APPROACH TO THYROID NODULES

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DISCLOSURES

- I have no conflicts of interest to disclose

CASE 1

- 33 y.o. female w/ PMH multinodular goiter who presents for initial visit for evaluation of goiter. She was previously evaluated for goiter in Albania. She was on an unknown medication for the thyroid that was stopped (she was told it might shrink the nodules). She underwent thyroid biopsy twice in Albania but does not recall which nodule was biopsied. She states the first biopsy was an inadequate sample due to bleeding, the second biopsy had some abnormal attributes and was Bethesda 3 (patient has records in Albanian and the Albanian interpreter is unable to interpret the medical language). She reports some difficulty swallowing due to the goiter, denies difficulty breathing due to goiter (has issues with breathing through her nose), no voice changes. No radiation exposure, no FH of thyroid cancer. Father had laryngeal cancer.
- What else would you like to know about her?
- What medication could she have been on?

INITIAL EVALUATION OF THYROID NODULES

- Is it functional?
  - Check TFT
- What does it feel like?
  - Physical Exam
- What does it look like?
  - Thyroid ultrasound

CASE 1

- What else would you like to know about her?
  - Thyroid function tests
- What medication could she have been on?
  - Levothyroxine aka Synthroid

OUTLINE

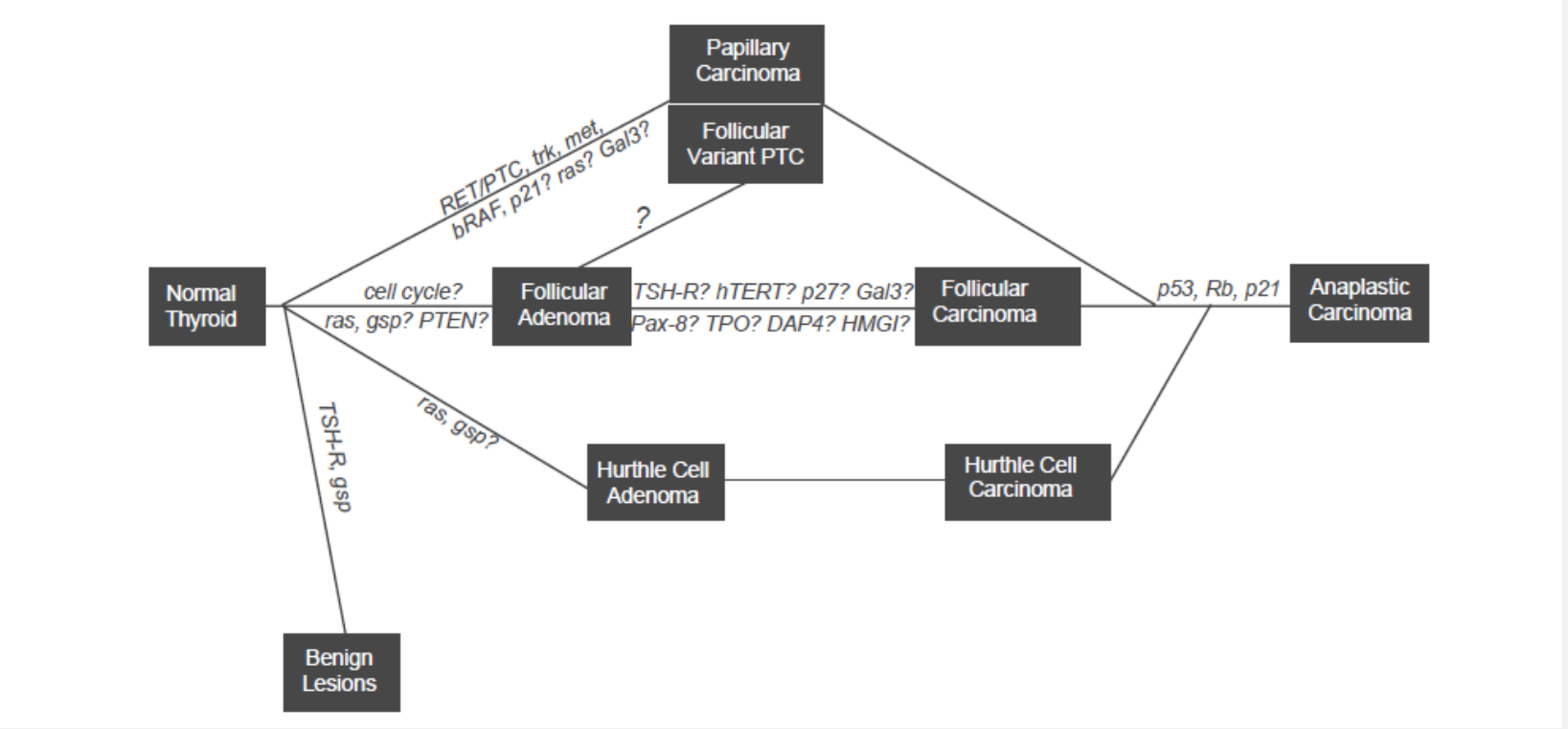
- EPIDEMIOLOGY
- CLINICAL EVALUATION
- LABORATORY TESTING
- IMAGING
- CYTOLOGY
- MOLECULAR TESTING
- MANAGEMENT

EPIDEMIOLOGY

- 68% of the general population, 5% by palpation
  - 65% with ultrasonography,
  - 15% with CT or MRI
  - 1% to 2% with ^{18}fluorodeoxyglucose PET
- Increases with age, female sex, and body mass index
- 10% malignant……55% if PET avid
  - Risk factors: childhood irradiation, exposure to ionizing radiation, family history of thyroid cancer or hereditary syndromes that include thyroid cancer (eg, MEN2, FAP) rapid nodule growth or hoarseness
  - Less well established/controversial-Obesity, metabolic syndrome, thyroid autoantibodies
- SCREENING???
  - No……common disease, low prevalence of cancer, excellent 10 year survival

PATHOGENESIS

- Sequential accumulation of alterations in the genes involved in the control of cell proliferation, differentiation or death
- A sequence of somatic mutational events leads to the clonal expansion of genetically modified cells that progressively show a selective growth advantage over normal non-transformed cells and acquire an invasive and metastatic potential



CLINICAL EVALUATION- WHAT DOES IT FEEL LIKE?

- Symptoms:
  - Globus sensation (sensation of a lump or foreign body in the throat)
  - Dysphagia or swallowing complaints (stasis, choking, odynophagia)
  - Dyspnea
  - Dysphonia or hoarseness
  - Pain (due to acute increase of nodule size)

- Physical examination of the thyroid
  - Size, consistency, lymph nodes
  - Firm, fixed, matted, or rapidly growing
  - Mostly normal!! Nodules are too small, too posterior or same consistency as the gland

LABORATORY TESTING- IS IT FUNCTIONAL?

- TSH, Free T4 (5% hyperfunction)
  - TSH low-thyroid uptake and scan
  - TSH high-thyroid antibodies
- TSH normal
- ?Thyroglobulin
- ?Calcitonin

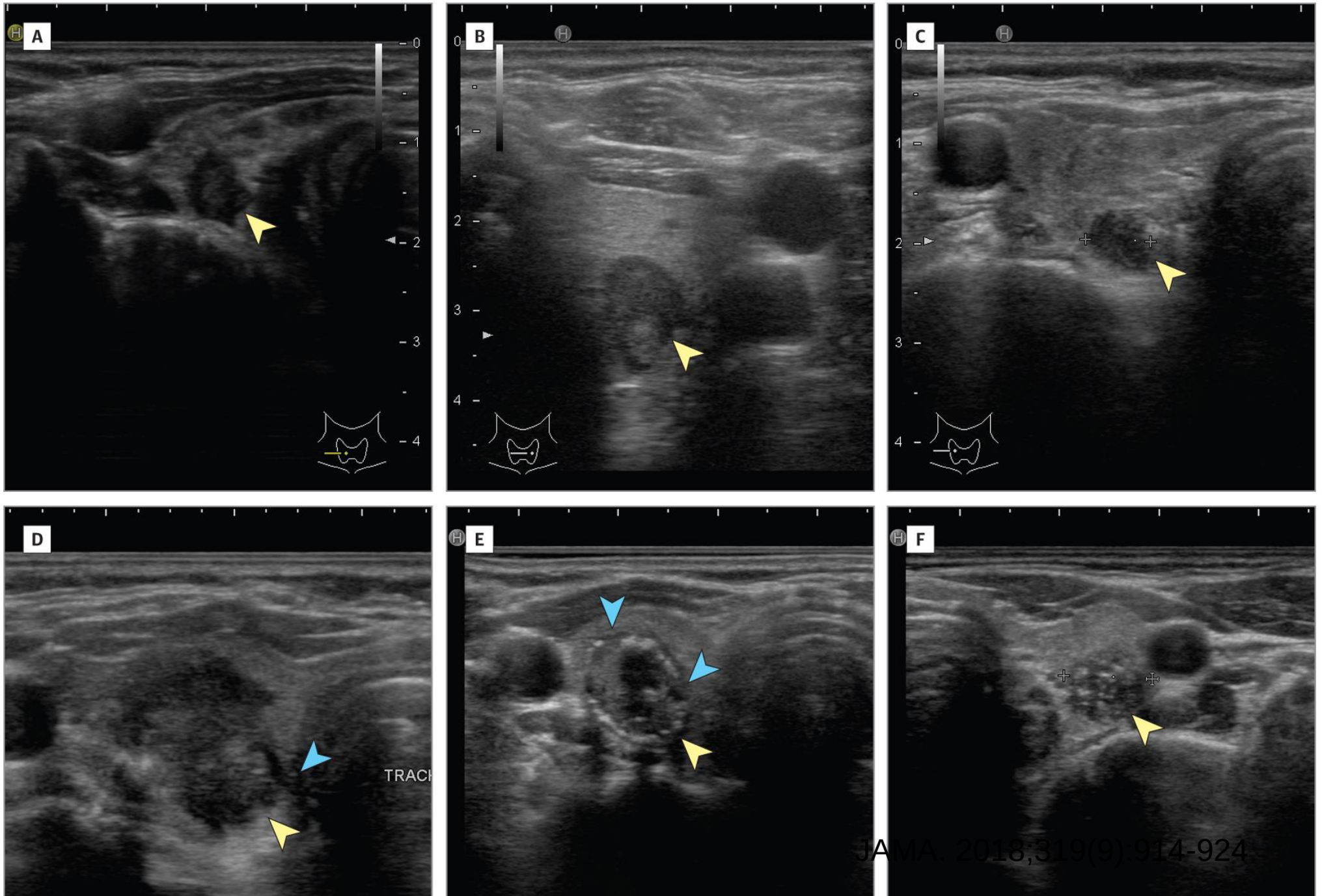
IMAGING-
WHAT DOES IT LOOK LIKE?

- TSH is normal
  - Do you need a thyroid ultrasound? Yes
    - When thyroid is palpably abnormal or a thyroid nodule is incidentally detected on another radiological study.
    - Nonspecific symptoms or abnormal laboratory test results are NOT indications for sonography.
  - Do you need an thyroid uptake and scan? No, only if TSH is low OR making a diagnosis of Graves disease or Thyroiditis

THYROID ULTRASOUND

- Best test!
- Highly sensitive
- Increased risk of malignancy-
  - solid
  - hypoechoic
  - intranodular flow
  - micro-calcification, interrupted rim calcification
  - irregular infiltrative borders
  - taller than wide
- Decreased risk of malignancy-
  - pure cysts
  - spongiform appearance
  - solid, regular borders with isoechoic or hyperechoic echogenicity

HIGH SUSPICION FEATURES ON THYROID US



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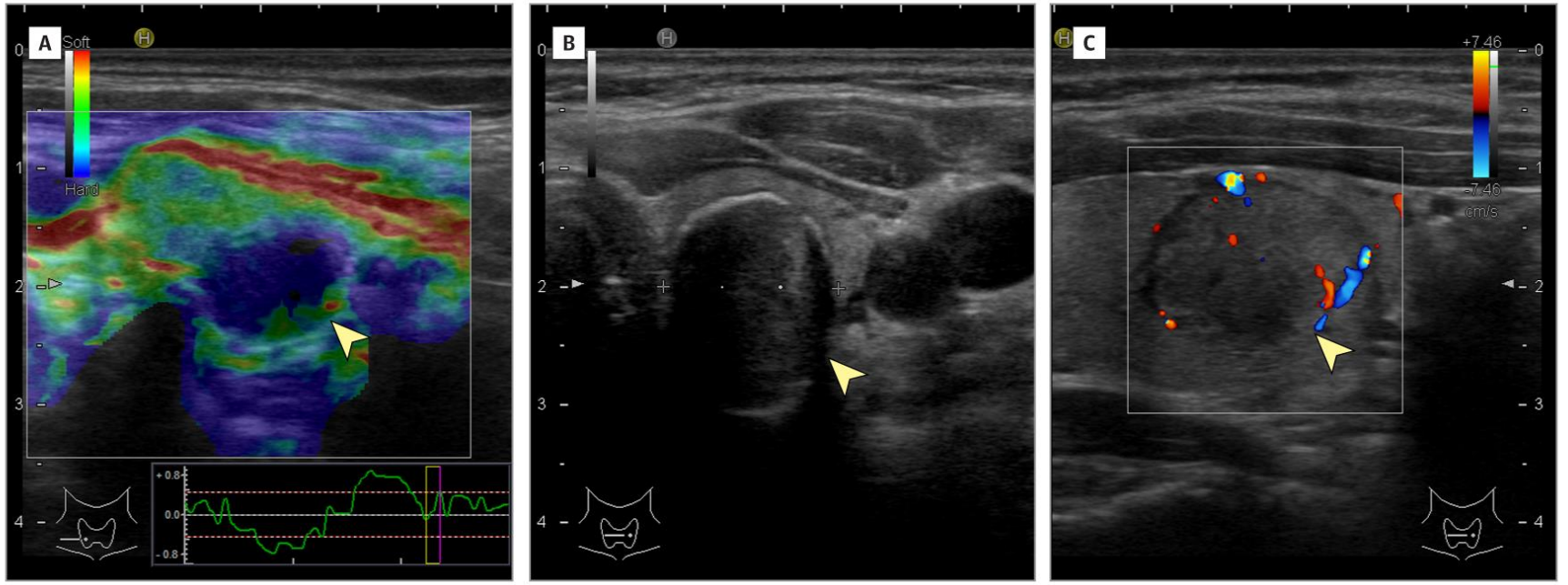
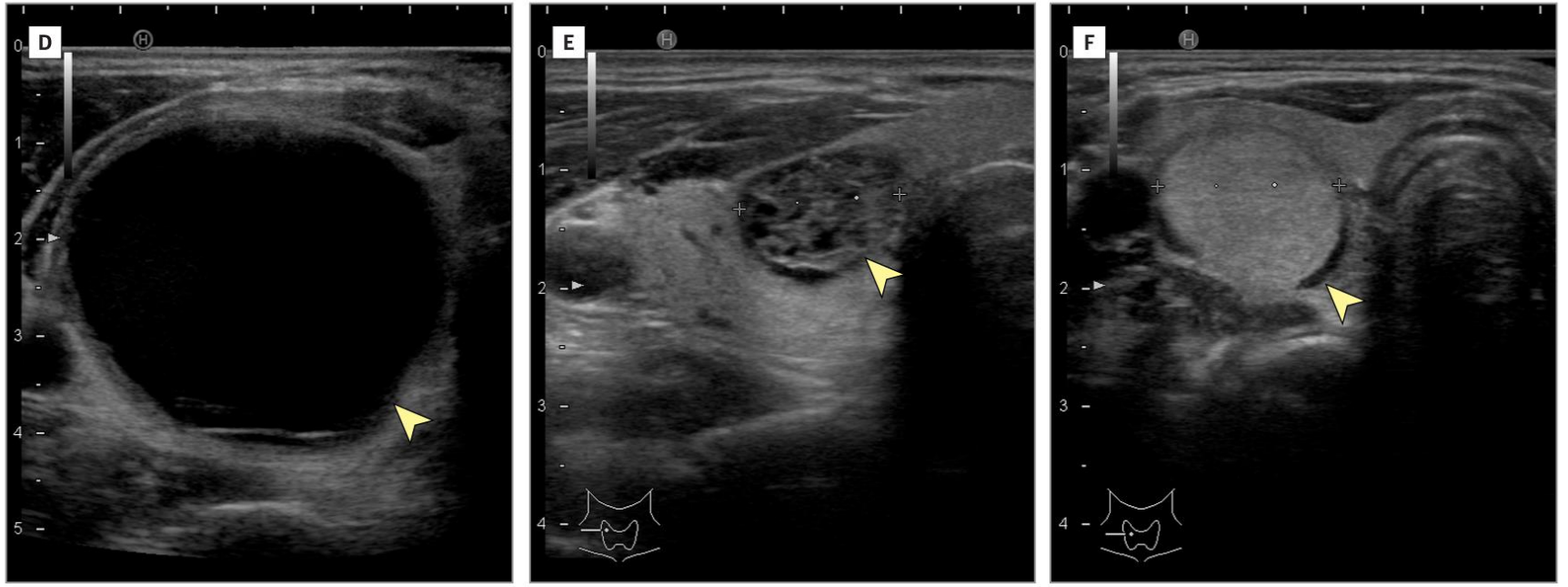
Imaging features of indeterminate thyroid nodules



Ultrasonographic features of low or very low suspicion thyroid nodules



EVALUATION OF THYROID NODULES BASED ON ATA GUIDELINES-WHEN TO BIOPSY?

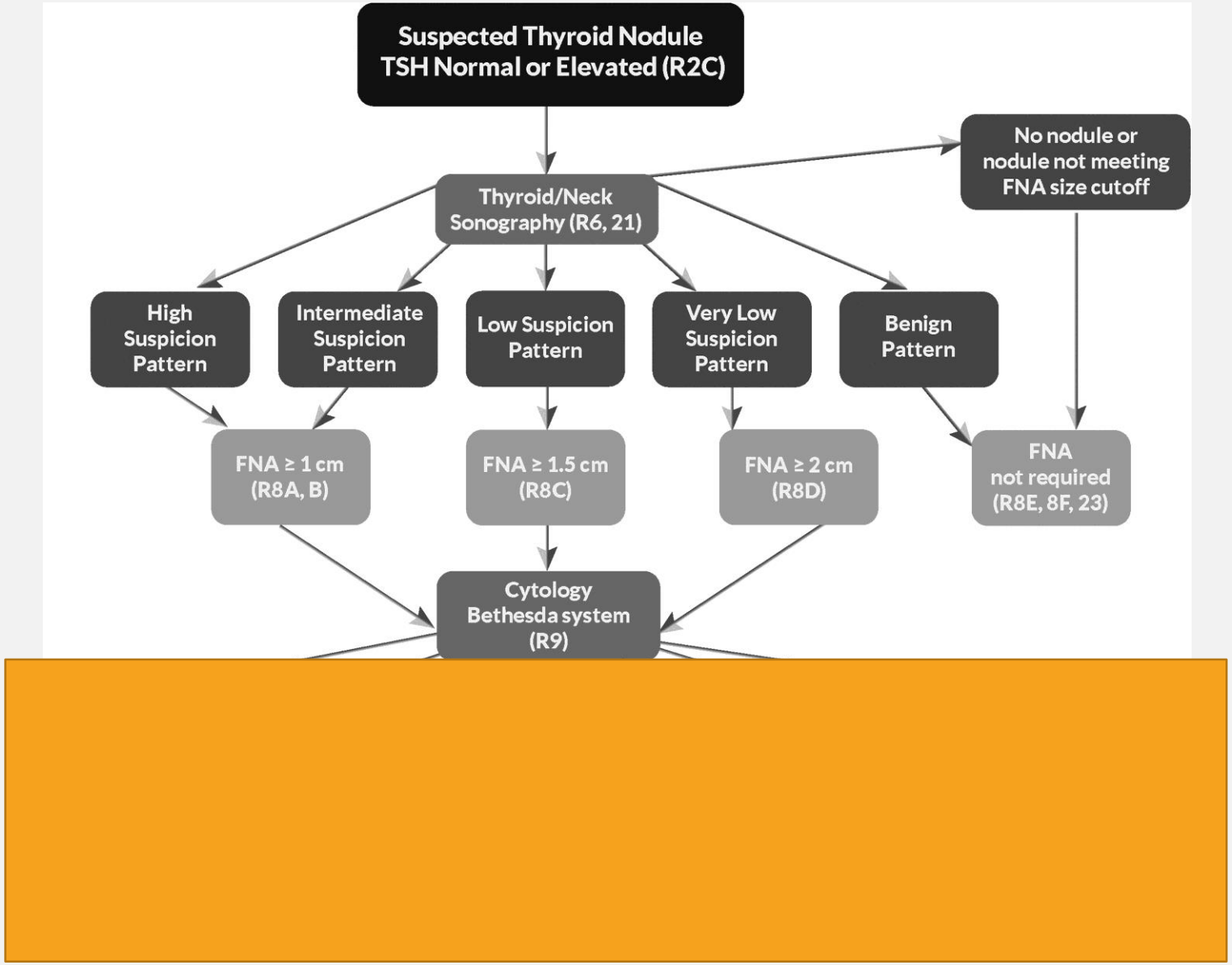


Table 1. Standardized Sonographic Scoring Systems Proposed or Endorsed by Practice Guidelines for Risk-Based Fine-Needle Aspiration Biopsy Guidance for Thyroid Nodules

AACE, ACE, and AME, 2016[22]	ATA, 2015[1]	EU-TIRADS, 2017[31]	ACR TIRADS, 2017[30]
Low-Risk and Benign Thyroid Nodules			
Low-risk definition Risk of malignancy, 1% FNAB >20 mm (selective)[a] **Sonographic pattern** Cysts (fluid component >80%) Mostly cystic nodules with reverberating artifacts and not associated with suspicious ultrasound signs Isoechoic spongiform nodules, either confluent or with regular halo	**Benign definition** Risk of malignancy, <1% FNAB is not indicated **Sonographic pattern** Purely cystic nodules (no solid component)	**Benign (EU-TIRADS 2) definition** Risk of malignancy, ≈0% FNAB is not indicated **Sonographic pattern** Pure, anechoic cysts; Entirely spongiform nodules	**Benign (TR1) definition** Risk of malignancy, 2% FNAB is not indicated **Sonographic pattern** Spongiform Pure cyst
			Not suspicious (TR2) definition Risk of malignancy, 2% FNAB is not indicated **Sonographic pattern** Mixed cystic/solid noncalcified nodules with smooth margins and oval shape
	Very low-suspicion definition Risk of malignancy, <3% FNAB ≥20 mm or observation **Sonographic pattern** Spongiform/partially cystic nodules without any ultrasound features defining low-, intermediate-, or high-suspicion patterns	**Low-risk (EU-TIRADS 3) definition** Risk of malignancy, 2%-4% FNAB >20 mm **Sonographic pattern** Oval shape, smooth margins, isoechoic or hyperechoic, without any feature of high risk	**Mildly suspicious (TR3) definition** Risk of malignancy, 5% FNAB ≥25 mm **Sonographic pattern** Isoechoic solid or hypoechoic cystic noncalcified nodules with smooth margins and oval shape
	Low suspicion definitions Risk of malignancy, 5%-10% FNAB ≥15 mm **Sonographic pattern** Isoechoic/hyperechoic solid or partially cystic nodule with eccentric solid area without microcalcifications, irregular margin, extrathyroidal extension, taller than wide shape		

Intermediate or Moderately Suspicious Thyroid Nodules			
Intermediate-risk definition Risk of malignancy, 5%-15% FNAB >20 mm **Sonographic pattern** Slightly hypoechoic (vs thyroid tissue) or isoechoic nodules, with ovoid-to-round shape, smooth or ill-defined margins May be present Intranodular vascularization Elevated stiffness at elastography Macro or continuous rim calcifications Indeterminate hyperechoic spots	**Intermediate-suspicion definition** Risk of malignancy, 10%-20% FNAB ≥10 mm **Sonographic pattern** Hypoechoic solid nodule with smooth margins without microcalcifications, extrathyroidal extension or taller than wide shape	**Intermediate-risk (EU-TIRADS 4) definition** Risk of malignancy, 6%-17% FNAB >15 mm **Sonographic pattern** Oval shape, smooth margins, mildly hypoechoic, without any feature of high risk	**Moderately suspicious (TR4) definition** Risk of malignancy, 5%-20% FNAB >15 mm **Sonographic patterns** Hypoechoic solid noncalcified nodules with oval shape and either smooth or irregular or lobulated margins Isoechoic solid or mixed noncalcified nodules with either nonparallel orientation (taller than wide), lobulated or irregular margins, or punctate echogenic foci
High-Risk or Suspicious Thyroid Nodules			
High-risk definition Risk of malignancy, 50%-90%[b] FNAB ≥10 mm (5 mm, selective)[c] **Sonographic patterns** Nodules with ≥ 1 of the following: Marked hypoechogenicity (vs prethyroid muscles) Spiculated or lobulated margins Microcalcifications Taller-than-wide shape Extrathyroidal growth Pathologic adenopathy	**High-suspicion definiton** Risk of malignancy, >70%-90% FNAB ≥10 mm **Sonographic pattern** Solid hypoechoic nodule or solid hypoechoic component of partially cystic nodule with ≥1 of the following: Irregular margins (infiltrative, microlobulated) Microcalcifications Taller than wide shape Rim calcifications with small extrusive soft tissue Extrathyroidal extension	**High-risk (EU-TIRADS 5) definition** Risk of malignancy, 26%-87% FNAB >10 mm **Sonographic pattern** Nodules with ≥ 1 of the following: Nonoval shape Irregular margins Microcalcifications Marked hypoechogenicity	**Suspicious (TR5) definition** Risk of malignancy, ≥20% FNAB >10 mm **Sonographic pattern** Hypoechoic solid nodule with any of the following Nonparallel orientation (taller than wide) Extrathyroidal extension Punctate echogenic foci Isoechoic solid nodule with irregular or lobulated margins and either peripheral rim calcifications or punctate echogenic foci

THYROID FINE NEEDLE ASPIRATION

- Simple, safe, bedside procedure
- Endocrinologists or radiologists
- Complications are rare-bleeding, infection, pain
- Ultrasound guided

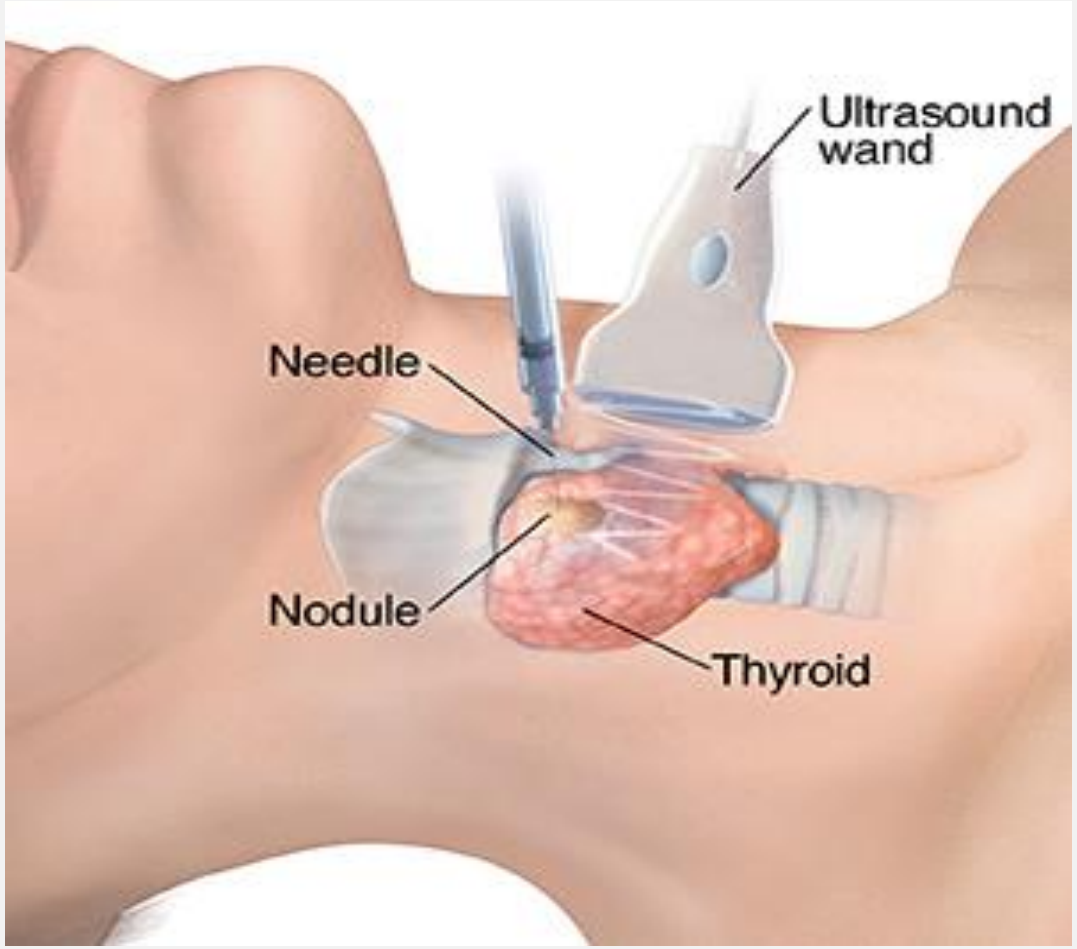


Table 2. The Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy and Recommended Clinical Management

Diagnostic Category	Risk of Malignancy, %	Usual Management[a]
Category 1: Nondiagnostic or Unsatisfactory		
Cyst fluid only Virtually acellular specimen Obscuring blood, artifacts	0-5[b]	Repeat FNAB with ultrasound guidance
Category 2: Benign		
Benign follicular nodule (eg, adenomatoid nodule, colloid nodule) Chronic lymphocytic (Hashimoto) thyroiditis Granulomatous (subacute) thyroiditis	0-3[c]	Clinical and sonographic follow-up[c]
Category 3: Atypia of Undetermined significance or Follicular Lesion of Undetermined Significance		
Focal nuclear atypia Predominance of Hurthle cells Microfollicular pattern in a hypocellular specimen	≈10-30[d]	Repeat FNAB, molecular testing, or lobectomy
Category 4: Follicular Neoplasm or Suspicious for a Follicular Neoplasm[f]		
Crowded and overlapping follicular cells some or most of which are arranged as microfollicles	25-40[e]	Molecular testing, lobectomy
Category 5: Suspicious for Malignancy		
Suspicious for papillary thyroid carcinoma Suspicious for medullary thyroid carcinoma Suspicious for metastatic carcinoma Suspicious for lymphoma	50-75	Near total thyroidectomy or lobectomy[g,h]
Category 6: Malignant		
Papillary thyroid carcinoma Poorly differentiated carcinoma Medullary thyroid carcinoma Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma Carcinoma with mixed features (to be described)	97-99	Near total thyroidectomy[h,i]

MOLECULAR TESTING

- *Genes in MAPkinase pathway*
  - *BRAF* gene (V600E) is found in approximately 40% of papillary thyroid cancers, as well as in some poorly differentiated (33%) and anaplastic cancers (45%)
  - *RAS* gene family are found in some papillary cancers (13%, generally the encapsulated follicular variant), follicular thyroid cancers (40%-50%), benign follicular adenomas (20%-40%),[54] as well as in NIFTP (30%).
  - *RET/PTC* oncogene Radiation induced ca and *PAX8/PPARG Follicular ca*
  - *TERT and TP53 Anaplastic carcinoma*
- Thyroseq : Mutational analysis/gene sequencing approach-rule in test.
  - NPV 91-94% PPV 94%
  - Sensitivity ThyroSeq v3 (92%) and Afirma GSC (91%)
- AFFIRMA gene expression analysis or gene expression classifier (GEC), 142 genes, rule out test
  - NPV 95% PPV 95%

MANAGEMENT:NON-OPERATIVE

- 90% of detected nodules are clinically insignificant
- The risk of malignancy based on the sonographic pattern guides FNA and also follow up

ATA GUIDELINES FOR FOLLOW UP

- **Recommendations for initial follow-up of nodules with benign FNA cytology**
- (A) Nodules with high suspicion US pattern: repeat US and US-guided FNA within 12 months.
- **(Strong recommendation, Moderate-quality evidence)**
- (B) Nodules with low to intermediate suspicion US pattern: repeat US at 12–24 months. If sonographic evidence of growth (20% increase in at least two nodule dimensions with a minimal increase of 2 mm or more than a 50% change in volume) or development of new suspicious sonographic features, the FNA could be repeated or observation continued with repeat US, with repeat FNA in case of continued growth.
- **(Weak recommendation, Low-quality evidence)**
- (C) Nodules with very low suspicion US pattern (including spongiform nodules): the utility of surveillance US is limited. If US is repeated, it should be done at ≥24 months.
- **(Weak recommendation, Low-quality evidence)**
- **Recommendation for follow-up of nodules with two benign FNA cytology results**
- (D) If a nodule has undergone repeat US-guided FNA with a second benign cytology result, US surveillance for this nodule for continued risk of malignancy is no longer indicated.
- **(Strong recommendation, Moderate-quality evidence)**

FOLLOW-UP FOR NODULES THAT DO NOT MEET FNA CRITERIA

- (A) Nodules with high suspicion US pattern: repeat US in 6–12 months.
- **(Weak recommendation, Low-quality evidence)**
- (B) Nodules with low to intermediate suspicion US pattern: consider repeat US at 12–24 months.
- **(Weak recommendation, Low-quality evidence)**
- (C) Nodules >1 cm with very low suspicion US pattern (including spongiform nodules) and pure cyst: the utility and time interval of surveillance US for risk of malignancy is not known. If US is repeated, it should be at ≥24 months.
- **(No recommendation, Insufficient evidence)**
- (D) Nodules ≤1 cm with very low suspicion US pattern (including spongiform nodules) and pure cysts do not require routine sonographic follow-up.
- **(Weak recommendation, Low-quality evidence)**

MANAGEMENT-SURGICAL

- Lobectomy, Total thyroidectomy +/- Lymph node dissection
- Complications of surgery
  - Hypocalcemia (8%)
  - Recurrent laryngeal nerve damage (2.5%)
  - Hemorrhage

MANAGEMENT-SURGICAL

- Bethesda classes 3 and 4: Indeterminate: Thyroid lobectomy followed by completion thyroidectomy if needed
- Bethesda classes 5 and 6-Thyroidectomy +/- lymph node dissection

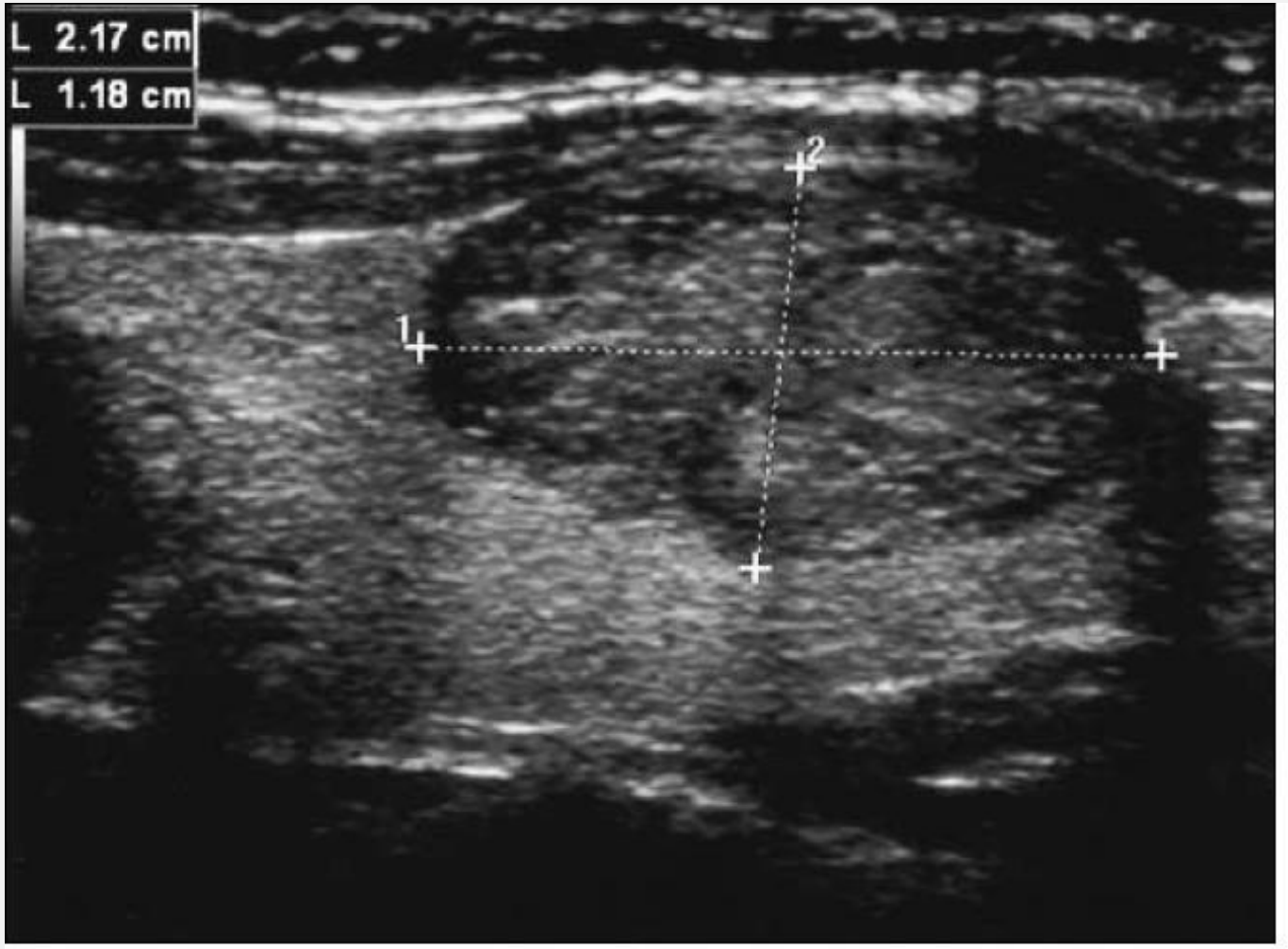
MANAGEMENT: ALTERNATIVE TO SURGERY

- percutaneous ethanol ablation
- radiofrequency, laser, microwave ablation, and
- high-intensity focused ultrasound
- Radioactive iodine therapy

CASE 2

- 42 y/o woman with obesity and prediabetes presented to the primary care clinic with URI symptoms. She takes no medications. She complains of pain in her throat and hoarseness of voice. She also states that sometimes she has difficulty swallowing. You examine her and feel that there is a lump in her neck. You reassure her that pain in her throat will improve. You decide to get TFT's and a neck ultrasound.
- TSH is 1.2

CASE 2 IMAGE

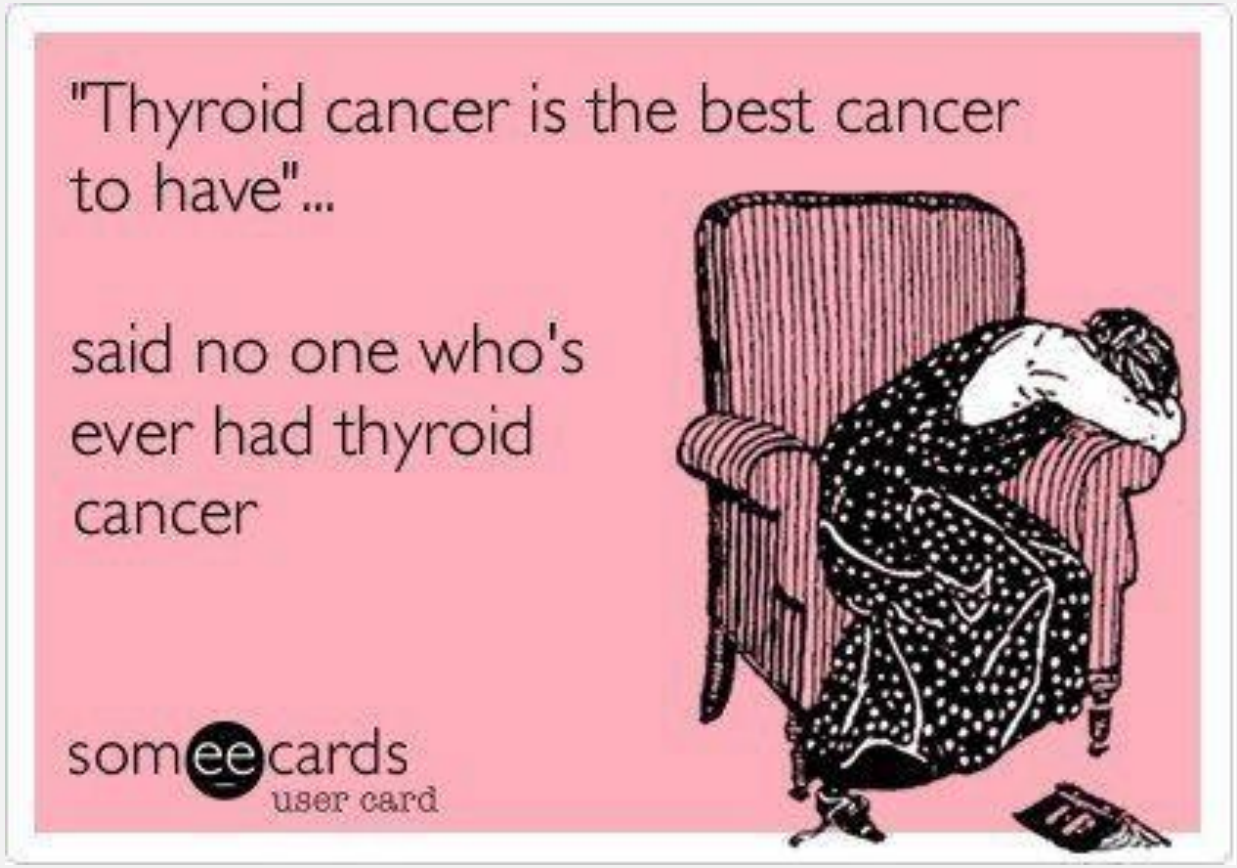


>2cm
Hypoechoic
Microcalcification

CASE 2 QUESTION

- A) Repeat US in 1 year
- B) Thyroid uptake and scan to determine if the nodule is cold
- C) Thyroid FNA
- D) Referral to ENT

QUESTIONS?


"Thyroid cancer is the best cancer to have"...
said no one who's ever had thyroid cancer
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