Role of surgery and minimally invasive techniques in thyroid nodule managements

Thyroid Cytology and Microhistology: how to manage persisting grey areas

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Indeterminate nodules

- In about 25% of nodules, FNA cytology cannot reliably exclude cancer, and such cases are placed in one of the **indeterminate categories**.
- Indeterminate lesions are further subdivided into **2 subclasses with significantly different estimated risks of cancer**, to better stratify the risk of malignancy associated with the “indeterminate” nodules.

ITALIAN CONSENSUS 2014	Risk of malignancy %	USA Bethesda 2008	Risk of malignancy %
TIR 1		Non-diagnostic	
TIR 1C			
TIR 2	<3	Benign	<3
TIR 3A	<10 *	AUS/FLUS	5-15
TIR 3B	15-30	FN/SFN	15-30
TIR 4	60-80	Suspicious of malignancy	60-75
TIR 5	>95	Malignant	97-99

** Mild focal cytologic features of PTC are included in TIR 3B while in Bethesda classification are included in AUS/FLUS*

Bethesda system for Thyroid Cythology. Ed 2018

Table 1.2 The Bethesda System for Reporting Thyroid Cytopathology: implied risk of malignancy and recommended clinical management

Diagnostic category	Risk of malignancy (%)	Usual management[a]
Nondiagnostic or Unsatisfactory	5–10[b]	Repeat FNA with ultrasound guidance
Benign	0–3[c]	Clinical and sonographic follow-up
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	~10–30[d]	Repeat FNA, molecular testing, or lobectomy
Follicular Neoplasm or Suspicious for a Follicular Neoplasm[e]	25–40[f]	Molecular testing, lobectomy
Suspicious for Malignancy	50–75	Near-total thyroidectomy or lobectomy[g,h]
Malignant	97–99	Near-total thyroidectomy or lobectomy[h]

- Reinforce that AUS and FLUS are synonymous terms

Risk of malignancy based on post 2007 literature

Italian Consensus for the Classification and Reporting of Thyroid Cytology

Code	Diagnostic category	Expected risk of malignancy (%)	Suggested actions
TIR1	Non-diagnostic	Not defined	Repeat US-guided FNA after at least 1 month
TIR1C	Non-diagnostic-cystic	Low (variable on the basis of clinical findings)	Evaluate the clinical setting and/or repeat FNA
TIR2	Non-malignant/benign	<3	Follow-up
TIR3A	Low-risk indeterminate lesion (LRIL)	<10[a]	Repeat FNA/clinical follow-up
TIR3B	High-risk indeterminate lesion (HRIL)	15–30[a]	Surgery
TIR4	Suspicious of malignancy	60–80	Surgery (consider frozen section)
TIR5	Malignant	>95	Surgery

[a] Expected rate of malignancy for the TIR3 subcategories is mainly found on clinical experience and is only partially based on the evidence of the published data

Mild focal cytological features of PTC are included in TIR 3B while in Bethesda classification are included in AUS/FLUS

J Endocrinol Invest, 2014

Endocrine
DOI 10.3007/s12020-017-1362-6
META-ANALYSIS

Performance of Italian Consensus for the Classification and Reporting of Thyroid Cytology (ICCRTC) in discriminating indeterminate lesions at low and high risk of malignancy. A systematic review and meta-analysis

Results of histologic examination reported in the included studies

	TIR3A		TIR3B	
	cases	cancers	cases	cancers
Tot	180	29(17%)	243	127(52%)

P Trimboli A Crescenzi L Giovannella - Endocrine 2017

TIR3 A (SIAPEC-AIT 2014)

- Increased cellularity with numerous microfollicular structures in a background of poor colloid amount; the proportion of microfollicles is not sufficient to diagnose a follicular neoplasm.
- Sparse cellular samples containing microfollicles.
- Partially compromised specimens (blood contamination) with mild cytologic or architectural alterations.
- Other samples (i.e. atypical cyst-lining cells) showing mild cytologic or architectural alterations.

Expected risk of malignancy <10%

Repeat FNA

- A repeat FNA yields a more definitive cytological diagnosis in many cases, whereas 10%–30% of nodules are repeatedly AUS/FLUS.
- The rate of **malignancy on surgical follow-up** has been shown to be: single AUS/FLUS diagnosis (41%), two successive AUS/FLUS diagnoses (43%), and patients with a benign cytological interpretation following the initial AUS/FLUS diagnosis (29%).

VanderLaan PA, et al. Am J Clin Pathol 2011.

Repeat FNA

TABLE 2. RATE OF MALIGNANCY CONSIDERING THE RESULTS OF THE FIRST AND SECOND FINE-NEEDLE ASPIRATION

		Second FNA				
		36%	48.6%	7.3%	6.6%	
First FNA	*ND*	*Benign*	*FLUS/AUS*	*FN*	*Suspicion of malignancy*	
FLUS	0/1	1/42 (2.4%)	6/38 (15.8%)	3/11 (27.3%)	0	10/92 (10.8%)
AUS	0/1	1/12 (8.3%)	15/35 (42.8%)	0	8/10 (80%)	24/58 (41.3%)
FLUS/AUS	0/2	2/54 (3.7%)	21/73 (28.7%)	3/11 (27.3%)	8/10 (80%)	34/150 (22.6%)

AUS, atypia of undetermined significance; FLUS, follicular lesion of undetermined significance; FN, follicular neoplasm; FNA, fine-needle aspiration; ND, nondiagnostic.

2.4% 8.3% 15.8% 42.8%

Rosario PW. Thyroid. 2014 Jul;24(7):1115-20

TIR 3 B (SIAPEC-AIT 2014)

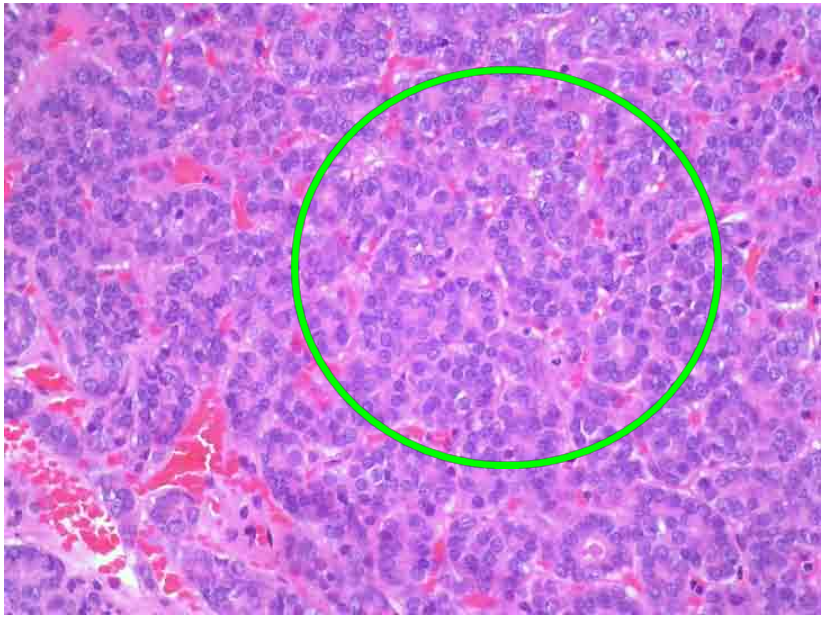
- High cellularity with a monotonous, repetitive microfollicular/ trabecular pattern with scant or absent colloid ("follicular neoplasm").
- Samples composed (almost) exclusively of Hurthle cells (Hurthle cell neoplasm).

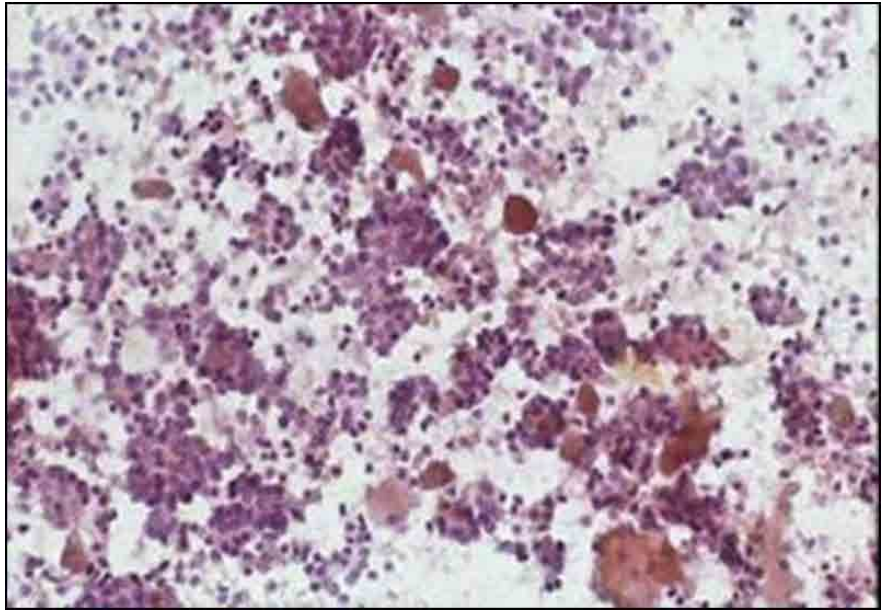
- Nuclear alterations often suggestive of papillary cancer but too mild or focal to be included in TIR 4.

Expected risk of malignancy: 15-30%

Follicular neoplasm

- Repeat FNA of nodules classified as follicular neoplasm is generally not recommended because it does not provide additional information for management.





WHO 2017 Follicular patterned thyroid tumors

		Capsular or vascular invasion		
		Present	**Questionable**	**Absent**
Nuclear features of PTC	**Present**	Invasive encapsulated follicular variant of PTC	Well-differentiated tumour of uncertain malignant potential	Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
	Questionable	Well-differentiated carcinoma, NOS		
	Absent	Follicular carcinoma	Follicular tumour of uncertain malignant potential	Follicular adenoma

Follicular patterned lesions without papillary nuclear features.

Hurthle cells neoplasm

Preoperative Diagnosis of Neoplastic or Malignant Hürthle Cell Lesions: A Chimera?

Cristina Díaz del Arco M. Jesús Fernández Aceñero

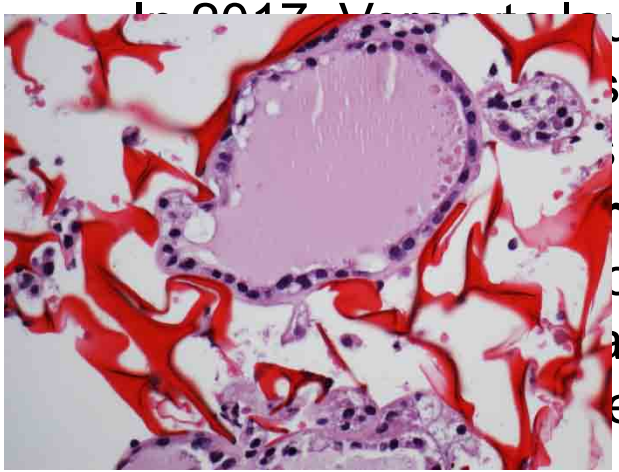
No cytological feature alone can predict histological outcome, but the authors found a significant association between neoplasia and highly cellular smears, the absence of colloid, the presence of microfollicles, large-cell dysplasia, prominent nucleoli or macronucleoli, > 25% of isolated HC, the presence of tridimensional groups, transgressing vessels and nuclear irregularity with coarse chromatin.

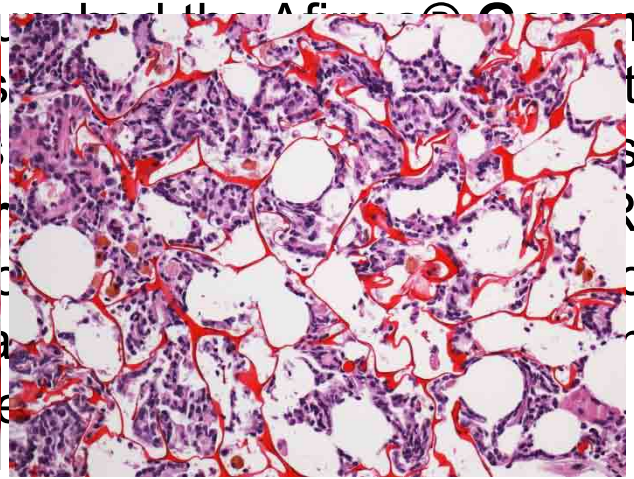
359 thyroid fine-needle aspiration cytology with Hurthle cells

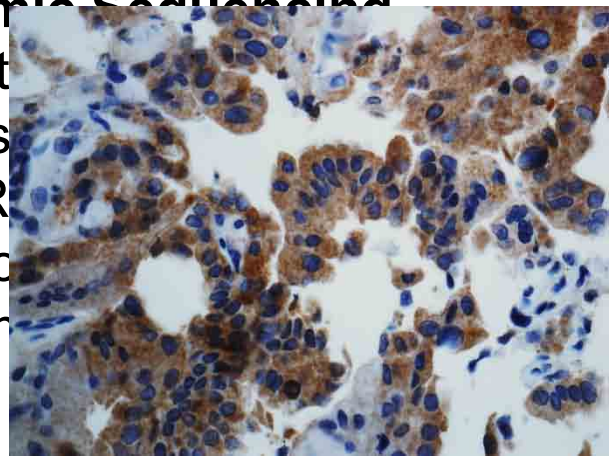
Acta Cytologica 2018;62:193–203

IHC and Molecular Test

- IHC panels (Gal3, HBME1, CK19, CD56) require cell block.
- Cautions in the interpretation of immunohistochemical results obtained in Hürthle cell tumours, because of their tendency to give rise to false-positive immunostaining with many antibodies (endogenous biotin).







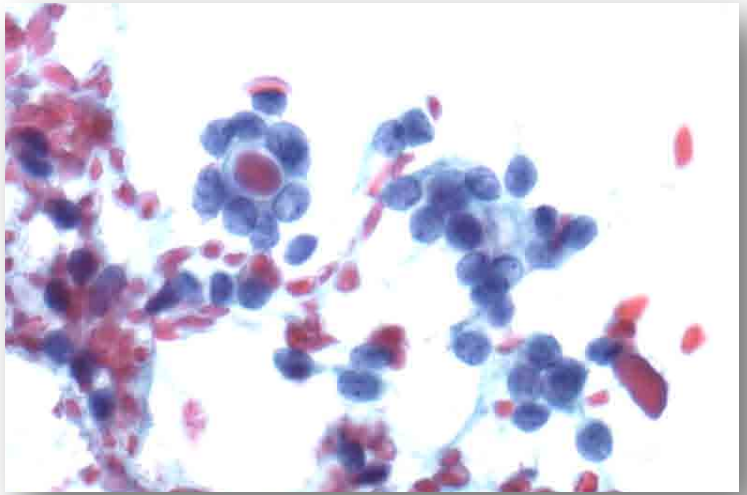
Preoperative Molecular Markers in Thyroid Nodules, Frontiers in Endocrinology, April 2018

IHC and Molecular Test

- In 2017, Veracyte launched the Afirma® **Genomic Sequencing Classifier (GSC)**, its newest product which tests a total of 10,196 genes. This includes **HC index** (mRNA expression and mitochondrial transcripts), and **Hürthle neoplasm index** (mRNA expression and chromosomal level loss of heterozygosity). Among HC lesions, specificity has increased from 11.8 to 58.8%, improving the diagnostic performance in HC lesions.

Preoperative Molecular Markers in Thyroid Nodules, Frontiers in Endocrinology, April 2018

TIR 3 B (SIAPEC-AIT 2014)



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Follicular patterned lesions with present or questionable nuclear papillary features.

Molecular Test

- Molecular testing of BRAF, (H,N,K)RAS and TERT
- Overall sensitivity was 60% and specificity 89%.

Decaussin-Petrucci M, Descotes F, Depaepe L, Lapras V, Denier ML, Borson-Chazot F, Lifante JC, Lopez J. Molecular testing of BRAF, RAS and TERT on thyroid FNAs with indeterminate cytology improves diagnostic accuracy. **Cytopathology. 2017 Dec**;28(6):482-487.

Nuclear versus architectural atypia

Am J Clin Pathol, Sep 2018

A Proposal for Separation of Nuclear Atypia and Architectural Atypia in Bethesda Category III (AUS/FLUS) Based on Differing Rates of Thyroid Malignancy

Daniel N. Johnson, MD,[1] Allison B. Cavallo, MD,[4] Imran Uraizee, MD,[1] Kevin Tanager, MD,[1] Ricardo R. Lastra, MD,[1,2,3] Tatjana Antic, MD,[1,2,3] and Nicole A. Cipriani, MD[1,3]

AUS (3N) is rendered for predominantly nuclear atypia while FLUS (3A) is for architectural microfollicles.

Table 2
Rate of Malignancy by Bethesda Category

Characteristic	Bethesda Category, No. (%)								
	I	II	III (All)	III (3A)	III (3N)	IV	V	VI	Total
Total FNAs	65 (4.7)	453 (32.4)	277 (19.8)	181 (13.0)	96 (6.9)	148 (10.6)	121 (8.7)	332 (23.8)	1,396 (100)
Total malignant	7 (10.8)	11 (2.4)[a]	46 (16.6)	14 (7.7)[a,b]	32 (33.3)[b,c]	37 (25.0)[c]	96 (79.3)	329 (99.1)	526 (37.7)
Total malignant, adjusted for NIFTP	No change, 7 (10.8)	7 (1.5)[a]	34 (12.3)	9 (5.0)[a,b]	25 (26.0)[b,c]	30 (20.3)[c]	84 (69.4)	327 (98.5)	489 (35.0)
PTC	4 (6.2)	10 (2.2)	38 (13.7)	11 (6.1)[d]	27 (28.1)[d]	19 (12.8)	93 (76.9)	311 (93.7)	475 (34.0)
PTC, adjusted for NIFTP	No change, 4 (6.2)	6 (1.3)	26 (9.4)	6 (3.3)[d]	20 (20.8)[d]	12 (8.1)	81 (66.9)	309 (93.1)	438 (31.4)
FTC	2 (3.1)	1 (0.2)	5 (1.8)	3 (1.7)[e,f]	2 (2.1)[f,g]	14 (9.5)[e,g]	0 (0.0)	0 (0.0)	22 (1.6)

Indeterminate FNA and nodule size

- Nodule volume is not a predictive factor for malignancy even if the risk of cancer and of more advanced disease is slightly higher in nodules >4 cm.
- Indeterminate lesions with a diameter exceeding 4 cm will be at least pT3 of TNM classification, if cancer is proved at final histology.

Second opinion

- A **second opinion** review of the cytopathology slides by a high-volume cytopathologist may be considered for patients with AUS/FLUS cytology. There is some evidence that this approach **may reclassify many of these patients**.

- Unfortunately, there is a relatively high inter-observer variability in this difficult diagnostic category.

ATA 2015

OUTCOME of cancer in indeterminate nodules

- Patients with Thy 3 cytology have better outcomes of thyroid cancer compared to patients with Thy 4 or Thy 5 cytology.
- Indeterminate cytology is commonly associated with the less aggressive FV-PTC.

Patients with indeterminate thyroid nodules at cytology and cancer at histology have a more favorable outcomes compared to patients with suspicious or malignant cytology. Rago et al**. Thyroid. 2018** Oct;28(10):1318-1324

OUTCOME of cancer in indeterminate nodules

Thy3
FV-PTC 64.5%

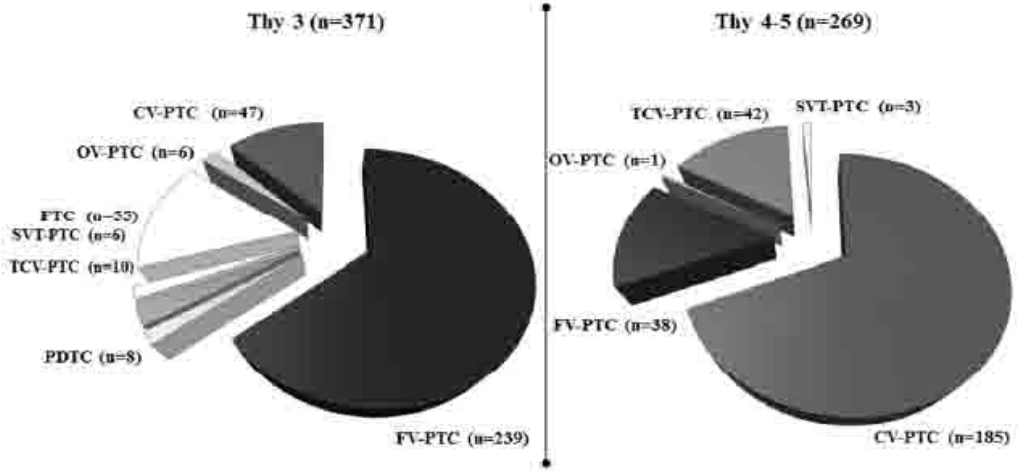

FIGURE 1. Distribution of histotype and variants of thyroid carcinoma in 371 Thy 3 and 269 Thy 4-5 patients. Classic Variant PTC: CV-PTC; Follicular Variant PTC: FV-PTC; Oxyphylic Variant PTC:OV-PTC; Tall Cell Variant PTC: TCV-PTC; Solid Variant with Trabecular PTC: SVT-PTC; Follicular Carcinoma: FC; Poorly differentiated Carcinoma: PDC

Thy 4-5
CV-PTC 68.7%

Structural and biochemical persistence of disease was less common in the Thy3 group at the end of the follow-up.

Conclusions

- Indeterminate nodules are very heterogeneous.
- **First, pay attention to the cause for indeterminate report:**
  - Poor cellularity or blood contamination. Repeat FNA
  - Microfollicular pattern. Repeat (TIR3A), FU, IHC, lobectomy (TIR3B)
  - Hurthle cells. 2nd opinion, clinical setting, lobectomy
  - Cytological atypia. IHC, molecular test, surgery
- Plan the treatment using all information from clinical data, US and cytology. You have the time to make the appropriate choice.

Thank you!