Papillary Thyroid Carcinoma: Follicular Variant Encapsulated Type
Replaced by:
Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclei (NIFTP)

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Overall Objectives

- Provide a review of the key histologic features to render the new diagnosis
- Specifically list exclusion criteria
- Give examples of the features from sample cases
- Provide the scoring system
- Allow for questions/discussion before the cases are scored
Thyroid Papillary Carcinoma: Classic Morphologic Features

**Architectural**
- Vascular or capsular invasion
- Variable growth patterns
- Elongated and/or twisted follicles
- Calcospherites (psammoma bodies)
- Intratumoral fibrosis
- Tincture of colloid (bright and rich) & scalloping
- Crystals or giant cells in the colloid

**Cytomorphologic/Nuclear**
- Enlarged cells (compared to normal thyroid)
- High nuclear to cytoplasmic ratio
- Nuclear overlapping, crowding
- Irregular placement around follicle
- Nuclear grooving/folding
- Intranuclear cytoplasmic inclusions
- Pale chromatin with chromatin margination/condensation and clearing
  - Orphan Annie Nuclei
Thyroid Papillary Carcinoma: Classic Morphologic Features

**Architectural**

- Vascular or capsular invasion
- Variable growth patterns
- Elongated and/or twisted follicles
- Calcospherites (psammoma bodies)
- Intratumoral fibrosis
- Tincture of colloid (bright and rich) & scalloping
- Crystals or giant cells in the colloid
Complex papillary structures
Overlapping nuclei in twisted follicles
Colloid and papillary structures
Psammoma body
Even/fine Chromatin; Colloid Crystalloids
Delicate Chromatin and Giant Cells
Thyroid Papillary Carcinoma: Classic Morphologic Features

Cytomorphologic/Nuclear

- Enlarged cells (compared to normal thyroid)
- High nuclear to cytoplasmic ratio
- Nuclear overlapping, crowding
- Irregular placement around follicle
- Nuclear grooving/folding/irregular contour
- Intranuclear cytoplasmic inclusions
- Pale chromatin with chromatin margination/condensation and clearing

✓ Orphan Annie Nuclei
Cellular enlargement with ↑↑ N:C ratio
Contour irregularities, folds, grooves
Nuclear crowding/overlapping; Grooves
Intranuclear cytoplasmic inclusions
EM of Intranuclear Cytoplasmic inclusion
Delicate, fine, even chromatin
Optically clear chromatin in large nuclei
NIFTP:
Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclei

Accepted term at March, 2015
The Endocrine Pathology Society Conference for Re-Examination of the Encapsulated Follicular Variant of Thyroid Papillary Carcinoma in Boston
Study Design

- International, multi-disciplinary study of 109 patients with non-invasive EFVPTC followed for 10-26 years and 101 patients with invasive EFVPTC followed for 1-18 years collected at 13 sites in 5 countries. Review of digitalized histologic slides by 24 thyroid pathologists from 7 countries.

- 24 experienced thyroid pathologists (representing 7 countries and 4 continents), two endocrinologists, one surgeon, and one psychiatrist. In addition, a molecular pathologist, a biostatistician, and a thyroid cancer survivor/patient advocate participated in the study.
A total of 268 tumors diagnosed as EFVPTC based on current criteria were contributed by working group pathologists from 13 institutions.

Potential cases for Group 1 included non-invasive EFVPTC with no radioiodine (RAI) treatment and at least 10 years of follow-up (n=138). Potential cases for Group 2 included EFVPTC with vascular invasion and/or tumor capsule invasion and ≥1 year of follow-up (n=130).

8 week series of weekly teleconferences aimed to refine groups 1 and 2 and to achieve consensus.

http://image.upmc.edu:8080/NikiForov%20EFV%20Study/view.apml
<table>
<thead>
<tr>
<th>Growth pattern</th>
<th>Nuclear features of PTC</th>
<th>Main oncogene</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>Yes</td>
<td>BRAF</td>
<td>Papillary microCA Classic PTC</td>
</tr>
<tr>
<td>Follicular</td>
<td>Yes</td>
<td>RAS</td>
<td>NIFTP Invasive EFVPTC</td>
</tr>
<tr>
<td>Follicular</td>
<td>No</td>
<td>RAS</td>
<td>FA FTC</td>
</tr>
</tbody>
</table>

Diagram:
- **Papillary**: BRAF -> Classic PTC
- **Follicular**: RAS -> NIFTP -> Invasive EFVPTC
- **Follicular**: RAS -> FA -> FTC
## Criteria used for NIFTP Diagnosis

<table>
<thead>
<tr>
<th>Major Features</th>
<th>Minor Features</th>
<th>Features NOT seen/Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Encapsulation or clear demarcation</td>
<td>1. Dark/hypereosinophilic colloid</td>
<td>1. “True” papillae &gt;1%</td>
</tr>
<tr>
<td>2. Follicular growth pattern (&lt;1% papillae)</td>
<td>2. Irregularly-shaped follicles</td>
<td>2. Psammoma bodies</td>
</tr>
<tr>
<td>3. Nuclear Features of PTC (Score 2 or 3):</td>
<td>3. Intratumoral acellular, eosinophilic fibrosis</td>
<td>3. Infiltrative border (capsular or lymphovascular invasion)</td>
</tr>
<tr>
<td>• Enlargement/crowding/overlapping</td>
<td>4. “Sprinkling” sign (multifocal involvement within a single nodule)</td>
<td>4. Tumor necrosis</td>
</tr>
<tr>
<td>• Elongation</td>
<td>5. Follicles cleft from stroma</td>
<td>5. High mitotic activity (&gt;3/10 HPFs)</td>
</tr>
<tr>
<td>• Irregular contours</td>
<td>6. Multinucleated giant cells within follicles</td>
<td>6. Cell/morphologic characteristics of other variants of PTC</td>
</tr>
<tr>
<td>• Grooves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pseudoinclusions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Chromatin clearing</td>
<td></td>
<td></td>
</tr>
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</table>

1. “True” papillae >1%
2. Psammoma bodies
3. Infiltrative border (capsular or lymphovascular invasion)
4. Tumor necrosis
5. High mitotic activity (>3/10 HPFs)
6. Cell/morphologic characteristics of other variants of PTC
Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclei

- Surrounded by thick, well formed capsule
  - Capsule may be thinned and attenuated
  - Partially encapsulated and incompletely encapsulated are equivalent
  - Smooth muscle-walled vessels within the fibrosis
Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclei

- Absent invasion
- By definition this must be “non-invasive”
  - No capsular invasion
  - No vascular invasion
- Must be adequately (completely) sampled
  - Tumor to capsule to parenchyma
  - 3 sections (not blocks) per cm of tumor
Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclei

- Exclusively follicular pattern of growth
  - Small to medium, round, twisted and elongated follicles
  - Follicles are often a monotonous size and shape (helpful feature)
  - Isolated or rare papillae may be seen
    - Must be ≤ 1% of overall tumor volume
    - If >1%, then it is NOT follicular variant
Rare/isolated papillary structure is OK
Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclei

- Hypereosinophilic colloid
- Scalloped colloid frequently present
- Internal, acellular, eosinophilic fibrosis between follicles
  - Dropping substage often creates a "bright" signal
Internal, acellular eosinophilic fibrosis
Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclei

- Absent psammoma bodies
- Absent necrosis
- No increased mitoses
  - $\leq 3$ mitoses/10 High Power Fields
- No other patterns present
  - Solid, insular, trabecular, morular
Excluded: solid pattern
Excluded: Oncocytic Papillary
Excluded: Columnar Variant
Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclei

Diagnosis rests on cytology

- **Size and shape**
  - Enlargement, elongation, overlapping/crowding

- **Membrane irregularities**
  - Irregular contours, grooves/folds, intranuclear cytoplasmic inclusions

- **Chromatin distribution**
  - Chromatin clearing, margination to membrane, “glassy” nuclei
Nuclear score: Sum of three nuclear features (each 0 or 1)
Thus, total score will vary between 0 and 3

Nuclear features:

1) Size and Shape
   - Enlargement
   - Elongation
   - Overlapping

Absent/insufficiently expressed (0) | Present/Sufficient (1)
Nuclear score: Sum of three nuclear features (each 0 or 1)
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<tr>
<td><strong>1) Size and Shape</strong></td>
<td><img src="image1.png" alt="Image" /> <img src="image2.png" alt="Image" /> <img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /> <img src="image5.png" alt="Image" /> <img src="image6.png" alt="Image" /></td>
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<tr>
<td>• Enlargement</td>
<td><img src="image7.png" alt="Image" /> <img src="image8.png" alt="Image" /> <img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /> <img src="image11.png" alt="Image" /> <img src="image12.png" alt="Image" /></td>
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<tr>
<td>• Elongation</td>
<td><img src="image13.png" alt="Image" /> <img src="image14.png" alt="Image" /> <img src="image15.png" alt="Image" /></td>
<td><img src="image16.png" alt="Image" /> <img src="image17.png" alt="Image" /> <img src="image18.png" alt="Image" /></td>
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<td>• Overlapping</td>
<td><img src="image19.png" alt="Image" /> <img src="image20.png" alt="Image" /> <img src="image21.png" alt="Image" /></td>
<td><img src="image22.png" alt="Image" /> <img src="image23.png" alt="Image" /> <img src="image24.png" alt="Image" /></td>
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<tr>
<td><strong>2) Membrane Irregularities</strong></td>
<td><img src="image25.png" alt="Image" /> <img src="image26.png" alt="Image" /> <img src="image27.png" alt="Image" /></td>
<td><img src="image28.png" alt="Image" /> <img src="image29.png" alt="Image" /> <img src="image30.png" alt="Image" /></td>
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<td>• Irregular contours</td>
<td><img src="image31.png" alt="Image" /> <img src="image32.png" alt="Image" /> <img src="image33.png" alt="Image" /></td>
<td><img src="image34.png" alt="Image" /> <img src="image35.png" alt="Image" /> <img src="image36.png" alt="Image" /></td>
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<tr>
<td>• Grooves</td>
<td><img src="image37.png" alt="Image" /> <img src="image38.png" alt="Image" /> <img src="image39.png" alt="Image" /></td>
<td><img src="image40.png" alt="Image" /> <img src="image41.png" alt="Image" /> <img src="image42.png" alt="Image" /></td>
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<td>• Intranuclear cytoplasmic inclusions</td>
<td><img src="image43.png" alt="Image" /> <img src="image44.png" alt="Image" /> <img src="image45.png" alt="Image" /></td>
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Thus, total score will vary between 0 and 3

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<td><strong>3) Chromatin Features</strong></td>
<td><img src="image49" alt="Absent" /> <img src="image50" alt="Absent" /> <img src="image51" alt="Absent" /></td>
<td><img src="image52" alt="Present" /> <img src="image53" alt="Present" /> <img src="image54" alt="Present" /></td>
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<tr>
<td>• Chromatin clearing</td>
<td><img src="image55" alt="Absent" /> <img src="image56" alt="Absent" /> <img src="image57" alt="Absent" /></td>
<td><img src="image58" alt="Present" /> <img src="image59" alt="Present" /> <img src="image60" alt="Present" /></td>
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<tr>
<td>• Margination to nuclear membrane</td>
<td><img src="image61" alt="Absent" /> <img src="image62" alt="Absent" /> <img src="image63" alt="Absent" /></td>
<td><img src="image64" alt="Present" /> <img src="image65" alt="Present" /> <img src="image66" alt="Present" /></td>
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<td>• Glassy nuclei</td>
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<td><img src="image70" alt="Present" /> <img src="image71" alt="Present" /> <img src="image72" alt="Present" /></td>
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</tbody>
</table>

Slight changes not sufficient to call “present”!
Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclei

• How much of the tumor must have nuclear feature?
  ◆ 3 foci per cm of tumor gross measurement
  ◆ This is not well defined or agreed upon
  ◆ May be multifocal within same nodule
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