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Turkish Society of Cytopathology
Department of Pathology, Clinical Centre of the University of Sarajevo, Bosnia and Herzegovina

ANCILLARY TESTS IN THYROID FNA

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THYROID CYTOLOGY

- FNA is the most useful test for thyroid nodules.
- FNA saves many patients unnecessary thyroid surgery while appropriately triaging patients with malignant nodules for surgery.
- Prior to the routine use of thyroid FNA, only 14% of surgically resected thyroid nodules were malignant. (Hamberger et al., 1982)
- With current thyroid FNA practice, >50% of resected nodules are malignant. (Yassa et al., 2007)

FINE-NEEDLE-ASPIRATION

- FNA is a method used worldwide for the diagnosis of palpable and non-palpable lesions in various organs.

- Despite being one of the most economical and reliable diagnostic procedures, in recent years there have been many attempts to replace FNA by core-needle biopsy.

THYROID CYTOLOGY

- There are two critical points in thyroid FNA:
  - The rates of inadequate material
  - Indeterminate cases in which cytology does not allow a definitive diagnosis of benignity or malignancy.

Ultrasound guidance improves the adequacy of our preoperative thyroid cytology but not its accuracy

P. Mehrotra[a], H. Viswanathan[†], S. J. Johnson[†], V. Wadehra[†], D. L. Richardson[§] and T. W. J. Lennard[a]

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Cytopathology 2006, 17, 137–141

CNB-US guided

FNA Freehand

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Cytopathology 2006, 17, 137–141

Histological diagnosis	Unsatisfactory freehand FNA cytology samples (%)	Unsatisfactory USS-guided core cytology samples (%)	Total (%)
Non-neoplastic	68 (81.0)	8 (66.7)	76 (79.1)
Multinodular goitre	58 (69.1)	6 (50.0)	64 (66.7)
Hashimoto's thyroiditis	7 (8.3)	1 (8.3)	8 (8.3)
Lymphocytic thyroiditis	1 (1.2)	1 (8.3)	2 (2.1)
Simple cyst	1 (1.2)	0	1 (1.0)
Hurthle cell hyperplasia	1 (1.2)	0	1 (1.0)
Benign	6 (7.1)	1 (8.3)	7 (7.3)
Follicular adenoma	5 (6.0)	1 (8.3)	6 (6.3)
Hurthle cell adenoma	1 (1.2)	0	1 (1.0)
Malignant	10 (11.9)	3 (25.0)	13 (13.5)
Papillary carcinoma	7 (8.3)	1 (8.3)	8 (8.3)
Follicular carcinoma	2 (2.4)	0	2 (2.1)
Lymphoma	1 (1.2)	2 (16.7)	3 (3.1)
Total	84 (100)	12 (100)	96 (100)

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Cytopathology 2006, 17, 137–144

Table 6. Overall comparison of combined accuracy of AC3, 4 and 5 cytology grades by freehand FNA and USS-guided core (excluding incidental PTCs)

	To predict neoplasia		To predict malignancy	
	FH	USS	FH	USS
Sensitivity	83.2	93.5	94.1	90.9
Specificity	46.6	26.0	41.9	22.0
Accuracy	63.0	51.9	54.5	40.7
Positive predictive value	56.0	47.9	34.0	30.3
Negative predictive value	77.1	86.7	95.7	86.7
False negative	22.9	13.3	4.3	13.3
False positive	44.0	56.1	66.0	69.7

Thyroid cytology: FNA is still the best diagnostic approach

➢ There is no evidence that core needle can replace FNA in, or even have a significant role in the evaluation of thyroid nodules. FNA remains the most accurate, cost-effective and reliable method to diagnose thyroid lesions, and represents a significant improvement in patient care.

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Cytopathology 2006, 17, 210–216 © 2006 The Authors
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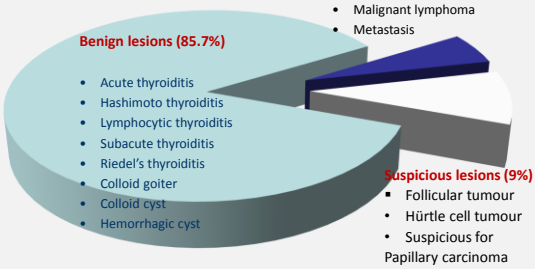
THYROID FNA: Cytopathological aspects

Malignant lesions (5.3%)
- Papillary carcinoma
- Medullary carcinoma
- Poorly dif. Carcinoma
- Anaplastic carcinoma
- Malignant lymphoma
- Metastasis

Benign lesions (85.7%)
- Acute thyroiditis
- Hashimoto thyroiditis
- Lymphocytic thyroiditis
- Subacute thyroiditis
- Riedel's thyroiditis
- Colloid goiter
- Colloid cyst
- Hemorrhagic cyst



Suspicious lesions (9%)
- Follicular tumour
- Hürtle cell tumour
- Suspicious for Papillary carcinoma

TBSRTC – DIAGNOSTIC CATEGORIES

- **NONDIAGNOSTIC or UNSATISFACTORY**
- **BENIGN**
- **ATYPIA OF UNDETERMINED SIGNIFICANCE or FOLLICULAR LESION OF UNDETERMINED SIGNIFICANCE**
- **FOLLICULAR NEOPLASM or SUSPICIOUS FOR A FOLLICULAR NEOPLASM**
  - specify if Hurthle cell (oncocytic) type
- **SUSPICIOUS FOR MALIGNANCY**
- **MALIGNANT**

TBSRTC 2- Probabilistic approach and Relationship to Clinical Algorithms

Category	Risk of Malignancy (%)	Usual Management
Nondiagnostic	(1-4) **0-5**	Repeat FNA w/ US
Benign	0-3	Follow
AUS or FLUS	(10-15) **10-30**	Repeat FNA, **molecular testing or lobectomy**
SFN	(15-30) **25-50**	Lobectomy or **molecular testing**
Suspicious for Malignancy (usually papillary CA)	(60-75) **50-75**	Lobectomy or total thyroidectomy
Malignant	97-99	Total thyroidectomy **(lobectomy)***

Problems not solvable by cytology

- Patients with indeterminate cytology typically undergo a lobectomy.
- After malignancy is established by histopathology these patients require to complete the thyroidectomy with additional costs and morbidity.
- In addition, 1-3% of nodules diagnosed as benign by FNA are later found to be malignant.
- Therefore, additional methods to improve the sensitivity and specificity of FNA diagnosis are highly desirable.

THE IDEAL TEST

- TEST + ⟹ HIGH PROBABILITY OF MALIGNANCY

⇩ SURGERY

BRAF
RET/PTC
ThyroSeq

- TEST + ⟹ LOW PROBABILITY OF MALIGNANCY

⇩ Avoid SURGERY

AFIRMA GEC

BRAF Mutations

- Most prevalent oncogenic mutation in PTC (V600E)
- BRAF mutation are not randomly distributed by PTC, it is especially observed in the classic variant (up to 69% vs 20% of follicular variant).

TABLE 2. Review of all thyroid FNA studies using the BRAF mutation prior to 2009.

Thyroid FNA studies	No. of samples	BRAF positive	Final diagnosis in BRAF-positive samples (%)
Prospective studies	1814	159	PTC = 159 (100%)
Retrospective studies	685	291	PTC = 291 (100%)
FNA on thyroid specimens	267	131	PTC = 130 (99.2%) Hyperplasia = 1 (0.8%)
Total	2766	581	PTC = 580 (99.8%)

Abbreviations: FNA, fine-needle aspiration; PTC, papillary thyroid carcinoma.
Note: Results of the prospective, retrospective, and FNA on surgically removed thyroid specimens are shown.
BRAF positivity shows an almost universal correlation with a final pathologic result of PTC.
Adapted from Nikiforova MN, Nikiforov YE. Molecular diagnostics and predictors in thyroid cancer. *Thyroid* 2009;19:1351–1361. doi: 10.1089/thy.2009.0240, with permission.

BRAF testing and Thyroid FNA

- BRAF testing alone is not effective in the lowest risk Bethesda indeterminate categories (AUS/FLUS and FN/SFN) for which the rate of BRAF positive lesions is very low and clinical management is most challenging.
- In contrast, BRAF is a component of the commercial panels for mutational testing of thyroid cancers. With the evolution of NGS can be integrate with other markers (TERT) to predict biological aggressiveness.

Song YS et al. Cancer 2016

- In the context of NI-FVPTC there may increased value in using BRAF mutation testing alone or in combination in cases of suspicious for malignancy and perhaps in the malignant category.

Pusztaszeri A et al. Cancer Cytopathology 2015

Triage of the Indeterminate Thyroid Aspirate: What are the Options for the Practicing Cytopathologist?

Table 1: Comparison of molecular testing for thyroid FNA

	Afirma[7, 22, 30, 31, 42, 44, 45]	ThyGenX[24]	ThyGenX/ThyraMIR[24]	ThyroSeq[25, 58]
Method	GEC (mRNA expression profile)	NGS	NGS/GEC (miRNA expression profile)	NGS
Sensitivity	83-100%	68.6%	89%	90-91%
Specificity	7-52%	86.5%	85%	92-93%
NPV	75-100%	85.3%	94%	96-97.2%
PPV	14-57%	70.6%	74%	76.9-83%
Clinical use	Rule out malignancy	Rule in malignancy/ determine the extent of surgery	Rule out and rule in malignancy/ determine the extent of surgery	Rule out and rule in malignancy/ determine the extent of surgery
Approximate Cost[25]	$4875 *	$1675	$3300	$3200

Onenerk A, Pusztaszeri M, Canberk S, Faquin W. Cancer Cytopathology, 2017

Will Molecular Testing Reduce Unnecessary Surgery and Overall Costs?

- Duick et al, Thyroid 22: 996-1001, 2012
  - ✓ 51 endocrinologists at 21 practice sites
  - ✓ Substantial drop in surgery rate for cytologically indeterminate nodules
  - ✓ From 74% to 7%
  - ✓ One surgery avoided for every two molecular tests
- Li et al. JCEM 96: 1719-1726, 2011
  - ✓ Modeling study to evaluate 5y cost-effectiveness of Afirma
  - ✓ 74% fewer surgeries for benign nodules
  - ✓ Overall lower costs to healthcare and improved quality of life

How molecular test helps in AUS/FLUS?

1. AUS/FLUS should get a repeat FNA
2. Decision for surgery can be selectively made based on patient's risk factors and subcategory of the AUS/FLUS
3. In centers with provision of GEC test, there is a definite value in GEC test.

Can a Gene-Expression Classifier With High Negative Predictive Value Solve the Indeterminate Thyroid Fine-Needle Aspiration Dilemma?

William C. Faquin, MD, PhD

Cancer Cytopathology March 2013

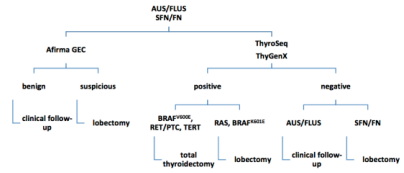
TABLE 1. Summary of the *Afirma* Test Applied to the Indeterminate Bethesda Categories[a]

Bethesda Category	No. (% of Total)	Sensitivity, %	Specificity, %	False-Negative Rate, %	NPV
AUS/FLUS	129 (48.7)	90	53	9.7	95
Suspicious for FN	81 (30.6)	90	49	10	94
Suspicious for malignancy	55 (20.8)	94	52	5.9	85
Total	265	92	52	8.2	93

Abbreviations: AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FN, follicular neoplasm; NPV, negative predictive value.
Summarized from Alexander EK, Kennedy GC, Baloch ZW, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. *N Engl J Med*. 2012;367:705-715.[10]

Triage of the Indeterminate Thyroid Aspirate: What are the Options for the Practicing Cytopathologist?

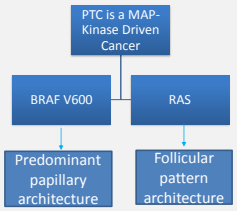
Table 2: Use of molecular testing to guide patient management for the FNA diagnosis of AUS/FLUS or SFN/FN



Onenerk A, Pusztaszeri M, Canberk S, Faquin W. Cancer Cytopathology, 2017

Diagnosis of Non-invasive Follicular Tumor with Papillary-like Nuclear Features (NIFTP): A Practice Changer for Thyroid Fine-needle Aspiration Interpretation

Sule Canberk[1*], Zubair W. Baloch[2*], Umit Ince[3], Fernando Schmitt[3,4]



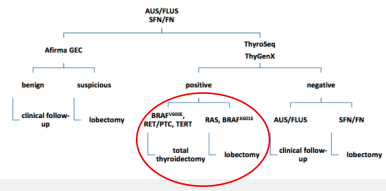
HOW THESE MOLECULAR STUDIES CAN BE HELPFUL FOR CLINICAL MANAGEMENT OF PATIENTS OF NIFTP

- UNDETERMINED CATEGORIES
- FEW STUDIES
- AFIRMA → ALL IN SUSPICIOUS
- THYROSEQ 2 → RAS MUTATIONS (+)
  BRAF MUTATIONS (-)

Jiang et al 2016

Triage of the Indeterminate Thyroid Aspirate: What are the Options for the Practicing Cytopathologist?

Table 2: Use of molecular testing to guide patient management for the FNA diagnosis of AUS/FLUS or SFN/FN



Onenerk A, Pusztaszeri M, Canberk S, Faquin W. Cancer Cytopathology, 2017

Mod Pathol. 2017 Mar 10. doi: 10.1038/modpathol.2017.9. [Epub ahead of print]

Molecular correlates and rate of lymph node metastasis of non-invasive follicular thyroid neoplasm with papillary-like nuclear features and invasive follicular variant papillary thyroid carcinoma: the impact of rigid criteria to distinguish non-invasive follicular thyroid neoplasm with papillary-like nuclear features.

Cho U[1], Mete O[2], Kim MH[3], Bae JS[4], Jung CK[1,5]

Author information

Abstract

Thyroid tumors formerly classified as non-invasive encapsulated follicular variant of papillary thyroid carcinoma were recently renamed 'non-invasive follicular thyroid neoplasm with papillary-like nuclear features'. The current study investigated the frequency of lymph node metastasis and mutational profile of encapsulated follicular variant in the setting of a clinical practice where central neck dissection was the standard of practice. We defined the impact of rigid diagnostic criteria by regrouping such tumors based on the complete absence of papillae or presence of ≤1% papillae. Of a total of 6,269 papillary thyroid carcinomas, 152 tumors fulfilled the criteria for encapsulated follicular variant. The results were stratified according to two different diagnostic cutoff criteria with respect to the extent of papillae. When the cutoff of 1% papillae was used, the rates of lymph node metastasis and $BRAF^{V600E}$ mutation were 3% and 10% in non-invasive tumors and 9% and 4% in invasive tumors, respectively. Despite the lack of invasive growth, one patient with $BRAF^{V600E}$ mutant-tumor displaying predominant follicular growth and subtle papillae developed a bone metastasis. When absence of papillary structure was applied as rigid diagnostic criteria, no $BRAF^{V600E}$ mutation was found in all tumors. However, central lymph node micrometastasis still occurred in 3% of non-invasive tumors. Non-V600E BRAF and RAS mutations were detected in 4% and 47% of non-invasive tumors, respectively. Our findings suggest that non-invasive follicular thyroid neoplasm with papillary-like nuclear features should not be regarded as a benign thyroid neoplasm as it can present with lymph node micrometastasis and should not be diagnosed in the presence of even a single papillary structure. Our findings underscore the original American Thyroid Association recommendation that defined non-invasive encapsulated follicular variants as low risk thyroid cancers. Clinical surveillance similar to low risk differentiated thyroid cancers and capture of this diagnostic category by Cancer Registries should be considered.Modern Pathology advance online publication, 10 March 2017; doi:10.1038/modpathol.2017.9.

Virchows Arch (2014) 465:119–133
DOI 10.1007/s00428-014-1608-4

REVIEW AND PERSPECTIVES

Telomerase promoter mutations in cancer: an emerging molecular biomarker?

João Vinagre · Vasco Pinto · Ricardo Celestino · Marta Reis · Helena Pópulo · Paula Boaventura · Miguel Melo · Telmo Catarino · Jorge Lima · José Manuel Lopes · Valdemar Máximo · Manuel Sobrinho-Simões · Paula Soares

TERT, BRAF and NRAS in primary thyroid cancer and metastatic disease

Miguel Melo; Adriana Gaspar da Rocha; Rui Batista; João Vinagre; Maria João Martins; Gracinda Costa; Cristina Ribeiro; Francisco Carrilho; Valeriano Leite; Cláudia Lobo; ...
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THYROID CYTOLOGY

- Despite the limitations of all the ancillary methods it is likely that in the future the number of indeterminate cases on FNA of thyroid will decline.
- However, it is worth remembering that even the histological criteria used for the diagnosis of these lesions are not entirely accurate.
- The histological diagnosis of adenomatoid goiter, follicular adenomas and carcinomas and FVPC/NIFT-P also have problems of reproducibility. With this in mind, is not surprising that different institutions may have different histological diagnoses for the same cytological diagnosis.