Background to the Thyroid Nodule

- Nodules of the thyroid are common:
  - 4-7% of the population have palpable nodules
  - Up to 70% have subclinical nodules
- Epidemiology:
  - Women
  - Older age
  - Radiation exposure
  - Diet - rich in goitrogens/deficient in iodine
- The majority of thyroid nodules are benign with a small fraction being malignant (includes undifferentiated carcinomas)

THYROID CARCINOMA

- Most common malignancy of endocrine system
- 1-2% of all malignancies
- Annual incidence: >63,000 cases (est) per year in USA
- Increasing incidence due to greater surveillance and more FVPTC - more to come on this (NIFTP)!
- >90% 10 year survival overall
The Overdiagnosis of Thyroid Carcinoma


Aggressive Thyroid Cancer

- Less focus on malignant vs benign
- More focus on identifying aggressive forms of thyroid cancer
- How to define aggressive thyroid carcinoma?
  - Microscopic analysis is mixed:
    - Works well for UTC, less well for PDTC, unsat. for DTC
  - Need for molecular indicators

FREQUENCY OF MAJOR THYROID MALIGNANCIES

- Papillary carcinoma: 70-80%
- Follicular carcinoma: 10-15%
- Medullary carcinoma: 2-5%
- Undifferentiated carcinoma: 2-5%
- Poorly differentiated carcinoma: 1-10%
FOLLICULAR-DERIVED THYROID CARCINOMA

Clinicopathologic Predictors of Aggressive Behavior:
- Patient age (> 45 yrs)
- Tumor size (> 4.0 cm)
- Presence of extrathyroidal extension
- Presence of distant metastatic disease

WHAT IS THE ROLE OF THYROID FNA

“FNA is the most accurate and cost effective method for evaluating thyroid nodules.”

Each year over 550,000 thyroid FNAs are performed in the U.S. !!!

**THYROID FNA RATIONALE**

**RATIONALE:**
- High prevalence of nodules (4-7%)
- Low incidence of malignancy (5%)
- Surgery for all nodules is not practical

**THYROID FNA: THE GOOD NEWS...**
- Reduced the number of surgeries by 50% [benign result in 60-70% of FNAs]
- Increased the yield of malignancies by 2-3X
- Decreased the costs of management by over 25%
- But with Bethesda and molecular testing, can we do better?
NORMAL THYROID ELEMENTS:
COLLOID
FOLLICULAR CELLS

COLLOID:
Usually a Benign Feature

- Watery colloid
- Dense colloid

Exception to the rule is the rare colloid-rich PTC

ARCHITECTURAL PATTERN:
MACROFOLLICLES VS MICROFOLLICLES

- MACROFOLLICLE
- MICROFOLLICLE

- BENIGN
- NEOPLASM
How are thyroid FNAs processed at various Harvard Hospitals?

**Thyroid FNA Processing**

**TECHNIQUE AND PROCESSING:**

- 3-5 separate passes per nodule
- Ethanol-fixed smears
- Air-dried smears
- Liquid based preparations
- Cell block
- Rinsings in saline or cytolyte

**MGH:** 4-6 fixed smears + 1 Surepath  
**BWH:** 1-2 Thin-Preps  
**BIDMC:** 1 Thin-Prep

**Reporting of Thyroid FNAs**

A major problem in the application of thyroid FNA has been the widespread inconsistency in reporting terminology.
### Bethesda Terminology: Relationship to Clinical Algorithms

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</tr>
<tr>
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A second edition of TBSRTC is currently being prepared and will be available by 2018.
Why are some thyroid FNAs signed-out as NON-DIAGNOSTIC or UNSATISFACTORY?

Too much blood, and not enough follicular cells!

Bethesda Criteria for Adequacy

Satisfactory smears: At least six groups of follicular cells with at least 10 cells per group

• Approx. 5-20% of thyroid FNAs are non-diagnostic.

**If your ND rate is too high, consider changing your FNA technique or switching to liquid-based preps.

EXCEPTION TO ADEQUACY RULE:

Colloid Nodule

Thyroid FNAs with abundant colloid only, can be placed into the BENIGN category.
EXCEPTION TO ADEQUACY RULE:
Inflammation only in Inflammatory Conditions
Thyroid FNAs with abundant inflammatory cells only,
can be placed into the BENIGN category.

Thyroid FNA Adequacy
Reducing your Non-Diagnostic rate:
• Ultrasound-guided FNA
• ROSE
• Use of liquid-based preparations
  • e.g. Thin Prep, Surepath
  • Concentrates cells into monolayer
  • Removes obscuring blood
  • Learning curve to interpret

PITFALL: THYROID CYSTS
• The accuracy of thyroid cyst FNAs is approximately 40%
• Can lead to false positive and false negative diagnoses
PITFALL: Cystic Thyroid Nodule

Some Cystic Thyroid Nodules Can Be Diagnosed as “BENIGN”

PITFALL: Cystic PTC may contain scant to absent epithelial cells

In the Bethesda System, cyst aspirates lacking follicular cells are classified as “Non-Diagnostic” or “cyst contents only”… no role for molecular testing
Helpful Note: Cystic Thyroid Lesions

Cystic degeneration is uncommon in follicular and Hurthe cell carcinomas!

INDETERMINATE THYROID FNAS (14-26%)

• 1) AUS/FLUS (8-12%)
• 2) Suspicious for Follicular Neoplasm/Follicular Neoplasm (+ oncocytic features) (2-8%)
• 3) Suspicious for Malignancy (4-6%)

What features are used to diagnose an FNA as “Suspicious for a follicular neoplasm” in the Bethesda System?
FNA as a Screening Test for Follicular Carcinoma

The Riddle
If the criteria for classifying these lesions are purely histologic, what hope is there for fine-needle aspiration cytology?

FNA as a Screening Test for Follicular Carcinoma

- Multinodular goiter
- Adenomatous nodule
- Follicular adenoma
  - Macrofollicular
  - Microfollicular
- Trabecular
- Solid
- Follicular carcinoma
EVALUATING FOLLICULAR LESIONS

- All follicular lesions are a mixture of micro- and macrofollicles.
- Focus on the predominant pattern.

BENIGN:
60-70% of Thyroid FNAs
Cytologic Reporting of Follicular Lesions

**BENIGN**

- Macrofollicles and colloid, consistent with a benign thyroid nodule.

Suspicious for a Follicular Neoplasm:
2-8% of All Thyroid Aspirates

Among the most difficult categories to address using molecular markers

Cytologic Reporting of Follicular Lesions

**SUSPICIOUS FOR A FOLLICULAR NEOPLASM**

*Note: Distinction between a follicular adenoma and follicular carcinoma is not possible based upon cytologic material.*
**Pitfall: Mixed Follicular Lesions**

- Mixed micro:macro lesions (50:50) may reflect contamination by normal thyroid macrofollicles (i.e. sampling), or the mixed nature of the nodule…Such samples are problematic!
- AUS/FLUS

**FNA as a Screening Test for Follicular/Hurthle Cell Carcinoma**

- Low false negative rate, <0.7%
- Low false positive rate, <5%
- High sensitivity, BUT............

**THYROID FNA: THE BAD NEWS... LOW SPECIFICITY!!!**

**Histologic Follow-up of FNAs Diagnosed as “Suspicious for a Follicular Neoplasm”**

- Carcinoma (FC & FVPTC) 20-30%
- Follicular adenoma/ 70-80%
- Adenomatous nodule
A sensitive and specific marker to distinguish follicular adenomas from carcinomas has yet to be identified.

Molecular testing is proving useful but expensive…. More on this topic later.

What are the features used to diagnose an FNA as “Suspicious for a Hurthle cell neoplasm” in the Bethesda System?

Hurthle cell adenomas and carcinomas are distinguished histologically by the presence of transcapsular and/or vascular invasion.
FNA OF HURTHLE CELL NEOPLASMS
Both Hurthle cell adenomas and carcinomas are diagnosed by FNA as “suspicious for a follicular neoplasm with oncocytic features.”

Cytologic Features of Hurthle Cell Neoplasms:
Pure Population of Hurthle Cells Without Background Lymphocytes

Cytologic Features of Hurthle Cell Neoplasms:
Blood Vessels Traversing Groups are Often Found
Hurthle cell neoplasms often have a single cell pattern.

Variation in cell size and nuclear size is usually seen in Hurthle cell neoplasia.

**PITFALL:**
Adenomatous Nodule With Oncocytic Changes

These lesions should be recognized as “BENIGN” in the Bethesda System.
Most cases of Hurthle cells in Hashimoto thyroiditis are easily recognized as BENIGN!

Oncocytic neoplasms in the DDX of Hurthle cell neoplasia

- Medullary Carcinoma
- Papillary Carcinoma
- Metastatic Renal Cell Carcinoma
- Parathyroid Adenoma

INDETERMINATE THYROID FNAS

- AUS/FLUS
- Suspicious for Follicular Neoplasm/Follicular Neoplasm (+ oncocytic features)
- Suspicious for Malignancy
Bethesda Terminology: A Probabilistic Approach to Thyroid FNA

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AUS/FLUS

- Cases that don’t fulfill criteria of other categories:
  - “The 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’.”
- 8 scenarios outlined in the Bethesda Atlas
- Heterogeneous category – WASTEBASKET
- Often a compromised specimen (obscuring blood, etc.)
  - Note: low cellularity, poor fixation, obscuring elements by themselves not sufficient for AUS/FLUS

AUS/FLUS - Scenario: Hypocellular but Microfollicular

Rare microfollicles
AUS/FLUS - Scenario: Mixed Architectural Pattern

AUS/FLUS - Scenario: Scant Hurthle Cells Only

AUS/FLUS – Scenario: Preparation Artifact and Mild Atypia

Air-drying of Pap-stained smear (Fig. 4.2, The Bethesda Atlas)
AUS/FLUS – Scenario: Prep Artifact
Obscuring blood and mild atypia

AUS/FLUS Scenario:
“Benign”…But Focal Features of Papillary Carcinoma

AUS/FLUS- Scenario:
Cyst Lining Atypia
AUS/FLUS:
Hurthle Cells in Setting of Hash or MNG

- Less than 7% of thyroid FNAs (range: 3-20% in lit.) – needs adjusting! ... probably 10-12%
- Potential for overuse/abuse –
  - Role for intralab monitoring (QA metric)
- Recommended management: Repeat FNA or molecular
  - >50% of cases are reclassified as BENIGN on repeat FNA
- Surgery for “repeat atypicals”
  - 27% malignant with repeat AUS/FLUS FNA
  [Fagin and Brandt, 2009]
- Should AUS/FLUS be further subdivided?
  - Nuclear atypia = increased risk for PTC
  - Architectural atypia only = lower risk for PTC

When do we diagnose an FNA as “Suspicious for malignancy” or “Malignant” in the Bethesda System?
**Papillary Thyroid Carcinoma is the Most Common Cause of a “Suspicious/Malignant” Dx**

- FNA is highly accurate:
  - >90% are diagnosed as positive or suspicious by FNA

**Papillary Thyroid Carcinoma**

*FNA is most useful as a diagnostic test for papillary thyroid carcinoma, probably better than frozen section!*

What are the BASIC features that we use to diagnose PTC by FNA?
Papillary Cytoarchitecture (88%): A Key Feature in View of NIFTP

Syncytial Groups (68%)

Longitudinal Nuclear Grooves (95%)
Dense, Hypereosinophilic Colloid (40%)

Multinucleated Giant Cells (53%)

PAPILLARY THYROID CARCINOMA

No single cytologic feature is **diagnostic** of papillary thyroid carcinoma!
PAPILLARY THYROID CARCINOMA: 5 Key Features for a “Malignant” FNA Diagnosis

“CONSERVATIVE” GUIDELINES
- Enlarged, oval nucleus with eccentric nucleolus
- Papillary structures
- Fine, pale chromatin
- Longitudinal nuclear grooves
- Intranuclear pseudoinclusions

PAPILLARY THYROID CARCINOMA

The risk for making a diagnosis of “Malignant” is that a total thyroidectomy is likely to be performed and central neck dissection!

What are the Factors Contributing to a Diagnosis of “Suspicious for Malignancy” vs “Malignant”?

- Inadequate sampling or preparation artifacts – A subset of these will be AUS/FLUS
- Cystic papillary thyroid carcinomas
- Variants of papillary carcinoma that are difficult to recognize – FVPTC and NIFTP
PAPILLARY THYROID CARCINOMA

Examples of papillary carcinoma mimics – False Positives

Papillary Architecture

Focal atypia partially obscured by blood – Not entirely convincing...be careful!
Papillary Hyperplastic Features in a Benign Thyroid Nodule

Nuclear Atypia & Lots of Intranuclear Pseudoinclusions: “Too good to be true!”

Dense Fibrous Stromal Material
Hyalinizing Trabecular Tumor
(Some consider this an indolent variant of PTC)

SUMMARY

• FNA is an essential initial test for evaluating thyroid nodules
• The Bethesda System for reporting FNAs is highly recommended and a new edition is forthcoming
• Be careful not to overuse the AUS/FLUS category!

Thank You!