). https://doi.org/10.1007/s00259-019-04332-5
20. L. Brammen. Medullary thyroid carcinoma: do ultrasonography and F-DOPA-PET-CT influence the initial surgical strategy? Ann Surgery Oncology, 3919–3927 (2018). https://doi.org/ 10.1245/s10434-018-6829-3
21. S. Rasul, 18 F DOPA PET /TC in diagnosis and stating of primary thyroid carcinoma prior to surgery. Eur J Nucl Mol Imaging **45**(12), 2159–2149 (2018). https://doi.org/ 10.1007/s00259-018-4045-9
22. M. Terroir, F-18-Dopa PET/CT is more sensitive than whole body MRI for the localization of persistent/recurrent disease of medullary thyroid. Thyroid, 29 (10), 1457–1464, https://doi.org/10.1089/thy.2018.0351
23. S. Lee. Comparison of 5 different PET radiopharmaceuticals for the detection of recurrent medullary thyroid carcinoma: a network meta-analysis. Clin. Nucl. Med.(45), 341–348 (2020). https://doi.org/ 10.1097/RLU.0000000000002940
24. G. Treglia, Comparison of 18-F DOPA, 18-F FDG and 68Ga-Somatostatin analogue PET/CT in patients with recurrent medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging **39**, 569–580 (2012). https://doi.org/ 10.1007/s00259-011-2031-6 569–580).
25. F. Castinetti. PET imaging in medullary thyroid carcinoma:time for reappraisal? Thyroid, 31(2), 151-155 (2021). https://doi.org/ 10.1089/thy.2020.0674
26. F. Calabria. ^{18} F- DOPA. In: Calabria F, Schillaci O (eds.) Radiopharmaceuticals. A guide to PET/CT and PET/MRI, pp. 37-57. Springer Nature Switzerland AG (2020, second edition)

Figures

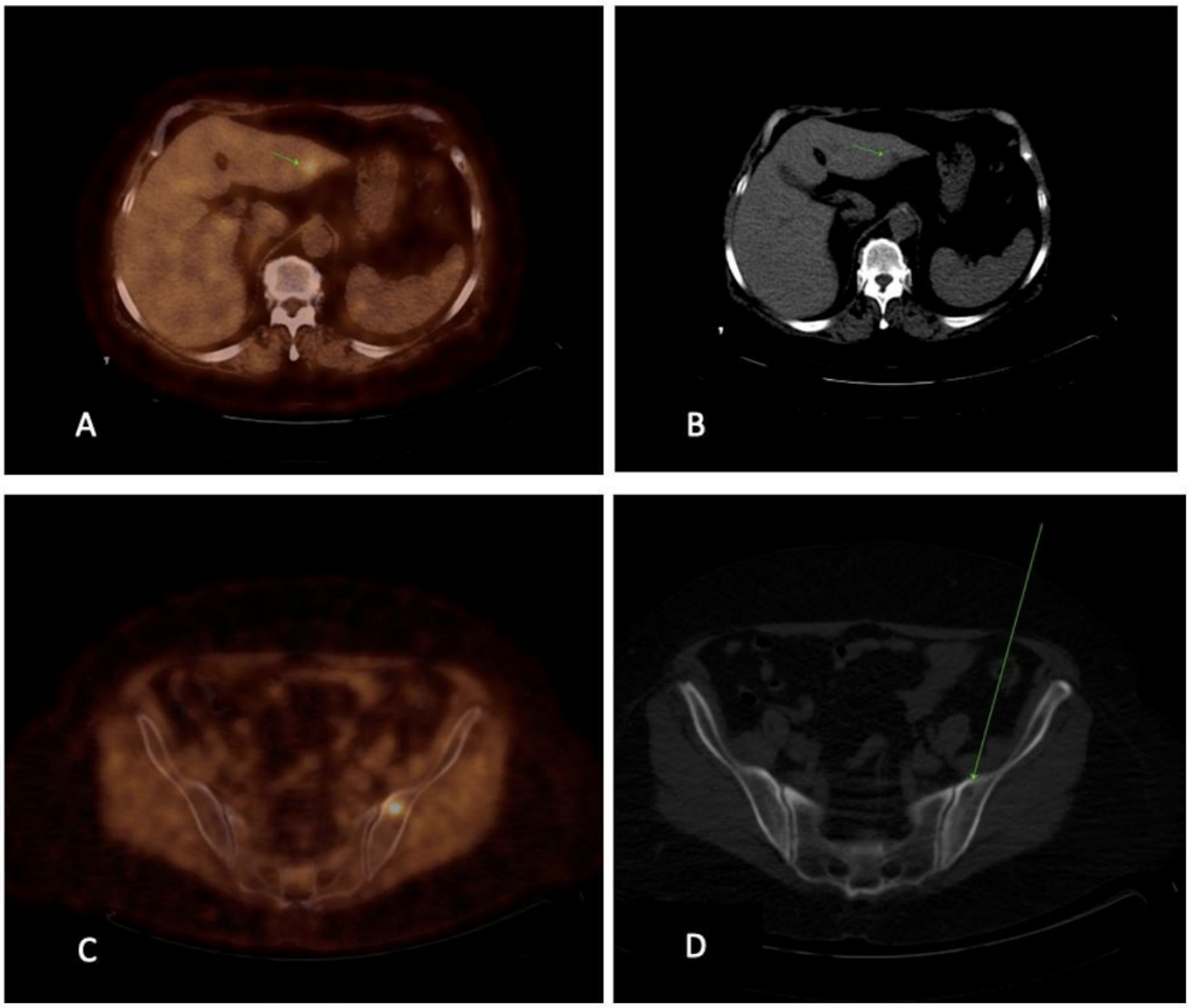

Figure 1

Sixty-nine year-old female with stage III sporadic medullary thyroid cancer. Ctn: 592pg/ml (Ctn DT:12.08 months); CEA:2.9 ng/ml (CEA DT: 16.44 months). A and B: Axial ^{18}F-DOPA PET/CT image showing one focus of uptake in the liver (seg III / 6mm) . SUV max 4.3. C and D: lytic lesion in left iliac bone, SUV max: 7.4.

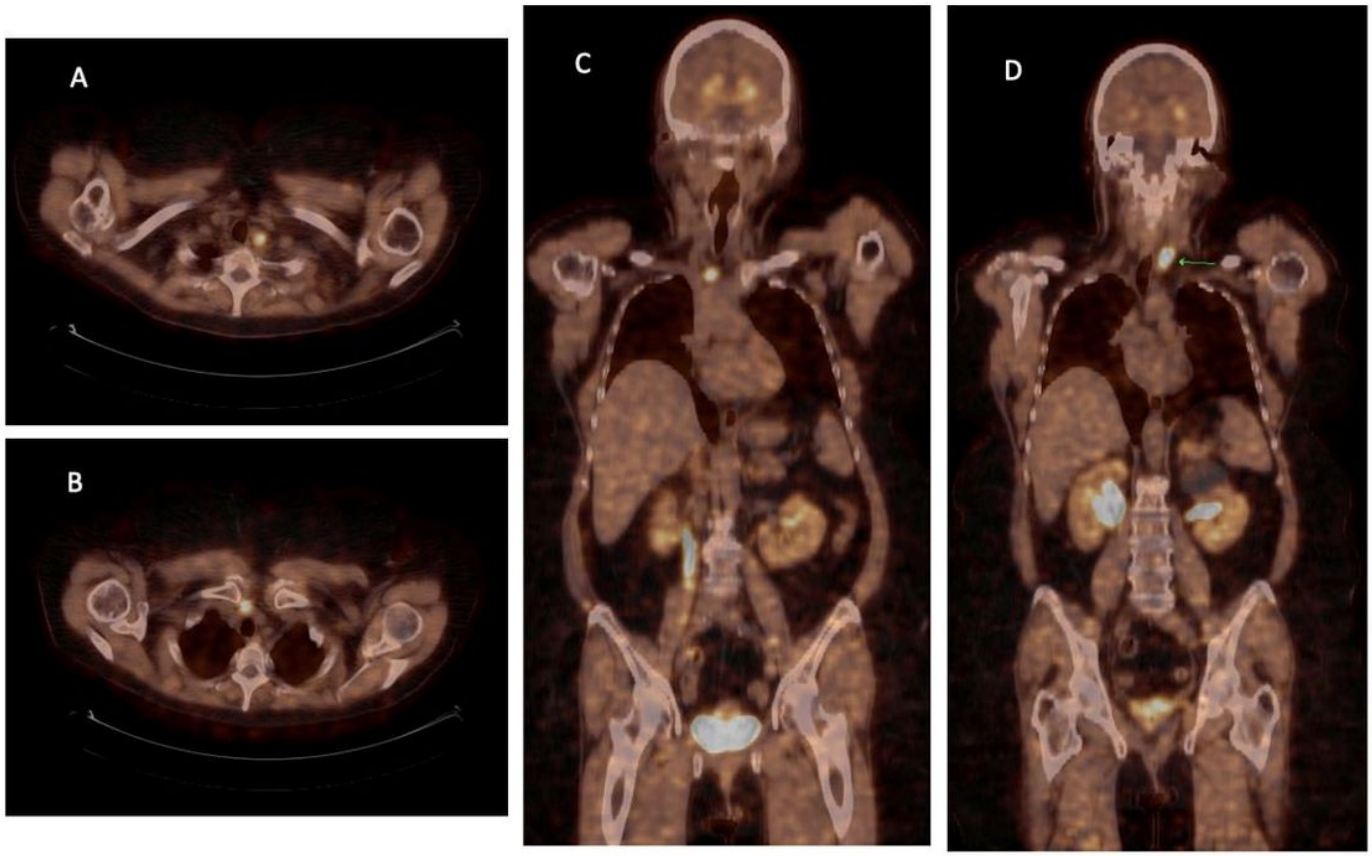

Figure 2

Sixty-five year-old female, stage III sporadic medullary thyroid cancer. Calcitonin: 1136pg/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)

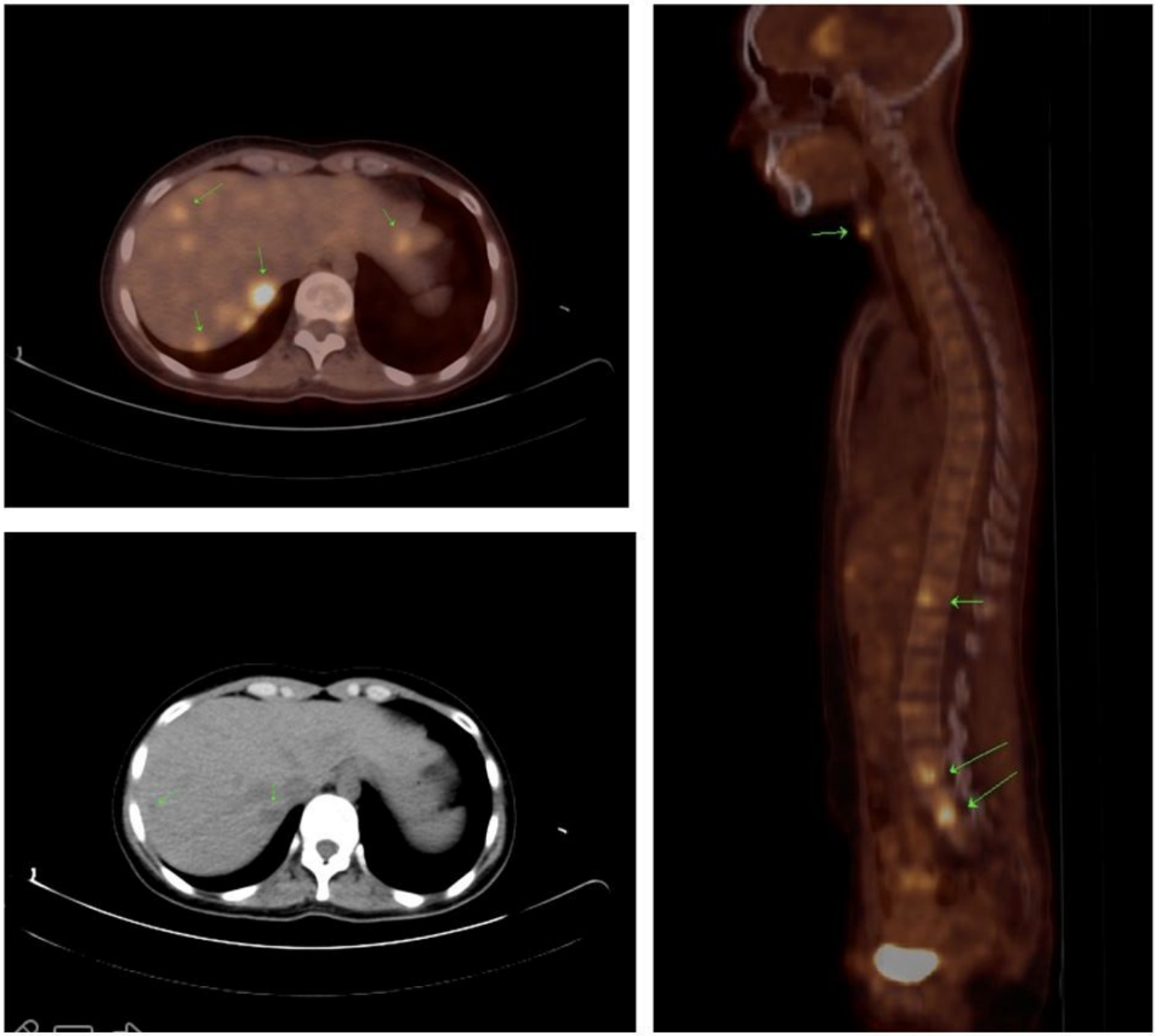

Figure 3

Thirty-six year-old female, stage II hereditary medullary thyroid cancer. Calcitonin: 11270pg/ml (Doubling time 15 months). CEA: 413ng/ml. (Doubling time 23 months). Multiple foci of ^{18}F DOPA uptake (cervical, liver and vertebrae)

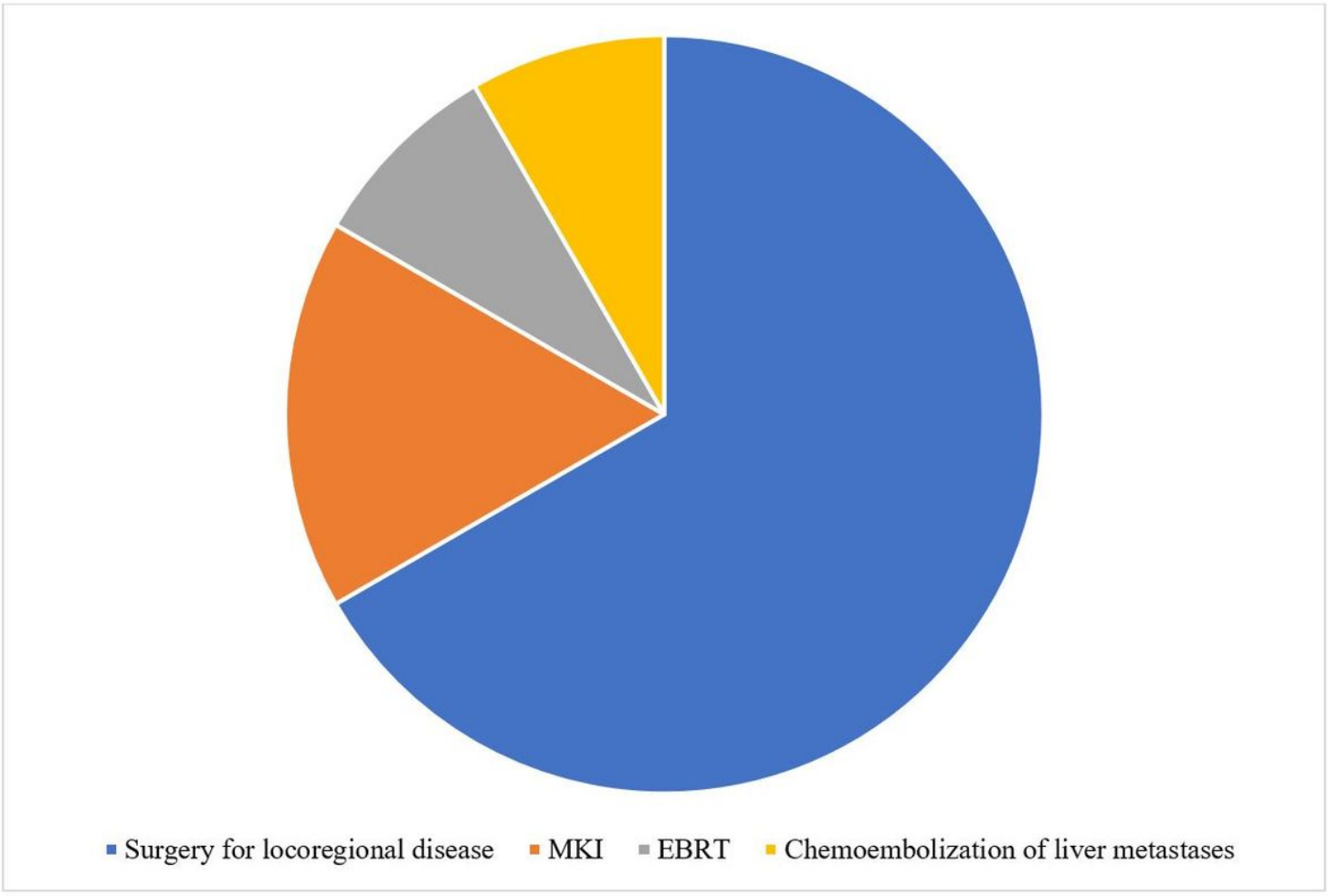

Figure 4

Changes in the management of 14 patients with MTC and positive findings in ^{18}F-DOPA PET/CT

MKI: multikinase inhibitor; EBRT: External beam radiotherapy