In the Name of GOD

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

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Medullary thyroid carcinoma

Background information:

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.

MTC occurs in sporadic or hereditary form, the latter being part of type 2 multiple endocrine neoplasia (MEN2) syndromes.

Lymph node metastases are present in 14% (central neck compartment) and 11% (lateral neck compartments) of patients with T1 tumors and in up to 86% and 93% of patients with T4 tumors, respectively.

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.

Serum tumor markers

Calcitonin (CT) and procalcitonin (PCT) are specifically secreted by parafollicular C cells and serve as valuable tumor markers in patients with MTC.

CEA is an aspecific tumor marker but it is a useful complementary tool to detect disease relapse and progression after primary treatment .

Notably, both calcitonin and CEA doubling times are useful prognostic predictors in patients with persistent disease after surgery.

Cytology and histology

Fine needle aspiration cytology (FNAC) is able to detect ~ 50% of MTCs .

Immunocytochemical (ICC) staining against CT and/or its measurement in the needle washouts significantly increase diagnostic accuracy when inconclusive cytological findings are rendered.

Sporadic MTCs are generally unifocal, whereas inherited tumours are multicentric and involve both lobes.

In case of microscopic features suggesting MTC additional immunostaining against specific biomarkers is warranted.

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 and tyrosine kinase inhibitors can be used and combined to treat progressive advanced MTC .

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 .

Whereas the role of functional radionuclide imaging is limited in preoperative staging , 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 (99mTc-(V)DMSA), somatostatin Indium-111/technetium 99m labelled somatostatin analogues (111In-pentetreotide, 99m Tc-depreotide) and iodine-123-labelled metaiodobenzylguanidine (123I-MIBG) were proposed to detect MTC relapse but overall sensitivity is unsatisfactory compared with conventional anatomic imaging and positron emission tomography/computed tomography .

However, current clinical guidelines recommend whole-body bone scan with 99mTc-diphosphonates to detect/ exclude bone metastases in MTC patients .

Finally, a positive 123I-MIBG scan in patients with relapsing/advanced MTC (about 30% of cases) predicts partial remission or stabilization of the disease after radiometabolic treatment with 131I-MIBG.

Radionuclide imaging in MTC:
positron emitting radiopharmaceuticals

Although several radionuclide imaging modalities are available,

- ✓ PET/CT using 18F-fluorodeoxyglucose (18F-FDG),
- ✓ 18F-fluoroDOPA (18F-FDOPA) and
- ✓ 68Ga-somatostatin analogues (68Ga-SSA)

offers higher sensitivity imaging compared with conventional nuclear medicine techniques, therefore these practice guidelines will be focused on PET/CT imaging in MTC.

Mechanism of uptake and rationale for PET tracers use in MTC

18F-FDG It is the most used PET radiopharmaceutical worldwide; as glucose analogue, the use of 18F-FDG for PET imaging allows to detect tumours with increased glucose metabolism. 18F-FDG uptake in MTC cells is linked to glucose transporters (GLUT) overexpression and increased hexokinase activity.

Furthermore, 18F-FDG uptake correlates with high proliferative activity and poor differentiation of MTC cells.

18F-FDOPA DOPA is the precursor of endogenous catecholamines.

18F-FDOPA is picked up by specific transporters (L type amino acid transporter, LAT) and converted to 18F-dopamine by cytosolic aromatic amino acid decarboxylase (AADC).

Both LAT expression and AADC activity are upregulated in MTC cells leading to increased 18F-FDOPA uptake in MTC lesions.

68Ga-SSA NET cells may overexpress somatostatin receptors (SSTRs) and this is the rationale for using radiolabeled SSA as targets for both radionuclide imaging (i.e. by using SSA labelled with positron-emitters such as 68Ga) and therapy (i.e. by using SSA labelled with beta-emitters such as 177Lu and 90Y) of NETs.

68Ga-SSA (i.e. DOTATOC, DOTATATE, DOTANOC, DOTALAN) have different affinities for the five SSTR subtypes.

Overall, all 68Ga-SSA can target SSTR subtype 2 efficiently, which is the SSTR subtype most overexpressed in NETs .

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.

Synthesis and quality control

18F-FDG

The synthesis and quality control of 18F-FDG have to conform to the criteria laid down in the European Pharmacopeia or the US Pharmacopeia.

18F-FDG can be prepared in-house or provided “ready to use”.

18F-FDOPAT

he synthesis of 18F-FDOPA requires up to 4 h and unfortunately it is characterized by a low labelling efficiency. 18F-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.

68Ga-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 68Ga is automated and requires between 20 and 30 min providing high radiochemical purity. The labelling procedure includes the following steps: 68Ga elution by 68Ge/68Ga 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 18F-FDG, 18F-FDOPA and 68Ga-SSA, respectively.

The amount of SSA injected should be less than 50 μg without any significant pharmacological effect expected.

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

18F-FDG

Fasting for at least 4 h prior to 18F-FDG injection is required to lower blood glucose and insulin levels and, in turn, reduce uptake by non-tumour cells.

18F-FDG can be administered if the glucose level is < 11 mmol/L.

Diabetic patients require specific instructions for glucose control.

In order to minimize 18F-FDG uptake in muscles strenuous exercise should be avoided for at least 6 h before 18F-FDG administration.

Additionally, patients are required to remain seated or recumbent and silent during the injection of 18F-FDG and the following uptake phase.

An adequate room temperature should be assured before the injection of 18F-FDG and throughout the subsequent phases to minimize 18F-FDG uptake in brown adipose tissue (BAT).

8F-FDOPA

On precautional basis, 18F-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 18F-FDOPA injection, to increase 18F-FDOPA uptake in MTC cells.

68Ga-SSA

There is no need of fasting before 68Ga-SSA injection.

The need of cold SSA discontinuation prior to 68Ga-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 18F-FDG injection; 30 to 60 min after 18F-FDOPA injection and 45 to 90 min after 68GaSSA 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 18F-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.

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:18F-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).

18F-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.

18Ga-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.

Pitfalls

18F-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. False positive findings may be due to inflammatory lesions (due to the high consumption of glucose by inflammatory cells) or other tumours.

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

18Ga-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. False positive results of 18Ga-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).

Other PET radiopharmaceuticals in MTC

Limited literature data are available about other PET radiopharmaceuticals in patients with MTC.

One study demonstrated the feasibility of anti-CEA immune-PET using a 68Ga-labelled radiotracer (IMP288) in MTC patients.

Another study evaluated the possible role of PET using the amino acid tracer 11C-methionine in patients with recurrent MTC but minimal additional information compared with combined 18F-FDG PET/CT and neck US has been reported.

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.

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

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.

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.

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.

Additionally, PET/CT using different radiopharmaceuticals (i.e. 18F-FDG, 18F-FDOPA and 68Ga-SSA) proved to be sensitive and accurate in detecting MTC recurrences/metastases and assess their biological and clinical aggressiveness.

Diagnostic performance of 18F-FDG-PET/CT

Basic characteristics, technical aspects and main findings of articles about 18F-FDG PET/CT in patients with MTC are briefly reported in. Several studies and two meta-analyses evaluated the role of 18F-FDG PET/CT in recurrent MTC, whereas limited data are available on preoperative MTC staging.

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.

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).

Basing on meta-analysis studies the patient-based detection rate of 18F-FDG PET or PET/CT in recurrent MTC ranges from 59% (95% confidence interval: 54–63%) to 69% (95% confidence interval: 64–74%).

Consequently, negative 18F-FDG PET/CT are reported in 30– 40% of MTC patients with increasing biomarkers levels.

It should be considered, however, that 18F-FDG PET/CT is generally required after previous negative cross-sectional anatomic studies.

Additionally, 18F-FDG PET/CT examination may correctly address the management of recurrent MTC when hypermetabolic lesions are detected.

Notably, a positive relationship exists between serum levels of CT and CEA and the sensitivity of 18F-FDG PET/CT.

Moreover, sensitivity of 18F-FDG PET/CT improves in patients with shorter serum calcitonin and CEA doubling times.

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

As demonstrated by some studies, 18F-FDG PET/CT is able to accurately identify MTC patients with poor prognosis and life expectancy.

Furthermore, this imaging method has been successfully used to evaluate response to targeted therapies in patients with advanced metastatic MTC treatment.

Diagnostic performance of 18F-FDOPA PET/CT

Several studies and one meta-analysis addressed the diagnostic performance of 18F-FDOPA PET/CT in recurrent MTC whereas few data are available about staging MTC before primary surgery.

Recently, however, 18F-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.

In summary, a consistently high specificity but a wide patient-based sensitivity range, from 45 to 93%, was reported in different studies using 18F-FDOPA PET/CT in patients with suspicious MTC recurrences.

Such differences are likely related to different techniques and different inclusion criteria among studies.

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.

Premedication with carbidopa was previously proposed to improve the tracer's bioavailability but its impact on the detection rate of 18F-FDOPA PET/CT was not demonstrated in MTC patients.

Interestingly, some authors demonstrated that, compared with standard acquisition obtained 30 to 60 min after 18F-FDOPA administration, early image acquisition (around 15 min after radiopharmaceutical injection) improves the detection rate of PET/CT in MTC patients.

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

A recent multicentric study demonstrated that 18F-FDOPA PET/CT may have a prognostic value in predicting disease progression and mortality rate in MTC.

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 68Ga-SSA PET/CT in staging and restaging MTC

Several studies and one meta-analysis evaluated the diagnostic performance of 68Ga-SSA PET/CT in patients with recurrent MTC whereas only sparse data are retrieved about the diagnostic performance of 68Ga-SSA PET/CT in preoperative MTC staging .

The diagnostic performance of 68Ga-SSA PET/CT is globally inferior in MTC compared with other NETs due to the variable SSTR expression in MTC.

The studies using 68Ga-SSA PET/CT in detecting recurrent MTC showed wide range of patient-based sensitivity, ranging from 25 to 100% .

Different technical aspects and inclusion criteria could likely explain the observed inter-studies heterogeneity. On a per patient-based analysis, the detection rate of 68Ga-SSA PET or PET/CT is 63.5% (95% confidence interval: 49–77) in suspected recurrent MTC .

Then, the surgical management of a significant number of patients with recurrent MTC can be modified by a positive 68Ga-SSA PET/CT .

This is particularly relevant when considering that 68Ga-SSA PET/CT examinations are often performed after previous multiple negative morphologic imaging studies .

The detection rate of 68Ga-SSA PET/CT has also exceeded that of bone scintigraphy and MRI in a small group of MTC patients with bone metastases . Finally, according to literature data, the detection rate of 68Ga-SSA PET/CT improves in patients with higher CT levels .

Other indications of 18Ga-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.

Treatments with cold or radiolabelled SSA are expected to be effective in patients with advanced/metastatic MTC lesions overexpressing SSTRs.

Then, 68Ga-SSA PET/CT could be proposed to assess SSTR-2A expression and select MTC patients for SSTR-2A targeting therapies.

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.

18F-FDOPA PET/CT has shown better sensitivity and specificity than 18F-FDG PET/ CT; nevertheless, a complementary/sequential use of these methods may improve the management of recurrent MTC.

18F-FDOPA tracks amino acid decarboxylation pathway, whereas 18F-FDG is a proliferation marker.

Accordingly, differentiated MTC cells are characterized by increased 18F-FDOPA uptake and absent 18F-FDG uptake while the opposite happen in de-differentiated MTC cells.

In summary, 18F-FDOPA-PET/CT is the most accurate method to assess the extent of the disease in patients with recurrent MTC while 18F-FDG PET/CT is a powerful prognostic toll and its positivity is associated to a more aggressive tumour phenotype and a worse prognosis.

A similar complementary role also exists for 68Ga-SSA and 18F-FDG PET/CT but no significant difference in detection rates of MTC lesions was proved.

Currently, only one head to head comparison of 18F-FDOPA, 18F-FDG and 68Ga-SSA PET/CT in patients with postoperative increased serum CT is available in literature.

The diagnostic performance of 18F-FDOPA PET/CT performance exceeded that of 18F-FDG and 68Ga-SSA PET/CT with a significantly higher proportion of change in the patient management.

The radiation dose is very similar for 18F-FDOPA, 18F-FDG and 68Ga-SSA PET/CT when the administered activity and the volume explored by CT are accounted.

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. 18F-FDG and 18F-FDOPA can be prepared in-house or provided “ready to use.”

The synthesis of 18F-FDOPA is difficult and this radiopharmaceutical is even the most expensive among those available for MTC evaluation while labelling of lyophilized peptides requires 68Ga and 68Ge/68Ga generator and radiochemical controls.

Overall, the availability of 18F-FDOPA and 68Ga-SSA is currently limited compared with 8F-FDG and, sometime, referral of MTC patients to specialized centres should be necessary for these examinations.

Costeffectiveness comparative studies on different PET/CT examinations in recurrent/metastatic MTC are warranted .

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).

If available, 18F-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 18F-FDOPA PET/CT, 18F-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).

- 68Ga-SSA PET/CT could be considered in selected cases with inconclusive anatomic imaging, 18F-FDOPA and 18F-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.


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