Multimodal imaging of thyroid cancer

Katrin Brauckhoff[a,b] and Martin Biermann[c,d]

Purpose of review
Thyroid cancer is the most common endocrine cancer in adults with rising incidence. Challenges in imaging thyroid cancer are twofold: distinguishing thyroid cancer from benign thyroid nodules, which occur in 50% of the population over 50 years; and correct staging of thyroid cancer to facilitate appropriate radical surgery in a single session. The clinical management of thyroid cancer patients has been covered in detail by the 2015 guidelines of the American Thyroid Association (ATA). The purpose of this review is to state the principles underlying optimal multimodal imaging of thyroid cancer and aid clinicians in avoiding important pitfalls.

Recent findings
Recent additions to the literature include assessment of ultrasound-based scoring systems to improve selection of nodules for fine needle biopsy (FNB) and the evaluation of new radioactive tracers for imaging thyroid cancer.

Summary
The mainstay of diagnosing thyroid cancer is thyroid ultrasound with ultrasound-guided FNB. Contrast-enhanced computed tomography and PET with [18F]-fluorodeoxyglucose (FDG) and MRI are reserved for advanced and/or recurrent cases of differentiated thyroid cancer and anaplastic thyroid cancer, while [18F]FDOPA and [68Ga]DOTATOC are the preferred tracers for medullary thyroid cancer.

Keywords
adult, follicular, medullary, papillary, thyroid cancer, thyroid nodule

INTRODUCTION

The greatest challenge in imaging thyroid cancer is distinguishing thyroid cancer from benign disease in the thyroid gland. Although thyroid cancer represents the most common endocrine malignancy in adults [1], it is still rare compared with benign thyroid nodules, which are seen on high-resolution ultrasound in more than 30% of men and 50% of women over 50 years [2]. The prevalence of thyroid cancer in typical patient cohorts may range from 1% in a general practice/radiology setting to 10% or higher in a specialist clinic [3], depending to a large extent on the referral pattern and the type of institution. When a patient presents with symptoms such as a palpable lateral neck mass or hoarseness, or has a genetic syndrome, the likelihood for malignancy is markedly increased. The clinical management of patients suspected for thyroid cancer is described in detail in the current guidelines of the American Thyroid Association (ATA) [4].

The present review will focus on imaging of the four common cancer types in the thyroid gland: papillary (PTC), follicular (FTC), poorly differentiated (PDTC) and anaplastic (ATC), as well as medullary (MTC) (Table 1) [5–7,8■,9–11]. PTC and FTC are both derived from the follicular epithelium. They share the ability to take up iodine due the expression of sodium-iodide-symporter (NIS) and are often grouped together as differentiated thyroid cancer (DTC) [4,12]. Generally, thyroid cancer imaging is performed in three different scenarios: primary detection and initial staging of thyroid cancer, to monitor therapy after surgery and to diagnose suspected recurrence.

[a]Department of Breast and Endocrine Surgery, Haukeland University Hospital, [b]Department of Clinical Science, University of Bergen, [c]Nuclear Medicine/PET-center, Department of Radiology, Haukeland University Hospital and [d]Department of Clinical Medicine, University of Bergen, Bergen, Norway

Correspondence to Martin Biermann, Nuclear Medicine/PET-centre, Department of Radiology, Parkbygget, Haukeland University Hospital, Jonas Liesvei, N-5021 Bergen, Norway. Tel: +47 5597 7643; e-mail: martin.biermann@uib.no

IMAGING OF DIFFERENTIATED THYROID CANCER: PRIMARY DETECTION AND STAGING

Primary imaging for DTC serves to establish the diagnosis of DTC, exclude malignancy in the contralateral thyroid lobe if hemithyroidectomy is considered, detect local invasion, and identify and map lymph node metastases to the lateral neck.

The mainstay for primary diagnosis thyroid cancer is high-resolution ultrasound of the thyroid gland including ultrasound-guided fine needle biopsy (FNB) of any suspect thyroid nodules [4]. Five criteria on brightness-mode (B-mode) ultrasound help identify malignancy in thyroid nodules: solidity, hypoechogenecity, taller than wide shape (anterior-posterior diameter larger than width in an axial scan; N. B. 92% of isthmic PTC are wider than tall [13]), irregular margin, and macro- and micro-calcification [14,15]. Note that follicular neoplasms including FTC often have a different appearance as a solitary, well defined, solid, homogeneous, isoechoic or hypoechoic nodule, with a peripheral halo,

parallel orientation to the skin surface and no lymph node enlargement [8■,16].

The major new advance in recent years has been the development of easy to use classification systems for thyroid nodules on thyroid ultrasound. The following dominate: The classifications proposed by the ATA [4] and American Association of Clinical Endocrinologists (AACE) [17], and the Thyroid Imaging Reporting and Data Systems (TIRADS) released by the Korean Society of Thyroid Radiology (K-TIRADS) [18], the European Thyroid Association (EU-TIRADS) [14] and the American College of Radiology (ACR-TIRADS) [15,19■]. In a recent meta-analysis comparing the performance of the three TIRADS, categories 4 and 5 had a sensitivity of about 90% for the detection of DTC with specificities between 50 and 60% [20]. In a recent prospective study comparing five common systems side-by-side with thyroid cytology as independent reference standard, ACR-TIRADS was the most specific [20]. In our opinion, it is also the easiest to apply and to teach.

Several other criteria of malignancy are not included in the above systems. Capsular abutment and loss of the hyperechogenic thyroid capsule may indicate local invasion [21]. Hard texture on ultrasound elastography and central vessels on Doppler ultrasound are rather machine-dependent [14,15]. Contrast-enhanced ultrasound, which is useful for visualization of parathyroid glands [22], entails additional costs for the contrast agent while it does not obviate FNB.

None of the common TIRADS take into account the functional state of a thyroid nodule. ATA and AACE guidelines recommend performing thyroid scintigraphy in addition to ultrasound in all patients evaluated for thyroid nodules who have subnormal serum thyrotropin (TSH) [4,17]. Hyperfunctioning 'hot' nodules are difficult to distinguish from hypofunctioning 'cold' nodules based on ultrasound alone (Fig. 1), and ultrasound classification systems

Table 1. Types of thyroid cancer

Thyroid cancer type	Origin	Relative incidence (%) [5]	Tumor marker	Iodine uptake	Heredity	Multifocal	LN met. [7,9]	Distant met.	5-year survival [6]
Differentiated									
Papillary	Follicular epithelium	90	Thyroglobulin	+	rare	+	++	Lung (miliary)	>95
Follicular		6		+		–	–	Lung, skeleton	>95
Poorly differentiated and anaplastic		1	–	–		(+)	+	Lung, skeleton, liver, brain	<10
Medullary	C-cell	2	Calcitonin, CEA	–	MEN II (30%)	+	+++	Lung, skeleton, liver	82

CEA, carcinoembryonic antigen; MEN, multiple endocrine neoplasia; met., metastases.
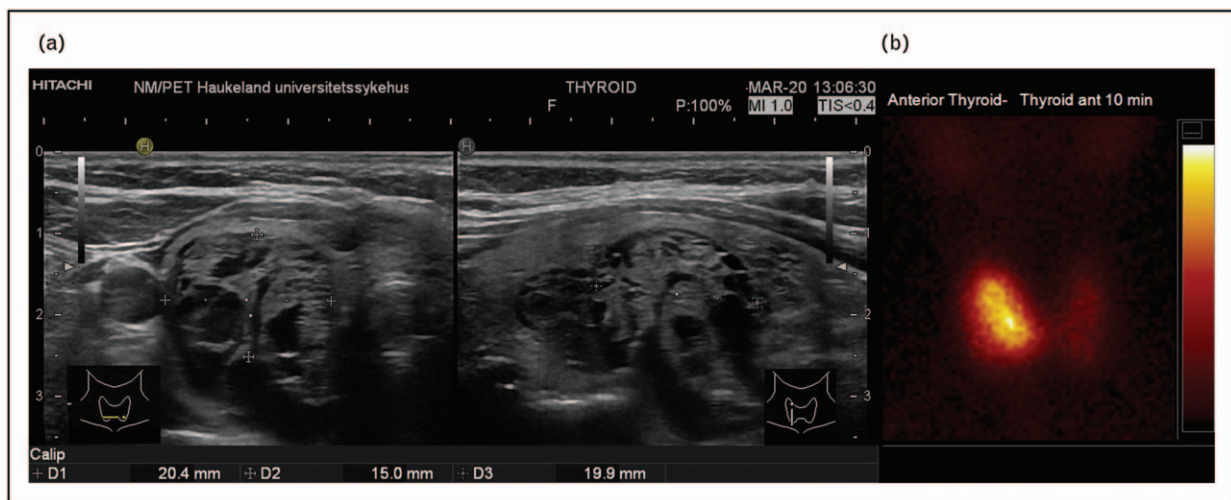
FIGURE 1. A 71-year-old woman referred for thyroid ultrasound and FNB because of a thyroid nodule detected on computed tomography. The patient's serum TSH of 0.2 μU/ml had not been not considered in the referral. Thyroid ultrasound (a) revealed a conglomerate of hypoechogenic nodules in the right thyroid lobe. ACR-TIRADS recommends FNB for this thyroid nodule. Scintigraphy (b) showed that the nodules were toxic, obviating the need for FNB. The patient was treated with radioiodine. FNB, fine needle biopsy. Adapted with permission from [25].

will recommend FNB in at least 25% [23■,24,25] even though hot nodules are nearly always benign [26,27]. Reversely, focal uptake of [^{18}F]fluorodeoxyglucose (FDG) on general oncology imaging [28] and of [^{99m}Tc]MIBI on parathyroid imaging [29] indicates thyroid malignancy (mostly PTC) in up to 30% of cases. The prognostic relevance of coincidently discovered secondary thyroid cancer is unclear [30,31]. A recent study suggests that EU-TIRADS may help avoid unnecessary FNB among FDG-positive nodules [32,33].

From a size of 10 mm and above, every suspicious thyroid nodule should undergo ultrasound-guided FNB [4]. Multinodular goiter does not appear to increase of risk DTC *per se* [34]. A pragmatic approach is to take FNB of the three most suspicious nodules [14]. The optimal technique for FNB is hotly debated. We prefer non-aspiration FNB, using three to four needle passes under local anaesthesia [35,36].

ATA guidelines recommend the Bethesda classification for thyroid cytology (Table 2) [37–39]. FNB works best for PTC, which has a characteristic appearance on cytology (Fig. 2). Cytological diagnosis of FTC is impossible, as the differential diagnosis of FTC versus follicular adenoma relies on the detection of vascular and or/or capsular invasion in a histological specimen. In both entities, cytology will only show varying degrees of atypia [39]. Similarly, the diagnosis of follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), a benign tumour, requires histopathology [39]. Finally, the cytological appearance of MTC is protean, and the follicular variant of PTC may be difficult to differentiate from follicular neoplasms [39].

Bethesda V and VI nodules will usually be treated by surgery with the possible exception of solitary PTC less than 10 mm in the absence of

Table 2. Bethesda-system for thyroid cytology [39]

Category	Designation	Risk of malignancy	Estimated frequency	Recommended
I	Nondiagnostic	5–10%	3%	Repeat FNB
II	Benign	0–3%	55%	No follow-up
III	Atypia	6–18%	7%	Repeat FNB
IV	Follicular neoplasm	10–40%	23%	Repeat FNB & molecular testing
V	suspicious	45–60%	6%	Hemithyroidectomy
VI	malignant	94–96%	5%	Total thyroidectomy

Estimated frequencies are highly dependent on the referral practice, while the frequency of Bethesda I is strongly related to the dexterity of the US operator [4,38].
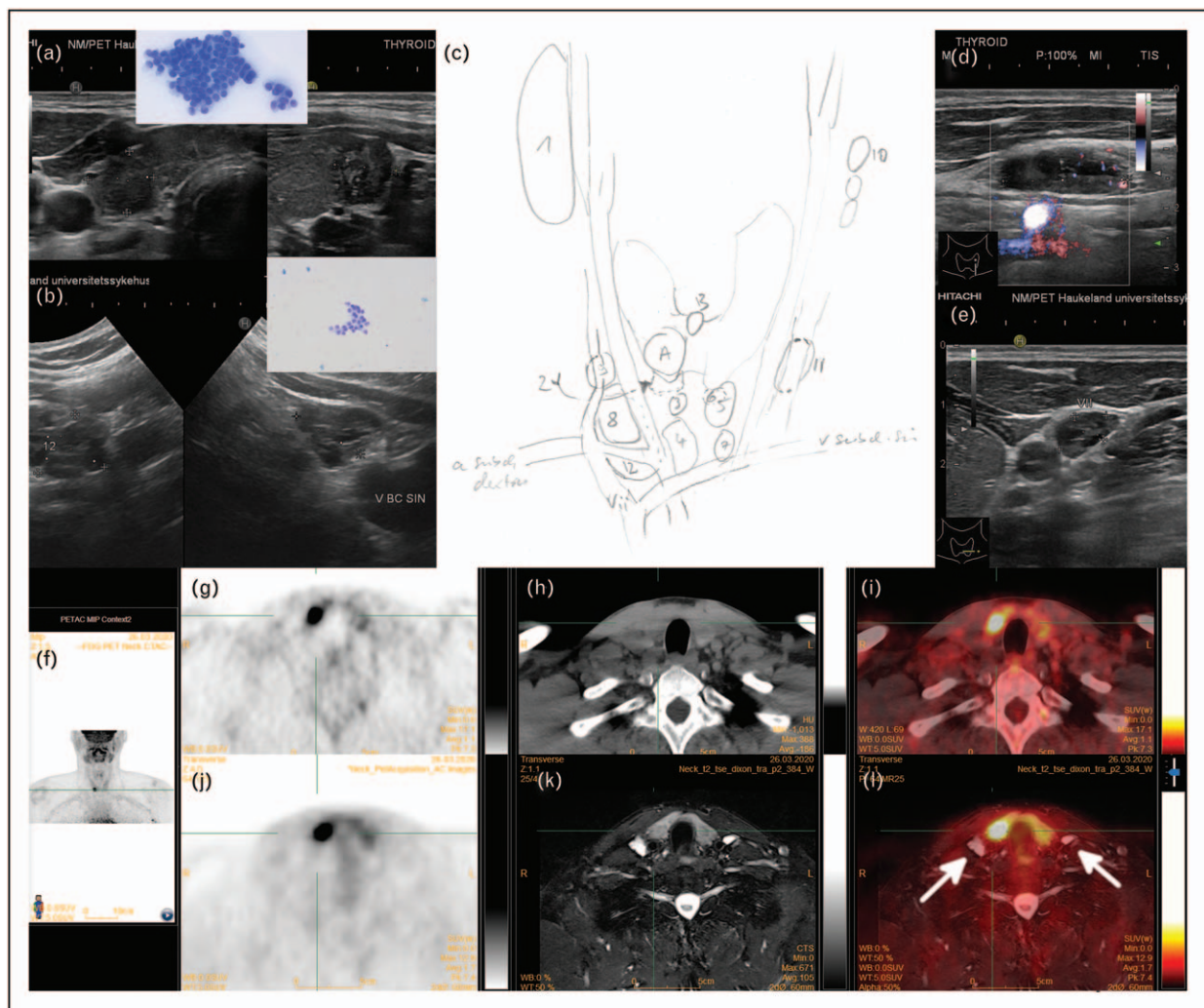FNB, fine needle biopsy.

FIGURE 2. A 34-year-old man presenting with a right lateral neck mass. Contrast-enhanced CT requested by the initially consulted otorhinolaryngologist had revealed multiple lesions in the right lateral neck. Ultrasound at our centre showed a 10 mm hypoechoic nodule 'A' (a) in the right thyroid lobe and multiple cystic LN on both sides of the neck (b–e). FNB of thyroid nodule 'A' (inset panel) and right cervical LN #8 (inset panel b) established the diagnosis of PTC. Thyroglobulin in the aspirate from LN #8 was more than 2000 ng/l. [^{18}F]FDG-PET/CT (f–i) revealed uptake only in thyroid nodule 'A' but not in the cystic LN. CT without intravenous contrast (h) did not add any relevant diagnostic information. On PET/MR (panels J-L), all cystic LN (arrows in panel l) were hyperintense on T2-weighted series. This helped us clarify the difficult anatomic relationships around LN #12 (b). Total thyroidectomy with systematic LN dissection confirmed a 12 mm PTC in the right thyroid lobe and LN metastases in 20/29 LN in the central, 4/12 in the right and 2/10 left neck, respectively. FNB, fine needle biopsy; LN, lymph node.

suspicious lymph nodes [40]. Categories Bethesda III and IV are 'cytologically indeterminate'. Bethesda III nodules should primarily undergo repeat cytology. The goal of category IV is to identify all potential follicular carcinomas, usually leading to hemithyroidectomy. ATA guidelines recommend molecular testing – when available – to rule in and out malignancy [4]. When there is a possibility for PTC, we routinely analyse samples for a somatic BRAF mutation. When positive, this will establish the diagnosis of PTC with more than 99% specificity (rule-in test). Rule-out-testing to exclude

malignancy in Bethesda III and IV nodules is expensive [41]. Functional imaging with [^{18}F]FDG-PET [42,43] and [^{99m}Tc]MIBI [44] will however have similar diagnostic performance. Cytology is unreliable for the detection of MTC. In our institution, we have chosen to screen all patients scheduled for surgery for elevated serum calcitonin. Likewise, cytology cannot be relied on to identify parathyroid adenomas [45]. In patients under evaluation for hyperparathyroidism, we therefore routinely analyse the washout from the FNB needle for parathyroid hormone [36,46].
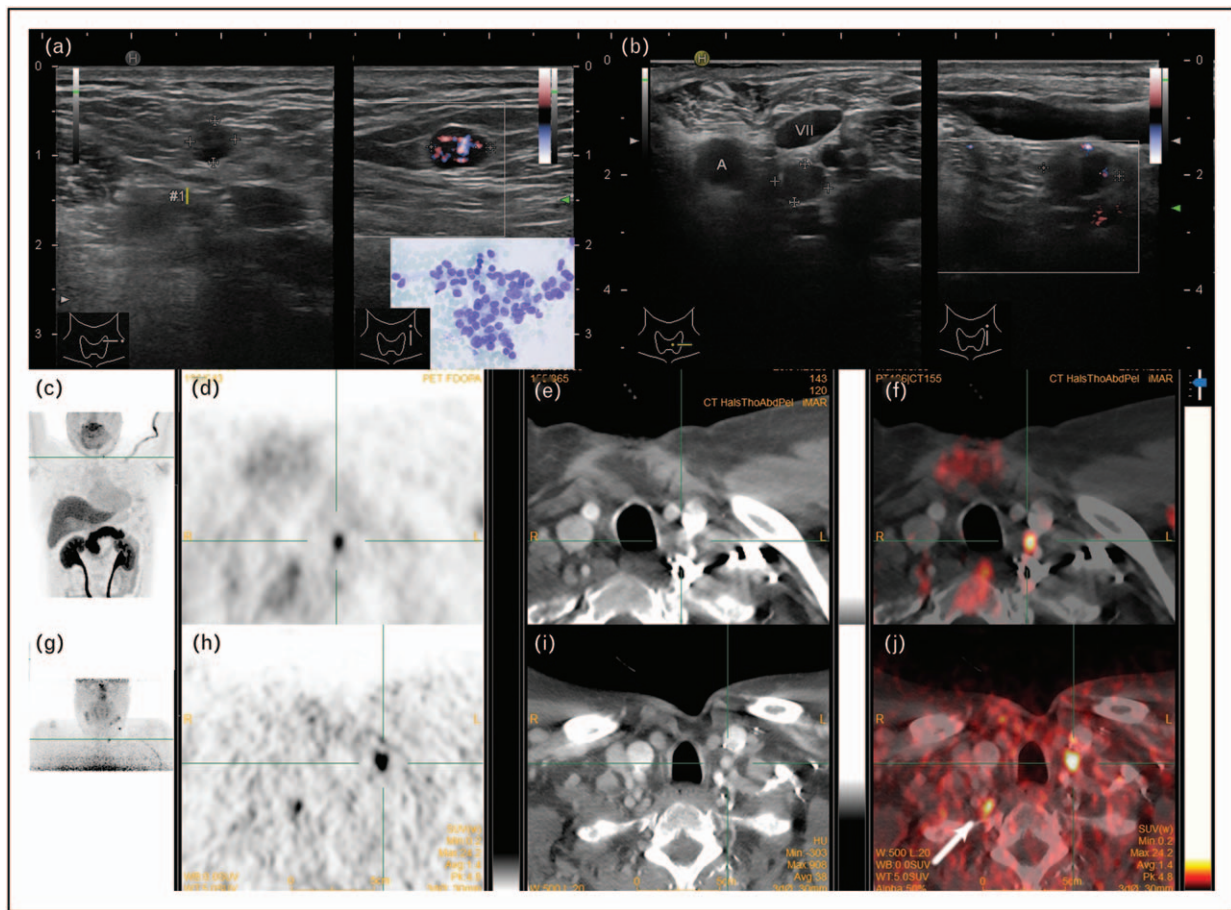
FIGURE 3. A 51-year-old man with medullary thyroid cancer pT1a (4 mm) pN1. Total thyroidectomy with left lateral LN dissection in 2003. In 2011, [^{18}F]FDG-PET including CT-CT showed two enhancing but FDG-negative LN metastases, which were confirmed on surgery. Rising serum calcitonin (25.1 pmol/l). Ultrasound in October 2019 showed a 5 mm hyperperfused LN (a). FNB revealed malignant cells (a), calcitonin from the aspirate was 3850 pmol/l. [^{18}F]FDOPA-PET in Aarhus/Denmark (c–f) revealed two foci: the known LN metastasis and a focus in the left central neck. Subsequent [^{68}Ga]DOTATOC-PET with a dedicated CE-CT of the neck with arms down (g–j) at our center confirmed both foci and allowed us to localize the central cervical lesion by US (b). The prevertebral focus (arrow in j) is physiological tracer uptake in the right stellate ganglion. CE-CT, contrast-enhanced CT; FNB, fine needle biopsy; LN, lymph node.

Cervical ultrasound for thyroid disease should always include screening for suspicious regional LN. The following three signs in B-mode ultrasound increase the likelihood of malignancy: round shape, hypoechogenicity, loss of hilar echo [47,48]. Cystic lymph nodes are almost pathognomonic of PTC (Fig. 2) but may also occur in squamous cell cancer. The hallmark of a malignant lymph node is focal hyperperfusion on Doppler ultrasound (Fig. 3a) [48,49].

When thyroid cancer is established based on FNB, we routinely perform a second ultrasound examination to specifically exclude lymph node metastases in the lateral neck, both ipsilateral and contralateral, with particular attention to lymph nodes at the edges of lymph node dissection regions. In addition to B-mode, every lymph node is examined with high-resolution Doppler (Fig. 3). In case of suspicious lymph nodes, we perform ultrasound-guided FNB of one lymph node per lateral cervical compartment. The technique is similar to FNB of thyroid lesions. However, cytology may only reveal lymphatic cells or fluid with macrophages in case of cystic lymph nodes. We therefore routinely supplement cytology with biochemistry: thyroglobulin in case of DTC, calcitonin in case of MTC [36,49]. Rarely, lymph node metastases can occur with a very small or no detectable primary in the thyroid gland [50]. In these cases, detection of malignancy rests on lymph node biopsy. Imaging of lymph nodes in the central compartment (level IV) is challenging to perform with ultrasound [51] but has limited relevance in institutions in which central lymph node dissection is part of the surgical routine.

Variations in vascular anatomy need to be recorded. We routinely document the common origin of right subclavian and carotid arteries from the innominate artery, as a subclavian artery originating directly from the aortic isthmus and passing behind the trachea (lusorian artery) is associated with a nonrecurrent inferior laryngeal nerve with major implications for surgical management [52].

In case of locally and regionally advanced disease, guidelines recommend computed tomography (CT) [4]. We prefer contrast-enhanced CT (CE-CT) for improved delineation of vascular anatomy and for the detection of regional lymph node metastases, especially in cases with MTC. The role of preoperative [18F]FDG PET/CT in addition to CE-CT is at present not firmly established [53–55]. However, we routinely perform [18F]FDG PET with coregistered CE-CT of neck and mediastinum down to the tracheal bifurcation. Since 2019, we also include PET/MR [56] for a better delineation the central viscera and of cystic lymph nodes (Fig. 2).

Error-free communication between endocrine surgeon and imaging specialist is paramount. We routinely summarize the findings in a hand drawing of all pertinent imaging findings in relation to the patient's vascular anatomy [57]. The drawings are scanned in and stored alongside the ultrasound images in the Picture Archival and Communications System and follow the patient into the operating theatre (Fig. 2).

IMAGING OF DIFFERENTIATED THYROID CANCER: THERAPY MONITORING

DTC expresses NIS. It has therefore the ability to take up radioactive iodine, at least under conditions of TSH stimulation, either endogenous (4 weeks' withdrawal of levothyroxine leading to a TSH >30 mU/l) or by intramuscular injection of recombinant human TSH (rhTSH) [4]. Three radioactive isotopes can be used: ^{131}I (physical half-life 8 days), which emits both gamma radiation, which is needed for conventional nuclear medicine imaging, and beta radiation, which irradiates the surrounding tissue with a maximum range of approx. 2 mm; ^{123}I (13 h), a gamma emitter; and ^{124}I (4 days), a positron emitter [58,59].

Until the turn of the millennium, many institutions routinely applied ^{131}I to ablate thyroid remnant tissue after total thyroidectomy apart from using it to treat regional or distant iodine-avid metastases [60]. Thyroid ablation has come under increasing scrutiny, at least for patients with low-risk thyroid cancer [4,61■■,62–64]. Following ablation, the distribution of radioactivity is documented by planar whole-body scintigraphy, and – ideally –

three-dimensional conventional imaging using single photon emission computed tomography (SPECT) in combination with CT [65].

Three aspects are important. First, we routinely perform cervical ultrasound in conjunction with SPECT/CT to detect regional lymph node metastases that were overlooked on preoperative staging. Small iodine-avid lymph node metastases can be followed up with ultrasound, as ^{131}I may be curative, while iodine-negative lymph node metastases require repeat surgery [66]. Second, SPECT/CT helps to identify iodine avid accessory thyroid tissue such a pyramidal lobe that may otherwise be mistaken for thyroid remnants [65]. Third, Post therapeutic ^{131}I scintigraphy can be the only imaging modality to detect – and treat – miliary pulmonary metastases in PTC, as the lung lesions are too small to be picked up by routine chest CT [67].

After ablation, routine imaging consists of periodic cervical ultrasound. Two retrospective series suggest that a follow-up regime including ultrasound performed 4 weeks, 1 year and 5 years after initial surgical therapy will detect about 90% of recurrences in low-risk DTC [68–70].

IMAGING OF DIFFERENTIATED THYROID CANCER: RECURRENCE

Distinguishing true recurrence from persisting disease that was overlooked on primary therapy can be difficult [57,71■■]. Recurrence of DTC is suspected when a patient detects a new painless lump in the neck, when there is a rise of serum thyroglobulin (Tg), and in case of persisting high levels of anti-thyro-globulin antibodies [4].

Initial imaging should include ultrasound of the neck including ultrasound-guided FNB of suspicious lesions [4,49]. Reactive lymph node at the edge of a previous systematic lymph node dissection may be difficult to distinguish from metastases, as they often are hypoechoic and enlarged with an abnormal shape. Doppler-ultrasound may help, but the definitive diagnosis often rests on FNB with determination of Tg in the washout from the biopsy needle [49].

Functional imaging of DTC has two components: demonstrating iodine avid disease that can be treated with high-dose ^{131}I, and demonstrating cancer tissue that has lost the ability to concentrate iodine and that needs to be treated by surgery or external beam therapy [12].

Imaging for iodine avid disease is performed under TSH stimulation using ^{123}I or ^{131}I whole-body scintigraphy, ideally supplemented by SPECT/CT of neck and mediastinum to both increase sensitivity and improve localization [4]. ^{124}I PET is the most

sensitive method for the detection or characterization of small lesions [72]. For pretherapeutic dosimetry, a small activity of ^{124}I, typically 37–74 MBq, is injected or ingested. Images are taken 48 h, and if positive, 96 h later [58]. Post therapeutic planar scintigraphy 72–96 h after the application at least 3000 MBq ^{131}I is still the most sensitive method for the detection of miliary pulmonary metastases in PTC [67], for which high-dose ^{131}I therapy is curative [73].

The mainstay for imaging recurrent DTC including iodine-refractory disease is [^{18}F]FDG PET [74]. When DTC de-differentiates, DTC may fail to express NIS, and glucose uptake is upregulated. An important caveat is that glucose uptake is also upregulated in inflammatory foci, which often leads to false positive findings in cervical lymph nodes [49]. Patient-based pooled sensitivity and specificity of [^{18}F]FDG for the detection of recurrent DTC are both 80% [74]. However, these estimates are probably overoptimistic, as diagnostic studies often lack a reference standard that is truly independent of imaging and/or sufficient follow-up [74]. In our own series of 51 patients imaged for suspected recurrent DTC from 2009 to 2014, lesion-based sensitivity of [^{18}F]FDG PET was 85% and specificity was 70%. Post-PET ultrasound including ultrasound-guided FNB of all suspicious lesions increased specificity to 90% while maintaining sensitivity [49]. TSH stimulation increases lesional uptake of [^{18}F]FDG [75], but it may no longer be needed due to the improved sensitivity of the most recent generation of PET scanners.

[^{68}Ga]DOTATOC has been used for DTC imaging [76,77] but without convincing evidence that it is superior to [^{18}F]FDG. Two recent case series show that ligands to prostate-specific membrane antigen (PSMA) may show focal uptake in patients with rising serum Tg, negative ^{131}I scintigraphy and [^{18}F]FDG-PET [78,79]. However, unspecific foci especially in the thorax are frequently encountered on imaging with [^{18}F]PSMA-1007, which has a higher resolution than the ^{68}Ga-labeled PSMA ligands [80]. PSMA PET for thyroid cancer therefore needs confirmation in larger series with a firm diagnostic standard that is independent of imaging, ideally cytology or histology. ^{68}Ga-labelled fibroblast activation protein inhibitor (FAPI) is an oligopeptide that has moderate uptake in thyroid cancer [81]. The tracer excels in imaging pancreatic cancer, as it is cancer-specific without uptake in inflammatory lesions [81]. Another new PET tracer, [^{18}F]tetrafluoroborate (TFB) is taken up by NIS [82■■]. In a recent study in 25 patients with suspected DTC, [^{18}F]TFB-PET showed focal uptake in recurrent tumor in 13 patients while ^{131}I SPECT-CT was positive only in 3 [82■■].

IMAGING OF MEDULLARY THYROID CANCER

The primary diagnosis of MTC follows the same principles as for DTC with two caveats: cytology is unreliable; micrometastases to cervical lymph node are common, and macrometastases to lymph node may be discontinuous and often contralateral [9]. Unlike DTC, MTC does not express NIS, and therefore has no iodine uptake. Three tracers are first choice for imaging MTC: [^{18}F]FDOPA, [^{68}Ga]DOTA-TOC (and analogues) and [^{18}F]FDG [83,84,85■]. The latter is least sensitive, but useful with increasing de-differentiation, particularly when S-CEA rises more rapidly than S-calcitonin [85■]. Only one study compared the three tracers in the same patients [86]. The most sensitive tracer for well differentiated MTC is [^{18}F]FDOPA [87■,88]. However, it is available only at very few select institutions. [^{68}Ga]DOTATOC, an increasingly ubiquitous tracer for neuroendocrine tumours, is not quite as sensitive, but more so than [^{18}F]FDG [85■]. Note that [^{68}Ga]DOTATOC may show physiological uptake in the stellate ganglia (Fig. 3 h.j) [89]. Other tracers that have been used for imaging MTC include radioactively labelled gastrin analogues [90], but there are at present no series that document the superiority of these new tracers over [^{18}F]FDOPA.

We use [^{68}Ga]DOTATOC rather than [^{18}F]FDG for staging before primary surgery, while we are eagerly awaiting the forthcoming production of [^{18}F]FDOPA in our own cyclotron unit. For staging-suspected recurrent disease, we routinely complement ultrasound and FNB at our own institution with [^{18}F]FDOPA with coregistered CE-CT of neck and mediastinum at a cooperating center abroad (Fig. 3).

IMAGING OF ANAPLASTIC THYROID CANCER

ATC is one of the most aggressive human cancers. Still, up to 20% of patients experience lasting cure after radical surgery in combination with radio-chemotherapy if cancer is limited to the thyroid gland and regional lymph nodes [91,92]. The main differential diagnosis is thyroid lymphoma, which is primarily treated with chemotherapy, often in combination with radiation. [^{18}F]FDG is the PET imaging agent of choice for both [93,94]. In case of ATC, we routinely perform [^{18}F]FDG PET/CT with CE-CT and PET/MR of neck and mediastinum, supplemented by core-needle biopsy (CNB) of the primary tumour for histological confirmation before surgery. In addition to CNB, we aspirate cells from the tumour and perform flow cytometry to exclude lymphoma [95]. MRI and endoscopy

are important to establish intactness of the central viscera.

CONCLUSION

The mainstay of thyroid cancer imaging is cervical ultrasound in combination with ultrasound-guided FNB. Thyroid scintigraphy with [^{99m}Tc]pertechnetate is used in patients with suppressed TSH for the detection of toxic nodules, which are nearly always benign. Imaging methods for DTC are scintigraphy with radioactive iodine isotopes and [^{18}F]FDG-PET. Recommended imaging methods for MTC are [^{18}F]FDOPA (when available), [^{68}Ga]DOTATOC and [^{18}F]FDG-PET.

Conflicts of interest

M. B. is an advisor (unpaid) for Segami Corp., Inc., Columbus/MD.
This manuscript has not been submitted elsewhere.

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- ■ of special interest
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