

Updates to The Bethesda System For Reporting Thyroid Cytopathology



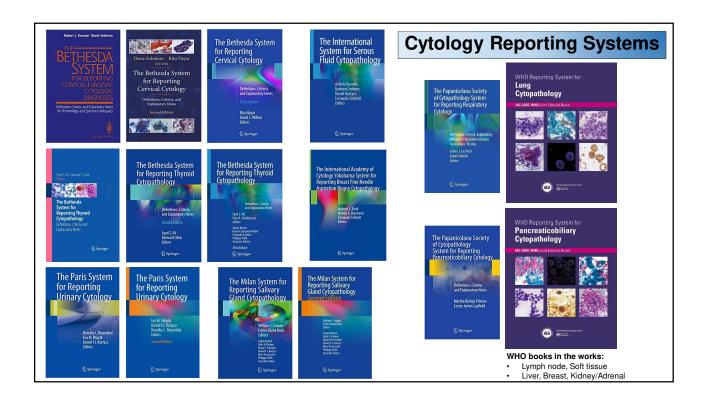
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* PVL has no relevant conflicts of interest relating to the content of this presentation to disclose.



Thyroid FNA Reporting

Reporting system must be succinct, unambiguous, and clinically helpful

✓ Clarity of communication:

• Facilitate clear and effective communication among cytopathologists, endocrinologists, surgeons, radiologists, and other health care providers

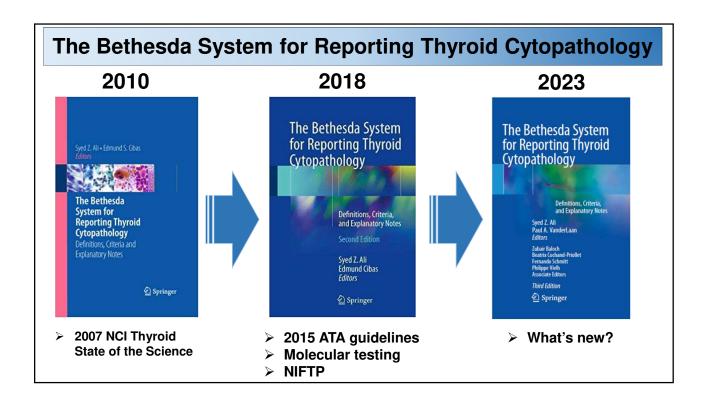
✓ Clinically relevant information:

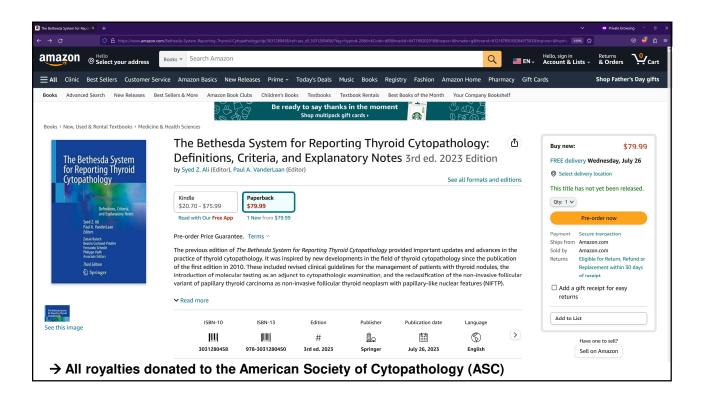
 Have well-defined ROMs for each diagnostic category, linked to a specific management recommendation

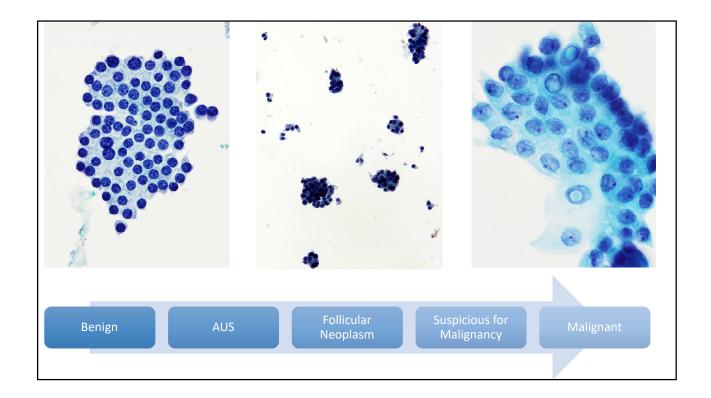
✓ Universal language:

 Allow effective and reliable sharing of data between laboratories and translatable results between studies

TIMELY REVIEW ection Editor: Andrea Abati, M.D. Pre Bethesda Era Reporting Thyroid Fine-Needle Aspiration: Literature Review and a Proposal elen H. Wang, M.D., DrPH Diagn. Cytopathol. 2006;34:67-76. PPV (%) Malignant: 99; suspected: 91; cellular atypia: 68; indeterm Literature review: 1966-2003 87 publications: PPV/NPV/Sen/Spec **Heterogenous practice:** Two tier reporting: 3 Three tier reporting: 41 Four tier reporting: 17 Five tier reporting: 8 on only indeterminate cases) Six + tier reporting: 10 (excluding ND category) Hürthle cell tumor Suspicion of malignant tumor Malignant tumor







TBS 3rd edition

Associate Editors

- Zubair Baloch MD, PhD
 - Hospital of the University of Pennsylvania, Philadelphia
- Beatrix Cochand-Priollet MD, PhD
 - Cochin Hospital, AP-HP Centre, University Paris-Cité-France
- Fernando Schmitt MD, PhD
 - University of Porto, Portugal
- Philippe Vielh MD, PhD
 - American Hospital of Paris, France









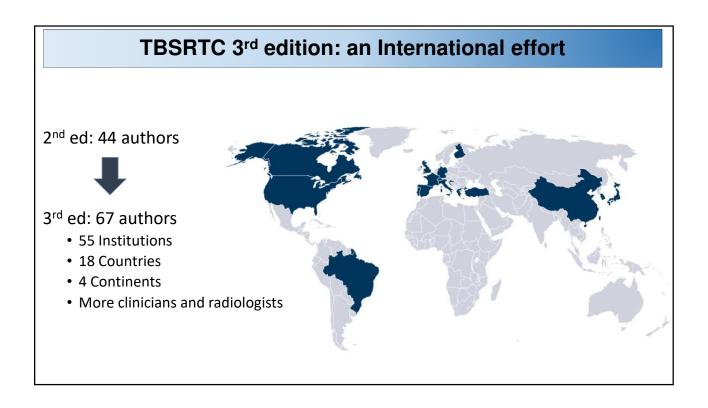


TABLE 1.1. The Bethesda System for Reporting Thyroid Cytopathology; diagnostic categories. **Diagnostic** I. Nondiagnostic Cyst fluid only **Category Names** Virtually acellular specimen Other (obscuring blood, clotting artifact, drying artifact, etc.) Benign Consistent with follicular nodular disease (includes adenomatoid nodule, colloid nodule, etc.) Consistent with chronic lymphocytic (Hashimoto) thyroiditis in the proper clinical context Consistent with granulomatous (subacute) thyroiditis One name per category III. Atypia of Undetermined Significance Specify if AUS-nuclear atypia or AUS-other IV. Follicular Neoplasm → Simplification The Bethesda System for Reporting Thyroid Specify if oncocytic (Hürthle cell) type V. Suspicious for Malignancy → Clarity Suspicious for papillary thyroid carcinoma Cytopathology Suspicious for medullary thyroid carcinoma Suspicious for metastatic carcinoma → Avoid confusion Suspicious for lymphoma → Align with other VI. Malignant Papillary thyroid carcinoma reporting systems High-grade follicular-derived carcinoma Medullary thyroid carcinoma Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma Carcinoma with mixed features (specify) Metastatic malignancy Non-Hodgkin lymphoma

The Bethesda System for Reporting Thyroid Cytopathology

Chapter 1

Overview of Diagnostic Terminology and Reporting

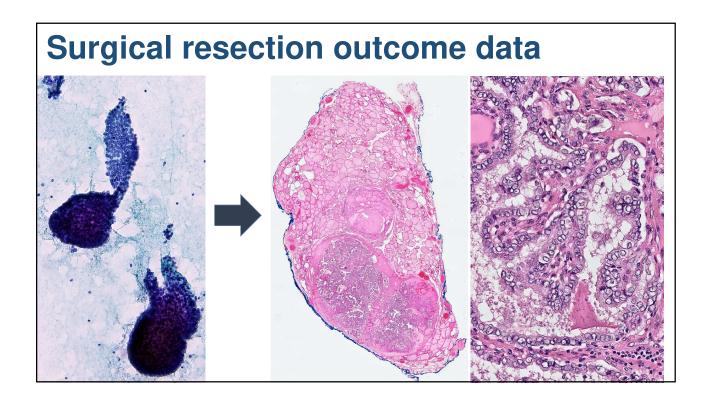
Refined ROM

→ New Data (Prospective Studies)

Zubair Baloch^{a*}, David Cooper^b, Martin Schlumberger^c, and Erik Alexander^d

TABLE 1.2. The Bethesda System for Reporting Thyroid Cytopathology: implied risk of malignancy (ROM) with expected ranges based on follow-up of surgically resected nodules with recommended clinical management.²³⁻⁵¹

Diagnostic category	ROM ^a	Usual management ^b	
	Ave% (range)		
Nondiagnostic	13 (5-20) ^c	Repeat FNA ^d with ultrasound guidance	
Benign	4 (2-7) ^e	Clinical and sonographic follow-up	
Atypia of Undetermined Significance ^f	22 (13-30)	Repeat FNA ^d , molecular testing, diagnostic	
5.000		lobectomy, or surveillance	
Follicular Neoplasmg	30 (23-34)	Molecular testingh, diagnostic lobectomy	
Suspicious for Malignancy	74 (67-83)	Molecular testingh, lobectomy or near-total	
		thyroidectomy ⁱ	
Malignant	97 (97-100)	Lobectomy or near-total thyroidectomyi	



Issues with Surgical Endpoints

- Not all nodules are resected (especially AUS)
 - ✓ Verification bias
- Lower risk nodules (B9, AUS) that are resected likely have other worrisome features
 - ✓ Inflated ROM for the category
- Additional layer of diagnostic subjectivity by the surgical pathologist
 - ✓ Multiple degrees of freedom to account for
- Temporal gap between FNA and resection
 - ✓ Lagging outcome indicator, difficulty in compiling data

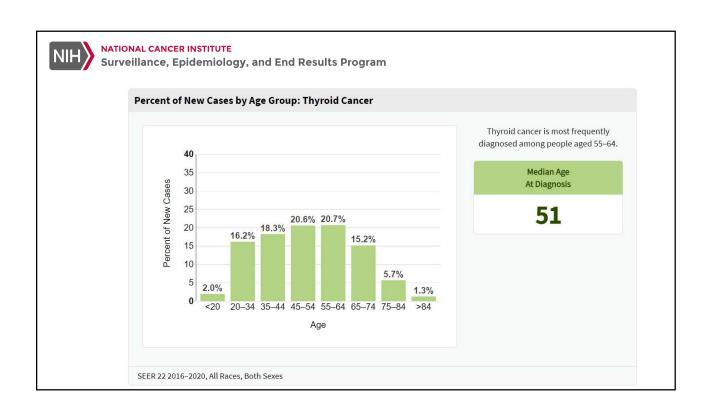
eview Article Cancer Cytopathol 2020;128:238-249.

Differences in Surgical Resection Rate and Risk of Malignancy in Thyroid Cytopathology Practice Between Western and Asian Countries: A Systematic Review and Meta-Analysis

Huy Gia Vuong, MD, PhD ^{10, 1}, Hanh Thi Tuyet Ngo, MD, PhD², Andrey Bychkox, MD, PhD ^{10, 14}, Chan Kwon Jung, MD, PhD ^{10, 14}, Trang Huyen Va, MD², Kim Bach Lu, MD⁴, Kennichi Kakudo, MD, PhD ^{10, 1}

TABLE 3. Resection Rate and Risk of Malignancy for 6 Categories of The Bethesda System for Reporting Thyroid Cytopathology in Western and Asian Series

	Pooled Proportion (95% CI), %		
	Western Series	Asian Series	Pa
FNA Category	(n = 22)	(n = 16)	
Nondiagnostic			
Frequency	11.9 (9.1-14.7)	12.6 (6.7-18.5)	.827
RR	14.9 (11.4-18.5)	11.5 (7.8-15.2)	.896
ROM	13.2 (9.6-16.7)	26.5 (16.4-36.6)	.151
Benign			
Frequency	64.2 (60.0-68.4)	59.8 (51.6-67.9)	.353
RR	11.0 (8.4-13.5)	16.0 (8.3-23.6)	.235
ROM	4.1 (2.8-5.4)	13.8 (9.0-18.6)	.001
AUS/FLUS	31 7	8	
Frequency	7.7 (5.1-10.2)	8.4 (5.5-11.4)	.647
RR	40.5 (32.2-48.8)	29.5 (21.0-38.0)	.354
ROM	21.5 (17.0-26.0)	45.0 (33.4-56.5)	.001
FN/SFN			
Frequency	7.9 (5.7-10.1)	3.5 (1.9-5.1)	.008
RR	63.4 (55.6-71.1)	55.5 (46.2-64.8)	.078
ROM	27.3 (24.4-30.2)	32.8 (27.5-38.1)	.335
Suspicious for malignancy	,		
Frequency	3.3 (2.6-4.1)	4.3 (2.6-6.1)	.291
RR	72.6 (65.4-79.9)	65.4 (56.4-74.4)	.310
ROM	75.1 (69.8-80.4)	88.1 (82.8-93.4)	.033
Malignant	(00.0 00.4)	55 (52.6-55.4)	.000
Frequency	4.9 (3.8-6.0)	10.9 (7.1-14.7)	.007
RR	74.8 (68.2-81.5)	68.6 (58.3-78.9)	.314
ROM	99.2 (98.8-99.5)	98.6 (97.6-99.5)	.633



Original Article

Cancer Cytopathol. 2012;120:342-350.

Cytomorphological and Molecular Genetic Findings in Pediatric Thyroid Fine-Needle Aspiration

Sara E. Monaco, MD¹; Liron Pantanowitz, MD¹; Walid E. Khalbuss, MD, PhD¹; Vanessa A. Benkovich, BS¹; John Ozolek, MD¹; Marina N. Nikiforova, MD¹; Jeffrey P. Simons, MD²; and Yuri E. Nikiforov, MD, PhD¹

Research

JAMA Oncol. 2022;8(9):1323-1327.

JAMA Oncology | Brief Report

Evaluation of the Molecular Landscape of Pediatric Thyroid Nodules and Use of a Multigene Genomic Classifier in Children

Jean-Nicolas Gallant, MD, PhD; Sheau-Chiann Chen, PhD; Carlos A. Ortega, BS; Sarah L. Rohde, MD; Ryan H. Belcher, MD; James L. Netterville, MD; Naira Baregamian, MD; Hulying Wang, MD; Jiancong Liang, MD, PhD; Fei Ye, PhD; Yuri E, Nikiforov, MD, PhD, Marian N, Nikiforov, MD; Vyran L. Wess, MD; PhD;

AJCP / ORIGINAL ARTICLE

Am J Clin Pathol. 2021:155(5):680-689.

Application of the Bethesda System for Reporting Thyroid Cytopathology in the Pediatric Population

A Multicenter Study in Asian Countries

Huy Gia Vuong, MD, PhD, ^{1,2} Ayana Suzuki, ³ Hee Young Na, MD, ⁴ Pham Van Tiryen, MD, ⁵ Doan Minh Khuy, MD, ⁵ Hiep Canh Nguyen, MD, PhD, ⁵ Tikamporn Jitpasutham, MD, ⁶ Agustina Abelando, MD, ^{8,5} Takashi Amano, ⁸ So Yeon Park, MD, ⁶ Chan Kwon Jung, MD, PhD, ¹⁰ Mitsuyoshi Hirokawa, MD, PhD, ³ Ryohei Katoh, MD, PhD, ⁹ Kennichi Kakudo, MD, PhD, ¹¹ and Andrey Bychkov, MD, PhD, ^{11,2,1,8}

Original Article

Cancer Cytopathol. 2022;130(5):330-335.

Subtype of atypia on cytology and risk of malignancy in pediatric thyroid nodules

Christine E. Cherella, MD $^{\bigcirc}$ ¹, Monica L. Hollowell, MD²; Jessica R. Smith, MD³; Benjamin Zendejas, MD, MSc³; Biren P. Modi, MD, MPH³; Edmund S. Cibas, MD $^{\bigcirc}$ ¹; and Ari J. Wassner, MD $^{\bigcirc}$ ¹

Bethesda System for Reporting Thyroid Cytopathology in Pediatric Thyroid Nodules

Experience of a Tertiary Care Referral Center

Amer Heider, MD; Stacy Arnold, MD; Xin Jing, MD

Arch Pathol Lab Med. 2020;144(4):473-477.



Chapter 1

Overview of Diagnostic Terminology and Reporting

Zubair Baloch^{a*}, David Cooper^b, Martin Schlumberger^c, and Erik Alexander^d

Refined ROM

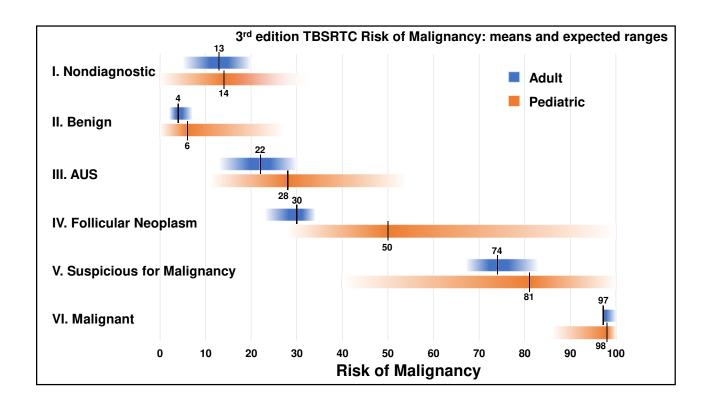
→ New Data (pediatric population)

TABLE 1.3. The Bethesda System for Reporting Thyroid Cytopathology in Pediatric Patients with implied risk of malignancy (ROM) and possible management recommendations. 10, 12-18, 64-69

Diagnostic category	ROM Ave% (range)	Possible Management Recommendations
Nondiagnostic	14 (0-33)	Repeat FNA with ultrasound guidance
Benign ^a	6 (0-27)	Clinical and sonographic follow-up
Atypia of Undetermined Significance	28 (11–54)	Repeat FNA or surgical resection
Follicular Neoplasm ^b	50 (28-100)	Surgical resection
Suspicious for Malignancy	81 (40–100)	Surgical resection
Malignant	98 (86–100)	Surgical resection

^a ROM is skewed by selection bias since a majority of thyroid nodules classified as benign do not undergo surgical excision.

^b Includes cases of follicular neoplasm with oncocytic features (Hürthle cell neoplasm).





Chapter 1

Overview of Diagnostic Terminology and Reporting

Refined ROM

→ Additional experience with NIFTP

Zubair Baloch^{a*}, David Cooper^b, Martin Schlumberger^c, and Erik Alexander^d

Table 1.4. Reported decreases in the risk of malignancy (ROM) of TBSRTC diagnostic categories if excluding nodules diagnosed on surgical pathology to be "Noninvasive Follicular Thyroid Neoplasm with Papillary Like Nuclear Features (NIFTP)". ^{21, 23, 70, 78}

Diagnostic category	% Decrease in ROM if excluding NIFTP ^a Ave% (range)	Estimated Final ROM if excluding NIFTP ^b Ave%
Nondiagnostic	1.3 (0-2)	12
Benign	2.4 (0-4)	2
Atypia of Undetermined Significance	6.4 (6-20)	16
Follicular Neoplasm	7.1 (0.2-30)	23
Suspicious for Malignancy	9.1 (0-40)	65
Malignant	2.6 (0-13)	94

 $^{^{}a}$ Based on weighted average (mean) reduction in malignancy with expected ranges calculated from refs 21 - 23 , $^{70-78}$

^b Based on estimated average ROM values from Table 1.2 minus values presented in this table

Terminology harmonized with latest 5th edition / 2022

with latest 5th edition / 2022 WHO classification of Thyroid Neoplasms

Benign (Chapter 2)

- Follicular Nodular Disease

FN-OFN (Chapter 6)

- Follicular neoplasm (Oncocytic follicular neoplasm)

High-Grade Follicular-Derived Thyroid Carcinoma (Chapter 10)

- Poorly differentiated thyroid carcinoma (PDTC) & differentiated high-grade thyroid carcinoma (DHGTC)

Malignant-PTC (Chapter 8)

- Cribriform morular thyroid carcinoma (CMTC) classified as malignant thyroid tumor of uncertain histogenesis
- NIFTP and HTT both classified as low-risk follicular cell derived neoplasms

International Agency for Research on Cancer

World Health
Organization

WHO Classification of Tumours online

Tionie Account Notes Lavourites About Contact Log

Endocrine and Neuroendocrine Tumours (5th ed.)

1. Forewords and introductions

2. Pituitary gland

3. Thyroid gland

Introduction

Developmental abnormalities

Thyroglossal duct cyst

Other congenital thyroid abnormalities

Follicular cell-derived neoplasms

Benign tumours

Thyroid follicular nodular disease

Follicular thyroid adenoma

Follicular thyroid adenoma with papillary architecture

Oncocytic adenoma of the thyroid

Low risk neoplasms

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features

Thyroid tumours of uncertain malignant potentia

Hyalinizing trabecular tumour of thyroid

Malignant neoplasms

Follicular thyroid carcinoma

Invasive encapsulated follicular variant papillary carcinoma

Papillary thyroid carcinoma

Oncocytic carcinoma of the thyroid Follicular-derived carcinomas, high-grade

Anaplastic follicular cell derived thyroid carcinoma

Thyroid C-cell derived carcinoma

Medullary thyroid carcinoma

Mixed medullary and follicular-cell derived carcinomas

Mixed medullary and follicular cell-derived thyroid carcinoma

Salivary gland-type carcinomas of the thyroid

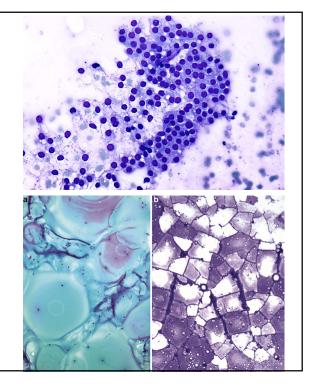
The Betherds System for Reporting Thyroid (ylippathology).

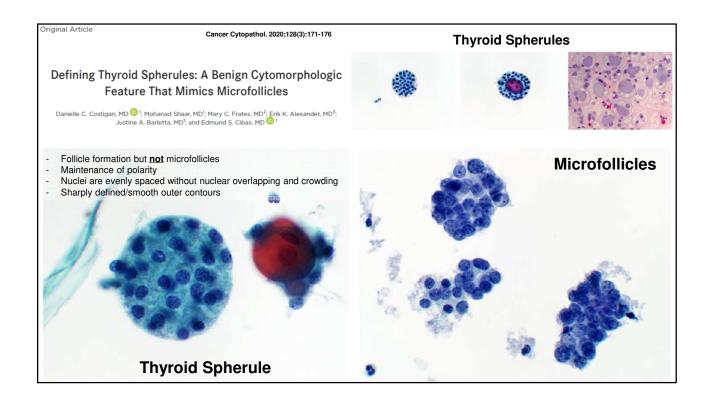
Chapter 3 Benign

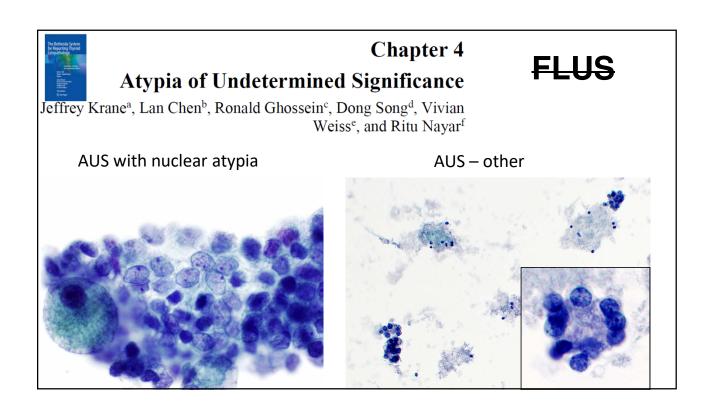
Tarik Elsheikh^a, SoonWon Hong^b, Christian Nasr^c, and Elena Vigliar^d

Follicular Nodular Disease (FND)

- recommended by the 2022 WHO classification of thyroid neoplasms
- refers to the spectrum of changes previously designated as colloid nodule, hyperplastic nodule, adenomatous nodule, or benign follicular nodule.
- several studies have shown that these nodules may or may not be clonal
 - > represent mixture of hyperplastic nodules and adenomas
- :. FND avoids designating these lesions as *hyperplastic* or *neoplastic* in nature.







Cancer Cytopathol 2014;122:368-76. The Prediction of Malignant Risk in the Category "Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance" of the Bethesda System for Reporting Thyroid Cytopathology Using Subcategorization and BRAF Mutation Results

Risk of malignancy according to sub-classification of the atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS) category in the Bethesda system for reporting thyroid cytopathology

S. J. Kim*, J. Roh*, J. H. Baek † , S. J. Hong ‡ , Y. K. Shong $^{\$}$, W. B. Kim $^{\$}$ and D. E. Song * Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, ¹Department of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, ¹Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, ¹Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Cytopathology, 2017;28(1):65-73. Cytopathology. 2017;28(1):65-73.

ORIGINAL ARTICLE

Differential outcomes of patients with thyroid FNA diagnoses of AUS/FLUS with and without nuclear atypia: The potential need for separation in the Bethesda System

Emily E. Waner MD, MPH 4,5 | Malak Itani MD 6,7 | Manjiri K. Dighe MD 6 | Tracy S. Tylee MD8

Georgios Deftereos MD^{1,2} | Stephen C. Schmechel MD, PhD^{1,3} |

Diagn Cytopathol. 2020;48(7):610-617.



ScienceDirect



WILEY

Utility of subcategorization of atypia of undetermined significance/follicular lesion of undetermined significance category in ultrasound-guided thyroid fine-needle aspiration in a large referral cancer center

Qiong Gan, MD°, Beth S. Edeiken, MD°, Melissa M. Chen, MD°, Elizabeth G. Grubbs, MD°, Naifa L. Busaidy, MD°, Mark Zafereo, MD°, Nancy D. Perrier, MD°, Maria D. Gule-Monroe, MD°, Savitri Krishnamurthy, MD°-a

CYTOLOGICA

Spectrum of Risk of Malignancy in Subcategories of 'Atypia of Undetermined Significance'

Matthew T. Olson^a Douglas P. Clark^a Yener S. Erozan^a Syed Z. Ali^{a, b}

Cancer Cytopathol. 2022;130(5):330-335.

Subtype of atypia on cytology and risk of malignancy in pediatric thyroid nodules

Christine E. Cherella, MD ¹⁰; Monica L. Hollowell, MD²; Jessica R. Smith, MD¹; Benjamin Zendejas, MD, MSc³; Biren P. Modi, MD, MPH³; Edmund S. Cibas, MD ¹⁰; and Ari J. Wassner, MD ¹⁰

Anatomic Pathology / AUS QUALIFIERS IN THYROID FNAs

Am J Clin Pathol. 2011;136:572

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

Paul A. VanderLaan, MD, PhD, Ellen Marqusee, MD, and Jeffrey F. Krane, MD, PhD

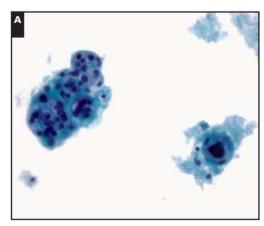
Key Words: Thyroid; Fine-needle aspiration; Cytology; Atypia of undetermined significance

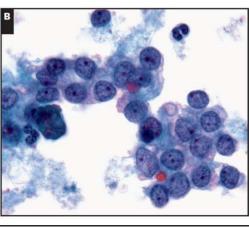
Nuclear (cytologic atypia)

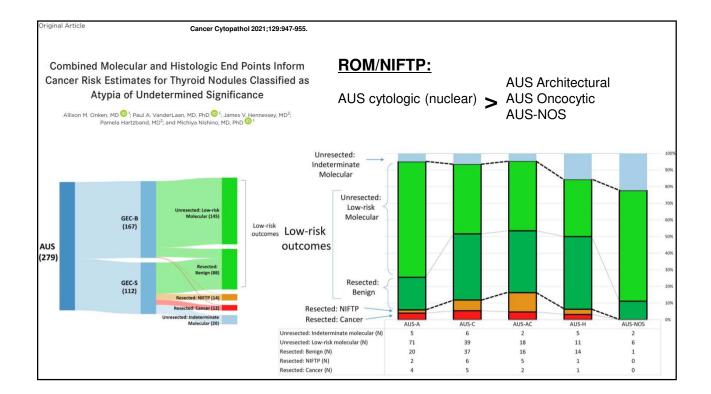
➤ ROM 20-40%

Architectural atypia

➤ ROM 10-15%









Chapter 4

FLUS

Atypia of Undetermined Significance

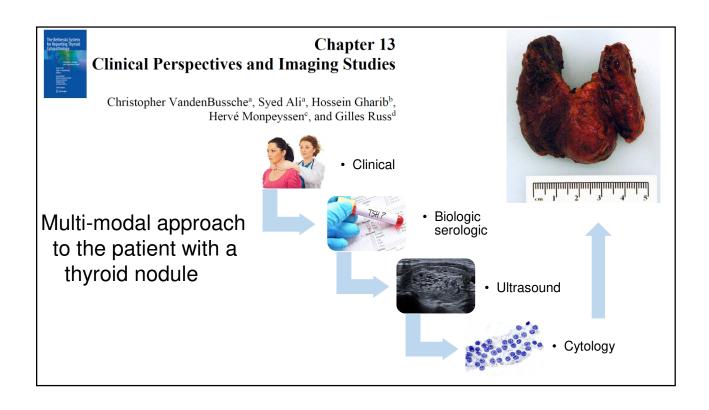
Jeffrey Krane^a, Lan Chen^b, Ronald Ghossein^c, Dong Song^d, Vivian Weiss^e, and Ritu Nayar^f

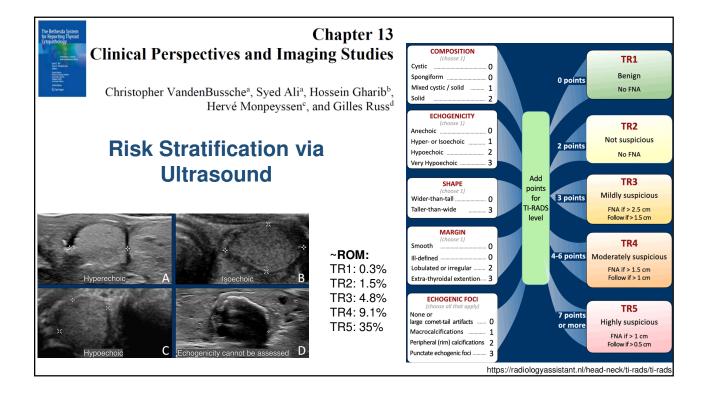
AUS with nuclear atypia

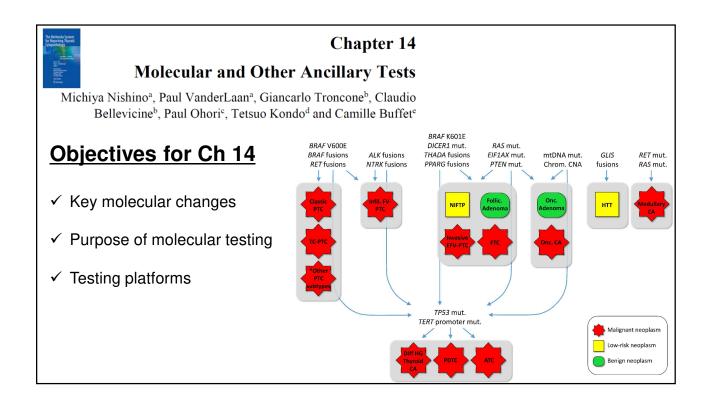
- Focal nuclear atypia
- Extensive but mild nuclear atypia
- Atypical cyst lining cells
- "Histiocytoid" cells
- Nuclear and architectural atypia

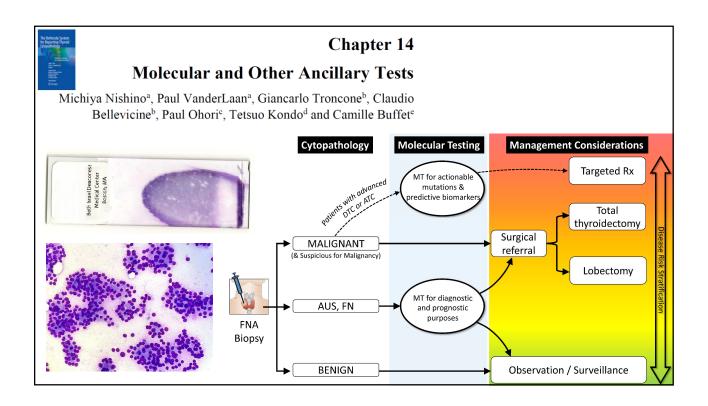
AUS – Other

- Architectural atypia
- Oncocytic/Oncocyte atypia
- Atypia NOS
- Nuclear changes not suggestive of PTC
- Psammoma bodies
- Atypical lymphoid cells, r/o lymphoma









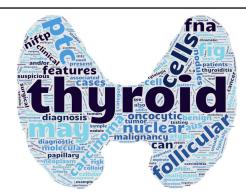
Summary

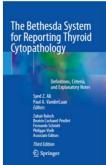
TBS 3rd ed: *evolution* and *maturation* of the most widely used thyroid FNA reporting system

- ✓ Single name for each category
- ✓ Refined ROM
- √ Changes in terminology (5th ed WHO)
- √ ~40% new/replaced images
- ✓ Literature update/refresh
- ✓ New chapters on Clin/Imaging and Molecular testing

Represents $^{\sim}2$ years of hard work by countless individuals from across the globe

→ Thank you!







Updates to The Bethesda System For Reporting Thyroid Cytopathology



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