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)

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.

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: 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.

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

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

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

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

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
  - BRAF RET/PTC ThyroSeq
  - SURGERY

- **TEST +** LOW PROBABILITY OF MALIGNANCY
  - AFIRMA GEC
  - Avoid SURGERY

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).

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.
- 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.

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

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

**Table 1:** Summary of the Afirma Test Applied to the Indeterminate Bethesda Categories

<table>
<thead>
<tr>
<th>Bethesda Category</th>
<th>No. (% of Total)</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>False-Negative Rate, %</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUS/FLUS</td>
<td>129 (100.0)</td>
<td>55 benign</td>
<td>46 suspicious</td>
<td>28 malignant</td>
<td>70</td>
</tr>
<tr>
<td>BRAF V600</td>
<td>118 (90.4)</td>
<td>55 benign</td>
<td>46 suspicious</td>
<td>28 malignant</td>
<td>70</td>
</tr>
<tr>
<td>RAS</td>
<td>105 (81.3)</td>
<td>55 benign</td>
<td>46 suspicious</td>
<td>28 malignant</td>
<td>70</td>
</tr>
<tr>
<td>Predominant papillary architecture</td>
<td>112 (86.7)</td>
<td>55 benign</td>
<td>46 suspicious</td>
<td>28 malignant</td>
<td>70</td>
</tr>
<tr>
<td>Follicular pattern architecture</td>
<td>107 (82.5)</td>
<td>55 benign</td>
<td>46 suspicious</td>
<td>28 malignant</td>
<td>70</td>
</tr>
</tbody>
</table>

**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

**Diagnosis of Non-invasive Follicular Tumor with Papillary-like Nuclear Features (NIFTP): A Practitioner's Guide for Thyroid Fine-needle Aspiration Interpretation**

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

**Afirma SEC**

BRAF V600

RAS

Predominant papillary architecture

Follicular pattern architecture

PTC is a MAP Kinase Driven Cancer

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 dual criteria to distinguish non-invasive follicular thyroid neoplasm with papillary-like nuclear features.

Jiang et al 2016

**Table 2:** Use of molecular testing to guide patient management for the FNA diagnosis of AUS/FLUS vs SPNFN

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afirma SEC</td>
<td>Thryoseq 2</td>
</tr>
<tr>
<td>BRAF V600</td>
<td>RAS Mutations (+)</td>
</tr>
<tr>
<td>RAS</td>
<td>BRAF Mutations (-)</td>
</tr>
</tbody>
</table>

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