Imaging of thyroid nodules

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The worldwide incidence of thyroid cancer has increased over the past several decades,[1] reaching an estimated incidence of 2.1% of all worldwide cancers in 2012.[2] In the U.S., the incidence has tripled from 4.8 to 15 of 100,000 people between 1975 and 2014[3] and was estimated to be 3.3% of all cancers in the United States in 2012.[2] This trend has been predominantly driven by a disproportionate increase in the diagnosis of small papillary thyroid cancers without a significant change in mortality (0.5 per 100,000 people).[3] This has led many people to believe that the higher incidence is due to the detection of subclinical disease[4-7] and possibly environmental factors.[8]

Diagnosis of subclinical disease in this situation has been termed over-diagnosis, defined as the detection of indolent thyroid cancer in asymptomatic patients or patients who will die from other causes. This increased detection of subclinical cancer may be harmful secondary to the psychological, physical, and financial burden associated with diagnostic testing and surgery.[8] Fortunately, there has been a plateau in incidence over the past several years, suggesting stabilization rather than a continued upward trend.[9]

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In this clinical context, the radiologist is faced with a difficult challenge -responsibly report clinically significant findings while balancing the fear of missing a cancer diagnosis. How can the radiologist differentiate benign and malignant thyroid nodules based on sonographic findings? The answer to that question determines recommendations for fine needle aspiration (FNA), surveillance, or nothing at all. Similarly, the radiologist is faced with the challenge of the incidental thyroid nodule (ITN), identified on computed tomography (CT), magnetic resonance imaging (MRI), or nuclear medicine studies, such as fluorodeoxyglucose-positron emission tomography (FDG-PET). When should the radiologist recommend dedicated thyroid ultrasonography for an ITN? Several multi-disciplinary professional societies have evaluated the available evidence and proposed guidelines to help the radiologist answer the above questions.

The purpose of this review is to provide the general radiologist with practical information regarding the management of thyroid nodules evaluated with ultrasonography while reviewing society guidelines. This review will also provide guidance on the management of ITNs detected on other imaging modalities (CT, MR, FDG-PET, and US) based on the American College of Radiology (ACR) Incidental Thyroid Findings Committee white paper.

Thyroid anatomy

Located superficially in the infrahyoid neck, the normal thyroid gland (Figure 1) is composed of right and left lobes joined centrally at their inferior thirds by the isthmus, a thin band of thyroid parenchyma that crosses the midline anterior to the trachea. The thyroid is sandwiched between the strap and sternocleidomastoid musculature anteriorly and the longus colli musculature posteriorly. The common carotid arteries and internal jugular veins are located laterally.[10]

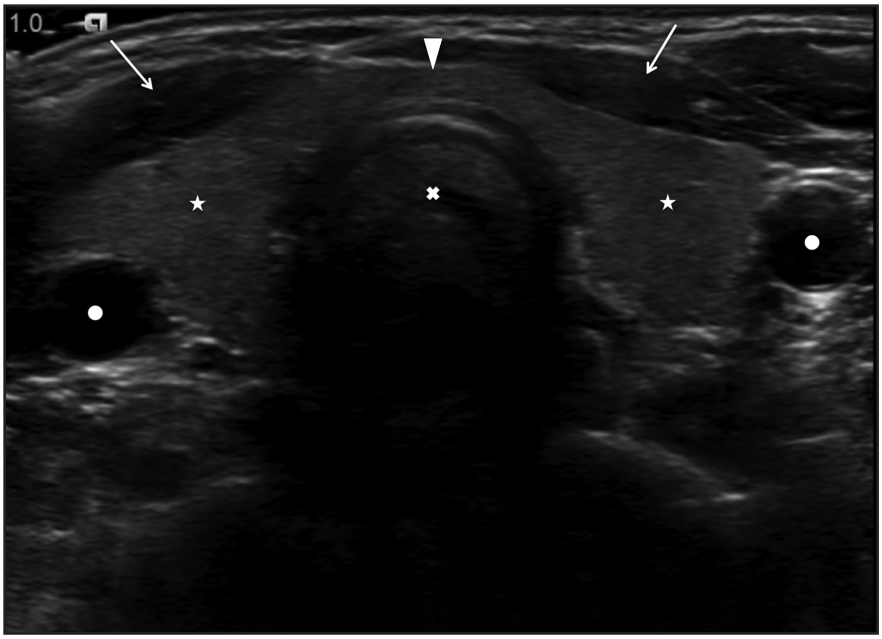

FIGURE 1. Normal thyroid anatomy. Thyroid ultrasound in the transverse plane depicting the right and left thyroid lobes (stars), thyroid isthmus (arrowhead), trachea (white "x"), strap muscles (arrows), and common carotid arteries (circles).

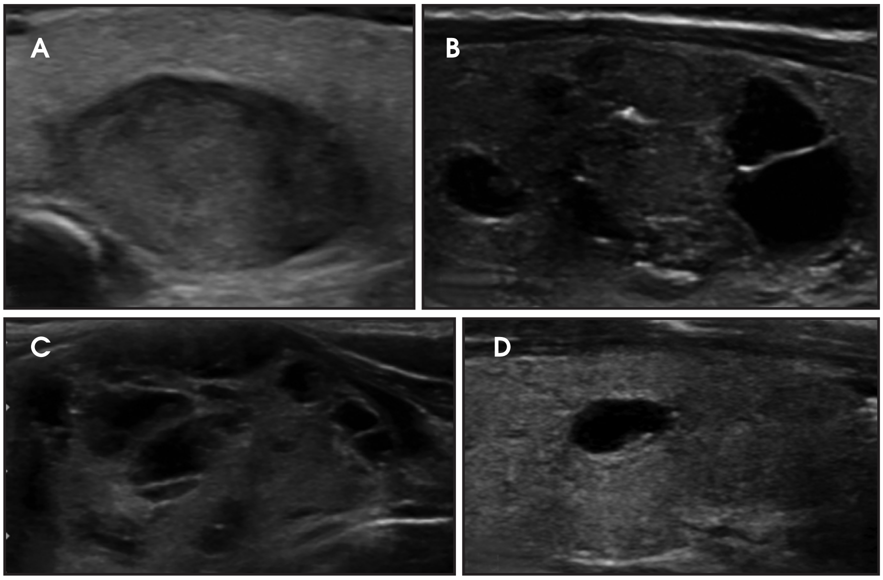

FIGURE 2. Composition is determined by the ratio of cystic to solid components. These are the imaging appearances for (A) solid, (B) predominantly solid, (C) predominantly cystic, and (D) cystic nodules.

Thyroid imaging

Ultrasonography

Ultrasonography is the imaging modality of choice for evaluating thyroid nodules because of its widespread availability, low cost, and lack of ionizing radiation. In addition, the thyroid's superficial location in the neck makes it accessible and amenable to high-frequency sonographic evaluation for accurate characterization. Lastly, visualization on ultrasonography is particularly useful for ultrasound-guided FNA. Multiple studies have reported a lower rate of nondiagnostic and false-negative cytology results from US-guided FNA compared to palpation-guided FNA.[11,12]

On ultrasonography, the normal thyroid gland is a well-circumscribed structure that is homogeneous in echotexture and hyperechoic relative to adjacent musculature. In the adult, each lobe measures 4-6 cm in length and up to 2 cm in width and thickness. The isthmus measures up to 3 mm in thickness.[10]

When evaluating a thyroid nodule, the location and size (in three dimensions) should be described. For nodules <0.5 cm, only the maximal diameter should be reported.[13] Complete evaluation of a thyroid nodule should include sonographic features such as composition, echogenicity, margins, orientation, presence and type of calcifications, vascularity, and extrathyroidal extension, if present. The overall sonographic pattern in conjunction with size confers a malignancy risk and provides a basis for the radiologist to make a management recommendation.[14,15] If there are multiple nodules, each nodule should be described and management decisions should be based on individual nodule suspicion, sometimes requiring multiple FNAs.[16]

Features associated with benignity include cystic or spongiform nodules as well as multiple nodules (without suspicious features) in an enlarged thyroid gland. Features associated with malignancy include hypoechogenicity, solid composition, irregular margins, taller-than-wide orientation and microcalcifications[17] with the latter three having the highest specificities.[16] The characteristics that should be included in the radiology report are described in more detail below and summarized in Table 1.

Multiple societies have created consensus statements to assist the radiologist and clinician in the management of thyroid nodules based on sonographic features, signifying the lack of a single generally accepted set of guidelines. These include the Society of Radiologists in Ultrasound,[18] the American Thyroid Association (ATA),[16] the American Association of Clinical Endocrinologists (AACE),[19] the National Comprehensive Cancer Network,[20] the ACR,[21] and the Korean Society of Thyroid Radiology (KSThR).[13] Several studies have compared and supported the

Table 1: Thyroid Nodule Characteristics on Ultrasonography

Feature	Associated with benignity	Associated with malignancy
Location – right or left lobe (upper, middle, lower thirds), isthmus	-	-
Size – measured in 3 dimensions	<1 cm	>1 cm
Composition – based on ratio of cystic to solid portion Solid: no cystic component Predominantly solid: ≤ 50% cystic Predominantly cystic: ≤ 50% solid Cystic: no solid portion Spongiform: ≥ 50% multicystic change	Cystic, Spongiform	Solid
Echogenicity – relative to adjacent thyroid parenchyma and strap musculature Hyperechoic: > thyroid parenchyma Isoechoic: = thyroid parenchyma Hypoechoic: < thyroid parenchyma Markedly hypoechoic: < strap muscles	Hyperechoic	Hypoechoic/ Markedly hypoechoic
Margin – border between nodule and uninvolved parenchyma Well-defined: distinct border Smooth Irregular margins Spiculated/infiltrative Microlobulated Ill-defined: indistinct border	Smooth	Irregular margins (spiculated, infiltrative, microlobulated)
Orientation Parallel: AP < transverse or longitudinal Non-parallel/Taller-than-wide: AP > transverse or longitudinal	Parallel	Non-parallel/ Taller-than-wide
Calcification – present or absent, type of calcification Microcalcifications: <1 mm Macrocalcifications: >1 mm Rim calcifications *Echogenic reflectors with comet tail artifact: colloid crystals	Colloid crystals	Microcalcifications/ Continuous rim/ Discontinuous rim calcifications with protruding soft tissue component
Vascularity – present or absent, can be further described as intranodular or peripheral	Absent	Present
Extrathyroidal Extension – extension into adjacent structures or lymph nodes	Absent	Present

validity of these guidelines.[22-25] Table 2 summarizes the management guidelines for these groups.[13,16,18-21]

Lesion characteristics on ultrasonography

Composition is based on the ratio of cystic to solid components (Figure 2). Cystic lesions have no solid components, predominantly solid lesions have ≤50% cystic components, predominantly cystic lesions have <50% solid comnents, and solid lesions have no cystic components. Spongiform nodules have multiple microcysts in >50% of the nodule and are seen in benign colloid cysts (Figure 3).[26]

Nodule echogenicity (hypoechoic, isoechoic, hyperechoic) is described relative to thyroid parenchyma with hypoechogenicity having an association with malignancy (Figure 4).[16] Markedly hypoechoic nodules are less echogenic than the adjacent strap muscles and been shown to have a higher malignancy risk (Figure 4D).[13]

Nodule margins may be smooth, irregular (microlobulated, infiltrative/spiculated), and ill-defined (Figure 5). Nodules with smooth or irregular margins have a well-demarcated border between nodule and uninvolved parenchyma. Ill-defined nodules do not have a clear border and are nonspecific.

Table 2: Summary of Consensus Guidelines

Society	Fine needle aspiration (FNA) Recommendations
2005 SRU[a]	1) ≥ 1 cm with microcalcifications
	2) ≥ 1.5 cm with solid composition or coarse calcifications
	3) ≥ 2 cm with mixed solid-cystic composition or "substantial growth"
	4) No biopsy for almost entirely cystic, none of the above, or no substantial growth
2015 ATA[b]	1) ≥ 1 cm if high suspicion (hypoechoic solid nodule or solid hypoechoic component of a partially cystic nodule with one or more suspicious features*) [>70-90% risk]
	2) ≥ 1 cm if intermediate suspicion (hypoechoic solid nodule with smooth margins without suspicious features*) [10-20% risk]
	3) ≥ 1.5 cm if low suspicion (isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without suspicious features*) [5-10% risk]
	4) FNA or observation if ≥ 2 cm with very low suspicion (spongiform or partially cystic nodule without any of the sonographic features described in low, intermediate, or high suspicion patterns) [<3% risk]
	5) No biopsy for benign (purely cystic nodule) [<1% risk]
	*****Suspicious features include irregular margins, microcalcifications, taller-than-wide orientation, rim calcifications with extrusive soft tissue component, extrathyroidal extension*.
2016 K-TIRADS[c]	1) ≥ 1 cm if high suspicion (solid hypoechoic nodules with any of 3 suspicious features#) [>60% risk]
	2) ≥ 1 cm if intermediate suspicion (solid hypoechoic nodules without any of 3 suspicious features# or partially cystic or iso/hyperechoic nodule with any of 3 suspicious features#) [15-50% risk]
	3) ≥ 1.5 cm if low suspicion (partially cystic or iso/hyperechoic nodule without any of 3 suspicious features#) [3-15% risk]
	4) >2 cm if benign (spongiform [<3% risk], partially cystic nodule with comet tail artifact [<1% risk], pure cyst)
	#Suspicious features include microcalcifications, taller-than-wide orientation, spiculated/microlobulated margins
2016 AACE[d]	1) ≥ 1 cm if Class 3^ – nodules with at least 1 of the following suspicious features: marked hypoechogenicity, spiculated or microlobulated margins, microcalcifications, taller-than-wide shape, evidence of extrathyroidal growth or pathologic adenopathy [50-90% risk]
	2) > 2 cm if Class 2^ – slightly hypoechoic nodules and isoechoic nodules with ovoid-to-round shape and smooth or ill-defined margins, intranodular vascularization, elevated stiffness at elastography, macro- or continuous rim calcifications, or hyperechoic spots of uncertain significance may be present [5-15% risk]
	3) > 2 cm and increase in size or associated with risk history if Class 1^ – mostly cystic nodules with reverberating artifacts that are not associated with suspicious US signs, isoechoic spongiform nodules confluent or with regular halo [1% risk]
	^Classes describe ultrasound feature suspicion as Class 1 (low risk), Class 2 (intermediate risk), and Class 3 (high risk).
2017 NCCN[e]	Solid nodules
	• ≥ 1 cm if suspicious sonographic features[x] are present
	• ≥ 1.5 cm if no suspicious sonographic features[x] are present
	Mixed cystic and solid nodules
	• >1 cm solid component if suspicious sonographic features[x] are present
	• > 1.5 cm solid component if no suspicious sonographic features[x] are present
	Spongiform ≥ 2 cm
	Simple cyst – not indicated
	[x]Suspicious features include hypoechoic, microcalcifications, infiltrative margins, and taller-than-wide orientation.
2017 ACR TI-RADS[f]	TR5 (highly suspicious)
	• FNA if ≥ 1 cm
	• Follow if ≥ 0.5 cm
	TR4 (moderately suspicious)
	• FNA if ≥ 1.5 cm
	• Follow if ≥ 1 cm
	TR3 (mildly suspicious)
	• FNA if ≥ 2.5 cm
	• Follow if ≥ 1.5 cm
	TR2 (not suspicious) or TR1 (benign) – no FNA
	TI-RADS categories determined by point total accrued for five nodule characteristics including composition, echogenicity, shape, margin, and calcifications. TR1 = 0 points, TR2 = 2 points, TR3 = 3 points, TR4 = 4-6 points, TR5 = 7+ points.

[a]Adapted from Frates et al. 2005, [b]Adapted from Haugen et al. 2015, [c]Adapted from Shin et al. 2016, [d]Adapted from Gharib et al. 2016, [e]Adapted from *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Thyroid Carcinoma 2017*, [f]Adapted from Tessler et al. 2017

Table 3: Management of Incidental Thyroid Nodules (ITNs)[a]

Category	Criteria	Recommendations
1 – highly suspicious for malignancy	FDG-avid thyroid nodule Suspicious lymphadenopathy[b] Extrathyroidal spread Lung metastases	Strongly consider ultrasonography (any size)
2 – indeterminate with risk factor of young age	Age < 35 years	Consider ultrasonography if ≥ 1 cm (adults) or any size (pediatric)
3 – indeterminate without risk factors	Age > 35 years	Consider ultrasonography if ≥ 1.5 cm

[a]Adapted from Hoang et al. 2015, [b] Suspicious lymph nodes are nodes > 1 cm in short axis (except jugulodigastric, which can be > 1.5 cm) or nodes containing calcification, cystic components, or irregular margins

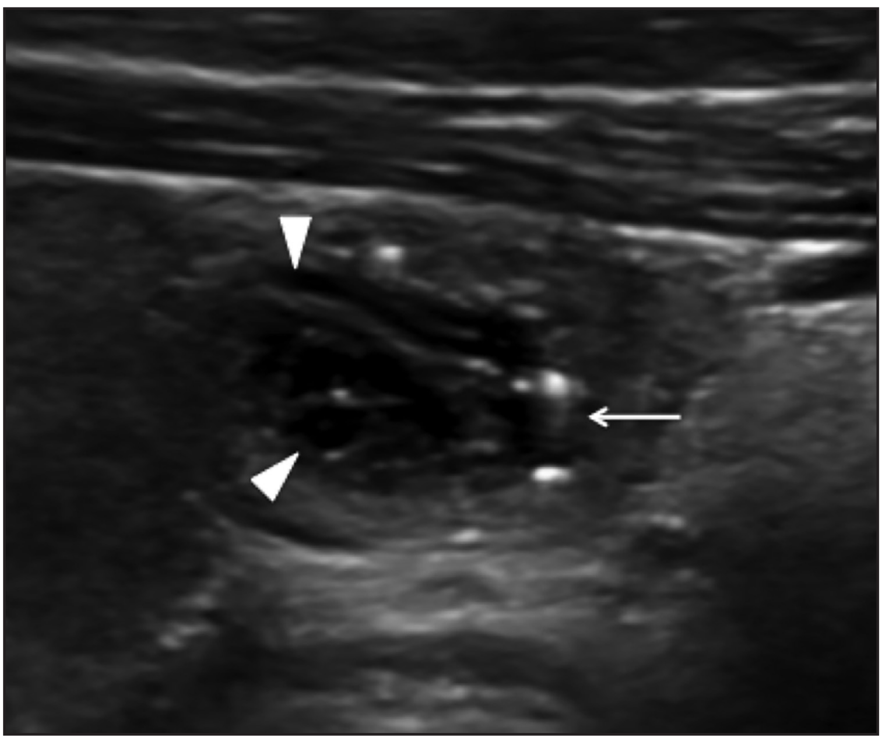

FIGURE 3. *Thyroid ultrasound demonstrates a nodule with microcystic areas occupying >50% of the nodule characteristic of a spongiform appearance (arrowheads). There are also echogenic foci with comet tail artifact (arrow) consistent with colloid crystals.*

Irregular margins (e.g. microlobulated, infiltrative/spiculated) are associated with malignancy.[13,16,21]

Orientation is defined as parallel (anteroposterior diameter is less than or equal to the transverse or longitudinal diameter) and non-parallel/taller-than-wide (anteroposterior diameter is greater than the transverse or longitudinal diameter) (Figure 6). A taller-than-wide orientation is less sensitive for malignancy although it is highly specific.[13,16,26,27]

Microcalcifications are echogenic foci less than 1 mm and do not demonstrate acoustic shadowing (Figure 7). They are highly specific for papillary thyroid carcinoma particularly when associated with solid, hypoechoic nodules.[13,21,28] Macrocalcifications (greater than 1 mm) are generally less worrisome, although discontinuous rim calcifications with a protruding soft-tissue component are concerning for malignancy.[13,16] Of note, echogenic foci with comet tail artifact represent benign colloid crystals (Figure 3) and can easily be confused with microcalcifications.[16,21]

The presence of vascularity (intranodular or peripheral) may be suggestive of malignancy, but data regarding its reliability are mixed.[13,16]

Interval growth

Interval growth is defined as a minimum increase in total volume of 50%, correlating with a 20% increase in diameter (minimal increase of 2 mm in at least two dimensions).[29] Although rapid growth of a nodule can be seen in high-grade malignancies such as anaplastic carcinoma and lymphoma, these are rare and typically show aggressive sonographic features. Multiple studies have shown that interval growth is not a reliable indicator of malignancy since both benign and malignant lesions can grow slowly or remain stable.[30-33] As a result, the ATA recommends the decision for initial FNA or repeat FNA after indeterminate or benign cytology be based on sonographic characteristics rather than size increase.[16]

Extrathyroidal imaging

Multiple societies recommend a cervical lymph node evaluation in all patients who undergo thyroid ultrasonography with known or suspected thyroid nodules.[16,21] Papillary thyroid carcinomas, which comprise 80% of all thyroid malignancies spread via the lymphatic system, as does medullary thyroid carcinoma.[34] Nodes that should be evaluated include the cervical chain lymph nodes in both the lateral (levels II, III, IV, V) and central (level VI) compartments. Similar to thyroid nodules, sonographic features and morphology are most important in determining risk of malignancy. Suspicious sonographic features include round shape, loss of the fatty hilum, calcifications, cystic change, increased echogenicity, and increased vascularity.[19,34] These sonographic features are more important in management than size, which is nonspecific. However, the radiologist's suspicion can be raised by nodes >1 cm in short axis or >1.5 cm for jugulodigastric nodes (level II).[34]

Ultrasound elastography

Ultrasound elastography differentiates thyroid nodules based on elasticity and comes in two forms, strain and shear wave elastography.[35,36] Many studies support the use of elastography;[37-43] however there are limitations[16] and it is not widely available. The AACE, ATA and KSThR recommend use of elastography as a supplementary study but not as a replacement for gray-scale ultrasound.[13,16,19]

CT and MRI of thyroid nodules

Cross-sectional imaging depicts the thyroid gland and its relationship to adjacent structures well. On non-contrast CT, the normal thyroid gland is homogeneously hyperattenuating relative to soft tissues in the neck due to its high iodine content. Following contrast administration, the thyroid enhances homogeneously and avidly because of its rich blood supply. On MRI, the thyroid gland is T1 hyperintense and T2 iso- to hypointense on noncontrast images and homogeneously enhances on post-gadolinium images (Figure 8).

Of note, iodinated contrast can interfere with the uptake of iodine-containing radionuclides, such as I-123 or I-131. Thus, timing of contrast-enhanced CT should be taken into consideration when diagnostic imaging or radionuclide ablation are planned. However, because iodine is cleared from the body within 4-8 weeks, nuclear imaging and therapy can

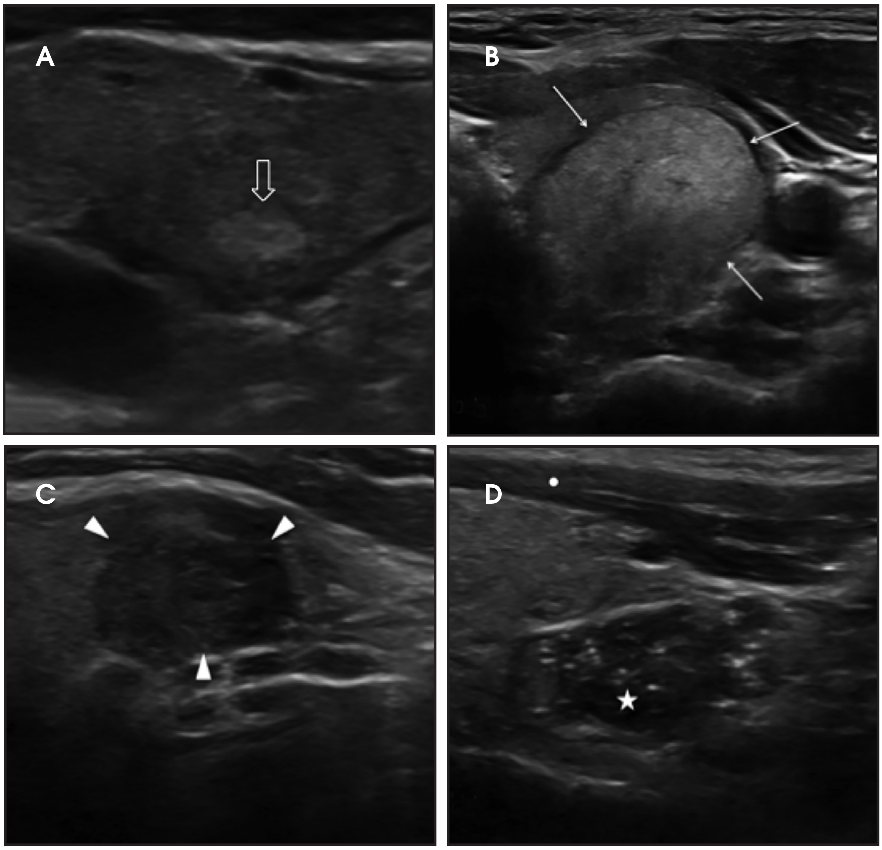

FIGURE 4. *Echogenicity of a nodule is compared to the echogenicity of adjacent thyroid tissue and strap muscles. These are the imaging appearances for (A) hyperechoic (empty arrow), (B) isoechoic (arrows), and (C) hypoechoic (arrowheads) nodules. (D) Markedly hypoechoic (star) nodules are hypoechoic compared to the strap muscles (circle).*

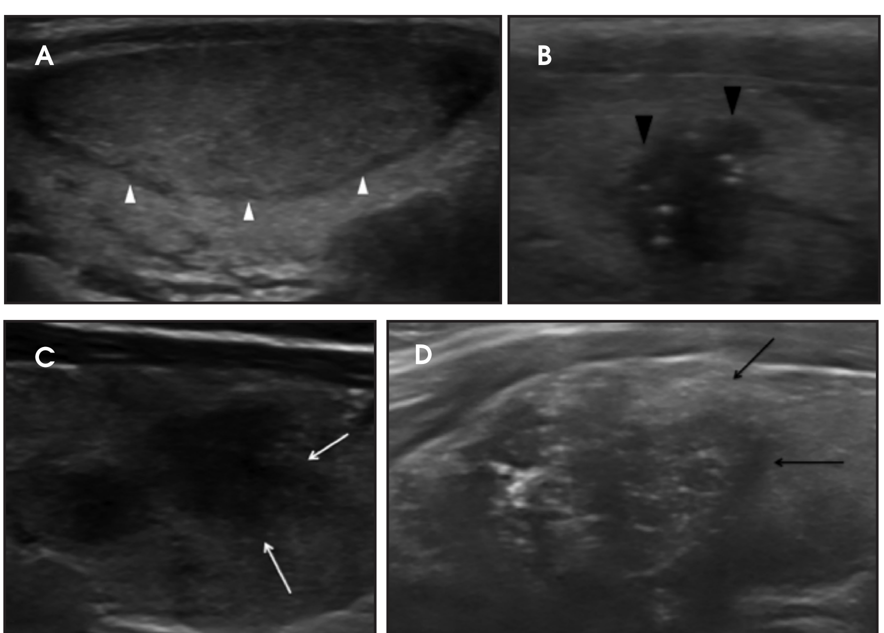

FIGURE 5. *Margins can be well-defined and may be (A) smooth (white arrowheads), (B) microlobulated (black arrowheads), or (C) spiculated/infiltrative (white arrows). Margins can also be (D) ill-defined (black arrows).*

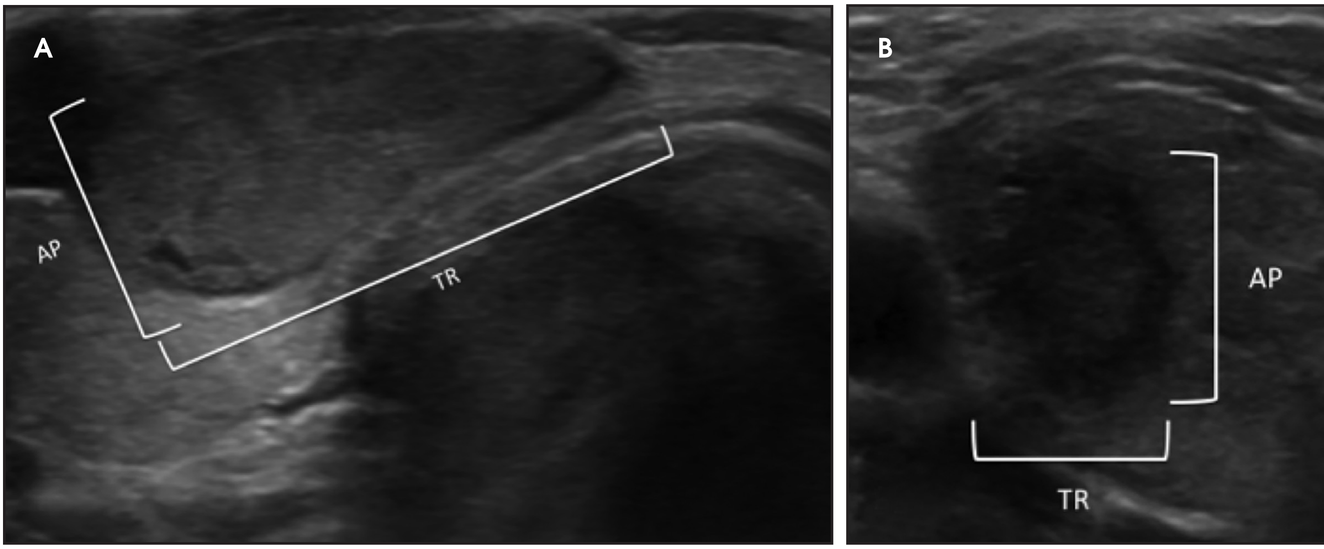

FIGURE 6. *(A) Parallel orientation is defined as an anteroposterior (AP) dimension less than the transverse (TR) or longitudinal (LO) dimensions. (B) Non-parallel or taller-than-wide orientation is defined as an AP dimension greater than the TR or LO dimensions.*

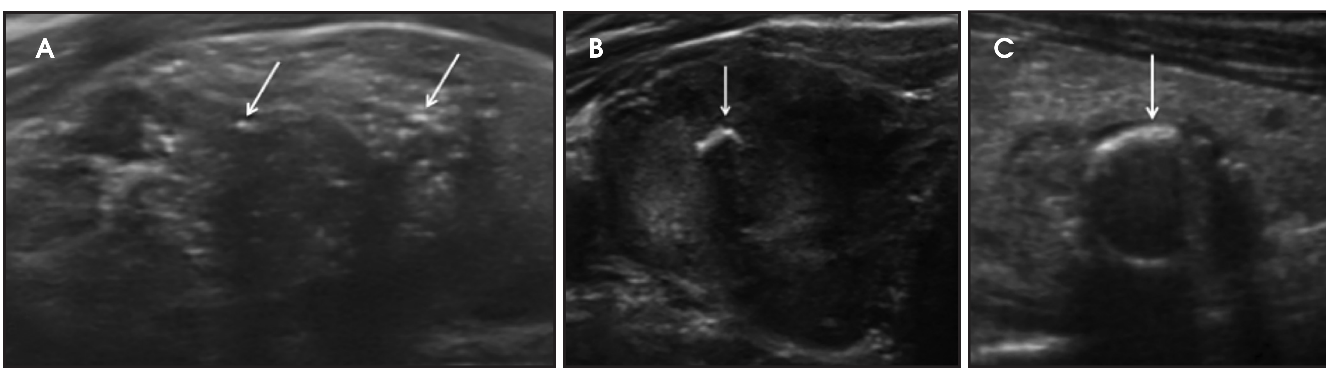

FIGURE 7. *(A) Echogenic foci <1 mm without shadowing (arrows) represent microcalcifications in this patient with papillary thyroid carcinoma. (B) Ultrasound images in different patients demonstrate macrocalcifications and (C) rim calcifications (arrows).*

be safely and successfully performed beyond this time period. If there is further concern about incomplete clearance, urine iodine sampling can be performed.[44-46] Unlike CT contrast, MRI contrast (gadolinium) does not interfere with iodine uptake.[47]

Computed tomography and MRI are not the studies of choice for evaluating thyroid nodules because of poor spatial resolution, and the inability to detect features such as irregular margins and microcalcifications. However, the radiologist must be familiar with the reporting of thyroid nodules identified on cross-sectional imaging because of the frequency of studies including the neck and upper mediastinum (eg. neck and chest CTs) and the frequency of ITNs on these studies (up to 25% on chest CT[48] and 16-18% on CT or MRI of the neck[49,50]). Apart from extra-thyroidal extension or lymphadenopathy, there are no reliable features that allow the radiologist to distinguish between benign and malignant thyroid nodules.[51] Size by itself is also an unreliable feature, but is useful in guiding further work-up in conjunction with patient age.[51]

Not surprisingly, the reporting of ITNs can be highly variable.[52-54] Fortunately, the three-tiered system proposed by Hoang et al. in 2012,[55] supported by other literature[49,56] and formalized in the ACR Incidental Thyroid Findings Committee white paper[51] provides the radiologist with a systematic approach to managing ITNs identified on CT, MRI, and nuclear imaging, including FDG-PET. Further evaluation with thyroid ultrasound is recommended for three categories of ITN as follows:[51,55]

1. Nodules with high risk characteristics such as lymphadenopathy, local invasion, or FDG avidity
2. Nodules ≥1 cm in patients <35 years of age and
3. Nodules ≥1.5 cm in patients >35 years of age

Ultrasonography of the neck in the evaluation of the carotid arteries, salivary glands, cervical lymph nodes, and other neck masses, can detect ITNs, as well. The sonographic features of the ITN should be described similarly to findings in a dedicated thyroid ultrasound. If there is insufficient evaluation of the thyroid, a full thyroid ultrasound should be recommended for complete characterization.[51]

Additional considerations in the reporting process include the presence of comorbidities and limited life expectancy

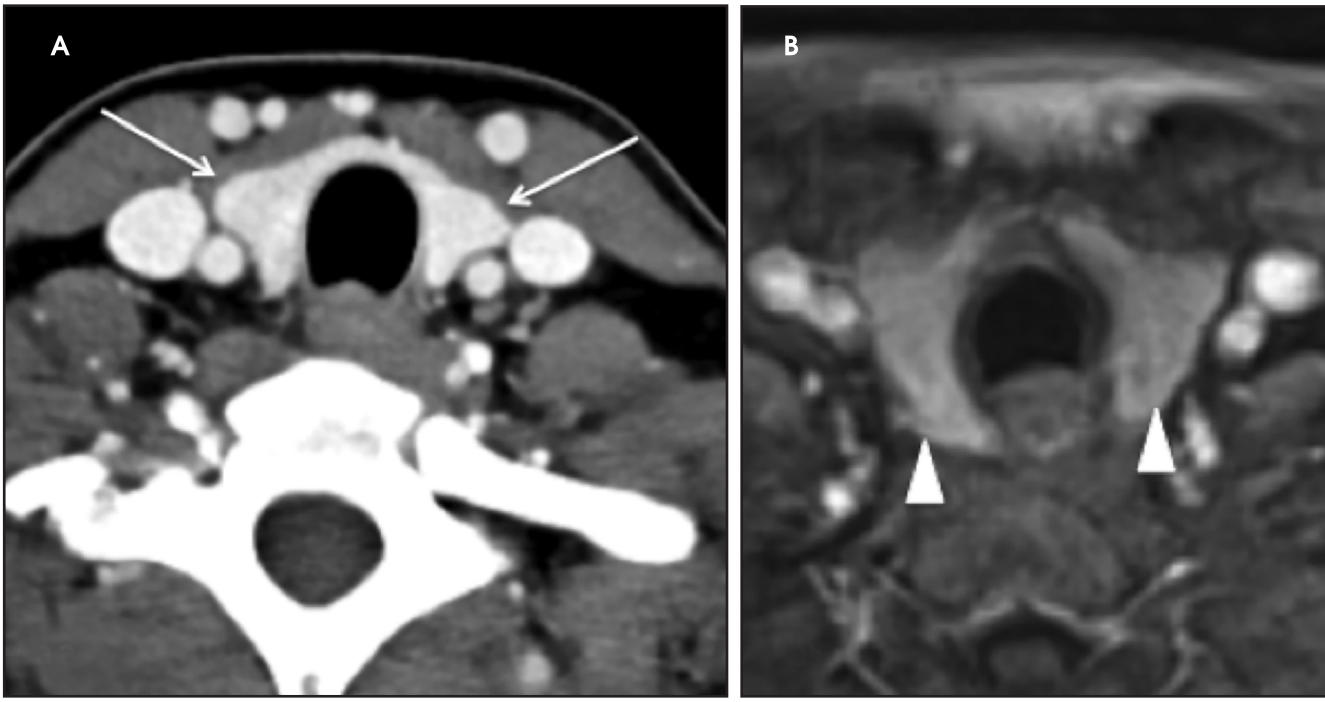

FIGURE 8. *Normal thyroid appearance on (A) contrast-enhanced axial computed tomography (arrows) and (B) T1-weighted contrast-enhanced magnetic resonance image (arrowheads).*

that would increase the risk of treatment or increase the patient's morbidity and mortality greater than a potential thyroid cancer. The ACR recommends that these patients do not undergo further evaluation.[51]

Nuclear imaging

The normal thyroid gland demonstrates homogeneous radiotracer uptake. Thyroid scintigraphy plays a role in the evaluation of a thyroid nodule in a patient who has low serum thyroid stimulating hormone levels. Thyroid scintigraphy with I-123 can identify a "hot" or hyperfunctioning nodule with radiotracer uptake greater than that of the surrounding thyroid. "Hot" nodules are rarely malignant and do not warrant cytologic analysis. A "warm" or iso-functioning nodule with radiotracer uptake equal to that of the surrounding thyroid, or a "cold" or hypofunctioning nodule with radiotracer uptake less than that of the surrounding thyroid, require further evaluation.[57]

Iodine-131 is useful as a therapeutic agent and imaging radionuclide. For diagnosis, I-131 is useful for whole body scanning to evaluate metastatic disease and for follow-up post-radioiodine ablation. High doses serve three purposes following thyroidectomy for malignancy: Ablate any remnant thyroid tissue, detect lymph node or distant metastases with high sensitivity, and ablate any tumor foci with uptake.[34]

Positron emission tomography with FDG is commonly performed in oncologic and non-oncologic settings. The normal thyroid gland has diffuse homogeneous low level FDG uptake similar to adjacent musculature. Incidental focal thyroid uptake occurs in 1-2% of cases[58-60] with a reported malignancy rate of 11-14%.[61,62] Due to this increased risk, the ACR and AACE recommend dedicated thyroid ultrasonography and FNA regardless of sonographic features[19,51] whereas the ATA recommends sonographic and clinical evaluation of all FDG avid thyroid nodules and FNA of nodules >1 cm.[16] There is no standard uptake value threshold that definitively distinguishes benign from malignant lesions.[59]

As mentioned previously, low-level FDG activity is normal. However increased diffuse radiotracer uptake occurs in 2% of patients.[58] It typically reflects benign inflammatory conditions such as Hashimoto's disease or other thyroiditis. Although thyroid nodules are rarely seen in these cases, the ATA recommends that diffuse uptake should prompt sonographic characterization.[16]

Conclusion

The incidence of thyroid cancer increased from 1975 to 2014 without a significant change in the mortality rate, most likely due to the earlier detection of indolent papillary thyroid cancers. Since the radiologist is often the first clinician to identify ITNs on cross-sectional imaging and is responsible for further characterization of nodules on ultrasonography, it is imperative that the radiologist be aware of the current data and recommendations with regards to thyroid nodule imaging. As described in this review, our recommendations are as follows:

Ultrasonography is the imaging modality of choice in the characterization of thyroid nodules because of its low cost, widespread availability, lack of ionizing radiation, ability to accurately depict nodule features, and ease of use for ultrasound-guided FNA.

Dedicated thyroid ultrasound should include a full survey of cervical lymph nodes.

Thyroid nodules are characterized by their location, size, composition, echogenicity, margins, orientation, calcifications, and vascularity. Benign features include predominantly cystic composition and an enlarged thyroid gland with multiple nodules. Irregular margins, taller-than-wide orientation, and microcalcifications are associated with malignancy. However, the overall pattern of sonographic features determines the risk of malignancy.

Risk stratification subsequently guides the radiologist recommendation for surveillance or FNA. Collaboration with the local referrers in your community may be helpful to standardize management recommendations.

We recommend the three-tiered approach to managing ITNs as described in the ACR Incidental Thyroid Findings Committee white paper (Table 3).[51]

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