Overall Objectives

- What is the current management of papillary carcinoma?
- What are the trends and what can we do differently?
- Supporting data
- Recommendations

Thyroid Neoplasms: General Considerations

- Thyroid carcinoma is most common endocrine malignancy (3.8% of all new US cancers; 9th most common cancer type)
  - Incidence = 62,980/year
  - Death rate = 1,890 (annual) (0.3% all deaths)
  - Age = 45 – 54 years old
  - Sex = F > M (3:1)
  - 14.7 /100,000 population /year
  - 1.1% will develop thyroid cancer during lifetime
  - 97.8% 5-year survival for all thyroid cancers

WHO Histological Classification of Thyroid Tumours

<table>
<thead>
<tr>
<th>Thyroid carcinoma</th>
<th>Follicular adenoma B330/9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary carcinoma B236/0</td>
<td>Hürthle cell neoplasm tumour B336/0</td>
</tr>
<tr>
<td>Follicular carcinoma B330/3</td>
<td>Other thyroid tumours</td>
</tr>
<tr>
<td>Poorly differentiated carcinoma B330/3</td>
<td>Teratoma 9080/1</td>
</tr>
<tr>
<td>Undifferentiated (anaplastic) carcinoma B320/3</td>
<td>Primary lymphoma and plasmacytoma</td>
</tr>
<tr>
<td>Squamous cell carcinoma B470/3</td>
<td>Ectopic thymus tissue B357/0</td>
</tr>
<tr>
<td>Mucopidermoid carcinoma B430/3</td>
<td>Angiosarcoma 9120/3</td>
</tr>
<tr>
<td>Sclerosing mucusoepidermoid carcinoma with eosinophilia B420/3</td>
<td>Smooth muscle tumours</td>
</tr>
<tr>
<td>Mucous carcinoma B440/3</td>
<td>Peripheral nerve sheath tumours</td>
</tr>
<tr>
<td>Medullary carcinoma B345/0</td>
<td>Paraganglioma B893/1</td>
</tr>
<tr>
<td>Medulloblastoma and medullary cell carcinoma B346/3</td>
<td>Sialolithiasis tumour 8815/0</td>
</tr>
<tr>
<td>Spindle cell tumour with thymus-like differentiation B336/3</td>
<td>Follicular dendritic cell tumour 9758/3</td>
</tr>
<tr>
<td>Carcinoma showing thymus-like differentiation B336/3</td>
<td>Langerhans cell histiocytosis 9751/1</td>
</tr>
</tbody>
</table>

Current Management

- Lobectomy or Thyroidectomy
  - Pre-op FNA dependent
  - Completion thyroidectomy if any of following:
    - Known distant metastases
    - Extrathyroidal extension
    - Tumor >4 cm
    - Confirmed cervical lymph node metastasis
    - Positive margins
    - Macroscopic multifocal disease (not microscopic)
    - Lymphovascular invasion
    - Poorly differentiated histology

Version 1, 2016 (07/2016): NCCN Clinical Practice Guidelines
Current Management

- NO completion thyroidectomy only if all are present:
  - Age between 15 – 45 years
  - No prior radiation
  - No lymphovascular invasion
  - No distant metastases
  - No cervical metastases (suspicious lymph node)
  - No extrathyroidal extension
  - Tumor 1-4 cm
  - Negative resection margins
  - No contralateral lesion
  - No aggressive variant
    - Tall, columnar, diffuse sclerosing, poorly differentiated

Version 1, 2016 (07/2016): NCCN Clinical Practice Guidelines

Thyroid Papillary Carcinoma: Histologic Types

- Usual or Conventional types
  - Occult, incidental, microcarcinoma, microscopic
  - Follicular
  - Macrofollicular
  - Oncocytic or oxyphilic
  - Clear cell
- “Biologically Aggressive” Variants
  - Diffuse sclerosing
  - Tall cell
  - Columnar cell
  - Insular or Poorly differentiated

Thyroid Papillary Carcinoma: Classic Clinical Features

- Most common malignant thyroid tumor
- Sex: F >> M (4:1)
- Age: 3rd – 5th decades (majority)
- Ethnicity: White > Black
- Symptoms:
  - Asymptomatic, palpable mass
    - Solitary nodule: 28x fold increased risk of tumor
  - Lateral neck mass (mets in up to 30%)
### Thyroid Papillary Carcinoma: Classic Pathology

**Macroscopic**
- Majority are solid and solitary
- May be cystic
- Encapsulated versus overt invasion
  - Adjacent tissues or extrathyroidal extension (pT3)
- Fibrosis and calcification may be present

**Size varies:**
- Occult, incidental, minute, microscopic
- < 1.0 cm by WHO definition
- Large: > 5 cm

### 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

---

**Architectural**

**Cytomorphologic/Nuclear**

---

**Architectural**

**Cytomorphologic/Nuclear**

---

**Architectural**

**Cytomorphologic/Nuclear**

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NIFTP: Noninvasive 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

Materials Reviewed

• All thyroid surgeries performed in 2002
• A minimum of 10 years of follow-up
• 721 cases reviewed
• All histology slides reviewed
  ◆ 7,977 primary slides
  ◆ 2,022 additional intraoperative, IHC, levels, specials, deepers
• Follow-up obtained from EMR or direct communication
Papillary carcinoma: Type/Variant Breakdown

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th># of Cases</th>
<th>% of all papillary cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical</td>
<td>106</td>
<td>32.7</td>
</tr>
<tr>
<td>Microscopic</td>
<td>98</td>
<td>29.6</td>
</tr>
<tr>
<td>Follicular variant</td>
<td>94</td>
<td>29.0</td>
</tr>
<tr>
<td>Tall cell</td>
<td>19</td>
<td>5.9</td>
</tr>
<tr>
<td>Diffuse sclerosing</td>
<td>4</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Study Design

- International, multi-disciplinary study of 138 patients with Noninvasive EFVPTC followed for 10-26 years and 130 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.
- 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.

Study Materials

- 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 Noninvasive 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

Mutations in Papillary Carcinoma and Phenotypical Associations
Molecular Alterations

- Point mutations involving RAS genes about 10% of papillary carcinomas
  - Almost exclusively the follicular variant
  - Seen in NRAS, HRAS, and KRAS genes
  - Strong correlation with
    - More frequent tumor encapsulation
    - Lower rate of lymph node involvement
- BRAF K601E mutation usually in follicular variant of papillary carcinoma
- PAX8/PPARγ
  - Usually follicular carcinoma
  - 5% of follicular variant papillary carcinomas

Gene Profiles and Histologic Variants

Histology Molecular

https://en.wikipedia.org/wiki/Noninvasive_follicular_thyroid_neoplasm_with_papillary-like_nuclear_features

Fine Needle Aspiration

- Most NIFTP were classified as Bethesda System for Reporting Thyroid Cytopathology:
  - III. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance
  - IV. Follicular Neoplasm or Suspicious for a Follicular Neoplasm
- Most will have molecular findings in RAS genes (KRAS, NRAS, HRAS)
  - But, not BRAF, PPARγ, RET/PTC

- V. Suspicious for Malignancy
  - Suspicious for papillary carcinoma
- VI. Malignant
  - Papillary thyroid carcinoma
- But – now these categories can only be used if you have 3-dimensional papillary structures and/or psammoma bodies – otherwise a NIFTP could be the diagnosis
Criteria

Major Features
1. Encapsulation or clear demarcation
2. Follicular growth pattern (<1% papillae)
3. Nuclear Features of PTC (Score 2 or 3):
   - Enlargement/crowding/overlapping
   - Elongation
   - Irregular contours
   - Grooves
   - Pseudoinclusions
   - Chromatin clearing
4. Follicular growth pattern (<1% papillae)
5. Nuclear Features of PTC (Score 2 or 3):
   - Enlargement/crowding/overlapping
   - Elongation
   - Irregular contours
   - Grooves
   - Pseudoinclusions
   - Chromatin clearing
6. Multinucleated giant cells within follicles

Minor Features
1. Dark colloid
2. Irregularly-shaped follicles
3. Intratumoral fibrosis
4. “Sprinkling” sign
5. Follicles cleft from stroma
6. Multinucleated giant cells within follicles

Features not seen/
Exclusion criteria
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

Noninvasive 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

ALGORITHM FOR DIAGNOSIS OF NIFTP

<table>
<thead>
<tr>
<th>Criteria</th>
<th>NIFTP</th>
<th>EFVPTC or PTC with invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encapsulated or Well-demarcated</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Capsular and/or Lymphovascular invasion</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>&gt;50% solid tumor/dyscohesive and/or &gt;5% true papillary pattern and/or Psammomma bodies identified and/or Tall cell or columnar cells/tumor</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Predominantly follicular pattern</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tumor necrosis and/or &gt;5 mitoses/10 HPFs</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nuclear features of papillary thyroid carcinoma (score 2 or 3)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Psammomma bodies identified and/or Tall cell or columnar cells/tumor</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Highly differentiated tumor</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Follicular adenoma and/or adenomatoid nodule</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Partially encapsulated—circumscribed

WHOse New in Thyroid Gland Pathology

L.D.R. Thompson
## Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclei

- Absent invasion
- By definition this must be “noninvasive”
  - No capsular invasion
  - No vascular invasion
- Must be adequately (completely) sampled
  - Tumor to capsule to parenchyma
  - 3 sections (not blocks) per cm of tumor

## Frozen section

- Unreliable and not meaningful
- You have to have the whole periphery sampled to be included in NIFTP category
  - Cannot be done during intraoperative assessment
- If a frozen is called “follicular variant of papillary carcinoma,” then it may be NIFTP at the time of permanents (if there is no invasion)
Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclei

- Predominantly 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

Sandison pseudopapillary structure OK

Single papillary structure is OK
Too many papillary structures

Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclei

- Hypereosinophilic colloid
- Scalloped colloid frequently present
- Internal, acellular, eosinophilic fibrosis between follicles
- Dropping substage condenser often creates a “bright” signal

Hypereosinophilic Colloid

Colloid scalloping

Internal fibrosis
Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclei

- Absent psammoma bodies
- Absent necrosis
- No increased mitoses
  - ≤ 3 mitoses/10 High Power Fields
- No other patterns or specific tumor types present
  - Solid, insular, trabecular, morular
  - Oncocytic, tall, columnar

Excluded: Tumor Necrosis

Excluded: >3 mitoses/10 HPFs

Excluded: Solid Pattern

Excluded: Cribriform-morula

Excluded: Tall cell papillary
Excluded: Columnar papillary

Thyroid Papillary Carcinoma: Encapsulated Follicular variant

- Must have nuclear features of papillary carcinoma
  - 1 point each = 3; 2 or more is diagnostic
- Size and shape (1 point)
  - Nuclear enlargement, overlapping, crowding, elongation
- Nuclear membrane irregularities (1 point)
  - Irregular contours, grooves, pseudoinclusions
- Chromatin characteristics (1 point)
  - Clearing with margination, glassy nuclei

Diagnosis rests on cytology

- Size and shape = 1 point
  - Enlargement, elongation, overlapping/crowding
- Membrane irregularities = 1 point
  - Irregular contours, grooves/folds, intranuclear cytoplasmic inclusions
- Chromatin distribution = 1 point
  - Chromatin clearing, margination to membrane, “glassy” nuclei

Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclei

Nuclear score: Sum of three nuclear features (each 0 or 1)

Thus, total score will vary between 0 and 3

<table>
<thead>
<tr>
<th>Nuclear features</th>
<th>Absent/insufficiently expressed (0)</th>
<th>Present/sufficient (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size and shape</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elongation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overlapping</td>
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</tr>
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<tbody>
<tr>
<td>Size and Shape</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Enlargement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Elongation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Overlapping</td>
<td></td>
<td></td>
</tr>
<tr>
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</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>• Grooves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Intranuclear cytoplasmic inclusions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromatin Features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Chromatin clearing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Margination to nuclear membrane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Glassy nuclei</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thus, total score will vary between 0 and 3

Absent/insufficiently expressed (0)
Present/Sufficient (1)

Slight changes not sufficient to call "present!"
Thyroid Papillary Carcinoma: Encapsulated Follicular Variant

- 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

<table>
<thead>
<tr>
<th>Diagnosis (= 324)</th>
<th># of Cases</th>
<th>Absent</th>
<th>Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical</td>
<td>106</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>Microscopic</td>
<td>98</td>
<td>63</td>
<td>35</td>
</tr>
<tr>
<td>FV: Encap/Inv.</td>
<td>94</td>
<td>80</td>
<td>14</td>
</tr>
<tr>
<td>Tall</td>
<td>19</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Diffuse sclerosing</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number with disease, %, average follow-up for diseased patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>p=0.0001 (chi square)</td>
</tr>
<tr>
<td>0/149 0%</td>
</tr>
<tr>
<td>20/175 11.4%</td>
</tr>
<tr>
<td>(11.1) (9.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Papillary carcinoma: Lymphovascular invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis (= 324)</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
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<td>(11.1) (9.3)</td>
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</table>

<table>
<thead>
<tr>
<th>Follicular Variant Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>71 cases</td>
</tr>
<tr>
<td>Surgery only</td>
</tr>
<tr>
<td>NO RAI</td>
</tr>
<tr>
<td>NED</td>
</tr>
<tr>
<td>11.1 years</td>
</tr>
</tbody>
</table>
NIFTP
Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features