Review

Update in thyroid imaging. The expanding world of thyroid imaging and its translation to clinical practice

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In recent years thyroid imaging has marked exponential progress, considerably changing the approach to diagnosis, prognosis, treatment, follow-up and evaluation of high prevalence thyroid diseases such as goitre, thyroid nodules and primary thyroid cancer. What is more, this notable technical advance has proven its ability to effectively confront such complex challenges as the identification of incidental thyroid nodules and the achievement of more accurate evaluation of recurrent/residual thyroid carcinoma.

Today, thyroid nodules constitute a frequently encountered problem with rates around 15% to 20% in the general population, its prevalence increasing up to 50% when detection is achieved via Ultrasound (US) rather than by palpation.[1] However, only 5% to 10% of thyroid nodules are malignant, even among those found incidentally.[2,3] Although the cornerstone of the evaluation of thyroid nodules is still based on clinical diagnosis and Fine-Needle Aspiration (FNA), in the last 10 years imaging techniques, especially Ultrasonography (US), have proven of great value.

Key words: Fine needle aspiration biopsy, Positron emission tomography, Thyroid imaging, Thyroid nodules, Thyroid ultrasonography

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Furthermore, lately new imaging modalities such as US elastography, new radionuclides for thyroid scintigraphy and Proton Emission Tomography (PET) are being included in the diagnostic algorithm of thyroid diseases.

ULTRASONOGRAPHY

A large number of reports have been published examining the clinical features of thyroid nodules as predictors of malignancy.[4,5] However, there is no single pathognomonic clinical characteristic indicating malignancy and great discrepancy at present exists amongst the various characteristics of thyroid cancer as presented in the medical literature. Hamming et al[6] described as high risk factors a fast growing firm nodule, vocal cord paralysis, lymph nodules metastasis and a familiy history of thyroid cancer. The presence of one risk factor represents a risk for malignancy of about 71% and the concurrence of any two or more factors denotes a probability close to 100%. Moreover, conventional imaging techniques such as Chest X-Ray or Computed Tomography (CT) have limited value in malignancy evaluation.

In this context, US has gained an important role in the evaluation of thyroid diseases. US does not use ionizing radiation and has no side effects; it is moreover less costly and is more widely available than other imaging modalities. In recent years, the rapid development of US equipment with high frequency transducers yield (7-13 MHz) and high-resolution images of the superficial neck structures has enabled a higher detection of clinically non-palpable nodules and a more accurate description of morphologic features.[7-11] Additionally, color-doppler imaging can determine the vascular pattern of a nodule or other thyroid diseases, while US examination allows fairly objective comparisons of nodule growth during clinical follow-up. Obviously, the improvement in US technical performance also facilitates the detection of very small thyroid lesions (2–3 mm) in up to 50% of the general population, raising the question of which nodules warrant evaluation by FNA.

High-resolution US characteristics of nodules have been shown to be useful for assessment of their malignancy potential.[10] The echographic patterns most frequently associated with thyroid carcinoma are microcalcifications, hypoechogenicity of the nodule compared to the surrounding parenchyma, irregular margins or absent halo sign, solid pattern, intranodular vascularization and certain shape (taller than wide) (Table 1). Nevertheless, it is widely recognized that any single echographic pattern cannot be considered specific for malignancy because of its low predictive value. However, when multiple patterns suggestive of malignancy are simultaneously present in a nodule, the specificity increases, though accompanied by a

Table 1. Sensitivity, specificity and predicitive value of various echographic patterns associated with thyroid carcinoma.

US patterns	Sensitivity %	Specificity %	PPV %	NPV %
Microcalcifications	6.1-59.1	85.8-95.0	24.3-70.7	41.8-94.2
Hypoechogenicity	26.5-87.1	43.4-94.3	11.4-68.4	73.5-93.8
Irregular margins or no halo sign	17.4-77.5	38.9-85.0	15.6-27.0	88.0-92.1
Solid appearance	26.5-87.1	43.4-94.3	11.4-68.4	73.0-93.8
Intranodular vascularity	54.3-74.2	78.6-80.8	24.0-41.9	85.7-97.4
Taller than wide	32.7	92.5	66.7	74.8

PPV: Positive Predictive Value, NPV: Negative Predictive Value. (From Rago T, et al,[10] with permission).

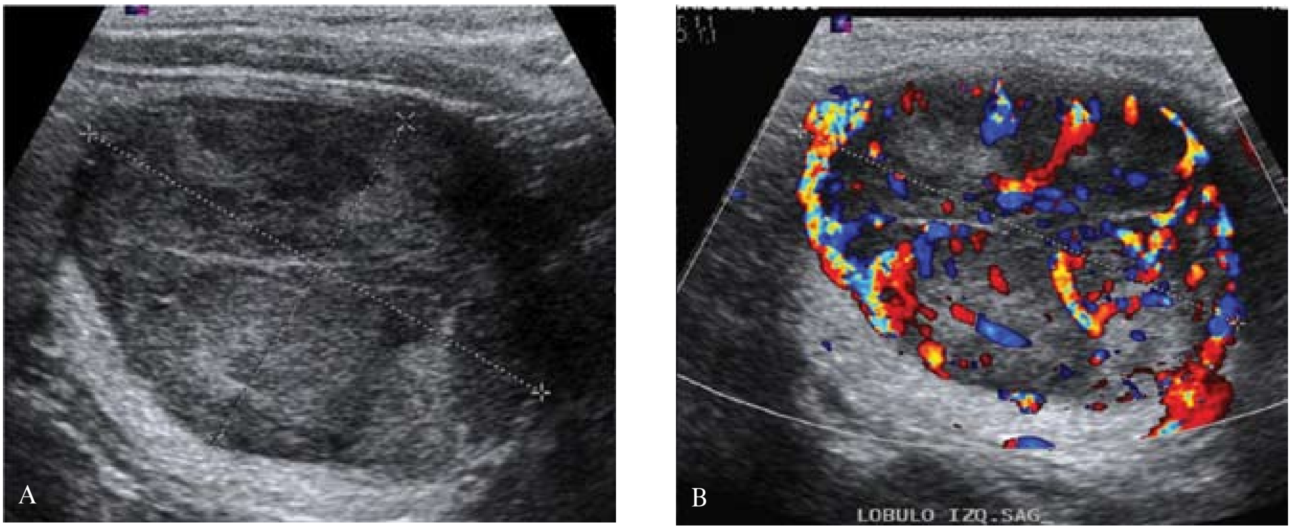


Figure 1. A. Transverse ultrasound scan shows a well-defined, homogeneous, solid iso-hypoechoic oval-shaped thyroid nodule, suggestive of a follicular lesion. **B.** T ransverse color-doppler scan demonstrates intranodular and peripheral vascularity.

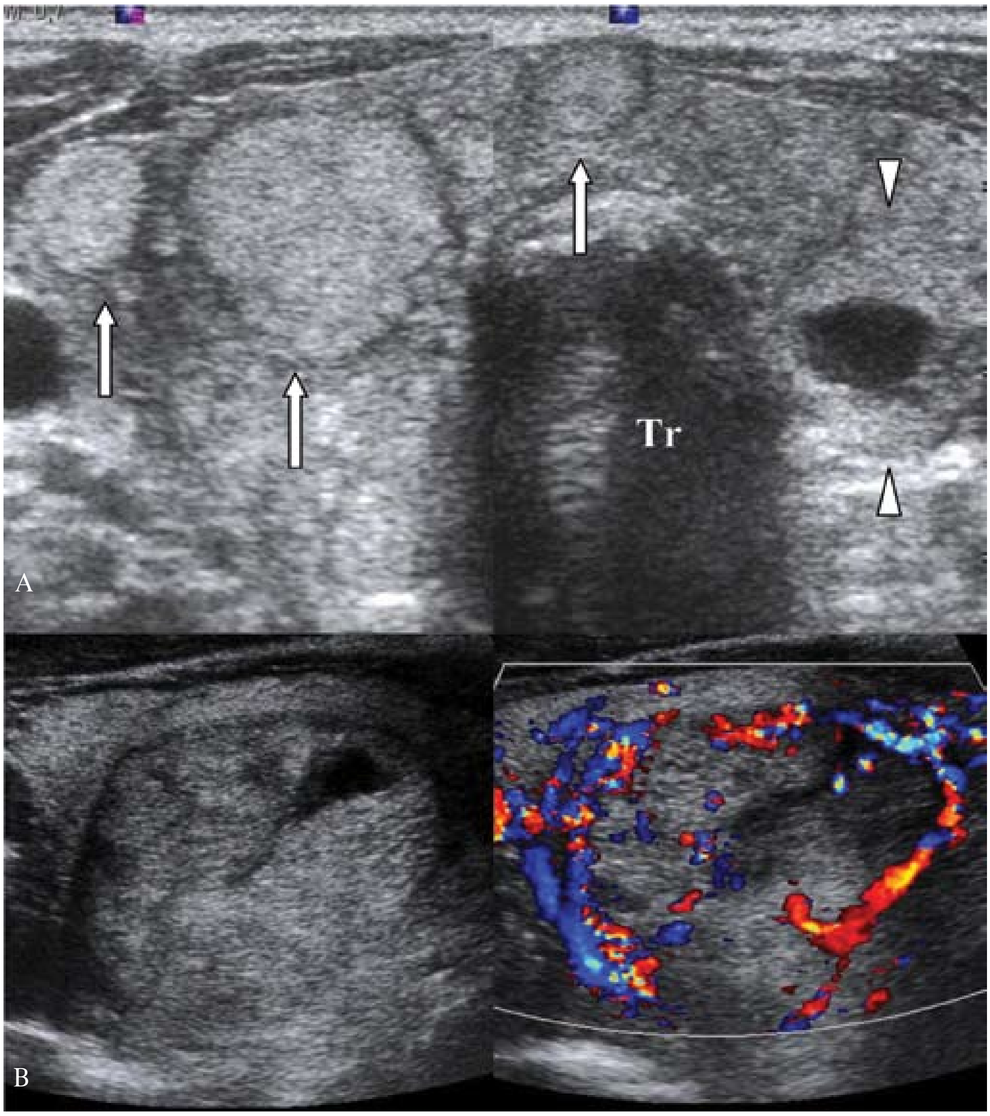


Figure 2. Multinodular goitre. **A.** Transverse dual ultrasound image shows enlargament of thyroid lobes and isthmus and multiple hyperechoic solid nodules with uniform thin halo (arrows). Mixed solid and cystic thyroid nodule in the left lobe. Tr: tracheal gas shadow. **B.** Transverse sonogram and color-doppler mode scan show a well-defined isoechoic thyroid nodule with thin complete hypoechoic halo, intranodular cystic/colloid space and peripheral vascularity, findings indicative of a hyperplastic nodule.

sensitivity decrease. US has gained such an important role in thyroid nodule evaluation that in all recent consensuses on the evaluation of thyroid nodules it has been agreed that thyroid US is essential for selection of nodules that warrant FNA[12-15] (Figures 1-4).

Furthermore, US is an important tool for the evaluation of cervical lymph nodes. Lymph nodes with metastatic lesion appear either rounded and solid with absence of the hyperechoic striae corresponding to the hilus, or cystic. Sometimes the pattern of such nodules is solid and non-homogeneous with spot calcifications.

At the beginning of the 90s, a new tool called US elastography was developed that enabled the evaluation of tissue elasticity.[16] The aim of this technique is to determine whether a nodule whose consistency is observed to be firm or hard is associated with an increased risk of malignancy. US elastography is based upon the principle that the softer parts of tissues deform more easily than the harder parts when

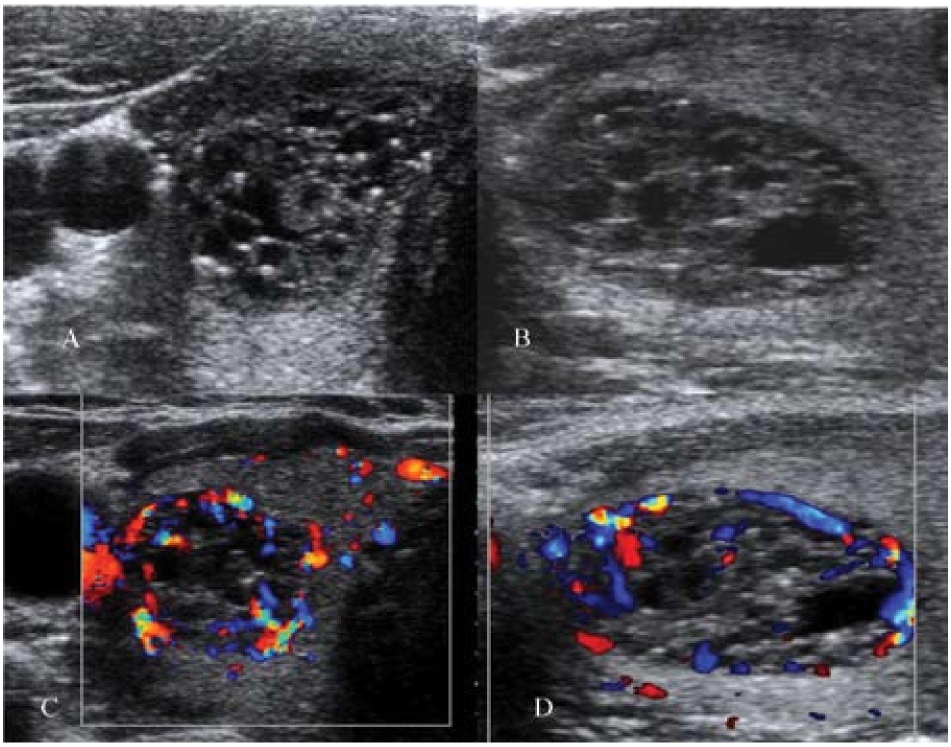


Figure 3. Spongiform nodule. **A.** Transverse and **B.** longitudinal ultrasound scan shows a thyroid nodule with multiple cystic spaces and punctuated ecogenic foci with comet tail artifact. **C.** Transverse and **D.** longitudinal color-doppler mode scan shows peripheral vascularity.

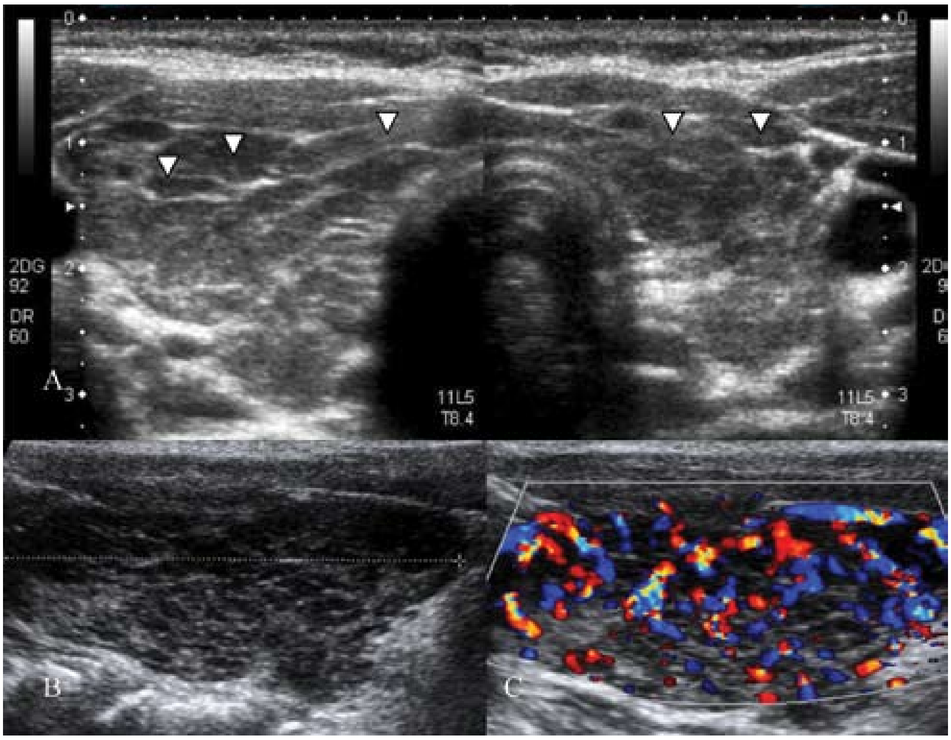


Figure 4. Hashimoto's thyroiditis. **A.** Tansverse dual ultrasound scan of the thyroid shows a diffusely enlarged hypoechoic gland with echogenic bands (arrowheads). **B.** Longitudinal sonogram of the left lobe shows multiple small hypoechoic nodules. **C.** Increased vascularity in color-doppler scan mode.

submitted to compression by an external force. This elasticity can be assessed by measuring the degree of distortion of the US beam. In fact, US elastography has been employed to differentiate cancers from benign lesions in prostate, breast, pancreas and lymph nodes.[17-20] However, US elastography has limitations, including the difficulty of assessing lesions that are not surrounded by sufficient normal tissue or located in areas—e.g., the retroareolar area—where pressure cannot be exerted evenly. In addition, there is a certain degree of subjectivity in the evaluation procedure. Nevertheless, despite these shortcomings and the fact that it is time-consuming, it has high specificity and sensitivity irrespective of the nodule size and its high predictive value is maintained in follicular lesions.[10]

Some studies[21-23] have demonstrated the usefulness of US elastography in evaluating thyroid nodules, suggesting that it is the best available non-invasive tool comparable to fine-needle aspiration (FNA). In general, conventional US retains pivotal importance in the initial evaluation and should be used in determining which nodules are suitable for US elastographic characterization. Indeed, nodules in which US reveals the presence of a calcified shell have to be excluded from the US elastographic evaluation. Similarly, in cystic nodules US elastography cannot give useful information. One other limitation is that the nodule to be examined must be clearly distinguishable from other nodules present in the thyroid. Thus, multinodular goitre with coalescent nodules is not suitable for this analysis. The US elastographic image is matched with an elasticity numbered on a scale from 1 to 5 and graded from elasticity in the whole nodule to no elasticity in the nodule and in the posterior shadowing, respectively.[21] In recent studies, a score from 4 to 5 has demostrated a highly predictive value for malignant lesion, reaching a sensitivity of 97%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 98%. The effectiveness of US elastographic measurement was independent of the nodule size and was also confirmed in an indeterminate (follicular) lesion on FNA.[22] In summary, US elastography has great potential as a new tool for the diagnosis of thyroid cancer, especially in nodules with indeterminate cytology.[10]

The development of ultrasound contrast as a novel methodology opens up new possibilities in diagnostic evaluation of thyroid nodules. The specific imaging contrast adds great clinical efficacy to ultrasound which allows differentiation between normal and pathological tissues by studying the dynamic macro- and microvasculature.

Recently, new ultrasound techniques, such as pulse inversion harmonic imaging and low mechanical index (<0.3), which are extremely sensitive to non-linear effects of US interaction with microbubble contrast agents, have been developed.[24] In fact, this enhanced contrast has already been shown to improve the accuracy of ultrasound in the evaluation of focal hepatic lesions.[25-27] Although studies with the first-generation, air-based, contrast agent SH U 508A (Levovist), equipped with color power doppler techniques to characterize solitary thyroid nodules, did not provide conclusive data, during the last few years the second generation contrast SonoVue has improved the results. SonoVue is a new, second generation, stabilized microbubble preparation containing sulphur hexafluoride. SonoVue has low solubility, is isotonic and does not contain potentially antigenic gas and, in comparison to radiographic contrast media or MRI, SonoVue does not come out of the vessel lumen, thus any echo received from a microbubble indicates the presence of a vessel.[28,29] Therefore, this US contrast agent allows the radiologist to perform continuous imaging at low acoustic power, providing an easier and more accurate depiction of tumour vascularity, especially with regard to microcirculation not assessable by means of color power doppler techniques; it could be an excellent tool for differentiation between benign and malignant thyroid nodules based on the differences in blood flow between normal and diseased tissues. What is more, SonoVue is well tolerated by the patient. Side effects have generally been mild and transient, resolving spontaneously without residual effect.[30] Nevertheless, although preliminary results are promising, more clinical trials are needed before this technique is incorporated in clinical practice.

FNA continues to be the cornerstone of thyroid nodule evaluation. In fact, FNA is a simple, useful and cost-effective diagnostic procedure, but the evaluation of non-diagnostic and insufficient FNA samples continues to be a problem.[31] Moreover, there is no universally accepted approach to follow-up of non-diagnostic thyroid FNAs[32,33] and it is well known that the false-negative rate for cytologically benign thyroid nodules is as high as 5%,[34] and around 5% to 10% in nodules defined as lesion of undetermined significance.[35] Furthermore, recent surveys of pathologists' and clinicians' perceptions of diagnostic terminology and cytopathology reports for thyroid FNAs demonstrated significant discordance between pathologists and clinicians.[36] In recent years, reports have suggested that the use of liquid-based cytology, inmunocytochemistry and more recently DNA analysis may improve diagnostic accuracy.[14,37-40] As described above, US has become an essential tool for nodule selection, diagnosis, follow-up and improvement of FNA.

Finally, in recent years tru-cut biopsy offers a higher diagnostic efficacy without important adverse effects and no reported cases of malignant seeding,[41] showing a sensitivity as high as 98% and specificity of 100%. The procedure involves the use of an 18G tru-cut needle usually performed under ultrasound guidance after application of local anaesthesia. Its application has been advised for those cases in which the cytology result is non-diagnostic or suspicious for malignancy. On the other hand, intraoperative frozen section evaluation is not recommended as a routine technique because of its low specifity.[42]

STRUCTURE CROSS-SECTIONAL IMAGING

CT and magnetic resonance imaging (MRI) play an adjuvant role in the evaluation of thyroid disease. Detection and characterization of a thyroid neoplasm is not the aim of CT and MRI, since these imaging techniques cannot differentiate benign from malignant thyroid lesions, unless invasion to adjacent organs is found. Furthermore, when CT imaging studies are performed and iodinated contrast agents are administrated, it will alter radioactive iodine uptake measurements for up to 6 weeks following the study and might precipitate thyroid storm in patients with subclinical hyperthyroidism.

In the setting of a benign nodular disease of the thyroid gland, CT and MRI are valuable imaging techniques for assessment of the presence and extension of substernal and mediastinal goitres and evaluation of secondary manifestations, such as compression and displacement of the aerodigestive structures and cervical vessels. They therefore constitute an invaluable guide for the surgeon in the preoperative approach.

Uncomplicated thyroid cancer is not routinely assessed by CT or MRI studies. When symptoms of extracapsular extension of the tumour such as dyspnea, hoarseness and dysphagia or neck pain radiated to the superior arm are present at clinical examination, cross-sectional imaging is recommended to assess loco-regional extension of the tumour. MRI or CT studies are otherwise recommended during post-thyroidectomy follow-up in the presence of an elevated serum TG and negative clinical and sonographic examination to rule out occult retropharyngeal or mediastinal metastatic involvement.[14]

Nevertheless, thyroid nodules are frequently detected incidentally during CT scan or MRI of the head and neck and the evaluation of such lesions represents a challenge. In a large retrospective study, Yoon el al[43] found that the presence of intranodular calcifications, contrast enhancement and a more tall than wide morphology were CT features associated with malignancy. In their study, sensitivity and negative predictive value based on a combination of these three CT features were 100%, but specificity and positive predictive value were low (46.7% and 21.1%, respectively). If one or more of these features are found in a CT examination, thyroid US and biopsy of the nodule is highly recommended. Further imaging studies to exclude malignancy are not indicated in the absence of these features.

The role of MRI in the evaluation of thyroid lesions has become more important in recent years because of the development of surface coils and functional MRI such as perfusion imaging and Diffusion Weighted MR imaging (DWI). DWI is a non-invasive diagnostic method which evaluates the mobility of water in different tissues to generate diffusion weighted images and Apparent Diffusion Coefficient (ADC) maps. In a recent study, Schraml et al[44] assessed parenchymal perfusion of the thyroid gland in patients with autoimmune thyroid diseases using MRI with no-contrast Arterial Spin Labelling perfusion techniques (ASL). Graves' disease showed elevated perfusion when compared with Hashimoto's thyroiditis and normal parenchyma. Although further studies are necessary to confirm these preliminary results, MRI combined with ASL techniques appears as a reliable tool for differentiating the various autoimmune thyroid disorders as well as for evaluating the response to medical treatment in Graves' disease. In another study using DWI, Schueller[45] found a significant difference in ADC values between benign and malignant thyroid nodules. Thyroid malignancy presents low signal intensities on DWI and high ADC, while benign adenomatous thyroid nodules show high signal intensities on DWI and low ADC.

NUCLEAR MEDICINE IMAGING

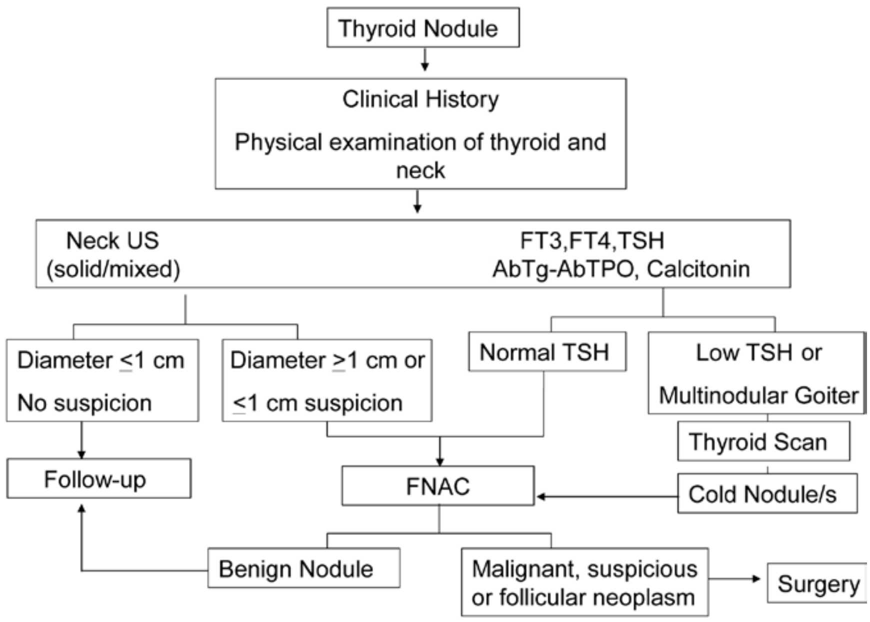
Nuclear medicine has played a central role in the evaluation of thyroid nodules since the advent of modern endocrinology, because it enables anatomic and functional evaluation of the thyroid. In fact, iodine or iodine analogues, such as thecnecium, are well suited for thyroid scintigraphy because these molecules play a key role in the physiology and pathophysiology of the thyroid gland, mainly on account of their trafficking through the sodium/iodine symporter (NIS) pathway.[46,47] In the clinical context, the most frequently used isotope for thyroid scintigraphy is ^{99m}technetium pertechnetate due to its better spatial resolution and its relatively lower radioactive burden compared with ^{131}I. Furthermore, compared with ^{123}I, it has a higher availability in the everyday nuclear medicine department workload, a shorter physical half-life (6 h vs 13 h) and an optimal energy (140 keV) for scintigraphic imaging.[48] However, the kinetics of ^{99m}technetium pertechnetate differ from those of iodine isotopes, as ^{99m}technetium pertechnetate is not organified in the gland, a fact which explains the discordance in the imaging of a nodule studied with radioiodine or pertechnetate, as an iodine organification defect may result in a rapid washout of the tracer.[49]

In the 1960s and 1970s scintigraphy was considered to be the most important test for the evaluation of thyroid nodules. However, as a consequence of the evolution of sonographic techniques and the increased availability and acceptance of fine-needle aspiration cytology, the role of scintigraphy has been redefined. As described in clinical guidelines, measurement of serum TSH—preferably associated with free thyroxine (FT4) and free triiodothyronine (FT3)—is indicated as the first-line diagnostic evaluation of thyroid nodules to rule out the presence of underlying hyperfunctioning thyroid disorders; if nodular autonomy is detected by a low-suppressed serum TSH, a scintigraphy must be performed in order to confirm the autonomous nature of the nodule, and a US with FNA cytology might be unnecessary because of the very low probability of malignancy.[12,14,15] Thyroid scintigraphy provides unique and inexpensive molecular-based information on nodular/thyroid function and is the only examination capable of establishing the presence of autonomously functioning thyroid tissue (Table 2). Due to its functional characteristics, scintigraphy is still useful in the evaluation of destructive acute/subacute thyroid diseases (De Quervain's thyroiditis, amiodarone thyroiditis type 2) through measurement of the radioiodine uptake. In such cases, the destructive hyperthyroidism would be shown as a reduced radioiodine uptake in the thyroid gland during the acute stage, as opposed to the increased radioiodine uptake in increased thyroid hormone synthesis diseases (Graves-Basedow). It is to be noted that these findings are not uniformly encountered in all patients.

The evaluation of thyroid cancer after surgery where remnant/recurrent disease detection by whole body ^{131}I -scintigraphy at low, non-therapeutic doses is controversial. The objective of post-surgical follow-up in patients with differentiated thyroid cancer is the early discovery and treatment of persistent/recurrent disease. However, as recommended in clinical guidelines,[12,14,15] this work-up should be mainly based on the information obtained by the combination of neck ultrasonography and stimulated serum thyroglobulin (Tg) after recombinant human TSH (rhTSH) or thyroid hormone withdrawal measurements.

A diagnostic whole body scan is recommended by some authors in high-risk patients or when the post-ablation whole body scan was poorly informative due to high uptake in thyroid remnants, or when it disclosed suspicious uptake. In fact, in the case of Tg increase and suspicion of remnant/recurrent disease during the follow-up, radioiodine therapy ablation dose and post-treatment scintigraphy is the prefered approach due to the obvious therapeutic effect and a higher sensitivity compared to an isolated diagnostic dose scan.[50] Therefore, in the event of elevated or increasing Tg, radioiodine therapy and post-therapy image acquisition without a previous diagnostic scan is preferred.

Table 2. European consensus for the study and follow-up of thyroid nodules.



From Pacini F, et al[15], with permission.

In recent years, other isotopes have been used in the evaluation of thyroid diseases, such as the somatostatin analogue depreotide (Figure 5), but its usefulness in the evaluation of thyroid pathology and in particular in thyroid cancer is still under investigation.[51]

Positron Emission Tomography

The use of PET in thyroid cancer evaluation has increased dramatically in recent years thanks to the characteristics of the most frequently used radiotracer F18-fluorodeoxyglucose (FDG), a glucose analogue which is accumulated in tissues with a high glucose metabolism due to an elevated membrane glucose transport and increased intracellular glycolytic pathway activity. Nowadays, FDG-PET is well established as an important imaging modality in oncology for tumour staging, restaging and detection of recurrence, as well as a good instrument for monitoring treatment response.[52] On whole body FDG-PET scans for non-thyroid disease, a normal thyroid gland demonstrates absent or low grade FDG uptake. Since its availability for clinical use in the follow-up of different diseases, especially in oncology, FDG-PET has incidentally identified thyroid uptake. In general, a diffuse uptake by the thyroid gland is considered to be benign and very likely secondary to thyroiditis and/or hypothyroidism, while a focal uptake of the thyroid on FDG-PET is defined as an incidentaloma, which is more clinically significant owing to its high risk of malignancy ranging from 25% to 50%. Further correlation or investigation of the thyroid function and/or ultrasound, together with a cytological diagnosis, should be advised in such cases.[53]

FDG-PET has demonstrated its greatest utility in the evaluation of thyroid cancer cases with dedifferentiated tumours which are radioiodine therapy resistant due to noniodine uptake by the lesions (Figure 6). In such cases in which, despite clearly elevated Tg levels, the radioiodine imaging is negative or demonstrates only faint iodine uptake, the best method of exploration is FDG-PET. In these instances, we will find a negative result on iodine scintigraphy but FDG-PET-positive uptake, a reflection of the accelerated metabolic state and the lower grade of radioiodine uptake in the dedifferentiated tumors. On the other hand, indolent slow-growing thyroid tumors will yield a positive result on iodine scintigraphy but a negative FDG-PET. This phenomenon, published in 1996, is called "flip-flop" and describes the reciprocal imaging relationship between radioiodine uptake and FDG-PET.[54] Therefore, FDG-PET uptake in thyroid cancer is a sign of bad prognosis as it reflects a dedifferentiated thyroid carcinoma with a higher metabolic rate.[55] In recent years, the combination of PET and computed tomography (PET/CT) has been introduced, allowing the fusion of the metabolic and

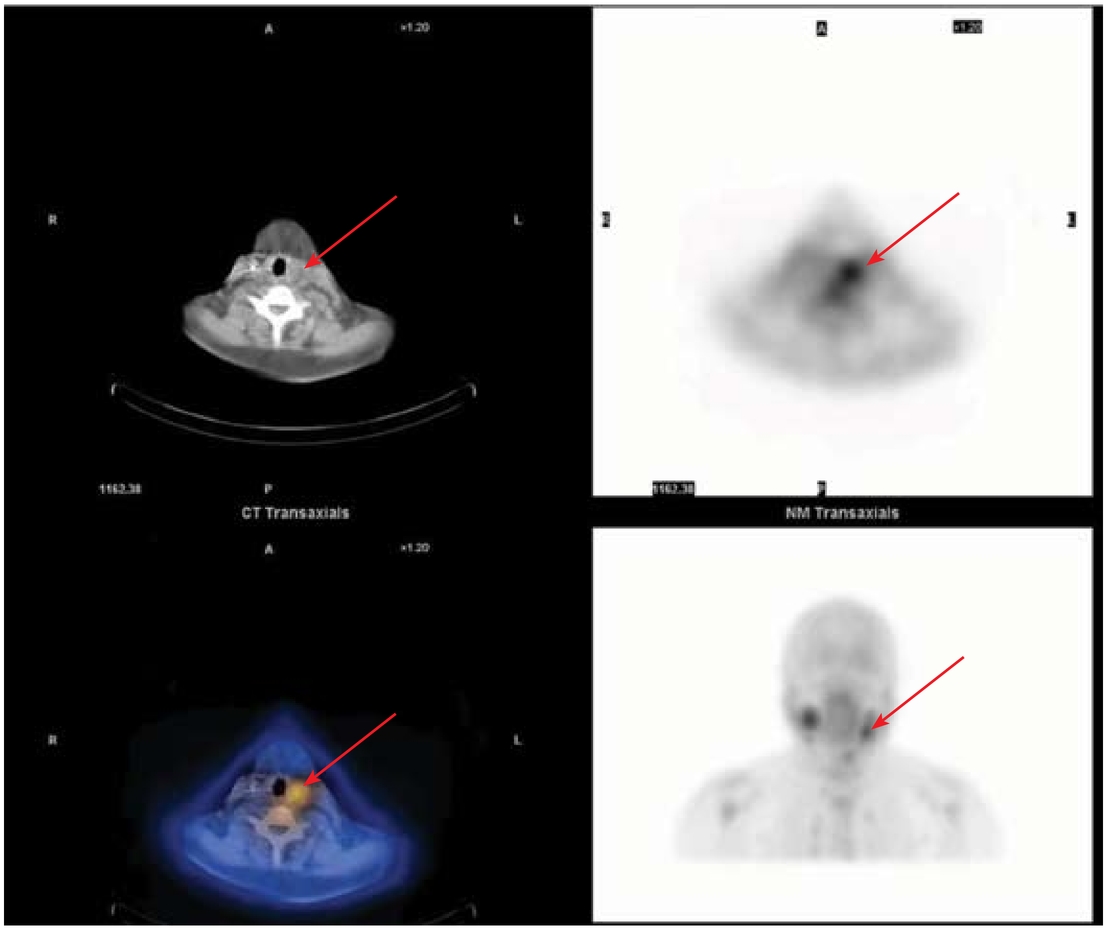


Figure 5. One hour post-injection of Depreotide, SPECT (single photon emission computed tomography), localization Computed Tomography and fusion imaging SPECT/CT in a 55-year old patient with recurrent papillary thyroid cancer and a pathological left cervical uptake.

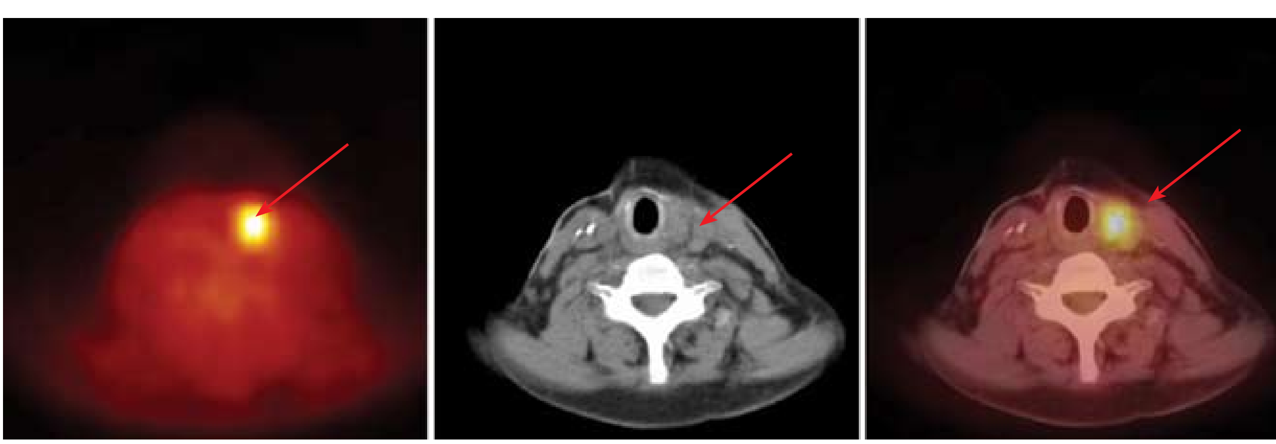


Figure 6. Pathological cervical uptake in FDG-PET and PET/CT fusion in a 60-year old woman with undifferentiated thyroid carcinoma.

morphologic information with preliminary good results in thyroid cancer and more recently with very promising results when combined with MRI.[56]

Moreover, some preliminary studies have confirmed the ability of ^{124}I to be used for lesion dosimetry.[57] The biggest pitfall of FDG-PET in thyroid cancer evaluation is its poor specificity due to the high glycolytic rate when the differential diagnosis is made between infectious or inflammatory processes and neoplasia, as well as its poor sensitivity for detection of micrometastases because of insufficient resolution capacity of the current technology.

For imaging purposes, a better anatomical localization of metabolically active tumour lesions might be achieved in the future by using different radionuclides and tracers such as $^{131}I/^{123}I/^{124}I$, FDG, or somatostatin receptor analogs.[58]

To summarize, in recent years imaging technologies have improved exponentially, changing the approach to the detection of thyroid diseases, especially thyroid nodules and thyroid carcinoma (Table 3). It is certain that in the next few years we will observe a revolution in thyroid nodule/cancer evaluation imaging, which in fact has already begun and is being increasingly incorporated in clinical practice.

Table 3. Advantages and disadvantages of thyroid imaging techniques in thyroid nodule evaluation.

	Summary of the thyroid imaging techniques				
	Malignancy evaluation	**Objectivity**	**Cost**	**Ionizing radiation**	**Availability**
Ultrasonography (US)	++	++	++	++	++
US Elastography	++	-	-	++	-
Contrast agents US	+/?	+	-	++	-
Conventional imaging techniques (CT/MRI)	-	++	-	-/+	+
Scintigraphy	-	+	+	-	+
Positron Emission Tomography	+	+	-	-	-

+/++ Useful/Very useful - Non Useful/Disadvantageous

Computed tomography (CT)/Magnetic resonance imaging (MRI)

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