Thyroid Fine Needle Aspiration and Bethesda Reporting Guidelines

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Why The Need For New Terminology?
- Increasing number of nodules being detected
- Hence, increasing numbers of Thyroid FNAs
- No consistent reporting terminology
- Clinical confusion
- Follow-up not evidence based

Incidence of Thyroid Nodules
- Palpable nodules in 5-10% of US population
- Incidentalomas in 42-67%
- Risk of malignancy in incidentalomas
  - Ultrasound-10%
  - PET-14-50%
  - Sestamibi-22-66%
  - CT & MRI-10%
Multidisciplinary NCI State of the Science Conference October 2007

- Pathologists (cyto and surgical), radiologists, endocrinologists, surgeons
- Preconference committees and online discussion
- Evidence based
- Summary document and atlas

Committees

- Indications for thyroid FNA and pre FNA requirements
- Training and credentialing
- Techniques (see video at http://thyroidfna.cancer.gov)
- Terminology and morphologic criteria for cytologic diagnosis
- Utilization of ancillary studies
- Post Thyroid FNA testing and treatment

Indications for Thyroid FNA

- Palpable nodule
- PET positive
- Hot on sestamibi scan
- Suspicious features on U/S or >1.5cm in diameter
- Detected on CT or MRI-need more data
NCI Thyroid FNA
State of the Science Conference
Bethesda, MD
October 22-23, 2007

• 154 registrants
• pathologists, surgeons, endocrinologists, radiologists
• moderated by Drs. Susan Mandel and Edmund Cibas

Slide courtesy Dr E Cibas

The Bethesda System Print Atlas

• Similar in size and format to cervix book
• Definitions, criteria, explanatory notes
• Over 40 contributing authors
• Edited by S. Z. Ali (chair of Atlas Committee) and E.S. Cibas
• 200 pages
• 200 color images
• $40.
• In print: Dec15th 2009

The Bethesda System:
Relationship to Clinical Algorithms

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk of Malignancy (%)</th>
<th>Usual Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient for Diagnosis</td>
<td>1-4</td>
<td>Repeat FNA w/ U/S</td>
</tr>
<tr>
<td>Benign</td>
<td>&lt;1</td>
<td>Follow</td>
</tr>
<tr>
<td>ACUS</td>
<td>~5-10</td>
<td>Repeat FNA</td>
</tr>
<tr>
<td>Sus for a Follicular Neo</td>
<td>20-30</td>
<td>Lobectomy</td>
</tr>
<tr>
<td>Sus for a Hürthle Cell Neo</td>
<td>20-45</td>
<td>Lobectomy</td>
</tr>
<tr>
<td>Suspicious for Malignancy</td>
<td>60-75</td>
<td>Lobectomy or total thyroidectomy</td>
</tr>
<tr>
<td>(usually papillary CA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99</td>
<td>Total thyroidectomy</td>
</tr>
</tbody>
</table>

Slide courtesy Dr Edmund Cibas
### Benign (>70% of cases)

- Adenomatous Nodules/multinodular goiter
- Hashimoto’s/lymphocytic thyroiditis
- Other benign entities like subacute thyroiditis, infection etc
- False negative rate <1%

### Benign: Adenomatous Nodule/Multinodular Goiter

- Most common cause of palpable and non-palpable thyroid nodules (2-50% depending upon definition and palpable vs microscopic)
- Histologically colloid lakes alternating with normal, attenuated or hyperplastic foci of thyroid epithelium
- Hemorrhage, siderosis, fibrosis, cystic change, degeneration, calcification and ossification.

### Benign: Adenomatous Nodule/Multinodular Goiter

- **Cellularity** - variable but usually low to moderate
- **Presentation** - Cohesive cells in flat sheets or macro follicles (fragmented or intact)
- **Colloid** - abundant, watery and thick
- **Cells** - Evenly spaced follicular cells with coarse chromatin
Adenomatous Nodule/Multinodular Goiter

Benign: Hashimoto’s/Lymphocytic Thyroiditis

- Autoimmune disease
- Thyroid parenchyma replaced by lymphoid infiltrate with germinal centers +/- fibrosis
- Autoantibodies (anti microsomal and TSH)
- Most hypothyroid after long standing disease
- Diffuse painless enlargement with or without nodularity

Benign: Hashimoto’s/Lymphocytic Thyroiditis

- Cellularity- variable
- Presentation- Dispersed cell population and lymphohistiocytic aggregates
- Colloid-scant to absent
- Cells- Lymphocytes, histiocytes, plasma cells and hurthle cells, some with atypia. Lymphocytes crawling over hurthle cells
Hashimoto’s Thyroiditis

Other Pitfalls…

Restrictive Light Chain Ratio by Flow Cytometry in Germinal Center B Cells in Hashimoto Thyroiditis

Benign: Granulomatous (de Quervain’s Thyroiditis)

- Subacute thyroiditis with pain and asymmetric enlargement
- Association with HLAB35 haplotype
- Little or no adherence to surrounding structures (unlike Reidel’s)
- Inflammation and non-caseating granulomas with foreign body giant cells
- CA19-9+ in late stage, CEA early (immuno)
Benign: Granulomatous Thyroiditis

- **Cellularity**: variable
- **Presentation**: Dispersed cell population and lymphohistiocytic aggregates and giant cells
- **Colloid**: scant to absent
- **Cells**: Giant cells, lymphocytes, histiocytes, plasma cells and follicular cells

Other Causes of Granulomas in Thyroid

- Sarcoidosis
- Mycosis
- Tuberculosis
- Post op necrotizing granulomas
- Palpation thyroiditis (no clinical significance)
Malignant (3-7\% of Thyroid FNAs)

- Papillary Carcinoma
- Medullary Carcinoma
- Poorly differentiated (Insular) carcinoma
- Undifferentiated(anaplastic) Carcinoma
- Lymphoma
- Metastatic Carcinoma

Papillary Carcinoma

- Most common thyroid malignancy (80\%)
- Any age but most between 30-50 yrs
- Most present as solitary and enlarging cold nodule
- Account for the largest number of malignant “incidentalomas”
- Ret/PTC gene

Malignant: Papillary Carcinoma

- **Cellularity**: Usually cellular with rare exceptions (intracystic Papillary)
- **Presentation**: Sheets, papillae or microfollicles with nuclear crowding/molding
- **Colloid**: Usually scant but can be variable
Malignant: Papillary Carcinoma

- Cells
  - Nuclei: Powdery chromatin with nuclear grooves, pseudoinclusions, nucleoli, membrane irregularity.
  - Cytoplasm: Variable. Could be scant, squamoid, Hurthle like or vacuolated.
  - Others: Psammoma bodies, histiocytes, multinucleated giant cells

Follicular Variant of Papillary Carcinoma

- Difficult to distinguish from follicular adenoma or carcinoma
- Microfollicular pattern but with nuclear and chromatinic characteristics of papillary or suggestive of papillary carcinoma
- If not diagnostic cytologically, may be classified under suspicious for Papillary or under susp for follicular (depending upon level of suspicion)
Malignant: Papillary Carcinoma (FV)

- **Cellularity**: Usually cellular
- **Presentation**: Microfollicles with nuclear crowding/molding
- **Colloid**: Usually scant but can be variable or even abundant
- **Cells**: Powdery chromatin, grooves, intranuclear inclusions

Medullary Carcinoma

- 5-10% of Thyroid Carcinoma
- 80-90% sporadic and in adults
- Rest in children with MEN syndromes
- Arise from parafollicular C cells and secrete Calcitonin
- Hence serum Calcitonin for screening
Malignant: Medullary Carcinoma

- **Cellularity**: Usually cellular
- **Presentation**: Dispersed single cells and loose clusters
- **Colloid**: Scant to absent
- **Cells**: Epitheloid, Plasmacytoid and/or spindle cells. Sporadic large cells.

Malignant: Medullary Carcinoma

- **Nuclei**: round or elongated with finely or coarsely granular chromatin, inconspicuous nucleoli, pseudoinclusions in 50% of cases, rarely multinucleation
- **Cytoplasm**: red cytoplasmic granules (70% of cases) especially on DQ.
- **Amyloid**

Medullary Carcinoma
Poorly Differentiated Carcinoma

- 4-7% of Thyroid carcinomas with prognosis intermediate between Papillary/follicular ca and anaplastic ca.
- Two types:
  - Poorly Differentiated Papillary or Follicular carcinoma
  - Insular carcinoma

Malignant: Insular Carcinoma

- **Cellularity**- Highly cellular
- **Presentation**- Single cells with some microfollicles, trabeculae and spheres
- **Colloid**- Scant to absent
- **Cells**- monomorphous round nuclei
Poorly Differentiated Carcinoma (Insular)

Lymphoma

- Primary Non Hodgkin’s lymphoma constitutes about 2% of Thyroid malignancies
- Older age
- Usually in setting of Hashimoto’s (40-80X risk compared to general population)
- 20-30 yrs after onset of Hashimoto’s

Lymphoma

- Most present with rapid enlargement and symptoms related to it
- Average size 7cms
- Three major types
  - Marginal zone B cell lymphoma of MALT type (MZL)
  - Diffuse large B cell lymphoma
  - Mixed MZL and DLBL
  - Others less common
Malignant: Lymphoma

- **Cellularity**: Cellular
- **Presentation**: Dispersed population of lymphocytes
- **Colloid**: Absent to scant
- **Cells**: Lymphocytes. MZL with small lymphoid cells interspersed with large lymphocytes. DLBL with large cells (centroblasts, immunoblasts, Burkitt like cells). Need Immunophenotyping.

Lymphoma

Anaplastic Carcinoma

- 10% of malignant thyroid tumors
- Rapidly fatal
- Rapidly growing mass involving adjacent structures
- 1/3rd associated with better differentiated areas like papillary or follicular
**Malignant: Anaplastic Carcinoma**

- **Cellularity** - Usually cellular
- **Presentation** - Dispersed single cells and loose clusters of large ugly cells.
- **Colloid** - Absent or rarely scant
- **Cells** - Epitheloid, spindle or squamoid. Tumor giant cells and osteoclasts may also be noted
- **Other** - Diathesis

**Metastatic Carcinoma**

- Usually Known history of Ca elsewhere
- 0.1-0.3% of thyroid aspirates
- Most frequent Primaries with Mets to Thyroid include
  - Breast
  - Kidney
  - Lung
Suspicious For

- Follicular Neoplasm
- Hurthle Cell neoplasm
- Papillary Carcinoma
- Other Malignancy

Suspicious for malignancy

- Excludes cases suspicious for a follicular or Hürthle cell neoplasm
- Suspicious for papillary carcinoma
  - Many papillary CAs (e.g., fol. variant) have subtle features and cannot be dx’d conclusively by FNA
- Suspicious for medullary carcinoma
  - Serum calcitonin level
- Suspicious for lymphoma
  - May include recommendation to repeat FNA with flow cytometry.
- Suspicious for metastatic tumor to thyroid

Slide courtesy Dr Cibas
SUSPICIOUS FOR MALIGNANCY.
Suspicious for Papillary Carcinoma
Predictive Value for Malignancy

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>n</th>
<th>% of cases called &quot;Sus for PC&quot;</th>
<th>% Malignant (PPV)*</th>
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</thead>
<tbody>
<tr>
<td>Gharib et al., 1993</td>
<td>288</td>
<td>3</td>
<td>60</td>
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<tr>
<td>Logani et al., 2000</td>
<td>52</td>
<td>?</td>
<td>77</td>
</tr>
<tr>
<td>Yang et al., 2007</td>
<td>84</td>
<td>3</td>
<td>76</td>
</tr>
<tr>
<td>Yassa et al., 2007</td>
<td>314</td>
<td>9</td>
<td>60</td>
</tr>
<tr>
<td>Raparia-Amrikachi/TMH 2009</td>
<td>180</td>
<td>1.5%</td>
<td>82</td>
</tr>
</tbody>
</table>

*Resected nodules only

Slide courtesy Dr Cibas

Suspicious for Follicular Neoplasm

- Follicular Adenoma
- Follicular Carcinoma (5-15% of thyroid malignancies)
- Follicular Variant of Papillary (if nuclear features not characteristic/suggestive of papillary to call suspicious for Papillary)
- Cellular Adenomatous nodules (sometimes)

Reserved for cases showing a microfollicular or crowded groups pattern
- Cannot distinguish Follicular adenoma from carcinoma (done on histology)
- Hence surgery (usually lobectomy) needed for definitive diagnosis
- Note: if suspicious for Papillary carcinoma, then excluded from this category
Suspicious for Follicular Neoplasm

- **Cellularity**: High
- **Presentation**: Microfollicles with nuclear crowding/molding or trabecular
- **Colloid**: Usually scant
- **Cells**: Lining microfollicles can be evenly spaced or may be irregularly spaced and even overlap.
Suspicious for Hurthle Cell Neoplasm

- Defined as any sample composed exclusively of Hurthle cells
- Risk of malignancy similar to susp for follicular category
- However Hurthle cell carcinomas are genetically different from Follicular carcinoma
- Cannot distinguish cytologically between adenoma Vs. carcinoma. Hence diagnostic lobectomy needed

Differential of Hurthle Cell Neoplasms

- Hurthle Cell Adenoma/Carcinoma
- Other lesions with Hurthle cell changes may creep into the differential ie
  - Follicular adenomas/carcinomas with hurthle cell change
  - Papillary and Medullary carcinomas
  - Hashimoto’s/Lymphocytic thyroiditis

Suspicious for Hurthle Cell Neoplasm

- Cellularity- High
- Presentation - Dyshesive population consisting exclusively of Hurthle cells or in small groups, trabeculae or follicles
- Colloid- Usually scant or absent
- Cells - Hurthle cells with prominent cherry nucleoli. Binucleation, nuclear holes, blue cytoplasmic granules on DQ
Atypical (Follicular) Cells of Undetermined Significance (ACUS) (<7% of FNAs)

- Reserved for cases that do not fit into Benign, Malignant or Suspicious categories
- Repeat FNA in 3-6 months is the recommended management
- If repeat ACUS or worse, then surgery

Atypical (Follicular) Cells of Undetermined Significance (ACUS)

- Mild changes suggestive of papillary carcinoma but only in rare cells.
- Sparsely cellular sample of microfollicles
- Atypical cyst lining cells
- Marked XRT
- Specimen compromised by obscuring blood etc.
- Obvious symplastic changes should not be included here
Insufficient for Diagnosis

- 10-30% of Thyroid FNAs
- Adequacy criteria
  - At least 6 groups, each with at least 10 benign appearing well visualized follicular cells or if the FNA is diagnostic of the lesion. Two groups of Insufficient listed below
- Cyst contents
- Unsatisfactory

Insufficient for Diagnosis

Adequacy criteria

- At least 6 groups, each with at least 10 benign appearing well visualized follicular cells or if the FNA is diagnostic of the lesion.
- Exceptions
  - Thyroiditis
  - Abundant colloid(colloid nodule)
  - Any atypia

Cyst Fluid only

- Cyst fluid with macrophages only (<6 groups of benign follicular cells) should be considered insufficient but identified as a distinct subset of “Insufficient for Diagnosis”
- Cannot exclude cystic papillary carcinoma if solid portion of nodule is not sampled
- 4% risk of malignancy
Unsatisfactory

- Blood only with rare or no follicular cells
- No colloid

Ancillary Techniques

- Not yet ready for regular clinical application
- BRAF mutation is very specific but not sensitive for Papillary thyroid ca
  - 60% conventional PTC
  - 77% tall cell PTC
  - 12% FVPTC
- May be useful in cases of ACUS. If +, then can upgrade to susp or +ve for malignancy. May also predict more aggressive behaviour and hence need for neck dissection.

Thyroid TBS Diagnostic categories, Expected Reporting Rates, Risk of malignancy and Management

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>RR</th>
<th>Risk</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>70%</td>
<td>&lt;1%</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>ACUS</td>
<td>&lt;7%</td>
<td>5-10%</td>
<td>Repeat FNA 3-6m</td>
</tr>
<tr>
<td>Susp for FN</td>
<td>20-30%</td>
<td></td>
<td>Dx lobectomy</td>
</tr>
<tr>
<td>Susp for HN</td>
<td>20-45%</td>
<td></td>
<td>Dx lobectomy</td>
</tr>
<tr>
<td>Susp for Malig</td>
<td>60-75%</td>
<td></td>
<td>Lob or Total Thyroidectomy</td>
</tr>
<tr>
<td>Malignant</td>
<td>3-7%</td>
<td>97-99%</td>
<td>Total Thyroid</td>
</tr>
<tr>
<td>Insufficient</td>
<td>10-30%</td>
<td>1-4%</td>
<td>Repeat FNA with Ultrasound</td>
</tr>
</tbody>
</table>
Clinical Outcomes for “Suspicious” Category in Thyroid Fine Needle Aspiration Biopsy
Patient’s Sex and Nodule Size are Possible Predictors of Malignancy

Azeb Zerga, MD; Jose Hay, MD; Pern-Arind, MD; Elia Fekry, MD; Margaret Amecheza, MD

Aims—Fine needle aspiration biopsy is the standard imaging test for the diagnosis of thyroid swellings. Approximately 32% of thyroid nodule diagnoses are "suspicious". We evaluated the role of patient’s age, sex, size of nodule, and ancillary and cytologic features as possible predictors of malignancy in patients with cytologic diagnoses of "suspicious" nodules. Methods—Cytologic biopsies and reports of 106 consecutive thyroid nodules from 2006-2009 interpreted as "suspicious" with follow-up were reviewed. The final histologic diagnosis was obtained by reviewing all histologic reports and comparing with the clinical data of all patients. Results—Thirty cases were suspicious for malignancy. Twenty had malignant histologic diagnoses. Among cases with malignant diagnoses, 19 presented as follicular or Hurthle cell neoplasms, one case of malignancy in female patients, one case of Hurthle cell neoplasms, and one case of benign lymphoma/leukemia were identified. Conclusion—Certain features were statistically significant for malignancy. Age, sex, and follow-up were associated with malignancy. Additionally, the role of ancillary and cytologic features in the diagnosis of thyroid fine needle aspiration biopsies were identified. The role of ancillary features in the diagnosis of thyroid fine needle aspiration biopsies were identified.