Review Article

PET Imaging in Recurrent Medullary Thyroid Carcinoma

Giorgio Treglia,1 Vittoria Rufini,1 Massimo Salvatori,1 Alessandro Giordano,1 and Luca Giovanella2

1 Institute of Nuclear Medicine, Catholic University of the Sacred Heart, 00168 Rome, Italy
2 Department of Nuclear Medicine and PET-CT Centre, Oncology Institute of Southern Switzerland, Street Ospedale 12, 6500 Bellinzona, Switzerland

Correspondence should be addressed to Luca Giovanella, luca.giovanella@eoc.ch

Received 23 April 2012; Accepted 21 May 2012

Academic Editor: Francesco S. Celi

Copyright © 2012 Giorgio Treglia et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Purpose. To perform an overview about the role of positron emission tomography (PET) or PET/computed tomography (PET/CT) using different radiopharmaceuticals in recurrent medullary thyroid carcinoma (MTC) based on biochemical findings (increased tumor marker levels after primary surgery).

Methods. A comprehensive literature search of studies published in PubMed/MEDLINE, Scopus, and Embase databases through February 2012 regarding PET or PET/CT in patients with recurrent MTC was performed.

Results. Twenty-nine studies comprising 714 patients with suspected recurrent MTC were retrieved. Twenty-seven articles evaluated the role of fluorine-18-fluorodeoxyglucose (FDG) PET or PET/CT in recurrent MTC with conflicting results. Diagnostic accuracy of FDG-PET and PET/CT increased in MTC patients with higher calcitonin and carcinoembryonic antigen values, suggesting that these imaging methods could be very useful in patients with more advanced and aggressive disease. Eight articles evaluated the role of fluorine-18-dihydroxyphenylalanine (FDOPA) PET or PET/CT in recurrent MTC reporting promising results. Overall, FDOPA seems to be superior but complementary compared to FDG in detecting recurrent MTC. Few studies evaluating other PET tracers are also discussed.

Conclusions. PET radiopharmaceuticals reflect different metabolic pathways in MTC. FDOPA seems to be the most useful PET tracer in detecting recurrent MTC based on rising levels of tumor markers. FDG may complement FDOPA in patients with more aggressive MTC.

1. Introduction

Medullary thyroid carcinoma (MTC) is a slow-growing neuroendocrine tumor originating from parafollicular C cells. MTC accounts for approximately 5% of thyroid carcinomas, occurring in either sporadic (75% of cases) or familial forms (25% of cases). This tumor is frequently aggressive; most frequent sites of metastatic disease are cervical and mediastinal lymph nodes, lungs, liver, and bone. The main treatment for MTC is surgical resection that is the only strategy for potential cure; in patients with metastatic disease therapeutic options are limited as this tumor does not concentrate radioiodine and shows poor response to chemotherapy and radiation therapy [1]. Also targeted therapy with vandetanib seems to show promising results in the treatment of patients with metastatic/recurrent MTC [1].

Serum calcitonin represents the most sensitive and accurate tumor marker in the postoperative management and surveillance of MTC. In about one third of patients with MTC lesions also carcinoembryonic antigen (CEA) levels may be increased and this finding has prognostic significance, as increased CEA levels are characteristic of advanced forms when the tumor tends to dedifferentiation. Serum calcitonin and CEA doubling times are efficient tools for assessing tumor progression and are useful prognostic factors of survival in patients with MTC [1].

The early detection of recurrence represents an important step in the management of patients with MTC, because identifying recurrent tumor tissue impacts in patient outcome [1–4]. Conventional imaging modalities are often negative or inconclusive in presence of rising levels of tumor markers. Therefore, functional imaging with PET using different radiopharmaceuticals was explored as a way to detect MTC recurrence.

Fluorine-18-Fluorodeoxyglucose (FDG), a glucose analog, accumulates in neoplastic cells allowing scintigraphic
visualization of tumors that use glucose as an energy source. FDG uptake in neoplastic cells correlates with poor differentiation and high proliferative activity. Neuroendocrine tumors usually show an indolent course, and consequently low FDG uptake [3, 4]. These tumors, however, when undergoing dedifferentiation become more aggressive and may show increased FDG uptake, and this is also the case in MTC as demonstrated by the immunoreactivity for KI-67 expression (KI-67 is a nuclear protein that is associated with cellular proliferation) in surgically removed lesions [3, 4].

Dihydroxyphenylalanine (DOPA) is an amino acid that is converted to dopamine by aromatic amino acid decarboxylase (AADC). Fluorine-18-DOPA (FDOPA) is taken up through ubiquitous transmembrane amino acid transporter systems that are significantly upregulated in neuroendocrine tumors, including MTC. This upregulation is presumably secondary to the increased activity of metabolic pathways involving the enzyme AADC which is a specific property of neuroendocrine tumors.

The aim of this paper is to perform an overview of the literature about the role of PET and PET/CT using different radiopharmaceuticals in patients with recurrent MTC based on biochemical findings (increased tumor marker levels after primary surgery).

2. Search Strategy and Data Abstraction

A comprehensive computer literature search of the PubMed/MEDLINE, Scopus and Embase databases was carried out to find relevant published articles on the role of PET or PET/CT using different radiopharmaceuticals in patients with recurrent MTC. We used a search algorithm based on a combination of the terms: (a) “PET” or “positron emission tomography” and (b) “medullary” or “thyroid”. No beginning date limit was used; the search was updated until February 29th 2012. To expand our search, references of the retrieved articles were also screened for additional studies. No language restriction was used.

Only those studies or subsets in studies that satisfied all of the following criteria were included: (a) PET or PET/CT performed in patients with suspected recurrent MTC after primary surgery; (b) sample size of at least 6 patients with MTC. The exclusion criteria were (a) articles not within the field of interest of this paper; (b) review articles, editorials or letters, comments, conference proceedings; (c) case reports or small case series (sample size of less than 6 patients with recurrent/residual MTC); (d) possible data overlap (in such cases the most complete article was included).

For each included study, information was collected concerning basic study (author names, journal, year of publication, and country of origin), patient characteristics (number of patients with suspected recurrent MTC performing PET or PET/CT, mean age, and sex), technical aspects (study design, device used, radiopharmaceutical used, injected dose, time interval between radiopharmaceutical injection and image acquisition, acquisition protocol, image analysis, and reference standard used), and diagnostic performance data (sensitivity and specificity). Patients evaluated with PET or PET/CT before primary surgery were excluded from the analysis. Only patients with a postoperative PET imaging were included.

3. Literature Data

Twenty-nine articles comprising 714 patients with suspected recurrent MTC were retrieved using the above cited criteria [5–33]. The characteristics of the included studies are presented in Table 1.

(A) PET and PET/CT Using Fluorine-18-Fluorodeoxyglucose. Twenty-seven articles evaluating the role of FDG-PET or PET/CT in patients with recurrent MTC were selected and retrieved from the literature (Tables 1 and 2) [5–8, 10, 12–33]. Other six articles were not included for possible data overlap [34–39]. Overall, the studies using FDG-PET or PET/CT have reported conflicting results about the diagnostic performance of these functional imaging methods in patients with suspected recurrent MTC. In particular, sensitivity of these methods ranged from 17% to 95% whereas specificity, when reported, ranged from 68% to 100% (Table 2). A possible explanation for these heterogeneous findings could be related to diversity between the studies in technical aspects (Table 2) and inclusion criteria (patients with known lesions versus patients with occult disease at conventional imaging methods; patients with slowly progressive disease versus patients with more aggressive disease) [40].

False negative results of FDG-PET and PET/CT could be related to small lesions or to the slow growth of neuroendocrine tumors. Both factors impact the diagnostic accuracy of these imaging modalities. False positive results also occurred by using FDG-PET and PET/CT, and were typically due to inflammatory lesions [3, 4, 40].

It should be noted that a significant number of recurrent MTC, based on rising levels of tumor markers, remained unidentified using FDG-PET or PET/CT. On the other hand, it should be considered that FDG-PET and PET/CT were often performed in patients with suspected recurrent MTC after negative conventional imaging studies, affecting the surgical management of patients with recurrent MTC when hypermetabolic lesions were detected [2–4, 40].

Based on literature findings, the diagnostic performance of FDG-PET or PET/CT in patients with recurrent MTC improved in patients with higher serum calcitonin and CEA levels [40]. Also, sensitivity of FDG-PET and PET/CT improved in patients with shorter tumor markers (calcitonin and CEA) doubling times [6, 10, 14, 16, 18], confirming the usefulness of these imaging methods in patients with more aggressive disease (with high glucose consumption and high FDG uptake) compared to those with slowly progressive disease (with low glucose consumption and low FDG uptake) [40].

FDG-PET or PET/CT were usually performed in the included studies if no disease sites were identified on conventional imaging in patients with biochemical evidence of MTC.
Table 1: Basic study and patient characteristics.

| Authors                        | Year | Country      | MTC patients performing PET for suspected recurrence | Mean age (years) | % Male | Tracers used for PET or PET/CT                                      |
|--------------------------------|------|--------------|------------------------------------------------------|------------------|--------|-------------------------------------------------------------------|
| Treglia et al. [5]             | 2012 | Italy        | 18                                                   | 53               | 33%    | FDG, FDOPA, and Gallium-68-DOTANOC/DOTATOC                        |
| Kauhanen et al. [6]            | 2011 | Finland      | 19                                                   | 52               | 53%    | FDG and FDOPA                                                      |
| Ozkan et al. [7]               | 2011 | Turkey       | 33                                                   | 50               | 27%    | FDG                                                               |
| Gómez-Camarero et al. [8]      | 2011 | Spain        | 31                                                   | 56               | 45%    | FDG                                                               |
| Palyga et al. [9]              | 2010 | Poland       | 8                                                    | 56               | 50%    | Gallium-68-DOTATATE                                               |
| Jang et al. [10]               | 2010 | Korea        | 16                                                   | 51               | 56%    | FDG and Carbon-11-methionine                                     |
| Luster et al. [11]             | 2010 | Germany      | 28                                                   | 48               | 46%    | FDOPA                                                             |
| Skoura et al. [12]             | 2010 | Greece       | 32 (38 scans)                                        | 52               | 31%    | FDG                                                               |
| Marzola et al. [13]            | 2010 | Italy        | 18                                                   | 51               | 44%    | FDG and FDOPA                                                      |
| Bogsrud et al. [14]            | 2010 | USA and Norway | 29                                             | 50               | 55%    | FDG                                                               |
| Conry et al. [15]              | 2010 | UK and Singapore | 18                                           | 54               | 72%    | FDG and Gallium-68-DOTATATE                                      |
| Beheshti et al. [16]           | 2009 | Austria      | 19*                                                  | 59               | 38%    | FDG and FDOPA                                                      |
| Faggiano et al. [17]           | 2009 | Italy        | 26                                                   | NR               | 49%    | FDG                                                               |
| Koopmans et al. [18]           | 2008 | The Netherlands | 21                                           | 56               | 48%    | FDG and FDOPA                                                      |
| Rubello et al. [19]            | 2008 | Italy        | 19                                                   | 53               | 42%    | FDG                                                               |
| Oudoux et al. [20]             | 2007 | France       | 33                                                   | 53               | 64%    | FDG                                                               |
| Giraudet et al. [21]           | 2007 | France       | 55                                                   | 56               | 62%    | FDG                                                               |
| Czepczyński et al. [22]        | 2007 | Poland and Italy | 13*                                         | 50               | 57%    | FDG                                                               |
| Beuthien-Baumann et al. [23]   | 2007 | Germany      | 15                                                   | 56               | 53%    | FDG and FDOPA                                                      |
| Ong et al. [24]                | 2007 | USA          | 28 (38 scans)                                        | 59               | 64%    | FDG                                                               |
| Iagaru et al. [25]             | 2007 | USA          | 13                                                   | 48               | 46%    | FDG                                                               |
| Gotthardt et al. [26]          | 2006 | Germany and the Netherlands | 26                                           | 45               | 58%    | FDG                                                               |
| De Groot et al. [27]           | 2004 | The Netherlands | 26                                           | 51               | 58%    | FDG                                                               |
| Szakáll et al. [28]            | 2002 | Hungary      | 40                                                   | 48               | 45%    | FDG                                                               |
| Diehl et al. [29]              | 2001 | Germany      | 85 (100 scans)                                       | 53               | 47%    | FDG                                                               |
| Hoegerle et al. [30]           | 2001 | Austria      | 10*                                                  | 57               | 55%    | FDG and FDOPA                                                      |
| Brandt-Mainz et al. [31]       | 2000 | Germany      | 17                                                   | NR               | 65%    | FDG                                                               |
| Adams et al. [32]              | 1998 | Germany      | 8                                                    | 49               | 50%    | FDG                                                               |
| Musholt et al. [33]            | 1997 | USA and Germany | 10                                           | 36               | 70%    | FDG                                                               |

NR: not reported; FDG: fluorine-18-fluorodeoxyglucose; FDOPA: fluorine-18-dihydroxyphenylalanine; *patients evaluated before primary surgery were excluded from the analysis.

reurrence or if calcitonin levels were elevated out of proportion to minor disease found on conventional imaging. The diagnostic performance of FDG-PET and PET/CT in recurrent MTC increased whether patients with known lesions at conventional imaging were included in the study population, because functional abnormalities are usually detectable by FDG-PET or PET/CT when anatomical changes are already evident.

(B) PET and PET/CT Using Fluorine-18-Dihydroxyphenylalanine. Eight articles evaluating the role of FDOPA-PET or PET/CT in patients with recurrent MTC were selected and retrieved from the literature (Tables 1 and 3) [5, 6, 11, 13, 16, 18, 23, 30]. Another article was not included for possible data overlap [41]. Overall, the studies using FDOPA-PET or PET/CT have reported promising results in recurrent MTC. In particular sensitivity of these methods ranged from 47% to 83% (Table 3); however, FDOPA-PET or PET/CT modified the surgical management of a significant number of patients with recurrent MTC when positive, because these functional imaging methods were often performed in patients with suspected recurrent MTC based on rising tumor markers after negative conventional imaging studies.

Differences in technical aspects (Table 3) and inclusion criteria could explain the heterogeneity between studies about the sensitivity values reported. False positive results of FDOPA-PET or PET/CT in recurrent MTC are uncommon.
Table 2: Technical aspects of the studies which used FDG-PET or PET/CT for detecting recurrent medullary thyroid carcinoma.

| Authors | Study design | Device | Injected activity | Time between tracer injection and image acquisition (min) | PET acquisition protocol | Image analysis | Reference standard | Sensitivity of FDG-PET or PET/CT | Specificity of FDG-PET or PET/CT |
|---------|--------------|--------|-------------------|----------------------------------------------------------|--------------------------|---------------|-------------------|-----------------------------|-------------------------------|
| Treglia et al. [5] | Retrospective multicenter | PET/CT | 259–407 MBq | 60 | Static acquisition | Qualitative | Histology and/or clinical/imaging followup | 17% | NC |
| Kauhanen et al. [6] | Prospective multicenter | PET/CT | 377 MBq | 60 | Static acquisition (3 min per bed position) | Qualitative and semiquantitative | Histology and/or clinical/imaging followup | 53% | NC |
| Ozkan et al. [7] | Retrospective single center | PET/CT | 296–370 MBq | 60 | Static acquisition (4 min per bed position) | Qualitative and semiquantitative | Histology and/or clinical/imaging followup | 93% | 68% |
| Gómez-Camarero et al. [8] | Retrospective single center | PET and PET/CT | 333–434 MBq | 60 | Static acquisition | Qualitative and semiquantitative | Histology and/or clinical/imaging followup | 88% | 85% |
| Jang et al. [10] | Prospective single center | PET/CT | 370 MBq | 60 | Static acquisition (4 min per bed position) | Qualitative | Histology and/or clinical/imaging followup | 63% | NC |
| Skoura et al. [12] | Retrospective single center | PET/CT | 370 MBq | 60 | Static acquisition (4 min per bed position) | Qualitative and semiquantitative | Histology and/or clinical/imaging followup | 47% | NC |
| Marzola et al. [13] | NR; multicenter | PET/CT | 2.2 MBq/kg | 60 | Static acquisition (3 min per bed position) | Qualitative and semiquantitative | Histology | 61% | NC |
| Bogsrud et al. [14] | Retrospective single center | PET and PET/CT | 740 MBq | 60–75 | Static acquisition (5 min per bed position) | Qualitative | Histology and/or clinical/imaging followup | 45% | 93% |
| Conry et al. [15] | Retrospective multicenter | PET/CT | 195–550 MBq | 50–75 | Static acquisition (1.5/5 min per bed position) | Qualitative and semiquantitative | Histology and/or clinical/imaging followup | 78% | NC |
| Beheshi et al. [16] | Prospective single center | PET/CT | 370 MBq | 60 | Static acquisition (4 min per bed position) | Qualitative and semiquantitative | Histology and/or clinical/imaging followup | 58% | NC |
| Faggiano et al. [17] | Retrospective multicenter | PET | 222–370 MBq | 60–90 | Static acquisition (4 min per bed position) | Qualitative | Histology and/or clinical/imaging followup | 50% | NC |
| Koopmans et al. [18] | Prospective single center | PET | NR | NR | Static acquisition (5 min per bed position) | Qualitative | Histology and/or clinical/imaging followup | 24% | NC |
| Rubello et al. [19] | Prospective multicenter | PET/CT | 5.5 MBq/kg | 60–90 | Static acquisition (4 min per bed position) | Qualitative and semiquantitative | Histology | 79% | 100% |
| Oudoux et al. [20] | Prospective multicenter | PET/CT | 310–450 MBq | 60 | Static acquisition | Qualitative and semiquantitative | Histology and/or clinical/imaging followup | 76% | NC |
| Authors                          | Study design | Device       | Injected activity | Time between tracer injection and image acquisition (min) | PET acquisition protocol | Image analysis                              | Reference standard                              | Sensitivity of FDG-PET or PET/CT* | Specificity of FDG-PET or PET/CT* |
|---------------------------------|--------------|--------------|-------------------|----------------------------------------------------------|--------------------------|---------------------------------------------|----------------------------------------------|----------------------------------|----------------------------------|
| Giraudet et al. [21]            | Prospective single center | PET/CT       | 5 MBq/Kg          | 60                                                       | Static acquisition       | Qualitative and semiquantitative            | Histology and/or clinical/imaging followup | 32%                              | NC                               |
| Czepczyński et al. [22]         | NR; single center | PET          | NR                | NR                                                       | Static acquisition       | Qualitative                                 | Histology and/or clinical/imaging followup | 58%                              | NC                               |
| Beuthien-Baumann et al. [23]    | Retrospective single center | PET          | 370 MBq           | 60                                                       | Static acquisition       | Qualitative                                 | Histology and/or clinical/imaging followup | 47%                              | NC                               |
| Ong et al. [24]                 | Retrospective single center | PET          | 555 MBq           | Minimum 45                                               | Static acquisition       | Qualitative and semiquantitative            | Histology and/or clinical/imaging followup | 62%                              | NC                               |
| Iagaru et al. [25]              | Retrospective single center | PET          | 550 MBq           | 45/60                                                    | Static acquisition       | Qualitative                                 | Histology and/or clinical/imaging followup | 86%                              | 83%                             |
| Gotthardt et al. [26]           | NR; multicenter | PET          | 350 MBq           | 60                                                       | Static acquisition       | Qualitative                                 | Histology and/or clinical/imaging followup | 70%                              | NC                               |
| De Groot et al. [27]            | Prospective single center | PET          | 400 MBq           | 90                                                       | Static acquisition       | Qualitative                                 | Histology and/or clinical/imaging followup | 41%                              | NC                               |
| Szakáll et al. [28]             | Retrospective single center | PET          | 5.55 MBq/Kg       | 40                                                       | Static acquisition       | Qualitative                                 | Histology and/or clinical/imaging followup | 95%                              | NC                               |
| Diehl et al. [29]               | Retrospective multicenter | PET          | 300–500 MBq       | Minimum 30                                               | Static acquisition       | Qualitative                                 | Histology and/or clinical/imaging followup | 78%                              | 79%                             |
| Hoegerle et al. [30]            | Prospective single center | PET          | 330 MBq           | 90                                                       | Static acquisition       | Qualitative                                 | Histology and/or clinical/imaging followup | 60%                              | 100%                            |
| Brandt-Mainz et al. [31]        | Prospective single center | PET          | 350 MBq           | 30                                                       | Static acquisition       | Qualitative                                 | Histology and/or clinical/imaging followup | 76%                              | NC                               |
| Adams et al. [32]               | Prospective single center | PET          | 374 MBq           | 60                                                       | Static acquisition       | Qualitative                                 | Histology and/or clinical/imaging followup | 87%                              | NC                               |
| Musholt et al. [33]             | NR; single center | PET          | 370–555 MBq       | 40                                                       | Static acquisition       | Qualitative                                 | Histology and/or clinical/imaging followup | 90%                              | NC                               |

NR: not reported; NC: not calculated; *sensitivity and specificity are reported on a per patient-based analysis.
| Authors               | Study design        | Device   | Injected activity | Time between tracer injection and image acquisition (min) | PET acquisition protocol                                                                 | Image analysis                  | Reference standard | Sensitivity of FDOPA-PET or PET/CT* | Specificity of FDOPA-PET or PET/CT* |
|----------------------|---------------------|----------|-------------------|-----------------------------------------------------------|-----------------------------------------------------------------------------------------|---------------------------------|-------------------|-----------------------------------|-------------------------------------|
| Treglia et al. [5]   | Retrospective       | PET/CT   | 4 MBq/kg          | 60                                                        | Static acquisition (3 min per bed position) no carbidopa premedication                  | Qualitative                     | Histology and/or clinical/imaging followup | 72%                   | NC                                 |
| Kauhanen et al. [6]  | Prospective         | PET/CT   | 243 MBq           | 60                                                        | Static acquisition (3 min per bed position) carbidopa premedication                    | Qualitative and semiquantitative | Histology and/or clinical/imaging followup | 58%                   | NC                                 |
| Luster et al. [11]   | Retrospective       | PET/CT   | 298 MBq           | 60                                                        | Static acquisition (4 min per bed position) carbidopa premedication                    | Qualitative and semiquantitative | Histology and/or clinical/imaging followup | 74%                   | 100%                               |
| Marzola et al. [13]  | Multicenter         | PET/CT   | 2.2 MBq/kg        | 60                                                        | Static acquisition (3 min per bed position) no carbidopa premedication                | Qualitative and semiquantitative | Histology                       | 83%                   | NC                                 |
| Beheshti et al. [16] | Prospective         | PET/CT   | 4 MBq/Kg          | 30                                                        | Static acquisition (4 min per bed position) no carbidopa premedication                | Qualitative and semiquantitative | Histology and/or clinical/imaging followup | 81%                   | NC                                 |
| Koopmans et al. [18] | Prospective         | PET      | 180 MBq           | 60                                                        | Static acquisition (5 min per bed position) carbidopa premedication                  | Qualitative                     | Histology and/or clinical/imaging followup | 62%                   | NC                                 |
| Beuthien-Baumann et al. [23] | Retrospective single center | PET      | 4.8 MBq/Kg        | 45                                                        | Static acquisition carbidopa premedication                                           | Qualitative                     | Histology and/or clinical/imaging followup | 47%                   | NC                                 |
| Hoegerle et al. [30] | Prospective         | PET      | 220 MBq           | 90                                                        | Static acquisition no carbidopa premedication                                        | Qualitative                     | Histology and/or clinical/imaging followup | 60%                   | NC                                 |

NC: not calculated; *sensitivity and specificity are reported on a per patient-based analysis.
On the other hand, possible causes of false negative results of FDOPA-PET or PET/CT should be kept in mind; they could be probably related to small MTC lesions or to de-differentiation, both factors affecting the diagnostic accuracy of these imaging methods.

Based on literature findings, the diagnostic performance of FDOPA-PET or PET/CT in recurrent MTC improved in patients with higher serum calcitonin levels [5, 6, 11, 13, 16, 18, 23, 30]. Comparative analyses between FDOPA and FDG have shown better results with FDOPA in terms of sensitivity and specificity and a complementary role of the two radiopharmaceuticals in the assessment of recurrent MTC. The different behavior of FDOPA and FDG in recurrent MTC can be explained by their different uptake mechanisms that, in turn, reflect the different metabolic pathways of neuroendocrine cells, including MTC cells. FDOPA is a marker of amino acid decarboxylation that is a feature of the neuroendocrine origin of MTC; so, it can be assumed that a higher FDOPA uptake is related to a higher degree of cell differentiation, whereas a higher FDG uptake is related to a high proliferative activity and a poor differentiation.

In the study of Hoegerle et al. [30], 10 MTC patients underwent both FDOPA-PET and FDG-PET after thyroidectomy. The sensitivity of both methods on a per-patient-based analysis was the same (60%), with discordant results in two patients (discordance rate was 20%: one case was positive at FDOPA-PET and negative at FDG-PET, another case was positive at FDG-PET and negative at FDOPA-PET). Nevertheless, FDOPA-PET revealed more lymph nodal metastases on a per lesion-based analysis compared to FDG-PET [30].

In the study of Beuthien-Baumann et al. [23], 15 MTC patients underwent both FDOPA-PET and FDG-PET after thyroidectomy. The sensitivity of both methods on a per-patient-based analysis was the same (47%), with discordant results in most of the patients on a per lesion-based analysis [23].

Koopmans et al. [18] performed both PET methods in 17 patients with recurrent MTC, reporting a higher sensitivity of FDOPA-PET compared to FDG-PET on a per-patient-based analysis (62% versus 24%, resp.); furthermore, these authors found discordant results in 7/17 (41%) patients. In particular in 6 patients FDOPA-PET was positive and FDG-PET was negative for MTC recurrence [18].

In 2009 Beheshiti et al. [16] found a superiority of FDOPA-PET/CT compared to FDG-PET/CT in 19 MTC patients evaluated after primary surgery (sensitivity on a per-patient-based analysis was 81% versus 58%, resp.). Discordant results between the two methods were found in most of the patients; in particular, FDOPA-PET/CT detected more lesions compared to FDG-PET/CT [16].

Marzola et al. [13] evaluated 18 patients who underwent both PET/CT methods for suspected MTC recurrence. These authors found a higher sensitivity of FDOPA-PET/CT compared to FDG PET/CT on a per-patient-based analysis (83% versus 61%, resp.). Discordant results were found in 6 cases (33%): in particular 5 patients were positive at FDOPA-PET/CT alone and one patient was positive at FDG-PET/CT alone [13].

Recently, Kauhanen et al. [6] evaluated 19 recurrent MTC patients with both methods, reporting a superiority of FDOPA-PET/CT compared to FDG-PET/CT (sensitivity on a per-patient-based analysis was 58% versus 53%, resp.). For most MTC patients with occult disease, FDOPA-PET/CT accurately detected metastases. In patients with an unstable calcitonin level, FDOPA-PET/CT and FDG-PET/CT were complementary. For patients with an unstable CEA doubling time, FDG-PET/CT was more feasible [6].

Lastly, in a recent multicentric study [5], 18 recurrent MTC performed both PET/CT methods. The sensitivity of FDOPA-PET/CT was superior compared to FDG-PET/CT on a per-patient-based analysis (72% versus 17%, resp.). Discordant results between FDOPA-PET/CT and FDG-PET/CT were found in 10/18 patients (56%), in whom FDOPA-PET/CT was positive and FDG-PET/CT was negative for MTC recurrence [5].

(C) PET and PET/CT Using Other Radiopharmaceuticals. Neuroendocrine tumors usually overexpress somatostatin receptors on their cell surface and this represents the rationale for using somatostatin analogues for diagnosis and therapy of these tumors. In fact, PET or PET/CT using somatostatin analogues labelled with Gallium-68 are valuable diagnostic tools for patients with neuroendocrine tumors [42]. Nevertheless, the experience with somatostatin analogues PET tracers in recurrent MTC is very limited [5, 9, 15]. A recent study comparing FDOPA, FDG, and somatostatin analogues labelled with Gallium-68 in recurrent MTC showed a significantly lower sensitivity of somatostatin receptor PET/CT (33%) compared to FDOPA-PET/CT (72%) [5]. Another study reported a complementary role of somatostatin receptor PET/CT compared to FDG-PET/CT in recurrent MTC [15].

However, somatostatin receptor PET could be a useful method in selecting patients for radioreceptor therapy to treat metastatic lesions showing a high expression of somatostatin receptors.

Lastly, Carbon-11-Methionine, a PET radiopharmaceutical used to evaluate the amino acid metabolism, was also used in detecting recurrent MTC, without significant advantages compared to FDG [10].

4. Conclusion and Future Perspectives

PET radiopharmaceuticals reflect different metabolic pathways and seem to show complementary role in detecting recurrent MTC.

There is an increasing evidence in the literature about the role of FDG-PET and PET/CT in recurrent MTC. FDG-PET and PET/CT should not be considered as first-line diagnostic imaging methods in patients with suspected recurrent MTC, but could be very helpful in detecting recurrence in those patients in whom a more aggressive disease is suspected.

To date, FDOPA seems to be the most useful PET radiopharmaceutical in detecting recurrent MTC based on rising levels of tumor markers. Nevertheless, the literature focusing
on the use of FDOPA-PET or PET/CT in the detection of recurrent MTC remains still limited.

Other PET radiopharmaceuticals, such as somatostatin analogues labelled with Gallium-68, were also evaluated for this indication in a limited number of studies.

Multicenter and prospective studies investigating a larger patient population and comparing different PET radiopharmaceuticals in recurrent MTC are needed.

**Conflict of Interests**

The authors declare that they have no conflict of interests.

**References**

[1] S. C. Pitt and J. F. Moley, “Medullary, anaplastic, and metastatic cancers of the thyroid,” *Seminars in Oncology*, vol. 37, no. 6, pp. 567–579, 2010.

[2] American Thyroid Association Guidelines Task Force, R. T. Kloos, C. Eng et al., “Medullary thyroid cancer: management guidelines of the American Thyroid Association,” *Thyroid*, vol. 19, no. 6, pp. 565–612, 2009.

[3] V. Rufini, G. Treglia, G. Perotti, L. Leccisotti, M. L. Calcagni, and D. Rubello, “Role of PET in medullary thyroid carcinoma,” *Minerva Endocrinologica*, vol. 33, no. 2, pp. 67–73, 2008.

[4] V. Rufini, P. Castaldi, G. Treglia et al., “Nuclear medicine procedures in the diagnosis and therapy of medullary thyroid carcinoma,” *Biomedicine and Pharmacotherapy*, vol. 62, no. 3, pp. 139–146, 2008.

[5] G. Treglia, P. Castaldi, M. F. Villani et al., “Comparison of [18F]DOPA, [18F]FDG and [68Ga]-somatostatin analogue PET/CT in patients with recurrent medullary thyroid carcinoma,” *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 39, pp. 569–580, 2012.

[6] S. Kauhanen, C. Schalin-Jäntti, M. Seppänen et al., “Complementary roles of [18F]-DOPA, [18F]-FDG and [68Ga]-somatostatin analogue PET/CT in medullary thyroid cancer,” *Journal of Nuclear Medicine*, vol. 52, pp. 1855–1863, 2011.

[7] E. Ozkan, C. Soydal, O. N. Kucuk, E. Ibis, and G. Erbay, “Impact of [18F]-FDG PET/CT for detecting recurrence of medullary thyroid carcinoma,” *Nuclear Medicine Communications*, vol. 32, pp. 1162–1168, 2011.

[8] P. Gómez-Camarero, A. Ortiz-de Tena, I. Borrego-Dorado et al., “Evaluation of efficacy and clinical impact of [18F]-FDG-PET in the diagnosis of recurrent medullary thyroid cancer with increased calcitonin and negative imaging test,” *Revista Española de Medicina Nuclear*. In press.

[9] I. Palgya, A. Kowalska, D. Gąsior-Perczak et al., “The role of PET-CT scan with somatostatin analogue labelled with gallium-68 ([68Ga]-DOTA-TATE PET-CT) in diagnosing patients with disseminated medullary thyroid carcinoma (MTC),” *Endokrynologia Polska*, vol. 61, no. 5, pp. 507–511, 2010.

[10] H. W. Jang, J. Y. Choi, J. I. Lee et al., “Localization of medullary thyroid carcinoma after surgery using 11C-methionine pet/ct: comparison with [18F]-FDG PET/CT,” *Endocrine Journal*, vol. 57, no. 12, pp. 1045–1054, 2010.

[11] M. Luster, W. Karges, K. Zeich et al., “Clinical value of 18-fluorine-fluorodihydroxyphenylalanine positron emission tomography/computed tomography in the follow-up of medullary thyroid carcinoma,” *Thyroid*, vol. 20, no. 5, pp. 527–533, 2010.

[12] E. Skoura, P. Rondogianni, M. Alevizaki et al., “Role of [18F]FDG-PET/CT in the detection of occult recurrent medullary thyroid cancer,” *Nuclear Medicine Communications*, vol. 31, no. 6, pp. 567–575, 2010.

[13] M. C. Marzola, M. R. Pelizzo, M. Ferdeghini et al., “Dual PET/CT with [18F]-DOPA and [18F]-FDG in metastatic medullary thyroid carcinoma and rapidly increasing calcitonin levels: comparison with conventional imaging,” *European Journal of Surgical Oncology*, vol. 36, no. 4, pp. 414–421, 2010.

[14] T. V. Bogsrud, D. Karantanis, M. A. Nathan et al., “The prognostic value of 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography in patients with suspected residual or recurrent medullary thyroid carcinoma,” *Molecular Imaging and Biology*, vol. 12, no. 5, pp. 547–553, 2010.

[15] B. G. Conry, N. D. Papathanasiou, V. Prakash et al., “Comparison of [68Ga]-DOTATATE and [18F]-fluorodeoxyglucose PET/CT in the detection of recurrent medullary thyroid carcinoma,” *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 37, no. 1, pp. 49–57, 2010.

[16] M. Beheshti, S. Förcher, R. Vali et al., “The value of [18F]-DOPA PET-CT in patients with medullary thyroid carcinoma: comparison with [18F]-FDG PET-CT,” *European Radiology*, vol. 19, no. 6, pp. 1425–1434, 2009.

[17] A. Faggiano, F. Grimaldi, L. Pezzullo et al., “Secretive and proliferative tumor profile helps to select the best imaging technique to identify postoperative persistent or relapsing medullary thyroid cancer,” *Endocrine-Related Cancer*, vol. 16, no. 1, pp. 225–231, 2009.

[18] K. P. Koopmans, J. W. B. De Groot, J. T. M. Plukker et al., “[18F]-dihydroxyphenylalanine PET in patients with biochemical evidence of medullary thyroid cancer: relation to tumor differentiation,” *Journal of Nuclear Medicine*, vol. 49, no. 4, pp. 524–531, 2008.

[19] D. Rubello, L. Rampin, C. Nanni et al., “The role of [18F]-FDG PET/CT in detecting metastatic deposits of recurrent medullary thyroid carcinoma: a prospective study,” *European Journal of Surgical Oncology*, vol. 34, no. 5, pp. 581–586, 2008.

[20] A. Oudoux, P. Y. Salau, C. Bournaud et al., “Sensitivity and prognostic value of positron emission tomography with F-18-fluorodeoxyglucose and sensitivity of immunoscintigraphy in patients with medullary thyroid carcinoma treated with anti-carcinoembryonic antigen-targeted radioimmunotherapy,” *Journal of Clinical Endocrinology and Metabolism*, vol. 92, no. 12, pp. 4590–4597, 2007.

[21] A. L. Giraudet, D. Vanel, S. Leboulleux et al., “Imaging medullary thyroid carcinoma with persistent elevated calcitonin levels,” *Journal of Clinical Endocrinology and Metabolism*, vol. 92, no. 11, pp. 4185–4190, 2007.

[22] R. Czepczyński, M. G. Pariseau, J. Kosowicz et al., “Somatostatin receptor scintigraphy using 99mTc-EDDA/HYNIC-TOC in patients with medullary thyroid carcinoma,” *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 34, no. 10, pp. 1635–1645, 2007.

[23] B. Beuthien-Baumann, A. Strumpf, J. Zessin, J. Bredow, and J. Kotzerke, “Diagnostic impact of PET with [18F]-FDG, [18F]-DOPA and 3-O-methyl-[18F]fluoro-D-glucose in recurrent or metastatic medullary thyroid carcinoma,” *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 34, no. 10, pp. 1604–1609, 2007.

[24] S. C. Ong, H. Schöder, S. G. Patel et al., “Diagnostic accuracy of [18F]-FDG PET in restaging patients with medullary thyroid carcinoma and elevated calcitonin levels,” *Journal of Nuclear Medicine*, vol. 48, no. 4, pp. 501–507, 2007.
[25] A. Iagaru, R. Masamed, P. A. Singer, and P. S. Conti, “Detection of occult medullary thyroid cancer recurrence with 2-Deoxy-2-[F-18]fluoro-d-glucose-PET and PET/CT,” Molecular Imaging and Biology, vol. 9, no. 2, pp. 72–77, 2007.

[26] M. Gotthardt, M. P. Béhé, D. Beuter et al., “Improved tumour detection by gastrin receptor scintigraphy in patients with metastasised medullary thyroid carcinoma,” European Journal of Nuclear Medicine and Molecular Imaging, vol. 33, no. 11, pp. 1273–1279, 2006.

[27] J. W. B. de Groot, T. P. Links, P. L. Jager, T. Kahraman, and J. T. M. Plukker, “Impact of 18F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in patients with biochemical evidence of recurrent or residual medullary thyroid cancer,” Annals of Surgical Oncology, vol. 11, no. 8, pp. 786–794, 2004.

[28] S. Szakáll Jr., O. Ésik, G. Bajzik et al., “18F-FDG PET detection of lymph node metastases in medullary thyroid carcinoma,” European Journal of Nuclear Medicine, vol. 43, no. 1, pp. 66–71, 2002.

[29] M. Diehl, J. H. Risse, K. Brandt-Mainz et al., “Fluorine-18 fluorodeoxyglucose positron emission tomography in medullary thyroid cancer: results of a multicentre study,” European Journal of Nuclear Medicine, vol. 28, no. 11, pp. 1671–1676, 2001.

[30] 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, vol. 28, no. 1, pp. 64–71, 2001.

[31] K. Brandt-Mainz, S. P. Müller, R. Görges, B. Saller, and A. Bockisch, “The value of fluorine-18 fluorodeoxyglucose PET in patients with medullary thyroid cancer,” European Journal of Nuclear Medicine, vol. 27, no. 5, pp. 490–496, 2000.

[32] S. Adams, R. Baum, T. Rink, P. M. Schumm-Dräger, K. H. Usadel, and G. Hör, “Limited value of fluorine-18 fluorodeoxyglucose positron emission tomography for the imaging of neuroendocrine tumours,” European Journal of Nuclear Medicine, vol. 25, no. 1, pp. 79–83, 1998.

[33] T. J. Musholt, P. B. Musholt, F. Dehdaští, and J. F. Moley, “Evaluation of fluorodeoxyglucose positron-emission tomographic scanning and its association with glucose transporter expression in medullary thyroid carcinoma and pheochromocytoma: a clinical and molecular study,” Surgery, vol. 122, no. 6, pp. 1049–1061, 1997.

[34] S. Adams, R. P. Baum, A. Hertel, P. M. Schumm-Dräger, K. H. Usadel, and G. Hör, “Metabolic (PET) and receptor (SPECT) imaging of well- and less well- differentiated tumours: comparison with the expression of the Ki-67 antigen,” Nuclear Medicine Communications, vol. 19, no. 7, pp. 641–647, 1998.

[35] R. Czepczyński, J. Kosowicz, K. Ziemiańska, R. Mikołajczak, M. Gryczyńska, and J. Sowiński, “The role of scintigraphy with the use of 99mTc-HYNIC-TOC in the diagnosis of medullary thyroid carcinoma,” Endokrynologia Polska, vol. 57, no. 4, pp. 431–435, 2006.

[36] M. Gotthardt, A. Battmann, H. Höffken et al., “18F-FDG PET, somatostatin receptor scintigraphy, and CT in metastatic medullary thyroid carcinoma: a clinical study and an analysis of the literature,” Nuclear Medicine Communications, vol. 25, no. 5, pp. 439–443, 2004.

[37] A. Boer, S. Szakáll Jr., I. Klein et al., “FDG PET imaging in hereditary thyroid cancer,” European Journal of Surgical Oncology, vol. 29, no. 10, pp. 922–928, 2003.

[38] S. Szakáll Jr., G. Bajzik, I. Repa et al., “FDG PET scan of metastases in recurrent medullary carcinoma of the thyroid gland,” Orvosi Hetilap, vol. 143, no. 21, pp. 1280–1283, 2002.