



# Challenges (Changes) in Thyroid Nodule Management

**3<sup>rd</sup> Italian AACE Chapter  
Endocrine Course**

**Rome**

November 8, 2018

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## Disclosures

- None

## Thanks

- To Italian AACE colleagues for the invitation, and the honor of speaking to your group today

Contemporary Endocrinology  
Series Editor: Leonid Poretsky

Hossein Gharib *Editor*

# Thyroid Nodules

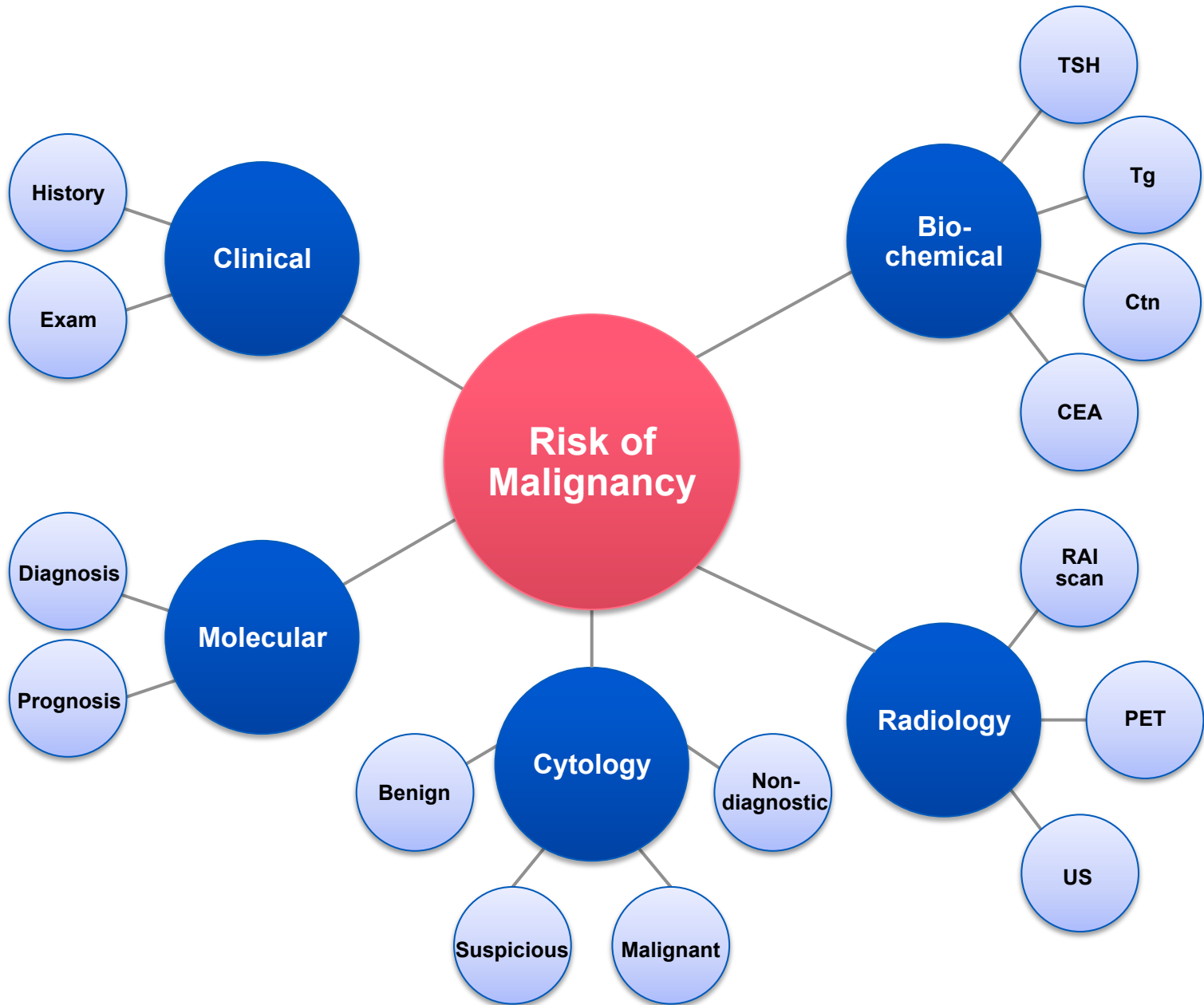
Diagnosis and Management

# Thyroid Nodule Rule of 5s

- 5% palpable
- 5% malignant
- 5% nondiagnostic
- 5% not evaluated by endocrinologists
- 5% of endocrine practice

# Multidisciplinary Approach to Thyroid Nodule

- Endocrinology: Clinical findings
- Radiology: US Characteristics
- Cytology: Diagnostic terminology
- Laboratory: Molecular findings
- Surgery: Conservative approach





A 30-year-old woman is referred for a recent thyroid nodule. US shows a solid, hypoechogenic lesion with intranodular vascularization & smooth borders.

What is the approximate risk of malignancy in this nodule based in US features?

A. Low <1%

B. Intermediate 5-15%

C. High 50-90%

D. Very high

# AACE Thyroid US ROM

US features (ROM)	High (70-90%)	Intermediate (5-15%)	Low (<1%)
Mostly cystic >50%			✓
Isoechoic			✓
Spongiform			✓
Hypoechoic	✓	✓	✓
Intranodular vascularization		✓	✓
Smooth/ill-defined margins		✓	✗
Marked hypoechogenicity	✓	✗	✗
Spiculated margins	✓	✗	✗
Microcalcifications	✓	✗	✗
Taller, than wide	✓	✗	✗
ETE and/or nodes	✓	✗	✗



A 69-year-old man is discovered to have a 1.8 cm thyroid nodule

Which of the following statements is true regarding thyroid nodule & advancing age?

- A. ↑ prevalence
- B. ↓ risk of malignancy
- C. ↑ aggressiveness of malignancy
- D. None of the above
- E. All of the above

## The Influence of Patient Age on Thyroid Nodule Formation, Multinodularity, and Thyroid Cancer Risk

Norra Kwong, Marco Medici, Trevor E. Angell, Xiaoyun Liu, Ellen Marqusee, Edmund S. Cibas, Jeffrey F. Krane, Justine A. Barletta, Matthew I. Kim, P. Reed Larsen, and Erik K. Alexander

Thyroid Section, Division of Endocrinology, Hypertension, and Diabetes (N.K., M.M., T.E.A., X.L., E.M., P.R.L., M.I.K., E.K.A.), and Department of Pathology (E.S.C., J.F.K., J.A.B.), The Brigham & Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115

**Introduction:** Although advancing age is known to influence the formation of thyroid nodules, the precise relationship remains unclear. Furthermore, it is uncertain whether age influences the risk that any thyroid nodule may prove cancerous.

**Aim:** The aim was to determine the impact of patient age on nodule formation, multinodularity, and risk of thyroid malignancy.

**Conclusion:** With advancing age, the prevalence of clinically relevant thyroid nodules increases, whereas the risk that such nodules are malignant decreases. Nonetheless, when thyroid cancer is detected in older individuals, a higher-risk histological phenotype is more likely. These data provide insight into the clinical paradox that confronts physicians managing this common illness.

higher risk histological phenotypes. Although nearly all malignancies in younger patients were well-differentiated, older patients were more likely to have higher risk papillary thyroid carcinoma variants, poorly differentiated cancer, or anaplastic carcinoma ( $P < .001$ ).

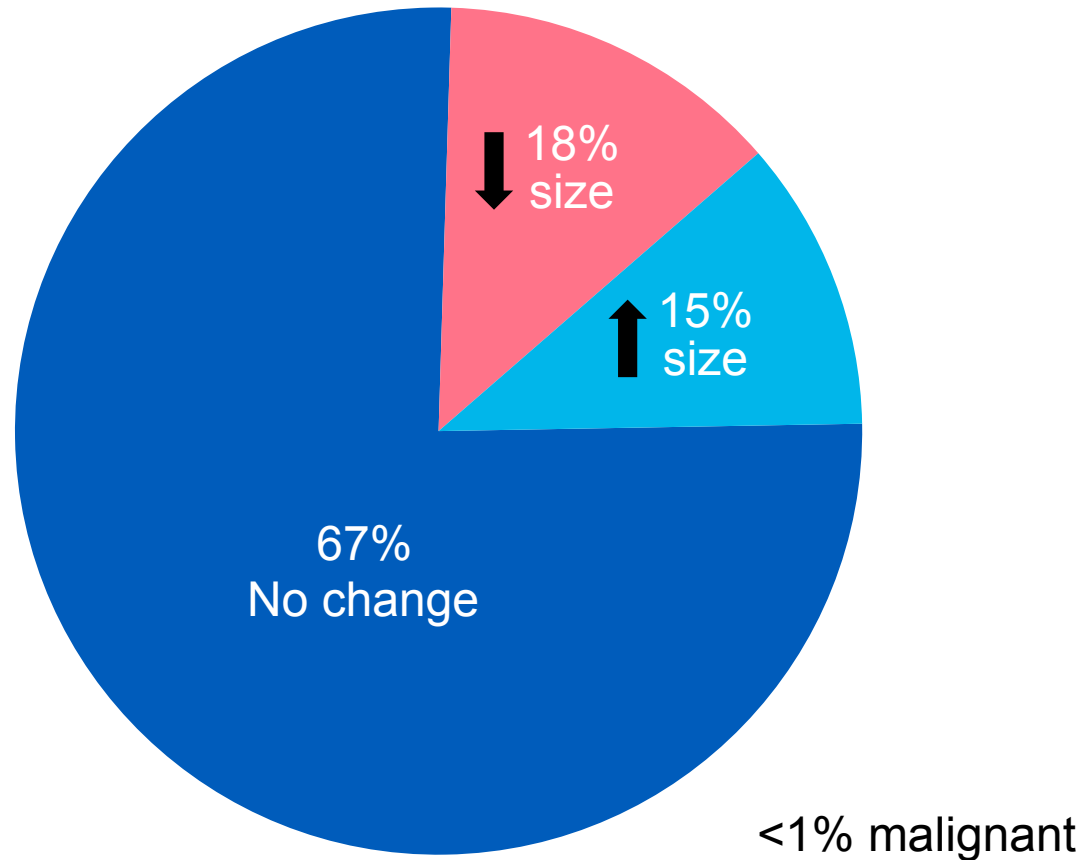
**Conclusion:** With advancing age, the prevalence of clinically relevant thyroid nodules increases, whereas the risk that such nodules are malignant decreases. Nonetheless, when thyroid cancer is detected in older individuals, a higher-risk histological phenotype is more likely. These data provide insight into the clinical paradox that confronts physicians managing this common illness. (*J Clin Endocrinol Metab* 100: 4434–4440, 2015)

A 44-year-old man is discovered to have a thyroid nodule, which on US appears solid, hypoechoic & measures 2.2 x 1.6 x 1.8 cm. FNA shows a colloid, benign nodule.

He was reassured and told to return in one year for follow-up. What will most likely be found on thyroid US one year later?

- A. 5% chance nodule increased in size
- B. 5% chance nodule decreased in size
- C. 70% chance nodule is stable in size
- D. 5% chance nodule is malignant
- E. 10% chance nodule has disappeared

# What Happens to Benign Thyroid Nodules One Year After Diagnosis?

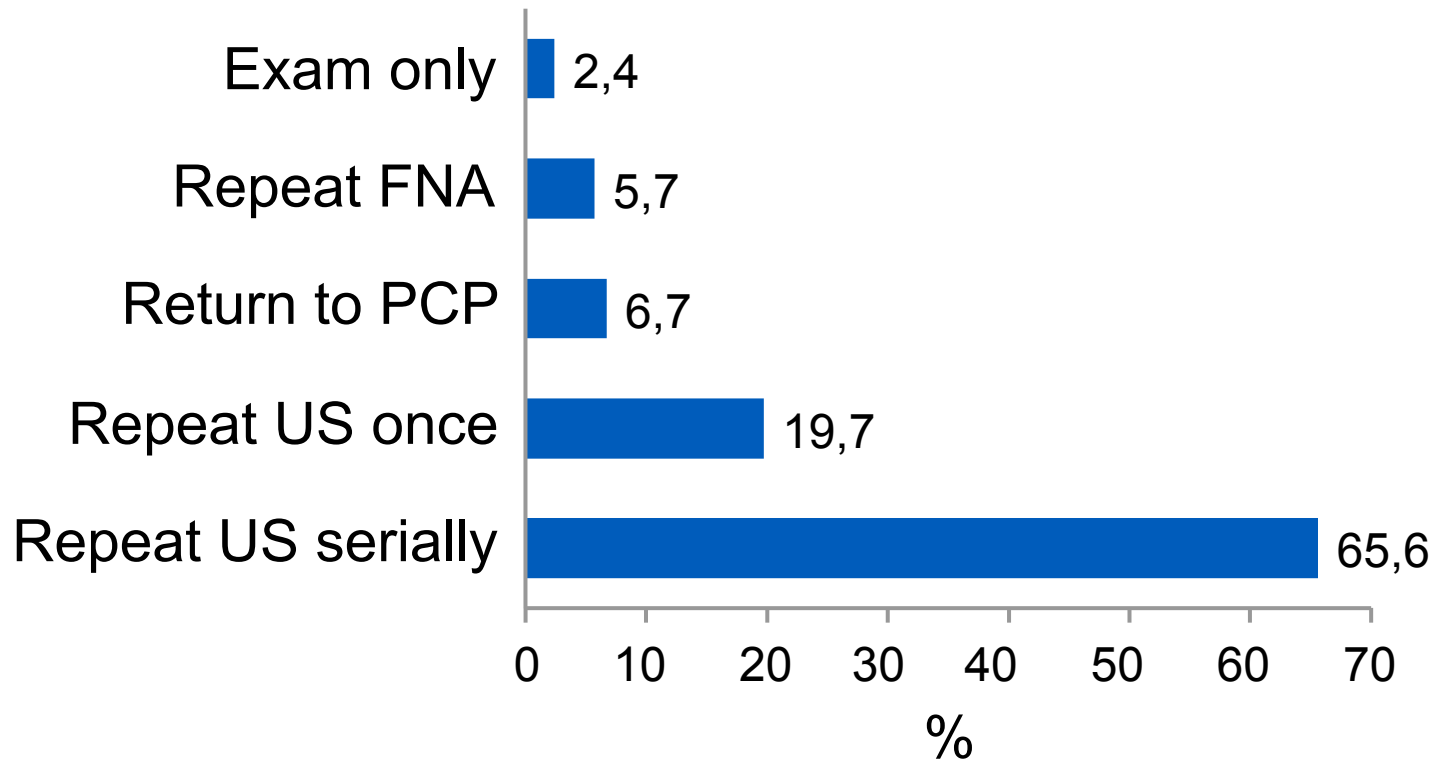


Durante et al: JAMA, 2015

# Clinical Practice Survey

## Management after a Benign FNA

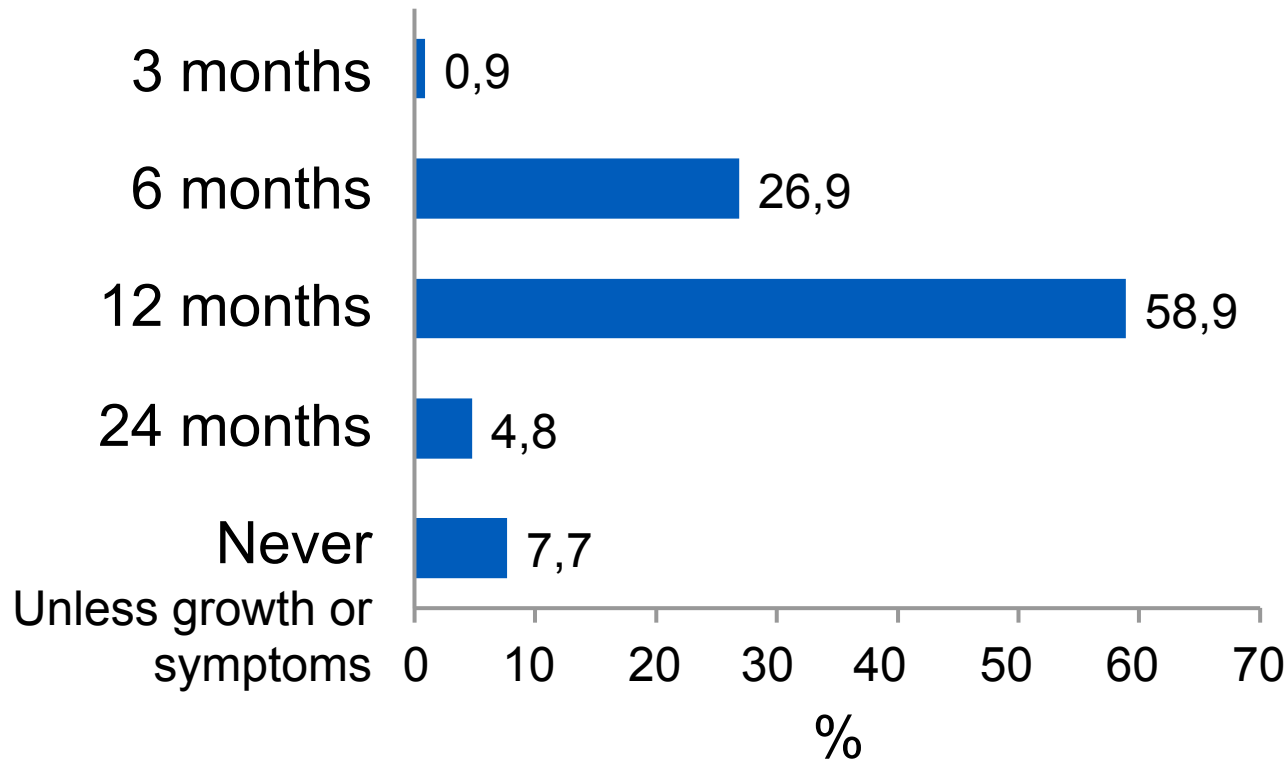
Index patient has a benign FNA; how are most patients with this finding managed at your institution?



# Clinical Practice Survey

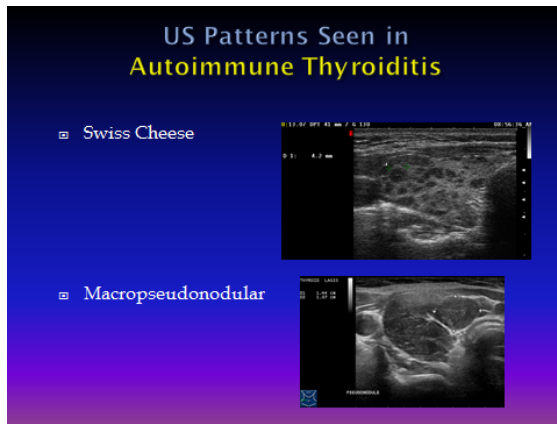
## Management after a Benign FNA

When would you next repeat a thyroid ultrasound after a benign FNA result?



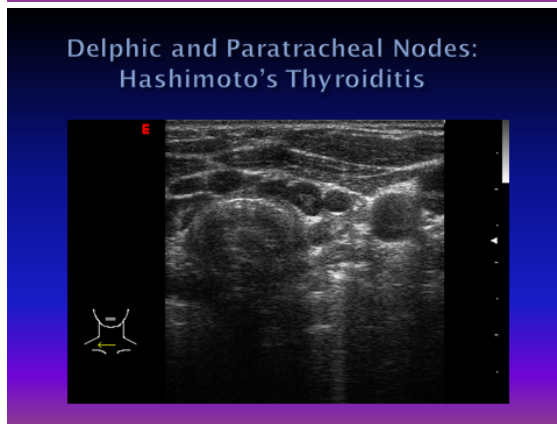
Unless growth or symptoms

A 30-year-old woman is discovered to have a small goiter on routine exam. TSH is 3.1 & FT4 1.5. Thyroid US shows a 1.5 cm solid left lobe nodule.



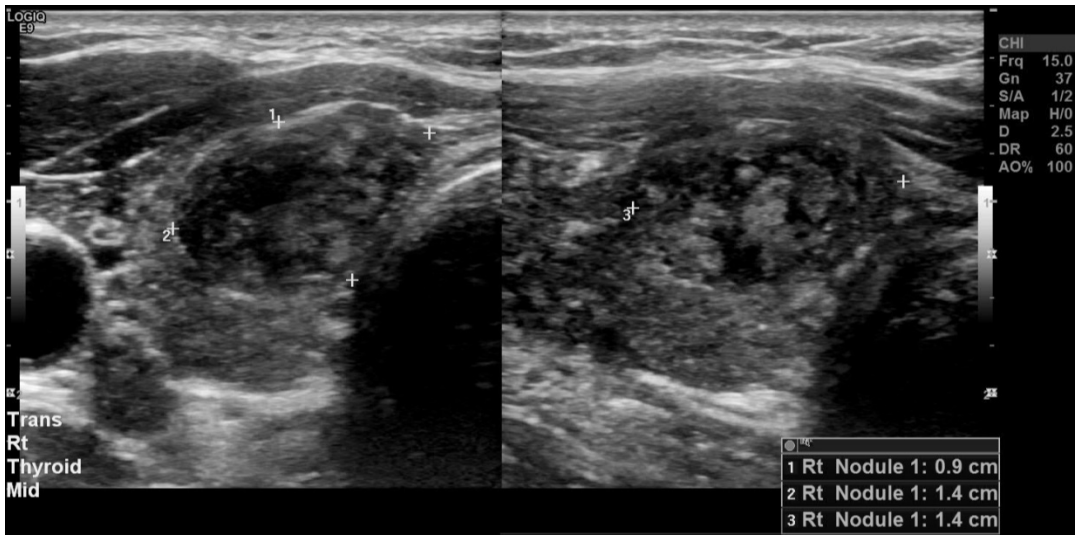
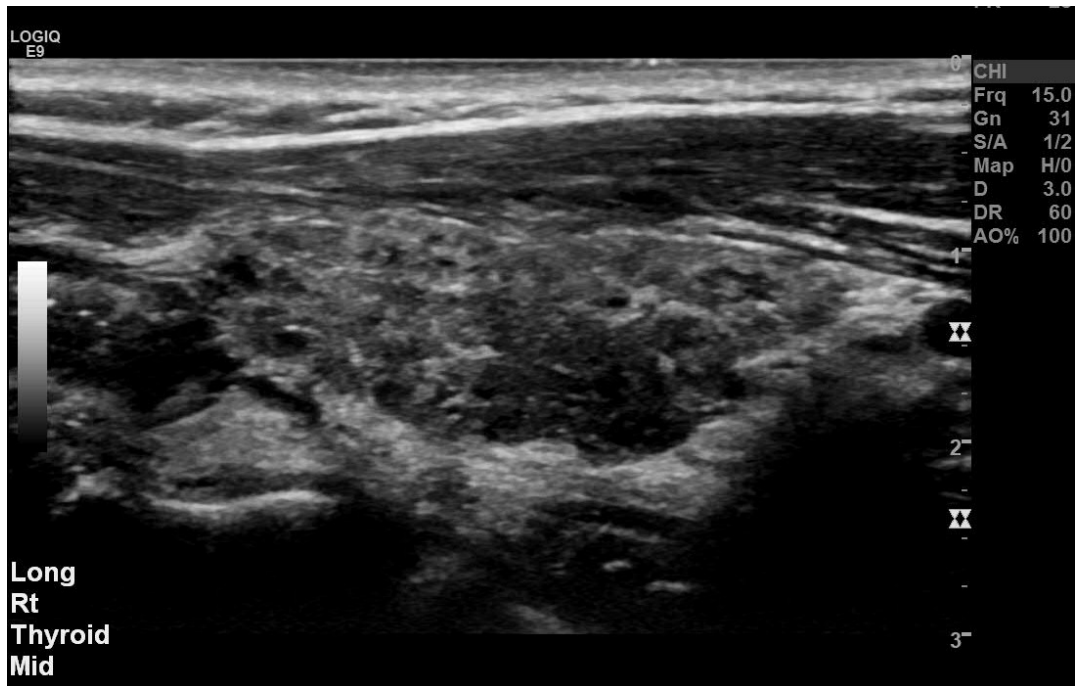
Would you FNA?

What about lymph nodes?



What if TPOAb is 560?



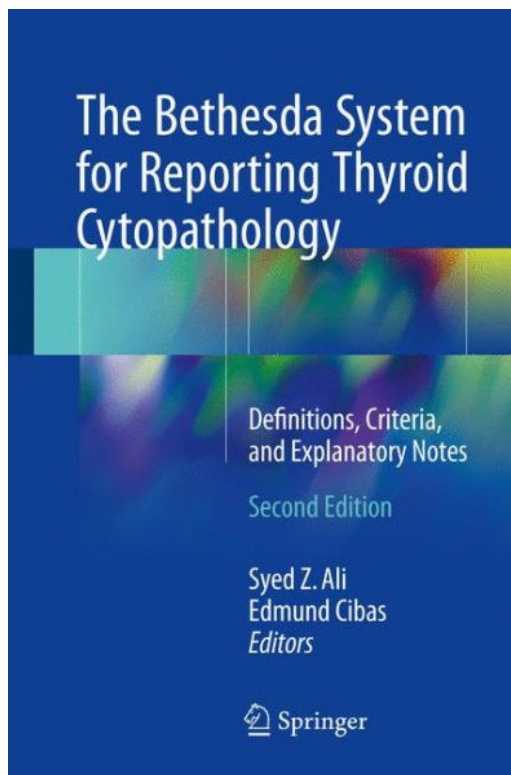


# Hashimoto Thyroiditis

- Also known as lymphocytic thyroiditis, chronic autoimmune thyroiditis, clinical lymphocytic thyroiditis, and struma lymphomatosa
- Described more than 100 years ago by Hakaru Hashimoto
- On US often see “hypoechoic micro-nodules (1-6 mm) with echogenic septation described as pseudo nodular or giraffe pattern”

## **The Bethesda System for Reporting Thyroid Cytopathology**

Edmund S. Cibas, MD,<sup>1</sup> and Syed Z. Ali, MD<sup>2</sup>



Cibas and Ali. *Am J Clin Pathol.* 2009; 132:658-665

Updated 2<sup>nd</sup> edition published last year

# Remember

NPV of FNA is extremely high at 97-99%  
which renders result very reliable

<b>Diagnostic Category</b>	<b>Risk of Malignancy (%)</b>	<b>Usual Management†</b>
Nondiagnostic or Unsatisfactory	1-4	Repeat FNA with ultrasound guidance
Benign	0-3	Clinical follow-up
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	~5-15‡	Repeat FNA
Follicular Neoplasm or Suspicious for a Follicular Neoplasm	15-30	Surgical lobectomy
Suspicious for Malignancy	60-75	Near-total thyroidectomy or surgical lobectomy§
Malignant	97-99	

# The Problem of AUS/FLUS

- Variability in Dx: Labs report AUS rate ranging from 1 to 22%
- BSRTC originally reported >7% but in 2017 recommends 10%
- This is a Dx of exclusion and should not be overused!
- Descriptive interpretation of “atypia” should accompany report

# AUS/FLUS

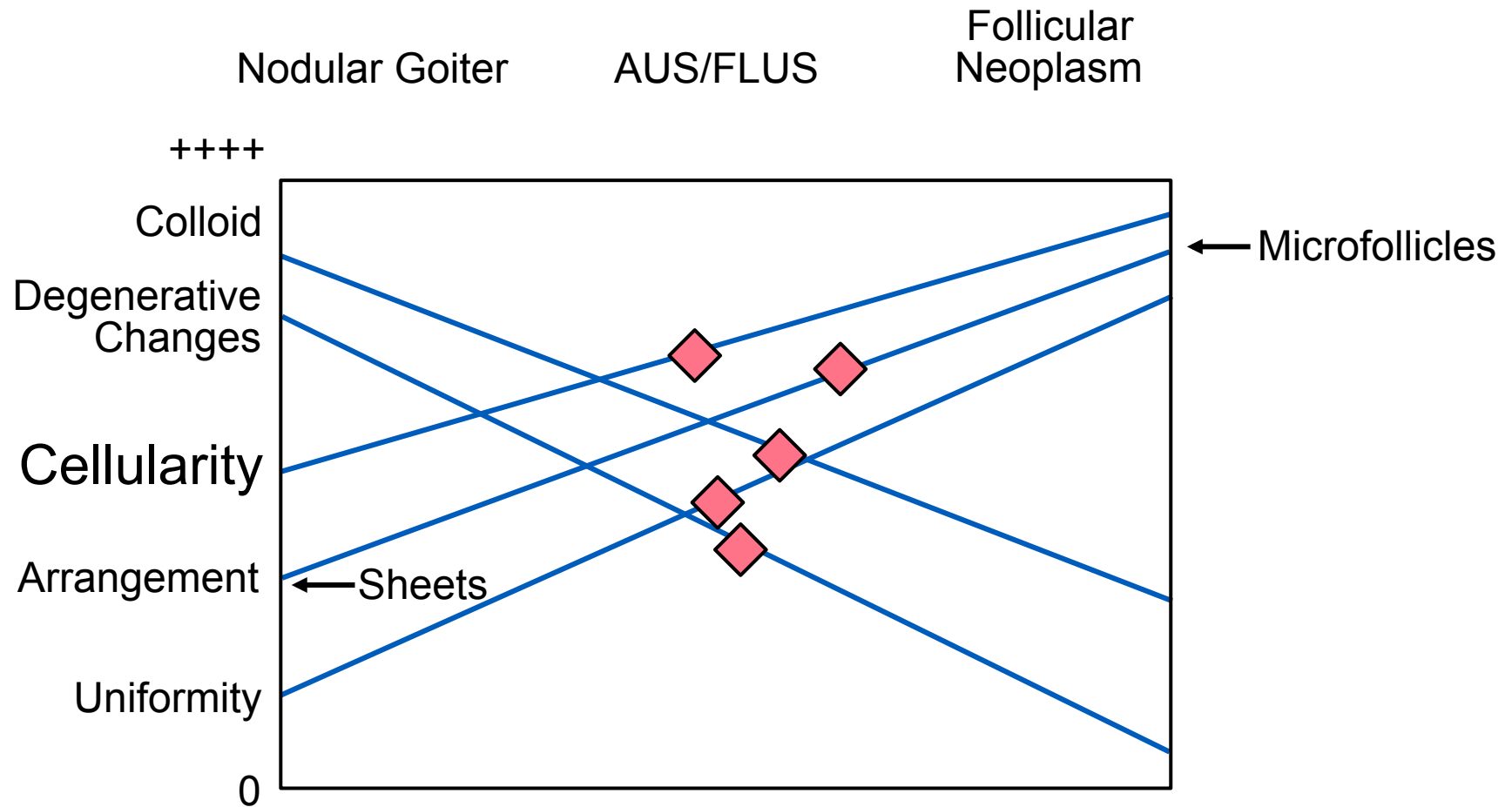
- Should be reserved for cases that fall between the benign and suspicious categories
- Qualitatively or quantitatively insufficient for a more definitive diagnosis
- Lack criteria to be classified as suspicious for FN, Hurthle cell, or malignant neoplasm



# AUS/FLUS

- Most “atypicals” (80-96%) resolve into benign or suspicious results after repeat FNA
- Malignancy rate (10-30%) is not sufficient to justify immediate surgery
- Avoid overuse of this category
- Understand what *your* cytopathologist means by AUS/FLUS

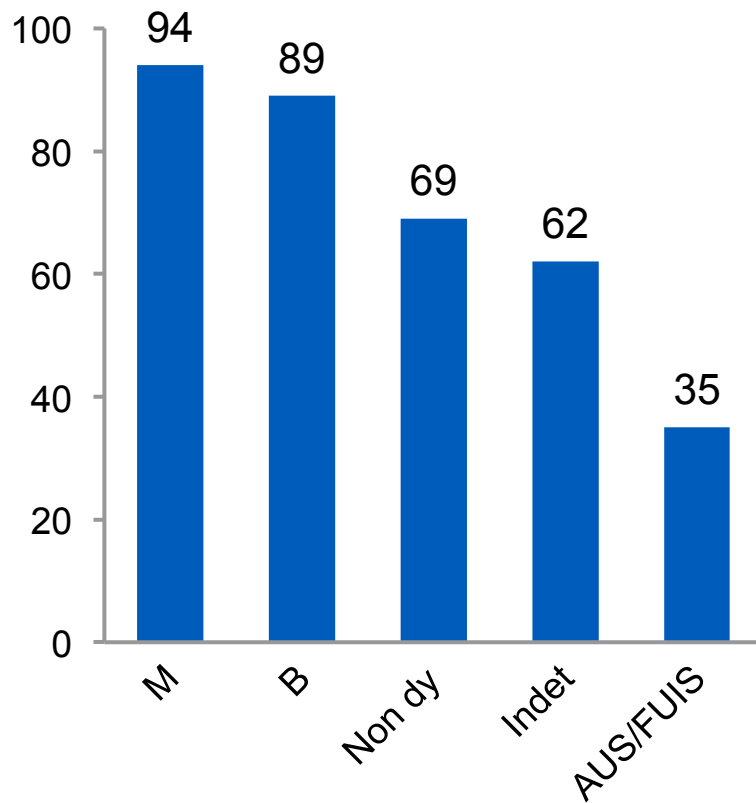
# Follicular Lesion of Uncertain Significance in Thyroid FNA



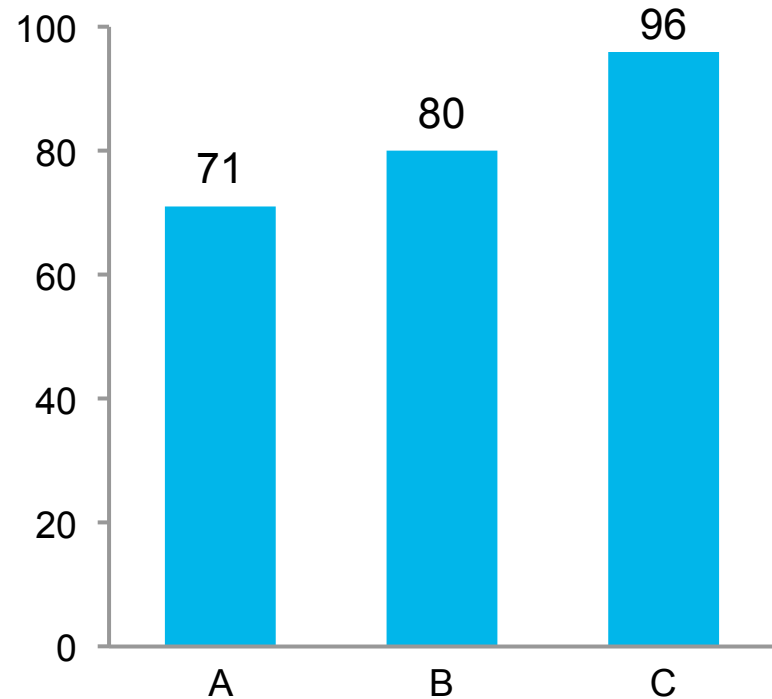
# How Good is Your Cytopathologist?

# Thyroid FNA

## Concordance of Local CP with Expert CP



## Intraobserver Concordance of Expert CP



Cibas et al: Ann Intern Med 159:325, 2013

# Molecular Markers

## Immunohistochemistry

- Galectin-3
- HBME-1
- CK19

## Mutations & gene rearrangements

- BRAF (V600E)
- RAS
- RET/PTC
- PAX8/PPAR $\gamma$
- ThyroSeqv2

## Gene expression

- Micro RNA
- Afirma GEC

# Molecular Markers

1. Afirma-Veracyte
2. ThyroSeq (2)-CBL Path
3. ThyGenX/ThyraMIR: NPV 94%; PPV 74%
4. RosettaGX: NPV 99%; sensitivity 98%

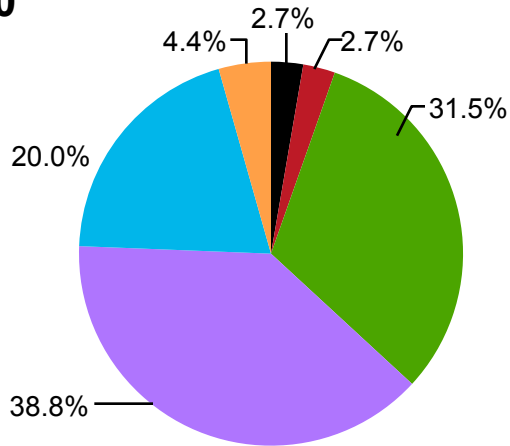
# Diagnostic Performance of Available Molecular Tests

Test	Markers used	Cytology (Bethesda)	Cases (no.)	NPV (%)	PPV (%)	Limitations of validation
<b>ThyroSeq v2</b>	Gene mutations	III	95	97	77	2 single-institution validation studies
	Gene fusions	IV	143	96	83	
	Gene expression	<b>Total</b>	<b>239</b>			
<b>Afirma</b>	Gene expression classifier	III	129	95	38	High post-unblinding exclusion rate (15%)
		IV	81	94	37	
		<b>Total</b>	<b>210</b>			
<b>Rosetta</b>	miRNAs	III+IV	<b>150</b>	92	43	Small validation set <u>No HCC tested</u>
<b>ThyGenX + ThyraMir</b>	7-gene panel miRNA	III	58	97	68	Small validation set
		IV	51	91	82	
		<b>Total</b>	<b>109</b>			

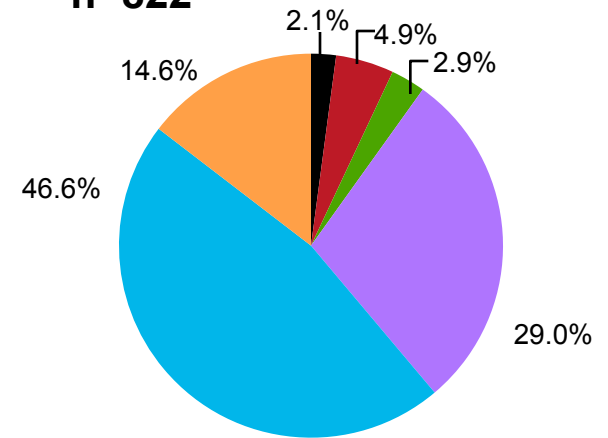


# Clinical Practice Survey

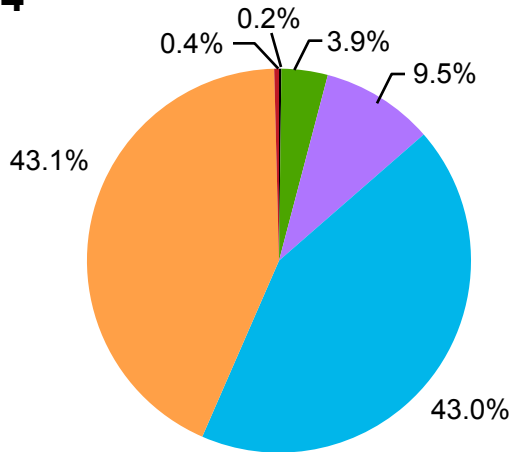
**A. AUS/FLUS**  
n=820



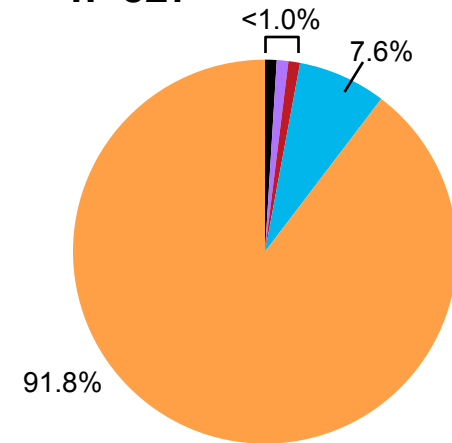
**B. Follicular neoplasm**  
n=822



**C. Suspicious for malignancy**  
n=824



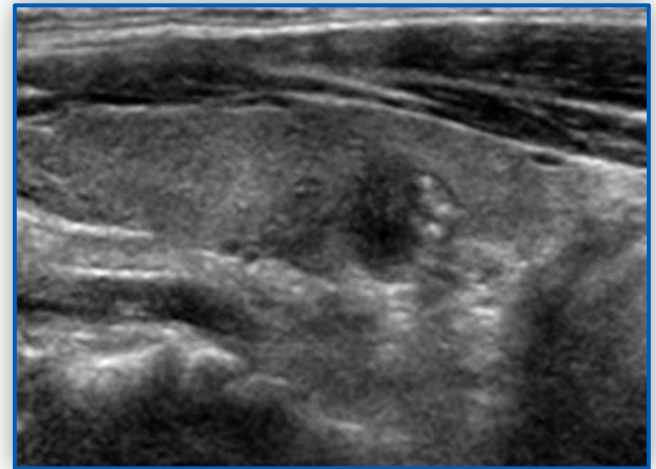
**D. Malignant**  
n=827



- Observe
- Thyroid scan
- Repeat FNA
- Molecular profile
- Lobectomy
- Total thyroidectomy

## 68-Year-Old Man

- Referred for an incidental thyroid nodule found on chest CT performed for cough; no radiation Hx and no FHx of thyroid disease; TSH 3.8 mIU/L.
- US shows a 1 cm solid, hypoechoic nodule with poorly defined margins and possible microcalcifications; no abnormal nodes were noted.



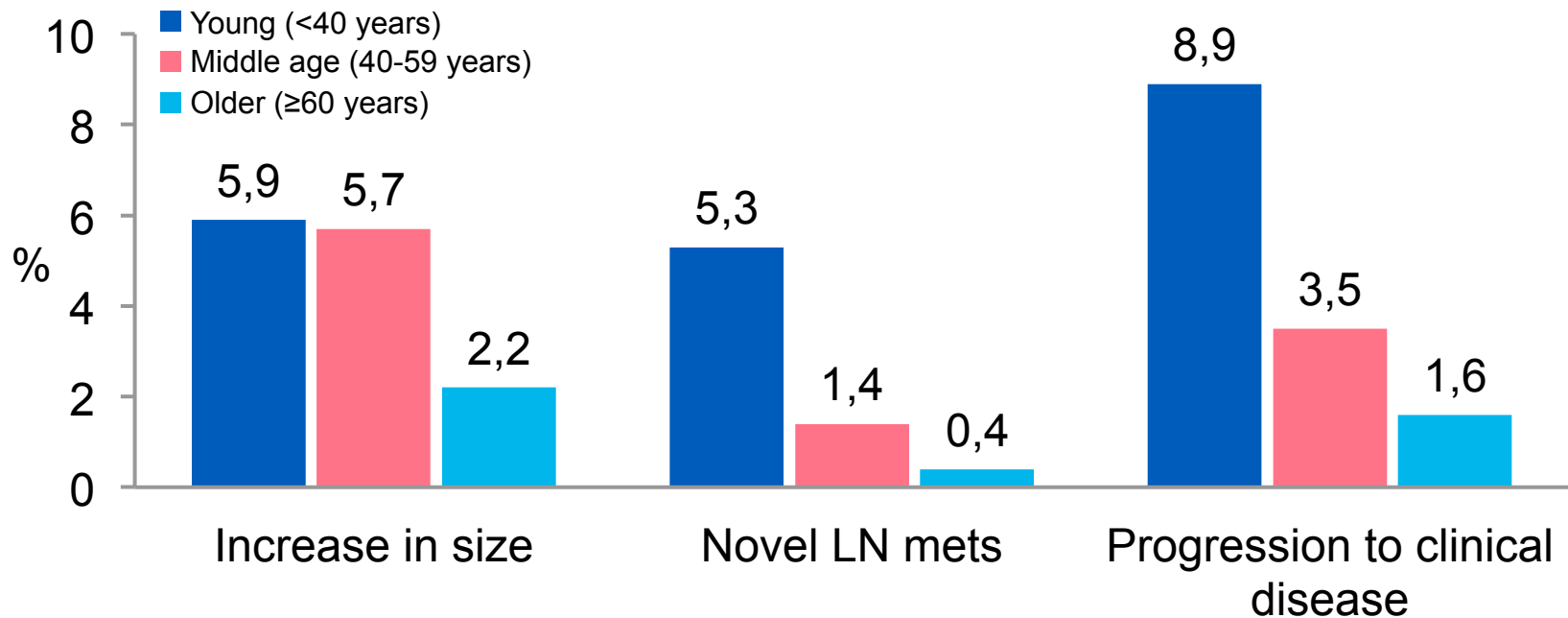
## How should we manage this patient now?

- A. Perform US-FNA & follow
- B. Proceed with thyroidectomy
- C. Active surveillance; repeat US in 6 months
- D. Begin LT4 Rx; repeat US in 6-12 months
- E. Dismiss without follow up

## Patient Age Is Significantly Related to the Progression of Papillary Microcarcinoma of the Thyroid Under Observation

Yasuhiro Ito, Akira Miyauchi, Minoru Kihara, Takuya Higashiyama,  
Kaoru Kobayashi, and Akihiro Miya

### Outcomes after 10 years of observation



# Favor Nonsurgical Management of PTMC, If Nodule

- $< 1$  cm
- Intrathyroidal but not subcapsular
- No LN
- Age  $> 60$  years
- Willing to defer immediate surgery
- Compliant with follow-up

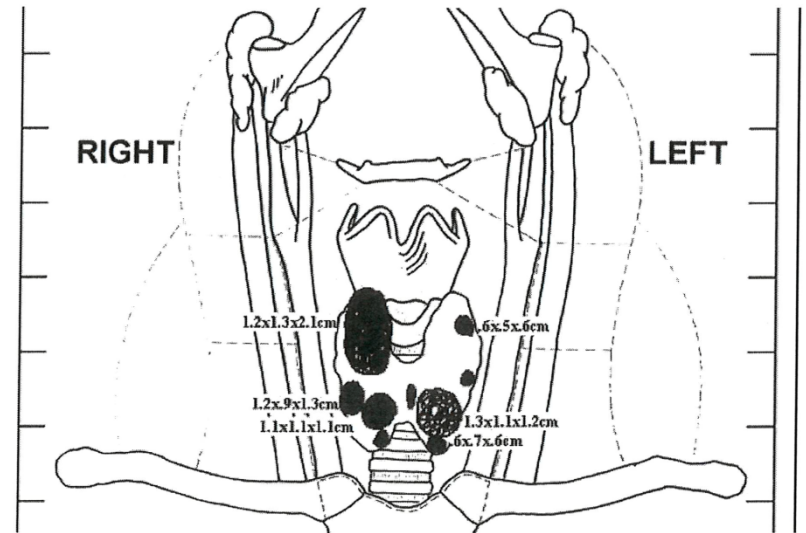
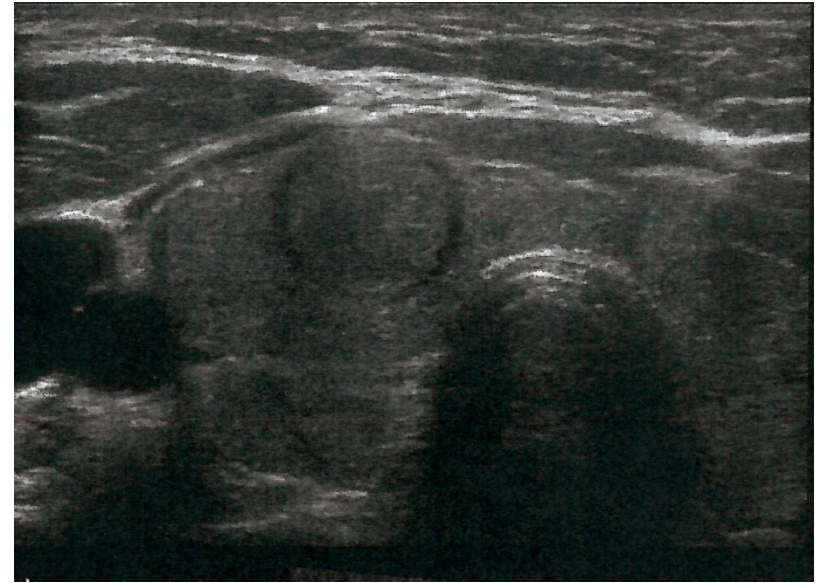
# Rationale for Avoiding Surgery for PTMC

- Mortality very low <0.5%
- Recurrence is low around 1-5% and only 1% if no nodes at dx
- Increased risk of recurrence if subcapsular lesion, ETE or multifocal disease
- BRAF mutations increase risk of local spread

66-year-old woman has a long history of a small goiter. She remains asymptomatic. Serum TSH is 2.2 mIU/L.

Thyroid US shows a small MNG; the largest nodular in the right is 2.1 cm, solid and hypoechoic. The largest nodule in the left lobe is 1.2 cm in greatest dimension; isoechoic and solid.

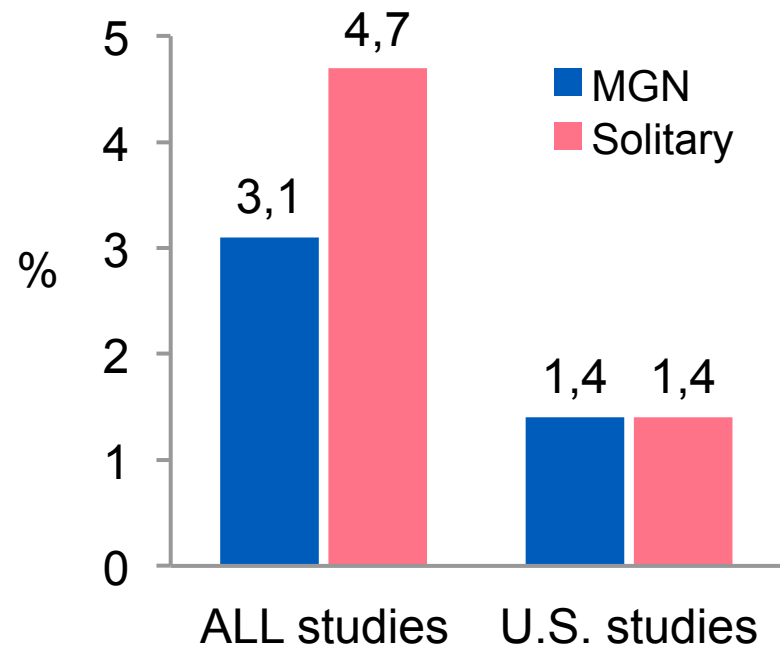
What is the risk of malignancy? Which nodule(s) to FNA?



# Risk of Cancer in a solitary nodule vs a Multinodular Gland

- Meta-analysis
  - 14 studies (44,288 pt)
  - 4 in US (2,442 pt)
  - 10 outside US
- 23,565 MNG pt
- 20,723 solitary nodule pt
- Overall lower risk of cancer in multinodular pt
- US subset: No difference

Cancer Prevalence MNG vs Solitary Nodule





# AACE Recommendations

- No more than 2 nodules, selected per criteria for single lesion, need FNA
- Do not FNA hot nodules if scan available
- With suspicious cervical adenopathy, FNA both nodule & node

A 46-year-old woman undergoes a left lobectomy after fine-needle aspiration of a 3.5 cm thyroid nodule showed follicular lesion of undetermined significance (FLUS) and molecular testing showed an NRAS mutation within the tumor. Histological examination is interpreted as showing a noninvasive follicular thyroid neoplasm with papillary-like nuclear features.

Which of the following is the most accurate description of this patient's tumor and recommended management strategy?

- A. Benign and no surveillance is needed
- B. Benign but he should undergo surveillance for recurrence
- C. Premalignant but no further therapy is needed
- D. Malignant but no further therapy is needed
- E. Malignant and further therapy is needed

# NIFTP Criteria

## Diagnostic Criteria for NIFTP

1. Encapsulation or clear demarcation<sup>a</sup>
2. Follicular growth pattern<sup>b</sup> with
  - <1% Papillae
  - No psammoma bodies
  - <30% solid/trabecular/insular growth pattern
3. Nuclear score 2-3
4. No vascular or capsular invasion<sup>c</sup>
5. No tumor necrosis
6. No high mitotic activity<sup>d</sup>

<sup>a</sup>Thick, thin, or partial capsule or well circumscribed with a clear demarcation from adjacent thyroid tissue

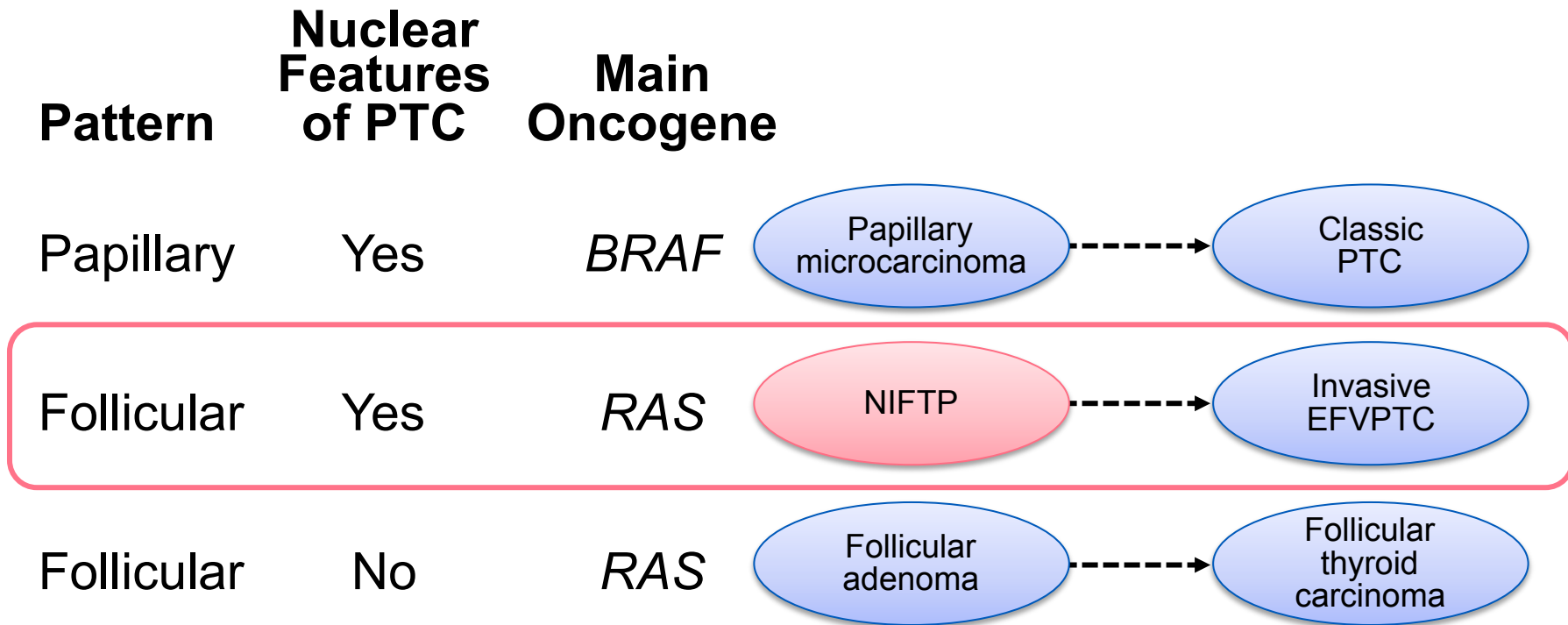
<sup>b</sup>Including microfollicular, normofollicular, or macrofollicular architecture with abundant colloid

<sup>c</sup>Requires adequate microscopic examination of the tumor capsule interface

<sup>d</sup>High mitotic activity defined as at least 3 mitoses per 10 high-power fields (400x)

# NIFTP as a Putative Premalignant Lesion

## Putative Scheme of Thyroid Carcinogenesis



EFVPTC indicates encapsulated follicular variant of PTC; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid carcinoma

# Conclusions-1

- A multidisciplinary approach to thyroid nodule is recommended
- Assess risk of malignancy (ROM) by clinical, biochemical, radiologic, cytologic and molecular means
- Thyroid nodule prevalence increases with age but ROM decreases
- Most (85%) benign thyroid nodules remain stable or decrease in size on follow-up

## Conclusions-2

- Watch for pseudonodules in patients with Hashimoto thyroiditis
- AUS/FLUS has a 10-30% risk of malignancy immediate surgery is not justified; molecular markers may help
- Do not FNA most nodules <1 cm even if high suspicion for malignancy
- PTMC may be followed by active surveillance in lieu of surgical intervention
- NIFTP is diagnosed by pathology after surgery; no further Rx is required

MAYO  
CLINIC



**Thank you**





# Questions & Discussion