Update on Thyroid FNA – The Bethesda System

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Thyroid Nodules

- Frequent occurrence
  - Palpable: 4-7% of adults
  - Ultrasound: 10-31%
- Majority benign
- FNA has proven to be an effective management tool in patients with thyroid nodules
Thyroid FNA

- Safe, inexpensive, easily performed, minimal patient discomfort
- High diagnostic accuracy rate ~ 90-100%
- False positive diagnoses: <1%
  - over-interpretation of reparative and reactive nuclear changes as papillary thyroid carcinoma (PTC)
- False negative rates: 1-11%
  - unsatisfactory specimens
  - sampling errors
  - interpretation errors
  - cystic neoplasms, especially PTC
- Major limitations include:
  - difficulty to distinguish hypercellular non-neoplastic nodules from follicular neoplasm
  - difficulty to obtain an adequate specimen on some occasions
THYROID FNA

- Its main purpose is
  - to provide a rational approach to management and
  - to determine the correct surgical procedure when surgery is required
The Bethesda Conference

- Aim: to provide the current “state of the science” in the practice of thyroid FNA.
- Held - Oct 2007 Bethesda, Maryland
- 6 committees were formed for review of English medical literature extending back to 1995
- Final document containing the review and conclusions – posted on Feb 2008
- The text was not endorsed as standard of practice guidelines
Fine Needle Aspiration Biopsy Technique

HIGH Quality smears are essential for diagnosis
Thyroid FNA

- Needles: 27-25G
  - Dwell time in nodule – 2-5 secs
  - Biopsy cadence – 3/sec;
  - 1-2 slides per pass
- Zajdela Technique
- 2-5 passes
### Needle size and Follicles

Follicular cell nucleus = 8-10 µ
Follicle = 200 µ

<table>
<thead>
<tr>
<th>Needle Gauge</th>
<th>Internal diameter (mm)</th>
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<tbody>
<tr>
<td>22</td>
<td>0.394</td>
</tr>
<tr>
<td>23</td>
<td>0.318</td>
</tr>
<tr>
<td><strong>25</strong></td>
<td><strong>0.241</strong></td>
</tr>
<tr>
<td>28</td>
<td>0.165</td>
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</table>
Zajdela Technique

Diagn Cytopath 2:17, 1986
Adequate number of passes
## Adequacy Rate in Relation to Number of Passes

<table>
<thead>
<tr>
<th>Reference</th>
<th>No of Passes</th>
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<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Hamburger et al. Arch Pathol Lab Med 1989 113(9):1035-41.</td>
<td>36</td>
</tr>
<tr>
<td>Redman et al. Thyroid 2006; 16(1):55-60</td>
<td>5</td>
</tr>
</tbody>
</table>

- Not enough data reported to assess the role of the no. of passes on sensitivity within individual studies.
- From discussions at the meeting, it was felt that the small incremental increase in adequacy reported beyond 5 passes did not out-weight the potential increased morbidity and trauma associated with additional passes, and, as such, the consensus among all specialists in attendance was to **stop at 5 passes**.
Optimal Number of Passes for Solid or Cystic Lesions

- 2-5 biopsies from different sites
- representative tissue from each pass smeared on a slide (or 2) and the remaining rinsed into a collection tube with transport fluid medium
Preparing a good smear is as important as performing the procedure
Material to Path

- **Direct smears**: 1-2 slides per pass
- **Material in liquid preservative** (needle rinses or dedicated pass)
  - CytoRich Red – Concentrated smears and cell blocks
  - RPMI (special medium required in work up of cases with lymphoma)
Diagnostic terminology / classification scheme and morphologic criteria for cytologic diagnosis of thyroid lesions
Cytopathologist Review of Slides

- Presence of colloid
- Cellularity
- Cytomorphology
What most of us have been saying on our reports

- Benign
- Indeterminate (Don’t know)
  - Follicular lesion/nodule
- Suspicious
- Malignant
- Non Diagnostic
## Tiered Classification

### Suggested Categories

<table>
<thead>
<tr>
<th>Category</th>
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<tr>
<td>Benign</td>
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<tr>
<td>Atypia of Undetermined significance or Follicular lesion of Undetermined significance</td>
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<tr>
<td>Follicular/Hurthle cell Neoplasm or Suspicious for Follicular/Hurthle Neoplasm</td>
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<td>Suspicious for Malignancy</td>
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<tr>
<td>Malignant</td>
</tr>
<tr>
<td>Non-diagnostic</td>
</tr>
</tbody>
</table>
1. Benign

- Low risk of malignancy <1%
- The diagnostic terms include:
  - nodular goiter
  - chronic lymphocytic thyroiditis
  - hyperplastic/adenomatoid nodule in goiter
  - colloid nodule.
- Follow up:
  - by clinical and periodic radiologic exam
  - repeat FNA due to increase in the size of nodule.
1a. Colloid nodule
Ia. Colloid nodule
1a. Colloid nodule
1b. Lymphocytic thyroiditis
1b. Lymphocytic thyroiditis
1b. Lymphocytic thyroiditis
1b. Lymphocytic thyroiditis
D/D of lymphocytes in thyroid

- Chronic inflammation in goiter
- Chronic lymphocytic thyroiditis
- Graves disease
- Radiation/drug induced thyroiditis
- Intrathyroidal lymph node
- Malignant lymphoma – NHL, HD
3. Follicular Neoplasm/ Suspicious for Follicular Neoplasm

- Low to intermediate *risk of malignancy 20-30%* (higher in Hurthle cell lesions if the nodule is equal to or larger than 3.5 cm)

- **Includes:**
  - *Non-papillary* follicular patterned lesions/neoplasms
  - Hurthle cell lesions/neoplasms.
  - Other suggested diagnostic terms - micro-follicular proliferation/lesion, suggestive of neoplasm and follicular lesion.

- **Lobectomy/hemithyroidectomy**

- Diagnosis rendered on surg. pathology exam - adenomatoid nodule or adenoma or carcinoma
3a. Follicular neoplasm

Microfollicle - <15 cells in a circle that is at least 2/3 rd complete
3a. Follicular neoplasm
3a. Follicular neoplasm
3a. Follicular neoplasm
3b. Follicular neoplasm
3b. Follicular neoplasm
Cellular Follicular Patterned Lesions

- Hyperplastic (adenomatous) nodule
- Hyperplasia (Graves’ disease)
- Hurthle cell nodule in thyroiditis
- Follicular adenoma
- Follicular carcinoma, well diff
- Papillary carcinoma, follicular variant
3b. Hurthle cell neoplasm
3b. Hurthle cell neoplasm
3b. Hurthle cell neoplasm
Hurthle Cell Proliferations

- Hurthle cell nodule in thyroiditis
- Hurthle cell adenoma
- Hurthle cell carcinoma
- Papillary carcinoma, oncocytic variant
- Medullary carcinoma
2. Follicular Lesion/Atypia of Undetermined Significance

- **Risk of malignancy 5-10%**
- **Heterogeneous category** that includes
  - cases where cytologic findings are not convincingly benign, yet the degree of cellular or architectural atypia is not sufficient for an interpretation of "Follicular Neoplasm" or "Suspicious for Malignancy".
  - compromised specimen (e.g. low cellularity, poor fixation, obscuring blood).
- Benefit from **repeat FNA** and correlation with clinical and radiologic findings.
- When utilized should ideally represent <7% of all thyroid FNA interpretations.
2a. Follicular atypia
2a. Follicular atypia
2a. Follicular atypia
2a. Follicular atypia
2a. Colloid goitre...
2a. Papillary carcinoma
2a. Papillary carcinoma
2b. Follicular lesion
2b. Follicular lesion
2c. Hurthle cell lesion
2c. Hurthle cell lesion
2c. Hurthle cell lesion
4. Suspicious for Malignancy

- **Suspicious for papillary carcinoma**
  - majority of cases (50-75%) are found to be follicular variant of papillary carcinoma

- **Suspicious for medullary carcinoma**
  - applies to cases with limited specimen for confirmatory immunostains – calcitonin
  - the cytology report should include a recommendation to assay serum calcitonin levels to confirm cytologic impression

- **Suspicious for other primary and secondary malignancies**

- **Suspicious for neoplasm because of total necrosis of the lesional cells** (anaplastic carcinoma).
4a. Suspicious for Malignancy
4a. Suspicious for Malignancy
4a. Suspicious for Malignancy
4a. Papillary carcinoma
4b. Suspicious for Malignancy
4b. Suspicious for Malignancy
4b. Suspicious for Malignancy
5. Malignant

- Papillary carcinoma and its variants
- Poorly differentiated carcinoma
- Anaplastic carcinoma
- Medullary carcinoma
- Lymphoma
- Metastases
5c. Malignant: Papillary Ca
5c. Malignant: Papillary Ca
5a. Malignant: Papillary Ca
5a. Malignant: Papillary Ca
5a. Malignant: Papillary Ca
5b. Malignant: Medullary Ca
5b. Malignant: Medullary Ca
5b. Malignant: Medullary Ca
5b. Malignant: Medullary Ca
Metastatic carcinoma

- Rare - <10% of thyroid neoplasms sampled by FNA
- Multiple/solitary lesion/s
- Most common primaries – Breast, Lung, Kidney, Colon, Melanoma
- History of primary neoplasm is usually present
6. Non-diagnostic

- Processed and examined, but non-diagnostic due to
  - limited cellularity
  - no follicular cells or
  - poor fixation and preservation

- Repeat FNA can be recommended in these cases (6-18 mos)
6a. Non-diagnostic – insufficient follicular cells
6b. Non-diagnostic- poor preservation
6b. Non-diagnostic - poor preservation
6b. Non-diagnostic - poor preservation
Adequacy

- All thyroid FNAs must be technically adequate with well preserved and well prepared tissue for examination
- Solid nodules with less than abundant colloid:
  - 5-6 groups with at least 10 cells is recommended
- Minimum no. of follicular cells are not required
  - Smears with abundant thick colloid
  - Inflammatory processes eg thyroiditis
  - Cystic lesions
Colloid nodule
Cystic lesions

- Most commonly occur as a result of cystic degeneration of adenomatous nodule
- Low risk of malignancy (1-4%) in simple non complex cysts
- Higher risk of malignancy (~14%) in
  - Mixed cystic and solid nodules
  - Cysts > 3cm
  - Recurring cysts
- Of all aspirated cysts 1% are malignant
Cystic lesion contd.

- Because of low potential of false negative it is recommend that cysts be interpreted as
  
  **Negative for malignancy**

Clinical and radiologic correlation is a must
- Cyst size, complexity
- Disclaimer of cystic papillary ca
Cystic degn. in colloid nodule
Cystic degn. in colloid nodule
Cystic degn. in Papillary ca
Cystic degn. in Papillary ca
Causes of Diagnostic Failures

- Unsatisfactory samples ~ 50%
- Remaining 50%:
  - shortcomings in interpretation of adequate samples or
  - pathologists issuing diagnoses on samples with inadequate material

Thus unsatisfactory specimens were the cause or a contributing factor in the majority of failed diagnoses.
Factors Affecting Adequacy

- Operator's skill
- Nature of the nodule (size, location, cystic, fibrotic, etc)
- Gauge of the needle
- Whether the needle is aspirated or only capillary suction is used
- The number of passes
- Other technical factors
- The criteria for adequacy
- The patient's tolerance of the procedure
Unsatisfactory sample rate of <10% is a conservative measure of proficiency

(cyst contents that may be categorized as “non-diagnostic” due to a lack of follicular cells should not be considered “unsatisfactory” samples)
## Tiered Classification Scheme

<table>
<thead>
<tr>
<th>Suggested Categories</th>
<th>Alternate Category (s) terms*</th>
<th>Risk of Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign</strong></td>
<td></td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
| **Follicular lesion of undetermined significance** | Atypia of undetermined significance  
R/O Neoplasm  
Atypical follicular lesion  
Cellular Follicular Lesion | 5-10%              |
| **Neoplasm**                                 | Suspicious for Neoplasm                                         | 20-30%             |
| **Suspicious for Malignancy**                |                                                                 | 50-75%             |
| **Malignant**                                |                                                                 | 100%               |
| **Non-diagnostic**                           | Unsatisfactory                                                 |                    |
Ancillary studies

Suspected medullary carcinoma
- IHC panel (calcitonin, thyroglobulin, CEA, chromogranin)
- Serum calcitonin

Suspected anaplastic carcinoma
- IHC for pan-cytokeratin

Suspected metastatic carcinoma
- IHC for TTF-1
- If TTF-1 negative, expand IHC panel based on cytomorphology and clinical setting to identify primary
Ancillary studies

Suspected metastatic thyroid carcinoma to lymph node
- IHC for TTF-1, thyroglobulin, calcitonin
- May consider thyroglobulin level assessment on FNA sample

Suspected lymphoma
- Flow cytometric immunophenotyping