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Update on Management of Medullary Thyroid Carcinoma: Focus on Nuclear Medicine

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Currently, there is a discrepancy among the available guidelines on the usefulness of nuclear medicine techniques in medullary thyroid cancer (MTC) diagnosis and treatment. Aim of this review is to provide an update on diagnostic and therapeutic nuclear medicine techniques in this setting. Evidence-based data clearly demonstrates the usefulness of PET/CT with different radiopharmaceuticals in recurrent MTC (in particular when serum calcitonin is higher than 150 pg/mL or calcitonin doubling time is shortened) and ^{18}F-FDOPA should be the preferred PET radiopharmaceutical. If ^{18}F-FDOPA PET/CT is negative or unavailable, ^{18}F-FDG PET/CT or ^{68}Ga-DOTA-peptides PET/CT could be performed for MTC restaging. There is currently insufficient evidence to recommend PET/CT with several radiopharmaceuticals for MTC staging. Clinical experience on PET/MRI with different radiopharmaceuticals in MTC is still limited. Several investigational nuclear medicine therapeutic options are currently under evaluation in metastatic MTC. More data are needed to evaluate the efficacy, toxicity, and role of these therapeutic options in the management of MTC patients.

Introduction

Medullary thyroid carcinoma (MTC) is an uncommon neuroendocrine tumor arising from the thyroid parafollicular C cells which produce and release calcitonin (Ctn), a hormone which influences calcium homeostasis by inhibiting osteoclasts. MTC accounts for about 1%-5% of all thyroid malignancies.[1-4]

MTC can be sporadic in 75% of cases and familial in 25% of cases. The sporadic form is most often caused by somatic

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mutations in the RET gene or, less frequently, in the RAS genes. MTCs may also be inherited into the context of autosomal-dominant multiple endocrine neoplasia (MEN) syndromes 2a and 2b or isolated familial MTC syndrome. These syndromes are also caused by mutations in the RET gene, but they occur in germline cells. The onset of sporadic MTC is between 50 and 60 years, whereas hereditary MTCs usually present earlier.[1-4]

MTC shows a less favorable prognosis and a higher mortality rate than well-differentiated thyroid cancer. Lymph node metastases are already present at diagnosis in 30%-60% of MTC patients and recurrences occur in up to 50% of patients. Several factors may influence the prognosis of MTC including genotype, baseline biomarkers (Ctn and carcinoembryonic antigen [CEA]) levels including their doubling time, histological findings, tumor extent, metastatic spread, gender, and age.[1-4]

The clinical presentation of MTC is rather nonspecific. One of the most common symptoms is a palpable neck lump. The nodule may cause complaints (ie, dysphagia, pain, dyspnea or speech impediment) or it may be asymptomatic.[1-4]

About the diagnosis of MTC a variety of diagnostic tests, including biochemical, genetic and imaging methods, can be used. According to current guidelines, fine-needle aspiration biopsy (FNAB), neck ultrasound (US), serum Ctn and CEA levels and RET gene mutation analysis are the most important diagnostic tools for MTC detection and management. Depending on the results of these analyses, a decision is made about the treatment procedure and the search for metastatic foci using cross-sectional imaging methods.[2,5] The pivotal role of imaging is to address therapy. Neck US is the first imaging method used in the diagnosis of thyroid tumors and it can also serve as the initial tool to evaluate MTC metastasis on regional neck lymph nodes.[1-4] Computed tomography (CT) is used mainly in the search for distant metastases of MTC, whereas magnetic resonance imaging (MRI) may be used as a tool for the evaluation of liver and bone metastases even if it is not a standard diagnostic option for MTC.[1-4] About nuclear medicine techniques, there is a discrepancy among the available guidelines on the usefulness of these techniques in MTC diagnosis.[2,5]

Surgery is the primary therapy of MTCs: complete surgical resection of the tumor and nodal metastases with a curative intent remains the mainstay of treatment. In MTC patients with distant metastases, therapeutic options are limited as MTC does not concentrate radioiodine and shows poor response to chemotherapy and radiation therapy. Currently, there is ongoing research on the use of tyrosine kinase inhibitors (TKIs), highly specific RET inhibitors, radionuclide therapy and immunotherapy.[1-4] However, the lack of consensus in the available guidelines regarding the most appropriate diagnostic, therapeutic and follow-up strategies has caused substantial variability in clinical practice.[5-7]

Aim of this review is to provide an update on diagnostic and therapeutic nuclear medicine techniques and their role in the management of MTC taking into account available evidence-based data.

Nuclear Medicine Imaging in MTC

Nuclear medicine imaging techniques are non-invasive methods able to early detect pathophysiological changes in MTC which usually precede morphological changes detected by conventional imaging modalities. Hybrid imaging techniques such as SPECT/CT, PET/CT and PET/MRI provide both functional and morphological information in the same imaging session allowing a clear advantage compared to stand-alone nuclear medicine imaging or conventional imaging methods.[8-10]

Whole body scintigraphy with SPECT radiopharmaceuticals such as Technetium-99m pentavalent dimercaptosuccinic acid (^{99m}Tc-(V)DMSA), somatostatin analogues labeled with Indium-111 or Technetium-99m, radioiodinated metaiodobenzylguanidine (MIBG) or radiolabeled anti-CEA antibodies, which have been extensively used in past years, are not sensitive enough to detect MTC relapse when compared to PET imaging for MTC. Bone scintigraphy using diphosphonates labeled with Technetium-99m is still recognized as a useful imaging technique in MTC staging and restaging, whereas promising results were obtained with cholecystokinin-B/gastrin receptor scintigraphy.[8,9]

Considering the advantages in terms of spatial resolution of PET compared to SPECT, several PET radiopharmaceuticals evaluating different metabolic pathways or receptor status have been developed and used to detect MTC lesions (Table 1). According to evidence-based data, the most used PET radiopharmaceuticals in this setting are Fluorine-18 fluorodeoxyglucose (^{18}F-FDG), Fluorine-18 dihydroxyphenylalanine (^{18}F-FDOPA) and somatostatin analogues labeled with Gallium-68 (^{68}Ga-DOTA-peptides).[11] These PET radiopharmaceuticals are mainly used for restaging MTC in cases of increased serum tumor markers levels after treatment.[8-10]

^{18}F-FDG, a radiolabeled glucose analogue, is currently the most used radiopharmaceutical for PET imaging in oncology. The ability of ^{18}F-FDG PET/CT to identify MTC lesions is

Table 1 PET Radiopharmaceuticals in Detecting MTC Lesions According to Literature Data

PET radiopharmaceuticals
^{18}F-FDG
^{18}F-FDOPA
^{68}Ga-DOTA-somatostatin analogs
^{18}F-fluoride
Radiolabeled anti-CEA antibodies (labeled with ^{68}Ga or ^{64}Cu)
Cholecystokinin-2 receptor targeting tracers (labeled with ^{68}Ga)
Fibroblast activation protein-targeting radiopharmaceuticals (labeled with ^{68}Ga)
Prostate specific membrane antigen-targeting radiopharmaceuticals (labeled with ^{68}Ga or ^{18}F)
Amyloid targeting radiopharmaceuticals ([^{18}F]AV-45)
^{18}F-Fluorocholine
^{11}C-methionine

The most used PET radiopharmaceuticals are reported in italics.

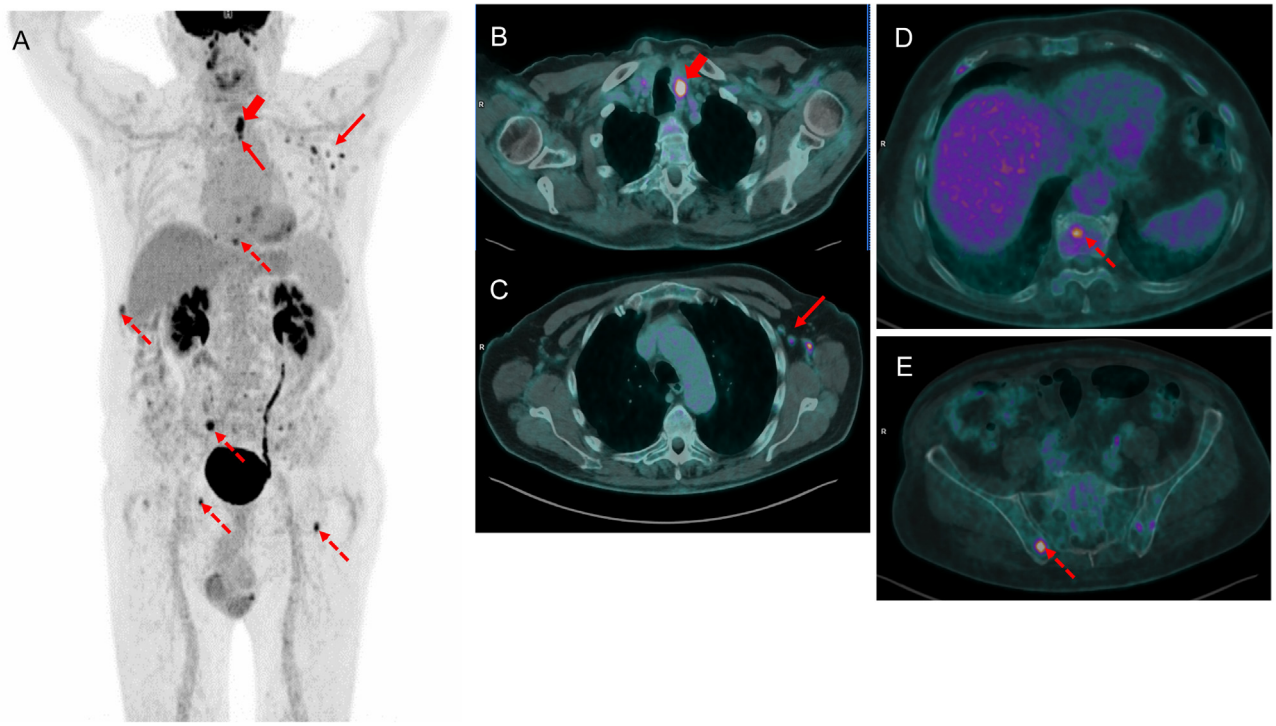

Figure 1 A 80-year-old male with a cytological diagnosis of MTC in a left thyroid nodule. ^{18}F-FDG PET/CT (A: maximum intensity projection PET image; B-E: axial PET/CT images) performed at initial diagnosis showed focal tracer uptake in the left thyroid lobe (short arrow) as well as in multiple lymph nodes (arrows) and multiple bone lesions (dashed arrows). (Color version of figure is available online.)

mainly related to the increased glycolytic activity of tumor cells. ^{18}F-FDG uptake in MTC cells correlates with high proliferative activity and poor differentiation (Fig. 1).[12,13] According to evidence-based data, the detection rate of recurrent MTC on a per patient-based analysis by using ^{18}F-FDG PET/CT is suboptimal with a pooled value of 56%.[12] False negative findings of ^{18}F-FDG PET/CT in MTC could be due to small or slow-growing MTC lesions with reduced ^{18}F-FDG uptake. Conversely, inflammatory lesions characterized by increased glucose metabolism are the main source of false positive findings for MTC on ^{18}F-FDG PET/CT.[12,13] Notably, the detection rate of ^{18}F-FDG PET/CT in patients with recurrent MTC significantly improves in patients with higher serum Ctn and CEA levels and shorter Ctn and CEA doubling times, demonstrating the usefulness of this imaging method in patients with rapidly progressive disease compared to those with slowly progressive disease.[12,13] Interestingly, ^{18}F-FDG PET/CT has a relevant predictive and prognostic value in recurrent MTC being able to identify patients with poor survival and to distinguish progressive from stable MTC disease.[14] Moreover, the combined use of ^{18}F-FDG PET/CT and Ctn doubling time may improve the identification of high-risk MTC patients for which a close monitoring is required. Furthermore, ^{18}F-FDG uptake is an independent predictive factor related to the response to radioimmunotherapy or tyrosine kinase inhibitors in metastatic MTC.[14]

^{18}F-FDOPA is a PET radiopharmaceutical useful to assess the uptake, decarboxylation and storage of amine precursors which are features of neuroendocrine tumors. This radiopharmaceutical is taken up through transmembrane amino acid transporter systems that are upregulated in neuroendocrine tumors. MTC, as other neuroendocrine tumors, shows increased activity of aromatic amino acid decarboxylase converting DOPA to dopamine.[15] According to evidence-based data, the detection rate of recurrent MTC on a per patient-based analysis by using ^{18}F-FDOPA PET/CT is 72%.[16] Possible sources of false negative findings for MTC on ^{18}F-FDOPA PET/CT may be small MTC lesions or dedifferentiation. On the other hand, false positive findings of ^{18}F-FDOPA PET/CT in recurrent MTC are uncommon.[16] Notably, the detection rate of ^{18}F-FDOPA PET/CT in patients with recurrent MTC significantly improves in patients with serum Ctn levels > 150 pg/mL and Ctn doubling times < 24 months, whereas it is not affected by the use of premedication with carbidopa (a selective extracerebral decarboxylase inhibitor which could improve the bioavailability of ^{18}F-FDOPA).[16] The acquisition time of ^{18}F-FDOPA PET/CT may influence the diagnostic performance of this imaging method. When performed, early acquisition of ^{18}F-FDOPA PET/CT (around 5-15 minutes after radiopharmaceutical injection) showed a higher detection rate and increased radiopharmaceutical uptake in MTC lesions compared to late acquisition (around 45-60 minutes after radiopharmaceutical injection) (Fig. 2).[17-20] ^{18}F-FDOPA PET/CT may affect the management of a significant number of patients with recurrent MTC when positive, because this imaging technique is often performed in patients with recurrent MTC based on rising tumor markers after negative conventional morphological imaging methods.[16] Moreover, in patients with MEN2A or

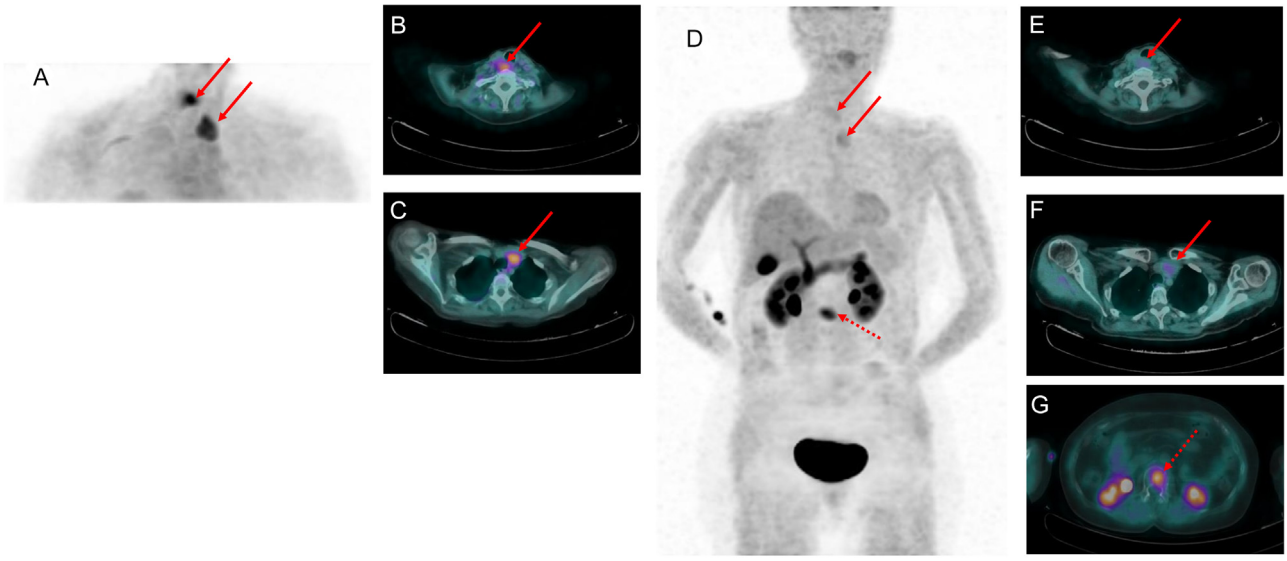

Figure 2 ^{18}F-FDOPA PET/CT performed for increased calcitonin levels in a 62-year-old female submitted to total thyroidectomy and cervical lymphadenectomy for MTC 14 years before. Coronal (A) and fused PET/CT images (B, C) obtained 5 minutes after radiopharmaceutical injection showed high ^{18}F-FDOPA uptake in two cervical/mediastinal lymph nodes (arrows). Maximum intensity projection PET image (D) and fused PET/CT images obtained 45 minutes after radiopharmaceutical injection showed faint uptake in the two lymph nodes (E, F), and increased uptake in a bone lesion in the second lumbar vertebra (G, dashed arrow). (Color version of figure is available online.)

MEN2B syndrome, ^{18}F-FDOPA PET/CT is useful to identify associated pheochromocytomas, which occur in approximately 50% of these patients and usually are benign and bilateral (Fig. 3).[21] In this setting, ^{18}F-FDOPA PET/CT has the advantage of low physiologic uptake in the adrenal medulla, when compared to ^{68}Ga-DOTA-peptides as well as that of specific uptake in the neurosecretory granules of adrenal medulla cells, when compared to ^{18}F-FDG. A predictive and prognostic value of ^{18}F-FDOPA PET/CT has been suggested in recurrent MTC: progression-free survival and disease-specific survival were significantly longer in patients with an unremarkable ^{18}F-FDOPA PET/CT compared with those with positive PET/CT scans.[22]

Several somatostatin analogues (DOTA-TATE, DOTA-TOC, DOTA-NOC, DOTA-LAN) labeled with ^{68}Ga have been used as PET radiopharmaceuticals for detecting MTC based on the overexpression of somatostatin receptors on the cell surface of neuroendocrine tumor cells.[11,23] According to evidence-based data, the detection rate of recurrent MTC on a per patient-based analysis by using ^{68}Ga-DOTA-peptides PET/CT is suboptimal with a pooled value of 63.5%.[24] Possible sources of false negative findings for MTC on ^{68}Ga-DOTA-peptides PET/CT may be small MTC lesions or lesions with no or mild expression of somatostatin receptors (Fig. 4). On the other hand, false positive findings of ^{68}Ga-DOTA-peptides PET/CT in recurrent MTC may be due to inflammatory lesions or other than neuroendocrine tumors due to the possible overexpression of somatostatin receptors in activated lymphocytes or other than neuroendocrine tumor cells, respectively.[24] Overall, the sensitivity of somatostatin receptor PET/CT in detecting recurrent MTC seems to be inferior compared to other neuroendocrine tumors (ie, well-differentiated pulmonary and gastroenteropancreatic neuroendocrine tumors) due to the variable somatostatin receptor expression in MTC.[11] Notably, the detection rate of ^{68}Ga-DOTA-peptides PET/CT in patients with recurrent MTC significantly improves in patients with higher serum Ctn levels (Fig. 5).[24] A clear advantage of ^{68}Ga-DOTA-peptides PET/CT compared to ^{18}F-FDOPA or ^{18}F-FDG PET/CT could be its theranostic value: as this imaging method may detect lesions with high somatostatin receptor expression it could be useful in selecting metastatic MTC patients for whom treatment with somatostatin analogues could be an option.[23,24]

Even if ^{18}F-FDOPA, ^{18}F-FDG and ^{68}Ga-DOTA-peptides may provide complementary information in the assessment of recurrent MTC, comparative studies and a network meta-analysis clearly demonstrate the superiority of ^{18}F-FDOPA PET/CT in terms of detection rate compared to the ^{18}F-FDG-PET/CT and ^{68}Ga-DOTA-peptides PET/CT in this setting (Fig. 6).[25,26] The superior diagnostic performance of ^{18}F-FDOPA PET/CT in recurrent MTC is also associated with a significantly higher proportion of change in the patient management compared to ^{18}F-FDG PET/CT and ^{68}Ga-DOTA-peptides PET/CT.[26] However, a significant percentage of recurrent MTC patients shows negative PET/CT imaging using both ^{18}F-FDOPA, ^{18}F-FDG or ^{68}Ga-DOTA-peptides.[26] For this reason, several other PET radiopharmaceuticals beyond those cited above were evaluated in MTC.

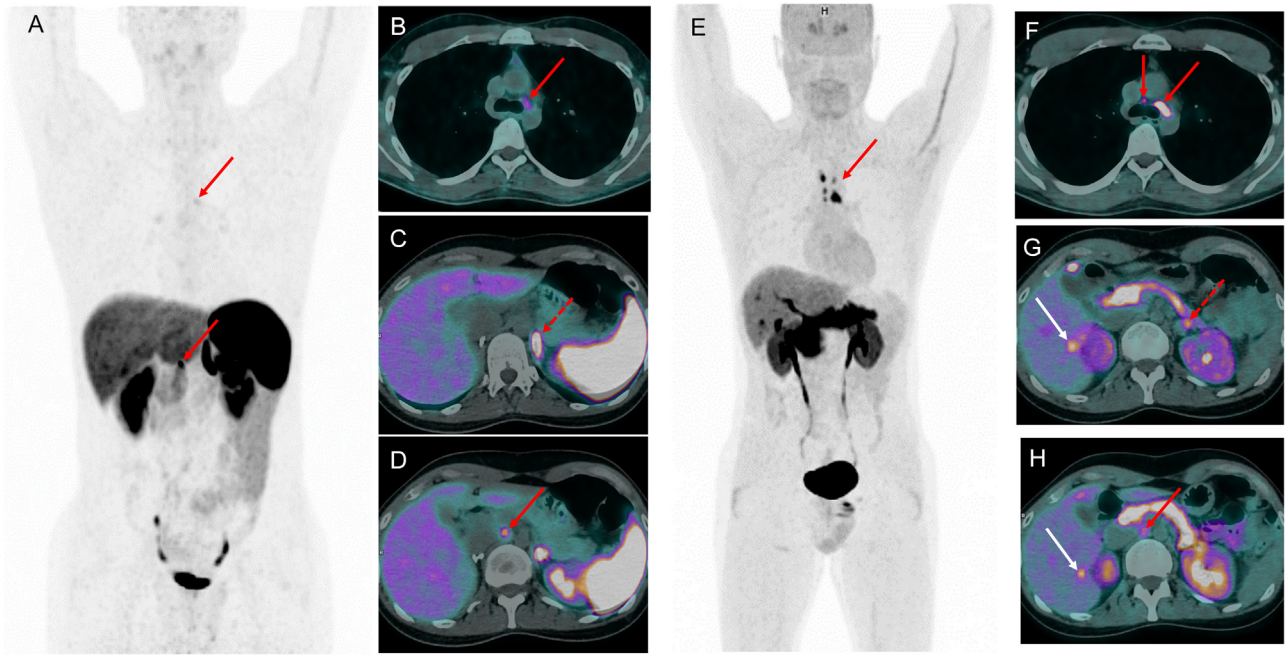

Figure 3 A 30-year-old man with MEN2A syndrome previously submitted to right adrenalectomy for pheochromocytoma and subsequent total thyroidectomy with bilateral cervical lymphadenectomy and resection of one liver metastasis. ^{68}Ga-DOTANOC PET/CT (A: MIP PET) performed for restaging after surgery showed faint radiopharmaceutical uptake in one mediastinal lymph node (B), high uptake in one celiac (D) lymph node (red arrows) as well as high physiologic tracer uptake in the left adrenal medulla masking a small adrenal nodule (C, dashed arrow). ^{18}F-FDOPA PET/CT (E), maximum intensity projection PET image showed focal tracer uptake in multiple mediastinal lymph nodes (F), and one celiac (H) lymph node (red arrows), in multiple liver lesions as well as abnormal tracer uptake in the left adrenal nodule (G, dashed arrow), which was associated with high levels of urinary metanephrines. The patient underwent left adrenalectomy, which confirmed the presence of a 1.5 cm pheochromocytoma. (Color version of figure is available online.)

Few reports underlined the role of PET/CT with ^{18}F-fluoride, a radiopharmaceutical evaluating the bone metabolism, in assessing bone metastases of MTC reporting a superior diagnostic performance in this setting compared to other imaging methods and a potential prognostic value.[27,28] However, the main limitations of this imaging method are the low level of evidence on its clinical utility in MTC and its inability to correctly evaluate extra-skeletal lesions (even if few cases of soft tissues metastases with ^{18}F-fluoride uptake are reported in the literature).[29]

Promising results are available on PET/CT with radiolabeled anti-CEA antibodies in MTC as example of immuno-PET/CT,

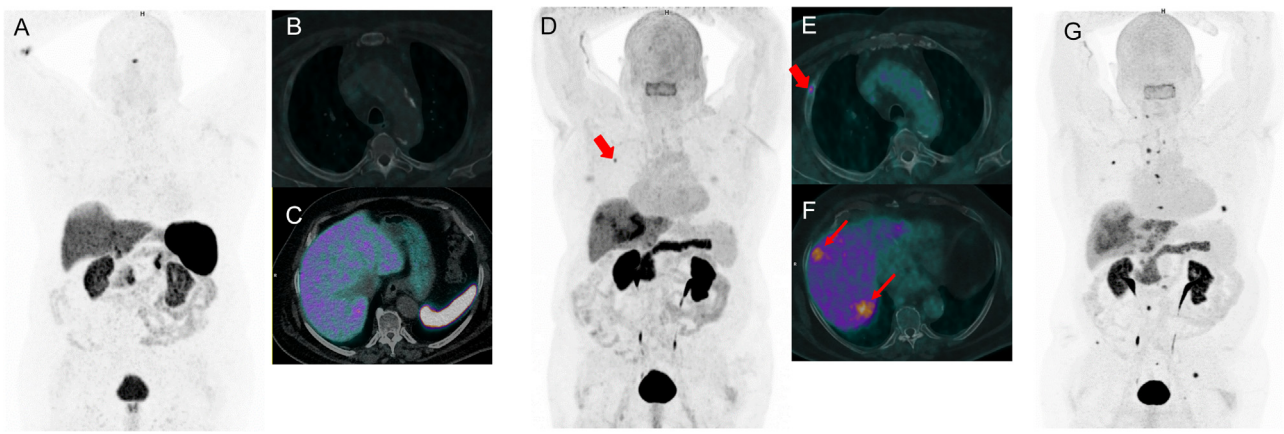

Figure 4 Restaging for progressive increase of Ctn levels in a 78-year-old man after surgery (total thyroidectomy and lymphadenectomy) for MTC. ^{68}Ga-DOTANOC PET/CT was negative (A, B, C). ^{18}F-FDOPA PET/CT showed focal tracer uptake in the III right rib (D, E, short arrow) and multiple liver lesions (D, F, arrows). Subsequent ^{18}F-FDOPA PET/CT (G) performed 2 years later showed progressive disease with multiple lymph nodal, liver and bone metastases. (Color version of figure is available online.)

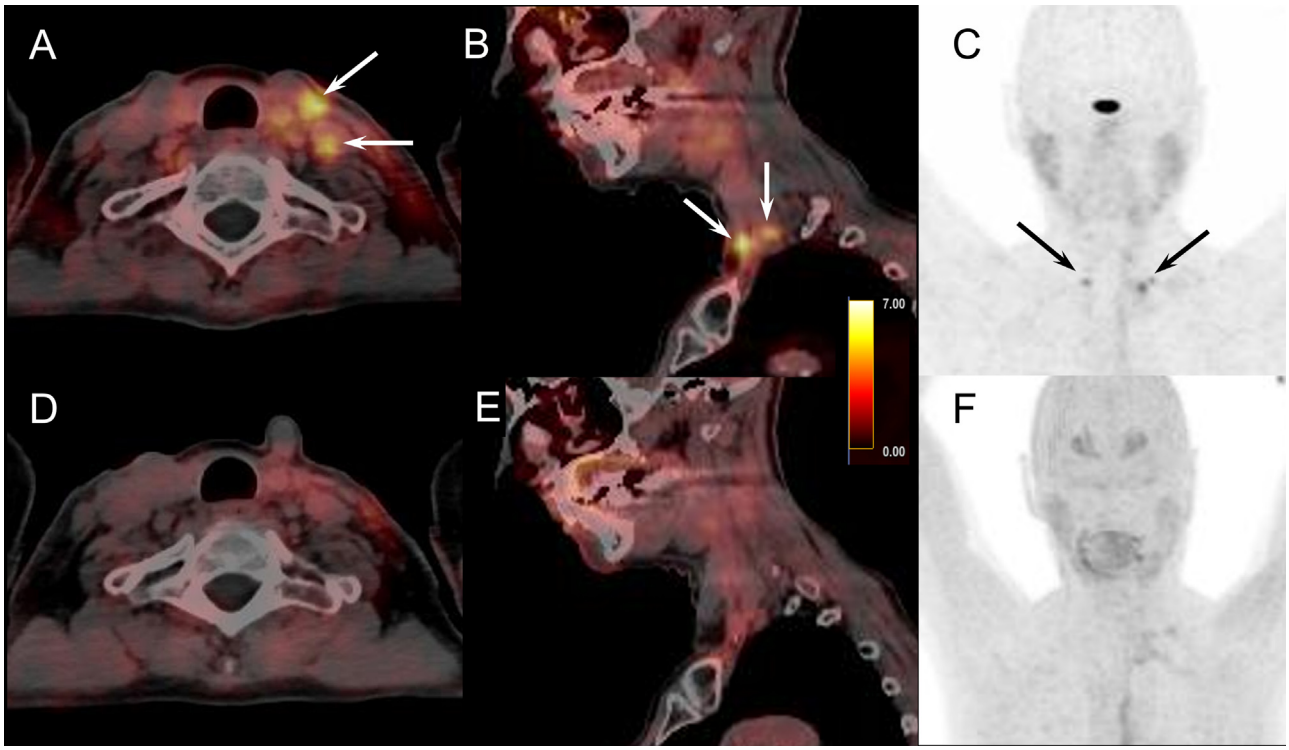

Figure 5 Head-to-head comparison between ^{18}F-FDOPA (upper panel) and ^{68}Ga-DOTATOC (lower panel) PET/CT in a 45-year-old woman with metastatic sporadic MTC, previous history of thyroidectomy and cervical lymph nodal dissection (central and left compartments, N+: 22/43), and increased serum calcitonin. Cervical bilateral lymph nodal relapse was revealed only by ^{68}Ga-DOTATOC PET (arrows). (A, D) Axial PET/CT, (B, E), sagittal PET/CT, (C, F) maximum intensity projection PET images. (Color version of figure is available online.)

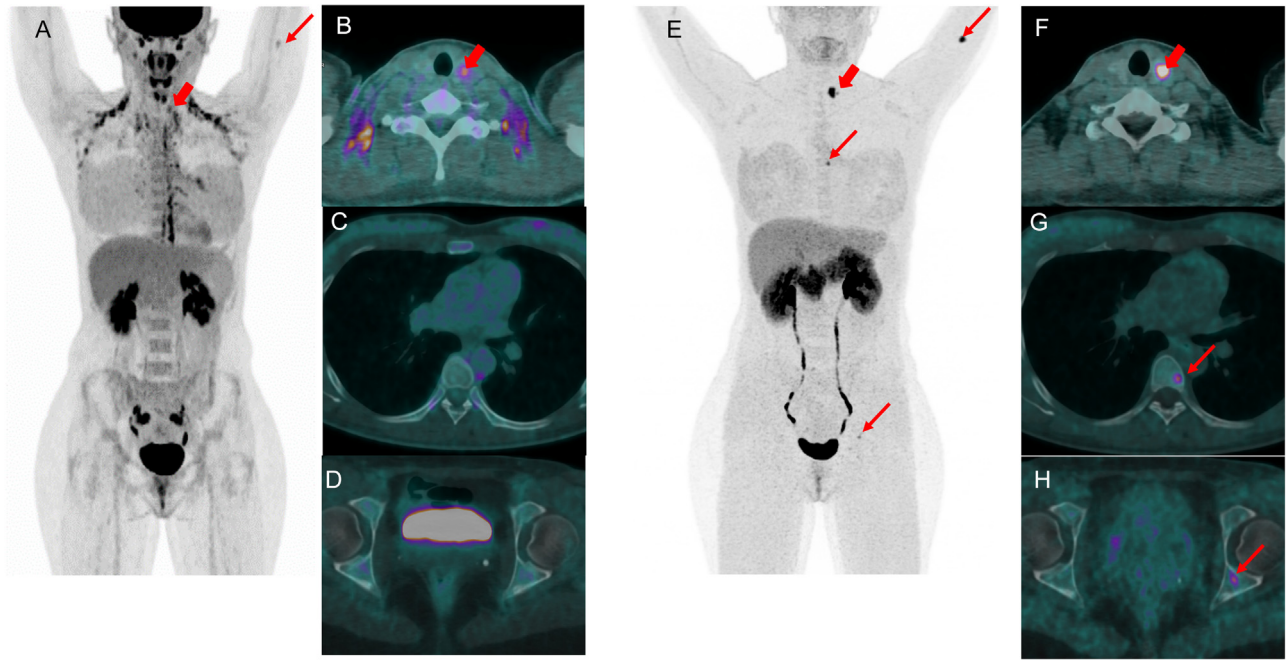

Figure 6 A 38-year-old female with incidental finding of MTC cells in a breast nodule. ^{18}F-FDG PET/CT performed after breast surgery showed focal tracer uptake in the left thyroid nodule (A, B, short arrow) and in the left humerus (A, arrow). No abnormal uptake is evident in the seventh dorsal vertebra (C) and in the left acetabulum (D). ^{18}F-FDOPA PET/CT showed focal tracer uptake in the left thyroid nodule (E, F, short arrow) and in the left humerus (E, arrow) as well as in the seventh dorsal vertebra (G) and in the left acetabulum (H) (arrows). (Color version of figure is available online.)

which combines the high sensitivity and resolution of a PET tomography with the specificity of a monoclonal antibody. Recent studies demonstrated that immuno-PET/CT is an effective procedure for detecting metastatic MTC lesions showing a higher sensitivity than other PET/CT and morphological imaging methods for disclosing metastases, except for the lung, where CT remains the most effective examination.[30-33] Immuno-PET could be a diagnostic tool for MTC detection, but also a theranostic companion approach to select patients to be treated with radioimmunoconjugates or antibody-drug conjugates.[32] However, the use of immuno-PET/CT in MTC is still limited to research protocols.

Cholecystokinin 2 receptor (CCK2R, or gastrin receptor) is overexpressed in MTC. Several PET radiotracers have been developed to target CCK2R, with promising results regarding the theranostic value of subsequent therapy with minigastrin labeled with ^{177}Lu. However, this diagnostic option is currently under evaluation in clinical trials.[34-36]

Further PET radiopharmaceuticals under evaluation in MTC but with very limited finding according to the literature include: fibroblast activation protein (FAP)-targeting radiopharmaceuticals,[37,38] prostate-specific membrane antigen (PSMA)-targeting radiopharmaceuticals,[39-41] amyloid-targeting tracers,[42] radiolabeled choline,[43] and ^{11}C-methionine.[44]

Most of literature data on PET in MTC are related to PET/CT with different radiopharmaceuticals mainly in the restaging setting. Although, the role of the molecular imaging procedures to restage MTC is supported by several evidence-based studies, the role of these procedures at the time of first staging is still not recognized. However, interesting studies analyzed the role of ^{18}F-FDOPA PET/CT in staging MTC prior to total thyroidectomy and lymph node dissection reporting that this imaging procedure is able to identify primary malignancy with high sensitivity and to disclose lymph node metastases with higher sensitivity than that of neck US.[45,46]

Another interesting topic is the possible advantage of PET/MRI on PET/CT in MTC evaluation. PET/MRI combines the functional information obtained with PET with the high soft tissue contrast resolution provided by MRI. This hybrid imaging method could provide advantages compared to PET/CT with different radiopharmauceuticals mostly in detecting liver metastases of MTC (Figs. 7 and 8). However, clinical experience on PET/MRI in MTC is still limited.[8]

Nuclear Medicine Therapy in MTC

Radio-immunotherapy using radiolabeled anti-CEA monoclonal antibodies, peptide receptor radionuclide therapy (PRRT) using ^{177}Lu-labeled or ^{90}Y-labeled somatostatin analogues, CCK2R-ligands labeled with ^{177}Lu and FAP- or PSMA-ligands targeted with ^{177}Lu have been developed as investigational nuclear medicine therapeutic options in metastatic MTC. However, few guidelines currently recommend nuclear medicine therapeutic options in metastatic MTC and just in very selected cases.[5] Overall, the efficacy, toxicity and

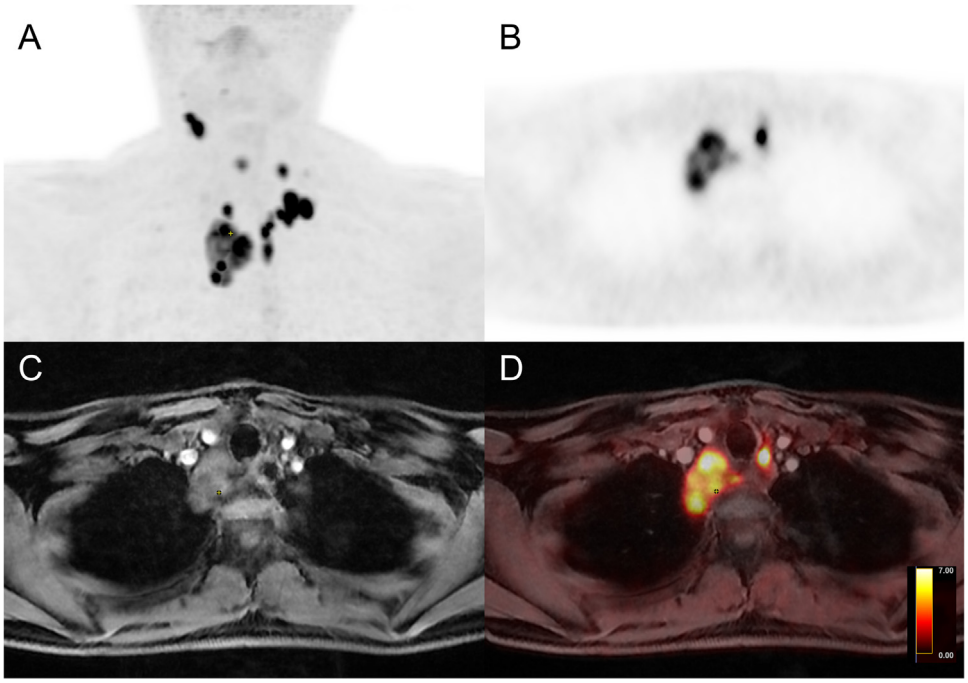

Figure 7 A 40-year-old man with metastatic sporadic MTC and previous history of thyroidectomy and central and bilateral cervical lymph node compartment dissection, presenting with increased serum calcitonin level and almost normal CEA. Patient underwent ^{18}F-FDOPA PET/MRI showing several foci of pathologic radiotracer uptake suggesting a massive mediastinal lymphatic relapse (A) anterior maximum intensity projection PET image, (B) axial PET, (C) contrast enhanced axial T1-weighted MRI (arterial phase), (D) axial PET/MRI. (Color version of figure is available online.)

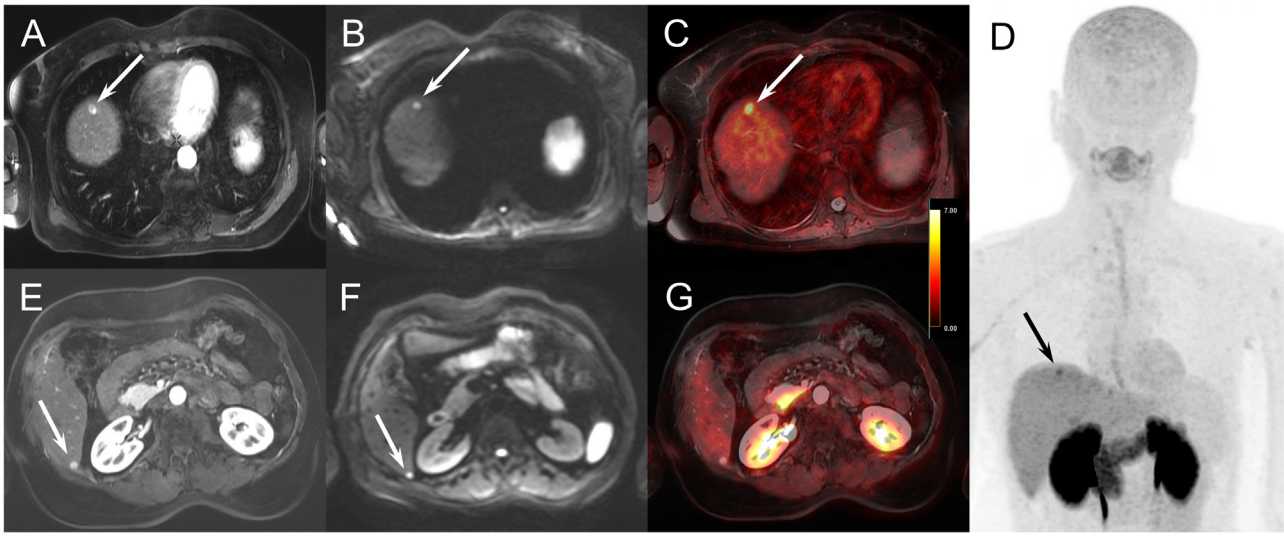

Figure 8 Results of ^{18}F-FDOPA PET/MRI of a 57-year-old man with metastatic sporadic MTC and previous history of thyroidectomy and right cervical lymph node compartment dissection. Abnormal ^{18}F-FDOPA uptake was showed only in one liver lesion (arrow, upper panel). Several other liver nodules of few mm were detected exclusively by MRI in right liver (arrow, lower panel), underlying the interest of hybrid PET/MRI imaging for optimal restaging and therapeutic strategy optimization. (A, E) Contrast enhanced axial T1-weighted MRI (arterial phase), (B, F) axial diffusion MRI, (C, G) axial PET/MRI, (D) maximum intensity projection PET image. (Color version of figure is available online.)

role of these therapeutic options remain to be determined in MTC patients.[8]

PRRT with radiolabeled somatostatin analogues has the potential to be an effective and safe modality for treating patients with somatostatin receptor positive MTC.[47,48] A recent evidence-based article demonstrated that PRRT could be effective in MTC with few adverse events.[49] Among 220 patients with metastatic MTC, biochemical and objective responses were observed in 37.2% and 10.6% of the patients, respectively.[49] However, the prevalence of high tumor avidity on ^{68}Ga-DOTA-peptides is low in the setting of metastatic MTC, and PRRT could be a viable treatment option in very selected metastatic MTC patients.[50]

Conclusions

To summarize, according to EANM guidelines, there is currently insufficient evidence to recommend PET/CT with several radiopharmaceuticals for staging MTC before treatment or for evaluating treatment response in metastatic MTC. Conversely, consistent evidence-based data support the use of PET/CT with different radiopharmaceuticals in MTC restaging when serum Ctn is higher than 150 pg/mL or Ctn doubling time is shortened. When PET/CT is indicated, ^{18}F-FDOPA should be the preferred PET radiopharmaceutical. If ^{18}F-FDOPA PET/CT is negative or unavailable, ^{18}F-FDG PET/CT or ^{68}Ga-DOTA-peptides PET/CT could be performed.[9] ^{18}F-FDG PET/CT is particularly useful when Ctn and CEA levels are rapidly rising or an aggressive behavior of the disease is expected. ^{68}Ga-DOTA-peptides PET/CT is particularly useful to assess the feasibility of targeted therapy with somatostatin analogs in highly selected patients.[9] Clinical experience on PET/MRI with different radiopharmaceuticals in MTC is still limited.

Several investigational nuclear medicine therapeutic options are currently under evaluation in metastatic MTC. More data are needed to evaluate the efficacy, toxicity, and role of these therapeutic options in the management of MTC patients.

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