Thyroid Ultrasound
Diffuse and Nodular Disease

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KEYWORDS

• Thyroiditis • Thyroid nodules • Thyroid cancer • Diffuse thyroid disease
• Thyroid imaging reporting and data system • Ultrasound

KEY POINTS

- Thyroid ultrasound can diagnose diffuse thyroid disease by evaluating glandular size, echogenicity, echotexture, margins, and vascularity.
- Ultrasound of chronic lymphocytic thyroiditis shows a diffusely heterogeneous gland with patchy, nodular hypoechoic areas intermixed with echogenic parenchymal bands, giving the gland a micronodular appearance.
- The classic sonographic appearance of Graves disease is an enlarged gland with increased parenchymal vascularity and arteriovenous shunting creating a "thyroid inferno" appearance with a smooth or scalloped glandular contour.
- Ultrasound assessment of thyroid nodules should include description of internal composition, echogenicity, margins, shape, and presence of any echogenic foci.
- Thyroid nodule morphologic features suspicious for malignancy include hypoechoic and very hypoechoic echogenicity, taller-than-wide shape, irregular margins, echogenic foci in solid nodules, and focal increased ^{18}FDG activity on PET imaging.

INTRODUCTION

The normal thyroid gland lies in the anterior neck, superficial to the trachea, deep to the strap muscles, and medial to the carotid arteries and jugular veins. The superficial location of the thyroid makes high-resolution ultrasound the imaging modality of choice for evaluation of diffuse and focal processes. Patients may be referred for imaging because of laboratory or palpable abnormalities. The anatomy and sonographic technique to evaluate the thyroid gland is discussed in detail in the Danielle M. Richman and Mary C. Frates' article, "Ultrasound of the Normal Thyroid with Technical Pearls and Pitfalls," elsewhere in this issue. This article focuses on diffuse and focal abnormalities of the thyroid parenchyma, and an approach to thyroid nodules for an understanding of how ultrasound can guide management of thyroid pathology.

DIFFUSE THYROID DISEASE

Thyroid ultrasound with gray-scale and color Doppler is the most helpful imaging modality to differentiate normal thyroid parenchyma from diffuse or nodular thyroid disease by evaluating glandular size, echogenicity, echotexture, margins, and vascularity. The various causes of diffuse thyroid disease often have overlapping sonographic imaging features.[1]

The adult thyroid can vary in size with patient body habitus, ranging from 4 to 6 cm cranial to caudal length, 2 to 3 cm transverse width, and 1.5 to 2.0 cm anteroposterior depth.[1] The anteroposterior diameter of the thyroid can also be divided into categories that consist of normal range (1–2 cm), decreased size (<1 cm), and enlarged size (>2 cm).[2] With diffuse thyroid diseases, the thyroid is often enlarged. The term "goiter" is defined as generalized enlargement of

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Fig. 1. A 66-year-old woman with multinodular goiter. (*A*, *B*) Gray-scale images demonstrate enlarged nodular goiter with coalescent nodules virtually replacing the gland without discrete suspicious-appearing nodule in the right lobe transverse (*A*) and longitudinal planes (*B*). (*C*) Transverse image of both enlarged, lobular thyroid lobes. Cursors on (*A*), (*B*) represent thyroid lobe measurements in the transverse and longitudinal planes.

the thyroid, and refers to both normal parenchyma and diffuse or nodular disease. Patients with a diffuse multinodular goiter have an enlarged gland with multiple hyperplastic or adenomatous nodules of variable size, usually all similar in appearance, with or without normal-appearing tissue between the nodules[3,4](**Fig. 1**).

Thyroid parenchymal echogenicity is described as isoechoic, hypoechoic, markedly hypoechoic, or hyperechoic using the strap musculature as an internal reference.[2] The normal thyroid is usually homogeneous and slightly hyperechoic due to its follicular composition, with a thin echogenic border and smooth margins.[4] The term border is preferred over capsule,[5] as the thin connective tissue along the outer surface of the thyroid has heterogeneous thickness and composition, and discontinuous distribution, consistent with a pseudocapsule rather than a true fibrous capsule.[6] Thyroid echotexture is described as fine, coarse, or micronodular pattern.[2] In diffuse thyroid disease, the thyroid can have increased or decreased parenchymal echogenicity and coarsened echotexture with nodular (micro- or macrolobulated) margins.[2,7]

Glandular vascularity with color Doppler sonography is categorized as normal, mildly increased, markedly increased, or decreased. Normal thyroid color Doppler flow should be fairly symmetric and evenly distributed. Diffuse thyroid disease presents with variable vascularity that can be normal, increased, or decreased.[1,2,4,7]

A combination of 2 or more abnormal features had 82% sensitivity and 84% specificity for diffuse thyroid disease in one multicenter study.[7] Kim and colleagues[2] demonstrated that a combination of 3 or more ultrasound characteristics of diffuse thyroid disease had a high sensitivity and specificity (88% and 92%, respectively) for the identification of diffuse thyroid disease over 2 sonographic features. No single feature provided both high specificity and sensitivity, but the absence of any sonographic features of diffuse thyroid disease essentially excluded asymptomatic diffuse thyroid disease.[2,7] The most specific features of diffuse thyroid disease include anteroposterior diameter greater than 2 cm, marked hypoechogenicity, coarse echotexture, markedly increased (or decreased) vascularity, and macrolobulated margins.[2]

Box 1
Types of thyroiditis

- Autoimmune
  - Chronic autoimmune lymphocytic (Hashimoto disease)
  - Subacute granulomatous (DeQuervain disease)
  - Graves disease
- Medication induced
  - Amiodarone
  - Interleukins (IL-2)
  - Interferon-alpha
  - Tyrosine kinase inhibitors
  - Immunomodulating cancer therapies
- Infectious
  - Acute suppurative
- Uncertain etiology
  - Riedel thyroiditis

THYROIDITIS

Thyroiditis encompasses a wide group of disorders that cause inflammation of the thyroid gland and diffuse thyroid disease (**Box 1**). These

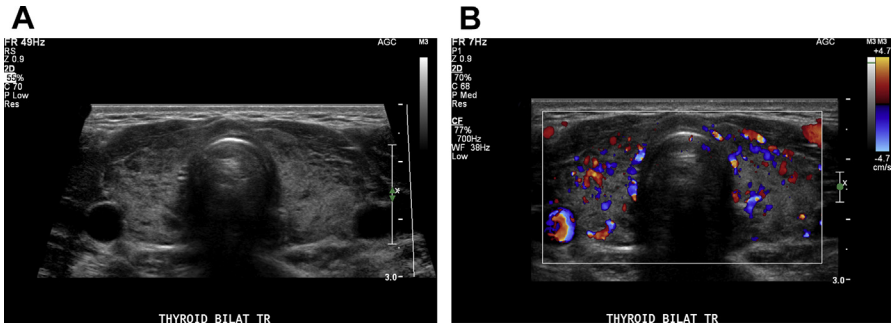

Fig. 2. A 39-year-old woman with Hashimoto thyroiditis. (*A*) On gray-scale, mall patchy hypoechoic nodules scattered diffusely throughout the gland in the transverse plane. (*B*) Color Doppler can be increased in the acute phase, as in this patient, shown in the transverse plane.

conditions have various etiologies, clinical symptomatology, imaging findings, and treatment.

Chronic Lymphocytic (Hashimoto) Thyroiditis

Chronic lymphocytic thyroiditis, or Hashimoto thyroiditis, is the most common autoimmune disorder of the thyroid and the most common cause of hypothyroidism in iodine-sufficient areas, affecting up to 10% of individuals in the United States with an overall female predominance of 8 to 9:1. Patients develop antibodies targeting thyroglobulin, thyroid peroxidase (TPO), an enzyme for thyroid hormonogenesis, and the thyroid-stimulating hormone (TSH) receptor. The thyroid becomes infiltrated with lymphocytes, which incite progressive replacement of follicular cells with eventual fibrosis and atrophy.[1,3,7,8]

The typical sonographic appearance of chronic lymphocytic thyroiditis is a diffusely heterogeneous gland with patchy, nodular hypoechoic

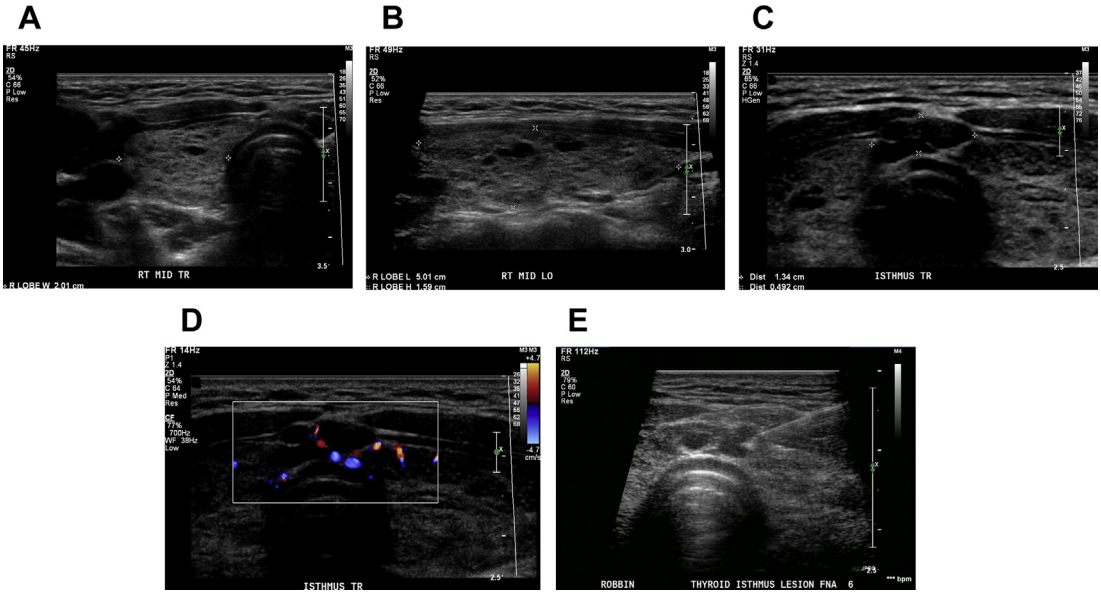

Fig. 3. A 17-year-old girl with Hashimoto thyroiditis and a focal nodule. (*A*, *B*) Hypoechoic nodules are scattered throughout the gland with increased echogenic bands in-between the nodules, the "giraffe skin" appearance, in the right lobe transverse (*A*) and longitudinal planes (*B*) on gray-scale imaging. (*C*, *D*) Focal 2.1-cm hypoechoic nodule in the isthmus, on gray-scale (*C*) with internal color Doppler flow (*D*), classified as ACR TI-RADS TR-4. (*E*) FNA is shown with needle in the nodule; sampling revealed focal lymphocytic infiltrate consistent with Hashimoto thyroiditis, without features of a focal nodule. Cursors on (*A*, *B*) represent thyroid lobe measurements in the transverse and longitudinal planes; (*D*) Isthmus nodule measurement is shown in the transverse plane. Longitudinal measurement of the nodule was 2.1 cm, not shown.

areas of lymphocytic infiltration intermixed with echogenic parenchymal bands between the nodules, giving the gland a micronodular or "giraffe skin" appearance[4,9] (**Figs. 2** and **3**). In the acute phase, this thyroiditis can present with a painless, lobular goiter; normal size gland; or small gland, sometimes with increased vascularity.[4] As inflammation and fibrosis progresses, hyperechoic linear and curvilinear bands can occur with heterogeneous appearance while the surface contour becomes more nodular and the gland more atrophic at end stage, sometimes with the appearance of "pseudonodules" (see **Fig. 3**; **Fig. 4**).[1] Ultrasound often identifies an increased number of benign, hyperplastic lymph nodes in cervical levels II, III, and IV compared with patients without thyroid disease.[10,11]

Patients with chronic lymphocytic thyroiditis are at risk for developing primary thyroid lymphoma, which is usually a B-cell lymphoma and represents less than 5% of all thyroid malignancies.[12] This diagnosis should be suspected if an atrophic gland quickly enlarges or develops hypoechoic masses with increased through transmission, particularly in the setting of systemic symptoms[1,12] (**Fig. 5**).

Subacute Granulomatous (DeQuervain) Thyroiditis

DeQuervain or subacute thyroiditis is a rare, often self-limiting condition likely due to an immune response following a viral or upper respiratory tract infection (**Box 2**) and represents approximately 3% to 6% of all thyroid diseases.[1,3] The classic presentation is an acutely painful neck with tender glandular swelling, jaw and ear pain, and occasional systemic symptoms, such as fever, fatigue, weight loss, elevated erythrocyte sedimentation rate or C-reactive protein, suppressed TSH level, and dysphagia.[1,3,4,13] In the acute phase, patients may be hyperthyroid but often later become hypothyroid until returning to a euthyroid state after approximately 6 to 18 months.[1,3]

The typical ultrasound appearance of the gland includes patchy, ill-defined hypoechoic regions in one or both lobes with significantly decreased vascularity within the thyroid parenchyma

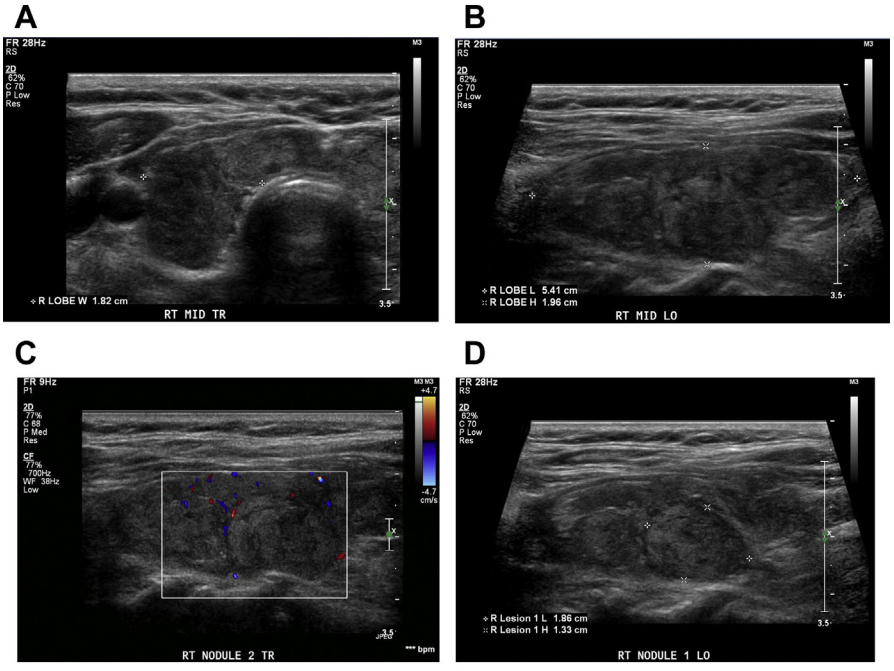

Fig. 4. A 67-year-old woman with Hashimoto thyroiditis and discrete possible nodule. (*A*, *B*) Heterogeneous gland with hypoechoic nodules diffusely in the right lobe on gray-scale in the transverse (*A*) and longitudinal planes (*B*). (*C*) On color Doppler, there is little flow in the nodule and thyroid in this chronic phase. (*D*) Discrete 1.9-cm ACR TI-RADS TR-3 nodule was biopsied (before TI-RADS implementation); pathology was benign lymphocytic infiltration. Note that nodule measurement was made before ACR TI-RADS implementation in the longitudinal plane; note that TI-RADS nodule measurement requires only cranial-caudal measurement in the longitudinal plane, and both AP and transverse measurements should be obtained in the transverse plane, as in **Fig. 3**. Cursors on (*A*, *B*) represent thyroid lobe measurements in the transverse and longitudinal planes.

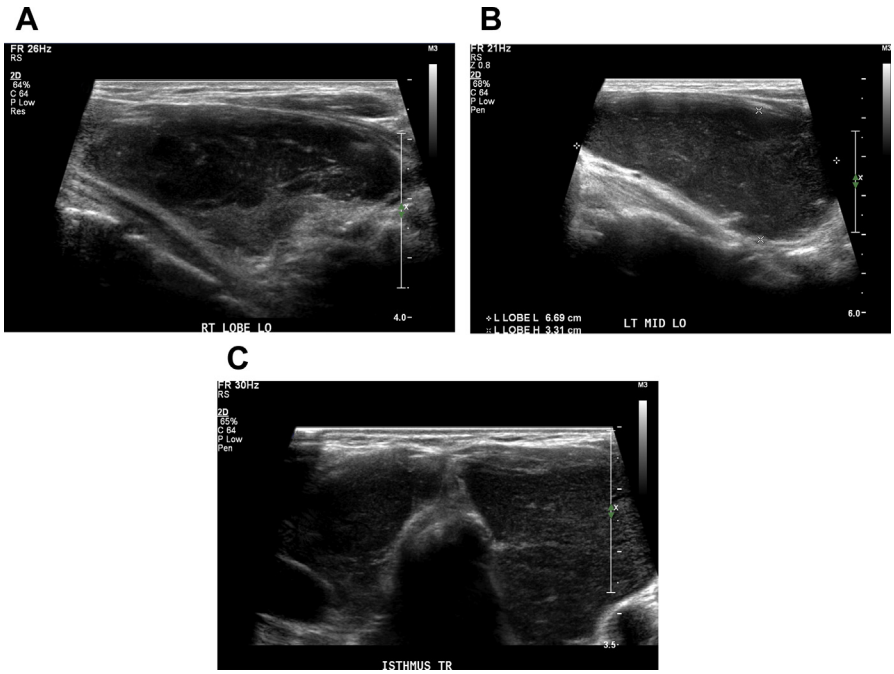

Fig. 5. An 84-year-old woman with large B-cell lymphoma on gray-scale ultrasound of the thyroid. (*A–C*) Thyroid gland is enlarged with near-complete replacement of gland with hypoechoic infiltrate in the right longitudinal (*A*), left longitudinal (*B*), and bilateral lobe transverse view (*C*). Biopsy showed large B-cell lymphoma. Cursors on (*B*) represent thyroid lobe measurement in the longitudinal plane.

(**Fig. 6**). Often, these hypoechoic areas elongate and do not result in discrete nodules but have a "pseudonodule" appearance.[3] Sometimes the appearance is described as "lava flow," with diffuse and confluent hypoechoic areas.[13,14] The acute phase may demonstrate hypervascularity, whereas the subacute phase may reflect diffuse hypovascularity. Imaging features may take weeks to months to resolve.[1]

Box 2
Viruses associated with subacute granulomatous thyroiditis

Hepatitis B
Hepatitis C
Mumps
Cytomegalovirus
Coxsackie virus (A and B)
Enterovirus

Data from Dighe M, Barr R, Bojunga J, et al. Thyroid Ultrasound: State of the Art Part 1 - Thyroid Ultrasound reporting and Diffuse Thyroid Diseases. *Med Ultrason.* 2017;19(1):79-93.

Graves Disease

Graves disease is an autoimmune disorder with female predominance, in which antibodies stimulate the TSH and cause epithelial hyperplasia, glandular enlargement, bowing of the anterior margin, parenchymal coarsening, and hyperthyroidism, occasionally with the presence of a pyramidal lobe due to gland hypertrophy.[1,3] The classic sonographic appearance of Graves disease is an enlarged gland with increased parenchymal vascularity and arteriovenous shunting creating a "thyroid inferno" appearance with a smooth or scalloped glandular contour[1,4] (**Fig. 7**). The gland may demonstrate decreased echogenicity due to increased blood flow, increased cellularity, and decreased colloid.[3,4]

Medication-Induced Thyroiditis

Various medications result in thyroid dysfunction (see **Box 1**), with sonographic features that overlap with other causes. Amiodarone is an iodine-rich medication used in the treatment of cardiac arrhythmia with side effects of both hyperthyroidism and hypothyroidism. Thyrotoxicosis can occur in up to 15% of patients on this therapy independent of dose or duration of therapy. Despite stopping amiodarone when possible, patients often require additional medical treatment for the

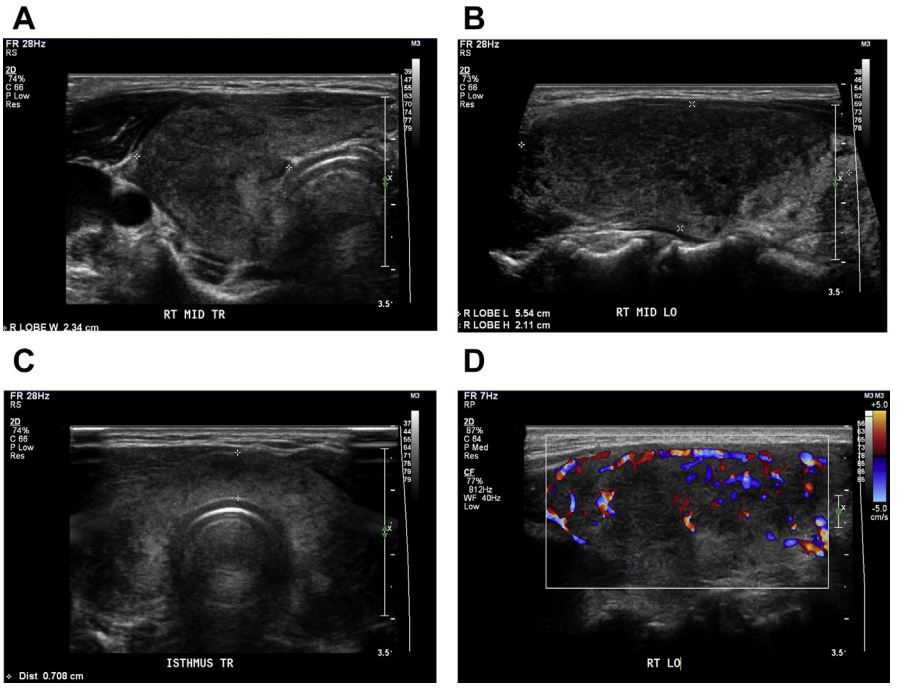

Fig. 6. A 51-year-old woman with subacute thyroiditis, likely post viral. (*A–C*) Gray-scale images in transverse (*A*, *C*) and longitudinal (*B*) planes show diffuse small hypoechoic areas throughout an enlarged thyroid, with focal areas of overall decreased echogenicity, so-called "lava flow" pattern. (*D*) In the acute phase, increased color Doppler flow is present in the right lobe between the hypoechoic areas. Cursors on (*A*, *B*) represent thyroid lobe measurements in the transverse and longitudinal planes; cursors on (*C*) show the measurement of isthmus thickness, which is enlarged at greater than 3 mm.

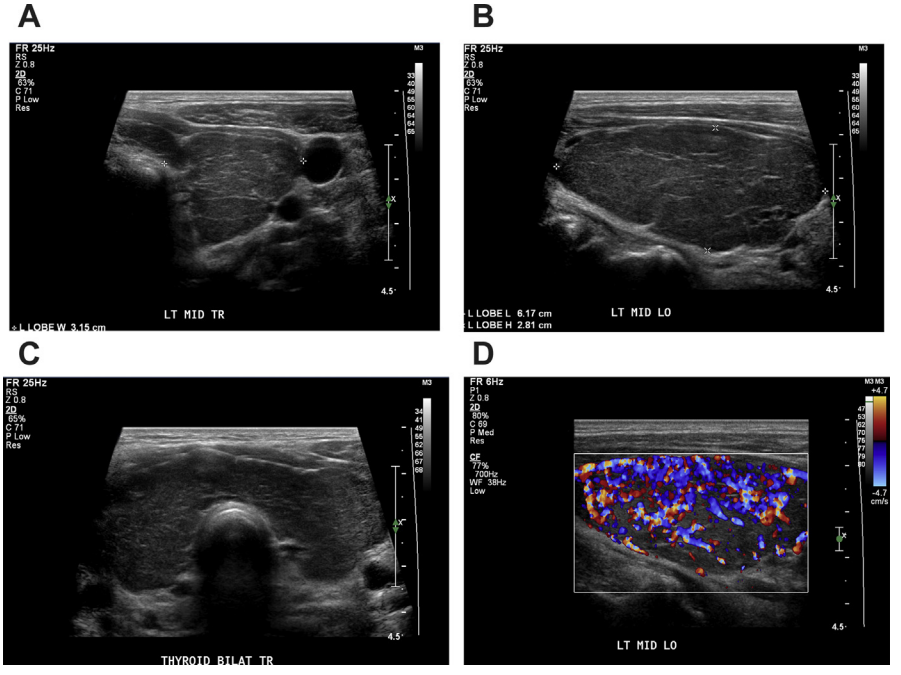

Fig. 7. A 42-year-old woman with Graves disease. (*A–C*) Enlarged, mildly heterogeneous gland with decreased echotexture, and a scalloped, nodular contour without focal nodules on gray-scale. (*D*) Increased color Doppler flow due to hyperemia is shown in the left lobe, longitudinal plane. Cursors on (*A*, *B*) represent thyroid lobe measurements in the transverse and longitudinal planes.

hyperthyroidism.[15–17] Interferon medication can induce thyroid disease with sonographic features detectable even before abnormal thyroid function or antibody status could be measured, occurring with increased incidence in female individuals and patients with a preexisting thyroglobulin or TPO antibodies and viral load. It presents as a destructive process on ultrasound with no specific imaging features.[3]

Immunotherapy-related thyroiditis may be increasing in prevalence given the wider use of immunotherapy for various malignancies. These agents can induce autoimmune responses beyond the malignant target, known as immune-related adverse events (IRAEs), usually occurring within 3 to 6 months of initiation of therapy. Approximately 5% to 10% of patients experience endocrine IRAEs, most commonly reported to affect thyroid and pituitary hormones, with typical thyroid disorder presenting as thyrotoxicosis and eventual hypothyroidism if the IRAE causes inflammatory damage to the gland.[18,19] The imaging features can overlap with other types of thyroiditis, including heterogeneous glandular tissue with increased or decreased vascularity and hypoechoic nodular areas.[20,21]

Riedel Thyroiditis

Riedel thyroiditis is a rare, local form of fibrosclerosis of the thyroid that presents in patients 30 to 50 years of age with uncertain etiology, thought to be due to an autoimmune process.[3] It results in very firm neck swelling due to thyroid fibrosis and invasion of adjacent neck soft tissue structures with inflammatory cell infiltrates.[3,22] This condition is most common in women and can be associated with mediastinal or retroperitoneal fibrosis like immunoglobulin G4–mediated diseases.[3] The gland is enlarged, hypoechoic, hypovascular, and coarsened with a pseudonodular appearance that has fibrotic bands and perithyroid extension.[3]

Acute Suppurative Thyroiditis

This is a rare disease that occurs in immunosuppressed patients or children and young adults with branchial anomalies. It presents with inflammation including fever, sore throat, painful swelling, skin erythema, and lymphadenopathy in a euthyroid state. On ultrasound, the thyroid gland has nonspecific hypoechoic and anechoic areas with normal or increased vascularity. Occasionally, an abscess can occur and can be cured with antibiotic therapy or drainage.[3]

FOCAL THYROID ABNORMALITIES

The American Thyroid Association (ATA) defines a nodule as "a discrete lesion within the thyroid gland that is radiographically distinct from the surrounding thyroid parenchyma."[23] The incidence and prevalence of thyroid nodules can be difficult to pin down due to the overall increase in imaging studies and the goal of the imaging study, as nodules may be identified incidentally on chest computed tomography imaging or carotid ultrasound, or as part of a dedicated thyroid study for abnormal laboratory values or physical examination. Detection of nonpalpable nodules by imaging studies may be as high as 70%[24] and can vary by imaging modality. Thyroid nodules may be hyperplastic or neoplastic, with most due to benign hyperplastic changes in architecture and benign follicular adenomas; only a small percentage are malignant. Occasionally, focal thyroiditis can mimic a nodule.

Thyroid malignancies are listed in **Box 3**. In 2016, there were an estimated 822,242 people living with thyroid cancer in the United States. The American Cancer Society estimates approximately 52,070 new cases in 2019, which has tripled over the past 3 decades. Death rates remain low, with estimated 2170 deaths in 2019, and overall 5-year survival of 98%.[25,26]

Box 3
Thyroid malignancies

Follicular epithelial cell origin
- Papillary
- Follicular
- Hurthle cell
- Poorly differentiated
- Anaplastic

Neuroendocrine C-cell origin
- Medullary

Metastases (from)
- Lung
- Renal cell
- Breast
- Melanoma

Lymphoma

Data from Refs.[4,28]

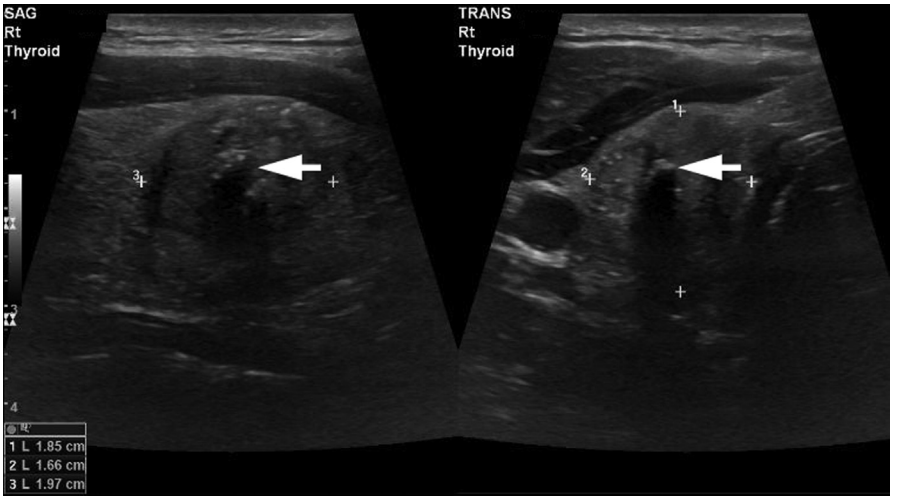

Fig. 8. A 40-year-old man with biopsy-proven follicular variant papillary thyroid cancer. Transverse and longitudinal gray-scale ultrasound images show a hypoechoic nodule with ill-defined margins, PEF, and shadowing calcifications (*arrow*), and taller-than-wide shape, as measured by the calipers. Taller-than-wide shape is a highly specific indicator of malignancy.

Differentiated thyroid cancers arise from the follicular epithelial cells, and include papillary, follicular, and Hurthle cell subtypes.

Papillary thyroid cancer is the most common subtype in the United States, accounting for up to 90% of all thyroid cancers. This cancer occurs more frequently in women, with peak incidences in the third and seventh decades. The tumors are hypoechoic due to closely packed cells, and up to 35% have calcified psammomatous bodies, which are not found in follicular or medullary carcinoma[27] (**Figs. 8** and **9**). Metastases occur most commonly by lymphatic spread to cervical lymph nodes, which should be carefully assessed for cystic change and echogenic foci indicative of metastases even in the setting of normal nodal size.[27,28] Papillary microcarcinoma presents as small tumors of less than 10 mm, often with metastatic adenopathy. With high-resolution scanning, these small tumors can be identified by their suspicious features[4] (**Fig. 10**).

Follicular carcinoma accounts for 5% to 15% of cancers and also occurs more frequently in women. Tumors are often homogeneous and well-encapsulated, making them difficult to differentiate from hyperplastic nodules by imaging. The Bethesda System for Reporting Thyroid Cytopathology is a category-based reporting system for specimens obtained with fine-needle aspiration (FNA) to allow for clear communication between pathologists and referring clinicians that samples fall into 1 of 6 diagnostic categories: (I) nondiagnostic or unsatisfactory; (II) benign; (III) atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS); (IV) follicular neoplasm or suspicious for a follicular neoplasm; (V) suspicious for malignancy; and (VI) malignant. Because follicular tumors cannot be

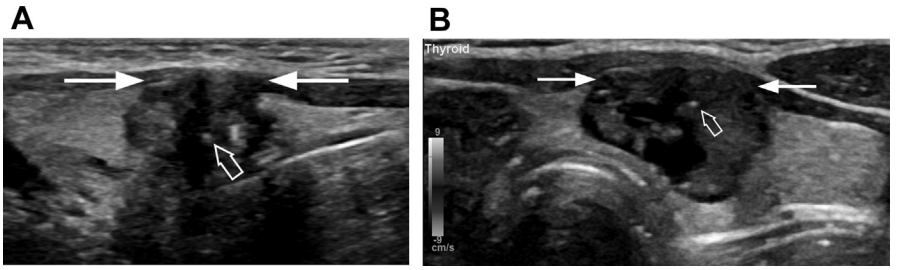

Fig. 9. A 41-year-old woman with bilateral papillary thyroid cancer. (*A*) Longitudinal (*A*) and transverse (*B*) gray-scale image demonstrates a right hypoechoic nodule with calcifications (*open arrow*) and extrathyroidal extension into the adjacent sternothyroid muscle (*arrows*).

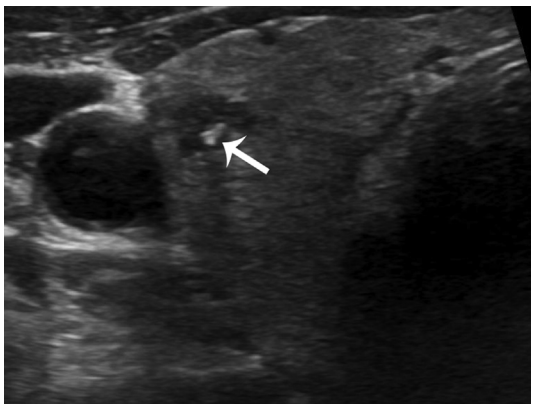

Fig. 10. A 66-year-old woman with a 4-mm papillary thyroid carcinoma in the mid-right thyroid on gray-scale image. Although small, the nodule is hypoechoic with irregular margins and contains a shadowing macrocalcification (*arrow*).

reliably categorized by FNA alone, they may be characterized as a Bethesda III or Bethesda IV.[29] Molecular testing can be used for additional risk stratification at the time of initial FNA to reduce the number of surgeries for benign nodules.[30] Follicular carcinoma is more likely to metastasize by hematogenous spread.[4,28]

Medullary thyroid cancer arises from the neuroendocrine C-cells and represents approximately 2% to 5% of cancers. Up to 20% of these cancers occur in patients with multiple endocrine neoplasia type 2. Metastatic lymph nodes can be found in up to 70% of patients at presentation.[28]

Anaplastic thyroid cancer is an aggressive malignancy that presents with widespread involvement rather than as a focal nodule and carries a poor prognosis. Patients often present with a rapidly enlarging neck mass, and often have metastatic disease to the lungs, bone, or brain at presentation.[28]

Metastases to the thyroid are more commonly found in autopsy specimens than with a clinical presentation. Tumors that most commonly spread to the thyroid include renal cell carcinoma, lung, breast, and gastrointestinal tract malignancies. These lesions tend to present similarly to other thyroid nodules, as either a palpable finding or incidentally on a diagnostic imaging study.[31]

APPROACH TO THYROID NODULES

Because thyroid malignancies most commonly present as focal nodules, multiple endocrinology and radiology societies have developed morphologic and size criteria to identify nodules most suspicious for underlying malignancy, guide follow-up examinations, and reduce unnecessary biopsies.[5,32–40] The development of these risk-stratification systems over the past 2 decades, from qualitative and pattern approaches to quantitative scoring systems, is nicely reviewed by Ha and colleagues.[41]

Although a detailed review of all the thyroid nodule scoring systems is beyond the scope of this article, a common theme among the scoring systems is the description of morphologic features that determine suspicion of malignancy, to guide further assessment with FNA and imaging follow-up. Because the morphologic features that are suspicious for malignancy overlap between scoring systems, we focus on the features of the American College of Radiology Thyroid Imaging, Reporting and Data System (ACR TI-RADS) released in 2017,[5] which defines 5 morphologic categories to assess at ultrasound (**Box 4**). For each nodule, the categories are evaluated and scored, and the final score corresponds to a suspicion for malignancy, guiding the decision of whether to perform FNA based on nodule size and features (**Fig. 11**).[5]

Composition

Nodule composition describes the internal material in the nodule as 1 of the following: (1) cystic or almost completely cystic, (2) spongiform, (3) mixed cystic and solid, or (4) solid or almost completely solid.[5] A cystic nodule is well circumscribed and anechoic with increased through transmission (**Fig. 12**). Spongiform nodules are composed of small cystic spaces that account for greater than 50% of the nodule; the cystic spaces are relatively similar in size and distributed throughout the nodule[35] (**Fig. 13**). Larger cystic spaces can be a part of spongiform nodules, but if large solid components are present, the nodule is mixed cystic and solid, not spongiform.[42] Both cystic and spongiform nodules are nearly always benign.[43,44] The solid component of mixed cystic and solid nodules should be carefully analyzed for suspicious features such as nodularity or calcification. Color Doppler flow of these areas can

Box 4
Sonographic features to assess risk of malignancy in thyroid nodules

Composition
Echogenicity
Margin
Shape
Echogenic foci

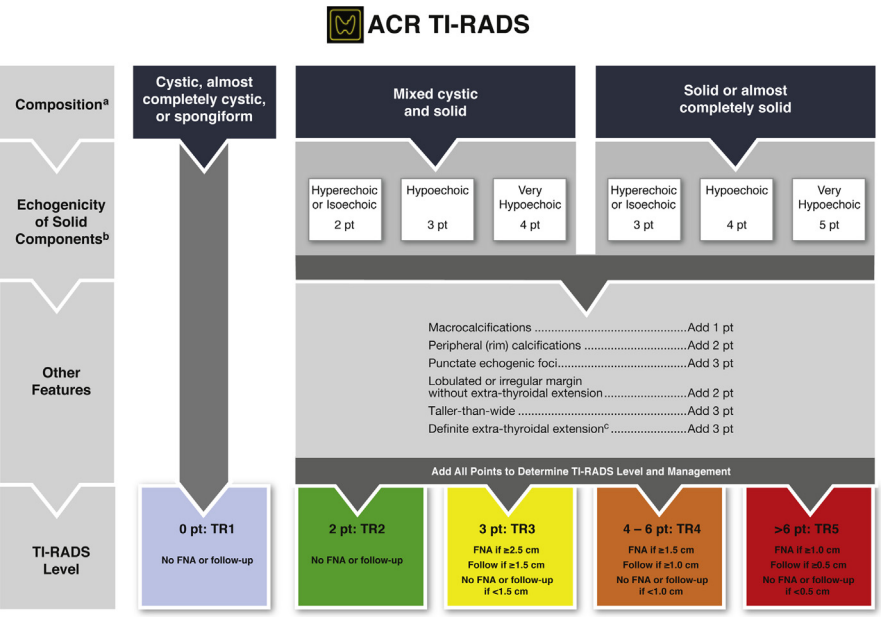

Fig. 11. ACR TI-RADS scoring system flow chart. [a] Classify nodule as solid if composition cannot be determined. [b] Classify nodule as isoechoic if echogenicity cannot be determined. [c] Nodules with definite extrathyroidal extension should be considered malignant until proven otherwise. (*From* https://www.acr.org/-/media/ACR/Files/RADS/TI-RADS/TI-RADS-Alternative-chart.pdf from ACR Thyroid Imaging, Reporting and Data System (TI-RADS™); with permission.)

help differentiate solid tissue from blood products or layering debris. Solid nodules may have a small cystic component, usually 5% or less, when the nodule is viewed in its entirety.[45]

Echogenicity

The echogenicity of solid nodules is determined by comparison with adjacent thyroid tissue, and nodules may be hyperechoic, isoechoic, or hypoechoic based on the appearance of most of the nodule (**Fig. 14**). The "very hypoechoic" descriptor refers to hypoechoic nodules that are more hypoechoic than the adjacent neck strap musculature.[35] Anechoic is included in the lexicon for description of cystic nodules.[5] Color Doppler flow can differentiate solid, very hypoechoic nodules from avascular cysts.

Fig. 12. A 76-year-old woman with a history of amiodarone thyrotoxicosis. Longitudinal gray-scale image of the left upper thyroid demonstrates a colloid cyst with multiple echogenic foci demonstrating large comet-tail artifact (*arrows*). There is an adjacent anechoic cyst (*curved arrow*).

Shape

The shape of the nodule should be assessed in the transverse plane with measurement of the transverse and anterior-posterior (AP) dimensions. "Taller-than-wide" nodule shape has longer AP length compared with transverse (**Fig. 15**), with low sensitivity but high specificity for malignancy,[34,35,46,47] as many malignant nodules have round or oval shape that is longer in the AP direction compared with the transverse. Although this appearance can be assessed visually, a recent study suggests than an AP-to-transverse ratio greater than 1.2 can improve specificity.[48] Three-dimensional measurement is completed by a cranial-caudal measurement of the nodule in the longitudinal plane. The largest of these 3 measurements is used to determine subsequent management.

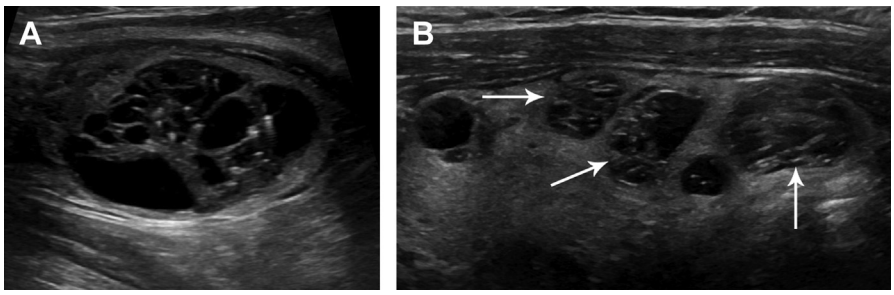

Fig. 13. Spongiform nodules. (*A*) 66-year-old woman with a multinodular goiter. Longitudinal gray-scale image shows a spongiform nodule characterized by multiple small cystic spaces. Spongiform architecture is strongly associated with benign cytology. (*B*) A 66-year-old man with metastatic papillary thyroid cancer (not shown) also has multiple spongiform nodules (*arrows*) in the right thyroid on longitudinal gray-scale ultrasound. Note the nodules contain PEF indicating the backwalls of small simple cysts.

Margin

The nodule margin, or its border with the adjacent parenchyma, can be categorized as (1) smooth, with well-defined and uninterrupted curvilinear edge; (2) ill-defined, or unable to distinguish from neighboring tissue; or (3) irregular (spiculated, jagged, or angulated margins) or lobular (focal rounded protrusions) (**Fig. 16**). Of note, for partially cystic nodules, the margin of the solid component should be assessed, not the entire nodule margin.[49] If the nodule has an interface with the borders of the thyroid, this margin should be assessed for extrathyroidal extension.[5,35] Minimal extrathyroidal extension can be suspected if the nodule abuts the thyroid border, bulges the thyroid contour, or there is loss of the echogenic thyroid border at the nodule-thyroid border interface[50]

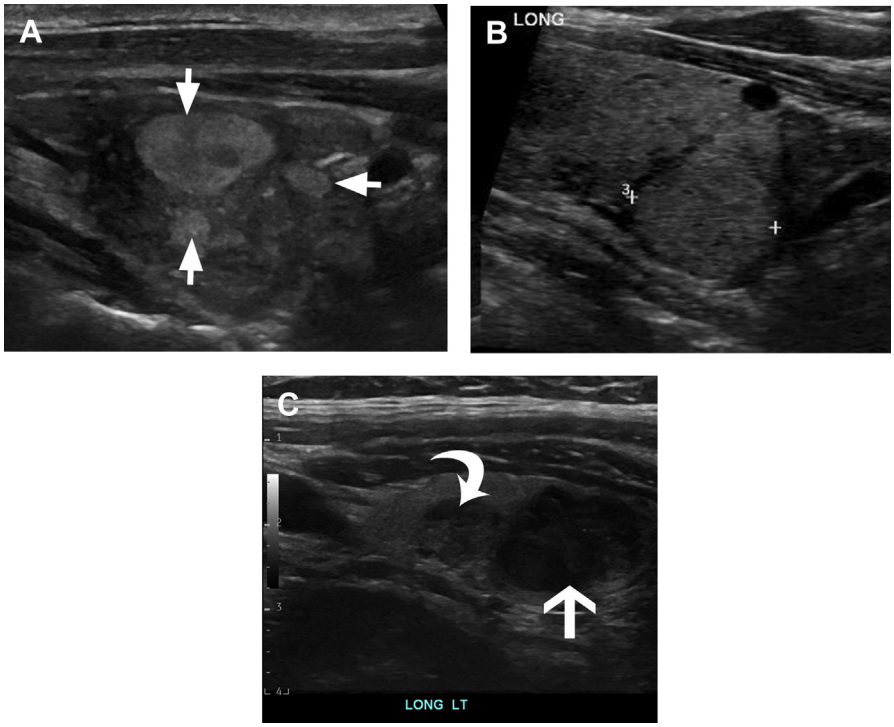

Fig. 14. Nodule echogenicity on gray-scale ultrasound. (*A*) An 88-year-old man with hyperechoic nodules (*arrows*) and Hashimoto thyroiditis. (*B*) A 65-year-old woman with an isoechoic nodule (*calipers*). (*C*) A 51-year-old woman with nodules that are hypoechoic (*curved arrow*) and very hypoechoic (*arrow*).

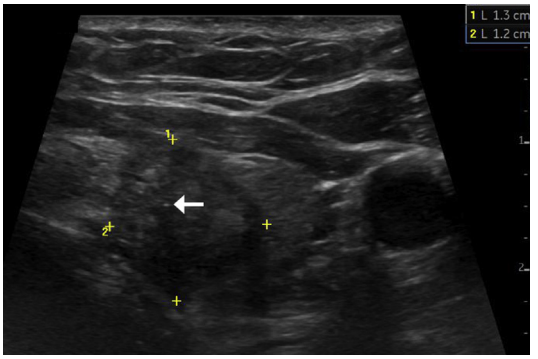

Fig. 15. A 58-year-old woman with well-differentiated papillary thyroid cancer in the left thyroid. Transverse gray-scale image demonstrates a taller-than-wide shape (*calipers*) and PEF (*arrow*).

(**Fig. 17**). Clear invasion of soft tissues beyond the thyroid is characterized as extensive extrathyroidal extension, which is highly associated with malignancy, and a poor prognostic factor[51] (**Fig. 18**).

Echogenic Foci

Nodules can contain echogenic foci, defined as focal areas with markedly increased echogenicity within or along the margins of the nodule, and these foci may represent calcification, colloid, or microcyst wall interfaces. Macrocalcifications are coarse, echogenic foci that produce posterior acoustic shadowing and may be within the nodule or around the periphery (see **Figs. 8** and **10**). The

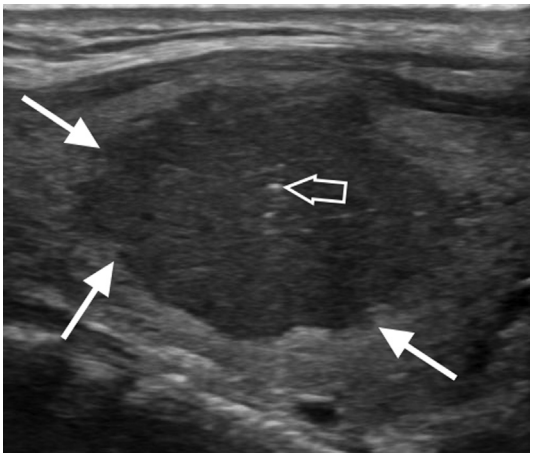

Fig. 16. A 42-year-old woman with palpable right thyroid nodule detected on annual physical exam. Longitudinal gray-scale ultrasound shows a hypoechoic solid nodule with irregular margins (*arrows*) and PEF without shadowing or comet-tail artifact (*open arrow*). Final pathology was medullary thyroid carcinoma.

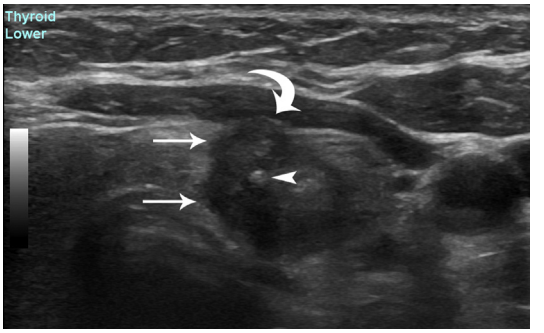

Fig. 17. A 58-year-old woman with well-differentiated papillary thyroid cancer. Transverse gray-scale ultrasound image shows a hypoechoic solid nodule with irregular margins (*arrows*), extension to the thyroid capsular surface (*curved arrow*), and central calcification (*arrowhead*). On pathology evaluation, the tumor focally extended beyond the thyroid border.

prevalence of malignancy associated with macrocalcifications in one study was 17.2% for clumped calcification within the nodule and 19.5% for peripheral calcifications.[52] Peripheral calcification can obscure the internal composition and echogenicity of the nodule, and ACR TI-RADS suggests these nodules should be scored as solid and isoechoic in the algorithm. Peripheral calcifications that are interrupted with protruding soft tissue have higher rates of malignancy,[53] and the margin of this soft tissue can be characterized as lobulated.[5]

Punctate echogenic foci (PEF) are nonshadowing, echogenic foci measuring less than 1 mm and should be assessed for posterior features and composition of surrounding nodule material. The term "microcalcification" should be avoided, as colloid and microcyst wall interfaces have similar appearance. Cystic fluid that contains PEF with large comet-tail artifact, or triangular or V-shaped echoes extending more than 1 mm posterior to the PEF, are highly likely to be benign[52] (see **Fig. 12**). Similarly, small echogenic foci within spongiform nodules are not suspicious, as they likely represent reflectors at the backwalls of tiny cysts. PEF found in solid nodule components with small (<1 mm) or no posterior artifact are suspicious, as they may represent the psammomatous calcifications found in papillary carcinoma[27] and have a 15% prevalence of malignancy[52] (see **Figs. 8** and **15**; **Fig. 19**). In a recent study, PEF had a positive predictive value of only 45% to 48% for the presence of psammomatous calcifications, as dystrophic calcifications and colloid also can give this appearance.[54]

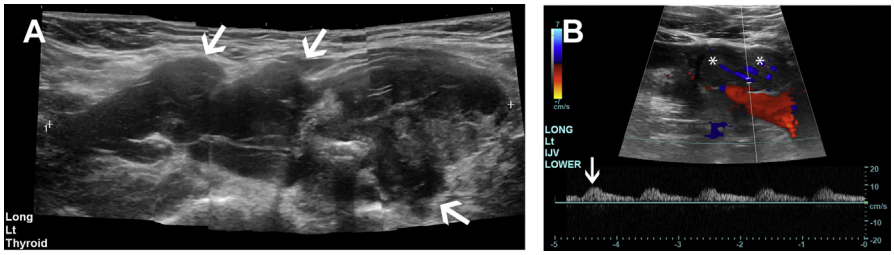

Fig. 18. A 59-year-old woman with metastatic follicular carcinoma with Hurthle cell features. (*A*) Longitudinal gray-scale extended view image shows a large (11 cm) hypoechoic left thyroid mass (*calipers*) with irregular margins and extrathyroidal extension (*arrows*). (*B*) Longitudinal spectral Doppler of the left lower internal jugular vein demonstrates an intraluminal hypoechoic solid mass (*asterisk*) with arterial flow (*arrow*) indicating tumor invasion into the left internal jugular vein.

Features Not Part of the American College of Radiology Thyroid Imaging, Reporting and Data System Scoring Algorithm

Nodule vascularity is not part of ACR TI-RADS lexicon, as lesion vascularity has not been found to consistently correlate with papillary thyroid cancer; however, there is an association with follicular cancers.[5,23,35] Color Doppler can be helpful to differentiate solid tissue from debris or hemorrhage within a cystic nodule, or delineate a subtle isoechoic nodule.

Nodule size does not contribute to suspicion of malignancy in the ACR TI-RADS algorithm, but size is used as part of the decision to biopsy or follow the nodule once the level of suspicion has been determined.[5] Nodule size is not a specific feature of malignancy and the various society guidelines have different size thresholds when combined with morphologic features, other patient factors such as comorbidities, and shared decision making with the patient to guide decision to perform nodule FNA, nodule imaging follow-up frequency, and duration or no follow-up at all.

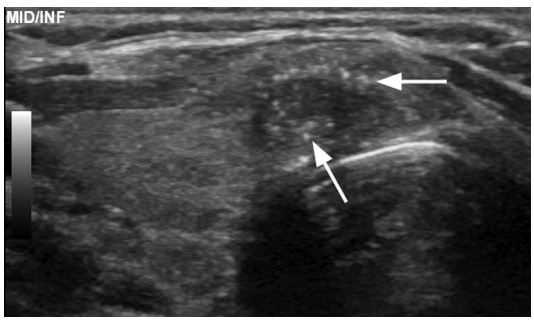

Fig. 19. A 39-year-old woman with papillary thyroid carcinoma confirmed by FNA after transverse gray-scale ultrasound demonstrated a hypoechoic nodule with multiple PEF (*arrows*).

There is general agreement that nodules smaller than 1.0 cm should not undergo FNA.[5,32–40,55]

The ACR TI-RADS documents do not specifically address nodules with increased [^{18}F]fluorodeoxyglucose (^{18}FDG) activity on PET studies. In patients undergoing PET examinations, 1.6% to 2.5% of patients have focal hypermetabolic activity in the thyroid, and a range of 11% to 35% of these nodules are subsequently diagnosed as malignant.[56–58] The ATA guidelines recommend FNA of hypermetabolic nodules $\geq$1 cm independent of other ultrasound features.[23]

Although cervical lymph nodes are not part of the ACR TI-RADS system, the thyroid ultrasound examination should include survey of neck lymph nodes in levels I to VI and documentation of size and location of any suspicious nodes.[59] Suspicious features include round or globular shape, short axis measurement $\geq$1 cm, loss of echogenic hilum, peripheral instead of hilar flow, cystic areas, and PEF[5] (**Figs. 20** and **21**).

Summary of Features Suspicious for Thyroid Malignancy

In summary, features suspicious for malignancy include hypoechoic and very hypoechoic echogenicity, taller-than-wide shape, irregular margins, PEF in solid nodules, macrocalcifications, and focal increased ^{18}FDG activity on PET imaging.[5,23,46,47,52] In addition, risk factors for thyroid cancer should be considered when evaluating patients with nodules (**Box 5**).[23] The overall degree of suspicion in the ultrasound report and the decision to biopsy will depend on the thyroid algorithm used by the radiologists, which can be selected in consensus with the referring clinicians to ensure clear and consistent communication within the care team.

Because the prevalence of benign thyroid nodules is so high, the risk-stratification systems aim to reduce unnecessary biopsies with benign

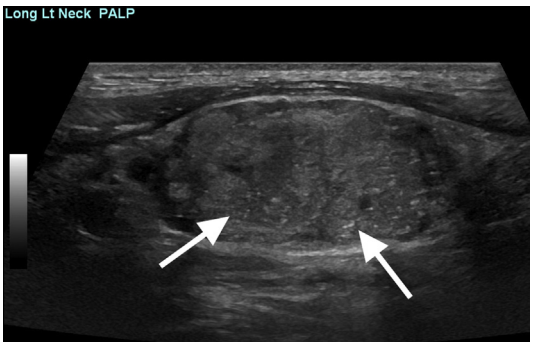

Fig. 20. A 30-year-old man with slowly enlarging left neck mass, with biopsy results of metastatic papillary thyroid carcinoma. Longitudinal gray-scale ultrasound showed an enlarged lymph node with loss of echogenic hilum and multiple PEF (*arrows*).

results. Several recent studies have shown ACR TI-RADS performs well to reduce biopsies with higher accuracy, when applied alone or when compared with other systems.[55,60–63] Hoang and colleagues[62] retrospectively compared individual practice patterns with ACR TI-RADS for 15 malignant and 85 benign nodules with reduction in recommended biopsies and improved accuracy by both private practice radiologists and expert consensus readers. Middleton and colleagues[61] applied ACR TI-RADS[5], ATA 2015 guidelines[23], and Korean Society of Thyroid Radiology (KSThR) TI-RADS[37] to 3422 nodules with diagnostic FNA. All nodules could be classified with ACR TI-RADS, but 3.9% with KSThR TI-RADS and 13.9% with ATA guidelines could not be classified. The application of ACR TI-RADS would have resulted in reduction in FNA of benign nodules of nearly 53%, compared with 22% reduction for the ATA guidelines, and 20% for the KSThR system.[61] Grani and colleagues[55] applied 5 international scoring systems (ATA,[23] the American Association of Clinical Endocrinologists,[38] ACR,[5] the European Thyroid Association,[39] and KSThR[37]) to evaluate 502 nodules $\geq$1.0 cm with diagnostic FNA. ACR TI-RADS had the greatest reduction in biopsies and lowest false negative rate.[55]

PITFALLS IN NODULE EVALUATION

Although cystic, almost completely cystic, and spongiform nodule compositions are consistently benign,[43,44] the nodule in its entirety must be carefully assessed to ensure no suspicious areas or overestimation of cystic or spongiform components. Spongiform nodules should have the appearance of a cut sponge or honeycomb with cyst fluid making up 50% or more of the nodule. The mixed cystic and solid nodules should be further characterized by features in the solid component, and FNA should target the solid

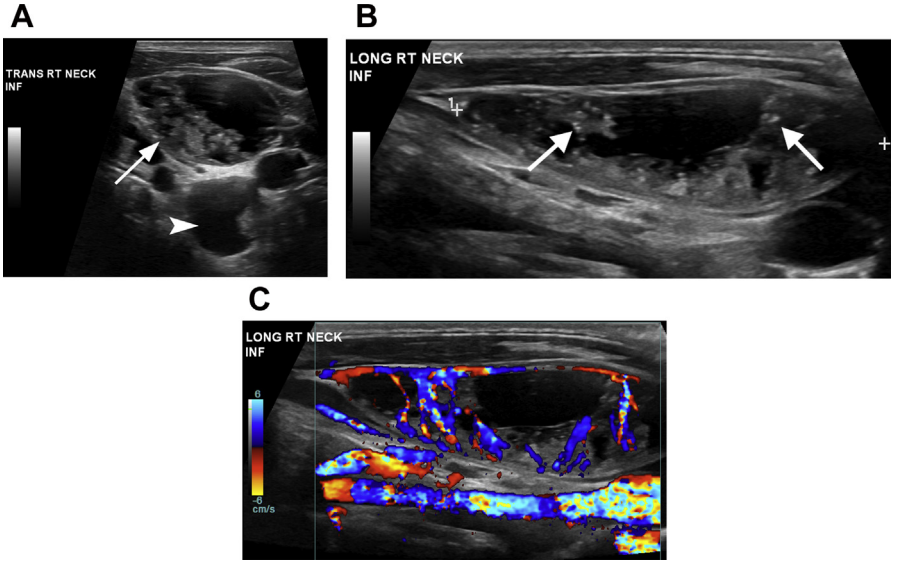

Fig. 21. A 20-year-old man presented with a right neck mass initially thought to be a branchial cleft cyst. Surgical excision revealed metastatic papillary thyroid cancer. (*A*) Transverse gray-scale ultrasound demonstrates 2 abnormal lymph nodes. The larger lymph node shows solid and cystic changes (*arrow*), and the smaller lymph node is entirely cystic (*arrowhead*). (*B*) Longitudinal gray-scale image demonstrates multiple PEF (*arrows*) in the solid component. (*C*) Color Doppler ultrasound shows hypervascularity within the solid portions of the metastatic lymph node.

Box 5
Risk factors for thyroid malignancy

Total body radiation (ie, for bone marrow transplantation)

Childhood or adolescent radiation exposure (ie, nuclear fallout or head and neck radiation therapy)

Familial syndromes associated with thyroid cancer (ie, Cowden syndrome, familial adenomatous polyposis, multiple endocrine neoplasia 2)

component if that area meets criteria for sampling, as up to 7% of papillary thyroid cancers can have cystic components.[64]

Occasionally, cystic or almost completely cystic nodules can undergo degenerative changes over time with decreasing size, replacement of cyst fluid with hypoechoic or very hypoechoic solid material, ill-defined margins and PEF, resulting in a highly suspicious appearance. Similar changes may occur in nodules that have undergone previous aggressive sampling. Color Doppler may help differentiate debris from vascularized tissue. In isolation, these nodules will likely meet criteria for FNA; however, if a prior study can precisely confirm a previously benign cystic nodule in the same location, follow-up imaging may be sufficient.[65,66]

A diffuse thyroid disease can present as only focal nodular abnormalities. Subacute thyroiditis may have scattered focal hypoechoic regions. The typical reticular pattern of chronic lymphocytic thyroiditis can be variable within the gland, mimicking nodules. The echogenic "white knight" nodules in chronic lymphocytic thyroiditis are benign[43] (**Fig. 22**); however, solid isoechoic and hypoechoic nodules should be evaluated by their morphologic criteria for possible FNA the same as nodules in a background of normal parenchyma[9] (see **Figs. 3** and **4**).

Fig. 22. A 13-year-old girl with focal echogenic nodule (*white arrows*) on gray-scale ultrasound; the "white knight" pattern is benign in the setting of Hashimoto disease (right lobe longitudinal plane). Arrowheads show the thyroid border.

SUMMARY

Thyroid ultrasound with gray-scale and color Doppler can differentiate normal thyroid parenchyma from diffuse or nodular thyroid disease by assessing gland size, echogenicity, echotexture, margins, and vascularity. The various causes of diffuse thyroid disease often have overlapping sonographic imaging features. Most thyroid nodules result from benign hyperplastic changes or benign follicular adenoma, with a much smaller percentage that is malignant. A systematic approach to nodule morphology should include evaluation of composition, echogenicity, margin, shape, and any echogenic foci. Because the prevalence of benign thyroid nodules is so high, consistent use of a risk-stratification system can reduce unnecessary biopsies with benign results.

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DISCLOSURE

The authors have nothing to disclose.

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