Challenges in the Diagnosis of Thyroid Cancer – An Update

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Speaker Disclosure
No Dislosures to make.

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Selected Problems in Diagnosis
* Min. invasive follicular carcinoma
* Variants of papillary thyroid carcinoma
* Poorly differentiated thyroid carcinoma

THYROID

Background to Thyroid Neoplasia
**THYROID CARCINOMA**

- Most common malignancy of endocrine system
- Annual incidence = 122,000 cases worldwide
- Young and middle-age adults
- More common in women (2-4x; 1:120 risk in U.S.)
- >90% 10 year survival

**Aggressive Thyroid Cancer**

- Less focus on malignant vs benign (NIFT)
- 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
Follicular Adenoma vs “Hyperplastic”

- Variety of names for benign follicular nodules:
  - Follicular adenoma
  - Adenomatous nodule
  - Adenomatoid nodule
  - Hyperplastic nodule
- Up to 60% of nodules in multinodular goiters have been shown to be clonal
- Follicular adenoma at MGH:
  - Solitary or dominant, well-defined fibrous capsule, histologically different from surrounding normal.

PROCESSING SOLITARY THYROID NODULES

For a single or dominant thyroid nodule, submit the entire capsule.

FOLLICULAR ADENOMA

Histologic variants:
- Toxic adenoma
- Adenoma with papillary hyperplasia
- Adenoma with bizarre nuclei
- Signet-ring adenoma
- Adenoma with spindle cell metaplasia
- Adenolipoma/adenochondroma
- Hurthle cell adenoma
Follicular Adenoma With Adipose Tissue: Lipoadenoma

Follicular Adenoma With Bizarre Nuclei: Can Mimic Anaplastic or PD carcinoma

Follicular Adenoma With Signet Ring Cells: Can Mimic Metastatic Disease

Follicular Adenoma With Spindle Cell Metaplasia: Can Mimic Medullary Carcinoma
FOLLICULAR CARCINOMA

Two distinct histologic types:

- Minimally invasive (COMMON)
  - up to 98% 10-year survival
- Widely invasive (RARE)
  - 30-45% 10-year survival
  - Often shows “poorly differentiated histologic features”

Histology:
- Thick, irregular capsule
- Microfollicular, trabecular, or solid patterns
- Unequivocal transcapsular and/or angioinvasion
Minimally Invasive Follicular Carcinoma

FOLLICULAR CARCINOMA

Capsular Invasion:
- Full thickness invasion through capsule
- "Mushrooming" appearance
- New fibrous capsule along leading edge

Transcapsular Invasion

Transcapsular Invasion with Mushroom Appearance
Mimic: Incomplete Capsular Invasion

Mimic: FNA ARTIFACT
Small capillaries, hemosiderin, fibrosis

Mimic: Vessel entering capsule:
Get Levels!

Follicular Carcinoma with Angioinvasion

**Angioinvasion:**
- Considered by some a more reliable sign of malignancy
- Vessel is within or immediately outside the capsule - *Vessels within the tumor do not count!*
- Intravascular tumor covered by endothelial layer or associated with thrombus
- *I do not require thrombus to be present!*
**FOLLICULAR CARCINOMA**

Minimally invasive follicular carcinoma

= Grossly encapsulated follicular carcinoma with angioinvasion

Mimic: Artifactual tumor within ectatic vessel

Mimic: Artifactual retraction of tissue

IHC for CD34 & TTF1
Tips/Comments for Problem Cases: Invasion versus Artifact

- Deeper H&E levels x 3 will resolve the problem in a majority of cases
- Is “atypical” or “uncertain malignant potential” an option? Yes, but…
- What about Hurthle cell tumors?
  - Be cautious with tumors over 3 cm!
  - Solid and trabecular HC tumors
  - Mitotically active HC tumors

EXTRATHYROIDAL EXTENSION: Be Conservative!

- Extrathyroidal extension = T3
- Extension into surrounding muscle, fibrovascular, and neural tissues
- Significance of extension into perithyroidal adipose tissue is uncertain (minimal EE)
- Unreliable in the isthmus

Selected Challenges in the Diagnosis of Papillary Thyroid Carcinoma

PAPILLARY THYROID CARCINOMA

- 70-80% of thyroid carcinomas
- Indolent (although certain variants are aggressive) - <6.5% mortality
- Young to middle-aged (20-50 years)
- Women:men (4:1)
- Prior radiation exposure, Hashimoto thyroiditis, 4-fold increase among offspring of affected
Frozen Section: To Freeze or Not to Freeze???

At the MGH, a subset of thyroidectomy specimens are sent for frozen section:
- Limited to those that were indefinite for PTC by FNA
- Many frozen section pitfalls!!
- Intraoperative smears are routinely performed to compliment the frozen section

To Freeze or Not to Freeze???
Can easily be mistaken for PTC in frozen section
Artifactual inclusion

Cytology of Papillary Thyroid Carcinoma

Oval, pale, grooved nuclei

PAPILLARY THYROID CARCINOMA: Many Variants!

- Encapsulated
- Follicular
- Macrofollicular
- Diffuse sclerosing
- Warthin-like
- Solid
- Trabecular
- Cribriform-Morular
- Oncocytic
- Hobnail
- Tall cell
- Columnar cell
It is important to recognize certain variants of PTC:
* May pose a diagnostic problem
* May be associated with syndromes such as FAP
* May suggest an aggressive clinical behavior.

**PAPILLARY THYROID CARCINOMA**

**Follicular variant:**
- Most common variant: 10-15% of PTC
- RAS mutations are most common
- Many are encapsulated - NIFT
- The DDX is with follicular adenoma

**Histologic Features:**
- Classic PTC nuclear features (Subtle in 30% of cases):
  - Pale oval nuclei
  - Crowded/overlapping nuclei
  - Longitudinal nuclear grooves
- Intranuclear pseudoinclusions are **RARE**
- Small amounts of dense hypereosinophilic colloid
- Intraluminal histiocytes/giant cells

**Easily Recognizable FVPTC**

**FVPTC:** Irregularly spaced & overlapping oval nuclei
Encapsulated FVPTC: Many nuclear grooves, nuclei are somewhat hyperchromatic

FVPTC: A Good Clue…. Overlapping oval nuclei and abortive papillae

Clues to FVPTC:
- Hypereosinophilic Colloid
- Multinucleate Histiocytes in lumen

Immunohistochemical Markers to Help Diagnose FVPTC: Galectin-3, CD117, and HBME-1
- Galectin-3+
- CD117-
The Follicular Variant of Papillary Carcinoma

- Sample the capsule well to search for invasion
- Get levels x 3 on blocks with susp for invasion
- Compare nuclear features to surrounding normal thyroid tissue
- Search for nuclear overlap, intraluminal histiocytes, and abortive papillae
- Last resort: galectin-3+, HBME-1+, CD117 –
- Molecular features are generally not useful

In over 1/3 of cases, the encapsulated/non-invasive FVPTC can pose a significant diagnostic challenge!

NIFT

A consensus group of thyroid experts led by Dr. Nikiforov is drafting a recommendation to suggest:
Non-Invasive Follicular Thyroid (NIFT) Neoplasm with Papillary-Like Nuclear Features

- Solves an important thyroid pathology issue
- Redefines a large set of low-risk cancers as “neoplasms” [or “uncertain malignant potential”]
- Non-invasive
- Follicular-patterned
- Dx is independent of molecular profile
  - Pax8-PPARg, RAS, BRAF
Non-invasive: encapsulated, partially encapsulated, unencapsulated
Risk of malignant behavior is low
- Low metastatic potential (0%) Vivero et al 2013
- Low recurrence risk (3%)
Management would likely be lobectomy alone

Encapsulated FVPTC - NIFT:
Mild nuclear overlap and grooves

Manuscript in preparation
Validation/comment period
?Role of molecular studies
Reassessment of FNA and ROM
Implications for medicolegal risk

Four variants of PTC that are often more aggressive, but NOT independent predictors of an aggressive behavior.
Hobnail Variant:
- Rare aggressive variant
- Average age 54 years
- Female predominance
- 63% Stage III or IV at presentation
  - Large size, extrathyroidal extension, LN mets
  - Subset with tall cell features or UTC
- BRAF+ in 80% of cases; RET/PTC in 20%

Hobnail Variant of PTC: Cells often are dyshesive

Hobnail Variant of PTC: Cells show a clinging pattern
Hobnail Variant of PTC:
Nuclei tend to be more hyperchromatic than classical PTC

PAPILLARY THYROID CARCINOMA

Diffuse Sclerosing Variant:
- Uncommon
- Occurs in children and young adults
- Widely invasive with extrathyroidal extension
- RET-PTC rearrangements most common
- More aggressive than conventional PTC: LN mets & frequent distant mets.

Diffuse Sclerosing PTC:
Extensive Lymphatic Involvement

Diffuse Sclerosing PTC:
Diffuse involvement and dense sclerosis

Lymphoid stroma
Lymphatic with tumor
Sclerosis
Psammoma body

Diffuse Sclerosing PTC: Many Psammoma Bodies

Diffuse Sclerosing PTC: Squamous Morules

Pitfall: Avoid misinterpreting the usual stromal hyalinization of PTC as DSV.

PAPILLARY THYROID CARCINOMA

• **Tall cell variant:**
  - Uncommon
  - Elderly patients
  - Large size (usually >5.0 cm)
  - Often more aggressive than conventional PTC
  - BRAF mutations common

Histologic Features:
  - >50% tall cylindrical cells (2-3x tall as wide)
  - Papillary fronds of cells
  - Abundant acidophilic (pink) cytoplasm
  - Basally-located nuclei with conventional PTC nuclear features
  - Mitotic activity and necrosis
Tall Cell Variant of PTC:
Cells are 2-3x as tall as wide

TCV PTC: Mitoses and Tumor Necrosis are Common

Tall Cell Variant of PTC

If the tall cell component is less than 50%, we use the term “PTC with tall cell features.”
Columnar Cell Variant of PTC: Resembles an Intestinal Neoplasm

Columnar Cell Variant of PTC: Feathered Appearance of Columnar Cells

Columnar Cell Variant of PTC: Often Includes Squamous Morules

Diagnosing poorly differentiated thyroid carcinoma
Poorly Differentiated Thyroid Carcinoma

- Insular type is the classic form
- Approx. 4% of thyroid carcinomas
- Mean survival = 3.9 years
- Metastasis to LN, lung, bone, liver, brain
- Poor prognosis even when encapsulated or focal
- An aggressive subset contains ALK gene rearrangements or TERT mutations

Poorly Differentiated Carcinoma with Characteristic Insular Pattern

Poorly Differentiated Carcinoma with Extensive angioinvasion is often present
Poorly Differentiated Carcinoma with High N/C ratio cells

- Frequent mitoses

ATYPIA

Microfollicles

Necrosis

Poorly Differentiated Carcinoma

- Can arise de novo or in association with a well differentiated carcinoma
- Can be a precursor of anaplastic carcinoma.

Insular Carcinoma and Papillary Thyroid Carcinoma
Even when focal, a poorly differentiated component should be mentioned in the pathology report.

**DDX:**
- Medullary carcinoma
- Metastatic neuroendocrine carcinoma
- Solid variant of papillary carcinoma
Poorly Differentiated Thyroid Carcinoma

Ancillary Markers:
- Positive for thyroglobulin, TTF-1, & PAX-8
- Shows increased reactivity for MIB-1 and p53
- Usually negative for neuroendocrine markers
- Negative for calcitonin
- + B-catenin

Thyroglobulin +

The Turin Proposal for Diagnosing Poorly Differentiated Thyroid Carcinoma

The Turin Proposal

- Malignant follicular neoplasm
- Solid, trabecular or insular growth pattern
- Absence of conventional nuclear features of papillary carcinoma
- Presence of at least one of the following:
  - Convoluted nuclei
  - Mitotic activity ≥ 3 per 10 HPF
  - Tumor Necrosis

Necrosis

Convoluted Nuclei
The Turin Proposal

- Does not account for encapsulated non-invasive forms
- Does not account for “high grade” forms of PTC
- More markers needed to distinguish the bad actors - ? TERT and ALK

SUMMARY

- Use deeper H&E levels liberally in the assessment of capsular and angioinvasion
- Beware of certain variants of PTC which can cause a diagnostic pitfall or are more aggressive
- Prepare for the arrival of NIFT
- Poorly differentiated thyroid carcinoma should be recognized and reported even when focal
- Longterm goal: More emphasis on aggressive disease and less overdiagnosis of indolent cancer!

Thank You!