



What is the Evidence Behind The Ultrasound Systems?

Rachel Pessah-Pollack, MD, FACE

Assistant Clinical Professor of Medicine
Mount Sinai School of Medicine, New York

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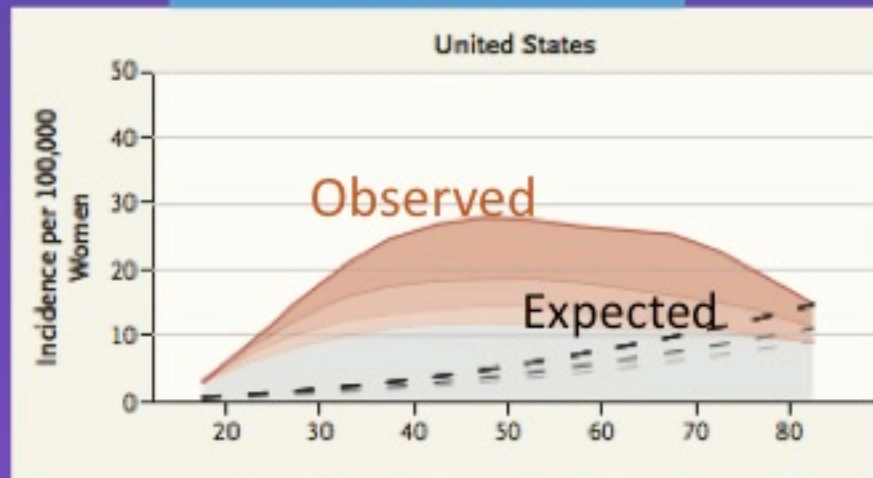
Objectives

- 1. Discuss major thyroid ultrasound classification systems and indications for biopsy
- 2. Recognize the limitations to the evidence behind US systems
- 3. Highlight future directions: AACE/AME Guideline Update and App

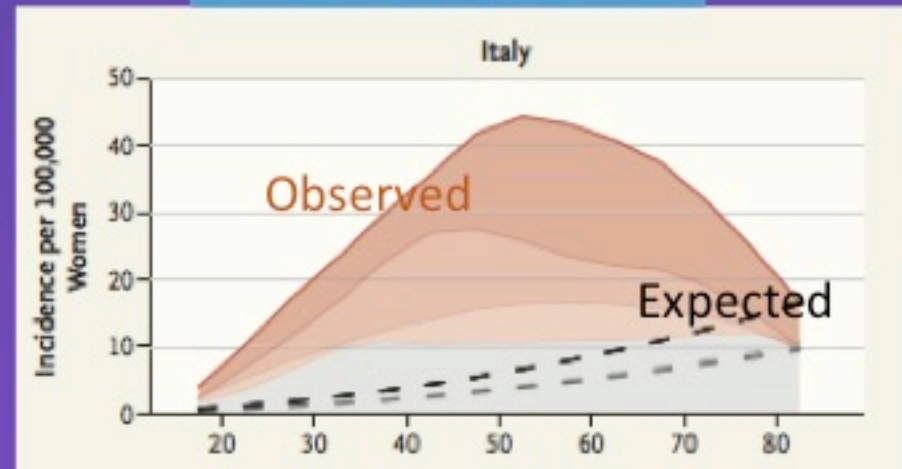
Increasing Impact of Over Diagnosis

- Dramatic increases in incidence... without substantial changes in thyroid-cancer-related mortality rates

United States



Italy



Observed	Expected
—	- - - 2003-2007
—	- - - 1998-2002
—	- - - 1993-1997
—	- - - 1988-1992

Need To Identify Which Nodules Require FNA Versus Do Not Require FNA

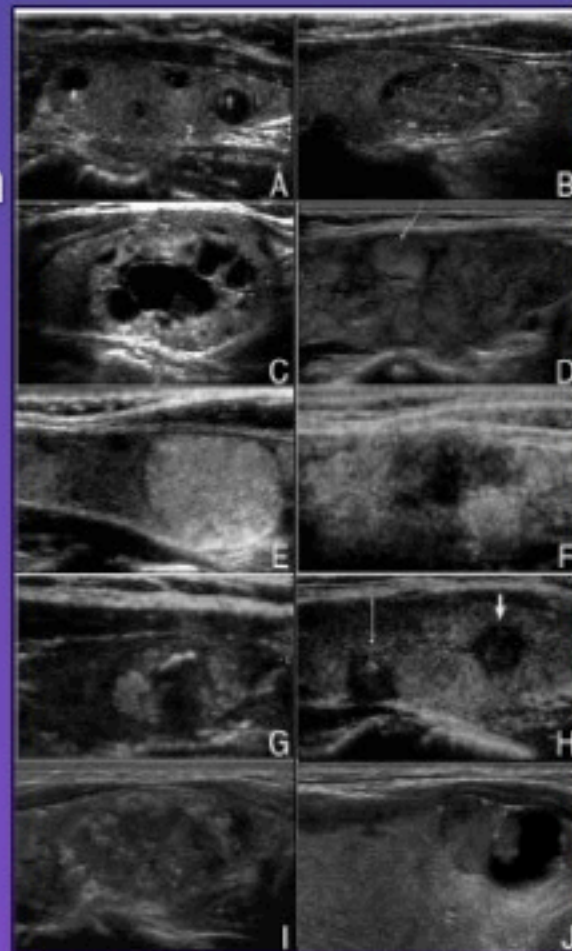
- Sharp rise in diagnosis and treatment of thyroid cancer from increased detection and biopsy...but lack of improvement in long-term outcomes
- Identify and treat the small group of patients with malignancy
Avoid unnecessary procedures in the majority with benign nodules



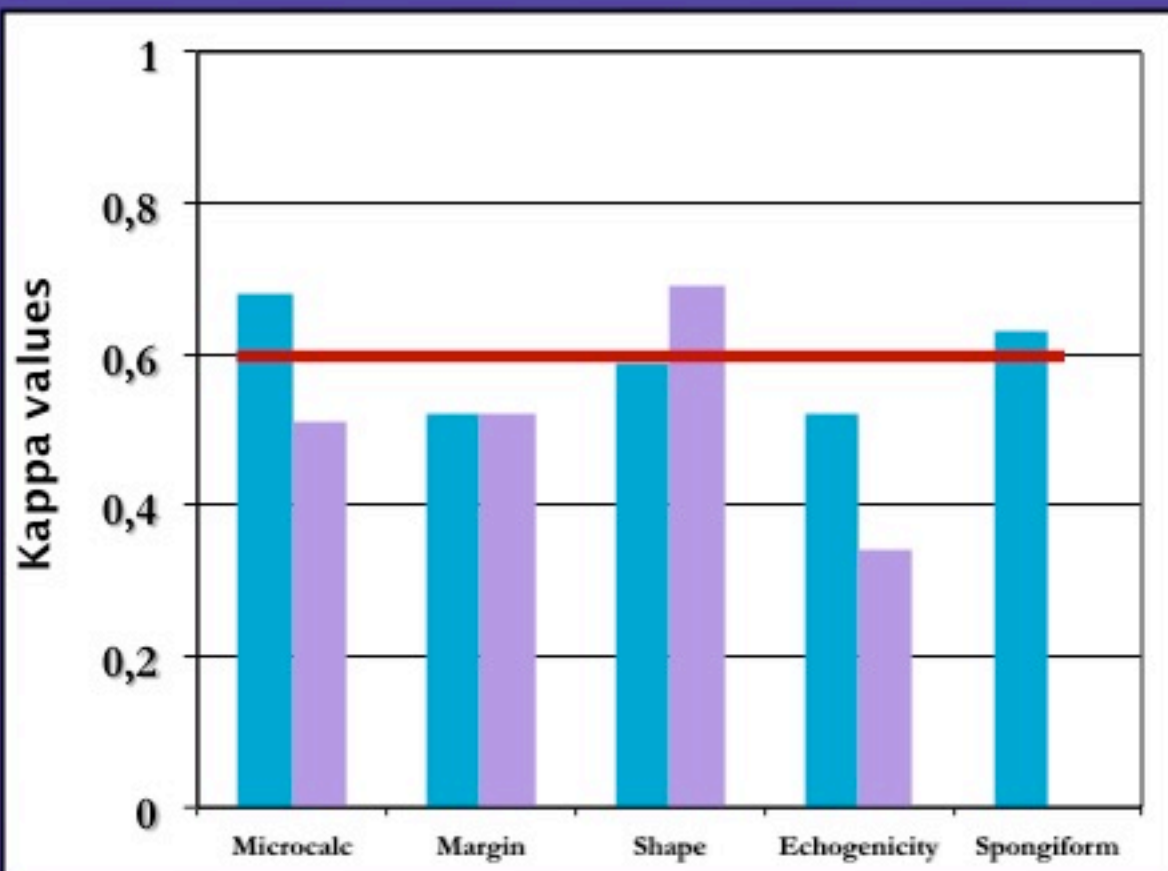
**Which Nodules
Need FNA?**

Recognize Variability in US Reporting Due To Many Factors

- US machine properties
 - Probe Frequency
 - Gain, Power Output
 - Harmonics or post image acquisition software e.g. smoothing
- Image interpretation
 - Static vs. Real Time
 - Use of Video
- Patient factors
 - Depth of Nodule
- Interobserver variability
- Nonstandardized lexicon




Interobserver Variability Of US Features: Experienced Radiologists Show Moderate Agreement



Kappa Values Agreement

<0.2 slight
0.21-0.4 fair
0.41-0.6 moderate
0.61-0.8 substantial
>0.8 ~perfect!

 = Moon

 = Choi

How Sensitive and Specific are Ultrasound Findings Predictive of Thyroid Cancer?

	Sensitivity	Specificity
Microcalcifications	45%	85%
Absence of Halo	66%	46%
Poorly Defined Margins	64%	77%
Hypoechoic	80%	45%
Increased Doppler flow	67%	81%
Taller than Wide	48%	92%
MicroCa²⁺ and Irreg margins	30%	95%
MicroCa²⁺ and Hypoechoic	28%	95%
Solid and Hypoechoic	73%	69%
FNA	92%	84%

≥ 2 Suspicious Features Increases Risk

Common Ultrasound Classification Systems Used



Many qualitative and quantitative systems
No consensus on a single US system

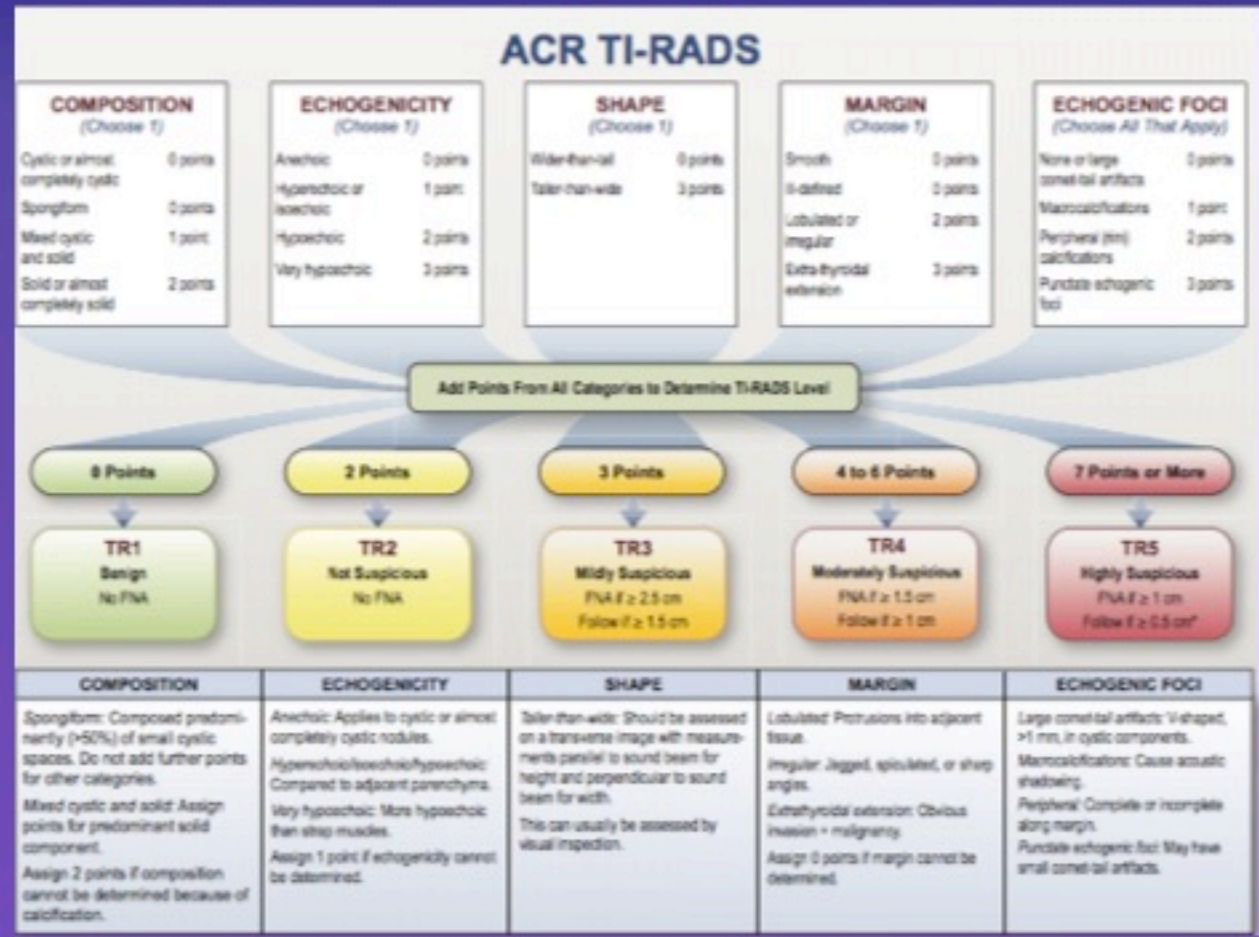
TIRADS has had numerous adaptations since 2009

Category	US PATTERN	MALIGNANCY RISK %
TIRADS 1	Normal thyroid gland	0
TIRADS 2	Cyst with or without comet tail Spongiform Mixed cystic/solid with solid portion mixed	0
TIRADS 3	Hashi's pseudonodule	<5
TIRADS 4		5-80
4A	Solid or mixed hyper/isoechoic with thin capsule	5-10
4B	Hypoechoic with irreg margins Hyper/iso/hypo with thick capsule	10-80
TIRADS 5	Hypo/Iso nonencapsulated with microcalcs	>80

Five Categories in ACR TI-RADS 2017

Points given for all US features

Add Points To Determine TIRADS Level



“Our Motto Was No Nodule Left Behind” –
 Dr Franklin Tessler

TI-RADS FNA Indications

3 points **TR3**
Mildly Suspicious
FNA if ≥ 2.5 cm
Follow if ≥ 1.5 cm

4-6 points **TR4**
Moderately Suspicious
FNA if ≥ 1.5 cm
Follow if ≥ 1 cm

7 points or More **TR5**
Highly Suspicious
FNA if ≥ 1 cm
Follow if ≥ 0.5 cm

TR3



Isoechoic partially cystic

TR4a



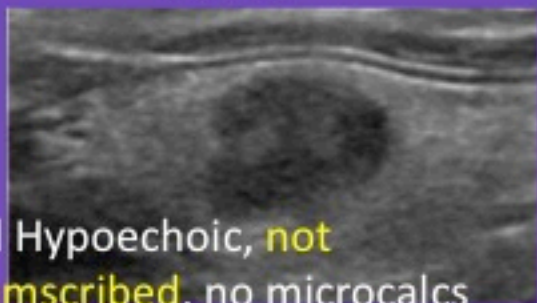
Solid Isoechoic circumscribed,
no microcalcs

TR4b



Solid Hypoechoic circumscribed,
no microcalcs

TR4c



Solid Hypoechoic, **not**
circumscribed, no microcalcs

TR4c



Markedly Hypoechoic, **not**
circumscribed, Microcalcs

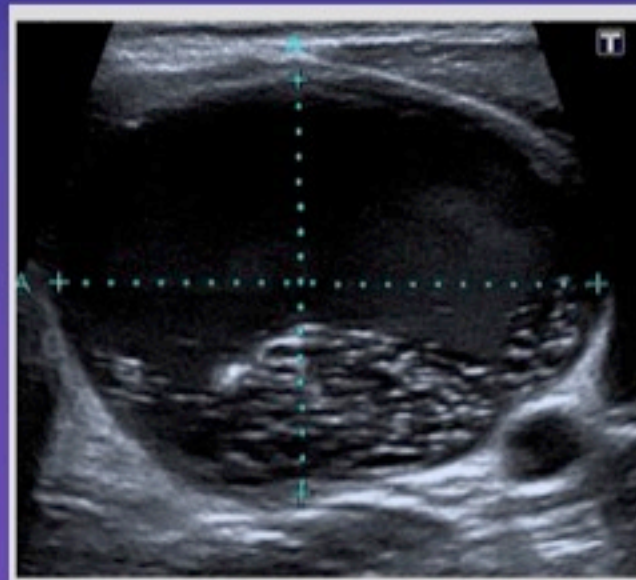
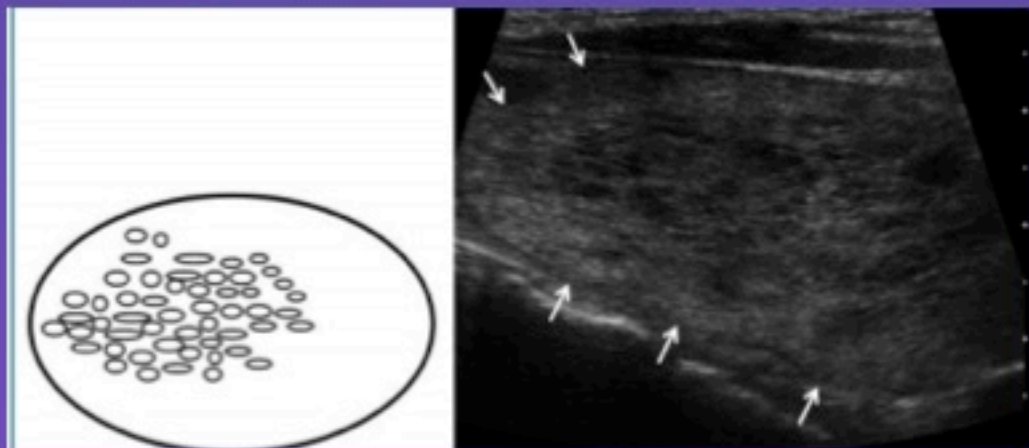
Spongiform, predominantly cystic, cystic nodules ~100% benign and no FNA needed

TR1

0 points
Benign
No FNA

TR2

2 points
Not Suspicious
No FNA

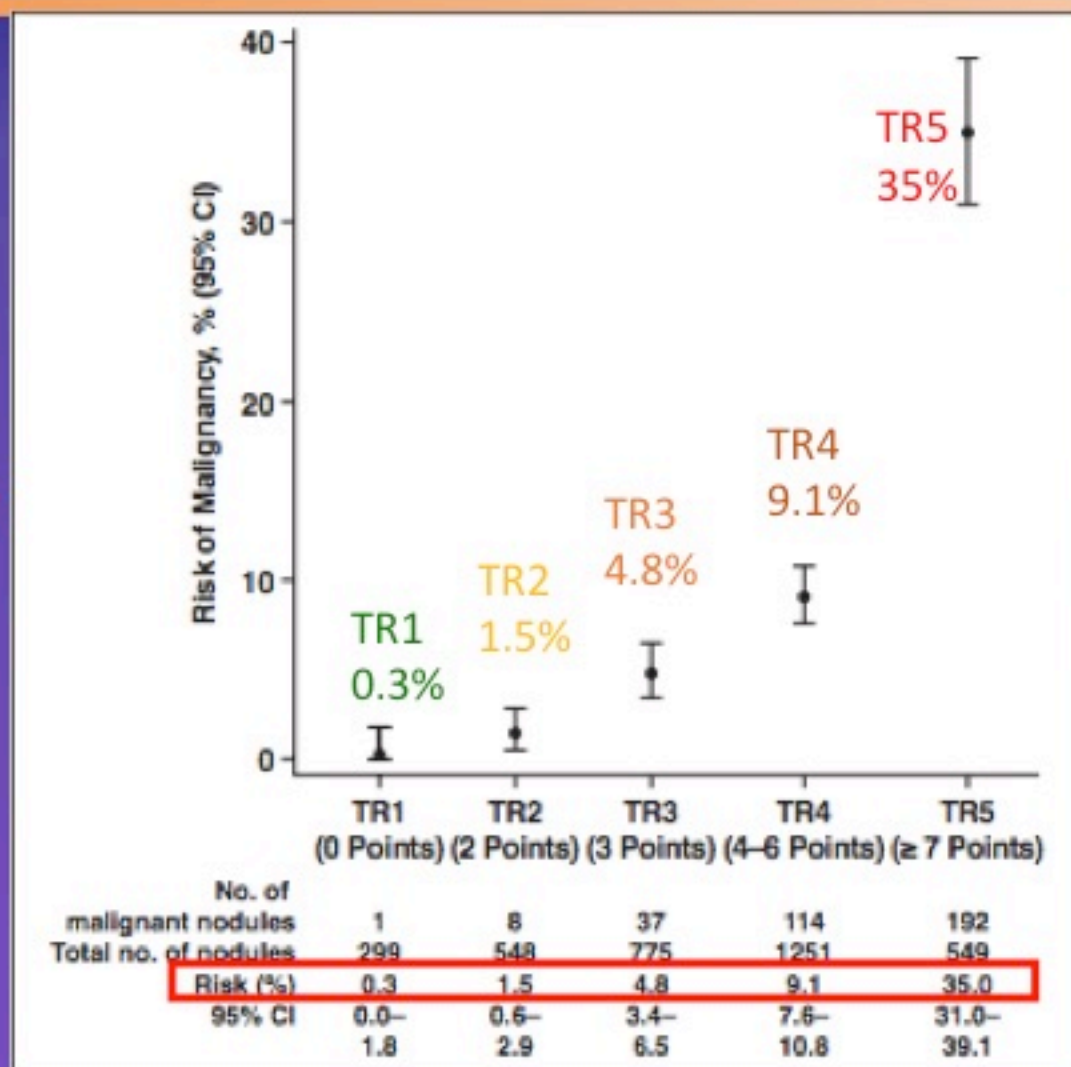


Spongiform:
Aggregation of multiple
microcystic components >
50% volume

~ 100% Benign Rate
1/360 Spongiform Nodules Malignant
99.7% specificity -Moon

Risk of Malignancy Validated Retrospectively With ACR TI-RADS System

Risk of Malignancy



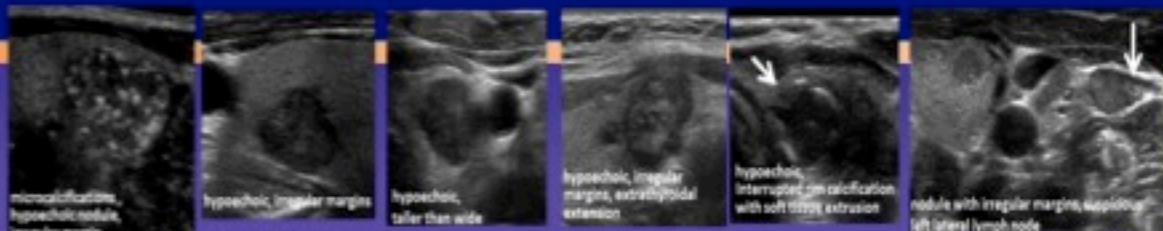
Inter-observer Studies
Ongoing With
2017 TI-RADS

TIRADS Classification

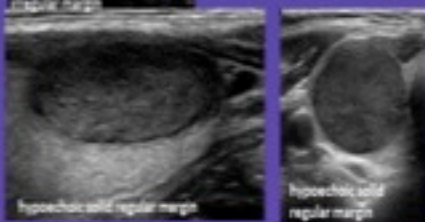


ATA 2015: Nodule Sonographic Pattern Risk of Malignancy

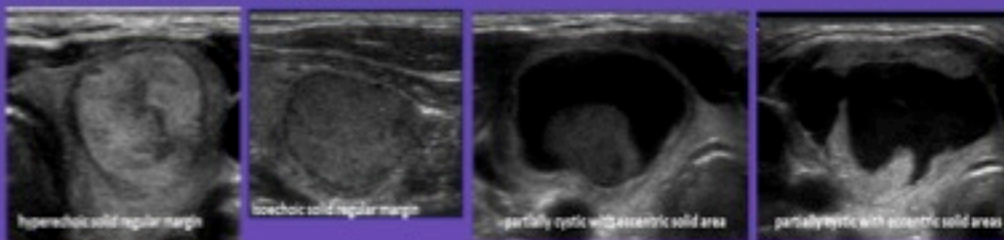
High
Suspicion
70-90%



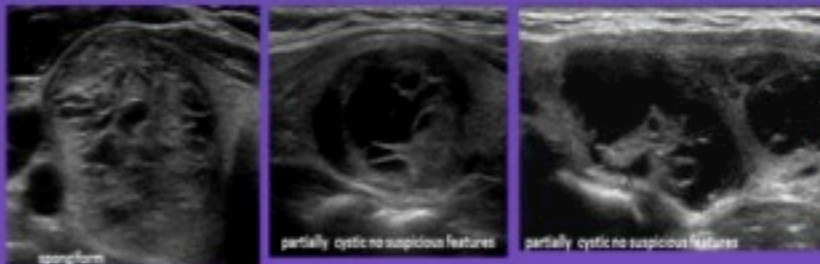
Intermediate
Suspicion
10-20%



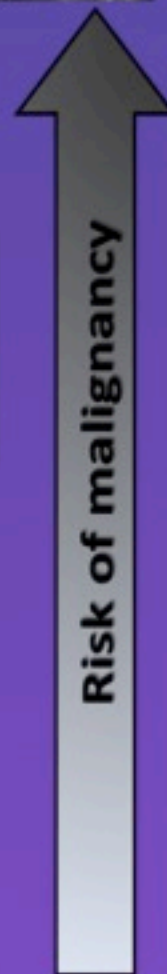
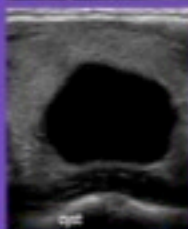
Low
Suspicion
5-10%



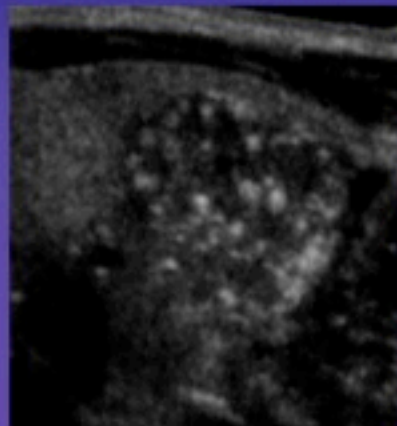
Very low
Suspicion
<3%



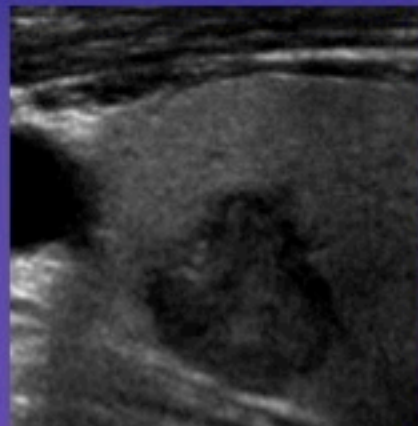
Benign
<1%



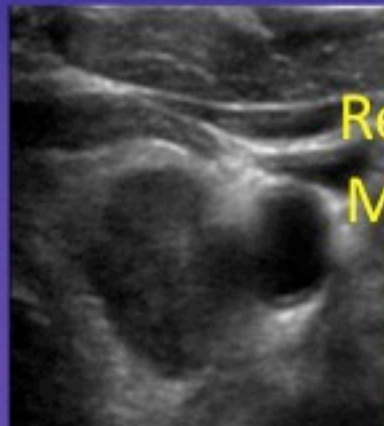
High Suspicion Pattern Risk of Malignancy 70-90%: Diagnostic FNA Nodules ≥ 1 cm



hypoechoic,
microcalcs, irreg
margin

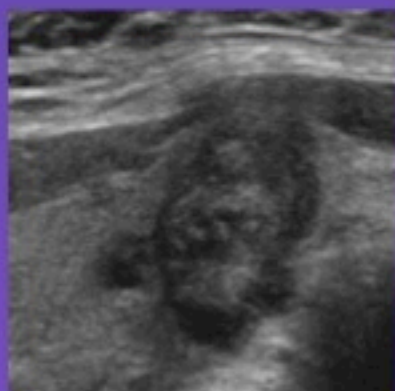


hypoechoic, irreg margin
(microlobulated/
spiculated)

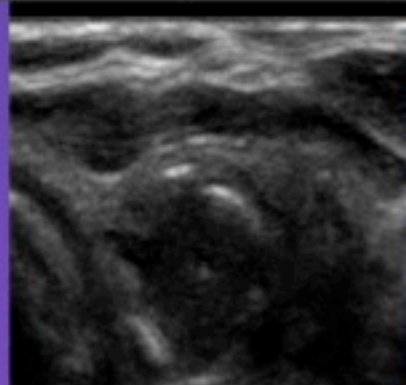


hypoechoic, irreg
margin, taller than
wide

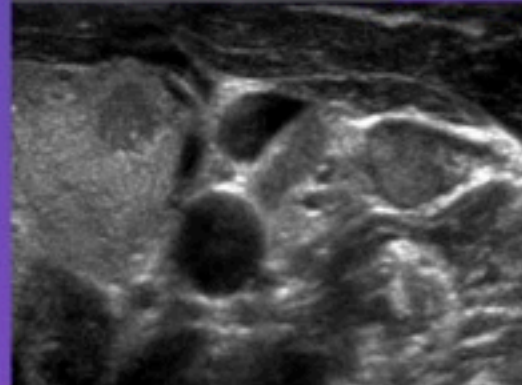
Strong
Recommendation,
Moderate-Quality
Evidence



hypoechoic, irreg margin,
extrathyroidal extension



hypoechoic, interrupted
rim calcification with
soft tissue extrusion

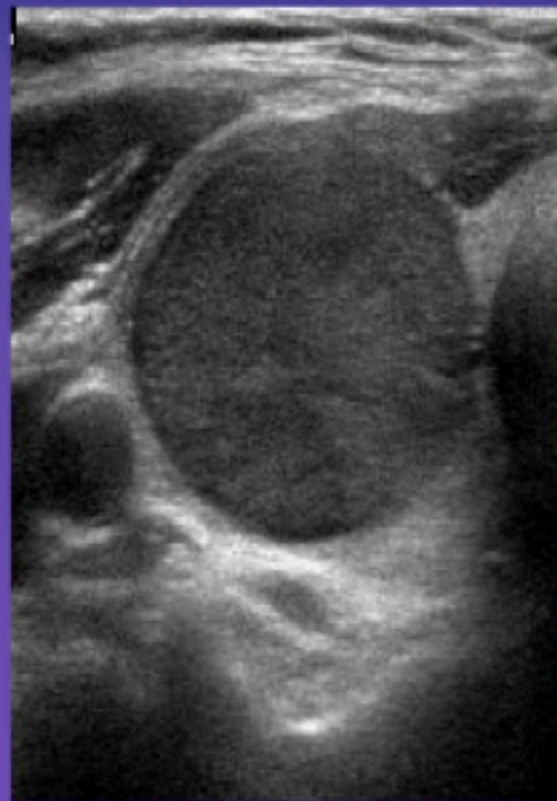
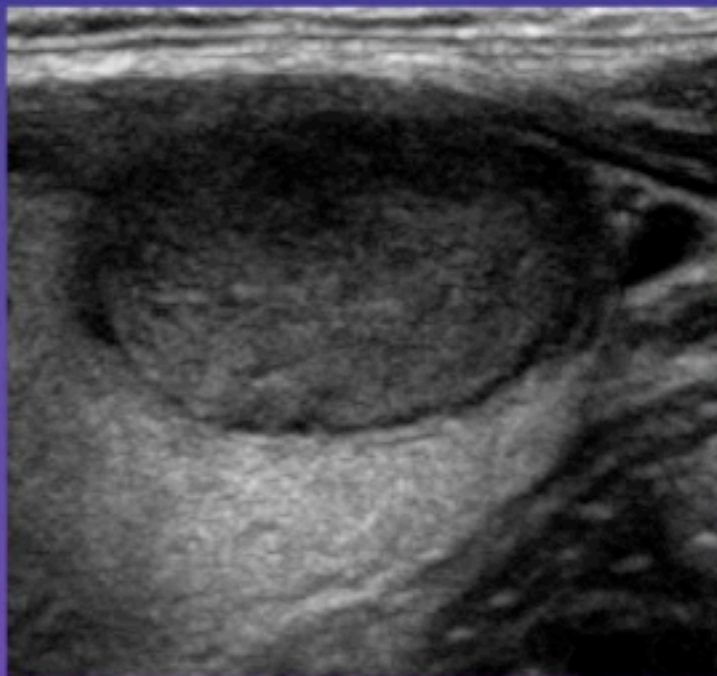


irregular margins, suspicious left
lateral lymph node



AMERICAN
THYROID
ASSOCIATION
FOUNDED 1922

Intermediate Suspicion Pattern Risk of Malignancy 10-20%: Diagnostic FNA ≥ 1 cm



Hypoechoic Solid Nodules With Smooth Margins

Without Microcalcifications, ExtraThyroidal Extension, or T>W

Strong Recommendation, Low-Quality Evidence

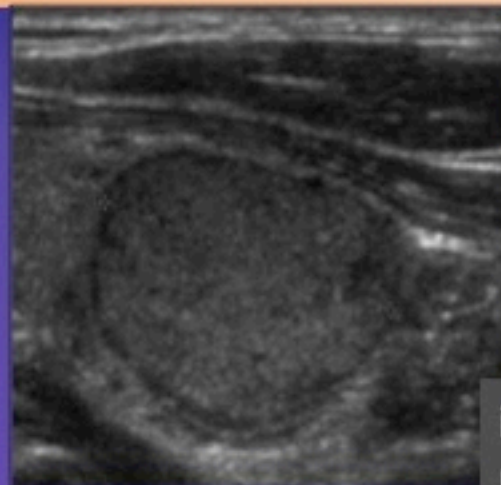


AMERICAN
THYROID
ASSOCIATION
FOUNDED 1923

Low Suspicion Pattern Risk Of Malignancy 5-10%: Diagnostic FNA ≥ 1.5 cm



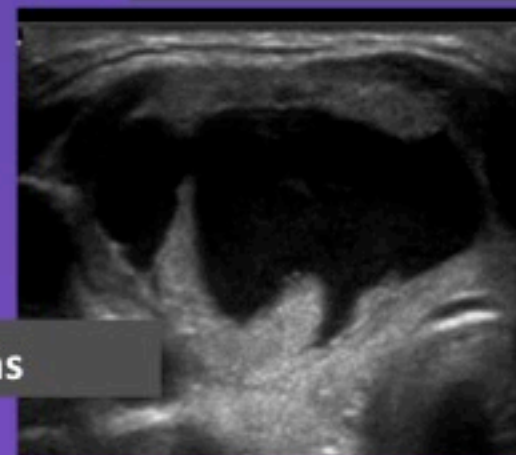
hyperechoic solid reg margins



isoechoic solid reg margins



partially cystic with eccentric solid areas



Without Microcalcifications, Irregular Margins, ETE, or T>W

Weak Recommendation, Low-Quality evidence



R8 US Pattern and suggested FNA cutoffs

Sonographic Pattern	Estimated malignancy risk	FNA size cutoff	Strength of rec	Quality of evidence
High suspicion	>70-90%	≥ 1 cm	Strong	Moderate
Intermediate suspicion	10-20%	≥ 1 cm	Strong	Low
Low suspicion	5-10%	≥ 1.5 cm	Weak	Low
Very low suspicion	< 3%	≥ 2 cm	Weak	Moderate
One option is surveillance				
Benign	< 1%	No biopsy	Strong	Moderate

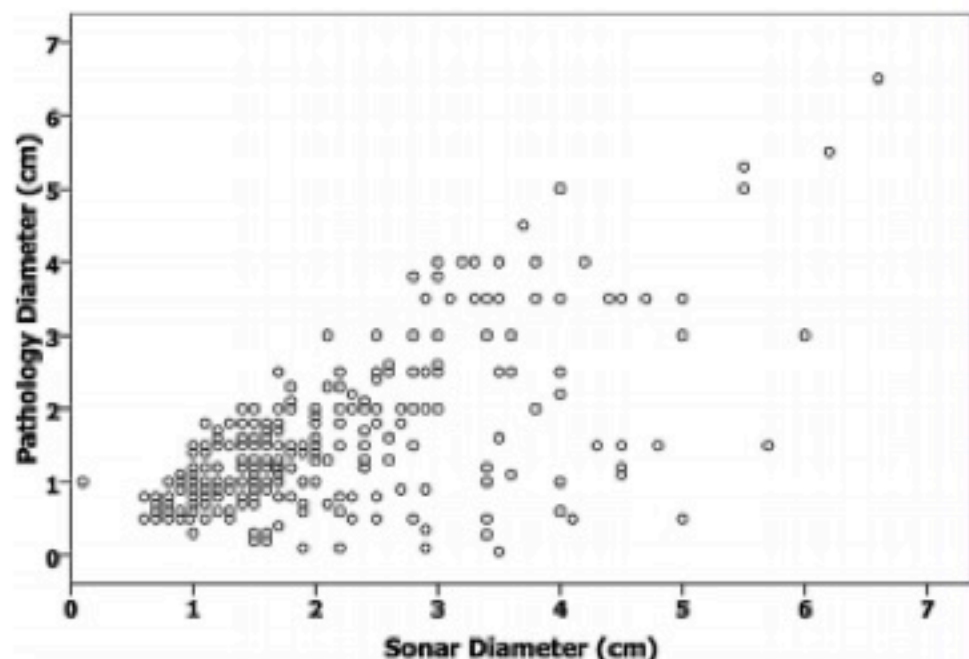
FNA not recommended for nodules not meeting above criteria and nodules < 1 cm

Strong

Moderate

Discrepancy Between Biopsy Thresholds For Mildly Suspicious Nodules: TIRADS 2.5 cm Vs. ATA 2.0 cm

- ATA based on retrospective data
 - - cumulative risk distant metastases PTC and FTC higher at 2 cm
- ACR reviewed data – different interpretation
 - prior analysis tumor size in resected specimens, not US dimensions



Lack of concordance US
and pathologic sizing

US tendency to result in
larger measurements

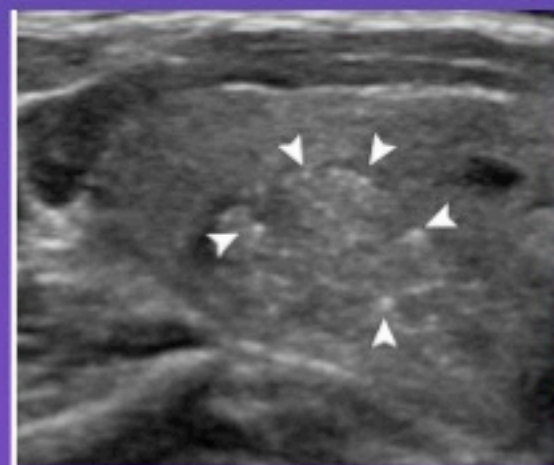
ATA Limitations in Classifying Isoechoic Nodules With Other Concerning Features Vs. TIRADS

-Comparison ATA 2014 vs. TIRADS 2011

3.4% (of 1,293 nodules) **without** ATA Classification
 Isoechoic with irregular margins, microcalcifications, and/or T>W

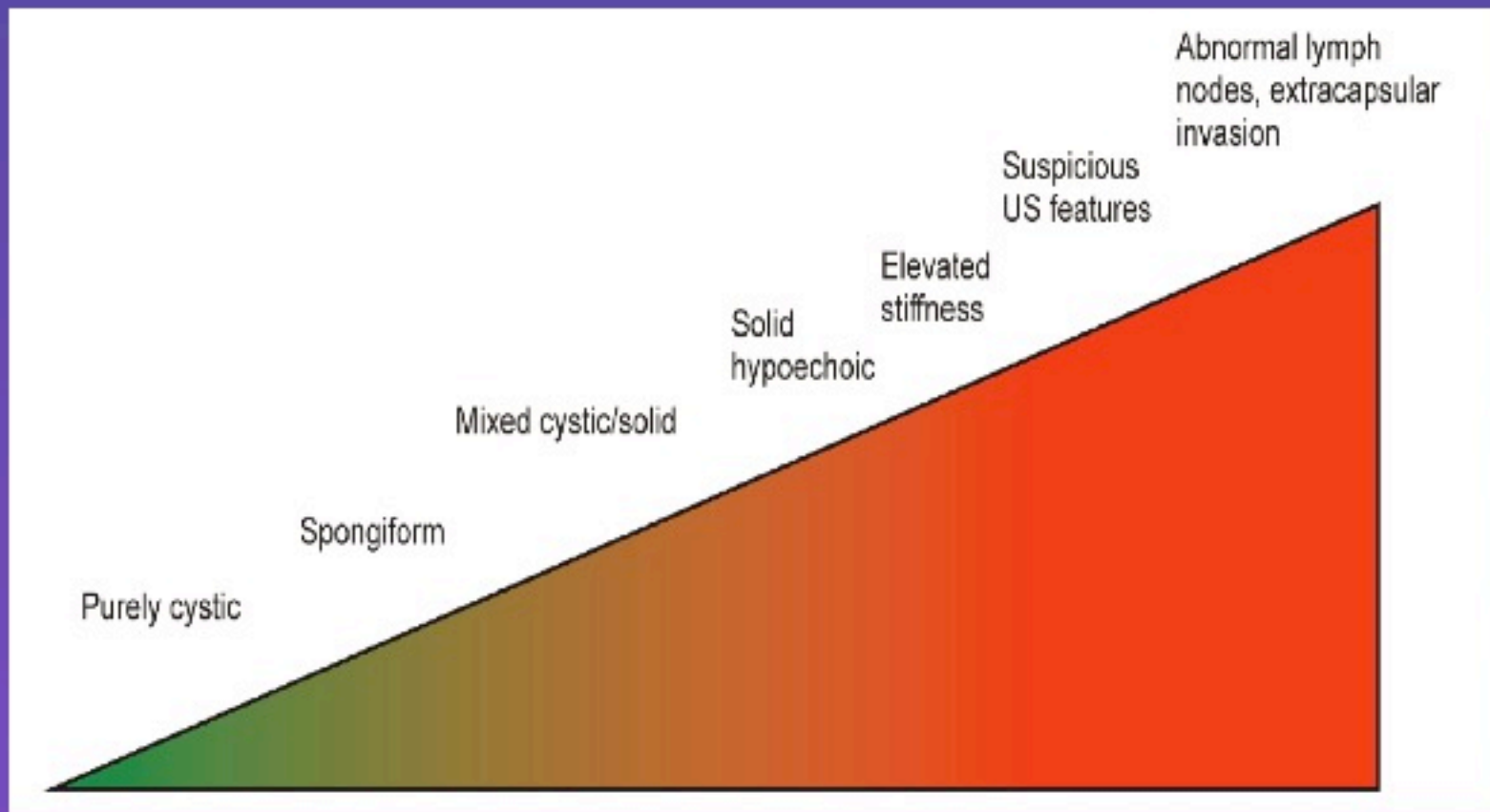
18.2% of “not specified” ATA nodules malignant

Scoring System and Category	Characteristics	Final Diagnosis*		Recommended Malignancy Risk (%)	Calculated Malignancy Rate (%)†	P Value
		Benign (n = 1059)	Malignant (n = 234)			
TIRADS						
3	No suspicious US features	310 (29.3)	6 (2.6)	1.7	1.9 (0.8)	<.001
4a	One suspicious US feature	391 (36.9)	17 (7.3)	3.3	4.2 (1.0)	
4b	Two suspicious US features	223 (21.1)	33 (14.1)	9.2	12.9 (2.2)	
4c	Three or four suspicious US features	131 (12.4)	130 (55.5)	44.4–72.4	49.8 (3.2)	
5	Five suspicious US features	4 (0.3)	48 (20.5)	87.5	92.3 (3.7)	
ATA guidelines						
Very low suspicion	Spongiform or partially cystic nodule without any suspicious US features	396 (37.4)	11 (4.7)	<3	2.7 (0.8)	<.001
Low suspicion	Iso- or hyperechoic solid nodule or partially cystic nodule without microcalcifications, irregular margin or extrathyroidal extension, and taller-than-wide shape	313 (29.6)	10 (4.3)	5–10	3.1 (1.1)	
Intermediate suspicion	Hypoechoic solid nodule with smooth regular margin	194 (18.3)	39 (16.7)	10–20	16.7 (2.5)	
High suspicion	Solid hypoechoic or partially cystic hypoechoic nodule with irregular margins, microcalcifications, taller-than-wide shape, disrupted rim calcification with hypoechoic soft-tissue extension, and extrathyroidal extension	120 (11.3)	166 (70.9)	>70–90	58.0 (3.0)	
Not specified	Solid isoechoic or partially cystic isoechoic nodule with irregular margins, microcalcifications, and taller-than-wide shape	36 (3.4)	8 (3.4)	Not mentioned	18.2 (5.8)	





2016 AAACE/AME Nodule Guidelines: FNA Indications Based on US Findings

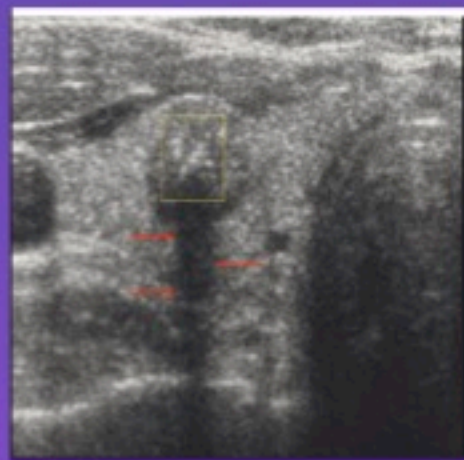
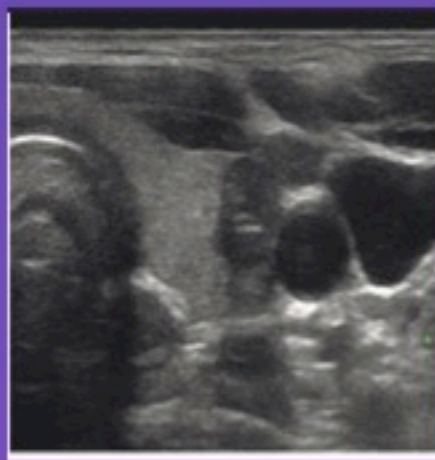
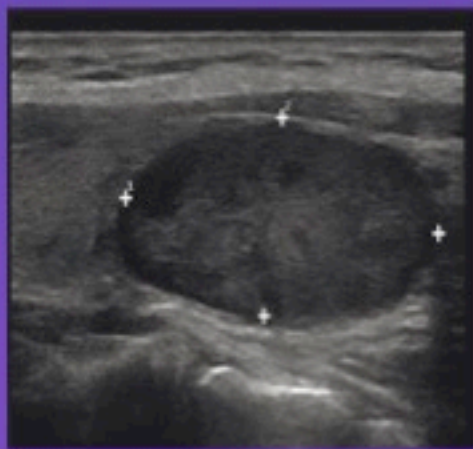


AAACE Guidelines Mapping Protocol For Evidence

Best Evidence Level	Predominantly Negative SF and/or RQ	Predominantly Positive SF and/or RQ	Consensus for Recommendation and for Grade	EL to Grade Mapping	Map to Final Recommendation Grade
1	No	No	>66%	Direct	1 → A
Any ^b	No	No	100%	Rule	Any → A (new)
2	No	Yes	>66%	Adjust up	2 → A
2	No	No	>66%	Direct	2 → B
1	Yes	No	>66%	Adjust down	1 → B
3	No	Yes	>66%	Adjust up	3 → B
3	No	No	>66%	Direct	3 → C
2	Yes	No	>66%	Adjust down	2 → C
4	No	Yes	>66%	Adjust up	4 → C
4	No	No	>66%	Direct	4 → D
3	Yes	No	>66%	Adjust down	3 → D
Any ^b	Yes/no	Yes/no	≤66%	Rule	Any → D (new)

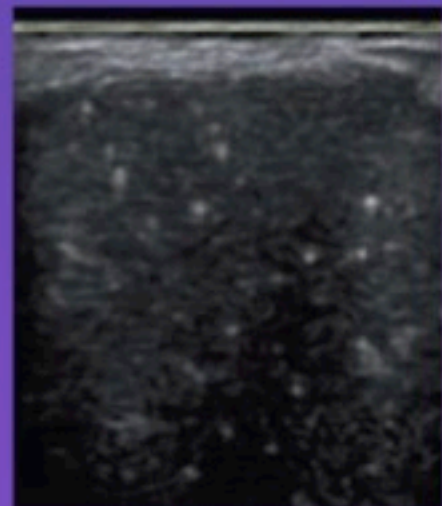
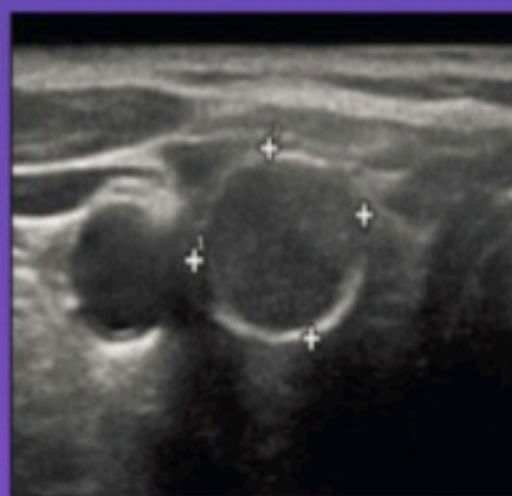
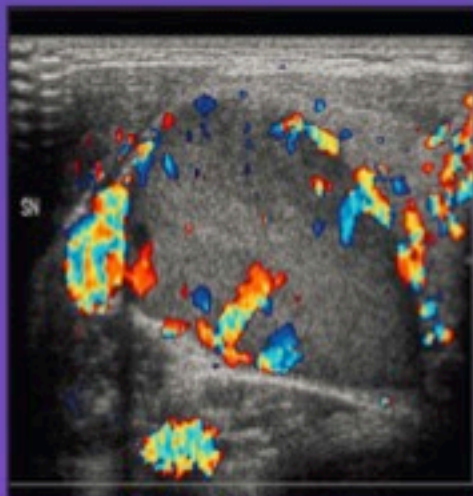
All guidelines require expert opinion

- At least 1 of the following:
 - Marked hypoechogenicity
 - Spiculated or microlobulated margins
 - Microcalcifications
 - Taller-than-wide shape
 - Extrathyroidal growth or pathologic adenopathy
- Evidence:
BEL 2, GRADE A**



- Slightly hypoechoic nodules or isoechoic nodules with ovoid-to-round shape, smooth or ill defined margins
- May be present: intranodular vascularization, elevated stiffness, macro-or continuous rim calcifications, or indeterminate hyperechoic spots

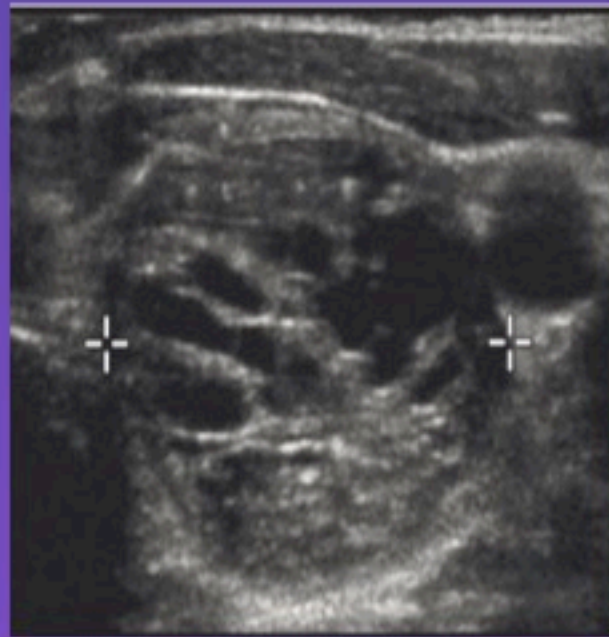
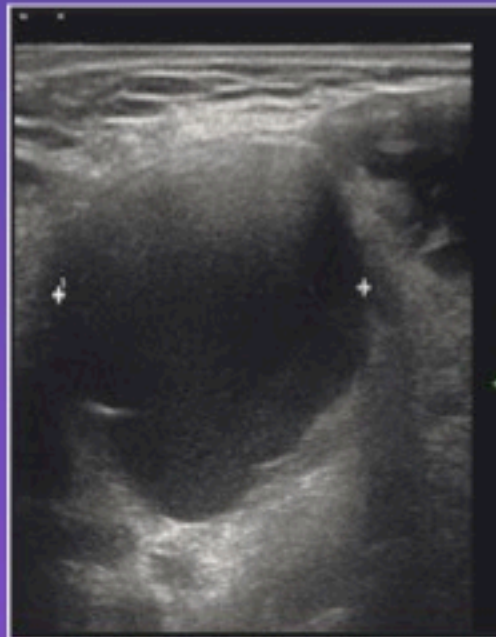
Evidence
BEL 2,
GRADE A



Class 1: Low-Risk ~ 1% ROM

- Cysts or mostly cystic (> 50%) nodules with reverberating artifacts without suspicious US signs
- Isoechoic spongiform nodules either confluent or with regular halo

Evidence:
BEL 2, GRADE A





US Risk of Malignancy, Suggested FNA Recommendations and Evidence



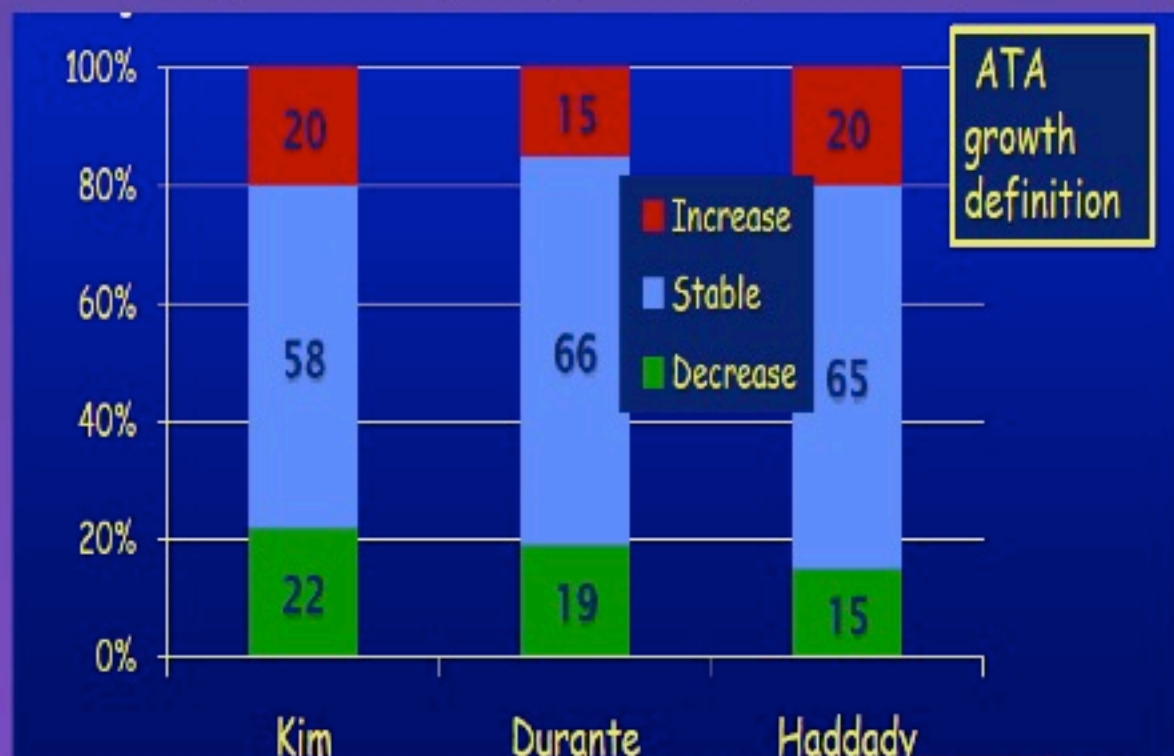
Sonographic Pattern	Estimated malignancy risk	FNA size cutoff	AACE Level of Evidence	AACE Strength of Rec
High Risk US	50-90%	≥ 1 cm	2	A
Intermediate Risk US	5-15%	>2 cm	2	A
Low Risk US	~1%	>2 cm or growing	2	A

Ultrasound classification systems for risk stratification

ATA 2015	AACE/ AME	TIRADS Horvath	TIRADS Kwak	TIRADS Russ
Benign 0%	Low Risk <1%	2 0%	2 0%	2 0%
Very Low Suspicion <3%			3 2%	
Low Suspicion 5-10%	Intermediate Risk 5-15%	4a 5-10%	4a 3-12%	3 0.25%
Intermediate Suspicion 10-20%			4b 7-38%	4a 6%
High Suspicion >70-90%	High Risk 50-90%	4b 10-80% 5 >80%	4c 44-72% 5 89-98%	4b 69% 5 ~100%

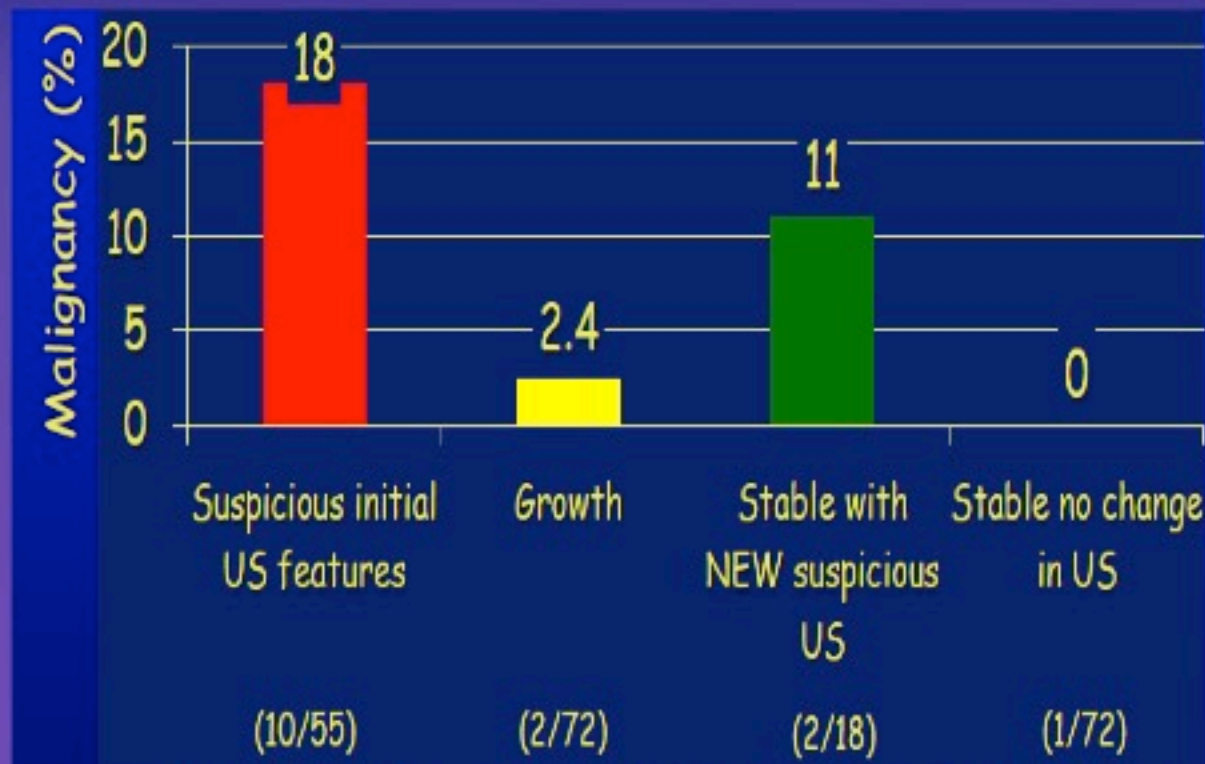
How Often Should We Follow Benign Cytology Nodules?

- Majority asymptomatic, sonographic/cytologic benign nodules no significant size increase 4-5 years
- Kim: 854 cytological benign nodules, 4 yr mean f/u, 3 US exams
- Durante: 630 cytologic, 937 US benign nodules in 992 pts, 5 yr f/u, US annual
- Haddady: 1078 cytologic benign nodules, 64 mo f/u; avg time growth 52 mos



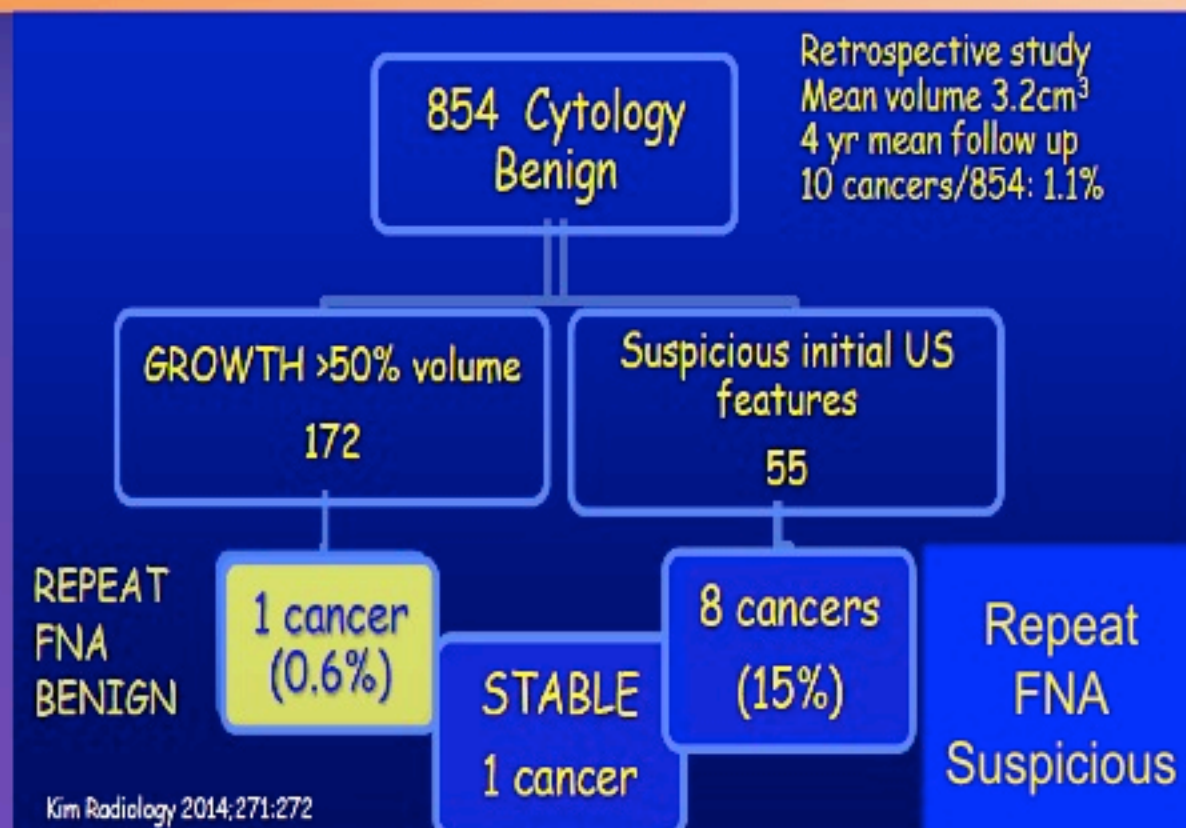
Kim et al *Radiology* 2014; 272-281
Durante et al. *JAMA* 2015; 313: 926-935
Haddady 2015 AACE

Cancer Detection Rates in Nodules With Initial Benign Cytology out of 217 nodules



Of the 14 missed cancers, 13 had suspicious US features (10 on initial US, 1 with growth, 2 new on follow up US)

R23 ATA: Follow-up Thyroid Nodules with Benign Cytology- Ultrasound Appearance Most Important



Given low false-negative rate US guided FNA cytology and higher yield missed malignancies based upon **nodule sonographic pattern** rather than growth, follow-up...benign cytology diagnoses...

risk stratification based upon US pattern

AACE/AME 2018 Approach to Thyroid Nodules Update and App Planned



AACE/ACE/AME Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS,
AMERICAN COLLEGE OF ENDOCRINOLOGY, AND
ASSOCIAZIONE MEDICI ENDOCRINOLOGI MEDICAL GUIDELINES FOR
CLINICAL PRACTICE FOR THE DIAGNOSIS AND MANAGEMENT OF
THYROID NODULES – 2016 UPDATE

APPENDIX



- US characteristics similar to ACR (TIRADS) features
- Comprehensive Rating of Risk of Malignancy with Combined Scoring System
- 3 US Categories – 1=Benign, 2=Intermediate, 3=High Risk
- 2 Clinical Categories/Scenarios – For or Against FNA
- 5 Sizes based on TNM :<5 mm; 5-10 mm;<10-20 mm;> 20-40 mm; > 40 mm

Final Score: Indication to Perform FNA

AAACE/AME 2018 Update and App Based on 5 Different Decisions

- 1. Follow: Yes/No
 - If Yes: US when and for how long?
- 2. Indications For Repeat FNA
- 3. Cyst Management
- 4. Indications For Surgery
- 5. Utility/Role of Molecular Markers

Future Studies:

Validation Studies Needed

Retrospective Databases Available for Rapid

Preliminary Assessment

Conclusions

- Many US Systems with no consensus on a single system
- Many limitations exist in current US Systems: interobserver variability, wide range in nodule feature classifications, wide range in risk of malignancy
- Ultrasound features are most important in decision-making regarding when to FNA
- Ongoing studies to validate US systems and assess interobserver variability

Stay Tuned in 2018:

AACE/AME Guidelines Update and Mobile App

Special Thanks...

- Dr Jeffrey Garber
- Dr Mark Lupo
- AME Organizing Committee

