EFSUMB – European Course Book

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Thyroid Ultrasound

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Content

Introduction

High-resolution ultrasound (US) is the most sensitive imaging test available for the examination of the thyroid gland, to detect thyroid lesions, accurately calculate their dimensions, identify the internal structure and vascularization and evaluate diffuse changes in the thyroid parenchyma. Thyroid US is able to confirm the presence of a thyroid nodule when the physical examination is equivocal and differentiate between thyroid nodules and cervical masses from other origin, like cystic hygroma, thyroglossal duct cyst and lymphadenopathy. Thyroid US is able to detect thyroid nodules in especial clinical scenarios like patients with a history of head and neck radiation, multiple endocrine neoplasias (MEN) type II and to diagnose lymphadenopathy in jugular, submandibular and supraclavicular chains.

Clinical indications

Indications for thyroid US, following the American Asociation of Clinical Endocrinologists and Associazione Medici Endocrinologi recommendations [(1)] are synthetized in Table 1.

Thyroid sonography is recommended in:
1. All patients with a palpable thyroid nodule or with multinodular goiter (MNG).
2. High risk patients for thyroid malignancy : history of familial thyroid cancer, MEN type II and irradiated neck in childhood.
3. Patients with palpable cervical adenopathy suspiscious of malignancy.

Thyroid sonography is not recommended in:
1. Patients with a normal thyroid on palpation and low risk of thyroid cancer.
2. As a screening test in the general population.

Table 1   Indications for Thyroid US.

Indication	Recommendation
Screening test in the general population	(-)
Normal thyroid on palpation and low risk for thyroid cancer	(-)
Palpable thyroid nodule or MNG	(+)
High risk patients (history of familial thyroid cancer, MEN type II or external irradiation)	(+)
Adenopathy suggestive of malignancy	(+)

(-) not recommended (+) recommended

Role of thyroid ultrasound

The role of thyroid US may be resumed into 3 main issues:
1. *To detect* thyroid and cervical masses, including relapse in the thyroid bed and cervical adenopathy after thyroidectomy.
2. *To differentiate* between possible benign and probably malignant masses, based on their sonographic appearance.
3. *To guide* the performance of FNA biopsy and percutaneous treatment.

Thyroid US is able to provide answers to several clinical questions:
1. Is the palpable mass within or adjacent to the thyroid?.
2. Is the tumor confined to the thyroid or locally invades nearby structures?.
3. Are cervical lymph nodes involved?.
4. Is there a primary focus in the thyroid gland in a patient with cervical adenopathy?.
5. Is there a post-operative residual or recurrent tumor in the thyroid bed or metastases to neck lymph nodes?

Technical guidelines

The patient is examined supine, the neck hyperextended (a pillow may be placed below the shoulders to achive neck hyperextension), with a high frequency linear transducer (7-15 MHz) [Figure 1] that provides enough penetration (about 5 cm depth) and excellent resolution (0.7-1 mm). This level of resolution is not achieved by any other imaging method. Images are performed on gray scale and color Doppler.

Figure 1   High resolution linear transducer (7-15 MHz) for the performance of thyroid sonography.


The recommended protocol for thyroid US [(2)] [Thyroid/Parathyroid Ultrasound. American College of Radiology Practice Guideline. Revised 2007. http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/us/us_thyroid_parathyroid.aspx] is as follows:
1. Transverse scans of the whole gland at the upper, mid, lower poles and the isthmus, and side-by-side images of each lobe, to compare echogencity and size of both lobes. Each lobe width and AP diameters are measured [Figure 2a].
2. Longitudinal scans through each lobe, on medial, mid and lateral planes. The length of the lobes is measured [Figure 2b].
3. Identify focal lesions, measure the main lesions and identify the dominant one (according to size).
4. Document the presence of enlarged lymph nodes or thrombosed jugular vein.

Standardized US reporting criteria should be followed indicating: position, shape, size, margins, content, echogenicity and vascular pattern of the whole gland and, when present, the focal lesions. Nodules with malignant potential should be identified, and FNA biopsy should be suggested to the referring physician [(2;3)].

Figure 2   Thyroid measurement on transverse (A) and longitudinal (B) scans.

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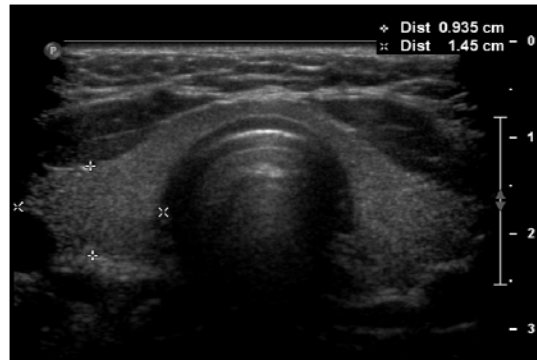
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Normal anatomy

The normal thyroid is comprised of two lobes and the isthmus, bridging the lobes, ahead the trachea. Size and shape are variable, according to age [Table 2]. It has a medium to high level echogenicity. The relationships with the sorrounding structures are as follows: ahead, the strap muscles and sterno-cleido-mastoid muscle, behind, the trachea and longus colli muscles, on both sides, the common carotid artery and jugular vein and lastly,the esophagus, behind the left thyroid lobe [Figure 3].

Table 2   Normal thyroid dimensions

Age	Longitudinal	A-P	Volume	Isthmus
Newborn	18-20 mm	8-9 mm		
1 year	25 mm	12-15 mm		
Adult	40-60 mm	13-18 mm (up to 20 mm)	18.6 mL or gram (SD:4.5) M: 19.6 (4.7) F: 17.5 (4.2	4-6 mm A-P

Figure 3   Normal thyroid and sorrounding structures on transverse scans. A. RL: right lobe. LL: left lobe. I: isthmus. E: esophagus. B. T: trachea. SM: strap muscles. SCM: sterno-cleido-mastoid muscle. JV: jugular vein. CCA: common carotid artery.

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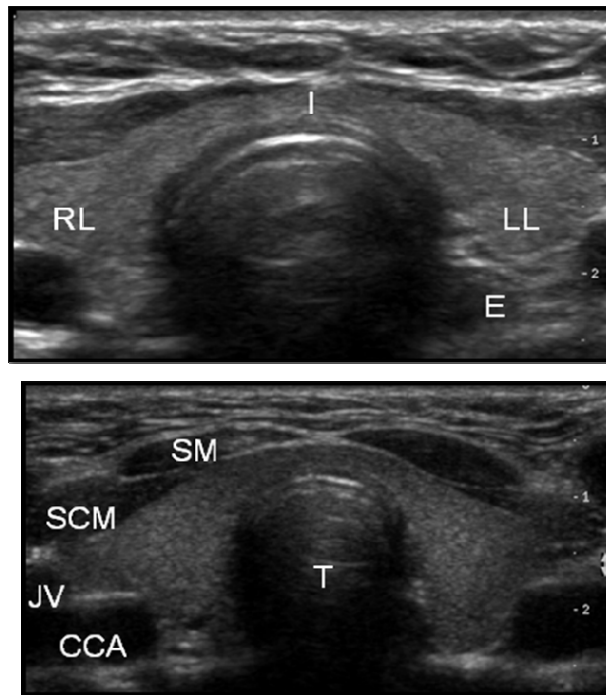
Color and/or power Doppler US are useful to evaluate the vascularity of the thyroid gland and focal masses. The thyroid gland is a richly vascularized organ. The arterial supply is provided on each side by the superior thyroid artery (a branch of the external carotid artery) and the inferior thyroid artery (a branch of the thyro-cervical trunk, which is a branch of the subclavian artery). The thyroid arteries may be localized on color or power Doppler. A low resistance flow is demonstrated on spectral Doppler in these visceral arteries. A peak systolic velocity in the intrathyroid arteries is on the range of 15-30 cm/second and is the highest velocity found in any superficial organ [Figure 4].

Figure 4   Arterial vascularization of the thyroid gland. A: On color Doppler, the inferior thyroid artery is seen. B: On spectral display, a low resistance flow with a high systolic velocity is obtained.

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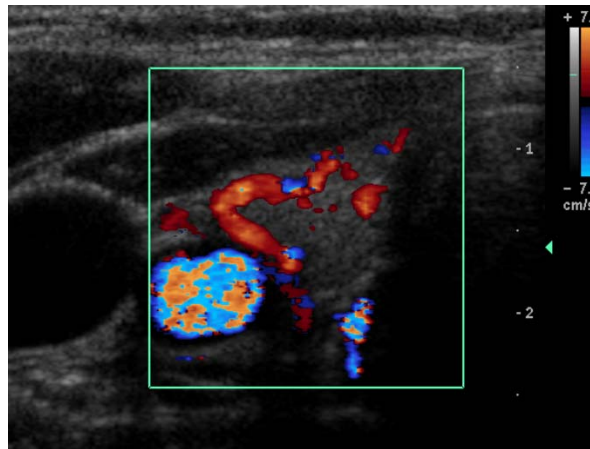
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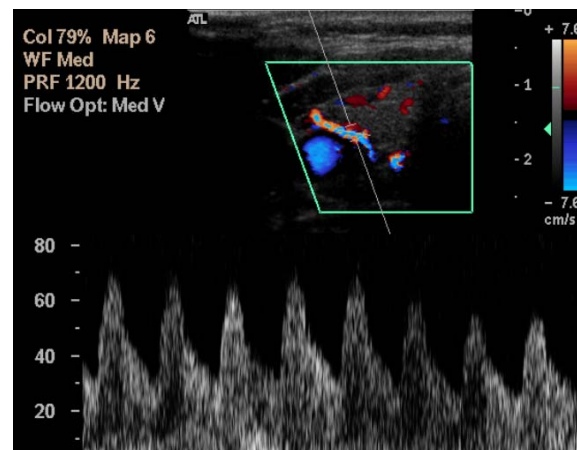
Congenital anomalies

Congenital agenesia or hypoplasia of the thyroid gland may include the whole gland or just one of the lobes. Ectopic thyroid, a deficit in migration of the thyroid gland to the lower neck from its origin at the base of the tongue, develops most commonly at a sublingual or a suprahyoid position [(4)] [Figure 5]. Ectopic thyroid may be easily detected on radionuclide scans [Figure 6].

Figure 5   **Congenital developmental defects and clinical outcomes. Development of the thyroid gland begins at the first and second weeks of intrauterine life and is completed by week 11. A and B. The thyroid gland arises as an endodermal thickening at the junction of the developing anterior and posterior tongue, at the level of the foramen cecum, between the first and second branchial arches. C and D. The aortic sac of the heart descends and pulls the thyroid caudally, its pharyngeal connection elongates as a stalk, the thyroglossal duct, which normally disappears by the fifth to sixth week of intrauterine life.**
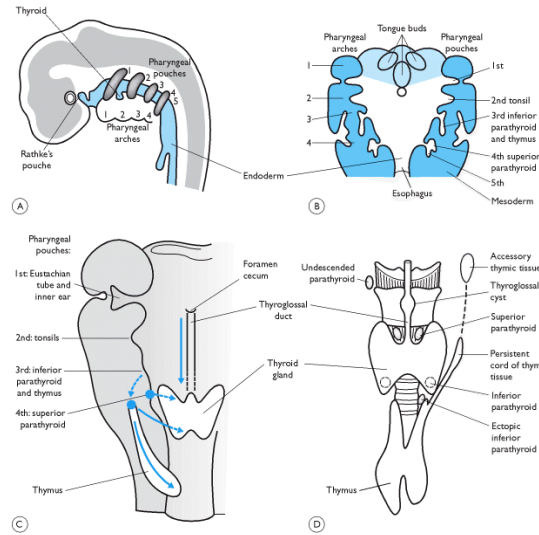
Figure 6   **Ectopic (sublingual) thyroid seen on thyroid scintigraphy (I^{123}).**
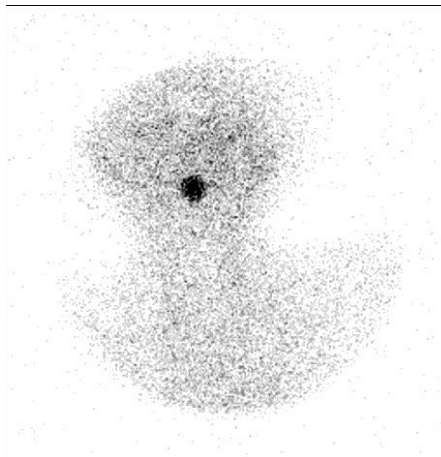
A thyroglossal cyst, forming from a persistent thyroglossal duct, appears as a neck lump at the middline [Figure 7]. The normal placed thyroid gland must be searched for to exclude thyroid agenesia. In the absence of a normal thyroid, the cyst will be the only present thyroid tissue.

Figure 7   **Midline neck lump in a 2 years- old male. A: A normal thyroid gland at the base of the neck is present. A cyst (cursors) is seen ahead the isthmus of the gland. B: The cyst (arrow) is demonstrated between the thyroid isthmus and the hyoid bone. The submandibular salivary gland (SG) is shown above the cyst. Thyroid radionuclear**

scan was performed preoperatively to confirm that the thyroid gland is present and normally functioning.

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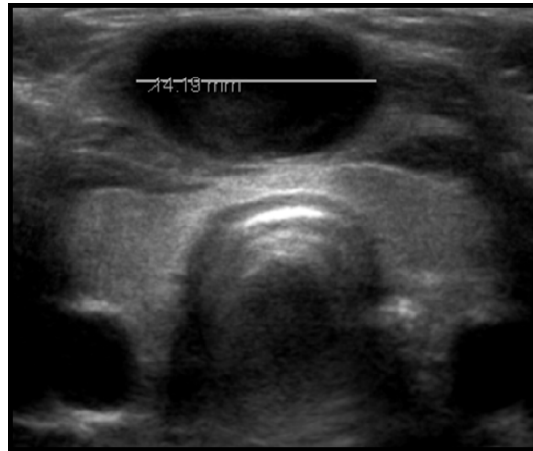
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Benign nodules

Nodularity

Nodularity within the thyroid is the norm, the development of nodules can be regarded as part of the normal maturation process of the thyroid. The incidence correlates directly with age (see illustration below).
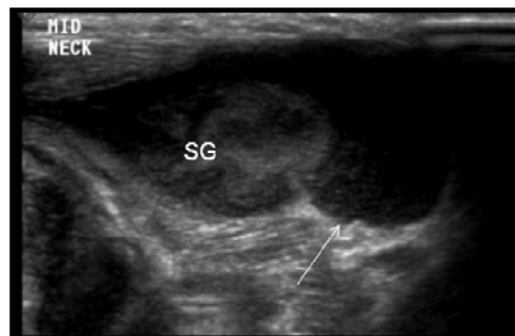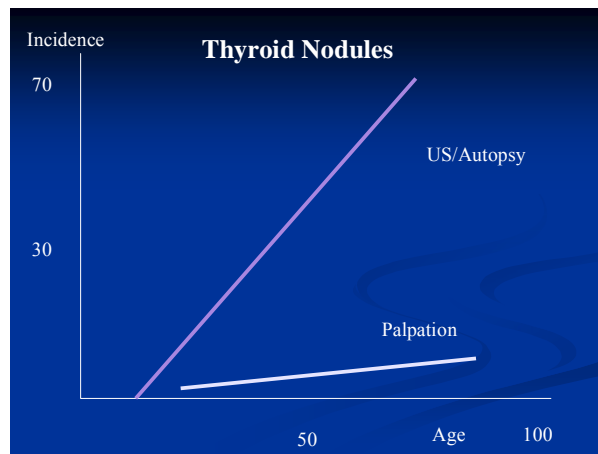
Figure 8   Incidence of thyroid nodules *(x)* at US/autopsy and palpation related to patient age *(y)*.


Ultrasound is an extremely sensitive tool in the detection of nodules and is equal to that of pathologists at post-mortem/autopsy. Thus the operator may be faced with an incidence of 30-70% of thyroid nodules on ultrasound examination, depending on the age of their patient population being scanned.

However while the incidence of nodularity within the thyroid is high ie ranging from 50 to 70%, the incidence of thyroid cancer is low. In the United Kingdom, the quoted incidence of thyroid carcinoma is one new case per 50,000 patients per annum. Therefore a radiologist or thyroid surgeon working in a large hospital with a catchment population of 500,000 patients would expect to see just 10 new cases of thyroid cancer per annum. However a radiologist could reasonably expect to see thyroid nodules in approximately half of the necks that he or she scans in a year. The dilemma for the radiologist or sonographer is how to identify the few thyroid cancers present within a multitude of benign thyroid nodules.

Fortunately, there are well documented signs that can be used in the differentiation of benign from malignant thyroid nodules on ultrasound. Thyroid nodules are formed as a result of hyperplasia and involution within the thyroid, these hyperplastic nodules frequently undergo a process of cystic degeneration ie they frequently contain cystic areas as they mature. As the nodules evolve, haemorrhage may occur within the nodule, which can increase the cystic component within nodules [Figure 8].

Figure 9   Thyroid nodularity. A. Normal thyroid-absence of nodules, uncommon. B. Benign thyroid nodule- iso and hyper- echoic, halo present, cystic degeneration.

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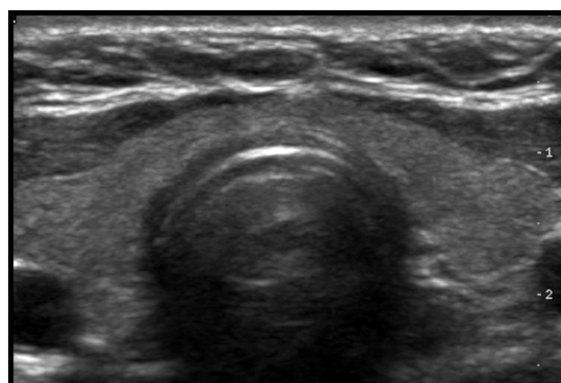
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"Ring down" sign of colloid

A major constituent of benign thyroid nodules is colloid. Colloid causes a "ring down" artifact or sign, typically within the cystic element of a nodule. Ahuja et al [(5)] were the first to describe the sign on ultrasound. When seen -it identifies the presence of colloid within a nodule ie implies that this is a benign colloid nodule [Figure 9].

Figure 10   "Ring down" sign within solid component of a cystic colloid nodule.
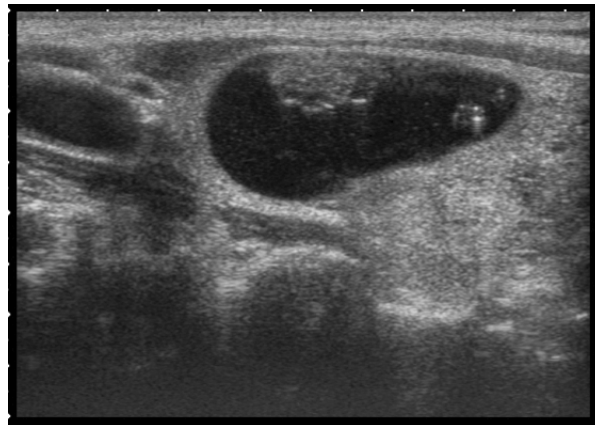
Care needs to be taken by the operator however in ensuring that the echogenic "ring down" sign is not mistaken for the microcalcification that is pathognomonic of papillary carcinoma of the thyroid. Operators need to be aware of the various software applications present in modern ultrasound machines which can impair the detection of both microcalcification and the colloid "ring down" sign. The "ring down " sign is also frequency dependent. It is good practice to have multiple presets on your machine to allow the user to review equivocal nodules and signs both with and without the various processing software applications.

Calcification

Calcification within benign thyroid nodules is typically "eggshell" or peripheral in its distribution ie curvilinear calcification around the periphery of the nodule [Figure10]. Occasionally, large aggregates of calcification identified within benign thyroid nodules, it is

thought that this may occur following haemorrhage and all fibrosis within a nodule. The distinction that needs to be made is from the fine punctate calcification of papillary carcinoma and the punctate or slightly more globular calcification that is seen in medullary carcinoma of the thyroid.

Figure 11   Patterns of calcifications in a thyroid nodule.   A. Typical benign calcification – peripheral/ "egg shell". B. Solid hypoechoic lesion containing micro-calcification – diagnosis – papillary carcinoma

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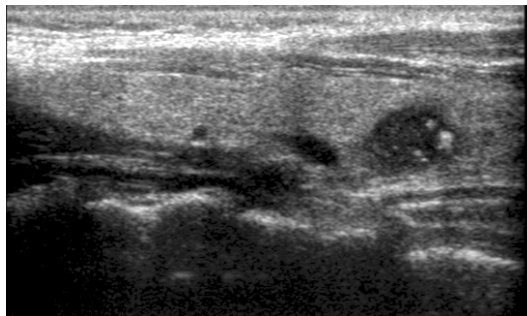
Echogenicity

The majority of benign thyroid nodules will be iso-or hyper -echoic relative to the normal "background" echotexture of the thyroid. If a solid thyroid lesion is hyper echoic relative to normal thyroid tissue, the incidence of malignancy is quoted as only 4%. If the lesion is iso-echoic the incidence of malignancy increases to 26% whereas malignancy is said to occur in 63% of hypo- echoic nodules. A significantly hypoechoic solid lesion should always be viewed with suspicion, the presence of an irregular margin, punctate calcification within or intra-nodular colour flow are additional features that indicate malignancy.

Figure 12   Benign nodules- hyper- or iso-echoic to background echotexture. Cystic change is common.
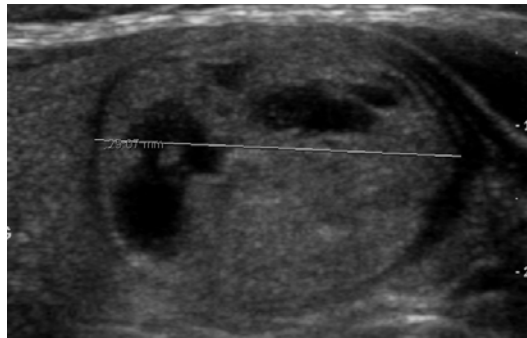
Multiplicity of nodules

Is the presence of multiple nodules and indicator of benignity? In three of the largest seria [(6-8)] on the use of of thyroid ultrasound in the detection of malignancy, the incidence of malignancy in solitary nodules as compared to multiple nodules is similar [Table 3].

Table 3   Incidence of thyroid carcinoma

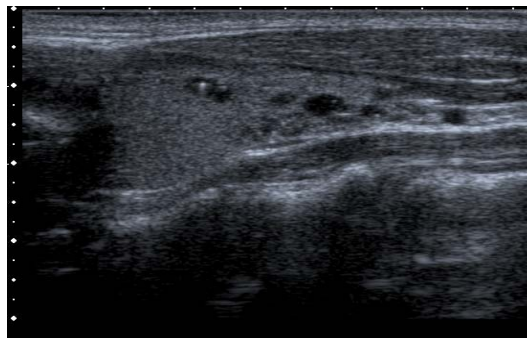| Reference	Solitary [%]	Multiple [%]
Cochand	13	14
Marqusee	7	9
Papini	9	6

Figure 13   Multiple colloid nodules within the thyroid. Note ring down sign.

Thus the presence of multiple nodules within a thyroid cannot be taken as an indicator of benignity. The sensitivity of ultrasound for thyroid nodules means that the presence of multiple nodules is the norm on ultrasound examination, the true solitary nodule is an ultrasound rarity (Figure12). The ultrasound detection of multiplicity of thyroid nodules should not be confused with the clinician's assertion that there is an increased likelihood of a clinically detected "solitary" thyroid nodule being malignant as compared to an obvious multinodular goiter on clinical examination. However, Marqusee [(7)] has shown that clinical examination is poor at the distinction of solitary versus multiple thyroid nodules. Ultrasound

will usually identify other nodules in the patient with a "solitary thyroid nodule" which cannot be detected on palpation.

Halo/margin

The margin of the thyroid nodule needs to be reviewed in the ultrasound assessment. In benign nodules a hypo-echoic halo is typically identified surrounding hyper- or iso-echoic nodules. This "halo" is caused either by the capsule of the nodule or is due to adjacent compressed thyroid tissue. The presence of a halo infers benignity of the nodule- a complete halo is said to be 12 times more likely to indicate the nodule is benign rather than malignant ([Figure 13). As with all the signs being discussed-the halo sign is not an absolute sign of benignity-it may be seen in thyroid malignancy [(9)]. If, as stated, the sign is a result of adjacent compressed thyroid tissue it is not surprising that given the indolent nature of papillary carcinoma-there will be adjacent compressed thyroid tissue which could manifest itself as a halo surrounding a papillary carcinoma.

Figure 14   Halo- surrounding a hyper echoic homogenous lesion-follicular lesion.
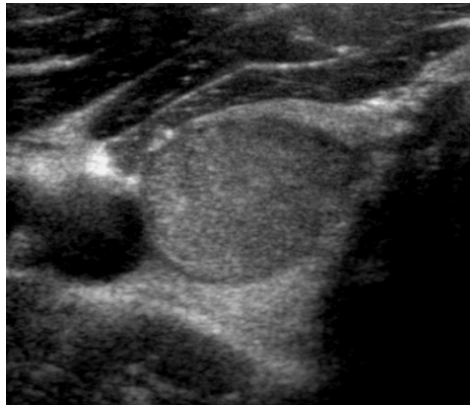
Colour flow patterns

The last feature to discuss in the consideration of benign thyroid nodules is the colour flow patterns detected on colour flow imaging. Assessment of colour flow should be an adjunct to the spectrum of signs which help in the differentiation of benign from malignant nodules. As such, the operator should ensure their machines are set up with a readily available preset to detect low/medium velocity flow within nodules with little motion artefact. Both standard colour flow assessment or power Doppler assessment can be used-the principle is the detection of a flow pattern rather than direction of flow. (This author (R.E.) advises adjusting the colour flow parameters to detect flow within the lingual artery, deep to the hyoglossus muscle-once the parameters are set for this flow velocity, it is usually a satisfactory preset for colour flow assessment within a thyroid nodule).

Originally [(10)] three colour flow patterns were described within thyroid nodules:
1. Type I-no flow detected within the nodule
2. Type II- peri-nodular arterial flow pattern
3. Type III- intra-nodular flow with multiple vascular poles, chaotic arrangement, with or without peri-nodular flow

Type I and II are mostly seen in benign hyperplastic nodules whereas Type III flow pattern is generally identified in malignant nodules.

Given the high colour sensitivity of modern ultrasound machines, vessels are now detected within the majority of thyroid nodules. It is probably easier to think in terms of predominantly peripheral flow as typical of a benign colour flow pattern [Figure 14a] whereas a chaotic intra nodular pattern as more indicative of malignancy [Figure14b].

Figure 15.   A. Benign colour flow pattern – note hyperechoic nodule relative to thyroid, halo, peripheral colour flow with no significant intra nodular flow B.- Malignant intra nodular, chaotic blood flow pattern.

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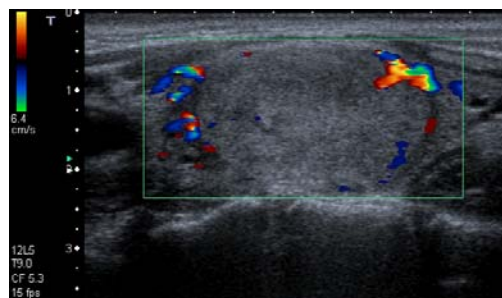
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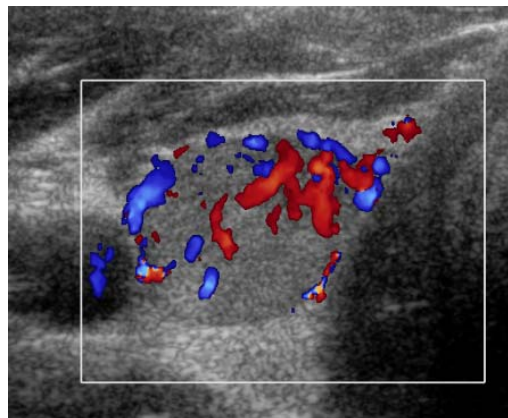
There are therefore a spectrum of signs that can be used in the assessment of thyroid nodules which are indicators of benignity. However no sign can be taken as absolute, but if the signs are used in summation, they are indicators of the likelihood of a thyroid nodule being benign.
In summary, benign nodules are typically iso-or hyper-echoic in comparison to the background echotexture of the thyroid, they will often contain areas of cystic degeneration and will be typically surrounded by a hypoechoic halo [(11)]. If calcification is present - it is eggshell like or peripheral in its distribution, this is an added sign that the nodule is benign. If a "ring down" sign is demonstrated within the cystic element, this can be taken as a sign of colloid-a constituent of benign thyroid nodules. The colour flow pattern detected in benign thyroid nodules is characteristically a predominantly peripheral flow pattern. And finally, whether the nodule is a solitary nodule on ultrasound examination or whether it is one of multiple nodules within the thyroid, cannot be used as a criterion for the differentiation of benign or malignant disease.

Malignant nodules

Thyroid cancer represents less than 1% of all malignancies, with an average annual incidence of 5 per 100.000 inhabitants. The incidence of thyroid cancer in the United States increased from 3.6 per 100 000 in 1973 to 8.7 per 100 000 in 2002, a 2.4-fold increase [(12)]. Mortality from thyroid cancer is approximately 0.5 per 100 000, with a 4-8% 20 years cumulative mortality, and was stable between 1973 and 2002, suggesting that changes in the diagnostic approach to thyroid nodules resulted in an increased detection of subclinical disease.

The incidence of cancer among thyroid nodules is low, 10-13%, with a same incidence between occult and papable nodules. Thyroid cancer is more frequent in females and has two peaks of prevalence, the first under 20 year-age and the second over 60. Histologically, 75-80% are papillary and mixed papillary and follicular, 10-20% are follicular, 3-5% medullary and 1-2% anaplastic carcinomas. Two histological types, papillary and follicular. are included in the subgroup of differentiated thyroid carcinoma (DTC).

Thyroid cancer spreads first to to the lymphatic cervical nodes; distal metastases are infrequent-2-3% of cases, mostly to bones and lungs.

Papillary carcinoma

The described sonographic appearance of thyroid cancer is related to the most frequent histological type, the papillary carcinoma [Table 4].

The malignant nodule echogenicity as seen on B-mode gray scale is low in 90% of the cases. Microcalcifications, with or without acoustic shadow, when present, is a reliable diagnostic criterion. Hypervascularity with a disorganized pattern is seen on color Doppler sonograhy in 90% of the cases [Figure 15].

Cervical lymph nodes must be systematically searched for. Metastatic cervical lymph nodes are round, hypoechogenic and sometimes cystic, with absent hilum. Hypervascularity in the lymph nodes is frequently shown on color Doppler. Microcalcifications, when present in the primary malignancy, may be also seen in the metastatic lymph nodes [Figure 16 -18].

When a suspiscious nodule is incidentally discovered in the thyroid, FNA should be performed from this nodule, even if the patient was referred for another palpable lesion [Figure 19].

Table 4   Sonographic features for the characterization of malignant and benign nodules.

US FEATURE	Malignant	Benign
Solid	++++	++
Mixed	++	+++
Cystic-purely, thin septa	+	++++
Hypoechogenic	+++	+++
Isoechogenic	++	+++
Hyperechogenic	+	++++
Thick incomplete halo	+++	+
Thin halo	++	++++
Poorly defined margins	+++	++
Well defined margins	++	+++
Microcalcifications	++++	++
Eggshell calcifications	+	++++
Coarse calcifications	+	+++

| Internal flow pattern | +++ | ++ |
| Peripheral flow pattern | ++ | +++ |

+ very low probability ++ low probability +++ intermediate probability ++++ high probability

Figure 16   **Incidentally discovered papillary carcinoma in a 54 years-old woman during carotid US-Doppler examination. a. A hypoechogenic nodule with poorly defined margin without a sorrounding halo is detected in the right thyroid lobe. b. Microcalcifications without acoustic shadowing are seen (arrowheads). c. A disorganized rich internal vascularity is seen on Power Doppler. Papillary carcinoma was diagnosed on fine needle aspiration biopsy (FNAB).**
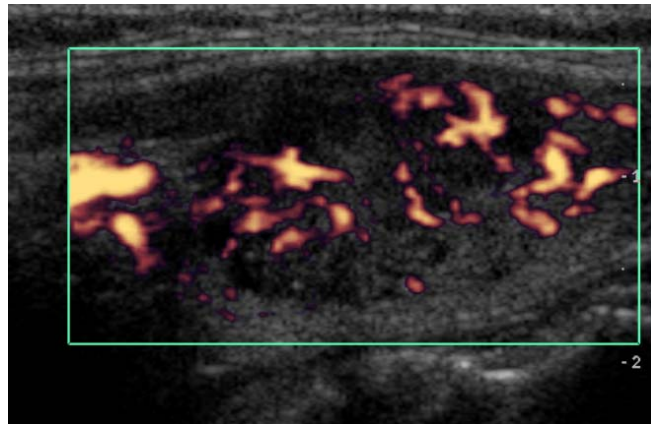
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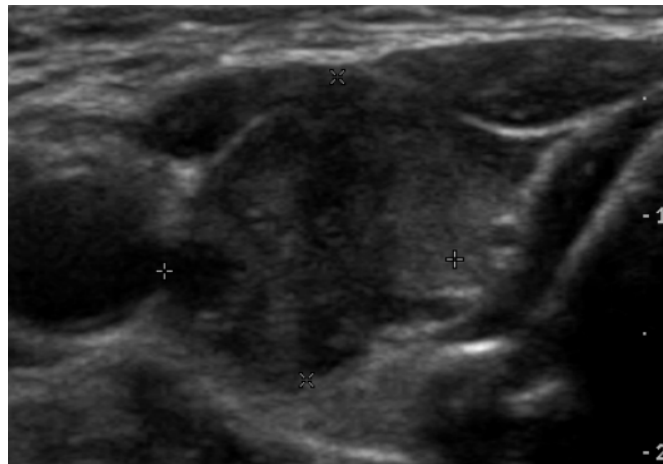
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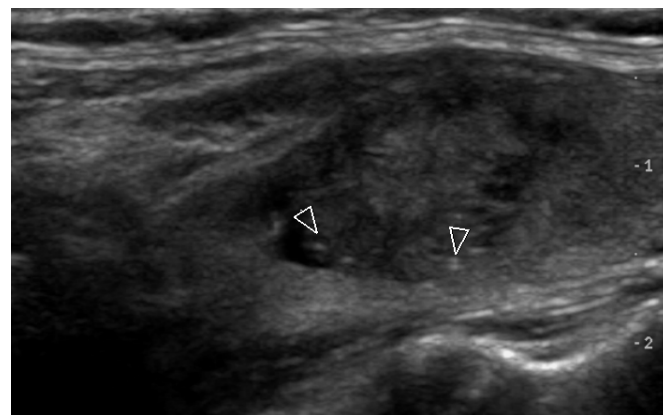
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Figure 17   **Papillary carcinoma metastatic to cervical lymph nodes in a 34 year- old frmale with a palpable nodule in the right lobe. A mixed cystic and solid nodule with microcalcifications is seen on transverse view (a and b) and longitudinal view (c) of the thyroid gland. d. Transverse scan of lymph nodes at the jugular chain. Round small lymph nodes with microcalcifications, without echogenic hilus are seen. Papillary carcinoma was diagnosed on FNA performed from the thyroid nodule and one of the cervical lymph nodes.**

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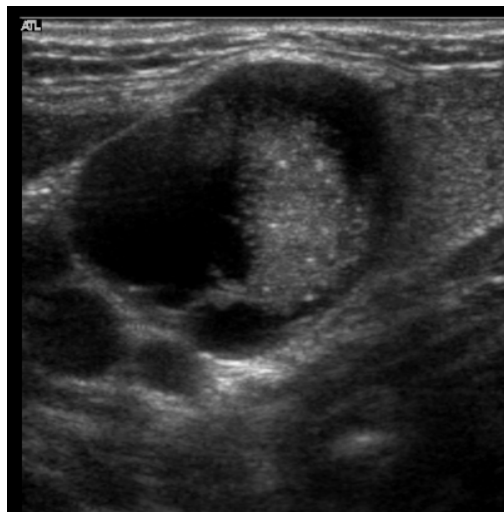
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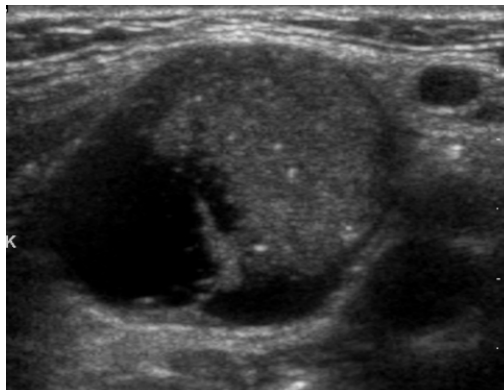
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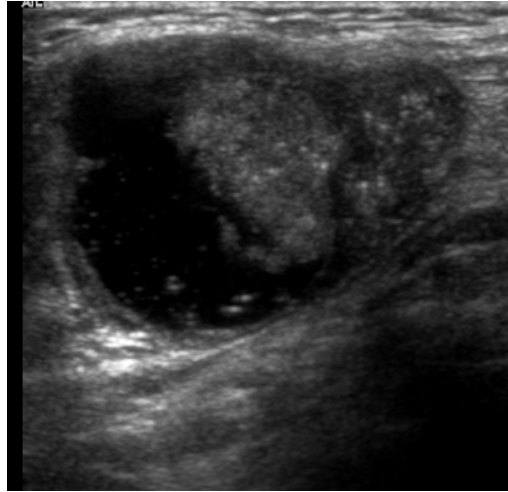
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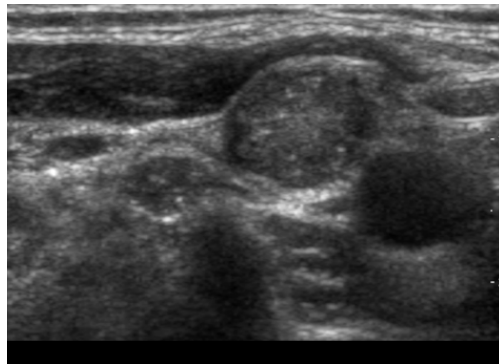
Figure 18   Non palpable bilateral papillary carcinoma spread to cervical lymph nodes in a 32-year-old female with a history of neck radiation in childhood due to Hodgkin's lymphoma. a and b. Hypoechogenic, heterogeneous texture of both thyroid lobes with foci of sparced (thin arrows) and clustered (thick arrow) microcalcifications. c. Enlarged rounded submandibular lymph nodes with microcalcifications (arrow). Multifocal invasive papillary carcinoma was diagnosed on FNA from the thyroid gland and one of the abnormal lymph nodes.

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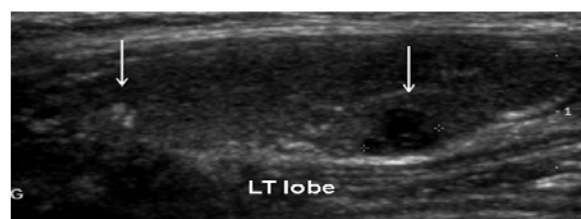
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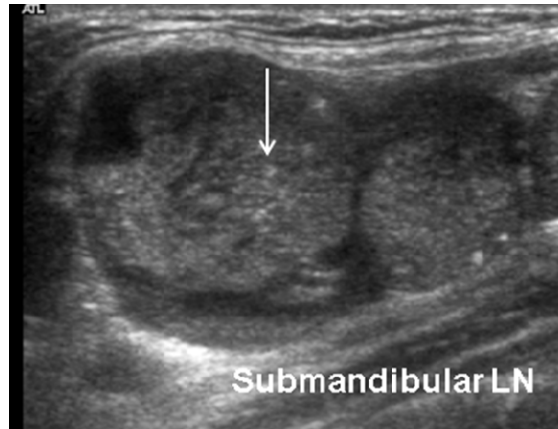
Figure 19   Palpable diffusely enlarged thyroid gland in a 18 year- old female. a. Enlarged right lobe and isthmus. b. Enlarged left lobe. Microcalcifications are spread over the whole gland. c. Distorted vessels on color Doppler. d. Supraclavicular enlarged lymph node with microcalcifications. Papillary carcinoma was diagnosed on FNA.

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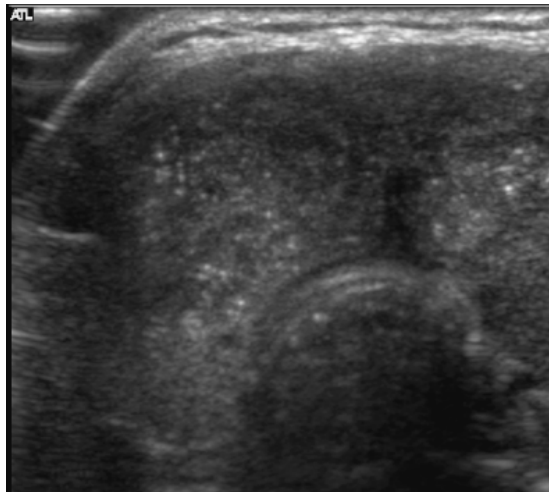
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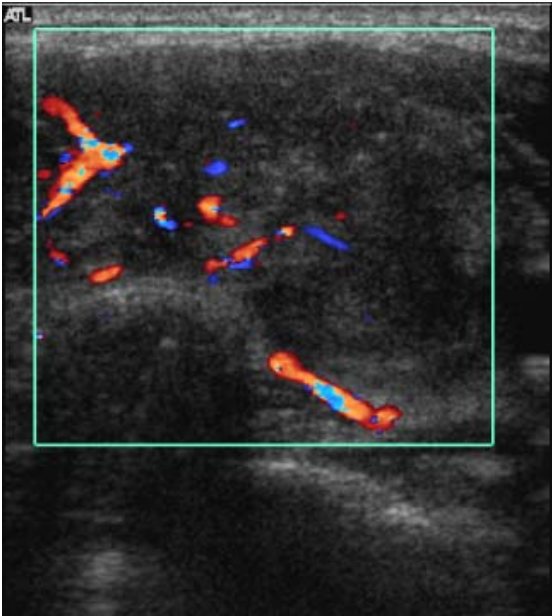
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Figure 20   **Incidentally discovered papillary carcinoma in a 70 year-old female referred to thyroid sonography for a palpable nodule at the isthmus. a. An oval well defined nodule with a hypoechogenic halo is seen at the isthmus, corresponding with the clinical finding. b and c. On transverse and longitudinal scans, a hypoechogenic ill-defined nodule(arrow in b) is seen in the right lobe on transverse (b) and longitudinal (c) scans, highly suspicious for malignancy. d. FNA from the suspicious nodule was performed (small arrow) and papillary carcinoma was diagnosed on cytology.**

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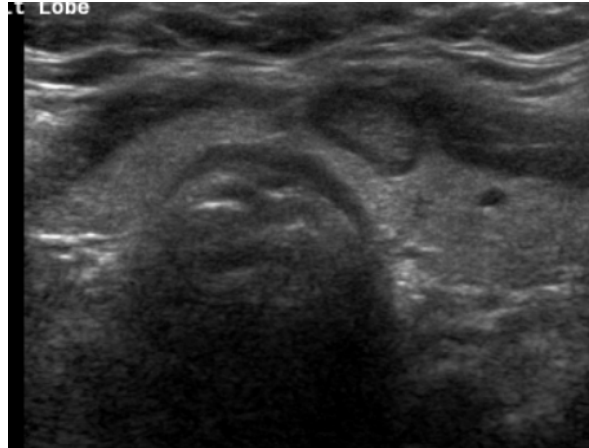
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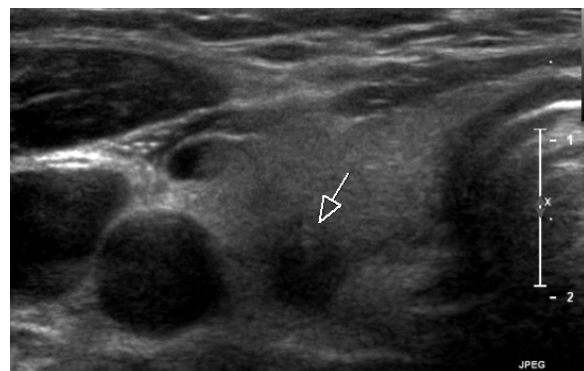
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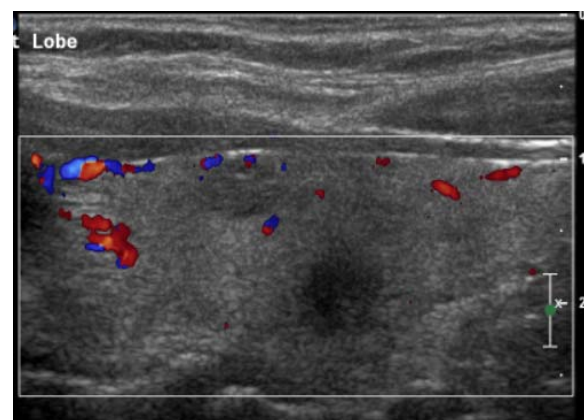
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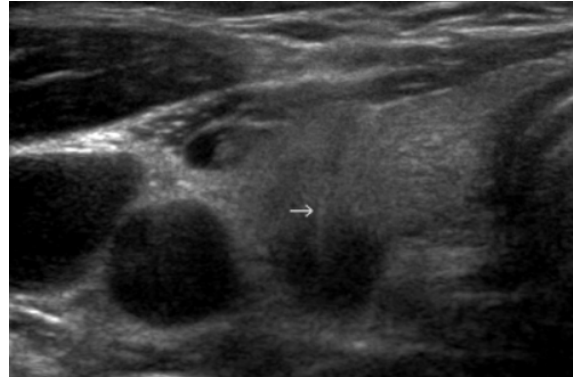
In 1/3 of the cases, multiple nodules coexist with a malignant nodule. In 2/3 of the cases, at least one additional nodule is seen. A " dominant" nodule is the one with features suggestive of malignancy or different from the other nodules. In 20% of cases, papillary carcinoma may be multicentric [Figure 17 and 18]. In 48% of cases, papillary carcinoma may be occult (non-palpable)[Figure 19].There is no evidence for a better outcome when an occult carcinoma (less than 1-1.5 cm) is detected.

Thyroid carcinoma may develop in chronic autoinmune lymphocytic thyroiditis (Hashimoto's thyroiditis), where benign and malignant nodules may coexist. A "dominant" nodule, with one or more centimeter in diameter must be biopsed (FNA) to rule out carcinoma [Figure 20].

Figure 21   **Palpable nodule at isthmus in a 40 year-old female with hypothyroidism. Multiple tiny hypoechoic nodules spread in the thyroid gland are seen in transverse (a) and longitudinal (b) scans, compatible with Hasimoto's thyroiditis. A 6 mm hypoechoic nodule is seen in the isthmus (cursors) in transverse (c) and longitudinal (d) scans through the palpable nodule. e. Papillary carcinoma was diagnosed on US-guided FNA (small arrow) of this nodule.**

a
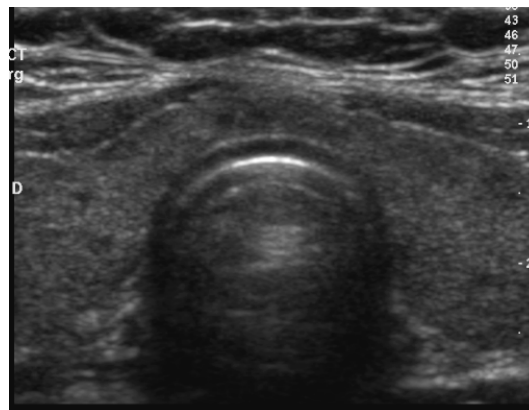
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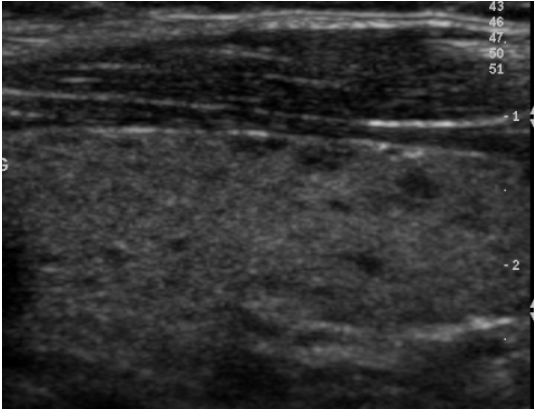
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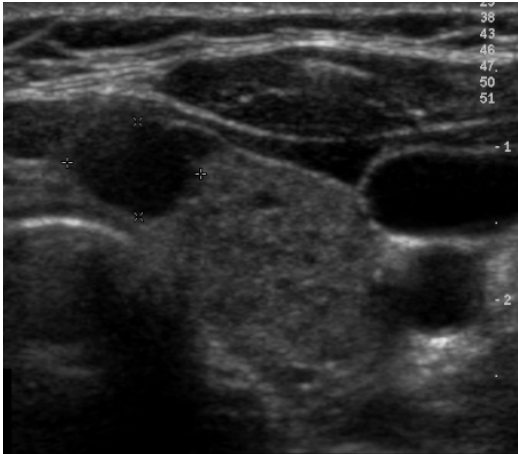
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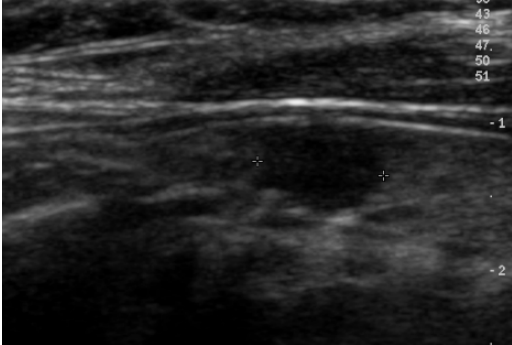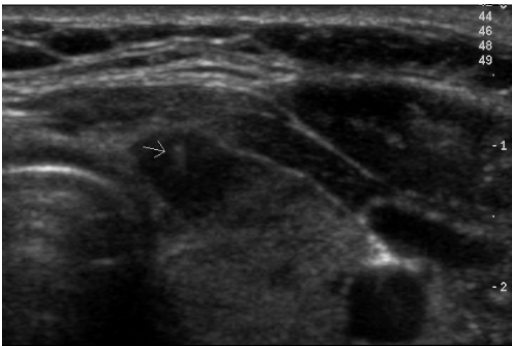
Follicular Carcinoma

Follicular carcinoma represents a 5-15% of thyroid cancers. Like papillary, follicular carcinoma is more common in females. Two types are described: 1-Minimially invasive type, encapsulated and only invasive to capsular vessels. 2- Widely invasive type, non-encapsulated and invasive to adjacent tissues and vessels. Metastatic spread to bones, lung, brain and liver may occurr, with a frequency of 5-10% of cases in the minimally invasive type and 20-40% in the widely invasive type. The overall mortality at 20 years is in the range of 20-30%.

Follicular carcinoma is similar to follicular adenoma on sonographic exam. However, presence of irregular margins, thick irregular halo and caotic vessels are suggestive of follicular carcinoma.

FNA fails to distinguish between benign and malignant follicular tumor. A follicular "adenoma" must be excised for a definitive diagnosis on hystological analysis [Figure 21 and 22].

Figure 22   Follicular adenoma in a 42 year-old male. A single nodule was seen in the right lobe. On Doppler color, peripheral to central vessels with a "spoke-and-wheel-like" appearance were seen. On FNA, a follicular adenoma was diagnosed, although, due to the inability of cytology to differentiate between follicular adenoma and carcinoma, surgery was performed. Hystological analysis confirmed the diagnosis of adenoma.
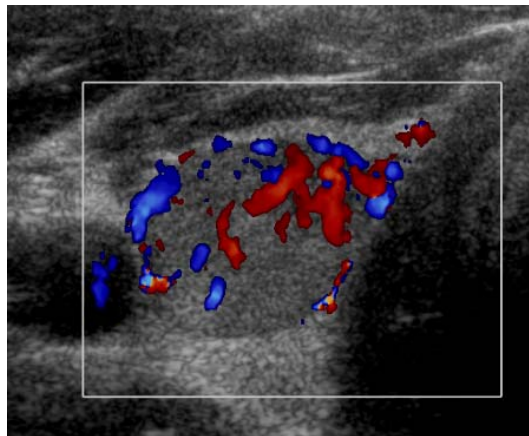
Figure 23   Follicular carcinoma. Non-palpable incidentally discovered solitary thyroid nodule in a 56 year-old female during carotid sonography. a. A bilobular hypoechoic nodule with coarse calcifications (arrow) is seen in the left lobe. b. Disorganized hypervascular network on power Doppler in transverse (b) and longitudinal (c) scans. FNA was performed yielding a diagnosis of follicular tumor. Partial thyroidectomy was performed, although, due to the presence of sparced malignant cells on histology, a total thyroidectomy was followed.

a

b

c
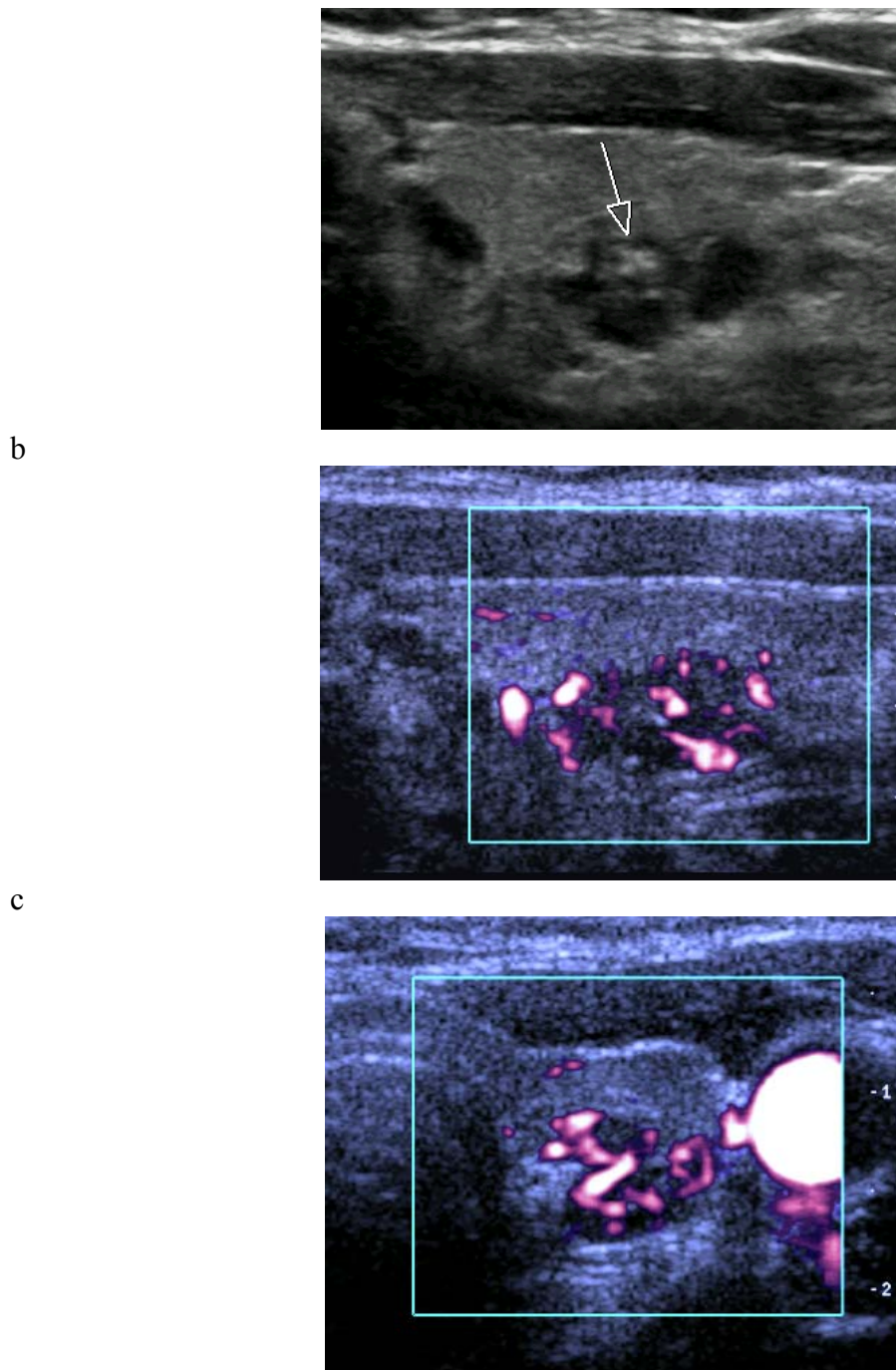
Medullary carcinoma

Medullary carcinoma of thyroid represents 5% of all malignancies. A familial history of thyroid cancer, especially associated with MEN type-II is present in 20%. Medullary carcinoma may secret calcitonin and frequently spreads to lymph nodes. The prognosis is worse than for follicular neoplasms. A hypoechoic mass ins seen on US [Figure 23]. Microcalcifications may be present, that are coarser than in papillary carcinoma.

Figure 24   Medullary carcinoma of thyroid in a 38 year-old female. a. A solitary highly hypoechoic well delimited oval nodule is seen in the left lobe. b. Sparced peripheral

and central vascularization seen on color Doppler. c. Medullary carcinoma was diagnosed on US-guided FNA (echogenic needle inside the nodule).

a
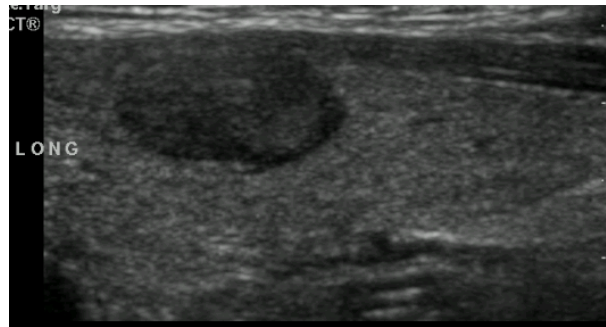
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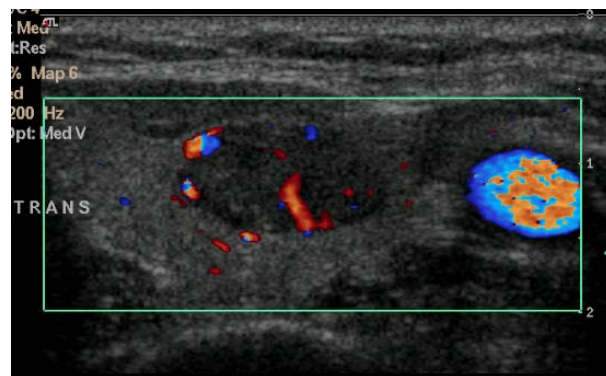
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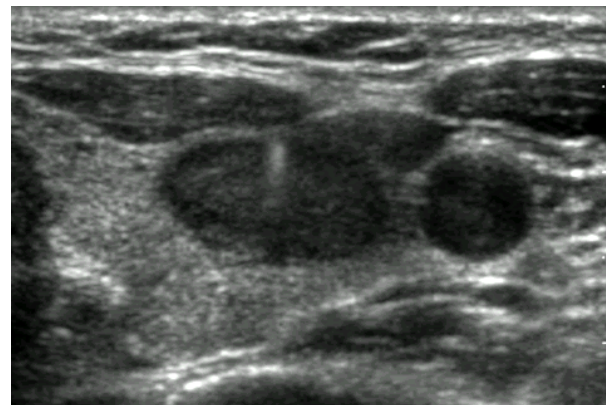
Anaplastic carcinoma

Anaplastic carcinoma represents 2% of thyroid cancers and is seen mostly in elderly patients. It has the worst prognosis of all thyoird malignancies, with a less than 5% 5 years-survival rate. Sonographically, the tumor is hypoechogenic, ill-defined and in general, invasive to adjacent structures [Figure 24].

Figure 25   Anaplastic carcinoma of thyroid in a 86 year-old female. a. Transverse scan. b. Longitudinal scan. A large hypoechoic undefined tumor invading the adjacent muscles is seen in the right lobe. c. US-guided needle biopsy with a 18 gauge tru-cut needle (echogenic line into the nodule) was performed due to a suspiscion of

lymphoma. The histological diagnosis was anaplastic carcinoma of the thyroid gland.

a
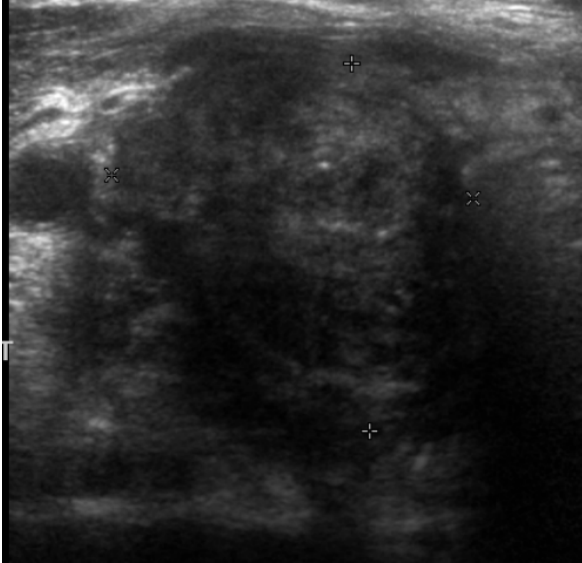
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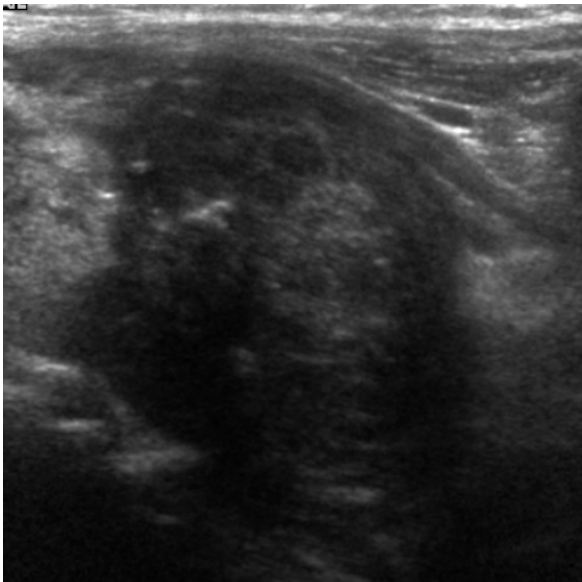
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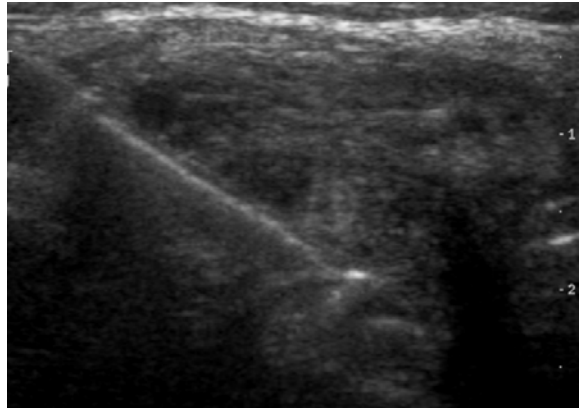
Thyroid lymphoma

Thyroid lymphoma represents 4% of all malignancies. Histologically, it is a non-Hodgkin's type. Patients are mostly elderly women; and in 60-70% develops on the basis of a chronic lymphatic thyroiditis. It is rapidly growing and survillance depends on the clinical stage.

It appears as one or more markedly hypoechoic lobulated masses [Figure 25], sometimes with cystic necrosis. On color Doppler they are hypovascular with caotic vessels. Neck vessels encasement may be seen.

Figure 26   **Thyroid lymphoma in a 43 year-old female with Non-Hodgkin's lymphoma. Thyroid nodules were seen on neck CT. a and b. Multiple hypoechoic nodules seen on transverse and longitudinal scans. c. FNA under ultrasound guidance from the dominant nodule in the left lobe (arrow) rendered Non-Hodgkin's lymphoma.**

a
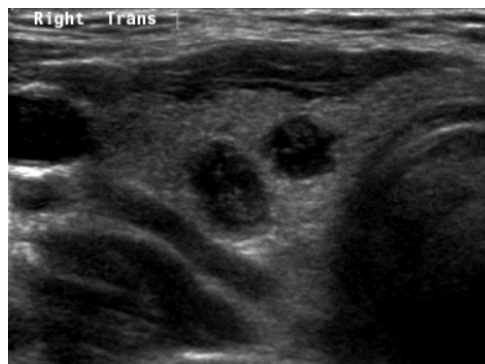
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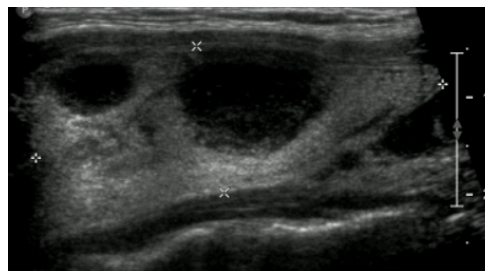
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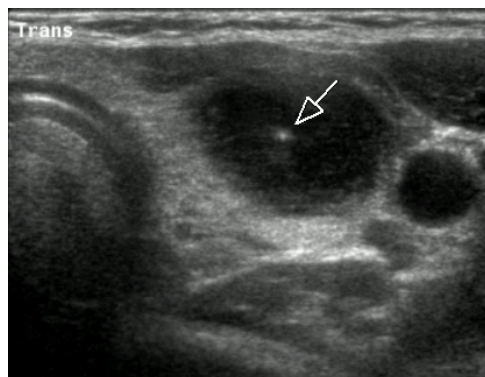
Thyroid metastases

Metastases to the thyroid gland are infrequent and generally associated with an advanced stage of malignancy. The main primary tumors spreading to the thyroid gland are malignant

melanoma (39% of cases), breast carcinoma (21% of cases) and renal cell carcinoma (10% of cases).

Sonographically, metastases are present as a solitary or multiple hypoechoic homogeneous mass without calcifications [Figures 26 and 27].

Figure 27   **Relapse of squamous cell carcinoma of esophagus at the cervical anastomosis, invading the thyroid gland in a 76 years-old male. A. On a transverse scan, a lobulated highly hypoechoic mass (M) infiltrating the right lobe of the thyroid (T) is seen. (CCA: common carotid artery, JV: jugular vein). B. On longitudinal scan, the mass (M) infiltrates the lower pole of the thyroid (T).**

a
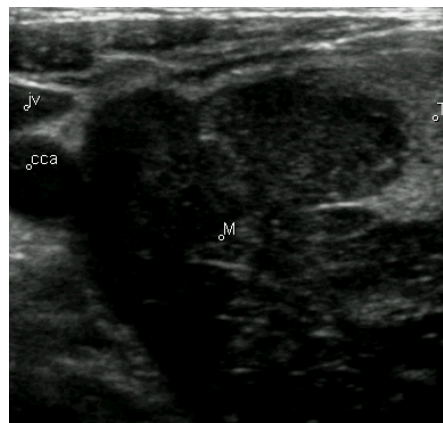
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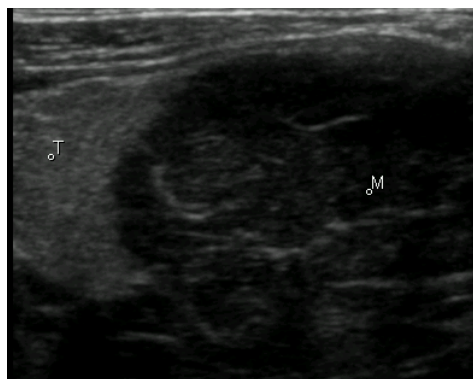
Figure 28   **Metastases from gastrointestinal adenocarcinoma. Bilateral thyroid nodules were seen in a computerized tomography performed in a 55 year-old female suspected for malignancy of unknown origin. a. Transverse scan of the right thyroid lobe shows several small hypoechoic nodules. b Transverse scan of the left lobe showing a big hypoechoic nodule. Adenocarcinoma most probably from gastrointestinal origin was diagnosed on FNA.**

a
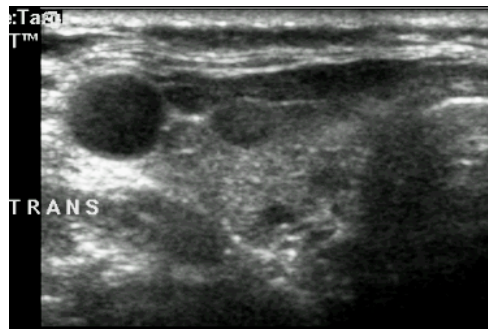
b

Monitoring after thyroidectomy

Two techniques are recommended for monitoring after thyroidectomy for malignancy: I ^{131} whole-body scanning and/or thyroid sonography imaging and measurement of serum Tg. Suggested surveillance and maintenance protocol for differentiated thyroid carcinomas (DTC-papillary and follicular types) include periodic neck ultrasonography and chest radiography [Figure 28]. Ultrasonography performed by an experienced operator is the most sensitive means for detecting neck recurrences of DTC [(13)].

Figure 29   Recurrent papillary carcinoma in thyroid bed with a retrojugular lymph node metastasis in a 48 year-old female on survillance after thyroidectomy. a.Non – palpable 6 mm width (cursors) hypoechogenic and ill- defined nodule (arrow) with microcalcifications (open arrow) at isthmus bed. b. Retrojugular round lymph node (arrows) with microcalcifications. c. US-guided FNA (small arrow) from the lymph node yielded the diagnosis of relapsing papillary carcinoma.

a

b
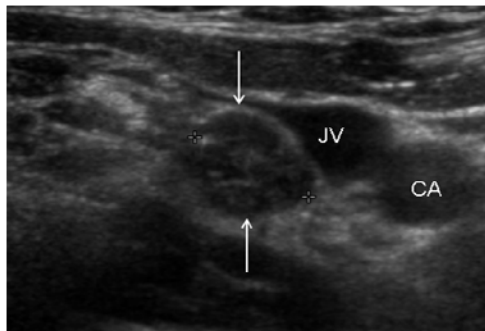
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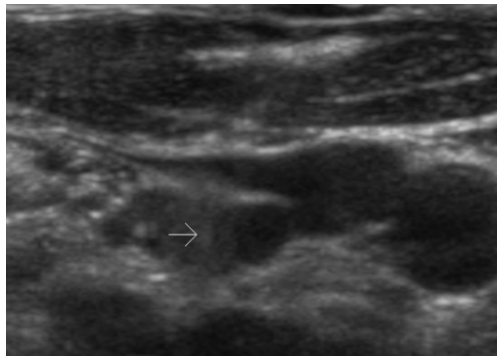
Ultrasound Reporting Criteria

When reporting a thyroid sonography, some general rules should be fulfilled:
1. Describe:a- size; b- echogenicity; c- vascularity, of the whole gland.
2. Describe: a- position; b- shape; c- size; d- margins; e- content; f- echogenic pattern g- vascular characteristics, of the nodules.
3. Identify the nodule at risk to be malignant.

Clinical work up

In the clinical work up of thyroid nodules, two main questions should be asked:
1. Is the nodule suspiscious for malignancy?.
2. Is there an history of MEN II, previous neck radiation or thyroid resection?

Ahead of a positive answer, FNAB must be performed, either blindly by palpation or under US guidance. Recommendations for FNA of thyroid nodules based on US features were published by a panel of radiologist in ultrasound [(14)] [Table 5].

Table 5   Recommendations for work-up of thyroid nodules 1 cm or larger in maximum diameter [(14)].

US Feature	Recommendation
Solitary nodule	
Microcalcifications	Strongly consider US-guided FNA if ≥1 cm
Solid (or almost entirely solid) or coarse calcifications	Strongly consider US-guided FNA if ≥1.5 cm
Mixed solid and cystic or almost entirely cystic with solid mural component	Consider US-guided FNA if ≥2 cm
None of the above but substantial growth since prior US examination	Consider US-guided FNA
Almost entirely cystic and none of the above and no substantial growth (or no prior US)	US-guided FNA probably unnecessary
Multiple nodules	Consider US-guided FNA of one or more nodules, with selection prioritized on basis of criteria (in order listed) for solitary nodule*

FNA is likely unnecesary in a diffusely enlarged gland with multiple nodules of similar sonographic appearance, without intervening parenchyma.

Presence of abnormal lymph nodes overrides US features of thyroid nodule(s) and should prompt US-guided FNA of the lymph node and/or the ipsilateral thyroid nodule.

Differential diagnosis

Attempts to differentiate probably benign from probably malignant thyroid nodules are based basically on 6 parameters:
1. Internal consistency (solid, mixed solid and cystic, purely cystic).
2. Echogenicity (hyperechogenic, isoechogenic, hypoechogenic).
3. Margins (well differentiated, poorly differentiated).
4. Sorrounding halo (thin, thick, incomplete, no halo).
5. Calcifications (eggshell, coarse, microcalcifications).
6. Vascularization (peripheral, internal flow pattern).

Sonographic features associated with thyroid cancer are:
1. Solid (highest sensitivity but low positive predictive value).
2. Hypoechogenic.
3. Irregular margins.
4. Absent halo.
5. Microcalcifications (highest positive predictive value (PPV) but low sensitivity- feature present in 26-59% of cancers).

6. Intranodal vascularity.

Nodule size is not predictive of malignancy. Regarding nodule shape, malignant nodules are frequently more tall than wide.
Ultrasound examination for differentiation of benign from malignant nodules, according to the literature, has a sensitivity of 63-94%, a specificity of 61-95% and an accuracy of 80-94%. Multiple signs present in a nodule, e.g.absent halo, microcalcifications and intranodular flow, increase the probability for cancer, with a specificity of 97%. A solid nodule with microcalcifications has a 30% positive predictive value while a cystic nodule without microcalcifications lowers it to 1%. An increased probability for cancer was seen when combining calcifications with : 1- Age older than 40 years; 2- Solitary nodule; 3- MEN II with high calcitonin values.
The detection of multiple thyroid nodules when examining the neck with ultrasound presents an immediate and potentially large clinical problem. Should the Radiologist/Sonographer advise that all patients who have incidentally detected thyroid nodules be sent to an endocrinologist or a thyroid surgeon for review? Such action could result in 30 - 70% of patients being subsequently referred for an opinion. Given the low incidence of thyroid malignancy such actions are clearly a waste of resources and clinically inefficient. Should all "dominant" nodules undergo a fine needle aspiration in order to try and establish a cytological diagnosis-this is the favoured approach and the proffered guidelines of many Thyroid Surgical Associations. However, given the incidence of nodules on thyroid ultrasound examination, a dominant nodule is a common ultrasound finding and to follow this guideline would involve large numbers of patients undergoing an invasive procedure with a low diagnostic yield for malignancy and with great potential for inducing patient anxiety.
Some would advocate a "wait and see" policy and recommend that a thyroid nodule that is thought to be benign should undergo regular ultrasound review; however unless the ultrasound service is funded on a "paid per fee" basis and income generation is the driver for a service, there is no obvious health gain for the patient population. Such a policy would result in a large cohort of patients undergoing follow up scans, being performed for little diagnostic gain. Papillary carcinoma is an indolent tumour, the fact that a nodule has not changed in size over a one or two-year period cannot and should not be interpreted as effectively excluding a carcinoma.
The solution lies in the realisation that ultrasound can assess the morphology of thyroid nodules and detect signs that can indicate the probability of a nodule being either benign or malignant. If a nodule is thought to display characteristics of a malignant thyroid nodule ie represent a possible carcinoma then a decision should be made to proceed to either a fine needle aspiration or a core biopsy (the decision as to which technique is used will be influenced by local factors e.g. whether cytological expertise is present) in order to obtain cytological or histological proof of malignancy or in order to definitively exclude malignancy. The vast majority of nodules detected on ultrasound will be benign and require no further follow-up. The use of positive signs plus detectable risk factors for the detection of malignancy has been advocated by several authors [(8)] previously. Such an approach is advocated [(15)] in response to the realisation that unless a pragmatic approach is adopted, ultrasound and clinical services could be overrun by an epidemic of nodules detected on ultrasound examination.
The spectrum of signs that are available in the differentiation of benign and malignant thyroid nodules can be incorporated into a radiological classification system similar to the classification system used by breast radiologists for the radiological differentiation of breast masses on imaging. A similar system could be used for thyroid nodules, as outlined below-diagrammatically.

Radiological classification of thyroid nodules
R1 - normal
R2 - probably benign
R3 – indeterminate
R4 - suspicious
R5 – malignant

R1- normal thyroid gland
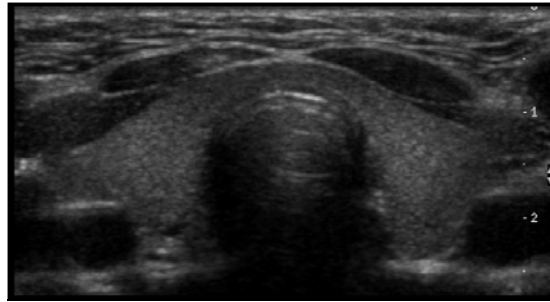
R2 – Probably benign. Colloid ring down sign.
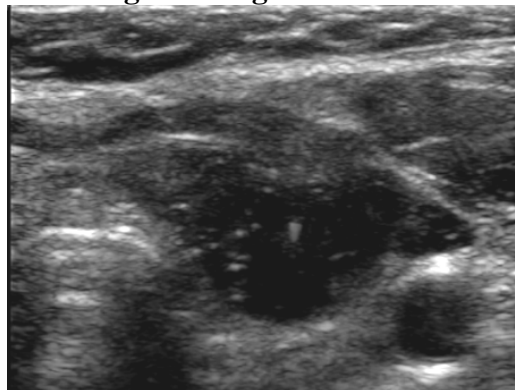
R2 – Probably benign. R2 - benign calcification

R2 – Probably benign. R2 – peripheral flow
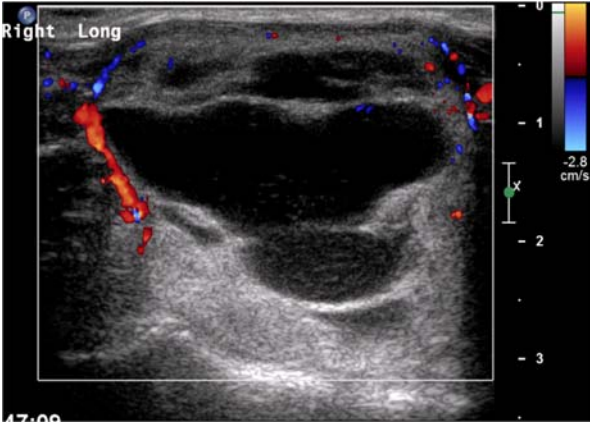
R3- Indeterminate. Follicular lesion-small percentage will be malignant.
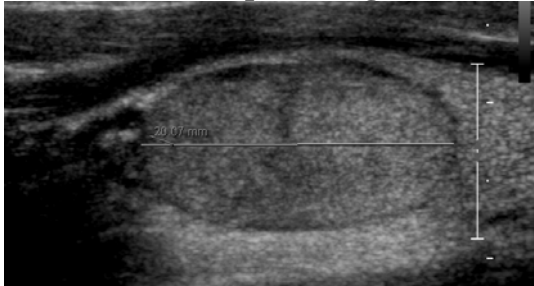
R4 – Suspicious. R4-Suspiscious lesion, homogeneous hypoechoic but peripheral flow.
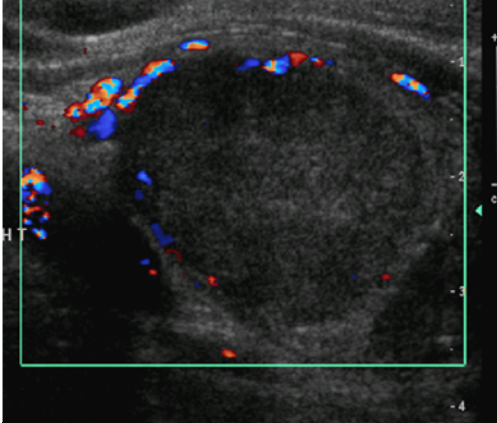
R5 – Malignant. R5 – solid hypoechoic,microcalcification.
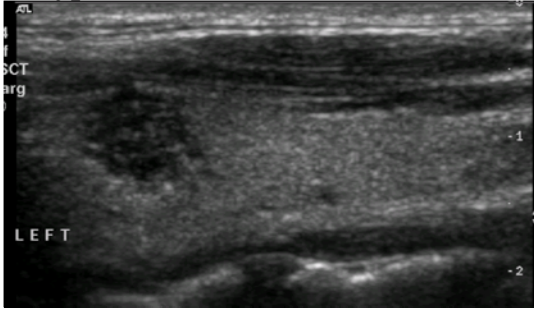
R5 – microcalcification in nodal metastases

If a working classification is used that identifies the probability on ultrasound of malignant disease, nodules can be selected for biopsy. This would mean that the indeterminate, suspicious and malignant group would undergo biopsy. The use of a radiological classification system provides the clinician with a report identifying the probability of underlying malignant disease. The radiological findings can then be reviewed in conjunction with the clinical findings and where a biopsy has been taken -the cytological or histological diagnosis.This would then allow the patient to be managed appropriately.

Follicular lesions will be by necessity classified as indeterminate lesions (R3), while the ultrasound appearances of a follicular lesion are well defined ie they are typically homogenous solid lesions with a well-defined halo. Typically the echotexture of a follicular lesion is hyperechoic relative to normal thyroid tissue. However follicular lesions encompasses a spectrum from the more predominant benign follicular adenoma (80% of all follicular lesions) to the less common (20%) follicular carcinoma (if there are areas of hypo echogenicity within, this should be regarded as suspicious for malignant change, ie this would be regarded as suspicious-R4).

Ultrasound and cytology cannot differentiate between a follicular adenoma and a follicular carcinoma. Capsular invasion and vascular invasion have to be identified on histological assessment of the surgical specimen in order to diagnose follicular carcinoma.

Therefore when a solid homogenous hyper-echoic lesion with a well-defined halo is identified, a diagnosis of probable follicular lesion should be made These will be classified as indeterminate lesions (R 3), management of these lesions is debatable. While most surgeons will advocate excision, there may be a role in some cases for ultrasound review if a "wait and see" policy is being followed in certain patients.

Predictors of cancer

A review of the literature of the radiological signs that could predict thyroid carcinoma presented at RSNA in 2005, confirmed that the presence of a solid hypoechoic lesion containing punctate calcification is a strong indicator of malignancy. Intra-nodular colour flow and irregular margins are strong additional signs indicating malignancy [Table 6].

Table 6   Predictors of malignancy [(16)].

Feature	Sensitivity	Specificity

Microcalcifications	40%	90%
Absence of halo	66%	46%
Irregular margins	64%	84%
Hypo-echoic	83%	49%
Intra-nodular flow	70%	65%
MicroCa.&irregular margins	30%	95%
MicroCa.&hypoechoic	28%	95%
Solid & hypoechoic	73%	69%

http://www.headandneckultrasound.co.uk/presentations/Thyroid%20Ultrasound.pdf]

These criteria are similar to the criteria and risk factors identified by Papini et al [(8)] in their description of how the use of risk factors identifiable on ultrasound can select those nodules that are likely to be malignant and should undergo fine needle aspiration. Papini proposed that the adoption of such a policy in the selection of which nodules to biopsy would result in a more appropriate selection of patients undergoing biopsy and would ultimately lead to a higher diagnostic yield for thyroid carcinoma.

Knowledge of the relevant signs of benignity and malignancy in thyroid nodules can therefore be used to provide a helpful ultrasound diagnosis, identify which nodules should undergo biopsy and allow patients to be triaged safely [(17)].

Examples of how the radiological classification works in practice are outlined in cases below. The following cases are illustrating the radiological classification.

Case 1   **Female, early 50s presents with a thyroid mass. Ultrasound – solid/cystic nodule,relatively iso –echoic – Diagnosis R2. No indication for FNA.**

Case 2   **Female in mid thirties – vague history of left thyroid swelling. Ultrasound - iso - echoic nodule within left lobe of the thyroid, halo present. Some early cystic change developing within. No warning features for malignancy – R2 – No ultrasonic signs for malignancy. Diagnosis - benign hyperplastic nodule.**

Case 3   **Middle aged female,referred in for right thyroid mass,patient says she has had the lump for years.Ultrasound – predominantly cystic nodule, benign colour flow pattern,"ring down " signs identified on real time imaging - no signs of anything sinister – Ultrasound diagnosis - degenerative colloid nodule. R2, no FNA.**
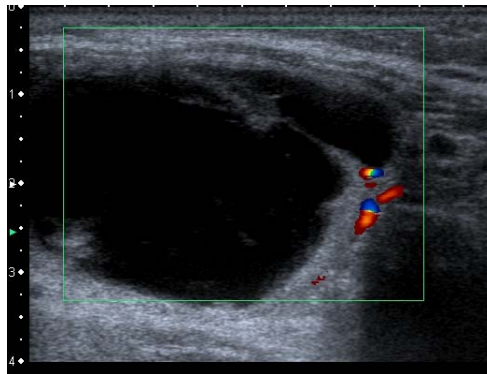
Case 4   **Young female in her early thirties,right thyroid swelling – present off and on "for years".Ultrasound – predominantly cystic nodule,echogenic foci within solid and cystic components – ring down sign identified. Ultrasound diagnosis: R2 – degenerative colloid nodule.**
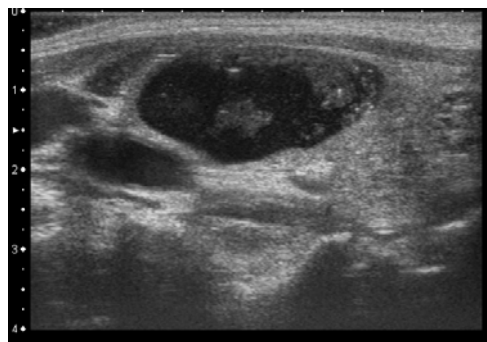
Diffuse disease

There are several conditions that can be thought of as causing a diffuse abnormality within the thyroid. This section will deal with only the most common conditions that present as a diffuse enlargement of the thyroid namely multinodular goitre, Hashimotos thyroiditis, de Quervain's sub acute thyroiditis and Graves' disease. Many of these processes will have some ultrasound characteristics but have widely differing clinical presentations. For example Hashimotos thyroiditis and Graves' disease can look very similar on ultrasound yet clearly will have widely differing biochemical profiles and clinical presentations. The operator needs to be aware that the ultrasound findings choose to be viewed in isolation from the clinical and biochemical status of the patient

Ultrasound has no primary role in the management of the hyper- thyroid patient or of the hypo- thyroid patient, biochemistry is the mainstay in determining management. However the ultrasound operator needs to be aware of the manifestations of these conditions as many diffuse diseases of the thyroid may present as a "thyroid nodule".

Multinodular goiter (MNG)

Multinodular goiter is the commonest pathological condition of the thyroid. The ultrasound diagnosis rests on the finding of multiple nodules within an enlarged thyroid. The features that indicate that the nodules are benign are as described in the previous section.

In order to understand the ultrasound morphology one needs to review the basic pathological processes which occurred during the development of a MNG. Hyperplasia with the subsequent formation of nodules occurs, there is associated fibrosis and calcification within the nodules. Vascular compression due to the follicular hyperplasia leads to focal ischaemia, necrosis and inflammatory change. Cystic areas containing colloid identified microscopically, alternating with hyperplastic foci of thyroid tissue, haemorrhage, fibrosis and calcification. Secondary to the inflammatory change present, a lymphocytic infiltration may be found [(11)].

The ultrasound features are therefore understandable in the light of the histological changes that occur during the development of MNG [Figure 29]. They are:

1. Iso-or hyper- echoic nodules with cystic degeneration
2. Well-defined halo surrounding nodules-due to compressed adjacent tissue
3. Colloid component of cystic elements-"ring down" sign
4. Heterogenous background echotexture of the thyroid
5. Calcification-nodules often contain florid dysplastic central calcification or well- defined peripheral curvilinear calcification.

Figure 30   MNG. Diffuse parenchymal inhomogeneity over the two lobes and the isthmus- that were imaged separetely due to their big size and afterwards joined to show the whole gland- without any recognizable normal tissue.
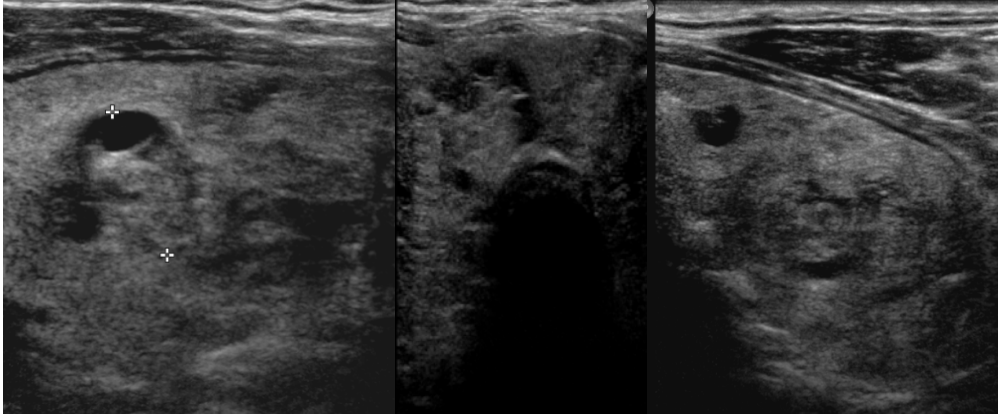
What is the role of ultrasound in the management of MNG? Frequently the only role is to confirm the clinical diagnosis. The radiologist or sonographer can add value to the examination by assessing the nodules to ascertain whether there are any features to suggest that there is a malignant nodule within. If there are no features to suggest a malignant nodule, biopsy/FNA is of little value in the confirmation of a MNG and should be discouraged. An assessment of retrosternal extension should be carried out as part of the examination by scanning inferiorly to the level of the manubrium, if necessary while asking the patient to swallow-to identify the lower margin of the thyroid. If retrosternal extension is detected, CT would be required in order to define the mediastinal extent.

Thyroiditis

The commonest types of thyroiditis encountered are Hashimoto's thyroiditis and de Quervain's thyroiditis. This section will restrict itself to discussion of these two conditions plus a discussion of Graves' disease.

Hashimoto's thyroiditis

Hashimoto's thyroiditis is the most common of the chronic thyroiditides, and the most common cause of hypothyroidism in the United Kingdom. It is an autoimmune condition. Hypothyroidism is diagnosed at presentation or subsequently develops in 50% of cases. The biochemical picture can be that of hyper thyroidism in the acute, initial phase.
Ultrasound appearances
Acute phase
Focal nodular thyroiditis-small hypo echoic nodules with ill defined margin- is seem. representing lymphocytic infiltration [Figure 30]. Features typically starts in the anterior portion and isthmus of the thyroid.

Figure 31   Early Hashimotos thyroiditis – note hypoechoic changes commencing in isthmus and anterior portion of right lobe of the thyroid.
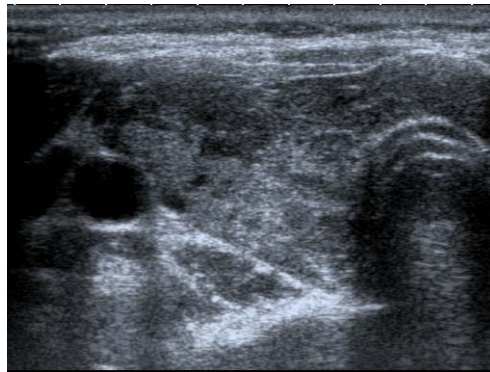
Sub acute phase
The infiltration proceeds to involve the whole of the thyroid gland, the gland is enlarged and slightly rounded in outline. It can be hypervascular on colour flow imaging [(18-20)].

Chronic phase
1. Enlarged, slightly lobular outline, the thyroid is diffusely hypoechoic with fine echogenic septae within [Figure 31].
2. Small atrophic gland with heterogenous echogenicity.

Figure 32   Established Hashimotos thyroiditis - note echogenic striae against the hypoechoic background diffuse changes throughout the gland. a. Axial scan. b Longitudinal scan.

a
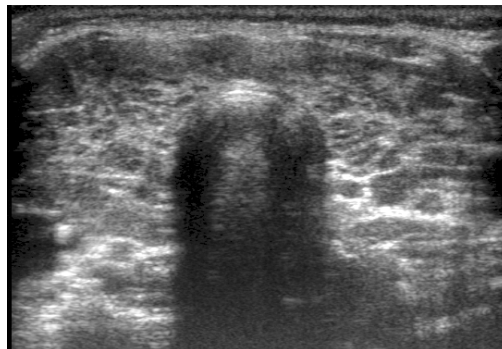
b
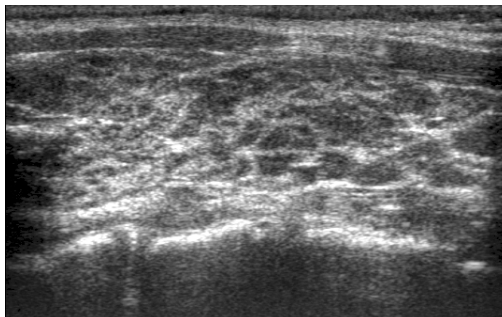
De Quervain's sub acute thyroiditis

The clinical scenario differs in that the patient characteristically presents with a painful swelling in the lower neck, fever and lethargy; typically following a viral illness. The biochemistry in the acute phase is that of thyro toxicity, usually followed by a period of hypo-thyroidism. Typically (after a period of six months from acute onset) the patient recovers and becomes euthyroid.
Ultrasound features
Acute phase
A hypoechoic ill-defined mass, usually tender. The adjacent thyroid tissue is heterogenous in echotexture.
Subacute phase
The hypo echoic area increases in size to involve the ipsilateral thyroid lobe and sometimes extends to the contralateral lobe.
Recovery phase
Thyroid appearances returns to normal or atrophy may develop.

Graves disease

The typical biochemical thyrotoxic profile is matched by a diffuse enlargement of the thyroid gland with rounding of the normal angular outline. The gland is diffusely hypoechoic and colour flow imaging reveals an often spectacular "thyroid inferno" with marked hyper vascularity [Figure 32]. The ultrasound picture can be indistinguishable from Hashimotos thyroiditis in the sub acute phase or can be indistinguishable from de Quervain's thyroiditis if both lobes are involved. However the clinical picture varies significantly between these three conditions, making an ultrasound distinction between the conditions academic.

Figure 33   Hypervascularity identified in early Graves disease – appearances non specific, can be seen in any acute thyroiditis (anterior distribution could be seen in early Hashimotos for example).
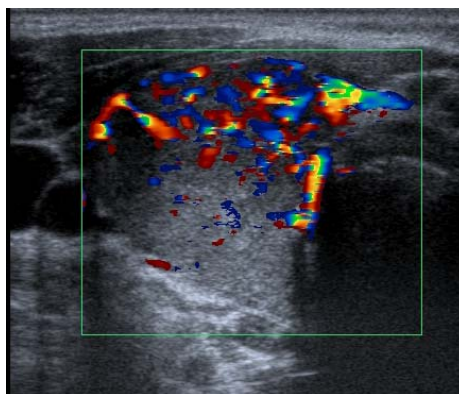
Fine needle aspiration cytology

Cytological examination of material obtained by fine needle aspiration (FNA), due to its high sensitivity and specificity, is the best single test for differentiating malignant from benign thyroid lesions. FNA was first used in Sweden in the 1950s, but it did not become widely used until 1980s. FNA is performed under ultrasound guidance using 21-27 gauge needles. In

the classic approach of fine needle cytology the biological specimen is obtained by repetitively moving a needle attached to a 10-20mL syringe for constant or intermittent suction. A more recent variant collects the specimen by moving through and twirling within the nodule a small needle, not attached to a syringe, in order to aspirate the material by capillary action. The material is air dried, stained with Papanicolaou and May-Grünwald-Giemsa (MGG) or hematoxylin-eosin and interpreted by a cytologist or cytopathologist. Ultrasound imaging guidance enables introduction of the needle into the core of the lesion, in real-time, thus considerably improving diagnostic accuracy and sensitivity compared to blinded aspirations [(21)]. In our experience [E.R.M.], 22 gauge needles provide excellent results, without major complications. Bleeding occurs in some 1% of aspirations and is usually self-limiting. The practice of thyroid FNAC varies in different countries and institutions. In most institutions samples are taken by cythologists, cytopathologists or cystotechnologists, while radiologists position the needle within the lesion under ultrasound guidance. The needle should be closely monitored by the ultrasound beam, continuously during the procedure. Therefore we recommend to insert the needle from the edge of the transducer, and not in the middle. By inserting the needle from the edge one can visualize the whole length of the shaft of the needle during the whole procedure, and be sure that the needle tip is in the desired position. If the needle is inserted in the midline of the transducer, the tip of the needle might not be accurately visualized during the procedure [Figure 33].

Figure 34   The needle is introduced from the side of the linear transducer, and is clearly visible in its whole length (arrows) within the nodule during the procedure
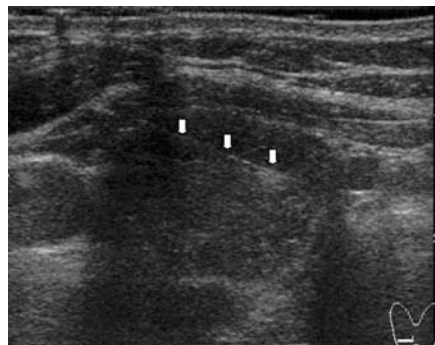
The Society of Radiologists in Ultrasound defines recommendations based on nodule size and ultrasound characteristics for those thyroid nodules that should undergo ultrasound guided FNA and for those nodules that should not undergo FNA [(14)]. The recommendations for thyroid nodules 1 cm and larger in maximum diameter are presented in the following table [Table 7].

Table 7   Recommendations for FNA [(14)].

Feature	Recommendation
Microcalcifications	FNA
Solid or coarse calcifications	FNA if ≥ 1.5 cm
Mixed solid and cystic or cystic with solid mural component	FNA if ≥ 2 cm
Enlarging	FNA
Mainly cystic	FNA probably unnecessary
Internal or central vascularization	FNA

According to the standard criteria [(22-24)] cytological results are subdivided as follows:

Class 1: not diagnostic or suggestive of colloid nodule (macrophages and colloid with or rare follicular cells).

Class 2: benign nodule (monomorphic thyroid follicular cells without nuclear changes, abundant colloid macrophages with or without hemosiderin); in this class were also classified the nodules fulfilling the typical cytological criteria for Hashimoto's thyroiditis (monolayered sheets and small groups of follicular cells, sometimes with oncocytic features, often with nuclear pleomorphism, admixed with or in close proximity to lymphocytes and occasional plasma cells).

Class 3: indeterminate follicular lesion (increased cellularity with microfollicular pattern, scanty or absent colloid, moderately pleomorphic follicular and/or Hürthle cells with mild nuclear changes).

Class 4: suspect or frankly malignant (presence of atypical cells with abnormal nuclear shape, nuclear enlargement, nuclear polymorphism and prominent nucleoli or cellular nests loosely cohesive with the marked overlap). In this class a cytological diagnosis of papillary thyroid carcinoma is included, on the basis of classical features (papillae and/or characteristic nuclear changes such as grooves and pseudoinclusions).

There is limited literature regarding the use of core biopsy needles, but so far it suggests that it is safe, well tolerated and associated with a low incidence of complications. FNA remains todate the best technique available for the initial evaluation of thyroid nodules. Ultrasound guided core biopsy should not be seen as a competitor of FNA, but rather as a complementary investigational tool. Core needle biopsy under ultrasound guidance utilizing modern needles may be advantageous in cases rendered "unsatisfactory" by FNA [(23)].

Percutaneous ultrasound-guided ethanol injection for the treatment of thyroid toxic and autonomous nodules

Thyroid toxic adenomas and toxic nodular goiters have traditionally been treated with radioiodine therapy or surgical resection. According to the numerous literature reports both methods are associated with potentially serious, permanent and relatively frequent complications [(25)]. Ethanol is a well established sclerosing agent in the treatment of hepatocellular carcinomas using ultrasound guidance [(26)] and in the neck, Solbiati et al. introduced this technique for parathyroid glands sclerosations in patients with secondary hyperparathyroidism [(27)]. In 1990 Livraghi et al. started with US-guided percutaneous ethanol injection (PEI) for sclerosation of autonomous and toxic thyroid adenomas [(28)]. This method is utilized in our department since 1996 [G.I.], and we treat mostly single autonomous and toxic adenomas, since results of the treatment of the toxic nodular goiter were poor. We perform the PEI procedure in two sessions per week, until the total calculated volume is injected. PEI is performed under US guidance using state-of-the-art scanners; color and power Doppler US is used to evaluate increased intra and perinodular vascularization that can be observed in the vast majority of autonomous (scintigraphically "hot") thyroid nodules [Figure 34]. The needle is introduced into the nodule using a "free-hand" technique without the use of local anesthesia. Side-hole needles are preferably used, although end-hole needles are suitable too. Sterile 96% ethanol is used as the sclerosing agent. The total volume of ethanol should equal 1.5 times the nodular volume. The nodular volume (in cm^3) is calculated in a standard fashion (length x width x depth x 0.5 = volume in cm^3). The number of injections (sessions) is calculated according to the nodular size and usually varies from 1 to 8 injections for the therapy cycle. The volume of ethanol being injected per session depends

from the patient's compliance with the procedure; in large nodules it is up to 30% of the nodular volume, while in small nodules the total ethanol volume can be injected in one to two sessions. At each session ethanol is injected with the needle being directed to different areas of the nodule to ensure equal distribution. The procedure is repeated twice a week until the calculated volume of ethanol has been injected into the nodule. Injection and distribution of ethanol within the nodule are clearly visible using US control as tiny intranodular hyperechoic foci [Figure 35].

Thyreostatic medication is not routinely prescribed prior to PEI. In all patients, thyroid hormones, TSH and thyroid antibodies in the serum are measured using standard laboratory methods and thyroid scintigraphy using 99m Tc pertechnetate is performed. Scintigraphic and US/color Doppler findings are compared prior to PEI, so that the ethanol could be injected in the specific nodule, which proved to be particularly beneficial in cases of multinodular thyroids.

Follow-up after PEI includes measurement of serum thyroid hormones and control US examination at 1,3,6 and 12 months. Thyroid scintigraphy is performed 3-4 months after completion of PEI. Evaluation of PEI success is based on hormonal status and scintigraphic findings. If the procedure was not successful upon the first cycle of injections, ethanol can be reinjected once more. If new autonomous nodules develop during the period of follow-up PEI can be repeated.

Possible complications are minor and transitory. Some patients develop local hematoma after the procedure that usually resolves spontaneously. All patients experience pain during the ethanol injection and 30-40% experience pain few hours to 1-2 days after the procedure. Pain is usually well tolerated, but about 5% of patients refuse further treatment. Pain is projected towards the jaw, ear or sternum, and is stronger when more ethanol is injected. Transient dysphonia may result after injection of ethanol in posterior parts of the lobe.

The outcome of PEI can be categorized into three groups [(28-30)]:

1. Complete cure with normalization of serum thyroid hormones and TSH levels, normalization of the clinical status and reappearance of the extranodular uptake on scintigraphy, while the node is either "cold", or invisible on the scan
2. Partial recovery with remission of clinical symptoms, normalization of serum thyroid hormones and TSH levels, reappearance of the extranodular uptake on scintigraphy, with node (or part of the node) still "hot" on scintigraphy
3. Hormonal remission – clinical status improved, serum thyroid hormone levels normal, TSH still suppressed; scintigraphically "hot" nodule, with suppressed extranodular uptake.

In our experience, complete cure is achieved in some 60% of patients, partial recovery in 28-30% of patients, and failure of the procedure is observed in 10-12%. Both complete cure and partial recovery are considered a successful treatment. The results are the best for autonomous nodules where some uptake of technetium is seen in extranodal thyroid tissue on scintigraphy. The success rate for toxic nodular goiter is below 50%. In more than 90% of patients we observed significant reduction of initial nodular volume during the follow-up, with volume reduction >50% due to coagulation necrosis induced by ethanol and subsequent nodular fibrosis. In all patients with successful procedure outcome, a considerable flow reduction or even disappearance of intranodular flow was observed with color and power Doppler [Figure 36 and 37]. B-mode echogenicity increased in all successfully sclerosed nodules [(30;31)].

Figure 35 **Color Doppler demonstrates hypervascularisation of thyroid toxic adenoma before treatment.**
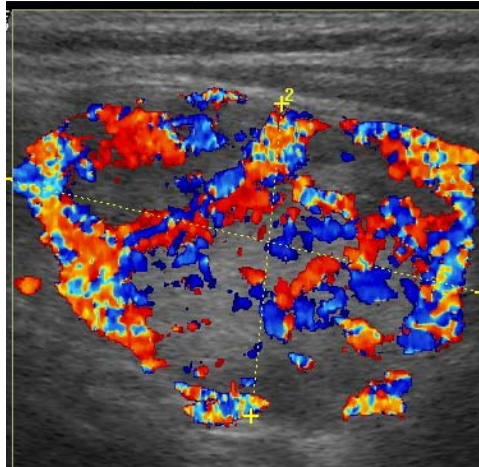
Figure 36 **During ethanol injection, hyperechoic foci are seen within the nodule (arrows). Equal intranodular distribution of ethanol can be achieved by modifying the position of the needle.**
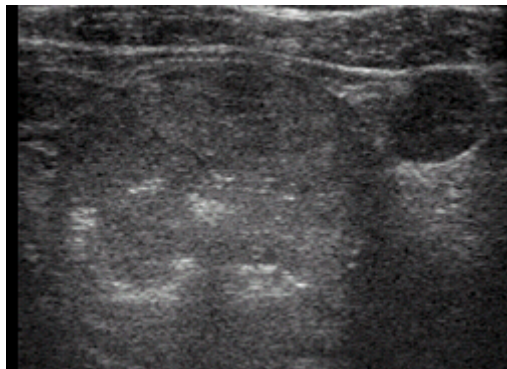
Figure 37 **After 2 days from the first PEI session, nodule vascularization is markedly decreased.**

Figure 38   Power Doppler demonstrates almost completely absent internal vascularisation after successful completion of the procedure.
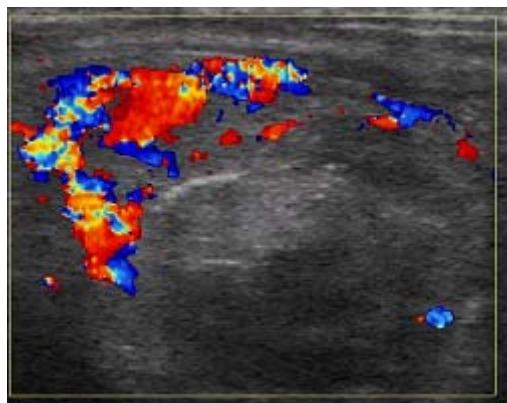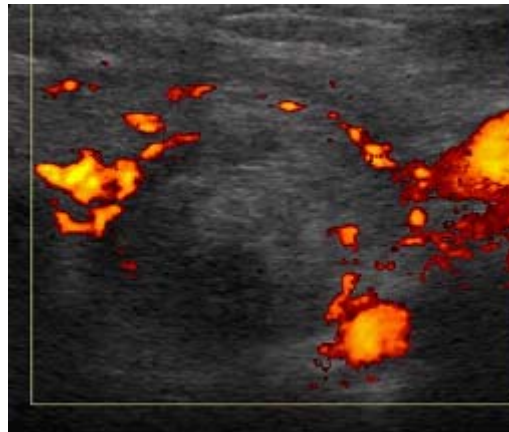

One might speculate whether PEI should be used only in patients with toxic adenomas, as patients with autonomous adenomas rarely disclose clinical symptoms and may undergo spontaneous degeneration, involution and self-healing. However, PEI in developing autonomous adenomas prevents development of overt hyperthyreosis in the future.

Young female patients with solitary hyperfunctioning nodules seem to be ideal candidates for PEI, especially those with autonomous adenomas. This is a group of patients where exposure to radioactive isotopes should be avoided because of long-lasting hypothyreosis that follows this particular therapy. Hypothyreosis following PEI is extremely rare, < 1% [(28;32;33)]. Unlike PEI, radioiodine therapy causes hypothyreosis in 5-30% of patients, and is also known to increase the incidence of gastric carcinoma. After thyroid gland surgery hypothyreosis can be observed in 11% of cases; other serious complications include permanent recurrent laryngeal nerve damage and hypoparathyroidism [(25)]. Both radioiodine therapy and surgery are considerably more expensive as compared to PEI.

In conclusion, US-guided PEI is a safe and effective method for the treatment of autonomous and toxic thyroid nodules, enabling permanent inactivation of autonomous nodules in up to 90% of patients, with minimal and transitory side effects. The best results are observed in patients with small and solitary nodules and it may become the treatment of choice for toxic and autonomous solitary nodules, especially in young patients.

Other imaging modalities

Elastography

Elastography is a newly developed sonographic dynamic technique that uses ultrasound to estimate the stiffness of tissues by measuring the degree of distortion under application of a external force. US elastography has been mostly applied in studies of liver and breast pathology. In thyroid gland elastography has been applied to study the hardness/elasticity of thyroid nodules to differentiate malignant from benign lesions [(34)]. There are several elastography techniques that utilize external compression, carotid artery pulsations, etc. [(35)]. In one method (Sonoline Elegra, Siemens) strain images are built by measuring the local displacement induced by a compressive force applied to the tissue surface [(36)9. Fields displacements are estimated by using a correlation technique that tracks the echo delays in segmented waveforms recorded before and after the quasi-static compression. Tissue

compression is displayed as an image called elastogram on which the hard areas appear dark and the soft areas appear bright. Biomechanical tests on samples of excised tumors and normal thyroid gland tissue are performed to validate the results of thyroid strain imaging and elastic modulus using special equation is calculated.

The values, expressed in kilopascals (kPA,) for normal thyroid gland tissue, benign nodules and malignant nodules are presented in Table 8.

Table 8   Elastography values for normal thyroid, benign nodules and malignant nodules

	kPA	Range (kPa)	Ratio
Normal thyroid	12,3±4,8	5,8-18.7	
Benign nodule	22,5±9,6	11,9-37,4	2,3±1,7
Malignant nodule	99,7±79,8	15,9-590,4	8,8±4,6

Another method used in clinical practice (Hitachi Medical Systems) acquires two ultrasonic images, before and after tissue compression by the probe, and tracks tissue displacement by assessing imaging beam propagation [(34)]. A dedicated software provides an accurate measurement of tissue distortion. The ultrasound elastogram is displayed over the B-mode image in a color scale that ranges from red, for components with greatest elastic strain (softest components) to blue, for those with no strain (hardest components).

The latest method, shear-elastography mode (Aixplorer, Supersonic) simultaneously uses ultrasound waves and shear waves to better characterize and quantify tissue stiffness. Shear wave velocity is directly related to the quantifiable measurement of tissue elasticity. The scanner can generate, capture and quantify the velocity of a shear wave by acquiring data much faster than conventional ultrasound technology. A quantitative color coded map displaying local tissue elasticity for a large image region is produced in real-time a. An easy-to-read color scale indicates tissue elasticity in kilopascals, displayed usually in the range of 0-200 kPa. Elastography image indicates local tissue elasticity: very soft (blue) and very hard (red) [Figure 38]. It's worth to note that color encoded elastography images are different in Hitachi and Aixplorer. In Hitachi hard is blue, while it is th opposite in Aixplorer (shear wave), where soft is blue. The following figures [Figure 38 to 45] illustrate the elastographic features of different tissues using Aixplorer, Supersonic (share wave).

Figure 39   Thyroid elastography: very soft area (blue) and hard area (red).
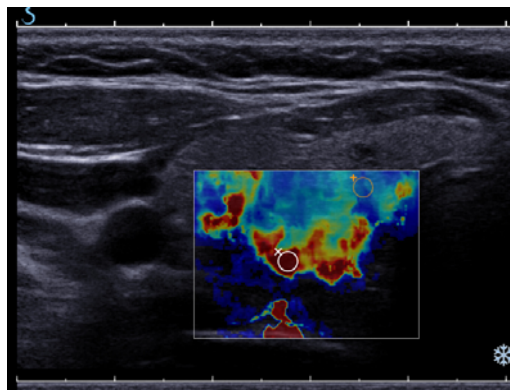
No manual compression is required. Pulses are successively focused at different depths in tissue at supersonic speed. Shear wave propagation is captured with plane waves. Shear wave propagation speed relates directly to the local elasticity of tissue and can be measured in kilopascals. So called "Q-Box" quantification tool accurately measures, in real-time, true tissue elasticity in kilopascals, by placing a region of interest (ROI) in the desired area. Multiple areas of interest can be compared, and ratios of stiffness between these areas measured (E-ratio) [Figure 39].

Figure 40   Goiterous benign nodule. The stiffness of the hypoechoic thyroid nodule is lower than the thyroid parenchyma (8,6 kPa vs 13,5 kPa;. E ratio: 0.6). Q-Box elastography compares the stiffness of two regions as a ratio (nodule (large ROI) to parenchyma (small ROI)). FNA demonstrated nodular goiter (benign nodule).
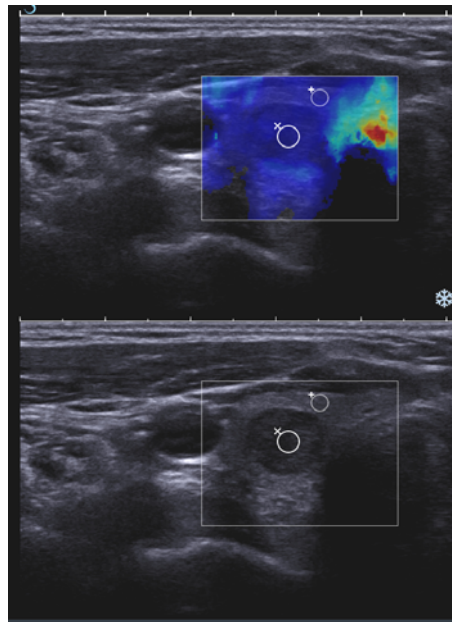
Even though the hypoehogenic nodule demonstrated on the figure 39 was morphologically moderately suspicious, elastography demonstrated a very soft nodule, softer than the surrounding parenchyma. FNA confirmed that the nodule was benign.
In figure 40 the elastographic image of papillary cancer is presented. The nodule is quite hard (red on color display) and quantification of its elastic properties demonstrated that it is much harder than the surrounding thyroid gland parenchyma.
The elastographic presentation of Hürtle-cell tumor [Figure 41], simple thyroid cyst [Figure 42], thyroid cyst with solid component [Figure 43], calcifications within a thyroid nodule [Figure 44] and Hashimoto's thyroiditis[Figure 45] are illustrated.

Figure 41   Thyroid papillary cancer. The nodule is very stiff (red on color display). The measured stiffness of the nodule is 201,9 kPa, while adjacent normal parenchymal stiffness is 28,4 kPA. The E-ratio is 7,1, indicating that cancer is seven times harder than normal parenchyma.
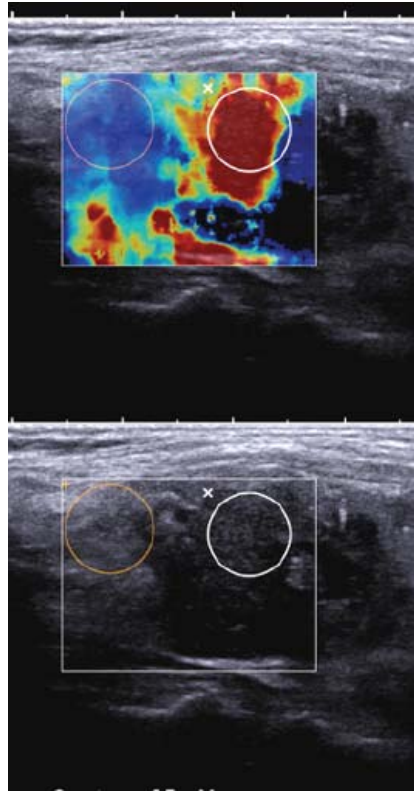
Figure 42 **Hürtle-cell tumor. A mixed solid and cystic nodule is seen. The Q-Box is positioned in the solid part of the tumor that probably contains some calcifications. A very high stiffness value of 279,4 kPa is measured, while the adjacent area of the tumor measures only 25,1 kPa. The colour image displays these differences clearly, with the hard area encoded in the red colour.**
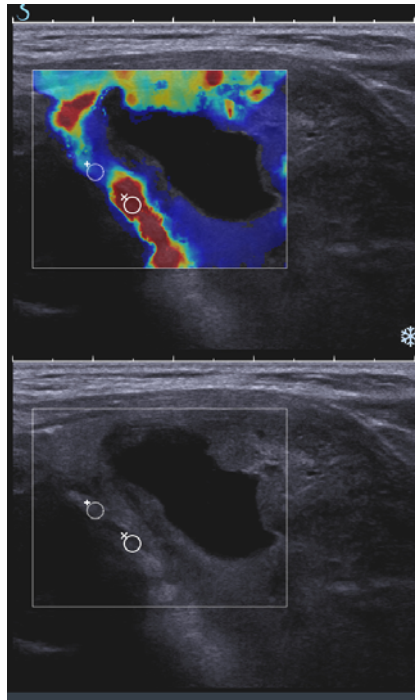
Figure 43 **Simple thyroid cyst. The Q-Box within the cyst measures 12,6 kPa, and in normal parenchyma, slightly harder than the cyst, it measures 16,6 kPa. The E ratio is 0,8.**
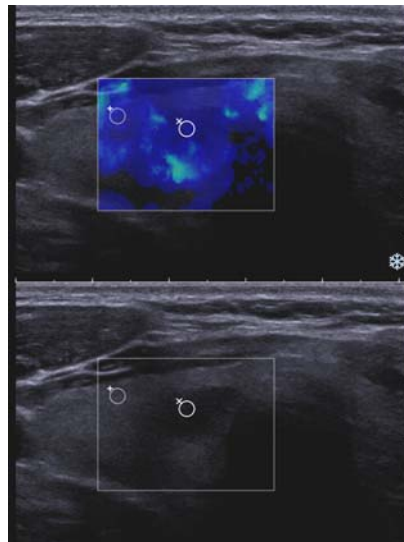
Figure 44   Thyroid cyst with solid protrusion. The solid part within the cyst is harder (20,6 kPa) compared to values in the liquid part of the cyst (12 kPa).
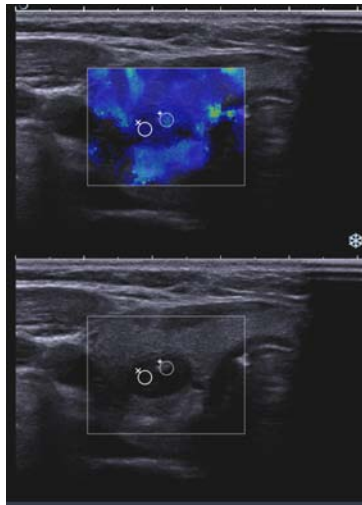
Figure 45   Calcification within a nodule. Calcium deposit is very hard, appearing in red; Q-Box positioned at the edge of the calcification measures a high stiffness of 217,3 kPa.
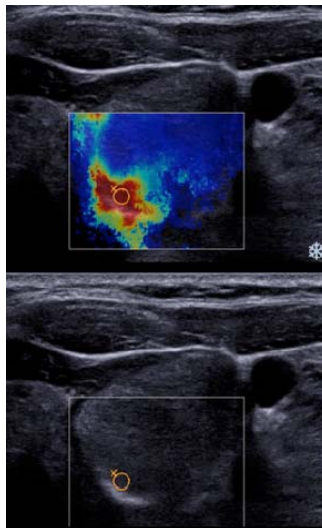
Figure 46   Diffuse thyroid disease (Hashimoto disease). The red color represents tracheal cartilage. Measurements in two areas of the thyroid lobe demonstrate 17,5 and 18,4 kPa.
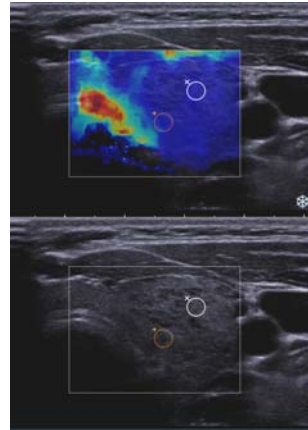
Contrast enhanced ultrasound

Contrast enhanced ultrasound (CEUS) provides only ancillary data for the diagnosis of malignant thyroid nodules. Variation of time-intensity curves during the transit times of the injected microbbubles offers a modest improvement over the information obtainable with traditional US color or power Doppler examinations. New specifically designed microbubbles and new models of US equipment with specific software are needed to improve the predictive value of CEUS for small parts applications [(1)].

Scintigraphy

Thyroid scintigraphy (^{123}I or ^{99m}TcO$_4$) for a thyroid nodule or multinodular goiter is less requested nowadays because of the availability of US and the aggressive use of FNA of thyroid nodules. A normal thyroid scintigraphy shows homogeneous distribution of the radiotracer throughout the gland [Figure 46].

The clinical indications for thyroid scintigraphy, according to American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and management of thyroid nodules [(1)], are: 1- TSH level below the normal range. 2- Iodine-deficient areas even if the TSH level is in the low-normal range. 3- Suspected ectopic thyroid tissue or retrosternal goiter [Figure 47].

Findings on thyroid scintigraphy are unspecific. A cold nodule may represent a benign lesion (like adenoma, cyst or hemorraghe) or a malignant one (well differentiated carcinoma, medullary or anaplastic carcinoma)[Figure 48]. Less than 20% of cold nodules are actually a malignant nodule. A hot nodule is generally an autonomous or hypertrophic adenoma [Figure 49].

Figure 47 **Normal thyroid scintigraphy. A homogeneous distribution of the radiotracer throughout the gland is seen. Note esophageal activity (arrow)on the left plot.**
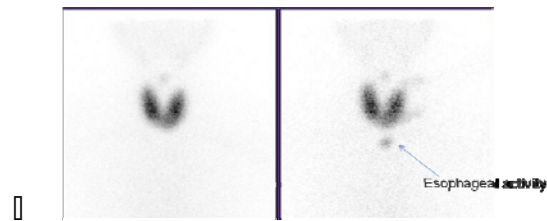
Figure 48 **Lingual thyroid. Ectopic thyroid tissue uptake at the level of the formaen cecum.**
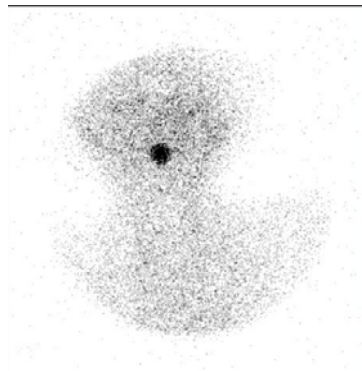
Figure 49 **Cold nodule. a. Benign cold nodule on cytology. b. Malignant cold nodule on cytology. Scintigraphy is unspecific for the differentiation between benign and malignant cold nodules.**

a   b
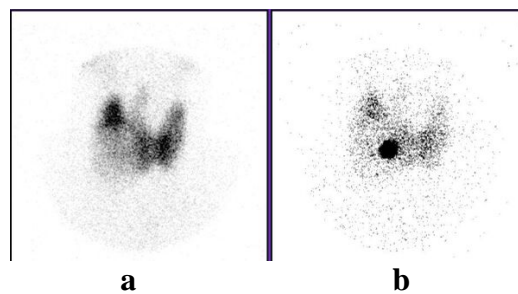
Figure 50 **Hot nodule. a. Single nodule in left lobe (arrow). b. Multiple nodules in both lobes. Note the retrosternal placement of the nodule in the right lobe (arrow). On cytology, autonomous or hyperthrophic adenoma/s were diagnosed.**

a   b
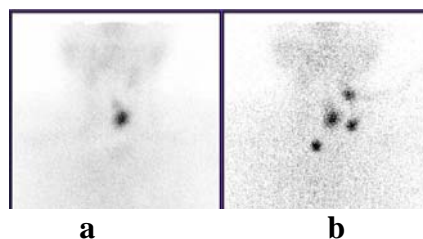
Computed tomography

Computed tomography (CT) is inferior to ultrasound in the differential diagnosis of thyroid nodules. The purpose of performing CT examination is largely limited to the preoperative evaluation of tumors too large to be assessed by ultrasound alone, in order to determine the presence of extracapsular or mediastinal invasion [(37;38)]. CT also carries considerable radiation dose to the radiosensitive thyroid gland.

Multidetector row CT (MDCT) provides higher spatial resolution than conventional CT scanners and allows assessment of tumor extension on 3D reformatted images, with excellent image quality [(39)].

CT exam of the thyroid gland is performed according to the standard protocol. No contrast medium is administered for the thyroid, which is easily discriminated from its adjacent tissue due to the high density of the gland, meanwhile, to avoid interference with hormonal function and radioiodine-related diagnostic tests or treatment. Image acquisition is done at 3 mm thickness. Thin sections (1mm) are used for 3D and multiplanar reconstructions (MPR). When indicated, iodinated contrast medium (100 ml) is injected via an antecubital vein at a 4ml/sec injection rate), and images aquired in arterial and late phases. MDCT provides accurate data on invasion of surrounding tissues, including muscles, trachea, esophagus and blood vessels [Figure 50]. MDCT cannot distinguish between benign and malignant nodules. The dynamic of thyroid nodules contrast enhancement is not studied in details, although differences in density are observed between normal parenchyma and benign and malignant thyroid nodules in the late imaging phase.

On MPR morphological distortion of the trachea or esophagus by the thyroid tumor can be evaluated on multidirectional images. As these structures run in the cranio-caudal direction, coronal and sagittal reformatted images are effective to see compression or invasion by the tumor [Figure 51]. Oblique sections in which the plane is freely are particularly effective for evaluating tracheal invasion. With 3D imaging, the entire thyroid gland can be observed at the same time, and the number and location of nodules are therefore easily determined. 3D imaging is also useful to display the irregularity of the nodule surface and tracheal distortion [(37)].

Figure 51   An inhomogeneous thyroid nodule with regular margins, internal cystic changes and small calcifications is seen in the left lobe. It is a benign nodule, as diagnosed by US –guided FNA. The nodule is clearly delineated from the surrounding thyroid parenchyma, which can be seen in both benign and malignant nodules.
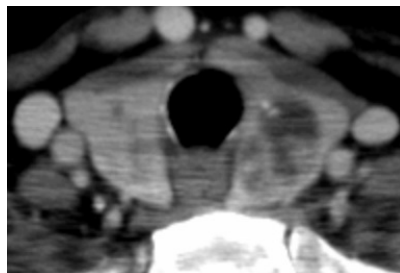
Figure 52   Coronal MPR through the thyroid nodule in the left lobe seen in figure 50 The trachea is slightly compressed by the nodule and displaced towards the right side.
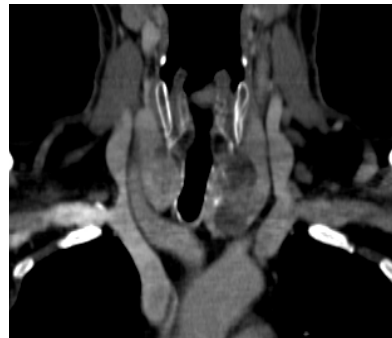
Positron emission tomography

Positron emission tomography (PET) is a rapidly evolving imaging modality that has gained widespread acceptance in oncology, with several radionuclides applicable to thyroid cancer. Thyroid cancer patients have been studied most commonly using 18F-Fluorodeoxyglucose (FDG-PET), with perhaps the greatest utility being the potential localization of tumor in differentiated thyroid cancer (DTC) patients who are radioiodine whole body scan (WBS) negative and thyroglobulin (Tg) positive. Several studies have evaluated sensitivity and specificity of FDG accumulation in thyroid cancer. Some studies demonstrated FDG accumulation in all cancers, while in other studies accumulation was observed in benign nodules, as well as in malignant nodules. The conclusion is that FDG-PET is useful in patients in whom the FNA results are inconclusive, and positive accumulation on PET indicates probable cancer and the need for surgery. Emerging data suggest that PET/CT fusion studies provide increased accuracy and modify the treatment plan in a significant number of DTC cases when compared to PET images alone [(40)].

Magnetic resonance imaging (MRI)

To date, little information is available about the use of magnetic resonance imaging (MRI) in the diagnosis of thyroid cancer. The conventional MRI protocol includes the following sequences: T1-weighted spin-echo imaging, T2-weighted fast spin-echo imaging and inversion recovery imaging [(41)]. Cystic areas of the lesion are defined by characteristic T1- and T2-weighted images and correlate with sonographic findings. Recently, diffusion-weighted imaging (DWI) has evolved as a helpful diagnostic tool for assessing tumor characterization, not only in neural but also in extraneural lesions, such as bone marrow pathologies, lymph nodes, and liver tumors. DWI is based on the random translational motion of water protons, which reflects the tissue-specific diffusion capacity. The diffusion capacity is indirectly proportional to diffusion barriers. Structural changes characteristic of malignancies or benign tissue result in different signals on DWI, which may be quantified by calculating the apparent diffusion coefficient (ADC). In general, rapidly growing tumors are characterized by increased cell attenuation and increased amount of diffusion barriers [(42)]. The initial results indicate that DWI has the potential to enable differentiation between thyroid carcinoma, adenoma, and normal parenchyma [(43;44)]

Dynamic contrast medium–enhanced magnetic resonance imaging (DCE-MRI) is useful to differentiate malignant and benign lesions of brain, breast, endometrium, and salivary glands. Thyroid carcinoma or thyroid nodules with a high cell proliferation index demonstrate

delayed washout pattern on DCE-MRI [(45)]. DCE-MRI is useful to detect or exclude thyroid carcinoma with high diagnostic accuracy in patients with multinodular goiter when results of other diagnostic methods are inconclusive [(44)].

Diagnostic Algorithm

Fine needle aspiration cytology (FNA) is the most important test in the management of thyroid nodules. FNA has a 85% (65-98% range) sensitivity, 99% (72-100% range) specificity and 95% overall accuracy for the diagnosis of focal thyoid lesions. FNA can be performed blindly by palpation or ultrasound-guided to increase confidence if the lesion is palpable. In addition, US-guided FNA can be used to help localize non-palpable lesions, lesions less than 1 cm or when initial free-hand FNA was non-diagnostic. Well trained and experienced cytologist has to evaluate the specimen. Core biopsy should be considered after two aspiration procedures showing non-diagnostic specimen or when thyroid lymphoma is suspected.

Ultrasound allows detection of thyroid and cervical masses, gross dfferentiation of benign from malignant masses based on image features and guidance for FNA biopsy and percutaneous treatment. Ultrasound can accurately document the size of a thyroid swelling and therefore, thanks to its non-invasiveness, serial scans may be performed, allowing better assessment of growth.

Computed tomography (CT) and magnetic resonance imaging (MRI) are indicated in selected cases to determine staging and local extent of the disease for planning surgery. CT and MRI are indicated when there is a potential infiltration of surrounding tissues by the thyroid mass. Other important indications include cervical lymphadenopathy or cases when limits of the goiter cannot be determined clinically or by US, such as retrosternal goiter. CT and MRI can demonstrate involvement of the larynx, pharynx, trachea, esophagus or major blood vessels. MR imaging is used to plan the surgical procedure in a patient with symptoms of extrathyroidal tumor extension (usually voice change or dysphagia). MR is better than CT for evaluating the relationship of tumor to the larynx, esophagus, trachea, spine, and major vessels both prior to thyroidectomy and at local-regional recurrence. It is important to avoid iodine-contrast media in CT to ensure that subsequent radioiodine treatment uptake by the remaining thyroid tissue is not compromised. This difficult may be overcome by gadolinium-enhanced MRI scan [(46;47)]. In the majority of cases a CT or MR scan is not performed prior to thyroidectomy. In the absence of symptoms of tumor invasion of adjacent structures, preoperative CT or MR imaging does not add useful information. It is not necessary to obtain a CT or MR scan to look for adenopathy prior to thyroidectomy. Unlike other head and neck malignancies, it is not necessary to stage the neck with CT or MR scans. The extent of node dissection is determined by cervical ultrasonography and palpation of the nodes

PET-CT has a significant role in the overall post-surgery management especially in patients with elevated serum thyroglobulin (Tg) but negative radioiodine whole body scans. PET-CT should be a part of the routine tests in the Tg positive/ radioiodine scan negative patient [(48)].

In conclusion, in the clinical work-up of a patient with suspicion of thyroid pathology, US should be the first imaging test. When US demonstrates a nodule suspicious for malignancy or there is a history of radiation, MEN II type or thyroidectomy, FNA should be the second diagnostic exam, blind by palpation or under US-guidance.

In the pre-operative planning, CT or MRI should be performed in the presence of symptoms of tumor invasion of adjacent structures.

Pearls and pitfalls

1. Thyroid sonography is able to detect thyroid and cervical masses and to differentiate between probably benign and probably malignant masses based on sonographic criteria.
2. Papillary thyroid tumor is the most prevalent type of thyroid cancer and generally has a favorable prognosis.
3. Sonography is able to guide FNA biopsy and percutaneous treatment of thyroid nodules.

Main limitations of thyroid sonography:
1. Some overlapping in sonographic features of benign and malignant masses.
2. Difficult identification of suspected lesions in multinodular goiter.
3. Operator and equipment quality dependence.

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