HHS Public Access

Author manuscript

Curr Opin Endocrinol Diabetes Obes. Author manuscript; available in PMC 2023 March 27.

Published in final edited form as:

Curr Opin Endocrinol Diabetes Obes. 2022 October 01; 29(5): 456–465. doi:10.1097/MED.0000000000000740.

Advanced imaging and theranostics in thyroid cancer

Molly E. Roseland[a,b], **Yuni K. Dewaraja**[a], **Ka Kit Wong**[a]

[a]Division of Nuclear Medicine, Department of Radiology, Michigan Medicine, University of Michigan, Ann Arbor, Michigan, USA

[b]Division of Body Imaging, Department of Radiology, Michigan Medicine, University of Michigan, Ann Arbor, Michigan, USA

Abstract

Purpose of review—Thyroid cancers are endocrine neoplasms with diverse gene expression and behavior, for which constantly evolving anatomic and functional imaging/theranostic agents have an essential role for diagnosis, staging, and treatment.

Recent findings—To achieve definitive diagnosis, neck ultrasound and associated risk stratification systems, notably Thyroid Imaging Reporting and Data System (TI-RADS), allow improved thyroid nodule characterization and management guidance. Radioactive iodine-131 (RAI) has long played a role in management of differentiated thyroid cancer (DTC), with recent literature emphasizing its effectiveness for intermediate-high risk cancers, exploring use of dosimetry for personalized medicine, and potential for retreatment with RAI following tumor redifferentiation. Iodine-124 positron emission tomography/computed tomography (PET/CT) has promising application for DTC staging and dosimetry. F18-fluorodeoxyglucose (FDG) PET/CT is used for staging of high risk DTC and identification of noniodine-avid disease recurrences, with metabolic uptake consistently portending poor prognosis. Poorly differentiated and anaplastic thyroid cancers are best assessed with anatomic imaging and F18-FDG PET/ CT, though recent studies show a potential theranostic role for Ga68/Lu177-prostate-specific membrane antigen. Medullary thyroid cancers are evaluated with ultrasound, CT, magnetic resonance imaging, and various positron-emitting radiotracers for PET imaging (F18-DOPA, F18-FDG, and recently Ga68-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)–octreotate (DOTATATE)); the latter may enable treatment with Lu177-DOTATATE.

Summary—Multidisciplinary collaboration is essential to streamline appropriate management, given the wide array of available imaging and new therapies for metabolic and genetically complex cancers.

Keywords

dosimetry; FDG-PET; Ga68-DOTATATE; Ga-68-PSMA; Iodine-124; Iodine-131; theranostics; thyroid cancer; thyroid ultrasound; TI-RADS

Correspondence to Ka Kit Wong, MBBS, Division of Nuclear Medicine, Department of Radiology, University of Michigan, 1500 E. Medical Center Drive, B1G505 UH, Ann Arbor, MI 48109-0028, USA. Tel: +1 734 936 5388; kakit@med.umich.edu.

Conflicts of interest

Y.K.D. is a consultant for MIM software.

INTRODUCTION AND EPIDEMIOLOGY

Thyroid cancer is the most common endocrine malignancy, frequently affecting younger women. Incidence rates tripled in the USA between 1974 and 2013, primarily due to increased diagnosis of well differentiated papillary thyroid cancers [1,2], with relatively stable incidence of follicular, medullary, and anaplastic cancers. A slight decline in incidence was recently observed in 2016–2019, potentially reflecting changing management guidelines (increased surveillance of small, low-risk thyroid nodules) to reduce overdiagnosis [3,4]. Although prognosis remains excellent for patients with early-stage papillary tumors (98% overall 5-year survival), outcomes are much poorer for patients with distant metastases (53% 5-year survival), or anaplastic subtypes (9–34% 5-year survival) [3]. This emphasizes the importance of accurate imaging to identify aggressive cancers, as well as appropriate use of functional imaging for complete staging and potential theranostic treatment.

In this review, we provide an overview of current best-practices and recent advances in thyroid cancer imaging, emphasizing how imaging can complement clinical staging, pathologic evaluation, and how new molecular diagnostics/therapies developments have potential to improve outcomes.

THYROID NODULE WORKUP: THYROID IMAGING REPORTING AND DATA SYSTEM AND INCIDENTAL THYROID NODULES

While thyroid cancer screening is no longer recommended for asymptomatic patients by the USA Preventive Services Task Force as of 2017 [4], abnormal physical examination and thyroid function tests often prompt further evaluation with high frequency, linear-array thyroid ultrasound, revealing one or more thyroid nodules. Likewise, thyroid nodules are frequently observed incidentally on imaging (computed tomography/magnetic resonance imaging, MRI/PET) obtained for unrelated concerns. Since most nodules are benign and no single feature can definitively diagnose malignancy, accurate nodule characterization and risk determination are essential, enabling a delicate balance of the benefits of early cancer diagnosis with the morbidity of overdiagnosis and aggressive treatments [5,6].

To standardize reporting and management recommendations of thyroid sonography, the American college of radiology (ACR) Thyroid Imaging Reporting and Data System (TI-RADS) was released in 2017 [7■■,8], and has since become a widely accepted system for thyroid nodule risk stratification [alongside the American Thyroid Association (ATA), EU-TIRADS in Europe, etc.]. TI-RADS uses a points-based system to assign scores to up to four dominant nodules based on five main features, including composition, echogenicity, shape, margin, and echogenic foci. Any nodule can be classified, in contrast to the ATA system (which uses morphologic patterns), by which up to 14% of nodules are not categorizable [9]. Nodules are then assigned categories of TR-1 to TR-5, with higher scores indicating increasing risk [8].

Because TI-RADS uses relatively higher size thresholds for fine-needle aspiration (FNA), it has been shown to decrease rates of biopsy recommendations by 19.9–46.5%, with the

highest specificity among classification systems [7■■,10,11]. It manages to avoid increased rates of missed cancers by suggesting surveillance for potentially suspicious nodules: a 2021 study of 352 malignant nodules showed 98% met criteria for either FNA (68%) or follow-up (20%) per TI-RADS [12]. Therefore, the system appears to help prevent unnecessary interventions and overdiagnosis while maintaining patient safety. Variability in scoring and scanning technique remains a potential challenge for TI-RADS (for example, increasing points assigned for nodules with colloid/comet tail artifact misclassified as punctate echogenic foci, or a cystic nodule misclassified as solid due to suboptimal image quality) [7■■]. However, this is not a problem unique to TI-RADS, as many ultrasound features are shared among classification systems, and all systems have been shown to have similar interobserver variability [13,14].

TI-RADS is likely to be updated as more data emerge to refine its ability to distinguish between benign and malignant nodules. In particular, new ultrasound technology, as well as advanced analytics (deep learning, radiomics) have shown favorable results and improved nodule risk stratification in various recent studies [7■■]. These include ultrasound shear-wave elastography to assess elevated tissue stiffness, a feature common in various cancers, with high sensitivities (75–89%) [7■■,15–19], and contrast-enhanced ultrasound (CEUS) for real-time visualization of blood-flow (morphology, intensity, kinetics) with inert intravascular microbubbles. Features, such as hypo-enhancement, heterogeneous enhancement, and slow wash-in/wash-out are indicative of malignancy, with high sensitivity (78–90%) and specificity (83–99%) for cancer [20■]. CEUS may also have value for diagnosis of extrathyroidal extension [21] and metastatic cervical lymph nodes; nonetheless, routine use may be limited due to its operator-dependence, need for direct radiologist supervision, higher cost, and longer imaging times [7■■,20■]. Superb microvascular imaging (SMI) is an ultrasound technique similar to power Doppler that enables improved visualization of small, low-velocity blood vessels, and neovascularity in tumors. Diagnostic efficiency of TI-RADS (pooled sensitivity and specificity of 80% and 82%) improved with addition of SMI (sensitivity and specificity of 88% and 89%) [22]. Finally, machine learning and artificial intelligence is a topic of recent research, and may enable more accurate nodule classification than TI-RADS and manual radiologist scoring alone [23,24].

While TI-RADS provides objective risk assessment based on anatomic features for individual nodules, its recommendations may be modified by other available imaging features. For example, ‘cold’ hypofunctioning nodules with absence of uptake on thyroid scintigraphy (I-123 or Tc-99m pertechnetate) are classically associated with an increased risk of malignancy; increased late uptake on Tc-99m sestamibi (MIBI) scanning (uptake values >5.9) is a reproducible, potentially valuable method to identify cancer in the setting of prior indeterminate or nondiagnostic nodule cytology [25]. Incidental focal thyroid nodule uptake on positron emission tomography/computed tomography (PET/CT) indicates an increased risk of malignancy [26]. A large retrospective study of 52,693 oncology patients undergoing F18-fluorodeoxyglucose (FDG) PET/CT showed 1003 (1.9%) hypermetabolic thyroid nodules; although only 47 patients ultimately underwent thyroid surgery, 31 (66%) were found have thyroid cancer. However, death was largely related to pre-existing malignancy, with only one due to medullary thyroid cancer [27■■]. A study assessing FDG-avid lymph nodes with TI-RADS showed an overall rate of malignancy

of 34%; the majority of FDG-avid thyroid nodules were classified as TR-4 and 5 (71%), which had particularly high rates of malignancy (24–68%) [28]. Recent studies of Ga-68 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)–octreotate (DOTA-TATE) show focal thyroid uptake in 4–6% of scans, with 18–21% risk of cancer (particularly medullary) among biopsied nodules [29,30]. Likewise, a small study of 341 patients undergoing Ga-68 prostate-specific membrane antigen (PSMA) PET for prostate cancers showed focal thyroid uptake in seven cases (3%), with only 2 (0.5%) diagnosed with thyroid cancer [31]. Accordingly, focal thyroid uptake on PET/CT in a patient without life-limiting malignancy warrants ultrasound evaluation, according to 2015 recommendations from the ACR Incidental Thyroid Findings Committee [32]. However, subsequent management, including FNA, may be conservative, based on the status of the patient's other malignancy [26].

The ACR also suggests thyroid ultrasound as the next step for incidental nodules on computed tomography or MRI ≥ 1 cm for patients <35 years, and ≥ 1.5 cm inpatients ≥ 35 years [32]; smaller nodules are considered low risk and require no follow-up. When indicated, ultrasound-guided FNA (using multiple passes with 25–27-gauge needles) with cytology enables diagnosis of the majority of suspicious thyroid nodules [33,34]. For nondiagnostic samples, repeat FNA is recommended, but larger core needle biopsy also has potential to improve tissue yield in larger TR-4/5 nodules >2cm [35]. While molecular testing is often performed for nodules with indeterminate-risk cytology, a new 2022 trial also showed F18-FDG PET can help risk-stratify indeterminate nodules, avoiding up to 40% of unnecessary thyroid surgeries [36].

DIFFERENTIATED THYROID CANCER (PAPILLARY THYROID CANCER AND FOLLICULAR THYROID CANCER)

Differentiated thyroid cancer (DTC) is the most common subtype of thyroid cancer (>90%), consisting of ubiquitous papillary and less common follicular cancers. Diagnosis is established with ultrasound and FNA, with concurrent FNA also performed for any suspicious cervical lymph nodes prior to surgery [37]. Contrast-enhanced neck computed tomography may be performed for large invasive tumors or clinically apparent lymphadenopathy: a recent metanalysis of PTC showed similar sensitivity and specificity of ultrasound (73%, 89%) and computed tomography (77%, 88%) for lateral compartment cervical lymph node metastases, but higher sensitivity and lower specificity of computed tomography (39%, 87%) compared to ultrasound (28%, 95%) for central compartment metastases [38■]. Definitive management is thyroidectomy: small PTC (<4cm) without nodal metastases may undergo thyroid lobectomy, but larger tumors or those with clear lymph nodal metastases typically undergo total thyroidectomy with variable lymph node dissection [37]. There is also an increasing role for active surveillance or minimally invasive percutaneous ablation (laser, microwave, radiofrequency) by interventional radiology, which have been proposed as a viable option for small, low-risk cancers or isolated metastases in older patients who are poor surgical candidates [37,39].

RADIOACTIVE IODINE IMAGING, THERAPY, AND DOSIMETRY

Radioactive iodine-131 (RAI) has been used for thyroid cancer since the 1940 s, and represents the first true theranostic agent, targeting the Na-I symporter (NIS) expressed in DTC and normal thyroid tissue. I-131 emits 364 KeV gamma rays for imaging with planar gamma cameras and single photon emission computed tomography (SPECT)/computed tomography systems, as well as damaging beta particles to induce tumor cell death and tissue ablation. Today, RAI remains a mainstay for DTC restaging, remnant gland ablation, and adjuvant therapy. While considered optional for patients with low risk or micropapillary tumors (and has not been shown to improve outcomes), it is typically recommended for ATA intermediate-high risk patients [37] based on surgical pathology tumor classification (WHO, to be updated in 2022) [40], staging (AJCC/ATA 8th edition guidelines) [41], and ATA risk classification [37].

Adequate patient preparation for RAI [low-iodine diet and thyroid stimulating hormone (TSH) stimulation] is essential to ensure sufficient therapeutic uptake. A recent study shows that a low-iodine diet for 4 days provides equivalent thyroid stimulating hormone (TSH) stimulation to 7 days [42], which may improve patient compliance. RAI should also be delayed at least four weeks following computed tomography with iodinated contrast [43]. TSH stimulation may be performed either by withdrawal of thyroid hormone supplementation for 4–5 weeks or rh-TSH (Thyrogen) injections for 1–2 days, the latter of which may be better tolerated by patients. A recent multicenter retrospective study affirmed similar outcomes for recombinant human thyroid stimulating hormone (rhTSH)-stimulation among patients with and without nodal metastases [44]. Hypothyroidism with thyroid hormone withdrawal may still be preferable for extensive metastatic disease to ensure maximal tumor uptake.

Initial pretherapy diagnostic whole body iodine scans (WBS) are typically performed 1–2 days after low doses of I-131 (1–5 mCi) or I-123 in order to identify any unsuspected metastatic disease, which may prompt higher RAI doses [37,43,45]. While diagnostic WBS is somewhat controversial, and not performed at all institutions, a 2015 study affirmed their impact on therapeutic decision-making [46], and diagnostic WBS are endorsed by the ATA/society of nuclear medicine and molecular imaging in consensus guidelines [47]. Nonetheless, posttherapy I-131 scan has higher sensitivity for metastases due to higher doses administered.

RAI therapeutic dosing is usually determined empirically, based on individual patient and disease factors [47]. Typical activity prescribed is as low as 30–50 mCi for low-risk remnant ablation, 100–150 mCi for metastatic neck lymph nodes, and 200 mCi for distant lung/bone metastases [48]. Successful ablation rates and recurrence rates are not significantly different at various dose ranges, and biological heterogeneity between individuals is well recognized; therefore, there is no consensus for a fixed activity approach [49]. Increasing radioactivity is required for high risk metastatic disease, but carry an increased risk for unintended side effects, such as salivary gland damage, lacrimal gland injury, lung fibrosis, or leukopenia [50■■], prompting ongoing interest in using dosimetry to optimize tumor dose based on individual patient pharmacokinetics while limiting critical organ damage.

Available only at select academic institutions with dedicated physicists [51], dosimetry may be performed with various techniques prior to I-131 therapy or using posttherapy scans. Dosimetry is based on the premise that absorbed radiation dose is dependent on the number of radioactive decays in the source region, the energy emitted by each decay event, and the energy absorbed by the target region [52■]. Using scans showing anatomic distribution of radioactivity over time to estimate residence time (time-integrated activity coefficient), the radiation absorbed dose to tumor and normal organs can be estimated. Quantitative SPECT/computed tomography is more accurate than two-dimensional planar images for precise assessments of absorbed dose, but planar imaging is sometimes used due to the higher cost and longer scan times associated with SPECT.

Two primary dosimetry paradigms are utilized: maximum targeted activity (MTA), to give the highest overall activity without causing toxicity, and lesion-based dosimetry, to give the lowest overall dose to deliver a minimum threshold of radiation to a tumor [52■]. MTA dosimetry methods in RAI include limiting the maximal activity resulting in <2 Gy exposure to the blood (used as a surrogate for bone marrow toxicity) as originally described by Benua [53], or targeting a whole-body maximum retained activity at 48 h of 120 mCi (or 90 mCi in patients with lung metastases) [54]. A study assessing effectiveness of MTA dosimetry (using a combination of serial blood-draws to assess beta radiation and planar WBS to assess gamma radiation) showed that DTC patients with dosimetry-guided activity administrations had increased rates of complete response and similar side effects compared to those undergoing empiric treatment [55]. However, a 2017 study using similar dosimetry methodology showed no significant differences in survival [56]. Figure 1 illustrates an example of RAI treatment with dosimetry-guided dose escalation.

Lesion-based dosimetry for RAI was first performed by Maxon in 1983 demonstrating effective responses with > 300 Gy absorbed dose to remnant thyroid tissue and > 80 Gy to metastases [57]. A dosimetry study of the effects of high-activity 250 mCi RAI therapy reported higher absorbed dose to bone marrow under hypothyroid stimulation compared to rhTSH-stimulation. Lesion-based dosimetry also confirmed that bone metastases were difficult to treat, with only 55% receiving >100 Gy activity, suggesting that increasing dose to iodine-avid bone lesions would exceed safety margin to bone marrow [58]. Posttherapy dosimetry in patients with distant M1 metastatic disease based on post-RAI imaging at 2, 3, 7 days was performed in a cohort of 30 patients with 102 radioiodine therapies; complete response (biochemical and radiological) occurred in only 10%, partial response in 33%, and the remainder had progressive disease. Absorbed dose of >20 Gy to metastases was considered supportive of continued RAI treatments, whereas lesser absorbed doses were indicative of iodine-refractory tumor, for which ineffective RAI could be discontinued [59]. Dosimetry can therefore provide quantitative guidance for efficacious and safe radioiodine treatments while avoiding futile treatments or excess toxicity.

I-124 PET/CT is a promising newer modality with particular value in lesion-based dosimetry [60,61] due to its long half-life (4.2 d) and high spatial resolution. Despite challenges in quantitative imaging (complex decay scheme with multiple gamma-rays, low positron yield), prompt gamma correction has been used successfully to create diagnostic-quality PET imaging [62]. The higher spatial resolution of PET over SPECT is particularly attractive

for lesion-based dosimetry before RAI therapy in DTC because lesion size can be very small. I-124 PET imaging is also valuable for clinical trials, and was previously used in a ground-breaking study treating noniodine-avid thyroid cancers with I-131 following re-sensitization with the MEK-kinase inhibitor selumentinib; PET uptake was predictive of I-131 uptake and improved outcomes [63]. I-124 PET with dosimetry was similarly used in a more recent trial inducing iodine sensitivity in BRAF-mutant thyroid cancers treated with a BRAF-kinase inhibitor, identifying patients with sufficient tumor uptake for RAI treatment [64]. However, I-124 is still not currently Food and Drug Administration (FDA) approved, therefore limiting its applications in routine clinical practice [52■].

RECURRENT, IODINE-REFRACTORY, AND NONIODINE AVID DIFFERENTIATED THYROID CANCER

Following surgery and RAI therapy, patients without evidence of residual DTC undergo routine clinical and laboratory follow-up. Rising thyroglobulin levels typically prompts neck ultrasound to evaluate for structural evidence of recurrent disease, as well as a diagnostic I-131 scan to identify iodine-avid metastases that could be targeted for RAI therapy. However, such iodine scans are frequently negative due to tumor dedifferentiation and down-regulation of the NIS after RAI, conferring ‘iodine resistance’ [65]. Empiric retreatment of such patients with RAI was not shown to induce substantial tumor response or improve survival [66]. Lack of iodine uptake on radioiodine scintigraphy is often accompanied by an upregulation of GLUT-1 glucose transporters, known as the ‘flip-flop’ phenomenon, resulting in increased tumor uptake on FDG-PET/CT [65,67]. FDG uptake in recurrent DTC tumors is independently associated with increased risk of disease progression and poorer thyroid cancer survival [68–71].

Several metanalyses of FDG-PET/CT among patients with biochemical evidence of recurrent DTC and negative iodine scanning showed pooled sensitivity of 80–89% and specificity of 75–84% in detecting metastases [72–74]. rhTSH (Thyrogen)-stimulation, extensive metastases, higher thyroglobulin levels, and shorter Tg doubling time (<1 year) are all associated with increased likelihood of metastatic lesion identification on FDG-PET/computed tomography [75–77]. Current ATA guidelines recommend FDG-PET/CT only in patients with elevated Tg >10ng/mL and negative iodine scan [37] although 10–20% of patients with Tg levels less than this threshold may show evidence of disease [76]. PET findings guide subsequent management: localized FDG-avid metastases may be targeted for surgical resection or external beam radiation (EBRT), whereas more widespread metastases prompt treatment with systemic tyrosine kinase inhibitors, including lenvatinib and sorafenib [65]. Follow-up FDG-PET/CT may then be used to monitor functional tumor response to therapy [78]. Interestingly, FDG-PET/MRI may be valuable for local recurrence and neck lymph node metastases [79], but does not improve distant metastatic DTC diagnosis, given its poor sensitivity for lung metastases [80].

Of note, while FDG-PET is not recommended for initial staging, some DTC may be FDG-avid at diagnosis, particularly noniodine avid subtypes (BRAFV600E mutations, Hurthle cell carcinoma), large tumors, high risk features on histopathology, or widely metastatic

tumors (high proliferative rates, variable gene expression) [65,81,82]. A study of patients with intermediate and high risk DTC undergoing both iodine scanning and FDG-PET at diagnosis revealed additional lesions FDG-avid lesions in 14% of patients, potentially altering management and prognosis [83]. However, because of low sensitivity and negative predictive value for most metastases [84], FDG-PET is not routinely recommended for DTC initial staging.

Several other novel PET agents have been investigated for DTC. FDA-approved Ga-68 DOTA peptides (such as DOTATATE, targeting somatostatin receptors) may be administered for iodine-negative cancers. A 2014 analysis showed Ga-68 DOTA PET detected fewer lesions relative to FDG (65% vs. 90%), although both modalities detected lesions that changed management in 20–30% of cases [85]. Somatostatin receptor expression in thyroid cancer metastases may also allow a patient to receive theranostic treatment with Lu-177 DOTATATE peptide receptor radionuclide therapy (PRRT). Smaller studies of the newly FDA-approved Ga-68-PSMA for prostate cancer (and promising Ga-68 FAPI) also showed variable DTC uptake with potential theranostic implications [86,87■,88]. Experimental, non-FDA approved PET agents specifically targeting DTC include Ga-68 DOTA-(RGD)2, targeting an integrin marker in angio-neogenesis [89], and F-18 tetrafluoroborate, a substrate for the NIS [90].

POORLY DIFFERENTIATED (PDTC) AND ANAPLASTIC THYROID CANCER (ATC)

ATC is a rare subtype primarily affecting older patients, comprising <5% of newly diagnosed thyroid cancers. It is characterized by rapid growth, extensive local invasion, and very poor survival (6–8 month median survival). PDTC represents an intermediate histologic subtype between DTC and ATC, also with poor prognosis [65]. Both tumors are typically diagnosed with ultrasound or computed tomography, followed by FNA. Surgical resection provides the best chance for disease control and survival, but may not be possible for large tumors with extensive infiltration. External beam radiation, cytotoxic chemotherapy, and/or targeted molecular therapies may be used for adjuvant therapy or for palliative treatment of unresectable disease [91].

The ATA recommends F18-FDG PET/CT (and/or anatomic computed tomography) for initial staging of these cancers, given excellent sensitivity and high frequency of metastases at diagnosis [92]. Radioiodine scanning and radioiodine therapy play a very limited role given usual lack of NIS expression, which portends an adverse prognosis. A small study of 16 patients with ATC showed F18-FDG-PET was positive in 100% of cases and affected clinical management in half of cases [93]. Prognostically, both tumor volumes and high SUV max at FDG-PET are negative predictors of ATC survival, whereas negative posttreatment PET was predictive of long-term remission [94■]. PET also enabled improved diagnosis of bone metastases, which were not always visible on anatomic computed tomography [94■].

Theranostics are of particular interest for such aggressive cancers, but are challenging to evaluate in such rare malignancies; clinically available radiotracers have been used in few

patients on an experimental basis. Ga68-PSMA PET/CT and MRI were recently performed among a small cohorts of patients with PDTC and ATC [95,96], with variable results: 74% of poorly differentiated tumor metastases were detected in one small study, while only 11% of PDTC metastases (and no ATC metastases) were detected in another. In the latter study, only one patient underwent treatment with Lu-177 PSMA, stabilizing their disease for 7 months [96].

MEDULLARY THYROID CANCER

Medullary thyroid cancer (MTC) is a rare neuroendocrine neoplasm arising from parafollicular C thyroid cells, accounting for only 1–2% of thyroid cancers. It is associated with mutations in the RET oncogene, either sporadic or occurring in the context of autosomal dominant MEN 2A or MEN 2B (20–30% of cases) [97]; therefore, all MTC patients should undergo genetic testing to detect germline mutations . While patients with known predisposition may undergo screening or prophylactic thyroidectomy, all other patients are diagnosed similarly to other thyroid cancers (diagnostic ultrasound or computed tomography), with subsequent FNA. Calcitonin and carcinoembryonic antigen (CEA) are common tumor markers, and FNA samples should be analyzed specifically for elevated calcitonin if there is clinical suspicion for MTC [98]. Standard therapy consists of total thyroidectomy with variable neck dissection, with consideration of EBRT or tyrosine kinase inhibitors if gross residual disease.

Initial staging is performed with anatomic imaging. Neck ultrasound is required in all patients, and more extensive testing is ordered if there is suspected high volume disease, including contrast-enhanced computed tomography neck/chest, multiphasic computed tomography abdomen/pelvis or liver MRI, and pelvic MRI [97]. Tc-99 MDP bone scan is also suggested for detection of osseous metastases, though may have limited sensitivity. Radioiodine scintigraphy has no role in MTC. PET imaging has replaced conventional nuclear medicine imaging with limited sensitivity for MTC, notably In-111 pentetreotide, I-123 mIBG and Tc99m-pentavalent dimercaptosuccinic acid.

Restaging and suspected recurrence typically begins with a similar imaging workup, and functional imaging with PET/CT (F18-FDG, F18-DOPA, and/or Ga68-DOTATATE tracers) subsequently used to detect occult disease or characterize indeterminate anatomic imaging findings. F18-DOPA is an alternate PET agent that targets the L-type amino acid transporter, which is expressed in MTC as well as pheochromocytomas [65]. While it is considered the most accurate modality to detect recurrent/metastatic MTC [99■,100–102], particularly liver and cervical lymph node metastases, it has limited availability outside specialized academic institutions. F18-DOPA PET is most likely to show uptake in MTC metastases among patients with elevated calcitonin (>150 ng/mL), with an overall sensitivity of 47–83% [103]. F18-FDG PET has moderate sensitivity for MTC metastases (59–69%) [104], with highest yield among patients with short tumor marker doubling times (<1 year). A study of F18-FDG PET found sensitivity 92%, specificity 86% in MTC with elevated calcitonin, with significant impact on management decisions [105].

Finally, given its theranostic potential, Ga-68 DOTATATE, a somatostatin analogue with high affinity for SSTR2, widely available for neuroendocrine imaging, may be used to evaluate for metastatic MTC [106]. This tracer displays less reliable uptake compared to other neuroendocrine neoplasms, with only limited sensitivity for MTC (64%) [106], particularly bone metastases. However, a recent study of Ga68-DOTATATE PET actually found greater performance than conventional imaging in 37% of 14/38 patients, altering patient management by detecting neck nodes and bone metastases [107]. Nonetheless, identification of somatostatin receptor type 2 expression may also qualify a patient with refractory disease for Lu-177 PRRT: a recent small series reported 62% of patients with confirmed DOTATATE uptake (27/43) showed imaging evidence of disease response following PRRT [108]. Targeted new PET agents with Ga-68/Lu-177 theranostic pairs are also currently being investigated, including those targeting cholecystokinin-2 (CCK2R) receptors (DOTA-PPF11) and minigastrin (DOTA-MGS5) [99■].

Examples of PET/CT uptake in patients with MTC are shown in Fig. 2.

CONCLUSION

Imaging of thyroid cancer continues to evolve, and accordingly, radiologists and nuclear medicine physicians must be able to provide thoughtful interpretation of such advanced functional imaging techniques to ensure optimal patient outcomes. Furthermore, with rapid developments in the field, a multidisciplinary approach is necessary to ensure appropriate workup, management, and treatment recommendations.

Financial support and sponsorship

Y.K.D. would like to acknowledge grant funding from NCI R01 CA240706.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

1. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. JAMA 2006; 295:2164–2167. [PubMed: 16684987]
2. Lim H, Devesa SS, Sosa JA, et al. Trends in thyroid cancer incidence and mortality in the United States, 1974–2013. JAMA 2017; 317:1338–1348. [PubMed: 28362912]
3. American Cancer Society. Cancer Statistics Center. http://cancerstatisticscenter.cancer.org. Accessed April 17, 2022.
4. Powers AE, Marcadis AR, Lee M, et al. Changes in trends in thyroid cancer incidence in the United States, 1992 to 2016. JAMA 2019; 322:2440–2441. [PubMed: 31860035]
5. Hoang JK, Nguyen XV. Understanding the risks and harms of management of incidental thyroid nodules: a review. JAMA 2017; 143:718–724.
6. Vaccarella S, Franceschi S, Bray F, et al. Worldwide thyroid-cancer epidemic? the increasing impact of overdiagnosis. New Engl J Med 2016; 375:614–617. [PubMed: 27532827]
7■■. Hoang JK, Middleton WD, Tessler FN. Update on ACR TI-RADS: successes, challenges, and future directions, from the AJR special series on radiology reporting and data systems. AJR

Am J Roentgenol 2021; 216:570–578. [PubMed: 33112199] update on performance of TI-RADS ultrasound evaluation of thyroid nodules.

8. Tessler FN, Middleton WD, Grant EG, et al. ACR thyroid imaging, reporting and data system (TI-RADS): white paper of the ACR TI-RADS committee. J Am Coll Radiol 2017; 14:587–595. [PubMed: 28372962]
9. Middleton WD, Teefey SA, Reading CC, et al. Comparison of performance characteristics of American College of Radiology TI-RADS, Korean Society of Thyroid Radiology TIRADS, and American Thyroid Association Guidelines. AJR Am J Roentgenol 2018; 210:1148–1154. [PubMed: 29629797]
10. Grani G, Lamartina L, Ascoli V, et al. Reducing the number of unnecessary thyroid biopsies while improving diagnostic accuracy: toward the 'Right' TIRADS. J Clin Endocrinol Metab 2019; 104:95–102. [PubMed: 30299457]
11. Koseoglu Atilla FD, Ozgen Saydam B, Erarslan NA, et al. Does the ACR TI-RADS scoring allow us to safely avoid unnecessary thyroid biopsy? single center analysis in a large cohort. Endocrine 2018; 61:398–402. [PubMed: 29744655]
12. Middleton WD, Teefey SA, Tessler FN, et al. Analysis of malignant thyroid nodules that do not meet ACR TI-RADS criteria for fine-needle aspiration. AJR Am J rRentgenol 2021; 216:471–478.
13. Grani G, Lamartina L, Cantisani V, et al. Interobserver agreement of various thyroid imaging reporting and data systems. Endocr Connect 2018; 7:1–7. [PubMed: 29196301]
14. Seifert P, Görges R, Zimny M, et al. Interobserver agreement and efficacy of consensus reading in Kwak-, EU-, and ACR-thyroid imaging recording and data systems and ATA guidelines for the ultrasound risk stratification of thyroid nodules. Endocrine 2020; 67:143–154. [PubMed: 31741167]
15. Dong FJ, Li M, Jiao Y, et al. Acoustic radiation force impulse imaging for detecting thyroid nodules: a systematic review and pooled meta-analysis. Med Ultrasonogr 2015; 17:192–199.
16. Hu X, Liu Y, Qian L. Diagnostic potential of real-time elastography (RTE) and shear wave elastography (SWE) to differentiate benign and malignant thyroid nodules: a systematic review and meta-analysis. Medicine 2017; 96:e8282. [PubMed: 29068996]
17. Lin P, Chen M, Liu B, et al. Diagnostic performance of shear wave elastography in the identification of malignant thyroid nodules: a meta-analysis. Eur Radiol 2014; 24:2729–2738. [PubMed: 25113648]
18. Liu BJ, Li DD, Xu HX, et al. Quantitative shear wave velocity measurement on acoustic radiation force impulse elastography for differential diagnosis between benign and malignant thyroid nodules: a meta-analysis. Ultrasound Med Biol 2015; 41:3035–3043. [PubMed: 26371402]
19. Zhan J, Jin JM, Diao XH, Chen Y. Acoustic radiation force impulse imaging (ARFI) for differentiation of benign and malignant thyroid nodules–a meta-analysis. Eur J Radiol 2015; 84:2181–2186. [PubMed: 26259701]
20■. Radzina M, Ratniece M, Putrins DS, et al. Performance of contrast-enhanced ultrasound in thyroid nodules: review of current state and future perspectives. Cancers (Basel) 2021; 13:5469. [PubMed: 34771632] Summary of contrast-enhanced ultrasound of thyroid nodules.
21. Zhang Y, Zhang X, Li J, et al. Contrast-enhanced ultrasound: a valuable modality for extracapsular extension assessment in papillary thyroid cancer. Eur Radiol 2021; 31:4568–4575. [PubMed: 33411051]
22. Zhu C, Zhong L, Lin M, et al. The value of TI-RADS combined with superb micro-vascular imagine in distinguishing benign and malignant thyroid nodules: a meta-analysis. PloS one 2022; 17:e0261521. [PubMed: 35041691]
23. Buda M, Wildman-Tobriner B, Hoang JK, et al. Management of thyroid nodules seen on US images: deep learning may match performance of radiologists. Radiology 2019; 292:695–701. [PubMed: 31287391]
24. Wildman-Tobriner B, Allen BC, Maxfield CM. Common resident errors when interpreting computed tomography of the abdomen and pelvis: a review of types, pitfalls, and strategies for improvement. Curr Probl Diagn Radiol 2019; 48:4–9. [PubMed: 29397268]

25. Benderradji H, Beron A, Wémeau JL, et al. Quantitative dual isotope (123) iodine/(99m)Tc-MIBI scintigraphy: a new approach to rule out malignancy in thyroid nodules. Annales d'endocrinologie 2021; 82:83–91.
26. Corn S, Mitmaker E, Tabah R, et al. Incidental thyroid uptake on PET scanning: epidemiology, clinical significance, and management challenge. J Cancer Metastasis Treat 2021; 7:41.
27■■. Piek MW, de Boer JP, Vriens MR, et al. Retrospective analyses of (18)FDG-PET/CT thyroid incidentaloma in adults: incidence, treatment, and outcome in a tertiary cancer referral center. Thyroid 2021; 31:1715–1722. [PubMed: 34340567] Large study of incidental FDG uptake in thyroid nodules on PET with outcome analysis.
28. Felder GJ, Naeem M, Shady W, et al. Risk stratification of (18)F-fluorodeoxyglucose-avid thyroid nodules based on ACR thyroid imaging reporting and data system. J Am Coll Radiol 2021; 18:388–394. [PubMed: 33137296]
29. Kohlenberg JD, Panda A, Johnson GB, Castro MR. Radiologic and clinicopathologic characteristics of thyroid nodules with focal 68Ga-DOTATATE PET activity. Nucl Med Commun 2021; 42:510–516. [PubMed: 33481508]
30. Nockel P, El Lakis M, Gaitanidis A, et al. Preoperative 18F-FDG PET/CT in pheochromocytomas and paragangliomas allows for precision surgery. Ann Surg 2019; 269:741–747. [PubMed: 29334561]
31. Gossili F, Petersen LJ, Zacho HD. The frequency of thyroid incidental findings and risk of malignancy detected by (68)Ga-labeled prostate-specific membrane antigen PET/CT in prostate cancer. Hell J Nucl Med 2020; 23:240–245. [PubMed: 33306753]
32. Hoang JK, Langer JE, Middleton WD, et al. Managing incidental thyroid nodules detected on imaging: white paper of the ACR Incidental Thyroid Findings Committee. J Am Coll Radiol 2015; 12:143–150. [PubMed: 25456025]
33. Ohori NP, Wolfe J, Carty SE, et al. The influence of the noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) resection diagnosis on the false-positive thyroid cytology rate relates to quality assurance thresholds and the application of NIFTP criteria. Cancer Cytopathol 2017; 125:692–700. [PubMed: 28678437]
34. Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid 2017; 27:1341–1346. [PubMed: 29091573]
35. Hahn SY, Shin JH, Oh YL, et al. Comparison between fine needle aspiration and core needle biopsy for the diagnosis of thyroid nodules: effective indications according to US findings. Sci Rep 2020; 10:4969. [PubMed: 32188891]
36. de Koster EJ, de Geus-Oei LF, Brouwers AH, et al. [(18)F]FDG-PET/CT to prevent futile surgery in indeterminate thyroid nodules: a blinded, randomised controlled multicentre trial. Eur J Nucl Med Mol Imaging 2022; 49:1970–1984. [PubMed: 34981165]
37. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016; 26:1–133. [PubMed: 26462967]
38■. Alabousi M, Alabousi A, Adham S, et al. Diagnostic test accuracy of ultrasonography vs computed tomography for papillary thyroid cancer cervical lymph node metastasis: a systematic review and meta-analysis. JAMA 2022; 148:107–118.Metanalysis comparing ultrasound to neck computed tomorgraphy for thyroid cancer.
39. Mauri G, Hegedüs L, Bandula S, et al. European Thyroid Association and Cardiovascular and Interventional Radiological Society of Europe 2021 Clinical Practice Guideline for the use of minimally invasive treatments in malignant thyroid lesions. Eur Thyroid J 2021; 10:185–197. [PubMed: 34178704]
40. Baloch ZW, Asa SL, Barletta JA, et al. Overview of the 2022 WHO Classification of Thyroid Neoplasms. Endocr Pathol 2022; 33:27–63. [PubMed: 35288841]
41. Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on cancer/tumor-node-metastasis staging system for differentiated and anaplastic thyroid cancer (eighth edition): what changed and why? Thyroid 2017; 27:751–756. [PubMed: 28463585]

42. Dekker BL, Links MH, Muller Kobold AC, et al. Low-iodine diet of 4 days is sufficient preparation for 131I therapy in differentiated thyroid cancer patients. J Clin Endocrinol Metab 2022; 107:e604–e611. [PubMed: 34534327]
43. Klain M, Zampella E, Nappi C, et al. Advances in functional imaging of differentiated thyroid cancer. Cancers (Basel) 2021; 13:4748. [PubMed: 34638232]
44. Leenhardt L, Leboulleux S, Bournaud C, et al. Recombinant thyrotropin vs levothyroxine withdrawal in 131i therapy of n1 thyroid cancer: a large matched cohort study (ThyrNod). J Clin Endocrinol Metab 2019; 104:1020–1028. [PubMed: 30398518]
45. Schlumberger M, Leboulleux S. Current practice in patients with differentiated thyroid cancer. Nat Rev Endocrinol 2021; 17:176–188. [PubMed: 33339988]
46. Avram AM, Fig LM, Frey KA, et al. Preablation 131-I scans with SPECT/CT in postoperative thyroid cancer patients: what is the impact on staging? J Clin Endocrinol Metab 2013; 98:1163–1171. [PubMed: 23430789]
47. Tuttle RM, Ahuja S, Avram AM, et al. Controversies, consensus, and collaboration in the use of (131)i therapy in differentiated thyroid cancer: a joint statement from the American Thyroid Association, the European Association of Nuclear Medicine, the Society of Nuclear Medicine and Molecular Imaging, and the European Thyroid Association. Thyroid 2019; 29:461–470. [PubMed: 30900516]
48. Silberstein EB, Alavi A, Balon HR, et al. The SNMMI practice guideline for therapy of thyroid disease with 131I 3.0. Soc Nucl Med 2012; 53:1633–1651.
49. Alan Selcuk N, Toklu T, Beykan S, Karaaslan SI. Evaluation of the dosimetry approaches in ablation treatment of thyroid cancer. J Appl Clin Med Phys 2018; 19:134–140. [PubMed: 29858536]
50■■. Singer MC, Marchal F, Angelos P, et al. Salivary and lacrimal dysfunction after radioactive iodine for differentiated thyroid cancer: American Head and Neck Society Endocrine Surgery Section and Salivary Gland Section joint multidisciplinary clinical consensus statement of otolaryngology, ophthalmology, nuclear medicine and endocrinology. Head Neck 2020; 42:3446–3459. [PubMed: 32812307] Consensus guidelines on adverse radioiodine effects to the salivary and lacrimal glands.
51. Van Nostrand D. Sites performing dosimetry for selection of activity for (131)I therapy for differentiated thyroid cancer. J Nucl Med 2019; 60:20N–22N.
52■. Lawhn-Heath C, Hope TA, Martinez J, et al. Dosimetry in radionuclide therapy: the clinical role of measuring radiation dose. Lancet Oncol 2022; 23:e75–e87. [PubMed: 35114134] Concise review on dosimetry methodology.
53. Benua RS, Cicale NR, Sonenberg M, Rawson RW. The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer. Am J Roentgenol Radium Ther Nucl Med 1962; 87:171–182.
54. Atkins F, Van Nostrand D, Moreau S, et al. Validation of a simple thyroid cancer dosimetry model based on the fractional whole-body retention at 48 hours post-administration of (131)I. Thyroid 2015; 25:1347–1350. [PubMed: 26357962]
55. Klubo-Gwiezdzinska J, Van Nostrand D, Atkins F, et al. Efficacy of dosimetric versus empiric prescribed activity of 131I for therapy of differentiated thyroid cancer. J Clin Endocrinol Metabolism 2011; 96:3217–3225.
56. Deandreis D, Rubino C, Tala H, et al. Comparison of empiric versus whole-body/-blood clearance dosimetry-based approach to radioactive iodine treatment in patients with metastases from differentiated thyroid cancer. Soc Nucl Med 2017; 58:717–722.
57. Maxon HR, Thomas SR, Hertzberg VS, et al. Relation between effective radiation dose and outcome of radioiodine therapy for thyroid cancer. New Engl J Med 1983; 309:937–941. [PubMed: 6621620]
58. Abuqbeitah M, Demir M, Kabasakal L, et al. Indirect assessment of the maximum empirical activity (250 mCi) with respect to dosimetry concepts in radioiodine therapy of metastatic differentiated thyroid cancer. Nucl Med Commun 2018; 39:969–975. [PubMed: 30180046]
59. Sun F, Gerrard GE, Roberts JK, et al. Ten year experience of radioiodine dosimetry: is it useful in the management of metastatic differentiated thyroid cancer? Clin Oncology 2017; 29:310–315.

60. Jentzen W, Freudenberg L, Eising EG, et al. Optimized 124I PET dosimetry protocol for radioiodine therapy of differentiated thyroid cancer. Soc Nucl Med 2008; 49:1017–1023.
61. Sgouros G, Kolbert KS, Sheikh A, et al. Patient-specific dosimetry for 131I thyroid cancer therapy using 124I PET and 3-dimensional-internal dosimetry (3D-ID) software. J Nucl Med 2004; 45:1366–1372. [PubMed: 15299063]
62. Preylowski V, Schlögl S, Schoenahl F, et al. Is the image quality of I-124-PET impaired by an automatic correction of prompt gammas? PloS one 2013; 8:e71729. [PubMed: 24014105]
63. Ho AL, Grewal RK, Leboeuf R, et al. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. New Engl J Med 2013; 368:623–632. [PubMed: 23406027]
64. Dunn LA, Sherman EJ, Baxi SS, et al. Vemurafenib redifferentiation of BRAF mutant, RAI-refractory thyroid cancers. J Clin Endocrinol Metab 2019; 104:1417–1428. [PubMed: 30256977]
65. Bal C, Chakraborty D, Khan D. Positron emission tomography/computed tomography in thyroid cancer. PET Clin 2022; 17:265–283. [PubMed: 35256297]
66. Tramontin MY, Nobre GM, Lopes M, et al. High thyroglobulin and negative whole-body scan: no long-term benefit of empiric radioiodine therapy. Endocrine 2021; 73:398–406. [PubMed: 33570724]
67. Feine U, Lietzenmayer R, Hanke JP, et al. Fluorine-18-FDG and iodine-131-iodide uptake in thyroid cancer. Soc Nucl Med 1996; 37:1468–1472.
68. Deandreis D, Al Ghuzlan A, Leboulleux S, et al. Do histological, immunohistochemical, and metabolic (radioiodine and fluorodeoxyglucose uptakes) patterns of metastatic thyroid cancer correlate with patient outcome? Endocr Relat Cancer 2011; 18:159–169. [PubMed: 21118976]
69. Nagamachi S, Wakamatsu H, Kiyohara S, et al. Comparison of diagnostic and prognostic capabilities of ^{18}F-FDG-PET/CT, ^{131}I-scintigraphy, and diffusion-weighted magnetic resonance imaging for postoperative thyroid cancer. Jpn J Radiol 2011; 29:413–422. [PubMed: 21786097]
70. Robbins RJ, Wan Q, Grewal RK, et al. Real-time prognosis for metastatic thyroid carcinoma based on 2-[18F]fluoro-2-deoxy-D-glucose-positron emission tomography scanning. metabolism Clin Endocrinol Metab 2006; 91:498–505.
71. Vural GU, Akkas BE, Ercakmak N, et al. Prognostic significance of FDG PET/CT on the follow-up of patients of differentiated thyroid carcinoma with negative 131I whole-body scan and elevated thyroglobulin levels: correlation with clinical and histopathologic characteristics and long-term follow-up data. Clin Nucl Med 2012; 37:953–959. [PubMed: 22899202]
72. Dong MJ, Liu ZF, Zhao K, et al. Value of 18F-FDG-PET/PET-CT in differentiated thyroid carcinoma with radioiodine-negative whole-body scan: a meta-analysis. Nucl Med Commun 2009; 30:639–650. [PubMed: 19512954]
73. Haslerud T, Brauckhoff K, Reisæter L, et al. F18-FDG-PET for recurrent differentiated thyroid cancer: a systematic meta-analysis. Acta radiologica (Stockholm, Sweden: 1987) 2016; 57:1193–1200. [PubMed: 26163534]
74. Miller ME, Chen Q, Elashoff D, et al. Positron emission tomography and positron emission tomography-CT evaluation for recurrent papillary thyroid carcinoma: meta-analysis and literature review. Head Neck 2011; 33:562–565. [PubMed: 20665734]
75. Abraham T, Schöder H. Thyroid cancer–indications and opportunities for positron emission tomography/computed tomography imaging. Sem Nucl Medicine 2011; 41:121–138.
76. Giovanella L, Ceriani L, De Palma D, et al. Relationship between serum thyroglobulin and 18FDG-PET/CT in 131I-negative differentiated thyroid carcinomas. Head Neck 2012; 34:626–631. [PubMed: 21850699]
77. Giovanella L, Trimboli P, Verburg FA, et al. Thyroglobulin levels and thyroglobulin doubling time independently predict a positive 18F-FDG PET/CT scan in patients with biochemical recurrence of differentiated thyroid carcinoma. Eur J Nucl Medicine Mol Imaging 2013; 40:874–880.
78. Ahmaddy F, Burgard C, Beyer L, et al. (18)F-FDG-PET/CT in patients with advanced, radioiodine refractory thyroid cancer treated with lenvatinib. Cancers (Basel) 2021; 13:317. [PubMed: 33467085]
79. Vrachimis A, Burg MC, Wenning C, et al. [(18)F]FDG PET/CT outperforms [(18)F]FDG PET/MRI in differentiated thyroid cancer. Eur J Nucl Med Mol Imaging 2016; 43:212–220. [PubMed: 26419851]

80. Santhanam P, Khthir R, Solnes LB, Ladenson PW. The relationship of BRAF (v600e) mutation status to FDG PET/CT avidity in thyroid cancer: a review and meta-analysis. Endocr Pract 2018; 24:21–26. [PubMed: 29144823]
81. Lee JW, Lee SM, Lee DH, Kim YJ. Clinical utility of 18F-FDG PET/CT concurrent with 131I therapy in intermediate-to-high-risk patients with differentiated thyroid cancer: dual-center experience with 286 patientsJT J Nucl Med. 2013; 54:1230–1236. [PubMed: 23813775]
82. Pryma DA, Schöder H, Gönen M, et al. Diagnostic accuracy and prognostic value of 18F-FDG PET in Hürthle cell thyroid cancer patients. J Nucl Med 2006; 47:1260–1266. [PubMed: 16883003]
83. Kim BS, Kim SJ, Kim IJ, et al. Factors associated with positive F-18 flurodeoxyglucose positron emission tomography before thyroidectomy in patients with papillary thyroid carcinoma. Thyroid 2012; 22:725–729. [PubMed: 22524470]
84. Kundu P, Lata S, Sharma P, et al. Prospective evaluation of (68)Ga-DOTANOC PET-CT in differentiated thyroid cancer patients with raised thyroglobulin and negative (131)I-whole body scan: comparison with (18)F-FDG PET-CT. Eur J Nucl Med Mol Imaging 2014; 41:1354–1362. [PubMed: 24562651]
85. Heitkötter B, Steinestel K, Trautmann M, et al. Neovascular PSMA expression is a common feature in malignant neoplasms of the thyroid. Oncotarget 2018; 9:9867–9874. [PubMed: 29515776]
86. Fu H, Fu J, Huang J, et al. 68Ga-FAPI PET/CT in thyroid cancer with thyroglobulin elevation and negative iodine scintigraphy. Clin Nucl Medicine 2021; 46:427–430.
87■. Pitalua-Cortes Q, García-Perez FO, Vargas-Ahumada J, et al. Head-to-head comparison of (68)Ga-PSMA-11 and (131)I in the follow-up of well differentiated metastatic thyroid cancer: a new potential theragnostic agent. Front Endocrinol 2021; 12:794759.Original study of PSMA and DOTATATE PET in thyroid cancer.
88. Verma P, Malhotra G, Meshram V, et al. Prostate-specific membrane antigen expression in patients with differentiated thyroid cancer with thyroglobulin elevation and negative iodine scintigraphy using 68Ga-PSMA-HBED-CC PET/CT. Clin Nucl Med 2021; 46:e406–e409. [PubMed: 33883490]
89. Parihar AS, Mittal BR, Kumar R, et al. (68)Ga-DOTA-RGD(2) positron emission tomography/computed tomography in radioiodine refractory thyroid cancer: prospective comparison of diagnostic accuracy with (18)F-FDG positron emission tomography/computed tomography and evaluation toward potential theranostics. Thyroid 2020; 30:557–567. [PubMed: 31870227]
90. Dittmann M, Gonzalez Carvalho JM, Rahbar K, et al. Incremental diagnostic value of [(18)F]tetrafluoroborate PET-CT compared to [(131)I]iodine scintigraphy in recurrent differentiated thyroid cancer. Eur J Nucl Med Mol Imaging 2020; 47:2639–2646. [PubMed: 32248325]
91. Bible KC, Kebebew E, Brierley J, et al. 2021 American Thyroid Association Guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2021; 31:337–386. [PubMed: 33728999]
92. Bogsrud TV, Karantanis D, Nathan MA, et al. 18F-FDG PET in the management of patients with anaplastic thyroid carcinoma. Thyroid 2008; 18:713–719. [PubMed: 18630999]
93. Poisson T, Deandreis D, Leboulleux S, et al. 18F-fluorodeoxyglucose positron emission tomography and computed tomography in anaplastic thyroid cancer. Eur J Nucl Med Mol Imaging 2010; 37:2277–2285. [PubMed: 20694463]
94■. Kim HJ, Chang HS, Ryu YH. Prognostic role of pre-treatment [(18)F]FDG PET/CT in patients with anaplastic thyroid cancer. Cancers (Basel) 2021; 13:4228. [PubMed: 34439382] Original study of FDG PET in anaplastic thyroid cancer.
95. Lawhn-Heath C, Yom SS, Liu C, et al. Gallium-68 prostate-specific membrane antigen ([(68)Ga]Ga-PSMA-11) PET for imaging of thyroid cancer: a feasibility study. EJNMMI Res 2020; 10:128. [PubMed: 33090273]
96. Wächter S, Di Fazio P, Maurer E, et al. Prostate-specific membrane antigen in anaplastic and poorly differentiated thyroid cancer-a new diagnostic and therapeutic target? Cancers (Basel) 2021; 13:5688. [PubMed: 34830843]

97. Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 2015; 25:567–610. [PubMed: 25810047]

98. Kihara M, Hirokawa M, Kudo T, et al. Calcitonin measurement in fine-needle aspirate washout fluid by electrochemiluminescence immunoassay for thyroid tumors. Thyroid Res 2018; 11:15. [PubMed: 30450128]

99■. Asa S, Sonmezoglu K, Uslu-Besli L, et al. Evaluation of F-18 DOPA PET/CT in the detection of recurrent or metastatic medullary thyroid carcinoma: comparison with GA-68 DOTA-TATE PET/CT. Ann Nucl Med 2021; 35:900–915. [PubMed: 33993425] Original study of F-DOPA and DOTATATE PET in medullary thyroid cancer.

100. Castinetti F, Taïeb D. Positron emission tomography imaging in medullary thyroid carcinoma: time for reappraisal? Thyroid 2021; 31:151–155. [PubMed: 33191866]

101. 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; 45:341–348. [PubMed: 32049723]

102. 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; 19:1290–1299. [PubMed: 22819076]

103. 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; 16:362–372. [PubMed: 29518756]

104. Rubello D, Rampin L, Nanni C, et al. The role of 18F-FDG PET/CT in detecting metastatic deposits of recurrent medullary thyroid carcinoma: a prospective study. Eur J Surg Oncol 2008; 34:581–586. [PubMed: 17892923]

105. Saponjski J, Macut D, Saranovic DS, et al. Clinical relevance of (18)F-FDG PET/CT in the postoperative follow-up of patients with history of medullary thyroid cancer. Radiol Oncol 2020; 55:18–25. [PubMed: 33885241]

106. Pajak C, Cadili L, Nabata K, Wiseman SM. (68)Ga-DOTATATE-PET shows promise for diagnosis of recurrent or persistent medullary thyroid cancer: A systematic review. Am J Surg 2022. S0002-9610(22)00224-0. Online before print.

107. Tuncel M, Kılıçkap S, Süslü N. Clinical impact of (68)Ga-DOTATATE PET-CT imaging in patients with medullary thyroid cancer. Ann Nucl Med 2020; 34:663–674. [PubMed: 32602032]

108. Parghane RV, Naik C, Talole S, et al. Clinical utility of (177) Lu-DOTATATE PRRT in somatostatin receptor-positive metastatic medullary carcinoma of thyroid patients with assessment of efficacy, survival analysis, prognostic variables, and toxicity. Head Neck 2020; 42:401–416. [PubMed: 31755622]

KEY POINTS

- Improvements in ultrasound technology and TI-RADS risk stratification have influenced management of thyroid nodules, optimizing radiologic diagnosis of clinically relevant cancers.
- I-131 scintigraphy and RAI therapy continues to play a crucial role in patients with DTC, enabling remnant ablation and therapy for patients at higher risk for recurrence, and both I-131 scintigraphy and I-124 PET/CT, allow dosimetry for personalized management.
- F18-FDG PET/CT is valuable for recurrent/noniodine avid DTC, all PDTC/ATC, and recurrent medullary thyroid cancer (MTC), with metabolic uptake indicating poor prognosis in these thyroid cancers.
- F18-DOPA PET/CT is valuable for diagnosing recurrent MTC with the highest sensitivity.
- Ga68-DOTATATE PET has potential applications in MTC or noniodine avid thyroid cancers; with potential role for identifying patients who may benefit from PRRT.

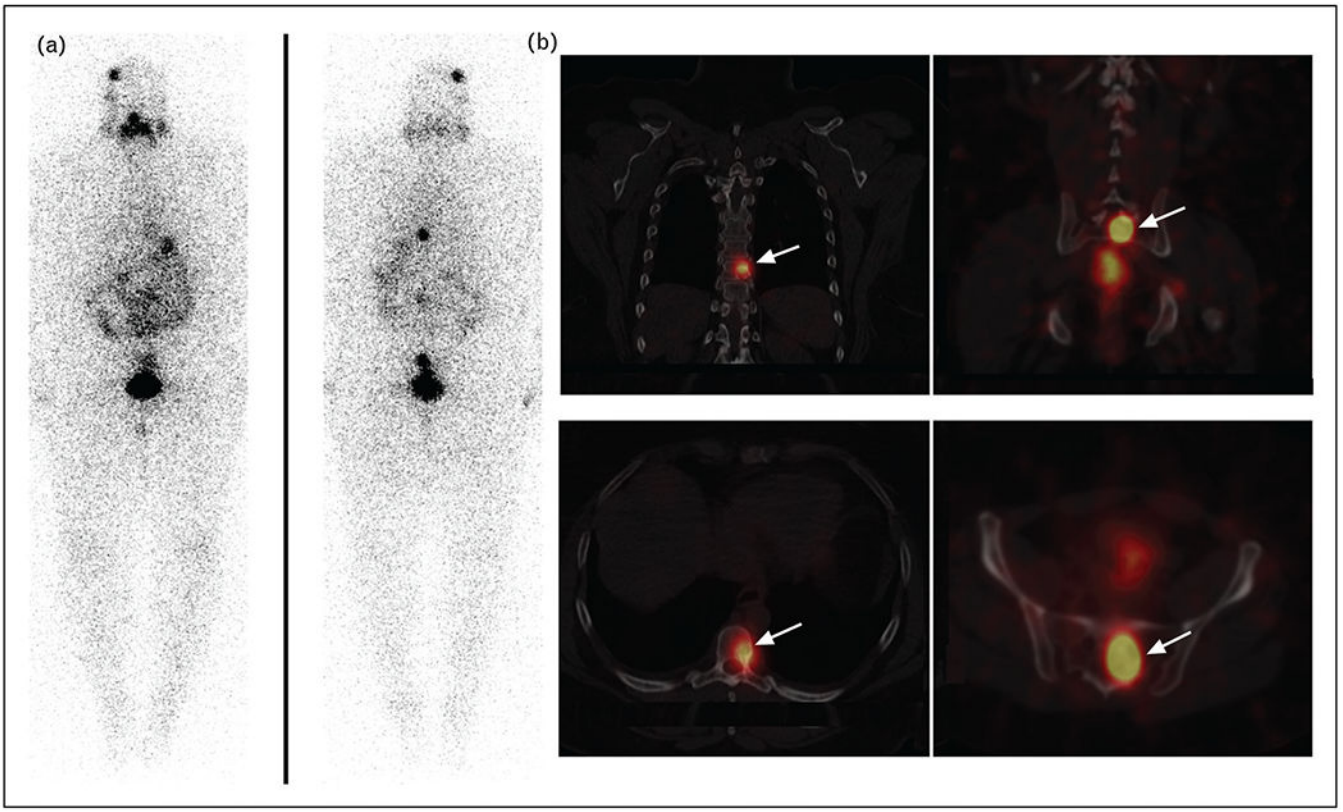

FIGURE 1.

Hypothyroid diagnostic I-131 scan (1 mCi dose) (a) anterior and posterior whole body and (b) fused axial SPECT/computed tomography in a 38 year old female with an 8 cm invasive follicular thyroid cancer, status posttotal thyroidectomy and 120 mCi I-131, now presents with for second radioiodine therapy with dosimetry-guidance. Thyroglobulin was 22 ng/mL with a TSH of 37 mIU/L. Stage 2, T3, N1, M1 disease. Planar scan demonstrates iodine-avid disease in the lower thoracic spine (T8), lumbar spine (L2), sacrum, left iliac crest, left acetabulum, and calvarium; representative examples are shown with arrows on SPECT/ computed tomography. Full body dosimetry with three time points was performed (24 h, 48 h, 72 h). The blood dosimetry estimated 0.35 cGy per mCi, indicating maximum of 565 mCi I-131 to limit blood exposure to < 2 Gy. Based on dosimetry, 350 mCi dose of I-131 was administered, which was tolerated and there was a durable response.

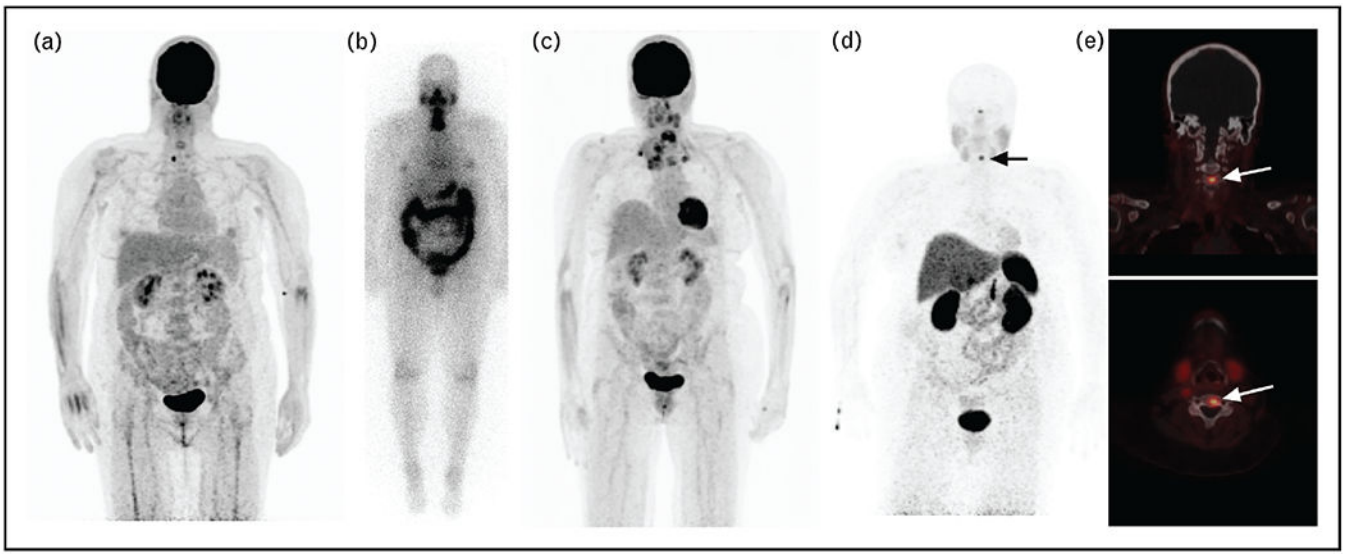

FIGURE 2.

(a) F18-FDG PET MIPS and (b) I-131 diagnostic whole body scan in a 54 year old. female with both medullary thyroid cancer and papillary thyroid cancer, an unusual combination. Patient had a strong family history of MEN2, elevated CEA levels to 2.1 pg/mL, and genetic testing was positive for RET mutation. Initial F18-FDG PET scan (a) was performed, showing a hypermetabolic right thyroid lobe nodule concerning for malignancy. Total thyroidectomy was performed. The surgically resected pathology specimen demonstrated a 2.0 cm classic variant papillary thyroid cancer in the right thyroid lobe (corresponding to the FDG-avid nodule), 1 +/26 metastatic lymph nodes with central compartment lymph nodes, and a 1.8 cm medullary thyroid carcinoma confined to the left lobe of the thyroid (no PET correlate). Her I-131 thyroid cancer scanned showed remnant thyroid tissue and she received medium dose RAI therapy to facilitate surveillance of her papillary thyroid cancer. (c) F18-FDG PET scan in a 61 year old female with medullary thyroid carcinoma. There is uptake in neoplastic disease in the right thyroid bed, bilateral neck and thoracic inlet nodes. Her calcitonin was elevated at 102 pg/mL and CEA 6 ng/mL. She had a notable prior history of total thyroidectomy and bilateral central compartment dissection for MTC 20years earlier. She had a recurrence 11 years earlier with multiple re-excisions of left supraclavicular lymph nodes. She had further recurrence and reoperative neck dissection of bilateral cervical and supraclavicular lymph nodes followed by XRT with 70 Gy in 35 fractions to residual disease in the neck and superior mediastinum 6years earlier. She also had a second course of XRT 1 year earlier. (d) Ga-68-DOTATATE PET MIPS and (e) axial and coronal fused PET/CT images in a 63 y.o. female with medullary thyroid cancer. There is somatostatin receptor type 2 expression in bony metastases with focal uptake in the skull and cervical spine (arrows). Her calcitonin was elevated at 884 pg/mL and CEA 6 ng/mL at time of imaging. CEA, carcinoembryonic antigen; CT, computed tomography; 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)--octreotate (DOTATATE); FDG, 18F-fluorodeoxyglucose; MIP, maximum intensity projection; PECT, positron emission tomography.