European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-019-04458-6

GUIDELINES

EANM practice guideline for PET/CT imaging in medullary thyroid carcinoma

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Received: 6 July 2019 / Accepted: 22 July 2019

Abstract

Background Medullary thyroid carcinoma (MTC) is a malignant tumour derived from the para-follicular thyroid C cells. It may occur in sporadic or hereditary forms and surgery represent the primary cure.

Methods Ultrasound examination and, in selected cases, cross-sectional anatomic imaging procedures, are adopted to stage the disease before primary surgery while different anatomic/morphologic and functional/molecular imaging procedures can be adopted in detecting persistent/recurrent disease. Positron emitting radiopharmaceuticals including fluorine-18 fluorodeoxyglucose (^{18}F-FDG), fluorine-18 dihydroxyphenylalanine (^{18}F-FDOPA) and somatostatin analogues labelled with gallium-68 (^{68}Ga-SSA) tracks different metabolic pathways or receptor expression/functioning, and proved to be useful in detecting MTC recurrences/metastasis.

Conclusions This practice guideline from the Thyroid Committee of the European Association of Nuclear Medicine (EANM), with involvement of external experts, provides recommendations based on updated literature's evidences. The purpose of this practice guideline is to assist imaging specialists and clinicians in recommending, performing and interpreting the results of PET/CT with various radiopharmaceuticals in patients with MTC.

Keywords Medullary thyroid carcinoma · PET/CT · Fluorodeoxyglucose · Dihydroxyphenylalanine · Somatostatin

Preamble

The European Association of Nuclear Medicine (EANM) is a nonprofit association pursuing clinical and research excellence in nuclear medicine. The EANM defines guidelines to improve the quality of nuclear medicine practice and research in order to provide the most appropriate care for patients. Such guidelines, however, are neither inflexible rules nor requirements of practice nor established legal standard of care. Practitioners may diverge from guidelines when different actions are required by the condition of the patient, resources availability or new insights. This practice guideline has been developed to assist imaging specialists and clinicians in recommending, performing and interpreting the results of PET/CT with different radiopharmaceuticals in patients with MTC. An additional aim is to facilitate future prospective multicentre studies. To obtain an evidence-based practice guideline, a preliminary systematic search of the literature was performed through PubMed and Cochrane library database (search date: 31.12.2017). The key words combination used for the literature search was: A) "PET" OR "positron emission tomography" AND B) "medullary" AND C) "thyroid". Articles in English language were selected and reported in the reference list. Case reports and articles reporting data on non-hybrid modalities (PET only) were excluded. The recommendations on the use of PET/CT with different radiopharmaceuticals in MTC were developed by a panel of experts and underwent multiple rounds of revision until consensus was achieved.

This article is part of the Topical Collection on Oncology – Head and Neck

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Published online: 04 September 2019

Medullary thyroid carcinoma: background informations

Epidemiology, tumour origin and genetics

Medullary thyroid carcinoma (MTC) is a neuroendocrine tumour originating from the neural crest-derived parafollicular C cells of the thyroid gland and accounts for about 1 to 2% of thyroid malignancies [1, 2]. MTC occurs in sporadic or hereditary form, the latter being part of type 2 multiple endocrine neoplasia (MEN2) syndromes. MEN2 syndromes are caused by different germline mutations in RET protooncogene (located on chromosome 10q11.2), encoding a transmembrane receptor of the tyrosine kinase family, associated with different biological and clinical behaviour [1, 3–5]. About 50% of sporadic MTCs carried somatic RET mutations while RAS mutations are detected in a significant proportion of remaining tumours [3–7].

Clinical presentation

Classical MEN2A syndromes (95% of cases, incidence 1/1,973,500) include MTC, pheochromocytoma (PHEO) and hyperparathyroidism (HPTH). Cutaneous lichen amyloidosis or Hirschsprung's disease may also coexist in some cases (MEN2A variants). Patients with MEN2B (5% of cases, incidence 1/38,750,000), develop aggressive MTC in infancy, associated with PHEO [4]. Inherited MTC may also present in families or individuals with RET germline mutations but neither PHEOs nor HPTH (i.e. familial MTC, FMTC) [3]. MEN2-related MTCs are generally multicentric and involve both thyroid lobes whereas sporadic MTCs occur in adults (~ 40–60 years) and are usually unifocal and monolateral [4, 6–8]. About 7% of patients with presumed sporadic MTC carry germline mutations [1]. Accordingly, genetic testing, that is mandatory in patients with MEN2 syndromes and their first-degree relatives should be also offered to patients with presumed sporadic MTC. Lymph node metastases are present in 14% (central neck compartment) and 11% (lateral neck compartments) of patients with T1 tumours and in up to 86% and 93% of patients with T4 tumours, respectively [9, 10]. Ten years after MTC diagnosis survival rates of 100%, 93%, 71% and 21% were observed in patients with AJCC stage I, II, III and IV MTC [11].

Serum tumour markers

Calcitonin (CT) and procalcitonin (PCT) are specifically secreted by parafollicular C cells and serve as valuable tumour markers in patients with MTC [1, 12–14]. CEA is an aspecific tumour marker but it is a useful complementary tool to detect disease relapse and progression after primary treatment [1]. Notably, both calcitonin and CEA doubling times are useful prognostic predictors in patients with persistent disease after surgery [1].

Cytology and histology

Fine needle aspiration cytology (FNAC) is able to detect ~ 50% of MTCs [15]. Immunocytochemical (ICC) staining against CT and/or its measurement in the needle washouts significantly increase diagnostic accuracy when inconclusive cytological findings are rendered [1, 16, 17]. Sporadic MTCs are generally unifocal, whereas inherited tumours are multicentric and involve both lobes [17, 18]. In case of microscopic features suggesting MTC additional immunostaining against specific biomarkers (i.e. CT, CEA, chromogranin A) is warranted [19].

Role of imaging methods in MTC

The only potentially curative treatment for MTC is surgery, consisting in total thyroidectomy and with risk-adapted neck dissections. Surgery and imaging-guided local treatments (i.e. external beam radiotherapy, thermal ablations, cementoplasty) and thyrosine kinase inhibitors can be used and combined to treat progressive advanced MTC [12]. Different anatomical and functional imaging procedures may be used in patients with MTC to stage the disease before surgery as well as to detect persistent/recurrent disease [1, 12, 20, 21]. Whereas the role of functional radionuclide imaging is limited in preoperative staging [22], its role may be valuable to detect and localize recurrent disease in front of postoperative increase of serum levels of MTC markers with corresponding negative or inconclusive morphologic imaging.

Radionuclide imaging in MTC: gamma emitting radiopharmaceuticals

Technetium-99m-labelled pentavalent dimercaptosuccinic acid (^{99m}Tc-(V)DMSA), somatostatin Indium-111/technetium-99m labelled somatostatin analogues (^{111}In-pentetreotide, ^{99m}Tc-depreotide) and iodine-123-labelled metaiodobenzylguanidine (^{123}I-MIBG) were proposed to detect MTC relapse but overall sensitivity is unsatisfactory compared with conventional anatomic imaging (i.e. US, CT, MRI) and positron emission tomography/computed tomography [12, 21–31]. However, current clinical guidelines recommend whole-body bone scan with ^{99m}Tc-diphosphonates to detect/exclude bone metastases in MTC patients [32]. Finally, a positive ^{123}I-MIBG scan in patients with relapsing/advanced MTC (about 30% of cases) predicts partial remission or

stabilization of the disease after radiometabolic treatment with ^{131}I-MIBG [21, 22, 31].

Radionuclide imaging in MTC: positron emitting radiopharmaceuticals

Although several radionuclide imaging modalities are available, PET/CT using ^{18}F-fluorodeoxyglucose (^{18}F-FDG), ^{18}F-fluoroDOPA (^{18}F-FDOPA) and ^{68}Ga-somatostatin analogues (^{68}Ga-SSA) offers higher sensitivity imaging compared with conventional nuclear medicine techniques, therefore these practice guidelines will be focused on PET/CT imaging in MTC.

PET/CT imaging in MTC patients: procedure guidelines

PET/CT examinations should be performed according to existing procedure guidelines for ^{18}F-FDG PET/CT tumour imaging [33] and for PET/CT imaging of neuroendocrine neoplasms with ^{18}F-FDOPA and ^{68}Ga-SSA [34], respectively.

Mechanism of uptake and rationale for PET tracers use in MTC

^{18}F-FDG It is the most used PET radiopharmaceutical worldwide; as glucose analogue, the use of ^{18}F-FDG for PET imaging allows to detect tumours with increased glucose metabolism. ^{18}F-FDG uptake in MTC cells is linked to glucose transporters (GLUT) overexpression and increased hexokinase activity. Furthermore, ^{18}F-FDG uptake correlates with high proliferative activity and poor differentiation of MTC cells [35–39].

^{18}F-FDOPA DOPA is the precursor of endogenous catecholamines. ^{18}F-FDOPA is picked up by specific transporters (L-type amino acid transporter, LAT) and converted to ^{18}F-dopamine by cytosolic aromatic amino acid decarboxylase (AADC). Both LAT expression and AADC activity are upregulated in MTC cells leading to increased ^{18}F-FDOPA uptake in MTC lesions [38, 39].

^{68}Ga-SSA NET cells may overexpress somatostatin receptors (SSTRs) and this is the rationale for using radiolabelled SSA as targets for both radionuclide imaging (i.e. by using SSA labelled with positron-emitters such as ^{68}Ga) and therapy (i.e. by using SSA labelled with beta-emitters such as ^{177}Lu and ^{90}Y) of NETs. ^{68}Ga-SSA (i.e. DOTATOC, DOTATATE, DOTANOC, DOTALAN) have different affinities for the five SSTR subtypes. Overall, all ^{68}Ga-SSA can target SSTR subtype 2 efficiently, which is the SSTR subtype most overexpressed in NETs [34]. Radiolabelled SSA binding and retention in MTC cells is related to some specific aspects including density of SSTRs on the cell surface and degree of internalization of the SSA-SSTR complex [34].

Synthesis and quality control

^{18}F-FDG The synthesis and quality control of ^{18}F-FDG have to conform to the criteria laid down in the European Pharmacopeia or the US Pharmacopeia. ^{18}F-FDG can be prepared in-house or provided "ready to use".

^{18}F-FDOPA The synthesis of ^{18}F-FDOPA requires up to 4 h and unfortunately it is characterized by a low labelling efficiency. ^{18}F-FDOPA can be prepared in-house or it can be supplied in two different formulations that conforms the criteria laid down in the European Pharmacopoeia: "ready to use" or neutralized using a bicarbonate buffer kit supplied by the manufacturer.

^{68}Ga-SSA ^{68}Ga-SSA synthesis can be performed in-house and must fulfil the criteria laid down in the European Pharmacopoeia monographs and/or good radiopharmaceutical practice. Radiolabelling of SSA with ^{68}Ga is automated and requires between 20 and 30 min providing high radiochemical purity. The labelling procedure includes the following steps: ^{68}Ga elution by ^{68}Ge/^{68}Ga generators, SSA radiolabelling, purification, sterilization and quality controls.

Dosage/activity and administration

All the PET radiopharmaceuticals for MTC are intravenously administered with activities dependent on several factors as the patient's weight, the PET/CT scanner, the acquisition time and in adult patients usually range from 2 to 5 MBq/kg, 2 to 4 MBq/kg and 100 to 200 MBq for ^{18}F-FDG, ^{18}F-FDOPA and ^{68}Ga-SSA, respectively. The amount of SSA injected should be less than 50 μg without any significant pharmacological effect expected.

Radiation dosimetry

The effective doses are 0.020–0.025 mSv/MBq for ^{18}F-FDG, ~ 0.020 mSv/MBq for ^{18}F-FDOPA and ~ 0.025 mSv/MBq for ^{68}Ga-SSA, respectively (ICRP publication 128, 2015). Additional radiation exposure originates from the CT scan carried out in the ^{18}F-FDG PET/CT study and the effective dose by this exposure depends on the characteristics of the CT system (diagnostic/low dose attenuation) and may differ strongly from patient to patient.

Precautions

In female patients with known or suspected pregnancy, the decision to perform or not PET/CT examinations should take into account the benefits against the possible harm. It is suggested to discontinue breastfeeding for 12 h after PET/CT imaging.

Patient preparation

^{18}F-FDG Fasting for at least 4 h prior to ^{18}F-FDG injection is required to lower blood glucose and insulin levels and, in turn, reduce uptake by non-tumour cells. ^{18}F-FDG can be administered if the glucose level is < 11 mmol/L. Diabetic patients require specific instructions for glucose control. In order to minimize ^{18}F-FDG uptake in muscles strenuous exercise should be avoided for at least 6 h before ^{18}F-FDG administration. Additionally, patients are required to remain seated or recumbent and silent during the injection of ^{18}F-FDG and the following uptake phase. An adequate room temperature should be assured before the injection of ^{18}F-FDG and throughout the subsequent phases to minimize ^{18}F-FDG uptake in brown adipose tissue (BAT).

^{18}F-FDOPA On precautional basis, ^{18}F-FDOPA should be administered to patients fasting for at least 4 h without limiting water intake to avoid interactions with amino acids from food. No consensus exists about the oral administration of carbidopa (i.e. a decarboxylase inhibitor) 1 h before ^{18}F-FDOPA injection, to increase ^{18}F-FDOPA uptake in MTC cells.

^{68}Ga-SSA There is no need of fasting before ^{68}Ga-SSA injection. The need of cold SSA discontinuation prior to ^{68}Ga-SSA PET/CT is still debated.

In all cases, for radiation safety reasons, low urinary concentration of PET radiopharmaceuticals should be assured providing adequate patients' hydration. In addition, the bladder activity must be reduced asking the patients to void immediately prior to the PET/CT examination. Patients should be also able to lie still for during the entire examination.

Image acquisition

PET/CT scans are usually obtained 60 min (from 45 to 90 min) after ^{18}F-FDG injection; 30 to 60 min after ^{18}F-FDOPA injection and 45 to 90 min after ^{68}Ga-SSA injection, respectively. The imaging field ranges from the base of the skull to the mid-thighs (or whole-body imaging, depending on the clinical setting). First topogram, then low-dose CT images and finally PET images are acquired. Early ^{18}F-FDOPA images (at 15 min after radiopharmaceutical injection) centred over the neck may also be acquired in patients with MTC. In fact, MTC lesions often show rapid washout and are better visualized on these early PET images [40, 41]. Usually, a low-dose CT scan protocol is adopted for attenuation correction and anatomical correlation. Additional standard contrast-enhanced CT scan should be performed in the same setting if clinically appropriate and justified (e.g. suspicion of local invasive disease or vascular invasion or suspicious metastases in sites of physiological tracer uptake).

Image analysis

PET/CT scans must be visually evaluated and interpreted by a board-certified nuclear medicine physician. Maximum intensity projection (MIP) PET images, as well as fused PET/CT slices in different projections (transaxial, sagittal and coronal) should be visualized. Physiological radiopharmaceutical uptake or excretion and abnormal findings should be evaluated. In particular:

^{18}F-FDG Physiological uptake or excretion can be seen in the brain cortex, salivary glands, lymphatic tissue of the Waldeyer's ring, muscles, brown fat, myocardium, mediastinum, liver, kidneys and bladder, gastrointestinal tract, testes, uterus and ovaries (before menopause) [33].

^{18}F-FDOPA Physiological uptake or excretion can be seen in the striatum, pancreas, liver, gallbladder, biliary tract, bowel, kidneys and urinary tract. Adrenal glands can be faintly visible [39, 42, 43].

^{18}Ga-SSA Physiological uptake or excretion can be seen in the liver, spleen, pituitary, thyroid, kidneys, adrenal glands, salivary glands, stomach wall, bowel, pancreas, prostate gland and breast. The differences among various radiolabelled SSA (due to different affinities for SSTR subtypes) have no significant impact on the interpretation of the PET scans [34].

A PET finding is considered abnormal when focal tracer accumulation is greater than background blood-pool activity and located outside of organs with physiologic tracer uptake or when exceeding the physiological background activity within an organ. Abnormal PET tracer accumulation, especially focal accumulation, should be evaluated in combination with intensity of uptake and anatomical findings at co-registered CT scan. Additionally, semi-quantitative PET analysis can be performed by reporting the maximal standardized uptake value (SUVmax) of the PET findings, calculated based on measured activity, decay-corrected injected dose and patient body weight. However, the contribution SUVmax to patients' assessment is debated mainly due to the wide methodological variability [33].

Pitfalls

^{18}F-FDG Possible causes of false negative findings are small, slow-growing, necrotic, calcified or sclerotic MTC lesions or located near or in sites of physiological radiopharmaceutical uptake [40]. False positive findings may be due to inflammatory lesions (due to the high consumption of glucose by inflammatory cells) or other tumours [40].

^{18}F-FDOPA Possible causes of false negative findings are small MTC lesions or located near or in sites of physiological radiopharmaceutical uptake or tumour dedifferentiation [41–44]. False positive results are uncommon and they may be related to radiopharmaceutical uptake by other NETs beyond MTC. Rarely, ^{18}F-FDOPA uptake may be due to inflammation, since high levels of amino acid transport have also been found in macrophages [42–44].

^{18}Ga-SSA Possible causes of false negative findings are small MTC lesions or located near or in sites of physiological radiopharmaceutical uptake or expressing low amount of SSTRs or tumour dedifferentiation [34, 45, 46]. False positive results of ^{18}Ga-SSA PET/CT may be related to radiopharmaceutical uptake by residual thyroid tissue, non-specific uptake in jugulodigastric lymph nodes, benign bone lesions (hemangioma and fractures), ectopic spleen tissue, other tumours or inflammation (since activated lymphocytes may overexpress SSTRs) [34, 45].

Other PET radiopharmaceuticals in MTC

Limited literature data are available about other PET radiopharmaceuticals in patients with MTC [47, 48]. One study demonstrated the feasibility of anti-CEA immune-PET using a ^{68}Ga-labelled radiotracer (IMP288) in MTC patients [47]. Another study evaluated the possible role of PET using the amino acid tracer ^{11}C-methionine in patients with recurrent MTC but minimal additional information compared with combined ^{18}F-FDG PET/CT and neck US has been reported [48].

Preoperative imaging

Neck US is useful to evaluate the risk of malignancy of thyroid nodules. However, even if solid hypoechoic nodules with intra-nodular coarse calcifications may be suspicious for MTC, no pathognomonic US features are available and serum CT measurement should be promptly required in case of US suspicious features [1]. All patients with suspicious MTC deserve a careful neck US to evaluated capsular infiltration and/or lymph node metastases. Preoperative staging of MTC Neck US is mostly based on neck US and serum CT levels [1, 12, 20]. Additional cross-sectional imaging (computed tomography and/or magnetic resonance imaging) is recommended in patients with positive US examination and/or serum CT > 500 pg/mL [12].

Imaging for detection of persistent/recurrent MTC

According to current clinical guidelines, a careful clinical examination and neck US are required in patients with detectable serum CT with levels < 150 pg/mL as cervical lymph nodes are generally involved in such cases. Patients with a negative assessment are followed by serum CT and CEA measurement and neck US examination every 6 to 12 months [12]. Patients with postoperative CT > 150 pg/mL and/or shortened CT/CEA doubling times deserve more extensive evaluation by anatomic imaging procedures (US, CT, MRI) and bone scintigraphy to promptly detect MTC metastases [12, 21]. Additionally, PET/CT using different radiopharmaceuticals (i.e. ^{18}F-FDG, ^{18}F-FDOPA and ^{68}Ga-SSA) proved to be sensitive and accurate in detecting MTC recurrences/metastases and assess their biological and clinical aggressiveness [1, 12, 47-73].

Diagnostic performance of ^{18}F-FDG-PET/CT

Basic characteristics, technical aspects and main findings of articles about ^{18}F-FDG PET/CT in patients with MTC are briefly reported in Tables 1 and 2. Several studies [27, 32, 46, 70–73] and two meta-analyses [44, 45] evaluated the role of ^{18}F-FDG PET/CT in recurrent MTC, whereas limited data are available on preoperative MTC staging [65–68]. Overall, conflicting results were described in patients with recurrent MTC with reported patient-based sensitivity and specificity ranging from 17 to 93% and from 68 to 92%, respectively (Table 2). Such heterogeneous findings are likely related to different procedures and technical protocols and different inclusion criteria adopted in different studies (i.e. previously known lesions versus occult disease; smouldering versus aggressive disease) [38]. Basing on meta-analysis studies the patient-based detection rate of ^{18}F-FDG PET or PET/CT in recurrent MTC ranges from 59% (95% confidence interval: 54–63%) to 69% (95% confidence interval: 64–74%) [69, 70]. Consequently, negative ^{18}F-FDG PET/CT are reported in 30–40% of MTC patients with increasing biomarkers levels. It should be considered, however, that ^{18}F-FDG PET/CT is generally required after previous negative cross-sectional anatomic studies. Additionally, ^{18}F-FDG PET/CT examination may correctly address the management of recurrent MTC when hypermetabolic lesions are detected [69, 70, 71]. Notably, a positive relationship exists between serum levels of CT and CEA and the sensitivity of ^{18}F-FDG PET/CT [1, 12, 32]. Moreover, sensitivity of ^{18}F-FDG PET/CT improves in patients with shorter serum calcitonin and CEA doubling times,

Table 1 Basic study and patient characteristics of relevant articles about ^{18}F-FDG PET/CT in MTC

Authors	Year	Country	Study design	Indication of ^{18}F-FDG PET/CT	Patients evaluated	Mean age (years)	%Male	Type of MTC
Werner et al. [49]	2017	Germany	Retrospective multicentric	Treatment response	18	48	67%	17 sMTC (94%), 1 hMTC (6%)
Romero-Lluch et al. [50]	2017	Spain	Prospective monocentric	Restaging	18	48	28%	10 sMTC (55%), 8 hMTC (45%))
Putzer et al. [51]	2017	Brazil	Retrospective monocentric	Restaging	17	49	29%	10 sMTC (59%), 7 hMTC (41%)
Łapińska et al. [52]	2017	India	Prospective monocentric	restaging	7	NR	NR	NR
Pałyga et al. [53]	2016	Italy	Retrospective monocentric	Staging or restaging	25	60	48%	NR
Traub-Weidinger et al. [46]	2015	Austria	Retrospective monocentric	Restaging	8	NR	NR	NR
Golubić et al. [54]	2014	China	Retrospective monocentric	Restaging	50	49	72%	NR
Archier et al. [55]	2014	France	Prospective monocentric	Treatment response	42	54	60%	NR
Gomez-Camarero et al. [56]	2012	Spain	Retrospective monocentric	Restaging	31	56	45%	17 sMTC (55%), 14 hMTC (45%)
Skoura et al. [57]	2012	Greece	Prospective monocentric	Restaging	51	53	28%	33 sMTC (65%), 18 hMTC (35%)
Rasul et al. [58]	2012	India	Prospective monocentric	Restaging	41	45	73%	NR
Treglia et al. [59]	2012	Italy	Retrospective multicentric	Restaging	18	53	33%	16 sMTC (89%), 2 hMTC (11%)
Kauhanen et al. [60]	2011	Finland	Prospective multicentric	Restaging	19	52	53%	16 sMTC (84%), 3 hMTC (16%)
Ozkan et al. [61]	2011	Turkey	Retrospective monocentric	Restaging	33	50	27%	28 sMTC (85%), 5 hMTC (15%)
Jang et al. [62]	2010	Korea	Prospective monocentric	Restaging	16	51	56%	15 sMTC (94%), 1 sMTC (6%)
Carr et al. [63]	2010	USA	Prospective monocentric	Treatment response	7	NR	NR	NR
Lam et al. [64]	2010	USA	Prospective monocentric	Treatment response	9	NR	NR	NR
Skoura et al. [65]	2010	Greece	Retrospective monocentric	Restaging	32	52	31%	22 sMTC (69%), 10 hMTC (31%)
Marzola et al. [66]	2010	Italy	Prospective monocentric	Restaging	18	51	44%	16 sMTC (89%), 2 hMTC (11%)
Bogsrud et al. [67]	2010	USA and Norway	Retrospective monocentric	Restaging	29	50	55%	21 sMTC (72%), 8 hMTC (28%)
Beheshti et al. [68]	2009	Austria	Retrospective monocentric	Restaging	32	42	38%	17 sMTC (53%), 11 hMTC (34%), 4 NR (13%)
Rubello et al. [69]	2008	Italy	Prospective monocentric	Restaging	19	53	42%	14 sMTC (74%), 5 hMTC (26%)
Oudoux et al. [70]	2007	France	Prospective multicentric	Restaging	33	53	64%	NR
Giraudet et al. [32]	2007	France	Prospective monocentric	Restaging	55	56	62%	43 sMTC (78%), 12 hMTC (22%)
Ong et al. [48]	2007	USA	Retrospective monocentric	Restaging	16	59	64%	NR

NR, not reported; *hMTC*, hereditary medullary thyroid carcinoma; *sMTC*, sporadic medullary thyroid carcinoma

Table 2 Technical aspects and main findings of relevant articles about ^{18}F-FDG PET/CT in MTC

Authors	Injected activity	Time interval between radiotracer injection and image acquisition	Image analysis	Other nuclear medicine techniques performed	Reference standard	Sensitivity	Specificity	Change of management	Prognostic role	Role in treatment response assessment
Werner et al. [49]	NR	60 min	Visual and semi--quantitative	–	RECIST	NR	NR	–	Yes	Yes
Romero-Lluch et al. [50]	164–444 MBq	60 min	Visual and semi--quantitative	^{18}F-FDOPA PET/CT	Pathology and/or clinical/imaging follow-up	50%(p)	NR	–		
Putzer et al. [51]	NR	NR	Visual and semiquantitative	–	Pathology and/or clinical/imaging follow-up	65%(p)	NR	–	Yes	–
Łapińska et al. [52]	NR	NR	Visual and semiquantitative	MIBG	Pathology and/or clinical/imaging follow-up	72%(p)	NR	–	–	–
Pałyga et al. [53]	370 MBq	60 min	Visual and semiquantitative	SRS	Pathology and/or clinical/imaging follow-up	63%(l)	NR	–	–	–
Traub-Weidinger et al. [46]	370 MBq	60 min	Visual	Somatostatin receptor PET/CT	Pathology and/or clinical/imaging follow-up	NR	NR	–	–	–
Golubic et al. [54]	7.4 MBq/Kg	60 min	Visual and semiquantitative	–	Pathology and/or clinical/imaging follow-up	66%(p), 73%(l)	92%(p), 67%(l)	Yes (16%)	–	–
Archier et al. [55]	250–450 MBq	60 min	Visual and semiquantitative	–	RECIST	NR	NR	–	Yes	Yes
Gomez-Camarero et al. [56]	333–434 MBq	60 min	Visual and semiquantitative	–	Pathology and/or clinical/imaging follow-up	88%(p)	85%(p)	Yes (45%)	–	–
Skoura et al. [57]	5 MBq/Kg	60 min	Visual and semiquantitative	–	Pathology and/or clinical/imaging follow-up	44%(p)	NR	–	–	–
Rasul et al. [58]	370 MBq	45–60 min	Visual and semiquantitative	Somatostatin receptor PET/CT	Pathology and/or clinical/imaging follow-up	63%(p)	NR	–	–	–
Treglia et al. [59]	259–407 MBq	60 min	Visual and semiquantitative	^{18}F-FDOPA PET/CT and somatostatin receptor PET/CT	Pathology and/or clinical/imaging follow-up	17%(p), 28%(l)	NR	No	–	–
Kauhanen et al. [60]	377 ± 30 MBq	60 min	Visual and semiquantitative	^{18}F-FDOPA PET/CT	Pathology and/or clinical/imaging follow-up	53%(p), 47%(l)	NR	–	–	–
Ozkan et al. [61]	296–370 MBq	60 min	Visual and semiquantitative	–	Pathology and/or clinical/imaging follow-up	93%(p)	68%(p)	–	–	–

Table 2 (continued)

Authors	Injected activity	Time interval between radiotracer injection and image acquisition	Image analysis	Other nuclear medicine techniques performed	Reference standard	Sensitivity	Specificity	Change of management	Prognostic role	Role in treatment response assessment
Jang et al. [62]	370 MBq	60 min	Visual	SRS, MIBG, bone scan, ^{11}C-methionine PET/CT	Pathology and/or clinical/imaging follow-up	63%(p), 80%(l)	NR	–	–	–
Carr et al. [63]	NR	60 min	Visual and semiquantitative	–	RECIST	NR	NR	–	–	Yes
Lam et al. [64]	NR	75 min	Visual and semiquantitative	–	RECIST	NR	NR	–	–	Yes
Skoura et al. [65]	370 MBq	60 min	Visual and semiquantitative	–	Pathology and/or clinical/imaging follow-up	47%(p)	NR	–	–	–
Marzola et al. [66]	2.2 MBq/Kg	60 min	Visual and semiquantitative	SRS, MIBG, ^{18}F-FDOPA PET/CT	Pathology	61%(p), 58%(l)	NR	–	–	–
Bogsrud et al. [67]	740 MBq	60–90 min	Visual	–	Pathology and/or clinical/imaging follow-up	45%(p)	NR	–	Yes	–
Beheshti et al. [68]	NR	NR	NR	SRS, MIBG, MIBI, bone scan	Pathology and/or clinical/imaging follow-up	NR	NR	Yes	–	–
Beheshti et al. [68]	370 MBq	60 min	Visual and semiquantitative	^{18}F-FDOPA PET/CT	Pathology and/or clinical/imaging follow-up	overall: 58%(p-), 62%(l)				
restaging: 53%(p)	NR	–	–	–						
Rubello et al. [69]	5.5 MBq/Kg	60–90 min	Visual and semiquantitative	SRS	Pathology	79%(p); 93%(l)	NR	Yes (21%)	–	–
Oudoux et al. [70]	5–7 MBq/Kg	60 min	Visual and semiquantitative	Anti-CEA immunoscintigraphy	Pathology and/or clinical/imaging follow-up	76%(l)	NR	–	Yes	–
Giraudet et al. [32]	5 MBq/Kg	60 min	Visual and semiquantitative	Bone scan	Pathology and/or clinical/imaging follow-up	58%(p)	NR	–	No	–
Ong et al. [48]	555 MBq	minimum 45 min	Visual and semiquantitative	SRS	Pathology and/or clinical/imaging follow-up	62%(p)	NR	–	No	–

(p) = on a per patient-based analysis; (l) = on a per patient-based analysis; *NR*, not reported; *MBq*, megaBequerel; *SRS*, somatostatin receptor scintigraphy; *MIBG*, radiolabelled metaiodobenzylguanidine scintigraphy; *MIBI*, ^{99m} Tc-methoxyisobutylisonitrile scintigraphy; *(V)DMSA*, pentavalent dimercaptosuccinic acid scintigraphy

confirming the usefulness of this imaging method in patients with more aggressive disease compared with those with slowly progressive disease [1, 12, 35, 38, 39].

Other indications of ^{18}F-FDG PET/CT in MTC

As demonstrated by some studies, ^{18}F-FDG PET/CT is able to accurately identify MTC patients with poor prognosis and life expectancy [68–70]. Furthermore, this imaging method has been successfully used to evaluate response to targeted therapies in patients with advanced metastatic MTC treatment [62–64].

Diagnostic performance of ^{18}F-FDOPA PET/CT

Basic characteristics, technical aspects and main findings of articles about ^{18}F-FDOPA PET/CT in MTC patients are summarized in Tables 3 and 4. Several studies [61, 62, 67, 70] and one meta-analysis [44] addressed the diagnostic performance of ^{18}F-FDOPA PET/CT in recurrent MTC whereas few data are available about staging MTC before primary surgery [70]. Recently, however, ^{18}F-FDOPA PET/contrast-enhanced CT (PET/ceCT) was reported to be highly sensitivity to stage MTC before surgery. Notably, its sensitivity exceeded that of neck US in detecting cervical lymph node metastases [60]. In summary, a consistently high specificity but a wide patient-based sensitivity range, from 45 to 93%, was reported in different studies using ^{18}F-FDOPA PET/CT in patients with suspicious MTC recurrences (Table 4). Such differences are likely related to different techniques and different inclusion criteria among studies. As reported in a meta-analysis of the literature, the per patient detection rate of ^{18}F-FDOPA PET or PET/CT is 66% (95% confidence interval, 58–74%) in patients with suspected recurrent MTC. When PET-alone studies were excluded this value increases to 72% [44]. All in all, ^{18}F-FDOPA PET/CT may address the surgical management in a significant number of patients with recurrent MTC when positive [59]. Notably, its detection rate further improves in patients with higher levels and shorter doubling time of serum CT, reaching a detection rate of 86% in patients with calcitonin doubling time < 24 months [44, 55–58]. Premedication with carbidopa was previously proposed to improve the tracer's bioavailability but its impact on the detection rate of ^{18}F-FDOPA PET/CT was

Table 3 Basic study and patient characteristics of relevant articles about ^{18}F-FDOPA PET/CT in MTC

Authors	Year	Country	Study design	Indication of ^{18}F-FDOPA PET/CT	Patients evaluated	Mean age (years)	%Male	Type of MTC
Caobelli et al. [72]	2018	Italy	Retrospective multicentric	Restaging and prognosis	60	64	7%	58 sMTC (97%), 2 hMTC (3%)
Romero-Lluch et al. [50]	2017	Spain	Prospective monocentric	Restaging	18	48	28%	10 sMTC (55%), 8 hMTC (45%))
Golubic et al. [54]	2017	Croatia	Prospective monocentric	Restaging	28	57	39%	25 sMTC (89%), 3 hMTC (11%)
Archier et al. [55]	2016	France	Retrospective multicentric	Restaging	86	51	48%	76 sMTC (88%), 10 hMTC (12%)
Sesti et al. [73]	2014	Austria	Retrospective monocentric	Restaging	39	62	54%	NR
Treglia et al. [41]	2013	Italy	Prospective monocentric	Restaging	15	59	40%	NR
Soussan et al. [40]	2012	France	Retrospective monocentric	Staging or restaging	14	50	29%	NR
Chondrogiannis et al. [43]	2012	Italy	Retrospective monocentric	Restaging	43	NR	NR	NR
Treglia et al. [44]	2012	Italy	Retrospective multicentric	Restaging	18	53	33%	16 sMTC (89%), 2 hMTC (11%)
Kauhanen et al. [60]	2011	Finland	Prospective multicentric	Restaging	19	52	53%	16 sMTC (84%), 3 hMTC (16%)
Luster et al. [75]	2010	Germany	Retrospective monocentric	Restaging	26	48	46%	15 sMTC (58%), 11 hMTC (42%)
Marzola et al. [66]	2010	Italy	Prospective monocentric	Restaging	18	51	44%	16 sMTC (89%), 2 hMTC (11%)
Beheshti et al. [68]	2009	Austria	Prospective monocentric	Staging or restaging	26	59	38%	25 sMTC (96%), 1 hMTC (4%)

NR, not reported; *hMTC*, hereditary medullary thyroid carcinoma; *sMTC*, sporadic medullary thyroid carcinoma

Table 4 Technical aspects and main findings of relevant articles about ^{18}F-FDOPA PET/CT in MTC

Authors	Injected activity	Time interval between radiotracer injection and image acquisition	Image analysis	Other nuclear medicine techniques performed	Reference standard	Sensitivity	Specificity	Change of management	Prognostic role	Role in treatment response assessment
Caobelli et al. [72]	209 ± 67 MBq	60 min	Visual and semi--quantitative	–	Pathology and/or clinical/-imaging follow-up	45%(p)	NR	–	Yes	–
Romero-Lluch et al. [50]	174–288 MBq	60 min	Visual and semi--quantitative	^{18}F-FDG PET/CT	Pathology and/or clinical/-imaging follow-up	67%(p)	NR	Yes (61%)-	–	–
Golubic et al. [54]	2–3 MBq/Kg	10 min	Visual and semi--quantitative	.	Pathology and/or clinical/-imaging follow-up	57%(p)	NR	Yes (57%)	–	–
Archier et al. [55]	3 MBq/Kg	10 min and 30 min	Visual and semi--quantitative	–	Pathology and/or clinical/-imaging follow-up	76%(p), 24%(l)	NR	–	–	–
Sesti et al. [73]	NR	NR	Visual	–	Pathology and/or clinical/-imaging follow-up	52%(p)	NR	–	–	–
Treglia et al. [41]	4 MBq/Kg	15 min and 60 min	Visual and semi--quantitative	–	Pathology and/or clinical/-imaging follow-up	73%(p)	NR	–	–	–
Soussan et al. [40]	4 MBq/Kg	15 min and at least 60 min	Visual and semiquantita-tive	–	Pathology and/or clinical/-imaging follow-up	93%(p)	NR	–	–	–
Chondrogiannis et al. [42]	185 MBq	60 min	Visual and semiquantita-tive	–	Pathology and/or clinical/-imaging follow-up	NR	NR	–	–	–
Treglia et al. [59]	165–370 MBq	60 min	Visual and semiquantita-tive	^{18}F-FDG PET/CT and somatostatin receptor PET/CT	Pathology and/or clinical/-imaging follow-up	72%(p), 85%(l)	NR	Yes (44%)	–	–
Kauhanen et al. [60]	243 ± 46 MBq + CP	60 min	Visual and semiquantita-tive	^{18}F-FDG PET/CT	Pathology and/or clinical/-imaging follow-up	58%(p), 52%(l)	NR	–	–	–
Luster et al. [75]	186–431 MBq + CP	NR	Visual	–	Pathology and/or	74%(p)	100%(p)	–	–	–

Table 4 (continued)

Authors	Injected activity	Time interval between radiotracer injection and image acquisition	Image analysis	Other nuclear medicine techniques performed	Reference standard	Sensitivity	Specificity	Change of management	Prognostic role	Role in treatment response assessment
					clinical/-imaging follow-up					
Marzola et al. [66]	2.2 MBq/Kg	60 min	Visual and semiquantitative	SRS, MIBG, ^{18}F-FDG PET/CT	Pathology	83%(p), 76%(l)	NR	–	–	–
Beheshti et al. [68]	4 MBq/Kg	30 min	Visual and semiquantitative	^{18}F-FDG PET/CT	Pathology and/or clinical/-imaging follow-up	overall: 81%(p), 94%(l) restaging: 73%(p)	NR	Yes (27%)	–	–

(p) = on a per patient-based analysis; (l) = on a per patient-based analysis; *NR*, not reported; *MBq*, megaBequerel; *CP*, carbidopa premedication; *SRS*, somatostatin receptor scintigraphy; *MIBG*, radiolabelled metaiodobenzylguanidine scintigraphy

not demonstrated in MTC patients [44]. Interestingly, some authors demonstrated that, compared with standard acquisition obtained 30 to 60 min after ^{18}F-FDOPA administration, early image acquisition (around 15 min after radiopharmaceutical injection) improves the detection rate of PET/CT in MTC patients [40, 41].

Other indications of ^{18}F-FDOPA PET/CT in MTC

A recent multicentric study demonstrated that ^{18}F-FDOPA PET/CT may have a prognostic value in predicting disease progression and mortality rate in MTC [54]. Conversely, there are not significant data about the usefulness of this imaging method in evaluating treatment response in patients with metastatic MTC.

Diagnostic performance of ^{68}Ga-SSA PET/CT in staging and restaging MTC

Basic characteristics, technical aspects and main findings of articles about ^{68}Ga-SSA PET/CT in MTC patients are reported in Tables 5 and 6. Several studies [49–53, 76] and one meta-analysis [45] evaluated the diagnostic performance of ^{68}Ga-SSA PET/CT in patients with recurrent MTC whereas only sparse data are retrieved about the diagnostic performance of ^{68}Ga-SSA PET/CT in preoperative MTC staging [73]. The diagnostic performance of ^{68}Ga-SSA PET/CT is globally inferior in MTC compared with other NETs due to the variable SSTR expression in MTC [34–37]. The studies using ^{68}Ga-SSA PET/CT in detecting recurrent MTC showed wide range of patient-based sensitivity, ranging from 25 to 100% (Table 6). Different technical aspects and inclusion criteria could likely explain the observed inter-studies heterogeneity. On a per patient-based analysis, the detection rate of ^{68}Ga-SSA PET or PET/CT is 63.5% (95% confidence interval: 49–77) in suspected recurrent MTC [45]. Then, the surgical management of a significant number of patients with recurrent MTC can be modified by a positive ^{68}Ga-SSA PET/CT [27, 73, 76,]. This is particularly relevant when considering that ^{68}Ga-SSA PET/CT examinations are often performed after previous multiple negative morphologic imaging studies [45]. The detection rate of ^{68}Ga-SSA PET/CT has also exceeded that of bone scintigraphy and MRI in a small group of MTC patients with bone metastases [49]. Finally, according to literature data, the detection rate of ^{68}Ga-SSA PET/CT improves in patients with higher CT levels [45].

Other indications of ^{18}Ga-SSA PET/CT in MTC

On a pathological basis, expression of SSTR-2A was found to be correlated with increased overall survival in patients with MTC [72]. Treatments with cold or radiolabelled SSA are expected to be effective in

Table 5 Basic study and patient characteristics of relevant articles about somatostatin receptor PET/CT in MTC

Authors	Year	Country	Study design	Indication of somatostatin receptor PET/CT	Patients evaluated	Mean age (years)	%male	Type of MTC
Yamaga et al. [77]	2017	Brazil	Prospective monocentric	Restaging	15	44	40%	10 sMTC (67%), 5 hMTC (33%)
Tran et al. [79]	2015	UK	Retrospective monocentic	Staging or restaging	7	45	43%	NR
Traub-Weidinger et al. [46]	2015	Austria	Retrospective monocentric	Restaging	8	NR	NR	NR
Ozkan et al. [61]	2015	Turkey	Retrospective monocentric	Restaging	22	43	50%	17 sMTC (77%), 5 hMTC (23%)
Budiawan et al. [78]	2013	Germany	Retrospective monocentric	Restaging and treatment response	8	47	50%	NR
Putzer et al. [51]	2013	Austria	Retrospective monocentric	Restaging	8	57	NR	NR
Rasul et al. [58]	2012	India	Prospective monocentric	Restaging	52	45	73%	NR
Treglia et al. [45]	2012	Italy	Retrospective multicentric	Restaging	18	53	33%	16 sMTC (89%), 2 hMTC (11%)
Łapińska et al. [52]	2011	Poland	Retrospective monocentric	Restaging	4	NR	NR	NR
Palyga et al. [53]	2010	Poland	Prospective monocentric	Restaging	8	56	50%	NR

NR, not reported; *hMTC*, hereditary medullary thyroid carcinoma; *sMTC*, sporadic medullary thyroid carcinoma

patients with advanced/metastatic MTC lesions overexpressing SSTRs. Then, ^{68}Ga-SSA PET/CT could be proposed to assess SSTR-2A expression and select MTC patients for SSTR-2A targeting therapies. However, its usefulness in assessing the response of MTC patients to peptide receptor radionuclide therapy was only reported in one study [50] and there are no studies demonstrating the prognostic value of ^{68}Ga-SSA PET/CT in MTC patients.

Comparison of different PET radiopharmaceuticals in MTC

Comparative analyses between PET/CT examinations performed with different radiopharmaceuticals in the setting of MTC restaging are available in the literature [27, 46, 48, 60, 61, 67, 70, 78] (Tables 2, 4 and 6). ^{18}F-FDOPA PET/CT has shown better sensitivity and specificity than ^{18}F-FDG PET/CT; nevertheless, a complementary/sequential use of these methods may improve the management of recurrent MTC [54, 63, 64, 67, 77]. ^{18}F-FDOPA tracks amino acid decarboxylation pathway, whereas ^{18}F-FDG is a proliferation marker. Accordingly, differentiated MTC cells are characterized by increased ^{18}F-FDOPA uptake and absent ^{18}F-FDG uptake while the opposite happen in de-differentiated MTC cells [54, 63, 64, 67, 77]. In summary, ^{18}F-FDOPA-PET/CT is the most accurate method to assess the extent of the disease in patients with recurrent MTC while ^{18}F-FDG PET/CT is a powerful prognostic toll and its positivity is associated to a more aggressive tumour phenotype and a worse prognosis [54, 60, 61, 63, 64, 67, 77]. A similar complementary role also exists for ^{68}Ga-SSA and ^{18}F-FDG PET/CT but no significant difference in detection rates of MTC lesions was proved [27, 46, 60, 77]. Currently, only one head to head comparison of ^{18}F-FDOPA, ^{18}F-FDG and ^{68}Ga-SSA PET/CT in patients with postoperative increased serum CT is available in literature. The diagnostic performance of ^{18}F-FDOPA PET/CT performance exceeded that of ^{18}F-FDG and ^{68}Ga-SSA PET/CT with a significantly higher proportion of change in the patient management [35].

The radiation dose is very similar for ^{18}F-FDOPA, ^{18}F-FDG and ^{68}Ga-SSA PET/CT when the administered activity and the volume explored by CT are accounted for. Moreover, the actual effective dose is currently decreasing with a trend to reduce the injected activity of radiopharmaceuticals by using time of flight PET/CT tomographs.

^{18}F-FDG and ^{18}F-FDOPA can be prepared in-house or provided "ready to use." The synthesis of ^{18}F-FDOPA is difficult and this radiopharmaceutical is even the most expensive among those available for MTC evaluation while labelling of lyophilized peptides requires ^{68}Ga and ^{68}Ge/^{68}Ga generator and radiochemical controls. Overall, the availability of ^{18}F-FDOPA and ^{68}Ga-SSA is currently limited compared with

Table 6 Technical aspects and main findings of relevant articles about somatostatin receptor PET/CT in MTC

Authors	Injected activity and type of peptide	Time interval between radiotracer injection and image acquisition	Image analysis	Other nuclear medicine techniques performed	Reference standard	Sensitivity	Specificity	Change of management	Prognostic role	Role in treatment response assessment
Yamaga et al. [77]	185 MBq DOTATATE	60 min	Visual and semiquantitative	SRS	Pathology and/or clinical/imaging follow-up	100% (p)	NR	–	–	–
Tran et al. [79]	52–89 MBq DOTATATE	45 min	Visual and semiquantitative	^{18}F-FDG PET/CT, MIBG	Pathology and/or clinical/imaging follow-up	86%(p)	NR	–	–	–
Traub-Weidinger et al. [46]	95–150 MBq DOTATOC/LAN	90 min	Visual	^{18}F-FDG PET/CT	Pathology and/or clinical/imaging follow-up	75%(p)	NR	–	–	–
Ozkan et al. [61]	111–148 MBq	45–60 min	Visual	^{18}F-FDG PET/CT, (V)DMSA	Pathology and/or clinical/imaging follow-up	68%(p), 91%(l)	NR	Yes (18%)	–	–
Budiawan et al. [78]	NR DOTATOC/NOC/TATE	NR	Visual and semiquantitative	–	EORTC response assessment criteria	NR	NR	–	–	Yes
Putzer et al. [51]	150–200 MBq DOTATOC	60 min	Visual and semiquantitative	SRS	Pathology and/or clinical/imaging follow-up	75%(p)	NR	–	–	–
Rasul et al. [58]	148–222 MBq DOTANOC	45–60 min	Visual and semiquantitative	^{18}F-FDG PET/CT	Pathology and/or clinical/imaging follow-up	81%(p)	NR	Yes (11%)	–	–
Treglia et al. [45]	1.5–2.5 MBq/Kg DOTANOC/ TOC	50–70 min	Visual and semiquantitative	^{18}F-FDOPA PET/CT and ^{18}F-FDG PET/CT	Pathology and/or clinical/imaging follow-up	33%(p), 20%(l)	NR	No	–	–
Lapinska et al. [52]	111–185 MBq DOTATATE	45–60 min	Visual and semiquantitative	–	Pathology and/or clinical/imaging follow-up	25% (p)	NR	–	–	–
Palyga et al. [53]	120–185 MBq DOTATATE	60 min	Visual and semiquantitative	Bone scintigraphy	Pathology and/or clinical/imaging follow-up	25%(p)	NR	Yes (25%)	–	–

(p) = on a per patient-based analysis; (l) = on a per patient-based analysis; *NR*, not reported; *MBq*, megaBequerel; *SRS*, somatostatin receptor scintigraphy; *MIBG*, radiolabelled metaiodobenzylguanidine scintigraphy; *(V)DMSA*, pentavalent dimercaptosuccinic acid scintigraphy

^{18}F-FDG and, sometime, referral of MTC patients to specialized centres should be necessary for these examinations. Cost-effectiveness comparative studies on different PET/CT examinations in recurrent/metastatic MTC are warranted [78].

PET/CT in MTC: practical recommendations

There is no sufficient evidence to recommend PET/CT with several radiopharmaceuticals for staging MTC before treatment or for evaluating treatment response in metastatic MTC and more studies investigating these indications are needed. Conversely, consistent evidences support the use of PET/CT with different radiopharmaceuticals to restage MTC patients with rising tumour markers. PET/CT imaging with available radiopharmaceuticals is suggested when serum CT exceed 150 pg/mL or CT doubling time is shortened (i.e. < 24 months) [1, 12, 19, 32, 68, 70, 75, 77, 78]. If available, ^{18}F-FDOPA PET/CT is preferred as first-line procedure due to its superior diagnostic performance compared with other PET tracers. In cases of negative or unfeasible ^{18}F-FDOPA PET/CT, ^{18}F-FDG PET/CT should be performed, in particular if calcitonin and CEA levels are rapidly rising (i.e. doubling time < 1 year) or an aggressive behaviour of the disease is expected (e.g. CEA levels disproportionately high compared with calcitonin levels). ^{68}Ga-SSA PET/CT could be considered in selected cases with inconclusive anatomic imaging, ^{18}F-FDOPA and ^{18}F-FDG PET/CT results and to assess the feasibility of peptide receptor radionuclide therapy in highly selected patients considered for this targeted treatment.

Suggested PET/CT reporting in MTC

As for other NETs, the nuclear medicine physician should record: the clinical question (i.e. staging, restaging, evaluation of treatment response), a brief clinical history (including type and chronology of previous therapies if any), type and date of examination, radiopharmaceutical and administered activity, CT parameters and dosimetry, relevant medications, laboratory data (in particular for MTC the last serum calcitonin and CEA values and their doubling times should be reported) and results of other imaging studies [34].

As for other NETs, the PET/CT report should describe as follows:

- the procedure;
- the findings including site and size of the lesion(s), uptake intensity (qualitatively and semi-quantitatively assessed by using the SUV);
- comparative analysis (to previous imaging studies);
- interpretation with a clear diagnosis whenever possible or, alternatively, study limitations precluding a clear conclusion (i.e. potential false negative or false positive results). Complementary diagnostic procedure or an adequate PET/CT follow-up should be also suggested [34].

Acknowledgements This practice guideline summarizes the views of EANM Thyroid Committee and produces recommendations for which the EANM cannot be considered responsible. The recommendations should be adopted in the context of good nuclear medicine practice of nuclear and do not substitute national and international regulations. Before approval, this practice guideline was available to all EANM Committees and EANM National Societies of Nuclear Medicine. All comments, criticisms and suggestions have been considered for this EANM practice guideline.

Compliance with ethical standards

Conflict of interest L.G. is member of Roche Diagnostics advisory board and received research grants and speaker fees from Roche Diagnostics, IBSA and Sanofi-Genzyme. F.A.V. has received research grants from Sanofi-Genzyme and speaker honoraria from Sanofi-Genzyme, Diasorin and Jubilant Draximage. M.L. has received research grants and speaker honoraria from Sanofi-Genzyme, Bayer and Astra Zeneca. G.T declares that he has no conflict of interest. I.I declares that he has no conflict of interest. JM declares that she has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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