REVIEW

OPEN

CURRENT OPINION

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 [^{18}F]-fluorodeoxyglucose (FDG) and MRI are reserved for advanced and/or recurrent cases of differentiated thyroid cancer and anaplastic thyroid cancer, while [^{18}F]FDOPA and [^{68}Ga]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

Curr Opin Endocrinol Diabetes Obes 2020, 27:335–344

DOI:10.1097/MED.0000000000000574

KEY POINTS

- Primary detection and staging of thyroid cancer relies on thyroid ultrasound supplemented by ultrasound-guided FNB. The various TIRADS help in selecting which nodules to biopsy.
- The preoperative evaluation of advanced thyroid cancer should include contrast-enhanced CT for improved detection of regional lymph node metastases, ideally supplemented by functional imaging on a hybrid scanner in the same session.
- The preferred tracers are [^{18}F]FDG for DTC and [^{18}F]FDOPA – when available – or [^{68}Ga]DOTATOC and analogues for MTC. Radioactive iodine isotopes are used for therapy monitoring and imaging recurrences in DTC.

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 microcalcification [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.

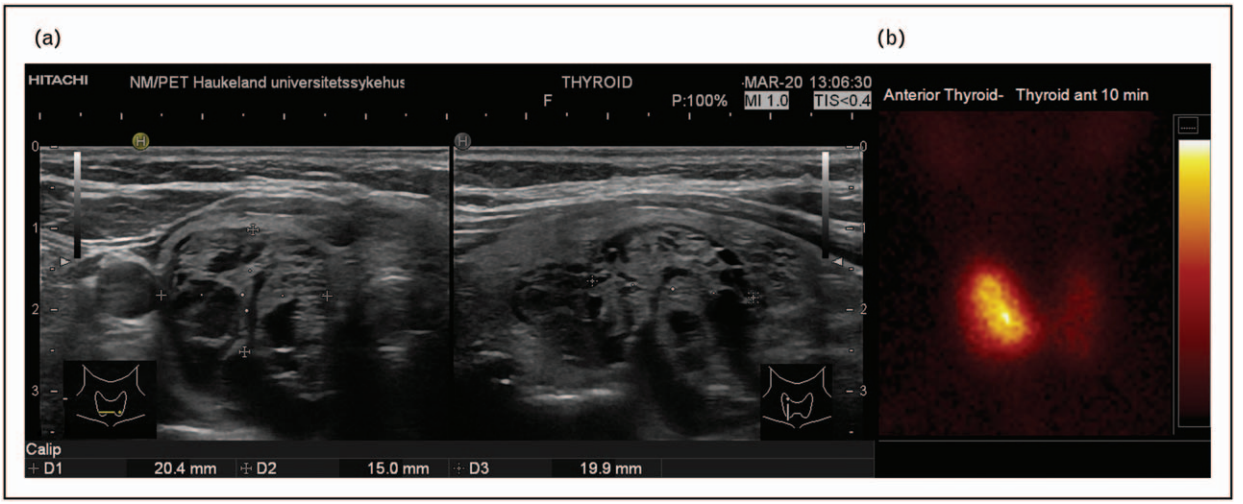

FIGURE 1. A 71-year-old woman referred for thyroid ultrasound and FNB because of a thyroid nodule detected on computed tomography. The patient's serum TSH of 0.2 μU/ml had not been not considered in the referral. Thyroid ultrasound (a) revealed a conglomerate of hypoechogenic nodules in the right thyroid 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.

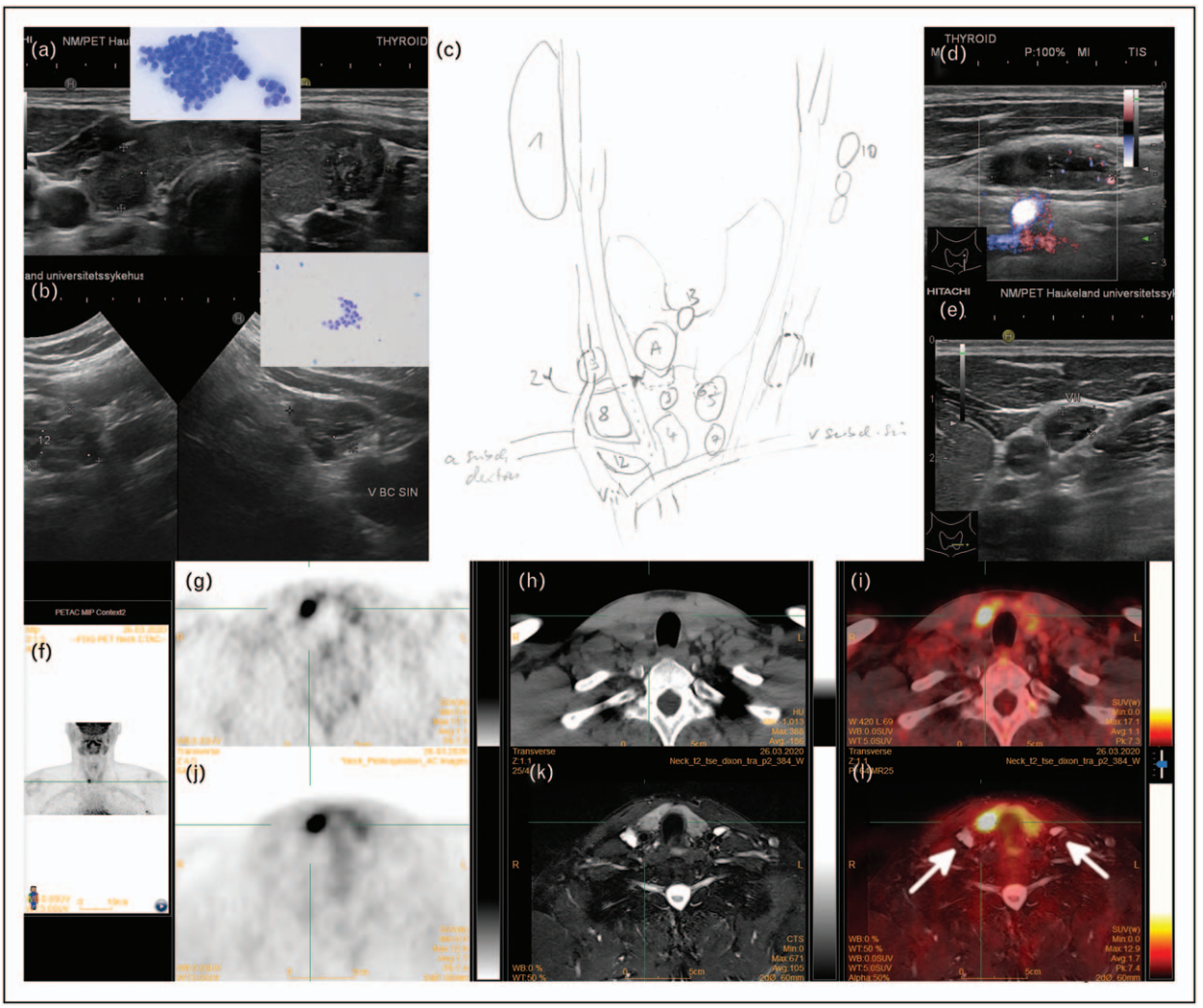

FIGURE 2. A 34-year-old man presenting with a right lateral neck mass. Contrast-enhanced CT requested by the initially consulted otorhinolaryngologist had revealed multiple lesions in the right lateral neck. Ultrasound at our centre showed a 10 mm hypoechoic nodule 'A' (a) in the right thyroid lobe and 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].

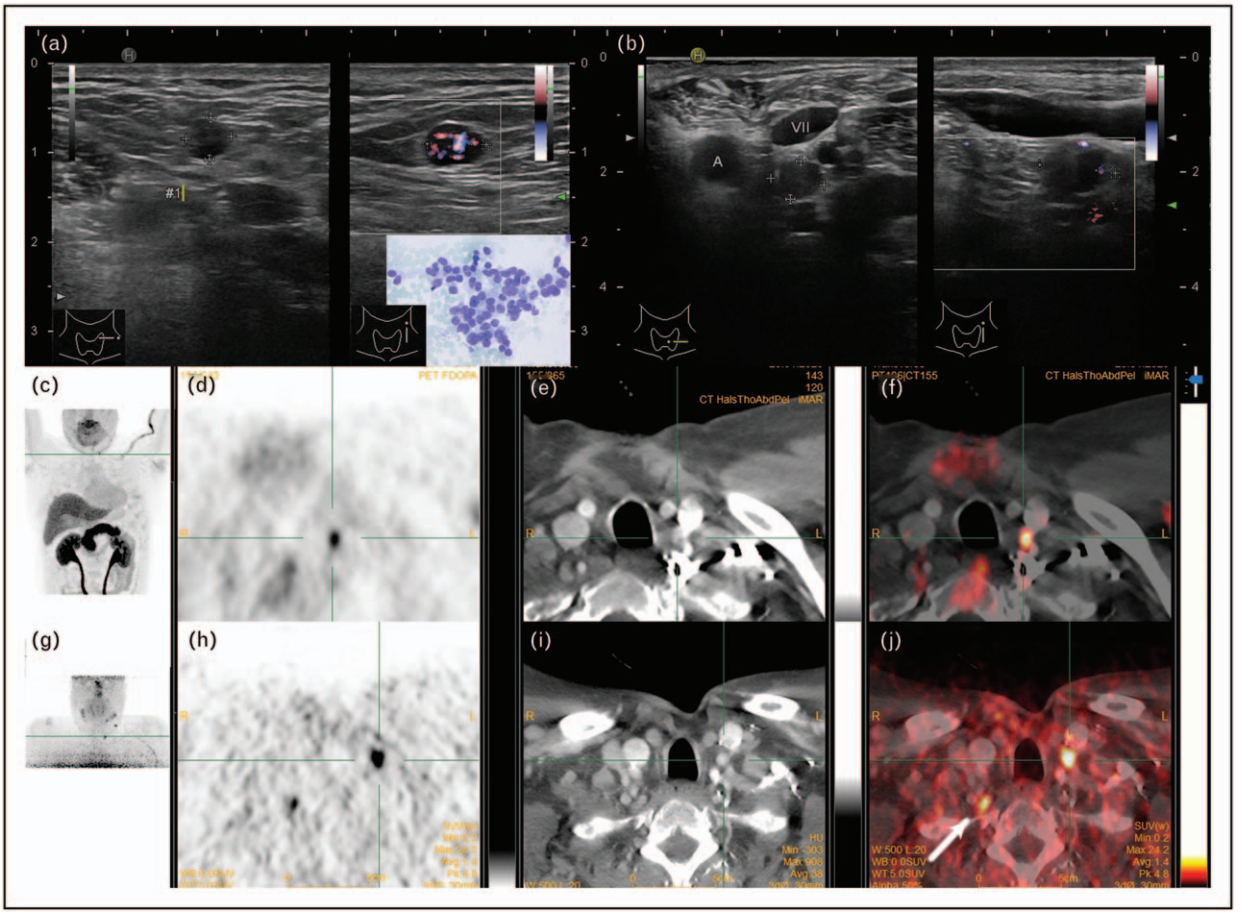

FIGURE 3. A 51-year-old man with medullary thyroid cancer pT1a (4 mm) pN1. Total thyroidectomy with left lateral LN dissection in 2003. In 2011, [^{18}F]FDG-PET including CT-CT showed two enhancing but FDG-negative LN metastases, which were confirmed on surgery. Rising serum calcitonin (25.1 pmol/l). 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 [^{18}F]FDG PET/CT in addition to CE-CT is at present not firmly established [53–55]. However, we routinely perform [^{18}F]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]DOTATOC (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 radiochemotherapy 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.

Acknowledgements

We thank Hans Kristian Haugland, PhD, from the Department of Pathology at Haukeland University Hospital for the cytology images and valuable advice regarding cytology, and Lars Rokne Reisæter, MD, from the Department of Radiology for helpful review of our manuscript.

Financial support and sponsorship

None.

Conflicts of interest

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

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. Olson E, Wintheiser G, Wolfe KM, *et al.* Epidemiology of thyroid cancer: a review of the National Cancer Database. Cureus 2019; 11:e4127.
2. Moon JH, Hyun MK, Lee JY, *et al.* Prevalence of thyroid nodules and their associated clinical parameters: a large-scale, multicenter-based health check-up study. Korean J Intern Med 2018; 33:753–762.
3. Ha SM, Baek JH, Choi YJ, *et al.* Malignancy risk of initially benign thyroid nodules: validation with various Thyroid Imaging Reporting and Data System guidelines. Eur Radiol 2019; 29:133–140.
4. 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.
5. Howlader N, Noone AM, Krapcho M *et al.* SEER Cancer Statistics Review 1975-2017. Bethesda/MD: National Cancer Institute. https://seer.cancer.gov/csr/1975_2017 (accessed May 17, 2020).
6. Mathiesen JS, Kroustrup JP, Vestergaard P, *et al.* Survival and long-term biochemical cure in medullary thyroid carcinoma in Denmark 1997-2014: a nationwide study. Thyroid 2019; 29:368–377.
7. Zaydfudim V, Feurer ID, Griffin MR, *et al.* The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma. Surgery 2008; 144:1070–1077discussion 1077–1078.
8. ■ Grani G, Lamartina L, Durante C, *et al.* Follicular thyroid cancer and Hürthle cell carcinoma: challenges in diagnosis, treatment, and clinical management. Lancet Diabetes Endocrinol 2018; 6:500–514.

An in-depth review of follicular and oncocytic (Hürthle cell) thyroid cancer.

9. Machens A, Dralle H. Prognostic impact of N staging in 715 medullary thyroid cancer patients: proposal for a revised staging system. Ann Surg 2013; 257:323–329.
10. Iyer NG, Shaha AR. Management of thyroid nodules and surgery for differentiated thyroid cancer. Clin Oncol (R Coll Radiol) 2010; 22:405–412.
11. Paschke R, Lincke T, Müller SP, *et al.* The treatment of well differentiated thyroid carcinoma. Dtsch Arztebl Int 2015; 112:452–458.
12. Van Nostrand D. Radioiodine refractory differentiated thyroid cancer: time to update the classifications. Thyroid 2018; 28:1083–1093.
13. Hahn SY, Han B-K, Ko EY, *et al.* Ultrasound findings of papillary thyroid carcinoma originating in the isthmus: comparison with lobe-originating papillary thyroid carcinoma. AJR Am J Roentgenol 2014; 203:637–642.
14. Russ G, Bonnema SJ, Erdogan MF, *et al.* European Thyroid Association Guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: the EU-TIRADS. Eur Thyroid J 2017; 6:225–237.
15. 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.
16. Kobayashi K, Hirokawa M, Yabuta T, *et al.* Tumor protrusion with intensive blood signals on ultrasonography is a strongly suggestive finding of follicular thyroid carcinoma. Med Ultrason 2016; 18:25–29.
17. Gharib H, Papini E, Garber JR, *et al.* American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules – 2016 update. Endocr Pract 2016; 22:622–639.
18. Shin JH, Baek JH, Chung J, *et al.* Ultrasonography diagnosis and imaging-based management of thyroid nodules: revised Korean Society of Thyroid Radiology Consensus Statement and Recommendations. Korean J Radiol 2016; 17:370–395.
19. ■ Tessler FN, Middleton WD, Grant EG. Thyroid Imaging Reporting and Data System (TI-RADS): a user's guide. Radiology 2018; 287:29–36.

This pictorial guide explains how to use ACR-TIRADS to assess the need for FNB in thyroid nodules.

20. 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.
21. Kamaya A, Tahvildari AM, Patel BN, *et al.* Sonographic detection of extracapsular extension in papillary thyroid cancer. J Ultrasound Med 2015; 34:2225–2230.
22. Agha A, Hornung M, Stroszczynski C, *et al.* Highly efficient localization of pathological glands in primary hyperparathyroidism using contrast-enhanced ultrasonography (CEUS) in comparison with conventional ultrasonography. J Clin Endocrinol Metab 2013; 98:2019–2025.
23. ■ Noto B, Eveslage M, Pixberg M, *et al.* Prevalence of hyperfunctioning thyroid nodules among those in need of fine needle aspiration cytology according to ATA 2015, EU-TIRADS, and ACR-TIRADS. Eur J Nucl Med Mol Imaging 2020; 47:1518–1526.

In a series of 566 patients with serum TSH in the normal range, the prevalence of hyperfunctioning nodules in thyroid scintigraphy was 8%. There were no criteria on B-mode US that allowed the identification of toxic nodules, while three of the most commonly used US classification systems spuriously recommended FNB in 25–50% of hyperfunctioning nodules.

24. Schenke S, Seifert P, Zimny M, *et al.* Risk stratification of thyroid nodules using the Thyroid Imaging Reporting and Data System (TIRADS): the omission of thyroid scintigraphy increases the rate of falsely suspected lesions. J Nucl Med 2019; 60:342–347.
25. Biermann M. Ultrasound classification systems estimating thyroid malignancy fail to recognize hyperfunctional nodules. Clin Thyroidol 2020; 32:225–228.
26. Schröder S, Marthaler B. Autonomy and malignancy of thyroid gland tumors. A critical analysis of the literature on the existence of hyperfunctioning follicular and papillary thyroid gland carcinomas. Pathologe 1996; 17:349–357.
27. Mirfakhraee S, Mathews D, Peng L, *et al.* A solitary hyperfunctioning thyroid nodule harboring thyroid carcinoma: review of the literature. Thyroid Res 2013; 6:7.
28. Nayan S, Ramakrishna J, Gupta MK. The proportion of malignancy in incidental thyroid lesions on 18-FDG PET study: a systematic review and meta-analysis. Otolaryngol Head Neck Surg 2014; 151:190–200.
29. Greilsamer T, Blanchard C, Christou N, *et al.* Management of thyroid nodules incidentally discovered on MIBI scanning for primary hyperparathyroidism. Langenbecks Arch Surg 2015; 400:313–318.
30. Pattison DA, Bozin M, Gorelik A, *et al.* 18F-FDG-avid thyroid incidentalomas: the importance of contextual interpretation. J Nucl Med 2018; 59:749–755.
31. Biermann M. FDG-avid thyroid incidentalomas on PET–CT ordered for other malignancies have no prognostic significance in a large retrospective cohort. Clin Thyroidol 2017; 29:461–464.
32. Trimboli P, Paone G, Treglia G, *et al.* Fine-needle aspiration in all thyroid incidentalomas at 18 F-FDG PET/CT: can EU-TIRADS revise the dogma? Clin Endocrinol (Oxf) 2018; 89:642–648.
33. Biermann M. EU-TIRADS can decrease unnecessary fine-needle aspirations of ^{18} F-FDG-positive thyroid nodules. Clin Thyroidol 2019; 31:65–68.
34. Frates MC, Benson CB, Doubilet PM, *et al.* Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. J Clin Endocrinol Metab 2006; 91:3411–3417.

35. Moss WJ, Finegersh A, Pang J, *et al.* Needle biopsy of routine thyroid nodules should be performed using a capillary action technique with 24- to 27-gauge needles: a systematic review and meta-analysis. Thyroid 2018; 28:857–863.

36. Biermann M. Needle biopsy of thyroid nodules is best performed using capillary action techniques rather than suction. Clin Thyroidol 2018; 30:418–421.

37. Cibas ES, Ali SZ. The Bethesda System for reporting thyroid cytopathology. Am J Clin Pathol 2009; 132:658–665.

38. Bongiovanni M, Crippa S, Baloch Z, *et al.* Comparison of 5-tiered and 6-tiered diagnostic systems for the reporting of thyroid cytopathology: a multiinstitutional study. Cancer Cytopathol 2012; 120:117–125.

39. Cibas ES, Ali SZ. The 2017 Bethesda System for reporting thyroid cytopathology. Thyroid 2017; 27:1341–1346.

40. Oda H, Miyauchi A, Ito Y, *et al.* Incidences of unfavorable events in the management of low-risk papillary microcarcinoma of the thyroid by active surveillance versus immediate surgery. Thyroid 2016; 26:150–155.

41. Sciacchitano S, Lavra L, Ulivieri A, *et al.* Comparative analysis of diagnostic performance, feasibility and cost of different test-methods for thyroid nodules with indeterminate cytology. Oncotarget 2017; 8:49421–49442.

42. Merten MM, Castro MR, Zhang J, *et al.* Examining the role of preoperative positron emission tomography/computerized tomography in combination with ultrasonography in discriminating benign from malignant cytologically indeterminate thyroid nodules. Thyroid 2017; 27:95–102.

43. Castellana M, Trimboli P, Piccardo A, *et al.* Performance of 18F-FDG PET/CT in selecting thyroid nodules with indeterminate fine-needle aspiration cytology for surgery. A systematic review and a meta-analysis. J Clin Med 2019; 8:1333.

44. Treglia G, Caldarella C, Saggiorato E, *et al.* Diagnostic performance of (99m)Tc-MIBI scan in predicting the malignancy of thyroid nodules: a meta-analysis. Endocrine 2013; 44:70–78.

45. Heo I, Park S, Jung CW, *et al.* Fine needle aspiration cytology of parathyroid lesions. Korean J Pathol 2013; 47:466–471.

46. Biermann M. Integrated cervical ultrasound by the same specialist who performed parathyroid scintigraphy improves parathyroid adenoma detection. Clin Thyroidol 2018; 30:471–475.

47. Vassallo P, Wernecke K, Roos N, *et al.* Differentiation of benign from malignant superficial lymphadenopathy: the role of high-resolution US. Radiology 1992; 183:215–220.

48. Leboulleux S, Girard E, Rose M, *et al.* Ultrasound criteria of malignancy for cervical lymph nodes in patients followed up for differentiated thyroid cancer. J Clin Endocrinol Metab 2007; 92:3590–3594.

49. Biermann M, Kråkenes J, Brauckhoff K, *et al.* Post-PET ultrasound improves specificity of 18F-FDG-PET for recurrent differentiated thyroid cancer while maintaining sensitivity. Acta Radiol 2015; 56:1350–1360.

50. Ito Y, Hirokawa M, Fukushima M, *et al.* Occult papillary thyroid carcinoma: diagnostic and clinical implications in the era of routine ultrasonography. World J Surg 2008; 32:1955–1960.

51. Kim K-E, Kim E-K, Yoon JH, *et al.* Preoperative prediction of central lymph node metastasis in thyroid papillary microcarcinoma using clinicopathologic and sonographic features. World J Surg 2013; 37:385–391.

52. Iacobone M, Viel G, Zanella S, *et al.* The usefulness of preoperative ultrasonographic identification of nonrecurrent inferior laryngeal nerve in neck surgery. Langenbecks Arch Surg 2008; 393:633–638.

53. Kwon SY, Choi EK, Kong EJ, *et al.* Prognostic value of preoperative 18F-FDG PET/CT in papillary thyroid cancer patients with a high metastatic lymph node ratio: a multicenter retrospective cohort study. Nucl Med Commun 2017; 38:402–406.

54. Chong A, Ha J-M, Han Y-H, *et al.* Preoperative lymph node staging by FDG PET/CT with contrast enhancement for thyroid cancer: a multicenter study and comparison with neck CT. Clin Exp Otorhinolaryngol 2017; 10:121–128.

55. Kim BS, Ryu HS, Kang KH. The value of preoperative PET-CT in papillary thyroid cancer. J Int Med Res 2013; 41:445–456.

56. Galgano SJ, Marshall RV, Middlebrooks EH, *et al.* PET/MR imaging in head and neck cancer: current applications and future directions. Magn Reson Imaging Clin N Am 2018; 26:167–178.

57. Biermann M, Brauckhoff K. Most 'recurrences' of thyroid cancer represent persistent rather than recurrent disease. Clinical Thyroidology 2018; 30:108–111.

58. Weber M, Binse I, Nagarajah J, *et al.* The role of 124I PET/CT lesion dosimetry in differentiated thyroid cancer. Q J Nucl Med Mol Imaging 2019; 63:235–252.

59. Kuker R, Sztejnberg M, Gulec S. I-124 imaging and dosimetry. Mol Imaging Radionucl Ther 2017; 26:66–73.

60. Mazzaferri EL, Kloos RT. Current approaches to primary therapy for papillary and follicular thyroid cancer. J Endocrinol Metab 2001; 86:1447–1463.

61. ■■ Schlumberger M, Leboulleux S, Catargi B, *et al.* Outcome after ablation in patients with low-risk thyroid cancer (ESTIMABL1): 5-year follow-up results of a randomised, phase 3, equivalence trial. Lancet Diabetes Endocrinol 2018; 6:618–626.

This study presents the long-term clinical outcomes of the four-armed randomized ESTIMABL trial in patients with low-risk PTC. The trial compared thyroid remnant ablation with 1.1 versus 3.7 GBq ^{131}I and under endogenous versus exogenous TSH-stimulation in a 2 x 2 factorial design. After 5 years of follow-up, recurrence rates in all four arms of the trial were below 2%.

62. Cooper DS, Doherty GM, Haugen BR, *et al.* Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009; 19:1167–1214.

63. Cooper DS, Doherty GM, Haugen BR, *et al.* Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006; 16:109–142.

64. Pacini F, Schlumberger M, Dralle H, *et al.* European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006; 154:787–803.

65. Zeuren R, Biagini A, Grewal RK, *et al.* RAI thyroid bed uptake after total thyroidectomy: a novel SPECT-CT anatomic classification system. Laryngoscope 2015; 125:2417–2424.

66. Sabet A, Binse I, Grafe H, *et al.* Prognostic impact of incomplete surgical clearance of radioiodine sensitive local lymph node metastases diagnosed by postoperative (124)I-NaI-PET/CT in patients with papillary thyroid cancer. Eur J Nucl Med Mol Imaging 2016; 43:1988–1994.

67. Freudenberg LS, Jentzen W, Müller SP, *et al.* Disseminated iodine-avid lung metastases in differentiated thyroid cancer: a challenge to 124I PET. Eur J Nucl Med Mol Imaging 2008; 35:502–508.

68. Durante C, Montesano T, Torlontano M, *et al.* Papillary thyroid cancer: time course of recurrences during postsurgery surveillance. J Clin Endocrinol Metab 2013; 98:636–642.

69. Ryoo I, Kim DW, Lee CY, *et al.* Analysis of postoperative ultrasonography surveillance after total thyroidectomy in patients with papillary thyroid carcinoma: a multicenter study. Acta Radiol 2018; 59:196–203.

70. Biermann M. How often does a thyroid cancer patient need to undergo surveillance with cervical ultrasound? Clinical Thyroidology 2017; 29:173–175.

71. ■■ Bates MF, Lamas MR, Randle RW, *et al.* Back so soon? Is early recurrence of papillary thyroid cancer really just persistent disease? Surgery 2018; 163:118–123.

This retrospective series from a single institution shows that many cases with 'recurrent' thyroid cancer represent cases with persistent disease missed on initial staging. This implies that some 30–40% of all 'recurrences' can potentially be avoided by optimum preoperative staging.

72. Giraudet A-L, Taïeb D. PET imaging for thyroid cancers: current status and future directions. Ann Endocrinol (Paris) 2017; 78:38–42.

73. Durante C, Haddy N, Baudin E, *et al.* Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab 2006; 91:2892–2899.

74. Haslerud T, Brauckhoff K, Reisæter L, *et al.* F18-FDG-PET for recurrent differentiated thyroid cancer: a systematic meta-analysis. Acta Radiol 2016; 57:1193–1200.

75. van Tol KM, Jager PL, Piers DA, *et al.* Better yield of (18)fluorodeoxyglucose-positron emission tomography in patients with metastatic differentiated thyroid carcinoma during thyrotropin stimulation. Thyroid 2002; 12:381–387.

76. Binse I, Poeppel TD, Ruhlmann M, *et al.* 68Ga-DOTATOC PET/CT in patients with iodine- and 18F-FDG-negative differentiated thyroid carcinoma and elevated serum thyroglobulin. J Nucl Med 2016; 57:1512–1517.

77. Middendorp M, Selkinski I, Happel C, *et al.* Comparison of positron emission tomography with [(18)F]FDG and [(68)Ga]DOTATOC in recurrent differentiated thyroid cancer: preliminary data. Q J Nucl Med Mol Imaging 2010; 54:76–83.

78. Lütje S, Gomez B, Cohnen J, *et al.* Imaging of prostate-specific membrane antigen expression in metastatic differentiated thyroid cancer using 68Ga-HBED-CC-PSMA PET/CT. Clin Nucl Med 2017; 42:20–25.

79. Verma P, Malhotra G, Agrawal R, *et al.* Evidence of prostate-specific membrane antigen expression in metastatic differentiated thyroid cancer using 68Ga-PSMA-HBED-CC PET/CT. Clin Nucl Med 2018; 43:e265–e268.

80. Kuten J, Fahoum I, Savin Z, *et al.* Head-to-head comparison of 68Ga-PSMA-11 with 18F-PSMA-1007 PET/CT in staging prostate cancer using histopathology and immunohistochemical analysis as a reference standard. J Nucl Med 2020; 61:527–532.

81. Kratochwil C, Flechsig P, Lindner T, *et al.* 68Ga-FAPI PET/CT: tracer uptake in 28 different kinds of cancer. J Nucl Med 2019; 60:801–805.

82. ■■ Dittmann M, Gonzalez Carvalho JM, Rahbar K, *et al.* Incremental diagnostic value of [^{18}F]tetrafluoroborate PET-CT compared to [131I]iodine scintigraphy in recurrent differentiated thyroid cancer. Eur J Nucl Med Mol Imaging 2020. (ePub).

This landmark study in 25 patients with suspected recurrent DTC showed that [^{18}F]TBF PET revealed recurrences in 13 patients while 131I SPECT-CT was positive only in 3.

83. Biermann M. ^{18} F-FDOPA-PET is more sensitive than F-18-FDG-PET in persistent or recurrent medullary thyroid cancer. Clin Thyroidol 2017; 29:301–304.

84. Kushchayev SV, Kushchayeva YS, Tella SH, *et al.* Medullary thyroid carcinoma: an update on imaging. J Thyroid Res 2019; 2019:1893047.

85. ■ Giovanella L, Treglia G, Iakovou I, *et al.* EANM practice guideline for PET/CT imaging in medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging 2020; 47:61–77.

The new guidelines on imaging MTC by the European Association of Nuclear Medicine include a detailed overview of the available literature regarding the different PET tracers.

86. Treglia G, Castaldi P, Villani MF, *et al.* Comparison of 18F-DOPA, 18F-FDG and 68Ga-somatostatin analogue PET/CT in patients with recurrent medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging 2012; 39:569–580.

87. ■ Brammen L, Niederle MB, Riss P, *et al.* Medullary thyroid carcinoma: do ultrasonography and F-DOPA-PET-CT influence the initial surgical strategy? Ann Surg Oncol 2018; 25:3919–3927.

An impressive large series documenting the utility of preoperative staging for MTC with [^{18}F]FDOPA at a single tertiary institution.

88. Terroir M, Caramella C, Borget I, *et al.* F-18-Dopa positron emission tomography/computed tomography is more sensitive than whole-body magnetic resonance imaging for the localization of persistent/recurrent disease of medullary thyroid cancer patients. Thyroid 2019; 29: 1457–1464.

89. Berg Z, Koppula BR. 68Ga-DOTATATE uptake by cervicothoracic (stellate) ganglia. Clin Nucl Med 2019; 44:810–811.

90. Roosenburg S, Laverman P, Joosten L, *et al.* PET and SPECT imaging of a radiolabeled minigastrin analogue conjugated with DOTA, NOTA, and NODAGA and labeled with (64)Cu, (68)Ga, and (111)In. Mol Pharm 2014; 11:3930–3937.

91. Smallridge RC, Ain KB, Asa SL, *et al.* American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2012; 22:1104–1139.

92. Fan D, Ma J, Bell AC, *et al.* Outcomes of multimodal therapy in a large series of patients with anaplastic thyroid cancer. Cancer 2020; 126:444–452.

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.

94. 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.

95. Hirokawa M, Kudo T, Ota H, *et al.* Preoperative diagnostic algorithm of primary thyroid lymphoma using ultrasound, aspiration cytology, and flow cytometry. Endocr J 2017; 64:859–865.