



# Thyroid Nodules

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# Disclosures

- None



# Let's Talk Nodules...

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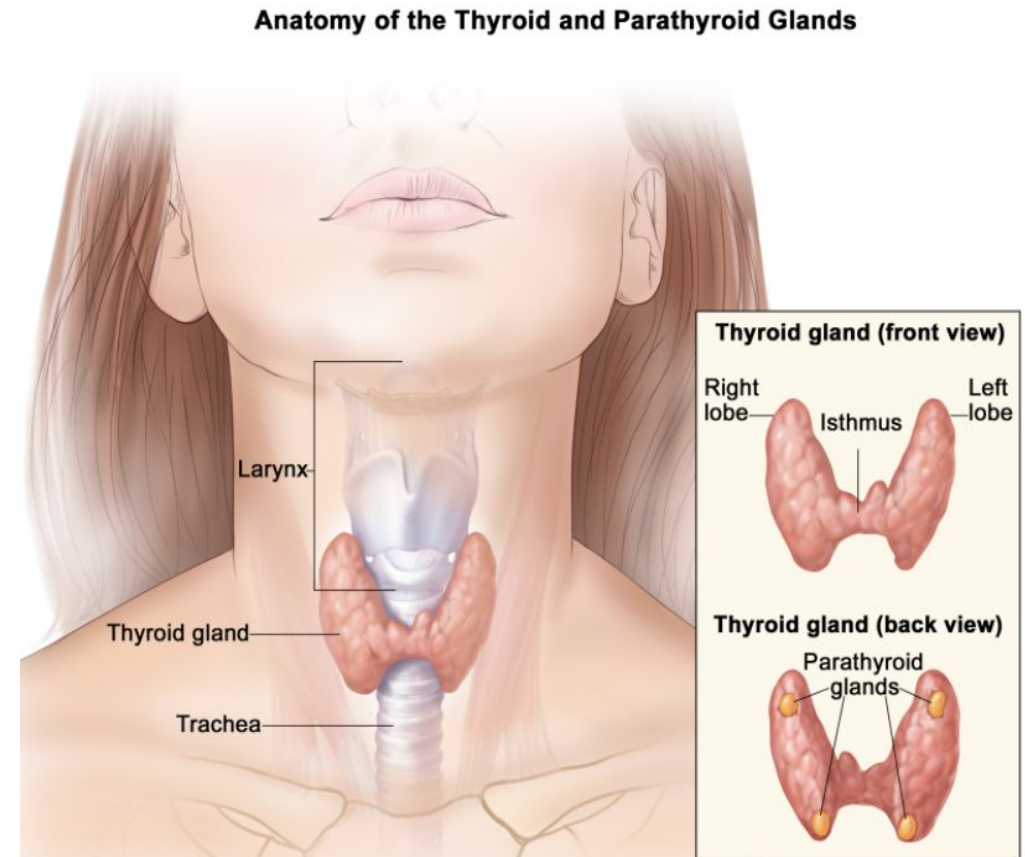
1. Brief overview of the thyroid.
2. What are thyroid nodules?
3. Thyroid Ultrasound
4. How to risk stratify thyroid nodules.
5. What nodules get biopsied?
6. How to interpret biopsy results.
7. Follow up recommendations.
8. Cases



# Thyroid Gland Basics

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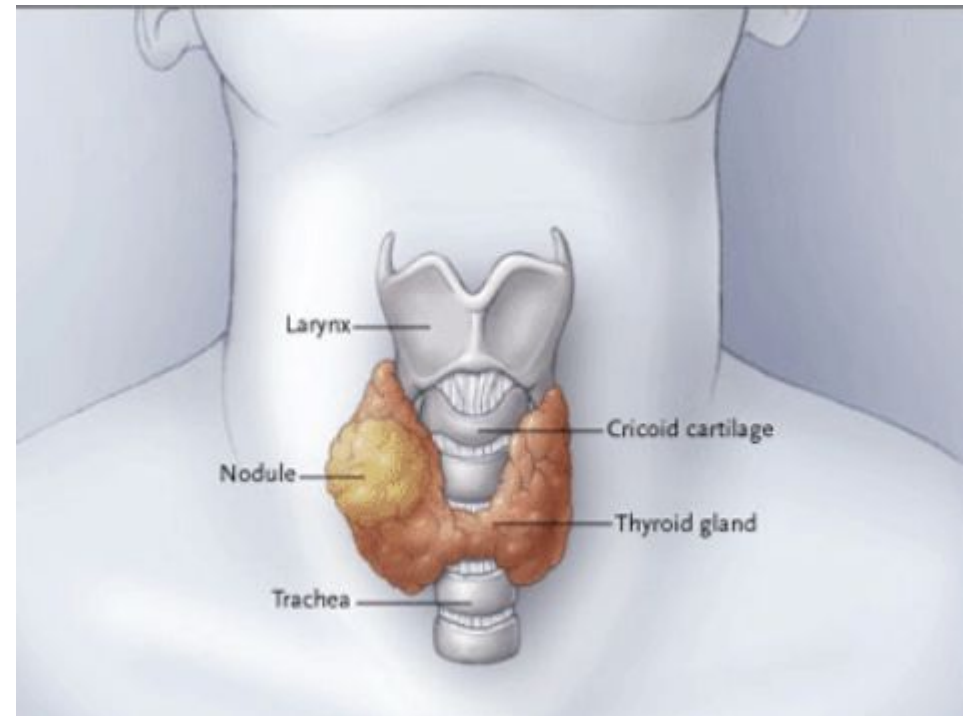
- Gland structure: left and right half connected by the isthmus.
- Sits in front of the trachea and larynx.
- Made of follicles that contain colloid. Colloid makes thyroglobulin. When stimulated thyroglobulin makes T4 and T3.



# Thyroid Nodules

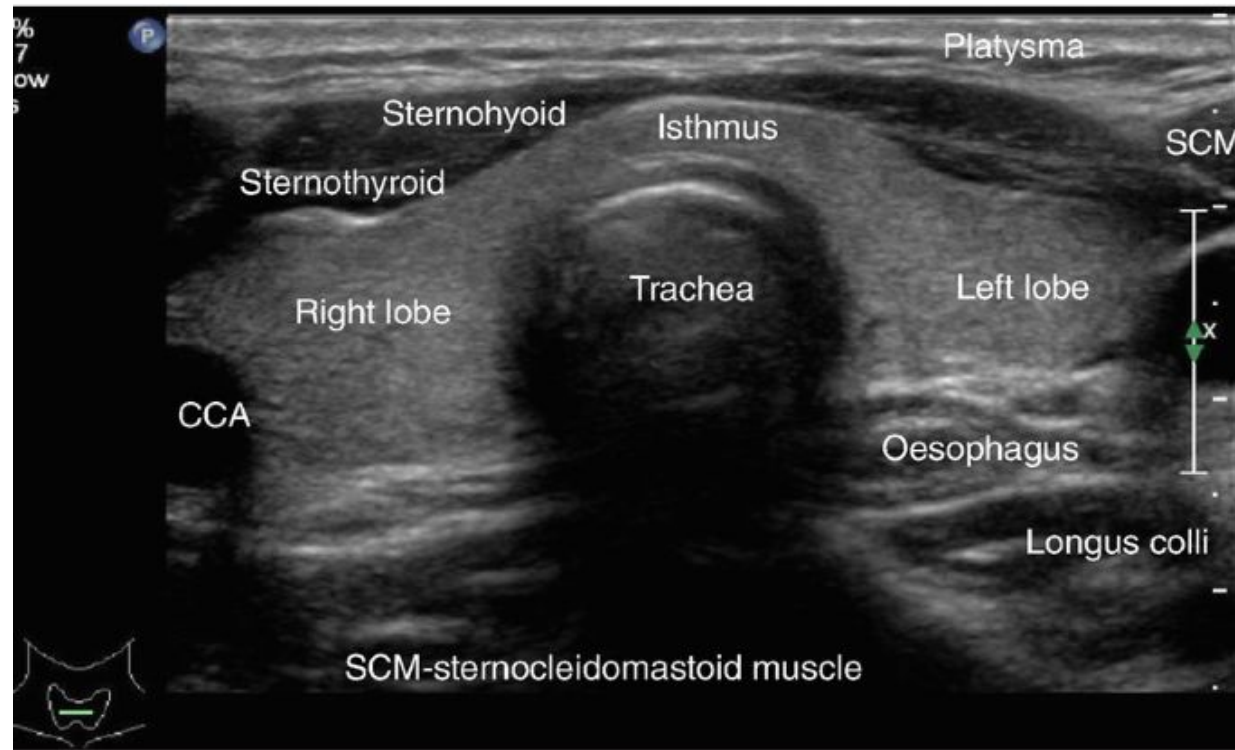
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- Common: by age 60 up to half of all people have thyroid nodules.
- Most nodules are benign (>90%)
- ~5% thyroid nodules are malignant
- Most often found on exam or incidentally on imaging.
- Females > Males



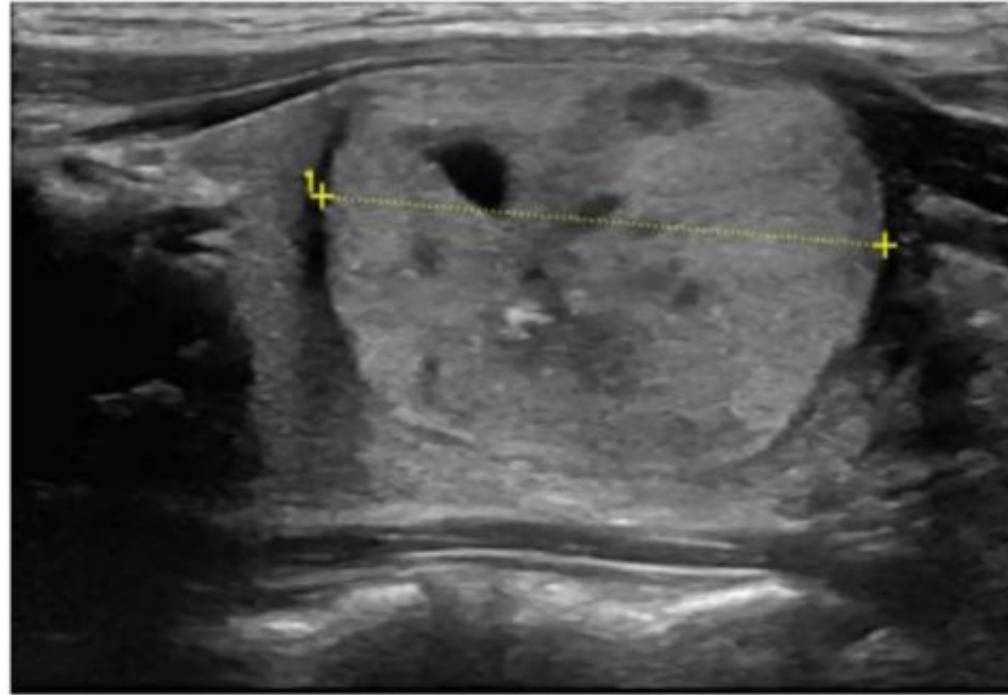
# Thyroid Ultrasound

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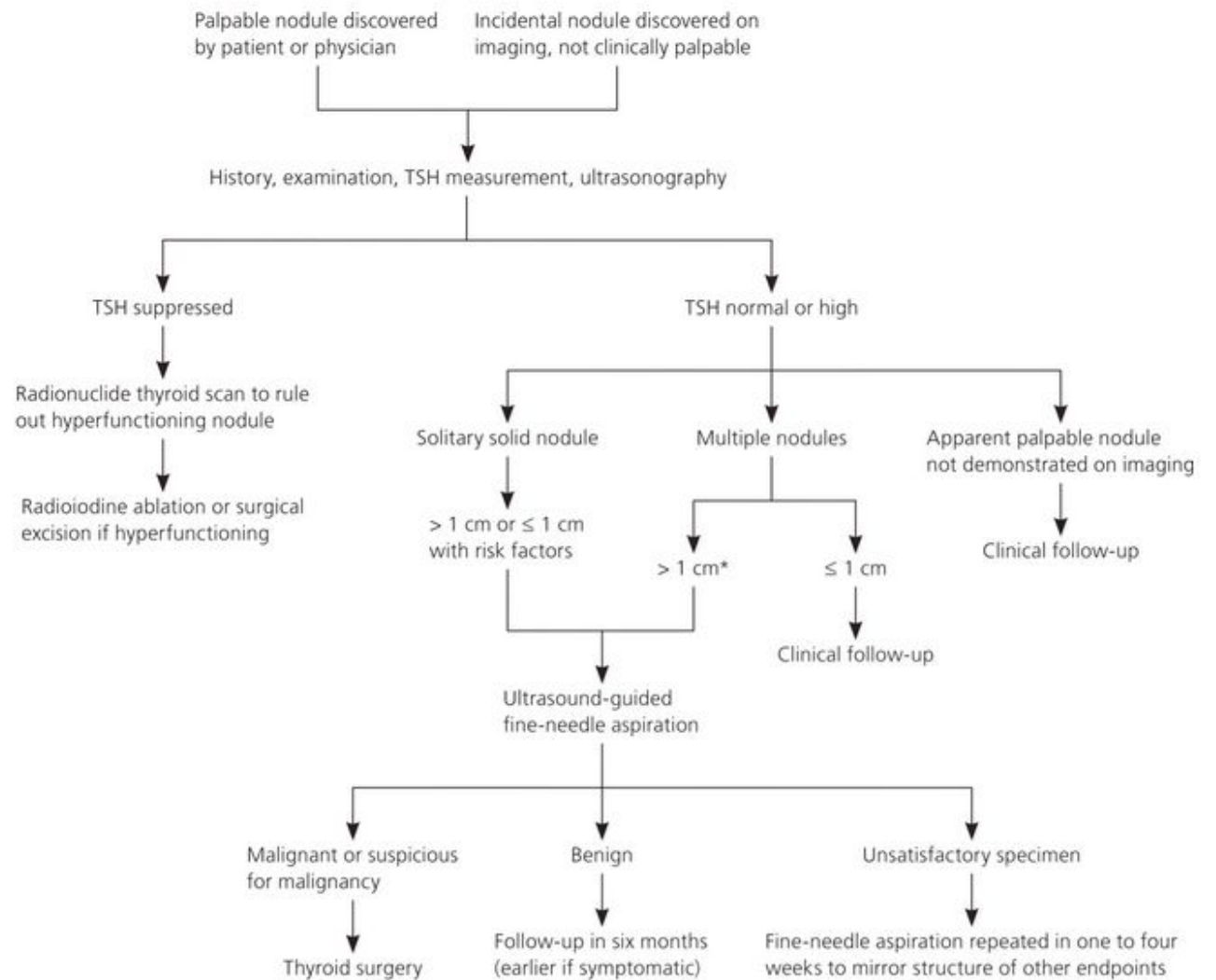
# Thyroid Nodules

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# I found a Thyroid nodule. What next?

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\*—Cutoff size for biopsy with multiple nodules not clearly established.

Suggested diagnostic and treatment approach for thyroid nodules. (TSH = thyroid-stimulating hormone.)

Adapted with permission from Weiss RE, Lado-Abeal J. Thyroid nodules: diagnosis and therapy. *Curr Opin Oncol.* 2002;14(1):50.



# **What features do you look for on ultrasound?**

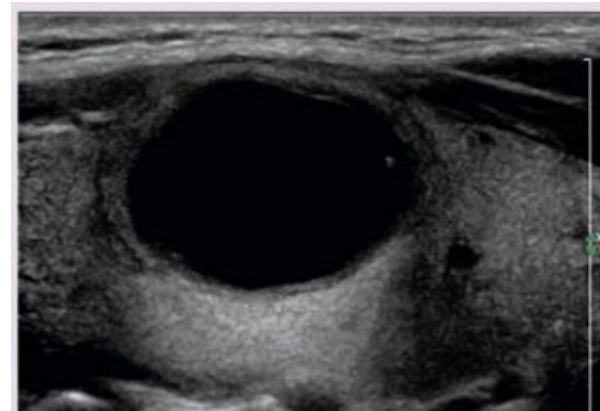
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- 1. Composition**
- 2. Shape**
- 3. Echogenicity**
- 4. Margins**
- 5. Echogenic Foci  
(Microcalcifications)**

# Composition

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- Composition refers to presence of tissue or fluid in the nodules. Nodules can be:
  - Cystic (fluid-filled)
  - Solid (soft tissue)
  - Mixed (solid + cystic)
  - Spongiform (looks like small cysts in a sponge)

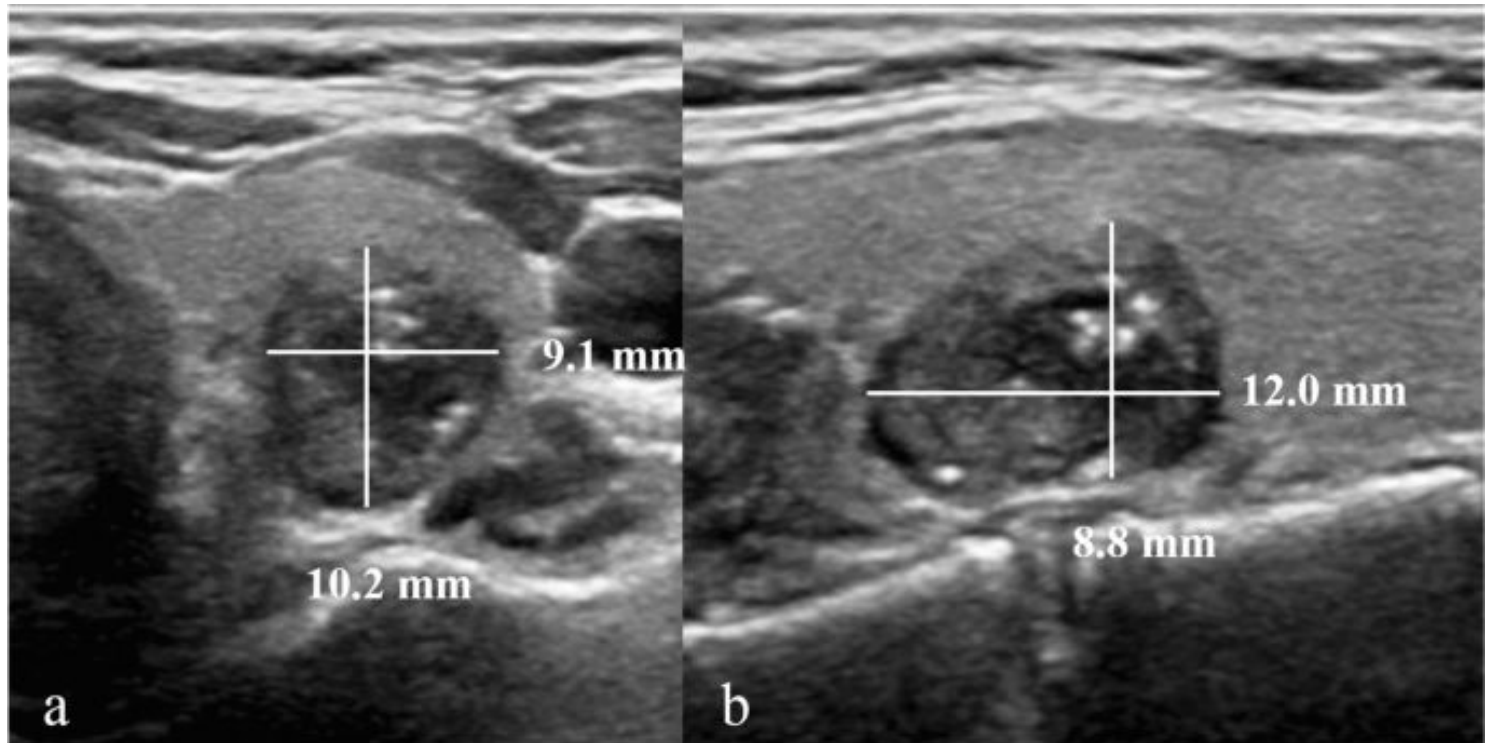


# Shape

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- Shape:

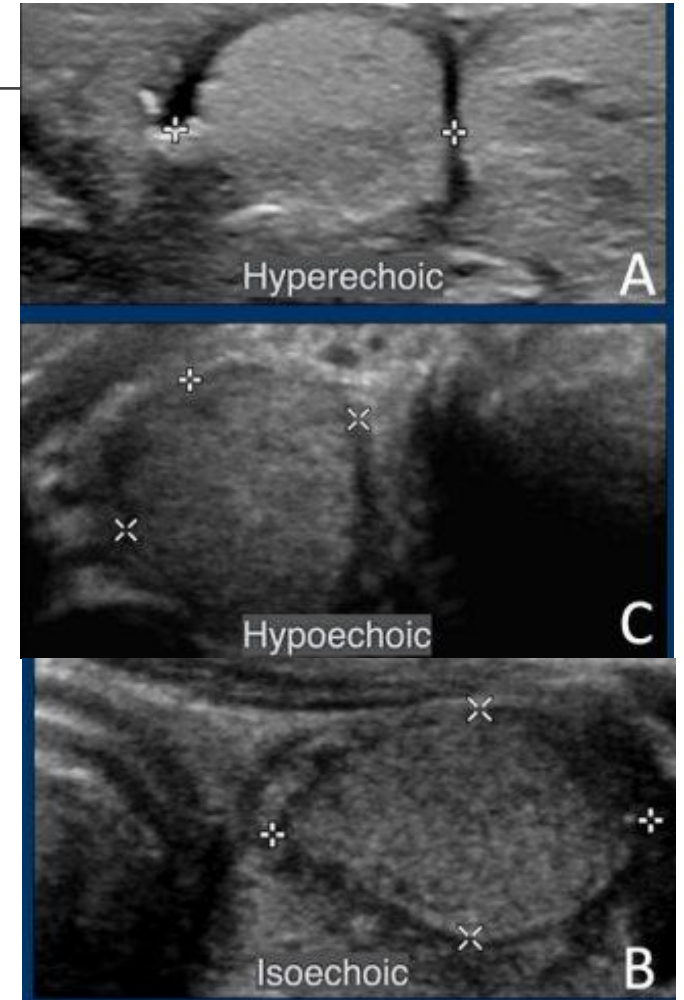
- Round vs Oval
- Taller-than-wide vs wider-than-tall



# Echogenicity

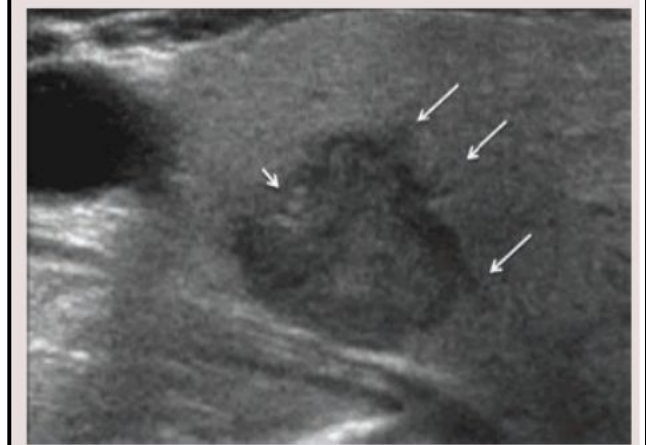
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- Echogenicity refers to the “look” of the solid component of the nodule compared to the remaining thyroid tissue:
  - Looks like surrounding tissue = Isoechoic
  - Looks brighter than surrounding tissue= Hyperechoic
  - Looks darker/not as bright as the surrounding tissue= Hypoechoic



# Margins

- Margins are how a nodules borders are described.
  - Poorly-defined/ill-defined = look to blend with surrounding, without discrete borders; probably a benign finding.
  - Micro-lobulated, spiculated or infiltrating = concerning for malignancy

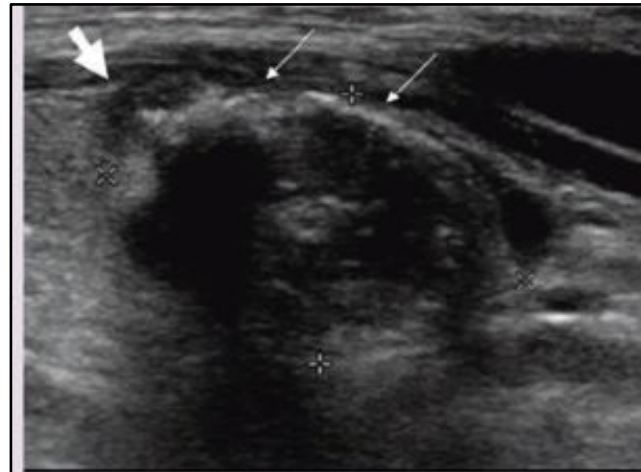


**Figure 6. Infiltrating margins.** A sagittal view of the thyroid demonstrates a solid, markedly hypoechoic papillary thyroid cancer that has infiltrating soft tissue (long arrows) extending into the parenchyma, which represents the aggressive growth pattern of this tumor. This nodule also contains multiple microcalcifications (short arrow), which appear as small less than 1 cm bright foci throughout the nodule.

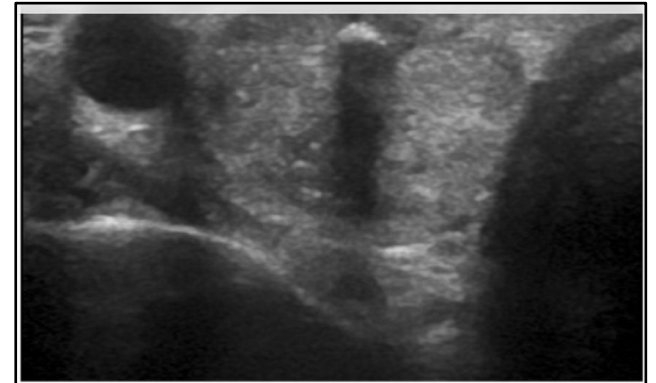


# Calcifications

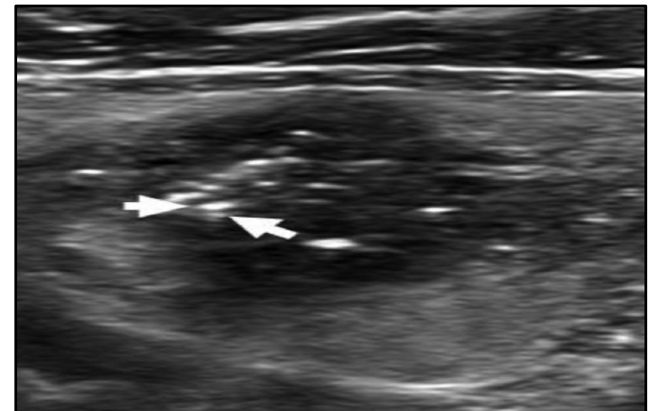
- Calcifications occur in benign and malignant nodules.
  - Called punctate echogenic foci.
- Certain calcifications are more concerning than others.
- Differentiate microcalcifications from hyperechoic foci-seen in colloid-containing nodules/cysts.  
(Posterior-acoustic shadowing vs enhancement).



**Figure 9. Peripheral calcifications.** A sagittal view shows a papillary thyroid carcinoma (outlined by electronic calipers) that has irregular peripheral calcifications (arrows). At the superior margin of the nodule, a small focus of soft tissue (large arrow), which is hypoechoic and contains microcalcifications, extends through the peripheral calcifications and provided an optimal region in which to perform an ultrasound-guided fine-needle aspiration of this lesion.



Solitary thyroid nodule was solid hypoechoic with macrocalcification and punctate calcification TR5; papillary carcinoma was evident after surgical removal



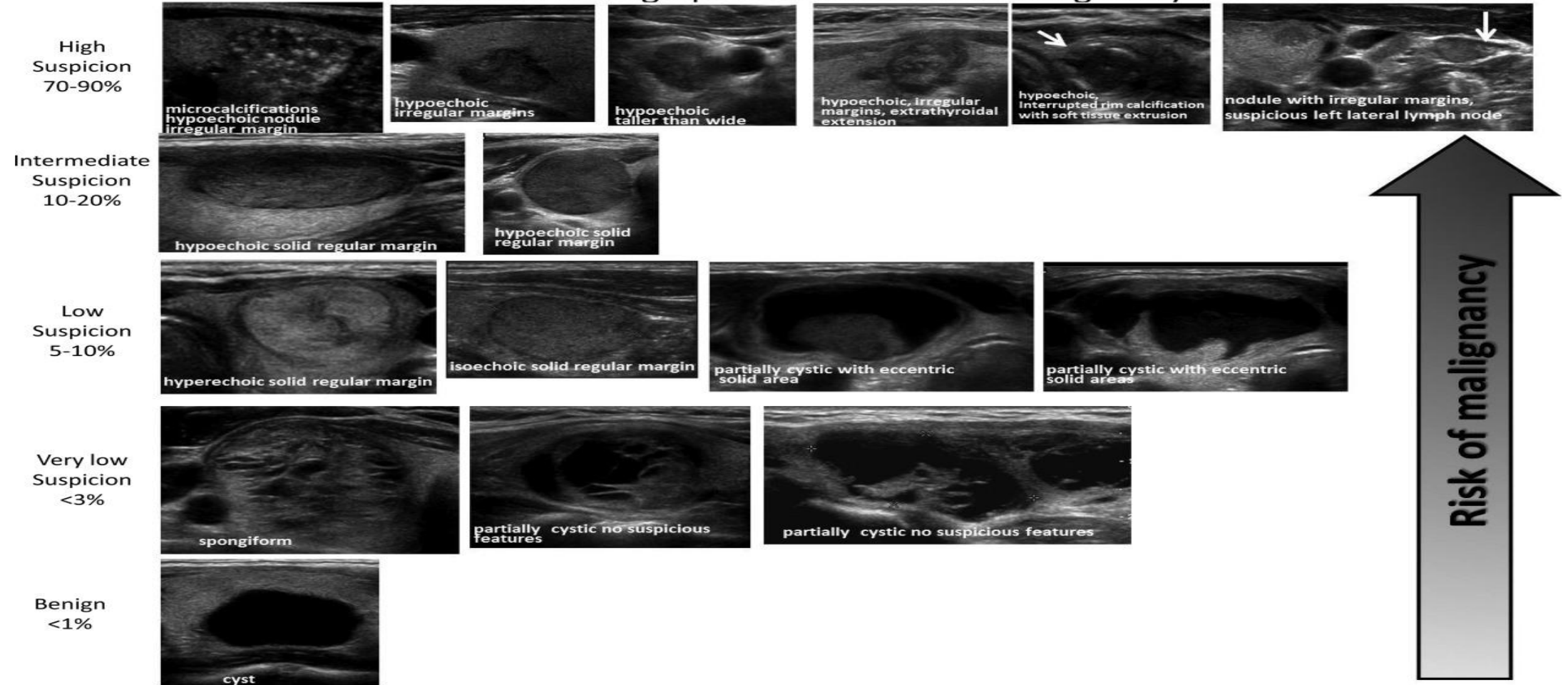
# How to risk stratify Thyroid Nodules

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- There are two major classification systems for thyroid nodules:
  - **ATA Classification** (American Thyroid Association)
  - **ACR TI-RADS** (American College of Radiology Thyroid Imaging Reporting and Data Systems)
- Endocrinologists for the most part use ATA classification.  
TIRADS is best for reporting nodules done by Radiologists.
  - TI-RADS concept is like BI-RADS for breast mammography.

# ATA Classification

ATA Nodule Sonographic Pattern Risk of Malignancy

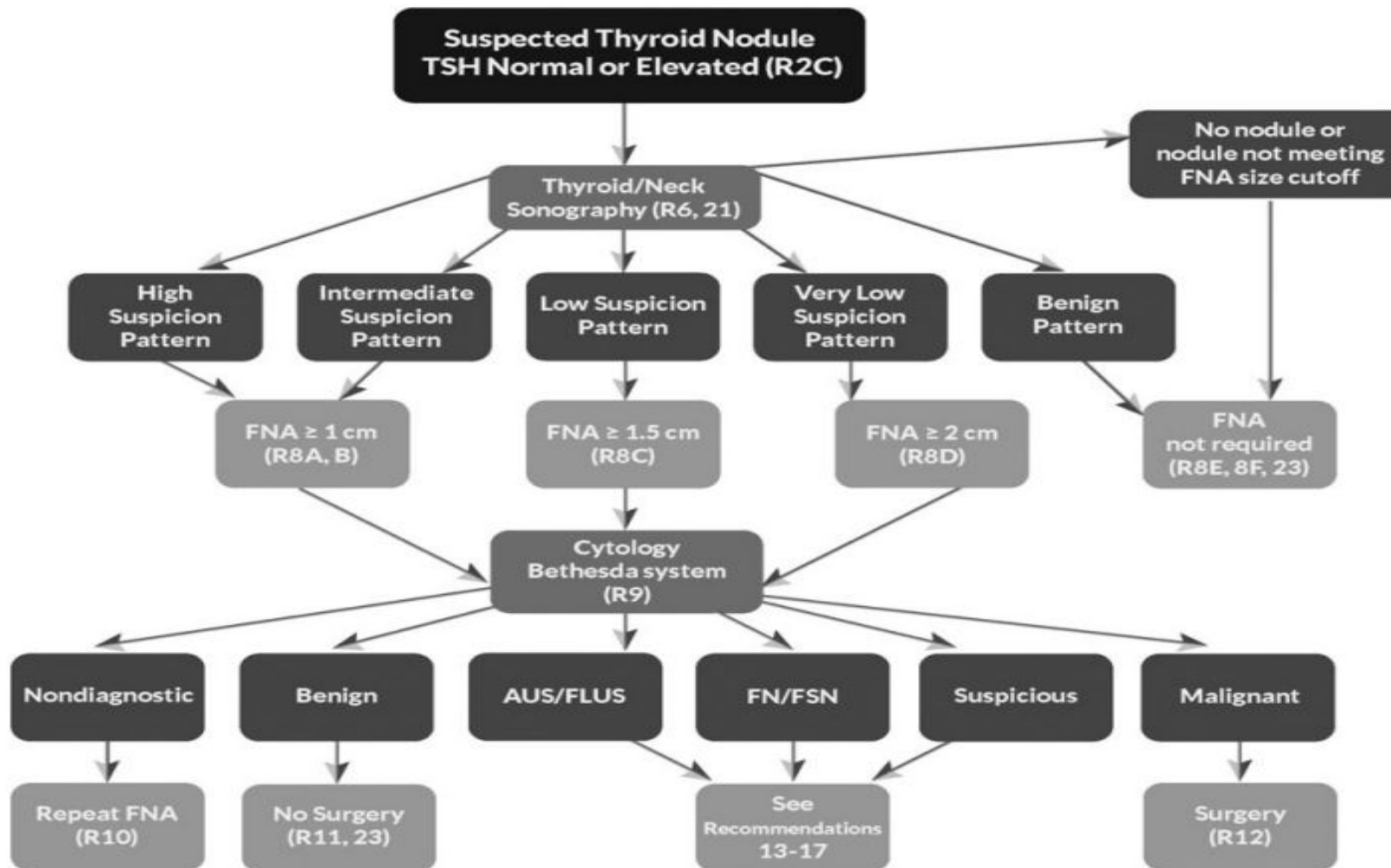


# ATA Classification

TABLE 6. SONOGRAPHIC PATTERNS, ESTIMATED RISK OF MALIGNANCY, AND FINE-NEEDLE ASPIRATION GUIDANCE FOR THYROID NODULES

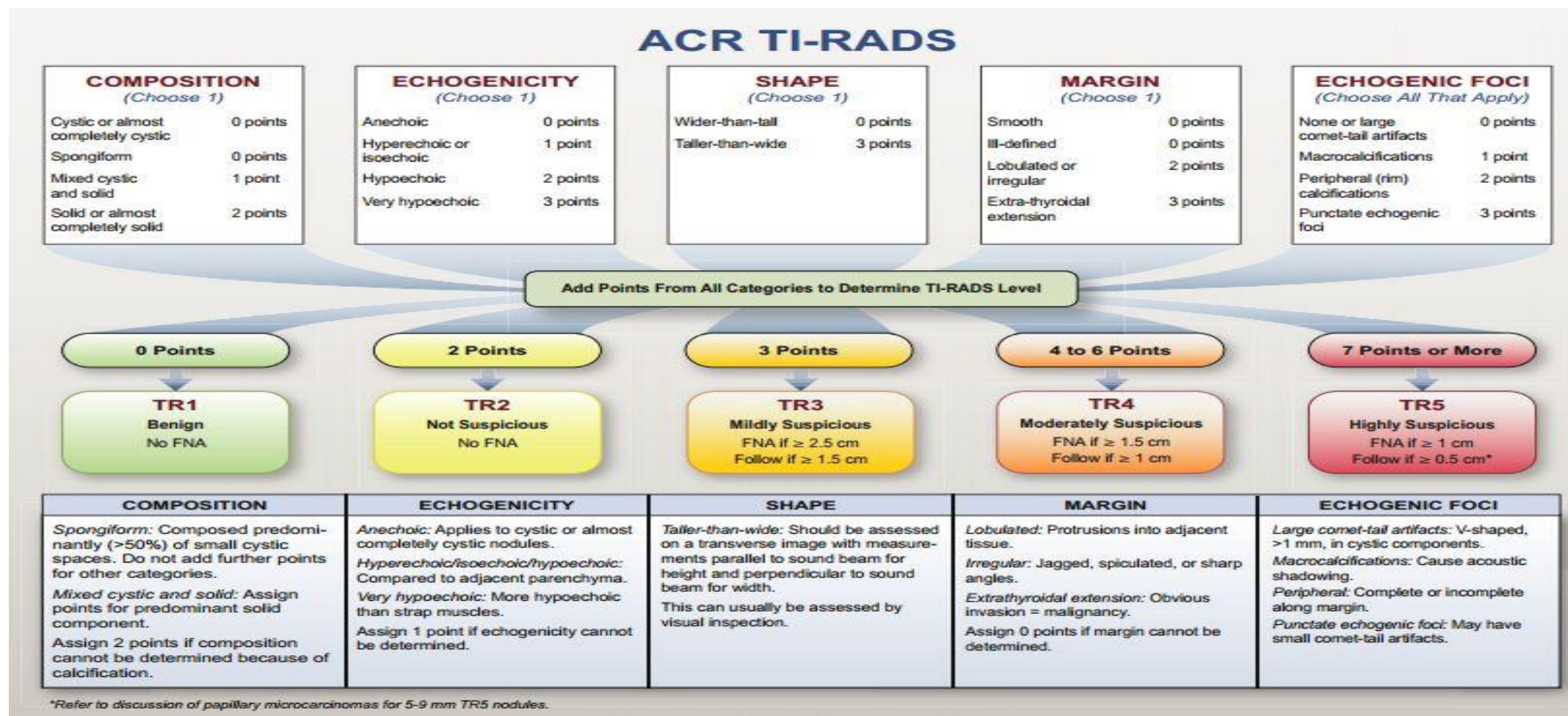
<i>Sonographic pattern</i>	<i>US features</i>	<i>Estimated risk of malignancy, %</i>	<i>FNA size cutoff (largest dimension)</i>
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule <b>with</b> one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of ETE	>70–90 <sup>a</sup>	Recommend FNA at $\geq 1$ cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins <b>without</b> microcalcifications, ETE, or taller than wide shape	10–20	Recommend FNA at $\geq 1$ cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, <b>without</b> microcalcification, irregular margin or ETE, or taller than wide shape.	5–10	Recommend FNA at $\geq 1.5$ cm
Very low suspicion	Spongiform or partially cystic nodules <b>without</b> any of the sonographic features described in low, intermediate, or high suspicion patterns	<3	Consider FNA at $\geq 2$ cm Observation without FNA is also a reasonable option
Benign	Purely cystic nodules (no solid component)	<1	No biopsy <sup>b</sup>

# Who Gets a Biopsy?





# ACR TI-RADS



**American Thyroid Association (ATA) 2016**

Pattern based

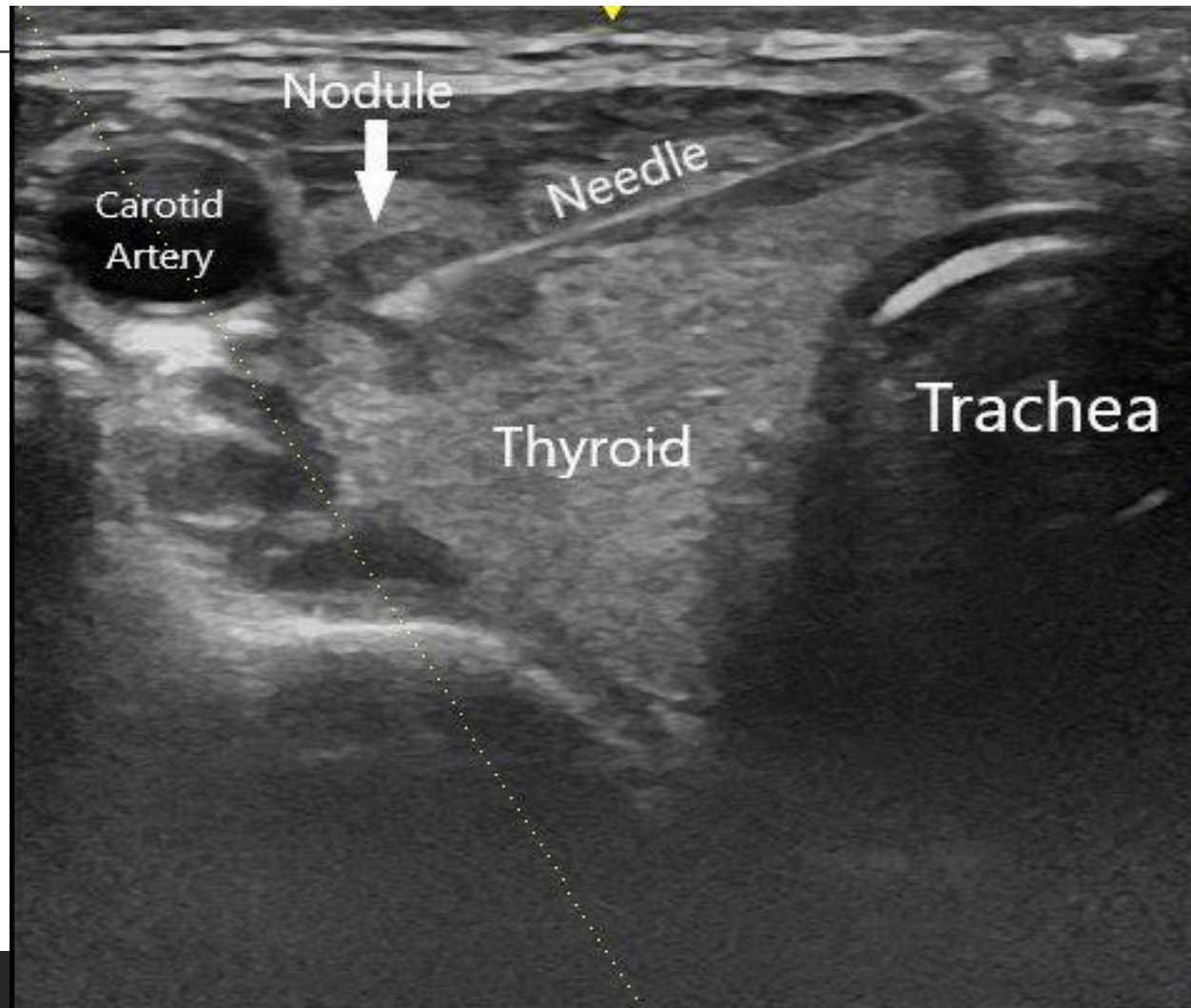
**American College of Radiology (ACR)**

Sum of points assigned to features

	Benign	No FNA	TR1 Benign	No FNA
	Very Low Suspicion	No FNA or $\geq 2\text{cm}$	TR2 Not Suspicious	No FNA
	Low Suspicion	$\geq 1.5\text{cm}$	TR3 Mildly Suspicious	$\geq 2.5\text{cm}$
	Intermediate Suspicion	$\geq 1\text{cm}$	TR4 Moderately Suspicious	$\geq 1.5\text{cm}$
	High Suspicion	$\geq 1\text{cm}^*$	TR5 Highly Suspicious	$\geq 1\text{cm}^*$

# Fine-Needle Aspiration (FNA)

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# Biopsy Results

Table 2. The 2023 Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy with Expected Ranges Based on Follow-Up of Surgically Resected Nodules with Recommended Clinical Management

Diagnostic category	ROM <sup>a</sup> Mean % (range)	Usual management <sup>b</sup>
Nondiagnostic	13 (5–20) <sup>c</sup>	Repeat FNA <sup>d</sup> with ultrasound guidance
Benign	4 (2–7) <sup>e</sup>	Clinical and ultrasound follow-up
Atypia of undetermined significance <sup>f</sup>	22 (13–30)	Repeat FNA, <sup>d</sup> molecular testing, diagnostic lobectomy, or surveillance
Follicular neoplasm <sup>g</sup>	30 (23–34)	Molecular testing, <sup>h</sup> diagnostic lobectomy
Suspicious for malignancy	74 (67–83)	Molecular testing, <sup>h</sup> lobectomy or near-total thyroidectomy <sup>i</sup>
Malignant	97 (97–100)	Lobectomy or near-total thyroidectomy <sup>i</sup>

- Bethesda classification used for thyroid nodules.
  - *Bethesda category 1*: Nondiagnostic
  - *Bethesda category 2*: Benign
  - Bethesda category 5-6: Suspicious for malignancy, malignancy
  - *Bethesda category 3-4*: Indeterminate area; usually send for genetic testing.



# Bethesda III & IV

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- Atypia of undetermined significance (Bethesda III) and suspicious for follicular neoplasm (Bethesda IV) are considered indeterminate thyroid nodules (ITN).
  - Occur in 20-25% of nodules
  - Cancer risk if 6-40%
- Send for genetic testing; Affirma<sup>®</sup> or Thyroseq<sup>®</sup>
  - These tests use the cells from the biopsy to determine if any molecular markers associated with cancer are present.
- Gives the likelihood of cancer. The goal is to prevent unnecessary surgery.
  - The past all ITNs went to surgery
- What to do with ~50% risk:
  - Discussion with patient and surgeon
  - Total/partial thyroidectomy or monitoring (must acknowledge they are aware of risks).



Molecular Test	Genomic sequencing classifier	Multigene genomic classifier	Multiplatform test
Trade Name	Afirma – GSC	ThyroSeq GC (v3)	ThyGeNEXT / ThyraMIR
What is tested?	<p>RNA-seq to assess gene expression with upstream mutation (BRAF v600E), 2 fusions (RET-PTC1/3)</p> <p>Xpression Atlas: 346 genes (761 variants), 130 fusions</p>	<p>NGS DNA and RNA 112 genes (12,135 variants) 120+ fusions Gene expression alterations (19 genes) Copy number alterations (10 chromosomal regions)</p>	<p>NGS DNA and RNA 10 genes 38 fusions 10 miRNAs</p>

## THE CHALLENGE



Indeterminate Diagnosis



Surgery Performed



**24%\***  
Malignant

**76%**  
Benign

Thyroid surgery  
is avoidable

## THE SOLUTION



Indeterminate Diagnosis



Thyroid FNA Analysis Performed *Without Surgery*



**~50%<sup>†</sup>**  
Benign



**~50%<sup>†</sup>**  
Suspicious



Surgery Performed



~40% of suspicious results will go on  
to be diagnosed as malignant\*

# Surgical + Medical Management

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- **Surgical Management:**

- Total thyroidectomy and neck dissection for Bethesda V & VI
- Hemithyroidectomy is discussed with surgeon

- **Medical Management:**

- Post-op treatment with thyroid replacement if total thyroidectomy done
- Monitor post-op calcium and PTH (potential for hypocalcemia)
- Patients with thyroid cancer:
  - Ultrasound
  - Follow up path to determine if RAI needed

- **Follow up recommendations for non-surgical patients:**

- Ultrasounds yearly; earlier based on your discretion.

# Thyroid Nodule Follow up

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- If classified as **ATA high risk** or **TR5**: Ultrasound surveillance recommended in 12 months.
- If classified **ATA low/intermediate** or **TR3/4**: Ultrasound surveillance recommended 12-24 months.
- If classified **ATA very low risk** or **TR2**: Indication for ultrasound surveillance is unknown.



**CASES**



# Case #1

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- **Case 1:**

- 76-year-old female
- Consult for incidentally noted thyroid nodules on CT.
- Dedicated US showed 3cm right nodule and several small cysts
- In-house US revealed nodule to the right.





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- **Classify Nodule:**

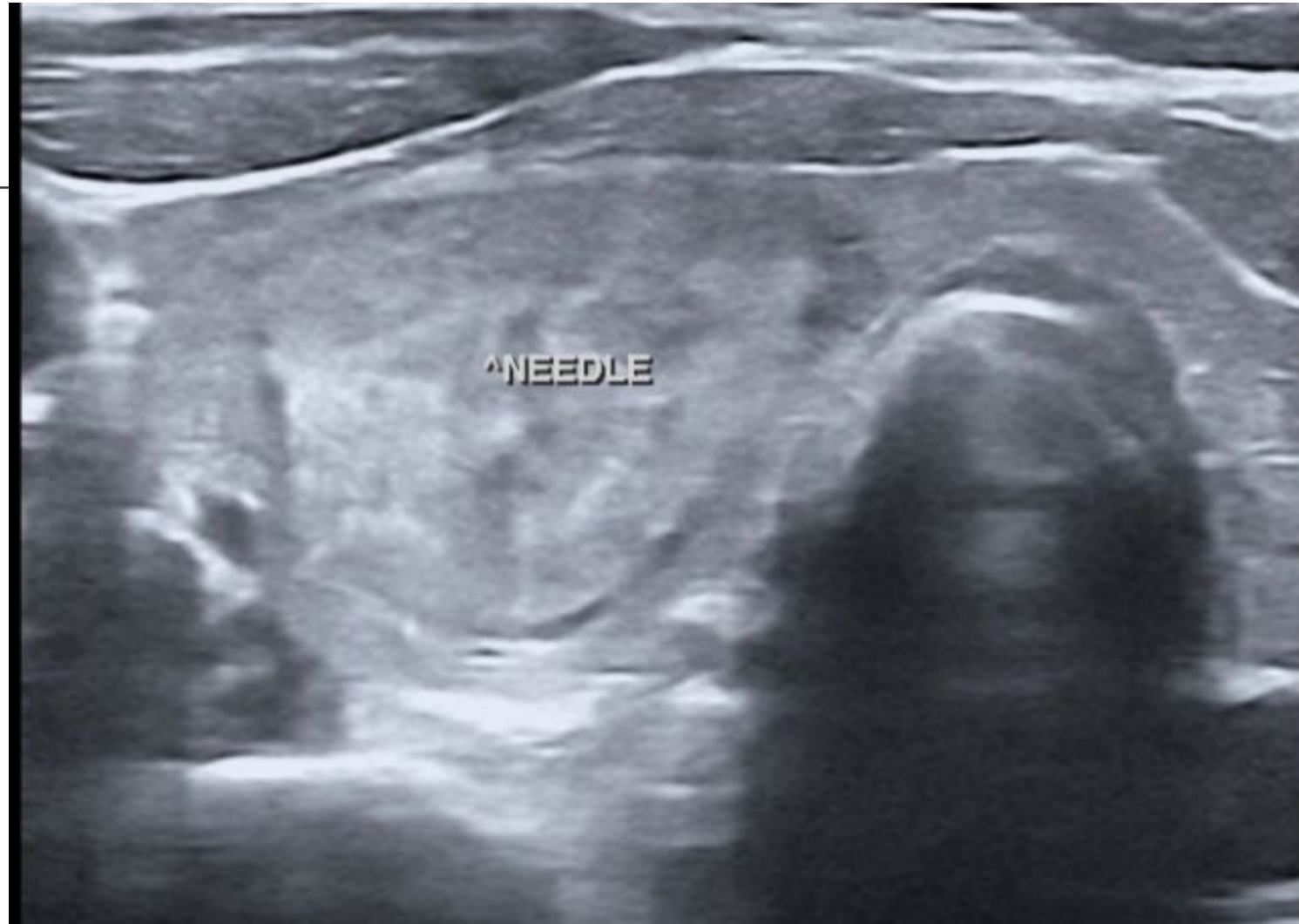
- Composition:
- Shape:
- Echogenicity:
- Margins:
- Calcification:
  
- ATA category:
- TIRADS:
- Do you biopsy?



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- **Classify Nodule:**

- Composition: solid, small cystic areas
  - Shape: round/wider-than-tall
  - Echogenicity: iso/hyperechoic
  - Margins: well-defined/smooth
  - Calcification: macrocalcification (see shadowing)
- 
- ATA category: Low-suspicion
  - TIRADS: TR3
  - Do you biopsy? Yes for both ATA ( $\geq 1.5\text{cm}$ ) & TIRADS ( $\geq 2.5\text{cm}$ )



# Final Path + Follow up

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RESULTS					
<b>Nodule:</b> <span style="border: 1px solid black; padding: 0 2px;">A</span> Thyroid, Right Side, 2.65 cm					
CYTOPATHOLOGY					
I Non Diagnostic	II Benign	III Atypia of Undetermined Significance	IV Suspicious for Follicular Neoplasm	V Suspicious for Malignancy	VI Malignant
<b>Cytopathology Diagnosis:</b> Benign (Bethesda Category II)					
<b>Diagnostic Comments:</b> The features are consistent with a benign hyperplastic/adenomatoid nodule.					
<b>Microscopic Description:</b> The cytologic and cell block preparations are moderately cellular and show groups of follicular cells, scattered lymphocytes and some colloid.					

- Follow up Recommendations? 1 year follow up Ultrasound.

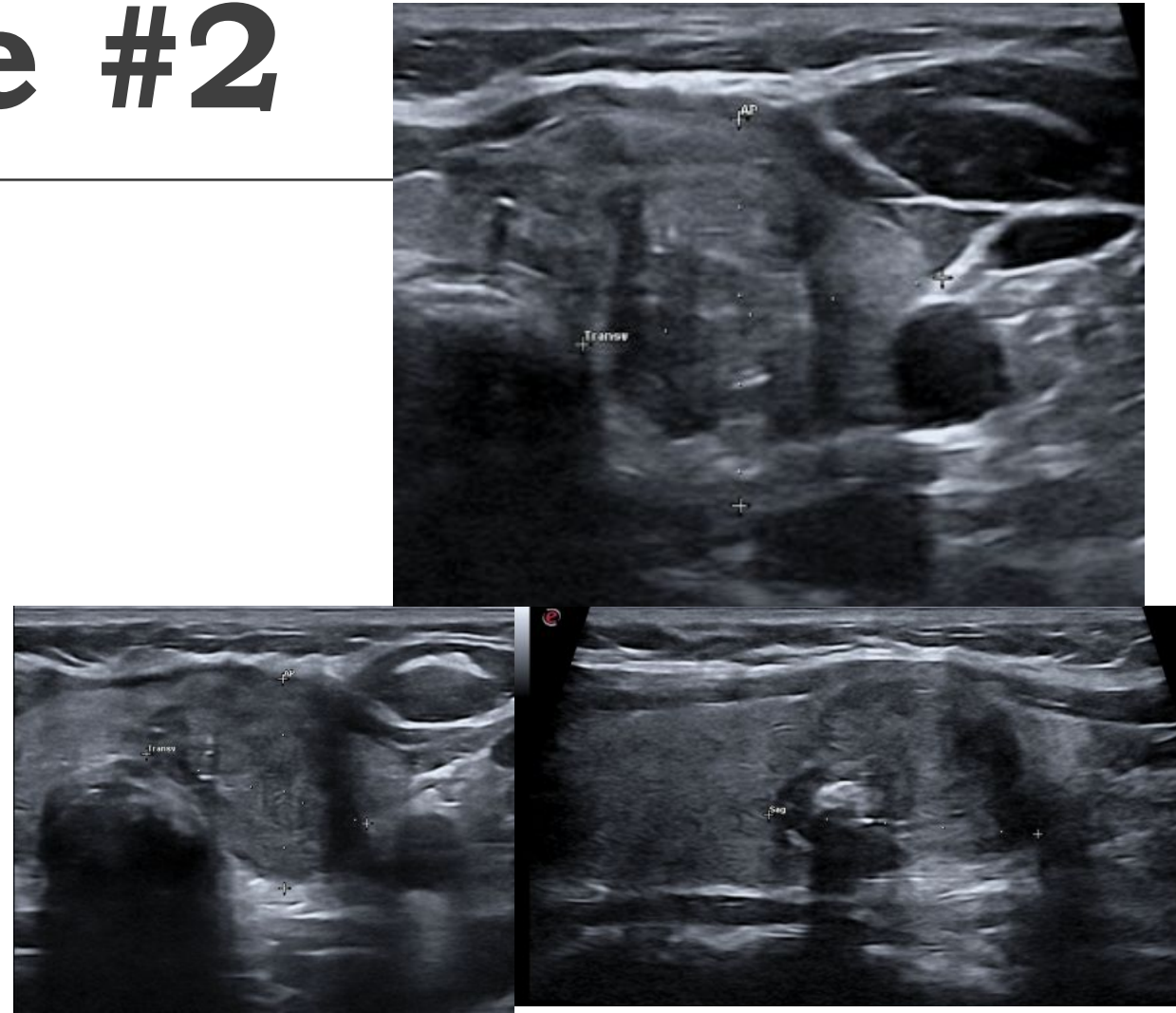


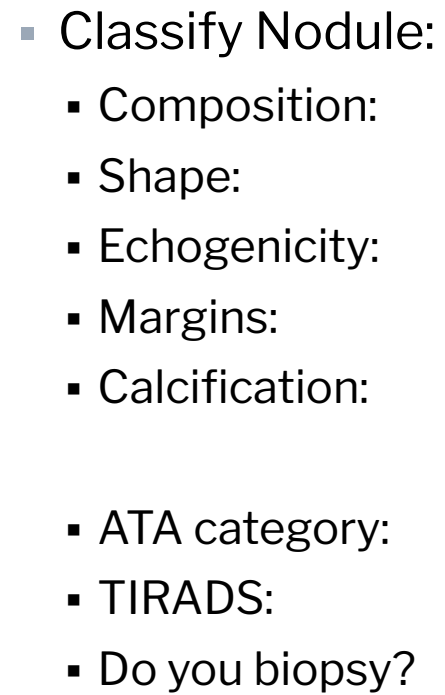
# Case #2

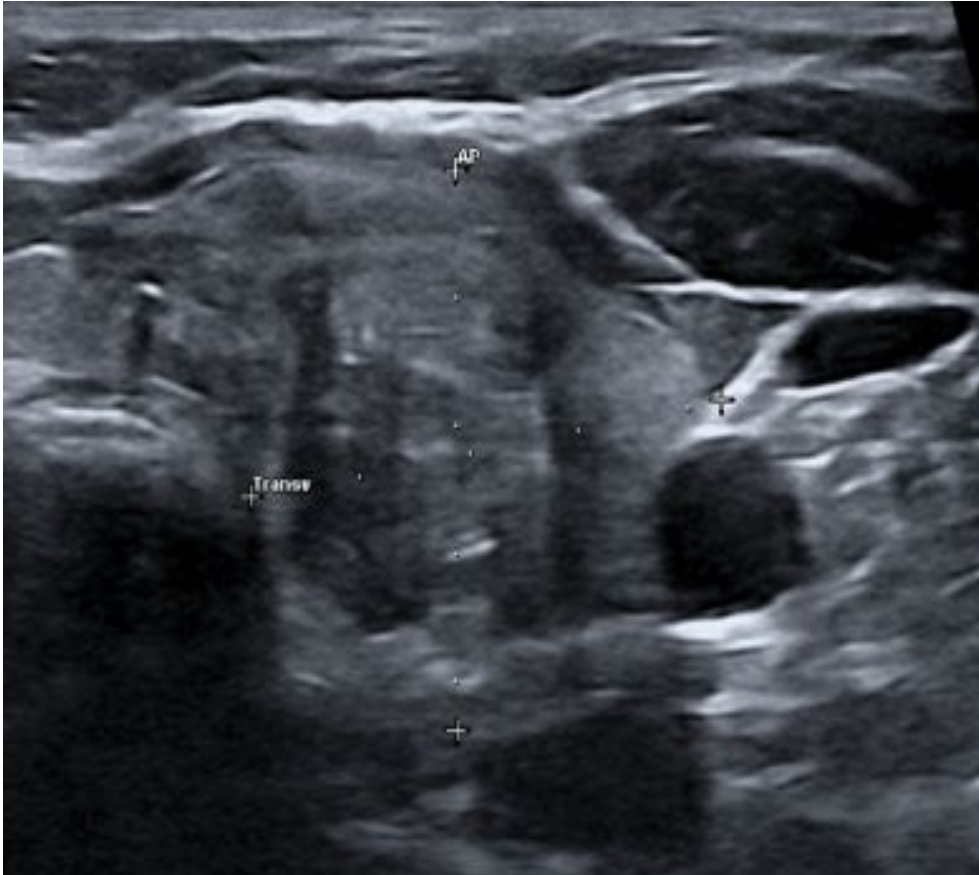
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## ■ Case 2:

- 37-year-old female
- Consult: Thyroid nodule palpated on examination. Ultrasound noted 2.2cm left nodule, hypoechoic with internal calcifications.
- In-house ultrasound showed 2.23cm left mid nodule. Seen on right.







- Classify Nodule:
  - Composition: Solid
  - Shape: Oval/Taller-than-wide
  - Echogenicity: Slightly hypoechoic
  - Margins: Defined/ halo
  - Calcification: Punctate echogenic foci
- ATA category: High suspicion
- TIRADS: TIRADS 5 (total 10 points)
- Do you biopsy? FNA ATA ( $\geq 1\text{cm}$ ) & TIRADS ( $\geq 1\text{cm}$ )

# Final Path + Follow up

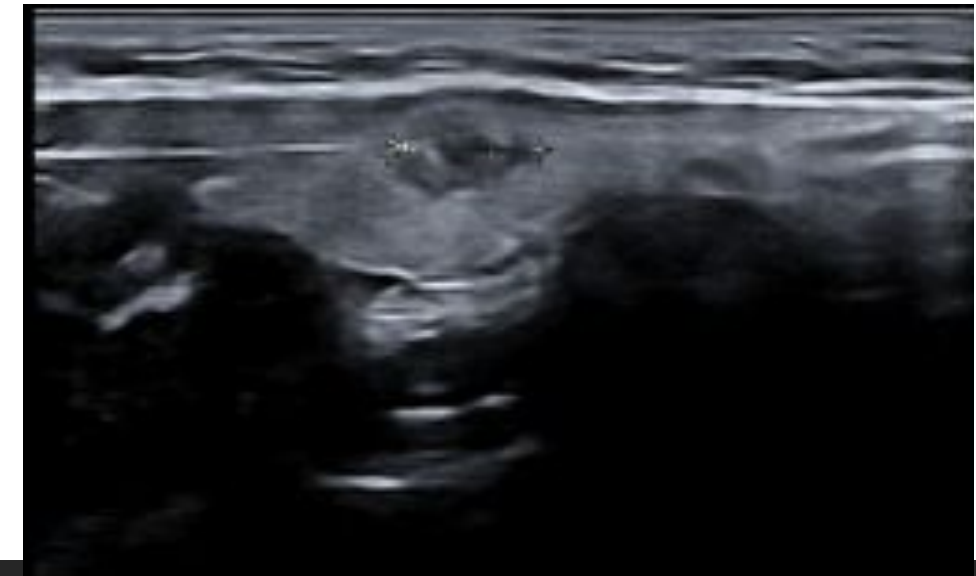
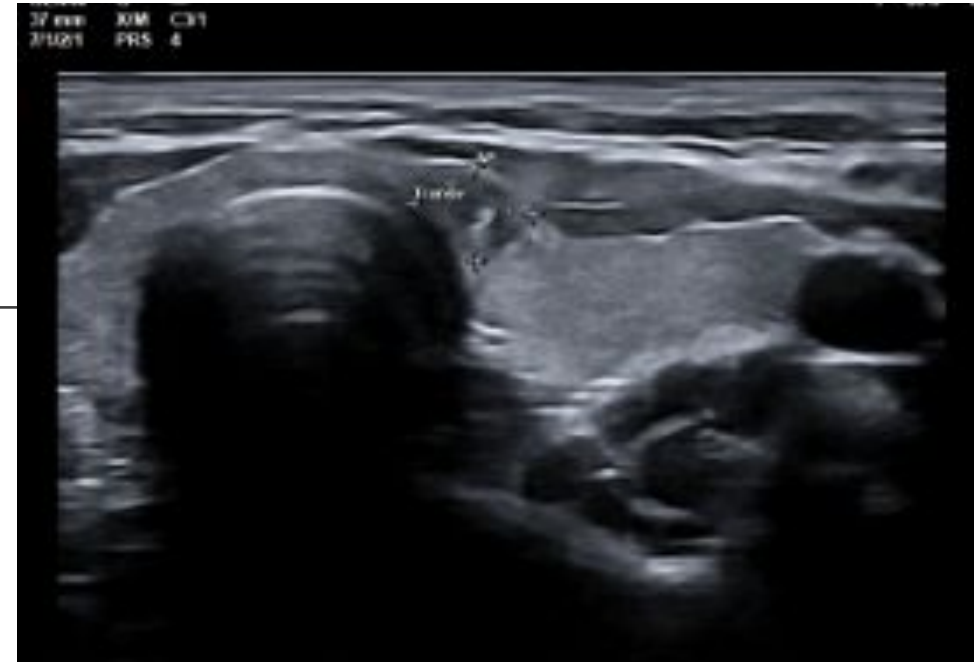
RESULTS					
Nodule: <b>A</b> Thyroid, Lower Left, 2.32 cm					
CYTOPATHOLOGY					
I Non Diagnostic	II Benign	III Atypia of Undetermined Significance	IV Suspicious for Follicular Neoplasm	V Suspicious for Malignancy	VI Malignant
<b>Cytopathology Diagnosis: Malignant</b> (Bethesda Category VI)					
<b>Diagnostic Comments:</b> The features are consistent with papillary carcinoma. ATA and AACE Guidelines recommend referral for surgical consultation.					
<b>Microscopic Description:</b> The cytologic and cell block preparations are moderately cellular, and contain sheets and groups of follicular cells with crowded, enlarged round to ovoid nuclei. The nuclei show pale chromatin and variable numbers of grooves, intranuclear inclusions and pinpoint nucleoli.					

- Follow up Recommendations? [Sending for total thyroidectomy.](#)

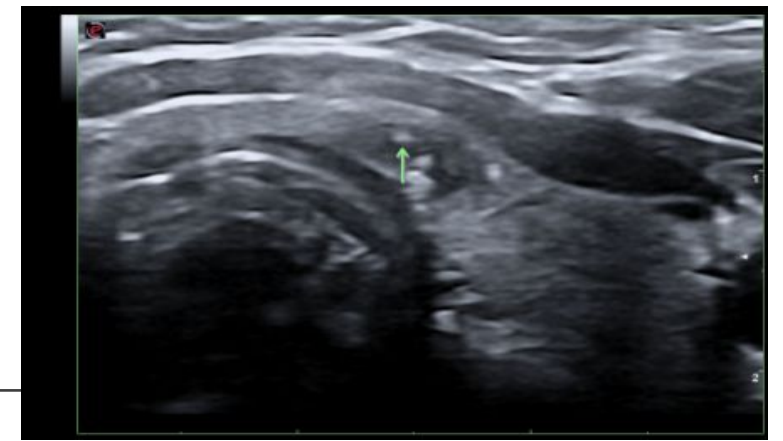
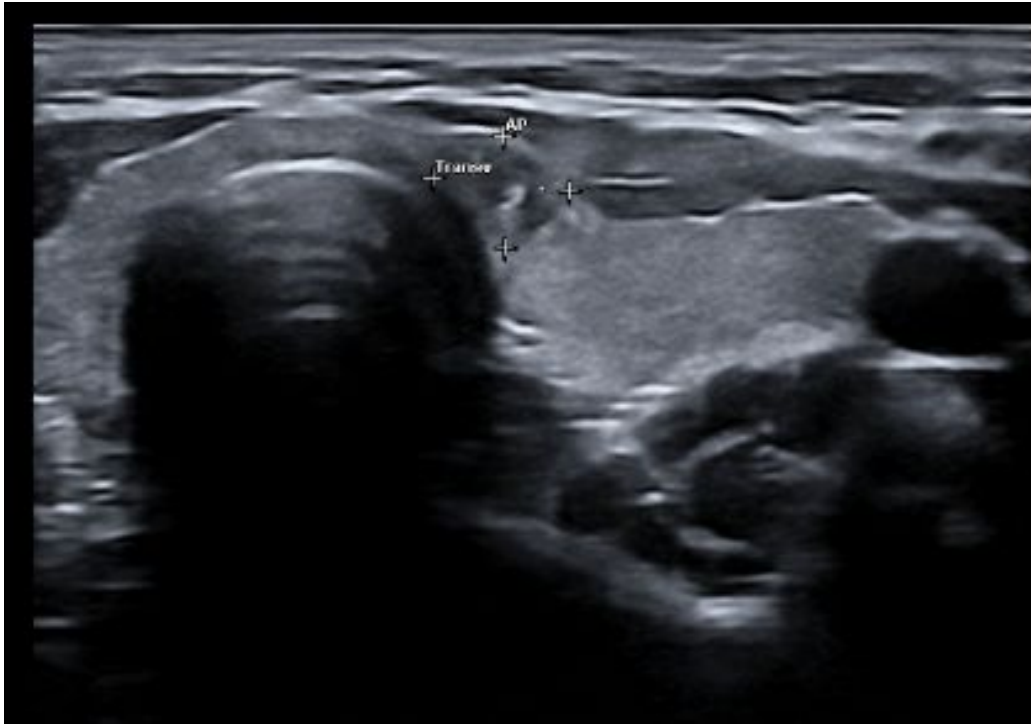
# Case

## ■ Case 3:

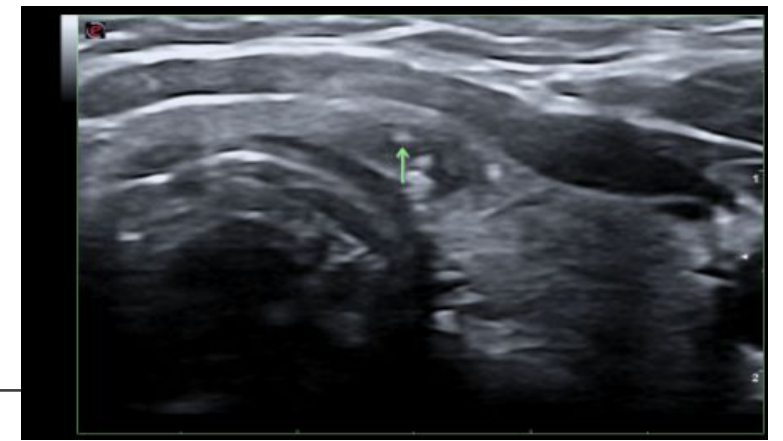
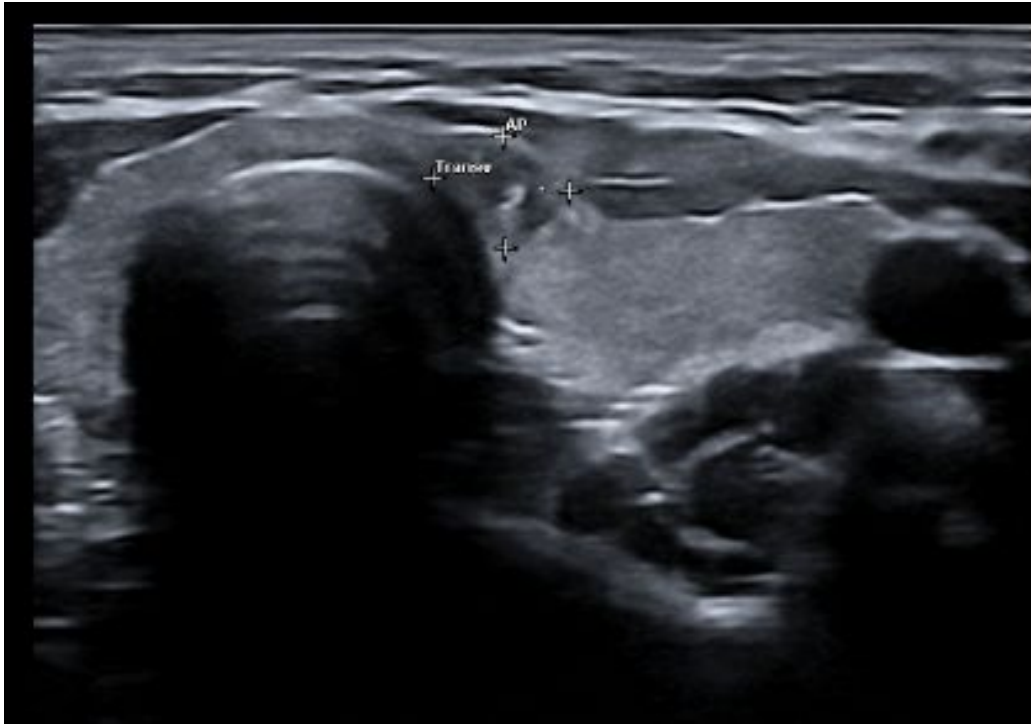
- 19-year-old female
- Consult: Hypothyroidism treated with Synthroid. Patient with ongoing symptoms of hypothyroidism.
- Exam noted fullness left thyroid.
- In-house ultrasound showed 0.52 x 0.63 x 0.74cm isthmus left nodule. Shown on the right.







- Classify Nodule:
  - Composition:
  - Shape:
  - Echogenicity:
  - Margins:
  - Calcification:
  
- ATA category:
- TIRADS:
- Do you biopsy?



- Classify Nodule:
  - Composition: Solid
  - Shape: Wider-than-tall (by the numbers)
  - Echogenicity: Hypoechoic
  - Margins: Well-defined
  - Calcification: Macrocalcifications
  
- ATA category: High suspicion
- TIRADS: TR4
- Do you biopsy? No. Not  $\geq 1\text{cm}$  (ATA) or  $\geq 1.5\text{cm}$  TIRADS

# Patient Discussion +Decision

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- *Discussion with patient:* Informed of high-risk features but technically does not meet FNA criteria.
- Ultimately recommended FNA.
  - ATA says biopsy suspicious nodule regardless of size).

# Final Path

RESULTS				
<b>Nodule:</b> <b>A</b> Thyroid, Isthmus, 0.74 cm				
CYTOPATHOLOGY				
<b>I</b> Non Diagnostic	<b>II</b> Benign	<b>III</b> Atypia of Undetermined Significance	<b>IV</b> Suspicious for Follicular Neoplasm	<b>V</b> Suspicious for Malignancy
<b>Cytopathology Diagnosis:</b> Indeterminate - Atypia of Undetermined Significance (AUS - Bethesda Category III)				
<b>Diagnostic Comments:</b> These features are best classified as atypia of undetermined significance, cannot exclude papillary thyroid carcinoma.				
<b>Microscopic Description:</b> The cytologic preparations are cellular and show a few clusters of follicular cells with scattered nuclear palor in crowded or microfollicular groups, preservation artifact and some colloid. Cell block is noncontributory.				
AFIRMA GENOMIC SEQUENCING CLASSIFIER*		AFIRMA XPRESSION ATLAS		
<b>Suspicious</b>		<b>BRAF p:V600E c.1799T&gt;A</b>		
<b>MTC:</b> Negative <b>Parathyroid:</b> Negative		<b>BRAF p. V600E c. 1799T&gt;A:</b> Positive <b>RET/PTC1, RET/PTC3:</b> Not Detected		
		<b>Clinical Relevance</b>	<b>Risk of Malignancy</b>	<b>Associated Neoplasm Type</b>
		Evidence of clinical significance in thyroid cancer	>95% <sup>11</sup>	PTC
		<b>FDA Approved Therapy<sup>2</sup></b> Only in Anaplastic Thyroid Carcinoma. See medication prescribing information for appropriate patient selection.		
<b>NODULE A RESULTS SUMMARY</b>				
<p>The result of this 0.74cm Bethesda III nodule A is Afirma GSC Suspicious and <b>BRAF p:V600E</b> positive which suggests a risk of cancer of &gt;95%<sup>11</sup>. This genomic alteration is associated with PTC and a BRAF V600E-like profile, which includes a higher rate of lymph node metastases and extrathyroidal extension than alterations that are RAS-like, or Non-BRAF-Non-RAS-like<sup>9, 10</sup>. Clinical correlation and surgical resection should be considered. Consider visiting <a href="http://clinicaltrials.gov">clinicaltrials.gov</a> to see if there are any available clinical trials relevant to the described molecular variant/fusion discovered on Afirma testing.</p> <p>*This Afirma result is outside indication (OI) due to sample being received with wrong cold brick. Performance characteristics have not been established for this OI condition. * This Afirma result is outside indication (OI) due to the nodule size being less than 1 cm; performance characteristics have not been established for this OI condition. * This Afirma result is outside indication (OI) due to the patient being less than 21 years of age; performance characteristics have not been established for this OI condition.</p>				

■ Follow up Recommendations?

# Management

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- S/p total thyroidectomy and neck dissection
- Final Pathology: Metastatic papillary thyroid cancer, tall cell variant
- Completed RAI 30mCi
- Post-treatment scan without metastatic disease noted.



*Thank You!*