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# Evolving Management of Thyroid Nodules

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Disclosure: No conflict of Interest

# Learning Objectives

- Discuss an updated approach to management of patients with thyroid nodules.
- Recognize the role of diagnostic tests available for the evaluation of thyroid nodular disease.
- Review the standardized sonographic criteria guidelines for risk based thyroid nodule FNAB performance.
- Understand the FNAB cytology report and the role of molecular markers in the evaluation and management of thyroid nodules.

## Approach to Thyroid Nodular Disease

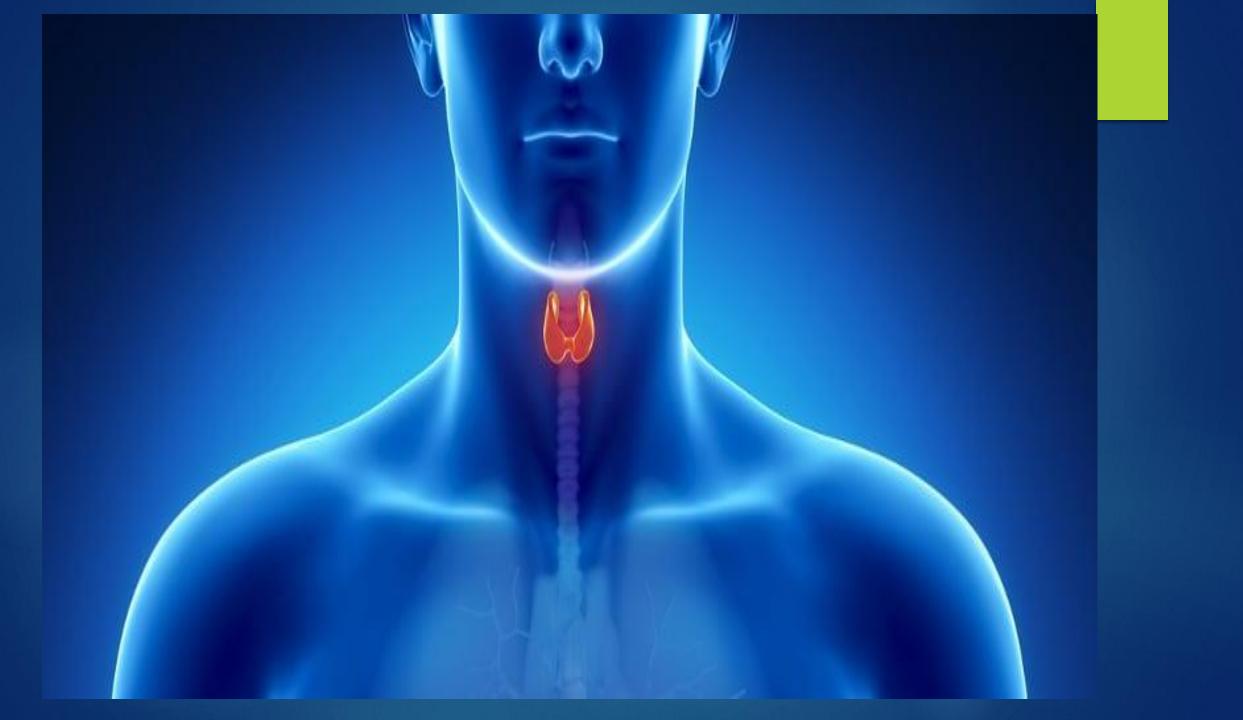
46 y/o surgeon with incidentally found nodule on Rt superior lobe of thyroid. Patient has history of thyroidectomy 17 years ago due to dominant nodule. Patient is euthyroid. Denies family hx of thyroid cancer. Refers history of radiation exposure at OR. Thyroid Sonogram shows a 2.5 cm hypoechoic nodule with irregular margins and calcifications. FNA biopsy done: Bethesda Class 2: Benign.

Next step in the management of this patient:

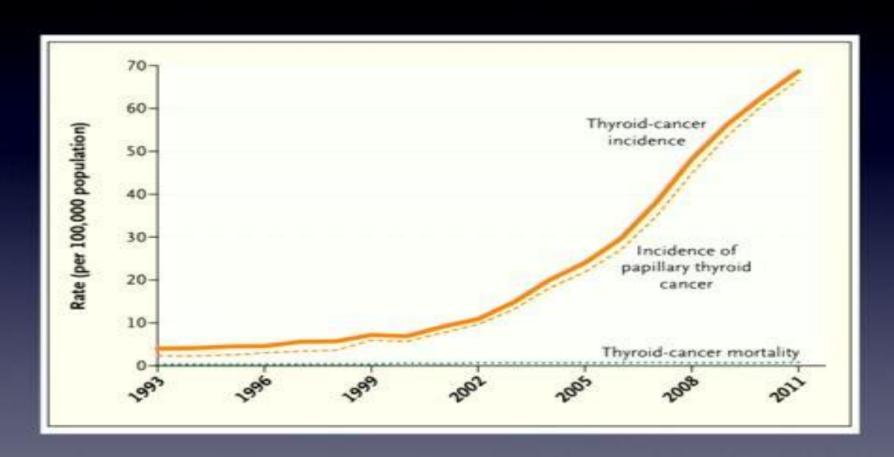
- A) Repeat FNA in 6 months
- B) Repeat sonogram in 6 months.
- C) Surgery consultation
- D) Repeat FNA with molecular markers
- ▶ E) A and C

## Thyroid nodule cases

- ▶ 35 y/o lawyer who presented with incidentally found thyroid nodule on left lobe. No previous hx of thyroid disease. He has no family hx of thyroid cancer and history of cervical discogenic disease and diagnostic studies and multiple dental procedures and braces for 10 years. Thyroid sonogram shows a .9x .5 x .7 cm hypoechoic nodule taller than wide on left lobe. TIRADS 5.
- Next step:
- A) FNA biopsy with molecular markers
- B) Surgery
- c) FNA biopsy
- D) Sonogram in 12 months
- E) Observation



## Thyroid cancer is over-diagnosed



## Prevalence of Thyroid Nodules

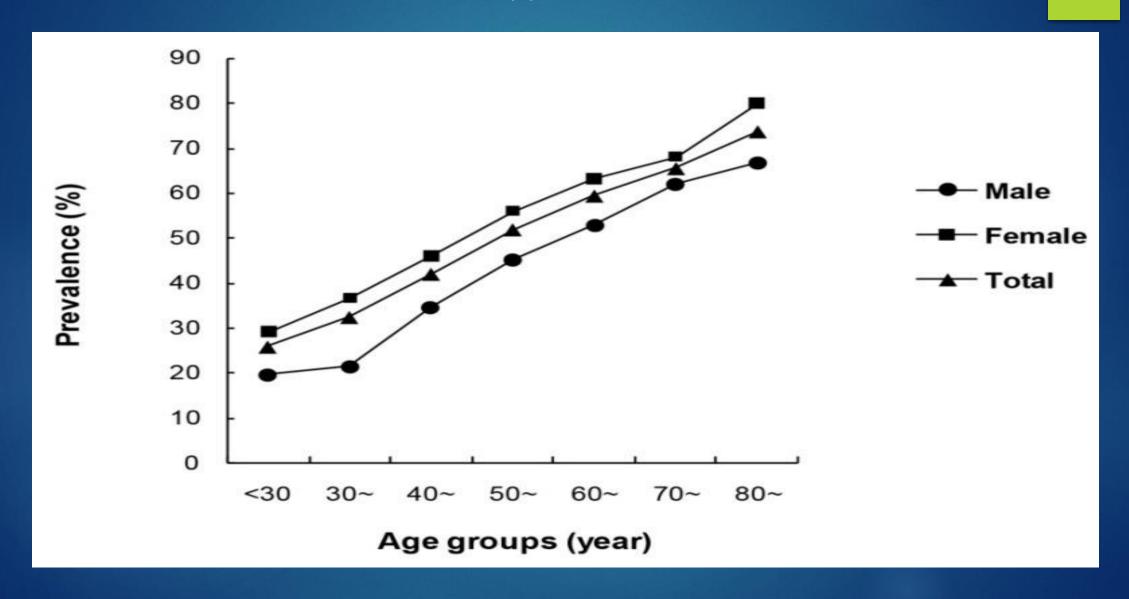


North America 67% Brazil 17%
China 49%
Finland 27% Belgium 19%

- Thyroid Nodule prevalence in iodine sufficient areas is approximately 5-7 % depending on age and sex.
- Prevalence and multi-nodularity increases with age, female sex, iodine deficiency, after radiation exposure, may increase with BMI, sedentary lifestyle, and smoking status in areas of iodine deficiency.
- ▶ 68% of general population harbor occult thyroid nodules discovered on diagnostic imaging (thyroid incidentalomas) or in autopsies.
- Risk of Malignancy (ROM) from 5-13% in patients with US, CT or MRI detected thyroid incidentalomas.
- JAMA March 6,2018 Vol 319 (9)
- Int J Environ Res Public Health; April 13 (4)

# Prevalence of Thyroid Nodules

Int J Environ Res Pub Health April 2016 13 (4)



# Thyroid Incidentalomas Prevalence

Ultrasonography – 65%
Computed Tomography or MRI --- 15%
PET 18 Fluorodeoxiglucose 1-2% ----ROM 55%
Risk of Malignancy of Incidentalomas 5-13%

2017 US Preventive Services Task Force Recommendation Statement: Against screening of thyroid cancer in adults without signs and symptoms of the disease. The potential harms outweigh any potential benefit. Recommendation does not apply to patients with risk factors.

JAMA 2017: 317(18): 1882-1887

# Malignancy in Thyroid Nodules Risk Factors

- Childhood irradiation to head and neck.
- lonizing Irradiation exposure in childhood and adolescence
- ► Family history of thyroid cancer
- Hereditary syndromes with associated DTC:
- Hamartoma Tumor Syndrome, Familial Adenomatous Polyposis, MEN 2, Werner Syndrome, Carney Complex
- ► Familial DTC 5-10%- genetic anticipation
- Rapid Nodule growth, hoarseness

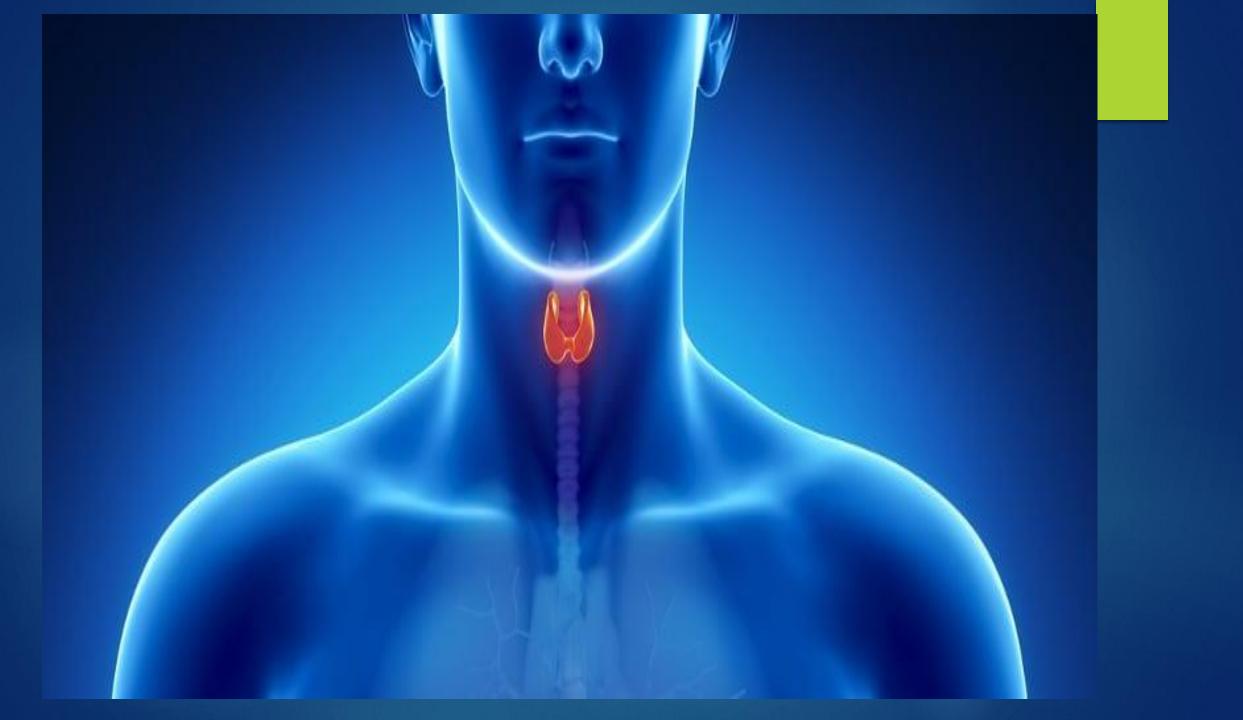


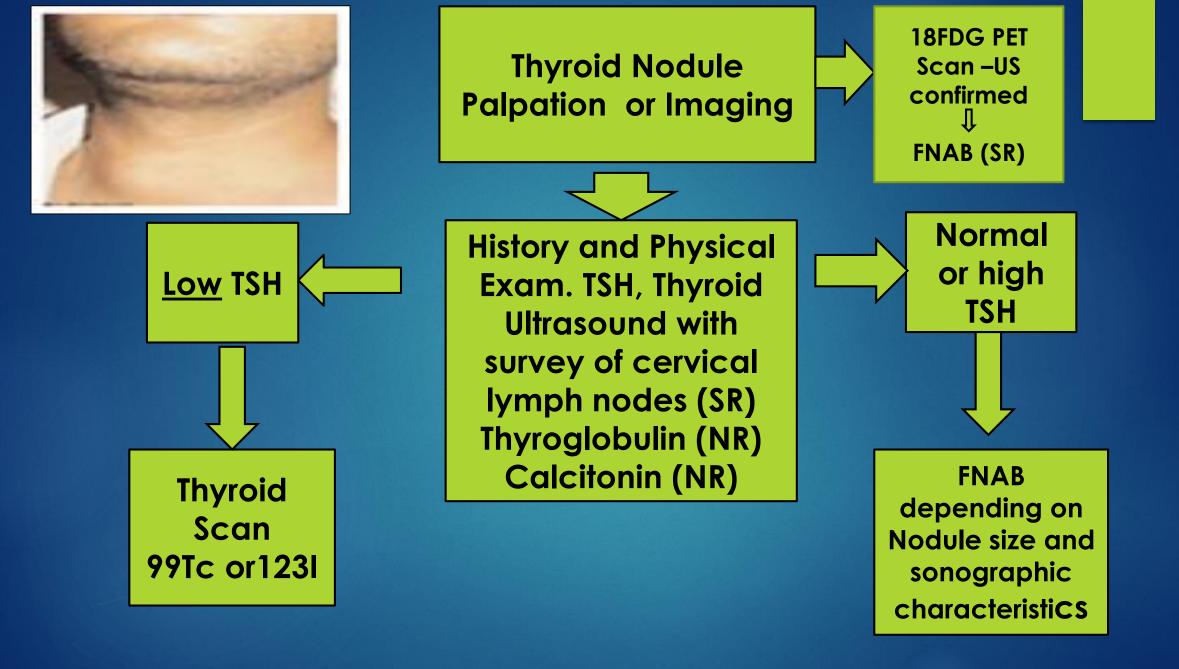
# Challenges in the Management of Thyroid Nodules

- Overdiagnosis
- ► Thyroid Incidentalomas
- Risks and harms of management of incidental thyroid nodules
- Costs of evaluation
- Individual variability in diagnostic reports
- Follow up guidelines

# Indications for Thyroid Sonogram

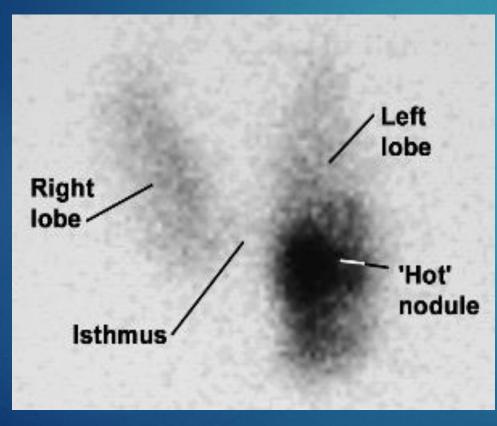
- Palpable thyroid nodule
- Asymmetric thyroid
- Incidentally found thyroid nodule characteristics
- ► Focal lesion on PET Scan
- ► Family members with thyroid cancer or MEN2
- History of external radiation
- Rapid nodule growth , hoarseness





# Hyperfunctioning Nodules rarely harbor malignancy

### Low TSH



### Thyroid Scan 123 I or 99TC

To determine hyperfunctioning nodule ( HOT) vs

Isofunctioning nodule (WARM)

Non functioning nodule (COLD)

If hot nodule present corresponds to the nodule in sonogram evaluation, NO cytology evaluation is needed.

Repeat US in 12-24 m to assess nodule stability.

## Multinodular Goiter



- Each nodule carries an independent risk of malignancy.
- When multiple nodules ≥ 1cm are present, FNA should be performed based upon nodule sonographic pattern and size.
- ▶ If none of the nodules has a high or moderate suspicion sonographic pattern, the likelihood of malignancy is low. It is reasonable to aspirate the largest nodule (≥2 cm) or continue surveillance without FNA.
- Radionuclide scanning may also be considered in patients with multiple thyroid nodules with the goal of identifying and aspirating appropriate hypo functioning nodules.

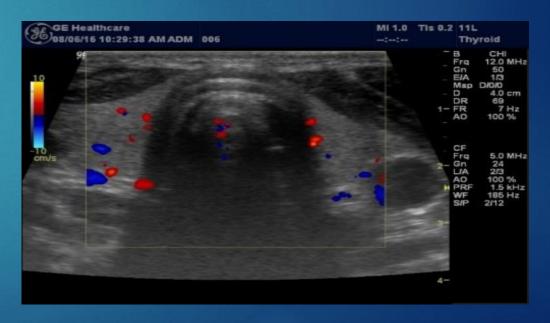
# Ultrasound Scanning of the Thyroid

<u>Ultrasonics.</u> 1967 Jul;5:177-80.

Ultrasound scanning of the thyroid gland as a new diagnostic approach.

<u>Fujimoto Y</u>, <u>Oka A</u>, <u>Omoto R</u>, <u>Hirose M</u>.



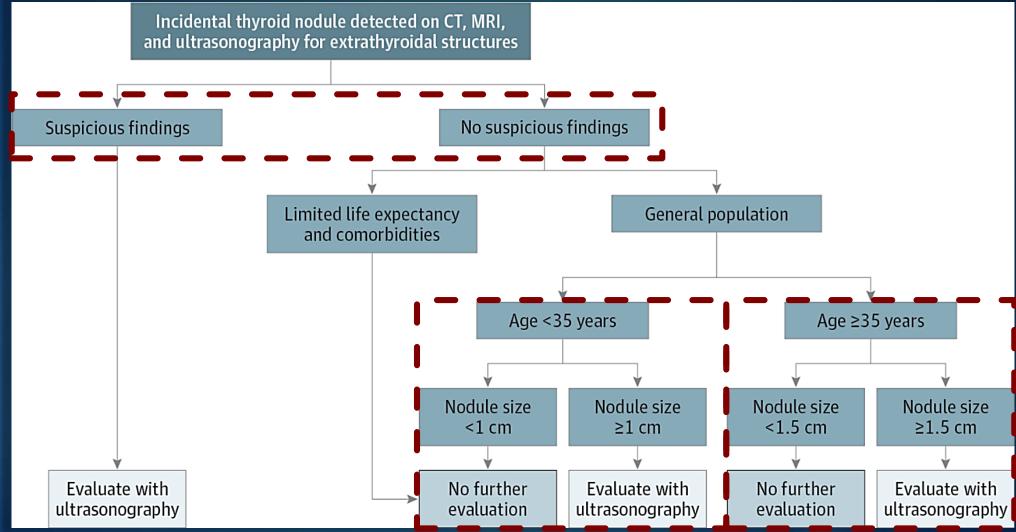


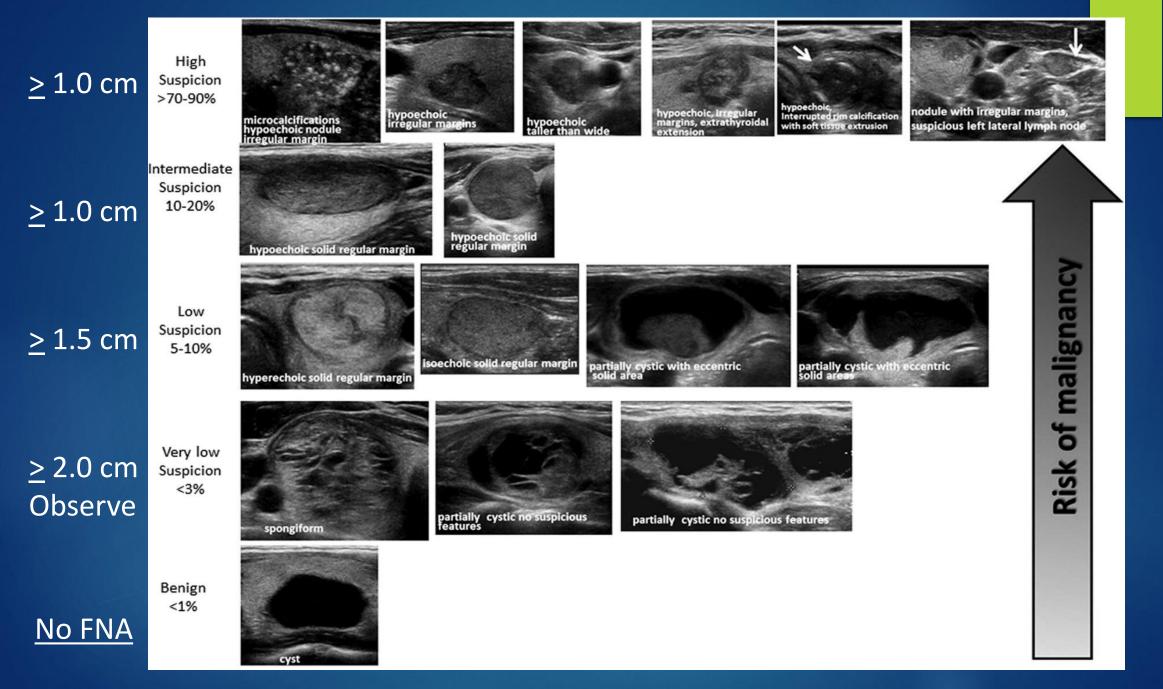
# Thyroid ultrasound report should include:

- Description of background thyroid parenchyma
- Nodule location
- Size (3 dimensions)
- Sonographic features of the nodule if present
- Survey of cervical lymph nodes

Malignancy Stratification	US Features	Malignancy Risk	Cutoff For FNA
High Risk	Solid, hypoechoic with 1 or more of the following: Irregular margins or poorly defined margins (infiltrative, micro lobulated), Microcalcifications, Taller than wide in transverse view, Rim calcifications with extrusive soft tissue, Extrathyroidal extension	>70-90%	≥ 1.0 cm
Intermediate	Hypoechoic without High Risk Features	10-20%	≥ 1.0 cm
Low	Isoechoic, hyperechoic, or partially cystic with eccentric solid areas without High Risk Features	5-10%	≥ 1.5 cm
Very Low	Spongiform or partially cystic without High Risk Features	<3%	> 2.0 cm Or Observe.
Benign	Purely cystic Haugen BR, et al. <i>Thyroid</i> 2016;26:1-132	<1%	No Biopsy

# American College of Radiology Recommendations for Incidental Thyroid Nodules





# Ultrasound Score System Proposed for Risk Based FNAB Thyroid Nodules

AACE, ACE, AME 2016

Low Risk and Benign

Risk of Malignancy 1%

FNAB >20mm

Sonography: Cysts with reverberating artifacts, no suspicious US signs

Isoechoic spongiform-confluent or with regular halo

### ATA 2015

Benign Risk of malignancy <1%

**FNAB** not indicated

Sonography: purely cystic

Very low suspicion Risk of malignancy <3% FNAB >20 mm or observation

Spongiform, partially cystic without US features suspicious

Low Suspicion Risk 5-10% FNAB >15 mm. Isoech, hyperechoic or partially cystic with eccentric solid area, without calcification, irreg margins, taller than wide, extrathyroidal extension.

# ACR TIRADS, 2017 Benign (TR1) definition

Risk of Malignancy 2%

**FNAB** not indicated

Sonographic pattern: Spongiform, pure cyst

#### Not suspicious (TR2)

Risk of malignancy 2%

**FNAB** not indicated

Sonographic pattern: mixed cystic, solid, not calcified, smooth margins, oval shape

## TR3- mild suspicious ROM 5%

FNAB >25mm Isoechoic, hypoechoic, cystic, non calcified, oval shape, smooth margin

# Intermediate or Moderately Suspicious Nodules US Scoring

# AACE, ACE, AME 2016

ROM 5-15% FNAB > 20mm

Sonographic pattern: Slightly hypoechoic or isoechoic, ovoid to round shape, smooth or ill defined margins

May be present: intranodular vascularization, elevated stiffness at elastography

Macro or continuous ring calcification, indeterminate hyperechoic spot

### ATA 2015

**ROM 10-20%** 

**FNAB > 10 mm** 

Sonography: Hypoechoic solid nodule with smooth margins w/out microcalcifications, extrathyroidal extension or taller than wide shape

### **ACR TIRADS 2017**

**ROM 5-20%** 

FNAB > 15 mm

Sonography: Hypoechoic solid non calcified with oval shape and smooth or irregular or lobulated margins. Isoechoic, solid or mixed non calcified nodules with either non parallel orientation(taller than wide), lobulated or irregular margins, or punctate echogenic foci

# High Risk or Suspicious Thyroid Nodules

# AACE, ACE, AME 2016

**ROM 50-90%** 

FNAB > or = 10 mm 0r 5 mm selective

Sonography: Nodules with 1 or more of the following:
Marked hypoechogenicity (vs prethyroid muscles)

Spiculate or lobulated margins

**Microcalcifications** 

Taller than wide shape

Extrathyroidal growth

Pathologic adenopathy

### ATA 2015

ROM >70-90%

FNAB > or = 10 mm

Sonography: Solid

hypoechoic nodule or solid hypoechoic component of partially cystic nodule with one or more of: Irregular margins (infiltrative, micro lobulated),

Microcalcifications,

Taller than wide,

Rim calcifications with small extrusive soft tissue

Extrathyroidal extension

### **ACR TIRADS 2017**

Suspicious (TR5)

ROM > 20%

FNAB > 10 mm

Sonography: Hypoechoic solid nodule with any of the following: Non parallel orientation (Taller than wide),

Extrathyroidal extension

Punctate echogenic foci

Isoechoic solid nodule with irregular or lobulated margins, peripheral rim calcifications or punctate echogenic foci

# Thyroid Nodule Location on US as a Predictor of Malignancy

The results of a retrospective study of 219 patients with FNAB suggested that thyroid nodules found in the superior pole appeared to confer 4X higher risk of cancer than other regions of the thyroid gland. (ROS/ AKT/Rad exposure)

The location of the nodule may be considered an additional factor in the decision making process regarding performing FNA and how to proceed with suspicious and enlarging nodules. Zhang, F.

Endocrine Practice 2019;25(No2)

## <u>Thyroid Imaging Reporting and Data System</u> TIRADS: American College of Radiology

### **ACR TI-RADS**

#### COMPOSITION

(Choose 1)

Cystic or almost 0 points completely cystic

Spongiform 0 points

Mixed cystic 1 point

and solid

Solid or almost 2 points

completely solid

#### **ECHOGENICITY**

(Choose 1)

Anechoic 0 points

Hyperechoic or 1 point isoechoic

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

III-defined 0 points

Lobulated or 2 points

3 points

irregular

Extra-thyroidal extension

ECHOGENIC FOCI

(Choose All That Apply)

None or large 0 points comet-tail artifacts

Macrocalcifications 1 point

Peripheral (rim) calcifications

> Punctate echogenic 3 points

2 points

foci

Add Points From All Categories to Determine TI-RADS Level

0 Points

TR1 Benign

No FNA

2 Points

TR<sub>2</sub> **Not Suspicious** No FNA

3 Points

TR3 Mildly Suspicious FNA if > 2.5 cm

Follow if ≥ 1.5 cm

4 to 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\*

## **US Elastography**

- Ultrasound elastography differentiates thyroid nodules based on elasticity: strain and shear wave elastography.
- It measures stiffness which may predict malignancy. Many studies support the use of elastography as an independent predictor of thyroid cancer in unselected thyroid nodules. There are limitations and it is not widely available.
- The AACE, ATA and KSThR recommend use of elastography as a supplementary study but not as a replacement for gray-scale ultrasound.
- ▶ <u>J Ultrasound Med.</u> 2014 Mar;33(3):495-502.
- ▶ Thyroid Volume 23, number 6, 2013

### Elastography

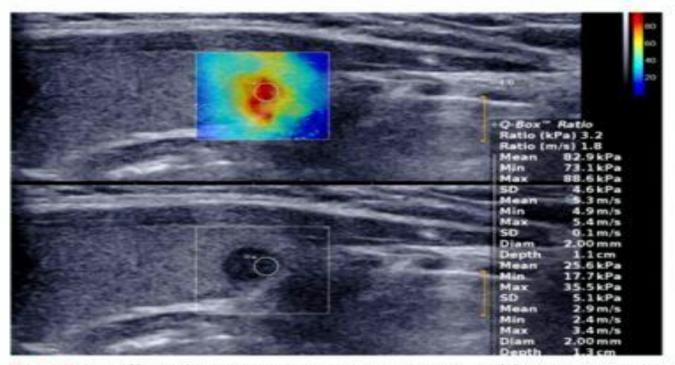
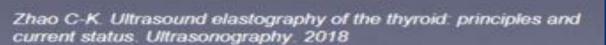


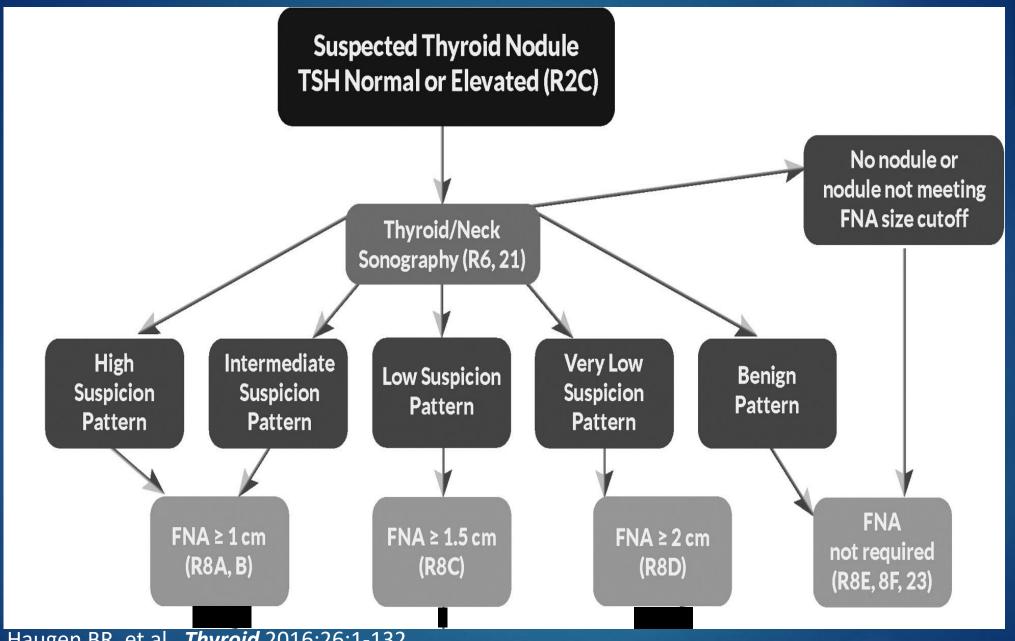
Fig. 12. Papillary thyroid carcinoma in a 28-year-old woman. Grayscale ultrasonography (lower side) shows a solid hypoechoic 6-mm thyroid nodule with poor margin and microcalcifications. SuperSonic shear-wave elastography (upper side) shows a heterogeneously stiff (red and yellow) nodule with a maximum elasticity of 88.6 kPa.



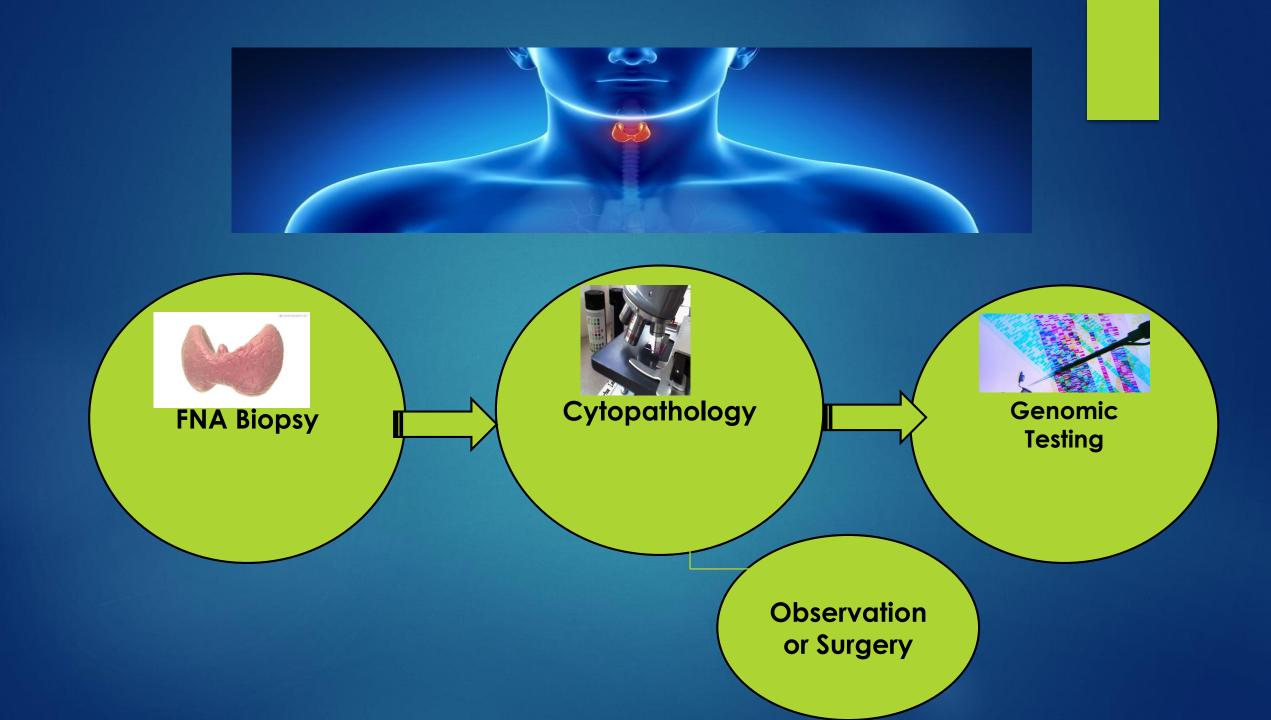
# US Elastography for Differentiation of Benign and Malignant Thyroid Nodules

- > 5481 nodules in 4468 patients were evaluated for elasticity score.
- 1063 nodules in 983 patients for strain ratio.
- ▶ Mean Sensitivity and Specificity of ultrasound elastography for differentiation of thyroid nodules were 0.79 (95% confidence interval [CI], 0.77-0.81) and 0.77 (95% CI, 0.76-0.79) for elasticity score assessment and 0.85 (95% CI, 0.81-0.89) and 0.80 (95% CI, 0.77-0.83) for strain ratio assessment. The areas under the curve for the elasticity score and strain ratio were 0.8941 and 0.9285.
- ▶ UE has high sensitivity and specificity for identification of malignant thyroid nodules. It is a promising tool for reducing unnecessary fineneedle-aspiration biopsy. NPV was 97.2%.
- ▶ <u>J Ultrasound Med.</u> 2014 Mar;33(3):495-502
- ► Thyroid Volume 23, number 6, 2013





Haugen BR, et al. *Thyroid* 2016;26:1-132



## Bethesda Classification of Thyroid Nodules

Bethesda Group	Diagnostic category	Abbreviation	Malignancy rate	
			Before NIFTP reclassification (NIFTP malignant)	After NIFTP reclassification (NIFTP benign)
1	Non-diagnostic unsatisfactory		5–10%	No change
II	Benign	NPV 95-98%	0–3%	No change
III	Atypia of undetermined significance, follicular lesion undetermined significance (AUS/FLUS)	Nuclear atypia, mixed macro- microfollicular Hurtle cells	10–30%	6–18%
IV	Follicular neoplasm suspicious for follicular neoplasm (FN/SFN)	Microfollicular nodules and Hurtle cell nodules	25–40%	10–40%
V	Suspicious for malignancy		50–75%	45–60%
VI	Malignant -3-5%	PPV 95%	97–99%	94–96%

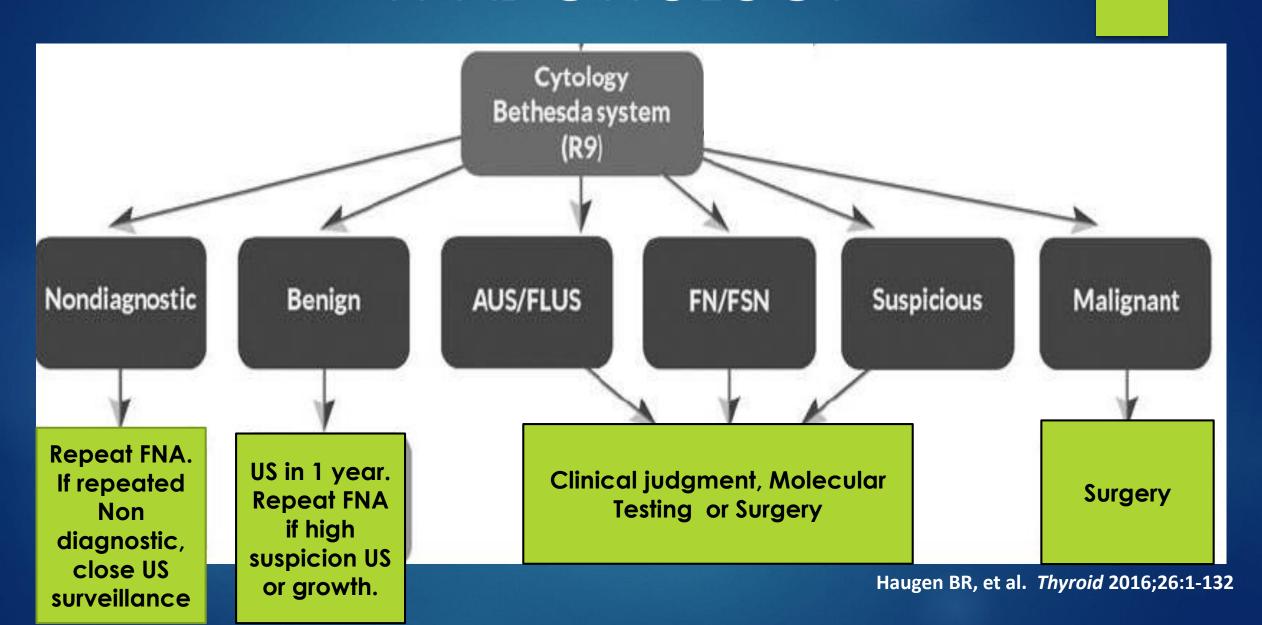
# NIFTP Reclassification: Non Invasive Follicular Thyroid Neoplasm.

- ▶ Follicular variant of Papillary Carcinoma: Described in 1970's as a tumor with predominant follicular growth pattern and nuclear cytomorphology of PTC.
- Subtypes: infiltrative (aggressive) and encapsulated (benign course).
- Procent clinical follow up and case control studies confirmed that non invasive EFVTPTC behaves in benign fashion and may be overtreated. Recent molecular analysis shows a unique set of genetic mutations and fusions (RAS (M)30%,PPARG or THADA(GF)44%. NIFTP Reclassification: Non Malignant Entity by Endocrine Pathology Society Working Group.
- Follow up for 10-26 years post op no evidence of disease. No RAI ablation and the majority was treated with lobectomy. Represents 5% of thyroid of FNAB diagnosed as malignant.

## NIFTP Diagnostic Criteria

- Well demarcated/ encapsulated follicular patterned tumor
- Nuclear cytology of PTC
- Non invasive characteristics:
  - ▶ No tumor capsule invasion or invasion in surrounding thyroid parenchyma
  - No lymphovascular invasion.
- Exclusion: Invasion , tumor growth pattern, Psammoma bodies , tumor necrosis or mitosis
- ▶ Long term prospective studies are needed to validate this change in thyroid cancer diagnosis and treatment.
- Endocrine Practice 2017:23 (No. 9).

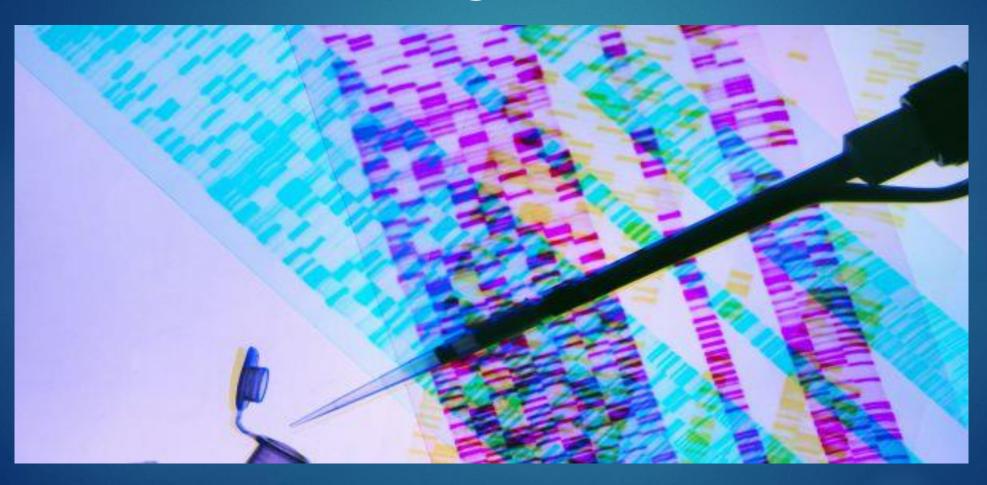
### FNAB CYTOLOGY



### Follow-Up of Nodules with Benign FNA

- Based on sonographic stratification:
  - ▶ High Suspicion: Repeat US and FNA within 12 months
  - ▶ Low to Intermediate Suspicion: Repeat US at 12-24 months
    - ▶ If new suspicious sonographic feature or growth, then repeat FNA
      - Growth:
        - ▶20% increase in at least 2 dimensions with a minimal increase of 2mm
        - More than 50% increase in volume
- ▶ **Two benign FNA** No US surveillance indicated

# Indeterminate Cytology and Molecular Testing



## Molecular Genetics and Diagnosis of Thyroid Cancer

Activation of MAPK and PI3K-AKT signaling pathways
(THYROID CANCER INITIATION AND PROGRESSION)
Oncogenic Stimuli-----Mutated BRAF, RAS, RET/PTC, TRK
INITIATING EVENT IN DTC PTC AND SOME FOLLICULAR CA
Thyroid Cancer Mutational Mechanisms:

**Point Mutations**: RAS, BRAF GENES (high I intake, volcanic chemicals exposure)

Chromosomal rearrangements: RET/PTC, PAX8/PPARG

Radiation exposure: RET/PTC, BRAF/AKAPq

**Chromosomal Fragility**: RET/PTC

Nat Rev Endocrinol . 2011 Aug 30; 7 910) : 569-580

## Molecular Testing

#### Benefits

- Better Risk stratification
- Reduces the need of diagnostic thyroid surgery
- Distinguishes high risk cancers from premalignant or low intermediate risk nodules.

#### **Commercially Available**

- AFIRMA GEC + MTC (Veracyte Inc)
- ThyroSEq v3 (CBL Path Pittsburg)
- ThyGenX/ ThyraMIR (Interpace Diagnostics, Inc New Jersey)
- Rosetta GX Reveal( Rosetta Genomics Inc, Philadelphia, Pennsylvania)

### **Molecular Tests**

#### **AFIRMA**

Methodology: Analysis 167 mRNA(25 genes in screening) 142 genes in classifier by microarray.

Report: Benign or Suspicious

Validation study:

51 positive/210 indeterminate FNA =24% cancer prevalence

% Sensitivity: 92

% Specificity:52

% NPV 94

% PPV 37

\$\$ BRAF \$450 MTC \$975

**GEC + MTC \$6400** 

#### **Thyroseq**

DNA and RNA target sequencing (56 genes) for Mutations, gene fusions and gene expression

Specific gene mutation or translocation

61 positive/239 indeterminate FNA =26% cancer prevalence

%Sen 90

%Spec 93

% NPV 89

%PPV 85

\$4056

Arch Pathol Lab Med vol 142 April 2018

## ThyGen X/ ThyraMIR

Targeted sequencing for Mutations ( $\overline{5}$  genes), 3 gene fusions, expression analysis of 10 miRNA/

Report: Negative/Positive

Valid: 35 positive/109 indeterminate

Prevalence of cancer = 32%

Sens 89 Spec 85 NPV 94

**PPV 74** 

#### Rosetta GX Reveal

**Expression of 24 miRNA** 

31 positive/150 indeterminate Prevalence of cancer 21%

Sens 74 Specificity 74

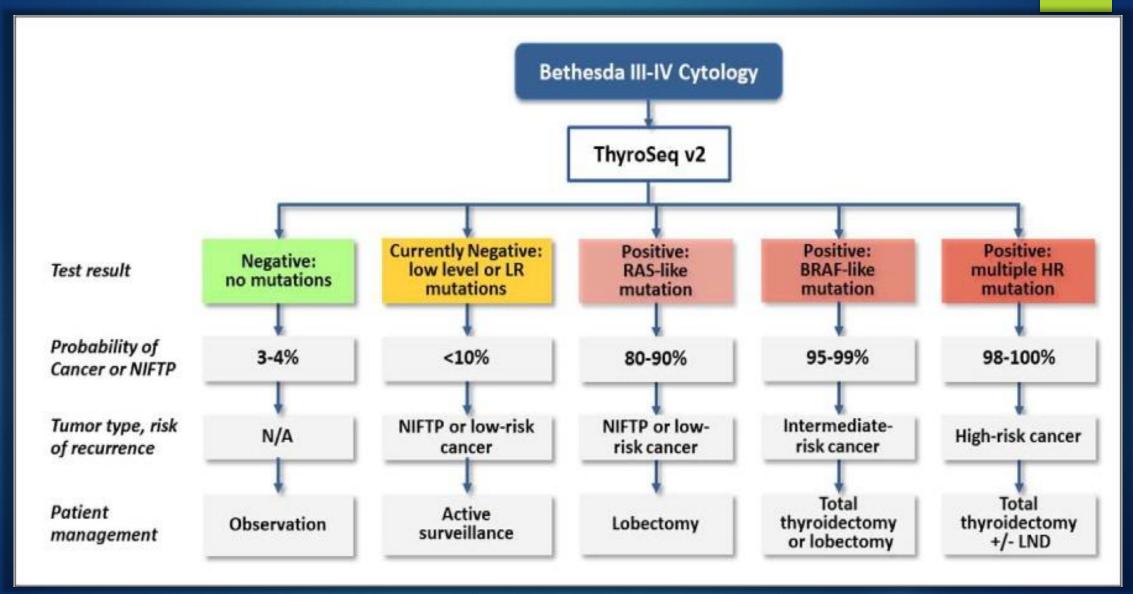
**NPV 92** 

**PPV 43** 

\$ 3700



### **Molecular Markers**





Management of Benign Thyroid Nodules

## Thyroid Hormone Therapy

- Routine TSH suppression for benign thyroid nodules in iodine sufficient populations is NOT recommended.
- "There are no data to guide recommendations on the use of thyroid hormone therapy in patients with growing nodules that are benign on cytology."
- ▶ TSH suppression
  - † risk of cardiac arrhythmias, osteoporosis, and adverse symptomatology.
  - Risks outweigh the benefits

# Ultrasound guided Sclerotherapy in Benign Cystic Nodules

- A preliminary prospective study on the efficacy and safety of ultrasoundguided percutaneous Lauromacrogol sclerotherapy in benign cystic or predominantly cystic thyroid nodules.
- Prospective study First Hospital of Wenzhou Medical University from October 2012 to Dec 2015 with percutaneous Lauromacrogol sclerotherapy. Therapeutic success rate >50% nodule volume reduction mean volume reduction 12.5 cm to .3 cm in cystic and predominantly cystic 10.5 cm to 2.0 cm at 12 m post PLI p <.001 with 93.4% of therapeutic success rate. No significant difference in thyroid function before and after PLI in two groups of patients p>0.05.

# Comparison of Ultrasound-Guided Percutaneous Polidocanol Injection Versus Percutaneous Ethanol Injection for Treatment of Benign Cystic Thyroid Nodules. Retrospective study: May 2010-March 2016

Efficacy, safety, and cost-effectiveness of US guided PPI and PEI injection for treatment of benign cystic and predominantly cystic thyroid nodules were compared.

135 cystic thyroid nodules  $\rightarrow$  PEI vs 136 cystic thyroid nodules  $\rightarrow$  PPI F/U 1,3,6,12 post Tx.

Nodule volumes, symptoms, and cosmetic scores before Rx and at F/U

Therapeutic success rate, safety, and cost-effectiveness compared.

No significant differences in the reduction of the nodule volume, volume reduction rate, and therapeutic success (P > .05), cosmetic scores nor symptom scores.

Complication rates for Ethanol higher than those for Polidocanol (P < .05).

The cost of PPI was higher than that of PEI(mean  $\pm$  SD, US\$97.18  $\pm$  US\$22.17 versus US\$43.36  $\pm$  US\$5.51; P < .01).

Ultrasound-guided percutaneous polidocanol injection can be an alternative for sclerotherapy of cystic or predominantly cystic thyroid nodules.

# Radiofrequency Ablation Therapy for Large Benign Thyroid Nodules

- Mayo Clinic Rochester Dec 2013-2016 experience:
- US guided thyroid nodule RFA is an effective and safe outpatient treatment in patients with symptomatic steadily growing benign, large, predominantly solid nodules.
- Results: nodule volume reduction, alleviates compressive symptoms and improve esthetic appearance, preserves normal thyroid function.
- In Centers with expertise could become an alternative for the management of benign large toxic and non toxic nodules.
- Mayo Clinic Proceedings 2018.

# Radiofrequency Ablation Therapy for Large Benign Thyroid Nodules

- Safety of radiofrequency ablation of benign thyroid nodules and recurrent thyroid cancers: a systematic review and meta-analysis.
- 24 eligible studies included with a sample size of 2421 patients and 2786 thyroid nodules.
- ▶ 41 major complications and 48 minor complications of RFA were reported, giving a pooled proportion of 2.38% for overall RFA complications [95% confidence interval (CI): 1.42%-3.34%] and 1.35% for major RFA complications (95% CI: 0.89%-1.81%). On subgroup analysis, the overall and major complication rates were significantly higher for malignant thyroid nodules than for benign thyroid nodules (p = 0.0011 and 0.0038, respectively).
- RFA was found to be safe for the treatment of benign thyroid nodules and recurrent thyroid cancers

## Ultrasound-Guided Percutaneous Microwave Ablation for Solid Benign Thyroid Nodules:

- ▶ The results among 75 patients with 90 nodules undergoing MWA in this study were superior to those among patients acting as control 49 pts with 56 nodules). It revealed that MWA significantly decreased TN volume in comparison with untreated patients who did experience TN size increase. Complications: Horner syndrome (1 case/90 nodules treated), transient voice change and laryngeal nerve paralysis (2), pain (10), edema, cervical burn (1), transient thyrotoxicosis (1)
- The magnitude of volume reduction in this study is similar to studies conducted by RFA and other MWA studies, though there is no head-to-head studies which thermal modality is superior.

## In Summary

- There are clear indications for thyroid sonography.
- Sonographic characteristics of a thyroid nodule should be used to determine the probability of malignancy and guide decisions on FNAB, surgery or follow up studies.
- Molecular markers are available for indeterminate nodules with highly suspicious characteristics to aid in evaluation before surgery to guide extension of surgery.
- Evaluation of Thyroid Nodular disease in collaboration with an experienced radiologist, cytopathologist and surgeon is key to early diagnosis of malignancy, follow up of high risk nodules, and therapy of suspicious and benign lesions as needed. The patient is an active participant in this decision process.

声引导下经皮穿刺聚桂醇硬化治疗甲状腺囊性和囊实性结节的前瞻性初步研究

### THANKS FOR YOUR ATTENTION

