Ultrasound Systems:

the available evidence and the clinical role

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Diagnostica per Immagini e Radiologia Interventistica

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Conflitti di interesse

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

Background

- Ultrasound is the diagnostic modality of choice in the study of diffuse and focal thyroid disease

- The sensitivity of US produced unexpected dilemmas in the management of thyroid nodules

Background

- Thyroid nodule can be detected by US in >68% of population
- Most of this nodule are benign and do not require surgery
- Small PTC can be indolent and may be not “clinical significant”
- Overtreatment of thyroid cancer is a main issue
- This problem is expected to boost up in the future as the incidence of thyroid neoplasm (PTC) has a positive trend.

FNA

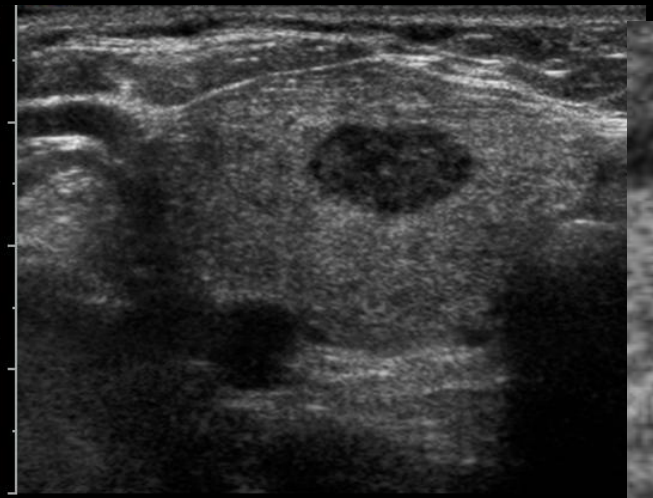
- FNA is the best triage system for malignancy but we cannot perform FNA on all detected nodules
- Also after FNA uncertainty on the nature of nodule can remain
- Surgery can be required to reach a definitive diagnosis

US: The Revolution

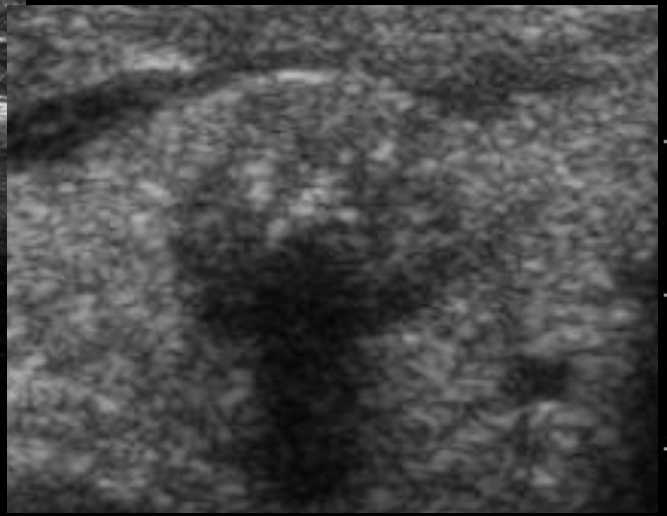
- It was soon evident that in some cases we were able to predict the nature of thyroid nodules

- Some nodule features or single US finding were obviously predictive of malignant or benign lesions

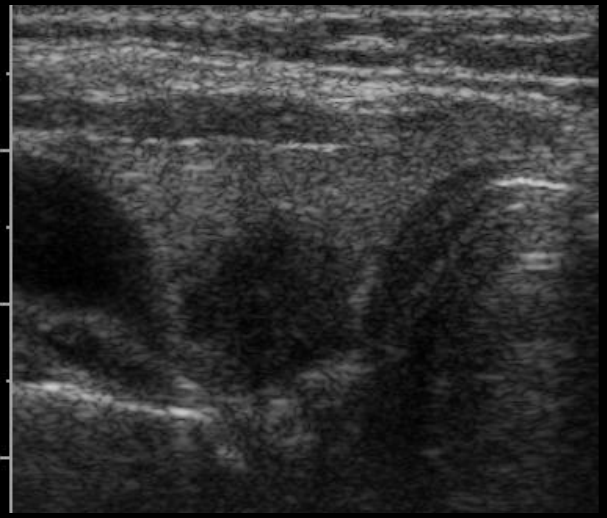
US: The Revolution



Marked Hypoechoic Appearance



Microcalcifications



Irregular Margins

Papini E et al. JCE&M 2002
Kim et al. Radiology 2002

US: The First Step

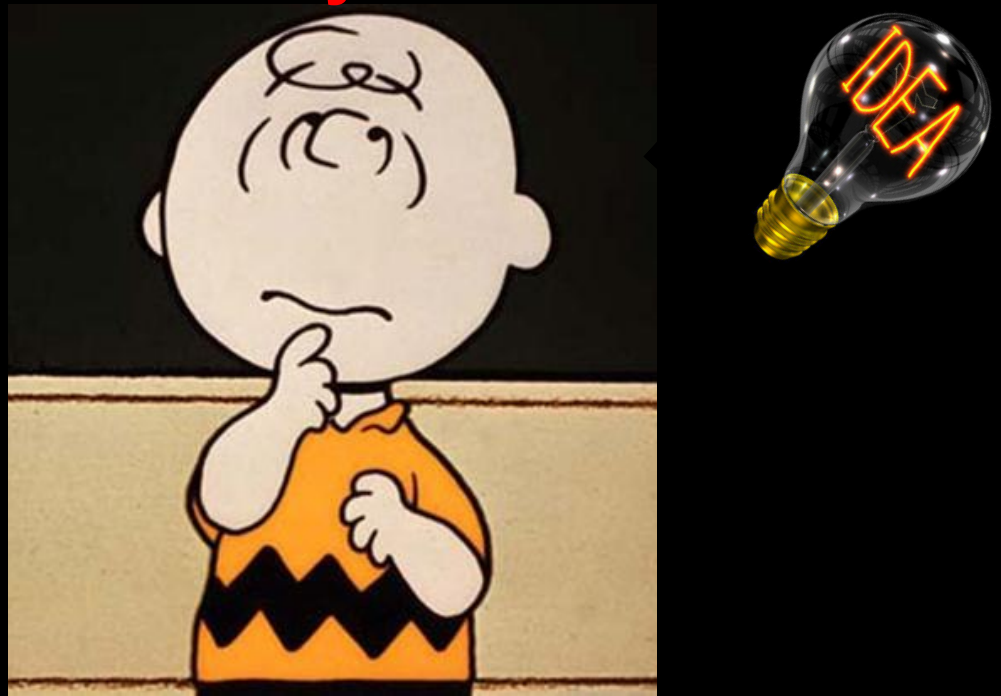
In 2002 Kim firstly reported a combination of four sonographic risk features and an attempt to standardize lexicon

TABLE 1 Sonographic Findings in 155 Malignant or Benign Thyroid Nodules

Sonographic Characteristics	Malignant Nodules (%) (n = 49)	Benign Nodules (%) (n = 106)
Microcalcification	29 (59.1)	15 (14.2)
Irregular or microlobulated margin	27 (55.1)	28 (26.4)
Marked hypoechogenicity	13 (26.5)	6 (5.6)
More tall than wide	16 (32.7)	8 (7.5)

Kim EK, Park CS, Chung WY, Oh KK, Kim DI, Lee JT, et al. New sonographic criteria for recommending fine-needle aspiration biopsy of nonpalpable solid nodules of the thyroid. AJR Am J Roentgenol. 2002;178:687–691.

US classifications of thyroid nodules? Why not?



US: The Inflation

- Many criteria for US classification of thyroid nodules were proposed
- Looking back, many of them had a pattern-oriented qualitative (analogical) approach while few were based on discrete sonographic finding (digital)

US: The Evolution

- Standardize terminology/improve communication
- Force the sonographers to think about risk categories
- Give a concise information on the risk of malignancy
- Help the care team in managing thyroid nodules
- Limit unnecessary FNAB and surgery
- Support cancer research statistics and “RADIOMICS”

US: The Drawback

- Difficult to be implemented
- Time consuming (complex systems and multiple nodules)
- Generate patient concern
- Difficult to understand for patients or for the referring physician

US: The Inflation

AMERICAN THYROID ASSOCIATION

DEDICATED TO SCIENTIFIC INQUIRY, CLINICAL EXCELLENCE, PUBLIC SERVICE, EDUCATION, AND COLLABORATION.

- ATA guidelines were published in 2006 and revised in 2009
- The last revision of ATA guidelines was published in 2015 with substantial changes especially regarding the indication for FNA

Haugen B et al. Thyroid , January 2016; 26: 1 - 133

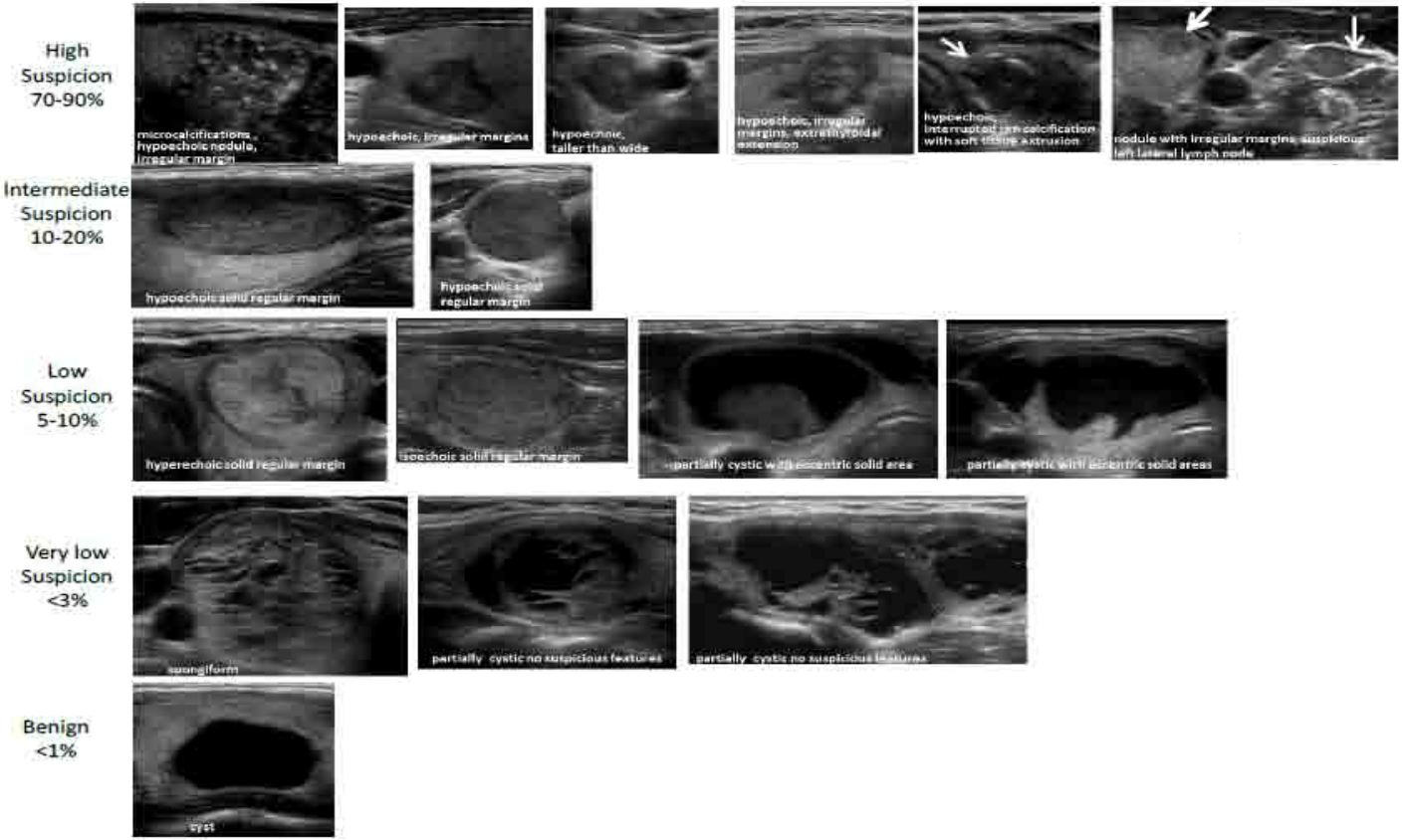
V

IV

III

II

I



Indication to FNA

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**

Dimension threshold

US: The Inflation

Ultrasound was no more a simple detection tool for thyroid nodule but now could influence

- Indication to FNA
- follow-up strategy
- surgical approach

US: The Sequel

Thyroid Imaging Reporting and Data System (TIRADS)

The first TIRADS was proposed in 2009 with a scheme similar to BIRADS (Breast-Imaging Reporting and Data System) proposed by the ACR in late 1980

Horvath et s. J Clin Endocrinol Metab, May 2009, 90(5):1748–1751

US: The Sequel

Thyroid Imaging Reporting and Data System (TIRADS)

- Shortly after, Park proposed an equation for predicting the probability of malignancy in thyroid nodules based on 12 US features
- It appeared difficult to be implemented in clinical practice

JY Park **Thyroid**. **2009** Nov;19(11):1257-64

US: The Sequel

Thyroid Imaging Reporting and Data System (TIRADS)

- In 2011 Kwak proposed a new simplified version of TIRADS.
- Complex US patterns of thyroid nodules were abandoned and risk stratification was mainly based on the number of simple suspicious US features

Kwak JY, Han KH, Yoon JH, et al. Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk. Radiology 2011;260(3):892–899.

US: The Sequel

Thyroid Imaging Reporting and Data System (TIRADS)

1. solid component
2. hypoechogenicity or marked hypoechogenicity
3. microlobulated or irregular margins
4. microcalcifications
5. taller-than-wide shape

Kwak JY, Han KH, Yoon JH, et al. Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk. Radiology 2011;260(3):892–899.

US: The Stoke of Genius

Thyroid Imaging Reporting and Data System (TIRADS)

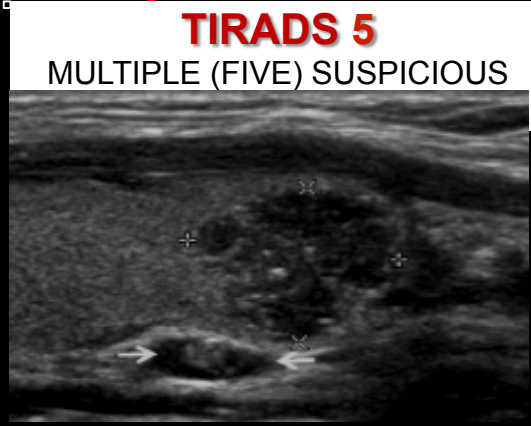
"As the number of suspicious US features increased, the fitted probability and risk of malignancy also increased"

Kwak JY, Han KH, Yoon JH, et al. Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk. Radiology 2011;260(3):892–899.

US: The Sequel

Thyroid Imaging Reporting and Data System (TIRADS)

- 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: biopsy proven malignancy



US: Consideration

- The limit of nodule pattern oriented classifications is the complexity necessary to include all different possibilities and avoid some unclassified nodules

- What is the role TIRADS class 1?

BTA Guidelines for the Management of Thyroid Cancer

In 2014 the British Thyroid Association proposed a risk stratification with 5 classes on the base of complex US patterns of thyroid nodules

CLINICAL ENDOCRINOLOGY

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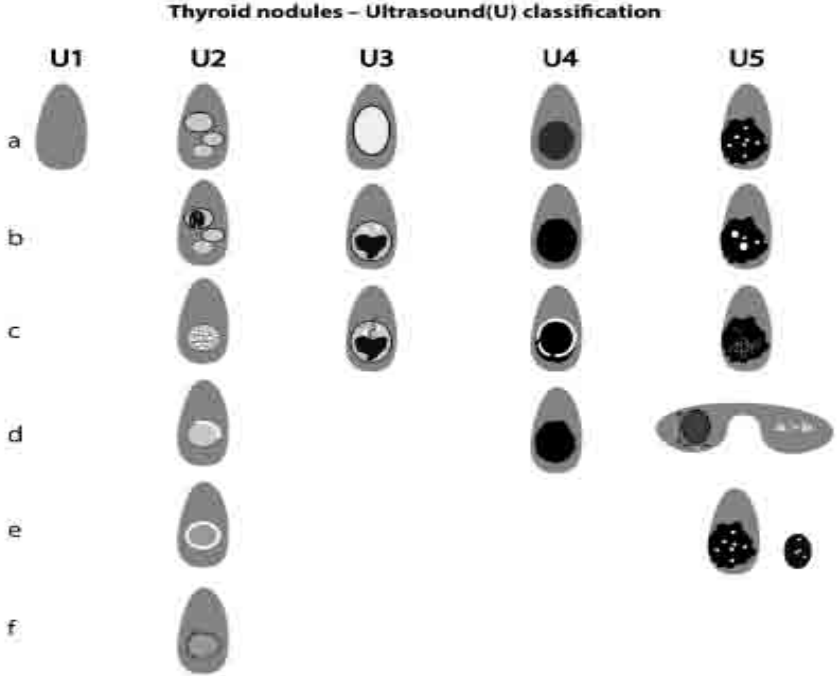
THE CLINICAL JOURNAL OF THE SOCIETY FOR ENDOCRINOLOGY AND THE ENDOCRINE SOCIETY OF AUSTRALIA

Graphic Compilation of BTA Thyroid Nodules Classification



U1. Normal

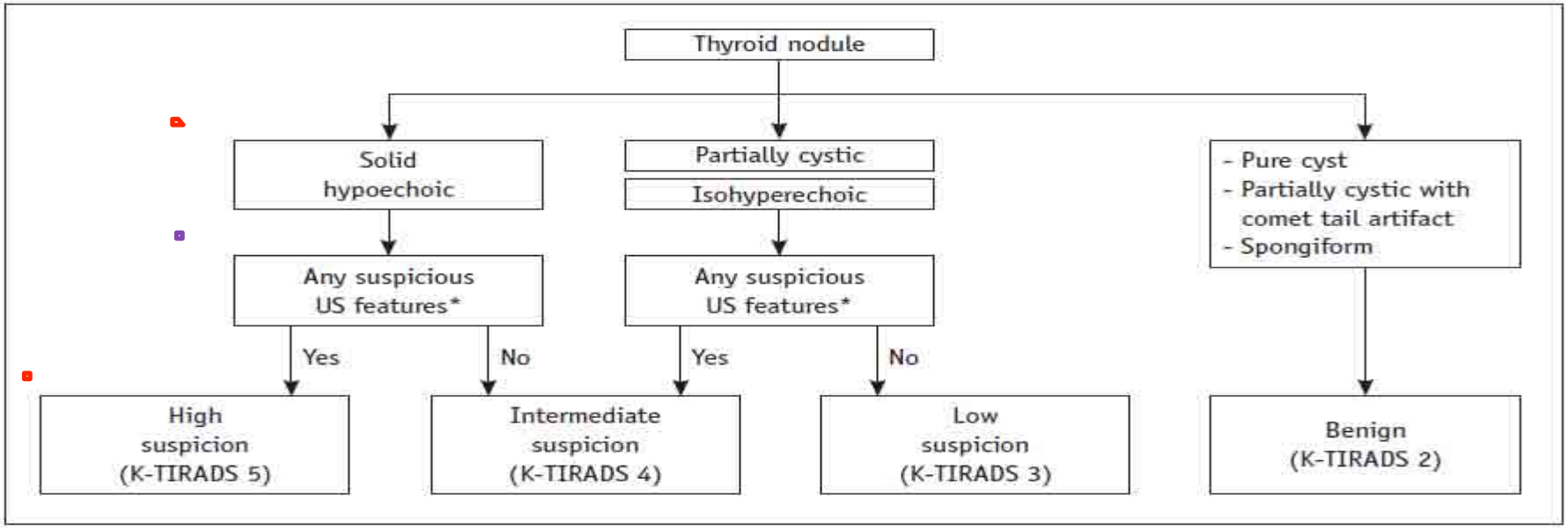
U2. Benign:
(a) halo, hyper- / iso-echoic
(b) cystic change +/- ring down sign (colloid)
(c) micro- cystic / spongiform
(d & e) peripheral egg shell calcification
(f) peripheral vascularity.

U3. Indeterminate/Equivocal:
(a) homogenous, hyper - echoic (markedly), solid, halo (follicular lesion).
(b) ? hypo-echoic, equivocal echogenic foci, cystic change
(c) mixed/central vascularity.

U4. Suspicious:
(a) solid, hypo-echoic (cf thyroid)
(b) solid, very hypo-echoic (cf strap muscle)
(c) disrupted peripheral calcification, hypo-echoic
(d) lobulated outline

U5. Malignant
(a) solid, hypo-echoic, lobulated / irregular outline, micro-calcification. (? Papillary carcinoma)
(b) solid, hypo-echoic, lobulated/irregular outline, globular calcification (? Medullary carcinoma)
(c) intra-nodular vascularity
(d) shape (taller >wide)
(e) characteristic associated lymphadenopathy

2016 South Korean K-TIRADS



Algorithm of K-TIRADS for malignancy risk stratification based on solidity and echogenicity of thyroid nodules.

Ultrasonography Diagnosis and Imaging-Based Management of Thyroid Nodules: Revised Korean Society of Thyroid Radiology Consensus Statement and Recommendations Jung Hee Shin et al. Korean J Radiol 2016;17(3):370-395

2016 South Korean K-TIRADS

Suspicious US features for K-TIRADS

a) microcalcification
b) non-parallel orientation
c) spiculated/microlobulated margins

Ultrasonography Diagnosis and Imaging-Based Management of Thyroid Nodules: Revised Korean Society of Thyroid Radiology Consensus Statement and Recommendations Jung Hee Shin et al. Korean J Radiol 2016;17(3):370-395

US: Consideration

Thyroid nodules risk stratification based mainly on the number of simple suspicious US features increase the PPV only for classic variant of papillary cancer but reduce overall sensitivity

2016 AACE-AME Thyroid US Classification

In 2016 AACE-AME issued a thyroid nodules classification based on

a) Simplification

b) US nodule pattern

c) Benign and suspicious US features

d) Precise indication for FNA

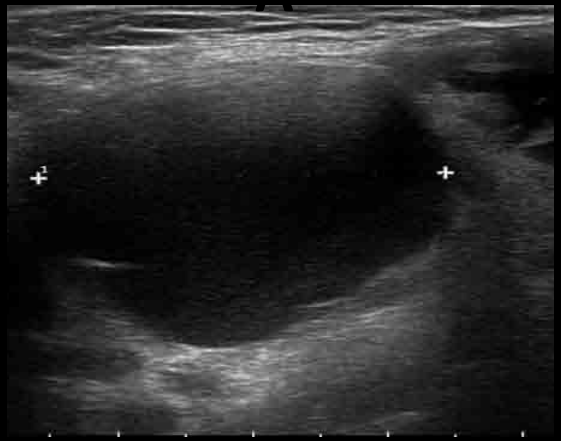
Endocrine Practice 2016

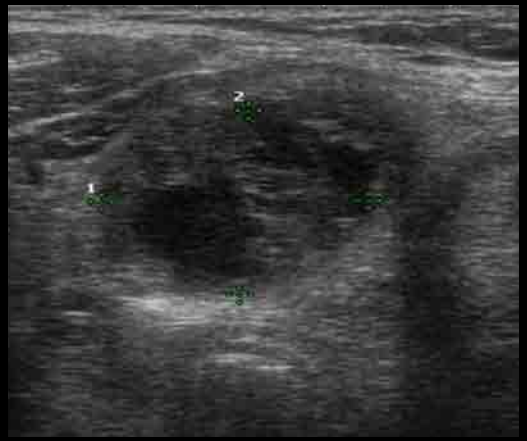
2016 AACE-AME Thyroid US Classification

- US class 1. Low-risk thyroid lesion
- US class 2. Intermediate-risk thyroid lesion
- US class 3. High-risk thyroid lesion

Endocrine Practice 2016

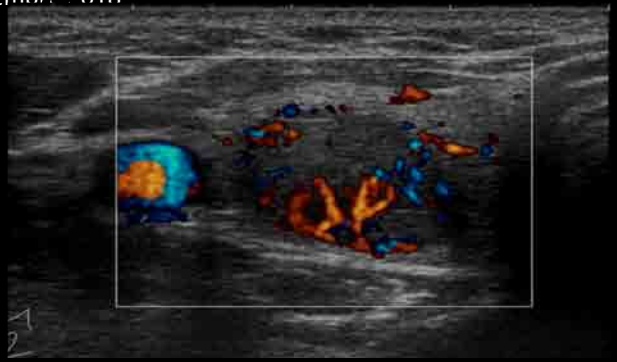
US class 1. Low-Risk nodules

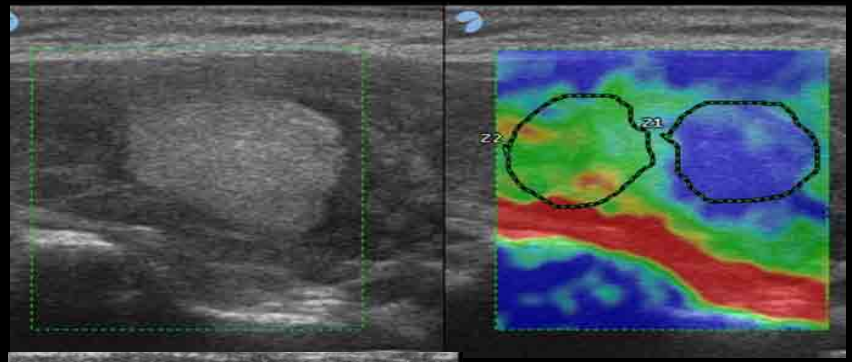


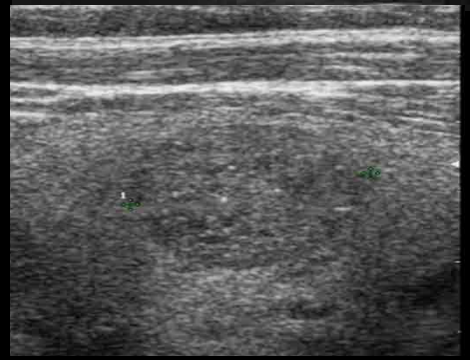


A. Thyroid cyst (fluid component >80% , regular margins)
B. Mostly cystic nodule with reverberating artifacts, no suspicious signs
C: Iso-echoic spongiform nodule , regular margins.

US class 2. Intermediate-risk nodules

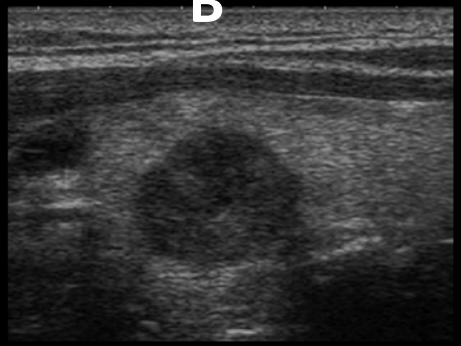


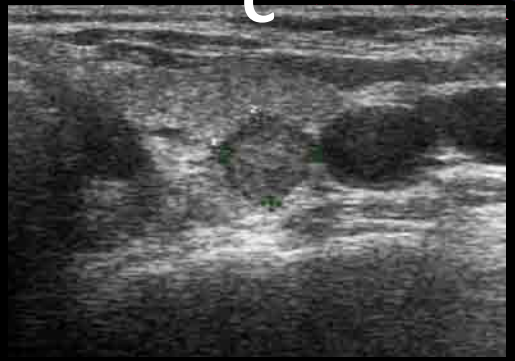


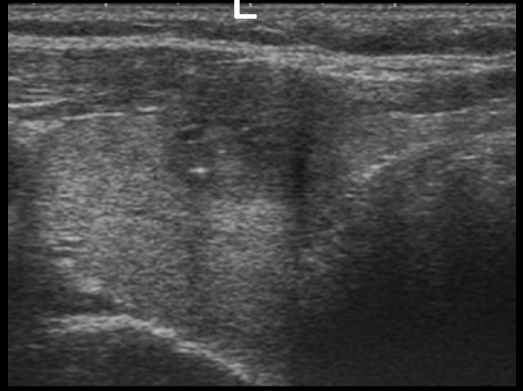


Slightly hypo- or iso-echoic nodules with smooth margins or halo. May be present:
A. intranodular vascularization: B. elevated stiffness at elastography; C. coarse or rim calcifications;
D. indeterminate hyperechoic spots.

US Class 3. High-Risk Nodules







A. Marked hypoechogenicity; B. Spiculated or lobulated margins; C. More tall than wide shape; D. Microcalcifications; E. Extracapsular growth; F. Pathologic adenopathy.

Indications for FNA

In high-risk nodules with 5-10 mm diameter consider FNA or surveillance on the basis of:

- ✓ US pattern (size and location)
- ✓ clinical setting
- ✓ patient preference.

Last but not least

Journal of the American College of Radiology 2017

ACR TI-RADS

COMPOSITION (Choose 1)		ECHOGENICITY (Choose 1)		SHAPE (Choose 1)		MARGIN (Choose 1)		ECHOGENIC FOCI (Choose All That Apply)	
Cystic or almost completely cystic	0 points	Anechoic	0 points	Wider-than-tall	0 points	Smooth	0 points	None or large comet-tail artifacts	0 points
Spongiform	0 points	Hyperechoic or isoechoic	1 point	Taller-than-wide	3 points	Ill-defined	0 points	Macrocalcifications	1 point
Mixed cystic and solid	1 point	Hypoechoic	2 points			Lobulated or irregular	2 points	Peripheral (rim) calcifications	2 points
Solid or almost completely solid	2 points	Very hypoechoic	3 points			Extra-thyroidal extension	3 points	Punctate echogenic foci	3 points

Add Points From All Categories to Determine TI-RADS Level

0 Points	2 Points	3 Points	4 to 6 Points	7 Points or More
TR1 Benign No FNA	**TR2** Not Suspicious No FNA	**TR3** Mildly Suspicious FNA if ≥ 2.5 cm Follow if ≥ 1.5 cm	**TR4** Moderately Suspicious FNA if ≥ 1.5 cm Follow if ≥ 1 cm	**TR5** Highly Suspicious FNA if ≥ 1 cm Follow if ≥ 0.5 cm*

COMPOSITION	ECHOGENICITY	SHAPE	MARGIN	ECHOGENIC FOCI
Spongiform: Composed predominantly (>50%) of small cystic spaces. Do not add further points for other categories. *Mixed cystic and solid:* Assign points for predominant solid component. Assign 2 points if composition cannot be determined because of calcification.	*Anechoic:* Applies to cystic or almost completely cystic nodules. *Hyperechoic/isoechoic/hypoechoic:* Compared to adjacent parenchyma. *Very hypoechoic:* More hypoechoic than strap muscles. Assign 1 point if echogenicity cannot be determined.	*Taller-than-wide:* Should be assessed on a transverse image with measurements parallel to sound beam for height and perpendicular to sound beam for width. This can usually be assessed by visual inspection.	*Lobulated:* Protrusions into adjacent tissue. *Irregular:* Jagged, spiculated, or sharp angles. *Extrathyroidal extension:* Obvious invasion = malignancy. Assign 0 points if margin cannot be determined.	*Large comet-tail artifacts:* V-shaped, >1 mm, in cystic components. *Macrocalcifications:* Cause acoustic shadowing. *Peripheral:* Complete or incomplete along margin. *Punctate echogenic foci:* May have small comet-tail artifacts.

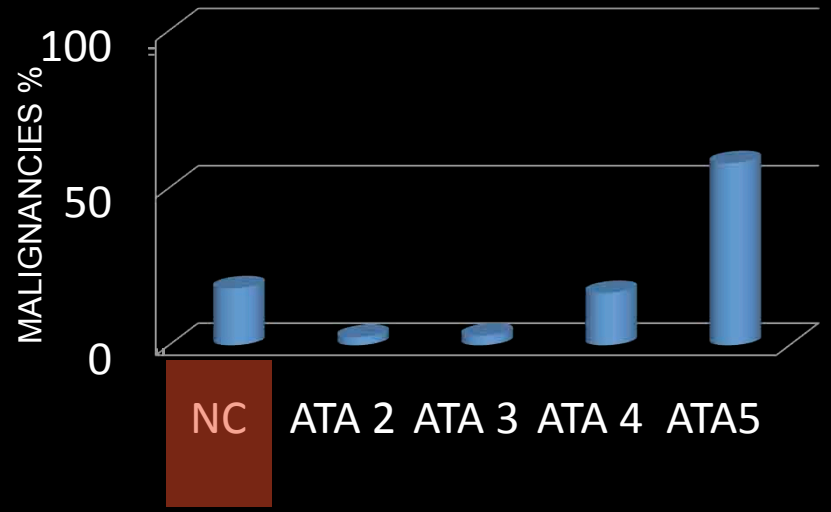
*Refer to discussion of papillary microcarcinomas for 5-9 mm TR5 nodules.

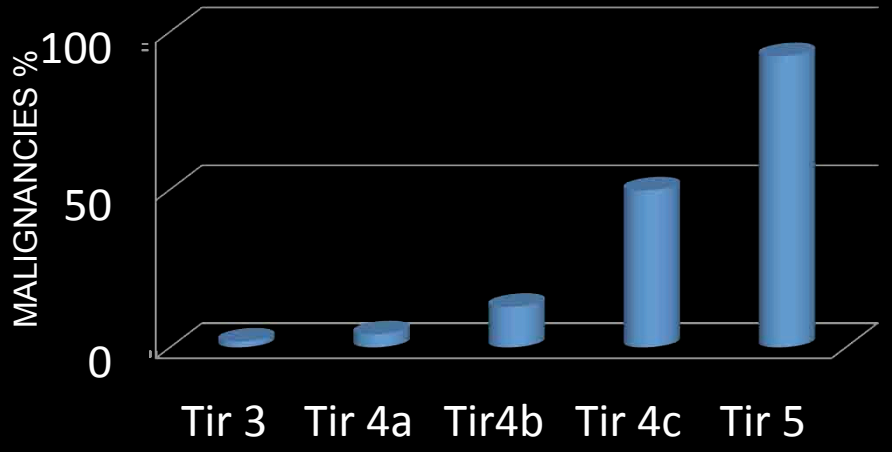
Journal of the American College of Radiology 2017 14, 587-595DOI: (10.1016/j.jacr.2017.01.046)

Question 1#

- Do US classifications of thyroid nodules work as expected ?

ATA 2014 vs TIRADS (Yoon 2016)

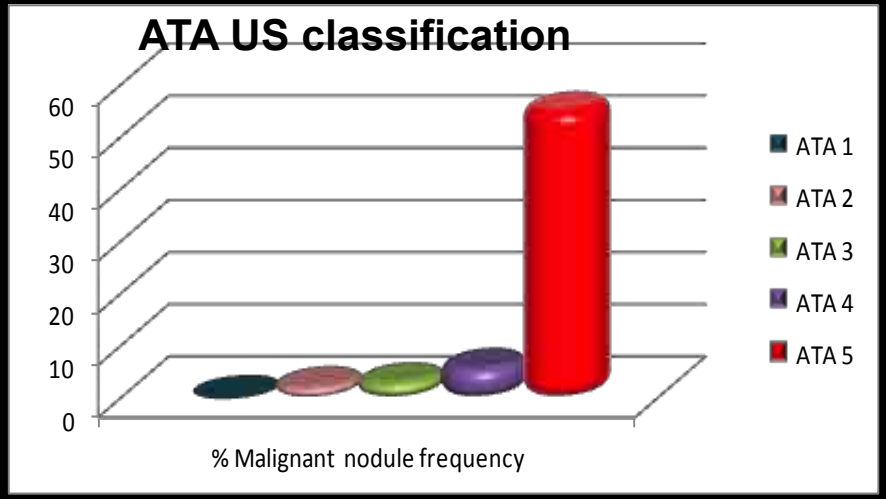


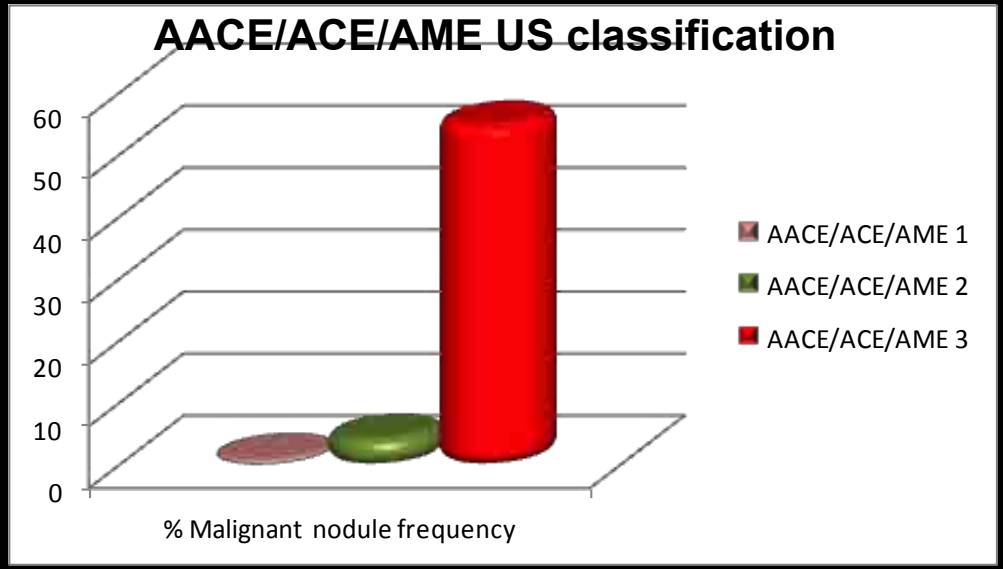


Malignancy Risk Stratification of Thyroid Nodules: Comparison between the Thyroid Imaging Reporting and Data System and the 2014 American Thyroid Association Management Guidelines.

Yoon JH, Lee HS, Kim EK, Moon HJ, Kwak JY Radiology.2016 Mar;278(3):917-24

ATA vs AACE/ACE/AME





Persichetti et al., JCE&M 2018

Malignancy rate in the US Classes

BTA		ATA		AACE/ACE/AME	
Benign	2.8%	Benign	0.0%	Low-risk	1.1%
		Very low suspicion	2.2%		
		Low-suspicion	3.3%		
Indeterminate	10%	Indeterminate	5.8%	Intermediate risk	4.4%
Suspicious	58.3%	High suspicion	55.0%	High-risk	54.9%
Malignant	80.9%				

Persichetti et al., J Clin Endocrinol Metab. 2018

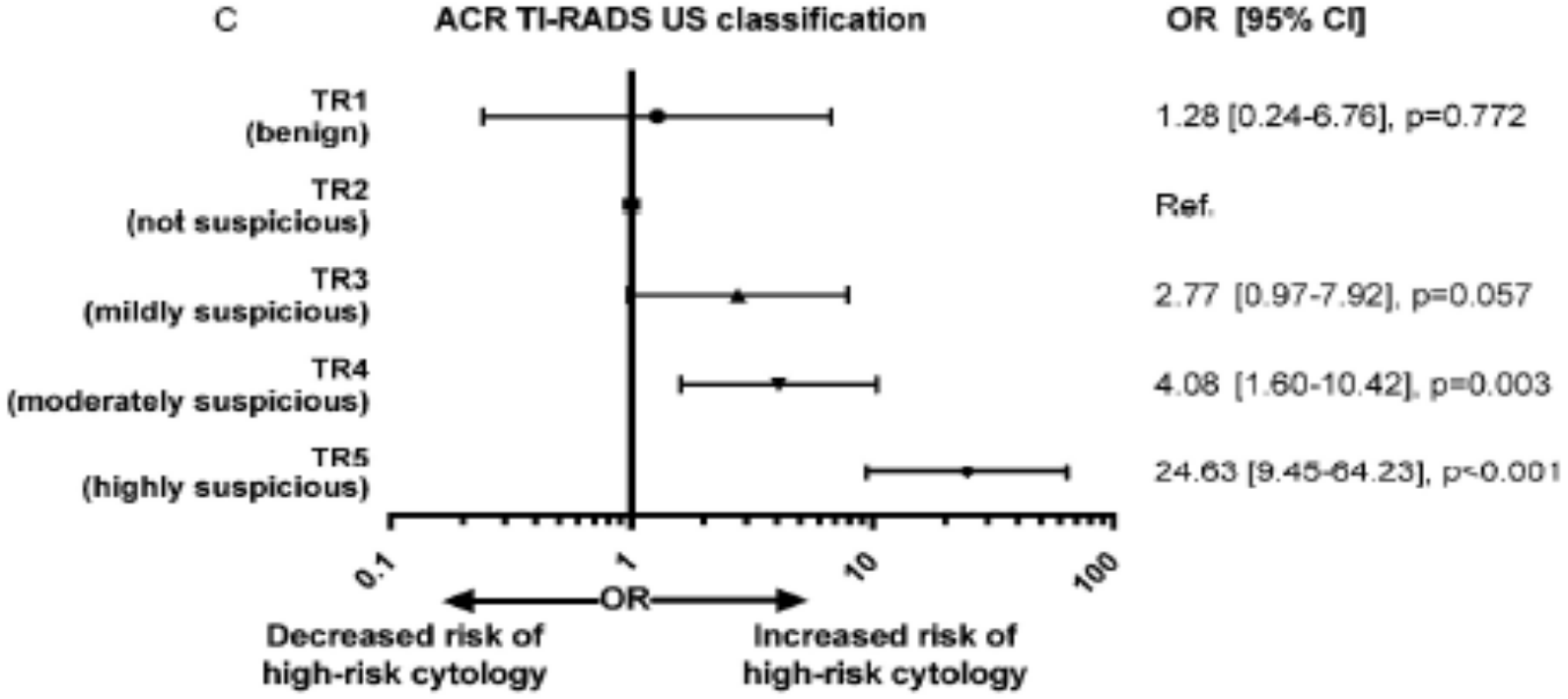
ATA, AACE/ACE/AME and ACR TI-RADS

- 1077 thyroid nodules undergone FNA
- Retrospective US classification according to ATA, AACE/ACE/AME and ACR TI-RADS
- OR and ROC curves for TIR3b, TIR4 and TIR5 were calculated for the different US categories
- Diagnostic performance (C-index) of ACR and AACE/ACE/AME improved when adding clinical data in the regression model
- ACR showed the highest C-index value, similar to AACE/ACE/AME, and significantly superior to ATA.

Differences between ATA, AACE/ACE/AME and ACR TI-RADS ultrasound classifications performance in identifying cytological high-risk thyroid nodules.

A. Lauria Pantano1*, E. Maddaloni1*, S.I. Briganti1, G. Beretta Anguissola1, E. Perrella2, C.Taffon2, A.Palermo1, P.Pozzilli1, S.Manfrini1, A.Crescenzi2

Odds ratio for cytological high risk nodules by ACR TI-RADS US classification systems



Pantano AL et al EJE 2018

Question # 2

What is the diagnostic performance of the higher risk classes?

Question # 2

	BTA	ATA	AACE/ACE/AME
Sensitivity	0.74	0.81	0.82
Specificity	0.92	0.87	0.87
Accuracy	0.89	0.86	0.86

Persichetti et al., J Clin Endocrinol Metab. 2018

Question 3#

- How many FNA can we spare with the combined use of US classes and size cut-offs
- what risk of missing malignancies?

ATA US classes and size cut-offs for thyroid FNA

US Class	Size cut-off	Number	Spared FNA	Malignancy rate
Benign	no	43	**100.0%**	**0.0%**
Very low Risk	≥ 20 mm	137	**48.9%**	**0.0%**
Low Risk	≥ 15 mm	263	**28.1%**	**0.8%**
Indeterminate	≥ 10 mm	313	**12.7%**	**0.7%**
High risk	≥ 10 mm*	231	**18.6%**	**25.5%**

Persichetti et al., J Clin Endocrinol Metab. 2018

AACE US classes and size cut-offs for thyroid FNA

US Class	Size cut-off	Number	Spared FNA	Malignancy rate
Low risk	> 20 mm	180	**42.8%**	**0.0%**
Intermediate risk	≥ 20 mm	572	**45.3%**	**2.0%**
High risk	≥ 10 mm*	235	**18.7%**	**25.5%**

* Virtual data: the actual AACE size cut-off for FNA is 6 mm in the US high-risk class

Persichetti et al., J Clin Endocrinol Metab. 2018

Question # 4

Are US Classification Systems useful for guiding the management of indetermined cytology?

ATA ultrasound system for the initial assessment of thyroid nodules: Use in stratifying the risk of malignancy of indeterminate lesions.

- 173 cytologically indeterminate lesions
- ATA high suspicion class showed a 75% cancer rate, significantly higher than other categories
- halo and microcalcifications were the most sensitive and specific findings
- at multivariate analysis, ATA high suspicion class and size > 4.1 cm were significantly associated with cancer (OR 19.4 and 5.4, respectively)
- ATA US system is reliable in risk stratification of indeterminate thyroid lesions.

Trimboli P et al. Head & Neck 2018; 40 (4):722-727

Rom

EJE

ITALIAN CHAPTER

Accepted Preprint (first posted online 27 April 2018)

CLINICAL STUDY

TIRADS score is of limited clinical valu… risk stratification of indetermin… cytological results

Emmanuelle Chaign…

Marie Bi…

However the high PPV of TIRADS 4b and V can suggest a surgical approach whatever Bethesda category is

…mate nodules. TIRADS …gnancy rate (p<0.0001). Risk …icant only in Bethesda V nodules (… …isk of malignancy in this Bethesda V category was al… …, whatever the TIRADS score.

Conclusion: For a clinician facing an indeterminate cytological result for a thyroid nodule, return to TIRADS score is of limited value in most conditions to rule in or rule out malignancy and to guide subsequent management of patients.

Question # 5

What about interobserver agreement for US classification systems?

Question # 5

Classification System	K correlation coefficient
BTA	78,9%
ATA	76,9%
AACE/ACE/AME	82%

Persichetti et al., J Clin Endocrinol Metab. 2018

CONCLUSION

Role of US Classifications

- US classifications Systems are an important tool and provide an effective malignancy risk stratification of thyroid nodules

BUT

Role of US Classifications

- the level of evidence is not yet adequate (retrospective studies, single center data, selection bias, final diagnosis based on cytology)
- Nodule pattern based systems can have different performance with respect to US feature based one
- US feature based systems (i.e. ACR TIRADS) are more oriented to classical variant of PTC
- Nodule pattern based classifications can have better performance for cytological indeterminate category

Role of US Classifications

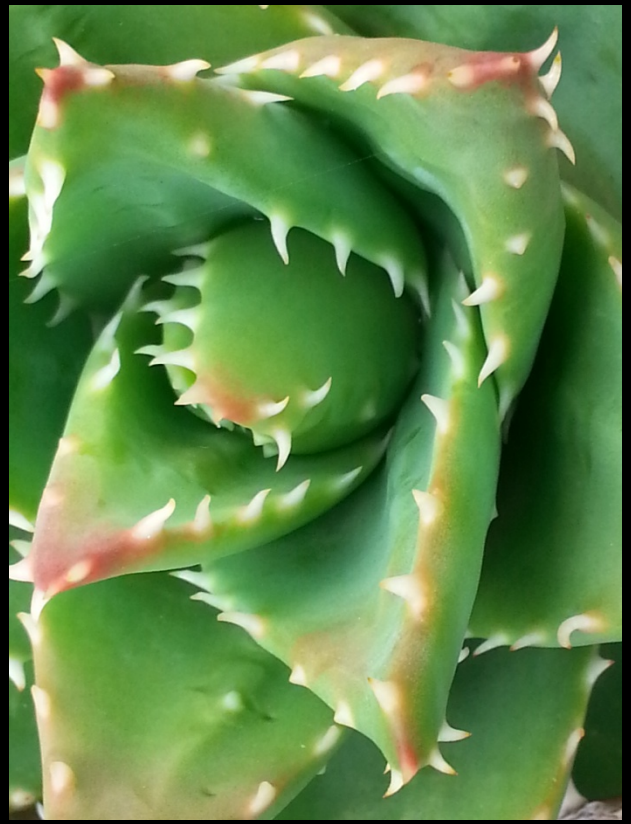
- The rate of malignancy in the different categories is progressive but is generally lower than expected
- the interobserver agreement is not elevated and should be tested in multicenter trials

Use in Clinical Practice

- AACE-ACE-AME is easy to be used and with elevated predictivity
- ATA classification may pose some difficulty in every day practice and is missing a few relevant features
- ACR TI-RADS is a promising US classification, based on a numeric score of the main US features, and is well suited for electronic algorithms (RADIOMICS)

Use in Clinical Practice

- Indication to FNA and the “FNA sparing criteria” should be always evaluated in the context of clinical setting and patient preferences.
- The high risk of missed malignancies with “FNA sparing criteria” should be reconsidered and mitigated on the basis of the concept of “Clinical Significant Tumor”



Thank you