ENDOCRINE TUMOURS

Imaging in the follow-up of differentiated thyroid cancer: current evidence and future perspectives for a risk-adapted approach

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Abstract

The clinical and epidemiological profiles of differentiated thyroid cancers (DTCs) have changed in the last three decades. Today's DTCs are more likely to be small, localized, asymptomatic papillary forms. Current practice is, though, moving toward more conservative approaches (e.g. lobectomy instead of total thyroidectomy, selective use of radioiodine). This evolution has been paralleled and partly driven by rapid technological advances in the field of diagnostic imaging. The challenge of contemporary DTCs follow-up is to tailor a risk-of-recurrence-based management, taking into account the dynamic nature of these risks, which evolve over time, spontaneously and in response to treatments. This review provides a closer look at the evolving evidence-based views on the use and utility of imaging technology in the post-treatment staging and the short- and long-term surveillance of patients with DTCs. The studies considered range from cervical US with Doppler flow analysis to an expanding palette of increasingly sophisticated second-line studies (cross-sectional, functional, combined-modality approaches), which can be used to detect disease that has spread beyond the neck and, in some cases, shed light on its probable outcome.

Introduction

The clinical and epidemiological profiles of differentiated thyroid cancers (DTCs) have evolved remarkably over the past 30 years. In the 1980s and 1990s, patients usually presented with palpable primaries, often accompanied by locoregional or even distant metastases (1, 2). Today's DTCs are more likely to be small, localized, asymptomatic papillary forms, many with subcentimeter diameters (3). These changes have been paralleled and in large part driven by advances in diagnostic imaging technology. Since the late 1980s, clinicians' toolboxes for examining

Invited Author's profile

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the interior of the human body have expanded rapidly to include gray-scale ultrasonography (US), Doppler flow analysis, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). Widespread clinical use of these new techniques for assessing structures in the head and neck (e.g. carotid arteries) has been responsible for the incidental discovery of many of the tiny, silent thyroid cancers being diagnosed and treated today (4, 5, 6).

The evolving profile of DTCs has been mirrored by changes in our approaches to their treatment and follow-up. The standard of care before the 2000s involved total thyroidectomy (often with neck dissection), liberal use of radioiodine remnant ablation (RRA), and life-long surveillance based chiefly on whole-body radioiodine scintigraphy (WBS) and serum thyroglobulin (Tg) assays. Support is now growing for more conservative strategies in selected cases: lobectomy, omission of RRA, even active surveillance alone, which is now an option for some papillary microcarcinomas (7, 8, 9). These changes, too, have been facilitated by the availability of new imaging tools and techniques. The frequent use in the past of aggressive treatments (e.g. total thyroidectomy followed by RRA) was dictated in part by the need to eradicate not only the neoplastic thyroid tissue but normal thyroid remnants as well, since their uptake of iodine and production of thyroglobulin diminished the diagnostic performance of WBS and Tg assays during postoperative surveillance. These constraints were attenuated by increasing reliance on US surveillance, freeing clinicians to consider more individualized treatments for DTCs.

Despite the relatively indolent nature of most thyroid cancers and the increasing prevalence of low-risk tumors, the early 2000s witnessed striking increases in the use of imaging technology for assessing DTCs. A recent analysis of over 23 000 cases of DTC diagnosed in the U.S. confirmed that, although the tumors identified between 2001 and 2009 were more likely to be small (<1 cm) and localized than in previous years, patients were more rather than less likely to undergo I-131 scintigraphy and cervical US (odds ratios, 1.44 (95% confidence interval (CI), 1.35–1.54) and 2.15 (95% CI: 2.02–2.28) respectively) (10). PET studies increased more than 30-fold between 1996–2004 and 2005–2009, even in patients with localized disease (11).

Efforts are needed to curb this 'diagnostic hyperactivity' and bring post-treatment management strategies more in line with the *current* challenges of thyroid cancer (9, 12). Aside from the increasing demands for cost-efficient healthcare policies, there is a growing awareness that the increased use of diagnostic imaging does not inevitably translate into increased overall survival. Greater consideration is being given to the potential risks of imaging-related radiation exposure (11) and the impact of excessive surveillance on patients' quality of life (13).

Signs of change are already in the air. Although the major goal of post-treatment surveillance of patients with DTC is still the timely detection and effective management of persistent or recurrent cancer, increasing emphasis is being placed on the need to reliably identify patients who are disease-free and therefore eligible for less-intensive surveillance. Recommendations by national and international bodies are increasingly based on assessments of the individual patient's risk of recurrence (rather than death) (Table 1). Emphasis is also being placed on the dynamic nature of these risks, which evolve over time, spontaneously and in response to treatment (14).

This review will provide a closer look at the evolving evidence-based views on the use and utility of imaging technologies in the post-treatment staging and the short- and long-term surveillance of patients with DTCs. The modalities considered range from whole-body radioiodine scintigraphy and cervical US with Doppler flow analysis – the 'work horses' in both settings – to an expanding palette of increasingly sophisticated cross-sectional, functional, combined-modality imaging approaches, which can be used to detect disease that has spread beyond the neck and, in some cases, shed light on its probable outcome.

Cervical ultrasonography

Cervical US includes gray-scale studies performed with high-resolution linear transducers (frequencies of 10 to 15–17 MHz) (15) and assessment of lesion vascularity with color or power Doppler. First used in the late 1980s to distinguish cystic from solid thyroid nodules

Table 1 American Thyroid Association criteria for assessing risk of recurrence in patients with DTC.

Risk	Features
Low	Intrathyroid tumor ≤5 lymph node micrometastases (<0.2 cm)
Intermediate	Aggressive histology, minor extrathyroid extension, vascular invasion >5 involved lymph nodes (0.2–3 cm)
High	Gross extrathyroid extension, incomplete tumor resection Lymph node metastases >3 cm Distant metastases

(15), ultrasound's popularity increased steadily. By the early 2000s, a growing body of evidence indicated that sonographic examination of the neck combined with serum thyroglobulin assays was the most sensitive approach for detecting locoregional DTC involvement (16, 17, 18, 19). In 2006, it was officially recommended for this purpose by the American Thyroid Association (ATA) (20), replacing WBS, which had been the procedure of choice for over 40 years.

Cervical US is inferior to WBS in terms of specificity, and it provides no information on extracervical recurrence, including the upper mediastinum. It is also unsuitable for exploring deep cervical structures (e.g. retro- or parapharyngeal areas) (12). However, high-resolution US can pinpoint lesions as small as 2–3 mm in the thyroid bed or cervical lymph nodes, where the vast amount of persistent/recurrent disease is found in DTC patients. In addition, its diagnostic yield is unaffected by the radioiodine-avidity of the lesions or the presence of anti-Tg antibodies, which can cause false-negative findings in WBS and serum Tg assays (19), and it offers a number of practical advantages, including low cost, wide availability, and no known adverse effects (21).

Its main shortcoming is operator dependency, a problem aggravated by the diverse profiles of the operators examining thyroid cancer patients (e.g. radiology technicians, radiologists, endocrinologists, and other clinical specialists caring for these patients). Efforts have thus been made to define minimum criteria for operators claiming expertise in cervical US and to standardize methods for conducting, interpreting, and documenting the examination results (12). A second important limitation of US is its relatively low specificity, which will be discussed at greater length below.

Normal, suspicious, and indeterminate findings

Numerous US findings have been analyzed over the years as markers of persistent and recurrent foci of thyroid cancer in the neck. Those considered most useful for this purpose by the European Thyroid Association (ETA) are shown in Figs 1 and 2. Their sensitivities and specificities vary widely, and 'suspicious' lesions are thus distinguished from 'indeterminate' findings, which are atypical but also relatively common in the absence of malignancy.

The low specificity of US findings for distinguishing benign and malignant lesions increases when they are confirmed by cytological analysis of US-guided FNA and/or assay of the needle washout fluid for Tg (22, 23, 24); the washout fluid can also be subjected to PCR-based assay of thyroid-specific gene (Tg, TSH receptor) transcripts (25). Current trends, however, are characterized by more cautious use of biopsy (9). Decisions are based on lesion size and/or growth and the likelihood that management will change if positive results emerge. These recommendations reflect a growing awareness of the stress, morbidity, and costs associated with biopsy (26). More importantly, in at least 30% of cases, reoperation for pathologically confirmed metastases fails to eradicate the disease. It also carries an increased risk of serious, often permanent complications, including nerve resection, hypoparathyroidism, and tracheal or esophageal damage (27, 28). Finally, analysis of surgical pathology data on prophylactic neck dissections indicate that up to 90% of patients with papillary microcarcinomas (<1 cm) have level VI lymph node metastases, and up to 40% have lateral compartment involvement (29, 30, 31). These figures far exceed the clinical locoregional recurrence rates reported for these patients, suggesting that a substantial portion of the cervical disease detected during follow-up is clinically insignificant. FNA should thus be undertaken only after careful consideration of costs, benefits, and the patient's own preferences.

Thyroid bed

Thyroid bed lesions are a particular concern owing to the proximity of vital structures that can be compressed/damaged by residual tumor growth (but also by repeat encounters with the surgeon's scalpel, owing to the presence of scar tissue). Postoperative exploration of this area should be postponed until at least 3 months after surgery (12, 32). Even then, distinguishing benign and malignant lesions in this area on the basis of US alone is undeniably difficult (Fig. 1). Hypoechogenicity alone may represent autoimmune thyroiditis, suture granulomas, benign reactive lymph nodes, parathyroid adenomas (12), and jugular chain LNs that have slid medially to occupy the bed (33).

Discordant findings have emerged from the few small studies that assessed the diagnostic value of US abnormalities against pathology findings. Lee et al. (34) concluded that benign and malignant lesions could indeed be distinguished on the basis of their margin characteristics, shapes, and calcification statuses. Margin irregularity (Fig. 2E) – a feature whose detection is associated with particularly high interoperator
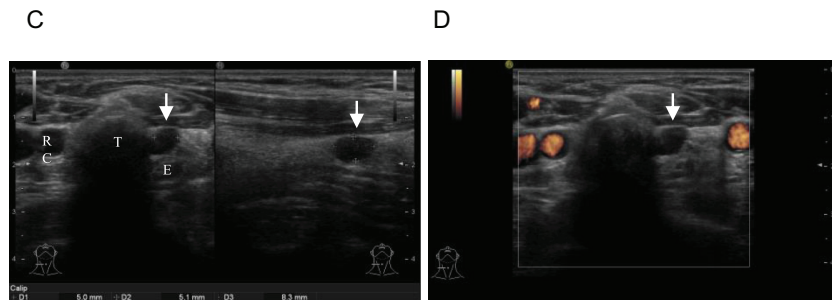
US findings	Images

Normal

- *Triangular or flattened area that is uniformly hyperechoic vs surrounding muscle tissue (A)*
- *Ovoid lesions, that is uniformly hyperechoic or isoechoic vs surrounding muscle tissue (B)*
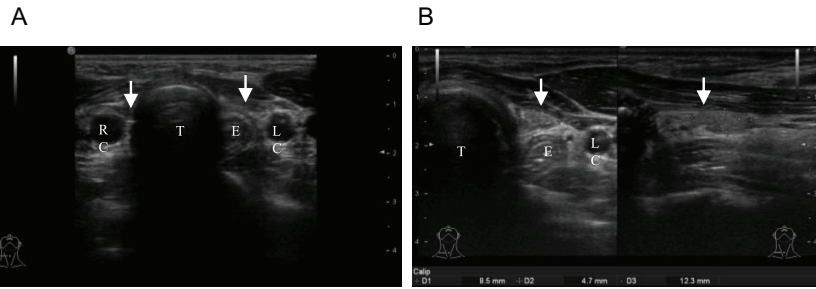
Indeterminate

- *Lesions displaying hypoechogenicity alone (C, D)*

Suspicious

- *Taller-than-wide in transverse plane (E)*
- *Irregular margins (E)*
- *Microcalcifications (F)*
- *Cystic changes (G)*
- *Increased vascularization*
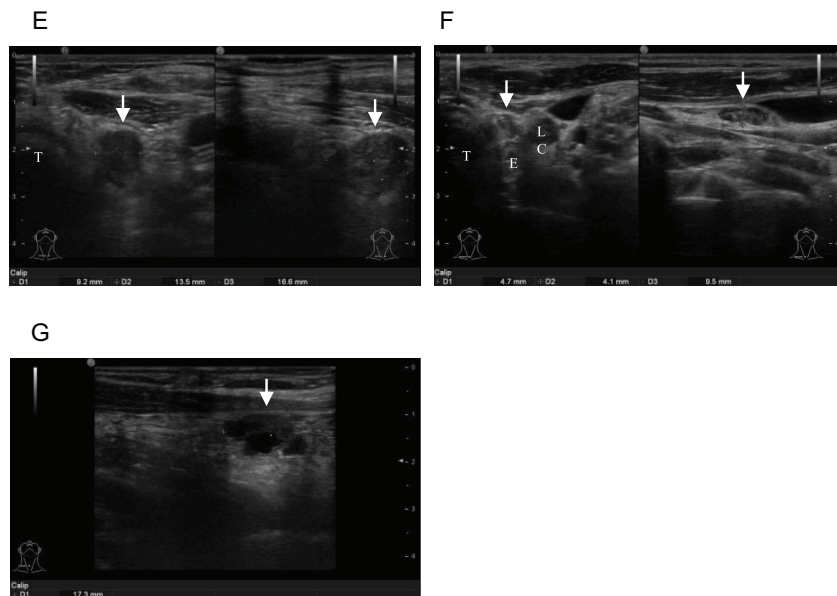
Figure 1

Classification of post-treatment sonographic findings in the thyroid bed. Panels A and B. *Normal findings*: (A) The thyroid bed after total thyroidectomy: the hyperechoic bilateral paratracheal areas are consistent with the postoperative proliferation of fibrofatty connective tissue (arrows); (B) normal left tracheal thyroid gland remnant (arrows): ovoid area, hyperechoic vs anterior muscle tissue. Panels C and D. *Indeterminate findings*: left tracheal thyroid bed nodule (arrows): small, ovoid, hypoecoic nodule, without signs of vascularization, and other US suspicious features. Panels E, F and G. *Suspicious findings*: (E) A hypoechoic nodule in the left tracheal thyroid bed (arrows) appears taller-than-wide with irregular margins; (F) suspicious left tracheal thyroid bed nodule (arrows) with hypoechoic areas and punctate hyperechogenicity representing microcalcifications; (G) left tracheal thyroid bed nodule (arrow): longitudinal scan of a cystic area, with posterior acoustic enhancement. E, esophagus; LC, left carotid artery; RC, right carotid artery; T, trachea; US, ultrasound.

US findings

Images

Normal

- *Identifiable (hyperechoic) hilum (A)*
- *Ovoid shape (A)*
- *Normal size (short axis diameter ≤8 mm for level II, ≤5 mm for levels III, IV and VI) (A)*
- *Absent or exclusively hilar vascularization (B)*
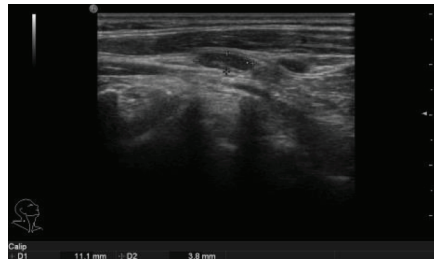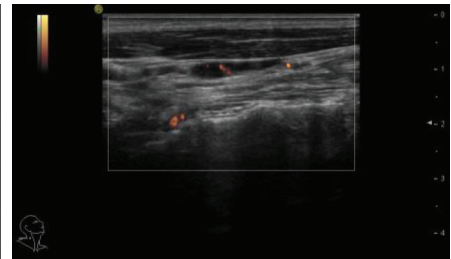
Indeterminate

Absence of hilum +1 or more of the following:
- *Round shape (C)*
- *Increased size (short axis diameter ≥8 mm for level II, ≥5 mm for levels III, IV and VI) (C)*
- *Increased central vascularization*
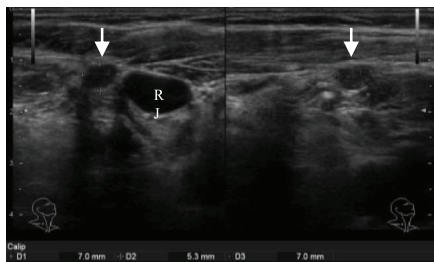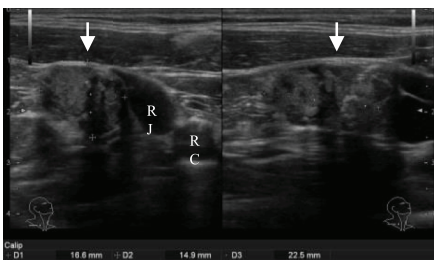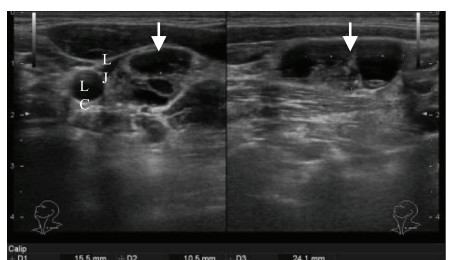
Suspicious

- *Hyperechoic thyroid-like tissue (D)*
- *Microcalcifications (D)*
- *Cystic changes (E)*
- *Peripheral vascularization (F)*
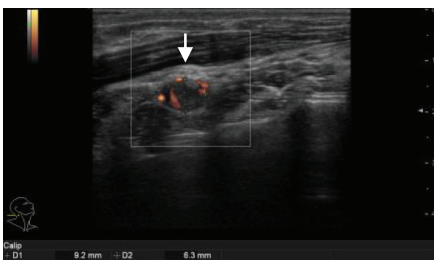
Figure 2

Classification of post-treatment sonographic findings of cervical lymph nodes. Panels A and B. *Normal findings*: This right cervical lymph node (arrows) has a hyperechoic hilum, an elongated shape, short axis ≤5 mm, and exclusively hilar vascularization. Panel C. *Indeterminate findings*: Right cervical lymph node (arrows) with loss of hilum, round shape, and short axis ≥5 mm. Panels D, E and F. *Suspicious findings*: (D) Right cervical lymph node (arrows): thyroid-tissue-like appearance and microcalcifications with posterior shadowing; (E) suspicious left cervical lymph node (arrows) with cystic areas with posterior acoustic enhancement; (F) round right cervical lymph node (arrows) displaying peripheral vascularization. LC, left carotid artery; LJ, left jugular vein; RC, right carotid artery; RJ, right jugular vein; US, ultrasound.

Low-risk patients[a]	Intermediate-risk patients[a]	High-risk patients[a]

First-line imaging studies

▪ *Neck US*	▪ *Neck US* ▪ *Consider DxWBS / SPECT-CT[b]*	▪ *Neck US* ▪ *Consider DxWBS / SPECT-CT[b]* ▪ *Consider CT/MRI*

In the presence of any of the following…

▪ *Structural evidence of disease on neck US* **and/or** ▪ *Non-stimulated Tg >5-10 ng/mL* ▪ *Rising Tg levels* ▪ *Rising Tg antibodies* ▪ *Symptoms referable to distant metastases*	▪ *Non-stimulated Tg >10 nd/mL and negative radioiodine imaging* **or** ▪ *As a prognostic/predictive tool in patients with metastatic disease[c]*

…consider performing:

Second-line imaging studies

▪ *DxWBS / SPECT-CT[b]* **and/or** ▪ *Chest CT without i.v. contrast (pulmonary parenchyma) and with i.v. contrast (mediastinum)* **and, if negative:** ▪ *CT/MRI of the abdomen and/or MRI brain/skeleton* **and/or** ▪ *[18]FDG/PET scan*	▪ *[18]FDG/PET scan*

variability (35) – emerged as the most sensitive (79%) and specific (100%) predictor of thyroid bed recurrence. This feature, however, was found in only 10% of the confirmed recurrences reported by Shin *et al.* and 6% of those classified as 'non-recurrences'. In fact, they found no significant differences between these two classes of lesions in terms of size, shape, echogenicity, margins, calcification, or vascularity and concluded that they could not be reliably differentiated without biopsy (36).

The ETA currently recommends FNA for sonographically suspicious thyroid bed lesions that measure 10 mm or more or display active growth (12). For smaller nodules (<11 mm), growth is actually rare (<10% of cases), particularly when they exhibit no suspicious features (Figs 1 and 2) and are not accompanied by cervical lymphadenopathy or detectable/increasing Tg production. The growth that does occur is typically quite slow (roughly 1 mm/year), suggesting that small thyroid bed nodules can be safely managed with cautious observation and serial sonographic examinations of the neck (37).

Cervical lymph nodes

Metastatic involvement is more commonly found in level III, IV, and VI nodes than in those of level II (38, 39). Normal nodes are typically oval, with short to long axis ratios of <0.5 (Fig. 2A) (15). Size provides limited information on the likelihood of malignancy. Normal ranges vary with the location, with larger nodes found in the submandibular region (level II), possibly because of reactive phenomena related to chronic oral cavity inflammation. Furthermore, many metastatic nodes are normal in size (40).

Studies correlating preoperative sonographic and surgical histology findings indicate that a nonvisualized hilus is the most sensitive predictor of lymph node malignancy (100%), but its specificity was dismally low (29%). The most specific findings are cystic changes (100%), punctuate hyperechogenicity (representing colloid or microcalcifications) (100%), and peripheral vascularization (82%), which also display relatively high sensitivity (86%) (38). In light of these findings, a productive strategy for pinpointing worrisome lymph nodes might begin with a thorough Doppler-based assessment of vascularity in all nodes lacking a hilus (15).

The ATA reserves FNA for sonographically suspicious lymph nodes that exceed 8–10 mm (smallest diameter) and/or display active growth (9). Nodes with suspicious and especially indeterminate findings do not generally increase in size. In a retrospective study on the natural course of US-detected lymph node abnormalities in 166 patients followed with serial US, only 20% of the abnormal nodes lesions grew ≥3 mm during the first 3 years after surgery; moreover, none caused pain or compression of vital structures, and 14% disappeared entirely over time, with no treatment at all (41).

Post-treatment staging and surveillance

Ultrasound plays an especially important role in the early surveillance of the growing subpopulation of DTC patients treated with lobectomy or with total/near total thyroidectomy without RRA (12, 42, 43). In the presence of normal thyroid tissue (even small remnants), the result of a single serum Tg assay is of limited use. In these cases, Tg assays provide reliable information on the presence of persistent/recurrent disease only later, when serial measurements are available, and can be analyzed to identify increases in Tg production over time (44, 45, 46, 47). Substantial rises are an indication for additional imaging work-up (US and/or second-line studies) (Fig. 3) (9, 12).

Normal findings in the initial post-treatment neck scan are strongly associated with excellent long-term outcomes (14). The negative predictive power is virtually 100% in very low-risk patients with microPTCs (48) and excellent in intermediate-risk patients as well. Peiling Yang *et al.* reviewed 90 cases of ATA intermediate-risk PTC treated with total thyroidectomy and RRA, with negative basal Tg and TgAb assays, and negative or only indeterminate findings (Figs 1 and 2) on the first post-treatment US.

Figure 3

Risk-stratified use of diagnostic imaging modalities in the initial post-therapeutic staging of differentiated thyroid cancer. (a) Risk of persistent/recurrent disease as reported in the 2015 American Thyroid Association Guidelines for the Management of Thyroid Nodules and Differentiated Thyroid Cancer (Haugen 2015). (b) In patients with uptake on DxWBS, SPECT–CT allows (i) more precise anatomical localization of radioiodine uptake, (ii) exclusion of nonspecific uptake, and (iii) identification of noniodine-avid lesions. (c) [18]FDG/PET helps identify patients at highest risk for rapid disease progression and disease-specific mortality (prognostic role) and/or those with radioiodine-refractory disease (predictive role). [18]FDG/PET, ^{18}F-fluorodeoxyglucose positron emission tomography; CT, computed tomography; DxWBS, diagnostic whole-body scan; MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography; Tg, thyroglobulin; US, ultrasound.

The rate of structural disease recurrence during follow-up (median 10 years) was 8% (4/49) in the subgroup whose initial US findings were negative (as opposed to 12% (5/41) in the group with indeterminate scan results) (49).

In many facilities, neck sonography is still done routinely, once or even twice a year, even when the risk of recurrence is low (12, 50). A recent retrospective analysis of over 1000 cases of PTC treated between 2000 and 2010 at Memorial Sloan Kettering Cancer Center found that during the first 3 years of surveillance, the number of US examinations per patient ranged from 1.3 in low-risk patients to 1.9 and 1.8 in intermediate- and high-risk groups – already appreciably lower than rates reported in other retrospective studies (51). Nonetheless, the number of scans needed to detect 1 recurrence event in the low-risk cohort (154.0) was 6–7 times higher than those of the intermediate and high-risk groups (23.9 and 13.0 respectively), indicating that there is substantial room for improving the cost-effectiveness of US surveillance of low-risk patients (50).

Similar conclusions were reached in the study cited above by Peiling Yang *et al.* (49). The 90 intermediate-risk patients they retrospectively reviewed were followed with *routine* cervical US and Tg assays at 6–12 month intervals, and structural recurrence emerged in only 9 (10%). All the lesions were sonographically detected. However, in 5/9 cases, the disease was also heralded by other findings (rising Tg levels in most cases) and would thus have been identified even if US had not been used so frequently. These authors also underscored the high probability of false-positive findings associated with frequent US examinations in populations of this sort. In 51 (57%) of the cohort patients, the routine scans yielded new or persistently atypical findings, which led to a host of additional diagnostic procedures (first- and second-line imaging procedures, FNA), none of which disclosed any clinically significant structural disease. On the basis of these findings, these authors suggest that in intermediate-risk DTC patients whose initial post-treatment assessment reveals no structural or biochemical evidence of disease, sonographic surveillance can be discontinued if the second assessment is also negative (49).

These conclusions are supported by recent findings confirming the strong associated between normal findings at the initial assessment and excellent long-term outcomes (14). They are also consistent with the ETA's current guidelines regarding the first 5 years of follow-up, when over three-quarters of recurrences are identified (3). During this period, yearly US scans are recommended only for patients meeting the ETA's high-risk criteria (some of whom are classified as intermediate-risk according to ATA criteria) and only when warranted by pTNM staging, serum Tg levels, and responses to therapy (12). For low- and very low-risk patients with normal findings at 6 months, 'regular' scans are considered unnecessary.

When doubts on the presence of distant metastases arise, additional imaging is required (Fig. 3). The following section provides a concise profile of the methods most commonly used.

Cross-sectional imaging

The cross-sectional imaging studies include CT and MRI scans. Both allow high-precision anatomic localization and measurement of disease foci and are especially useful for assessing the tumor burden in patients with extensive local disease or distant metastases. To identify the nature of the mass, however, the results have to be interpreted within the clinical context of the individual patient. When doubts arise or discordant findings emerge (e.g. a lesion compatible with metastatic lung disease in a low-risk patient with undetectable serum Tg and negative Tg antibody assays), cytological or histological confirmation is needed. When foci of metastatic disease are found, options include local or systemic therapy and simple surveillance alone. Lesions that represent no immediate threat to the patient should be treated only if the tumor burden is substantial or when there is obvious progression. The latter can be documented using the Response Evaluation Criteria in Solid Tumors, RECIST 1.1 system) (52).

Evidence supporting the utility of cross-sectional imaging modalities comes largely from experience with other solid tumors; data on their specific use in thyroid cancer are lacking. According to the ATA, cross-sectional imaging of the neck and chest should be considered in the following cases: (i) patients with extensive recurrent nodal disease; (ii) patients with negative findings on cervical US and WBS and a high serum Tg level (generally exceeding 10 ng/mL), or rising Tg or Tg antibodies values; and (iii) in cases where reliable assessment of potential aerodigestive tract invasion is needed (9). Rarer sites of thyroid cancer metastases should be explored when a clinical suspicion arises or in high-risk patients with high serum thyroglobulin levels (10 ng/mL) and no evidence of lung/mediastinal metastases (Fig. 3).

The optimal timing for cross-sectional imaging studies in patients with DTC is not well defined: recommendations range from 3 to 12 months after treatment, depending on the tumor burden, location of the disease,

histology, and Tg trend (9). Anyway, many thyroid cancer clinical trials have enrolled patients with progressive disease evaluated over a period of ≤12 months and baseline assessment performed no more than 4 weeks before treatment introduction (52).

Computed tomography

The anatomic resolution of a CT scan is sufficiently high to allow precise localization of disease foci, and compared with other second-line studies, it offers distinct advantages in terms of availability, cost, and examination times. The lungs can be explored with high-resolution CT without contrast (9), but contrast-enhancement with iodine is best for exploration of the mediastinum. Contrast-enhanced scans are also recommended before surgery to identify possible areas of vascular invasion; for assessment of the retrotracheal space, it is used as a complement to neck US (9).

The radiation exposure associated with CT imaging has been linked to an increased risk of cancer (53). This risk should be weighed against the aggressiveness of the patient's disease when decisions are being made on the use and frequency of CT in the post-treatment surveillance of DTC patients.

Magnetic resonance imaging

Unlike CT, MRI is associated with absolutely no radiation exposure. It offers excellent soft-tissue contrast, which is particularly useful when esophageal and/or tracheal invasion is suspected (54, 55). Although its specificity is relatively low (51%), MRI offers excellent sensitivity (95%) for the detection of metastatic lymphadenopathy in DTC patients (56). It is particularly useful for ruling out nodal involvement in the mediastinum (57), which is poorly visualized on ultrasound. Its main shortcomings are related to the duration of the examination and the possibility of false-negative findings related to movement artifacts.

MRI is the imaging modality of choice for identifying thyroid cancer metastases to the bone, brain, or liver. The bones most frequently targeted by these lesions (and metastases from other cancers as well) are those with high blood flow: the vertebrae, the ribs, and the hips (58). Its high soft-tissue contrast is very useful for exploring the marrow and paraosseous structures (e.g. spinal canal) with a detection limit of 2 mm (59). Whole-body MRI has displayed 100% sensitivity, 80% specificity of 80%, and 96% accuracy in the detection of bone metastases in cancer patients, and its performance is only slightly inferior in patients harboring more than one lesion (sensitivity, specificity, and accuracy: 94, 76, and 91% respectively (59). The addition of background body signal suppression (DWIBS) significantly increases the accuracy of MRI for bone metastasis detection, and the accuracy of this approach has proved to be similar to that of ^{18}F-fluorodeoxyglucose PET (94%) in a small cohort of 23 patients (60).

In patients with solid tumors, MRI is superior to CT for the detection of brain metastases because it provides higher soft-tissue contrast, no bone artifacts, and fewer partial volume effects. Paramagnetic contrast agents also produce significantly stronger enhancement than those used with CT (61). In the presence of multiple brain lesions, roughly 20% of the lesions identified with MRI are missed on CT (61).

Approximately, 0.5% of DTC metastases are located in the liver. They usually develop late in the course of the disease in patients with other distant metastases (62). Evidence-based guidelines recommend CT or MRI identification of liver metastases. Data are lacking in DTC, but MRI is considered preferable to CT for exploring liver metastases from most endocrine tumors (63, 64).

Functional imaging

Radioiodine imaging

Radioiodine imaging exploits the capacity of thyroid cells to take up iodine from the circulation, which is mediated by the sodium iodine symporter (NIS). This capacity is generally preserved in thyroid cancer cells although they might display decreased (65, 66) or even absent (67, 68) *NIS* expression. Iodine metabolism in thyroid cancer cells can also be influenced by somatic mutations, such as *BRAF* V600E, which is associated with downregulated expression of iodide-metabolizing genes (69). Radioiodine can be used to obtain planar or three-dimensional images (classic radioiodine scintigraphy vs single-photon emission computed tomography, SPECT).

Diagnostic whole-body radioiodine scintigraphy

Although the accuracy of a diagnostic WBS is approximately 84–90%, its specificity (91–100%) far exceeds its sensitivity (27–55%) (70, 71, 72, 73). It is the most sensitive tool for thyroid remnant detection and thyroid remnant ablation assessment (74, 75). It is also useful for early detection of distant metastases. These lesions, however, are relatively uncommon in DTC

patients: they are found in only ~3% of DTC patients at diagnosis and in 10% or less during follow-up (3, 76, 77). The ATA thus recommends routine diagnostic WBS during follow-up only when the risk of persistent/recurrent disease and extracervical metastases is intermediate or high (Fig. 3) (9). Even in these cases, there is no need to repeat the DxWBS if the RxWBS yields negative findings, especially if Tg production is undetectable and the Tg antibody assay is negative (17, 78, 79, 80, 81). In contrast, DxWBS can be useful for monitoring (and for planning additional imaging work-up) of distant and/or local foci of radioiodine uptake revealed on post-therapeutic WBSs, and it is also an option for assessing the presence of distant metastases when positive Tg antibody levels render serum Tg levels unreliable markers of disease (9).

DxWBS can also be helpful in calculating therapeutic doses of radioiodine (82). It is important to recall, however, that a diagnostic dose of ^{131}I (the isotope most widely used for diagnostic scans in DTC patients) can reportedly reduce the uptake of radioiodine subsequently administered for therapeutic purposes, particularly when the two administrations are separated by more than 3 days and fewer than 7 days – a phenomenon known as the 'stunning effect' (83). However, in a recent study of two consecutive cohorts of DTC patients undergoing RRA, ablation rates and detection rates of disease recurrence were similar in the patients whose ablations were or were not preceded by a diagnostic scan (84). Stunning is not caused by diagnostic scans performed with ^{123}I (85, 86, 87). This pure gamma emitter is ideal for use with modern gamma cameras and provides higher image resolution than ^{131}I. Its use is limited, however, by its high cost and low availability (due to its short half-life).

WBS has a number of practical drawbacks. The detection limit depends on several factors, including the activity administered, the timing of image acquisition following RAI administration, the type of equipment used (crystal thickness), and the patient's renal function status (88). A successful scan also requires a lengthy period of patient preparation (3–4 weeks) to maximize tracer uptake. This involves a low iodine diet and elevation of TSH levels by withdrawal of thyroid hormone replacement therapy. The latter is often associated with unpleasant symptoms of hypothyroidism. Administration of recombinant human TSH (rhTSH) is an effective alternative that is more expensive but decidedly better tolerated. In addition, patients who have recently undergone computed tomography scanning with iodinated contrast medium must wait 4–8 weeks before they have a radioiodine WBS (89). Radiation exposure is also a consideration. The examination involves administration of a radioactive tracer (albeit at low doses). The radiation risk also involves persons who are in contact with the patients, so radioprotection measures must be adopted for the 10–15 days following the scan. Disease is anatomically located based on the RAI uptake observed on the planar whole-body image and, if necessary, images of specific body regions, such as the neck. The precision of this approach is nonetheless limited. Because RAI can be concentrated by both normal and neoplastic thyroid tissue, RAI scintigraphy cannot be used to identify foci of persistent/recurrent disease in the thyroid bed. False-positive results can also be caused by the physiologic or pathologic accumulation of radioiodine in nonthyroidal tissues and body fluids (Table 2) (90). The sensitivity of WBS can be reduced in the presence of large amounts of normal thyroid tissue: these remnants can sequester almost all of the administered ^{131}I activity, thereby reducing visualization of smaller metastatic lesions (9). When a large remnant is visualized on post-therapeutic WBS, a diagnostic WBS can be evaluated to reassess the presence of local or distant metastases (9). WBS is also of no value in the patients whose tumors have lost the ability to concentrate RAI (91), a phenomenon encountered in up to two-thirds of patients with distant metastases (the subpopulation most likely to benefit from WBS) (92).

Single-photon emission computed tomography/computed tomography

In single-photon emission computed tomography (SPECT), the two-dimensional tomographic images acquired with the SPECT gamma camera are elaborated to provide a three-dimensional representation of the region being examined. SPECT–CT involves the co-registration and fusion of SPECT images and those acquired with a conventional CT scan. This dual-modality approach improves the localization

Table 2 False-positive radioiodine uptake.

Physiologic uptake
  Choroid plexus
  Lachrymal sac and tears
  Nasopharynx and nasal secretions
  Salivary glands and saliva, oral cavity, esophagus
  Breast and breast milk
  Liver, gallbladder, and biliary tract
  Kidneys, urinary tract, and urine
  Stomach
  Large bowel and feces
Pathologic uptake
  Inflammation
  Benign tumors
  Malignant tumors

and facilitates measurement of lesions seen on SPECT scintigraphy. The specificity of SPECT–CT is high (up to 100%) and the sensitivity is 50% (93).

Costs and availability are major considerations in decisions on the use of SPECT–CT. In the follow-up of patients with DTC, SPECT–CT is performed with diagnostic or therapeutic activities of radioiodine. Consequently, it has the same drawbacks as RAI WBS in terms of patient preparation and the need for postscan radioprotection measures. On the other hand, the SPECT–CT fusion images elaborated by the scanner software allow more precise localization of foci of RAI uptake as well as lesions that are not RAI-avid. For this reason, SPECT–CT is less likely to produce false-positive and indeterminate results (94, 95), and it reportedly provides a gain in information over that furnished by WBS alone in 35–68% of patients (94, 96, 97). In a recent study, SPECT–CT performed after RRA revealed additional disease foci (neck lymph nodes and/or distant metastases) in about 9% of the patients whose RxWBS showed uptake only in the thyroid bed. Results of this type were particularly common when stimulated Tg levels were ≥1.8 ng/mL. In patients with RxWBS findings suggestive of cervical lymph node metastasis, 40% of the lesions were reclassified as normal thyroid remnants on the basis of SPECT–CT results (98).

## ^{18}F-fluorodeoxyglucose positron emission tomography

Positron emission tomography is being employed more and more often for all types of cancers. The most common tracer used in clinical settings is ^{18}FDG, a glucose analog that is taken up by benign as well as neoplastic cells. The latter cells' demand for glucose, however, is markedly increased owing to their reliance on anaerobic glycolysis, which is far less efficient for energy production than oxidative phosphorylation. The metabolic information provided by this technique is the basis for PET's use as a diagnostic and prognostic tool in cancer patients (e.g. for evaluating the response to treatment and estimating the risk of death). The PET/CT is a more recently developed technique that uses integrated scanners to acquire PET and CT images in a single session. The combination of functional and morphologic data furnished by this approach substantially improves the anatomic localization of lesions. Two meta-analyses analyzed the diagnostic performances of ^{18}FDG PET and ^{18}FDG PET/CT for the detection of persistent/recurrent DTC in patients with detectable Tg and no evidence of RAI uptake (99, 100). In both cases, the patient-based sensitivity of PET/CT was appreciably higher than PET alone (93–94%

vs 83–84% for ^{18}FDG PET). The ATA strongly recommends ^{18}FDG PET/CT for high-risk DTC patients with elevated basal or stimulated serum Tg (generally >10 ng/mL) and negative findings on radioiodine imaging during follow-up (9). In case of lower thyroglobulin levels, ^{18}FDG PET/CT can be false negative due to the presence of microscopic disease. The specificities of ^{18}FDG PET alone and PET/CT methods were similar (81–84%) (99, 100). This is due to the fact that inflammation also increases FDG uptake. When ^{18}FDG PET is used to stage DTC, care must be taken to differentiate increased uptake by thyroid-derived neoplastic tissue from that observed in nonthyroid tumors (Fig. 4). Uptake can also be increased merely by the presence of inflammation (e.g. reactive lymph nodes, inflammatory joint changes) (Fig. 4).

Disease relapse and staging

^{18}FDG PET findings lead to changes in patient management strategies (generally involving the surgical plan) in about 30% of the cases (101, 102, 103). As noted, however, false positivity related to inflammation is possible. Therefore, if surgery is planned on the basis of FDG uptake, the true metastatic nature of cervical lymph nodes must always be verified intraoperatively or preoperatively via FNA.

^{18}FDG PET positivity in thyroid cancer is influenced by several other factors, including primary tumor histology, the presence of RAI-refractory disease, overall tumor burden, disease localization, and TSH levels at the time of the scan. ^{18}FDG avidity is most commonly seen in the more aggressive DTC forms. Histopathological analysis of distant metastases from 70 ^{18}FDG-avid thyroid tumors revealed that almost half were poorly differentiated cancers, 20% were tall-cell variants, and 9% were Hürthle cell carcinomas. However, almost one-fourth (23%) were well-differentiated cancers. In 16 (37%) of the 43 patients whose primary tumor was also analyzed, the ^{18}FDG-avid metastases presented more aggressive histological features than the primaries (104). Distant metastases that take up ^{18}FDG are frequently refractory to radioactive iodine therapy, even at high doses, and most of these lesions exhibit signs of metabolic progression during the first year after treatment (105). ^{18}FDG uptake in RAI-refractory thyroid cancer is correlated with loss or downregulation of *NIS* expression and increased expression of glucose transporter 1. The *BRAF* V600E mutation can also cause this metabolic pattern, and this may explain the ^{18}FDG uptake observed in well-differentiated thyroid cancer harboring this mutation (69). Patients with detectable thyroglobulin production and suspected recurrence are sometimes referred for empirical RAI treatment to search and treat disease localization. However,
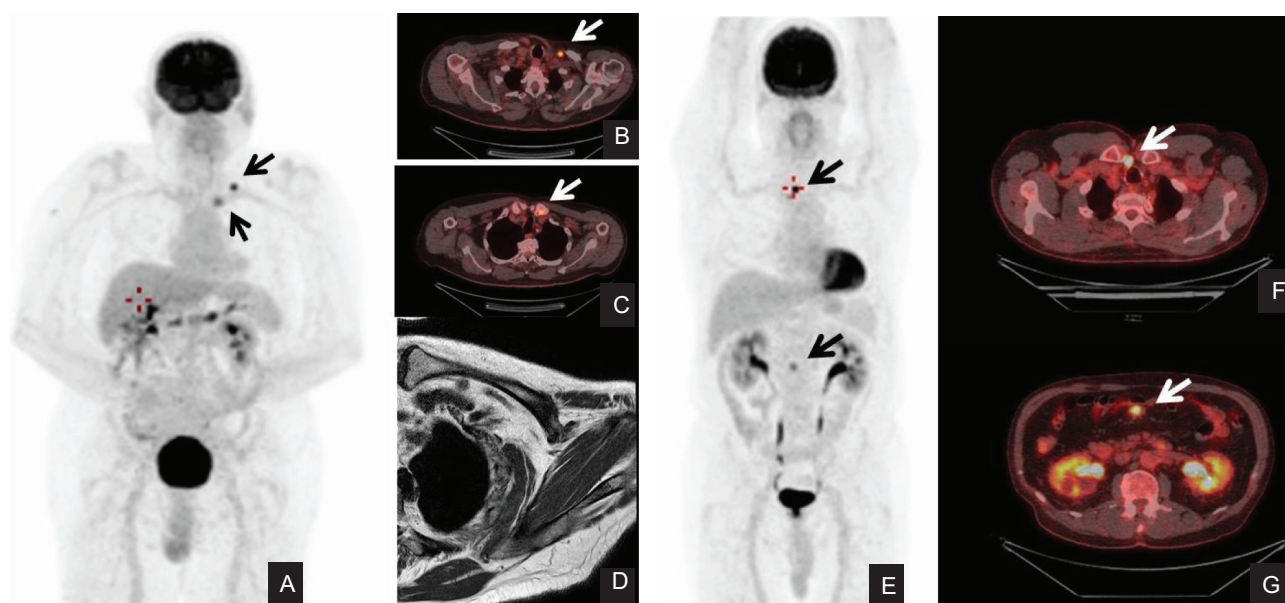
Figure 4

[18]FDG PET findings in the follow-up of differentiated thyroid cancer. [18]FDG PET/CT in a patient with tall-cell variant thyroid cancer (panel A) showed a retroclavicular left metastatic lymph node (panel B, axial view) and high and focal uptake also in the left clavicle (panel C, axial view) suspicious of bone metastases. MRI confirmed to be arthrosis (panel D). FDG PET in a patient with recurrent papillary thyroid cancer (panel E). High FDG uptake was detected in a superior mediastinal lymph node (panel F, axial view) and in mesenteric lymph node (panel G, axial view) suspicious for recurrence. Biopsy confirmed thyroid cancer recurrence in the mediastinal lymph node, but it was in favor of a B cells lymphoma in the mesenteric lymph node.

in roughly one-third of these patients, the post-treatment whole-body RAI scan is negative and [18]FDG PET is more sensitive to detect recurrence, suggesting that it might be useful to perform [18]FDG PET before giving empiric radioactive iodine treatment in these patients (106).

In addition to its recommended role in the follow-up of patients with aggressive histology and RAI-refractory disease, FDG PET is also potentially useful in the primary staging of high-risk patients (Table 1). Lee et al. retrospectively analyzed 258 patients who underwent RRA and [18]FDG PET/CT during the same period of time. Compared with the post-treatment WBS, [18]FDG PET/CT revealed additional positive findings in 25% of the patients with high- or intermediate-risk thyroid cancers (pT3-T4N1 and tumor size >2 cm) but only 3–6% of those with lower-risk tumors (T3-T4 N0 or T1-T2 N1 and size <2 cm), and the gain in information led to a change in management in 17% of the cases (107). Nascimento et al. retrospectively evaluated 38 patients with aggressive thyroid cancer histotypes and no evidence of disease after surgery. [18]FDG PET/CT performed after the first RRA revealed persistent disease in 15 (39%) of these patients; only 12 of these cases were identified with the post-therapeutic RAI WBS (108). Of the 86 lesions

detected in this cohort, 41% were detected only by [18]FDG PET/CT and 31% were seen only on the post-therapeutic WBS, indicating the two techniques play complementary roles (108). Additional studies are nonetheless necessary to validate the utility of this approach in routine practice.

The serum thyroglobulin level is an indirect index of the tumor burden. Current guidelines recommend [18]FDG PET/CT when Tg levels exceed 10 ng/mL (9), and this threshold has been used in several studies. However, FDG PET positivity is also associated with lower thyroglobulin levels (101, 109). For this reason, lower thresholds have been proposed. Giovanella et al., for example, suggested a level of 4.6 ng/mL, which was associated with a sensitivity of 96% (110). Based on a subsequent analysis of 102 cases, the same investigators also demonstrated that [18]FDG-PET positivity is predicted by a serum thyroglobulin doubling time of less than 1 year, regardless of the Tg level itself (111).

Ultrasonography is still the best tool for detection of cervical lymph node metastases, but [18]FDG PET can be useful for identifying recurrence in areas that are difficult or impossible to explore sonographically, such as the upper mediastinum or the retropharyngeal region (101, 112). As for distant metastases, [18]FDG PET can often

detect small bone lesions that are missed on CT or MRI scans. However, CT is still the method of choice for identifying lung metastasis, especially the micronodular form that is so common in thyroid cancer. These lesions are often [18]FDG-negative due to a partial volume effect (113).

The sensitivity of [18]FDG PET can be influenced by TSH stimulation. Conflicting results have been reported on this issue. However, in a recent meta-analysis of seven prospective controlled clinical trials (168 patients), per-patient and per-lesion analyses both revealed more positive findings and a better tumor/background ratio when [18]FDG PET was performed under TSH stimulation than when it was done during LT4 treatment (114). However, [18]FDG PET performed after the administration of rhTSH has also been associated with false-positive findings, especially in cervical lymph nodes. As noted above, positive [18]FDG findings must be interpreted with caution (102). If, for practical reasons, [18]FDG PET cannot be performed under TSH stimulation during follow-up, it can be done at the time of RAI treatment to take advantage of the TSH stimulation.

Prognostic value

In DTC patients with distant metastases, reported 10-year survival rates range from 25 to 42%, and the presence of RAI-refractory disease is a major determinant of mortality (92). [18]FDG uptake is currently considered an important tool for predicting overall survival and response to therapy in this population. In a study of 80 patients with distant metastases from thyroid cancer, [18]FDG uptake was the only independent predictor of overall survival: rates at 2 years were 100% in patients with [18]FDG-negative lesions but only 60% for those who were [18]FDG-positive. Furthermore, in the PET-positive subgroup, overall survival was unrelated to the lesions' RAI avidity. Mortality was also associated with the [18]FDG uptake level (SUV Max of >5) and number of [18]FDG-avid lesions (>10) (115), which is consistent with previous findings (116). Wang *et al.* found no significant response to radioactive iodine therapy in lesions that displayed [18]FDG uptake, even those that also took up radioactive iodine (105). [18]FDG uptake is also correlated with other clinical factors that predict nonsurvival and/or nonresponse to ^{131}I treatment, such as age over 45 years and the presence of necrosis (115, 116).

Other radiopharmaceuticals

PET can also be performed with iodine-124 ([124]I). The sensitivity of this approach exceeds that of diagnostic and therapeutic WBS done with ^{131}I not only because it provides tomographic images, but [124]I PET also offers higher resolution (117, 118, 119). Nonetheless, it has also been associated with false-negative findings in patients with miliary lung nodules (120). The half-life of [124]I (4.2 days) allows the acquisition of sequential images for uptake quantification over time. [124]I PET-guided lesional 3D dosimetry together with blood clearance studies can predict the absorbed lesion dose, improve selection of the safest and most effective ^{131}I activity to administer, and predict responses to RAI treatment (121, 122). Nowadays, [124]I PET is used almost exclusively in research settings owing to the limited availability of the tracer and the growing use of SPECT–CT for post-therapeutic ^{131}I scan. ^{18}F-Fluoride PET has been proposed for evaluating bone metastases from thyroid cancer, but the lytic nature of these lesions makes their evaluation difficult (123).

The performance of a new hybrid PET/MRI machine has recently been evaluated in thyroid cancer. Vrachimis *et al.* compared FDG PET/MRI with FDG PET/CT in DTC patients with detectable thyroglobulin production and found that the new method offered no diagnostic gains: recurrence detection rates were actually lower with FDG PET/MRI (85% vs 97% for FDG PET/CT) (124). Iodine 124 PET/MRI has also been used for lesion detection and dosimetry in high-risk thyroid cancer patients with lymph nodes metastases. The authors reported that MRI was superior to CT for identifying pathological lymph nodes, especially those smaller than 10 mm (125), but this issue requires further study.

Conclusions

The diagnostic imaging studies reviewed above play fundamental roles in post-treatment surveillance of patients with DTC. As in other settings, the key to success is selecting the proper tool(s) for the task at hand.

Figure 3 summarizes the current recommendations of the ATA for rational use of imaging studies during DTC follow-up assessments, including post-treatment staging and subsequent surveillance. The choice of first-line tools for this process may vary somewhat from center to center, depending on local resources. Cost and availability have to be considered. Studies available only in a few highly specialized centers may be useful in many patients, and depending on local resources, they may have a place in the first-line armamentarium (e.g. in a facility that includes a nuclear medicine department, WBS/SPECT–CT can be useful for routine use in several patient subsets).

However, they are likely to be problematic for repeated use on patients being followed in facilities not located in metropolitan areas. Likewise, safety and tolerability are always valid concerns, but they play particularly important roles in ensuring patients' continuing participation in routine surveillance activities.

In the end, however, the final choice will be determined largely by the likelihood and probable location of persistent/recurrent disease and the sensitivity of the test for detecting this type of disease. In this context, the fact that over 85% of all thyroid cancers are PTCs (126, 127) is highly pertinent since these tumors spread via the lymphatics. One out of four PTC patients will develop cervical lymph node metastases (http://seer.cancer.gov/stat-facts/html/thyro.html; last accessed 17 January 2016), whereas distant metastases are rare in PTC, particularly in the absence of cervical lymphadenopathy. Given its high sensitivity for thyroid bed and cervical lymph node lesions, its excellent safety and tolerability profiles, wide availability, and low cost, neck US is thus an ideal first-line imaging tool for use in almost all DTC patients and in almost all settings.

Second-line imaging studies are used more selectively and in cases where there is at least some reason to suspect metastasis (elevated or increasing levels of serum Tg, rising Tg antibody titers, atypical first-line imaging findings). The importance of specificity increases at the second-line level, and the higher risk status also justifies the use of methods that are most costly, less accessible, and/or more likely to be associated with some adverse effects.

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