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Review

Thyroid cytopathology: updates and molecular testing

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Summary

The utility of fine needle aspiration (FNA) is well described in the context of evaluating thyroid lesions. Among the various international systems of classification of thyroid cytology, the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) has also provided a sound framework to standardize the reporting of FNA cytology results. New molecular evidence and clinical studies demonstrated the need for revision of the nomenclature resulting in introduction of new categories, such as the noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP). Indeterminate thyroid cytology results pose a challenge for further management and the continued development of molecular markers may aid in the management of indeterminate thyroid lesions.

Key words

Fine needle aspiration • Noninvasive follicular thyroid neoplasms with papillary-like nuclear features • Atypical cytology • Molecular tests

Fine needle aspiration (FNA) cytology is important tool in diagnosing thyroid lesions. Ultrasound guided thyroid FNA is usually indicated in thyroid nodules greater than 1.0 cm with high risk imaging features, nodules greater than 2.0 cm with intermediate imaging features or with low risk imaging features but continuously increasing size, or if there is a positive family history of thyroid cancer [1]. Paratracheal lesions or enlarged lymph nodes also requires work up which may possibly include ultrasound guided FNA (US-FNA). The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) has introduced a uniform system of reporting thyroid FNA cytology results [2]. This system includes six defined categories, but it is comparable to other international systems, such as, the Royal College of Pathology (United Kingdom) system and the Italian consensus 2014. These systems describe five major categories with further subdivision of category 3 into either low risk or atypia and high risk or suggestive of follicular neoplasm [1]. The TBSRTC essentially classifies these subcategories as category III and IV, respectively. Below is a list of the TBSRTC categories and their descriptions [3]:

a. nondiagnostic;
b. benign;
c. atypical (atypia of undetermined significance/ follicular lesion of undetermined significance);
d. suspicious for follicular neoplasm/follicular neoplasm;
e. suspicious for malignancy;
f. malignant.

I. Nondiagnostic

The criteria for adequacy are the presence of six clusters of follicular cells consisting, ideally, of a minimum of 10 cells on one slide. Of note, this criterion is not required in colloid nodules with abundant colloid, lymphocytic thyroiditis consisting of lymphocytes with few or rare follicular cells, or inflammatory/infectious conditions presenting with any atypical cells. Lack of any of the above described adequacy or diagnostic features suggests a nondiagnostic sample (Fig. 1A). Additionally, due to the risk of cystic papillary carcinoma of the thyroid, samples of cystic fluid with less

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than six groups of follicular cells are also considered nondiagnostic. Finally, obscuring or air-drying artifacts which affect the diagnostic interpretation are classified as nondiagnostic. False negative FNA results can be avoid by sampling cystic and solid portions of a cyst and by targeting the periphery of larger nodules to avoid central areas of cystic degenerative changes. If FNA is nondiagnostic and imaging or clinical features are suspicious, then repeat FNA is suggested.

II. Benign

This category includes benign colloid nodules (Fig. 1B), lymphocytic thyroiditis, papillary hyperplasia, Graves' disease, and benign cysts. Benign nodules usually consists of mostly macrofollicles mixed with a few microfollicles and abundant colloid. Hurthle cell changes can be seen in large degenerative nodules. Atypia in Hurthle cell nodules or change is an unreliable feature. Treated cases of Graves' disease can show nuclear overlapping or more microfollicles. Nodules with benign cytology results but either continuously increasing in size or with high risk imaging features may require repeat ultrasound guided FNA [1]. However, cases with stable nodular lesions may need imaging follow-up after 24 months in appropriate clinical settings. If repeat FNA is benign in clinically stable nodule then no ultrasound surveillance is required.

III. Atypia

Atypia can be further subclassified into the following categories:

A Atypia of undetermined significance

This category includes features of cytologic atypia (Fig. 1C), such as, nuclear clearing, nuclear enlargement, sparsely cellular specimens with rare atypical cells, and focal cytologic atypia in lymphocytic thyroiditis. Sometimes, "histiocytoid cells" with focal atypia are seen in cystic papillary thyroid carcinoma (PTC) and they do not show classical nuclear features of PTC. These "histiocytoid cells" are difficult to differentiate from histiocytes [4]. In such instances, immunohistochemical stains can be performed on the cell block material, if available.

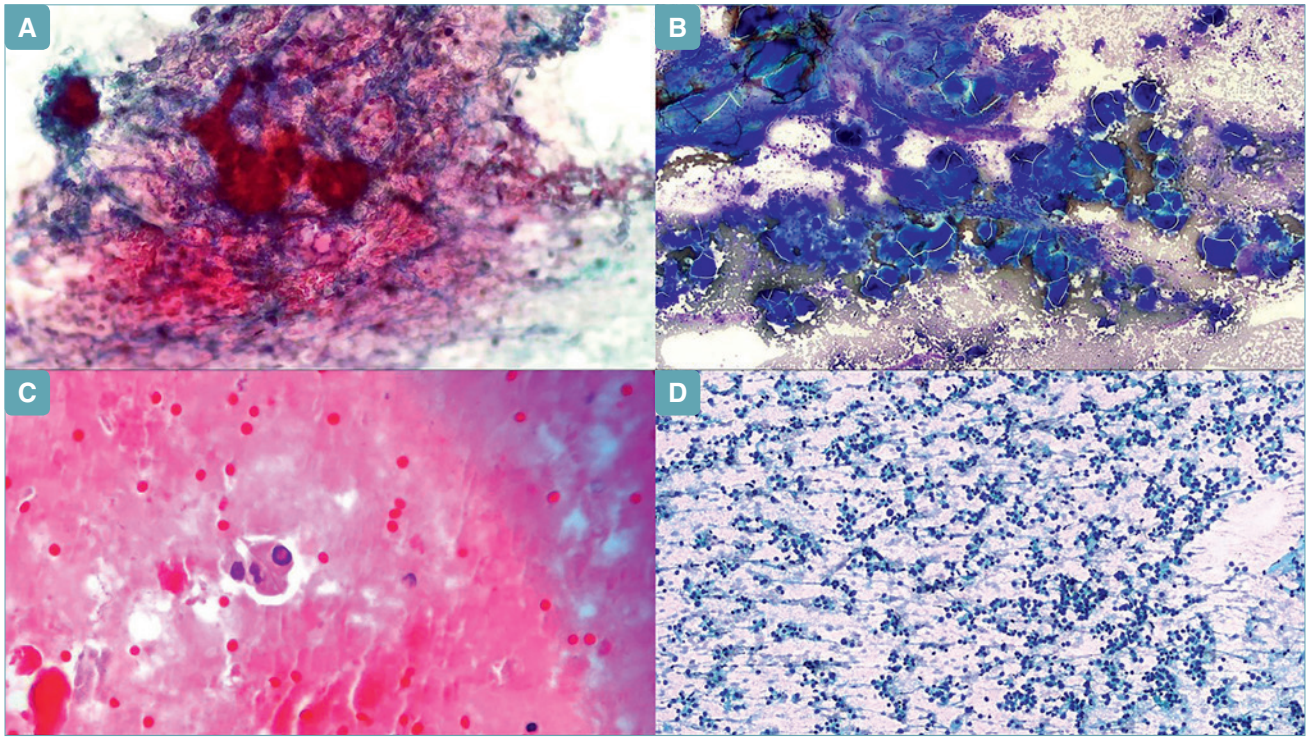

Fig. 1. (A) Nondiagnostic: Fragment of muscle (somewhat resembles colloid) (Papanicolaou stained smear) x 20, (B): Benign: Abundant colloid (Diff Quik smear) x 10, (C) AUS: Single atypical cell with nuclear inclusion (cell block) x 40, (D) Suspicious for follicular neoplasm/follicular neoplasm: Cellular specimen with microfollicles and abundant single cell with eccentrically located nuclei (Papanicolaou stained smear) x 10.

B Follicular lesion of undetermined significance

This category includes specimens with architectural atypia. Examples include small or inadequate specimens mostly exhibiting microfollicular architecture or Hurthle cell populations or primarily cellular specimens with a predominance of microfollicular architecture.

C Other

Atypia other than the aforementioned categories fall into this category. Additionally, cases previously treated with radioactive iodine and samples with lymphocytic proliferation or psammomatous calcifications fall here.

The overall risk of malignancy (ROM) is variable in this category, ranging between 6-30% [5 6]. However, it is important to recognize the institutional risk of malignancy. Categorizing architectural atypia separately from nuclear atypia may impact risk of malignancy. Recent study has suggested more risk of malignancy in cases with nuclear atypia (up to 33.3%) than architectural atypia (up to 7.7%) [7]. A conservative approach with follow-up is suggested for small and favorable lesions (e.g. those without family history). Repeat FNA will classify a majority of the atypical lesions into a definitive category [6]. According to the American Association of Clinical Endocrinologist and American College of Endocrinology guidelines for clinical practice and management, molecular testing may be helpful as an adjuvant test. If repeat FNA or molecular testing is inconclusive, then either surveillance or diagnostic surgery should be considered. Second opinion from a cytopathologist at a high-volume practice may be helpful in certain cases [1].

IV. Suspicious for follicular neoplasm/ follicular neoplasm (SFN/FN)

This diagnostic category consists of cellular aspirates with microfollicular architecture, scant or absent colloid, or exclusively Hurthle cell populations either in trabecular architecture or as single cells (Fig. 1D). Cystic changes are usually not seen unless a neoplastic nodule is large, which may allow for degenerative changes. If the neoplastic lesion is comprised of more than 75% Hurthle cells, according to WHO guidelines, it can be designated as a Hurthle cell neoplasm. Parathyroid lesions should be taken into consideration while investigating microfollicular architecture and correlation with clinical history is helpful.

The risk of malignancy reported in this category ranges from 25 to 40% [3]. Repeat FNA or core needle biopsy is unnecessary. Surgical management, via thyroid lobectomy and isthmectomy, is a preferable option. If the lesion is clinically favorable with low risk imaging features, then close follow-up may be considered. Molecular testing may be helpful in determining the need for surgery.

V. Suspicious for malignancy

Specimens in this category may be cellular with some features of PTC while not meeting the criteria for the diagnosis of carcinoma. This category also includes sparsely cellular specimens with most of the features of papillary thyroid carcinoma. Medullary carcinoma specimens which are largely cellular and contain monomorphic single cells with eccentrically located nuclei and smudged chromatin may fall into this category if they lack cell block which would allow for further characterization. Lymphoma and metastatic tumors should also be considered in the differential diagnosis of a lesion suspicious for malignancy. A surgical approach is recommended and the preferable treatment modality in most of the cases. Repeat FNA for additional sample or flow cytometry can be performed in cases concerning for lymphoma.

VI. Malignant

This diagnostic category includes carcinoma, lymphoma, other tumors, and metastatic tumors. In conventional papillary thyroid carcinoma (PTC), the specimen consists of cells arranged in papillae and/or monolayer sheets with a syncytial appearance. They show intranuclear cytoplasmic pseudoinclusions, nuclear crowding, intranuclear grooves, and pale nuclei with powdery chromatin (Fig. 2). If the tumor lacks papillae and contains mostly follicular architecture with nuclear feature of PTC, then differential diagnosis should include papillary thyroid carcinoma, follicular variant (PTC-FV) or noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP). In the latter category, the nuclear changes are mostly subtle and therefore the category “suspicious for follicular neoplasm” or “suspicious for malignancy” can be used. Surgical treatment is recommended management in most cases.

Recently, the NIFTP category was introduced in the thyroid tumor classification replacing encapsulated noninvasive papillary carcinoma follicular variant (NI-EFV-PTC). Nikiforov et al. compared 109 cases (with tumor size 1.1 cm-9.0 cm) of NI-EFV-PTC compared to 101 cases (0.6-5.5 cm) of invasive EFV-PTC. With

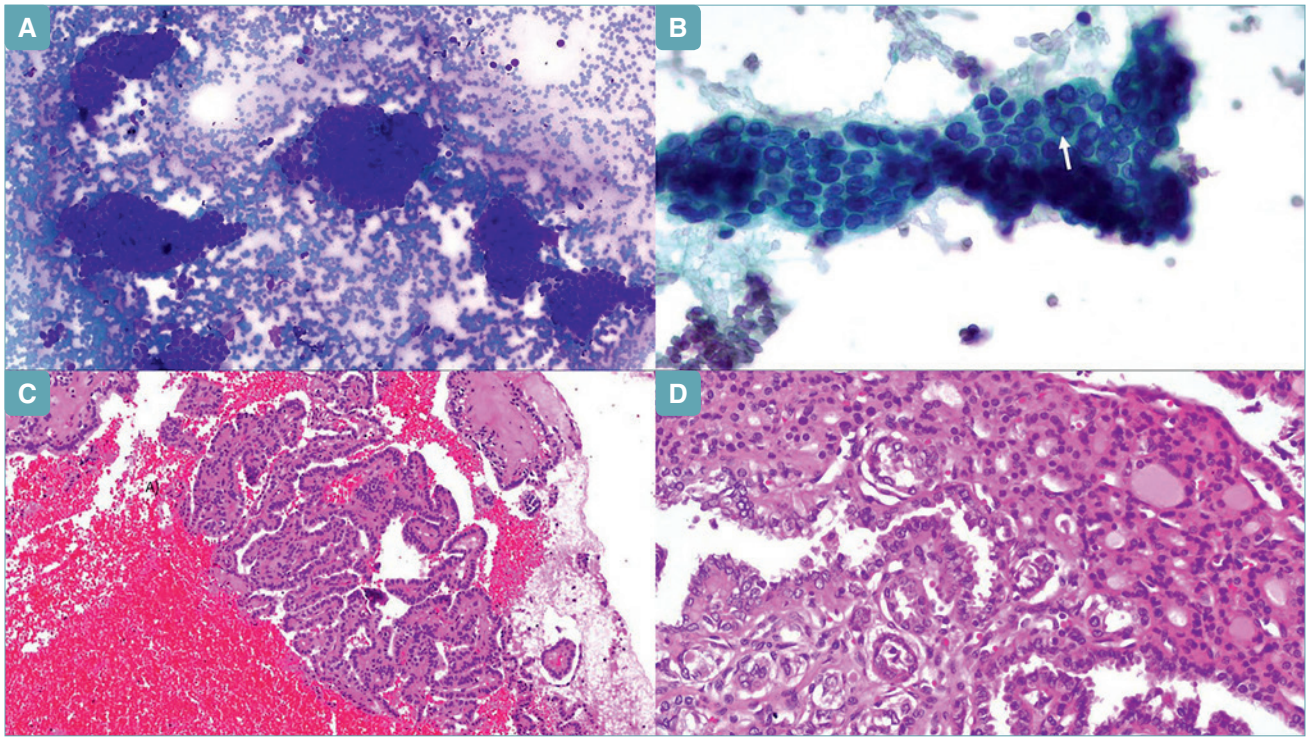

Fig. 2. Papillary carcinoma, (A) Clusters of papillary carcinoma with focal nuclear crowding x 10 (Diff-Quik smear), (B) Elongated and oval nuclei, nuclear overlapping and intranuclear inclusion (arrow)(Papanicolaou stained smear) x 40, (C) Fragment of papillary carcinoma (cell block) x 10, (D) Tissue section with focus of papillary carcinoma x 20.

a mean follow-up of 14.4 years, the authors did not find any cases of NI-EFV-PTC with any recurrence or metastasis. However, 12 cases with either metastasis or/and recurrence were noted in the comparison group (IEFV-PTC). The most frequent mutation in the NI-EFV-PTC was RAS, a commonly mutation seen in follicular adenoma (FA). These findings supported an indolent behavior for NI-EFV-PTC which resulted in recommendation for a nomenclature shift to NIFTP [7]. Johnson and colleagues found RAS mutation in FA (4/11) and NIFTP (20/32) but no cases in PTC with extensive follicular growth pattern and suggested molecular similarities between FA and NIFTP [8].

Specific histologic criteria are required to establish a diagnosis of NIFTP (Fig. 3). Neoplastic cells should be in microfollicular architecture, show some nuclear features of PTC, and either encapsulated or with demarcated outline and no capsular or vascular or intraparenchymal invasion noted. NIFTP usually show some nuclear features including irregular nuclear membrane, nuclear enlargement, and chromatin clearing. Intranuclear pseudoinclusions are very rare and infrequently seen [9 10]. No papillae, psammoma bodies, necrosis, or increased mitosis (> 3), or solid growth > 30% should be seen. NIFTP cases are BRAF600E and TERT negative and they usually show indolent behavior and do not metastasize [11]. In the original study suggesting NIFTP classification, all cases of NI-EFV-PTC cases were larger than 1.0 cm which raises concerns about the classification of lesions less than 1.0 cm as encapsulated/well circumscribed PTC (microPTC versus NIFTP) [7].

Another group compared 52 cases of encapsulated follicular variant of microPTC (EFV) and 57 invasive EFV-microPTC and followed the cases for two years. They did not find any recurrence in the first group (noninvasive) but found 5 cases with lymph node metastasis in the invasive EFV-PTC group. They concluded the study with suggestion to include noninvasive EFV-PTC in NIFTP category [12].

Cytologic evaluation of NIFTP cases poses a challenge when differential diagnosis includes PTC-FV. Most of the studies proposed classifying NIFTP as Bethesda category IV (suspicious for follicular neoplasm/ follicular neoplasm) or Bethesda Category V (suspicious for malignancy) with a disclaimer about

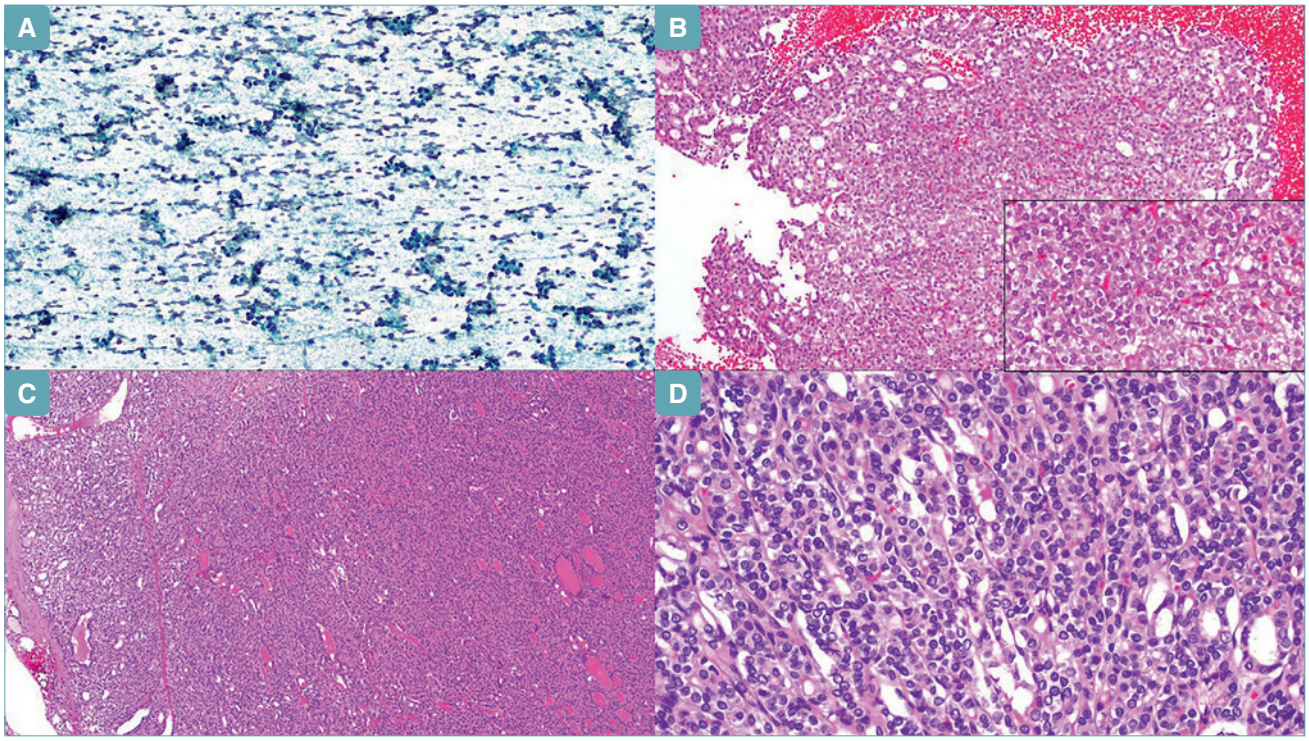

Fig. 3. Noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP), (A) Abundant microfollicles (Papanicolaou stained smear) x 10, (B) Tightly packed clusters of microfollicles with very scant colloid x 10 x. High magnification shows vague nuclear clearing (cell block) x 40x, (C) Histology sections shows encapsulated microfollicular neoplasm 4X, (D) There is some nuclear overlapping, nuclear groves and nuclear clearing x 20.

the differential diagnosis. Cytomorphologic features of NIFTP usually show microfollicular architecture and some nuclear features of PTC with rare pseudoinclusions [11 12]. On the other hand, they show RAS, BRAFK601, PPARG, and THADA gene fusions while being negative for BRAF600E. Due to the classification of NIFTP as an indolent neoplasm rather than malignant carcinoma, one would expect a decrease in risk of malignancy in indeterminate cytology cases. Bethesda classes III and V showed a decreases in the observed the risk of malignancy (Bethesda III: 10-30% to 6-18% and Bethesda V: 50-75% to 45-60%), while the risk of malignancy in category IV remained comparable [13-15]. This new understanding of the risk of malignancy of NIFTP raises questions about the use of lobectomy versus total thyroidectomy in future investigations and the use of molecular testing as an aid in determining the surgical approach.

Molecular markers are developed to guide further management in indeterminate thyroid lesions. Molecular tests can either be a rule in test or rule out test. A rule in test is used to predict malignancy and helps guide surgical management. They usually have a high positive predictive value (PPV) and specificity (confirmatory test). Rule out tests helps identify cases without disease and thereby avoiding unnecessary surgical treatment in patients with indeterminate cytology results. Rule out tests should have high negative predictive value (NPV) and sensitivity. There are some challenges associated with the use of molecular testing such as cost, insurance coverage, and collection and preservation of the sample. Currently, there are four clinically used molecular tests and they are described and listed below:

1. Afirma Gene Expression Classifier;
2. Thyroseq Genomic Classifier;
3. ThyGeNEXT and ThyraMIR;
4. RosettaGX.

1. Afirma Gene Expression Classifier

This is a DNA microarray-based test used for intermediate cytology results. Results are reported as BENIGN or SUSPICIOUS [16]. Initial FNA passes are utilized for cytologic diagnostic evaluation while two sep-

arate FNA passes are stored in a vial with nucleic acid preservative. The initial screening is performed with 25 genes, including those genes for metastatic tumors, parathyroid, and medullary carcinomas (MTC). If the latter is positive, it is reported as a positive result. If the initial screen is negative, then the specimen is examined for an additional 142 genes to complete the main GEC panel. Benign results are low risk (5%) while suspicious results are considered moderate risk (40%). If BRAF 600E is positive then the specimen is considered high risk (100%).

McIver et al. in a study of 105 indeterminate cytology cases evaluated Afirma GEC results in 36 cases and compared the ROM using histologic follow-up. Of the 32 GEC-suspicious cases, 5 were found to be malignant while 27 were benign. They reported statistical results (% sensitivity, specificity, PPV, and NPV) as follows: 83, 10, 16, and 75, respectively [16]. In one of the initially published studies of 265 indeterminate cytology results including AUS/FLUS (n = 129), SFN/FN (n = 81), and suspicious for malignancy (n = 55), the authors found Afirma GEC analysis of AUS/FLUS to have the following results (% sensitivity, specificity, PPV, and NPV): 90, 53, 38, and 95, respectively. For SFN/FN, the results (% sensitivity, specificity, PPV, and NPV) were as follows: 90, 49, 37, and 95, respectively [17].

In instances with indeterminate cytology results with negative Afirma GEC testing, it is appropriate to follow-up as if the lesions were benign [18]. Azizi et al. evaluated 151 indeterminate cytology results and found GEC suspicious results in 59 and GEC benign in 92 cases. Of the GEC-suspicious group, 28 (47.5%) were malignant while 17 cases in the benign group received follow-up surgery and 3 (3.3%) of these cases were found to be malignant on follow-up histology [19].

2. THYROSEQ Genomic Classifier

This method utilizes DNA and RNA next generation sequencing to detect hot spot mutation, gene fusions, gene alterations including copy number variations (CNV) with ThyroSeq v3. Currently, Thyroseq v2 (2014) uses a 56 gene panel and Thyroseq v3 (2017) has 112 gene panels available for clinical use. This test is reported as either NEGATIVE or POSITIVE. Specimen collection requires either a separate FNA pass into Thyroseq Preserve solution or formalin fixed paraffin embedded tumor sections. A recent study evaluated 247 indeterminate cytology results (Bethesda III and IV) and compared them to corresponding Thyroseq v3 and histology (cancer + NIFTP) results. They found overall sensitivity to be 94%, specificity 82%, PPV 66%, and NPV 97% [20]. For Bethesda category III, the different variables (%; sensitivity, specificity, PPV, and NPV) for Thyroseq v2 and v3 are compared as follows: 91, 92, 77, 97 and 91, 85, 64, 97, respectively [20-21].

3. ThyGeNEXT and ThyraMIR

This method requires DNA and RNA extraction by next generation sequencing (NGS). A dedicated FNA pass is required and the specimen is preserved in fixative (up to six weeks in a room temperature). ThyGeNEXT NGS Panel consists of DNA mutation panel (BRAF, PIK3A, HRAS, KRAS and NRAS) and chromosome rearrangements (RET-PTC1, RET-PTC3 and PAX8-PPARG). If initial testing with ThyGeNEXT shows either BRAF or TERT mutations, this is considered high risk and surgical options should be considered. If ThyGeNEXT shows other mutations, then ThyraMIR consisting of 10 miRNA (miR-29b-1-5p, miR-31-5p, miR-138-1-3p and others) is the next step and the result is reported as LOW or MODERATE risk. Labourier et al. studied 109 indeterminate cytology results (Bethesda III & IV) and found (%) sensitivity, specificity, PPV and NPV as follows: 94, 80, 68, 97 and 82, 91, 82, 91, respectively [22].

4. RosettaGX

This test measures 24 miRNA by using quantitative RT-PCR. Some of the miRNA overlap with ThyraMIR® miRNA classifier (hsa-miR-31-5p, hsa-miR-222-3p, hsa-miR-146b-5p, hsa-miR-375, hsa-miR-551b-3p). Testing requires cell acquisition directly from the ThinPrep slide and direct smears and results are reported as BENIGN or SUSPICIOUS. An initial validation study evaluated indeterminate thyroid cytology results (Bethesda III, IV and V) by dividing them in two categories; validation set (n = 189; when one out of two pathologists agree with the original pathologists diagnosis) and validation agreement set (n = 150; when all three pathologists agree with the diagnosis). They found (%) sensitivity, specificity, PPV and NPV in these two groups as follows: 85, 72, 59, 91 and 98, 78, 62 99, respectively [23].

According to the American Thyroid Association management guidelines, molecular testing should be performed in Clinical Laboratory Improvement Amendments (CLIA)/College of American Pathologist certified laboratories. In Bethesda III cases, repeat FNA and molecular testing may help in ROM assessment and should be performed based on clinical judgment and patient preferences. If repeat FNA or molecular

testing is inconclusive, then either surveillance or diagnostic surgery should be considered. On the other hand, in Bethesda category IV, surgical management is usually performed while molecular testing may be used to assess the ROM [24].

Conflict of interest statement

None declared.

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