Follicular Variant of Papillary Thyroid Carcinoma

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Follicular Thyroid Lesions and Neoplasms

- Hyperplastic nodule
- Follicular adenoma
- Adenomatous nodule
- Macrofollicular, microfollicular, oncocytic
- Follicular thyroid carcinoma
- Papillary thyroid carcinoma, follicular variant
- Non-invasive follicular thyroid neoplasm with papillary-like nuclei (NIFTP)
Follicular Variant of Papillary Thyroid Carcinoma: What is new?

NIFTP
Follicular Variant of PTC

• Clinical
  – Same age and gender as conventional
  – Slightly different prognosis
    • Lower lymph node metastases
    • 10-year: 90% (FV) vs. 96% (conventional)
Follicular Variant of PTC

- Histologic features
  - Pure follicular architecture
  - Papillary carcinoma nuclei
    - RARE to absent intranuclear pseudoinclusions
      - If present, r/o classical type, r/o oncocytic (Hürthle cell) neoplasm
  - Irregular nuclear membranes
  - Some encapsulated
    - +/- invasion
Follicular Variant of PTC

- Histologic features
  - Encapsulated
    - Without capsular invasion
    - With capsular invasion
    - With lymphovascular invasion
  - Well-circumscribed
  - Invasive
    - With fibrosis
Follicular variant PTC
Special Studies in Papillary Carcinoma

- Immunohistochemistry: HBME1
- Molecular mutations
BRAF mutations

• Tumors
  – Melanoma
  – Cholangiocarcinoma
  – Papillary thyroid carcinomas
  – etc

• Mutation
  – Activating mutation in exon 15
  – Valine > glutamate (V600E)
  – Simulates phosphorylation in activation site
BRAF in Papillary Carcinoma

![Graph showing BRAF expression in various types of papillary carcinoma.](image)
RET-PTC Translocations

- Tumors
  - Papillary thyroid carcinomas

- Translocation
  - Different partner genes
    - ELE1 and H4 most common
  - Constitutively activated tyrosine kinase
  - Fusion protein translocation to cytoplasm
RET/PTC in Papillary Carcinoma

![Bar chart showing the percentage of RET/PTC in FVPTCa, PTCa, FCa, and FA. PTCa has the highest percentage, followed by FVPTCa, FCa, and FA.]
Mutations in FVPTC

- RAS (N-K-H)
- PAX8-PPARγ

- Integrated genomic characterization of papillary thyroid carcinoma

- Implications for TCGA genomic characterization of papillary thyroid carcinoma: does follicular variant of papillary thyroid carcinoma exist?
Mutations in FVPTC

Follicular Variant

• Architecture:
  – Encapsulated
  – Well-circumscribed
  – Invasive
Follicular Variant

- Subtle histologic features
  - Low power assessment
    - Nuclear atypia at 4X (different from background)
    - Clustered atypia
    - Nuclear features more pronounced under capsule
  - Architecture
    - Perifollicular fibrosis
    - Thick colloid
    - Abortive papillae
Follicular variant PTC
Follicular variant PTC
Follicular Variant of PTC

• Subtle histologic features
  – Nuclei
    • Flattened or pushed in side
    • Irregular contours
    • Small peripheral nucleoli
Follicular variant PTC
Papillary Thyroid Carcinoma

Nuclear clearing

Crowded Overlapping

Nuclear grooves
Follicular variant PTC

Normal follicles
Challenging Follicular Variants

• Macrofollicular lesions
• Lesions with scattered nuclear features: sprinkling sign
Follicular variant PTC
Follicular variant PTC
Follicular variant PTC
Follicular variant PTC
Follicular variant PTC
Pitfalls in FVPTC

• Things to avoid
  – Exclude reactive areas
    • FNA area
    • Degenerative changes
  – Exclude microscopic papillary carcinoma within a nodule
  – Nuclear features that are just too good
  – Frozen section
Problem Areas in Follicular Variant

• Well-circumscribed tumors?
• Encapsulated tumors?
• Lesions with scattered nuclear features
  – Diagnosis?
  – Size of tumor?
Changes...

• Recent publication on this fastest growing subtype of the most common endocrine cancer
• Invasion rather than nuclear features correlates with outcome in encapsulated follicular tumors: further evidence for the reclassification of encapsulated papillary thyroid carcinoma follicular variant.
  Ganly I et al.; Hum Pathol. 2015 Feb 4.

• Identification of oncogenic mutations and gene fusions in the follicular variant of papillary thyroid carcinoma.

• Molecular alterations in partially-encapsulated or well-circumscribed follicular variant of papillary thyroid carcinoma.
International Consortium:
Working Group for Reclassification of the Encapsulated Follicular Variant of Papillary Thyroid Carcinoma

- Pathologists and a few clinicians (surgeons, endocrinologists)
- Over 200 cases of invasive carcinomas
- Non-invasive, encapsulated neoplasms
- Nuclear scoring
- Classification
- New name??
  - Meeting USCAP, Boston, 2015 (March 20-21)
May 25, 2015:

• Non-invasive follicular thyroid neoplasm with papillary-like nuclei
• Aka NIFTP (non-invasive follicular tumor, papillary-like)
• Would define the tumor to be biologically inert, regardless of degree of nuclear membrane irregularities
• Definition still in evolution
• Publication should be submitted shortly
Implications of NIFTP

• Reduced diagnosis of follicular variant of papillary thyroid carcinoma

• **Reduced over-treatment** of indolent thyroid tumors

• Reduced need for consultation due to **increased reproducibility** of morphological features – and reduced use of immunohistochemistry

• Update to Bethesda FNA criteria
Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma
A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

Yuri E. Nikiforov, MD, PhD; Raja R. Seethala, MD; Giovanni Tallini, MD; Zubair W. Baloch, MD, PhD; Fulvio Basolo, MD; Lester D. R. Thompson, MD; Justine A. Barletta, MD; Bruce M. Wenig, MD; Abir Al Ghuzlan, MD; Kennichi Kakudo, MD, PhD; Thomas J. Giordano, MD, PhD; Venancio A. Alves, MD, PhD; Elham Khanafshar, MD, MS; Sylvia L. Asa, MD, PhD; Adel K. El-Naggar, MD; William E. Gooding, MS; Steven P. Hodak, MD; Ricardo V. Lloyd, MD, PhD; Guy Maytal, MD; Ozgur Mete, MD; Marina N. Nikiforova, MD; Vanla Nosé, MD, PhD; Mauro Papotti, MD; David N. Poller, MB, ChB, MD, FRCPath; Peter M. Sadow, MD, PhD; Arthur S. Tischler, MD; R. Michael Tuttle, MD; Kathryn B. Wall; Virginia A. Livolsi, MD; Gregory W. Randolph, MD; Ronald A. Ghossein, MD

JAMA Oncology, published on line, April 14, 2016
Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: A Paradigm Shift to Reduce Overtreatment of Indolent Tumors.


Follicular variant of PTC

• Recognized in the mid-1970s
• Two types follicular variant of PTC:
  - Encapsulated /circumscribed (EFVPTC)
  - Infiltrative
• EFVPTC constitutes 10%-20% of all thyroid cancers diagnosed in Europe and North America.
Diagnostic criteria for EFVPTC

- **Major features:**
  - Encapsulation or clear demarcation
  - Follicular growth pattern
  - Nuclear features of PTC

- **Minor features:**
  - Dark colloid
  - Irregular shaped follicles
  - Intratumor fibrosis
  - Sprinkling sign
  - Multinucleated giant cells
  - Follicles cleft from the stroma

- **Exclusion features**
  - True papillae (>1%)
  - Psammoma bodies
  - Infiltrative border
  - Tumor necrosis
  - High mitotic activity (>3 /10 HPF)
  - Cell/morphology characteristic of other variants of PTC
Figure 1. Gross and Histopathologic Features of the Tumor Currently Known as Encapsulated Follicular Variant of Papillary Thyroid Carcinoma (EFVPTC)

A. Tumor with thin capsule

B. Encapsulation and microfollicular growth pattern of the tumor

C. Nuclear enlargement and elongation

D. Irregular nuclear contours and chromatin clearing
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (Noninvasive EFVPTC) (n = 109)</th>
<th>Group 2 (Invasive EFVPTC) (n = 101)</th>
</tr>
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<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>45.9 (21-81)</td>
<td>42.8 (8-78)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>91 (83)</td>
<td>71 (70)</td>
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<tr>
<td>Male</td>
<td>18 (17)</td>
<td>30 (30)</td>
</tr>
<tr>
<td>Tumor size, mean (range), cm</td>
<td>3.1 (1.1-9.0)</td>
<td>2.5 (0.6-5.5)</td>
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<tr>
<td>Extent of surgery</td>
<td></td>
<td></td>
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<tr>
<td>Lobectomy</td>
<td>67</td>
<td>15</td>
</tr>
<tr>
<td>Total thyroidectomy</td>
<td>42</td>
<td>86</td>
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<tr>
<td>Follow-up, y</td>
<td></td>
<td></td>
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<tr>
<td>Mean (range)</td>
<td>14.4 (10-26)</td>
<td>5.6 (1-18)</td>
</tr>
<tr>
<td>Median</td>
<td>13.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Adverse events during follow-up, No. (%)</td>
<td>0</td>
<td>12 (12)</td>
</tr>
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</table>
Endocrine Pathology Society Working Group

Conclusion

• Nomenclature revision needed
• Old term: Encapsulated follicular variant of papillary thyroid carcinoma
• New name: Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NFITP)
eTable 2. Results of molecular analysis of cases initially submitted to Group 1

<table>
<thead>
<tr>
<th>Gene mutation</th>
<th>Accepted to final Group 1</th>
<th>Excluded due to insufficient nuclear features</th>
<th>Excluded due to the presence of higher-grade exclusion criteria</th>
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<td>n=27</td>
<td>n=5</td>
<td>n=5</td>
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<tr>
<td>RAS*</td>
<td>8</td>
<td>2</td>
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</tr>
<tr>
<td>NRAS</td>
<td>(5)</td>
<td></td>
<td>(1)</td>
</tr>
<tr>
<td>HRAS</td>
<td>(2)</td>
<td></td>
<td>(1)</td>
</tr>
<tr>
<td>KRAS</td>
<td>(1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF K601E</td>
<td>1</td>
<td></td>
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</tr>
<tr>
<td>TERT</td>
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<td></td>
<td>1</td>
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<tr>
<td>PPARG fusion</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALK fusion</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>THADA fusion</td>
<td>6</td>
<td></td>
<td></td>
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<tr>
<td>TOTAL MUTATION POSITIVE</td>
<td>21 (78%)</td>
<td>0</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>TOTAL MUTATION NEGATIVE</td>
<td>6 (22%)</td>
<td>5 (100%)</td>
<td>1 (20%)</td>
</tr>
</tbody>
</table>

*Two cases had double mutations: RAS and EIF1AX*
The “capsule”

• NIFTP does not require a capsule
• Requires tumor to be well-circumscribed
• For NIFTP, the “capsule” becomes the tumor:non-tumor interface
• The interface should be “adequately sampled”
Case Presentation

53 year-old male with multinodular goiter with prominent nodules
Ultrasound

2.3 cm nodule #2

0.9 cm nodule #1
Histology

Nodule #1
- Infiltrative
- Follicular architecture
- Nuclear features of PTC

Nodule #2
- Well-circumscribed
- Follicular architecture
- Nuclear features of PTC
Nodule #1

- Follicular architecture
- Nuclear features of PTC

Nodule #2

- Follicular architecture
- Nuclear features of PTC
Nodule #1
• Positive

Nodule #2
• Positive
Diagnosis
Multifocal Papillary Thyroid Carcinoma, Follicular Variant
Our Patient

Nodule #1
- PTC nuclei
- Follicular architecture
- INFILTRATIVE GROWTH
- BRAF positive

Just like classical-type PTC

Nodule #2
- PTC nuclei
- Follicular architecture
- NON-INVASIVE, CIRCUMSCRIBED
- BRAF negative

Just like follicular adenoma/carcinoma
PTC, Follicular variant

Infiltrative Follicular Pattern
- BRAF-like
- Similar to classical-type molecularly and in behavior

Encapsulated Follicular Pattern
- RAS-like
- Similar to follicular adenoma/carcinoma molecularly and in behavior
Let's suppose..... these nodules were in separate patients....
Patient #1

- Morphology:
  - PTC nuclei
  - Follicular architecture
  - Infiltrative growth
- Molecular profile: BRAF positive (similar to classical-type)
- Diagnosis: Papillary thyroid carcinoma, follicular variant, invasive
- Behavior prediction: nodal spread (similar to classical type!)
- Treatment: Total lobectomy plus radioiodide treatment +/- lymph node dissection

Patient #2

- Morphology:
  - PTC nuclei
  - Follicular architecture
  - Confined growth
- Molecular profile: BRAF negative, RAS positive (similar to follicular adenoma)
- Diagnosis: NIFT
- Behavior prediction: indolent
- Treatment: Lobectomy alone
- NO radioiodine therapy!
- NO additional surgery!
- NO additional cost!
- NO psychological trauma!!
Molecular Pathways in Thyroid Papillary Carcinogenesis

Tall-cell, columnar cell, and hobnail variants PTC have a high prevalence of \textit{BRAF} mutation.

Follicular Variant of PTC have a low prevalence of \textit{BRAF}, higher \textit{RAS} mutation.

Classical Variant of PTC have a low prevalence of \textit{BRAF}, higher \textit{RET-PTC}.

- **BRAF**: 0-21%
- **RAS**: 29-77%
- **RET-PTC**: 13-43%
Progress in Identifying Driver Mutations in Thyroid Cancer

1990 2000 2005

- 20% RAS, RET/PTC
- 30% RAS, RET/PTC, TP53, TRK, PTEN, b-catenin
- 70% RAS, RET/PTC, TP53, TRK, PTEN, b-catenin, PAX8/PPARg, BRAF, PIK3CA, BRAF/AKAP9
Progress in Identifying Driver Mutations in Thyroid Cancer

- **1990**: 20% RAS, RET/PTC
- **2000**: 30% RAS, RET/PTC, TP53, TRK, PTEN, b-catenin
- **2005**: 70% RAS, RET/PTC, TP53, TRK, PTEN, b-catenin, PAX8/PPARg, BRAF, PIK3CA, BRAF/AKAP9
- **2014**: >90% RAS, RET/PTC, TP53, TRK, PTEN, b-catenin, PAX8/PPARg, BRAF, PIK3CA, BRAF/AKAP9, AKT1, STRN/ALK, ETV6/NTRK3, EIF1AX

Reduced “Dark Matter” of unknown driver mutations.
## Common Mutations in Types of Thyroid Cancer

<table>
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<tr>
<th></th>
<th>PTC, classical and tall cell</th>
<th>PTC, follicular variant</th>
<th>Follicular Carcinoma</th>
<th>Poorly-differentiated carcinoma</th>
<th>Anaplastic carcinoma</th>
<th>Follicular adenoma</th>
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<td><strong>BRAF V600E</strong></td>
<td>+++</td>
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<tr>
<td><strong>BRAF K601E</strong></td>
<td></td>
<td>+++</td>
<td>++</td>
<td>+</td>
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<td>+</td>
</tr>
<tr>
<td><strong>NRAS</strong></td>
<td></td>
<td>+++</td>
<td>++</td>
<td>+</td>
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<tr>
<td><strong>HRAS</strong></td>
<td></td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>KRAS</strong></td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
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<tr>
<td><strong>PTEN</strong></td>
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<td><strong>TSHR</strong></td>
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<td><strong>GNAS</strong></td>
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<tr>
<td><strong>RET/PTC</strong></td>
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<tr>
<td><strong>PAX8/PPARG</strong></td>
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<td>+++</td>
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<tr>
<td><strong>ALK FUSIONS</strong></td>
<td>+</td>
<td></td>
<td></td>
<td>++</td>
<td>++</td>
<td></td>
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<tr>
<td><strong>BRAF FUSIONS</strong></td>
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<tr>
<td><strong>ETV6/NTRK</strong></td>
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