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Molecular imaging and related therapeutic options for medullary thyroid carcinoma: state of the art and future opportunities

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Abstract

Due to its rarity and non-specific clinical presentation, accurate diagnosis, and optimal therapeutic strategy of medullary thyroid carcinoma (MTC) remain challenging. Molecular imaging provides valuable tools for early disease detection, monitoring treatment response, and guiding personalized therapies. By enabling the visualization of molecular and cellular processes, these techniques contribute to a deeper understanding of disease mechanisms and the development of more effective clinical interventions. Different nuclear imaging techniques have been studied for assessing MTC, and among them, PET/CT utilizing multiple radiotracers has emerged as the most effective imaging method in clinical practice. This review aims to provide a comprehensive summary of the current use of advanced molecular imaging modalities, with a particular focus on PET/CT, for the management of patients with MTC. It aims to guide physicians towards a rationale for the use of molecular imaging also including theranostic approaches and novel therapeutical opportunities. Overall, we emphasize the evolving role of nuclear medicine in MTC. The integration of diagnostics and therapeutics by in vivo molecular imaging represents a major opportunity to personalize treatment for individual patients, with targeted radionuclide therapy being one representative example.

Keywords Medullary thyroid carcinoma · Nuclear medicine · Molecular imaging · PET · ^{18}F-FDG · ^{18}F-DOPA · ^{68}Ga-DOTA peptides · Theranostics

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1 Introduction

1.1 Clinical overview

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor arising from the parafollicular C-cells of the thyroid gland [1] and accounts for 3–10% of all thyroid carcinomas [2]. MTC often develops from the upper-third of the posterior thyroid lobes, where C-cells are most concentrated, and frequently spreads to nearby lymph nodes [3]. C-cells secrete mainly thyrocalcitonin (TCT), carcinoembryonic antigen (CEA), and chromogranin A, with TCT and CEA being the two serum markers currently used for MTC screening and patient monitoring.

When screening for thyroid disorders, MTC may be suspected if hyper calcitoninemia is present. Nonetheless, it is important to note that increased TCT values can also be observed in other conditions such as chronic renal failure, C-cell hyperplasia (CCH) caused by thyroiditis, or as a side effect of certain medications. Procalcitonin measurement has been shown to improve diagnostic accuracy in such cases [4]. TCT levels are closely related to tumor mass and differentiation. MTC is usually suspected when serum TCT level is below the upper reference limit [5]. The levels of TCT tend to increase with the size and differentiation of the tumor. In dedifferentiated MTC, CEA can serve as a follow-up marker.

Patients with MTC may manifest thyroid mass, neck pain or fullness, difficulty swallowing or breathing, and hoarseness, or other more unusual symptoms such as bone pain, flushing, weight loss, or diarrhea, which result from distant metastases secreting high levels of TCT. The diagnosis of MTC can be confirmed by performing a fine-needle aspiration biopsy.

MTC has a worse prognosis than differentiated thyroid cancers, with approximately 10% of patients initially presenting with a palpable MTC nodule having distant metastases, and cervical lymphatic spread in 70% of cases. A significant association has been observed between the tumor size and the preoperative basal serum TCT levels. TCT below 20 pg/mL can rule out the risk of lymph node involvement, while TCT levels exceeding 20, 50, or 200 pg/mL are commonly linked with central and unilateral involvement, contralateral central diffusion, and contralateral lateral spread, respectively [6].

MTC can occur sporadically or as a result of germline activating RET proto-oncogene mutation, which is present in approximately 20–30% of cases and is associated with multiple endocrine neoplasia type 2 (MEN2) syndromes [7]. MEN2 is an inherited syndrome with an estimated prevalence of 1:20,000 [8]. There are two phenotypic forms of MEN2, both of which have MTC, which is primarily responsible for patient's prognosis [9]. MEN 2 A or Sipple syndrome is the most common form and is associated with the presence of pheochromocytoma (PCC) in 20–50% of cases and primary hyperparathyroidism (HPT1) in 5–20% of cases.

1.2 Current therapeutic strategy

The effective management of MTC depends significantly on the patient's age, the tumor stage at the time of diagnosis, and the expertise of the medical team involved. The primary treatment and the only curative option for MTC is surgery, especially in those patients without or with limited metastases. Surgery typically consists of a total thyroidectomy with central neck dissection to remove any affected lymph node, even if preoperative cervical ultrasound shows no evidence of disease, and irrespective of TCT levels [10]. The extent of lateral cervical lymphatic excision is a matter of debate and left to the discretion of the surgeons, who bases their decision on their experience, ultrasound results, and basal TCT levels [11].

Up to 40% (19.7–37.9%) of patients will experience metastatic relapse during follow-up, contrasting with de novo metastatic patients representing only 10% of all MTC patients [12, 13]. Local treatment should be used in patients with oligometastatic and progressive disease to postpone systemic treatments [14]. Systemic therapy includes drugs mainly targeting vascular endothelial growth factor receptor-2 (VEGFR2) and activating RET mutations. Cabozantinib and vandetanib are the two first-line systemic drugs approved by the EMA and the FDA based on an improvement in progression-free survival compared with placebo in large phase-3 trials [15, 16]. Vandetanib is a once-daily oral agent that selectively targets RET, VEGFR2, and EGFR signaling. The ZETA trial compared vandetanib (300 mg daily) with placebo (2:1) in 331 patients with locally advanced or metastatic medullary thyroid cancer [16]. The predicted modified progression-free survival (mPFS) in the vandetanib arm was significantly extended than that observed in the placebo group (30.5 vs. 19.3 months; HR, 0.46; 95% CI, 0.31 to 0.69; $p < 0.001$). Statistically significant advantages for vandetanib were observed for objective response rate (45% vs. 13%, $p < 0.001$), disease control rate at 24 weeks (87% vs. 71%, $p = 0.001$), and biochemical response ($p < 0.001$). The effect on overall survival was confounded by the crossover of patients on the placebo arm to receive vandetanib at investigator-assessed progression before confirmation by central review. Cabozantinib is a once-daily oral agent that targets kinase of c-MET, VEGFR2, and inhibits AXL and RET. The EXAM trial compared cabozantinib (140 mg daily) with placebo (2:1) in 330 patients with documented radiographic progression of metastatic

MTC [15]. Prior therapies including MKIs was permitted but patients receiving placebo were not allowed to crossover to cabozantinib in cases of progression. The predicted mPFS in the cabozantinib arm was significantly extended than that observed in the placebo group (11.2 vs. 4.0 months for placebo; HR 0.28; 95% CI, 0.19 to 0.40; $p < 0.001$) with a higher rate of responses (28% versus 0%, median duration of response 14.6 months). In the final analysis a 5.5-month increase in median overall survival (OS) with cabozantinib vs. placebo was reported (26.6 versus 21.1 months) without reaching statistical significance (HR 0.85, 95% CI 0.64–1.12; $p = 0.24$) [17]. Activating RET mutations is reported in almost all familial forms and 60% of cases of sporadic MTC [18]. In 2020, two selective RET inhibitors were incorporated into the therapeutic armamentarium based on the results of multicenter, open-label, multicohort clinical trials in patients with RET-altered tumors of various types [19, 20]. Selpercatinib is the first selective RET kinase inhibitor approved by the FDA for advanced or metastatic RET-mutant MTCs requiring systemic therapy and by the EMA only after prior treatment with cabozantinib or vandetanib. Accelerated approvals were based on the significant and durable responses observed in a phase 1–2 trial multicohort clinical trial (LIBRETTO-001): 69% in pretreated patients (cabozantinib and/or vandetanib, 55 patients) with more than 70% responses lasting ≥ 12 months, and 73% in naive patients (88 patients) [20]. Pralsetinib is the second selective RET kinase inhibitor approved by the FDA showing similar efficacy in another multicohort clinical trial (subgroup previously treated: ORR 60%, treatment-naive subgroup: ORR 71%) [19]. Finally, cytotoxic chemotherapy can be a treatment option after molecular targeted therapy, but the tumor response is low (about 15% with combination of 5-fluorouracil with dacarbazine) with short duration [21].

1.3 Role of imaging

Imaging plays a critical role in the management of MTC by enabling the accurate diagnosis and staging of the disease, as well as the monitoring of treatment response and disease progression. Imaging modalities such as ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) are utilized at various stages of the disease, as well as blood tests to monitor calcitonin and CEA levels. The comprehensive use of imaging aids in optimizing patient care by providing valuable information for decision-making and ensuring appropriate management strategies for individuals with MTC. A multidisciplinary approach utilizing radiological and nuclear medicine examinations is used in the management of patients with MTC. Modern hybrid imaging techniques like PET/CT play a crucial role in clinical practice by combining anatomical and functional imaging. They offer improved accuracy, unique information, and optimized therapeutic strategies, ultimately enhancing patient care and outcomes. Molecular imaging has also led to the development of theranostic approaches, which use a single agent for both imaging and therapy. This allows for personalized medicine by selecting patients who are most likely to benefit from targeted therapies and monitoring their response to treatment. Therefore, imaging is an integral part of the management of MTC and is critical to achieving optimal outcomes for patients with this rare form of thyroid cancer.

1.4 Morphological imaging

US is the first-line imaging to be proposed to patients with suspected MTC with reported overall diagnostic accuracy of 80.4% [22]. Moreover, it has been demonstrated that US is superior to cross-sectional (CT, MRI) and functional imaging in detecting primary tumor, neck lymph node metastases, and recurrent nodal metastases in the neck during post-surgical follow-up [22–24]. US semeiology of MTC include a hypoechoic aspect, an irregular shape with ill-defined margins, the presence of micro calcifications, a height/width ratio < 1 (lesion larger than taller), and an increased vascularity [22–24]. Studies comparing the US features of MTC with other malignant thyroid tumors have found that heterogeneity of echo-structure and increased tumor vascularity favor the identification of MTC compared with other more frequent thyroid tumors such as papillary tumors. Moreover, MTCs are usually larger than papillary tumors [23, 24]. In case of US features evoking a suspicious or malignant nodule, the examination should be extended to the neck to rule out the presence of nearby metastatic lymph nodes. US criteria in favor of a metastatic node include the absence of the typical hyperechoic adipose tissue within the hilum, the hypoechoic aspect, and a round (rather than oval) morphology. According to the US features, suspected or malignant thyroid nodules including MTC, should be referred for percutaneous sampling. In this perspective, the sonographic patterns (composition, echogenicity, margins, calcifications, presence of extrathyroidal nodules) proposed by the American Thyroid Association (ATA) to classify thyroid nodules perform well also for MTC [25]. However, US sensitivity remains suboptimal in MTC and only just over half of cases are considered as high risk according to Thyroid Imaging and Reporting Data Systems (TIRADS) [26]. From a recent systematic review including twenty-five papers, 65% of MTCs were categorized as having a high suspicion level, while 25% was considered as intermediate suspicion according to the ATA system. When considering all Risk Stratification Systems (RSS), approximately 54.8% of MTCs were considered high-risk/suspicion classification.

When pooling data from studies lacking RSS information, the prevalence of US suspicious MTCs was around 60% [26]. On the other hand, as showed by a recent meta-analysis, the studies assessing the precision of RSS mainly focus on histologically confirmed cancers, with the majority being papillary thyroid carcinoma (PTC), questioning the diagnostic adequacy of TIRADS application for patients with MTC [27]. The association of US and TCT levels seems the best diagnostic approach to suspect or rule out MTC [4].

The use of CT or MRI is limited to cases needing a systemic assessment to detect metastatic disease. High serum TCT level is the main criteria used to propose CT or MRI investigations [28]. Nevertheless, systemic metastases should be detected with cross sectional imaging in case of extensive neck disease, or signs and/or symptoms of distant metastases regardless of the TCT levels. CT is the most sensitive imaging modality to detect lung and mediastinal metastases. Moreover, contrast-enhanced CT or MRI are used to rule out liver metastases. MRI is the most sensitive exams to detect bone metastases [11, 29]. Finally, patients with newly diagnosed MTC should be evaluated for HPT and PCC prior to thyroid surgery.

In the recent years, 4D CT has been used to evaluate thyroid cancer recurrences. 4D CT combines three-dimensional CT imaging with the element of time, allowing for the assessment of dynamic changes in tissue over time. Nonetheless, there is currently a lack of data that specifically examines the application of 4D CT in cohorts of patients diagnosed with MTC. 4D CT can help differentiate with high accuracy between recurrent thyroid carcinoma and residual nonmalignant thyroid tissue [30]. The precontrast images and the arterial phase were more useful for accurate discrimination. Additionally, the utilization of 4D CT has been suggested for the characterization of thyroid nodules. in this case, precontrast nodule attenuation was significantly lower in malignant nodules when compared with benign nodules [31]. More recently, the utilization of early-phase enhanced CT and the incorporation of quantitative parameters obtained from multiphasic CT enhance the identification of cervical lymph node metastases originating from papillary thyroid cancer. This heightened detection capability holds significance in terms of accurate staging and formulating effective treatment strategies [32]. It's important to note that while the potential application of 4D CT in MTC seems logical, its clinical utility and widespread adoption would depend on factors such as technological feasibility, cost-effectiveness, and demonstrated benefits over existing imaging techniques.

In the follow-up of MTC, conventional imaging modalities are commonly used to assess the thyroid bed, evaluate regional lymph nodes, and detect distant metastases. The choice of imaging modality and the frequency of follow-up imaging studies depend on various factors, including the individual patient's clinical status, stage of disease, and treatment history. The decision is typically made by a multidisciplinary team of healthcare professionals specializing in thyroid cancer, who will tailor the follow-up schedule to the specific needs of the patient. The imaging findings are often correlated with clinical assessment and tumor marker measurements (such as TCT and ACE levels) to guide treatment decisions and monitor disease progression or recurrence.

1.5 Molecular imaging

The current modalities available for clinical investigation of patients with MTC comprise several nuclear imaging techniques. The use of radiopharmaceuticals for gamma camera-based investigations, including Technetium-99 m pentavalent dimercaptosuccinic acid (^{99m}Tc-(V)DMSA), Indium-111 or Technetium-99 m labeled somatostatin analogues, radioiodinated metaiodobenzylguanidine (^{123}I-MIBG) or radiolabeled anti-CEA antibodies, has been proposed in the past to detect MTC relapse, but they lack sensitivity compared to modern PET/CT imaging. Diphosphonate-labeled Technetium-99 m bone scintigraphy is still useful for MTC staging and restaging, while cholecystokinin-B/gastrin receptor scintigraphy has shown promising results [33, 34].

PET/CT is a superior nuclear imaging technique compared to conventional scintigraphic methods for investigating MTC in clinical settings. Latest generation of PET/CT devices with the use of several radiopharmaceuticals, such as ^{18} F-dihydroxyphenylalanine (^{18} F-DOPA), ^{18} F-fluorodeoxyglucose (^{18} F-FDG), and ^{68}Ga-labeled somatostatin analogues (^{68}Ga-DOTA-peptides), offer higher sensitivity also due to better spatial resolution and it is commonly used for restaging MTC when serum tumor markers levels increase after treatment [35, 36]. Accordingly, a personalized PET/CT exploration could be tailored for each patient taking into consideration both tumor characteristics and patient clinical presentation (Fig. 1).

However, there are also limitations to using nuclear medicine investigations for molecular diagnostic testing. First, these tests typically involve exposure to ionizing radiation. Second, the radiopharmaceuticals used may have limited availability and may be expensive. Finally, nuclear medicine investigations require specialized equipment and expertise, which may not be available at all medical centers.

1.6 ^{18}F-dihydroxyphenylalanine (^{18}F-DOPA) PET/CT

Neuroendocrine tumors take-up, accumulate, and decarboxylate amine precursors and amino acids. Radiolabeled amino acids such as DOPA have been successfully used

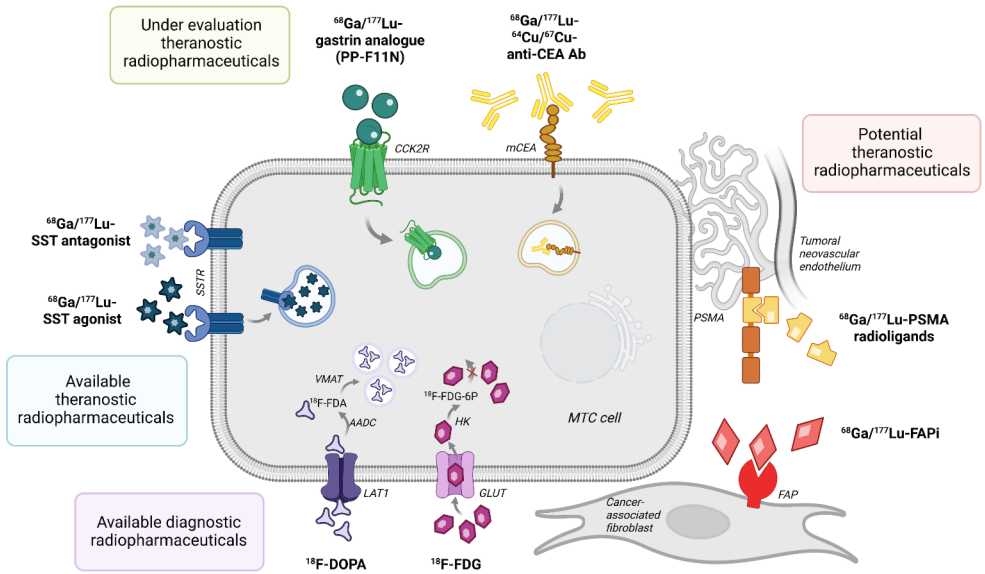

Fig. 1 Schematic representation of principal targets and related PET radiopharmaceuticals for radionuclide diagnostic imaging and therapeutics for medullary thyroid carcinoma (MTC). ^{18} F-FDG: ^{18} F-fluorodeoxyglucose, GLUT: glucose transporter, HK: hexokinase, ^{18} F-DOPA: ^{18} F-dihydroxyphenylalanine, LAT: L-amino acid transporter, AADC: aromatic L-amino acid decarboxylase, ^{18} F-FDA: ^{18} F-fluorodopamine, VAMT: vesicular monoamine transporter, SST: somatostatin, SSTR2: type-2 somatostatin receptor, CCK2R: cholecystokinin 2 receptor, CEA-Ab: anti carcinoembryonic antigen antibody, mCEA: membrane-bound carcinoembryonic antigen, PSMA: prostate-specific membrane antigen, FAPi: fibroblast activation protein (FAP) inhibitor. Created with BioRender.com.

as imaging agents after being labeled with fluorine-18 (^{18} F-FDOPA) for PET/CT investigations (Fig. 1). The L-amino acid transporters, particularly LAT-1 and LAT-2, are responsible for the uptake of ^{18} F-DOPA in neuroendocrine cells. Afterward, the aromatic L-amino acid decarboxylase (AADC) enzyme mediates its decarboxylation into ^{18} F-dopamine, which accumulates in intracellular vesicles through vesicular transporters (VMAT). In contrast to other types of neuroendocrine tumors, the AADC-mediated intracellular decarboxylation and storage mechanisms in MTC are less efficient, leading to a moderate uptake intensity and shorter tumoral retention. Therefore, early images are required at about 15–20 min after radiotracer injection, and the acquisition time duration needs to be extended [37, 38].

1.6.1 Preoperative screening

At present, there are no guidelines suggesting the use of ^{18} F-DOPA PET/CT before initial surgery (Fig. 2), mainly due to limited available literature [11, 34, 39, 40]. Indeed, the added value of ^{18} F-DOPA PET/CT prior to initial thyroidectomy has been only scarcely assessed and must be further evaluated. The initial results are promising in terms of detection rate for primary tumor and lymph node invasion, allowing the selection of patients who may benefit from operation with curative intent, as well as guiding further surgical procedures [39, 41]. According to Wells et al. [11], ^{18} F-DOPA PET/CT is more effective than ^{18} F-FDG PET/CT in preoperative and follow-up assessment of disease, but it does not provide additional value compared to cervical US in detecting nodal metastases. In a recent surgical study, the influence of neck US and contrast-enhanced ^{18} F-DOPA PET/CT prior to initial surgery in 50 MTC patients was assessed [42]. The surgical procedure involved total thyroidectomy with bilateral central neck dissection and bilateral lateral lymphadenectomy, including level V. For neck US, sensitivities based on nodal, central, and lateral compartments were 43%, 6%, and 56%, respectively. On the other hand, for ^{18} F-DOPA PET/CT, the sensitivities for the same compartments were 57%, 28%, and 75%, respectively. Patients with lateral lymph node involvement that were missed by PET/CT had small metastases with a mean size of 5.6 ± 5.1 mm, stressing that PET sensitivity can be negatively affected by lesion size and consequent partial volume effect for tiny lesions.

1.6.2 Post operative management and surveillance

Post-surgical persistent/recurrent disease is common in thyroidectomy patients, especially those with lymph node involvement. Serum calcitonin level measurement is crucial in detecting persistent or recurrent disease and determining the need for surgery. ^{18} F-DOPA PET is the preferred functional imaging modality for evaluating patients with persistent/recurrent MTC (Figs. 3 and 4; Table 1), but its sensitivity varies, and its spatial resolution is limited. The usefulness of ^{18} F-DOPA PET in identifying persistent MTC was initially demonstrated by Hoegerle et al. in 2001 [43],

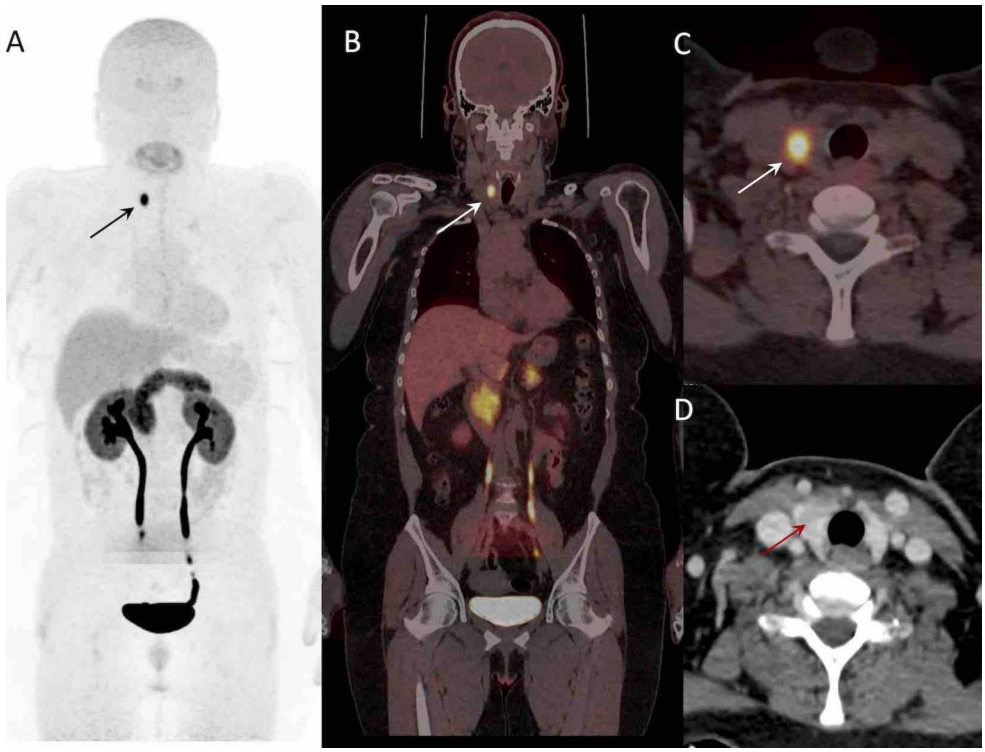

Fig. 2 Preoperative ^{18} F-DOPA PET/CT results in a 56-years-old woman with sporadic MTC. Patient showed increased plasma calcitonin (537 ng/L, N < 10) and CEA (33 ng/mL, N < 5) values. Intense radiotracer uptake (SUVmax-bW: 18.5) was revealed exclusively in one nodule (arrows) of 18 × 17 × 12 mm of inferior pole of right thyroid lobe, corresponding to MTC (A: anterior whole-body PET maximum intensity projection (MIP); B, C: coronal and axial PET/CT; D: axial contrast-enhanced CT (delayed phase)). Patient underwent total thyroidectomy, and central and right lymph node compartment dissection. Pathological examination confirmed the presence of MTC (pT1bN0 UICC 8th) without nodal involvement

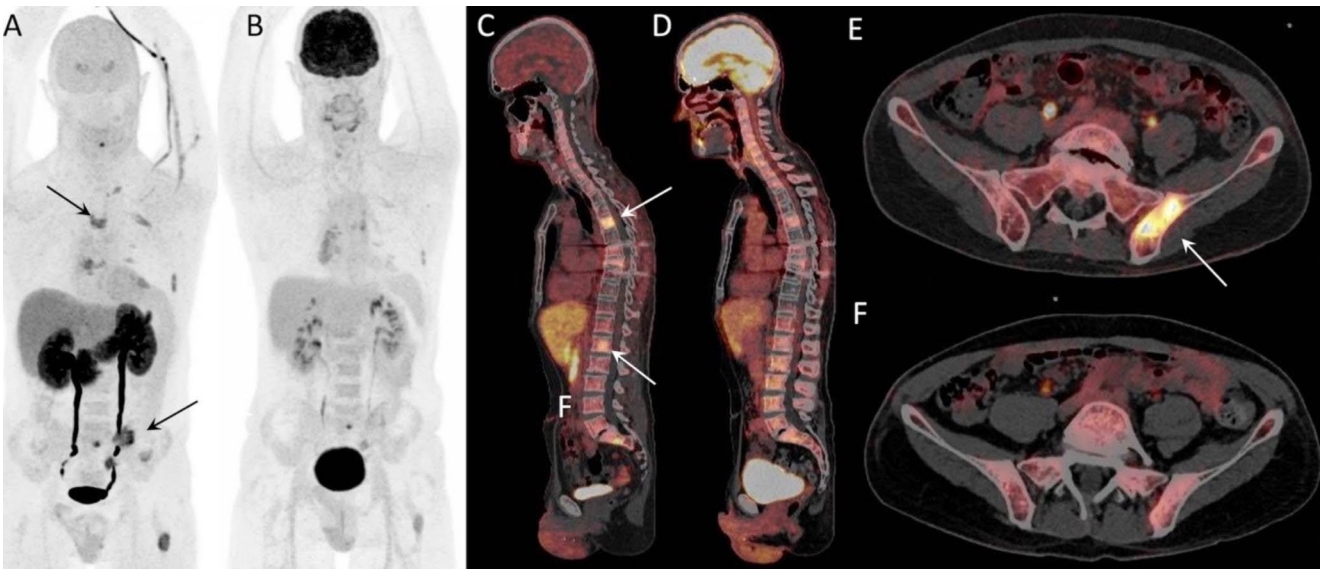

Fig. 3 A 48-years-old man with metastatic MTC and previous history of thyroidectomy and central and right lymph node compartment dissection, presenting with increased serum calcitonin level (193 ng/L, N < 10) and almost normal CEA. Patient underwent ^{18} F-FDOPA PET/CT (arrows, A: anterior maximum intensity projection (MIP); C, E: sagittal and axial PET/CT) showing higher detection rate than ^{18} F-FDG PET/CT for bone metastases (B, D, F). The following MRI investigation confirmed the presence of multiple spine lesions, and patient started treatment by tyrosine kinase inhibitor

and subsequent studies have confirmed its efficacy with reported sensitivities ranging from 47 to 83% [41, 44–46]. According to evidence-based data the detection rate *per patient* of ^{18} F-FDOPA PET/CT is estimated to be around 72% and is strongly influenced by serum TCT levels and tumor behavior [47]. Despite its utility, ^{18} F-FDOPA PET/CT is limited by its poor spatial resolution, leading to the underestimation of small nodes. This drawback can be particularly significant for nodes that are only a few millimeters in size. Interestingly, the effectiveness of ^{18} F-FDOPA PET/CT in detecting recurrent MTC increases in patients with high serum TCT levels (> 150 pg/mL) and TCT doubling

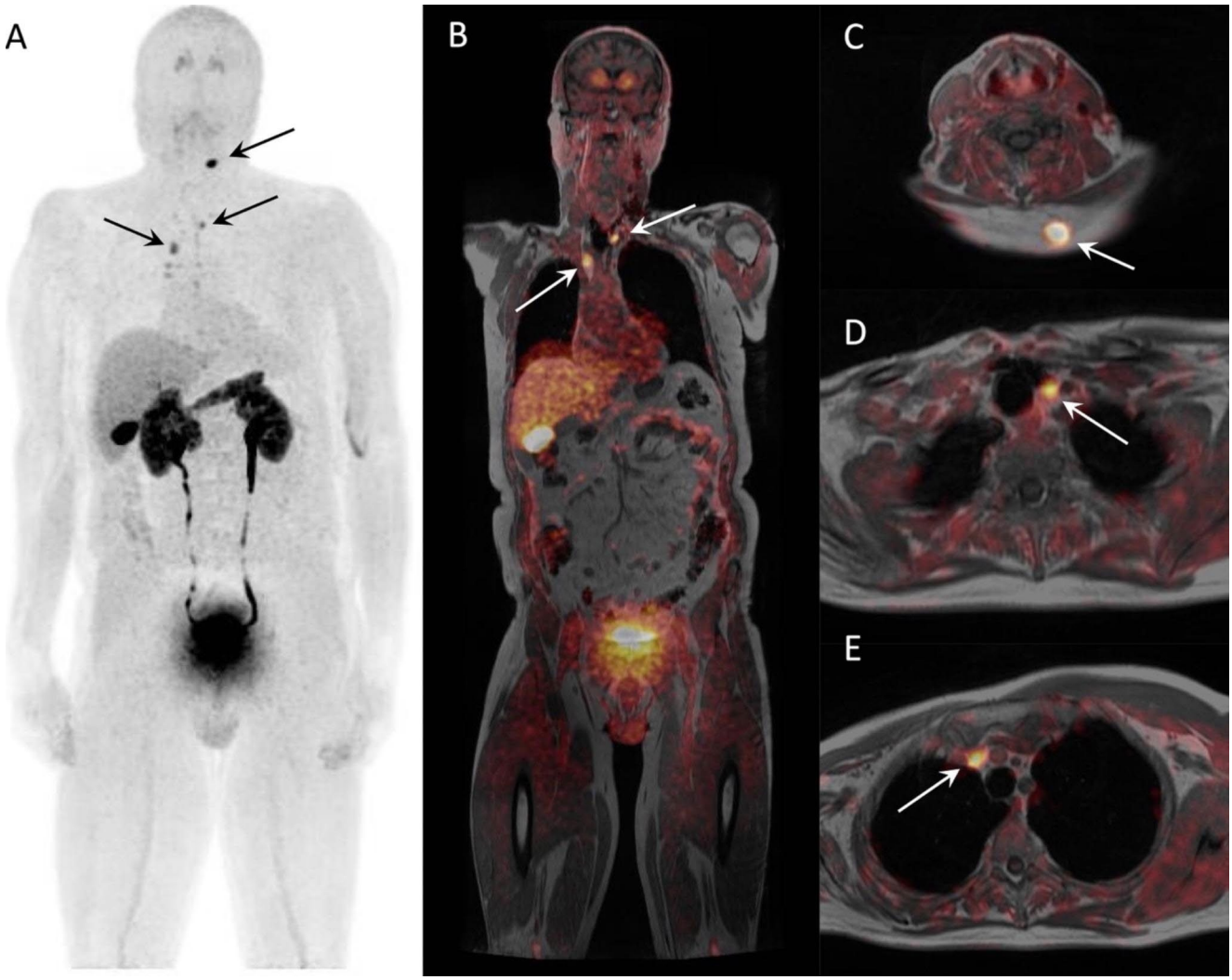

Fig. 4 A 57-year-old man with metastatic sporadic MTC and previous history of thyroidectomy and central and bilateral cervical lymph node compartment dissection, presenting with increased serum calcitonin level and almost normal CEA. Patient underwent whole-body ^{18} F-FDOPA PET/MRI showing several foci of pathologic radiotracer uptake suggesting lymphatic and subcutaneous relapse (arrows, A: anterior maximum intensity projection PET image, B: coronal PET/MRI, C-E: axial PET/MRI).

times of less than 24 months [47]. The threshold of 150 pg/mL for TCT should not be regarded as an absolute value that dictates the sensitivity of ^{18} F-DOPA PET/CT, but rather as a meaningful clinical parameter for deciding on the optimal timing of reoperative surgery. In relapsed MTC, ^{18} F-FDOPA PET/CT can accurately assess involved cervical lymphatic compartments, guiding surgical strategy (extended vs. limited neck dissection) [48]. Moreover, it can also detect PCC in MEN2 patients [49]. Compared to whole-body MRI and CT, ^{18} F-FDOPA PET/CT performed better in detecting disease in one study [50].

It's important to stress that false-positive results by ^{18} F-FDOPA PET/CT are uncommon in patients with recurrent MTC [47]. In contrast, inflammatory lesions, or tumors other than neuroendocrine tumors, due to possible overexpression of somatostatin receptors in activated lymphocytes or tumor cells other than neuroendocrine cells, are responsible for false-positive results of ^{18} F-FDG PET/CT and 68Ga-DOTApeptide PET/CT, reducing their diagnostic specificity [51, 52].

A recent work suggests the potential use of ^{18} F-DOPA PET/CT in predicting and prognosticating PFS and disease-specific survival (DSS) in patients with recurrent MTC, resulting significantly longer ($p < 0.001$and $p = 0.012$, respectively) in patients with normal ^{18} F-FDOPA PET/CT compared with those with positive studies [53]. Anomalies observed through visual analysis on ^{18} F-DOPA PET/CT are strongly linked to an increased likelihood of disease progression and a reduced DSS, irrespective of nodal or metastatic conditions. It's worth mentioning that solely an abnormal PET result has been recognized as a standalone prognostic indicator according to the multivariate analysis.

Table 1 Main findings of published meta-analyses on PET/CT with different radiopharmaceuticals in recurrent medullary thyroid cancer

Author	Year	Radiopharmaceuticals	Studies included	MTC patients	Pooled DRp of PET/CT (95%CI)	Correlation among MTC serum markers and DRp of PET/CT	Head-to-head meta-analysis among PET radiopharmaceuticals
Cheng et al. [49]	2012	^{18}F-FDG	15	428	69% (64–74%)	Yes	NR
Treglia et al. [48]	2012	^{18}F-FDG	24	538	59% (54–63%)	Yes	NR
Treglia et al. [42]	2012	^{18}F-DOPA	8	146	72% (62–81%)	Yes	NR
Treglia et al. [61]	2017	^{68}Ga-DOTA-peptides	9	152	63.5% (49–77%)	Yes	NR
Pajak et al. [60]	2022	^{68}Ga-DOTA-peptides and ^{18}F-FDG	14	306	NR	Yes	^{68}Ga-DOTA-peptides slightly better than ^{18}F-FDG
Lee et al. [59]	2020	^{18}F-FDG, ^{18}F-DOPA, ^{68}Ga-DOTA-peptides	5 (network meta-analysis)	113	NR	Yes	^{18}F-DOPA better than ^{68}Ga-DOTA-peptides and ^{18}F-FDG

Legend: 95%CI = 95% confidence interval values; MTC = medullary thyroid carcinoma; DRp = detection rate per patient; NR = not reported

Neither semi-quantitative PET measurements nor clinical/laboratory information demonstrated the ability to predict poorer PFS and DSS among patients with recurring MTC.

Although ^{18}F-DOPA PET/CT has been recommended in the 2009 American Thyroid Association (ATA) guidelines in patients with persistent/recurrent MTC and serum TCT > 150 pg/mL [54], this option was not retained in the revised version of 2015 [11]. However, the European Association of Nuclear Medicine (EANM) did not approve the revised recommendations due to contradictions between the versions, no new evidence against the use of ^{18}F-FDOPA PET/CT, and the body of scientific evidence in the literature [34].

1.7 ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT

^{18}F-FDG is a radiotracer commonly used for PET/CT investigations in clinical oncology, as it reflects cellular glycolytic activity. Once transported into cells by glucose transporters (GLUT1 and 3), it is phosphorylated by hexokinase and remains trapped in the cytoplasm (Fig. 1). When used to assess the metastatic extent of MTC, ^{18}F-FDG PET/CT has a pooled per-patient sensitivity of only 59% (95%CI, 54–63%) (Table 1). Small or slow-growing tumors could result in false-negative findings on ^{18}F-FDG PET/CT scans. On the other hand, ^{18}F-FDG PET/CT revealed more useful for detecting MTC recurrence in patients with aggressive disease and higher levels of TCT and CEA (Fig. 5). Indeed, tumoral ^{18}F-FDG uptake correlates with high proliferative activity and poor tumoral differentiation [52]. Using a cutoff value of 1000 pg/ml for serum calcitonin, the overall sensitivity per patient of ^{18}F-FDG PET/CT in patients exceeding this threshold increases to 86.7%, except for patients with MEN 2 A. In those cases, ^{18}F-FDG PET/CT sensitivity drops to 23% even if the calcitonin levels are exceeding 1000 pg/mL, suggesting that ^{18}F-FDG PET/CT is more beneficial in identifying recurrence in sporadic cases than in MEN 2 A patients. Notably, false positivity rate is highly increased in patients with calcitonin levels < 150 pg/mL underlining that ^{18}F-FDG PET/CT may be misleading and its use questionable in detection of minimal tumor load [55].

According to the latest U.S. recommendations [11], PET/CT is not advocated for initial staging of MTC due to its lower sensitivity, regardless of the radiotracer used. However, this conclusion is based solely on a single older study that used ^{18}F-FDG PET/CT results [56], highlighting the need for more clinical research using newer, more specific radiotracers that are currently available in clinical practice.

Remarkably, ^{18}F-FDG PET/CT has a significant prognostic and predictive capability in the recurrence of MTC, as it can differentiate patients with unfavorable outcomes and distinguish those with progressive disease from those with

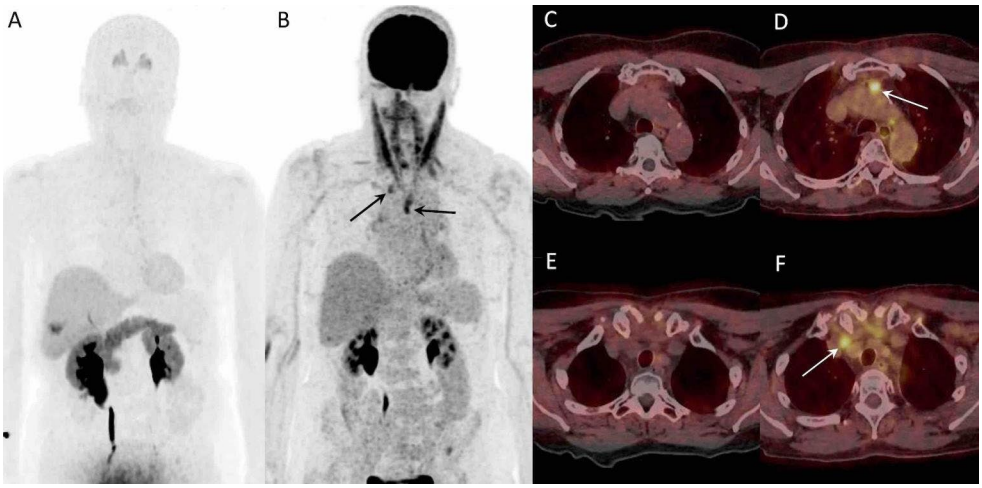

Fig. 5 A 76-years-old woman with metastatic MTC presenting with increased serum CEA level (108 ng/mL, N < 5) and a doubling time of about 8 months. Patient underwent ^{18} F-FDG (A, D: coronal PET slices; B, E: coronal PET/CT slices) and ^{18} F-FDOPA (C, F: coronal PET slices) PET/CT for primary staging and prognostication, showing exclusive ^{18} F-FDG tumor uptake (arrows). ^{18} F-FDOPA PET/CT was falsely negative (A, C, E)

stable disease [57]. Patient survival is significantly reduced in ^{18} F-FDG positive MTC compared to ^{18} F-FDG negative lesions, regardless of ^{18} F-DOPA PET/CT results. Thus, the combination of ^{18} F-FDG PET/CT and calcitonin doubling time can help identify high-risk MTC patients requiring close monitoring. Some authors have also proposed performing PET/CT with both ^{18} F-FDG and ^{18} F-FDOPA in patients with metastasis to better characterize tumor behavior [58].

Several studies have shown that ^{18} F-FDG PET can independently predict response to targeted radioimmunotherapy or tyrosine kinase inhibitors (TKI) for MTC patients. The analysis of the most metabolically active lesion on ^{18} F-FDG PET/CT can predict PFS, but not OS, in patients undergoing TKI treatment [59–61]. Recent research has demonstrated that certain parameters, such as intra-tumoral textural features and volumetric measurements obtained from pre-therapeutic ^{18} F-FDG PET, such as total lesion glycolysis (TLG), can be used to predict OS in patients with metastatic MTC [61]. This suggests that a radiomic approach to MTC may have a role in predicting treatment outcomes.

PET/MRI is a powerful imaging modality, potentially interesting in patients with MTC [62] (Fig. 4). However, its availability may be limited compared to conventional PET or MRI scanners, and it is still too early to define its clinical benefit.

1.8 68Ga-DOTA-peptides PET/CT

Neuroendocrine tumors typically express somatostatin receptor subtype 2 (SSTR2), which makes them suitable for somatostatin receptor imaging and targeted radionuclide therapy. SSTR2 is particularly important in the diagnosis and management of gastroenteropancreatic neuroendocrine tumors and various radiolabeled somatostatin analogs, such as ^{68}Ga-DOTA-peptides and ^{177}Lu-DOTATATE, have been developed for imaging and treatment purposes (Fig. 1).

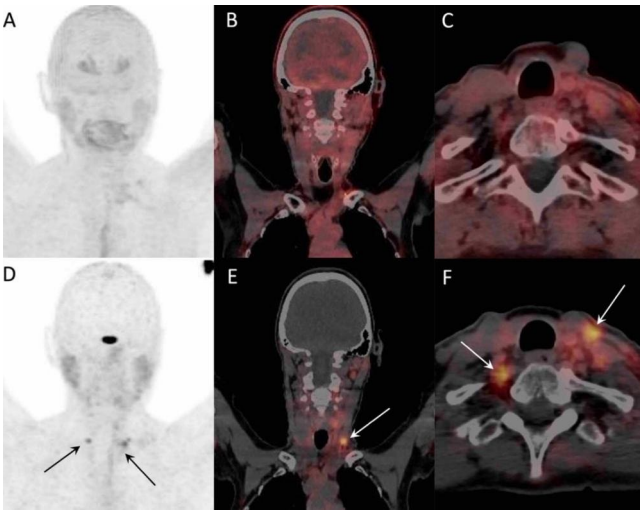

Fig. 6 Head-to-head comparison between ^{18} F-DOPA (upper panel) and ^{68}Ga-DOTATOC (lower panel) PET/CT in a 45-years-old woman with metastatic sporadic MTC and previous history of thyroidectomy and lymph node dissection (central and left compartments, N+: 22/43). Serum calcitonin (400 ng/L, N < 10) was disproportionately increased than CEA (6 ng/mL, N < 5). ^{68}Ga-DOTATOC PET/CT revealed cervical nodal relapse (arrows) missed by ^{18} F-DOPA PET/CT. A, D: PET anterior maximum intensity projection (MIP); B, E: coronal PET/CT; C, F: axial PET/CT.

The expression of SSTR2 appears to be inconsistent in MTC, and PET imaging using ^{68}Ga-DOTA-peptides seems to have limited usefulness as first line imaging with lower sensitivities compared to ^{18} F-DOPA and ^{18} F-FDG PET [63–66]. A recent meta-analysis [67] that assessed the diagnostic accuracy of ^{68}Ga-DOTA-peptides PET/CT in patients with recurrent MTC reported a sensitivity range of 25 to 100%. ^{68}Ga-DOTA-peptides PET may be considered in cases of biological relapse when ^{18} F-DOPA and ^{18} F-FDG PET results are inconclusive (Fig. 6). On a *per patient*-based analysis, the sensitivity of ^{68}Ga-DOTA-peptides PET or PET/CT in suspected recurrent MTC is 63.5%, with a 95% confidence interval ranging from 49 to 77% [67] (Table 1).

In addition, a small group of patients with bone metastases showed a higher detection rate with ^{68}Ga-DOTA-peptides PET/CT than with bone scintigraphy or MRI, according to a study by Werner et al. in 2018 [60].

^{68}Ga-DOTATOC PET/CT remains mandatory for patient selection before peptide receptor radionuclide therapy (PRRT). According to a recent study using in vitro receptor autoradiography, SSTR2 antagonists have been found to bind to a greater number of receptor sites than agonists. This finding opens new possibilities for imaging and PRRT with somatostatin antagonists in MTC [68, 69].

1.9 Other diagnostic PET radiotracers

PET/CT with ^{18} F-fluoride has been used in the evaluation of bone metastases in various types of cancer. In patients with MTC, ^{18} F-fluoride PET/CT has superior diagnostic performance in detecting bone metastases compared to other imaging methods, such as bone scintigraphy, also showing a potential prognostic value [70, 71]. However, its clinical utility in MTC is still not well established due to the limited number of studies on this topic. Additionally, PET/CT with ^{18} F-fluoride is not able to accurately evaluate extra-skeletal lesions, which limits its overall usefulness in the management of MTC.

Amyloid-targeting tracers, such as ^{18} F-Florbetapir, have been studied in MTC due to their potential to detect amyloid deposition in tumors, but the results have been limited and inconclusive [72]. Finally, radiolabeled choline and ^{11} C-methionine have been evaluated in other neuroendocrine tumors and may have some utility in MTC [73, 74], but further studies are needed to determine their usefulness.

1.10 Future direction for PET radiotracer development

Cholecystokinin 2 receptor (CCK2R), also known as gastrin receptor, is a G-protein-coupled receptor that is expressed in high levels in MTC. CCK2R is activated by gastrin, a peptide hormone that stimulates gastric acid secretion, and is also expressed in various other tumors, such as neuroendocrine tumors. In MTC, the overexpression of CCK2R has been related to tumor growth and progression. Interestingly, CCK2R can be used as a molecular target for molecular imaging and therapy in MTC (Fig. 1). Radiolabeled CCK2R antagonists have been developed for imaging of CCK2R-expressing tumors, including MTC, using PET or gamma camera imaging. This technique allows for the non-invasive detection of CCK2R-expressing tumors and may aid in the diagnosis, staging, and monitoring of MTC. However, more research is needed to further optimize these approaches and determine their clinical utility. Moreover, the theranostic value of subsequent therapy with minigastrin labeled with ^{177}Lu is currently under evaluation in clinical trials [75–77].

CEA is a glycoprotein that is expressed in high levels in MTC, making it a potential target for imaging and therapy. Radiolabeled anti-CEA antibodies can be administered to patients, and their binding to CEA-expressing tumor cells can be detected using PET/CT imaging (immuno-PET/CT) (Fig. 1). This allows for the visualization of both primary and metastatic MTC lesions. PET/CT with radiolabeled anti-CEA antibodies has high sensitivity and specificity for MTC lesions, including those that are too small to be detected using conventional imaging methods except for lung metastases, where CT remains the most effective examination. In addition, it has been used to monitor response to therapy and to detect disease recurrence [78–80]. While this imaging technique holds promise, it is not yet widely available and is still considered experimental. More research is needed to determine its clinical utility and to optimize its use in the management of MTC.

Several other PET radiopharmaceuticals have been evaluated for their potential use in imaging (and therapy) of MTC, but with limited findings in the literature (Fig. 1). Further research is needed to fully evaluate their utility in MTC. Fibroblast activation protein (FAP)-targeting radiopharmaceuticals have shown promising results, but their use in clinical settings for MTC has not yet been fully explored [81, 82]. Prostate-specific membrane antigen (PSMA)-targeting radiopharmaceuticals, which have shown utility in prostate cancer, have been investigated in a small number of MTC cases [83, 84].

1.11 PET/CT for MTC management: the appropriate tracer, the good patient, the right time

Based on the currently available imaging techniques, a complex and personalized approach is usually adopted to investigate a patient with suspected or known MTC (Fig. 7). At present, the routine use of PET/CT imaging for the pre surgical staging of MTC in patients with metastatic disease lacks sufficient evidence to support its recommendation. Nonetheless, PET/CT imaging has proven to be valuable in restaging MTC patients with biological relapse after surgery and serum TCT levels exceeding 150 pg/mL or the TCT doubling time is less than 24 months. If available, ^{18} F-DOPA PET/CT should be the preferred option due to its superior diagnostic performance in comparison to other PET tracers. The latest guidelines (2022) from NCCN Thyroid Carcinoma Panel acknowledges the potential use of various imaging methods to assess residual or metastatic tumors. However, there isn't enough conclusive evidence to endorse a specific selection or combination of tests. Therefore, considering the calcitonin/CEA doubling time,

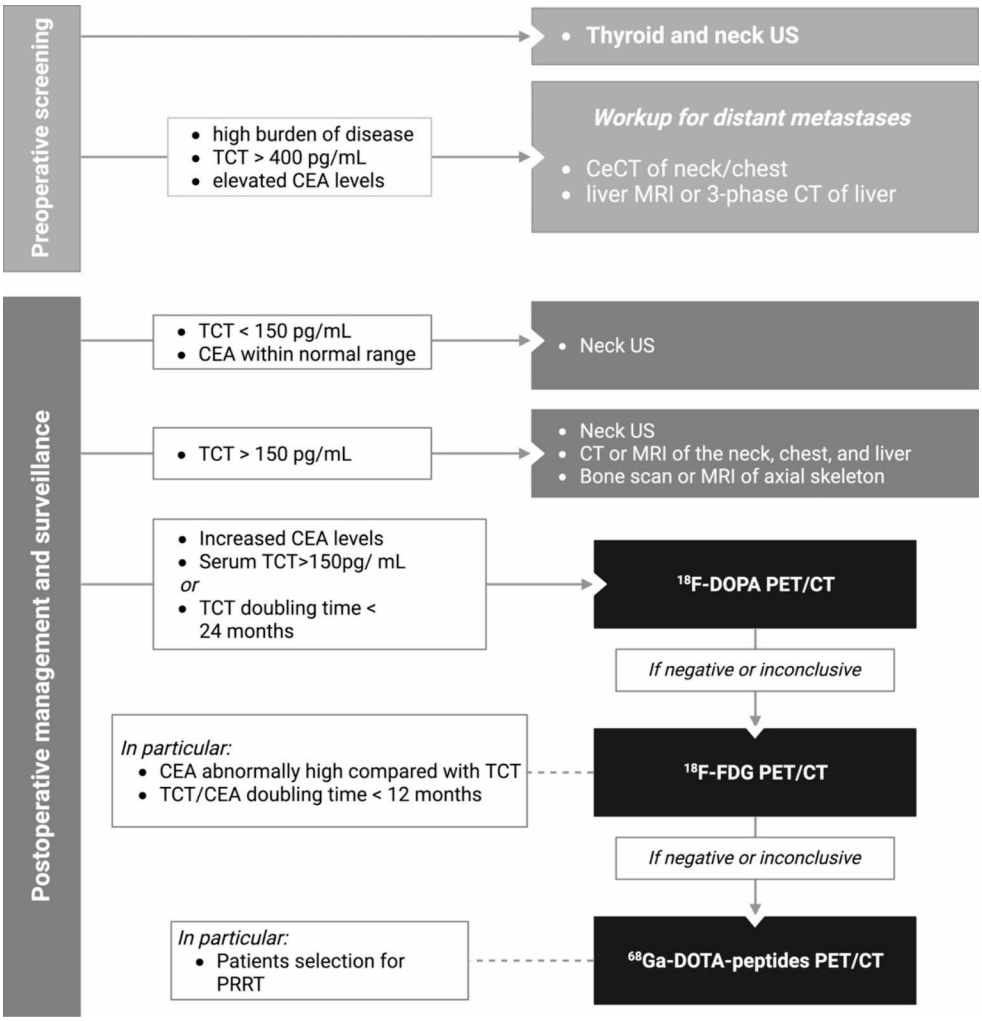

Fig. 7 Suggested imaging procedures for patients with MTC according to evidence-based data. TCT: serum calcitonin, CEA: anti carcinoembryonic antigen antibody, PRRT: peptide receptor radionuclide therapy, US: ultrasound, CeCT: contrast-enhanced computed tomography, MRI: magnetic resonance imaging, PET/CT: positron emission tomography/computed tomography, ^{18}F-DOPA: ^{18}F-dihydroxyphenylalanine, ^{18}F-FDG: ^{18}F-fluorodeoxyglucose. Created with BioRender.com.

particularly in cases of asymptomatic patients with detectable markers where initial imaging doesn't locate disease sites, options like ^{18}F-FDG PET/CT, or contrast-enhanced MRI of the neck, chest, and abdomen could be considered appropriate [85]. This is particularly important for patients with rapidly increasing calcitonin and CEA levels or those with CEA levels that are significantly higher than calcitonin levels. ^{68}Ga-DOTA-peptides PET/CT may also be considered for highly selected patients with inconclusive imaging results [85], and to evaluate the possibility of PRRT. Starting from these principles, the diagnostic algorithm should be adapted in each situation considering both availability of the various imaging studies and the own experience of medical team.

1.12 From diagnosis to treatment: is a theranostic approach for MTC possible?

The integration of diagnostics and therapeutics (theranostics) represents a major opportunity to personalize treatment for individual patients, with targeted radionuclide therapy being one representative example. Several radionuclide therapy options have been developed for MTC including somatostatin receptor based-PRRT, CCK2R targeted therapy, anti-CEA radioimmunotherapy.

PRRT with radiolabeled somatostatin analogs is a well-established second/third line theranostic treatment for SSTR-positive well-differentiated neuroendocrine tumors with remarkable clinical benefits [86]. This therapeutic option has also been suggested for metastatic MTC treatment. However, due to the variable expression of SSTRs in MTC [87], SSTR-based theranostics should be considered only in MTC cases with high levels of expression of SSTRs which could be demonstrated by SSTR PET (screening imaging method before SSTR-targeted therapy). Even if the prevalence of high uptake of radiolabeled somatostatin analogs is low in the setting of metastatic MTC, PRRT may still be a viable treatment option in selected patients [88]. The evidence on safety, effectiveness, and long-term outcome of PRRT with radiolabeled somatostatin analogs for MTC is still limited. A systematic review including 220 patients with metastatic MTC reported biochemical and objective

responses in 37.2% and 10.6% of MTC patients, respectively. In MTC patients treated with ^{177}Lu-DOTATATE mild and transient hematologic or renal complications were reported [89]. A recent study on 28 patients with progressive, SSTR-positive advanced MTC receiving PRRT with ^{177}Lu- or ^{90}Y-labeled somatostatin analogs demonstrated that this therapy was effective and well-tolerated. No acute or long-term grade 3/4 toxicity was recorded, except for one patient who suffered from grade 3 anemia possibly related to disease progression. The disease control rate after 3 to 4 months of PRRT was 56% and 72% using morphological and molecular response evaluation, respectively. Median overall survival (OS) and PFS were 63.7 and 10.1 months, respectively. Bone metastasis was an independent adverse prognostic factor for OS [90].

CCK2R has been a target of interest for molecular imaging and targeted radionuclide therapy for two decades. Recent clinical trials with novel radiolabeled minigastrin analogs demonstrate the potential for CCK2R targeted imaging and radionuclide therapy in metastatic MTC. The first clinical trials suggest that the use of CCK2R-targeted radiopharmaceuticals for MTC theranostics is reasonable [91]. Radiolabelled anti-CEA monoclonal antibodies have been used for theranostic approaches in metastatic MTC and several probes have been developed in the last decade with encouraging results [79, 80]. However, beyond clinical trials, the use of these molecules in clinical practice for MTC theranostics is still limited.

PSMA [83, 84, 92] and FAP [81, 82, 93] also represent potential theranostic targets for metastatic MTC and preliminary literature data seems promising but currently not sufficient for implementation of PSMA- or FAP-targeted therapies of MTC patients in the clinical routine. Currently, few guidelines recommend targeted radionuclide therapy in metastatic MTC patients and just in very selected cases [94].

Overall, the role of this therapeutic option in MTC patients remain to be clarified. Further investigations are required to evaluate the efficacy of targeted radionuclide therapy in MTC, including its impact on tumor response, progression-free survival, and overall survival rates. Clinical trials and retrospective studies involving larger patient cohorts are necessary to gather robust evidence and determine the patient selection criteria that would benefit most from this treatment approach. Additionally, it is important to explore potential combination therapies involving targeted radionuclide therapy, such as its use in conjunction with other systemic treatments. This could help determine whether a multimodal treatment approach, incorporating targeted radionuclide therapy, can provide superior outcomes compared to existing standard treatments. Furthermore, ongoing research efforts should focus on refining the dosimetry and radiopharmaceutical selection for targeted radionuclide therapy, ensuring optimized tumor targeting and minimal toxicity to healthy tissues. This will contribute to establishing standardized protocols and guidelines for its implementation, facilitating its widespread adoption in clinical practice.

1.13 Concluding remarks

In summary, we emphasize the dynamic and expanding role of nuclear medicine in the management of MTC. The integration of diagnostic and therapeutic modalities through in vivo molecular imaging could represent a significant avenue for tailoring treatment to individual patients. However, further investigations are necessary to elucidate the precise role of radionuclide therapy option, establish its efficacy, determine optimal treatment strategies, and evaluate its long-term benefits and potential toxicity. Continued research endeavors will enhance our understanding and ultimately lead to a more defined and evidence-based incorporation of targeted radionuclide therapy in the management of MTC.

Declarations

Competing interests The authors declare that they have no conflict of interest.

References

1. Hazard JB, Hawk WA, Crile G. Medullary (solid) carcinoma of the thyroid; a clinicopathologic entity. J Clin Endocrinol Metab. 1959;19:152–61.
2. Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S, Crocetti U, Attard M, Maranghi M, Torlontano M, Filetti S. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab. 2007;92:450–5.
3. Essig GF Jr, Porter K, Schneider D, Arpaia D, Lindsey SC, Busonero G, Fineberg D, Fruci B, Boelaert K, Smit JW, Meijer JA, Duntas LH, Sharma N, Costante G, Filetti S, Sippel RS, Biondi B, Topliss DJ, Pacini F, Maciel RM, Walz PC, Kloos RT. Thyroid. 2016;26:1563–72.
4. Trimboli P, Mian C, Piccardo A, Treglia G. Diagnostic tests for medullary thyroid carcinoma: an umbrella review. Endocrine. 2023;6 (ahead of print).
5. Scheuba C, Kaserer K, Moritz A, Drosten R, Vierhapper H, Bieglmayer C, Haas OA, Niederle B. Endocr Relat Cancer. 2009;16:243–53.
6. Machens A, Dralle H. Biological relevance of medullary thyroid microcarcinoma. J Clin Endocrinol Metab. 2012;97:1547–53.
7. Takahashi M, Ritz J, Cooper GM. Activation of a novel human transforming gene, ret, by DNA rearrangement. Cell. 1995;42:581–8.
8. Falchetti A, Marini F, Luzi E, Tonelli F, Brandi ML. Multiple endocrine neoplasms. Best Pract Res Clin Rheumatol. 2008;22:149–63.
9. Eng C, Clayton D, Schuffenecker I, Lenoir G, Cote G, Gagel RF, van Amstel HK, Lips CJ, Nishisho I, Takai SI, Marsh DJ,

Robinson BG, Frank-Raue K, Raue F, Xue F, Noll WW, Romei C, Pacini F, Fink M, Niederle B, Zedenius J, Nordenskjold M, Komminoth P, Hendy GN, Mulligan LM, et al. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. International RET mutation consortium analysis. JAMA. 1996;276:1575–9.
10. Moley JF. (2010) Medullary thyroid carcinoma: Management of lymph node metastases. J Natl Compr Canc Netw. 2010;8:549–556.
11. Wells SA, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, Lee N, Machens A, Moley JF, Pacini F, Raue F, Frank-Raue K, Robinson B, Rosenthal MS, Santoro M, Schlumberger M, Shah M, Waguespack SG, The American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma. Revised american thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25:567–610.
12. Pazaitou-Panayiotou K, Chrisoulidou A, Mandanas S, Tziomalos K, Doumala E, Patakiouta F. Predictive factors that influence the course of medullary thyroid carcinoma. Int J Clin Oncol. 2014;19:445–51.
13. Mehrotra PK, Mishra A, Mishra SK, Agarwal G, Agarwal A, Verma AK. Medullary thyroid Cancer: clinico-pathological Profile and Outcome in a Tertiary Care Center in North India. World J Surg. 2011;35:1273–80.
14. Hadoux J, Pacini F, Tuttle RM, Schlumberger M. Management of advanced medullary thyroid cancer. Lancet Diabetes Endocrinol. 2016;4:64–71.
15. Elisei R, Schlumberger MJ, Müller SP, Schöffski P, Brose MS, Shah MH, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol. 2013;31:3639–46.
16. Wells SA, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012;30:134–41.
17. Schlumberger M, Elisei R, Müller S, Schöffski P, Brose M, Shah M, et al. Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. Ann Oncol. 2017;28:2813–9.
18. Ciampi R, Romei C, Ramone T, Prete A, Tacito A, Cappagli V, et al. Genetic Landscape of somatic mutations in a large cohort of sporadic medullary thyroid Carcinomas studied by next-generation targeted sequencing. iScience. 2019;20:324–36.
19. Subbiah V, Hu MI, Wirth LJ, Schuler M, Mansfield AS, Curigliano G, et al. Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study. Lancet Diabetes Endocrinol. 2021;9:491–501.
20. 10, Wirth LJ, Sherman E, Robinson B, Solomon B, Kang H, Lorch J, et al. Efficacy of Selpercatinib in RET-Altered thyroid cancers. N Engl J Med. 2020;383:825–35.
21. Schlumberger M, Abdelmoumene N, Delisle MJ, Couette JE. Treatment of advanced medullary thyroid cancer with an alternating combination of 5 FU-streptozocin and 5 FU-dacarbazine. The Groupe d'Etude des Tumeurs a calcitonine (GETC). Br J Cancer. 1995;71:363–5.
22. Wang L, Kou H, Chen W, Lu M, Zhou L, Zou C. The diagnostic value of Ultrasound in Medullary thyroid carcinoma: a comparison with computed tomography. Technol Cancer Res Treat. 2020;19:153303382090583.
23. Liu MJ, Liu ZF, Hou YY, Men YM, Zhang YX, Gao LY, Liu H. Ultrasonographic characteristics of medullary thyroid carcinoma: a comparison with papillary thyroid carcinoma. Oncotarget. 2017;8:27520–8.
24. Lai X, Liu M, Xia Y, Wang L, Bi Y, Li X, Zhang B, Yang M, Dai Q, Jiang Y. Hypervascularity is more frequent in medullary thyroid carcinoma: compared with papillary thyroid carcinoma. Medicine. 2016;95:e5502.
25. Valderrabano P, Klippenstein DL, Tourtelot JB, Ma Z, Thompson ZJ, Lilienfeld HS, McIver B. New american thyroid Association Sonographic patterns for thyroid nodules perform well in medullary thyroid carcinoma: institutional experience, systematic review, and Meta-Analysis. Thyroid. 2016;26:1093–100.
26. Ferrarazzo G, Camponovo C, Deandrea M, Piccardo A, Scappaticcio L, Trimboli P. Suboptimal accuracy of ultrasound and ultrasound-based risk stratification systems in detecting medullary thyroid carcinoma should not be overlooked. Findings from a systematic review with meta-analysis. Clin Endocrinol (Oxf). 2022;97:532–40.
27. Trimboli P, Castellana M, Piccardo A, Romanelli F, Grani G, Giovanella L, Durante C. The ultrasound risk stratification systems for thyroid nodule have been evaluated against papillary carcinoma. A meta-analysis. Rev Endocr Metab Disord. 2021;22:453–60.
28. Machens A, Dralle H. Biomarker-based risk stratification for previously untreated medullary thyroid Cancer. J Clin Endocrinol Metab. 2010;95:2655–63.
29. Klain M, Hadoux J, Nappi C, Finessi M, Ambrosio R, Schlumberger M, Cuocolo A, Deandreis D, Salvatore D. Imaging medullary thyroid cancer patients with detectable serum markers: state of the art and future perspectives. Endocrine. 2022;75:330–7.
30. Debnam JM, Guha-Thakurta N, Sun J, Wei W, Zafereo ME, Cabanillas ME, Buisson NM, Schellingerhout D. Distinguishing recurrent thyroid Cancer from residual nonmalignant thyroid tissue using multiphasic multidetector CT. AJNR Am J Neuroradiol. 2020;41:844–51.
31. Fitzgerald RT, Kuruva M, David R, Samant RS, Kumar M, Van Hemert R, Angtuaco EJ, Bodenner D, Stack BC Jr. Characterization of thyroid nodules by 4-Dimensional Computed Tomography: initial experience. J Comput Assist Tomogr. 2017;41:195–8.
32. Gürsoy Çoruh A, Uzun Ç, Kul M, Akkaya Z, Halil Elhan A, Gökcan K. The impact of arterial phase on the detection of cervical lymph node metastasis from papillary thyroid carcinoma: a quantitative evaluation on multiphasic computed tomography. J Comput Assist Tomogr. 2020;44:262–8.
33. Skinner MA, Moley JA, Dilley WG, Owzar K, Debenedetti MK, Wells SA Jr. Prophylactic thyroidectomy in multiple endocrine neoplasia type 2A. N Engl J Med. 2005;353:1105–13.
34. Giovanella L, Treglia G, Iakovou I, Mihailovic J, Verburg FA, Luster M. EANM practice guideline for PET/CT imaging in medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging. 2020;47:61–77.
35. Castinetti F, Taïeb D. Positron emission tomography imaging in medullary thyroid carcinoma: time for reappraisal? Thyroid. 2021;31:151–5.
36. Treglia G, Sadeghi R, Giovinazzo F, Galiandro F, Annunziata S, Muoio B, Kroiss AS. PET with different radiopharmaceuticals in neuroendocrine neoplasms: an umbrella review of published meta-analyses. Cancers. 2021;13:5172.
37. Soussan M, Nataf V, Kerrou K, Grahek D, Pascal O, Talbot JN, Montravers F. Added value of early 18F-FDOPA PET/CT acquisition time in medullary thyroid cancer. Nucl Med Commun. 2012;33:775–9.
38. Fargette C, Imperiale A, Taïeb D. Molecular imaging of endocrine neoplasms with emphasis on 18F-DOPA PET: a practical approach for well-tailored imaging protocols. Q J Nucl Med Mol Imaging. 2022;66:141–7.
39. Rasul S, Hartenbach S, Rebhan K, Göllner A, Karanikas G, Mayerhoefer M, Mazal P, Hacker M, Hartenbach M. [18F]DOPA PET/ceCT in diagnosis and staging of primary medullary thyroid carcinoma prior to surgery. Eur J Nucl Med Mol Imaging. 2018;45:2159–69.

40. Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, Papotti MG, Berruti A. Guidelines Committee. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30:1856–83.
41. Beheshti M, Pocher S, Vali R, Waldenberger P, Broinger G, Nader M, Kohlfurst S, Pirich C, Dralle H, Langsteger W. The value of 18F-DOPA PET-CT in patients with medullary thyroid carcinoma: comparison with 18F-FDG PET-CT. Eur Radiol. 2009;19:1425–34.
42. Brammen L, Niederle MB, Riss P, Scheuba C, Selberherr A, Karanikas G, Bodner G, Koperek O, Niederle B. Medullary thyroid carcinoma: do Ultrasonography and F-DOPA-PET-CT influence the initial Surgical Strategy? Ann Surg Oncol. 2018;25:3919–27.
43. Hoegerle S, Altehoefer C, Ghanem N, Brink I, Moser E, Nitzsche E. 18F-DOPA positron emission tomography for tumour detection in patients with medullary thyroid carcinoma and elevated calcitonin levels. Eur J Nucl Med. 2001;28:64–71.
44. Treglia G, Rufini V, Piccardo A, Imperiale A. Update on management of medullary thyroid carcinoma: focus on Nuclear Medicine. Semin Nucl Med. 2023 (Ahead of print).
45. Beuthien-Baumann B, Strumpf A, Zessin J, Bredow J, Kotzerke J. Diagnostic impact of PET with 18F-FDG, 18F-DOPA and 3-O-methyl-6-[18F]fluoro-DOPA in recurrent or metastatic medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging. 2007;34:1604–9.
46. Luster M, Karges W, Zeich K, Pauls S, Verburg FA, Dralle H, Glatting G, Buck AK, Solbach C, Neumaier B, Reske SN, Mottaghy FM. Clinical value of 18-fluorine-fluorodihydroxyphenylalanine positron emission tomography/computed tomography in the follow-up of medullary thyroid carcinoma. Thyroid. 2010;20:527–33.
47. Treglia G, Cocciolillo F, Di Nardo F, et al. Detection rate of recurrent medullary thyroid carcinoma using fluorine-18 dihydroxyphenylalanine positron emission tomography: a meta-analysis. Acad Radiol. 2012;19:1290–9.
48. Archier A, Heimburger C, Guerin C, Morange I, Palazzo FF, Henry JF, Schneegans O, Mundler O, Abdullah AE, Sebag F, Imperiale A, Taieb D. (18)F-DOPA PET/CT in the diagnosis and localization of persistent medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging. 2016;43:1027–33.
49. Rotania M, Chabrier G, Imperiale A. Synchronous bilateral pheochromocytomas and bilobar medullary thyroid carcinoma revealed by 18F-FDOPA PET/CT in a MEN-2A asymptomatic patient. Endocrine. 2019;66:691–2.
50. Terroir M, Caramella C, Borget I, Bidault S, Dromain C, El Farsaoui K, Deandreis D, Grimaldi S, Lumbroso J, Berdelou A, Hadoux J, Hescot S, Hartl D, Baudin E, Schlumberger M, Leboulleux S. F-18-Dopa positron emission tomography/computed tomography is more sensitive than whole-body magnetic resonance imaging for the localization of persistent/recurrent disease of medullary thyroid cancer patients. Thyroid. 2019;29:1457–64.
51. Treglia G, Villani MF, Giordano A, Rufini V. Detection rate of recurrent medullary thyroid carcinoma using fluorine-18 fluorodeoxyglucose positron emission tomography: a meta-analysis. Endocrine. 2012;42:535–45.
52. Cheng X, Bao L, Xu Z, Li D, Wang J, Li Y. 18F-FDG-PET and 1-F-FDG-PET/CT in the detection of recurrent or metastatic medullary thyroid carcinoma: a systematic review and meta-analysis. J Med Imaging Radiat Oncol. 2012;56:136–42.
53. Caobelli F, Chiaravalloti A, Evangelista L, Saladini G, Schillaci O, Vadrucci M, Scalorbi F, Donner D, Alongi P, Young AIMN, Working Group. Predictive and prognostic value of 18F-DOPA PET/CT in patients affected by recurrent medullary carcinoma of the thyroid. Ann Nucl Med. 2018;32:7–15.
54. Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, Moley JF, Pacini F, Ringel MD, Schlumberger M, Wells SA Jr. ., and american thyroid Association Guidelines Task Force on Medullary thyroid carcinoma. Medullary thyroid cancer: management guidelines of the american thyroid Association. Thyroid. 2009;19:565–612.
55. Skoura E, Datseris IE, Rondogianni P, Tsagarakis S, Tzanela M, Skilakaki M, Exarhos D, Alevizaki M. Correlation between calcitonin levels and [(18)F]FDG-PET/CT in the detection of recurrence in patients with sporadic and Hereditary Medullary thyroid Cancer. ISRN Endocrinol. 2012;2012:375231.
56. Giraudet AL, Vanel D, Leboulleux S, Auperin A, Dromain C, Chami L, Ny Tovo N, Lumbroso J, Lassau N, Bonniaud G, Hartl D, Travagli JP, Baudin E, Schlumberger M. Imaging medullary thyroid carcinoma with persistent elevated calcitonin levels. J Clin Endocrinol Metab. 2007;92:4185–90.
57. Treglia G, Goichot B, Giovanella L, Hindié E, Jha A, Pacak K, Taïeb D, Walter T, Imperiale A. Prognostic and predictive value of nuclear imaging in endocrine oncology. Endocrine. 2020;67:9–19.
58. Marzola MC, Pelizzo MR, Ferdeghini M, Toniato A, Massaro A, Ambrosini V, Fanti S, Gross MD, Al-Nahhas A, Rubello D. Dual PET/CT with (18)F-DOPA and (18)F-FDG in metastatic medullary thyroid carcinoma and rapidly increasing calcitonin levels: comparison with conventional imaging. Eur J Surg Oncol. 2010;36:414–21.
59. Salaun PY, Campion L, Ansquer C, Frampas E, Mathieu C, Robin P, Bournaud C, Vuillez JP, Taieb D, Rousseau C, Drui D, Mirallié E, Borson-Chazot F, Goldenberg DM, Chatal JF, Barbet J. Kraeber-Bodéré F. 18F-FDG PET predicts survival after pretargeted radioimmunotherapy in patients with progressive metastatic medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging. 2014;41:1501–10.
60. Werner RA, Schmid JS, Higuchi T, Javadi MS, Rowe SP, Märkl B, Aulmann C, Fassnacht M, Kroiss M, Reiners C, Buck AK, Kreissl MC, Lapa C. Predictive value of FDG-PET in patients with advanced medullary thyroid carcinoma treated with vandetanib. J Nucl Med. 2018;59:756–61.
61. Werner RA, Bundschuh RA, Higuchi T, Javadi MS, Rowe SP, Zsótér N, Kroiss M, Fassnacht M, Buck AK, Kreissl MC, Lapa C. Volumetric and texture analysis of pretherapeutic 18F-FDG PET can predict overall survival in medullary thyroid cancer patients treated with Vandetanib. Endocrine. 2019;63:293–300.
62. Puhr-Westerheide D, Cyran CC, Sargsyan-Bergmann J, Todica A, Gildehaus FJ, Kunz WG, Stahl R, Spitzweg C, Ricke J, Kazmierczak PM. The added diagnostic value of complementary gadoxetic acid-enhanced MRI to 18F-DOPA-PET/CT for liver staging in medullary thyroid carcinoma. Cancer Imaging. 2019;14:19:73.
63. Treglia G, Castaldi P, Villani MF, Perotti G, de Waure C, Filice A, Ambrosini V, Cremonini N, Santimaria M, Versari A, Fanti S, Giordano A, Rufini V. Comparison of 18F-DOPA, 18F-FDG and 68Ga-somatostatin analogue PET/CT in patients with recurrent medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging. 2012;39:569–80.
64. Yamaga LYI, Cunha ML, Campos Neto GC, Garcia MRT, Yang JH, Camacho CP, Wagner J, Funari MBG. (68)Ga-DOTATATE PET/CT in recurrent medullary thyroid carcinoma: a lesion-by-lesion comparison with (111)In-octreotide SPECT/CT and conventional imaging. Eur J Nucl Med Mol Imaging. 2017;44:1695–701.
65. Lee SW, Shim SR, Jeong SY, Kim SJ. Comparison of 5 different PET radiopharmaceuticals for the detection of recurrent medullary thyroid carcinoma: a Network Meta-analysis. Clin Nucl Med. 2020;45:341–8.
66. Pajak C, Cadili L, Nabata K, Wiseman SM. 68Ga-DOTATATE-PET shows promise for diagnosis of recurrent or persistent medullary thyroid cancer: a systematic review. Am J Surg. 2022;224:670–5.

67. Treglia G, Tamburello A, Giovanella L. Detection rate of somatostatin receptor PET in patients with recurrent medullary thyroid carcinoma: a systematic review and a meta-analysis. Hormones (Athens Greece). 2017;16:262–72.
68. Reubi JC, Waser B, Maecke HR, Rivier JE. Highly increased 125i-Jr11 antagonist binding in vitro reveals novel indications for Sst2 targeting in human cancers. J Nucl Med. 2016;58:300–6.
69. Imperiale A, Jha A, Meuter L, Nicolas GP, Taïeb D, Pacak K. The emergence of somatostatin antagonist-based theranostics: paving the Road toward another success? J Nucl Med. 2023;64:682–4.
70. Ueda CE, Duarte PS, de Castroneves LA, Coura-Filho GB, Sado HN, Sapienza MT, Hoff AO, Buchpiguel CA. Comparison of 18F-NaF PET/CT with other imaging methods in the detection of bone metastases in patients with medullary thyroid cancer: a report of a series of 31 cases. Nucl Med Mol Imaging. 2020;54:281–91.
71. Ueda CE, Duarte PS, de Castroneves LA, Flávio J, Marin G, Sado HN, Sapienza MT, Hoff AO, Buchpiguel CA. Burden of metastatic bone disease measured on 18F-NaF PET/computed tomography studies as a prognostic indicator in patients with medullary thyroid cancer. Nucl Med Commun. 2020;41:469–760.
72. Li C, Zhang P, Nie R, Gong X, Xie J, Yu Z, Wang C, Zhang H, Yan R, Lu Z. Targeting amyloids with [18F]AV-45 for medullary thyroid carcinoma positron emission tomography/computed tomography imaging: a pilot clinical study. Mol Pharm. 2022;19:584–91.
73. Jamsek J, Hocevar M, Bergant D, Zaletel K, Rep S, Lezaic L. Diagnostic value of [18F]Fluorocholine PET/CT in detection of primary medullary thyroid cancer. Ann Nucl Med. 2021;35:429–37.
74. Jang HW, Choi JY, Lee JI, Kim HK, Shin HW, Shin JH, Kim SW, Chung JH. Localization of medullary thyroid carcinoma after surgery using (11)C-methionine PET/CT: comparison with (18) F-FDG PET/CT. Endocr J. 2010;57:1045–54.
75. Uprimny C, von Guggenberg E, Svirydenka A, Mikołajczak R, Hubalewska-Dydejczyk A, Virgolini IJ. Comparison of PET/CT imaging with FDOPA and cholecystokinin-2 receptor targeting 68Ga-DOTA-MGS5 in a patient with advanced medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging. 2021;48:935–6.
76. Sauter AW, Mansi R, Hassiepen U, Muller L, Panigada T, Wiehr S, Wild AM, Geistlich S, Béhé M, Rottenburger C, Wild D, Fani M. Targeting of the cholecystokinin-2 receptor with the minigastrin analog 177Lu-DOTA-PP-F11N:does the use of protease inhibitors further improve in vivo distribution? J Nucl Med. 2019;60:393–9.
77. von Guggenberg E, Uprimny C, Klingler M, Warwitz B, Sviridenko A, Bayerschmidt S, Di Santo G, Virgolini IJ. Preliminary clinical experience of cholecystokinin-2 receptor PET/CT imaging using the 68Ga-labeled minigastrin analog DOTA-MGS5 in patients with medullary thyroid cancer. J Nucl Med. 2023 (Ahead of print).
78. Wong JYC, Yamauchi DM, Adhikarla V, Simpson J, Frankel PH, Fong Y, Melstrom KA, Chen YJ, Salehian BD, Woo Y, Dandapani SV, Colcher DM, Poku EK, Yazaki PJ, Wu AM, Shively JE. First-In-human pilot PET immunoimaging study of 64Cu-anti-carcinoembryonic antigen monoclonal antibody (hT84.66-M5A) in patients with carcinoembryonic antigen-producing cancers. Cancer Biother Radiopharm. 2023;38:26–37.
79. Bodet-Milin C, Faivre-Chauvet A, Carlier T, Ansquer C, Rauscher A, Frampas E, Toulgoat F, Masson D, Bourgeois M, Cerato E, Rohmer V, Couturier O, Drui D, Goldenberg DM, Sharkey RM, Barbet J, Kraeber-Bodere F. Anti-CEA pretargeted immuno-PET shows higher sensitivity than DOPA PET/CT in detecting relapsing metastatic medullary thyroid carcinoma: Post hoc analysis of the iPET-MTC study. J Nucl Med. 2021;62:1221–7.
80. Bodet-Milin C, Bailly C, Touchefeu Y, Frampas E, Bourgeois M, Rauscher A, Lacoeuille F, Drui D, Arlicot N, Goldenberg DM, Faivre-Chauvet A, Barbet J, Rousseau C, Kraeber-Bodéré F. Clinical results in medullary thyroid carcinoma suggest high potential of pretargeted immuno-PET for tumor imaging and theranostic approaches. Front Med. 2019;6:124.
81. Ballal S, Yadav MP, Moon ES, Rösch F, ArunRaj ST, Agarwal S, Tripathi M, Sahoo RK, Bal C. First-in-human experience with 177Lu-DOTAGA.(SA.FAPi)2 therapy in an uncommon case of aggressive medullary thyroid carcinoma clinically mimicking as anaplastic thyroid cancer. Clin Nucl Med. 2022;47:e444–5.
82. Kuyumcu S, Isık EG, Sanli Y. Liver metastases from medullary thyroid carcinoma detected on 68Ga-FAPI-04 PET/CT. Endocrine. 2021;74:727–8.
83. Ballal S, Yadav MP, Roesch F, Raju S, Satapathy S, Sheokand P, Moon ES, Martin M, Agarwal S, Tripathi M, Bal C. Head-to-head comparison of [68Ga]Ga-DOTA.SA.FAPi and [68Ga]Ga-DOTANOC PET/CT imaging for the follow-up surveillance of patients with medullary thyroid cancer. Thyroid. 2023;12 (Ahead of print).
84. Arora S, Damle NA, Parida GK, Singhal A, Nalli H, Dattagupta S, Bal C. Recurrent medullary thyroid carcinoma on 68Ga-prostate-specific membrane antigen PET/CT: exploring new theranostic avenues. Clin Nucl Med. 2018;43:359–60.
85. Haddad RI, Bischoff L, Ball D, Bernet V, Blomain E, Busaidy NL, Campbell M, Dickson P, Duh QY, Ehya H, Goldner WS, Guo T, Haymart M, Holt S, Hunt JP, Iagaru A, Kandeel F, Lamonica DM, Mandel S, Markovina S, McIver B, Raeburn CD, Rezaee R, Ridge JA, Roth MY, Scheri RP, Shah JP, Sipos JA, Sippel R, Sturgeon C, Wang TN, Wirth LJ, Wong RJ, Yeh M, Cassara CJ, Darlow S. Thyroid carcinoma, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022;20:925–51.
86. Hofland J, Brabander T, Verburg FA, Feelders RA, de Herder WW. Peptide receptor Radionuclide Therapy. J Clin Endocrinol Metab. 2022;107:3199–208.
87. Czajkowski M, Kaemmerer D, Sänger J, Sauter G, Wirtz RM, Schulz S, Lupp A. Comparative evaluation of somatostatin and CXCR4 receptor expression in different types of thyroid carcinoma using well-characterised monoclonal antibodies. BMC Cancer. 2022;7:22:740.
88. Hayes AR, Crawford A, Al Riyami K, Tang C, Bomanji J, Baldeweg SE, Wild D, Morganstein D, Harry A, Grozinsky-Glasberg S, Oleinikov K, Khoo B, Caplin ME, Nicolas GP, Grossman AB. Metastatic medullary thyroid Cancer: the role of 68Gallium-DOTA-Somatostatin Analogue PET/CT and peptide receptor Radionuclide Therapy. J Clin Endocrinol Metab. 2021;106:e4903–16.
89. Maghsoomi Z, Emami Z, Malboosbaf R, Malek M, Khamseh ME. Efficacy and safety of peptide receptor radionuclide therapy in advanced radioiodine-refractory differentiated thyroid cancer and metastatic medullary thyroid cancer: a systematic review. BMC Cancer. 2021;20:21:579.
90. Liu Q, Kulkarni HR, Zhao T, Schuchardt C, Chen X, Zhu Z, Zhang J, Baum RP. Peptide receptor Radionuclide Therapy in patients with Advanced Progressive Medullary thyroid Cancer: efficacy, Safety, and survival predictors. Clin Nucl Med. 2023;48:221–7.
91. von Guggenberg E, Kolenc P, Rottenburger C, Mikołajczak R, Hubalewska-Dydejczyk A. Update on Preclinical Development and clinical translation of Cholecystokinin-2 receptor targeting Radiopharmaceuticals. Cancers (Basel). 2021;18:13:5776.
92. Hasenauer N, Higuchi T, Deschler-Baier B, Hartrampf PE, Pomper MG, Rowe SP, Fassnacht M, Buck AK, Werner RA. Visualization of Tumor Heterogeneity in Advanced Medullary thyroid carcinoma by Dual-Tracer Molecular Imaging: revealing the Theranostic potential of SSTR- and PSMA-Directed Endoradiotherapy. Clin Nucl Med. 2022;47:651–2.

93. Martin M, Ballal S, Yadav MP, Bal C, Van Rymenant Y, De Loose J, Verhulst E, De Meester I, Van Der Veken P, Roesch F. Novel generation of FAP inhibitor-based homodimers for Improved Application in Radiotheranostics. Cancers (Basel). 2023;21;15:1889.
94. Kim M, Kim BH. Current guidelines for management of medullary thyroid carcinoma. Endocrinol Metab (Seoul). 2021;36:514–24.