Review article

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How has the management of medullary thyroid carcinoma changed with the advent of ^{18}F-FDG and non-^{18}F-FDG PET radiopharmaceuticals

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Medullary thyroid cancer (MTC) arises from parafollicular C cells and is an elusive tumor to image. It occurs as a sporadic neoplasm in 70–80% of cases and is hereditary in 20–30% because of germline mutations of the rearranged during transfection proto-oncogene. Successful disease management relies on accurate staging. Tumor secretory biomarkers are highly sensitive to a disease; however, despite a wide variety of radiopharmaceuticals for molecular imaging that take advantage of hybrid SPECT/CT and PET/CT fusion imaging, imaging of MTC is still problematic. After initial surgical resection, the limited sensitivity of localization of small locoregional disease and the inability to detect early liver metastases hamper the success of later surgical approaches. ^{18}F-fluorodeoxyglucose PET has been used to detect MTC recurrences with modest success and may be best suited for only a small subset of more biologically aggressive MTCs. Recent developments in PET imaging with novel radiopharmaceuticals targeting specific cellular processes of MTC offer increased sensitivity for identifying recurrence, assessing prognosis, and guiding selection of optimal therapies. ***Nucl Med Commun*** **33:679–688** © **2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Medullary thyroid cancer (MTC) is a rare, neuroendocrine tumor (NET) derived from parafollicular C cells. MTC comprises only 5–12% of all thyroid cancers, expresses a variable phenotype and prognosis, and has an overall mean survival of 75–85% at 10 years after diagnosis [1–3]. Both age and tumor, node, and metastasis stage are strongly correlated with outcome. Excellent 10-year survival of 95% is seen with disease confined to the thyroid, falling to 75% survival for patients with regional disease and to 10–40% survival for those with distant metastases [1,2,4].

MTC is a hormonally active neoplasm producing the secretory peptides calcitonin (Ct) and carcinoembryonic antigen (CEA), which are useful tumor markers in diagnosis, surveillance, and prognosis. Management of MTC is challenging, as regional nodal (~50%) and distant metastases (up to 20%) at diagnosis are common [1,3]. Successful therapy for both sporadic and hereditary forms of MTC is dependent upon complete tumor resection; therefore, accurate preoperative staging is important [5–8]. However, unlike well-differentiated thyroid cancers, imaging and treatment with radioiodine has no role in the management of MTC. For imaging of MTC, neither discontinuation of replacement thyroid hormone nor administration of recombinant human thyroid-stimulating hormone to stimulate radiotracer uptake in tumor tissues is required. Unfortunately there have been too few randomized clinical trials to establish the optimal treatment approach for MTC, and present practice guidelines rely upon a small body of literature [9–11]. Nonetheless, guidelines are important to standardize the management of MTC as variable practice patterns have been previously documented [12].

It has been established that total thyroidectomy and lymph node dissection will effect a cure in ~60% of patients with tumor, node, metastasis stage N0 disease at diagnosis, which falls to 10–30% of patients with N1 disease [13]. Because of the potential for the presence of disease after thyroidectomy and lymph node dissection, management of MTC includes postoperative monitoring of Ct and CEA levels with estimations of their doubling times [1,3,10,11]. Despite the high sensitivity of Ct for predicting the presence of MTC, it continues to be a difficult neoplasm to image. Both computed tomography (CT) and MRI have limited sensitivity because of early

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and small metastases to locoregional lymph nodes and to the liver. Similarly functional scintigraphic techniques using a variety of radiopharmaceuticals that include thallium-201, ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin, ^{131}I/^{123}I-metaiodobenzylguanidine (MIBG), ^{99m}Tc-(V)-dimercaptosuccinic acid (DMSA), and ^{111}In-octreotide have not been uniformly successful in the imaging of MTC [14,15].

PET with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET has been used after thyroidectomy and after nodal resection to identify residual and/or recurrent MTCs [16,17]. However, given the heterogeneity of MTC phenotypic expression, ^{18}F-FDG PET may be best suited to detect only a small subset of biologically aggressive tumors that overexpress glucose transporter proteins [18]. Other novel non-^{18}F-FDG positron-emitting radiopharmaceuticals such as ^{18}F-fluorodihydroxyphenylalanine (^{18}F-DOPA) and ^{68}Ga-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) somatostatin analogues have been used to successfully image a wide variety of NETs, including MTC, and several studies have demonstrated superior sensitivity compared with ^{18}F-FDG PET for detection of MTC. As successful surgical management of recurrent disease rarely leads to normalization of Ct levels, sensitive imaging to detect remote metastases is crucial to identifying the subset of patients in whom additional surgery would be ineffectual [19].

Genetic testing

Over 20% of MTCs are hereditary, associated with germline mutations of the rearranged during transfection (RET) proto-oncogene that cause syndromes of multiple endocrine neoplasm (MEN)2A, MEN2B, and isolated familial MTC [1,20,21]. In ~50–60% of patients with sporadic MTC, a somatic mutation of the RET proto-oncogene is present. Somatic mutations in MTC unrelated to RET have also been reported, the most common being the M918T substitution in 20–50% of sporadic MTCs [3]. Genetic testing should be offered as part of the evaluation of patients with sporadic MTC, in which 4–10% will actually be inherited, with obvious implications for other family members and future generations [1,7,10,11].

Inherited MTC displays autosomal dominant transmission with near-complete penetrance of C-cell hyperplasia and MTC. Genetic testing of probands and their relatives provides important prognostic information that has proven to be useful in disease management. Present American Thyroid Association (ATA) risk stratification guidelines are based on classification of specific codon mutations that suggest optimal timing of prophylactic thyroidectomy in family members of index cases [10,22]. ATA (risk level D), including all MEN2B mutations, predicts more aggressive disease requiring early thyroidectomy and central compartment dissection before the age of 1 year [3]. In contrast, ATA (risk level A) mutations, which include familial MTC, may be delayed until Ct levels begin to rise, heralding the presence of C-cell hyperplasia or abnormal findings on thyroid ultrasound [10].

Preoperative evaluation

Diagnosis of MTC is usually made by fine-needle aspiration biopsy of thyroid nodules, whereas preoperative evaluation includes neck ultrasound and measurement of Ct, CEA, calcium, plasma, or urinary metanephrines and normetanephrines. A Ct level greater than 100 pg/ml in the presence of a thyroid nodule is considered as strong evidence for the presence of MTC [5], although a Ct level greater than 20 pg/ml should prompt further diagnostic evaluation [3]. Routine measurements of Ct in patients with thyroid nodules may not be cost-effective, as MTC is found in only 0.2–1.4% of thyroid nodules [3,10,11]. Furthermore, Ct can be elevated in C-cell hyperplasia, small cell lung cancer, carcinoid, chronic renal failure, and with proton pump inhibitor treatment. Although these potential false-positive circumstances would benefit from confirmatory pentagastrin stimulation, unfortunately this test is rarely performed [3,8,11] and not approved in the USA. Infrequently, MTC is suspected because of symptoms of flushing and diarrhea, or because of family history [10]. When lymph node metastases are present and/or Ct is greater than 400 pg/ml, evaluation for distant disease may be performed using neck and thorax contrast-enhanced CT and three-phase contrast CT of the liver [1,10]. Unlike the situation with radioiodine imaging and well-differentiated thyroid cancer, thyroidectomy before PET imaging of MTC is not a prerequisite, although to date the majority of studies on PET imaging have been limited to cohorts of postoperative patients. There are only two studies that included patients undergoing preoperative staging of MTC, one reporting three patients with ^{18}F-FDG PET before thyroidectomy [23] and the other reporting seven preoperative patients with ^{18}F-FDG and ^{18}F-DOPA PET/CT [24]. Unfortunately, the numbers of patients in these studies are too small to form conclusions on the role of preoperative PET imaging in MTC. Preoperative ^{18}F-FDG PET has been suggested for Ct greater than 400 pg/ml by some authors [8], although preoperative PET or somatostatin scintigraphy has not yet been included in contemporary practice guideline recommendations [10].

Thyroid cancer is increasingly being diagnosed incidentally on ^{18}F-FDG PET imaging in oncology patients undergoing staging of unrelated neoplasms [25]. A recent literature review of 18 studies found incidental thyroidal uptake of ^{18}F-FDG in 571 of 55 160 (1%) patients. A total of 322 of 571 (56.4%) patients with histological follow-up confirmed the rate of malignancy to be 33.2%. Although the majority of these incidentally discovered thyroid

cancers were papillary neoplasms in 82.2% of cases, MTC represented almost 2% of the total [26].

Careful preoperative staging of MTC is crucial, as surgical resection of all neoplastic tissues in the neck, with total thyroidectomy and central compartment lymph node dissection, with or without lateral compartment dissection, offers the best chance for a cure [1]. Surgery is curative in 90% of MTCs in primary lesions measuring less than 10 mm but falls markedly with increasing primary lesion size, where only 50% of patients with primary lesions more than 1 cm are cured of their disease [8]. MTC metastasizes to paratracheal and lateral cervical lymph nodes in 20–30% of cases with tumor size less than 1 cm (T1), 50% with size 2–4 cm (T2), and 90% for T3–T4 tumors [1]. Contralateral nodal metastases are reported to occur in 25–33% of cases [8]. There is general consensus that for N0 disease (around 30–40% of patients) total thyroidectomy with prophylactic central compartment dissection is the surgical procedure of choice [1,10,11]. This is because of the relative insensitivity of neck ultrasound, which may miss as many as 30–90% of nodal metastases before thyroidectomy because involved nodes are obscured by overlying thyroid tissue or because metastases are microscopic [3,27,28]. Moreover, the role of prophylactic lateral neck dissection is controversial in clinically N0 patients with advocates for varying extents of surgical dissection that include the central compartment and ipsilateral and bilateral neck compartments [13]. Furthermore, lateral dissection does not improve survival in N0 patients and can be performed at a second operation without increased morbidity [7,8]. Some authors favor lateral compartment dissection if central compartment disease is present [6–8] and also in the presence of T2 size more than 2 cm [6]. More aggressive recommendations favor bilateral neck dissection when Ct levels are elevated above 200 pg/ml, arguing that this offers the best chance for surgical cure [3]. Radio-guided surgical resection of MTC using handheld intraoperative probes has been reported using ^{99m}Tc-MIBG, ^{99m}Tc-(V)=DMSA, and ^{111}In-octreotide to assist in the surgical resection of regional nodal metastases; however, these techniques should be considered investigational and are not routinely practiced [29–31]. Radio-guided surgery in well-differentiated thyroid cancer using high-energy probes equipped with collimated lutetium oxyorthosilicate and bismuth germanate crystals optimized for detection of ^{18}F-FDG radioactivity has been described [32,33], and this technique appears to be feasible for MTC.

There is also controversy regarding the intraoperative management of parathyroid glands. In patients with sporadic MTC who are in the N0 stage, normal-appearing glands should be left in place [6]. In MEN2A, if hyperplasia is suspected then three glands are removed, with the remaining gland autotransplanted into the nondominant forearm [1]. If the inferior parathyroid glands become devascularized following central neck dissection, they may be autotransplanted into the sternocleidomastoid or brachioradialis muscle of the forearm [6,7]. In the case of hereditary MTC, it is important to screen for other endocrine disorders using hormonal and biochemical assessment of serum and urinary metanephrines to assess for pheochromocytoma or paraganglioma [1,10,11].

If distant metastases are present at diagnosis then less aggressive surgery may be appropriate to reduce iatrogenic morbidity [3,6].

Surveillance

The extent of initial surgery for MTC is important for ensuring locoregional disease control. Even if the extent of initial surgery is deemed adequate, recurrence rates remain high, up to 50% in most series [1–3,11]. To confirm biochemical remission, Ct levels should be measured 2–3 months after surgery, as Ct has a half-life of $\sim$30 h and elevated levels are highly sensitive for persistent or recurrent disease [1]. Reoperative procedures with unilateral or bilateral neck dissection as guided by neck and mediastinal imaging aim to reduce the risk of dissemination by removing gross metastastic nodal disease [6] or reduce the potential effects on cervical central neck structures by local tumor invasion. However, surgical treatment of recurrence(s) does not often result in normalization of Ct levels [11]. On the basis of present information, the imaging strategy is dependent on the Ct levels. It has been suggested that for Ct less than 150 pg/ml, imaging begins with neck ultrasound, as other imaging techniques are unlikely to be useful [3,6,10,11]. For Ct 150–400 pg/ml, contrast-enhanced neck and total body CT is recommended. If Ct is more than 400 pg/ml then multiphase CT liver protocol, contrast-enhanced MRI of the liver, MRI of the spine, bone scintigraphy, and ^{18}F-FDG PET may be considered [3,8,10,11]. The insensitivity of imaging has been attributed to small hypervascular hepatic metastases detected only on hepatic arteriography in a significant number of patients [16,17], which in one study reached 89% [34]. Therefore, the use of staging laparoscopy to detect surface metastases, hepatic venous sampling, and hepatic angiography has been previously investigated; however, all of these techniques should be used sparingly. Many patients with elevated Ct and disease undetectable by standard imaging methods appear to have an indolent course, spanning many years before the development of clinically apparent disease [10].

External beam radiation treatment has been used to manage metastatic MTC with limited efficacy [3,9,35,36]. Chemotherapy has low response rates that are unfortunately not durable [1,37,38]. ^{131}I-targeted or ^{90}Y-targeted radionuclide therapies have overall response rates of

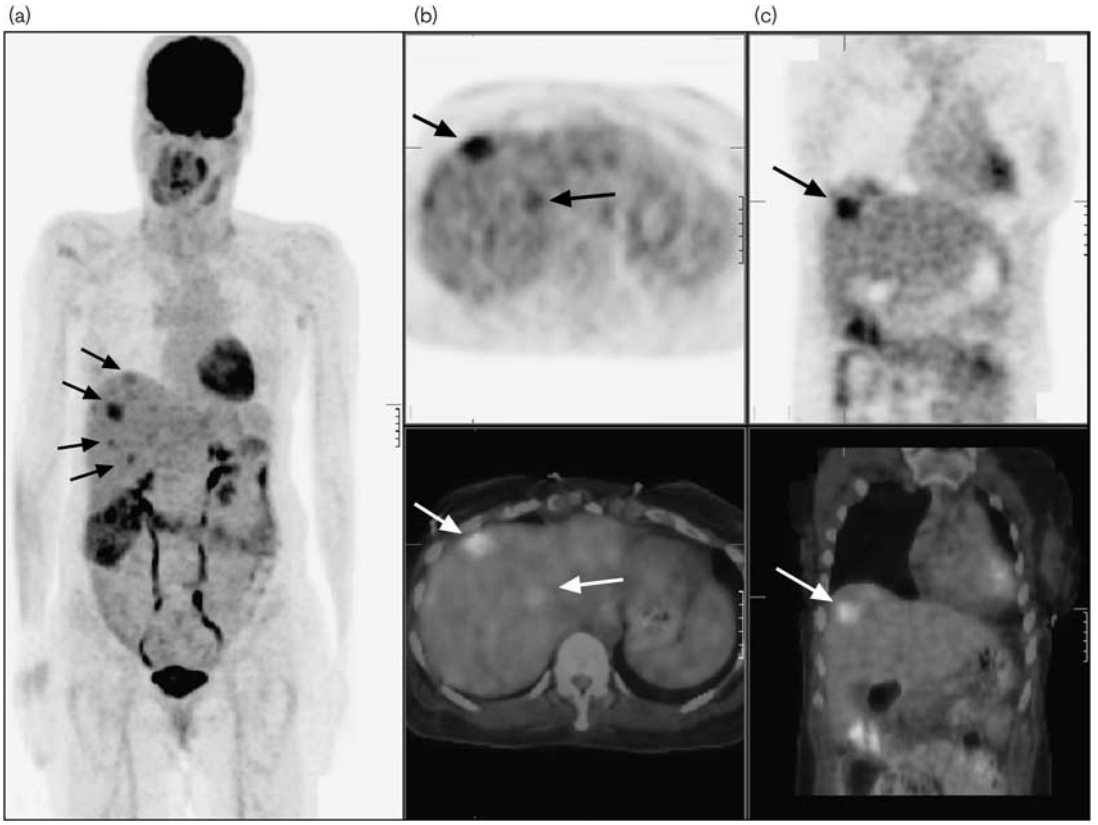
~30% and have had only a modest impact on the management of MTC [37]. The availability of novel multikinase inhibitors in clinical trials has modest efficacy for disease stabilization [19,39–42]. Clinical guidelines recommend enrollment in clinical trials on kinase inhibitors as the preferred best current practices for treatment of progressive MTC [10,11]. In April 2011, vandetanib was the first kinase inhibitor approved by the Food and Drug Administration in the USA for treatment of progressive MTC [39,40] and is generally well tolerated, although cardiovascular, dermatological, and gastrointestinal toxicities occur [41,43].

^{18}F-FDG PET

Reports have confirmed the use of ^{18}F-FDG PET and PET/CT for restaging MTC to detect tumor recurrence with patient-based sensitivities that range from 47 to 79% and lesion-based sensitivities that range from 76 to 96% [16–18,23,44–53]. Reported patient-based sensitivity ranges between 47 and 79% with higher lesion-based sensitivity between 76 and 96%. These data suggest a limited sensitivity of ^{18}F-FDG PET for detection of MTC recurrence, although a negative ^{18}F-FDG PET scan may also be negative by other imaging techniques and in this setting appears to imply a low disease burden and more favorable prognosis [18].

In contrast to ^{18}F-FDG PET for NET imaging, early studies of ^{18}F-FDG PET reported ^{18}F-FDG avidity for MTC [44,46]. One study showed ^{18}F-FDG uptake in 7/8 (88%) patients [54]. In an early multicenter trial of 85 patients with histopathological confirmation, ^{18}F-FDG PET exhibited a lesion-based sensitivity of 78% and specificity of 79%, whereas other imaging modalities – CT 50%, MRI 82%, SRS 25%, DMSA(V) 33%, and sestamibi 24% – were less successful [23]. However, in subsequent studies the sensitivity of ^{18}F-FDG PET for MTC fell to 40–60%, particularly when the value of Ct was less than 1000 pg/ml [16–18,45,47–53]. Comparative studies of ^{18}F-FDG PET versus CT and MRI have reported a lower sensitivity for ^{18}F-FDG PET [49,50]. Giradault *et al.* [49] found that ^{18}F-FDG PET was insensitive for detection of disease recurrence and did not provide additional value to an imaging strategy

Fig. 1



^{18}F-FDG PET/CT demonstrates multifocal hepatic metastases. A 40-year-old man with MTC status post total thyroidectomy underwent ^{18}F-FDG PET/CT scan for evaluation of suspected recurrent disease. Serum calcitonin levels were in excess of 17 000 pg/ml at the time of imaging. Anterior (a) MIP image demonstrates abnormal multifocal ^{18}F-FDG uptake in the liver (arrows). Widespread ^{18}F-FDG avidity hepatic metastases are demonstrated on selected axial (b) and coronal (c) PET and fused PET-CT images (arrows). CT, computed tomography; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; MIP, multiple intensity projection; MTC, medullary thyroid cancer.

combining neck ultrasound, lung CT, liver MRI, spine MRI, and bone scintigraphy.

The location of disease recurrence greatly influences the performance of different imaging modalities. ^{18}F-FDG PET demonstrates higher efficacy for disease in neck, supraclavicular, and mediastinal lymph nodes, identifying 240 foci in these locations compared with only 74 foci with CT and 79 with MRI [17]. However, CT was better for detection of liver and lung metastases, whereas ^{18}F-FDG PET and MRI were similar for localization of these sites [17]. Similarly, Oudoux *et al.* [52] reported that ^{18}F-FDG PET had an overall sensitivity of 76%, with a site-based sensitivity of 83% in the neck, 85% in the mediastinum, 75% in the lung, 60% in liver (Fig. 1), and 62% in bone.

As a means to select patients in whom ^{18}F-FDG PET has a greater likelihood for detection of disease, correlation of ^{18}F-FDG PET findings with Ct levels and doubling times has been performed. Ong and colleagues found that in patients with recurrent MTC, ^{18}F-FDG PET had an overall sensitivity of 62%; however, when Ct levels exceeded 1000 pg/ml, sensitivity increased to 78%. Patients with Ct less than 500 pg/ml had negative ^{18}F-FDG PET scans, suggesting microscopic metastases and low overall disease burden [16]. Rubello and colleagues described an overall patient sensitivity of 79% and high lesion sensitivity of 93% for ^{18}F-FDG PET, where significant cutoffs for positive findings were seen with Ct values in the range of 590–1350 pg/ml and negative PET scans with Ct values in the range of 58–600 pg/ml [53]. Skoura and colleagues in 38 patients found a sensitivity of 17/32 (47.4%) and reported only one false-positive case. Ct levels for patients with Ct less than 500 pg/ml had a PET scan sensitivity of 36.8%; for Ct levels between 500 and 1000 pg/ml, PET sensitivity was 33.3%; and for Ct levels greater than 1000 pg/ml, sensitivity increased to 80% [18]. Therefore, a Ct level of less than 500 pg/ml is more likely to be negative on ^{18}F-FDG PET. It should be noted, however, that determining universal thresholds of Ct for indicating timing of PET imaging may not be possible because of geographic differences in laboratory Ct measurement techniques [10].

Prognostic implications of ^{18}F-FDG PET have been explored by Oudoux and colleagues [52], where standardized uptake values were significantly correlated with Ct doubling times ($P = 0.025$); however, this finding was not confirmed by Ong and colleagues [16]. One study has reported on the prognostic value of ^{18}F-FDG PET with 6/11 (55%) PET-positive patients succumbing to their disease, whereas 13/14 (93%) PET-negative patients remained disease free with average follow-up of 44 months [55].

Although ^{18}F-FDG PET has confirmed superior sensitivity to SRS using ^{111}In-DTPA-octreotide, newer-generation somatostatin analogues such as ^{111}In-DOTA-lanreotide, ^{111}In-DOTA-NOC-ATE, ^{99m}Tc-EDDA/HYNIC-TOC, and

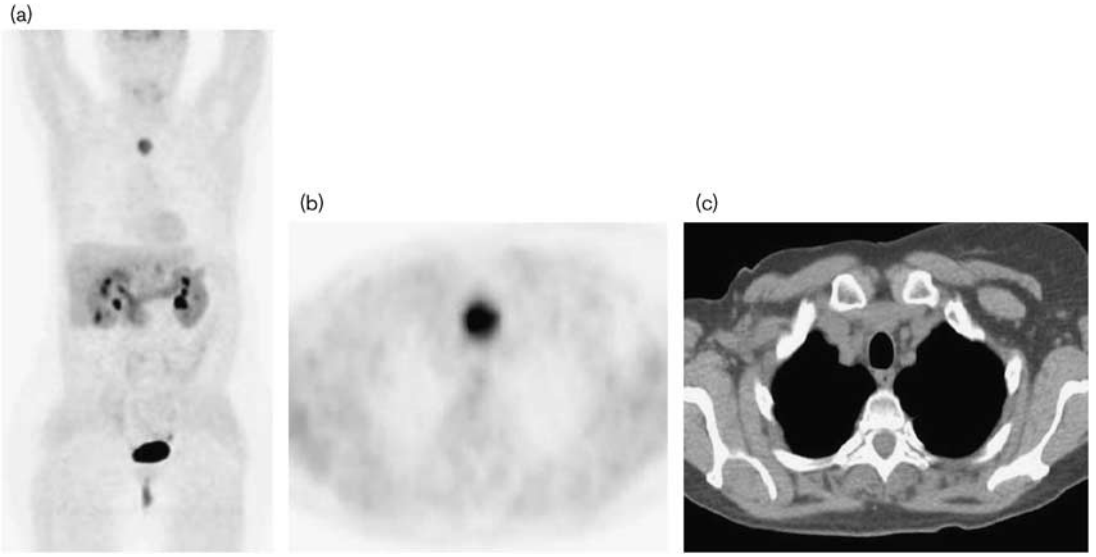
Table 1 Studies evaluating ^{18}F-FDG PET and PET/CT imaging of medullary thyroid cancer

References	Patient number	Group	Technique	Sensitivity	Specificity	Comment
Adams and colleagues [44,54]	8	MTC	^{18}F-FDG PET	88% (7/8) patients	NA	MTC is ^{18}F-FDG avid
Gasparoni *et al.* [48]	5	MTC	^{18}F-FDG PET	NA	NA	MTC is ^{18}F-FDG avid
Brandt-Mainz *et al.* [46]	20	MTC	^{18}F-FDG PET	76% (13/17) patients	NA	
Diehl *et al.* [23]	85	Postop MTC[a]	^{18}F-FDG PET	78% patients 68% foci	NA	^{18}F-FDG PET superior to CT, MRI, SRS, (V)DMSA
Szakall *et al.* [17]	40	Postop MTC	^{18}F-FDG PET MRI CT	270 foci 116 foci 141 foci	NA	^{18}F-FDG PET superior to CT, MRI
Bockisch *et al.* [45]	12	Postop MTC	^{18}F-FDG PET/CT	NA	NA	
Gotthardt *et al.* [50]	26	Postop MTC	^{18}F-FDG PET/CT	81% foci	NA	^{18}F-FDG PET same or slightly inferior to CT
De Groot *et al.* [47]	26	Postop MTC	^{18}F-FDG PET	50% patients 96% foci	NA	^{18}F-FDG PET superior to SRS and (V)DMSA
Iagaru *et al.* [58]	13	Postop MTC	^{18}F-FDG PET/CT	86% patients	83%	
Ong *et al.* [16]	28	Postop MTC	^{18}F-FDG PET	62% patients	1 false positive	
Giraudet *et al.* [49]	55	Postop MTC	^{18}F-FDG PET/CT Neck Mediastinum Lung Liver Bone	58% patients 55% patients 65% patients 42% patients 55% patients 76% patients	NA	Optimal work-up comprises neck US, chest CT, liver MRI, bone scan and spine MRI
Oudoux *et al.* [52]	33	Postop MTC	^{18}F-FDG PET/CT Neck Mediastinum Lung Liver Bone	76% foci 83% foci 85% foci 75% foci 60% foci 67% foci	NA	^{18}F-FDG PET superior for neck, CT superior for liver and lung, MRI superior for bone
Rubello *et al.* [59]	19	Postop MTC	^{18}F-FDG PET/CT	79% pts 93% foci	NA	
Skoura *et al.* [18]	32	Postop MTC	^{18}F-FDG PET/CT	47% patients	1 false positive	Sensitivity 80% for Ct >1000 pg/ml

CT, computed tomography; (V) DMSA, pentavalent dimercaptosuccinic acid; MTC, medullary thyroid cancer; postop, postoperative thyroidectomy; SRS, somatostatin receptor scintigraphy.

[a]Three of eighty-five patients in this study underwent preoperative ^{18}F-FDG PET for staging of MTC.

Fig. 2



^{18}F-DOPA PET/CT demonstrates solitary recurrent MTC focus in an upper anterior mediastinun. A 54-year-old woman previously operated for MTC underwent ^{18}F-DOPA PET/CT imaging for evaluation of suspected recurrent disease. Serum calcitonin levels were 85 pg/ml at the time of imaging. Anterior (a) MIP image: whole-body ^{18}F-DOPA PET/CT demonstrated a solitary focus of increased ^{18}F-DOPA uptake ($SUV_{max}=3.9$) consistent with recurrent disease. The solitary metastasis is demonstrated in axial PET (b) and CT (c) images. The patient underwent resection of this mediastinal lymph node. Following surgery, the calcitonin became undetectable and remained undetectable during the following 18 months, suggesting disease cure. CT, computed tomography; ^{18}F-DOPA, ^{18}F-fluorodihydroxyphenylalanine; MIP, multiple intensity projection; MTC, medullary thyroid cancer; SUV, standardized uptake value.

^{99m}Tc-depreotide have been developed. ^{99m}Tc-EDDA/HYNIC-TOC has been found to have good sensitivity of 79.5% and specificity of 83.3% for MTC [56]. In one study ^{99m}Tc-EDDA/HYNIC-TOC detected 15 lesions in five patients, compared with 11 lesions with ^{18}F-FDG PET; however, this observation will need to be confirmed in larger patient studies [57].

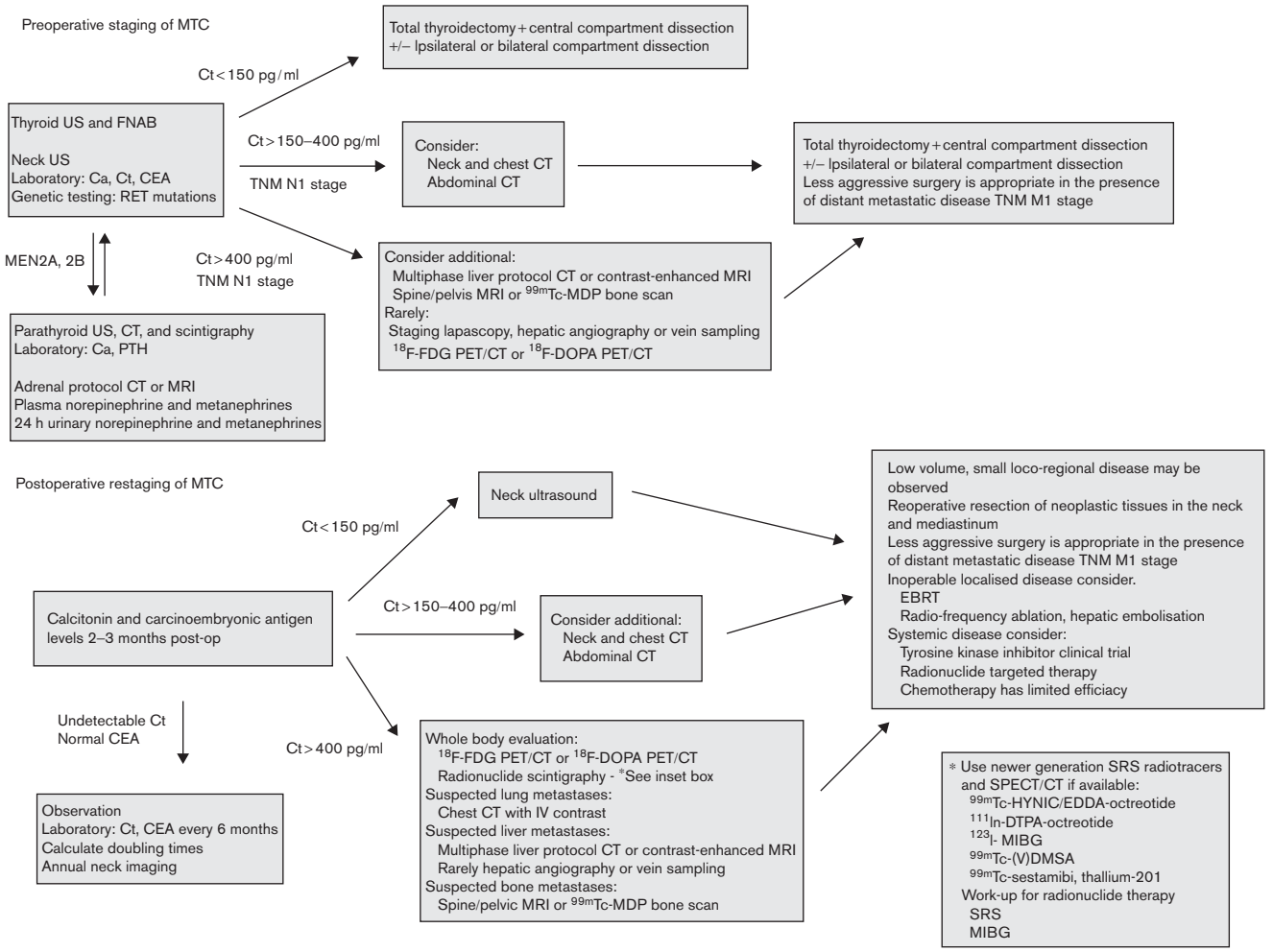
Table 1 summarizes the studies published on ^{18}F-FDG PET and PET/CT on MTC.

Non-^{18}F-FDG PET radiopharmaceuticals

^{118}F-DOPA has been successfully used for PET imaging of a variety of NETs, which include MTC [14,53,60]. L-DOPA is an intermediate in catecholamine biosynthesis and the ^{18}F-DOPA analogue is transported into cells by the large neutral amino acid transporter [61–66]. Intracellular retention depends upon decarboxylation by aromatic amino acid decarboxylase, whereas a portion of the metabolite ^{18}F-fluorodopamine (^{18}F-DA) may enter neurosecretory vesicles through uptake by vanillylmandelic acid transporter. Patients may be pretreated with oral carbidopa before ^{18}F-DOPA PET imaging, reducing peripheral conversion of ^{18}F-DOPA to its metabolites by AADC in liver and kidneys, with modest increases in tumor standardized uptake values and sensitivity [67].

Hoergle *et al.* [68] have reported ^{18}F-DOPA PET sensitivity of 63% for MTC, which in their series was superior to that of ^{18}F-FDG PET. More recent studies have demonstrated ^{18}F-DOPA PET sensitivity for MTC ranging between 74 and 87%, which in the majority of comparative studies is higher than that of ^{18}F-FDG PET [24,69–72], with some authors recommending ^{18}F-DOPA PET/CT using contrast-enhanced diagnostic CT for preoperative staging and postoperative surveillance [24]. Others have suggested a complementary role for ^{18}F-DOPA and ^{18}F-FDG PET, with the combination likely to provide the highest sensitivity and specificity [70]. The differences between ^{18}F-DOPA and ^{18}F-FDG avidity have been ascribed to MTC differentiation and proliferation, where ^{18}F-FDG PET may be more useful for patients with MTC expressing high Ki-67 indices and short (< 6 months) Ct doubling times [18]. Others have suggested that the higher tumor uptake seen with ^{18}F-DOPA PET allows detection of smaller lesions with higher sensitivity [24]. A cutoff of Ct greater than 500 ng/l has been suggested as predictive of a positive ^{18}F-DOPA PET scan, although another study suggests a lower Ct value of 150 pg/ml, and the actual cutoff value of Ct remains unconfirmed at this time [69,72]. Rubello and colleagues suggested the use of ^{18}F-DOPA PET/CT as the first-choice examination in biochemically recurrent MTC because it has, in some cases, proven to be able to detect relapse early when confined to the thyroid bed or locoregional lymph nodes; therefore, surgical reoperation may be planned with curative intent [73] (an example is reported in Fig. 2). As an alternative radiopharmaceutical, ^{18}F-DA has been shown to localize an MTC metastasis in

Fig. 3



A proposal diagnostic imaging and biochemical workup of medullary thyroid cancer in the preoperative (upper) and postoperative (lower) setting, according to authors' clinical experience. CEA, carcinoembryonic antigen; Ct, calcitonin; CT, computed tomography; (V) DMSA, pentavalent dimercaptosuccinic acid; ^{18}F-DOPA, ^{18}F-fluorodihydroxyphenylalanine; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; MIBG, metaiodobenzylguanidine; MTC, medullary thyroid cancer; postop, postoperative thyroidectomy; RET, rearranged during transfection; SRS, somatostatin receptor scintigraphy; TNM, tumor, node, metastasis.

a patient with MEN2A [74]. ^{18}F-DA has been shown to be sensitive for the evaluation of NETs of chromaffin origin, pheochromocytomas and paragangliomas, and may be an alternative to ^{18}F-DOPA PET [62,64,75].

Somatostatin is a regulatory peptide, with an affinity for G-protein-coupled membrane-bound somatostatin receptor subtypes 1–5. Peptide-based imaging with somatostatin analogues has been used to image MTC using ^{111}In-DTPA-octreotide with modest success [76]. As an alternative to fluorine-18, gallium-68 is a positron-emitting isotope that has been used to label somatostatin analogues such as ^{68}Ga-DOTA-Tyr-3-octreotide (DOTATOC), ^{68}Ga-DOTA-NaI-octreotide (DOTANOC), and ^{68}Ga-DOTA-octreotate (DOTATATE), with varying affinities for somatostatin receptor subtypes 1–5 [64,73]. Gallium-68 is a positron-emitting isotope with an 89% efficient positron yield and a half-life of 68 min and is readily available from a germanium-68/gallium-68 generator.

Conry *et al.* [77] have shown that ^{68}Ga-DOTATATE can be used to image MTC. In 18 patients with elevated Ct levels after thyroidectomy, ^{68}Ga-DOTATATE PET/CT had a sensitivity of 72% that was similar to an ^{18}F-FDG PET/CT sensitivity of 78%. In 10 patients a discordant pattern of recurrent disease per region and/or per lesion was observed, leading the researchers to conclude that ^{68}Ga-DOTATATE PET/CT could be used to complement ^{18}F-FDG PET and may identify a subset of patients for consideration of targeted radionuclide somotastatin analogue therapy [78]. An imaging approach using an amino acid radiotracer, ^{11}C-methionine (MET) PET/CT

Table 2 Alternative non-^{18}F-FDG PET/CT imaging of medullary thyroid cancer

Author	Patient number	Group	Technique	Sensitivity	Specificity	Comment
Hoegerle *et al.* [68]	11	Postop MTC	^{18}F-DOPA PET	63% foci	NA	^{18}F-DOPA PET is sensitive for MTC
			FDG PET	44% foci		
Beuthien-Baumann *et al.* [71]	15	Postop MTC	^{18}F-DOPA PET	47% (7/15) patients	NA	
			^{18}F-FDG PET	47% (7/15) patients		
Koopmans *et al.* [69]	21	Postop MTC	^{18}F-DOPA PET	62% patients, 71% foci	NA	
			^{18}F-FDG PET	24% patients, 30% foci		
Beheshti *et al.* [24]	26	Postop MTC[a]	^{18}F-DOPA PET/CT	81% patients	NA	^{18}F-DOPA PET/CT single best test
			FDG PET/CT	58% patients		
Luster *et al.* [72]	26	Postop MTC	^{18}F-DOPA PET/CT	74% patients	100%	PET/CT better than PET alone
Conry *et al.* [77]	18	Postop MTC	Ga-DOTA PET/CT	72% (13/18) patients	NA	Complementary role
			^{18}F-FDG PET/CT	78% (14/18) patients		
Marzola *et al.* [70]	18	Postop MTC	^{18}F-DOPA PET/CT	83% (15/18) patients	NA	Complementary role
			^{18}F-FDG PET/CT	61% (11/18) patients		
Jang *et al.* [79]	16	Postop MTC	^{11}C-MET PET/CT	63% patients, 73% foci	NA	MET PET unable to detect liver metastases
			^{18}F-FDG PET/CT	63% patients, 80% foci		

CT, computed tomography; ^{11}C-MET, methionine; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; ^{18}F-DOPA, fluorodiphenylalanine; Ga-DOTA, DOTA peptide; MTC, medullary thyroid cancer; postop, postoperative thyroidectomy.
[a]Seven of twenty-six patients in this series underwent preoperative ^{18}F-DOPA and ^{18}F-FDG PET/CT for staging of MTC.

was also successful in the detection of MTC metastases in postsurgical patients with elevated Ct [79]. ^{11}C-MET PET/CT had a lesion-based sensitivity of 73% that was similar to ^{18}F-FDG PET/CT of 80%, with both modalities exhibiting patient-based sensitivities of 63%. Both ^{11}C-MET PET/CT and ^{18}F-FDG PET/CT identified metastases when Ct levels were greater than 370 pg/ml. ^{11}C-MET PET/CT was superior to ^{18}F-FDG PET/CT for detection of cervical lymph nodes and failed to detect liver metastases due to the intense physiological ^{11}C-MET by the liver.

Figure 3 reports a proposal diagram or imaging technique to be used during preoperative staging and postoperative surveillance.

Table 2 reports studies on alternative non-^{18}F-FDG PET/CT imaging of MTC.

Conclusion

The management of MTC requires accurate staging and restaging imaging techniques to optimize surgical-based treatment strategies. For surveillance of both sporadic and hereditary MTC a combination of imaging modalities appears to provide the highest diagnostic sensitivity for all sites. The optimal selection of imaging is influenced by individualized phenotype profiles, based on genetic testing, tumor grade, proliferation indices, and consideration of Ct and CEA levels and their doubling times. ^{18}F-FDG and other novel positron-emitting radiopharmaceuticals integrated with CT, especially ^{18}F-DOPA and in future MRI techniques, provide a variety of imaging approaches to MTC that take advantage of unique cellular functions of this neoplasm that allow improved imaging to aid the surgeon and endocrinologist in the management of this elusive neoplasm.

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Conflicts of interest

There are no conflicts of interest.

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