Thyroid symposium: Implications for Thyroid Cytology of non-invasive follicular thyroid neoplasm with papillary-like nuclei (NIFTP)

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Lets Start with Basics
Thyroid Carcinoma

Well-Differentiated Carcinoma

- Differentiated architecture or growth pattern
- Cell type similar to normal thyroid components (Follicular, oncocytic, C-cells)
- Maintained Follicular or C-cell origin
- Produce related hormones
- Non-invasive or invasive
- Treatable disease – Papillary or follicular carcinoma
- Protracted prognosis in Medullary Carcinoma
Aggressive Thyroid Cancer-1

Well-Differentiated Carcinoma with (referred to as High Grade Carcinoma usually PTC)

- Multifocality with intra-thyroidal spread
- Multiple foci of vascular invasion and or extra-thyroidal invasion
- Mitoses
- Single cell or confluent necrosis
- Distant Mets at the time of Diagnosis
Aggressive Thyroid Cancer-2

Well-Differentiated Carcinoma with Nuclear and Architectural Hallmarks

- Tall cell variant
- Columnar cells variant
- Diffuse sclerosis variant
- Hobnail cell variant
- Solid variant
Well-Differentiated Follicular Derived Carcinoma
Morphologic Diagnosis

• **Papillary Thyroid Carcinoma** –
  Nuclear cytology – can be diagnosed in FNA specimens

• **Follicular Thyroid Carcinoma** –
  Invasion (capsular and or vascular invasion)
High Diagnostic Variability

- Nuclear cytology of papillary thyroid carcinoma—especially in Follicular Patterned Lesions (histopathology as well as cytopathology)
- Criteria for type and form of invasion
- Staging: Extra-thyroidal and Extra-nodal extension
Case of an Encapsulated Follicular Patterned Lesion
Case 1
Thyroid Experts Diagnoses
The Cytopathologists Gold Standard

Diagnoses:
- Hyperplastic nodule – Benign
- Follicular Adenoma – Benign
- Follicular Variant of Papillary Thyroid Carcinoma - Malignant

Lloyd RV et.al. AJSP 2004
Elshiekh TM et al. AJCP 2008
FVPTC Histologic Scenarios

FVPC Type 1

FVPC Type 2

FVPC Type 3

FVPC Type 4

FVPC Type 5

FVPC Type 6
Diagnostically challenging cases

- Encapsulated, no invasive features
- Seen in a background of nodular goiter
- Show admixture of micro and macro follicles
- Consists of areas diagnostic of papillary carcinoma and areas that appear benign
We Knew About Low Risk Tumors in Thyroid but Just Talked About it Very *Gently* *Afraid of Discussion*
Encapsulated follicular patterned lesions

- Minor nuclear changes of PTC
- Minor capsular penetration without nuclear changes of PTC
- Borderline diagnosis
- Extremely good prognosis
Important Questions/Issues?

• Is the current management of encapsulated FVPTC too aggressive?
  – Yes
• Is the diagnosis “WDTUMP” justifiable?
  – ?
• Role of molecular markers in the diagnosis of PTC
Clinicopathologic Data

Long term follow-up needed to modify the current management of encapsulated or noninvasive FVPTC
Approximately < 1% (0.5%) non invasive FVPTC have recurrence or metastasis (range of median f/u – 3 to 11.9 years)
Tumor recurrence and metastatic disease – incomplete submission of tumor capsule (grossing criteria)
The Thinking of Our Clinical Colleagues

The Traditional Management

- Same management for all thyroid cancers
- Total thyroidectomy
- RAI remnant ablation
The Thinking of Our Clinical Colleagues

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Risk Based Management

- Personalized risk assessment & Management recommendations & Predicting prognosis
Modified ATA 2015 Risk Assessment

High Risk
*Gross extrathyroidal extension, incomplete tumor resection, distant metastases or lymph node >3 cm*

Intermediate Risk
*Aggressive histology, minor extrathyroidal extension, vascular invasion, or > 5 involved lymph nodes (0.2-3 cm)*

Low Risk
*Intrathyroidal DTC ≤ 5 LN micrometastases (< 0.2 cm)*
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Low Risk
**Intrathyroidal DTC**
**≤ 5 LN micro-metastases (< 0.2 cm)**
Changes in Surgical Pathology Diagnosis / Classification of “Low Risk Tumor(s)"

- Non-Invasive Follicular Variant of PTC
- Low Risk Disease, Benign Clinical Course
The Perfect Timing of This Recommendation for Change in Nomenclature for Non-Invasive Follicular Variant of PTC
The Supporting Data

Follow-up studies

Molecular Data
Molecular and Follow-up Data

496 Papillary thyroid carcinomas

Mutations → Copy number alterations → mRNA expression → miR expression → Protein expression → DNA methylation

Braf^{V600E} v. Ras signaling

BRAF^{V600E}-RAS score → Thyroid differentiation score

Molecular classification of papillary carcinoma

RAS-like papillary carcinoma

BRAF^{V600E} -like papillary carcinoma

Subtypes of BRAF^{V600E} -like papillary carcinoma
## MUTATIONS

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<th>Classic PTC</th>
<th>Encapsulated-FVPTC</th>
<th>Foll Thy CA</th>
<th>Poorly Diff Thy CA</th>
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## GENE FUSIONS

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The Endocrine Society Working Group for Re-evaluation of the Encapsulated Follicular Variant of Papillary Thyroid Carcinoma

Project Goals
• **Review** a cohort of cases by experts in the field of endocrine pathology
• **Establish** a consensus on diagnostic histologic criteria
• **Define** the risk of adverse events based on long follow-up
• **Recommend** new terminology that reflects tumor biology and patient outcome
Study Logistics

Participants Led by Dr. Yuri Nikiforov
24 surgical pathologists
2 endocrinologists
1 surgeon
1 molecular pathologist, 1 biostatistician, 1 psychiatrist, 1 patient

• Review of 268 cases with f/u
• Face to face meeting in Boston & Multiple teleconferences 3/20-3/21/2015
• Discussion regarding nomenclature shift
Study Logistics

Consensus Group Proceedings

- **Inclusion and exclusion criteria** for non-invasive FVPTC
- **Nuclear scoring** scheme
- **109 cases** accepted as non-invasive FVPTC – no adverse outcomes (median f/u 13 years)
- **101 cases designated as encapsulated/well demarcated FVPTC with invasion** – 12% with adverse outcome, 2% death

Consensus Terminology

*Non Invasive Follicular Thyroid Neoplasm with Papillary Like Nuclear Features (NIFTP)*

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NIFTP Inclusion Criteria

1. **Well Demarcated**
   - Discrete interface from the surrounding thyroid parenchyma
   - Well-defined tumor capsule or unencapsulated but well-delineated

2. **Solid and cystic**

3. **Usually mixed macro and microfollicular growth pattern or predominance of one over other**

4. **Isolated papillae comprising <1% of tumor mass**

5. **Nuclear features of Papillary thyroid carcinoma**
   - Diffusely distributed throughout the tumor
   - Multifocal or patchy distribution (more prominent in microfollicular areas)

6. **Dense colloid in microfollicular and watery / thin in macrofollicular and cystic areas**
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1. **Invasion**
   - Encapsulated tumors: Invasion more than 50% of the tumor capsule thickness
   - Un-encapsulated tumors: Infiltration into adjacent non-tumoral thyroid parenchyma
   - Angio-invasion into tumor capsular vessels & lymphatic invasion
   - Perineural
   - Extrathyroidal

2. **Growth Pattern**
   - Solid, trabecular or insular cannot ≤30%
   - Papillae ≥1%
   - Any tall cell, columnar cell or cribriform architecture

3. **Psammoma bodies**

4. **Tumor necrosis**

5. **Increased mitoses, > 3 / 10 HPF**
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**Naming**

Non-Invasive Follicular Variant of PTC as anything but "Not Carcinoma"

**New Terminology Recommendation**

“Non-invasive follicular thyroid neoplasm with papillary-like nuclear features“ (NIFTP)

*Adequate sampling of entire tumor capsule is required to establish this diagnosis*

- Molecular profile - RAS and RAS-like mutations
- Non-invasive FVPTC – Negligible risk of recurrence
- Invasive EFVPTC - Increased risk of distant metastases
**Follicular Adenoma**
- Non-Invasive

**Follicular Carcinoma**
- Invasive (Tumor Capsule & Vascular Invasion)

**NIFTP**
- Well Demarcated
- Solid and cystic
- Usually mixed follicular growth pattern
- Isolated papillae comprising <1% of tumor mass

**Nuclear Features of PTC**
- Absent

**FVPTC**
- Invasive (Tumor Capsule & Vascular Invasion)

**Nuclear Features of PTC**
- Present

**Encapsulated / Well-Demarcated Follicular Patterned Lesions**
Questions

Possible Answers & Recommendations
Multifocal Tumors

• The diagnosis of NIFTP should not exclude the diagnosis of second or more tumors within the same gland
  – NIFTP + another carcinoma (usually microcarcinoma)
• Multiple NIFTP were not included in the study
• NIFTP is not included in the staging
Tumor Size

- Tumors measuring 1.0 cm or less have not been included in the NIFTP
  - Few studies have shown that encapsulated micro FVPTC can be included in NIFTP paradigm (Thompson, LD Mod Pathol 2016)
Strict vs. Reproducible
Morphologic Criteria

Invasion
Mitoses
Growth Pattern
Potential Issues with NIFTP Diagnosis

**Ethical issues & Legal implications**
– Should we reclassify cases diagnosed in the past as “Encapsulated FVPTC” to “NIFTP”?

**NO**

*Standard of care – Past vs. Present*
Potential Issues with NIFTP Diagnosis

Cytopathology Diagnosis Based on Nuclear Morphology

Increase in the number of False Positive diagnosis?

1. NIFTP is a Surgical Disease
2. Diagnosis based upon application of strict diagnostic criteria
   **Noninvasive nature has to be documented based on adequate sampling of tumor periphery and capsule**
Conclusions?

• NIFTP
  – Beneficial to patients
  – Stricter set of exclusion criteria
  – Grossing of encapsulated or well demarcated nodule
  – Initial pathologic approach to diagnose and manage low-risk thyroid neoplasms.