<u>Thyroid Cytomorphology</u> <u>Basic Concepts and Application in Everyday Practice</u>

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Conflict of Interest

• None to Report

Discussion Points

- Thyroid nodules
- Thyroid cytology
 - Patterned approach with correlation to surgical pathology.
 - Thyroid FNA Classification Scheme
 - Cytomorphology of common thyroid lesions based on various cytologic preparations

Thyroid Gland Enlargement Through Ages



Thyroid Nodules *<u>Are Common in Adults</u>*

- Clinically apparent nodules affect 4-7% of US population
- By Ultrasound up to 60% of US population has one or more nodules
- <u>More common in women and up to</u> <u>95% are benign -</u>







Pediatric Thyroid Nodule

Palpable thyroid nodules are less common in children than adults

- Sonographic or pathological abnormalities are common
 - 0.2–5% of children, 13% of adolescents
- Thyroid cystic lesions occur in 57% of children
- In adults, 7–15% of all thyroid nodules are malignant but the risk in children is higher -22–26%
- History, ultrasound features, and FNA cytology are used to identify nodules at risk for malignancy.



Pediatric Thyroid Nodule

<u>Risk Factors</u>



- Family history of thyroid nodules or thyroid cancer
 - 2.5-fold higher for children with a family history of benign thyroid disease
 - Four-fold higher for children with a family history of thyroid cancer
- Iodine deficiency
- Radiation exposure
 - Thyroid nodules develop in cancer survivors who:
 - Received radiation therapy at about 2% annually and *reach a peak after 15–25* years
 - A five-fold greater risk in patients with a history of neuroblastoma suggests the potential for genetic predisposition

Pediatric Thyroid Nodule

Risk Factors

- Thyroid disease
 - Autoimmune Thyroiditis
- Elevated serum thyrotropin (TSH)
 - Thyroid nodules and serum thyrotropin(TSH) in the upper tertile may be at increased risk for DTC
- <u>Genetic syndromes</u>
 - Familial adenomatous polyposis
 - Carney complex
 - Phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome (Cowden's disease)
 - Beckwith–Wiedemann Syndrome
 - Familial paraganglioma syndromes
 - Li–Fraumeni Syndrome
 - McCune-Albright syndrome
 - Werner syndrome/progeria
 - Peutz–Jeghers syndrome
 - DICER1 syndrome





PTEN (Cowden Syndrome)





Differential Diagnosis of Thyroid Nodules

- MALIGNANT (5-10%)
 - Papillary Ca(75%), Follicular Ca (15%), Medullary Ca(5%), Lymphoma, Poorly Differentiated & Analplastic Ca, Mets to thyroid (kidney)
- BENIGN (90%-95%)
 - Colloid or adenomatous nodules, Follicular adenomas, Chronic lymphocytic thyroiditis
- Developmental abnormalities
 - Unilateral lobe agenesis, thyroglossal duct cyst

Thyroid Nodule Management in the Era of Pre-Operative Risk Assessment

Everything Matters

<u>Clinical Features + Lab values + Ultrasound</u> + <u>Cytomorphology</u> + <u>Molecular Profiling</u> + Management Strategy

History

Radiation Family History Symptoms Thyroid Disease **Disorders of function** Structural abnormalities **Physical Exam** Initial Serial Laboratory determinations TSH levels Calcitonin levels Imaging: Ultrasound Standard B mode imaging Elastography Contrast Enhanced Ultrasound Artificial Intelligence **Computer Aided Diagnosis** Radiomics

Nuclear medicine **Radioactive Iodine** PET (FDG) **Clinical Practice Guidelines (CPGs) Risk Score Stratification Tools (Clinical Calculators)** Computer Interactive Guidelines **Fine Needle Aspiration** Molecular Marker/Diagnostics (mostly USA) **DNA (Mutations)** Messenger RNA micro-RNA Immunocytochemistry Principal Emerging

Garber JR, Frasoldati A, Patkar V and Papini E (2023) Editorial: Thyroid nodule evaluation: current, evolving, and emerging tools. Front. Endocrinol. 14:1276323.doi: 10.3389/fendo.2023.1276323

Thyroid Nodule Management in the Era of Pre-Operative Risk Assessment



Thyroid Ultrasound Risk Assessment



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Korean Society for Thyroid Radiology

AACE

Characteristics of major ultrasound risk stratification systems

<u>RSS</u>	Classification format	<u>Number of categories</u>	Categories and estimated RoM
2021 AACE/ACE-AME tool/ TNAPP	Electronic algorithmic tool that uses history, labs, and combinations of US features	Clinical 2; US features 3	US1 – 1% US2 – 5-15% US3 – 50-90%
2015 ATA	Pattern recognition	5	Benign - <1% Very low - <3% Low - 5–10% Intermediate - 10–20% High - 70–90%
2017 ACR-TIRADS	Point-based system	5	TR1 - <2% TR2 - <2% TR3 - <5% TR4 - 5–20% TR5 - >20%
2017 EU-TIRADS	Algorithmic (combinations of US features)	5	TR1 – None TR2 – 0% TR3 - 2-4% TR4 - 6-17% TR5 - 26-87%
2016 K-TIRADS	Algorithmic (combinations of US features)	5	K-TIRADS 1 – None K-TIRADS 2 – < 3% K-TIRADS 3 – 3-15% K-TIRADS 4 – 15-50% K-TIRADS 5 - > 60%
2020 C-TIRADS	Point-based system	6	C-TR 1 – None C-TR 2 – 0% C-TR 3 – <2% C-TR 4 A– 2-10% C-TR 4 B– 10-50% C-TR 4 C– 50-90% C-TR 5 – >90% C-TR 6 – Proven malignancy

AACE/ACE/AME, American Association of Clinical Endocrinology, American College of Endocrinology, Associazione Medici Endocrinologi; TNAPP, The Thyroid Nodule App; ACR TI-

RADS, American College of Radiology Thyroid Imaging Reporting and Data System; ATA, American Thyroid Association; EU-TIRADS, European Thyroid Imaging Reporting and Data System; K-TIRADS, Korean Society of Thyroid Radiology/Korean Thyroid Association Thyroid Imaging Reporting and Data System; K-TIRADS, Korean Society of Thyroid Radiology/Korean Thyroid Association Thyroid Imaging Reporting and Data System; K-TIRADS, Korean Society of Thyroid Radiology/Korean Thyroid Association Thyroid Imaging Reporting and Data System; RSS, risk stratification system; ROM, risk of malignancy.

Majety P (2023) Thyroid nodules: need for a universal risk stratification system. Front. Endocrinol. 14:1209631. doi: 10.3389/fendo.2023.1209631

Majety P, Garber JR. Ultrasound scoring systems, clinical risk calculators, and emerging tools. In: Handbook of thyroid and neck ultrasonography: an illustrated case compendium with clinical and pathologic correlation. (Cham, Germany: Springer International Publishing) (2023). p. 25– 52. doi: 10.1007/978-3-031-18448-2_2

Why is there a need for radiologists to characterize thyroid nodules and make follow up recommendations?

- Thyroid nodules are incredibly common, and most are detected by imaging exams
 - Incidental thyroid nodules (ITN)
- Most are detected in asymptomatic patients often undergoing imaging for another reason
- Clinicians want guidance as to what is the appropriate management when detected in low risk patients

Thyroid Nodules

- Sonography is best imaging test to assess features that help predict the likelihood of malignancy
 - Recommended for ITN > 1.5 cm in pts over 35 yo*
- Sonography can predict a benign nodule appearance
 - Entirely cystic nodule
 - Spongiform nodules
- Some nodules cannot be differentiated by appearance
 - Follicular adenoma vs Follicular histology cancers overlap in appearance on sonography

*ACR Incidental Thyroid Findings Committee Hoang JK et al., J Am Coll Radiol 2015;12:143-150

Imaging Features Associated with Malignancy

- Local invasion- the lesion extends beyond the thyroid capsule into the adjacent soft tissue
- Lymphadenopathyidentification of cervical Lymph nodes that have features of metastatic thyroid cancer
 - Cystic areas
 - Rounded Shape
 - Calcifications



Sonographic Features Associated with Thyroid Malignancy

- All solid consistency
- Hypoechogenicity (how dark the nodule appears)
- Infiltrating and lobulated nodule margins
- Taller- than -wide shape
- Large and coarse calcifications
- True microcalcifications
 - Representing psammoma bodies seen in PTC
 - These appear as tiny bright dots or punctate echogenic foci (PEF)
 - Concerning on solid and hypoechoic nodules

Margins Associated with Malignancy



Jagged/Irregular

Papillary cancer

Margins Associated with Malignancy



Macro-lobulated

Micro-lobulated

Types of Macrocalcifications



Central, large and dystrophic/coarse

High ROM

Peripheral & interrupted



Peripheral complete or "eggshell"



Central and linear

20 to 30% of Thyroid Cancers are solid and isoechoic or hyperechoic





Follicular variant papillary thyroid cancer

Pure Follicular Thyroid Cancer

Diagnosing & Interpreting FNA Specimens of Thyroid Nodules

<u>Reporting Framework / Scheme</u>





The Bethesda System for Reporting Thyroid Cytopathology Definitions, Criteria and Explanatory Notes

🖉 Springer



🖄 Springer

The Bethesda System for Reporting Thyroid Cytopathology

> Definitions, Criteria, and Explanatory Notes

Syed Z. Ali Paul A. VanderLaan *Editors*

Zubair Baloch Beatrix Cochand-Priollet Fernando Schmitt Philippe Vielh Associate Editors

Third Edition

Basic Concepts in Thyroid Cytology

- 1. Architecture
- 2. Cellular Features

Normal Thyroid - Histology

Follicular Çells



Let's Correlate

Thyroid Histology vs. Cytology



Colloid, Follicular cells & Macrophages/Histiocytes



Follicles, Papillary Formation & Colloid





Microfollicles



Oncocytic cells and Lymphocytes



Thyroid Lesions Encountered in Everyday Practice of Cytopathology

Colloid: Thyroid FNA



Cytomorphology of Adenomatous Nodule



Cytomorphology: Hyperplastic Nodule

Conventional - Smear Preparations





ThinPrep[®]

<u>Adenomatous Nodule</u> Colloid: Generally abundant . Follicular cells Variable morphology .Oncocytes, Macrophages Degeneration/regeneration: Calcification, stromal proliferation, mitoses



Hyperplastic Nodule - Heterogeneous Morphology




Chronic Lymphocytic Thyroiditis

Oncocytes + Lymphocytes. Lymphocytes In the background & infiltrating the cell groups



Chronic Lymphocytic Thyroiditis

Oncocytes + Lymphocytes: In the background & infiltrating the cell groups



Subacute Thyroiditis (GranulomatousThyroiidtis)

Most Relevant is history

• Painful enlargement of thyroid, usually bilateral

• Cytologic Findings

- Plump transformed follicular cells
- Epitheloid granulomas
- Multinucleated giant cells (97.2%)
- Follicular cells with intra-vacuolar granules (77.7%)
- Mature lymphocytes (100%)
- Macrophages (100%)
- Neutrophils (88.8%)
- Oncocytic cells
- Fire-flare follicular cells



Follicular Patterned Lesions/Neoplasms of The Thyroid Gland

- Adenomatous Nodule (Follicular Nodular Disease)
- Follicular Adenoma
- Follicular Lesion of Uncertain Malignant Potential
- Non-invasive Follicular Tumor with Papillary Like Nuclear Features (NIFTP)
- Follicular Thyroid Carcinoma
- Follicular Variant of Papillary Thyroid Carcinoma

Follicular Patterned Lesions/Neoplasms of the Thyroid Gland

Cytology – Reality Check

- Cannot differentiate between follicular adenoma and carcinoma
- Most are diagnosed as "Follicular Lesion / Neoplasm"
- Up to 80% of cases diagnosed as such are benign on histologic examination (hyperplastic nodule or adenoma)
- Approximately half of malignant cases are **NIFTP**



Fig 1C

<u>Cellular Follicular Patterned Lesion – AUS vs. Follicular Neoplasm</u>





<u>Cellular Follicular Patterned Lesion – Follicular Neoplasm</u>



Follicular Neoplasm



Follicular Neoplasm-Oncocytic (Hurthle Cell)

Cellular specimen. Monotonous population of oncocytic follicular cells. Singly scattered cells. Transgressing vessels. Can have enlarged nuclei with prominent nucleoli.



Suspicious for Malignancy

Diagnosis Suspicious for (Papillary Thyroid Carcinoma)

Focal nuclear features of papillary carcinoma

- 1. Diagnosis suspicious for papillary carcinoma
- 2. Up to 60-75% cases are malignant on histologic follow-up.
- 3. Most of the PTC cases are follicular variant of PTC, now >50% NIFTP

Suspicious for Papillary Thyroid Carcinoma Cytology

• Cytologic Features

- Colloid (thick & watery)
- Monolayer sheets and follicle formation
- Paucity of nuclear features of Pap ca
 - Elongated nuclei
 - chromatin clearing and nuclear membrane thickening
 - Nuclear grooves and rare to no inclusions
- Macrophages



Suspicious for Papillary Thyroid Carcinoma







59-year-old hypothyroid woman, FNA of a 1.9 cm, isoechoic/hypoechoic thyroid nodule – Intermediate Suspicion on US





Follow-up NIFTP

Malignant

Papillary Thyroid Carcinoma Medullary Thyroid Carcinoma Anaplastic Thyroid Carcinoma Secondary Tumors / Metastasis

Papillary Thyroid Carcinoma (PTC) Salient Features

Nuclear features – Major Diagnostic Criteria

- Elongation, intranuclear grooves, chromatin clearing
- Cytoplasmic invagination and inclusions
- Small peripheral nucleoli

Additional Features:

- Variable thick colloid
- Psammoma bodies
- Tissue fragments common
- Histiocytoid /squamoid / mesothelial type cells
- Variable # of macrophages

Papillary Thyroid Carcinoma: Cytomorphology



Papillary Thyroid Carcinoma



Papillary Thyroid Carcinoma





PTC – Cytomorphology. Smear Preparations vs. ThinPrep®

Conv - Smear Preparations



ThinPrep[®]





Papillary Thyroid Carcinoma



Papillary Thyroid Carcinoma. Nuclear features – Major Diagnostic Features Elongation, chromatin clearing, Nuclear membrane irregularities Intranuclear grooves, Inclusions Small peripheral nucleoli



Challenging Aspirates of Cystic PTC



PTC – Immunohistochemistry



Medullary Thyroid Carcinoma

Medullary Thyroid Carcinoma - Cytologic Features

- Cellular specimen: Loose tissue fragments. Single cells
- Heterogeneous Morphology: Round to oval cells. Spindle cells
- Amyloid: Acellular deposits (thick colloid)



Medullary Thyroid Carcinoma - Cytologic Features

Tumor cells with:

- Abundant eosinophilic cytoplasm. Plasmacytoid tumor cells. Neuroendocrine chromatin pattern
- 20% of cells can show cytoplasmic granules in Romanowsky stained-preps



Anaplastic Thyroid Carcinoma

Variable Cellularity. Easily diagnosable as "Malignant Neoplasm". Variably sized and shaped cells. Tumor necrosis. Squamous Differentiation. Infiltration by neutrophils



Variable Cellularity. Easily diagnosable as "Malignant Neoplasm". Variably sized and shaped cells. Tumor necrosis. Squamous Differentiation. Infiltration by neutrophils



Poorly Differentiated Thyroid Carcinoma (PDTCA)

WHO 5th edition

High-Grade Thyroid Carcinoma

Well-Differentiated High Grade Thyroid Carcinoma
Poorly Differentiated Thyroid Carcinoma

<u>PDTCA</u>: Cellular specimens. Monotonous cell population. Anisonucleosis, rare. Evenly dispersed nuclear chromatin. <u>*Most diagnosed as follicular*</u> <u>*neoplasm.*</u>



<u>PDTCA</u>: Cellular specimens. Monotonous cell population. Anisonucleosis, rare. Evenly dispersed nuclear chromatin.



<u>PDTCA</u>: Histologic Follow-up



What Else?
Things to Remember and be Reminded of...

Nodules measuring 1.0 cm or less

- Most are PTC (classic or follicular variant)
- Rarely Medullary microcarcinoma
- 1.0 cm or less Follicular Carcinoma non-existent
- Rare cases of Hürthle cell / Oncocytic follicular carcinoma measuring ≤ 1.0 cm have been reported
- Think of "Intrathyroidal Parathyroid Lesions"

Think long & hard before rendering a diagnosis of "Follicular Neoplasm" on a \leq 1.0 cm nodule with microfollicles.

Ectopic Tissues



Parathyroid Acini Mimicking Thyroid Follicles



Intrathyroidal Parathyroid

Think long & hard before rendering a diagnosis of "Follicular Neoplasm" on a ≤ 1.0 cm nodule with microfollicles.



Papillary Formation can be seen in Parathyroid FNA Specimens

Intrathyroidal Parathyroid FNA





<u>PTH Levels on portion of aspirate or</u> <u>Immunostain for PTH on Cell Block</u> (other stains GATA3, Chromogranin or TTF-1)

Nuclear & Architectural Atypia Can be Encountered In Benign Lesions Of Thyroid Gland



Graves' Disease

Chronic Lymphocytic Thyroiditis

Papillary Adenomatous Nodule / Papillary Adenoma

Mimics of Malignant Neoplasms – Hyalinizing Trabecular Tumor MIB1 IHC, GLIS - rearrangements



Clear Cells – Thinking of Metastatic Renal Cell



Clear Cell - Follicular Cell– Derived Neoplasm



Clear Cell Follicular Cell Derived - Neoplasm – Cystic PTC



Clear Cell Non-Follicular Cell Derived – Neoplasms





Colloid - Watery

Nuclear Atypia

Follicular Cells



Thyroid biopsy is usually done with a thin needle (fine needle biopsy) and is a welltolerated procedure with minimal to no complications and can be done in the office. *However, up to 10% of thyroid fine needle biopsies will not have enough cells for a diagnosis.*

An alternative method to evaluate thyroid nodules is a Core Needle Biopsy (CNB). This procedure uses a large needle and requires an experienced operator with specific training.

CNB also has a higher risk of complications than a fine needle biopsy, including injuries to the trachea and carotid artery.



Core needle device. A. Stylet and specimen notch (arrows). B. Cutting cannula.

Consensus Statement and Recommendations from the Korean Society of Thyroid Radiology

Indication of CNB

1. CNB could be alternative to FNA in evaluation of thyroid nodules in selected cases.

Device and procedure of CNB

- 1. Modern CNB devices, particularly 18–21-gauge, springactivated, core needles, are recommended for procedure.
- Patients with bleeding tendency, such as those taking anticoagulation medications or with disorders affecting coagulation cascade, should be thoroughly evaluated and any problems corrected before CNB.
- 3. CNB should be performed by experienced operators under ultrasound guidance.
- 4. Manual compression of biopsy site should be performed immediately after procedure for 20–30 min.

2017 & 2019 Practice guidelines for thyroid core needle biopsy: a report of the Clinical Practice Guidelines Development Committee of the Korean Thyroid Association: Diagnostic Categories

I. Nondiagnostic or unsatisfactory	
	Non-tumor adjacent thyroid tissue only
	Extrathyroid tissue only (e.g., skeletal muscle, mature adipose tissue)
	Acellular specimen (e.g., acellular fibrotic tissue, acellular hyalinized tissue, cystic fluid only)
	Blood clot only
	Other
II. Benign lesion	
	Benign follicular nodule
	Hashimoto's thyroiditis
	Subacute granulomatous thyroiditis
	Nonthyroidal lesion (e.g., parathyroid lesions, benign neurogenic tumors, benign lymph node)
	Other
III. Indeterminate lesion	
	IIIa. Indeterminate follicular lesion with nuclear atypia
	IIIb. Indeterminate follicular lesion with architectural atypia
	IIIc. Indeterminate follicular lesion with nuclear and architectural atypia
	IIId. Indeterminate follicular lesion with Hürthle cell changes
	IIIe. Indeterminate lesion, not otherwise specified
IV. Follicular neoplasm	
	IVa. Follicular neoplasm, conventional type
	IVb. Follicular neoplasm with nuclear atypia
	IVc. Hürthle cell neoplasm
	IVd. Follicular neoplasm, not otherwise specified
V. Suspicious for malignancy	
	Suspicious for papillary thyroid carcinoma, medullary thyroid carcinoma, poorly differentiated thyroid carcinoma, metastatic carcinoma, lymphoma, etc.
VI. Malignant	
	Papillary thyroid carcinoma, poorly differentiated thyroid carcinoma, anaplastic thyroid carcinoma, medullary thyroid carcinoma, lymphoma, metastatic carcinoma, etc

Thyroid Core Biopsy – Not an Uncommon Practice in Asia

Na DG, Baek JH, Jung SL, et al. Korean J Radiol. 2017;18:217–37Core needle biopsy of the thyroid: 2016 consensus statement and recommendations from Korean Society of Thyroid Radiology.



Jung CK et al. J Pathol Trans Med 2020 Jan; 54(1): 64–86. 2019 Practice guidelines for thyroid core needle biopsy: a report of the Clinical Practice Guidelines Development Committee of the Korean Thyroid Association. and Clinical Practice Guidelines Development

Committee of the Korean Thyroid Association

Jung Ck. J Pathol Transl Med 2023 Jul; 57(4): 208-216. Reevaluating diagnostic categories and associated malignancy risks in thyroid core needle biopsy

Ahn, S-H, Usage and Diagnostic Yield of Fine-Needle Aspiration Cytology and Core Needle Biopsy in Thyroid Nodules: A Systematic Review and Meta-Analysis of Literature Published by Korean Authors. Clin Exp Otolorhino, 2021

 Table 1. Number of papers on FNA or CNB in thyroid diseases published by authors from Korea

Index	Institute	FNA	CNB
1	Ajou University	2	0
2	Asan Medical Center	18	29
3	Busan Paik Hospital	17	0
4	Catholic University	10	3
5	Chung-Ang University	1	1
6	Chungbuk National University	1	0
7	Chungnam National University	4	0
8	Dong-A University	1	0
9	Ewha Womans University	1	0
10	Gacheon University	1	1
11	Yonsei University Gangnam Severance Hospital	7	0
12	Gangneung Asan Hospital	2	2
13	Gyeongsang National University	2	0
14	Hallym University	1	0
15	Human Medical Imaging	5	3
16	Inha University	2	0
17	Inje University	1	0
18	Kangbuk Samsung Hospital	1	0
19	Konkuk University	7	0
20	Korea University	7	0
21	Kyungpook National University	2	1
22	Myongji Hospital	1	0
23	National Cancer Center	2	0
24	Pusan National University	3	0
25	Samsung Medical Center	20	4
26	Seoul National University Boramae Hospital	2	0
27	Seoul National University Bundang Hospital	6	4
28	Seoul National University Hospital	8	2
29	Yonsei University Severance Hospital	65	4
30	Soonchunhyang University	1	0
31	Ulsan University Hospital	1	0
32	Yeouido St. Mary's Hospital	1	0
Total		204	54

- CNB led to a significantly lower proportion of non-diagnostic results than fine-needle aspiration (FNA).
- The **frequency of** atypia of undetermined significance/follicular lesion of undetermined significance **(AUS/FLUS) did not decrease** as a result of performing CNB in nodules with initial AUS/FLUS results, while **it increased in consecutive cases**.
- A subcategory analysis of AUS/FLUS showed that the increased frequency of AUS/FLUS findings on CNB was due to more frequent diagnoses of architectural atypia and follicular neoplasm, which resulted in a higher frequency of inconclusive findings in consecutive cases compared to FNA.
- Hospitals favoring CNB had a **higher proportion of AUS/FLUS diagnoses.**
- Although the complication rate did not differ significantly between CNB and FNA, serious complications of CNB did occur.

FNA, fine-needle aspiration; CNB, core needle biopsy.

Core Biopsy - Complications

Case Cohort of 6,168 patients with 6,687 thyroid nodules.

- The complication rate after US-guided CNB for thyroid lesions was 0.81% (50 / 6,169 pts).
- The rate of major complications was 0.06% (4 / 6,169).
- Vascular injury was the most common complication (47/6,169; 0.76 %).
- None of the patients experienced permanent problems resulting from complications.

Fig. 2 A 60-year-old woman with pseudoaneurysm after CNB. a Transverse US scan shows a left thyroid nodule in a posterior location. b-d US scan reveals a pulsatile cystic mass (arrowheads) with a typical swirling motion connecting to the superior thyroidal artery after CNB



Ha EJ et al. Eur Radiol 2017. Complications following US-guided core-needle biopsy for thyroid lesions: a retrospective study of 6,169 consecutive patients with 6,687 thyroid nodules

Benign vs. Indeterminate Lesions

Follicular Patterned Lesions. CNB – Not so helpful



FNA – AUS, CNB - Benign



Confirming Diagnosis

FNA x2: Non-Diagnostic. CNB – Anaplastic Ca, Paucicellular subtype



FNA x2: Non-Diagnostic. CNB – Anaplastic Ca, Paucicellular subtype



FNA Dx – Follicular Neoplasm, CNB – Poorly Differentiated Carcinoma



Multiple Passes Leading to Generous Cell Block – An Alternative to CNB



FNA x2: Non-Diagnostic. CNB – Medullary Thyroid Carcinoma



The Aftermath of CNB Post CNB Histologic Alterations



Post CNB Alterations



Conclusions

- Training to perform CNB
- Radiologic guidance
- The CNB can be considered in nodules with highly suspicious features especially prior non-diagnostic FNA.
 - Suspected diagnosis of Anaplastic Thyroid Carcinoma or Thyroid Lymphoma in a rapidly enlarging thyroid mass
- CNB has the potential to increase the % diagnosis of architectural atypia or follicular neoplasm.
- The literature on CNB ---?

Subtype-specific oncogenic drivers in thyroid cancer



Cancer Genome Atlas Research Network Cell. 2014 PMID: 25417114; Durante et al. JAMA. 2018 PMID: 29509871

FDA approved molecularly targeted therapies in thyroid cancer

Dabrafenib (BRAF inhibitor) & Trametinib (MEK inhibitor)	Larotrectinib (Selective TRK inhibitor)	Entrectinib (multi-kinase inhibitor NTRK1/2/3, ROS1, & ALK)	Selpercatinib (Selective RET kinase inhibitor)	Pralsetinib (Tyrosine Kinase Inhibitor)
 18 years old locally advanced, unresectable or metastatic solid tumors BRAFV600E mutant-positive 	 1 month old locally advanced or metastatic solid tumors Tumor agnostic NTRK fusion-positive 	 18 years old locally advanced or metastatic solid tumors penetrate blood-brain barrier Tumor agnostic NTRK fusion-positive 	 12 years old RET-driven advanced or metastatic cancer RET mutant-positive Medullary Thyroid Cancer RET fusion-positive radioactive iodine- refractory thyroid cancers 	 12 years old RET-driven advanced or metastatic cancer RET mutant-positive Medullary Thyroid Cancer RET fusion-positive radioactive iodine- refractory thyroid cancers

Patel J, Klopper J and Cottrill EE (2023) Molecular diagnostics in the evaluation of thyroid nodules: Current use and prospective opportunities. Front. Endocrinol. 14:1101410. doi: 10.3389/fendo.2023.1101410

Table 2. Comparison of testing methodology, biomarkers, and quality control measures for the three commercially available thyroid molecular testing platforms in the United States.

	ThyroSeq v3	ThyGeNEXT and ThyraMIR	Afirma GSC and Xpression Atlas
Test methodology	NGS for DNA and RNA	NGS for DNA and RNA; qRT-PCR for microRNA	NGS for RNA
SNV, insertions, deletions, and gene fusions	12,135 variants in 112 genes; 120+ fusions	42 variants in 10 genes; 38 gene fusions	905 variants and 235 gene fusions from 593 genes
Gene expression analysis	19 genes	4 genes	10,196 genes (1115 for the GSC classifier algorithm)
MicroRNA expression analysis	None	10 microRNAs	None
Copy-number alterations	10 chromosomal regions	None	Loss-of-heterozygosity analysis
QC for follicular cell content	Yes	Yes	Yes
Recognition of parathyroid	Yes	Yes	Yes
Recognition of MTC	Yes	Yes	Yes

Abbreviations: GSC, gene sequencing classifier; NGS, next-generation sequencing; qRT-PCR, quantitative real-time polymerase chain reaction; SNV, single nucleotide variant; QC, quality control; MTC, medullary thyroid carcinoma.

×

Patel J, Klopper J and Cottrill EE (2023) Molecular diagnostics in the evaluation of thyroid nodules: Current use and prospective opportunities. Front. Endocrinol. 14:1101410. doi: 10.3389/fendo.2023.1101410

Meta-analysis data of Afirma GSC and Thyroseq v3.

	<u>Afirma GSC®</u>	Afirma GSC®	<u>Thyroseq v3®</u>
<u>Meta-analysis</u>			
# Included Studies	7 studies	7 studies	6 studies
Sample Size	807	472	530
Specificity	43%	53%	50%
Sensitivity	94.3%	96%	95%
NPV	90%	96%	92%
PPV	63.1%	63%	70%

Vuong HG, Nguyen TPX, Hassell LA, Jung CK. Diagnostic performances of theafirma gene sequencing classifier in comparison with the gene expression classifier: A meta-analysis. Cancer Cytopathol (2021) 129:182–9. doi: 10.1002/cncy.22332

Lee E, Terhaar S, McDaniel L, Gorelik D, Gerhard E, Chen C, et al. Diagnostic performance of the second-generation molecular tests in the assessment of indeterminate thyroid nodules: A systematic review and meta-analysis. Am J Otolaryngol (2022) 43:103394. doi: 10.1016/j.amjoto.2022.103394

Vargas-Salas S, Martinez JR, Urra S, Dominguez JM, Mena N, Uslar T, et al. Genetic testing for indeterminate thyroid cytology: Review and meta-analysis. Endocrine-related Cancer (2018) 25:R163–77. doi: 10.1530/ERC-17-0405

Silaghi CA, Lozovanu V, Georgescu CE, Georgescu RD, Susman S, Nasui BA, et al. Thyroseq v3, afirma GSC, and microRNA panels versus previous molecular tests in the preoperative diagnosis of indeterminate thyroid nodules: A systematic review and meta-analysis. Front Endocrinol (2021) 12:649522. doi: 10.3389/fendo.2021.649522

Risk Based Assessment: we can all work together



WHO Classification of Thyroid Neoplasms, 5th ed

Developmental Abnormalities

- 1. Thyroglossal duct cyst
- 2. Other congenital thyroid abnormalities

Follicular Derived Neoplasms

- 1. Benign Tumors
 - a. <u>Thyroid follicular nodular disease*</u>
 - b. Follicular adenoma
 - c. Follicular adenoma with papillary architecture*
 - d. Oncocytic adenoma of the thyroid*

2. Low Risk Neoplasms

- a. Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
- b. Thyroid tumors of uncertain malignant potential
- c. Hyalinizing trabecular tumor
- 3. Malignant Neoplasms
 - a. Follicular thyroid carcinoma
 - b. Invasive encapsulated follicular variant papillary carcinoma*
 - c. Papillary thyroid carcinoma
 - d. Oncocytic carcinoma of the thyroid*
 - e. Follicular-derived carcinomas, high-grade*
 - i. Differentiated high-grade thyroid carcinoma
 - ii. Poorly differentiated thyroid carcinoma
 - f. Anaplastic follicular cell derived thyroid carcinoma

Thyroid C-cell Derived Carcinoma

1. Medullary thyroid carcinoma

Mixed Medullary and Follicular-cell Derived Carcinomas

Salivary Gland-type Carcinomas of the Thyroid*

- 1. Mucoepidermoid carcinoma of the thyroid
- 2. Secretory carcinoma of salivary gland type

Thyroid tumors of uncertain histogenesis*

- 1. Sclerosing mucoepidermoid carcinoma with eosinophilia
- 2. Cribriform morular thyroid carcinoma

Thymic Tumors Within the Thyroid

- 1. Thymoma family
- 2. Spindle epithelial tumour with thymus-like elements
- 3. Thymic carcinoma family

Embryonal Thyroid Neoplasms

1. Thyroblastoma
Macerola, E.; Poma, A.M.; Vignali, P.; Basolo, A.; Ugolini, C.; Torregrossa, L.; Santini, F.; Basolo, F.Molecular Genetics of Follicular-Derived Thyroid Cancer. Cancers **2021**, 13, 1139.

Gene	Advanced PTC			Advanced FTC				PDTC			ATC		
	n° Mutant/n° Total	Frequency Range	Pooled Frequency	n° Mutant/n° Total	Frequency Range	Pooled Frequency	Gene	n° Mutant/n° Total	Frequency Range	Pooled Frequency	n° Mutant/n° Total	Frequency Range	Pooled Frequency
BRAF	583/894	45-71%	65%	6/136 ¹	0–8%	4%	BRAF	57/220	15–33%	26%	166/395	20–56%	42%
RAS ²	68/890	1–23%	8%	83/136	8–90%	61%	RAS	48/220	9_39%	22%	100/395	20-33%	25%
EIF1AX	3/62	0–10%	5%	5/88	0–40%	6%	1045	+0/220	5 5570	2270	100/355	20 3370	2370
РІКЗСА	36/669	3–6%	5%	2/100	0–3%	2%	EIF1AX	11/125	5–11%	9%	22/181	8-14%	12%
PTEN	10/669	0–2%	1%	9/100	0–14%	9%	РІКЗСА	15/220	2–20%	7%	65/395	9–44%	16%
TERT	314/651	13–62%	48%	68/103	50-82%	66%	PTEN	6/220	4–33%	3%	45/395	11–20%	11%
TP53	64/669	3–13%	10%	9/100	0–12%	9%			/		/	/	
RET fusion	37/558	3–7%	7%	0/89	0%	0%	TERT	43/125	22–40%	34%	242/355	56-75%	68%
PPARG fusion	0/59	0%	0%	0/89	0%	0%	ТР53	45/220	8–67%	20%	244/395	25-80%	62%
							RET fusion	11/125	6–15%	9%	5/355	0–2%	1%
ALK fusion	3/527	<1–2%	1%	0/89	0%	0%		4/425	2 40/	20/	0/450	00/	00/
NTRK fusion	8/527	1–5%	2%	0/89	0%	0%	PPARG fusion	4/125	2–4%	3%	0/159	0%	0%
							ALK fusion	4/125	2–4%	3%	0/355	0%	0%
BRAF fusion	14/527	0–3%	3%	0/89	0%	0%	NTRK fusion	1/41	0–2%	2%	5/322	1-4%	2%

Personalized Approach to Thyroid Nodule Management

