

Thyroid Nodules: Evaluation & Initial Management

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Disclosures

- I have received research, speaking and/or consulting fees from
 - Quidel
 - Roche
 - Eisai
 - Abbvie
 - Horizon Therapeutics
 - Interpace Diagnostics
 - Takeda
 - Loxo/Lilly

Objectives

- Review ultrasound risk stratification
- Compare existing guidelines for risk stratification and FNA biopsy criteria
- Discuss the potential clinical utility of molecular markers in the evaluation of indeterminate thyroid nodules
- Outline initial management after comprehensive evaluation

Nodules: Palpable



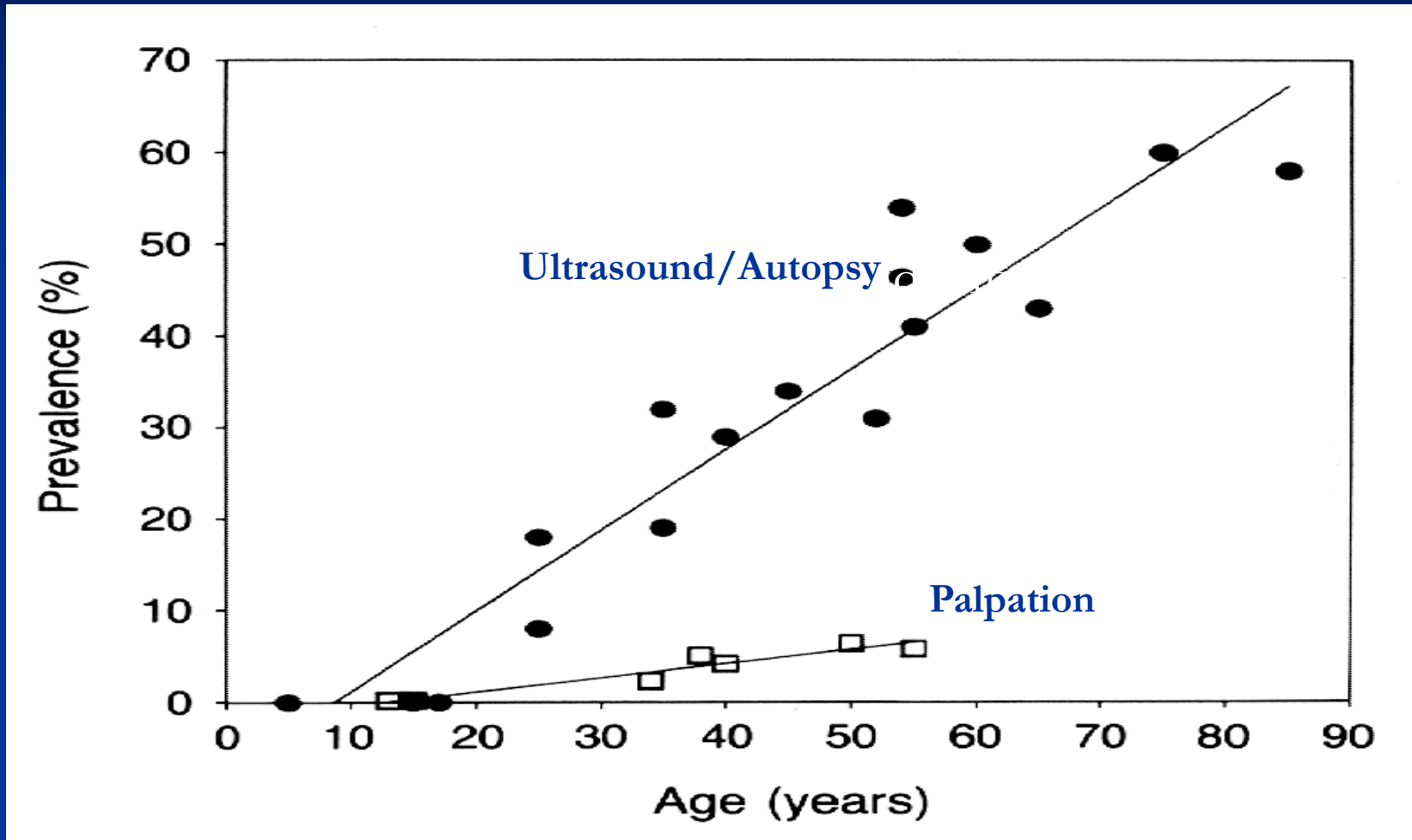
Incidental



CLINICAL QUESTIONS:

- Is it cancer?
- Does it cause symptoms?
- Is it impacting thyroid function?

How common are nodules?

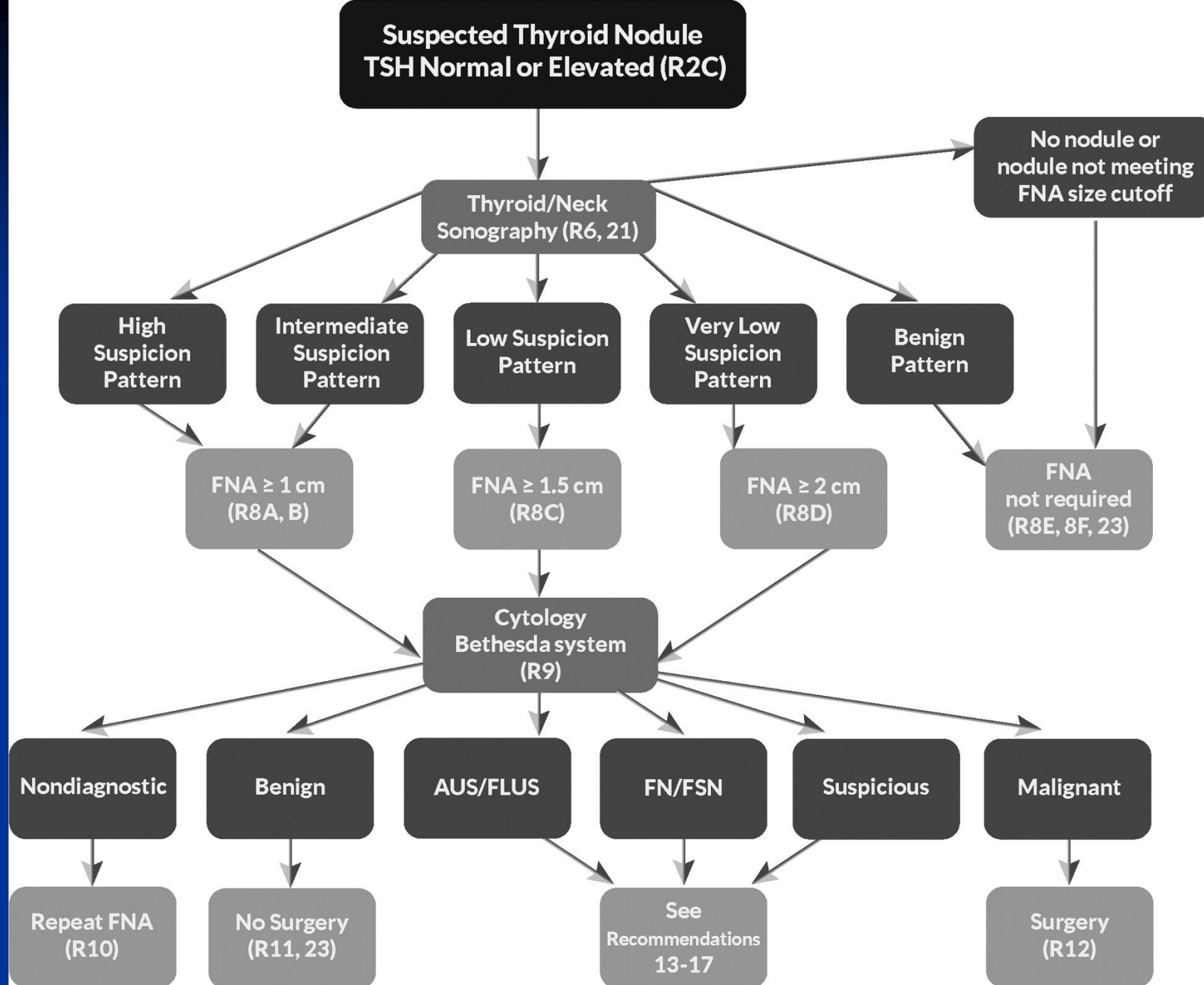


Mazzaferri, NEJM 1993

Why do I have these nodules?

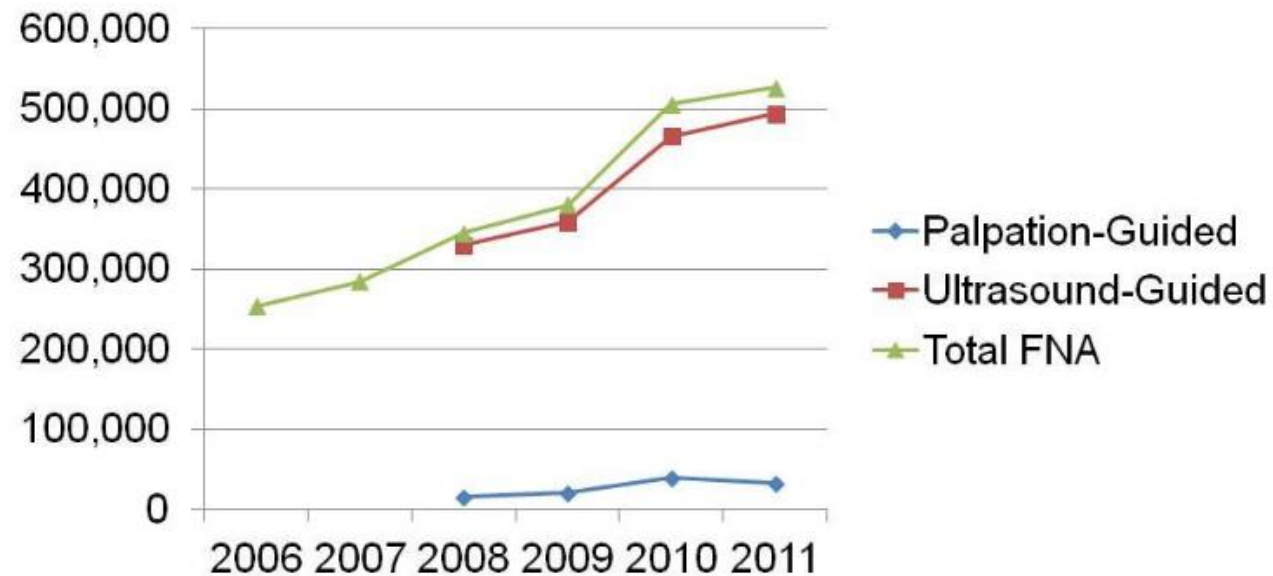
- Iodine Deficiency
- Autoimmune Thyroid Disease
- Family History of Nodules
- History of Smoking
- Radiation Exposure
- Insulin Resistance





Too many biopsies !

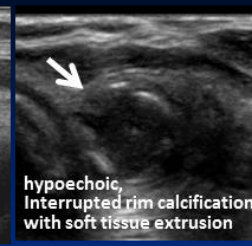
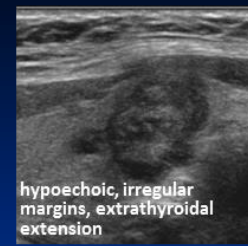
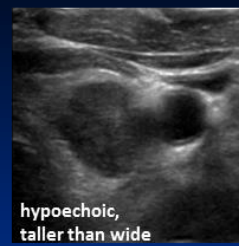
107% increase in thyroid FNAs, 2006-2011



- Thyroid FNAs more than doubled: 16% compounded annual percentage change
- Thyroid FNAs increased as a percentage of all FNAs, from 49% to 65%.

ATA 2015: Nodule Sonographic Pattern Risk of Malignancy

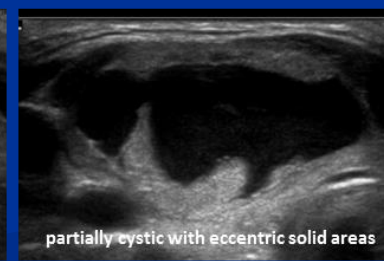
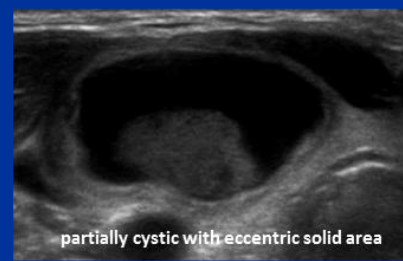
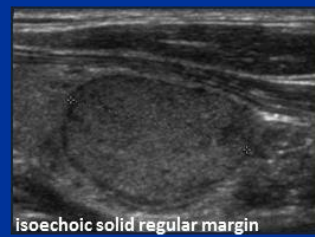
High
Suspicion
70-90%



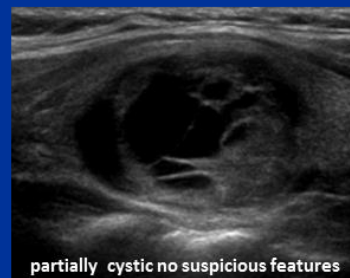
Intermediate
Suspicion
10-20%



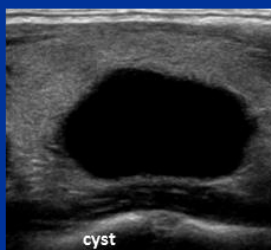
Low
Suspicion
5-10%



Very low
Suspicion
<3%



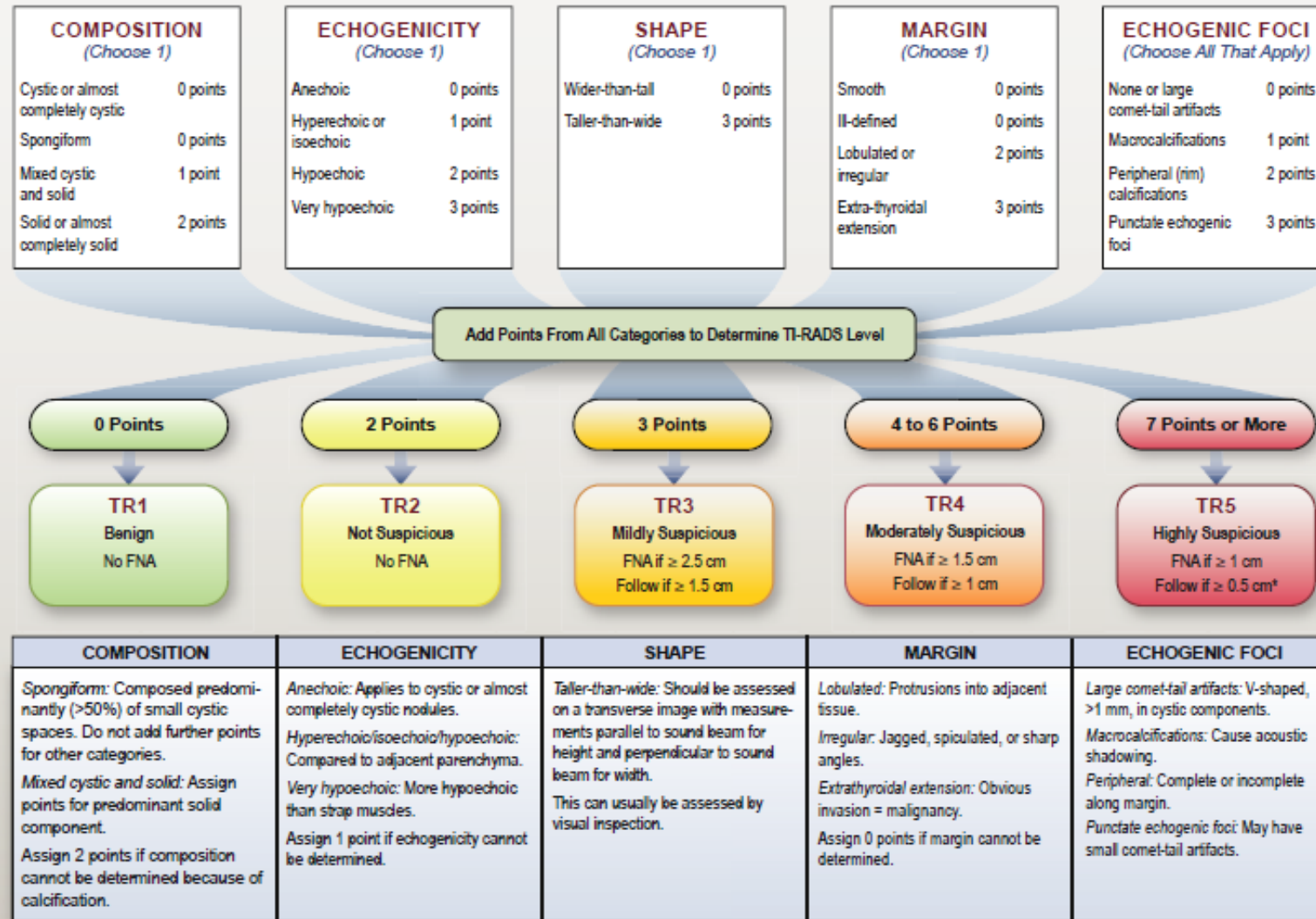
Benign
<1%



Risk of malignancy

Haugen et al. Thyroid; October 2015 (epub)

ACR TI-RADS



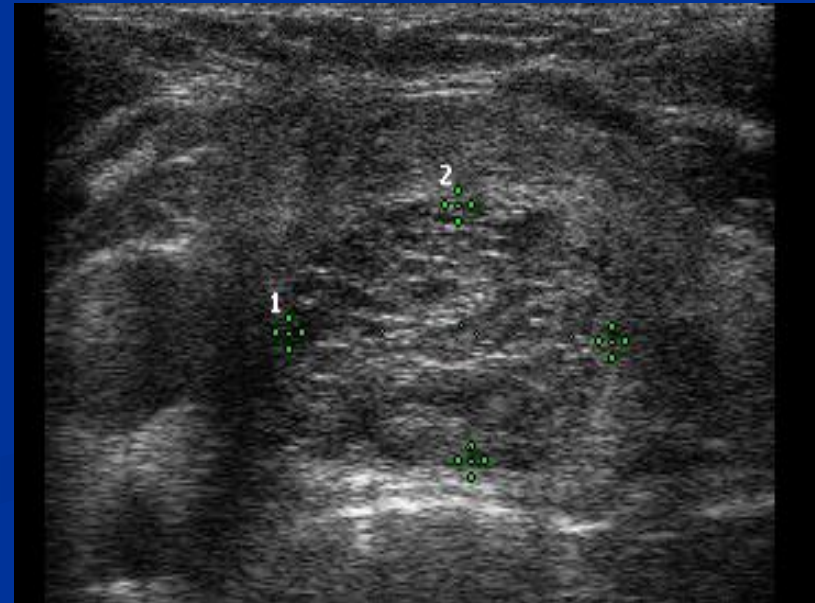
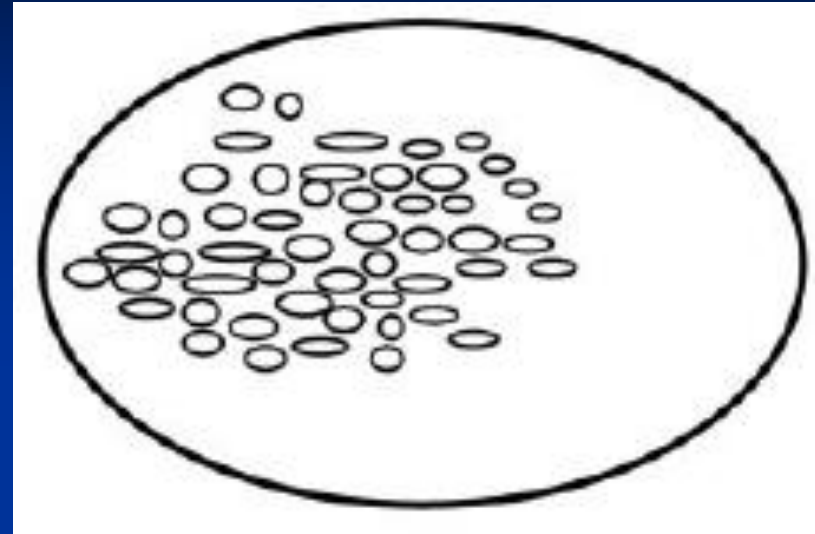
*Refer to discussion of papillary microcarcinomas for 5-9 mm TR5 nodules.

Composition

- Spongiform
- Pure Cyst
- Mixed Solid-Cystic
- Solid

“Spongiform” nodules

- aggregation of multiple microcystic components in more than 50% of the volume of the nodule
- “honeycomb of internal cystic spaces”
- Only 1 in 360 spongiform nodules malignant
 - 99.7% Specificity (Moon)

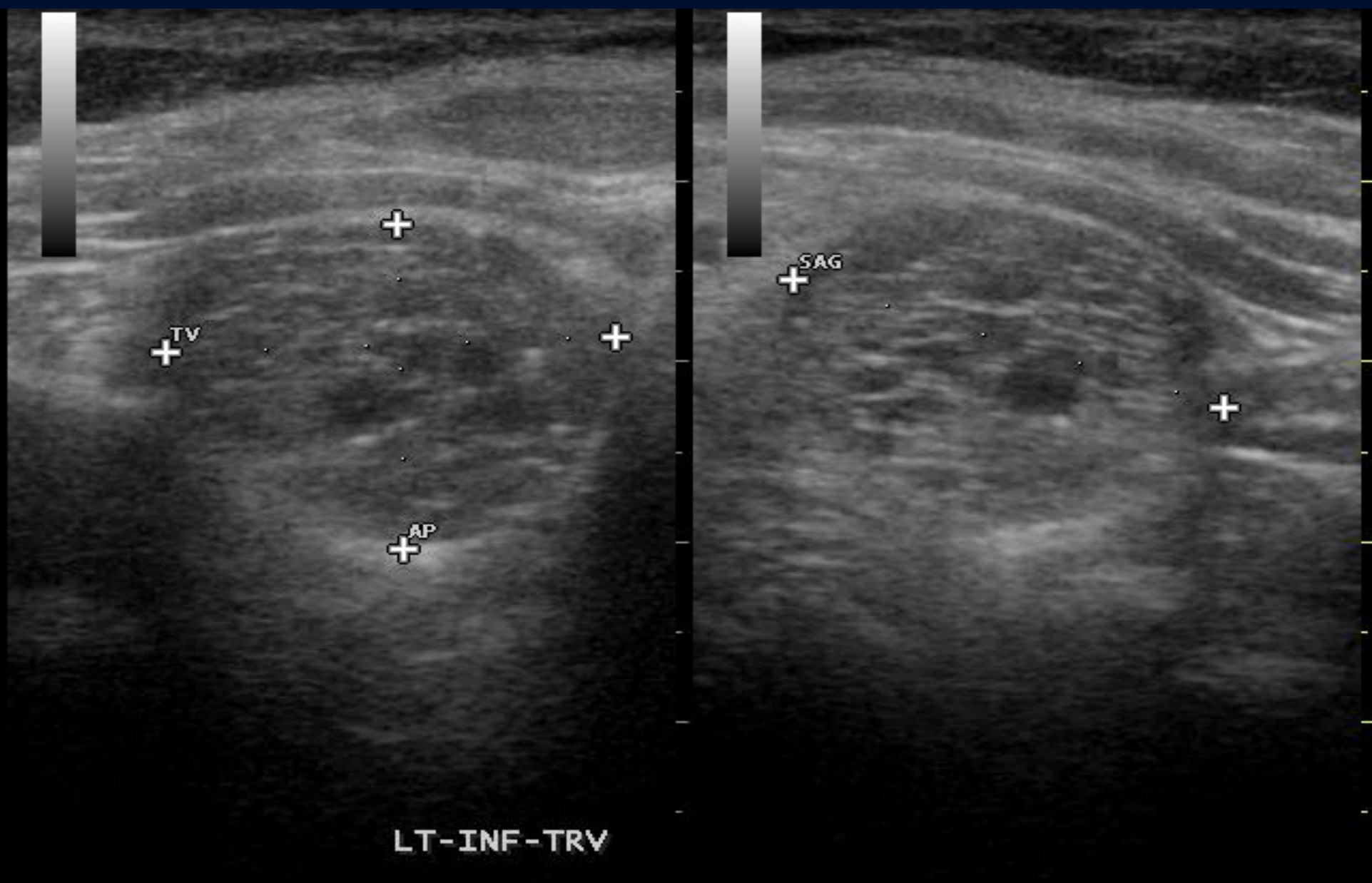


Moon Radiology 2008; 247: 762-70
Bonavita AJR 2009; 193:207-13

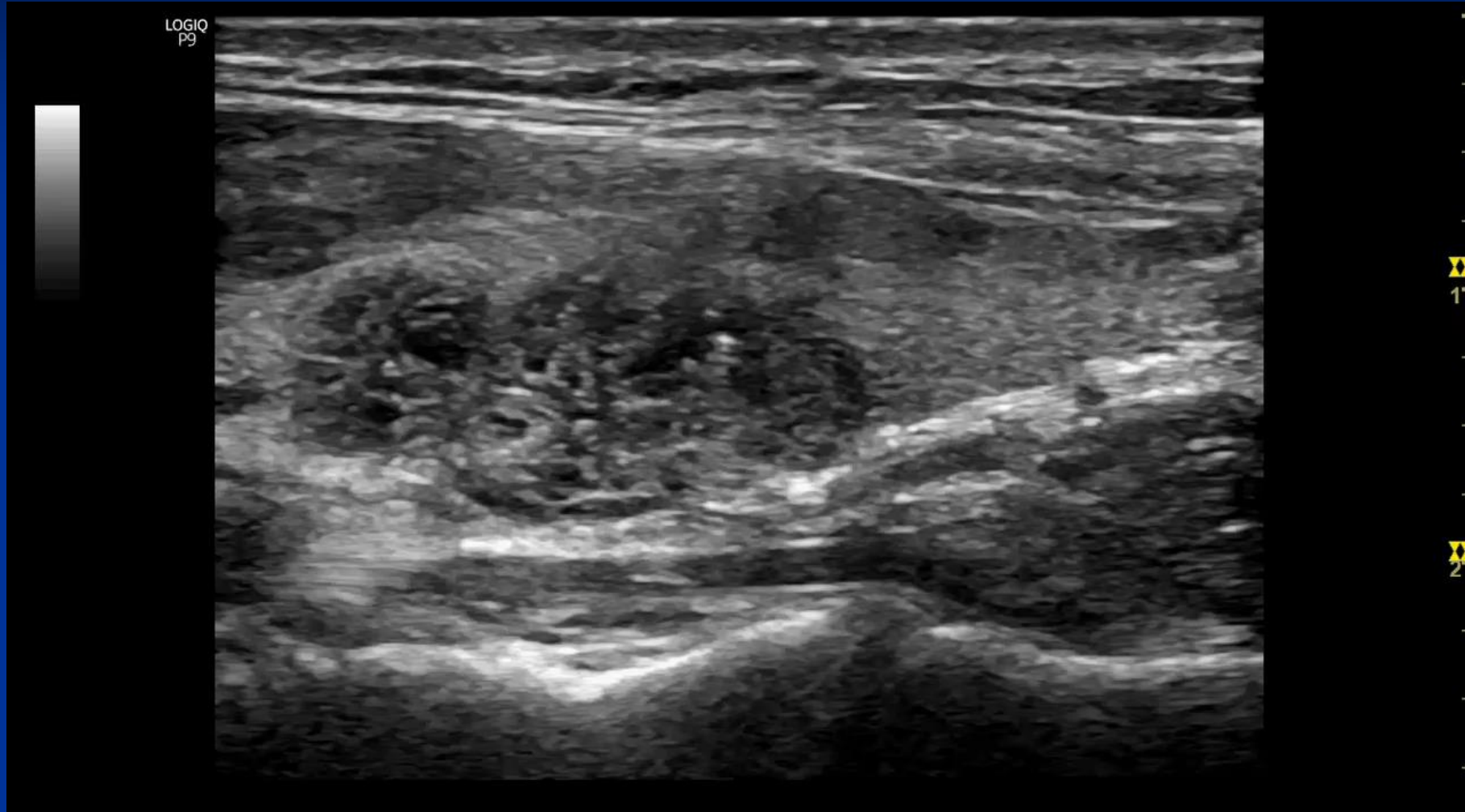
THYROID LA523

NOD 1

AP	1.80	cm
TV	2.23	cm
SAG	2.24	cm
V	4.7	ml



Spongiform

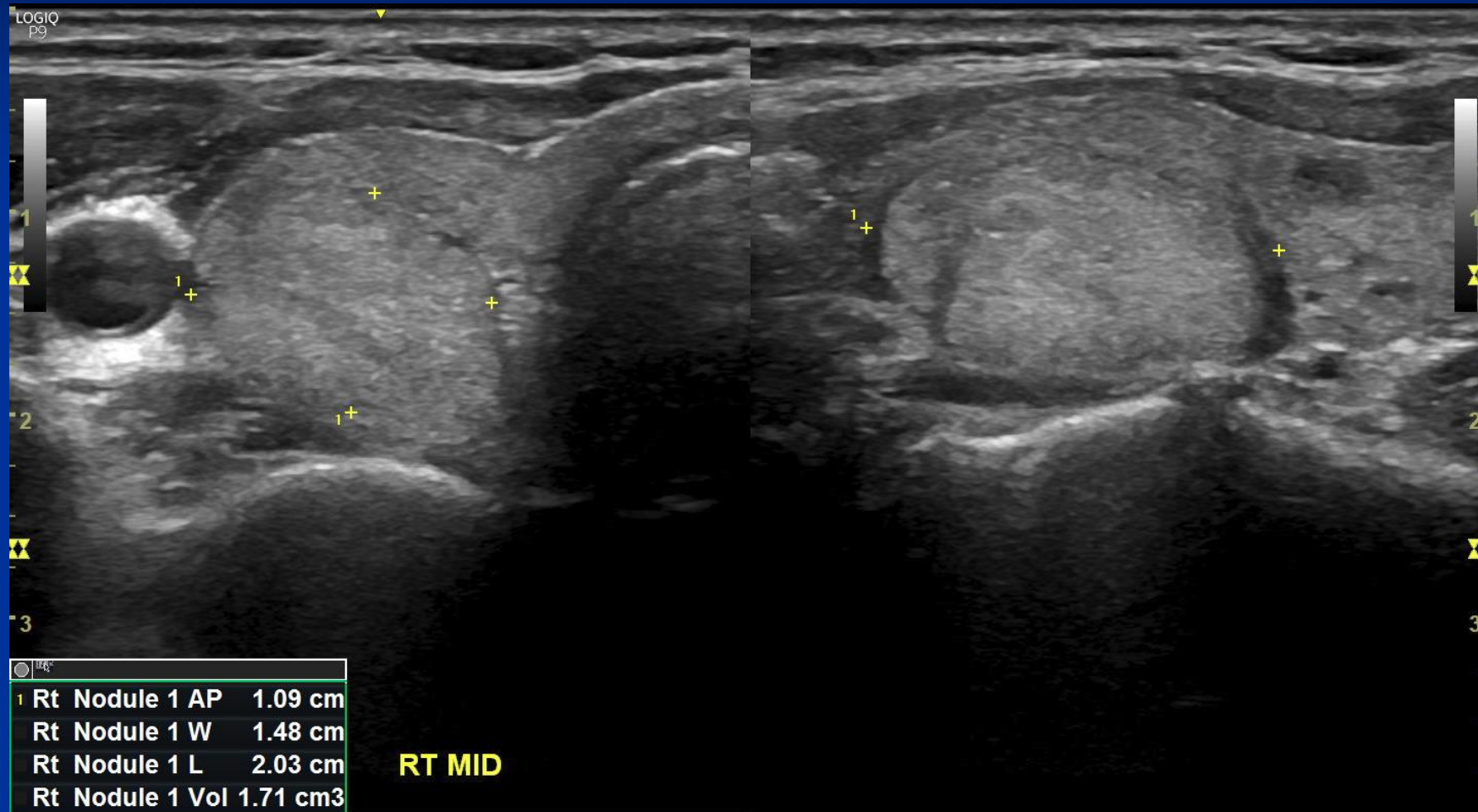


Echogenic foci often interpreted as micro-calcs

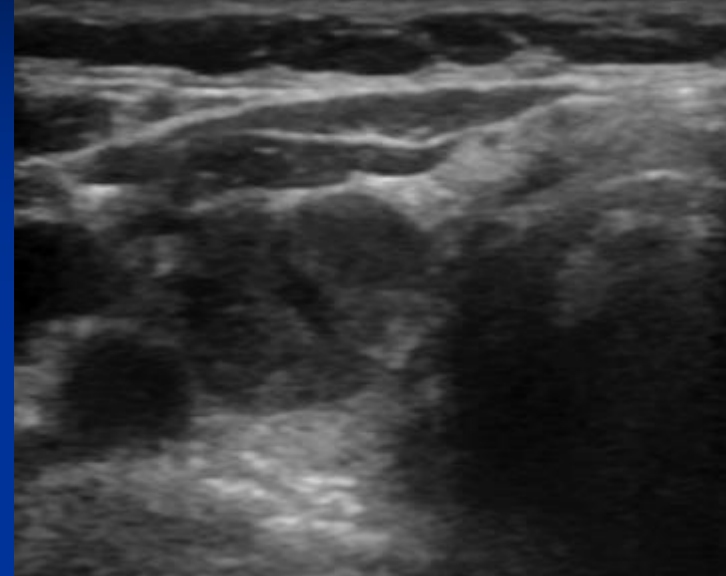
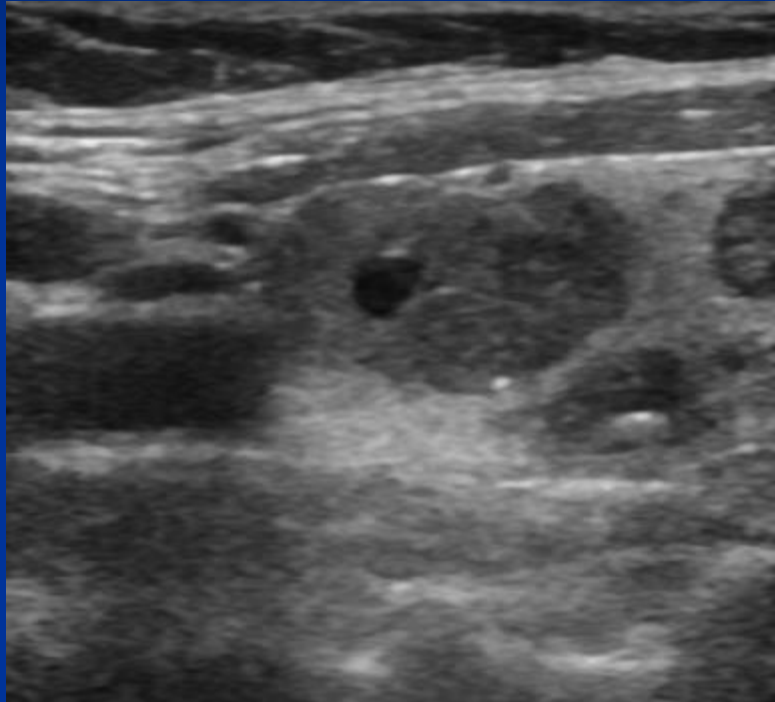
Echogenicity

- Hyperechoic
- Isoechoic
- Mildly Hypoechoic
- Markedly (very) Hypoechoic

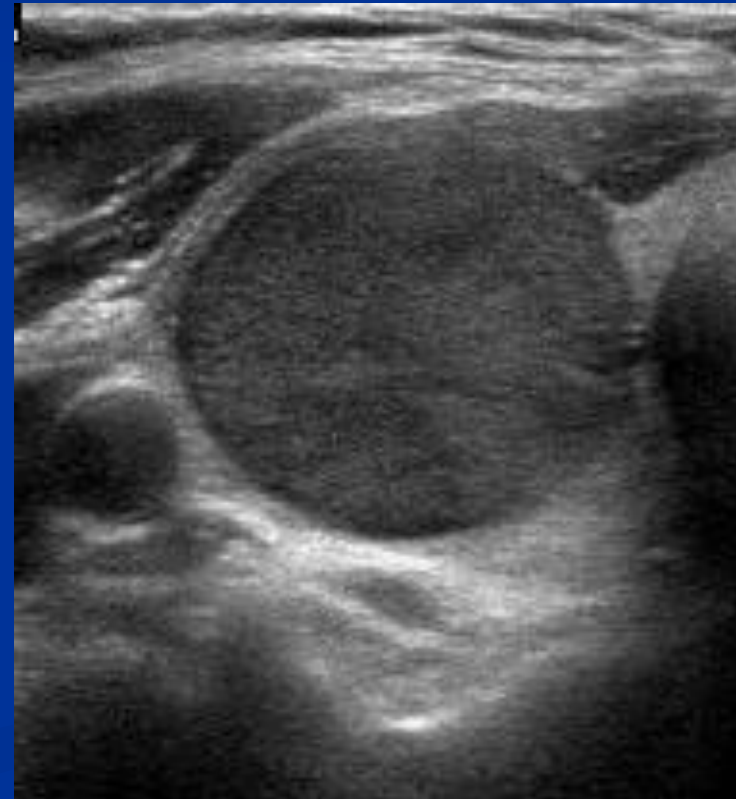
Isoechoic



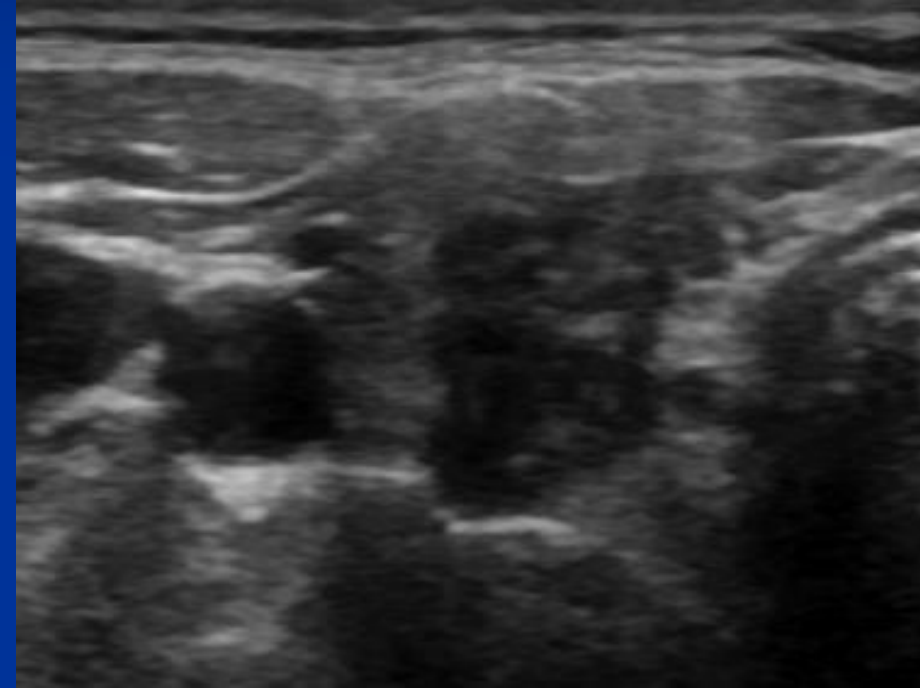
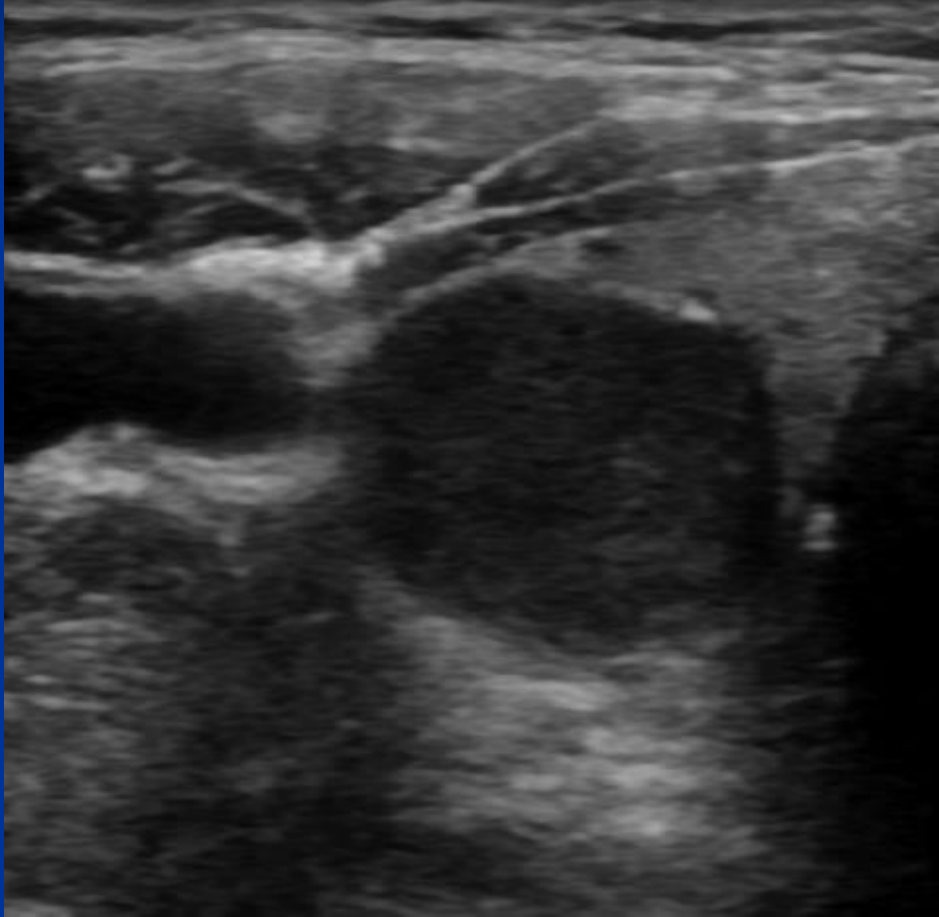
Hypoechoic



Hypoechoic



Markedly Hypoechoic

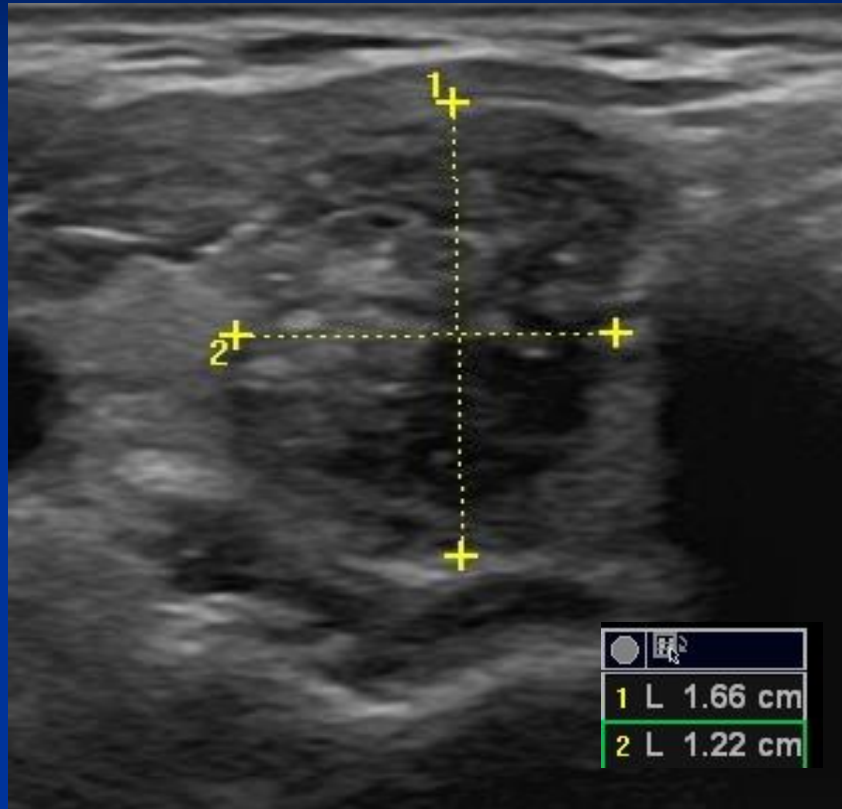


Compare to strap muscles and SCM

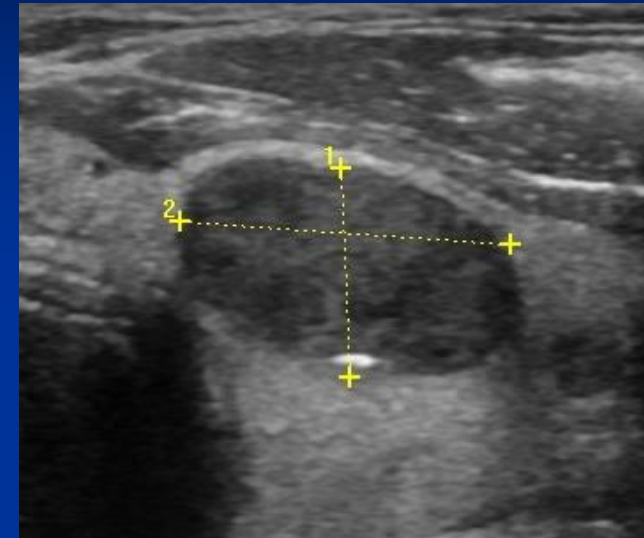
Shape/Orientation

- Parallel (wider than tall)
- Non-Parallel (taller than wide)

Taller than wide



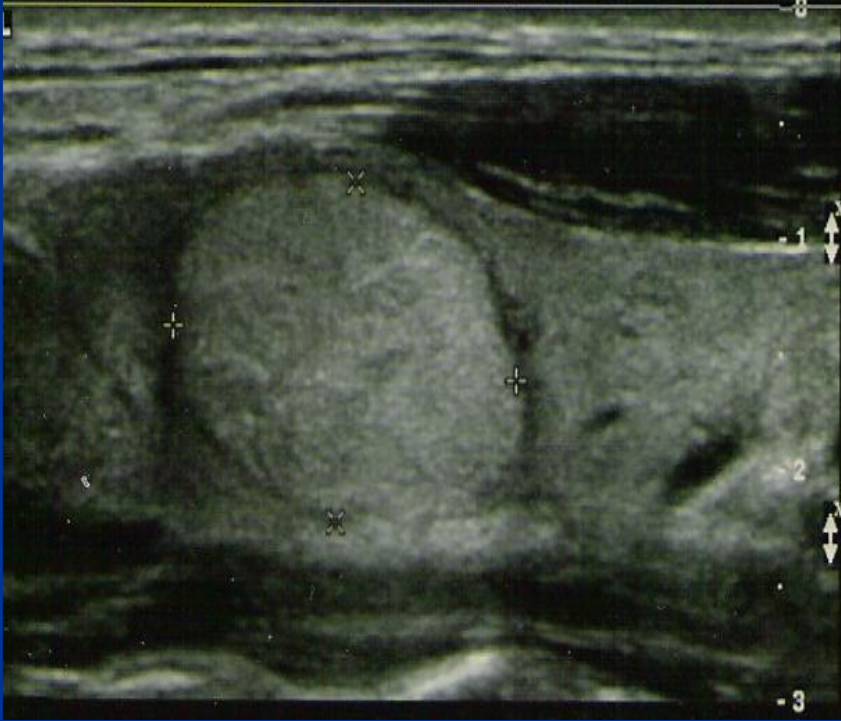
Nodule is taller than wide on the transverse view



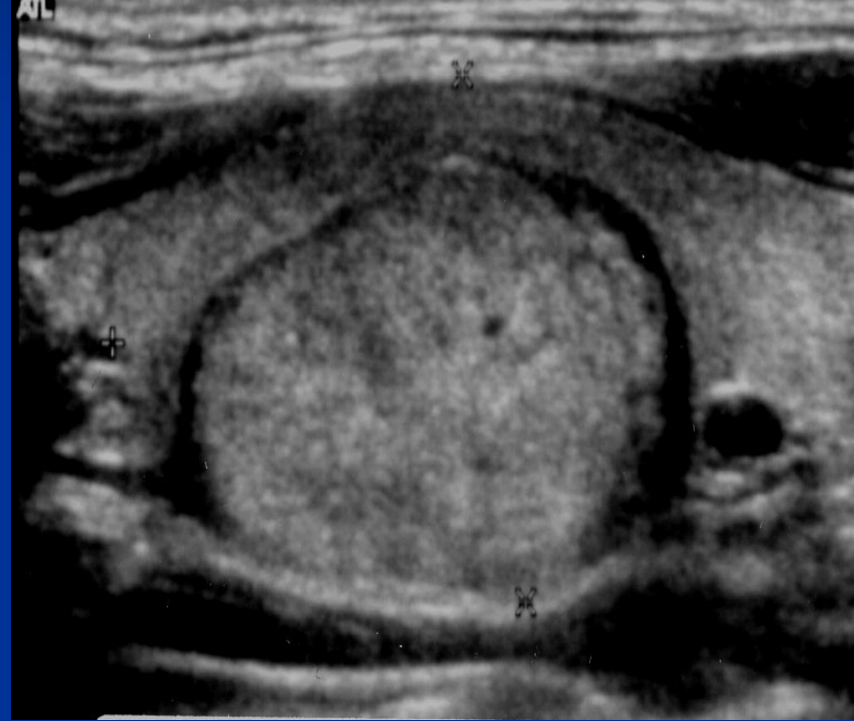
Margin

- Smooth
- Microlobulated
- Spiculated
- Ill-Defined
- Invasive

Halo

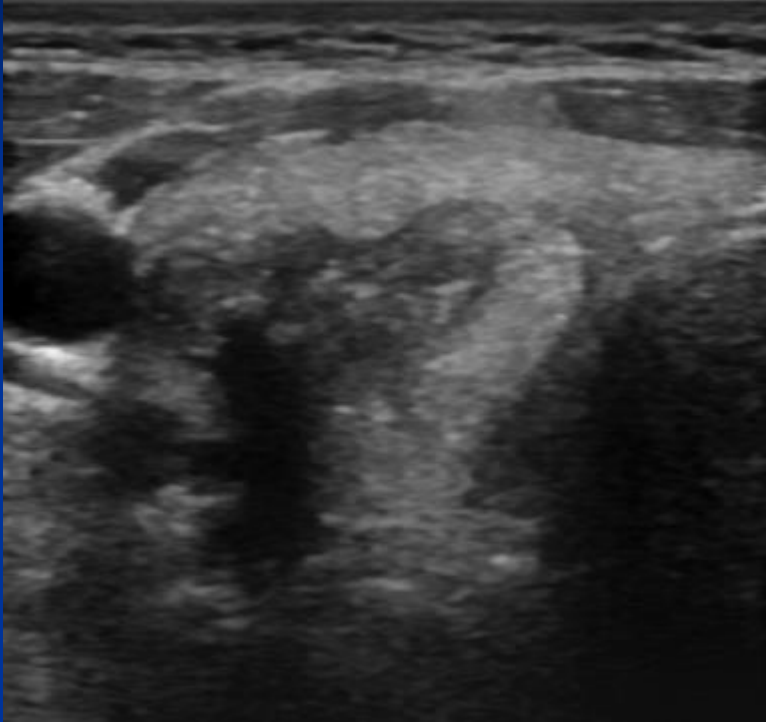


Thin Halo
Benign Follicular Adenoma

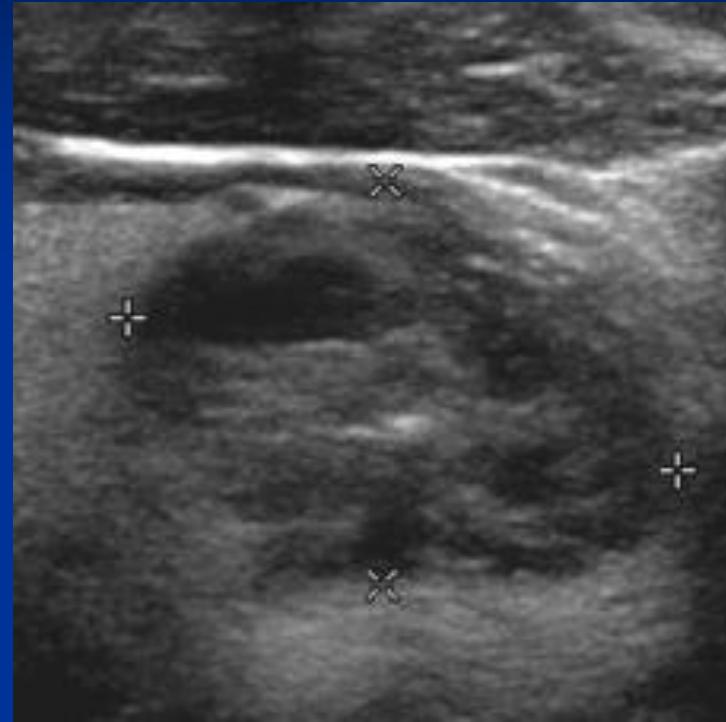


Thick, Irregular Halo
Follicular CA

Margins

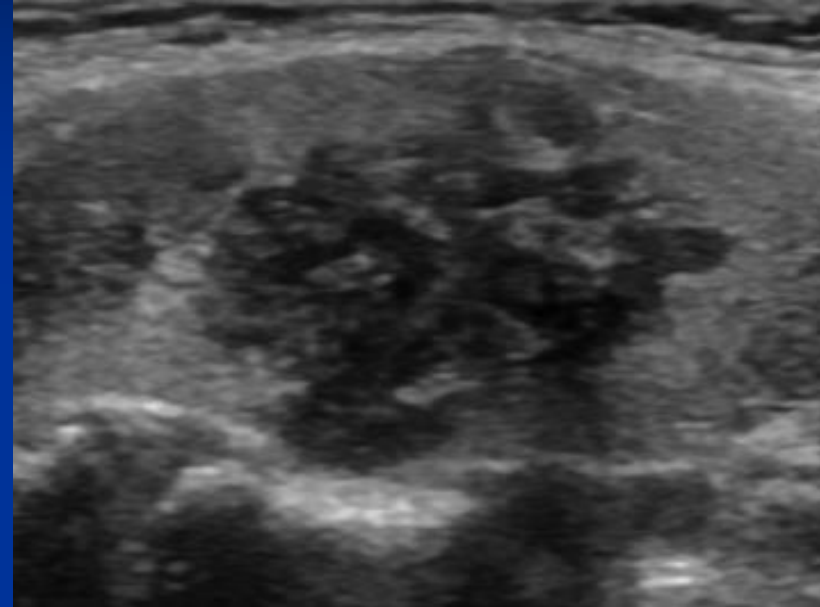
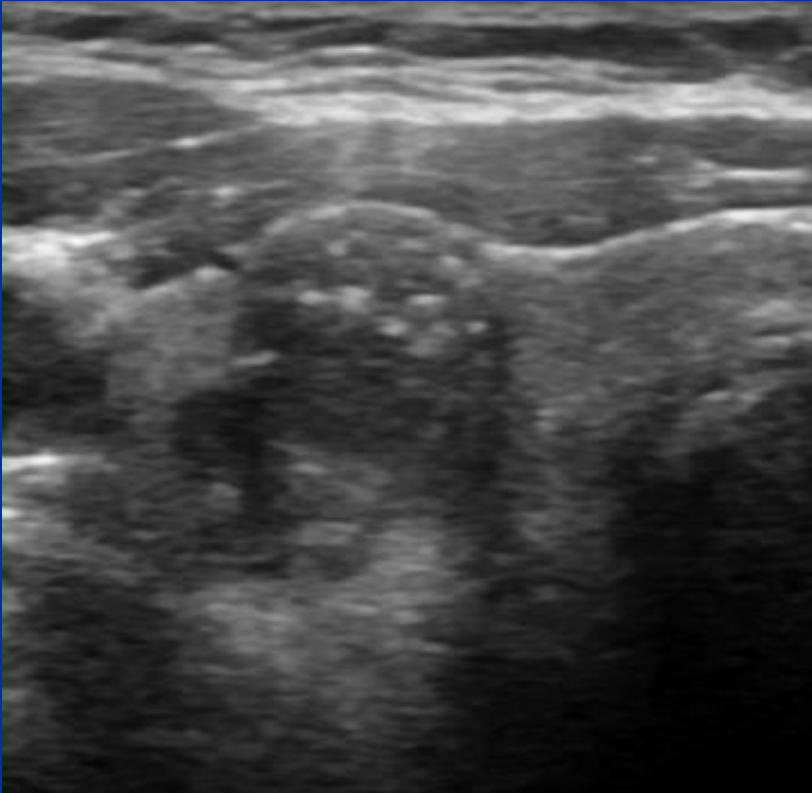


Irregular

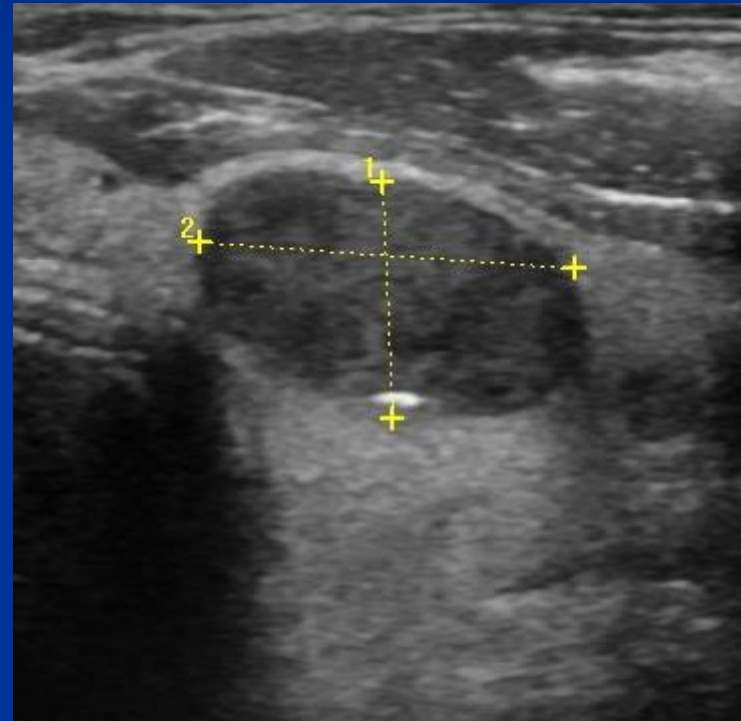
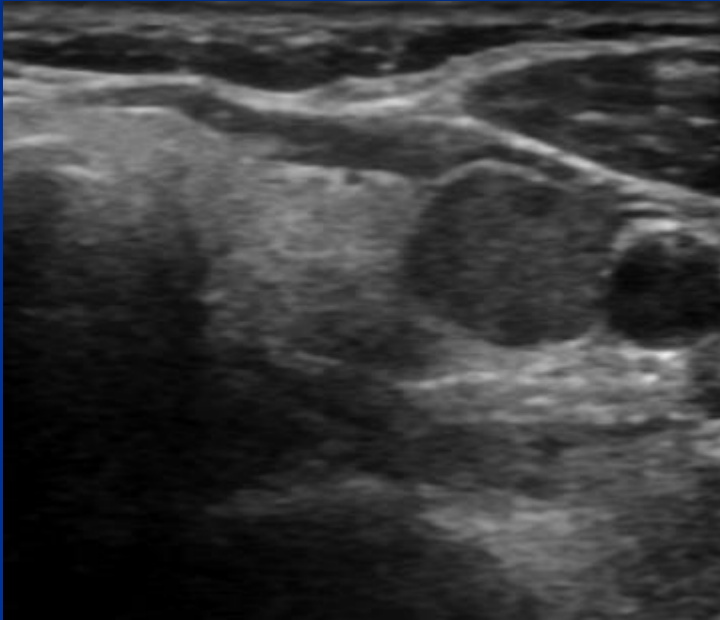


Poorly defined, but not infiltrative (spongiform)

Infiltrative/Irregular Borders



No Halo, but a Smooth Margin



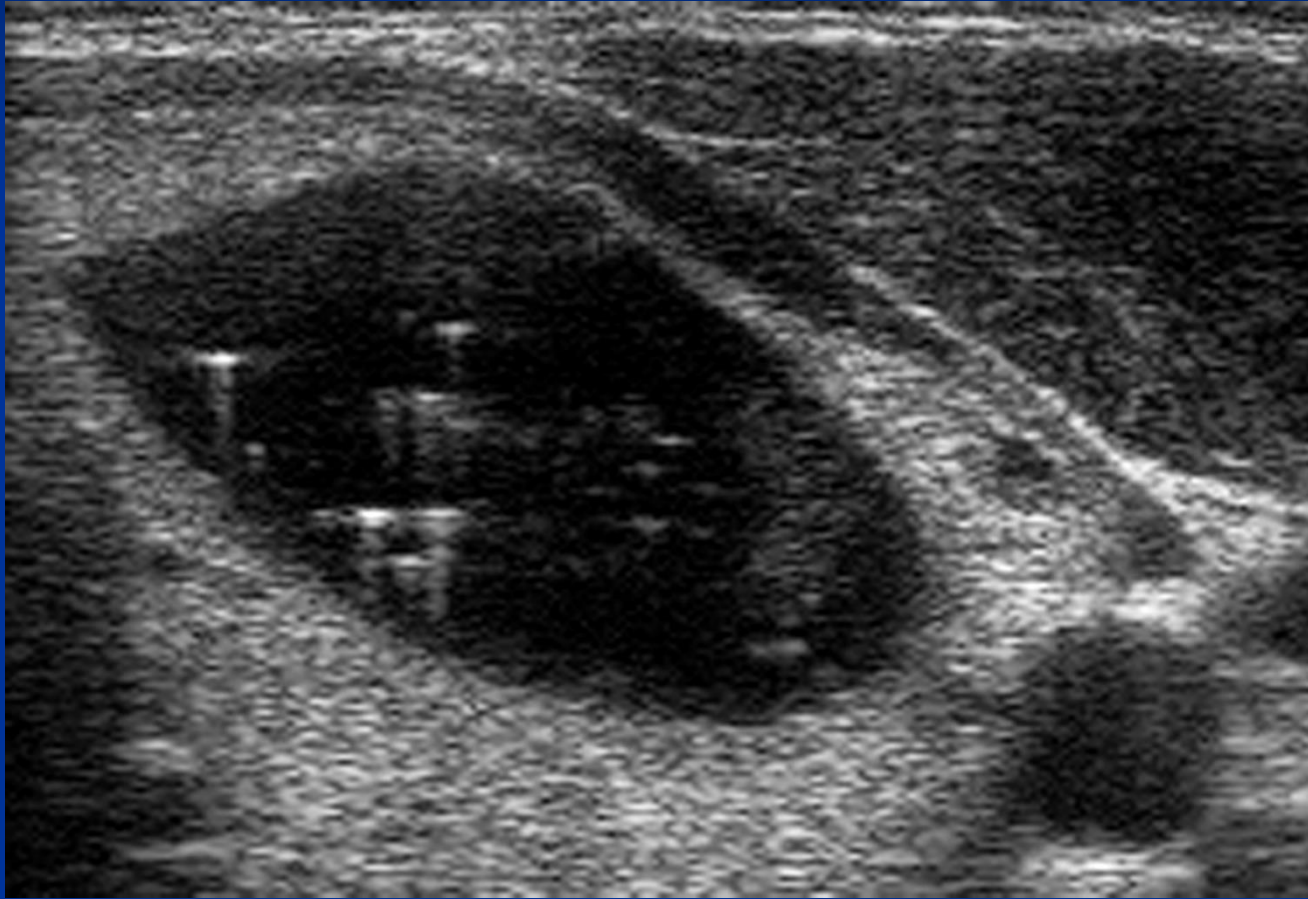
Gross Extra-Thyroidal Extension



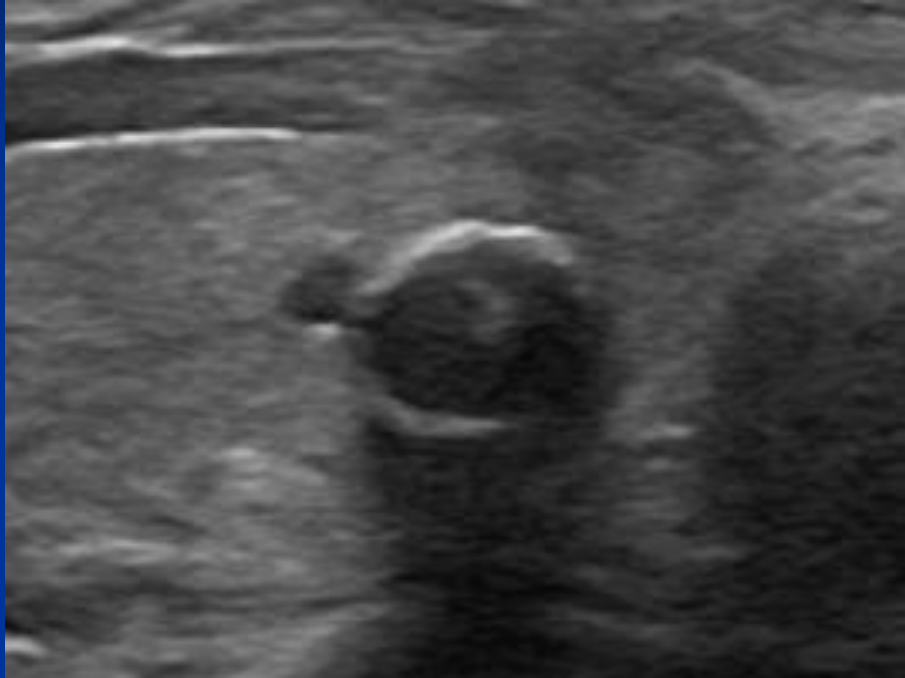
Echogenic Foci

- Punctate echogenic foci (“microcalcifications”)
- Intranodular macrocalcification
- Rim calcification
- Intracystic echogenic foci with comet tail

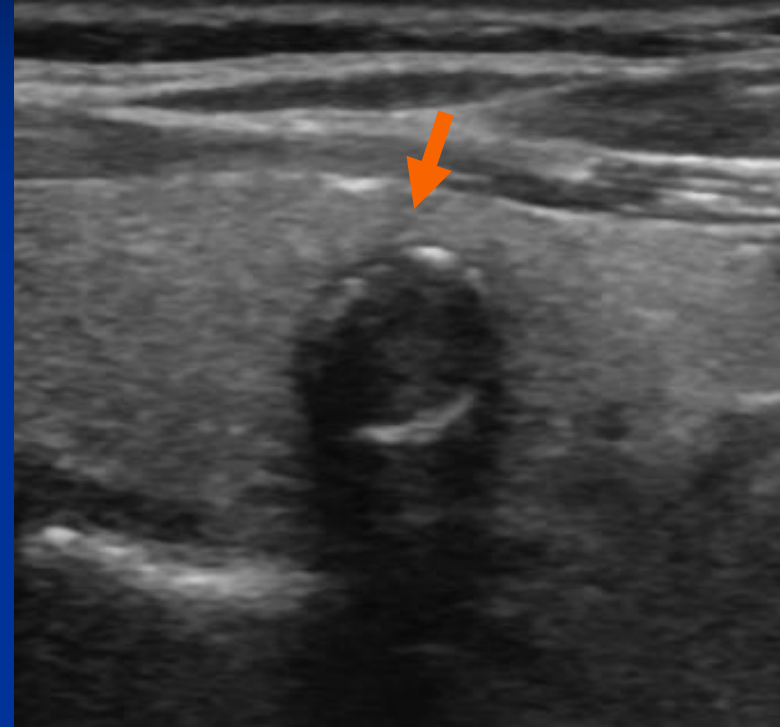
Colloid within Cystic Nodule with “Comet Tails”



Eggshell Calcifications with Shadowing

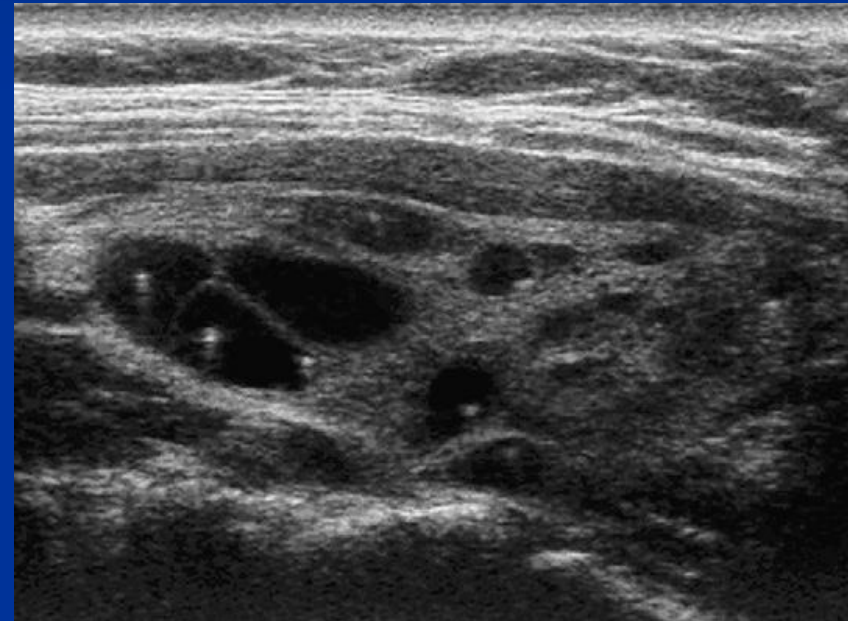
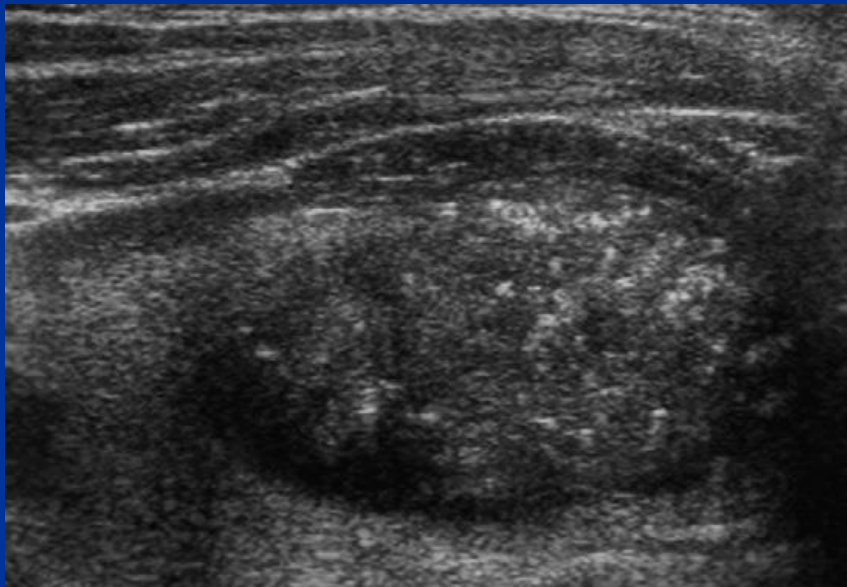


Smooth Eggshell
Maybe Reassuring

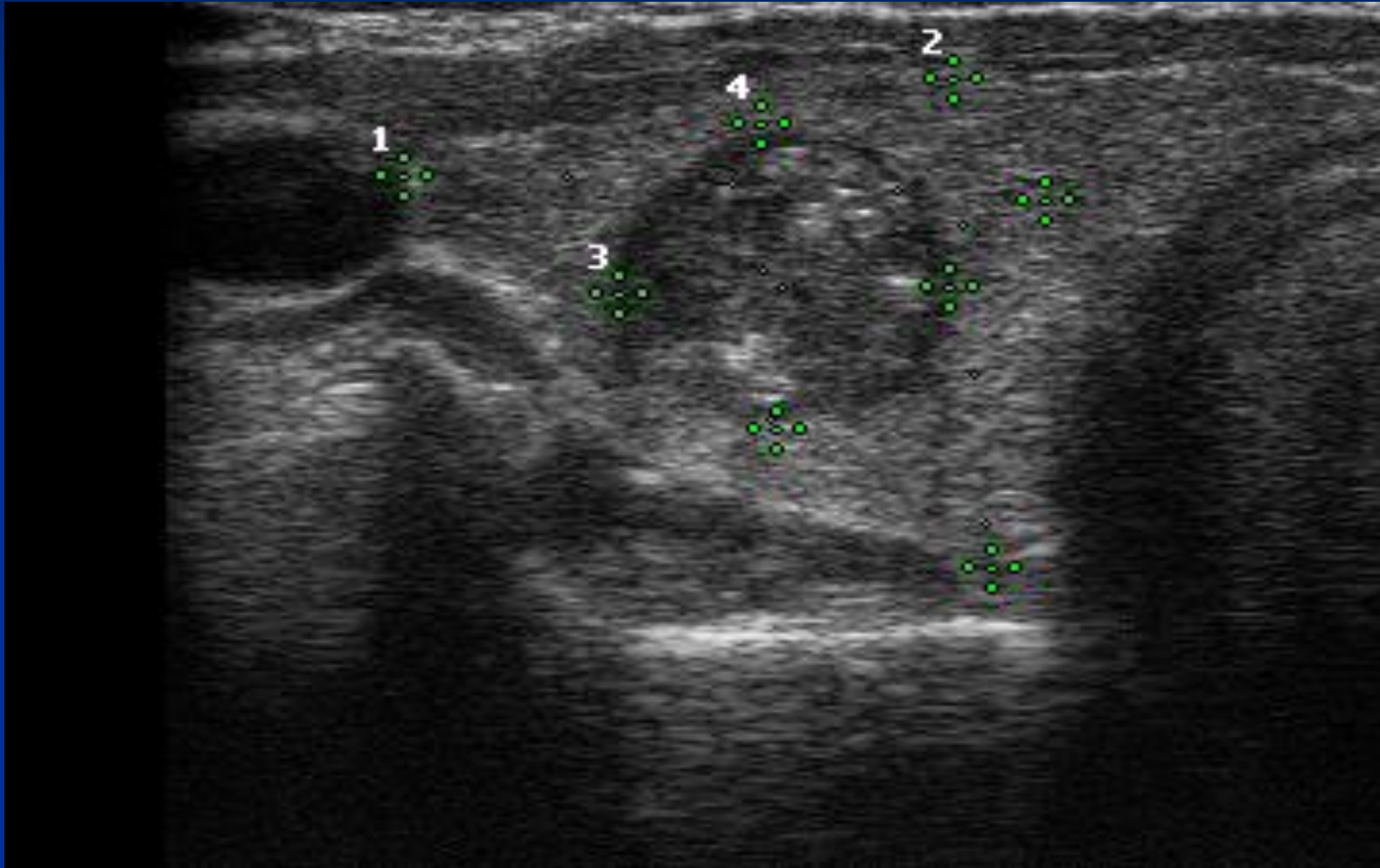


Interrupted Eggshell
Not reassuring

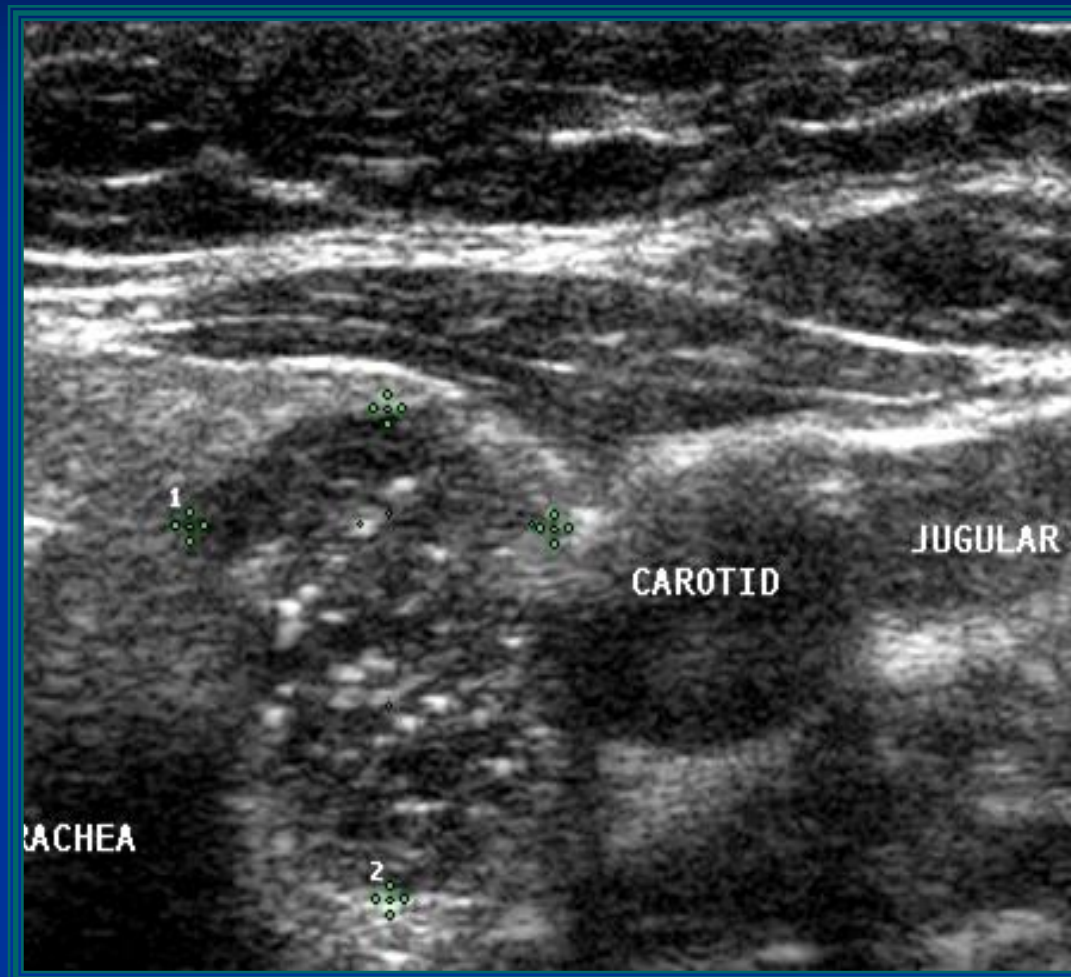
Microcalcification vs Comet Tail



Microcalcifications

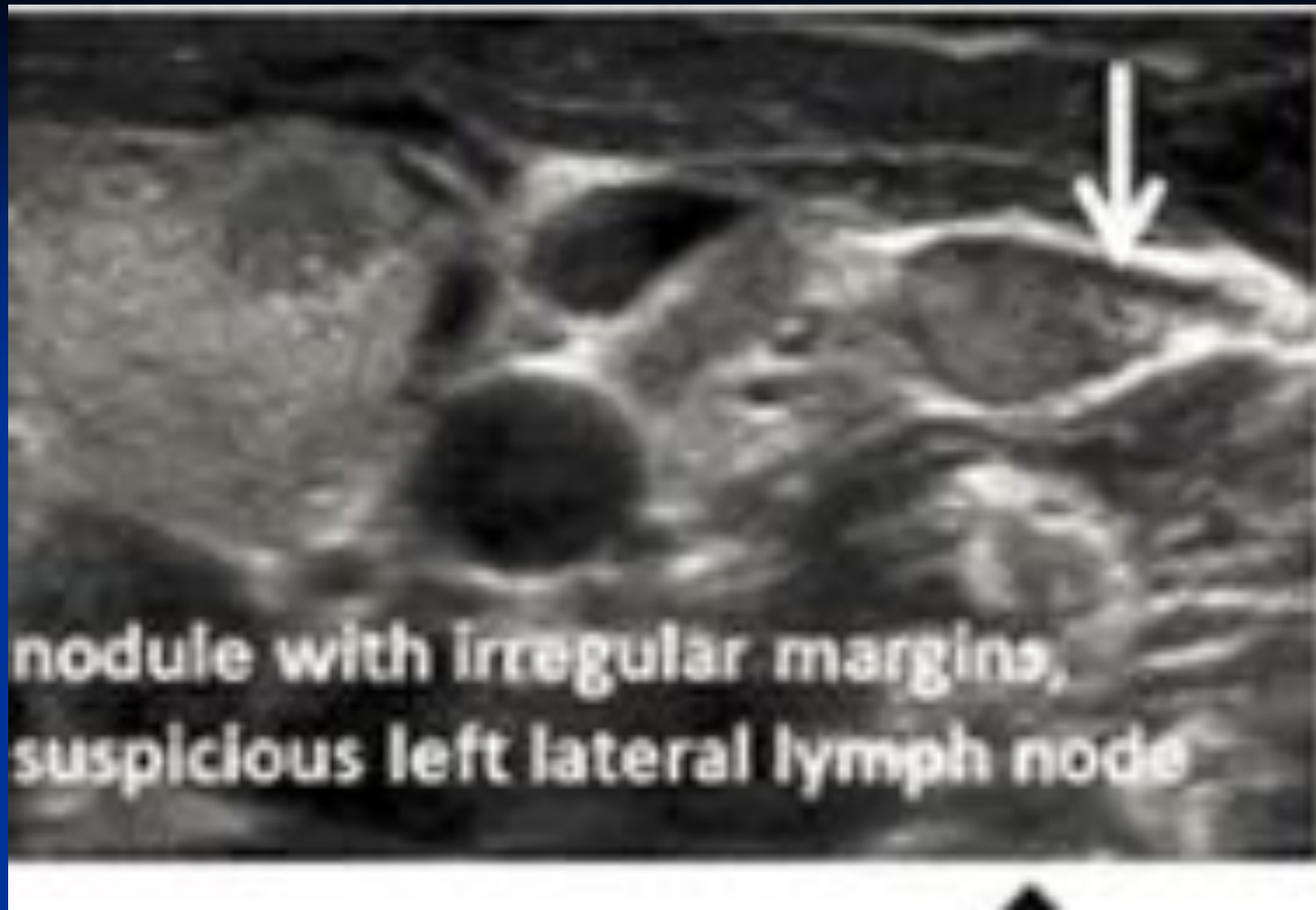


Microcalcifications



Suspicious Sonographic Features

- Hypoechoic
- Microcalcifications
- Infiltrative margins
- Taller than wide shape
- Abnormal cervical lymph nodes
- Extrathyroidal extension



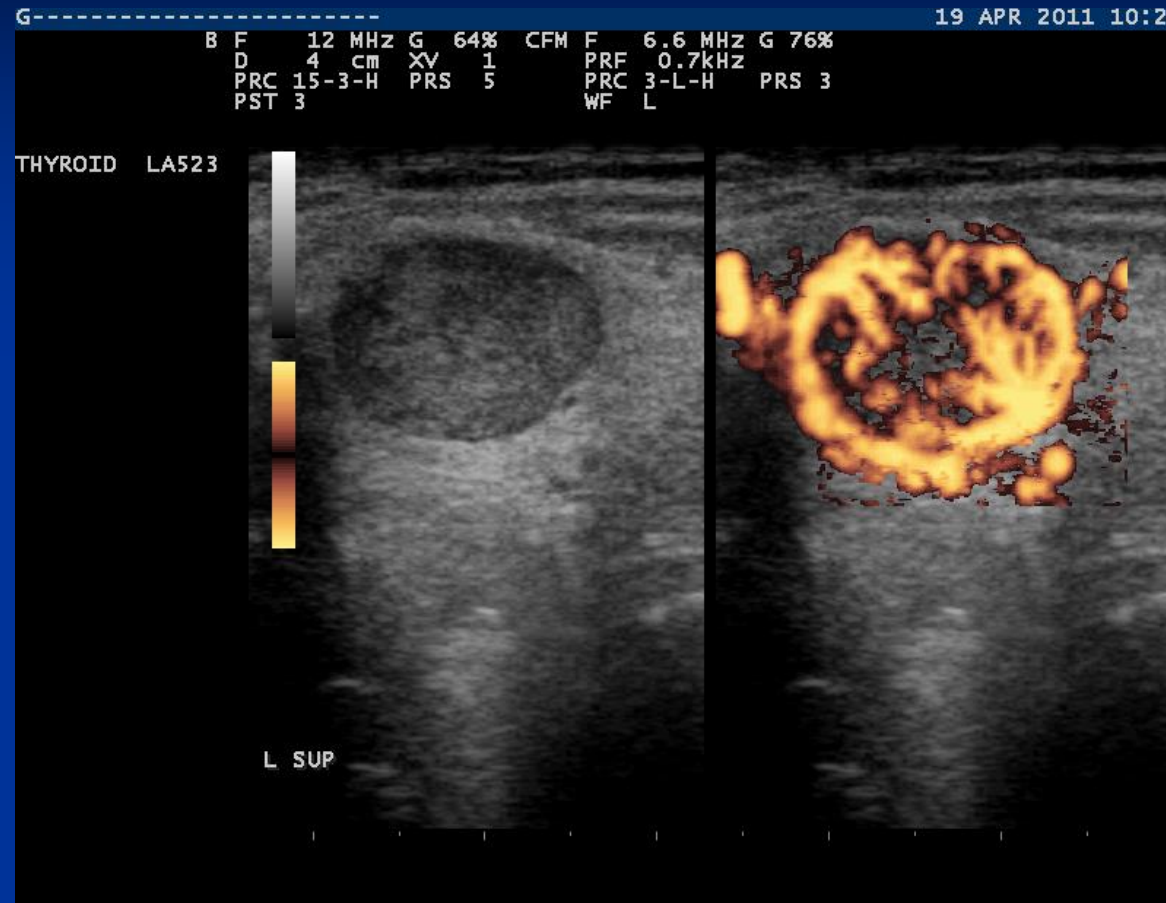
ALWAYS look for lymph nodes !

Suspicious Sonographic Features

- Hypoechoic
- Microcalcifications
- Infiltrative margins
- Taller than wide shape
- Abnormal cervical lymph nodes

NOT DOPPLER?

What About Intranodular Flow?

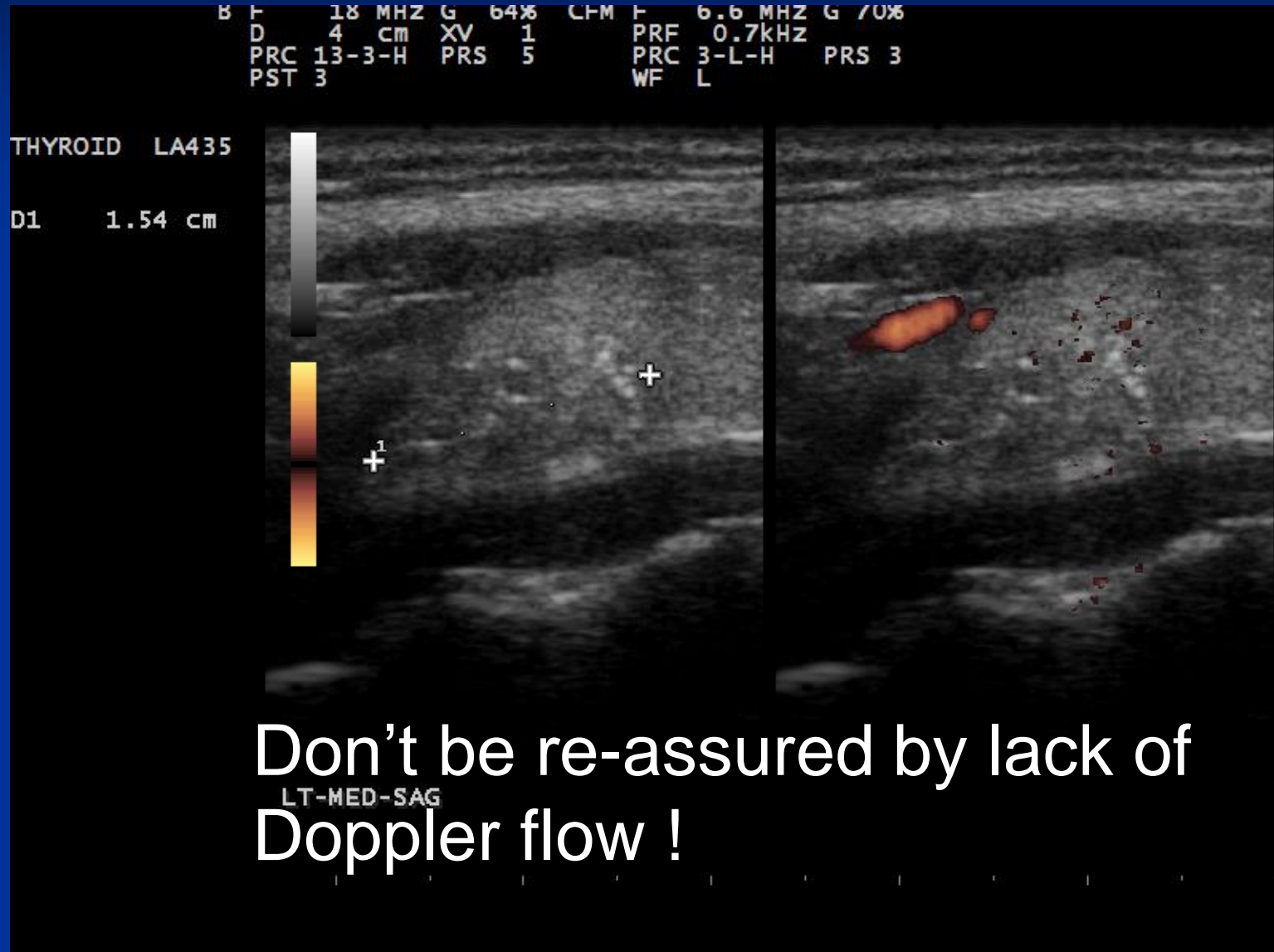


B-Mode

Power Doppler

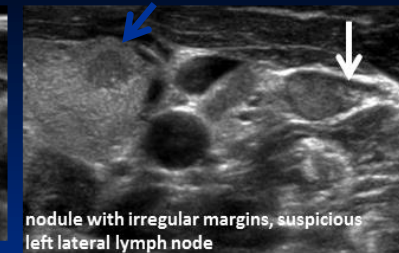
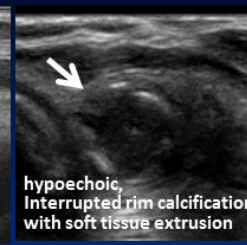
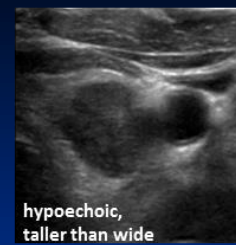
**NO LONGER CONSIDERED AN INDEPENDENT
RISK FACTOR WHEN DECIDING ON FNA**

PTC – lack of Doppler

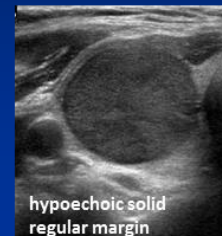


ATA 2015: Nodule Sonographic Pattern Risk of Malignancy

High
Suspicion
70-90%

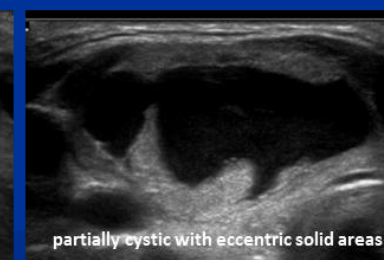
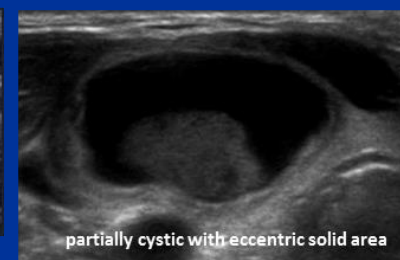


Intermediate
Suspicion
10-20%

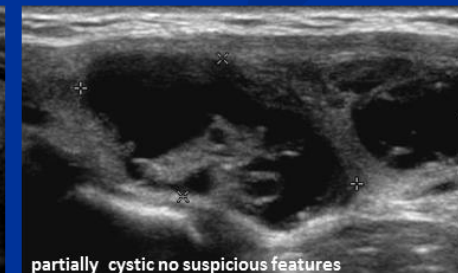
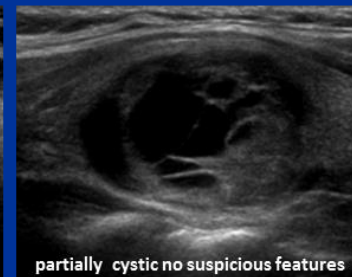
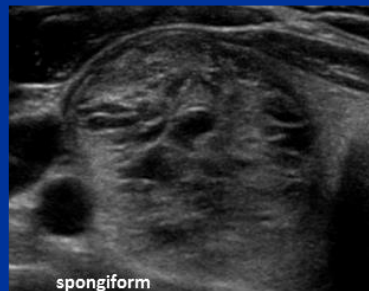


PATTERN BASED

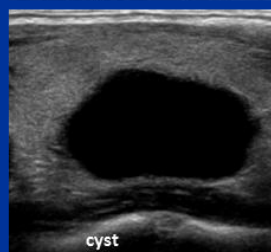
Low
Suspicion
5-10%



Very low
Suspicion
<3%



Benign
<1%



Haugen et al. Thyroid; October 2015

Risk of malignancy

ACR TI-RADS 2017

- Point based system
 - Composition
 - Echogenicity
 - Shape
 - Margins
 - Echogenic Foci
- “Leave no nodule behind”

Tessler et al; J ACR 2017

ACR TI-RADS

COMPOSITION

(Choose 1)

Cystic or almost completely cystic	0 points
Spongiform	0 points
Mixed cystic and solid	1 point
Solid or almost completely solid	2 points

ECHOGENICITY

(Choose 1)

Anechoic	0 points
Hyperechoic or isoechoic	1 point
Hypoechoic	2 points
Very hypoechoic	3 points

SHAPE

(Choose 1)

Wider-than-tall	0 points
Taller-than-wide	3 points

MARGIN

(Choose 1)

Smooth	0 points
Ill-defined	0 points
Lobulated or irregular	2 points
Extra-thyroidal extension	3 points

ECHOGENIC FOCI

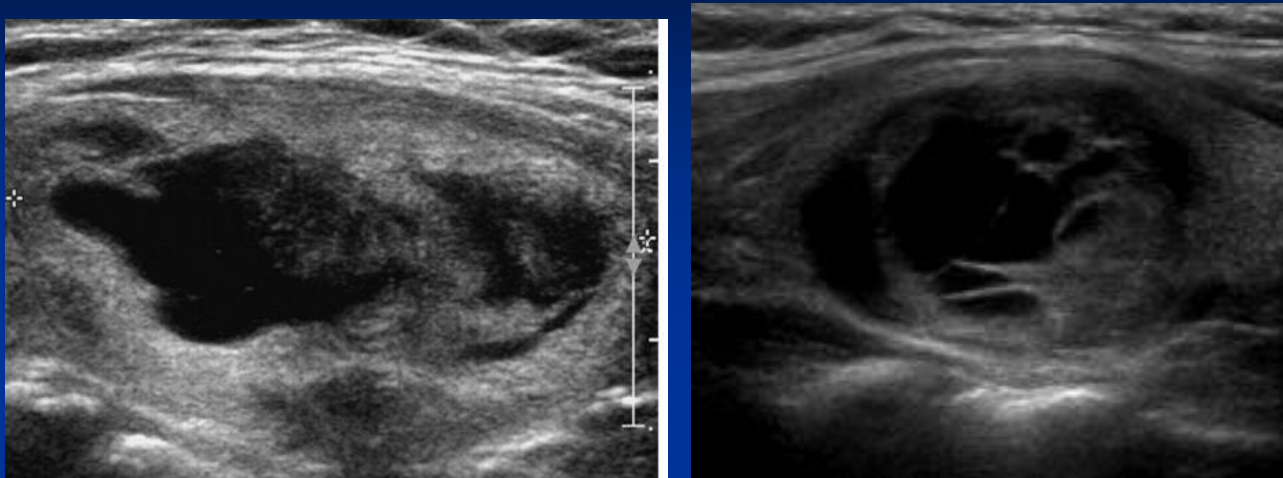
(Choose All That Apply)

None or large comet-tail artifacts	0 points
Macrocalcifications	1 point
Peripheral (rim) calcifications	2 points
Punctate echogenic foci	3 points

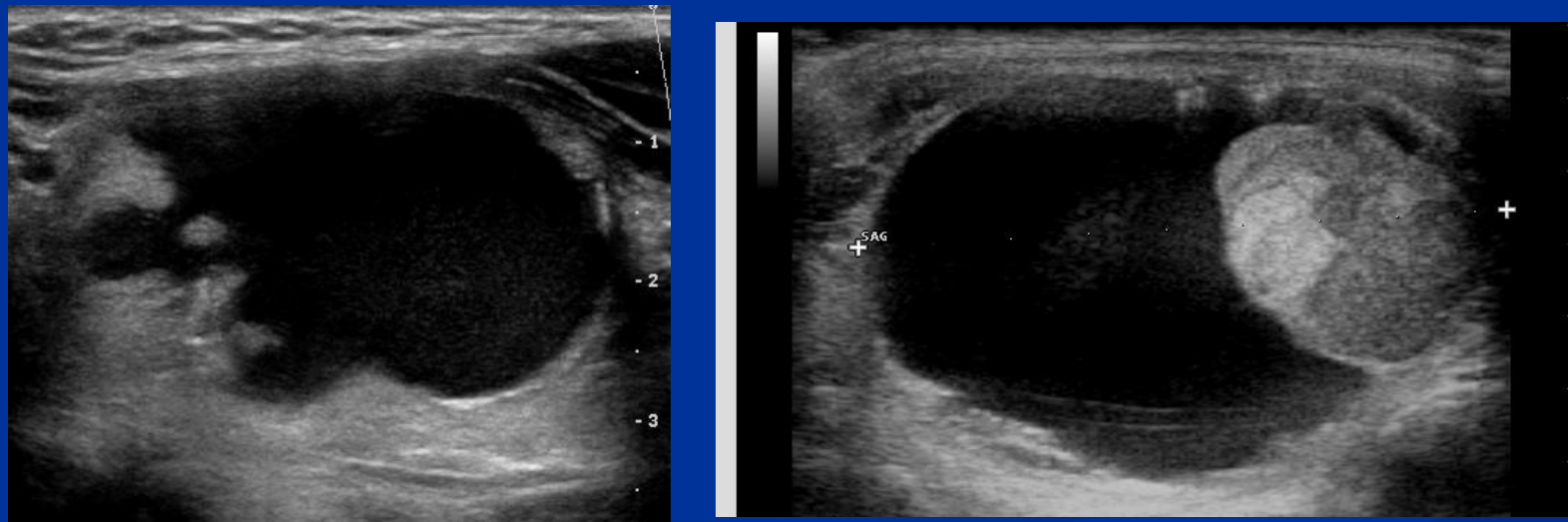
ACR TI-RADS



Partially cystic nodules—the solid part



Concentric



Uniformly solid area, abutting one side of cyst -- ECCENTRIC

Cystic PTC

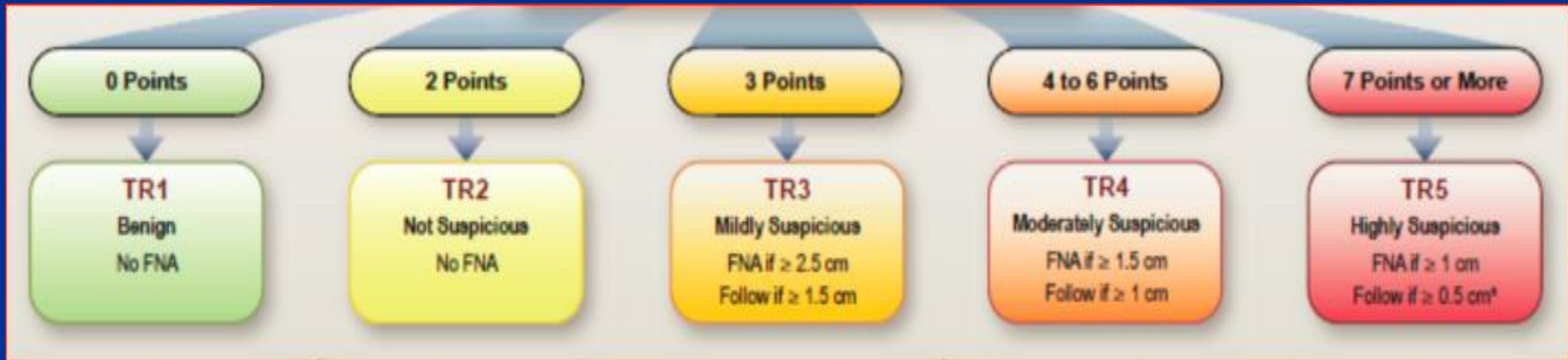


R8 US Pattern and suggested FNA cutoffs

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
<u>One option is surveillance</u>				
Benign	< 1%	No biopsy	Strong	Moderate
FNA is not recommended for nodules that do not meet the above criteria, including all nodules < 1 cm			Strong	Moderate

Haugen et al. Thyroid; January 2016

ACR TI-RADS FNA Recommendations



R24 Recommended follow-up of nodules that have not undergone FNA

Sonographic Pattern		Strength of rec	Quality of evidence
High suspicion	Repeat US 6-12 months	Weak	Low
Intermediate/ Low suspicion	Repeat US at 12-24m	Weak	Low
Very low suspicion	> 1cm: Utility and time interval of repeat US for risk of malignancy is not known. If repeated, do at ≥ 24 months	NO rec	Insufficient
	≤ 1 cm: Do not require routine US surveillance	Weak	Low

2017 Bethesda System for Reporting Thyroid Cytopathology

Diagnostic Category	ROM if NIFTP not cancer	ROM if NIFTP is cancer	Management
Nondiagnostic/unsatisfactory Cyst fluid only Acellular specimen Other: Obscuring factors	5–10%	5–10%	Repeat fine needle aspiration under ultrasound guidance
Benign Benign follicular nodule Chronic lymphocytic (Hashimoto) thyroiditis, in proper clinical setting Granulomatous (subacute) thyroiditis	0–3%	0–3%	Clinical and US follow-up until two negative
Atypia of undetermined significance/ follicular lesion of undetermined significance	6–18%	10–30%	Repeat FNA, molecular testing, or lobectomy
Follicular neoplasm/ suspicious for a follicular neoplasm (Specify if Hürthle cell type)	10–40%	25–40%	Molecular testing, lobectomy
Suspicious for malignancy	45–60%	50–75%	Lobectomy or near-total thyroidectomy
Malignant Papillary thyroid carcinoma Medullary thyroid carcinoma Poorly differentiated carcinoma Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma Carcinoma with mixed features Metastatic malignancy Non-Hodgkin lymphoma Other	94–96%	97–99%	Lobectomy or near-total thyroidectomy

Indeterminate Cytology – Bethesda Classes III and IV

Atypia of undetermined significance/ follicular lesion of undetermined significance	6–18%	10–30%	Repeat FNA, molecular testing, or lobectomy
Follicular neoplasm/ suspicious for a follicular neoplasm (Specify if Hürthle cell type)	10–40%	25–40%	Molecular testing, lobectomy

ATA 2015 Guidelines

[A17] AUS/FLUS cytology

■ **RECOMMENDATION 15**

(A) For nodules with AUS/FLUS cytology, after consideration of worrisome clinical and sonographic features, investigations such as repeat FNA or molecular testing may be used to supplement malignancy risk assessment in lieu of proceeding directly with a strategy of either surveillance or diagnostic surgery. Informed patient preference and feasibility should be considered in clinical decision-making.

(Weak recommendation, Moderate-quality evidence)

(B) If repeat FNA cytology, molecular testing, or both are not performed or inconclusive, either surveillance or diagnostic surgical excision may be performed for an AUS/FLUS thyroid nodule, depending on clinical risk factors, sonographic pattern, and patient preference.

(Strong recommendation, Low-quality evidence)

[A18] Follicular neoplasm/suspicious for follicular neoplasm cytology

■ **RECOMMENDATION 16**

(A) Diagnostic surgical excision is the long-established standard of care for the management of FN/SFN cytology nodules. However, after consideration of clinical and sonographic features, molecular testing may be used to supplement malignancy risk assessment data in lieu of proceeding directly with surgery. Informed patient preference and feasibility should be considered in clinical decision-making.

(Weak recommendation, Moderate-quality evidence)

(B) If molecular testing is either not performed or inconclusive, surgical excision may be considered for removal and definitive diagnosis of an FN/SFN thyroid nodule.

(Strong recommendation, Low-quality evidence)

Afirma GSC – Introduced 2018

JAMA Surgery | **Original Investigation**

Performance of a Genomic Sequencing Classifier for the Preoperative Diagnosis of Cytologically Indeterminate Thyroid Nodules

Kepal N. Patel, MD; Trevor E. Angell, MD; Joshua Babiarz, PhD; Neil M. Barth, MD; Thomas Blevins, MD;
Quan-Yang Duh, MD; Ronald A. Ghossein, MD; R. Mack Harrell, MD; Jing Huang, PhD; Giulia C. Kennedy, PhD;
Su Yeon Kim, PhD; Richard T. Kloos, MD; Virginia A. LiVolsi, MD; Gregory W. Randolph, MD;
Peter M. Sadow, MD, PhD; Michael H. Shanik, MD; Julie A. Sosa, MD; S. Thomas Traweek, MD; P. Sean Walsh, MPH;
Duncan Whitney, PhD; Michael W. Yeh, MD; Paul W. Ladenson, MD

JAMA Surg. 2018;153(9):817-824. doi:10.1001/jamasurg.2018.1153
Published online May 23, 2018.

Afirma GSC – BC III and IV

Table 2. Performance of the Genomic Sequencing Classifier (GSC)
According to the Final Histopathological Diagnoses
and Cytopathological Category

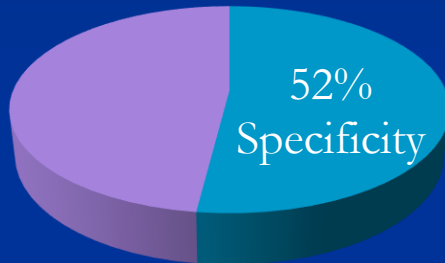
GSC Result	Reference Standard, % (95% CI)	
	Malignant	Benign
Performance across the primary test set of Bethesda III and IV indeterminate nodules (n = 190)		
Suspicious, No./total No.	41/45	46/145
Benign, No./total No.	4/45	99/145
Sensitivity	91.1 (79-98)	
Specificity	68.3 (60-76)	
NPV	96.1 (90-99)	
PPV	47.1 (36-58)	
Prevalence of malignant lesions, %	23.7	

NPV 96%

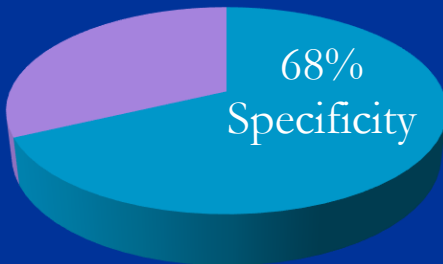
PPV 47%

Afirma GEC vs GSC for BC III/IV

GEC



GSC



Test	Sens	Spec	Ca %	NPV	PPV
GEC	92%	52%	24%	93%	37%
GSC	91%	68%	24%	96%	47%

Alexander EK et al, NEJM 2012
Patel KN et al, JAMA Surg 2018

Improved Specificity → Higher Benign Call Rate

Clinical Validation of ThyroSeq v3 GC

Research

JAMA Oncology | Original Investigation

Performance of a Multigene Genomic Classifier in Thyroid Nodules With Indeterminate Cytology A Prospective Blinded Multicenter Study

David L. Steward, MD; Sally E. Carty, MD; Rebecca S. Sippel, MD; Samantha Peiling Yang, MBBS, MRCP, MMed;
Julie A. Sosa, MD, MA; Jennifer A. Sipos, MD; James J. Figge, MD, MBA; Susan Mandel, MD, MPH;
Bryan R. Haugen, MD; Kenneth D. Burman, MD; Zubair W. Baloch, MD, PhD; Ricardo V. Lloyd, MD, PhD;
Raja R. Seethala, MD; William E. Gooding, MS; Simion I. Chiosea, MD; Cristiane Gomes-Lima, MD;
Robert L. Ferris, MD, PhD; Jessica M. Folek, MD; Raheela A. Khawaja, MD; Priya Kundra, MD;
Kwok Seng Loh, MBBS; Carrie B. Marshall, MD; Sarah Mayson, MD; Kelly L. McCoy, MD; Min En Nga, MBBS;
Kee Yuan Ngiam, MBBS, MRCS, MMed; Marina N. Nikiforova, MD; Jennifer L. Poehls, MD; Matthew D. Ringel, MD;
Huaitao Yang, MD, PhD; Linwah Yip, MD; Yuri E. Nikiforov, MD, PhD

ThyroSeq v3 GC Performance in Multi-Center Study

Table 1. Performance of the Genomic Classifier Test in Cytologically Indeterminate Thyroid Nodules

Performance in Bethesda III nodules (n = 154; disease prevalence 23%)			
Result	Cancer+NIFTP (n = 35)	Benign (n = 119)	Test performance, % (95% CI)
Positive	32	18	Sensitivity, 91 (77-97)
Negative	3	101	Specificity, 85 (77-90)
			NPV, 97 (92-99)
			PPV, 64 (50-77)
Performance in Bethesda IV nodules (n = 93; disease prevalence 35%)			
Result	Cancer+NIFTP (n = 33)	Benign (n = 60)	Test performance, % (95% CI)
Positive	32	15	Sensitivity, 97(85-100)
Negative	1	45	Specificity, 75(63-84)
			NPV, 98(89-100)
			PPV, 68 (54-80)
Performance in Bethesda III and IV nodules (n = 247; disease prevalence 28%)			
Result	Cancer+NIFTP (n = 68)	Benign (n = 179)	Result
Positive	64	33	Sensitivity, 94 (86-98)
Negative	4	146	Specificity, 82 (75-87)
			NPV, 97 (93-99)
			PPV, 66 (56-75)

eTable 7. Study characteristics and performance of ThyroSeq GC and Afirma GEC and GSC in Bethesda III and IV indeterminate cytology thyroid nodules

	<i>ThyroSeq GC¹</i>	<i>Afirma GSC³</i>
Study type	Multicenter, prospective, double-blind	Multicenter, retrospective, double-blind
Total number, samples	247	191
Total number, patients	223	183
Age, mean (range), years	51.7 (18-90)	51.6 (18-90)
Female, %	80	78
Nodule size by ultrasound, median (range), cm	2.1 (0.5-7)	2.6 (1.0-9.1)
Disease prevalence, %	27.5	23.7
Sensitivity, % (95%CI)	94.1 (86-98)	91.1 (79-98)
Specificity, % (95%CI)	81.6 (75-87)	68.3 (60-76)
NPV	97.3 (93-99)	96.1 (90-99)
PPV	65.9 (56-75)	47.1 (36-58)
Benign call rate	61%	54%
Avoidable surgeries for histologically benign nodules with indeterminate cytology	82%	68%

ThyGenX/ThyraMIR - Validation Study

Molecular Testing for miRNA, mRNA, and DNA on Fine-Needle Aspiration Improves the Preoperative Diagnosis of Thyroid Nodules With Indeterminate Cytology

Emmanuel Labourier, Alexander Shifrin, Anne E. Busseniers, Mark A. Lupo, Monique L. Manganelli, Bernard Andruss, Dennis Wylie, and Sylvie Beaudenon-Huibregtse

Asuragen, Inc (E.L., B.A., D.W., S.B.H.), Austin, Texas 78744; Jersey Shore University Medical Center (A.S.), Center for Thyroid, Parathyroid and Adrenal Diseases, Neptune, New Jersey 07753; Metropolitan Fine Needle Aspiration Service (A.E.B.), Washington, District of Columbia 20037 and Bethesda, Maryland 20814; Thyroid & Endocrine Center of Florida (M.A.L.), Sarasota, Florida 34231; and (M.L.M.) San Diego, California 92103

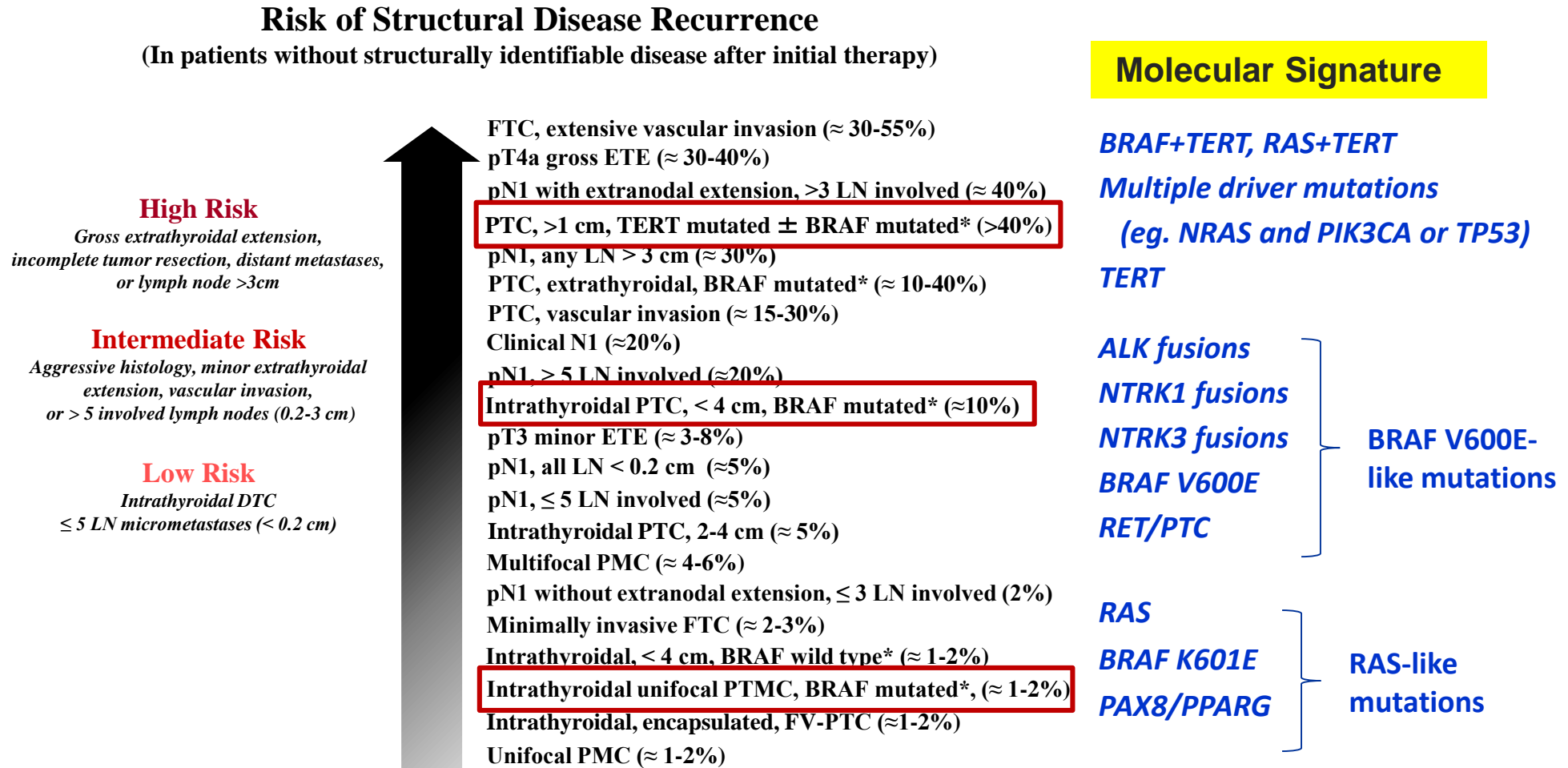
- Retrospective cross-sectional sampling
- Patients with thyroid nodule/s with Bethesda III or IV cytology and known surgical outcome
- 12 United States endocrine centers
- Local surgical pathology report used (blinded to molecular results)
- 109 nodules (58 BC III and 51 BC IV)

Table 3. Performance of the Multiplatform miRNA and Mutation Test

	Cohort, % (95% CI)	AUS/FLUS, % (95% CI)	FN/SFN, % (95% CI)
No. of cases	109	58	51
Sensitivity	89 (73–97)	94 (73–100)	82 (57–96)
Specificity	85 (75–92)	80 (64–91)	91 (76–98)
PPV	74 (58–86)	68 (46–85)	82 (57–96)
NPV	94 (85–98)	97 (84–100)	91 (76–98)
Odds ratio	44 (13–151)	68 (8–590)	48 (9–269)

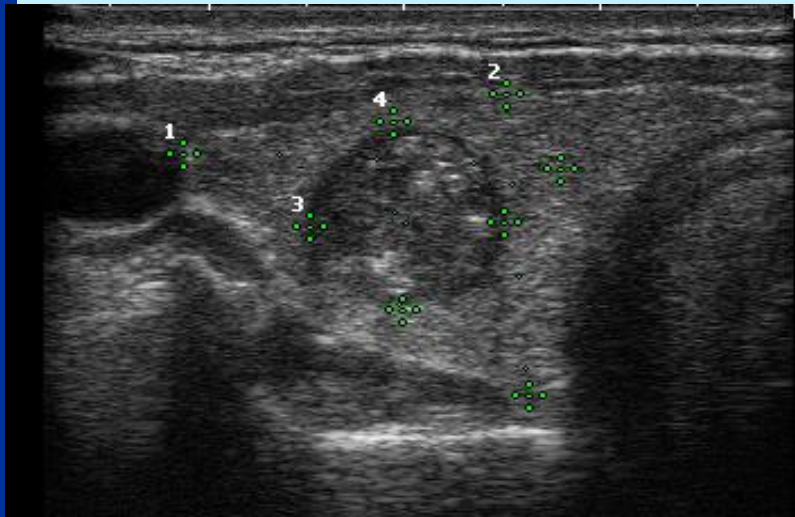
Prevalence – 32%

Molecular markers for cancer risk stratification



V600E BRAF-like PTC

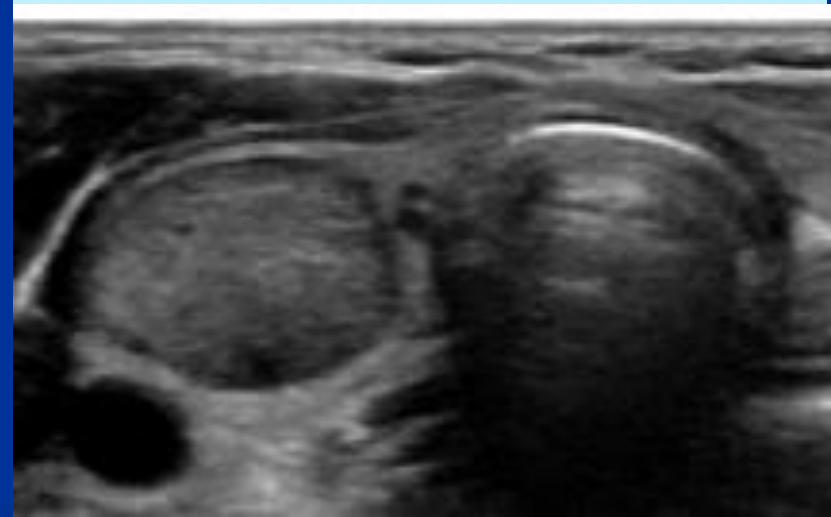
- Classic papillary/tall cell
- Infiltrative
- Spread to lymph nodes first, later to distant sites
- Prone to lose markers of thyroid differentiation



Cyto: BC V & VI

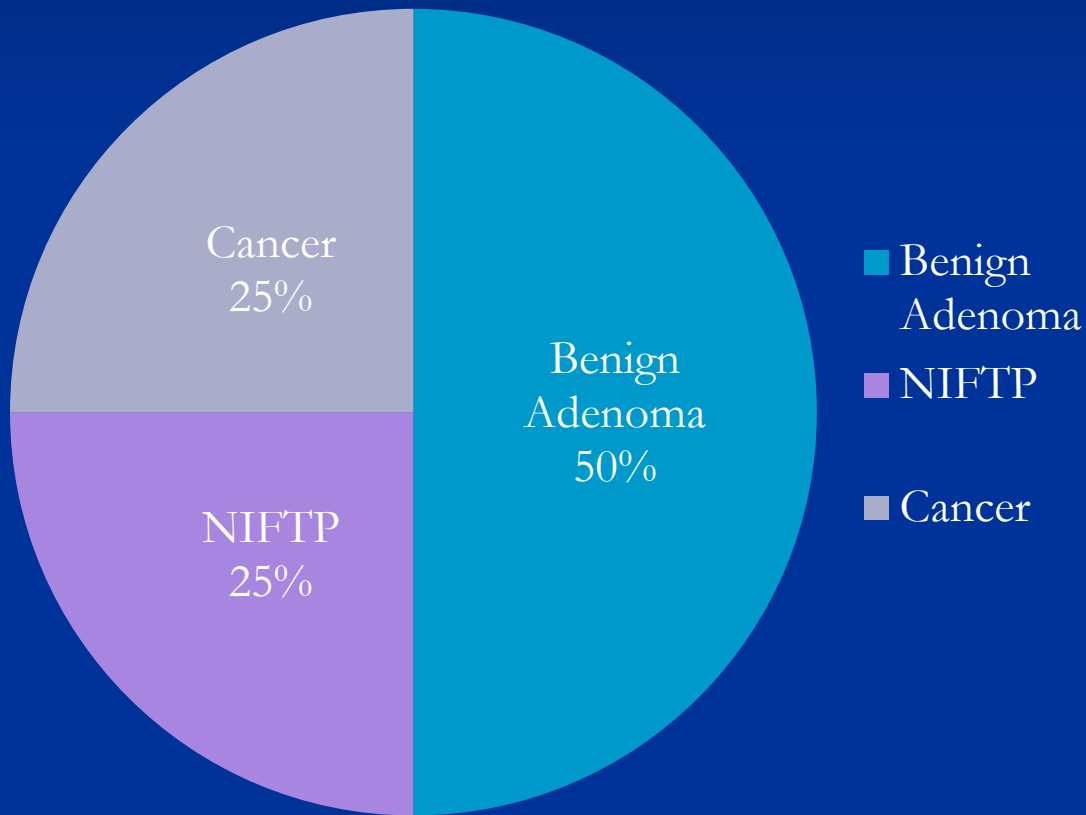
RAS-like PTC

- Follicular variant
- Encapsulated
- Spread to distant sites, rare to lymph nodes
- Retain markers of thyroid differentiation



Cyto: BC III & IV

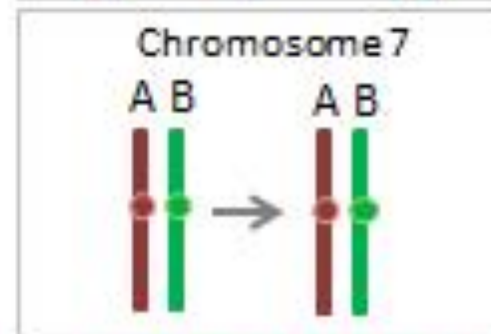
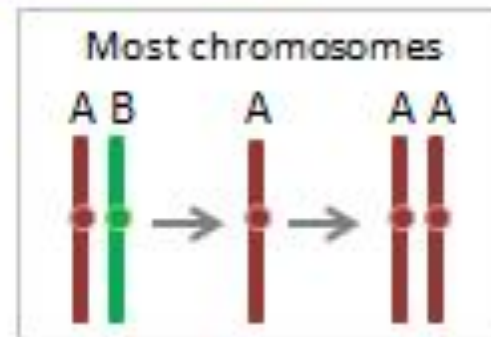
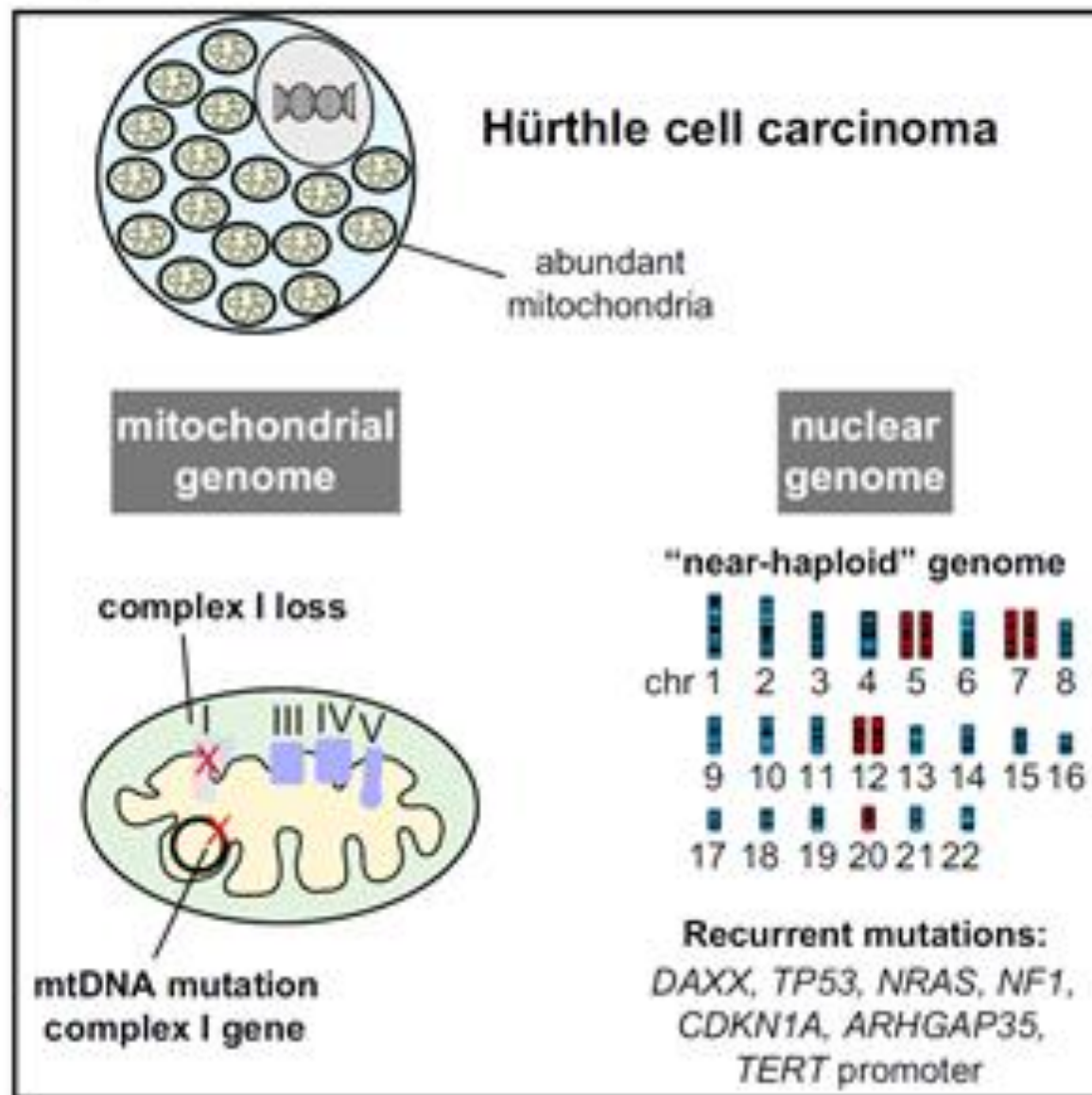
Tumors with isolated RAS mutations



- Most common mutation
- Most cancers with isolated RAS are low risk (FV-PTC)
- Lobectomy Appropriate

Genetic alterations in Hurthle cell carcinomas

Mitochondrial DNA mutations



Chromosomal copy number alterations



Nuclear DNA mutations



Gopal et al. Cancer Cell 2018

Afirma GSC and ThyroSeq v3 GC performance in Hurthle cell nodules

Afirma

Cohort	Sensitivity	Specificity
GSC Overall	91%	68%
GSC Hurthle	89%	59%
GEC Hurthle	89%	12%

Alexander EK et al, NEJM 2012
Patel KN et al, JAMA Surg 2018

ThyroSeq V3

	Hurthle cell hyperplasia n=11	Hurthle cell adenoma n=34	Hurthle cell carcinoma n=10
Accuracy of detection	100%	62%	100%

Steward DL et al. *JAMA Oncology* 2019;5:204-212

Practical Utilization of Markers

- Only order if will change the plan
- IF already decided on surgery, not useful
 - Patient preference
 - Compressive symptoms
 - Size, age, gender, risk factors
- Best Use: reasonable to avoid surgery w/ indeterminate FNA

After a Benign FNA Biopsy...

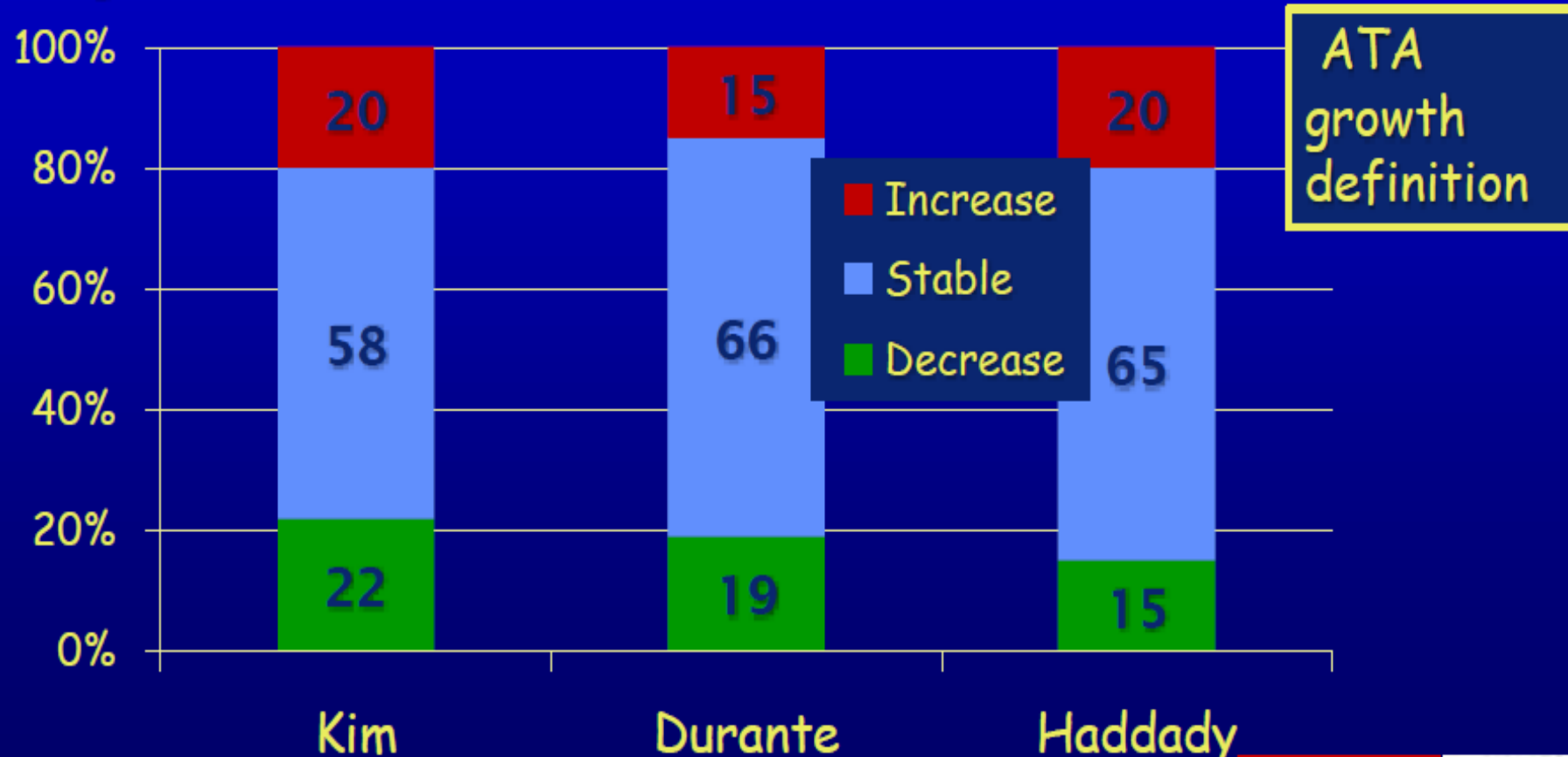
- Benign by cytology – Bethesda Class II
- Indeterminate (BC III or IV) with negative molecular

R23 Follow-up of nodules with benign cytology

Sonographic Pattern		Strength of rec	Quality of evidence
High suspicion	Repeat US and US FNA within 12 months	Strong	Moderate
Intermediate/ Low suspicion	Repeat US at 12-24m If growth or new suspicious US feature, repeat FNA OR continued observation	Weak	Low
Very low suspicion	Utility of surveillance US and assessment of nodule growth as an indicator for repeat FNA is not known. If repeated, US should at ≥ 24 months	Weak	Low
IF 2 nd US FNA done with benign cytology, US surveillance for continued risk of malignancy is no longer indicated		Strong	Moderate

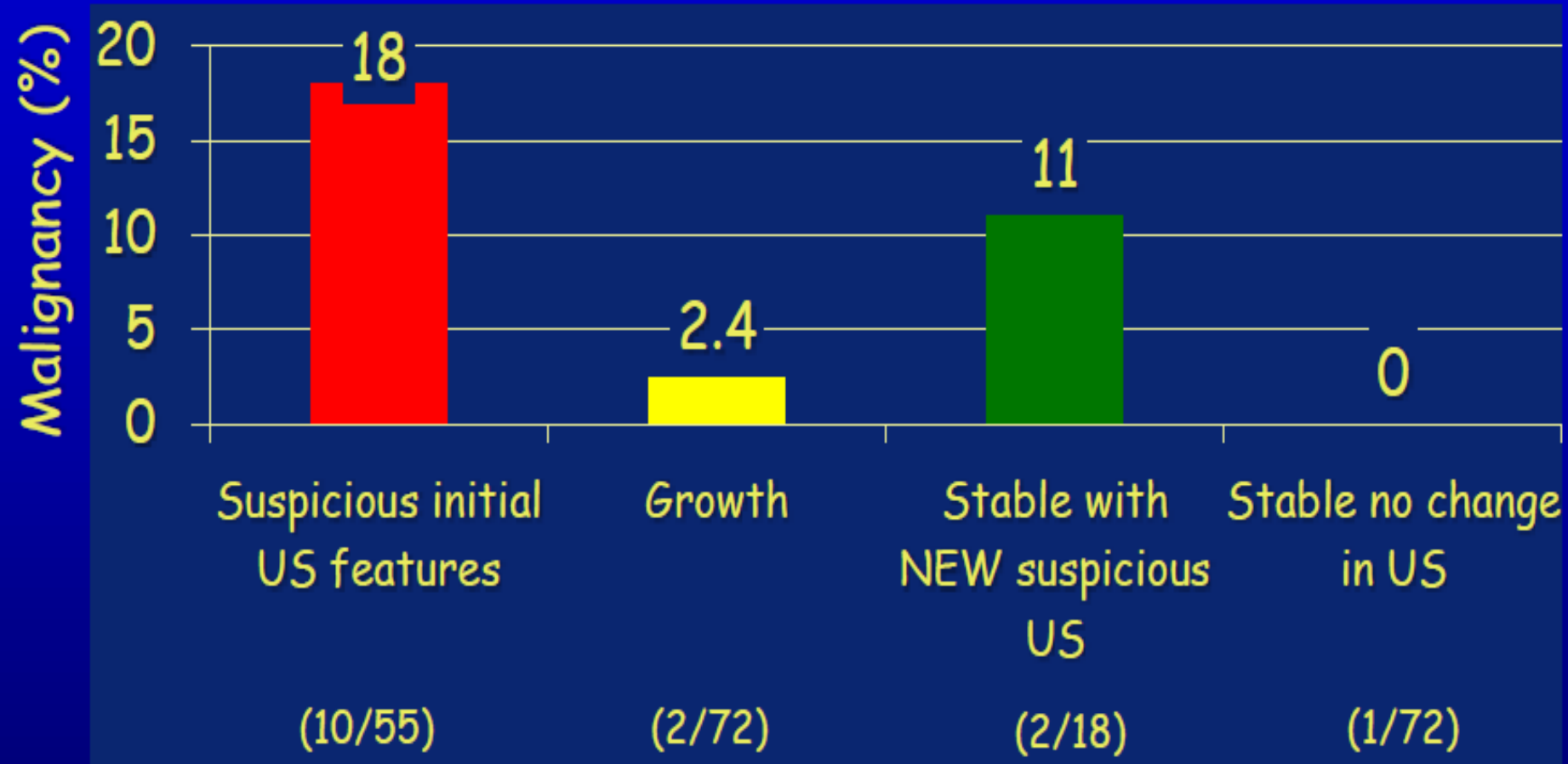
Growth of Benign Nodules with Benign Cytology

- Kim: 854 cytologically benign nodules, 4 yr mean fu, mean 3 US exams
- Durante: 630 cytologically and 937 sonographically benign nodules in 992 pts, 5 yr fu, annual US exam
- Haddady 1078 cytology benign nodules, minimum 64 mo fu; avg time to growth 52 mo



Kim Radiology 2014;271:272; Durante JAMA 2015;313:926;Haddady 2015 AACE

Cancer Detection Rates



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

Large nodules

THYROID
Volume 28, Number 12, 2018
© Mary Ann Liebert, Inc.
DOI: 10.1089/thy.2018.0221

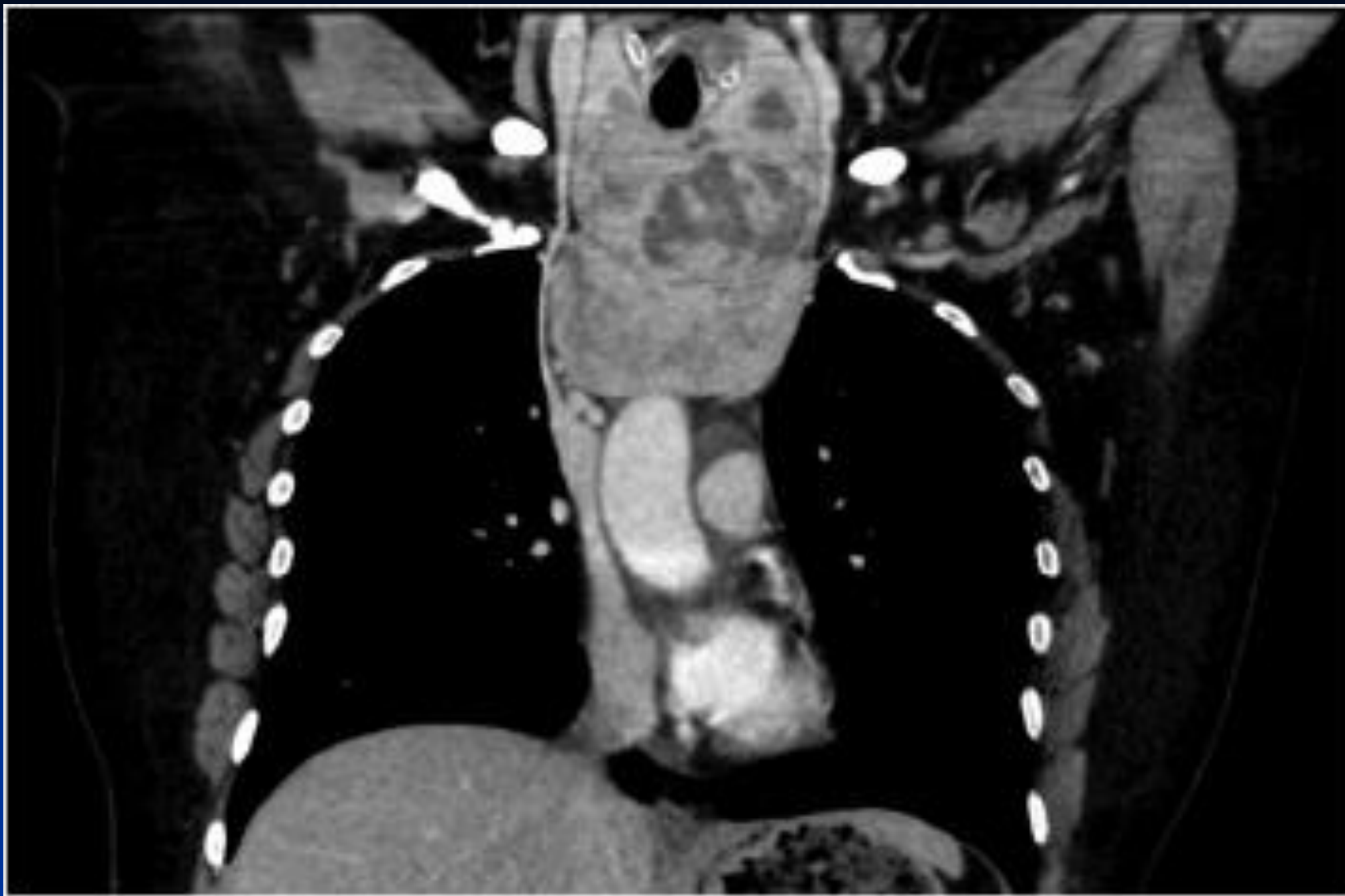
Large Cytologically Benign Thyroid Nodules Do Not Have High Rates of Malignancy or False-Negative Rates and Clinical Observation Should be Considered: A Meta-Analysis

Nicole A. Cipriani,¹ Michael G. White,² Peter Angelos,² and Raymon H. Grogan³

- Cytologically benign large nodules (>3,4 or 5cm) not recommended for resection in absence of other indications
- False negative rates are low and institution/practice dependent
- Resection may lead to increased morbidity compared to surveillance

Multinodular Goiter Considerations

- Evaluate each nodule individually
- Assess compressive symptoms
- Pemberton's sign and neck flexion
- Classic MNG/Hyperplasia – similar appearing coalescing nodules with little to no normal background parenchyma
- Evaluate for tracheal deviation and substernal extension



Indications for thyroid surgery

- Over-functioning nodule(s)
- Symptoms due to size
 - Trouble swallowing
 - Cough
 - Voice changes
 - Breathing difficulties
 - Cosmetic concerns
- Patient Preference
- Diagnosis or suspicion of clinically significant cancer

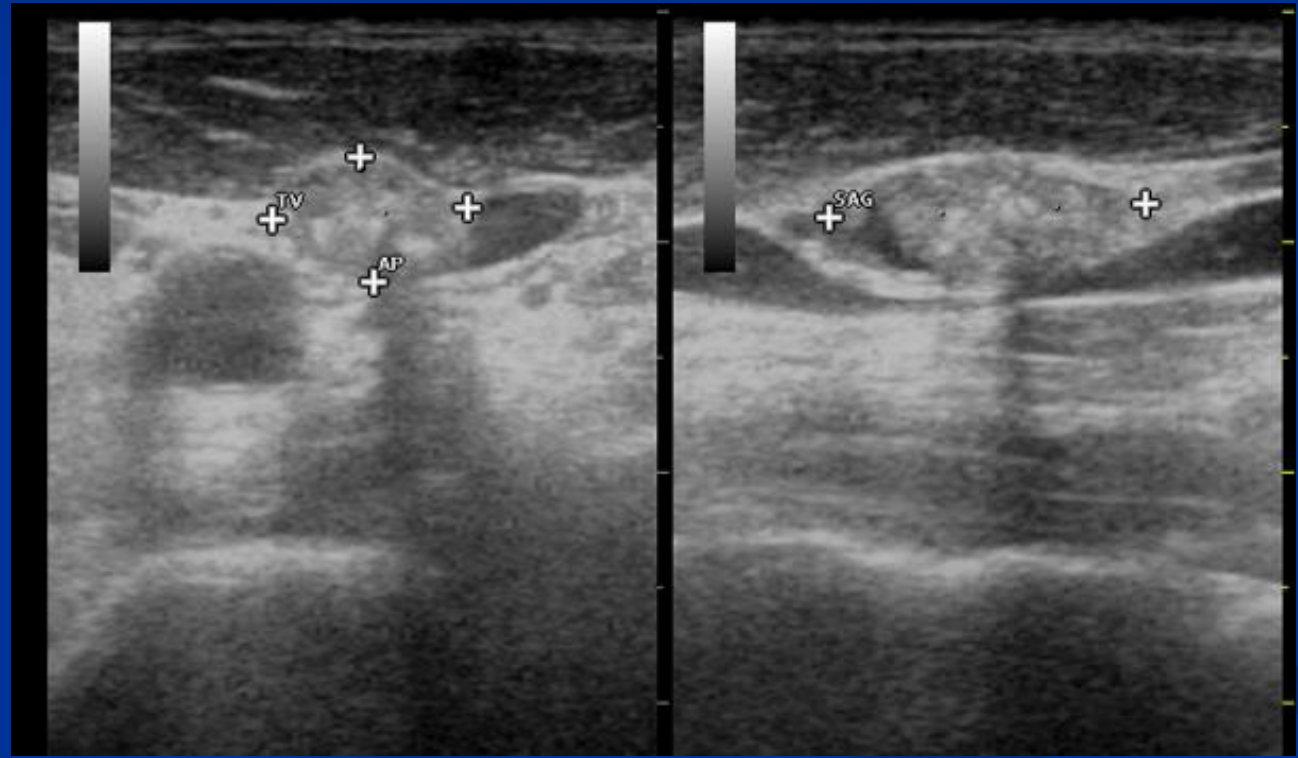
Non-Surgical Options for Benign Nodules

- Thyroxine medication (if hypothyroid)
- Iodine repletion (if deficient)
- Radioactive Iodine
- Percutaneous Ethanol Injection
- Radiofrequency Ablation
- High Frequency Ultrasound
- Laser

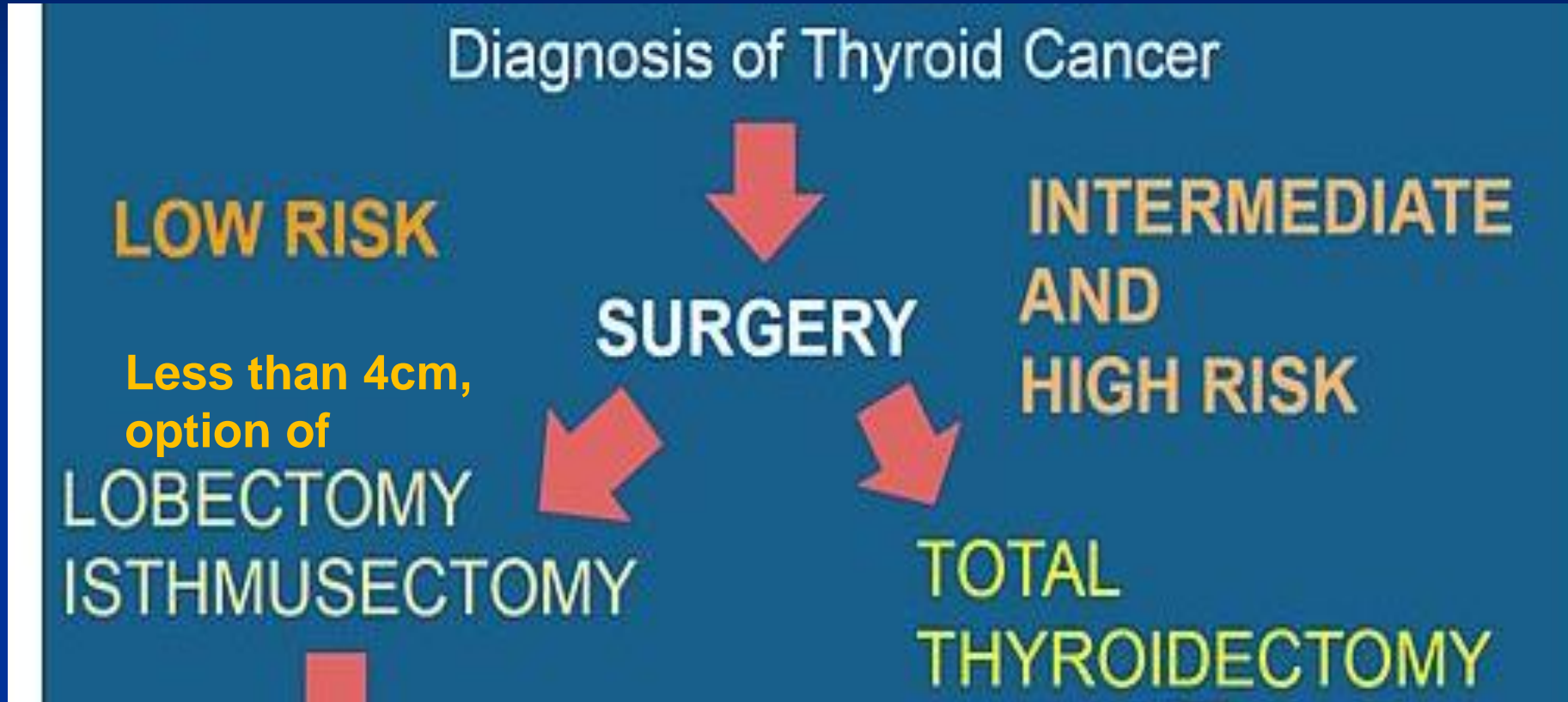
2017 Bethesda System

Suspicious for malignancy	45–60%	50–75%	Lobectomy or near-total thyroidectomy
Malignant Papillary thyroid carcinoma Medullary thyroid carcinoma Poorly differentiated carcinoma Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma Carcinoma with mixed features Metastatic malignancy Non-Hodgkin lymphoma Other	94–96%	97–99%	Lobectomy or near-total thyroidectomy

Lymph Node Assessment – MUST be performed pre-operatively !

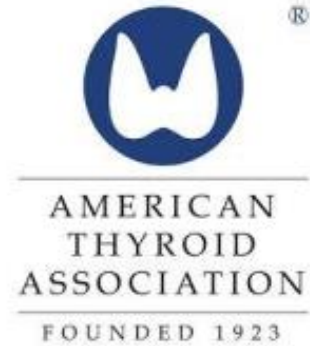


Initial Surgery for Thyroid Cancer



Critical to look at lymph nodes prior to surgery!

Total thyroidectomy (2009)



- 'For thyroid cancer >1 cm, initial surgery should be total thyroidectomy unless there are contraindications. Lobectomy may be sufficient for <1 cm, low-risk, unifocal, intrathyroidal PTCs w/o prior head/neck irradiation or nodal metastases.'
(Recommendation rating: A) -ATA Guidelines 2009

Total thyroidectomy or lobectomy (2015)



- 'For patients with thyroid cancer >1 cm and <4 cm w/o extrathyroidal extension, and cN0, the initial surgery can be ***either*** total thyroidectomy (high-risk tumors with nodal mets, requiring RAI), ***or thyroid lobectomy (low and medium-risk tumors)***.'

-ATA Guidelines 2015

Non DTC Initial Management

■ Medullary Thyroid Cancer

- Serum Calcitonin to guide pre-op staging
- CT w/ contrast to evaluate aero-esophageal invasion
- Total Thyroidectomy and Central Compartment Dissection

■ Lymphoma


- Diagnosed on Flow Cytometry – often with Core Biopsy
- Non-surgical management by Med Oncology

■ Anaplastic

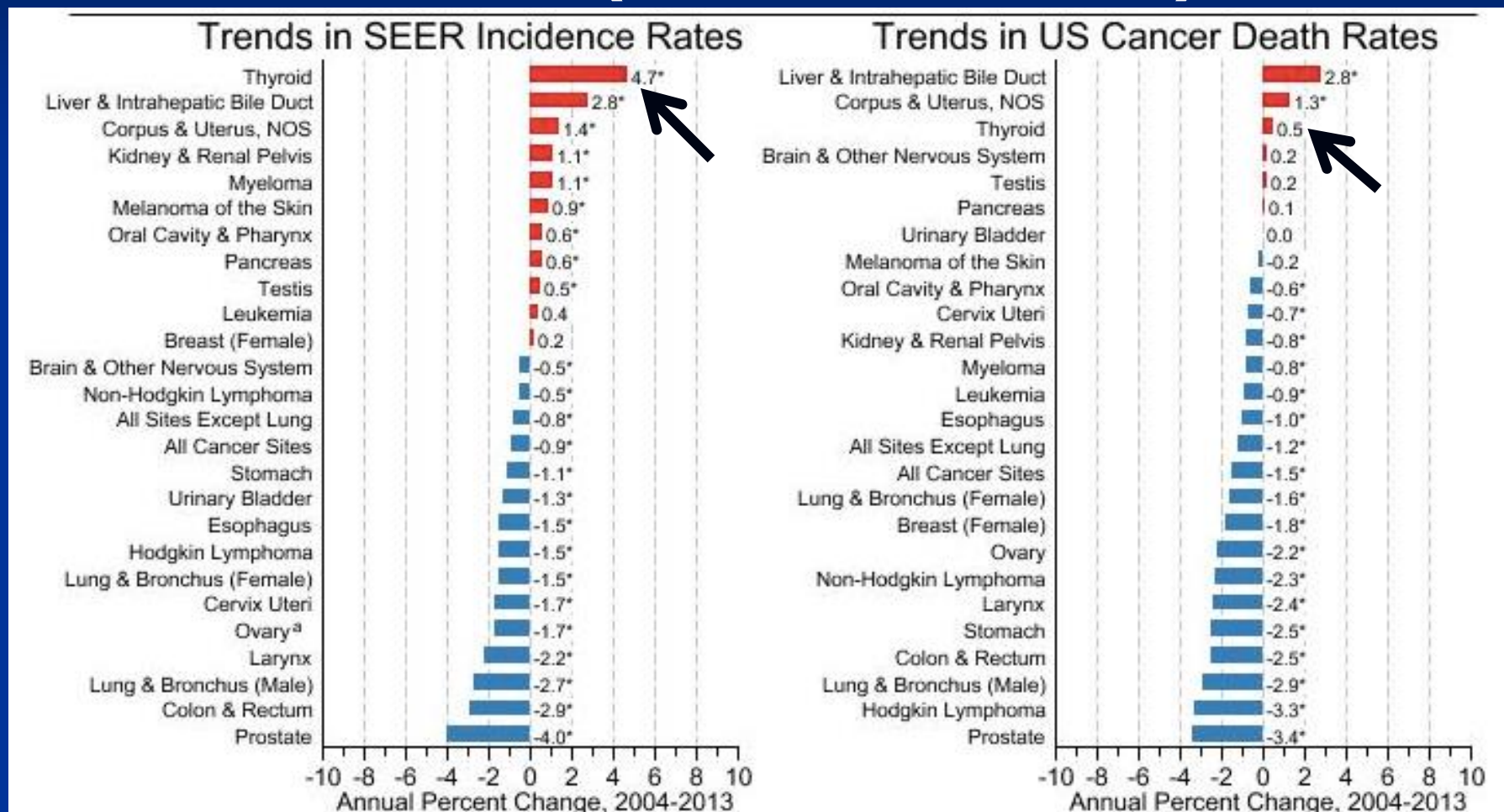
- Urgent referral to tertiary center

Increased risk of complications compared to a high-volume surgeon

Cases/yr	Surgeons	Increased complication risk
1	51%	68%
2-5	34%	55%
6-10	7%	35%
11-15	3%	19%
16-20	1%	9%
21-24	1%	2%

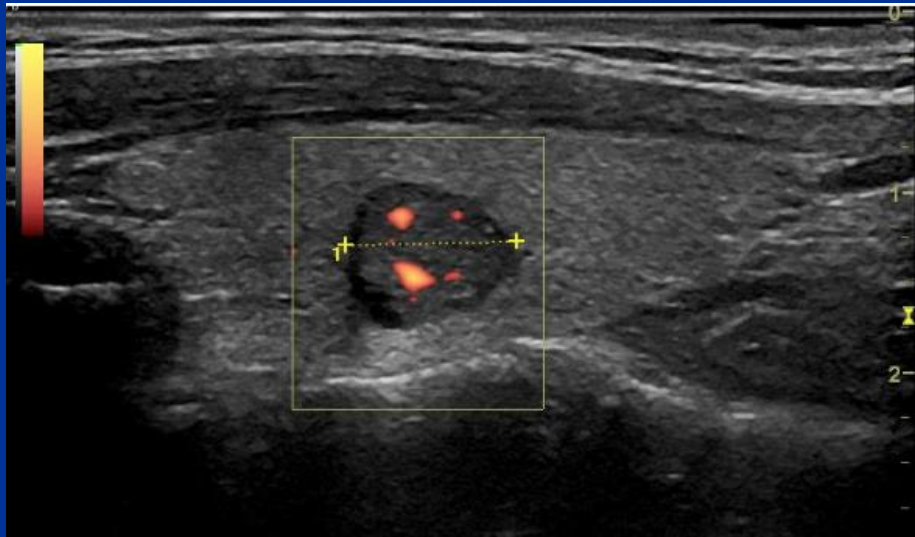


Trends in Incidence & Death (2004 – 2013)



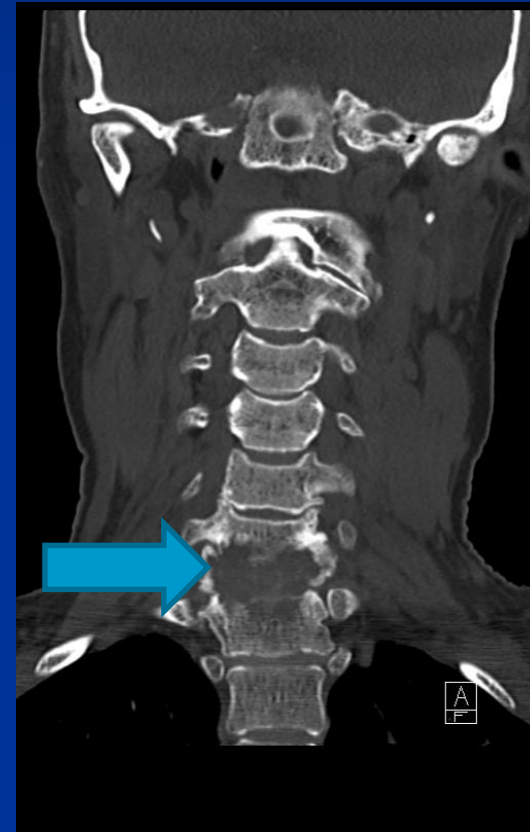
2 Different Thyroid Cancers !

9mm Nodule – incidentally discovered on CT scan



FNA thyroid
Papillary thyroid
cancer

Patient with arm numbness



Differentiated Thyroid Cancer
Presenting as Vertebral Met

Emergent spinal
cord decompression

SEER 2019

Estimated New Cases in 2019

52,070

% of All New Cancer Cases

3.0%

Estimated Deaths in 2019

2,170

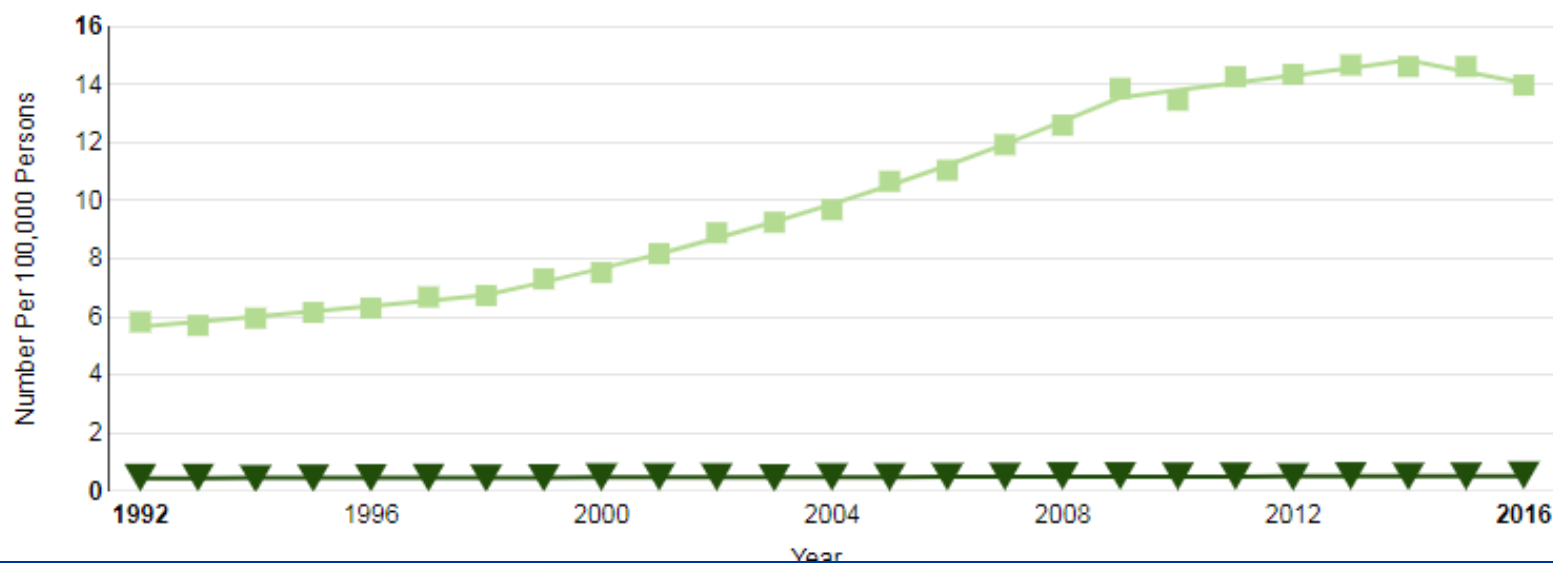
% of All Cancer Deaths

0.4%

Percent Surviving
5 Years

98.2%

2009-2015



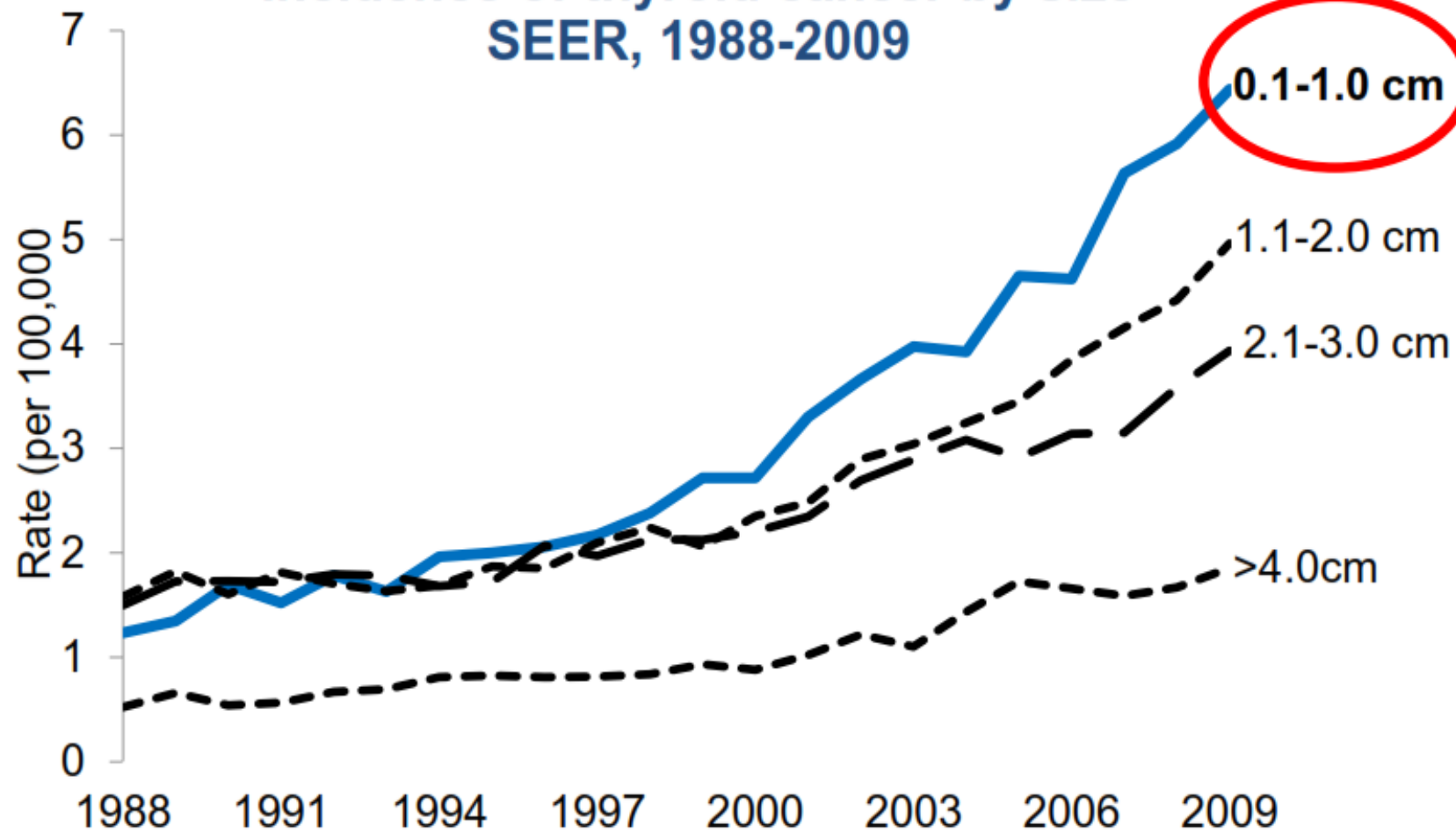
Increasing Incidence

Without Increased Mortality



OVERDIAGNOSIS

**Surveillance bias:
Incidence of thyroid cancer by size
SEER, 1988-2009**



2015 ATA Guidelines Based on Japanese Experience

A cytology diagnostic for a primary thyroid malignancy will almost always lead to thyroid surgery. However, an active surveillance management approach can be considered as an alternative to immediate surgery in:

- (a) patients with very low risk tumors (e.g. papillary microcarcinomas without clinically evident metastases or local invasion, and no convincing cytologic evidence of aggressive disease),
- (b) patients at high surgical risk because of co-morbid conditions,
- (c) patients expected to have a relatively short life span (e.g. serious cardiopulmonary disease, other malignancies, very advanced age), or
- (d) patients with concurrent medical or surgical issues that need to be addressed prior to thyroid surgery.

Observational Management Approach to Papillary Microcarcinoma

Tumor Progression During Active Surveillance

	n	Tumor size	Follow-Up	Increase ≥ 3 mm	Stable ± 3 mm	Decrease ≥ 3 mm	LN Mets
USA	291	≤ 1.5 cm	2 yrs	4%	92%	4%	0%
Korea	192	≤ 1 cm	2.5 yrs	2%	95%	3%	0.5%
Korea	370	≤ 1 cm	2.7 yrs	4%	96%	-	1%
Japan	1,235	≤ 1 cm	5 yrs	5%	95%	-	2%
			10 yrs	8%	92%	-	4%
Japan	415	≤ 1 cm	6.5 yrs	6%	91%	3%	1%

Ito, Thyroid 2014, Sugitani JCEM 2014, Kwon JCEM 2017,
Oh Thyroid 2018, Tuttle JAMA Otolaryngology 2017

Observational Management Approach to Papillary Microcarcinoma

Tumor Progression By Volume During Active Surveillance

	n	Tumor size	Median Follow-Up	Tumor Volume Increase $\geq 50\%$	Tumor Volume Stable $\pm 50\%$	Tumor Volume Decrease $\geq 50\%$
USA	291	≤ 1.5 cm	2 yrs	12%	79%	7%
Korea	192	≤ 1 cm	2.5 yrs	14%	69%	17%
Korea	370	≤ 1 cm	2.7 yrs	23%	77%	-
Japan*	169	≤ 1 cm	10 yrs	25%	57%	17%

Kwon JCEM 2017, Tuttle JAMA Otolaryngology 2017, Oh Thyroid 2018

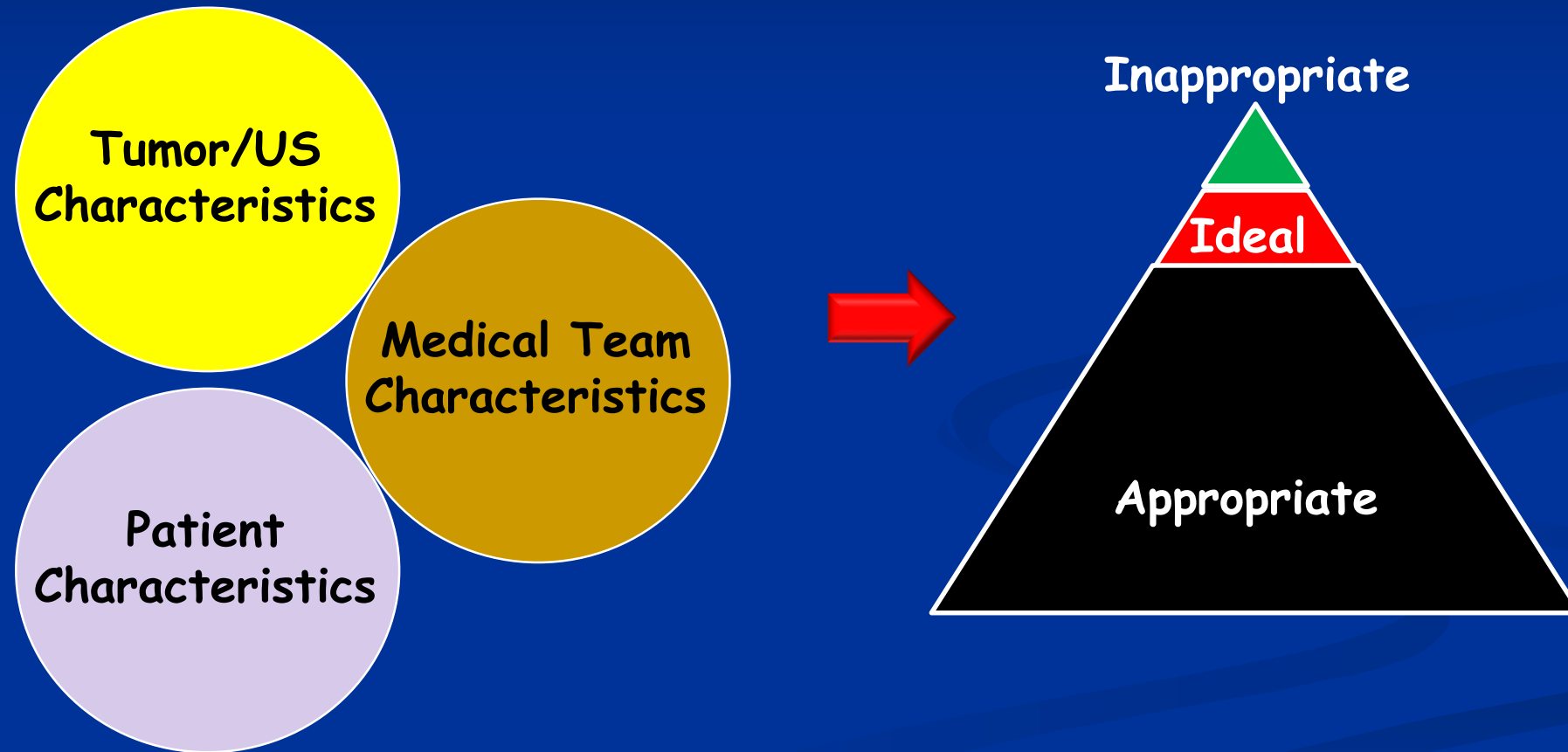
*Miyauchi, Surgery 2018 (tumor volume doubling rate/year)

Outcomes Similar: Japan, Korea and USA

- Active Surveillance of Low Risk PTC
 - 10-15% will have tumor volume increase
 - Younger patients more likely to progress
 - 1-2% will have clinically relevant nodal mets
 - Salvage therapy is effective

Implementing Active Surveillance in the US

Requires concurrent evaluation of three inter-related domains

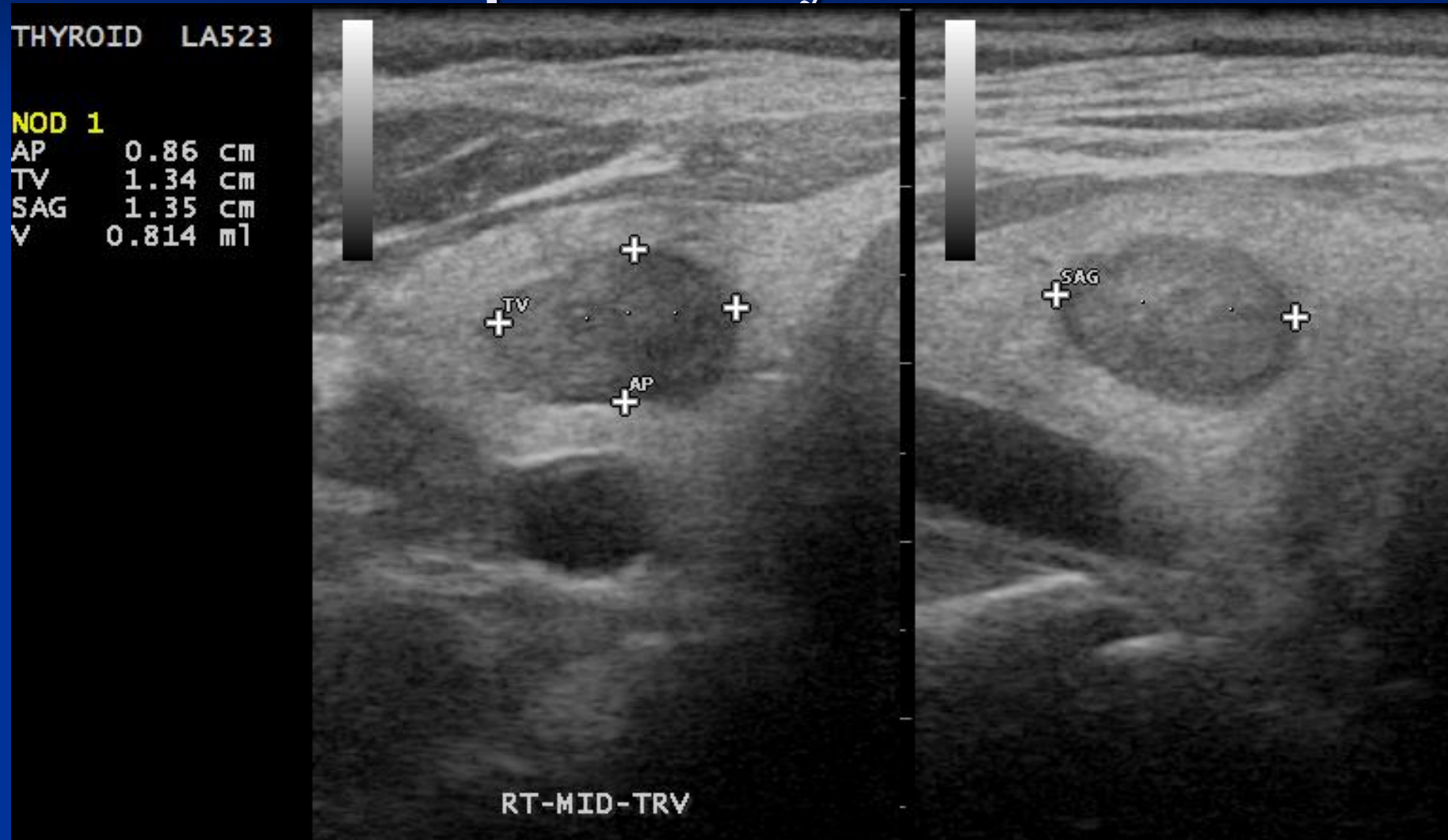


Slide Courtesy of Dr. Michael Tuttle

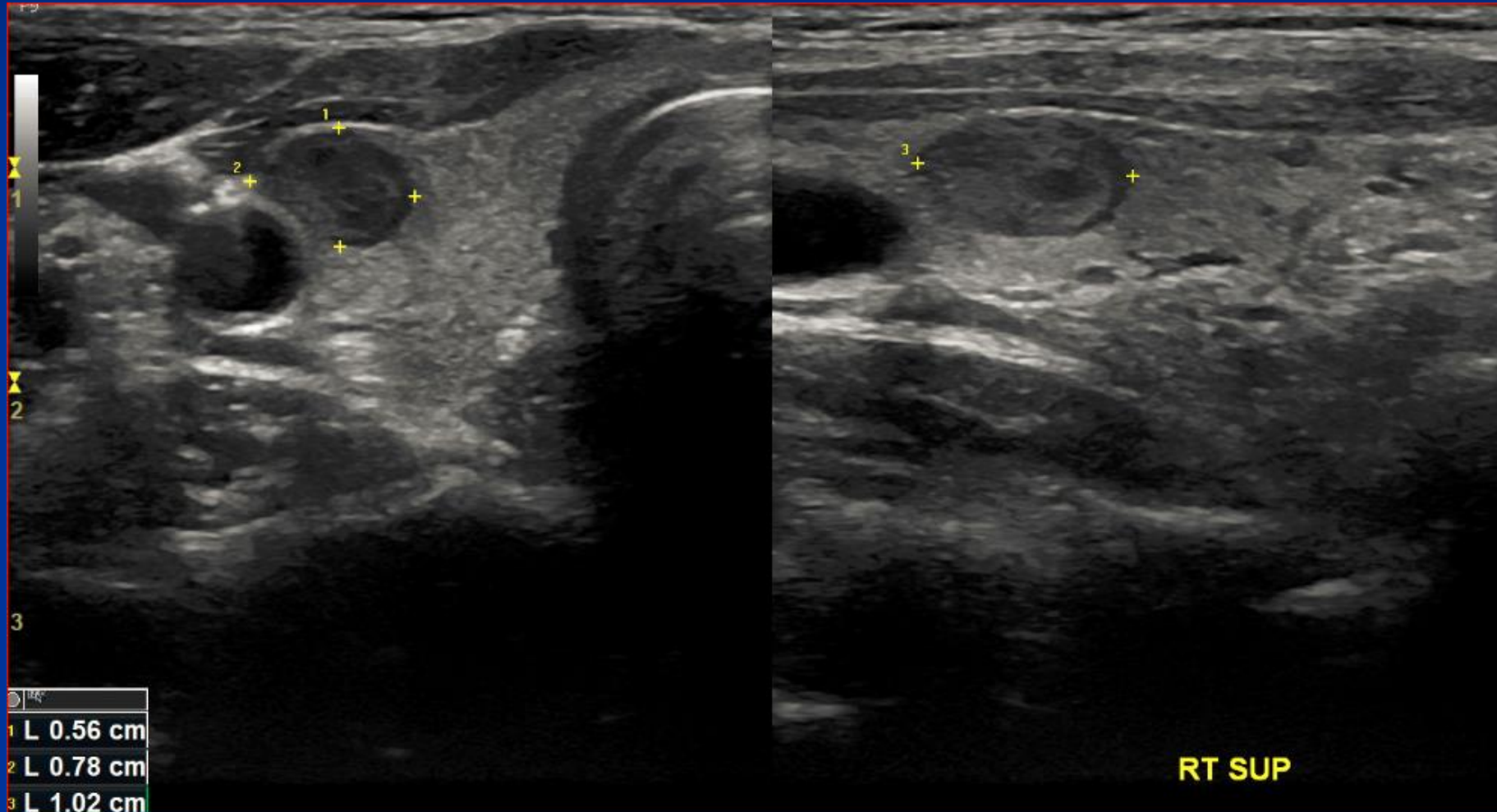
A clinical framework to facilitate risk stratification when considering an active surveillance alternative to immediate biopsy and surgery in papillary microcarcinoma.

JP Brito, Y Ito, A Miyauchi, RM Tuttle. Thyroid 2015

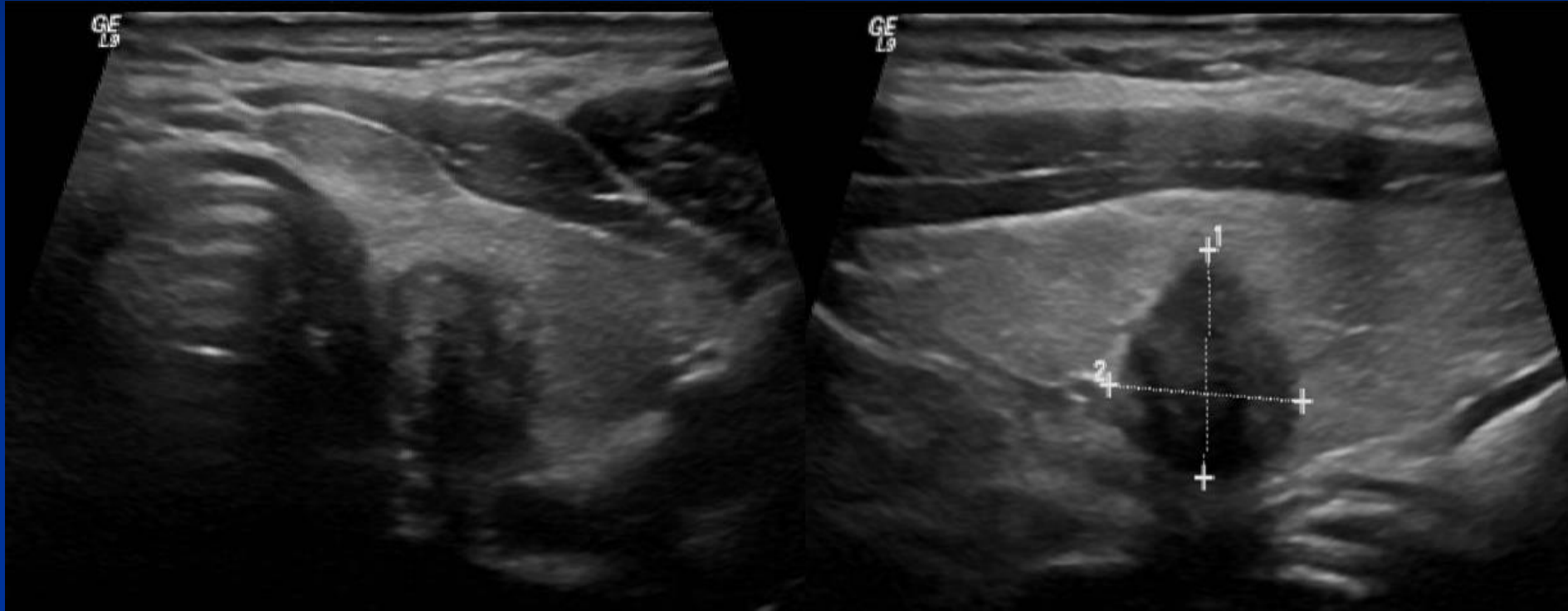
Ideal – low risk PTC, surrounded by thyroid parenchyma



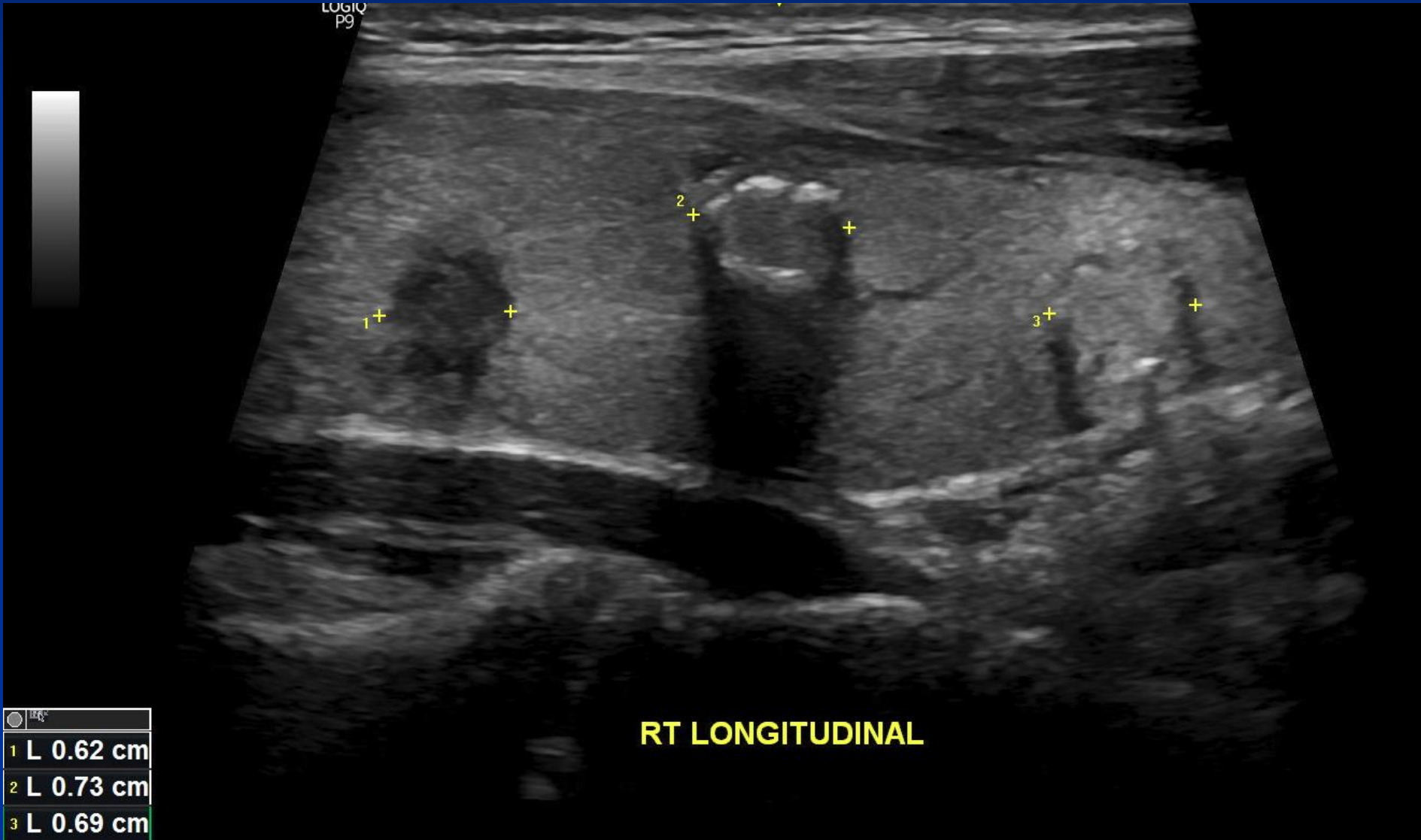
Abuts capsule but not invasive - appropriate



Not Appropriate



Multifocal Disease - appropriate



Indications for surgical intervention

- Increase in size of primary tumor*
 - $\geq 3\text{mm}$ increase in tumor diameter and/or
 - $\geq 100\%$ increase in tumor volume
- Identification of metastatic disease
- Direct invasion into surrounding structures
- Patient preference

May individualize decision for surgery depending on proximity to thyroid capsule and doubling time

Active Surveillance ≠ Do Nothing

- Requires diligent follow-up
- Committed multidisciplinary team
- Clear language and expectations
- Expert sonography

Barriers: fear, lack of education in community
 reluctance to de-escalate treatment

Summary: *Less is More*

- Epidemic of thyroid nodules demands a risk stratification scheme that reduces the number of biopsies
- Molecular testing may avoid surgery in cytologically indeterminate nodules
- Lobectomy is an option for PTC 1-4cm without imaging evidence of invasion or lymph node involvement
- Active Surveillance of low risk cancers will be more common