Thyroid Nodules: Patterns, Predictors, or Just Poke Them All

Mary Jennings Clingan, MD, LCDR, MC, USN, and Joel Robert Metzger, MD, CDR, MC, USN

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Thyroid nodules frequently are encountered incidentally, and although thyroid nodules are common, the prevalence of thyroid malignancy is relatively low. Considerable overlap exists between the appearance of benign and malignant thyroid nodules. Also, the varying guidelines among scientific associations, regarding when biopsy of a thyroid nodule is recommended, create a growing diagnostic dilemma. The initial approach to differentiate benign from malignant thyroid nodules focused on pattern recognition with a recent shift to individual feature analysis by ultrasound. Ultimately, fine-needle aspiration is required for definitive diagnosis; however, it is unrealistic to biopsy every thyroid nodule. The objective of this article is to emphasize the use of both pattern recognition and individual feature analysis to appropriately select candidates for biopsy and follow-up with a goal of identifying clinically significant thyroid cancer and of avoiding unnecessary workup of benign thyroid nodules.

Prevalence of Thyroid Nodules and Association With Cancer

Palpable thyroid nodules are reported in 4% to 8% of the adult population. Imaging detects an even greater number of thyroid nodules: up to 50% of patients imaged with ultrasound and 16% of patients imaged with CT and MRI. Despite the prevalence of thyroid nodules, the actual incidence of thyroid cancer is low, and the majority of thyroid nodules are benign with the reported risk of malignancy for all thyroid nodules ranging from 3% to 7%. Unfortunately, the risk of thyroid malignancy is the same whether or not the thyroid nodule is palpable or incidentally discovered. Likewise, the overall thyroid cancer rate per patient is the

Dr. Jennings Clingan is Medical Director Ultrasound, and Dr. Metzger is Medical Director MRI, Naval Medical Center Portsmouth, 620 John Paul Jones Circle, Portsmouth, VA 23708; E-mail: mary.clingan@med.navy.mil.

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same for those with multiple thyroid nodules as for those with a solitary thyroid nodule.4

The risk of thyroid malignancy is the same whether or not thyroid nodules are palpable, incidentally discovered, multiple, or single.

Rising Incidence of Thyroid Cancer and the Detection of Thyroid Nodules

Between 1973 and 2002, there was a greater than 2.5-fold increase in the incidence of thyroid cancer, with 87% of these new cases attributed to small papillary cancers.5 Despite earlier diagnosis, no change in mortality occurred over the same period, suggesting that changes in imaging have led to “over-diagnosis” as opposed to a true increase in biologic occurrence.5 Increased use of CT imaging of the neck, cervical spine, and chest also may result in increased diagnosis of small papillary thyroid cancers from a subclinical population. Thyroid nodules are seen in up to one in six neck CT studies, and total CT scanning in emergency departments increased by 227% from 2000 to 2008.5

Imaging Evaluation of Thyroid Nodules

Although CT and MRI may be the source of incidental thyroid nodule discovery, they are not used in the primary workup of a thyroid nodule. Ultrasound-guided fine-needle aspiration (FNA) is the most accurate evaluation for a thyroid nodule and is required for definitive diagnosis.3 However, there is controversy over whether the value of detecting subclinical thyroid cancer at an earlier time outweighs the risks and costs of screening, when the majority of incidental thyroid nodules are small papillary cancers.1,3,6 We cannot, and probably should not, fine-needle aspirate every thyroid nodule, and ultrasound helps to identify the most suspicious thyroid nodules to biopsy.

Ultrasound-guided fine-needle aspiration is the most accurate evaluation for a thyroid nodule and is required for definitive diagnosis.

Thyroid Nodules—Hot, Cold, or Who Cares?

I-123 radionuclide scans are not cost-effective or reliable in showing or characterizing a thyroid nodule.7 Cold thyroid nodules are more concerning for malignancy; however, up to 77% of cold thyroid nodules are benign.7 Therefore, if a patient is not hyperthyroid, I-123 scintigraphy is not part of the workup of an incidental thyroid nodule.

Focal Thyroid Lesions and Thyroid Cancer

On ultrasound, normal thyroid tissue is homogeneous in echotexture and hyperechoic to the adjacent strap muscles (Figure 1), with a thyroid nodule demonstrating a focal difference in echotexture. Thyroid nodules range from benign hyperplastic nodules and adenomas to focal thyroiditis and thyroid carcinoma. Thyroid cysts, intrathyroidal parathyroid tissue, and metastatic disease occur less frequently.7 Thyroid malignancy can be divided into several different types. The majority of thyroid cancers are papillary. Papillary thyroid carcinoma, which comprises 75% to 80% of thyroid cancer, includes mixed papillary and follicular subtypes and has an excellent prognosis.1 The remaining subtypes include pure follicular carcinoma (10%–20%); medullary carcinoma (3%–5%); and anaplastic carcinoma (1%–2%), which is more aggressive and rarely seen in patients younger than 60 years.1,2 Lymphoma also can occur in the thyroid as a part of generalized lymphoma or as a primary tumor, usually in the setting of longstanding Hashimoto thyroiditis.7

Figure 1. Normal thyroid. On ultrasound, the normal thyroid tissue is homogeneous in echotexture and hyperechoic to the strap muscles (*). C, carotid arteries; T, trachea.

The majority of thyroid cancers are papillary (75%–80%), and they have an excellent prognosis.
Classic Patterns for Thyroid Nodules

Reading et al. described eight classic patterns of thyroid nodules. The four patterns concerning for malignancy and warranting FNA/biopsy include a solid hypoechoic nodule containing discrete echogenic foci representing microcalcifications (papillary carcinoma) (Figure 2); a solid hypoechoic nodule with coarse echogenic foci (medullary or papillary carcinoma) (Figure 3); a solid and homogeneous egg-shaped nodule with a thin capsule (follicular neoplasm) (Figure 4); and a solid, hypoechoic nodule with refractive edge shadows (general characteristic for malignancy) (Figure 5).

The four patterns associated with benignity have cystic elements or diffuse changes and usually do not need FNA/biopsy. Three of these patterns are associated with benign nonneoplastic thyroid nodules and include small cystic nodules with or without internal echogenic foci or colloid (Figure 6), a nodule containing multiple cystic spaces with thin internal septations creating a “honeycomb” pattern (Figure 7), and large predominately cystic nodules (Figure 8). The final benign pattern is innumerable tiny hypoechoic nodules involving both lobes of the thyroid, which has a high certainty of Hashimoto thyroiditis (Figure 9).

Predictors for Thyroid Malignancy

Not all thyroid nodules will fit a classic pattern. Therefore, there has been a shift to focus on analysis of individual ultrasound features for malignancy, including composition, echogenicity, margins, calcification, and shape. Specific ultrasound

Figure 2. Solid, hypoechoic thyroid nodule, containing innumerable, discrete, echogenic foci representing microcalcifications. This ultrasound appearance has a high positive predictive value for papillary thyroid cancer.

Figure 3. Solid, hypoechoic thyroid nodule with coarse, echogenic foci representing dystrophic calcification. This ultrasound appearance is highly suggestive of thyroid malignancy.

Figure 4. Solid, homogeneous, egg-shaped thyroid nodule with a thin capsule. These ultrasound features are associated with follicular thyroid cancer.

Figure 5. Thyroid nodule with refractive edge shadowing, microcalcifications, and profound hypoechogenicity. All of these ultrasound features are associated with thyroid malignancy. A second smaller thyroid nodule is present. At thyroidectomy, the dominant nodule was medullary thyroid carcinoma, and the smaller nodule was benign.
Interval growth of a thyroid nodule is not indicative of thyroid malignancy, because up to 90% of thyroid nodules increase in volume 15% or more over 5 years.

Thyroid Cysts and Cystic Change

It has been reported that up to half of benign thyroid nodules contain cystic components and 3 of the 4 classic benign patterns hinge on a cystic composition. However, small cystic components have been reported in 13% to 25% of papillary thyroid cancers. But only 2.5% of thyroid cancers have sonographically visualized large cystic components of more than half the volume of tumor, and a cystic malignancy should have other concerning features, such as microcalcifications, a papillary solid component, or a mural nodule. Of note, cystic changes of papillary thyroid carcinoma are more common in cervical node metastasis (43% to 70% of cases) than in the primary thyroid tumor. Also, the composition of the nodal metastatic disease may be cystic when the primary tumor is solid.

Calcifications and Thyroid Cancer

Microcalcifications within a thyroid nodule are one of the most specific ultrasound predictors for thyroid malignancy, with a specificity of 85.8% to 95% and a PPV of 41.8% to

features concerning for malignancy include evidence of local lymphadenopathy/local invasion (Figure 10), the presence of calcification, marked hypoechogenicity (less than the strap muscles), taller-than-wide configuration (Figure 11), irregular or infiltrating margins, absence of a halo, predominately solid composition, and intranodular vascular flow. Solid composition is the most sensitive feature for thyroid malignancy, but it has a low positive predictive value (PPV), whereas microcalcifications are more specific with the highest PPV. Size and number of thyroid nodules are poor indicators for malignancy. In fact, in one third of the cases with multiple thyroid nodules, cancer is found in a nondominant nodule. Likewise, interval growth of a thyroid nodule often is included in criteria for rebiopsy but is not predictive of thyroid malignancy, as up to 90% of all thyroid nodules increase in volume 15% or more over 5 years. However, thyroid nodules that are predominately cystic are less likely to enlarge.

Figure 6. This ultrasound shows a small, cystic thyroid nodule with echogenic foci with comet-tail artifact representing inspissated colloid. This is a benign colloid cyst.

Figure 7. This ultrasound shows a thyroid nodule containing multiple cystic spaces separated by thin septations in a benign “honeycomb” pattern.

Figure 8. On this ultrasound, the large, predominately cystic thyroid nodule has benign features.

Figure 9. This ultrasound shows innumerable tiny hypoechogenic thyroid nodules. This is a benign pattern associated with Hashimoto thyroiditis.
94.2%.1,4,7 Macrocalcifications and peripheral rim calcifications (Figure 12) are less specific but also portend an increased risk, with large dystrophic calcifications associated with a malignancy rate of nearly 75% when seen with a solitary thyroid nodule.7

Microcalcifications within a thyroid nodule are one of the most specific ultrasound predictors for thyroid malignancy.

Vascular Flow

Intranodular vascularity has been described as an ultrasound feature of thyroid malignancy; however, up to 50% of hypervascular solid thyroid nodules in one series were benign.7 Likewise, peripheral vascularity, seen more commonly with benign thyroid lesions, also has been reported in up to 22% of thyroid malignancies.7 Rather, avascularity may be a more helpful predictor of benign disease, with one series finding that all cases of papillary thyroid carcinoma had some intrinsic vascular flow.7

No-Touch Thyroid Nodules

Taking the alternative approach, Bonavita et al.3 used individual feature assessment and pattern recognition to try to discern which thyroid nodules could be left alone. They concluded that the number of unnecessary thyroid biopsies could be decreased by approximately 60% if thyroid nodules with a spongiform configuration; cysts with colloid clot; nodules associated with Hashimoto thyroiditis (Figure 13), such as the “giraffe-hide” appearance (i.e., nodules seen in thyroiditis and composed of echogenic regions separated by hypoechoic bands, creating a giraffe-hide appearance); and hyperechoic nodules, were left alone.3 These four patterns were found to have 100% specificity for benignity in this series.3

No-touch thyroid nodules include those with a spongiform configuration, those with a colloid clot within a cyst, those associated with Hashimoto thyroiditis, and a hyperechoic mass.

Just Poke the Rest?

There is overlap between the sonographic features of benign and malignant nodules, and ultimately an FNA is required for definitive diagnosis. However, it is unrealistic to
biopsy every thyroid nodule. There are guidelines to help direct clinical practice, but these guidelines vary among organizations. The Society of Radiologists in Ultrasound (SRU), the American Association of Clinical Endocrinologists (AACE), and the American Thyroid Association (ATA) have slightly different recommendations in the management of thyroid nodules.

**Differing Criteria for FNA and Workup**

SRU recommends biopsy of mixed cystic and solid thyroid nodules 20 mm or larger, solid nodules or coarsely calcified nodules 15 mm or larger, and solid nodules 10 mm or larger with microcalcifications. SRU also recommends biopsy of any thyroid nodule with substantial growth or abnormal cervical nodes, noting that FNA probably is not needed for almost entirely cystic nodules without the above features or interval growth.4 AACE and ATA recommend biopsy of all solid thyroid nodules larger than 10 mm. AACE also recommends biopsy of any size thyroid nodule with one or more suspicious sonographic findings.5 The larger size thresholds for SRU result in higher specificity and lower sensitivity, with the aim to “diagnose cancers that have reached clinical significance while avoiding unnecessary tests and surgery in patients with benign nodules.”6 The 3-tiered system includes criteria proposed for the workup of incidental thyroid nodules seen on CT, MRI, or positron emission tomography (PET)/CT. Thyroid nodules with aggressive features such as suspicious cervical lymph nodes, local invasion, or focal metabolic activity on PET are evaluated with ultrasound. A solitary thyroid nodule 1 cm or larger in a patient younger than 35 years, or a solitary solid thyroid nodule 15 mm or larger in a patient 35 years or older, is recommended for evaluation with ultrasound.2

**Guidelines in Clinical Practice**

Hobbs et al.5 found that one of every four thyroid biopsies at their institution did not meet the SRU criteria. When they applied the SRU recommendations by ultrasound and the 3-tiered system for CT, MRI, or PET/CT to incidental thyroid nodules, the workup of incidental thyroid nodules was reduced by one third, and only one case of localized papillary carcinoma would have been missed.2 One institution looked at the application of the SRU guidelines to direct the workup of incidental thyroid nodules over a 10-year period and found that only 2% of thyroid malignancies would not undergo FNA or surgery. Furthermore, the SRU criteria-negative tumors were noted to be smaller and lower-stage malignancies.8

**What to Do? The SRU With Nuances**

In patients with risk factors, consider sampling solid subcentimeter-sized thyroid nodules, particularly if any are markedly hypoechoic or contain microcalcifications. Risk factors include family or personal history of thyroid cancer; Cowden syndrome; familial adenomatous polyposis; Carney complex; multiple endocrine neoplasia type 2; or external beam radiation including the thyroid in childhood or adolescence. Attempt to biopsy thyroid nodules that demonstrate peripheral calcifications, especially if the calcification appears interrupted. In the setting of abnormal cervical lymph nodes, biopsy any associated thyroid nodule. In addition, because of the increased risk of malignancy (27%–47%), biopsy all focally PET-positive thyroid nodules.2 In patients with multinodular goiter, assess each thyroid nodule, targeting the most suspicious nodule, not necessarily the largest.7 Finally, avoid the benign patterns (i.e., thyroid cysts with colloid, avascular spongiform nodules, and nodules related to Hashimoto thyroiditis, including hyperechoic nodules and giraffe-hide pattern nodules).

**Conclusion**

Thyroid nodules are ubiquitous and often are worked-up as incidental findings. This CME activity emphasizes that because most thyroid nodules are benign, and those that are malignant may never result in clinically significant disease, much consideration should go into which thyroid nodules can and should be biopsied. Established imaging patterns and predictors of malignancy, clinical risk factors, and institutional guidelines can be used to ensure that biopsy is performed in patients with thyroid nodules that have the potential to cause clinically significant disease.

**References**

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1. The thyroid ultrasound of a 40-year-old man reveals a solid thyroid nodule with an egg-shape and a thin capsule. The most likely diagnosis is
   A. thyroid adenoma
   B. intrathyroidal parathyroid tissue
   C. papillary thyroid carcinoma
   D. thyroid lymphoma
   E. pure follicular thyroid carcinoma

   See Reference No. 1 for further study

2. Primary thyroid lymphoma usually is associated with which one of the following diseases?
   A. Graves disease
   B. Long-standing Hashimoto thyroiditis
   C. Addison’s disease
   D. Hyperparathyroidism

   See Reference No. 7 for further study

3. Which one of the following is the most common type of primary thyroid malignancy?
   A. Medullary carcinoma
   B. Follicular carcinoma
   C. Papillary carcinoma
   D. Anaplastic carcinoma
   E. Lymphoma

   See Reference No. 1 for further study

4. Figure 14 is a Doppler ultrasound scan of a thyroid nodule. Which one of the following findings in this ultrasound scan is most likely to support the biopsy diagnosis of cystic papillary carcinoma in this patient?
   A. Shape of the cystic component
   B. Presence of the solid component
   C. Increased intranodular vascularity
   D. Size of the cystic component
   E. Peripheral vascularity

   See Reference No. 7 for further study

Figure 14.

CME quiz continues on p. 8.
5. In which one of the following situations should an I-123 radionuclide scan be used to evaluate a thyroid nodule?
   A. The patient has a history of Hashimoto thyroiditis.
   B. The patient is hypothyroid.
   C. The patient is euthyroid.
   D. The patient is hyperthyroid.
   E. There is a strong family history of thyroid cancer.

See Reference No. 2 for further study.

6. All of the following are clinical risk factors for thyroid cancer that should prompt consideration of biopsy of a solid, sub-centimeter thyroid nodule, except
   A. family history of thyroid cancer
   B. personal history of radiation therapy involving the thyroid in childhood or adolescence
   C. personal history of familial adenomatous polyposis
   D. personal history of thyroid cancer
   E. personal history of Graves disease

See Reference No. 2 for further study.

7. All of the following are ultrasound appearances of a thyroid nodule that support the “do not biopsy” treatment approach, except
   A. spongiform configuration of nodule
   B. refractive edge shadowing of nodule
   C. hyperechoic nodule
   D. nodules associated with Hashimoto thyroiditis

See Reference No. 3 for further study.

8. All of the following are classic ultrasound patterns of benign thyroid nodules, except
   A. small cystic nodules with or without internal echogenic foci or colloid
   B. a “honeycomb” pattern
   C. large, predominately cystic nodules
   D. innumerable, tiny hypoechogenic nodules in both lobes
   E. a solid mass with interrupted rim calcification

See Reference No. 4 for further study.

9. The thyroid ultrasound of a 32-year-old woman reveals a solid, hypoechogenic thyroid nodule containing innumerable, discrete, echogenic foci representing microcalcifications. The most likely diagnosis is
   A. papillary thyroid carcinoma
   B. thyroid adenoma
   C. thyroid cysts containing colloid
   D. parathyroid tissue within the thyroid
   E. Hashimoto thyroiditis

See Reference No. 8 for further study.

10. All of the following are ultrasound features of thyroid cancer, except
    A. solid, hypoechogenic thyroid nodule containing multiple microcalcifications
    B. solid, hypoechogenic thyroid nodule containing coarse, echogenic foci
    C. solid, homogeneous, egg-shaped thyroid nodule with a thin capsule
    D. thyroid nodule containing multiple cystic spaces with thin internal septations
    E. solid thyroid nodule with refractive edge shadows

See Reference No. 6 for further study.