



Rimini, 5-8 novembre 2015



ITALIAN CHAPTER



Controversies in Thyroid Nodule Guidelines

A. Crescenzi, A. Frasoldati, J. Garber,
L. Hegedus, E. Papini, M. Zini



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Conflitti di interesse



ITALIAN CHAPTER



Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiariamo che negli ultimi 2 anni abbiamo avuto rapporti di finanziamento rilevanti con soggetti portatori di interessi commerciali in campo sanitario.



How to Make Thyroid Nodule GLs Recommendations Consistent?

Rimini, 5-8 novembre 2015



Crescenzi, Frasoldati, Garber, Hegedus, Papini & Zini in 1963 (courtesy of F. Fellini)

Several Thyroid Nodule Guidelines are available

- BTA 2014
- NCCN 2015
- ATA 2015
- AACE/AME 2016

What shall we do in clinical practice?

Main Topics

- Ultrasound Report & Classification Systems
- Indications for US-guided FNA
- Management of Indeterminate Cytology

Main Topics

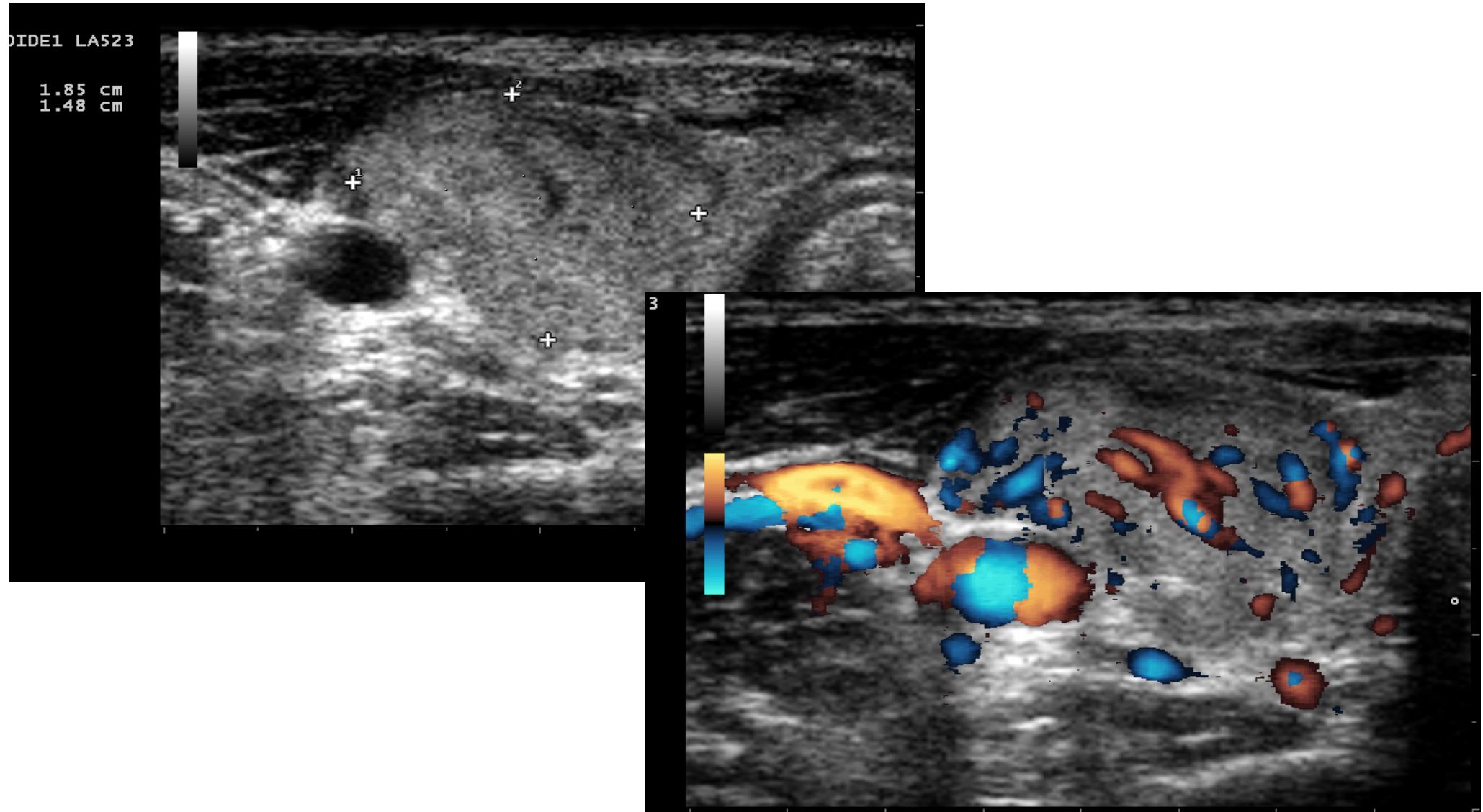
- Ultrasound Report & Classification Systems
- Indications for US-guided FNA
- Management of Indeterminate Cytology

Clinical Case: Paola

- Paola, age 35, teacher
- No relevant personal or family history
- Lump on the right side of the neck, firm, smooth, mobile, about 2 cm
- TSH: 2.3

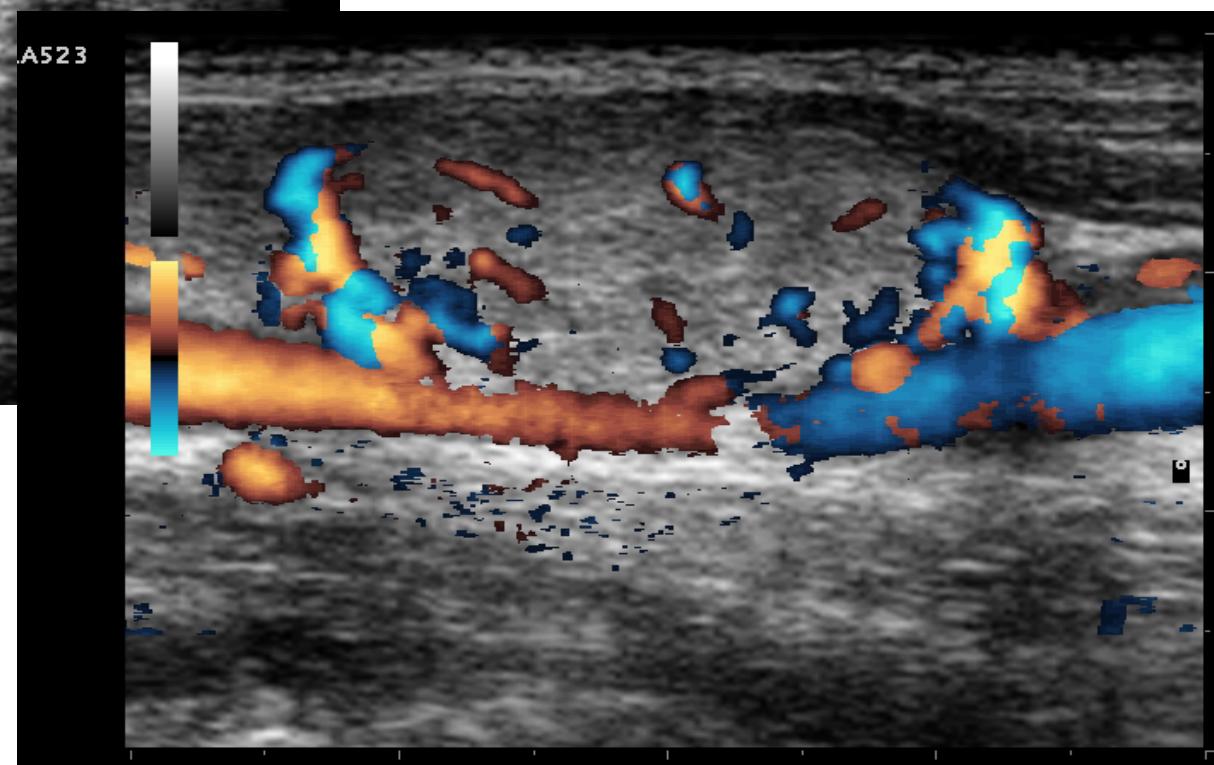
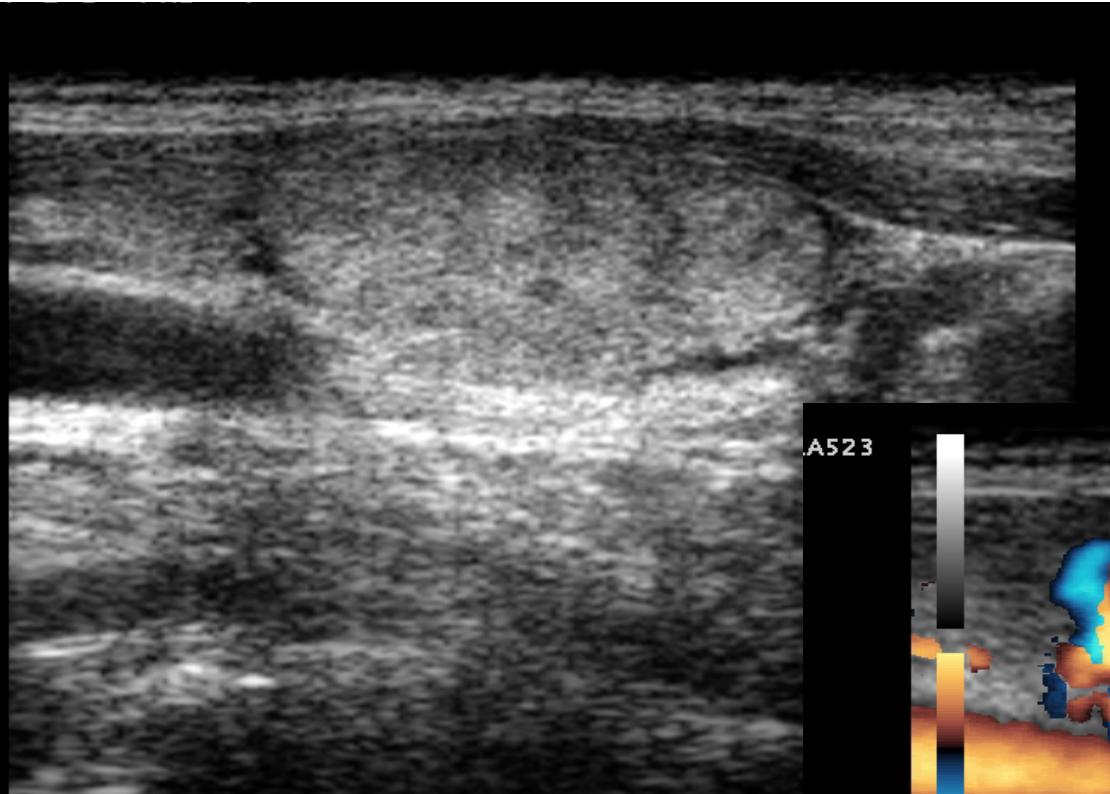


Paola: US Images



Paola: US Images

4



Paola: US Report

- Normal thyroid size
- Right thyroid lobe: solid nodule 21 mm Ø , isoechoic and homogeneous texture, well-defined and regular margins, peri- and intra-nodular vascularization. No calcifications.
- Left thyroid lobe: no nodules. Homogeneous texture.
- No suspicious cervical lymph nodes

The report is clear but ...
What is the risk of malignancy?





An Ultrasonogram Reporting System for Thyroid Nodules Stratifying Cancer Risk for Clinical Management

- TIRADS 1: normal thyroid gland.
- TIRADS 2: benign conditions (0% malignancy).
- TIRADS 3: probably benign nodules (5% malignancy).
- TIRADS 4: suspicious nodules (5–80% malignancy rate).
 - 4a (malignancy between 5 and 10%)
 - 4b (malignancy between 10 and 80%).
- TIRADS 5: probably malignant nodules (malignancy 80%).
- TIRADS 6: category included biopsy proven malignant nodules.



British Thyroid Association Guidelines for the Management of Thyroid Cancer

The practitioner should be competent in identifying the signs that allow a differentiation of thyroid nodules:

- **benign (U2)**
- **equivocal/indeterminate (U3)**
- **suspicious (U4)**
- **malignant (U5)**

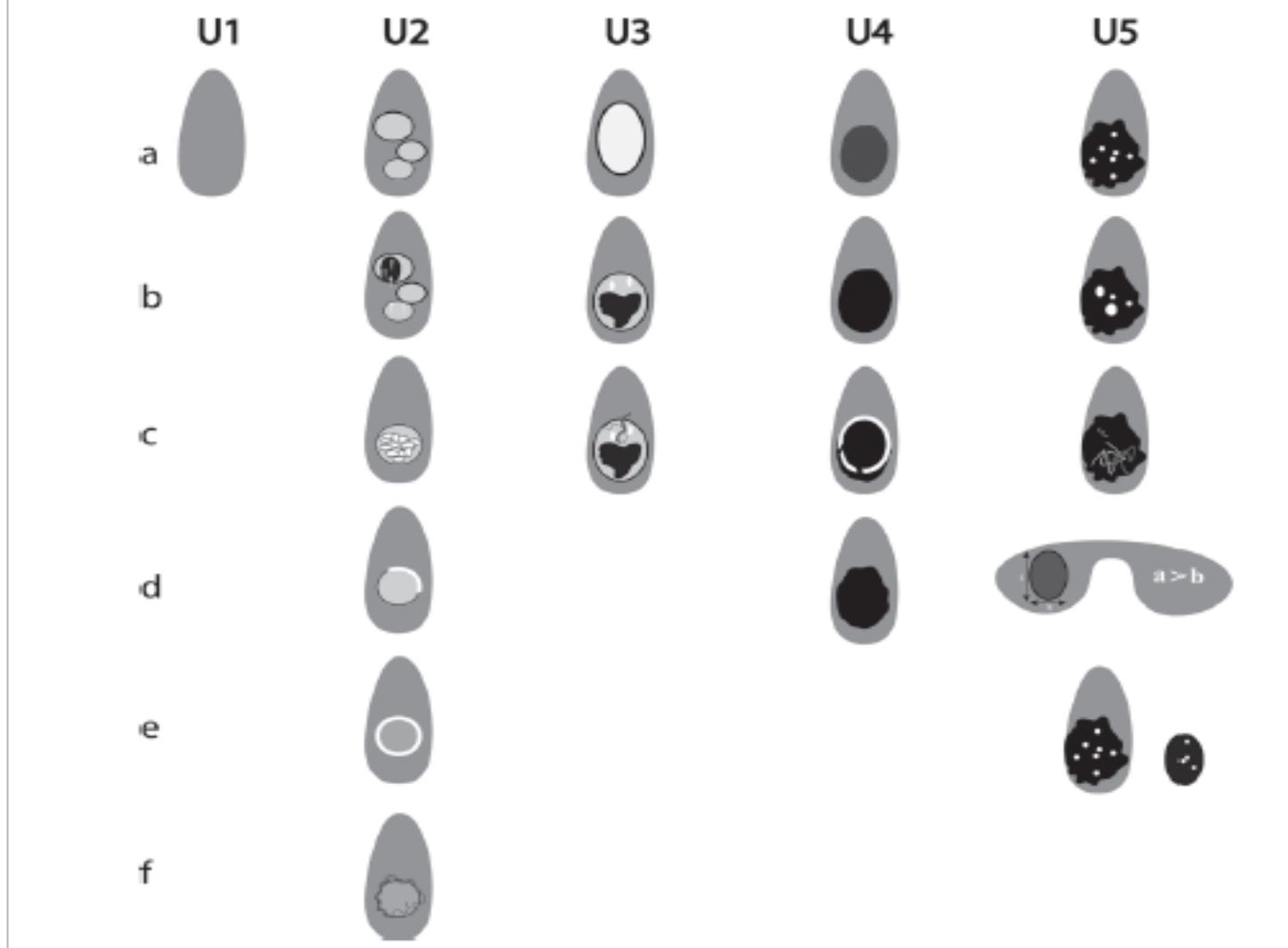
as outlined in the U classification.

In multinodular thyroids, the score for the most suspicious nodule should be recorded.



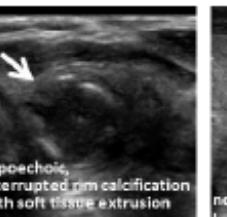
British Thyroid Association Guidelines for the Management of Thyroid Cancer

Ultrasound assessment of thyroid nodules

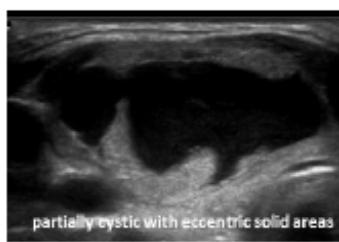
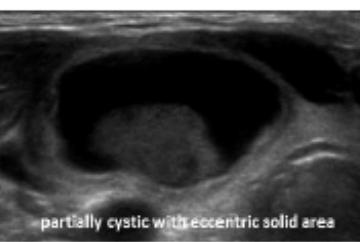




High
Suspicion
70-90%



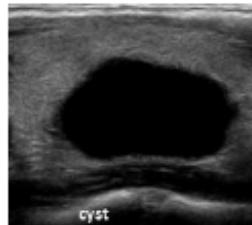
Intermediate
Suspicion
10-20%



Low
Suspicion
5-10%

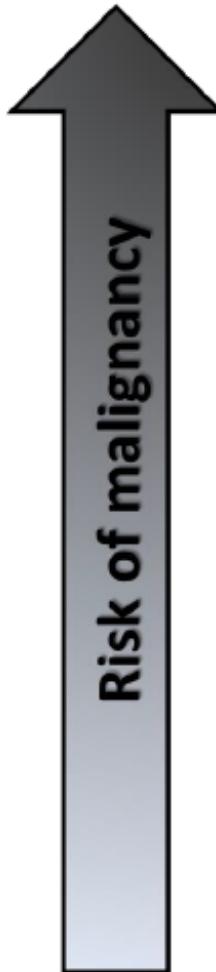


Very low
Suspicion
<3%



Benign
<1%

Risk of malignancy

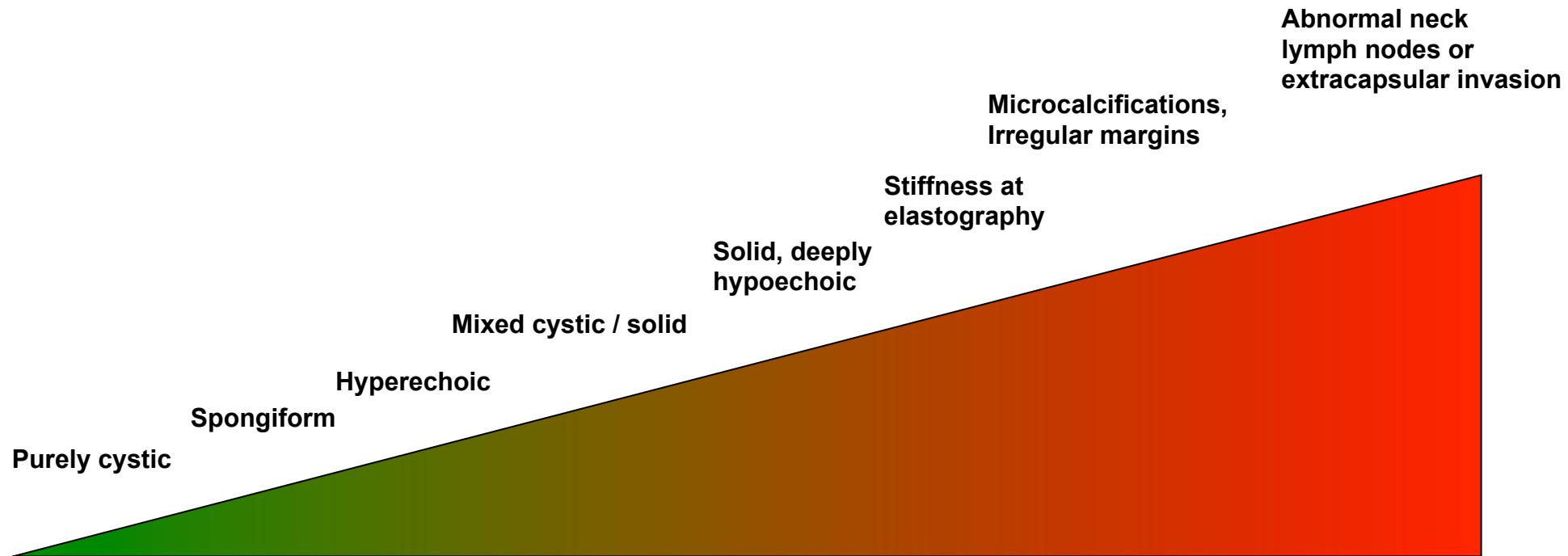




Sonographic Pattern	US features	Estimated risk of malignancy	Consider biopsy
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of extrathyroidal extension	>70-90%*	≥ 1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins without microcalcifications, extrathyroidal extension, or taller than wide shape	10-20%	≥ 1 cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without microcalcification, irregular margin or extrathyroidal extension, or taller than wide shape.	5-10%	≥ 1.5 cm
Very low suspicion	Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate or high suspicion patterns	< 3%	≥ 2 cm
Benign	Purely cystic nodules (no solid component)	< 1%	No biopsy**



2010 AACE/AME/ETA Guidelines US criteria for FNAB



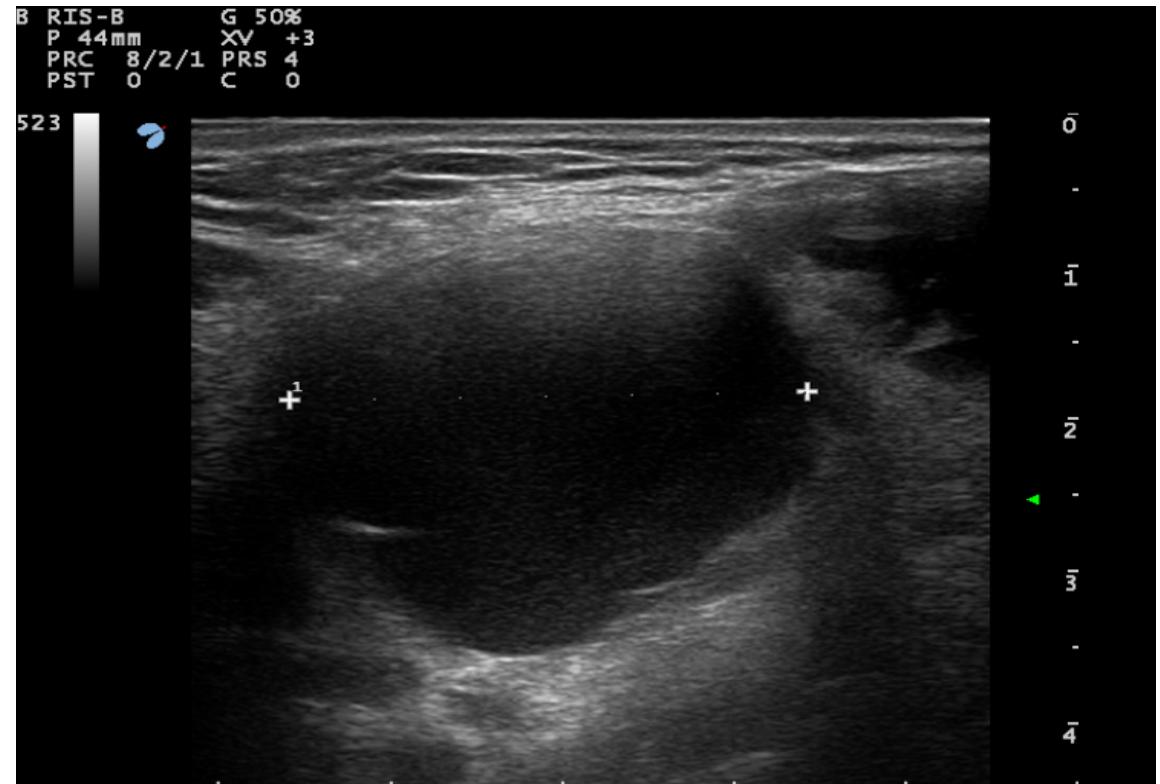
2016 AACE-AME US Classification

- Low-risk US Lesion
- Intermediate-risk US Lesion
- High-risk US Lesion

2016 AACE US Classification

Low risk lesion

- Cysts



2016 AACE US Classification

Low risk lesion

- Isoechoic spongiform nodules, confluent or with regular halo.



2016 AACE US Classification

Intermediate risk thyroid lesion

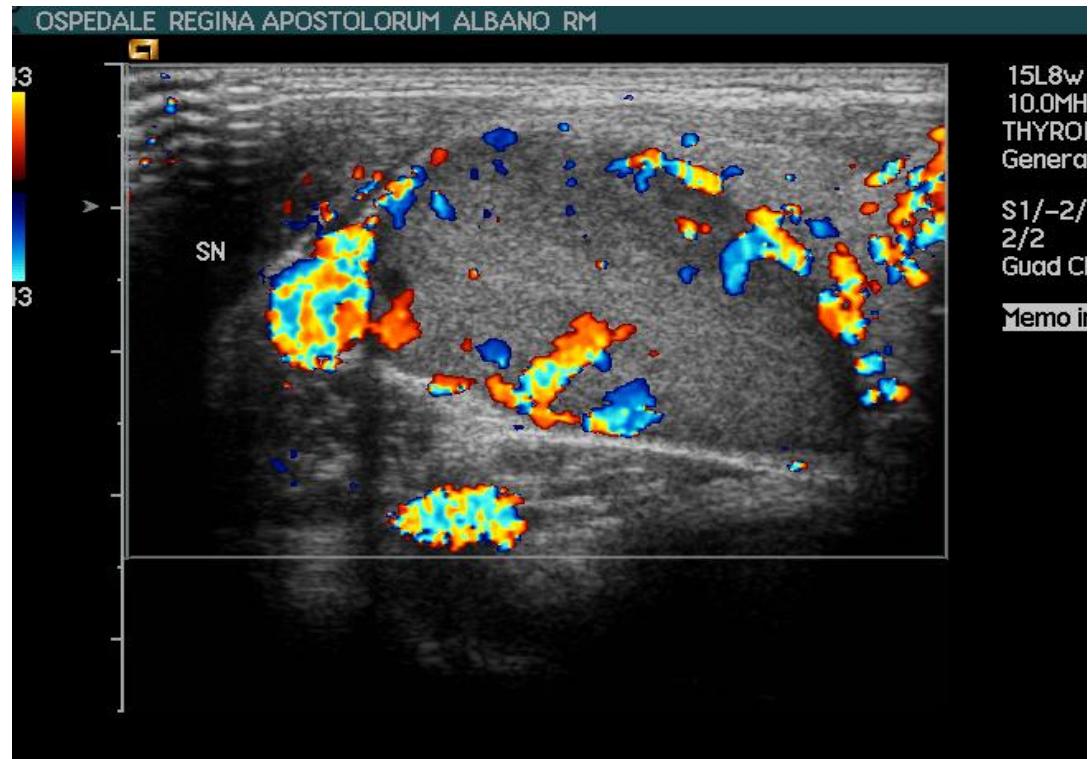
- Slightly hypoechoic nodules (vs surrounding thyroid tissue)



2016 AACE US Classification

Intermediate risk thyroid lesion

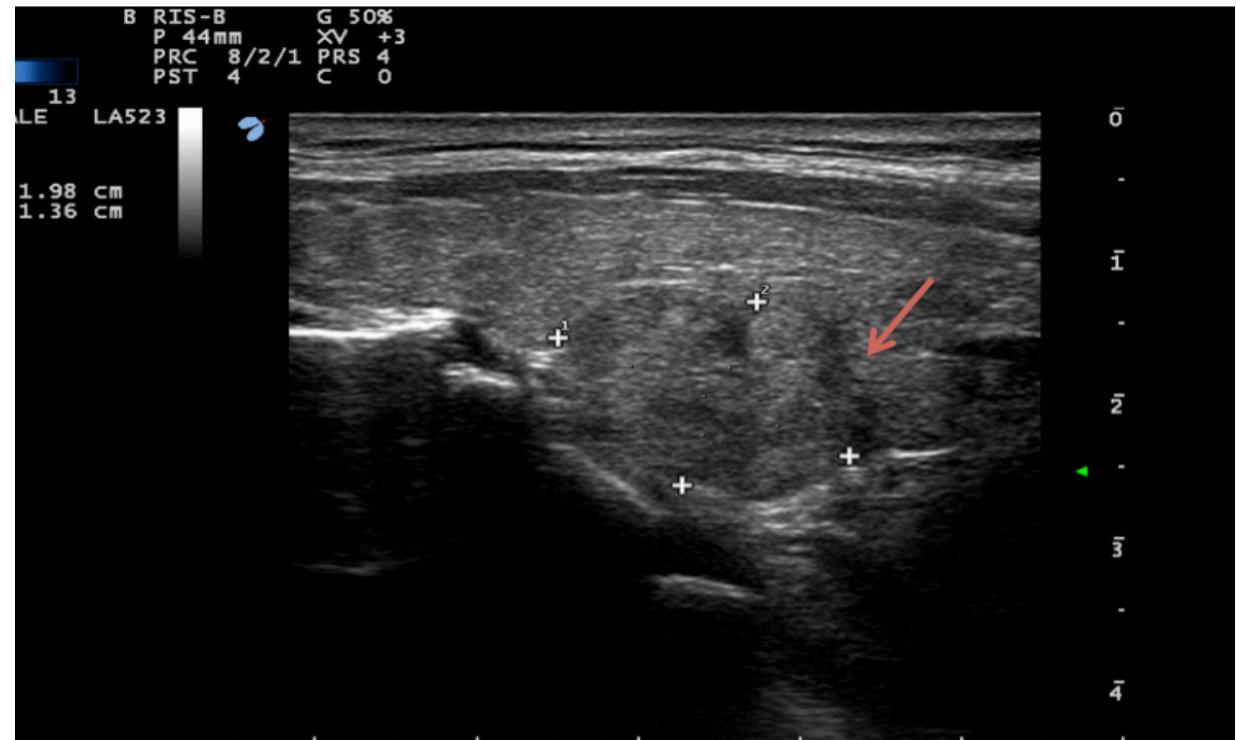
- May be present:
- ✓ Intranodular vascularization



2016 AACE US Classification

Intermediate risk thyroid lesion

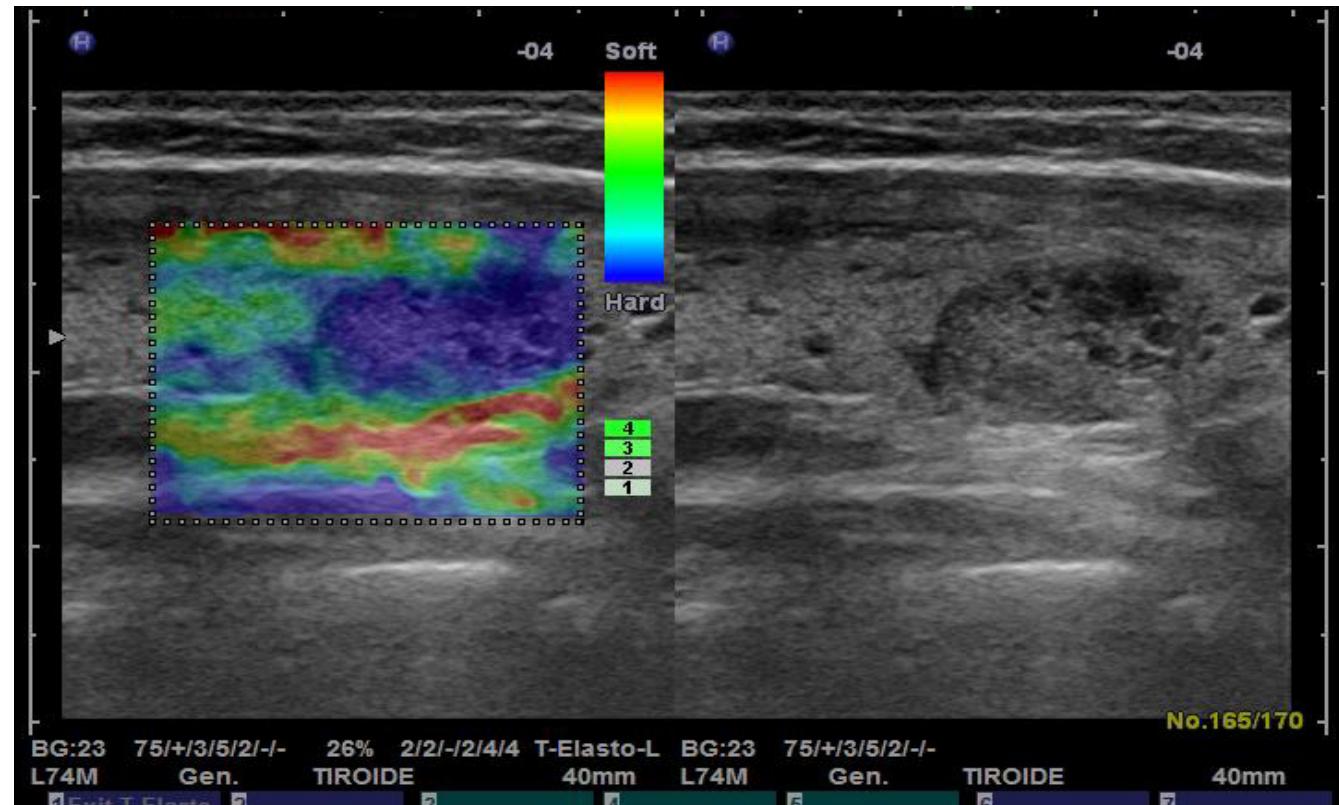
- Isoechoic nodules, with ovoid-to-round shape and smooth or ill-defined margins



2016 AACE US Classification

Intermediate risk thyroid lesion

- May be present:
- ✓ elevated stiffness at elastography

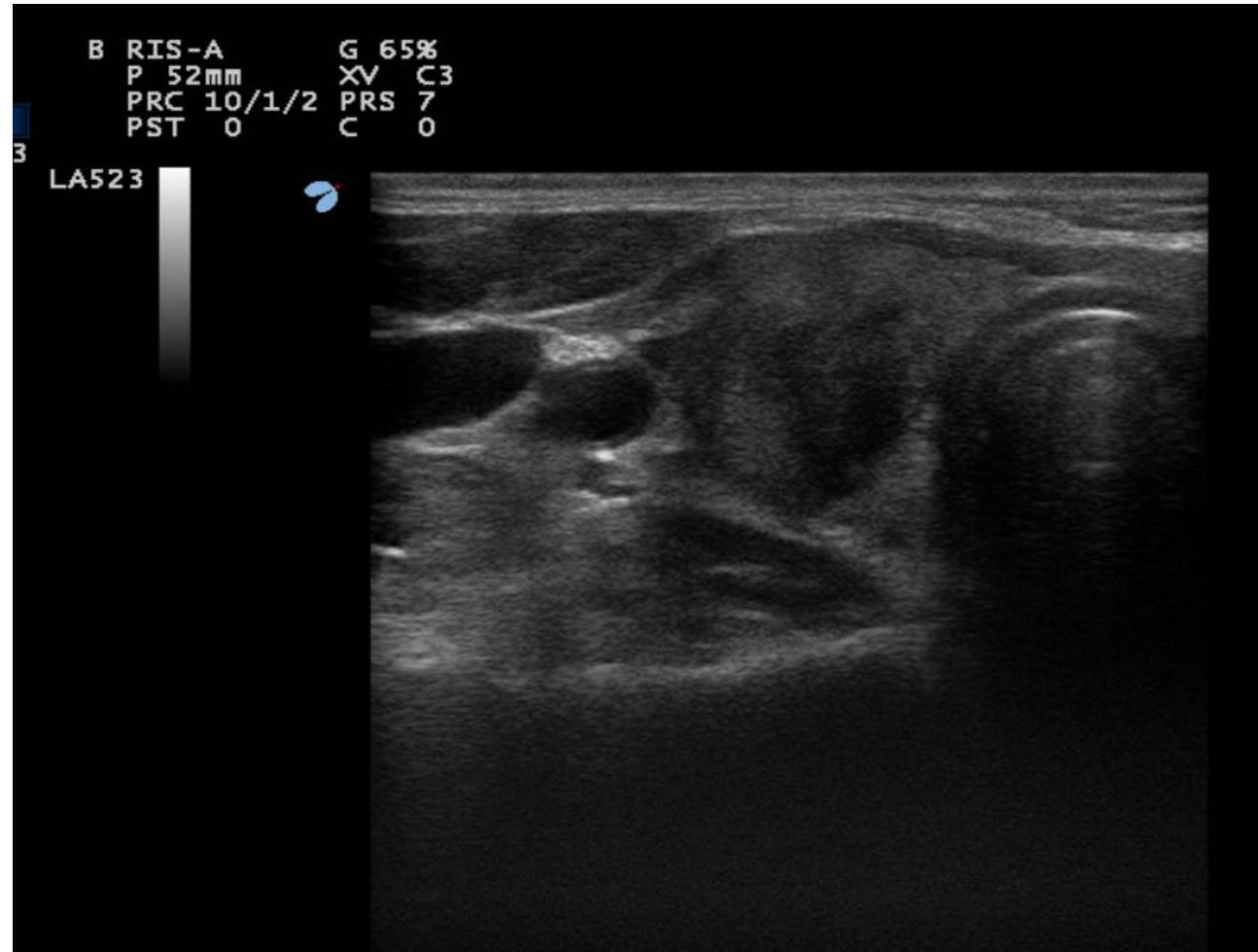


2016 AACE US Classification

High risk thyroid lesion

Nodules with at least one of the following features:

- ✓ Spiculated or lobulated margins (≥ 3)

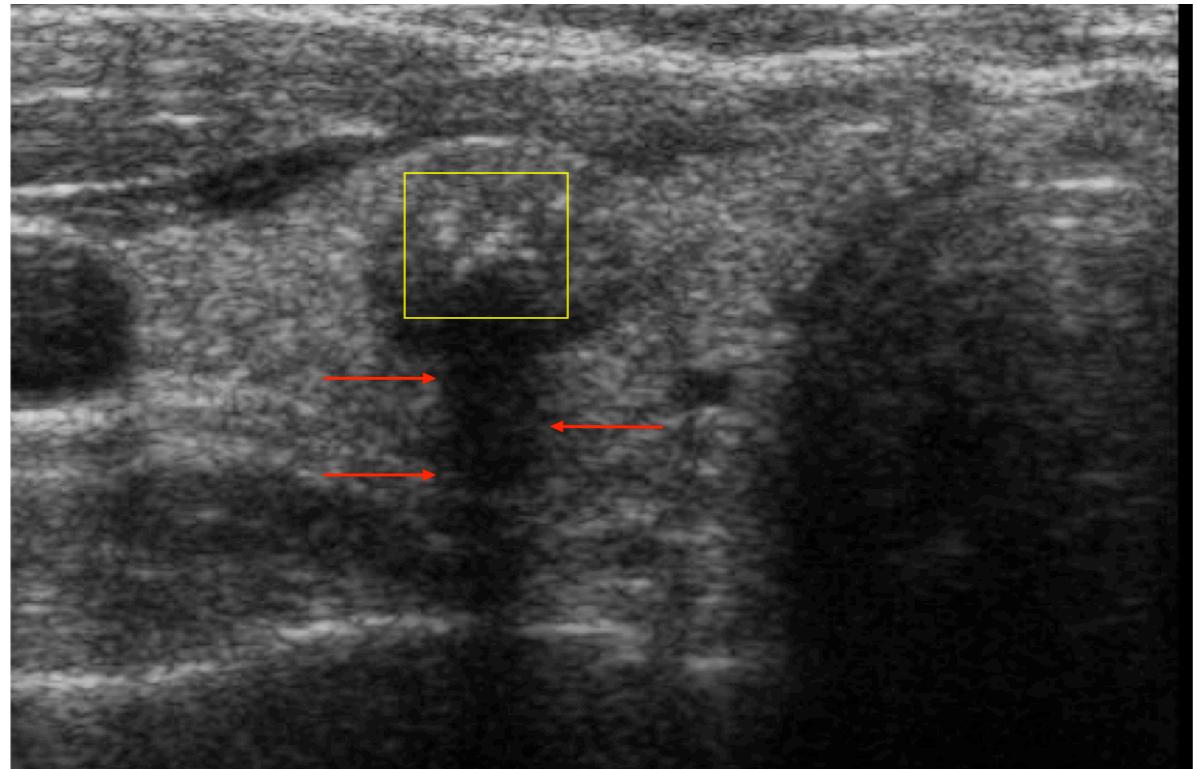


2016 AACE US Classification

High risk thyroid lesion

Nodules with at least one of the following features:

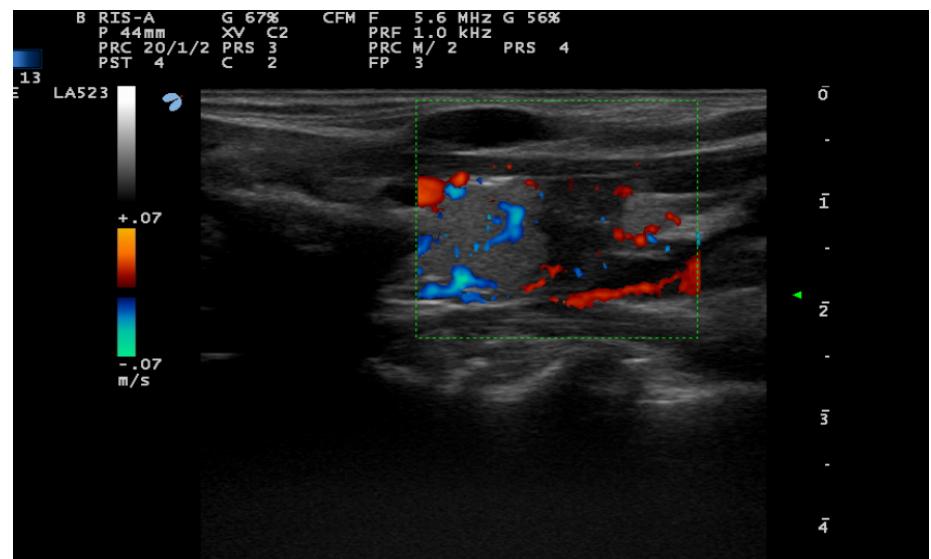
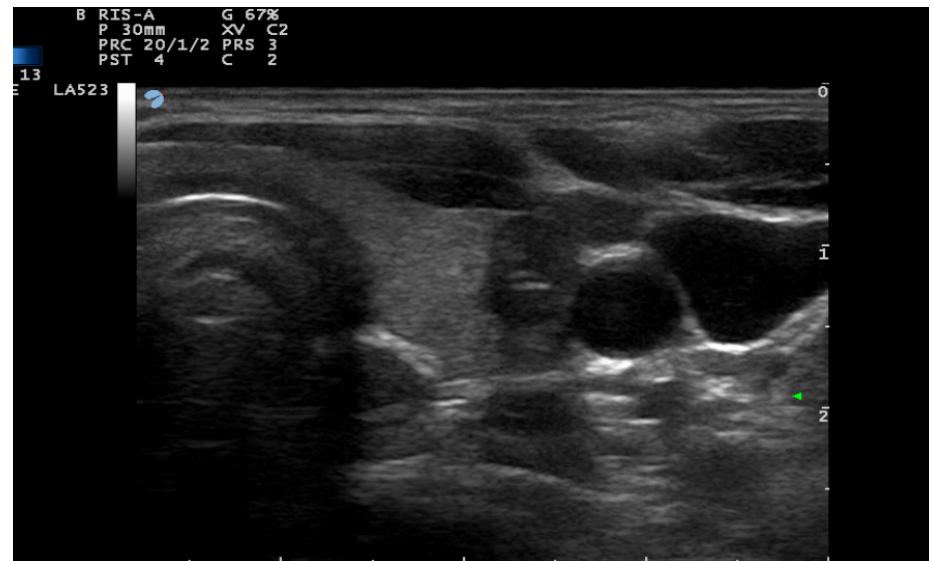
- ✓ **Microcalcifications**



2016 AACE US Classification

High risk thyroid lesion

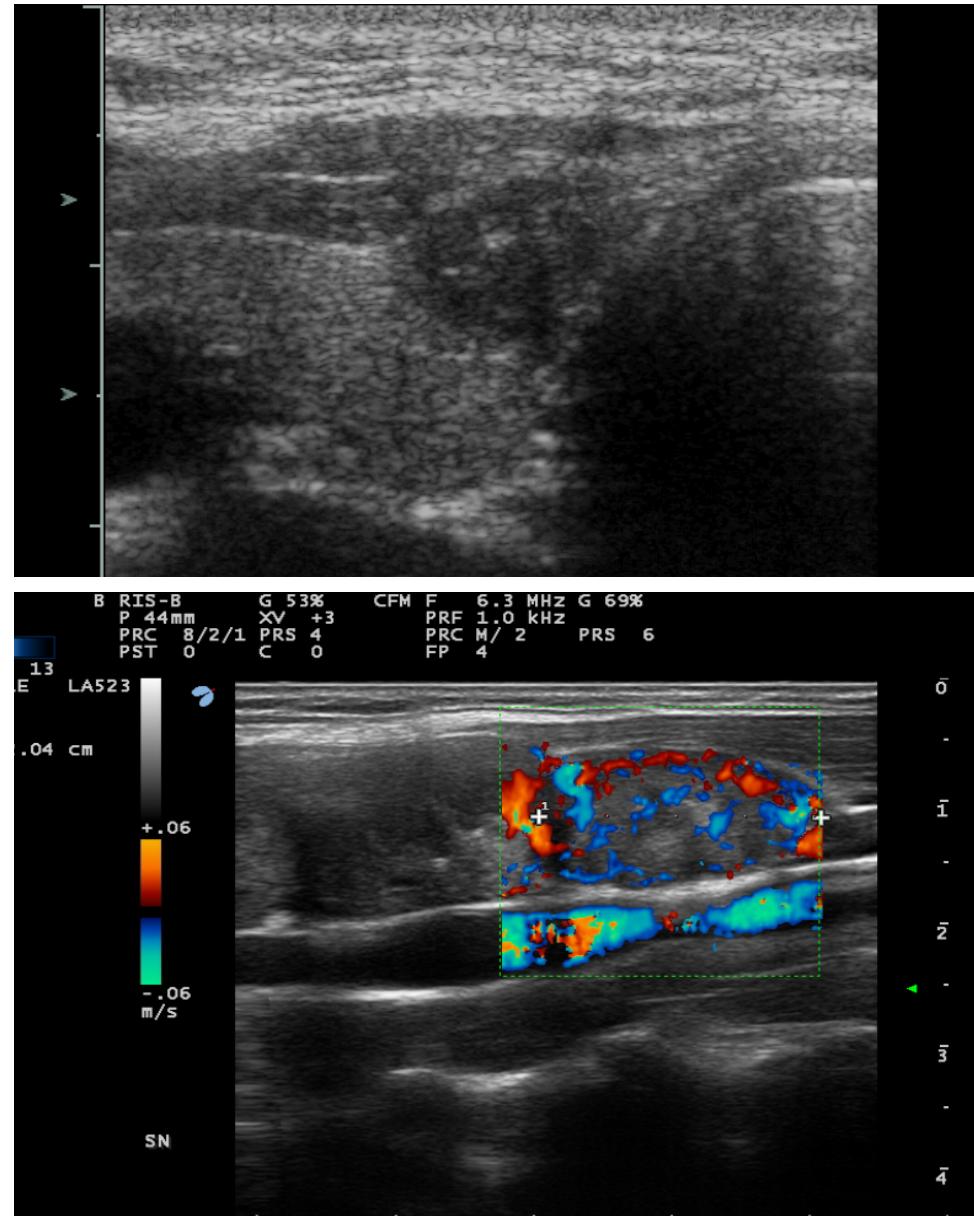
- **Nodules with at least one of the following features:**
- ✓ Taller-than-wide shape



2016 AACE US Classification

High risk thyroid lesion

- Nodules with at least one of the following features:
- ✓ Extrathyroidal growth or pathologic adenopathy



What is the Experts' Opinion?

Nothing more useful than
guidelines to help you fall
asleep...



Main Topics

- Ultrasound Report & Classification Systems
- Indications for US-guided FNA
- Management of Indeterminate Cytology

Back to Paola US Report

- Normal thyroid size
- Right thyroid lobe: solid nodule **21 mm Ø**, isoechoic and homogeneous texture, well-defined and regular margins, **peri- and intra-nodular vascularization**. No calcifications.
- Left thyroid lobe: no nodules. Homogeneous texture.
- No suspicious cervical lymph nodes.
- **Intermediate Risk Lesion (AACE/AME 2016)**

**So, we have a rating of the risk, but ...
Should we perform a FNA?**





British Thyroid Association Guidelines for the Management of Thyroid Cancer

- US appearances that are indicative of a benign nodule (U1–U2) should be regarded as reassuring not requiring FNAC, unless the patient has a statistically high risk of malignancy (2++, B)
- If the US appearances are equivocal, indeterminate or suspicious of malignancy (U3–U5), an US guided FNAC should follow (2++, B).

SONOGRAPHIC FEATURESThreshold for FNA**Solid nodule**

- With suspicious sonographic features^c ≥ 1.0 cm
- Without suspicious sonographic features^d ≥ 1.5 cm

Mixed cystic-solid nodule

- With suspicious sonographic features^c ≥ 1.5 – 2.0 cm
- Without suspicious sonographic features^d ≥ 2.0 cm

Spongiform nodule^e ≥ 2.0 cm**Simple cyst**Not indicated^g**Suspicious cervical lymph node^f**FNA node \pm FNA-associated thyroid nodule(s)

The above criteria serve as general guidelines. In patients with high-risk clinical features,^h evaluations of nodules smaller than listed may be appropriate depending on clinical concern. Allowance for informed patient desires would include excisional biopsy (lobectomy or thyroidectomy) for definitive histology, especially in larger nodules (>4 cm) or higher risk clinical situations.



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Thyroid nodule diagnostic FNA is recommended for :

- A) Nodules > 1cm with intermediate or high suspicion sonographic pattern (Strong recommendation)
- B) Nodules > 1.5 cm with low suspicion sonographic pattern (Weak recommendation)
- C) Nodules > 2.0 cm with very low suspicion sonographic pattern (i.e. - spongiform) (Weak recommendation)



Indications for US-Guided FNA

- In nodules >20 mm that are isoechoic, slightly hypoechoic, or hyperechoic with ovoid-to-round shape and smooth or ill-defined margins (intermediate-US-risk thyroid lesions), UGFNA is recommended

[GRADE B, BEL 3]



Indications for US-Guided FNA

- In nodules >10 mm that are associated with suspicious US signs (high-US-risk thyroid lesions), UGFNA is always recommended [GRADE A, BEL 2]



Indications for US-Guided FNA

- In light of the low clinical risk, nodules with a major diameter <5 mm should be monitored, rather than biopsied, with US, irrespective of their sonographic appearance



Indications for US-Guided FNA

- In nodules with a major diameter 5-10 mm that are associated with suspicious US signs, consider either UGFNA sampling or watchful waiting on the basis of the clinical setting and patient preference [GRADE B, BEL 3].



Indications for US-Guided FNA

Specifically, UGFNA is recommended for the following nodules ≤ 10 mm:

- Subcapsular or paratracheal lesions
- Suspicious lymph nodes or extrathyroid spread
- Positive personal or family history of thyroid cancer
- Coexistent suspicious clinical findings (eg, dysphonia)



Indications for US-Guided FNA

- UGFNA is recommended in spongiform or dominantly cystic nodules without suspicious US findings (low-US-risk thyroid lesions) **only** when >20 mm **and** increasing in size or associated with a high-risk history and before thyroid surgery or minimally invasive ablation therapy

[GRADE A, BEL 2]

What is the Experts' Opinion?

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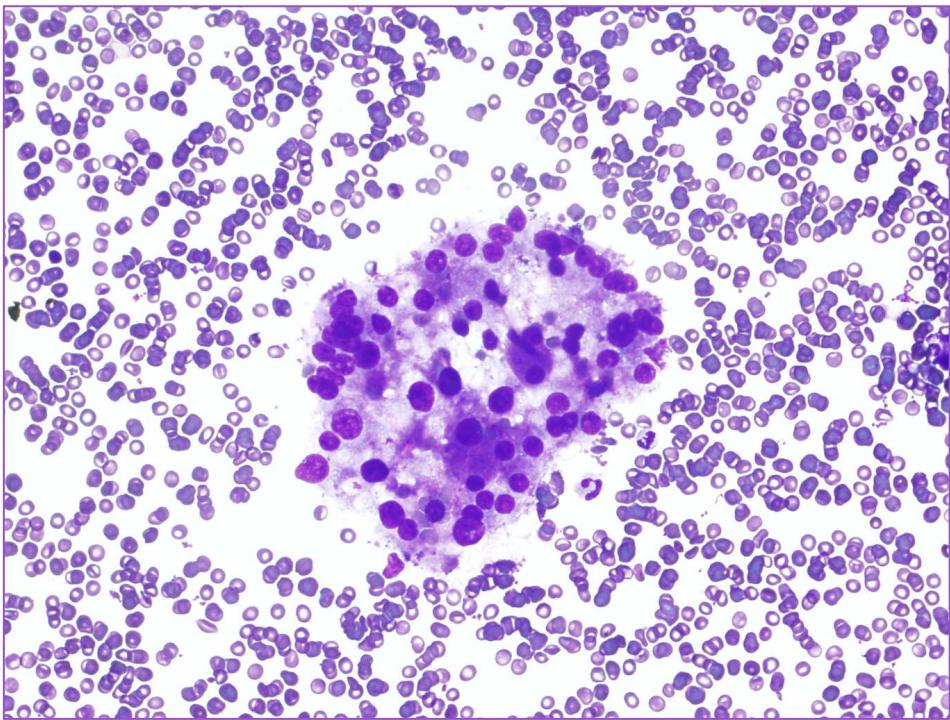
Main Topics

- Ultrasound Report & Classification Systems
- Indications to US-guided FNA
- Management of Indeterminate Cytology

Let's move back to Paola...



Paola FNA Report



“Sparse cellularity and dense colloid.

Architectural ‘atypia’ with microfollicles and focal nuclear changes”.

“Thy 3a” (BTA 2014)



Thy3a

- When there are atypical features present but not enough to place into any of the other categories.

Bethesda Classification Scheme

Diagnostic Category	Risk of Malignancy (%)	Usual Management
Non-diagnostic or Unsatisfactory		Repeat FNA with ultrasound guidance
Benign	0-3%	Clinical follow-up
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS)	~ 5-15%	Repeat FNA
Follicular Neoplasm or Suspicious for a Follicular Neoplasm (Specify if Hurthle type or Oncocytic)	15-30%	Surgical lobectomy
Suspicious for Malignancy	60-75%	Near-total thyroidectomy or surgical lobectomy
Malignant	97-99%	Near-total thyroidectomy

Comparison of the Italian Classification System for Thyroid Cytology with TBSRTC and the Royal college of Pathology Guidance for Reporting Thyroid Cytology

Italian Consensus 2014	USA BETHESDA	UK RCPATH
TIR 1 Non diagnostic TIR 1c Non diagnostic cystic	I. Non-diagnostic Cystic fluid only	Thy1 / Non-diagnostic Thy1c. Unsatisfactory, consistent with cyst
TIR 2 Non malignant	II. Benign	Thy2/Thy2c Non-neoplastic
TIR 3A Low-risk indeterminate lesion	III. AUS/FLUS Atypia or follicular lesion of undetermined significance	Thy 3a Neoplasm possible: atypia/non-diagnostic
TIR 3B High-risk indeterminate lesion	IV. Follicular neoplasm or suspicious for a follicular neoplasm	Thy 3f Neoplasm possible: suggesting follicular neoplasm
TIR 4. Suspicious of malignancy	V. Suspicious of malignancy	Thy 4 Suspicious of malignancy
TIR 5. Malignant	VI. Malignant	Thy 5 Malignant

CONSERVATIVE

SURGERY



RISK

VERY LOW

LOW

INTERMEDIATE

HIGH

VERY HIGH

CLASS

TIR 2
Thy2
Benign

TIR 3a
Thy3a
AUS FLUS

TIR 3b
Thy3f
FN

TIR 4
Thy4
Suspicious

TIR 5
Thy5
Malignant

ACTION

Follow up/
MIT

Repeat
FNA/
Mutational
testing

Surgery/
Close US
follow up

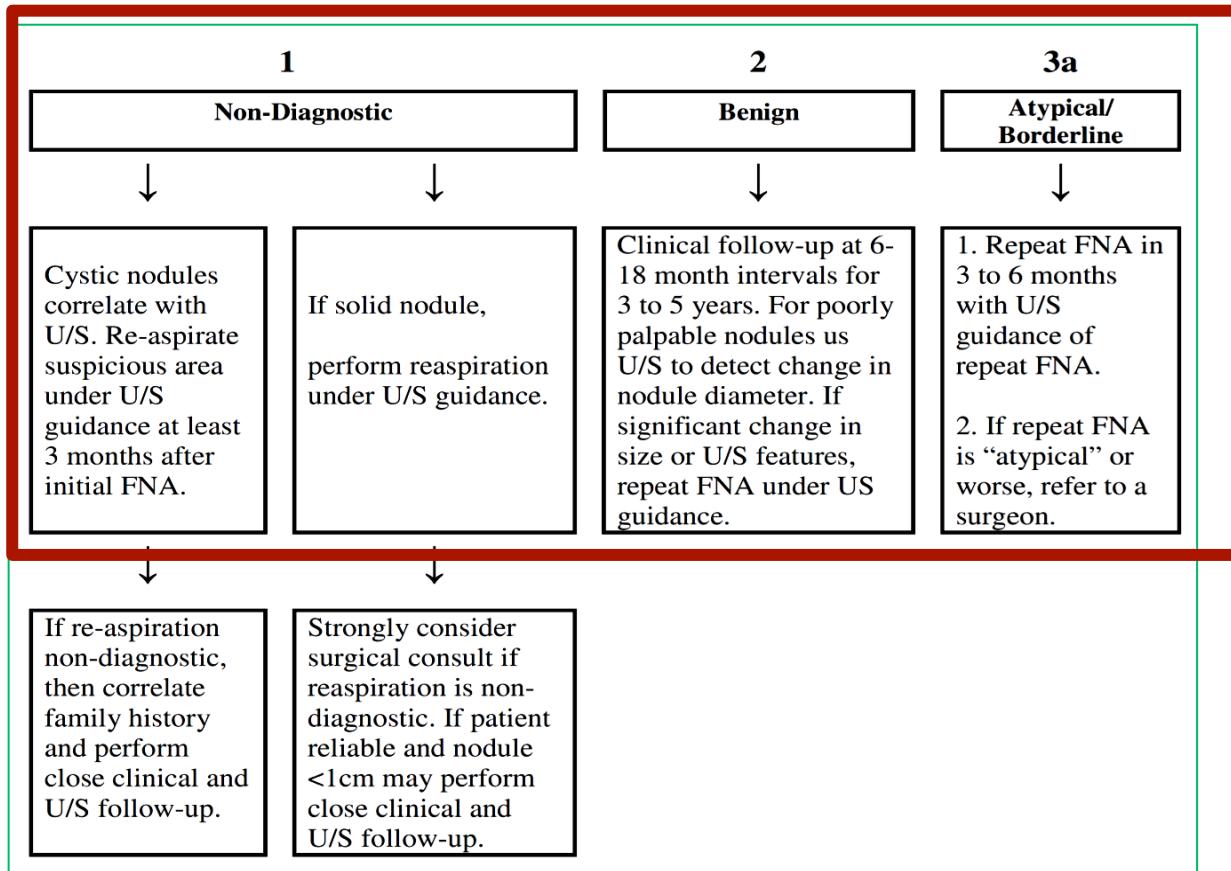
Surgery with
intraoperative
biopsy

Surgery,
total resection

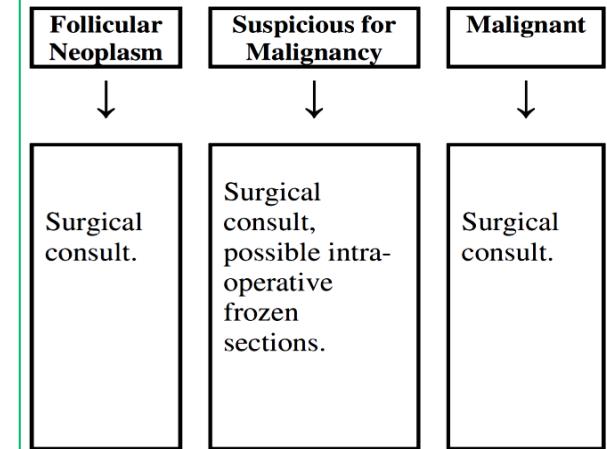


Post FNA Management for Different Reporting Categories

Conservative management



Surgical management





British Thyroid Association Guidelines for the Management of Thyroid Cancer

- Thy3a – further investigation, usually US assessment and repeat FNAC
- Thy3a FNAC on repeat sample requires MDT (multidisciplinary panel) discussion.



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AUS/FLUS cytology

- after consideration of worrisome clinical and US 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).

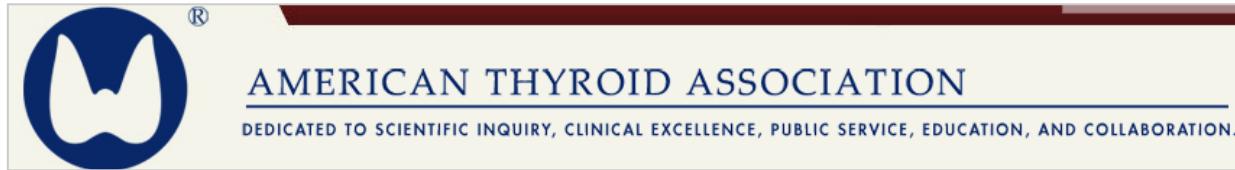


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AUS/FLUS cytology

- If repeat FNA cytology and/or molecular testing are not performed or inconclusive, either surveillance or diagnostic surgical excision may be performed depending on clinical risk factors, sonographic pattern, and patient preference (Strong Recommendation).

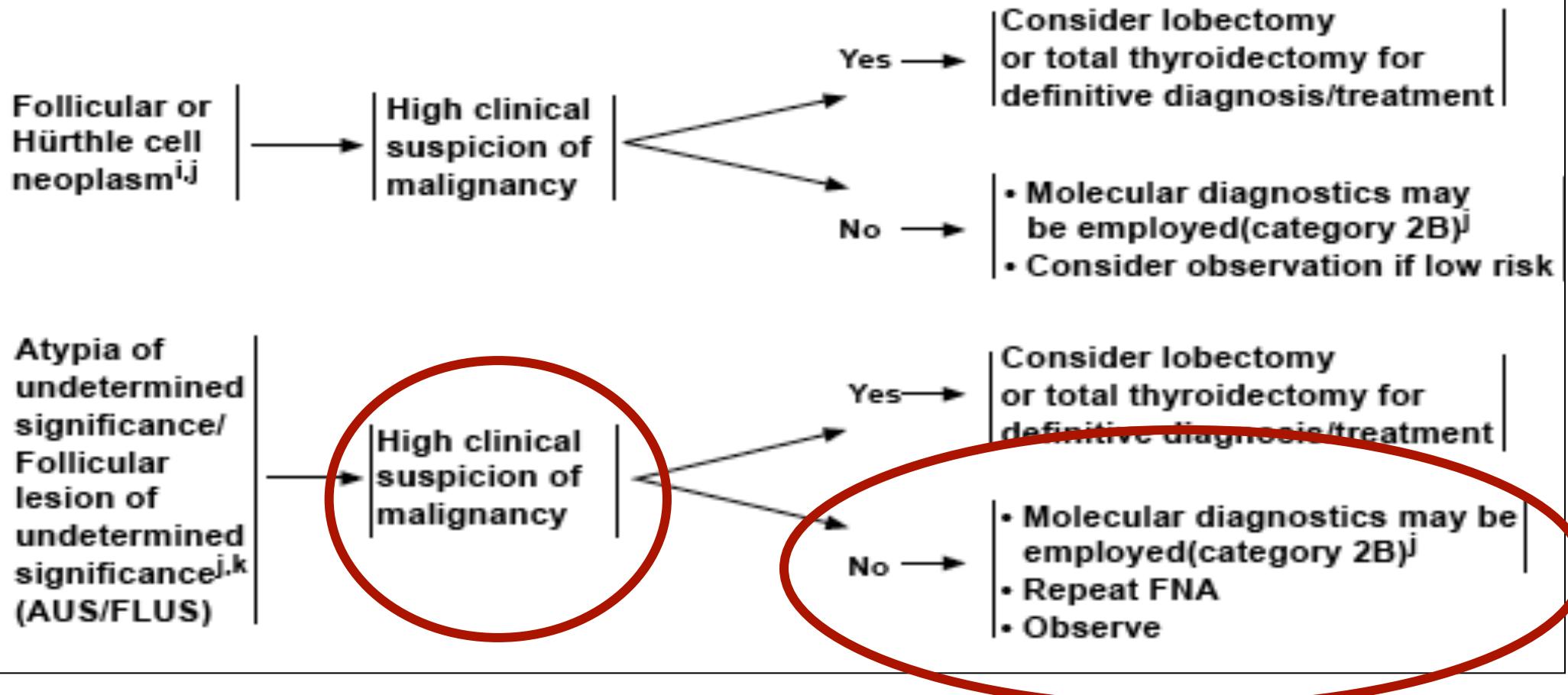


AUS/FLUS cytology

- 18FDG-PET imaging is not routinely recommended for the evaluation of thyroid nodules with indeterminate cytology (Weak recommendation).

NCCN Guidelines Version 2.2014 Table of Contents

Thyroid Carcinoma





When molecular testing should be considered

- To complement, not to replace, cytologic evaluation [GRADE A, BEL 2]
- The results are expected to influence clinical management [GRADE A, BEL 2]
- As a general rule, not recommended in nodules with established benign or malignant cytologic characteristics [GRADE A, BEL 2]



Molecular testing for cytologically indeterminate nodules

- Consider the detection of *BRAF* and *RET/PTC* and, possibly, *PAX8/PPARG* and *RAS* mutations if such detection is available [GRADE B, BEL 2]



How should patients with nodules that are negative at mutation testing be monitored?

- Since the false-negative rate for indeterminate nodules is 5% to 6% and the experience and follow-up for mutation-negative nodules or nodules classified as *benign* by a GEC are still insufficient, close follow-up is recommended [GRADE C, BEL 4]



Molecular testing for cytologically indeterminate nodules

- Because of the insufficient evidence and the limited follow-up, we do not recommend either in favor of or against the use of gene expression classifiers (GECs) for cytologically indeterminate nodules [GRADE B, BEL 2]



Management of low-risk indeterminate lesions

- Consider conservative management in the case of favorable clinical criteria, such as personal or family history and size of the lesion, and low-risk US and elastography features [GRADE C, BEL 3]
- Repeat UGFNA for further cytologic assessment, and review samples with an experienced cytopathologist [GRADE B, BEL 3]



Management of low-risk indeterminate lesions

- CNB may be considered to provide microhistologic information, but routine use is currently not recommended because its role in indeterminate lesions is still unsettled [GRADE D, BEL 4]
- We do not recommend either in favor or against the determination of molecular markers for routine use in this category [GRADE D, BEL 3].

3. What is the Experts' Opinion?

Nothing more useful than
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asleep...

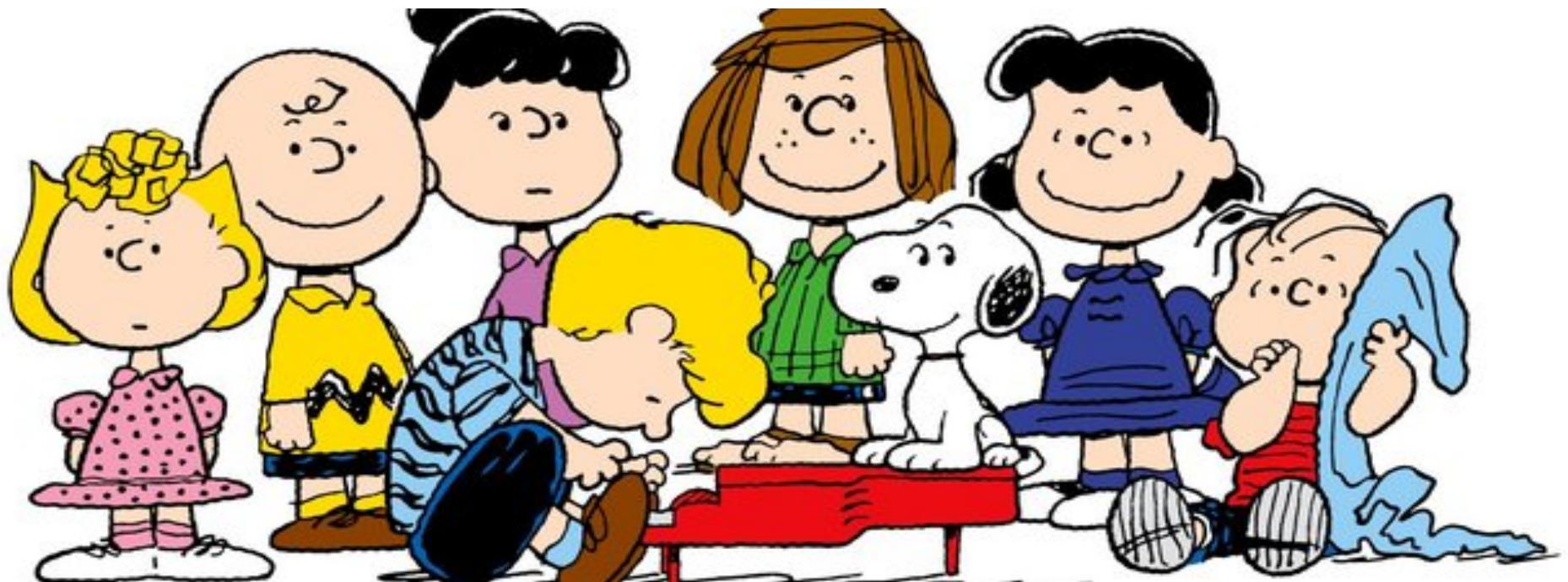


And ... what is the opinion of the participants?

**Molecular Tests for Indeterminate Cytology:
Yes or No in everyday practice?**



**So, we have just to think, discuss and
make the best choice all together!**



Comparison between Rating Systems: Benign

AACE-AME 2016	ATA 2015	British Thyroid Association 2014
<p>Low risk lesion</p> <ul style="list-style-type: none"> • Cysts • Mostly cystic nodules with reverberating artifacts that are not associated with intermediate or high risk US signs • Isoechoic spongiform nodules confluent or with regular halo 	<p>Benign Purely cystic nodules (no solid component)</p> <p>Very low suspicion Spongiform or partially cystic nodules without any of the US features described in low, intermediate or high suspicion patterns</p> <p>Low suspicion Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid area <u>without</u>:</p> <ul style="list-style-type: none"> ✓ Microcalcifications ✓ Irregular margin ✓ Extrathyroidal extension ✓ Taller than wide shape 	<p>U2 Benign</p> <ul style="list-style-type: none"> A. Halo, iso-echoic, mildly hyperechoic B. Cystic change (possible ring-down sign) C. Micro-cystic (spongiform) D.E. Macro and Peripheral egg-shell calcification F. Peripheral vascularity

Comparison between Rating Systems: Intermediate

AACE-AME	ATA	British Thyroid Association
<p>Intermediate risk thyroid lesion</p> <p>Slightly hypoechoic nodules (cf thyroid tissue) or isoechoic nodules, with ovoid-to-round shape and smooth or ill-defined margins</p> <p>May be present:</p> <ul style="list-style-type: none"> ✓ Intranodular vascularization ✓ elevated stiffness at elastography ✓ macro or continuos rim calcifications 	<p>Intermediate suspicion</p> <p>Hypoechoic solid nodule with smooth margins <u>without</u>:</p> <ul style="list-style-type: none"> ✓ microcalcifications ✓ extrathyroidal extension ✓ or taller than wide shape 	<p>U3 Indeterminate</p> <ul style="list-style-type: none"> A. Homogeneous, hyperechoic, solid, halo B. Hypoechoic, equivocal echogenic foci, cystic change (irregular) C. Mixed/central vascularity
		<p>U4 suspicious</p> <ul style="list-style-type: none"> A. Solid, hypoechoic (cf thyroid) B. Solid, very hypoechoic (cf strap muscle) C. Disrupted peripheral calcification with hypoechoic bulge D. Lobulated outline

Comparison between Rating Systems: Malignant

AACE-AME	ATA	British Thyroid Association
<p>High risk thyroid lesion</p> <p>Nodules <u>with</u> at least one of the following features:</p> <ul style="list-style-type: none"> ✓ Marked hypoechoicity (cf prethyroid muscles) ✓ Spiculated or lobulated margins (≥ 3) ✓ Microcalcifications ✓ Taller-than-wide shape ✓ Extrathyroidal growth or pathologic adenopathy 	<p>High suspicion</p> <p>Solid hypoechoic nodule or solid hypoechoic component of partially cystic nodule <u>with one or more</u> of the following :</p> <ul style="list-style-type: none"> ✓ Irregular margins (infiltrative, microlobulated) ✓ Microcalcifications ✓ Taller than wide shape ✓ Rim calcifications with small extrusive soft tissue component ✓ Evidence of extrathyroidal extention 	<p>U5 Malignant</p> <ol style="list-style-type: none"> A. Solid, hypoechoic, lobulated/irregular outline, B. microcalcification (papillary?) C. Solid, hypoechoic, lobulated/irregular outline, globular calcification (medullary?) D. Intranodular vascularity E. Taller (AP) > wide (TR) shape F. Characteristic associated lymphadenopathy



TIRADS classification algorithm

HIGH SUSPICIOUS ASPECTS

- Taller-than-wide shape
- Irregular or microlobulated margins
- Microcalcifications
- Marked hypoechoogenicity

≥ 3 signs and/or
adenopathy
TIRADS 5

1 or 2 signs and
no adenopathy
TIRADS 4B

LOW SUSPICIOUS ASPECT

- None of the high suspicious aspect
- Moderately hypoechoogenic

TIRADS 4A

PROBABLY BENIGN ASPECTS

- None of the high suspicious aspect
- Isoechoic
- Hyperechoic

TIRADS 3

BENIGN ASPECTS

- Simple cyst
- Spongiform nodule
- 'White knight' aspect
- Isolated macrocalcification
- Typical subacute thyroiditis

TIRADS 2

Normal thyroid US

TIRADS 1

And ... what is the opinion of the participants?

FNA: Yes or No?

