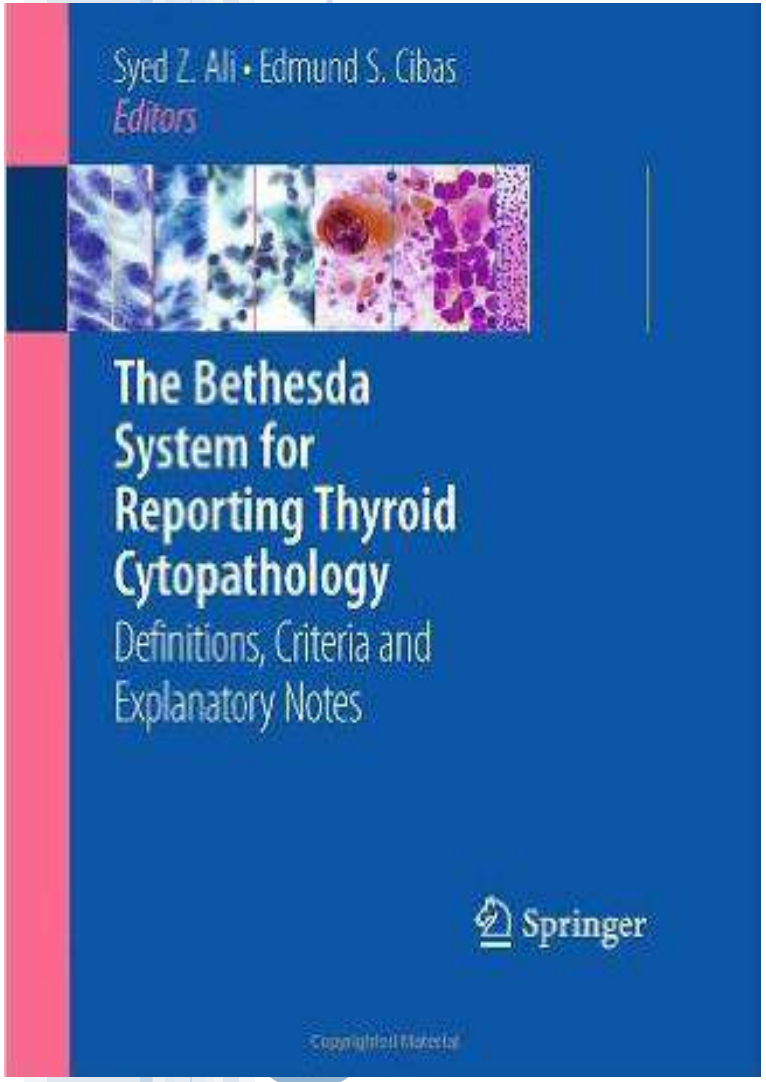


UPDATE ON THE Bethesda system for reporting thyroid cytology

Esther Rossi MD PhD MIAC

Division of Anatomic Pathology and Cytology

Catholic University of Sacred Heart

Rome, Italy

Present

< Current State and Global Impact of TBSRTC >

UK RCPath 2015	ITALY 2014	USA BETHESDA 2008	AUSTRALASIA CLASSIFICATION 2014	JAPAN THYROID ASSOCIATION 2013
Diagnostic category	Diagnostic category	Terminology	Categories	Terminology
Thy1/Thy1c Non-diagnostic for cytological diagnosis Unsatisfactory, consistent with cyst	TIR 1: Non-diagnostic TIR 1C: Cystic	I. Non-diagnostic	Non-diagnostic	Inadequate (non diagnostic)
Thy2/Thy2c Non-neoplastic, benign cystic	TIR 2: Non-malignant/benign	II. Benign	Benign	Normal or benign
Thy 3a Neoplasm possible – atypia present	TIR 3A: Low-risk indeterminate lesion (LRIL)	III. Atypia of undetermined significance (AUS) or follicular lesion u.s. (FLUS)	Indeterminate or Follicular lesion of undetermined significance	Indeterminate A. Follicular Neoplasm • A1 favor benign • A2 border-line • A3 favor malignant B. Others (atypia in non-follicular patterned lesions)
Thy3f Neoplasm possible - suggesting follicular neoplasm	TIR 3B: High-risk indeterminate lesion (HRIL)	IV. Follicular neoplasm or suspicious for a follicular neoplasm	Suggestive of a follicular neoplasm	
Thy 4 Suspicious of malignancy	TIR 4: Suspicious of malignancy	V. Suspicious of malignancy	Suspicious of malignancy	Malignancy suspected
Thy5 Malignant	TIR 5: Malignant	VI. Malignant	Malignant	Malignancy

TBSRTC

- Used world over
  - 2011 CAP Study – 77% of Labs in the US*
- 540,000 links on Google
- 115,000 citations on Google Scholar
- 1,751 articles on PubMed (unique)

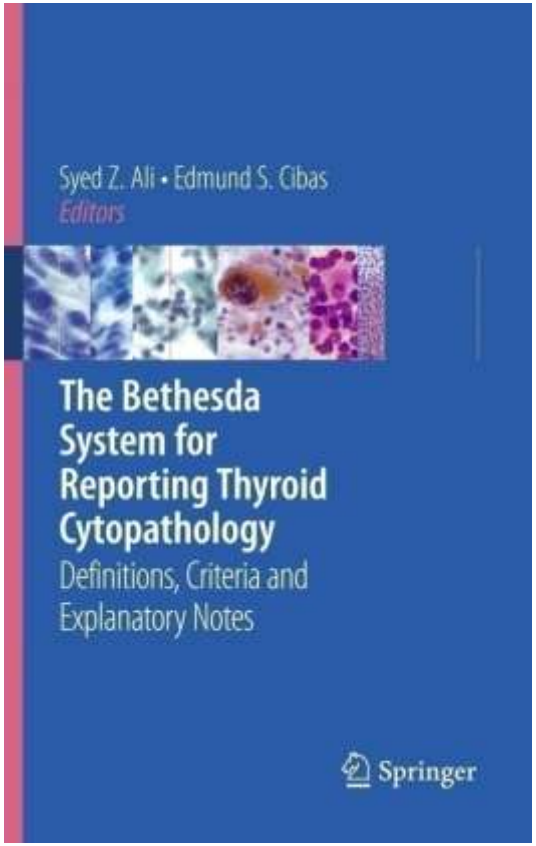
*Auger M, et al, Arch Pathol Lab Med 2013

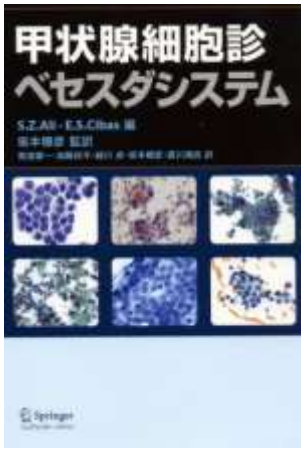
TBSRTC – Diagnostic Categories

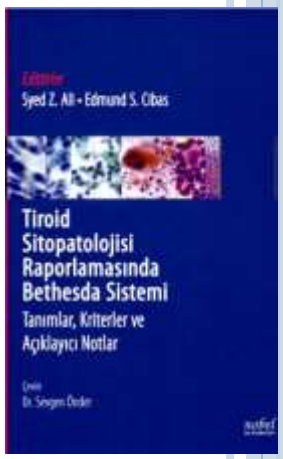
- Nondiagnostic/Unsatisfactory
- Benign
- AUS/FLUS *
- FN/SFN *
- Suspicious for Malignancy
- Malignant

* Why two names?

What Bethesda Really Said!







- Definitions, criteria, explanatory notes
- Over 40 contributing authors
- 170 pages
- 200 color images
- $40
- Chinese, Spanish, Japanese, Turkish

Digital Image Atlas – http://www.papsociety.org

TBSRTC - Probabilistic Approach and Relationship to Clinical Algorithms

	ROM (%)	Management
Nondiagnostic	1-4	Repeat FNA with US
Benign	0.5-5.5	Follow-up
AUS/FLUS	~5-10 (15-25)	Repeat FNA
FN/Suspicious for a FN	15-30	Lobectomy
Suspicious for Malignancy	60-77	Lobectomy or total thyroidectomy
Malignant	96-99	Total thyroidectomy

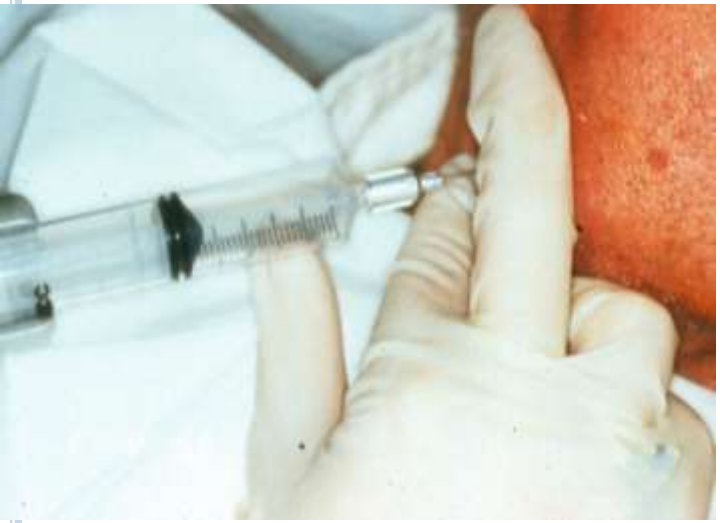
FUTURE

- TBSRTC II
  - March 2018
  - 200 pages, 200 figures
- Issues and Recommendations for possible modifications in TBSRTC 2 (Chapter based)
- Recent advances with potential impact on TBSRTC

TBSRTC Panel

- **Co-Leaders**
  - Bill Faquin (USA)
  - Marc Pusztaszeri (Switzerlan
  - Esther Diana Rossi (Italy)
- **Members**
  - Manon Auger (Canada)
  - Zubair Baloch (USA)
  - Justin Bishop (USA)
  - Massimo Bongiovanni (Switzerland)
  - Ashish Chandra (UK)
  - Guido Fadda (Italy)
  - M. Hirokawa (Japan)
  - Soonwon Hong (Korea)
  - Kennichi Kakudo (Japan)
  - Jeffrey Krane (USA)
  - Ritu Nayar (USA)
  - Sareh Parangi (USA)
  - Beatrix Cochand-Priollet (France)
  - Fernando Schmitt (Luxembourg)

Tasks of TBSRTC Panel:



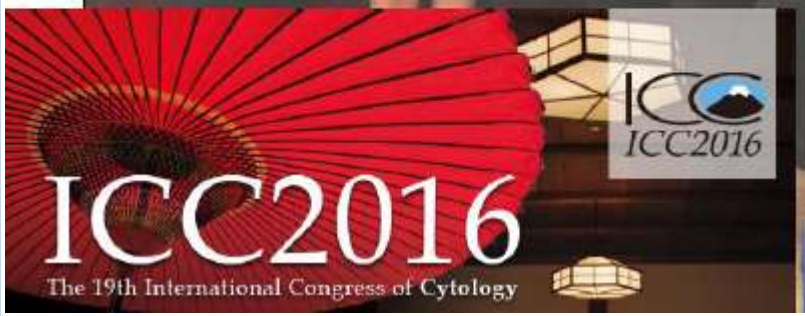
- Pubmed literature review of thyroid cytology from 2010 to present

- Divided efforts into subgroups corresponding to each of the 6 TBSRTC diagnostic categories
- 2-6 panel members per subgroup

- Email discussions among subgroup members, and face to face meeting at USCAP in Seattle

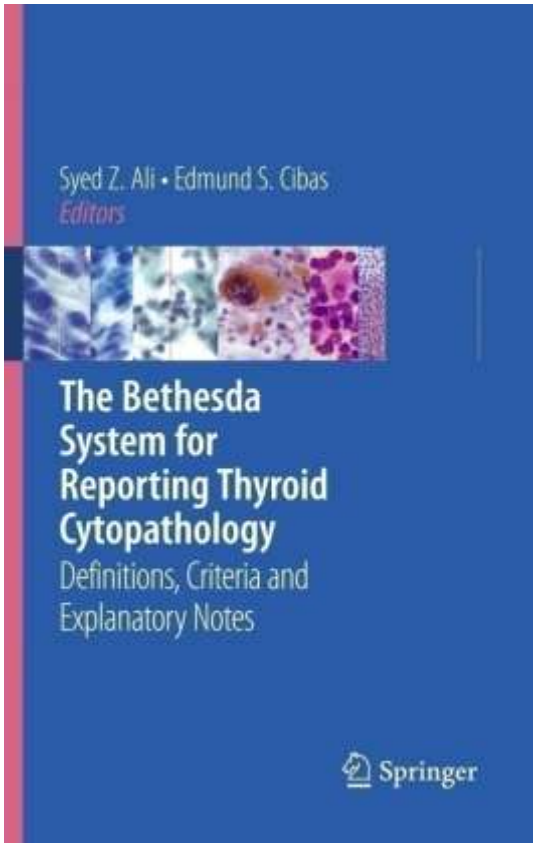
- IAC Symposium presentation – Yokohama, Japan
- Publication of manuscript detailing the panel's consensus recommendations for TBSRTC II

The Bethesda System for Reporting Thyroid Cytopathology: proposed modifications and updates for the second edition from an international panel



YOKOHAMA, JAPAN, June 2016

What are the prospects for the second edition of TBSRTC Atlas?



- **IAC Symposium organized by Drs. Syed Ali and Philippe Vielh to address past, present, & future of TBSRTC**
- **Many advances, large amount of published literature, and new questions for TBSRTC:**
  - **Reporting of selected uncommon entities (e.g. parathyroid adenoma)**
  - **Refinements to the ROM for each corresponding diagnostic category**
  - **NIFTP and its impact on the indeterminate categories of TBSRTC**
  - **2015 ATA Guidelines – impact on clinical management algorithms**
  - **Diagnostic category names – continue with multiple options or reduce to one?**
  - **Quality control: laboratory metrics for monitoring**
  - **Many more diagnostic category-specific issues…**

The Nondiagnostic Thyroid FNA: Criteria and Follow-up

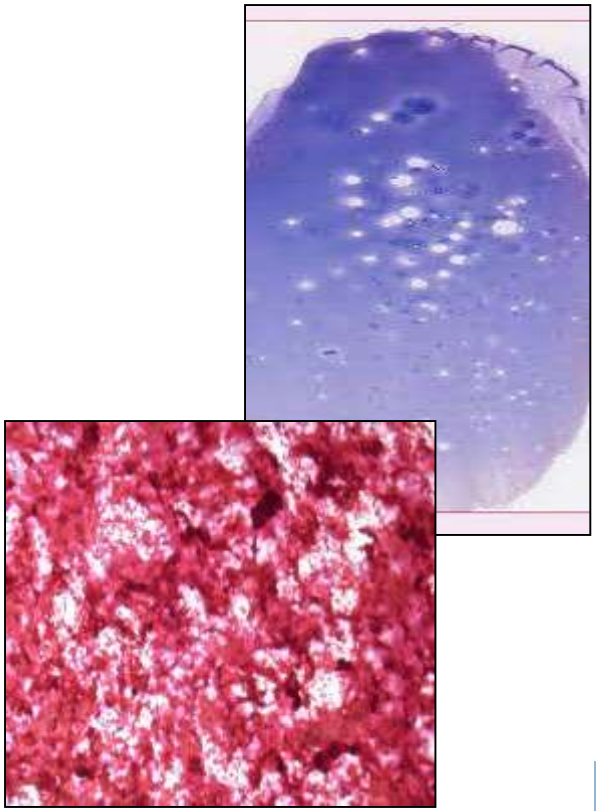
Rationale

Adequacy criteria

Frequency of Nondiagnostic

Management

Possible Future Scenario



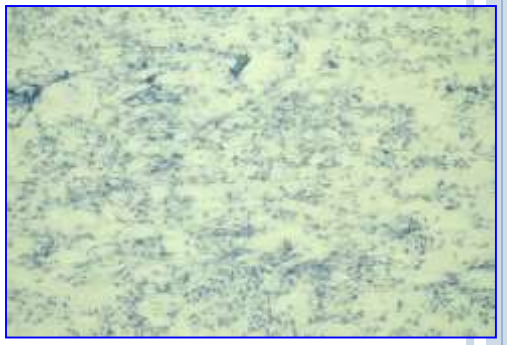
Factors Contributory to InadequateThyroid FNA

- **Inadequate history**

- **Inadequate specimen**

Quantity and quality of representative cells

- **Suboptimal preparation**



- **Interpretative and diagnostic errors**

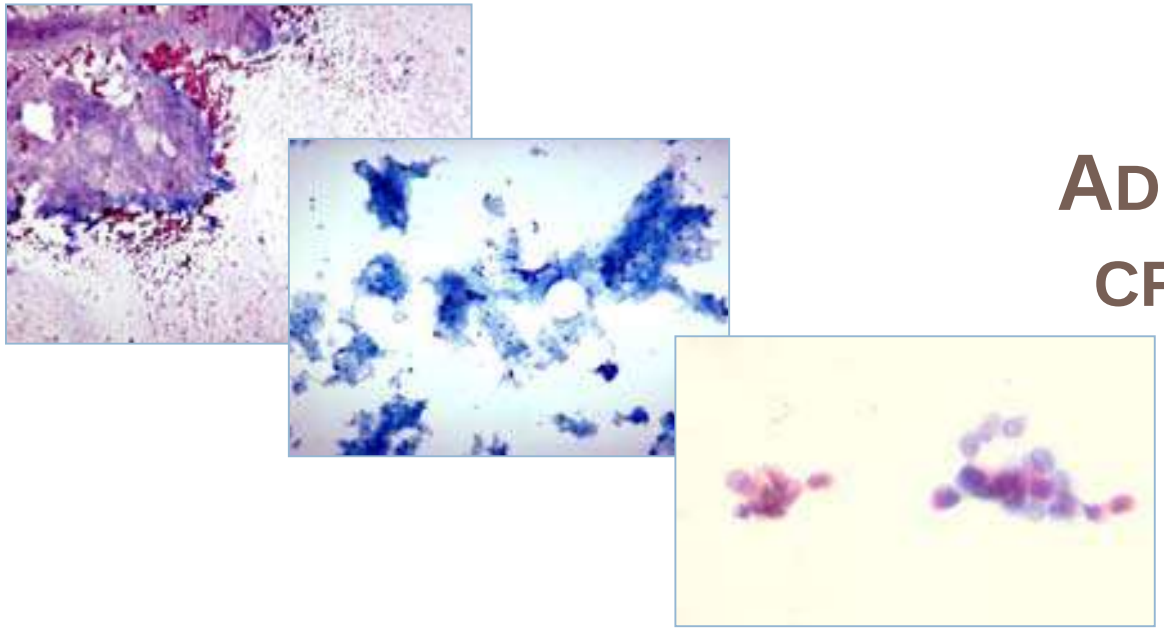
Rationale for a Non-Diagnostic category: Why is adequacy a problem in thyroid FNA?

1) TO REDUCE "FALSE NEGATIVE" DIAGNOSES ARISING FROM INSUFFICIENT SAMPLING

The Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy and Recommended Clinical Management

Diagnostic Category	Risk of Malignancy (%)	Usual Management[†]
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	Near-total thyroidectomy[§]

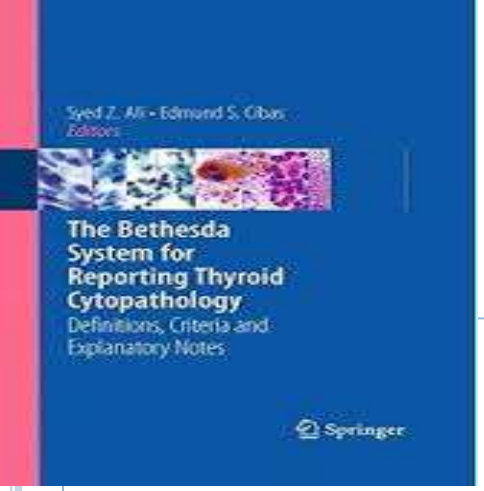
- cystic lesions are common
- Poor quality sampling by inexperienced aspirators
- Vascular components
- Colloid-rich nodules



ADEQUACY CRITERIA

- Criteria are not evidence-based

- Similar in all the current classification systems:
  - Bethesda
  - British
  - Italian
  - Japanese



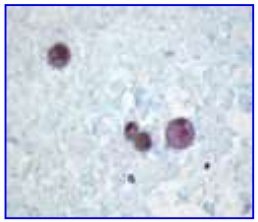
NONDIAGNOSTIC: BETHESDA CRITERIA

- **DEFINITION**: A specimen is Nondiagnostic if it fails to meet the adequacy criterion

  ADEQUACY CRITERION: At least 6 groups, each with at least 10 benign-appearing, well-visualized follicular cells

Same criteria irrespective of cytological preparation (smears, LBC, Cell-block)

"Cyst fluid (macrophages) only" cases included as a subset



EXCEPTION Thyroiditis = BENIGN

Abundant Colloid= BENIGN

Any atypia

Some attempts of different epithelial quantification

- Frost et al. *Cancer 1998;84:17-25*
  - ThinPrep - 6 clusters of 10 epithelial cells
  - 5% inadequate rate

- Renshaw. *Am J Clin Pathol 2002;118:518-521*
  - At least 10 follicular cells lacking atypia with no Hürthle cells

- Michael et. al. *Diagn Cytopathol 2007; 35:792-797*
  - ThinPrep cases
  - At least 200 cells

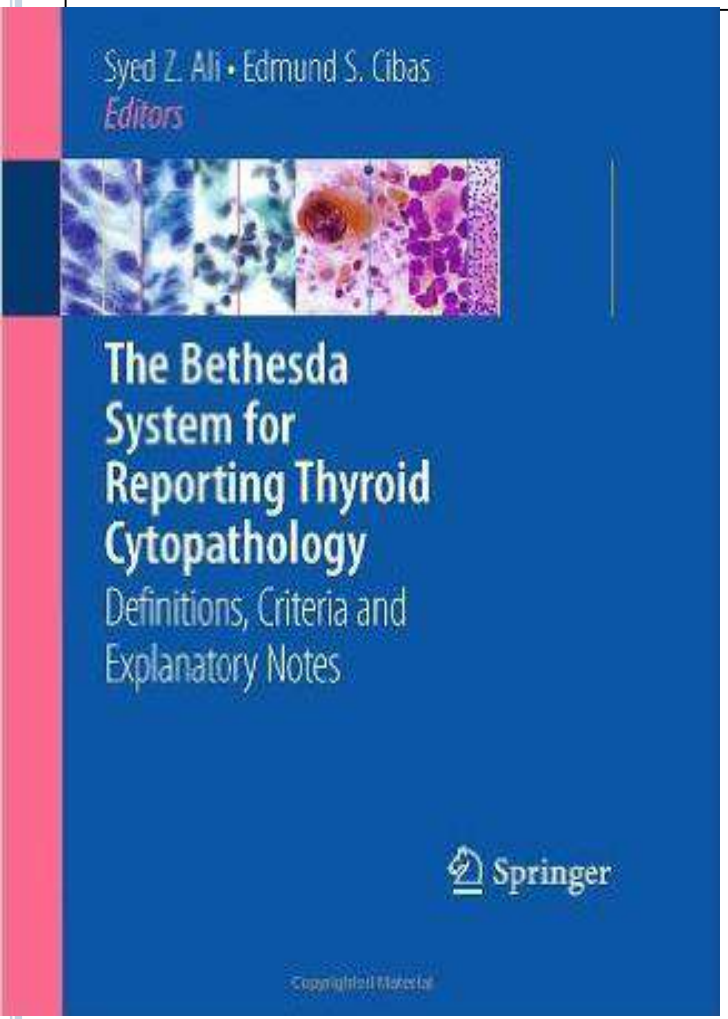
- Renshaw. *Diagn Cytopathol 2010*
- 30 epithelial cells lacking atypia with no Hürthle cells

Nondiagnostic* Rates

Study authors	Number of nodules biopsied	Nondiagnostic Rate (%)
Grant et al, 1988	8219	21
Yoder, et al, 2006	1043	5
Yassa et al, 2007	3589	13
Yang et al, 2007	4703	10
Theoharis et al, 2009	3037	12
Nayar et al, 2009	5194	5
Marchevsky et al, 2010	879	13
Hryhorczuk et al, 2011	1344	22
Renshaw, 2011	7089	24
Al Maqbali et al, 2012	1657	16
Coorough et al, 2013	4286	6
Ferreira et al, 2014	15,292	7
Range		**5-24%**

* defined using Bethesda System criteria

BTSRTC:Management of ND FNA



- Repeat FNA with ultrasound guidance no sooner than 3 month later
- Partially cystic nodules that are repeatedly ND need close observation or surgical excision

Thyroid ©2015 American Thyroid Association DOI: 10.1089/thy.2015.0020

2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid CancerBryan R. Haugen, M.D.[1] (Chair)*,

[A12] Nondiagnostic cytology

■ **RECOMMENDATION 10**

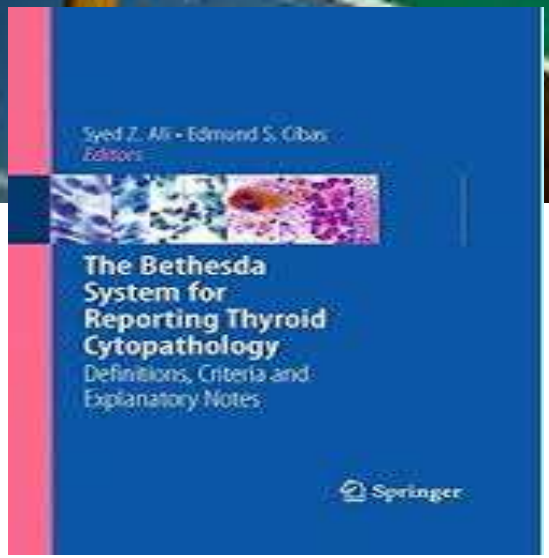
A) For a nodule with an initial nondiagnostic cytology result, FNA should be repeated with US guidance and, if available, on-site cytologic evaluation (**Strong recommendation, Moderate-quality evidence)**

B) Repeatedly nondiagnostic nodules without a high suspicion sonographic pattern require close observation or surgical excision for histopathologic diagnosis (**Weak recommendation, Low-quality evidence)**

C) Surgery should be considered for histopathologic diagnosis if the cytologically nondiagnostic nodule has a high suspicion sonographic pattern, growth of the nodule (greater than 20% in two dimensions) is detected during ultrasound surveillance, or clinical risk factors for malignancy are present (**Weak recommendation, Low-quality evidence)**


Here & Now


Future
Just Ahead


Syed Z. Ali · Edmund S. Cibas
Editors
The Bethesda System for Reporting Thyroid Cytopathology
Definitions, Criteria and Explanatory Notes
Springer

The Future of Adequacy

From the Composite outline of the key issues identified by our TBSRTC

- **Cystic lesions:**

Should still be reported as Non-diagnostic with an explanatory note. Update management according to revised ATA guidelines. The sample reports and the explanatory notes in TBSRTC regarding cystic lesions are adequate.

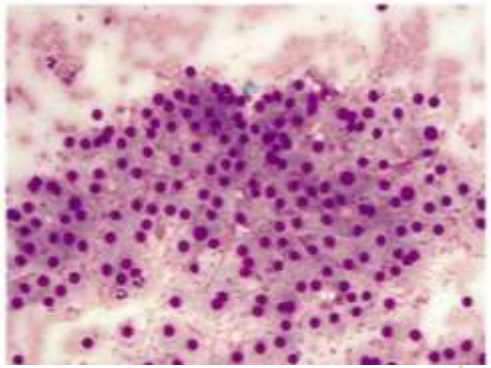
- **Repeat FNA after ND result:**

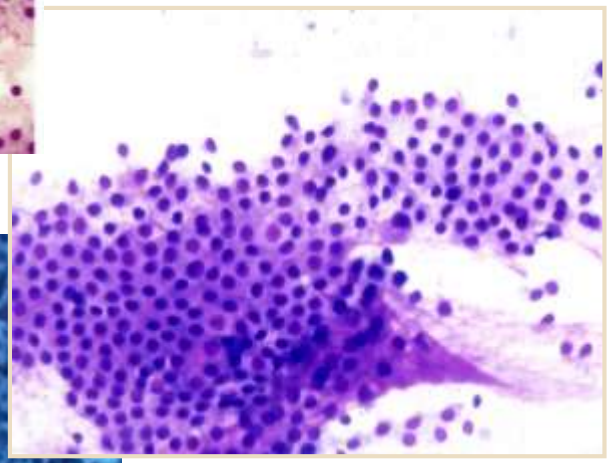
The wait time for repeating an FNA after a ND result can be less than 3 months (as suggested by the revised ATA guidelines). However, it should be explained that reactive atypia and cellular changes may be present if the delay to repeat FNA is shortened.

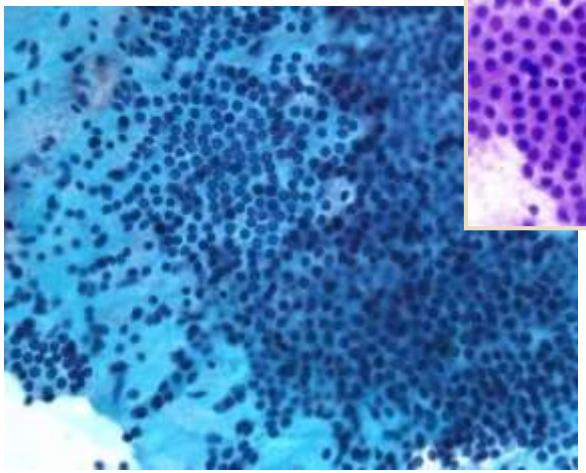
- **Adequacy criteria and preparation method:**

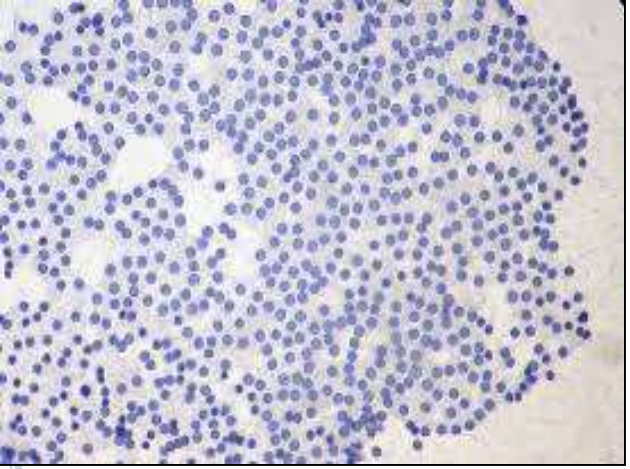
Clarification is needed pertaining to the specific adequacy criteria for smears vs. liquid based preparations: ThinPrep and Surepath alone or in combination with smears.

BENIGN NODULES









CATEGORY « BENIGN »

- **The most important category in terms of percentage of nodules**
- **percentage should be around 90-92% of all nodules**
- **Mostly concerns 60-70% of all nodules**

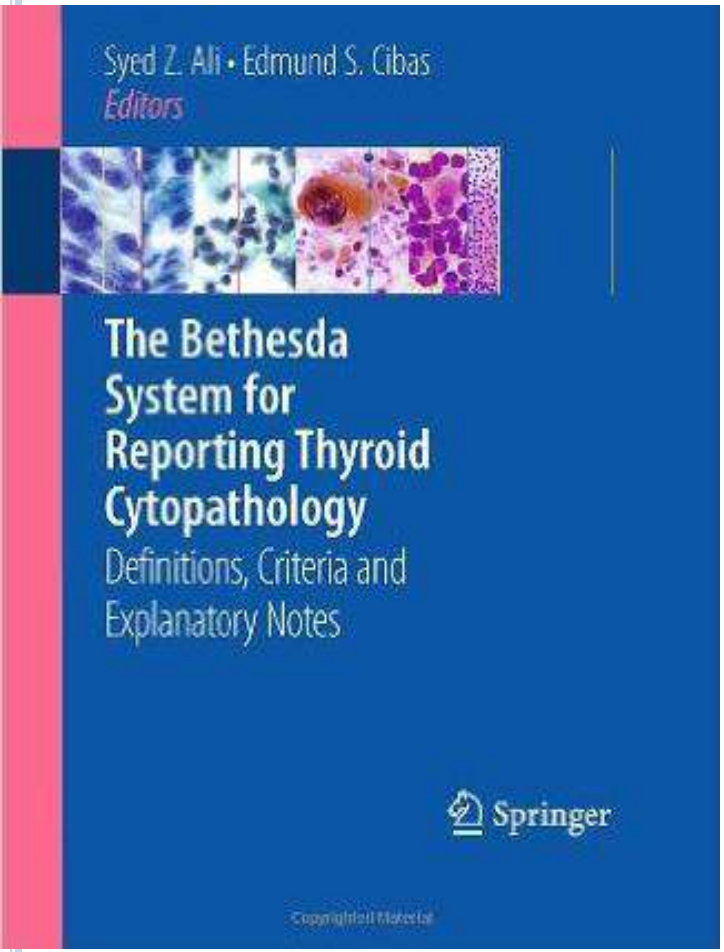
- **With some variations depending on:**

1. **the sampler performance**
2. **the cytopathologist training**
3. **The local epidemiological data**

Literature Results

Authors	Cases Number	Non diagn	Benign	FLUS or AUS	FN/ FNHC	SM	Malignant
Cochand-Priollet B et al 2012	2210	14.3%	65.5%	11% (23.6%)	4.9% (15.2%)	2.3% (58.7%)	2% (100%)
Mastorakis et al Cytopathology 2012	500	NA	49%	9.4% (23.4%)	1.2%	10.6% (96%)	26.8% (100%)
	500	NA	72.2%	5% (8%)	2.2%	3.2% (87.5%)	12.2% (100%)
Lacoste-Collin L et al 2012	1317	31.6%	48%	7.8% (18.5%)	7% (22.2%)	3% (55.6%)	2.6% (100%)
Bongiovanni et al 2012	7686	2%	54.7%	6.3% (14.4%)	25.3% 32.1%	6.3% (74.9%)	4% 99.4%
Park JH et al 2014	1730	13.3% (35.3%)	40.6% (5.6%)	9.1% (69%)	0.4% (50%)	19.3% (98.7%)	17.3% (98.9%)
Bethesda		<15% ?	60% 0 - 3%	<7% 5 -15%	6-11% 15 - 30%	2-8% 60 -75%	3-7% 97 - 99 %

BTSRTC:Management of BN FNA



- **Follow-up for 6-18 month intervals and for at least 3-5 years**
- **Repeat FNA for nodules with significant growth or US abnormalities**

Thyroid ©2015 American Thyroid Association DOI: 10.1089/thy.2015.0020

2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid CancerBryan R. Haugen, M.D.[1] (Chair)*,

RECOMMENDATION 11

If the nodule is benign on cytology, further immediate diagnostic studies or treatment are not required (Strong recommendation, High-quality evidence)

RECOMMENDATION 23

Given the low false negative rate of US-guided FNA cytology and the higher yield of missed malignancies based upon nodule sonographic pattern rather than growth, the follow up of thyroid nodules with benign cytology diagnoses should be determined by risk stratification based upon ultrasound pattern.

A)Nodules with high suspicion US pattern: repeat US and US-guided FNA within 12 months (Strong recommendation, Moderate-quality evidence)

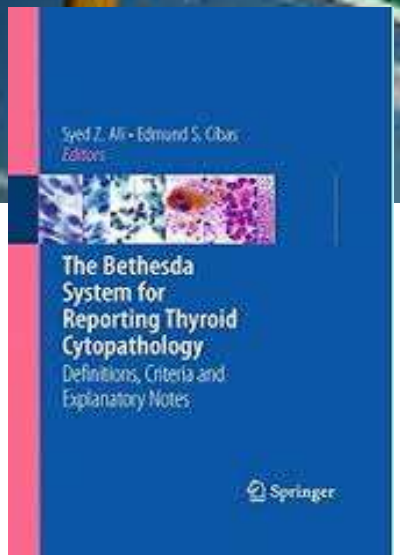
B) Nodules with low to intermediate suspicion US pattern: repeat US at 12-24 months.

If sonographic evidence of growth (20% increase in at least two nodule dimensions with a minimal increase of 2 mm or more than a 50% change in volume) or development of new suspicious sonographic features, the FNA could be repeated or observation continued with repeat US, with repeat FNA in case of continued growth (Weak recommendation, Low-quality evidence).

C) Nodules with very low suspicion US pattern (including spongiform nodules): the utility of surveillance US and assessment of nodule growth as an indicator for repeat FNA to detect a missed malignancy is limited. If US is repeated, it should be done at > 24 months (No Weak recommendation, Insufficient Low-quality evidence).


Here & Now


Future
Just Ahead


Syed Z. Ali · Edmond S. Cibas
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CONCLUSION

- **No major changes were suggested for this category**

- **ROM:**

Several recent studies have confirmed that the ROM is very low for this category (≤ 3%)

- **Diagnoses:**

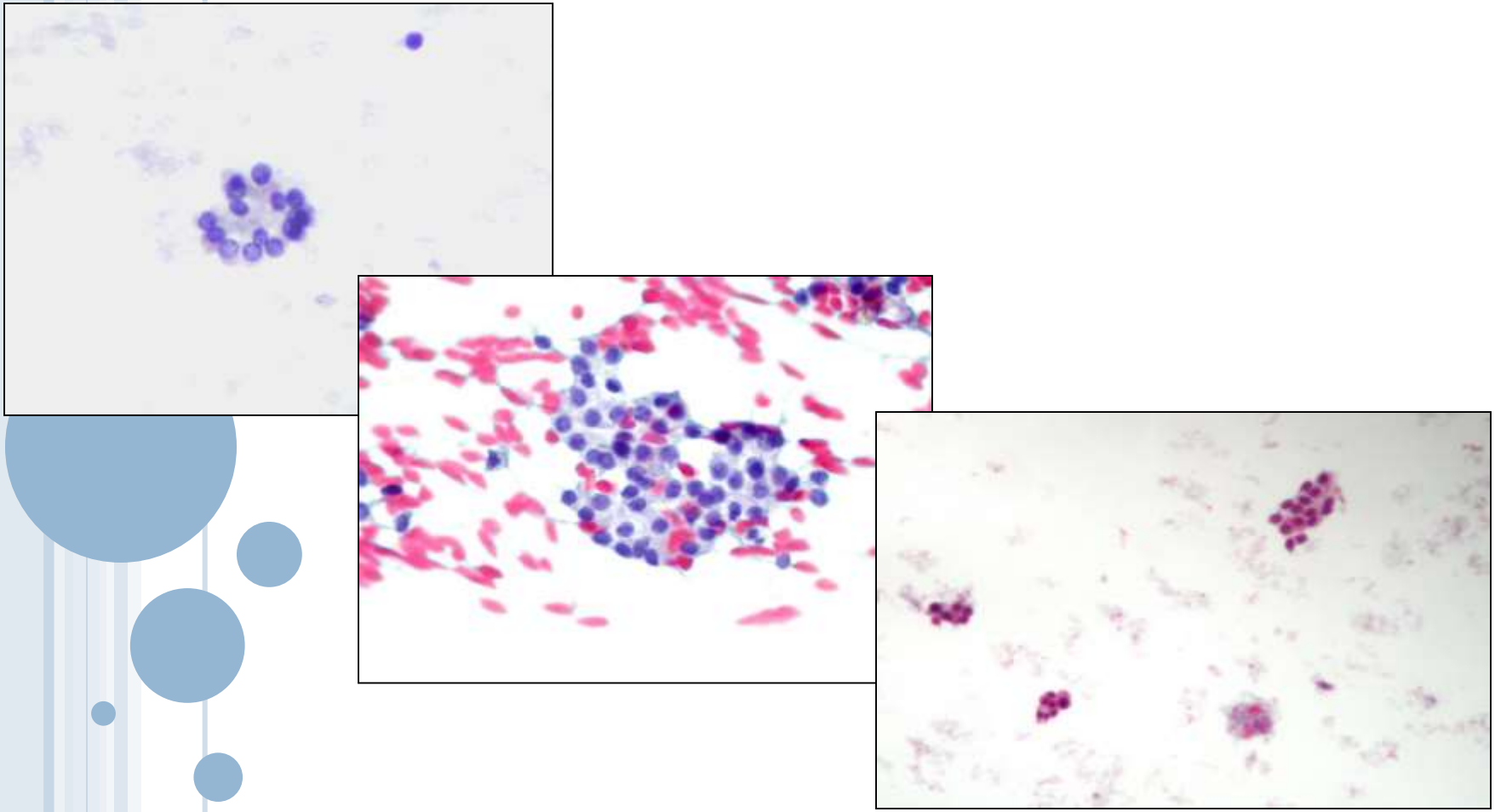
More LBC imagines

IgG4 thyroïditis should be included in the “thyroïditis” chapter

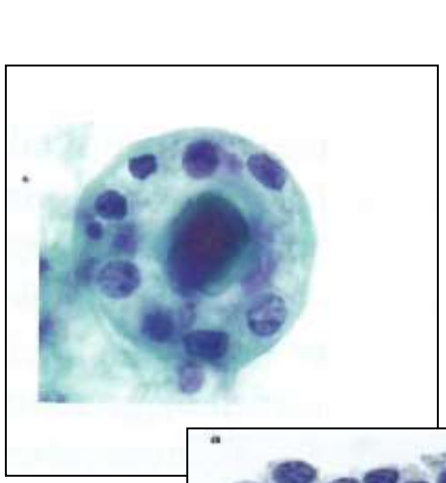
- **Follow-up:**

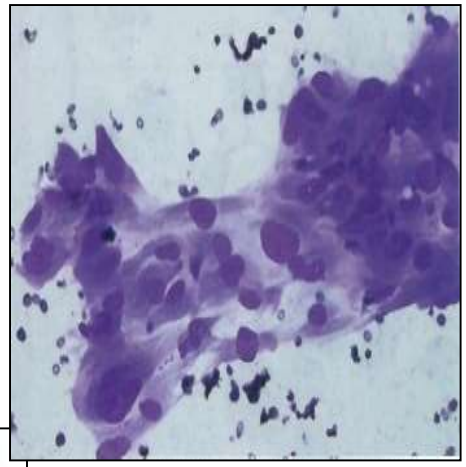
Risk stratification based upon ultrasound pattern (ATA 2015 revised guidelines) can be used to guide follow-up of thyroid nodules with benign cytology

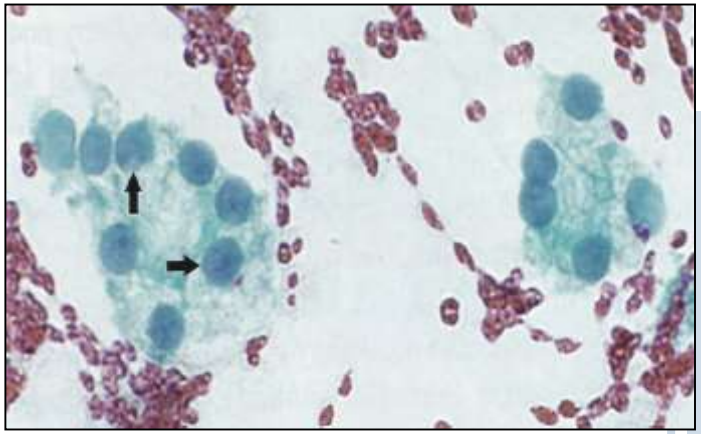
AUS/FLUS

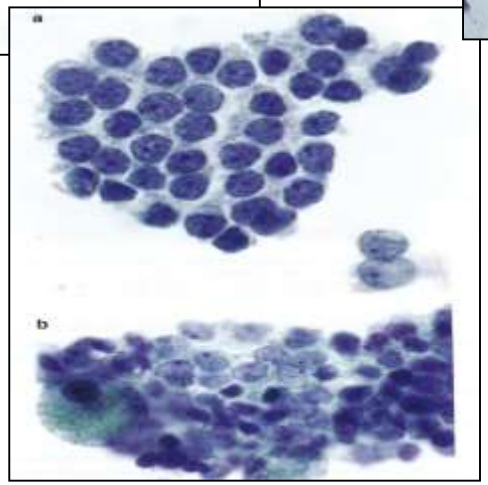


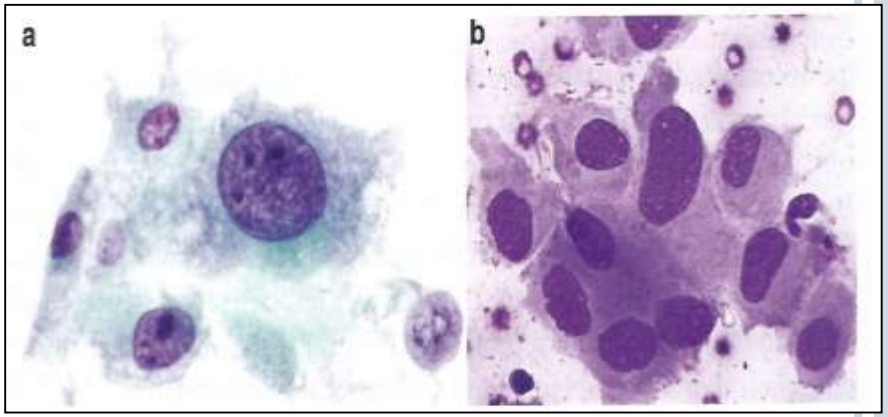
The classification of "indeterminate" lesions (those not clearly benign or malignant) in thyroid cytopathology has long been a source of confusion for both pathologists and clinicians.





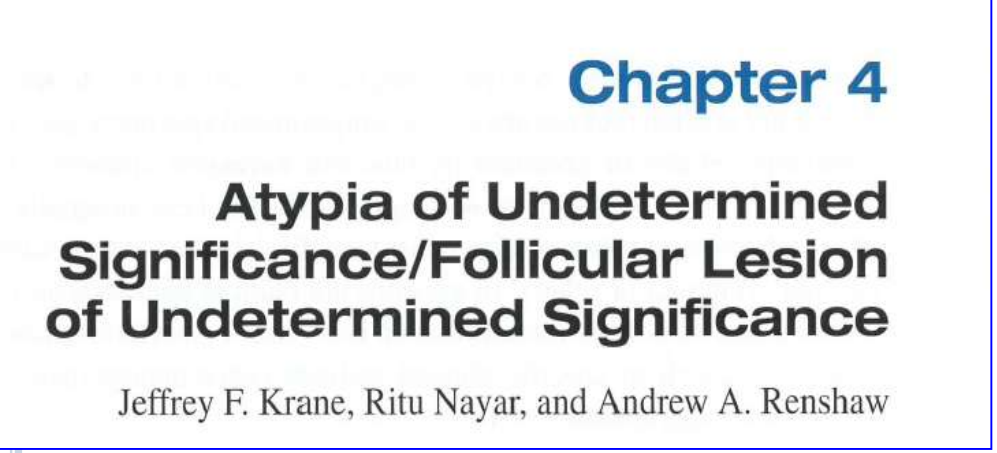






UK RCPath 2015	ITALY 2014	USA BETHESDA 2008	AUSTRALASIA CLASSIFICATION 2014	JAPAN THYROID ASSOCIATION 2013
DIAGNOSTIC CATEGORY	DIAGNOSTIC CATEGORY	TERMINOLOGY	CATEGORIES	TERMINOLOGY
Thy1/Thy1c Non-diagnostic for cytological diagnosis Unsatisfactory, consistent with cyst	TIR 1: Non-diagnostic TIR 1C: Cystic	I. Non-diagnostic	Non-diagnostic	Inadequate (non diagnostic)
Thy2/Thy2c Non-neoplastic, ben				Normal or benign
Thy 3a Neoplasm possible - present				Indeterminate A. Follicular Neoplasm • A1 favor benign • A2 border-line • A3 favor malignant B. Others (atypia in non-follicular patterned lesions)
Thy3f Neoplasm possible - follicular neoplasm				
Thy 4 Suspicious of malignancy	TIR 4: Suspicious of malignancy	V. Suspicious of malignancy	malignancy	Malignancy suspected
Thy5 Malignant	TIR 5: Malignant	VI. Malignant	Malignant	Malignancy

Indeterminate lesion or indeterminate pathologist??



"Indeterminate" or Grey Zone in Thyroid Cytopathology

Morphology and outcome differ from SFN/FNs and SMs

Not all Atypical Thyroid FNA's require surgical excision

Thyroid and atypia in TBSRTC

Reporting AUS/FLUS

AUS/FLUS both options to report this category

"Architectural" vs "Cytologic" atypia

Criteria (Describe 9 scenarios)

Recommended clarification of category

A narrative comment/ differential diagnosis

Avoid "buzz words" overlapping with SM or PM categories

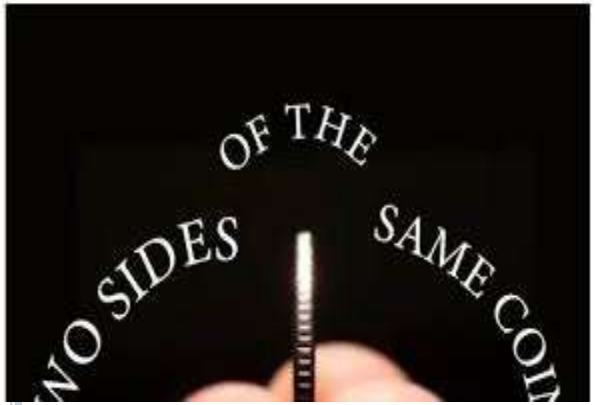
- **Recommended TBSRTC Rate**
  - Approx. 7% of all thyroid FNA

REPORTING RATES FOR TBSRTC CATEGORIES

Study	Total	Non-diagnostic I	Benign II (%)	AUS-FLUS III (%)	FN-SFN IV (%)	Suspicious V (%)	Malignant VI (%)
2	1382	278	539	376	116	36	37
		20.12%	39.00%	27.21%	8.39%	2.60%	2.68%
3	1000	56	671	8	172	24	69
		5.60%	67.10%	0.80%	17.20%	2.40%	6.90%
5	562	16	437	71	21	2	15
		2.85%	77.76%	12.63%	3.74%	0.36%	2.67%
6	3080	574	1817	104	298	71	216
		18.64%	58.99%	3.38%	9.68%	2.31%	7.01%
7	2468	230	1799	89	166	39	145
		9.32%	72.89%	3.61%	6.73%	1.58%	5.88%
8	442	36	223	25	35	42	81
		8.14%	50.45%	5.66%	7.92%	9.50%	18.33%
9	7089	1671	3829	548	606	134	301
		23.57%	54.01%	7.73%	8.55%	1.89%	4.25%
10	865	16	504	141	10	54	140
		1.85%	58.27%	16.30%	1.16%	6.24%	16.18%
11	3724	110	2064	248	886	224	192
		2.95%	55.42%	6.66%	23.79%	6.02%	5.16%
12	4703	488	3036	152	544	124	359
		10.38%	64.55%	3.23%	11.57%	2.64%	7.63%
13	3589	269	2361	144	328	314	173
		7.50%	65.78%	4.01%	9.14%	8.75%	4.82%
Total	28,904	3744	17,280	1906	3182	1064	1728
Mean		10.08%	60.39%	8.29%	9.80%	4.03%	7.41%

Overall ~ 8-10% seems to be the experience in labs with high volume experience

Which are the criteria used to diagnose an FNA as "AUS/FLUS?



AUS/FLUS

1. CYTOLOGIC ATYPIA

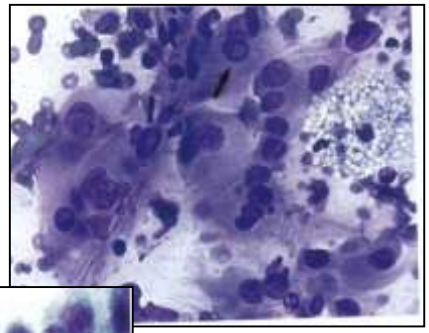
And/Or

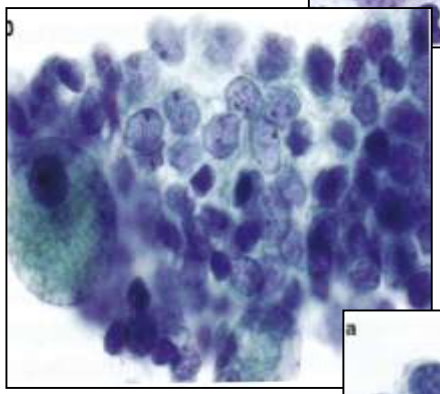
2. ARCHITECTURAL ATYPIA

Nuclear atypia in thyroid

Nuclear pleomorphism

- Nuclear enlargement
  - Hyperchromasia
  - Prominent nucleoli

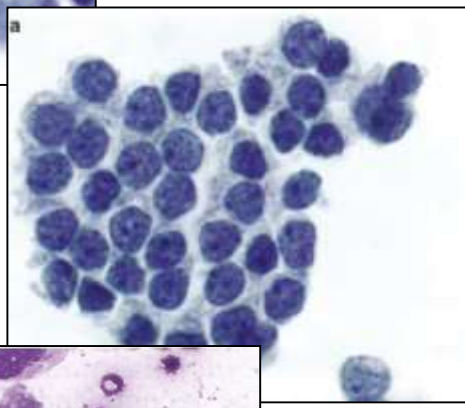




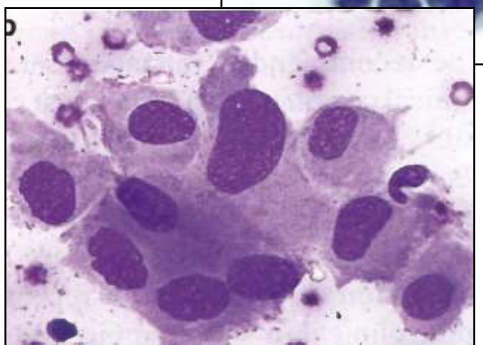
Nuclear Anaplasia

Changes in Nuclear Chromatin

- Reactive
- Neoplastic



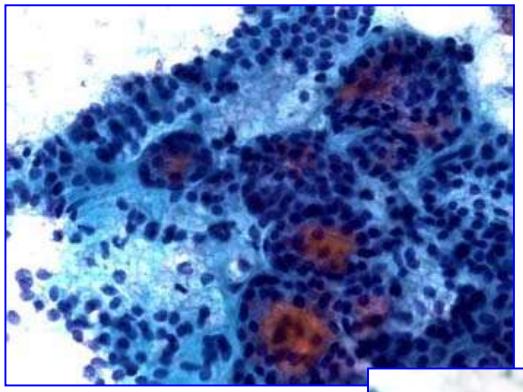
Nuclear atypia in benign thyroid lesions

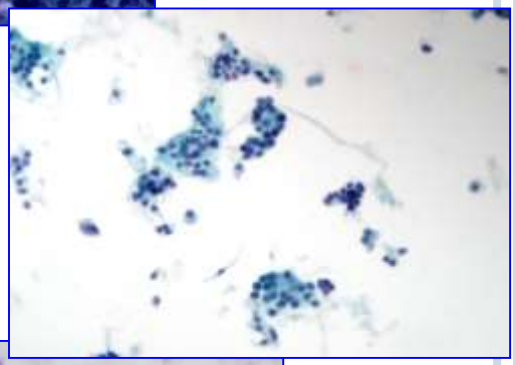


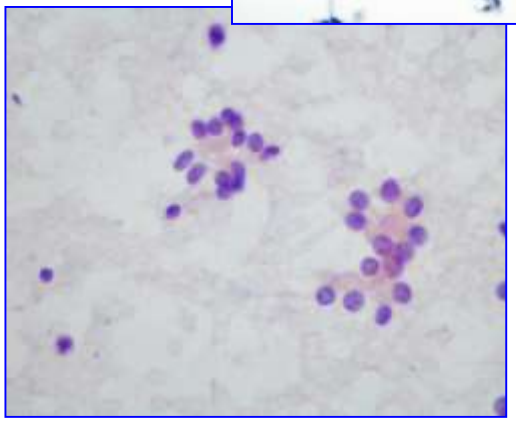
ARCHITECTURAL ATYPIA

Papillary Formations

Microfollicles







Am J Clin Pathol 2011; 136: 572-577

Usefulness of Diagnostic Qualifiers for Thyroid Fine-Needle Aspirations With Atypia of Undetermined Significance

Paul A. VanderLaan, MD, PhD,[1] Ellen Marqusee, MD,[2] and Jeffrey F. Krane, MD, PhD[1]

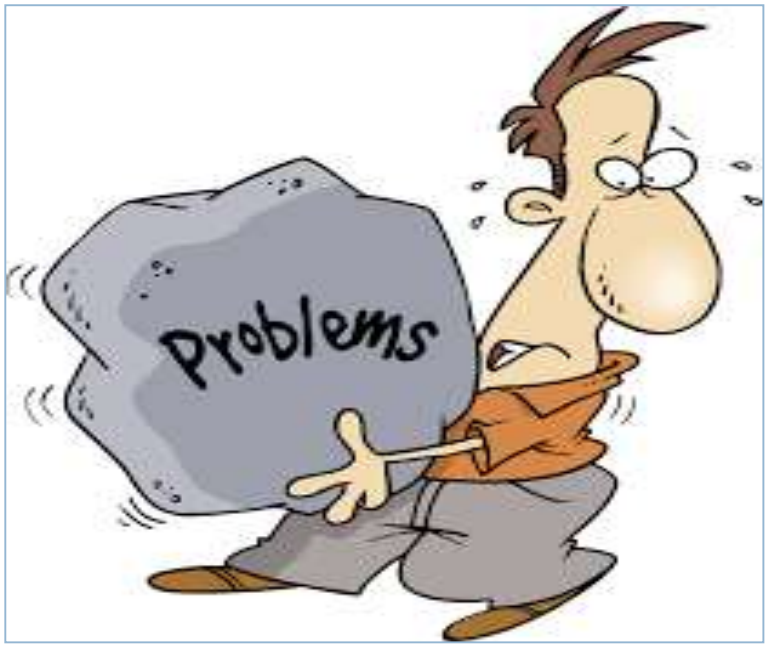
Table 2
Surgical Outcome Data for Atypia of Undetermined Significance in Thyroid Fine-Needle Aspirations Based on Atypia Qualifier*

Atypia Qualifier	Benign	Malignant	Total
Architectural	76 (34/45)	24 (11/45)	22.6 (45/199)
Cytologic	50 (17/34)	50 (17/34)†	17.1 (34/199)
Cytologic and architectural	54 (27/50)	46 (23/50)‡	25.1 (50/199)
Unspecified	36 (25/70)	64 (45/70)§	35.2 (70/199)
Total	51.6 (103/199)	48.2 (96/199)	100.0 (199/199)

* Data are given as percentage (number/total) of cases.
† Architectural atypia vs cytologic atypia, $P < .04$.
‡ Architectural atypia vs cytologic and architectural atypia, $P < .04$.
§ Architectural atypia vs atypia unspecified, $P = .0001$.

Architectural atypia: 24% risk of malignancy

Cytologic atypia: 50% risk of malignancy



How to manage AUS/FLUS lesion?

What to do with AUS/FLUS nodule?

Table 7. The Bethesda system for reporting thyroid cytopathology: Diagnostic categories and risk of malignancy[1]

Diagnostic category	Estimated/predicted risk of malignancy by the Bethesda system (%)[1]	Actual risk of malignancy in nodules surgically excised (%, median (range))[2]
Nondiagnostic or Unsatisfactory	1-4	20 (9-32)
Benign	0-3	2.5 (1-10)
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS)	5-15	14 (6-48)
Follicular Neoplasm or Suspicious for a Follicular Neoplasm (FN/SFN)	15-30	25 (14-34)
Suspicious for Malignancy (SUSP)	60-75	70 (53-97)
Malignant	97-99	99 (94-100)

[1]As reported in The Bethesda System by Ali &Cibas, 2009 (1076)

[2]Based on the meta-analysis of 8 studies reported by Bongiovanni et al. (103). The risk was calculated based on the portion of nodules in each diagnostic category that underwent surgical excision and likely is not representative of the entire population, particularly of non-diagnostic and benign diagnostic categories.

ATA guidelines 2015

MANAGEMENT -AUS/FLUS

1. **Repeat FNA**
   - is a suitable follow-up option in ATA 2015
   - limited cellularity contributes to the initial AUS/FLUS interpretation
   - Need clinical correlation (US findings, TSH/antibody titer correlation, etc.)

2. **Surgery**
   - Generally discouraged for initial AUS/FLUS
   - Reasonable option for second AUS

3. **Molecular testing**
   - Acceptable consideration for AUS/FLUS
   - Reflexive molecular testing is not mandated for all AUS/FLUS

ATA 2015- All clinical, radiologic, pathologic, and molecular findings must be integrated for the most informed, accurate, and individualized assessment

THE CHALLENGE

THYROID
Volume 25, Number 7, 2015

DOI: 10.1089/thy.2014.0502

American Thyroid Association Statement on Surgical Application of Molecular Profiling for Thyroid Nodules: Current Impact on Perioperative Decision Making

Robert L. Ferris,[1] Zubair Baloch,[2] Victor Bernet,[3] Amy Chen,[4] Thomas J. Fahey III,[5] Ian Ganly,[6] Steven P. Hodak,[7] Electron Kebebew,[8] Kepal N. Patel,[9] Ashok Shaha,[6] David L. Steward,[10] Ralph P. Tufano,[11] Sam M. Wiseman,[12] and Sally E. Carty[13]

for the American Thyroid Association Surgical Affairs Committee

TABLE 1. ESTIMATED LIKELIHOOD OF MALIGNANCY IN A THYROID NODULE WITH INDETERMINATE CYTOLOGY AND RECOMMENDED MANAGEMENT

Bethesda cytologic category	*Ancillary testing*		*Estimated[a] risk of malignancy; range (median)*	*Recommendation*
III (AUS/FLUS)	None		6–48% (14%)	Repeat FNA, ancillary testing, or diagnostic lobectomy
	GEC[b] (reported prevalence 24%)	Suspicious	38%	Diagnostic lobectomy
		Benign	5%	Active surveillance
	7-gene MT[c] (reported prevalence 14%)	Positive	88%	Oncologic thyroidectomy
		Negative	6%	Active surveillance or diagnostic lobectomy
IV (FN/FL)	None		14–34% (25%)	Ancillary testing or diagnostic lobectomy
	GEC[b] (reported prevalence 25%)	Suspicious	37%	Diagnostic lobectomy
		Benign	6%	Active surveillance
	7-gene MT[c] (reported prevalence 27%)	Positive	87%	Oncologic thyroidectomy
		Negative	14%	Diagnostic lobectomy
	ThyroSeq2.0 panel[d] (reported prevalence 27%)	Positive	87%	Oncologic thyroidectomy
		Negative	5%	Observation
V (SMC)	None		53–87% (70%)	Ancillary testing or oncologic thyroidectomy
	GEC[b] (reported prevalence 62%)	Suspicious	76%	Oncologic thyroidectomy
		Benign	15%	Diagnostic lobectomy
	7-gene MT[c] (reported prevalence 54%)	Positive	95%	Oncologic thyroidectomy
		Negative	28%	Diagnostic lobectomy

WHAT'S AGAIN?????

MEDICAL CONDITIONS

It's Not Cancer: Doctors Reclassify a Thyroid Tumor

Changes in Histopathology Nomenclature

JAMA Oncology

Home Current Issue All Issues Online First Collections CME Multimedia

Online First >

Original Investigation | April 14, 2016

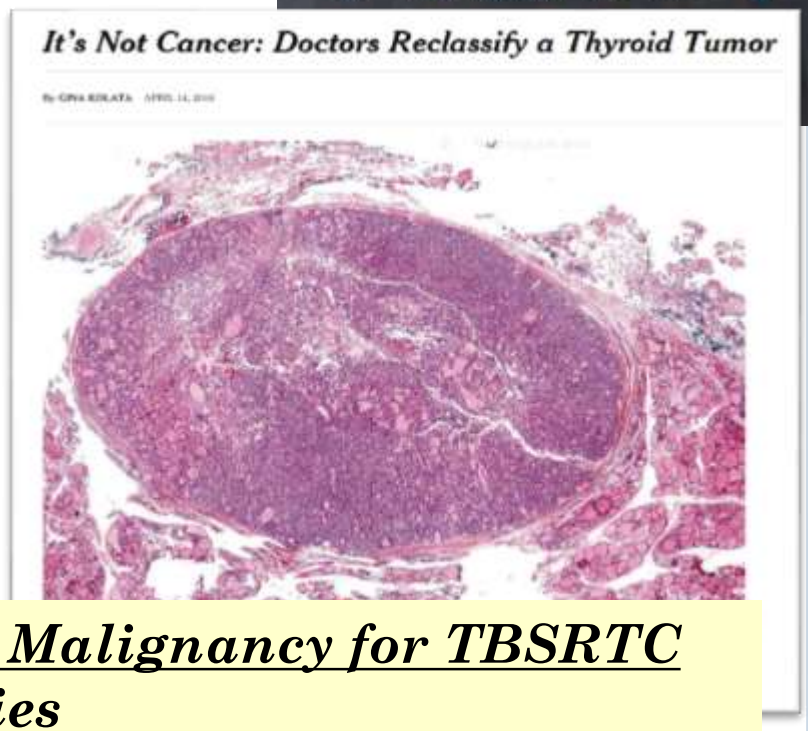
Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma

A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

OPEN ACCESS ONLINE FIRST

Yun E. Nikiforov, MD, PhD; Raja R. Seethala, MD; Giovanni Tallini, MD; Zubair W. Baloch, MD, PhD; Fulvio Basolo, MD; Lester D. R. Thompson, MD; Justina A. Barletta, MD; Bruce M. Wenig, MD; Abir Al Ghuzlan, MD; Kennichi Kakudo, MD, PhD; Thomas J. Giordano, MD, PhD; Venancio A. Alves, MD, PhD; Ehsan Khanafshar, MD, MS; Sylvia L. Asa, MD, PhD; Adel K. El-Naggar, MD, PhD; William E. Gooding, MS; Steven P. Hodak, MD; Ricardo V. Lloyd, MD, PhD; Guy Maytal, MD; Ozgur Mete, MD; Marina N. Nikiforova, MD; Vania Nosé, MD, PhD; Mauro Papotti, MD; David N. Poller, MB, ChB, MD, FRCPath; Peter M. Sadow, MD, PhD; Arthur S. Tischler, MD; R. Michael Tuttle, MD; Kathryn B. Wall; Virginia A. LiVolsi, MD; Gregory W. Randolph, MD; Ronald A. Ghossein, MD

[+] Author Affiliations



It's Not Cancer: Doctors Reclassify a Thyroid Tumor

By GINA KOLATA APRIL 14, 2016

Changes in the Implied Risk of Malignancy for TBSRTC Categories

AUS/FLUS

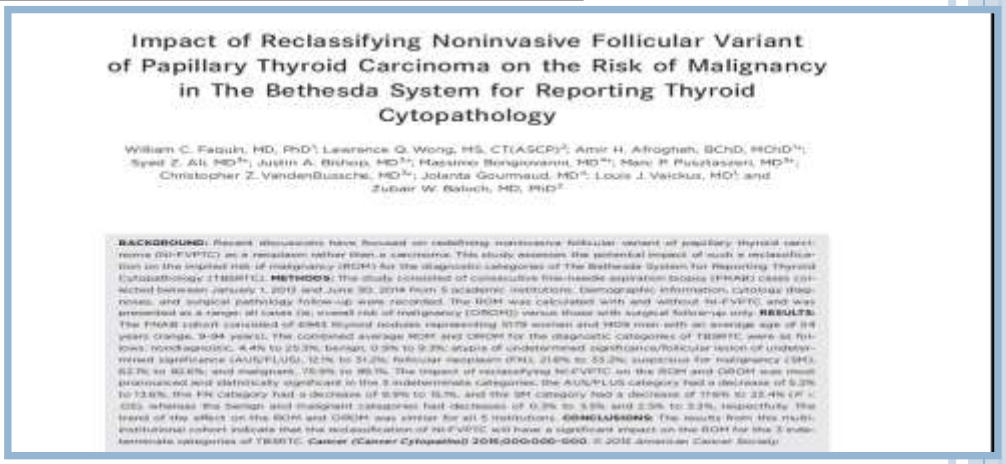
Suspicious for Follicular Neoplasm

Suspicious for Malignancy – 50% decrease

(Strickland et al. Thyroid 2015 & Faquin et al. Cancer Cytopathology 2015)

Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP)

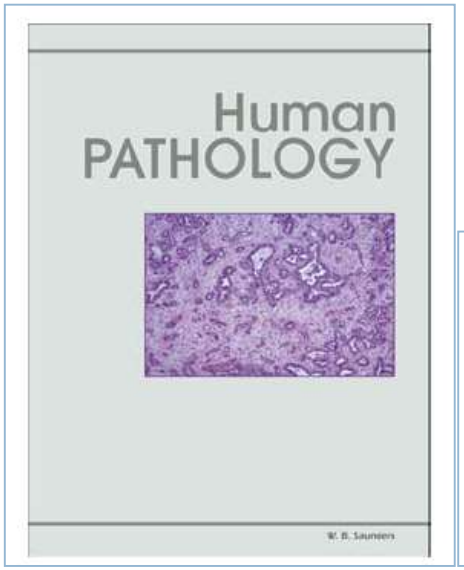
Cancer Cytopathology, 2015.



Impact of Reclassifying Noninvasive Follicular Variant of Papillary Thyroid Carcinoma on the Risk of Malignancy in The Bethesda System for Reporting Thyroid Cytopathology

William C. Faquin, MD, PhD[1]; Lawrence Q. Wong, MS, CT(ASCP)[2]; Amir H. Afroghteh, BChD, MOND[3]; Syed Z. Ali, MD[3]; Justin A. Bishop, MD[3]; Massimo Bongiovanni, MD[4]; Marc P. Pusztaszeri, MD[5]; Christopher Z. VandenBussche, MD[3]; Jolanta Gourmaud, MD[6]; Louis J. Vaickus, MD[1]; and Zubair W. Baloch, MD, PhD[7]

BACKGROUND: Recent discussions have focused on redefining noninvasive follicular variant of papillary thyroid carcinoma (NI-FVPTC) as a neoplasm rather than a carcinoma. This study assesses the potential impact of such a reclassification on the implied risk of malignancy (ROM) for the diagnostic categories of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). **METHODS:** The study consisted of consecutive fine-needle aspiration biopsy (FNAB) cases collected between January 1, 2010 and June 30, 2014 from 5 academic institutions. Demographic information, cytology diagnoses, and surgical pathology follow-up were recorded. The ROM was calculated with and without NI-FVPTC and was presented as a range: all cases (ie, overall risk of malignancy [OROM]) versus those with surgical follow-up only. **RESULTS:** The FNAB cohort consisted of 6941 thyroid nodules representing 5179 women and 1809 men with an average age of 54 years (range, 9-94 years). The combined average ROM and OROM for the diagnostic categories of TBSRTC were as follows: nondiagnostic, 4.4% to 25.3%; benign, 0.9% to 9.3%; atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), 12% to 31.2%; follicular neoplasm (FN), 21.6% to 55.2%; suspicious for malignancy (SM), 62.7% to 80.6%; and malignant, 76.9% to 96.1%. The impact of reclassifying NI-FVPTC on the ROM and OROM was most pronounced and statistically significant in the 6 indeterminate categories; the AUS/FLUS category had a decrease of 9.3% to 13.6%, the FN category had a decrease of 9.9% to 15.1%, and the SM category had a decrease of 19.6% to 22.4% (*P* < .05), whereas the benign and malignant categories had decreases of 0.3% to 3.5% and 2.5% to 3.3%, respectively. The trend of the effect on the ROM and OROM was similar for all 5 institutions. **CONCLUSIONS:** The results from this multi-institutional cohort indicate that the reclassification of NI-FVPTC will have a significant impact on the ROM for the 3 indeterminate categories of TBSRTC. *Cancer (Cancer Cytopathol)* 2015;000:000–000. © 2015 American Cancer Society.



Cytological features of "non-invasive follicular thyroid neoplasm with papillary-like nuclear features" and their correlation with tumor histology

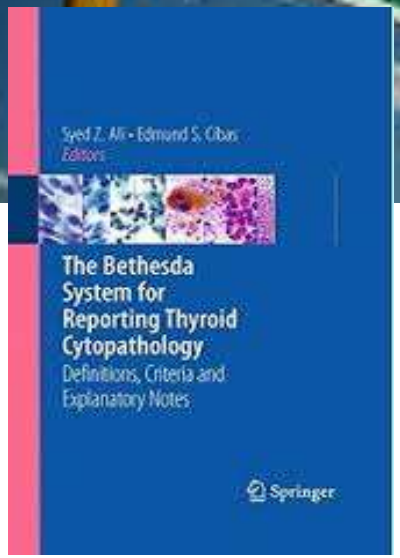
Francesca Maletta MD, Federica Massa MD, Liborio Torregrossa MD, PhD, Eleonora Duregon MD, PhD, Gian Piero Casadei MD, Fulvio Basolo MD, Giovanni Tallini MD, Marco Volante MD, PhD, Yuri E. Nikiforov MD, PhD, Mauro Papotti MD

The Impact of Non-Invasive Follicular Variant of Papillary Thyroid Carcinoma on Rates of Malignancy for Fine Needle Aspiration Diagnostic Categories

Kyle C. Strickland[1], Brooke E. Howitt[1], Ellen Marqusee[2], Erik K. Alexander[2], Edmund S. Cibas[1], Jeffrey F. Krane[1], and Justine A. Barletta[1]


Here & Now


Future
Just Ahead


Syed Z. Ali · Edmond S. Cibas
Editors
The Bethesda System for Reporting Thyroid Cytopathology
Definitions, Criteria and Explanatory Notes
Springer

The Bethesda System for Reporting Thyroid Cytopathology: proposed modifications and updates for the second edition from an international panel

- **The panel endorses AUS/FLUS**
- **Widely accepted and included in ATA 2015**
- **Only one term would be selected by a laboratory**

Recommendations for subclassifying AUS/FLUS

(importance of nuclear atypia)

The Bethesda System for Reporting Thyroid Cytopathology: proposed modifications and updates for the second edition from an international panel

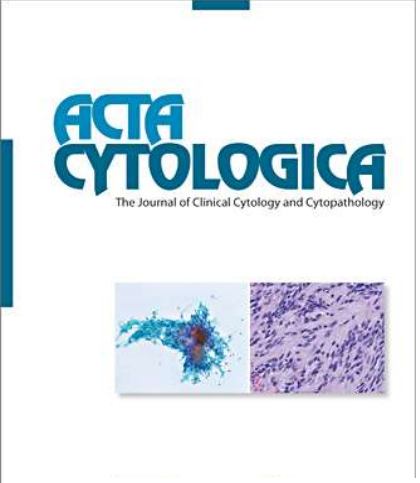
- **Common patterns include:**
  - **Architectural Atypia**
  - **Nuclear atypia**
  - **Oncocytic features**

Compromised samples lacking any Atypia should be classified as ND

FOLLICULAR NEOPLASMS/SUSPICIOUS FOR FOLLICULAR NEOPLASM

- **The panel favors the use of one term**
- **Widely accepted and included in ATA 2015**
- **Only one term would be selected by a laboratory**

Current diagnostic criteria could be further defined



The Bethesda System for Reporting Thyroid Cytopathology: proposed modifications and updates for the second edition from an international panel

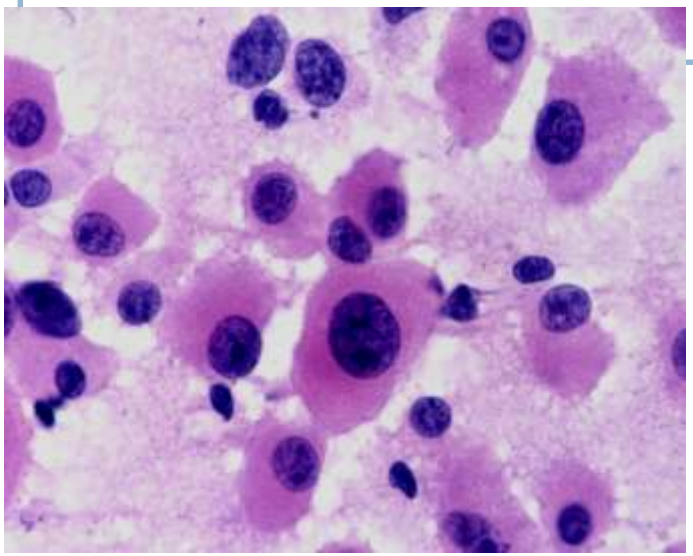
Due to NIFTPs, a follicular patterned lesion with nuclear atypia can be classified as FN rather than SM

Long-established standard of care is diagnostic surgical excision

ATA 2015 guidelines provide the option of molecular testing

Follicular Neoplasm, Hurthle Cell Type/ Suspicious for a Follicular Neoplasm, Hurthle Cell Type

- **Panel Recommendations:**
  - **Two names not ideal but accepted due to current use**
  - **Use of term “oncocytic” rather than “Hurthle cell” is preferred to coordinate with WHO terminology**

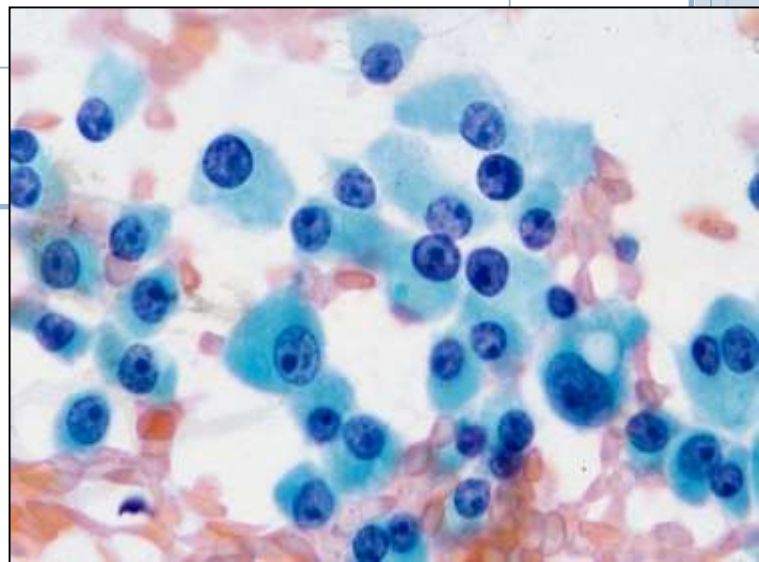


Follicular Neoplasm, Hurthle Cell Type/ Suspicious for a Follicular Neoplasm, Hurthle Cell Type

- **Panel Recommendations:**
  - **Rare cases reported containing abundant colloid**

Can abundant colloid exclude oncocytic (Hürthle cell) carcinoma in thyroid fine needle aspiration? Cytohistological correlation of 127 oncocytic (Hürthle cell) lesions.

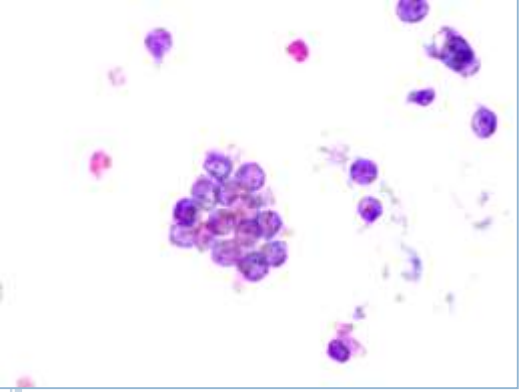
Yang GC[1], Schreiner AM, Sun W. Cytopathology, 2013 Jun;24(3):185-93



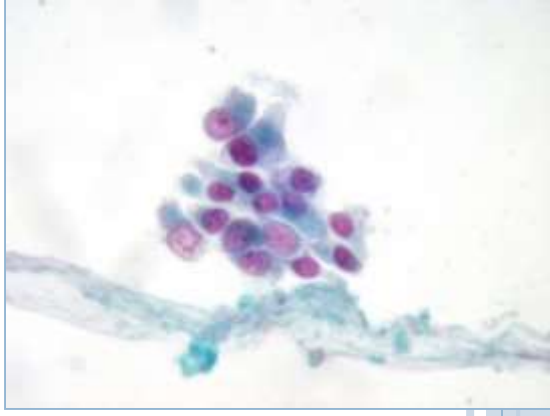
Follicular Neoplasm, Hurthle Cell Type/ Suspicious for a Follicular Neoplasm, Hurthle Cell Type

- **Panel Recommendations:**
  - **Molecular testing using Afirma may overestimate the ROM in aspirates of Hurthle cell neoplasms and lead to overtreatment**

Performance of the Afirma Gene Expression Classifier
in Hurthle Cell Thyroid Nodules Differs
from Other Indeterminate Thyroid Nodules
Eran Brauner,1,* Brittany J. Holmes,2,* Jeffrey F. Krane,3
Michiya Nishino,4 David Zurakowski,5James V. Hennessey,6
William C. Faquin,2,* and Sareh Parangi1,*



SUSPICIOUS FOR MALIGNANCY

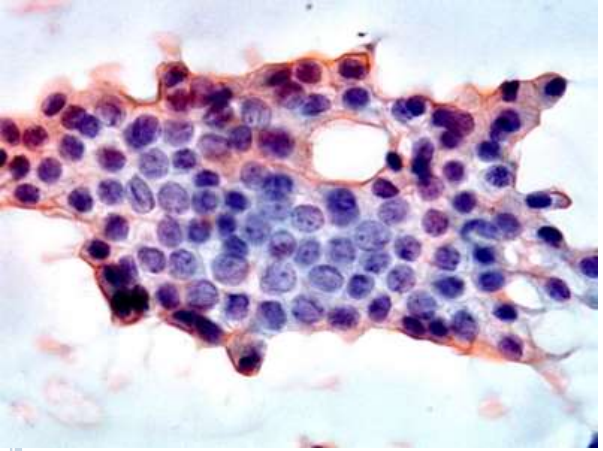


The group did not have major issues with this category, however, the following are suggested as footnote explanations and comments

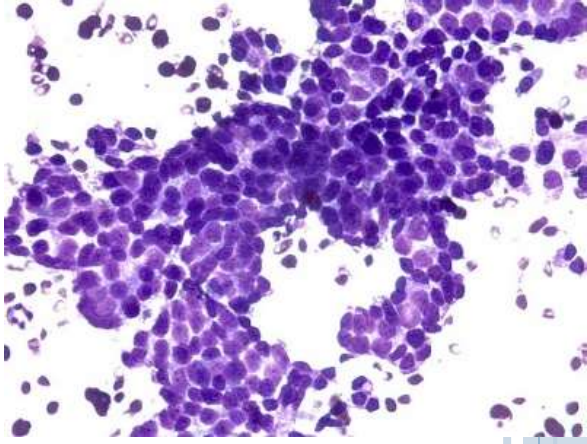
A major proportion of cases (>50%) classified as “SFM” are found to be follicular variant of PTC

The change in terminology of the encapsulated PTC to “Non-invasive Follicular Tumor with Papillary-like Nuclei (NIFT-P)” will cause a change in the absolute ROM

Several differential diagnoses



Suspicious For Malignancy:



- **Molecular testing:**

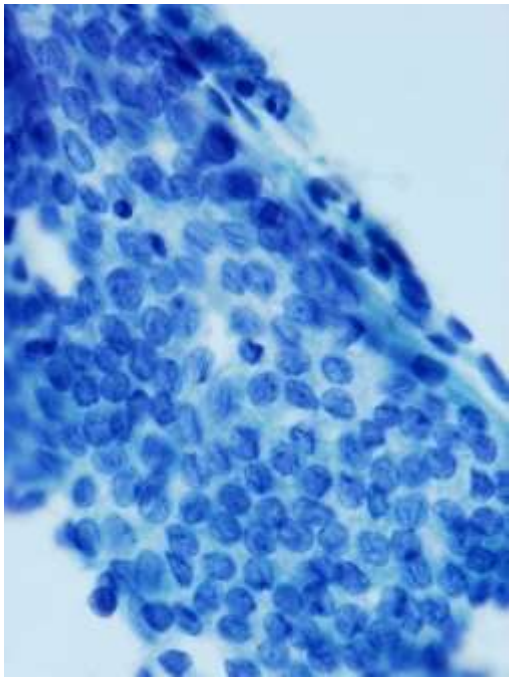
Utility of molecular testing using panels with high positive predictive value have future relevance for NIFTP (e.g. RAS vs BRAFV600E), and may be useful for management

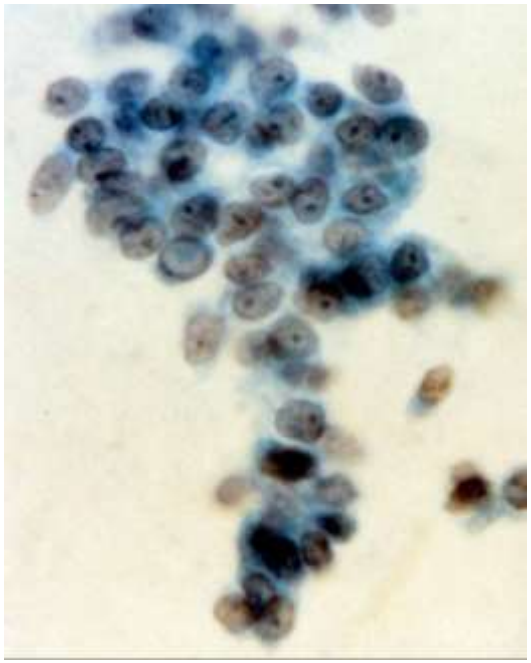
- **Liquid based preparations:**

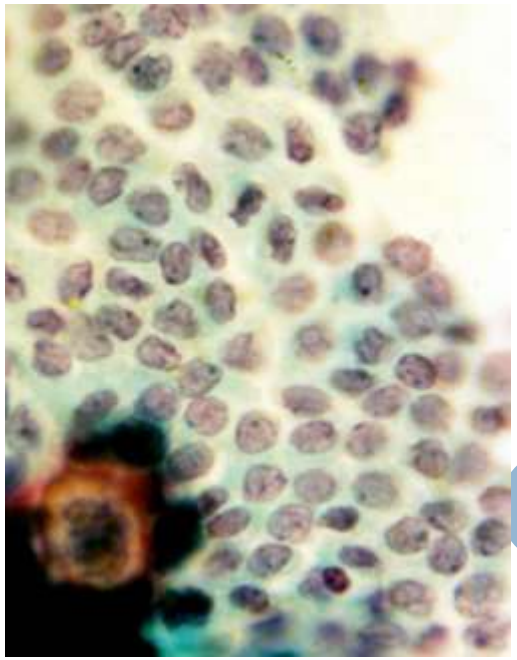
Differences in cytological features of PTC between conventional versus liquid-based preparations should be addressed

Update on PTC

- In general, essential diagnostic criteria for all types of PTC, conventional and variants, remain the same
  - only minor fine-tuning and wording







Update on PTC

- Key proposed modifications relate to
  - Liquid-based cytology (LBC)
  - PTC variants
  - Follicular variant PTC (FVPTC)
  - Hyalinizing trabecular tumor

PTC VARIANTS

- Since the implementation of TBSRTC in 2008, several PTC variants have been better characterized
  - histologically,
  - cytologically, and
  - molecularly
- Deserve more descriptions and illustrations

PDC
Key Issues for TBSRTC

- **An oncocytic variant of PDTC has also been described and mentioned in the new WHO classification of thyroid tumors**

- **The presence of Hürthle cells does not exclude a diagnosis of PDTC**

miR-150 and miR-23b differently expressed in WDTC vs PDTC

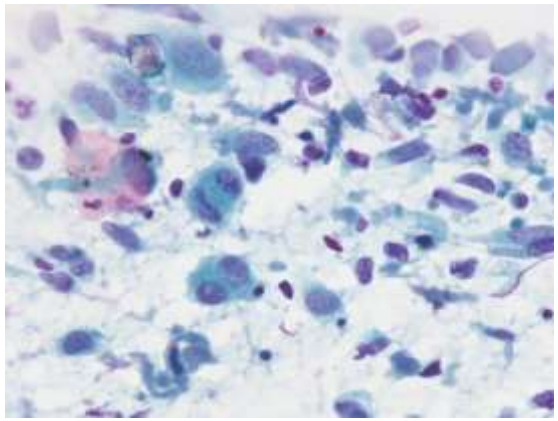
- **TERT promoter mutations are highly prevalent in advanced cancers.**

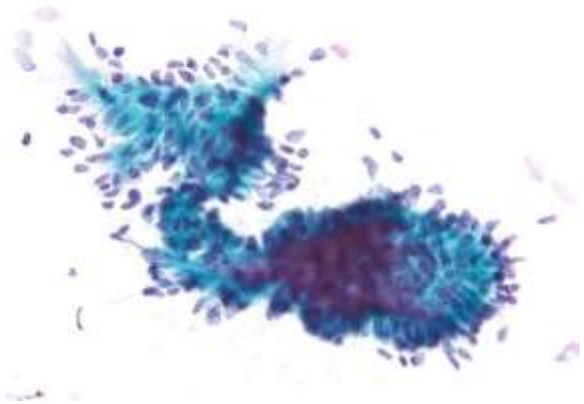
Undifferentiated Carcinoma
Key Issues for TBSRTC

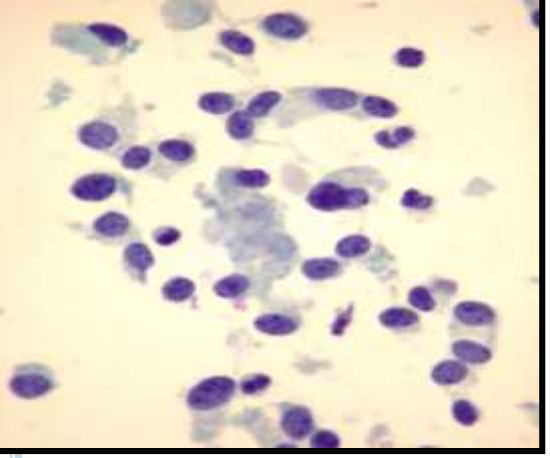
- **No major issues were suggested for this category.**

- **Molecular:**
  - **High rates of MAPK mutations, p53 mutations, and TERT mutations.**

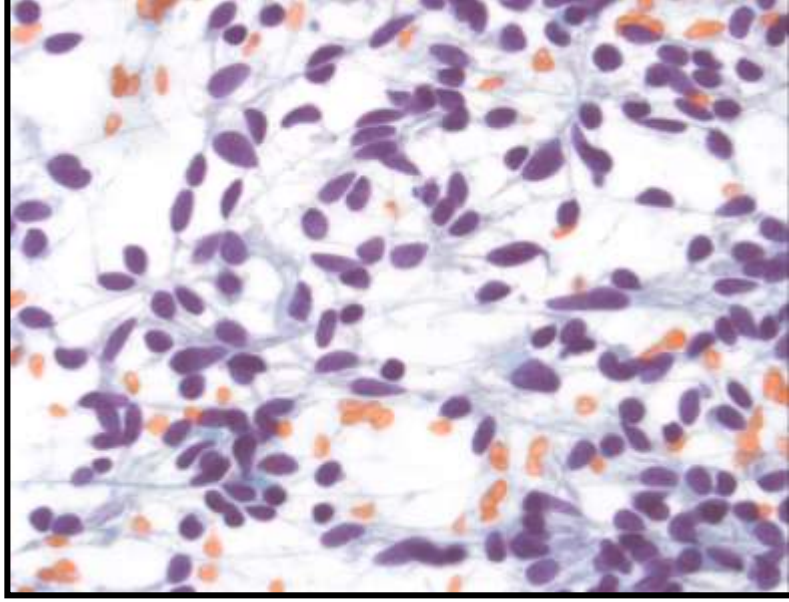
- **Immunohistochemistry:**
  - **PAX8 is usually retained in UTC while TTF-1 and thyroglobulin are usually negative.**



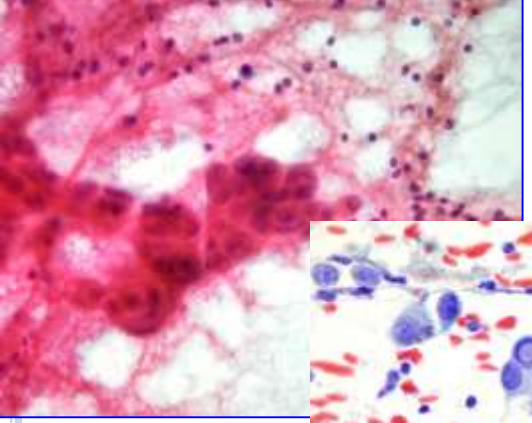


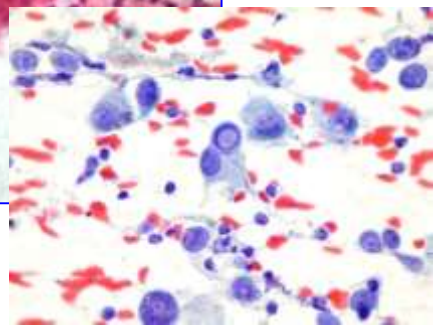


MTC



- No major changes
- 2015 ATA guidelines defined that calcitonin levels can be helpful (blood and FNA washout fluid)
- Rare morphological variants
- Overlaps with OFN, PDTC, neuroendocrine tumors
- Update from the 2015 ATA guidelines for management





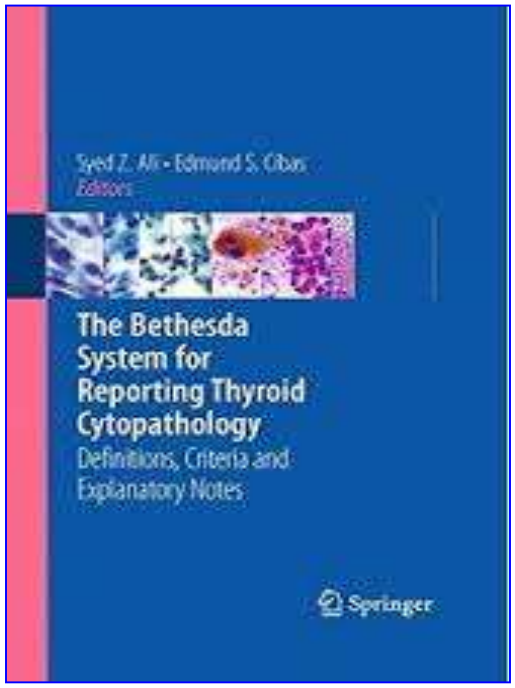
Metastatic Tumors Background

0.16% prevalence of all aspirated nodules

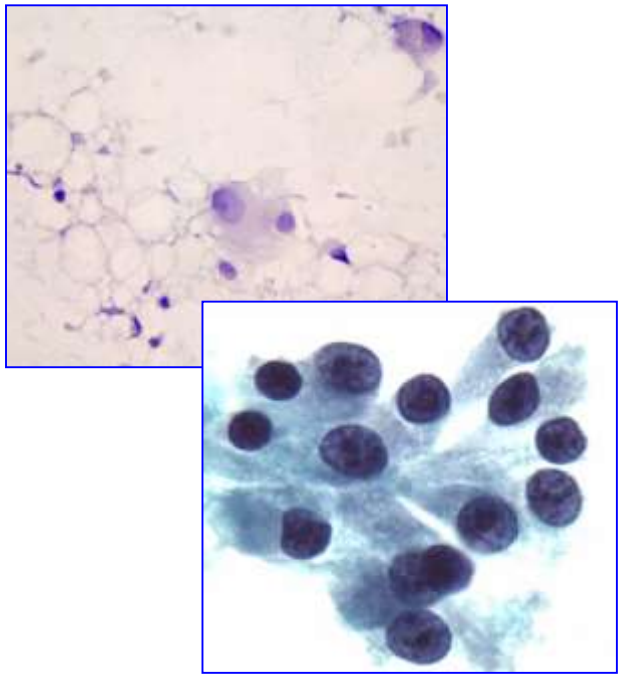
1.4 to 3% of all patients with surgical removed nodules

20-40% of cases with synchronous primary tumor

Most common malignancies : RCC (48.1%)
Colon-rectal Ca (10.4%)
Lung Ca (8.3%)
Breast Ca (7.8%)
Sarcoma (4%)



Diagnosis of Metastatic Tumors

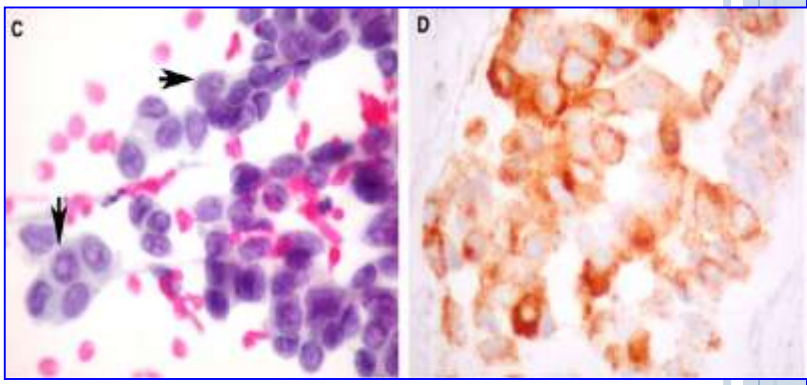


TBSRTC defines the criteria and explanatory notes for some metastatic tumors including:

- RCC
- Melanoma
- Breast Ca
- Lung Ca
- Other malignancies highlighted in the ATLAS pictures

DIAGNOSTIC CRITERIA FOR METS

- Moderately-highly cellular samples
- Single cell, small clusters, fragmented papillae, sheets
- Variable cellular size and shape
- Mostly depending on the primary tumor



Fine-Needle Aspiration Biopsy of Secondary Neoplasms of the Thyroid Gland: A Multi-Institutional Study of 62 Cases

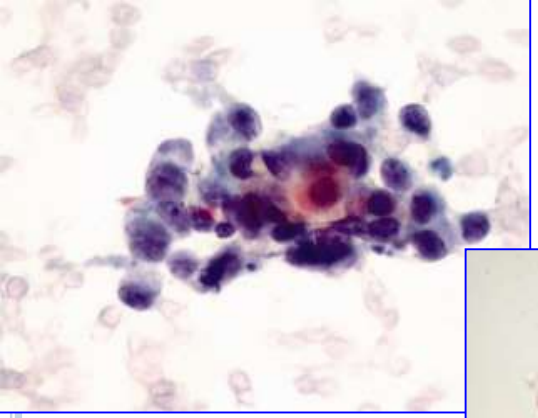
Marc Pusztaszeri, MD[1]; He Wang, MD, PhD[2]; Edmund S. Cibas, MD[3,4]; Celeste N. Powe
Massimo Bongiovanni, MD[6]; Syed Ali, MD[7]; Kamal K. Khurana, MD[8]; Paul J. Micha
and William C. Faquin, MD, PhD[4,9]

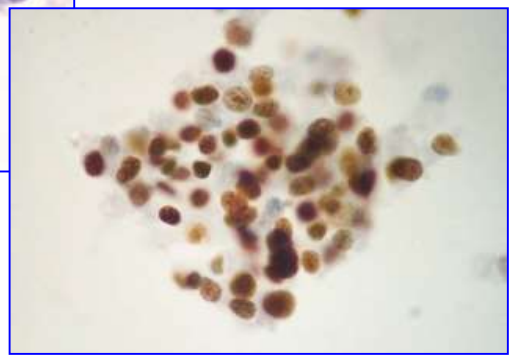
Adenocarcinomas from the kidney, lung, breast, and colon along with SCCs represent the majority of SNTGs. The current results indicate that FNAB is a sensitive and accurate method for diagnosing SNTG; however, diagnostic difficulties can occur. Knowledge of clinical history and the judicious application of ancillary studies can increase the sensitivity and accuracy of FNAB for detecting SNTGs. *Cancer (Cancer Cytopathol)* 2015;123:19-29. © *2014 American Cancer Society.*

Is Thyroid Gland Only a "Land" for Primary Malignancies? Role of Morphology and Immunocytochemistry

Esther Diana Rossi, M.D., Ph.D., M.I.A.C.,[1*] Maurizio Ma
Patrizia Straccia, B.D.,[1] Rene Gerhard, M.D.,[2,3] Antone
Alfredo Pontecorvi, M.D. Ph.D.,[4] Guido Fadda, M.D., M.I
Luigi Maria Larocca, M.D., Ph.D.,[1]
and Fernando Schmitt, M.D., Ph.D., F.I.A.C.[2,3]

Conclusions: *FNAC empowered the diagnostic workup of patients with TM avoiding useless surgical approach. The low sensitivity of cytology might be reinforced by the application of ancillary techniques.*



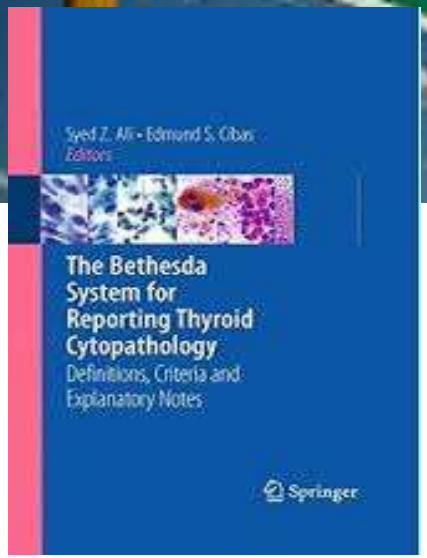


How much reliable is FNA for METs?

- Chung et al found 73.7% correct metastatic diagnoses
- Pusztaszeri M et al 87% correct secondary neoplasms
- Hegerova et al misdagnosed 6% as FNs or PTCs
- Rossi et al reported 100% correct diagnoses with the support of ancillary techniques


Here & Now


Future
Just Ahead


Syed Z. Ali • Edmund S. Cibas
Editors
The Bethesda System for Reporting Thyroid Cytopathology
Definitions, Criteria and Explanatory Notes
Springer


SUGGESTION BOX

Few suggestions for Chapter of metastatic lesions

- Extend to few other neoplasms (i.e metastatic neuroendocrine tumors)
- Some explanatory notes for other cytological preparations (LBC)
- Role of ancillary techniques (expanded array of markers: e.g. PAX-8 and GATA-3 and others)
- Distinction Between Primary Thyroid neoplasms (UTC) and Metastases
- Management section

LYMPHOMA

Primary (less frequent) or secondary malignancy (more frequent)

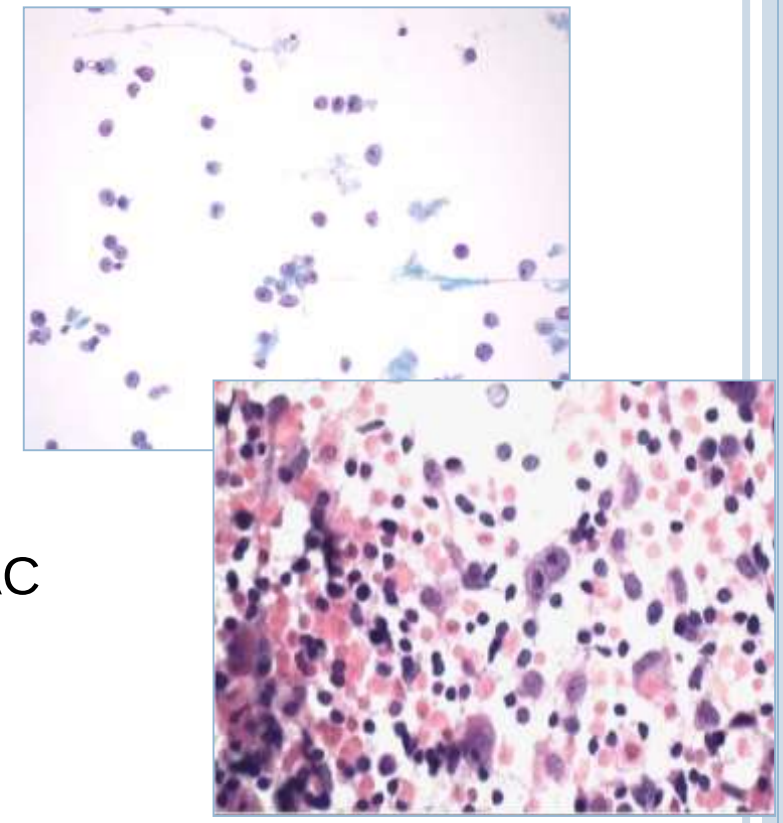
Mostly non-Hodgkin lymphomas (NHL) of B-cell phenotype (98%)

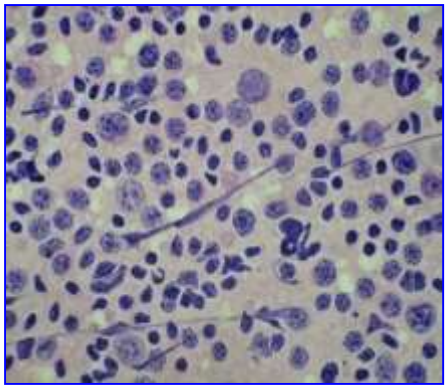
Two thirds preceded by HT

Most of them: Diffuse large B cell Lymphoma

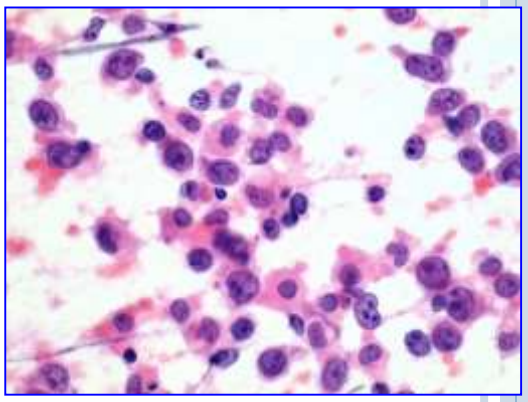
MALT

Three Different pattern of lymphomas on FNAC





TBSRTC FOR LYMPHOMA



CURRENT TBSRTC VERSION

- Definition of Lymphoma
- Explanatory notes
- Sample Reports

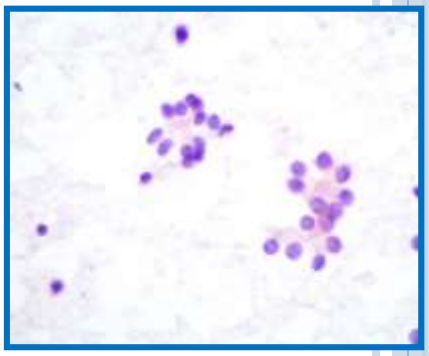
POSSIBLE TBSRTC REVISION

- No major issues for this category

Few additional explanatory notes for Ancillary techniques

Section on management

MOLECULAR MODELS



ORIGINAL ARTICLE

Endocrine Care

Molecular Testing for Mutations in Improving the Fine-Needle Aspiration Diagnosis of Thyroid Nodules

Yuri E. Nikiforov, D
Joshua P. Klopper,
and Marina N. Nik

ORIGINAL ARTICLE

Endocrine Care

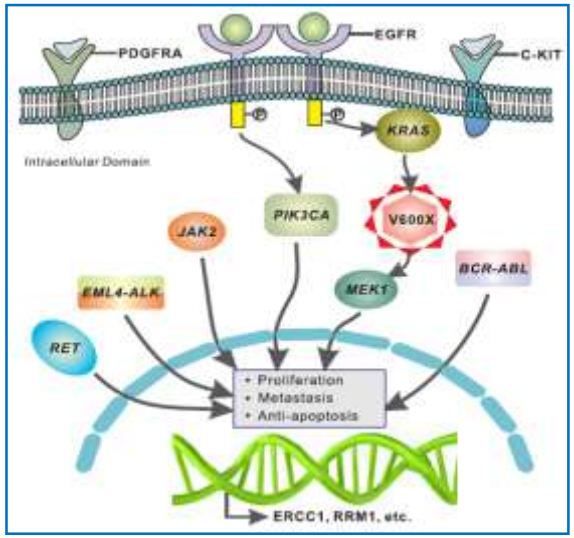
Impact of Mutational Testing on the Diagnosis and Management of Patients with Cytologically Indeterminate Thyroid Nodules: A Prospective Analysis of 1056 FNA Samples

Yuri E. Nikiforov, N. Paul Ohori, Steven P. Hodak, Sally E. Carty,

Original Article

Contribution of Molecular Testing to Thyroid Fine-Needle Aspiration Cytology of "Follicular Lesion of Undetermined Significance/Atypia of Undetermined Significance"

N. Paul Ohori, MD[1]; Marina N. Nikiforova
Raja R. Seethala, MD[1]; Sally E. Carty, MD



Journal of Surgical Oncology 2012;105:438–443

REVIEW ARTICLES

The Quest for Diagnostic Molecular Markers for Thyroid Nodules With Indeterminate or Suspicious Cytology

GUENNADI KOUNIAVSKY, MD,[1,2] AND MARTHA A. ZEIGER, MD[1,3,4]

[1]Division of Endocrine Surgery, Department of Surgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland
[2]Department of Surgery, Sheba Medical Center, Tel Hashomer, Israel
[3]Department of Oncology, The Johns Hopkins University School of Medicine, Baltimore, Maryland
[4]Department of Cellular and Molecular Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland

ROLE OF MOLECULAR ANALYSIS

Molecular Analysis

DIAGNOSIS OF CARCINOMA

Risk stratification

Personalized management

DX: BENIGN/INDETERMINATE

DX: MALIGNANT NEOPLASM

PROGNOSTIC PARAMETERS

THYROID
Volume 25, Number 7, 2015
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DOI: 10.1089/thy.2014.0502

American Thyroid Association Statement on Surgical Application of Molecular Profiling for Thyroid Nodules: Current Impact on Perioperative Decision Making

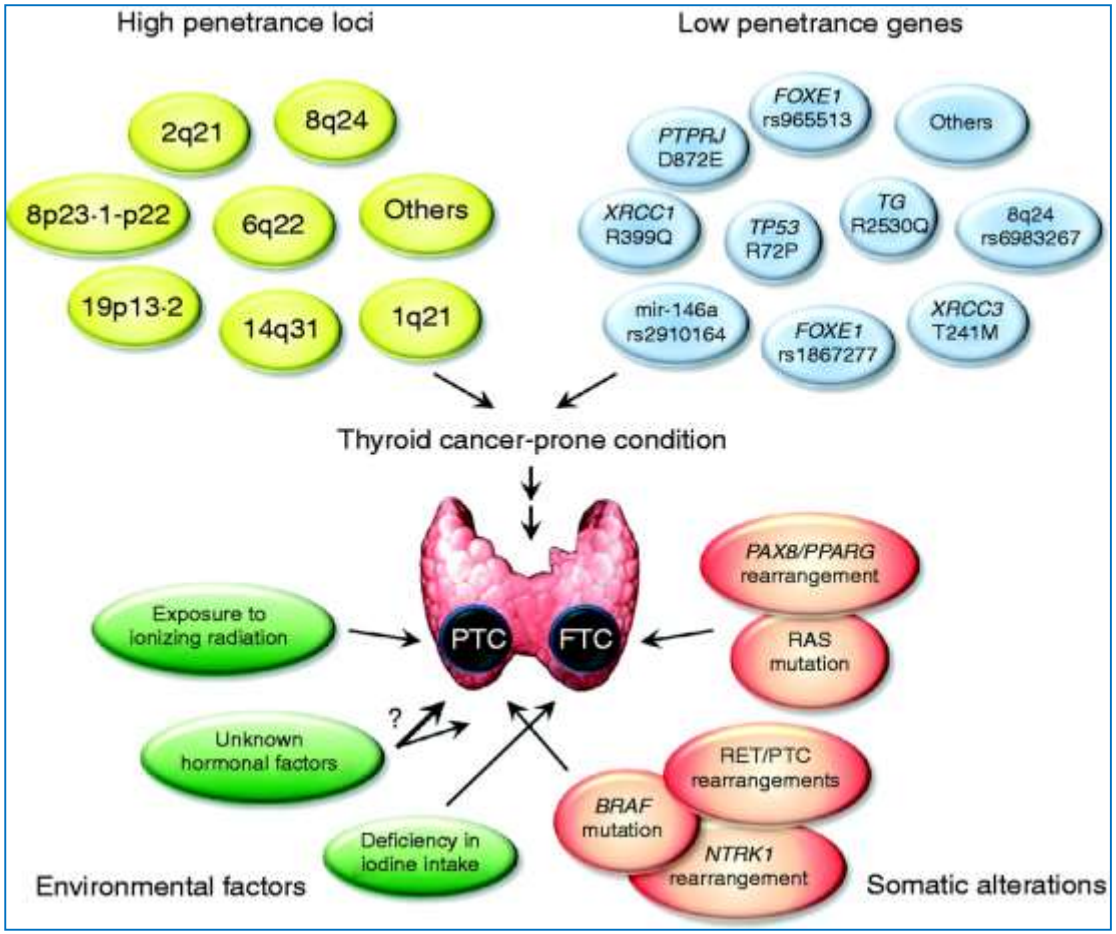
Robert L. Ferris,[1] Zubair Baloch,[2] Victor Bernet,[3] Amy Chen,[4] Thomas J. Fahey III,[5] Ian Ganly,[6] Steven P. Hodak,[7] Electron Kebebew,[8] Kepal N. Patel,[9] Ashok Shaha,[6] David L. Steward,[10] Ralph P. Tufano,[11] Sam M. Wiseman,[12] and Sally E. Carty[13]

for the American Thyroid Association Surgical Affairs Committee

TABLE 1. ESTIMATED LIKELIHOOD OF MALIGNANCY IN A THYROID NODULE WITH INDETERMINATE CYTOLOGY AND RECOMMENDED MANAGEMENT

Bethesda cytologic category	*Ancillary testing*		*Estimated[a] risk of malignancy; range (median)*	*Recommendation*
III (AUS/FLUS)	None		6–48% (14%)	Repeat FNA, ancillary testing, or diagnostic lobectomy
	GEC[b] (reported prevalence 24%)	Suspicious	38%	Diagnostic lobectomy
		Benign	5%	Active surveillance
	7-gene MT[c] (reported prevalence 14%)	Positive	88%	Oncologic thyroidectomy
		Negative	6%	Active surveillance or diagnostic lobectomy
IV (FN/FL)	None		14–34% (25%)	Ancillary testing or diagnostic lobectomy
	GEC[b] (reported prevalence 25%)	Suspicious	37%	Diagnostic lobectomy
		Benign	6%	Active surveillance
	7-gene MT[c] (reported prevalence 27%)	Positive	87%	Oncologic thyroidectomy
		Negative	14%	Diagnostic lobectomy
	ThyroSeq2.0 panel[d] (reported prevalence 27%)	Positive	87%	Oncologic thyroidectomy
		Negative	5%	Observation
V (SMC)	None		53–87% (70%)	Ancillary testing or oncologic thyroidectomy
	GEC[b] (reported prevalence 62%)	Suspicious	76%	Oncologic thyroidectomy
		Benign	15%	Diagnostic lobectomy
	7-gene MT[c] (reported prevalence 54%)	Positive	95%	Oncologic thyroidectomy
		Negative	28%	Diagnostic lobectomy

WHICH MOLECULAR TESTING??



rapidly evolving area and that no specific molecular test is preferred at present

HIGH PPV

ORIGINAL ARTICLE

Endocrine Care

Impact of Mutational Testing on the Diagnosis and Management of Patients with Cytologically Indeterminate Thyroid Nodules: A Prospective Analysis of 1056 FNA Samples

Yuri E. Nikiforov, N. Paul Ohori, Steven P. Hodak, Sally E. Carty, Shane O. LeBeau, Robert L. Ferris, Linwah Yip, Raja R. Seethala, Mitchell E. Tublin, Michael T. Stang, Christopher Coyne, Jonas T. Johnson, Andrew F. Stewart, and Marina N. Nikiforova

Departments of Pathology and Laboratory Medicine (Y.E.N., N.P.O., R.R.S., M.N.N.), Surgery (S.E.C., L.Y., M.T.S.), Otolaryngology and Head Neck Surgery (R.L.F., J.T.J.), and Radiology (M.E.T.), and Division of Endocrinology (S.P.H., S.O.L., C.C., A.F.S.), University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213

Asuragen Panel (ThyGenX)

- Done on FNA specimens
- Panel includes BRAF, N/H/K-RAS, RET/PTC, & PAX8/PPARγ
- Nikiforov et al, JCEM 2011, reported on 1,056 nodules with 87 positive mutations, risk of cancer was 87% to 95%; sensitivity was 60% (high PPV, low NPV)

HIGH PPV

Original Article

Highly Accurate Diagnosis of Cancer in Thyroid Nodules With Follicular Neoplasm/Suspicious for a Follicular Neoplasm Cytology by ThyroSeq v2 Next-Generation Sequencing Assay

Yuri E. Nikiforov, MD, PhD[1]; Sally E. Carty, MD[2]; Simon I. Chiosea, MD[1]; Christopher Coyne, MD[3]; Umamaheswar Duvvuri, MD[4]; Robert L. Ferris, MD, PhD[4]; William E. Gooding, MS[5]; Steven P. Hodak, MD[3]; Shane O. LeBeau, MD[3]; N. Paul Ohori, MD[1]; Raja R. Seethala, MD[1]; Mitchell E. Tublin, MD[6]; Linwah Yip, MD[2]; and Marina N. Nikiforova, MD[1]

7 GENES Asuragen → **12 GENES ThyroSeq v1** → **55 GENES ThyroSeq v2**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Preoperative Diagnosis of Benign Thyroid Nodules with Indeterminate Cytology

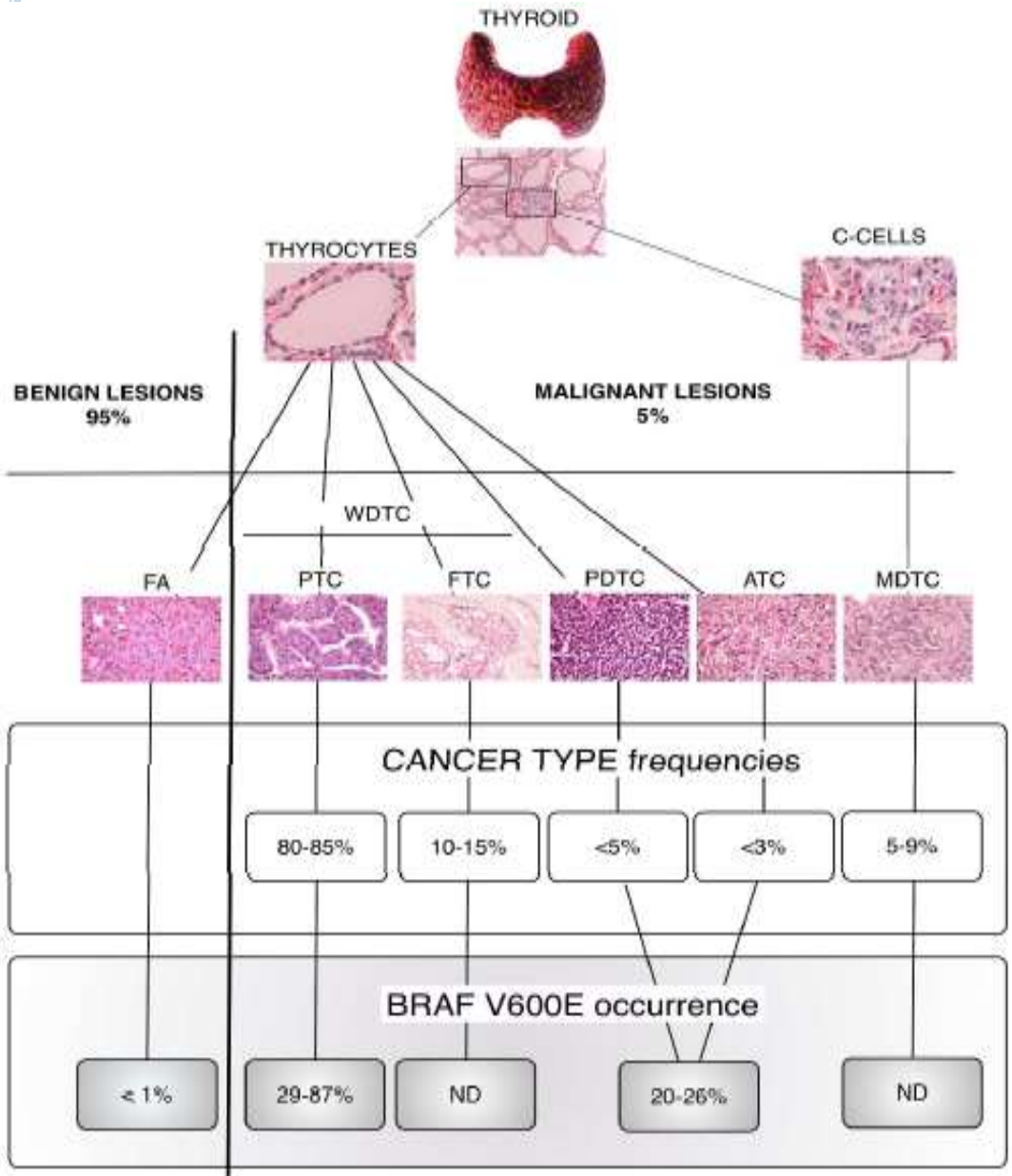
Erik K. Alexander, M.D., Giulia C. Kennedy, Ph.D., Zubair W. Baloch, M.D., Ph.D., Edmund S. Cibas, M.D., Darya Chudova, Ph.D., James Diggans, Ph.D., Lyssa Friedman, R.N., M.P.A., Richard T. Kloos, M.D., Virginia A. LiVolsi, M.D., Susan J. Mandel, M.D., M.P.H., Stephen S. Raab, M.D., Juan Rosai, M.D., David L. Steward, M.D., P. Sean Walsh, M.P.H., Jonathan I. Wilde, Ph.D., Martha A. Zeiger, M.D., Richard B. Lanman, M.D., and Bryan R. Haugen, M.D.

HIGH NPV

Veracyte Afirma Gene Expression Classifier

- Gene expression (167 genes) on FNA
- Alexander et al, NEJM 2012, showed that for 265 nodules, NPV was 95%
- McIver et al, JCEM 2014, did not confirm completely those results

MOLECULAR TESTINGS AND THYROID MALIGNANCIES



- **PTC and FVPTC:**the BRAFV600E mutation is 99.5% specific for PTC
- **Encapsulated FVPTC**: 80% risk of associating BRAFK601E mutation
- **FTC**: RAS mutations
- **MTC**: 1) all MEN2A, MEN2B,, FMTC and 50% of sporadic have *RET* germline mutations

  2)18%–80% of sporadic MTCs lacking somatic *RET* mutations have somatic mutations of *HRAS*, *KRAS*, or rarely *NRAS*
- **PDTC**: TERT mutations and microRNA
- **UDTC** : High rates of MAPK mutations, p53 mutations, and TERT mutations.

European Journal of Endocrinology (2012) 167 393–400 ISSN 0804-4643

CLINICAL STUDY

MicroRNA expression profile helps to distinguish benign nodules from papillary thyroid carcinomas starting from cells of fine-needle aspiration

Patrizia Agretti[1], Eleonora Ferrarini[1], Teresa Rago[1], Antonio Candelieri[4], Giuseppina De Marco[1], Antonio Dimida[1], Filippo Niccolai[1], Angelo Molinaro[1], Giancarlo Di Coscio[2,3], Aldo Pinchera[1], Paolo Vitti[1] and Massimo Tonacchera[1]

[1]Research Center of Excellence AmbiSEN and [2]Section of Cytopathology, Department of Oncology, University of Pisa, Via Paradisa 2, University Hospital of Pisa, Pisa, Italy and [4]Laboratory for Decision Engineering and Health Care Delivery, Department of Economics, University of Calabria, Cosenza, Italy

(Correspondence to T Massimo; Email: mtonacchera@hotmail.com)

Cancer Biomarkers 11 (2011/2012) 229–238
DOI 10.3233/CBM-2012-0273
IOS Press

The value of miRNA in diagnosing thyroid cancer: A systematic review

L. Lodewijk[1], A.M. Prins[1], J.W. Kist, G.D. Valk, O. Kranenburg, I.H.M. Borel Rinkes and M.R. Vri

Department of Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

Virchows Arch (2014) 464:333–346
DOI 10.1007/s00428-013-1521-2

INVITED REVIEW

Prognostic biomarkers in thyroid cancer

Paula Soares · Ricardo Celestino · Miguel Melo · Elsa Fonseca · Manuel Sobrinho-Simões

THYROID
Volume 22, Number 3, 2012
© Mary Ann Liebert, Inc.
DOI: 10.1089/thy.2011.0313

Evaluation of Candidate Diagnostic MicroRNAs in Thyroid Fine-Needle Aspiration Biopsy Samples

Mio Kitano,[1] Reza Rahbari,[1] Erin E. Patterson,[1] Seth M. Steinberg,[1] Nijaguna B. Prasad,[2] Yongchun Wang,[2] Martha A. Zeiger,[2] and Electron Kebebew[1]

The evaluation of miRNAs on thyroid FNAC: the promising role of miR-375 in follicular neoplasms
Rossi ED et al, Endocrine 2016

SUMMARY

Techniques for molecular profiling of thyroid cytology specimens have evolved as adjuncts to guide the management of cytologically indeterminate ever, it must be stressed that the test is only applicable clinically with clinical and sonographic malignancy and with understanding of malignancy for the Bethesda categories *at the reporting institution.*

Results/Conclusions: This review covers the clinical scenarios by cytologic category for which the thyroid surgeon may find molecular profiling results useful, particularly for cases with indeterminate fine-needle aspiration cytology.

7, 2015
ert, Inc., and the American Thyroid Association
ny.2014.0502

American Thyroid Association Statement on Surgical Application of Molecular Profiling for Thyroid Nodules: Current Impact on Perioperative Decision Making

Robert L. Ferris,[1] Zubair Baloch,[2] Victor Bernet,[3] Amy Chen,[4] Thomas J. Fahey III,[5] Ian Ganly,[6] Steven P. Hodak,[7] Electron Kebebew,[8] Kepal N. Patel,[9] Ashok Shaha,[6] David L. Steward,[10] Ralph P. Tufano,[11] Sam M. Wiseman,[12] and Sally E. Carty[13]

for the American Thyroid Association Surgical Affairs Committee

FUTURE DIRECTIONS

- Our working group has provided several conservative recommendations based on the available literature for potential changes and improvements of TBSRTC.

- The data from thyroid FNA studies based on changes in surgical pathology diagnoses were important for recommending additional changes in TBSRTC.

- The role of molecular tests still needs to be defined.
- They are not going to replace thyroid FNA cytology but they certainly play A ROLE in the current management.


THANK U FOR YOUR ATTENTION