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Standardized Ultrasound Report for Thyroid Nodules: The Endocrinologist's Viewpoint

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Key Words
Thyroid · Ultrasonography · Ultrasound · Nodule · Carcinoma · Tumor · Malignancy · Elastography

Abstract
Background: Ultrasonography (US) plays a crucial role in the diagnostic management of thyroid nodules, but its widespread use in clinical practice might generate heterogeneity in ultrasound reports. ***Objectives:*** The aims of the study were to propose (a) a standardized lexicon for description of thyroid nodules in order to reduce US reports of interobserver variability and (b) a US classification system of suspicion for thyroid nodules in order to promote a uniform management of thyroid nodules. ***Methods:*** Relevant published articles were identified by searching MEDLINE at PubMed combining the following search terms: ultrasonography, thyroid, nodule, malignancy, carcinoma, and classification system. Results were supplemented with our data and experience. ***Results:*** A standardized US report should always document position, extracapsular relationships, number, and the following characteristics of each thyroid lesion: shape, internal content, echogenicity, echotexture, presence of calcifications, margins, vascularity, and size. Combining the previous US features, each thyroid nodule can be tentatively classified as: malignant, suspicious for malignancy, borderline, probably benign, and benign. ***Conclusions:*** We propose a standardized US report and a tentative US classification system that may become helpful for endocrinologists dealing with thyroid nodules in their clinical practice. The proposed classification does not allow to bypass the required cytological confirmation, but may become useful in identifying the lesions with a lower risk of neoplasm.

Introduction

Nodular thyroid disease is a common finding, especially in females and in the elderly population. Thyroid nodules are found in 5% of the general population with the use of palpation [1], but high-resolution ultrasonography (US) allows their detections in up to 67% of subjects [2] and the number of discovered thyroid nodules is increasing over time. Malignancy comprises approximately 5% of all thyroid nodules [3] and its incidence is increasing all over the world in recent years [4]. Therefore, the correct identification of nodules that are malig-

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nant and avoidance of unnecessary procedures for those that are benign represent the challenge for endocrinologists.

Cytological examination of material obtained by fine-needle cytology (FNC), due to its high sensitivity and specificity, is still the best single test for differentiating benign from malignant thyroid lesions [5]. However, there is a recognized 5% false-negative rate [6] and, as compared with thyroid US, FNC has the disadvantage of being an invasive procedure. Moreover, thyroid US gives immediate information about the degree of suspicion of thyroid lesions. Originally, thyroid US was used almost exclusively to differentiate between the cystic and solid nature of thyroid lesions and to measure their size [7]. Afterwards, it was suggested that US could help identify characteristics suspicious for malignancy of thyroid tissue [8], and only recently, thyroid US has been widely recognized as the first-line diagnostic procedure for characterizing thyroid lesions [9].

Many studies had focused on how US can help distinguish benign and malignant lesions, and different guidelines and recommendations for the US management of thyroid nodules were proposed by different organizations [10, 11]. Unfortunately, even if there is an agreement on the central role of US in nodule work-up, there has been no universal consensus on a standardized terminology for thyroid US.

The need of uniform and standardized US reports is nowadays even greater due to the large number of physicians who perform thyroid US. In fact, with increased accessibility of high-resolution, portable US machines, thyroid US is being performed more commonly by non-radiologist physicians, e.g. surgeons, general physicians, and most of all endocrinologists. The latter, with their extensive knowledge about thyroid physiology and pathophysiology, are ideally suited to becoming more skilled in the use of thyroid US.

Therefore, this work is addressed to skilled physicians (endocrinologists and/or US operators) working in highly specialized centers for the management of thyroid nodules and was aimed to: (a) propose a universal standardized terminology for the description of thyroid nodules; (b) reduce US report variability between endocrinologists performing thyroid US; (c) provide endocrinologists not directly performing US, the needed terminology background for a correct interpretation and management of US reports, and (d) propose a US classification system of suspicion for thyroid malignancy to be validated in a prospective trial.

Methods

A literature search of English language journal articles in the MEDLINE database (PubMed) was undertaken. Search terms included: ultrasonography, thyroid, nodule, malignancy, carcinoma, and classification system. Consensus statements and recommendations for the US management of thyroid nodules, based on review of evidence and expert opinions, were also reviewed. We supplemented the search with records from personal files and our experience.

US Definition and Description of Thyroid Nodule

The echotexture of the normal thyroid is usually homogeneous and bright. A thyroid nodule is defined as a discrete lesion within the thyroid gland that is ultrasonographically distinct from the surrounding thyroid parenchyma [12]. A nodule usually differs from a pseudonodule for being always clearly distinguishable in both transverse and longitudinal planes.

In our opinion, a standardized and systematic description of US features of thyroid lesions makes the reports objective and more comparable over time. Moreover, a systematic report reduces the possibility of missing the description of some important thyroid lesions features. Therefore, if possible, US reports should always document position, extracapsular relationships, number and the following characteristics of each lesion: shape, internal content, echogenicity, echotexture, presence of calcifications, margins, vascularity, hardness, and size.

Position

The exact location of each nodule within the thyroid gland should always be described in US reports. Thyroid US usually permits a clear identification of an isthmus and of two lobes. Schematically, each thyroid lobe can be virtually divided into three portions: one *third superior*, one *third medium*, one *third inferior* and each portion can be further subdivided into two sub-portions: *anterior* and *posterior*. Isthmus can be divided into: *right parahistmic*, *left parahistmic* and *central part*. Any thyroid lesion can be described as approximately located in one of these sections. Seldom, thyroid nodules are located in the pyramidal lobe and more rarely they can be ectopic. Careful attention should be placed on nodules placed near the thyroid capsule. In this case, description of possible deformation or infiltration of the hyperechoic thyroid capsule and of invasion of adjacent structures is always rec-

ommended (see Extracapsular Relationships). Nodules localized in the posterior part of the two thirds inferior of thyroid lobes, close to the thyroid capsule, should be differentiated from parathyroid adenomas.

The systematic description of the thyroid nodule position is useful exclusively in monitoring the lesion during the follow-up. In fact, although medullary thyroid carcinoma is more frequently placed between the one third superior and the two thirds inferior of thyroid lobes [13], the localization of a thyroid lesion has no diagnostic importance in distinguishing between benign and malignant nodules.

Extracapsular Relationships

Extracapsular relationships of nodules placed near the thyroid capsule should be carefully described. Operators should observe whether the nodule deforms, infiltrates or even crosses the thyroid capsule invading the nearby structures. Therefore, it is important to distinguish simple *deformation* from *infiltration* of thyroid capsule, and to describe a possible *invasion* of the extracapsular areas for a presurgical US tumor staging (T of TNM) of thyroid cancer.

The thyroid capsule may be simply deformed by nodules without interruption of its hyperechogenicity (fig. 1.1). Deformation of the capsule does not indicate malignancy but it can be useful in assessing possible compression of adjacent structures. Infiltration of the thyroid capsule, instead, is defined as an interruption of its hyperechogenicity at the level of the tumor (fig. 1.2). This finding is always indicative of malignancy but does not necessarily mean an invasion of surrounding structures. In our experience, in fact, a clear US interruption of the capsule does not always correspond to extrathyroidal extension (T3) at postsurgical histological evaluation, indicating that US probably may overestimate tumor staging (T) in the TNM classification. Finally, invasion of the adjacent structures by invasive thyroid cancers is observed only occasionally (fig. 1.3). In these cases, the thyroid capsule is not only interrupted at the level of the tumor, but tumoral tissue is seen to penetrate into surrounding strap muscles or into close structures, e.g. trachea, esophagus, thyroid cartilage, and jugular vein. Extracapsular extension more frequently identified anaplastic carcinomas, thyroid lymphomas or intrathyroidal metastasis. On the contrary, extracapsular extension is less common in differentiated thyroid carcinoma in which associated metastatic lymphadenopathy is the most frequent finding [14].

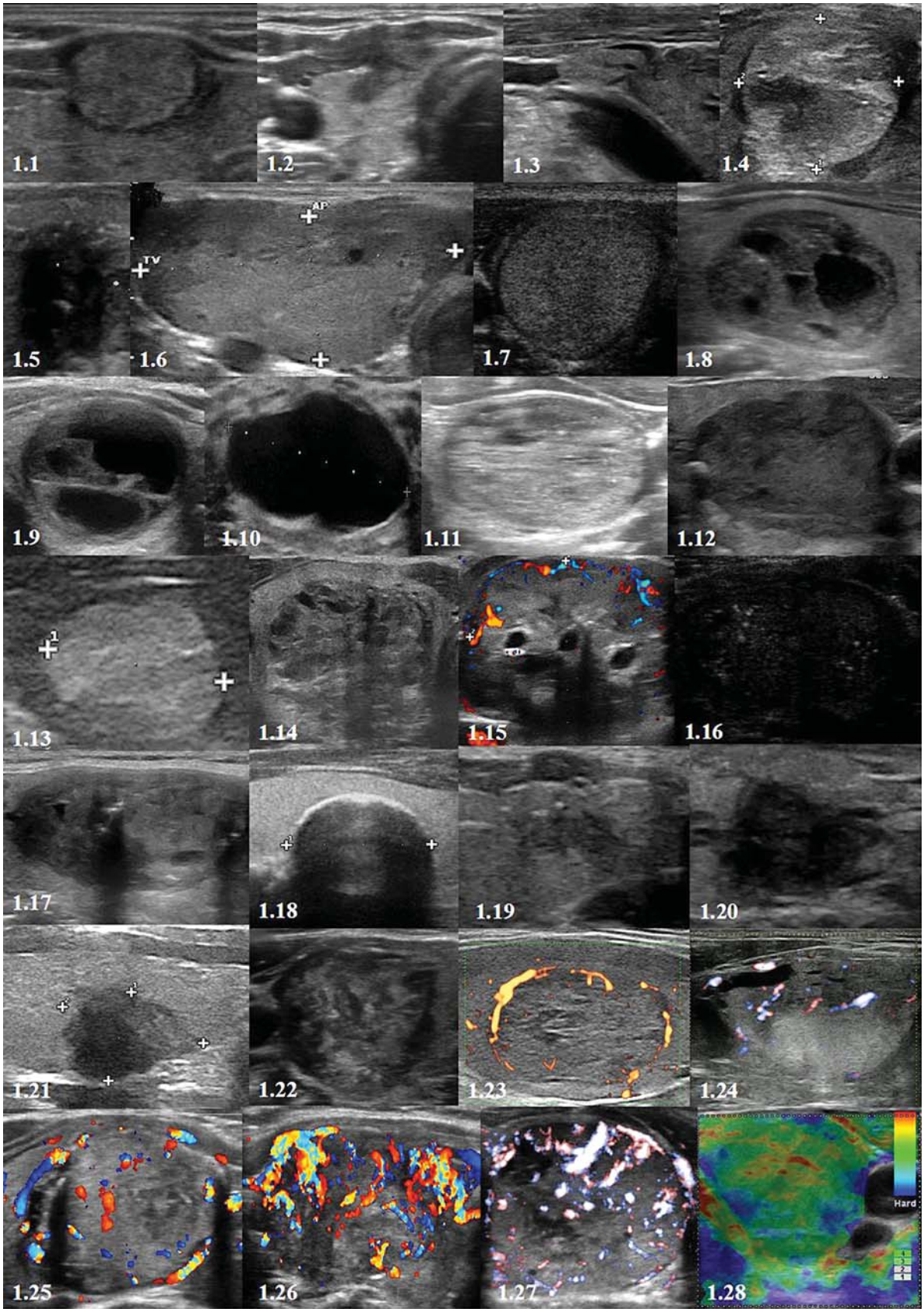
Number

Thyroid goiters may contain several nodules and in clinical practice endocrinologists often wonder if listing and describing all thyroid nodules, even those most likely benign, is really always necessary. It has been shown that the risk of malignancy in a multinodular thyroid gland compared to a gland with a solitary thyroid nodule is similar [3]. It follows that careful attention should be placed on all discovered thyroid nodules. Therefore, ideally, each nodule should be listed and analytically described. In clinical practice, instead, two exceptions may be granted when several thyroid lesions are present. First, when there are coalescent thyroid lesions not clearly distinguishable and a detailed characterization of each nodule is impossible to perform. Second, in case of clearly distinguishable thyroid lesions, with benign or probably benign features, when a detailed description of all nodules can result wearisome or may divert from more suspicious lesions. In these cases we suggest endocrinologists performing US to particularly focus their attention on lesions classifiable as malignant, suspicious for malignancy or borderline (see below) that should always be described in detail. The remaining lesions classifiable as benign or probably benign (see below) should be only listed indicating exclusively their position and size, but avoiding their overdetailed description. This approach is aimed to obtain clear and streamlined reports but containing all the information on the most suspicious lesions. In all other situations, a careful notation and description of each thyroid nodule is always recommended.

Shape

The shape of a nodule has gained diagnostic importance for the differentiation of benign and malignant nodules only recently [15]. Based on their shape, thyroid nodules can be classified as: *ovoid* (when the anteroposterior diameter of a nodule is less than its transverse diameter on a transverse or longitudinal plane) (fig. 1.1), r*ound* (when the anteroposterior diameter of a nodule is equal to its transverse diameter on a transverse or longitudinal plane) (fig. 1.4), *taller-than-wide* (when the anteroposterior diameter of a nodule is longer than its transverse diameter on a transverse or longitudinal plane) (fig. 1.5) or *irregular* (when a nodule is neither ovoid/round nor taller-than-wide) (fig. 1.6).

Both ovoid shape and round shape are reported in benign lesions but they do not obviously exclude malignan-



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cy. Instead, a taller-than-wide shape, although in which plane the ratio should be calculated is still a matter of debate, is reported to be associated with thyroid malignancy [15–17]. These findings reflect that malignant nodules grow across the normal tissue plane in a centrifugal and antigravitational way, in contrast to benign nodules usually growing along the tissue plane in a parallel fashion [15, 18, 19]. A nodule with irregular shape may be a malignant lesion, but irregular shape can also be noticed in benign conditions, such as focal thyroiditis [20].

Internal Content

Usually, internal content of thyroid nodules can be easily detected by US and it should always be reported because it is generally helpful in their differential diagnosis. The internal content of thyroid nodules can be classified following terminology based on the ratio of the cystic portion to the solid portion of the lesion: *solid* (liquid portion ≤10% of the nodule volume) (fig. 1.7), *mixed predominantly solid* (liquid portion >10% but ≤50% of the nodule volume) (fig. 1.8), *mixed predominantly cystic* (liquid portion >50% but ≤90% of the nodule volume) (fig. 1.9), *cystic* (liquid portion >90% of the nodule volume) (fig. 1.10), and *spongiform* (more than half of the nodule volume characterized by aggregation of multiple microcystic areas (<5 mm) separated by thin septations that are interspersed within solid tissue) (fig. 1.11) [20].

Cystic nodules can be described as *pure cysts* (if without internal septa) or as *polyconcamerated cysts* (if with one or more internal septa); predominantly solid or predominantly cystic nodule, instead, can also be called *complex nodules*. In general, pure cystic lesions are always thought to be benign; on the contrary, polyconcamerated cysts and complex nodules may harbor a risk of malignancy [21]. In pure cystic lesions, fluid usually appears homogeneously anechoic, with through transmission of sound waves and posterior acoustic enhancement. It usually consists of colloid and sometimes the sound wave interaction with the condensed colloid proteins may result in bright hyperechoic reverberation artifacts (i.e. *comet tails*) that may be useful in distinguishing the nature of the fluid [22]. A single comet tail artifact within a small cyst is usually called *'cat's eye artifact'* [22]. Sometimes, the content of some cystic nodules may appear less homogeneous due to its major density. The fluid content should be described as having the *'snow falls pattern'* when within it, multiple faint hyperechoic spots with brownian motion are present. In complex nodules, instead, the fluid component may also be the result of degeneration or hemorrhage. In these cases, it may change over time as the hematoma resolves, appearing isoechoic or hypoechoic, sometimes raising doubt as to whether the internal content is liquid or solid. Absence of blood flow is usually, but not always, helpful in this distinction. In the presence of internal solid components, distinguishing internal debris from viable tissue, which may present the same gray-scale imaging, is very important. In fact, the first are usually the result of organization processes, are always benign and should not be aspirated for diagnosis. On the contrary, the solid component of complex nodules composed of viable tissues may harbor a 3% risk of malignancy [21] and therefore they require more attention. Malignant US features of the solid component of complex nodules reported by literature include: an eccentric configuration, microlobulated or irregular free margins, microcalcifications within a solid component, perinodular infiltration, and a centripetal vascularity in the pedicle [23, 24].

Finally, a particular mention for the spongiform pattern. It usually appears finely inhomogeneous and it is always found in benign hyperplastic nodules. A spongiform nodule may relay the overall impression of iso- to hyperechogenicity, but it must be distinguished from iso-

Fig. 1. US images showing the main features of the thyroid nodules. **1.1** Ovoid nodule deforming thyroid capsule. **1.2** Nodule infiltrating thyroid capsule (see interruption of hyperechoic capsule). **1.3** Tumoral nodule invading perithyroidal tissue (see invasion of jugular vein). **1.4** Solid round nodule. **1.5** Markedly hypoechoic nodule with 'taller-than-wide' shape. **1.6** Large nodule with irregular shape. **1.7** Homogeneous, isoechoic, solid nodule with well-defined margins and thin halo sign. **1.8** Mixed nodule presenting predominantly solid internal content. **1.9** Mixed nodule presenting predominantly cystic internal content. **1.10** Anechoic pure cystic nodule. **1.11** Spongiform nodule with regular margins and finely inhomogeneous echostructure (see internal bright hyperechoic spots). **1.12** Hypoechoic nodule. **1.13** Hyperechoic nodule. **1.14** Nodule with markedly inhomogeneous echostructure. **1.15** Laser-treated nodule with inhomogeneous echostructure (see cavitations and hyperechoic scars). **1.16** Nodule containing microcalcifications. **1.17** Nodule containing coarse macrocalcifications (see posterior acoustic shadow). **1.18** Nodule with peripheral 'eggshell' calcification. **1.19** Nodule presenting ill-defined margins. **1.20** Nodule with spiculated margins. **1.21** Nodule presenting microlobulated edges. **1.22** Nodule with thick irregular halo. **1.23** Nodule presenting perinodular flow (PD). **1.24** Nodule with moderate intranodular flow (PD). **1.25** Nodule with moderate peri-intranodular flow (CD). **1.26** Nodule with increased intranodular flow (CD). **1.27** Nodule with increased peri-intranodular flow (PD). **1.28** US-E evaluation of predominantly elastic nodule (see prevalence of 'soft' areas within the nodule).

or hyperechoic complex nodules with isolated discrete cystic areas, because the first are benign and the latter may be malignant. Sometimes, spongiform nodules may also have hyperechoic foci (fig. 1.11) that may be confused with microcalcifications. Nevertheless, while in spongiform nodules hyperechoic foci are associated with the septations or in back wall of the small internal cystic spaces, the real microcalcifications, instead, are located within the solid stroma itself.

Echogenicity

Echogenicity is another important feature to be analyzed in thyroid nodules. The normal thyroid tissue is homogeneously hyperechoic and brighter than the surrounding muscles. Although the parenchymal echogenicity of thyroid glands can vary greatly among individuals, the echogenicity of a thyroid nodule should always be referred to the brightness of its solid component in comparison with the thyroid parenchyma [15, 20]. When the solid component of a nodule presents different degrees of echogenicity, the overall nodular echogenicity should be defined by that of the majority of the nodule.

Based on echogenicity a thyroid lesion can be classified as: *markedly hypoechoic* (nodule hypoechoic relative to the adjacent strap muscles) (fig. 1.5), *hypoechoic* (nodule hypoechoic relative to the thyroid parenchyma) (fig. 1.12), *isoechoic* (nodule with the same echogenicity as that of the thyroid parenchyma) (fig. 1.7), *hyperechoic* (nodule more echoic than thyroid parenchyma) (fig. 1.13), and *anechoic* (in cystic lesions with fluid content with through transmission of sound waves) (fig. 1.10).

Nodule echogenicity may be challenging to be classified in two situations: (a) in complex nodules in which the cystic area is not clearly distinct from the solid area, and (b) in some nodules when extranodular thyroid tissue is affected by Hashimoto's thyroiditis.

Pure cysts are always benign and appear anechoic. Hypoechogenicity, instead, is seldom reported in thyroid malignancies. Hypoechogenicity is thought to represent a cellular microfollicular histologic milieu, whereas the ultrasound appearance of macrofollicular benign nodules is usually isoechoic or hyperechoic [25]. Unfortunately, hypoechogenicity may also represent a typical feature of benign nodular fibrosis [26] and in fact almost a third of benign thyroid lesions are hypoechoic too. On the contrary, marked hypoechogenicity seems to be highly specific for malignant nodules [15, 20]. It follows that particular attention should be placed on markedly hypoechoic lesions.

Echotexture

Nodule echotexture plays a marginal role in differential diagnosis of thyroid lesions. Based on echotexture, nodules should be classified as *homogeneous* (fig. 1.7), *finely inhomogeneous* (fig. 1.11) and *markedly inhomogeneous* (fig. 1.14).

Although homogeneous nodules are often benign, even malignancy cannot be excluded. Similarly, inhomogeneous patterns (both finely and markedly), although more often observed in malignant nodules, are not exclusive of malignancies being observable in benign lesions too. For these reasons, the echotexture is widely recognized as not being a useful finding in distinguishing malignant from benign lesions [20].

Due to the spread of thermal ablation techniques for reducing the size of benign thyroid nodules (e.g. laser, radiofrequency) [27], endocrinologists may have to deal with US evaluation of previously thermal-treated thyroid lesions. Therefore, these nodules deserve a particular mention because they appear markedly inhomogeneous and for their peculiar US features that may change over time. In fact, immediately after the procedure, hyperechoic images due to tissue infiltration by gas may be noted. Peculiar cavitations, surrounded by charring, can be also noticed as result of positioning of fibers, especially in laser-treated lesions. Months after the treatment, thermal-ablated nodules are usually even more inhomogeneous for the presence of avascular hypoechoic necrotic areas and scars, as a normal result of thermal ablation (fig. 1.15). Scars appear as hyperechoic areas that can be confused with coarse calcifications, which differ because of the lack of posterior acoustic shadowing. These nodules should not be confused with malignancy [28], but their features should always be reported in follow-up US reports in order to monitor changes in their characteristics.

Presence of Calcifications

Calcifications may occur in up to a third of thyroid, both benign and malignant, nodules, and are defined as prominent echogenic foci on US, with or without posterior shadowing. Calcifications should be classified in: *microcalcifications*, *macrocalcifications* and *peripheral rim calcifications* (also called *'eggshell' calcifications*). The type of calcification should always be specified in the US reports.

Microcalcifications appear as small (<1 mm) intranodular punctate hyperechoic spots without posterior acoustic shadowing (fig. 1.16). Sometimes distinguishing microcalcifications from a benign punctuate echogenic foci may be difficult (see above). Reverberation artifacts due to colloid materials, i.e. comet tails, can be helpful in differential diagnosis. Microcalcifications are thought to represent the calcified psammoma bodies of papillary thyroid cancer and are highly specific for thyroid cancer. They are usually within malignant well-defined nodular thyroid lesions, but sometimes thyroid papillary carcinomas may also appear as a shaded area of grouped microcalcifications with no evidence of a clear nodular lesion. Microcalcifications should be differentiated from the microfibrotic hyperintense lesions and dense colloid microdeposits.

Macrocalcifications are coarse and large calcifications (>1 mm) that cause posterior acoustic shadowing (fig. 1.17). They occur most frequently in older patients or in 'old' degenerating benign nodules, representing perhaps a possible pathologic evolution of some thyroid lesions [29]. However, macrocalcifications, especially if associated with microcalcifications, within a hypoechoic nodule, may be worrisome for malignancy.

Peripheral rim calcifications ('eggshell') may be *complete* or *incomplete* (fig. 1.18). Peripheral eggshell calcifications surround the thyroid lesion and are thought to indicate a benign nodule. However, this has also been reported in malignant nodules [30], especially in cases of incomplete calcification. In fact, the interruption of the rim calcification may indicate probable invasion by the cancer. Therefore, outage in peripheral rim calcification should always be considered a worrisome finding [20, 31].

Margins

The margins of a thyroid nodule should be described on the basis of their *definition* and their *regularity*. It follows that thyroid nodule edges may appear: *well defined* (when there is a clear demarcation with normal thyroid tissue) (fig. 1.7) or *ill defined* (lack of clear demarcation with normal thyroid parenchyma) (fig. 1.19), *regular* (without irregularities and imperfections) (fig. 1.11) or *irregular* (with edges and irregularities), the latter further divided into *spiculated* (presence of one or more spiculations on its surface) (fig. 1.20) and *microlobulated* (presence of one or more smooth lobules on its surface) (fig. 1.21).

Ill-defined and irregular, both spiculated and microlobulated, margins are usually reported to be suggestive of malignancy [14, 15]. In fact, malignant nodules may present ill-defined margins due to the infiltration of the surrounding thyroidal parenchyma. Therefore, irregular margins, and most of all microlobulated appearance, are findings highly suggestive of malignancy [20]. Unfortunately, this finding is also reported in benign conditions such as thyroiditis [20] or in some benign thyroid nodules incompletely encapsulated that can merge with normal tissue [32].

The *halo sign* is another US pattern that should be described if present. The halo sign appears as a hypoanechoic ring that may completely or incompletely surround a nodule. It is comprised of a pseudocapsule formed by fibrous connective tissue, compressed thyroid tissue and chronic inflammatory change [33]. It can be a *regular thin halo* (fig. 1.7) or an *irregular thick halo* (fig. 1.22). The thin regular halo, which demonstrates the nodule's peripheral vascularity on color Doppler (CD) or power Doppler (PD), is a finding usually suggestive of benign lesion [34], but more than a half of benign nodules lack a halo [33]. On the other hand, even some papillary carcinomas may have a halo [34–36]. The *thick irregular halo*, instead, is usually avascular, and may signify the fibrous capsule surrounding a neoplastic growth. Therefore, a thick irregular halo may be suggestive of capsular invasion by a cancer and it is worthy of special attention [37].

Unfortunately, the definition of nodules' margins is probably the most difficult US feature to be described and it is highly operator-dependent. This finding explains the high interobserver variability in the definition of margins reported by several studies [38], but the use of CD and/or PD and the increase in expertise of endocrinologists dedicated to thyroid US might probably reduce this drawback.

Vascularity

In nodular goiter, Doppler imaging is used predominantly to assess the vascularity of nodular tissue. The leading use is to help determine the likelihood of a thyroid nodule being malignant. Vascularity of a thyroid lesion can be evaluated with CD and/or PD imaging. Based upon the Doppler effect, CD is a measure of the directional component of the velocity of blood moving through the sample volume. It provides information regarding both direction and velocity of blood flow within the nodule, but its shortcomings include the interference by noise

and angle dependence. PD analysis, instead, indicates the total amount of flow present, without information about velocity. PD is more sensitive for detection of flow in small vessels that would not be detected by CD. Furthermore, PD imaging is relatively independent of the angle of the probe and has less noise interference than CD. Therefore, PD should be the preferred imaging technique for assessing the vascularity of thyroid nodules [37]. CD and PD are frequently used to differentiate between solid thyroid nodules and avascular structures such as a blood clots or debris [10].

Several numeric flow-pattern classifications have been proposed but, in our opinion, they can be confounding. Indeed, we suggest a simply descriptive classification of nodule vascularity: *absent* (no or scarce blood flow); *perinodular* (vascular predominance in the periphery of the nodule) (fig. 1.23), further divided into *complete* or *partial*; *intranodular* (vascular predominance within the nodule), and *peri-intranodular* (flow in the periphery and within the nodule). The last two can be further divided by PD in two subtypes: (a) *moderate*: moderate blood flow with homogeneous structure and regular caliber of blood vessels (fig. 1.24, 1.25), and (b) *increased*: high blood flow with anarchical structure with tortuous caliber of vessels (fig. 1.26, 1.27).

Most benign nodules have absent or perinodular flow, but the new powerful US machines are now effective in also highlighting moderate blood flow even in benign lesions [14, 39]. Therefore, presence of vascularity does not necessarily indicate a tumor. Most thyroid cancers, instead, present increased vascularity in comparison with surrounding parenchyma, but the specificity of this character is low [37]. In fact, different investigators have used PD in attempts to determine the correlation between nodule vascularity and malignant involvement, but the results have been inconsistent [37]. The predictive value of blood flow for cancer is reported to be stronger only for nodules with cytology of follicular lesions in which the absence of vascularity reduces probability of malignancy from the generally accepted 20% for unselected ones to only 3% [40, 41].

In conclusion, based on literature [14, 39] and on our experience, nodular vascularity may also be present in up to half of benign nodules. We therefore suggest to carefully interpret CD and PD flow patterns along with other US characteristics as well as clinical features. We do not recommend using CD for differential diagnosis of thyroid cancer but only to differentiate between solid thyroid nodules and avascular structures [10].

Size

Thyroid nodules should be measured in all their three diameters, i.e. anteroposterior, transverse, and longitudinal. When measuring the nodule size, it is advisable to locate the calipers at the outer margin of the halo of the nodule [10].

The risk of malignancy does not change with the size of the nodule [42, 43] that should be precisely documented only for the purpose of follow-up and not for distinguishing a malignant lesion from a benign nodule.

There has been no clear consensus on the definition of nodule growth. We recommend the definition of nodule growth as a 20% increase in the nodule diameter (with a minimum increase in two dimensions of at least 2 mm) or a 50% increase in the nodule volume, according to the American Thyroid Association guidelines [3]. The previously mentioned criteria of nodular growth permits to overcome the reported interobserver's variability allowing the determination of true change in size [38, 44].

Cystic nodules usually show slower growth than solid nodules [45]. Moreover, although malignancy is believed to grow more frequently than benignancy, it should be remembered that the majority of benign thyroid nodules also grow with time [46, 47]. Therefore, a growing nodule does not necessarily indicate a tumor. On the contrary, differentiated thyroid cancers may remain unchanged in size for several years. Finally, a very rapid growth of a thyroid nodule should raise the suspicion of anaplastic thyroid carcinoma, thyroid lymphoma, or medullary thyroid carcinoma [48].

Elastosonography: Another Potential Parameter

Thyroid US is widely recognized as the first-line diagnostic procedure for characterizing thyroid lesions [9]. Nevertheless, sometimes, thyroid nodules may require a re-evaluation by second-level sonographers for better diagnostic characterization. In second-level centers, in fact, aside from clinicians particularly skilled in thyroid US, there are modern ultrasound machines equipped with software specifically developed for ultrasound research. It follows that in these centers it may be possible to obtain adjunctive information on nodule features. Thyroid nodule hardness, for example, is another feature that could be evaluated. Elastosonography (US-E) provides an estimation of tissue stiffness [49, 50]. Malignant lesions are often characterized by greater stiffness than normal tissue [51], and US-E has been proposed to differentiate cancers from

benign thyroid lesions. Results of recent studies seem to confirm US-E as a useful non-invasive tool for differential diagnosis [52–57], although, in our experience and as recently reported by literature [58], it seems to have lower sensitivity and specificity than that previously reported by some authors [53, 55, 59]. US-E may also play a role in differential diagnosis of indeterminate lesions [60] and in distinguishing nodules from pseudonodules in thyroiditis [61]. Unfortunately, US-E cannot be performed on partially cystic, calcific or coalescent nodules and its results should be interpreted with caution in some selected patient categories [62].

Many US machines with different software performing US-E are in commerce at the moment and each one presents peculiar characteristics and mode of use. In general, the US-E technique combines anatomic B-mode and elasticity images. The US-E elastogram is usually displayed over the B-mode image in a color scale depending on the magnitude of strain, usually red (soft tissue), green (intermediate degree of stiffness), and blue (hard, anelastic tissue) (fig. 1.28). Based on the overall pattern, the nodules can be immediately classified into different classes of hardness, hard being lesions more suspicious for thyroid cancer. This classification may be affected by a certain degree of subjectivity in assigning the grade of elasticity. To reduce this variability, classifications based on more objective numeric scores have been studied [63–65]. Unfortunately, at the moment, the proposed objective analyses are still too elaborate and time-consuming and also require further scientific confirmations. Moreover, it should be remembered that US-E software is not sufficiently widespread and therefore cannot be performed routinely yet.

In conclusion, US-E is a promising tool in the evaluation of thyroid nodules. More objective and immediate parameters of hardness are needed to definitely improve the diagnostic accuracy of this technique.

US Classification System

In some second-level centers, some ultrasonographers use a US classification systems for differentiating thyroid nodules [66, 67] as no single US feature of thyroid nodules retains a sufficient predictive value for the suspicion diagnosis of thyroid cancer. Some researchers have therefore proposed using a combination of features in order to improve the US sensitivity and specificity in this field [14, 15, 66, 67]. Nevertheless, when multiple patterns suggestive of malignancy are simultaneously present in a nodule, the specificity increases, but the sensitivity becomes unacceptably low [14]. It follows that a combination of features can be used only to stratify the risk. Some authors have evaluated the diagnostic accuracy of the combination of different US features and have proposed different US classification systems for differentiating thyroid nodules [68, 69].

In our opinion, a standardized US classification system, although not achieving the required diagnostic certainty, may improve the clinical thyroid nodule management of endocrinologists dealing with this finding. In fact, a standardized US classification system (a) may reduce differences in the risk evaluation of a thyroid nodule by physicians not directly performing US, (b) may better lead the choice of the nodules to be aspirated or to be followed up with more attention, and (c) may facilitate data comparison in scientific studies.

Combining current data of literature [68, 69] with our experience, we designed a US classification system of five categories based on thyroid nodule US characteristics and currently used in our center (table 1). Nodular US features are divided into: *US features of malignancy* including: marked hypoechogenicity, spiculated margins, microlobulated margins, microcalcifications, a taller-than-wide shape, perithyroidal infiltration, perithyroidal invasion, and associated metastatic lymphadenopathy; *borderline US features* including: hypoechogenicity, irregular shape, ill-defined margins, irregular thick halo, increased intranodular vascularity, increased peri-intranodular vascularity, macrocalcifications, and partially interrupted rim calcifications, and *US features of benignity* including: ovoid shape, round shape, isoechogenicity, hyperechogenicity, well-defined margins, regular margins, regular thin halo, perinodular vascularity, spongiform appearance and pure cystic lesion.

Therefore, by combining the previous US features, each thyroid nodule can be tentatively classified as follows: (1) *Malignant:* three or more US characteristics of malignancy regardless of the existence of borderline or benign US features. In nodules classified as malignant the possibility of a benign lesion can be reasonably ruled out. (2) *Suspicious for malignancy:* less than three US characteristics for malignancy regardless of the existence of borderline or benign US features. In this category the risk of malignancy is high, but the possibility of a benign lesion cannot be excluded. (3) *Borderline:* one or more borderline US features without US characteristics suggesting malignancy regardless of the existence of benign US patterns. This category includes most of all benign nodules but also malignant nodules. (4) *Probably benign:* two or

Table 1. US features and US classification system with five categories for the suspicion diagnosis of thyroid nodules

Malignant US features (US-Mal)	Borderline US features (US-Bor)	Benign US features (US-Ben)
Marked hypoechogenicity	Hypoechogenicity	Ovoid shape
Spiculated margins	Irregular shape	Round shape
Microlobulated margins	Ill-defined margins	Isoechogenicity
Microcalcifications	Irregular thick halo	Hyperechogenicity
Taller-than-wide shape	Increased intranodular flow	Well-defined margins
Perithyroidal infiltration	Increased peri-intranodular flow	Regular margins
Perithyroidal invasion	Macrocalcifications	Regular thin halo
Metastatic lymphadenopathy	Interrupted rim calcifications	Perinodular vascularity
		Spongiform appearance
		Pure cystic lesion

1 = *Malignant:* ≥3 US-Mal (regardless of the existence of US-Bor or US-Ben); 2 = *Suspicious for malignancy:* ≤2 US-Mal (regardless of the existence of US-Bor or US-Ben); 3 = *Borderline:* ≥1 US-Bor without US-Mal (regardless of the presence US-Ben); 4 = *Probably benign:* ≥2 US-Ben (except spongiform appearance and pure cystic lesion), with no US-Mal, and/or US-Bor; 5 = *Benign:* spongiform nodules, pure cystic lesions, without US-Mal and/or US-Bor.

more US characteristics that suggest a benign nodule (except spongiform appearance and pure cystic lesion), with no malignancy or borderline US features. Nodules belonging to this category have a low risk of malignancy. (5) *Benign:* nodules with a spongiform appearance or pure cystic lesions, with no malignancy or borderline US features. In lesions of this category the possibility of a malignant lesion can be reasonably ruled out.

Thyroid US Limits

Thyroid US presents some limitations. First of all, US is an observer-dependent method. Interobserver differences are reported, particularly on descriptions of echogenicity and border features of thyroid nodules [38]. Second, with the increased accessibility of high-resolution US machines, thyroid ultrasound is being performed more commonly by physicians different from radiologists (e.g. endocrinologists, surgeons, general physicians) resulting in a further increase of the variability in US reports. An adequate learning curve is advisable to obtain more uniformity in US thyroid execution and reporting, but no studies have yet examined it for non-radiologist physicians. US variability is further increased by the lack of a unique, standardized lexicon for the characterization of thyroid nodules. Technical limits of thyroid US are represented by thyroid nodules extending into substernal, retroclavicular, intrathoracic or retrotracheal locations that may not be easily imaged with US. Finally, although thyroid US has the advantage of being a non-invasive procedure and of giving immediate information about the degree of suspicion of a thyroid lesion, no single sonographic feature or combinations of features are adequately sensitive to identify all malignant nodules. It follows that FNC is required for ultimate diagnosis in any case.

Conclusions

Thyroid US is the major diagnostic modality for evaluation of thyroid lesions. Nevertheless, there is no clear consensus on the standardized terminology to be used in thyroid nodule US reports. Moreover, a univocal US classification system for differential diagnosis of thyroid lesions is still lacking.

An analytic approach in thyroid nodule US reports is now even more desirable because of the large number of physicians who actually perform US and the increasing number of detected thyroid lesions. The proposed approach may be particularly useful both for clinicians performing and not directly performing thyroid US in immediately and better identifying the nodules (those classified as borderline, suspicious of malignancy or malignant) worthy of further investigations (i.e. fine-needle aspiration and cytology), and distinguishing the lesions with very low or absent neoplastic risk. In these cases, the cytology may be avoided or deferred.

In summary, we combined data from literature with our experiences, and proposed a standardized US lexicon for reporting and classifying thyroid nodules which could

improve the management of the patients. Although the proposed US classification system still requires a scientific validation, we believe that this proposal can become useful for all clinicians dealing with nodular thyroid disease in their clinical practice.

Disclosure Statement

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