Diagnostic Snapshot

Indeterminate Thyroid Nodules: When to Worry?

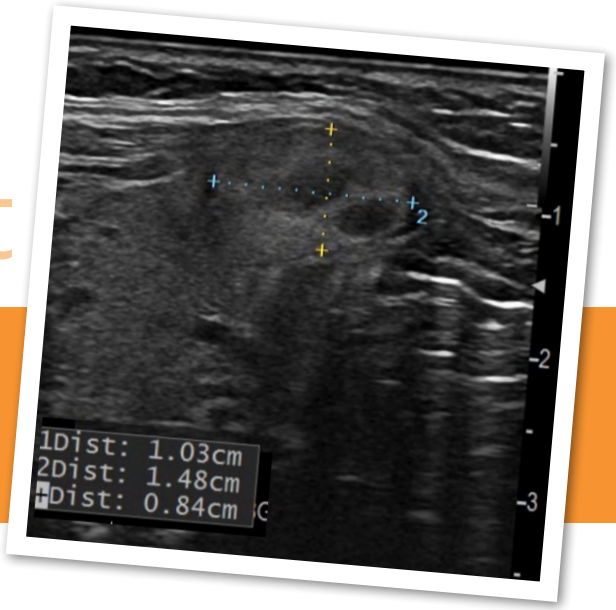

Figure 1. Ultrasound image of right superior thyroid nodule.

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Author's disclosure of conflict of interest is found at the end of this article.

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Abstract

Indeterminate thyroid nodules can present a confounding scenario for both provider and patient. Once a diagnosis of an indeterminate thyroid nodule is made, appropriate management can range from conservative observation to surgical resection. A thorough evaluation, including a dedicated history and physical examination, biochemical profile, pathologic information from a seasoned pathologist, and thyroid ultrasound by an experienced radiologist can help point health-care providers in the right direction. However, the ultimate diagnosis cannot be rendered unless surgical excision is performed. Provider and patient must agree on a personalized risk vs. benefit profile for the indeterminate thyroid nodule.

HISTORY

Mrs. C is a 56-year-old woman with a history of depression, anxiety, and kidney stones, and was diagnosed with multiple thyroid nodules in February 2020. She was seeing a local endocrinologist for abnormal thyroid function tests when the endocrinologist palpated the nodules on physical examination. Her thyroid function tests at the time were borderline hyperthyroid. Mrs. C denied any hyperthyroid symptoms, including heart palpitations, tachycardia, or recent weight loss. She also denied any compressive symptoms from the nodules, including dysphagia, hoarseness of voice, neck pain, or dyspnea while supine. Her grandmother had a goiter that was surgically removed, and her daughter has neurofibromatosis type 2 (an autosomal dominant syndrome that predisposes individuals to multiple tumors of the nervous system, most commonly schwannomas and meningiomas; Evans, 2009).

CHIEF COMPLAINT

Mrs. C presented to the clinic in July 2020 for surgical evaluation of two right-sided thyroid nodules. She was clinically asymptomatic and biochemically hyperthyroid.

PHYSICAL EXAM AND DIAGNOSTIC STUDIES

On physical examination, Mrs. C had two palpable nodules in the right thyroid lobe: one superior, and one inferior near the isthmus. There was no discernible cervical adenopathy or other noted abnormalities. Her blood pressure was 103/68 and heart rate 73 beats per minute. Her body temperature was 36.5°C (97.7°F). She was biochemically hyperthyroid with a thyroid stimulating hormone (TSH) of 0.29 and free thyroxine (free T4) of 1.23. On thyroid ultrasound, she had a 1.4-cm right isthmus nodule characterized as Thyroid Imaging Reporting and

Data System (TI-RADS) TR4 and a 1.0-cm right superior nodule characterized as TR5 (Figures 1 and 2). There was no lymphadenopathy detected on ultrasound. Fine-needle aspiration (FNA) biopsies of both nodules of interest were performed. Under pathology review, the 1.4-cm right isthmus nodule was described as atypical cells of undetermined significance (AUS; Table 1). The 1.0-cm right superior nodule was described as a follicular lesion.

According to the NCCN (2018) Guidelines, both AUS and follicular lesions with no suspicious molecular diagnostic findings warrant active surveillance. We decided with Mrs. C to conservatively follow up in 3 months, as she had two indeterminate nodules in the same thyroid lobe.

Table 1. The Bethesda System for Reporting Thyroid Cytopathology

Bethesda class	Diagnostic category	Cancer risk, %
I	Nondiagnostic (unsatisfactory)	1–4
II	Benign	0–3
III	Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS)	~5–15
IV	Follicular neoplasm (or suspicious for follicular neoplasm)	15–30
V	Suspicious for malignancy	60–75
VI	Malignant	97–99

Note. Information from Cibas & Ali (2009).

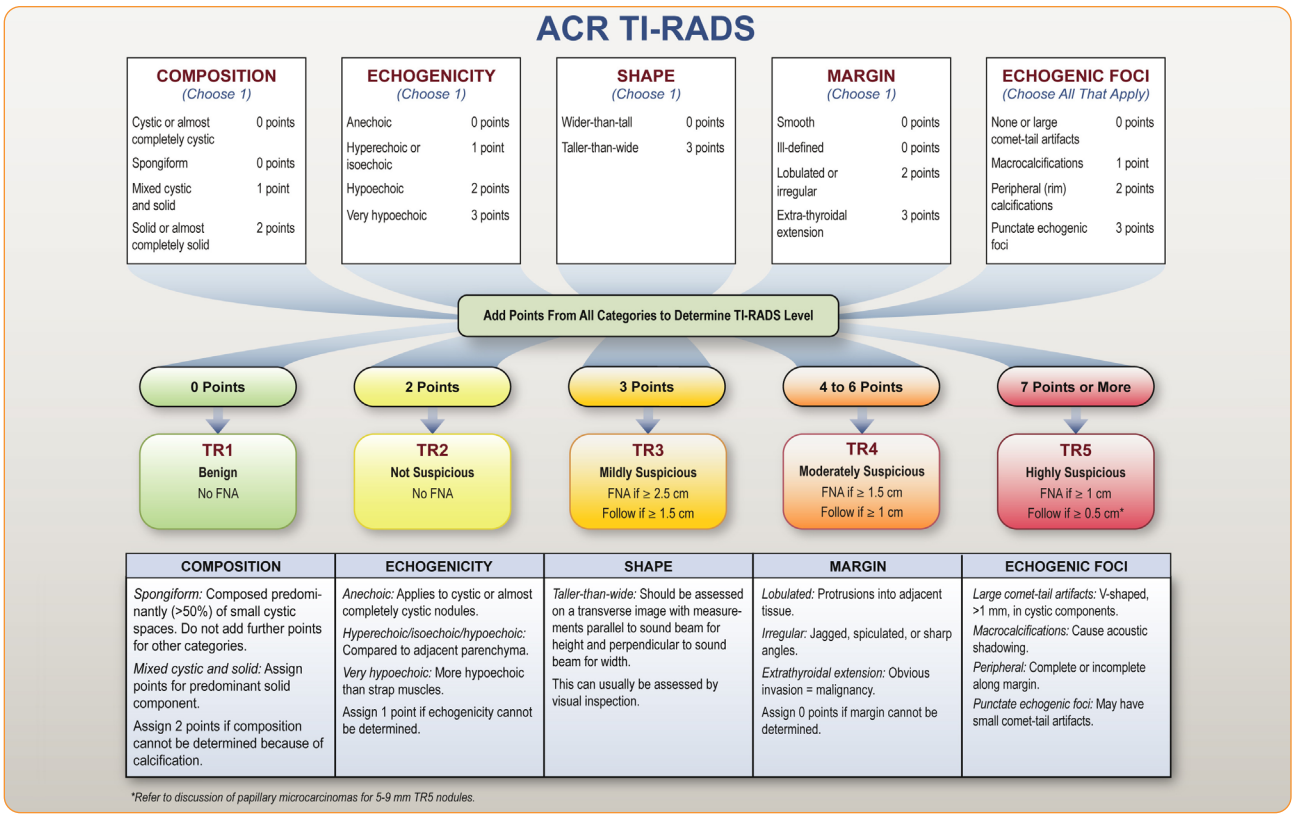

Figure 2. American College of Radiology (ACR) Thyroid Imaging Reporting and Data System (TI-RADS). Reprinted with permission from Tessler et al. (2017).

CLINICAL QUESTION

WHICH OF THE FOLLOWING FACTORS DOES *NOT* INCREASE A PATIENT'S CHANCE OF THYROID MALIGNANCY?

A. ☐ Family history
B. ☐ Size of the nodule
C. ☐ Bilateral thyroid nodules
D. ☐ History of radiation
E. ☐ Growth of the nodule

SEE BACK FOR ANSWER ▶

WHICH OF THE FOLLOWING FACTORS DOES *NOT* INCREASE A PATIENT'S CHANCE OF THYROID MALIGNANCY?

A. Family history

B. Size of the nodule

C. Bilateral thyroid nodules (correct answer)

D. History of radiation

E. Growth of the nodule

A Family history. Thyroid cancer can run in families. We specifically think of familial medullary thyroid carcinoma (MTC), multiple endocrine neoplasia type 2 (MEN2), Cowden syndrome, familial adenomatous polyposis (FAP), Werner syndrome, and Dicer 1 ribonuclease (DICER1) syndrome, among others (Fisher & Perrier, 2018). There is suspicion for a genetic link to familial papillary thyroid carcinoma that has not been clearly identified yet. When only two first-degree relatives are affected, the probability that the disease is sporadic is about 62% (Charkes, 2006).

B Size of the nodule. The false-negative rate for FNA biopsy increases with nodule size due to sampling error. In multiple studies, the false-negative rate can be as high as 13% for nodules greater than 4 cm in size (Gharib & Goellner, 1993). The American College of Radiology along with the American Thyroid Association provide helpful guidelines for FNA indications based on size and characteristics of thyroid nodules, commonly known as the TI-RADS classification system.

C Bilateral thyroid nodules (correct answer). The lone factor of having multiple and/or bilateral thyroid nodules does not inherently increase a patient's risk of malignancy. Thyroid goiter or multiple thyroid nodules are common and detectable in up to 68% of people (Haugen et al., 2016). There are helpful diagnostic tools such as the TI-RADS (Figure 2) guidelines from the American College of Radiology for ultrasound findings and the Bethesda classification system/cytopathology (Table 1) to stratify risk of malignancy for each individual nodule. However, if a cancer is detected in one nodule, it is more likely that the other nodules hold cancer as well.

D History of radiation. A history of radiation, especially in childhood, increases a patient's risk for thyroid cancer. There are many examples of this radiation including living near a radiation plant or other environmental exposures (e.g., Chernobyl), radiation for a previous cancer diagnosis, etc. (Bresciani et al., 2019).

E Growth of the nodule. Thyroid malignancies, although deemed a slow-growing cancer in most common cases, tend to grow over time. In the case of a growing thyroid nodule with indeterminate cytopathology, malignancy is more suspect. It is important to keep in mind that benign thyroid disease can also grow over time, so this is not an absolute certainty.

In a case of nodular growth, providers can choose to send the biopsy sample for molecular testing. Molecular testing is helpful in the case of true benign disease, as it has a negative predictive value of about 97% (Fisher & Perrier, 2018). However, it is far less helpful in the case of malignant disease, as the positive predictive value is anywhere from 30% to 60%. Therefore, molecular testing is a helpful "rule-out" tool: a negative result has a high correspondence with benign disease, but its ability to detect malignancy is limited. One major limitation to molecular testing is high cost.

MANAGEMENT

Three months later, Mrs. C's follow-up ultrasound indicated the nodules were stable in both size and characteristic. However, she remained biochemically hyperthyroid, now with a TSH of 0.05 and free T4 of 1.48. At this time, patient and provider agreed to proceed with a diagnostic right thyroid lobectomy with isthmusectomy to achieve a definitive diagnosis. According to the NCCN Guidelines

(2018), lobectomy is recommended in the setting of uninformative molecular diagnostic testing for atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS; Table 1). Mrs. C underwent surgery in March 2021. Surgical pathology revealed a 1.1-cm papillary thyroid carcinoma, follicular variant in the right superior lobe (biopsy follicular lesion), and a 1.4-cm non-invasive follicular thyroid neoplasm with papillary-like nuclear features (biopsy AUS). There was one lymph node removed, which was negative for tumor. There was no extrathyroidal extension nor lymphovascular invasion identified on histopathology. According to the American Joint Committee on Cancer (AJCC) 8th edition for differentiated thyroid carcinoma, this is a stage 1 (pT1b pN0a cM0) papillary thyroid cancer (Table 2; Tuttle et al., 2017). Further, according to the 2009 ATA Initial Risk Stratification System, her staging and pathology are categorized as low risk for disease recurrence (Haugen et al., 2016). Of note, had her histopathology indicated any lymphovascular invasion, extrathyroidal extension, or positive lymph nodes, she would have remained stage 1, but been deemed intermediate-risk disease. In this case, a total thyroidectomy would have been recommended in order to allow her candidacy for adjuvant radioactive iodine treatment (Haddad et al., 2018).

CONCLUSION

Mrs. C presented for follow-up in October 2021. Her ultrasound showed no evidence of recurrent or residual disease. She continues to be without any discrete nodules in the left thyroid lobe nor suspicious lymphadenopathy. She was started on low-dose levothyroxine supplementation due to a rising TSH of 3.39 and postoperative weight gain. She is doing well and will continue with active surveillance. According to the Bethesda classification system, Mrs. C had a malignancy risk of 5% to 15% for both thyroid nodules (Table 1; Cibas & Ali, 2009).

The evaluation of indeterminate thyroid nodules takes thoughtful collaboration of all information in tandem with excellent patient education. Medical decision-making must include not only the clinical thyroid picture, but also the patient's full clinical picture, including comorbidities, age, risk of a surgical operation, and patient preference. It is also wise to consider any compressive symptoms, the patient's risk of needing thyroid hormone supplementation or replacement after surgery, and patient compliance with both medication and follow-up care.

Disclosure

The author has no conflicts of interest to disclose.

Table 2. AJCC Prognostic Stage Grouping for Papillary Thyroid Carcinoma

When age at diagnosis is:	And T is[a]:	And N is[b]:	And M is[c]:	Then the stage group is:
< 55 years	Any T	Any N	M0	I
	Any T	Any N	M1	II
≥ 55 years	T1	N0/Nx	M0	I
	T1	N1	M0	II
	T2	N0/Nx	M0	I
	T2	N1	M0	II
	T3a/T3b	Any N	M0	II
	T4a	Any N	M0	III
	T4b	Any N	M0	IVA
	Any T	Any N	M1	IVB

Note. Information from Tuttle et al. (2017).

[a]Tumor size measured in greatest dimension and limited to the thyroid. T1: tumor ≤ 2 cm; T1a: tumor ≤ 1 cm; T1b: tumor > 1 cm but ≤ 2 cm; T2: tumor > 2 cm but ≤ 4 cm; T3: tumor > 4 cm or gross extrathyroidal extension invading only strap muscles; T3a: tumor > 4 cm; T3b: gross extrathyroidal extension invading only strap muscles from a tumor of any size; T4: gross extrathyroidal extension into major neck structures; T4a: gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve from a tumor of any size; T4b: gross extrathyroidal extension invading prevertebral fascia or encasing carotid artery or mediastinal vessels from a tumor of any size.

[b]NX: regional lymph nodes cannot be assessed; N0: no evidence of regional lymph node metastasis; N1: metastasis to regional nodes; N1a: metastasis to level VI or VII lymph nodes; this can be unilateral or bilateral disease; N1b: metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes or retropharyngeal lymph nodes.

[c]M0: no distant metastasis; M1: distant metastasis.

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