Diagnostic Challenges and Controversies of Follicular-Patterned Thyroid Neoplasms

Faqian Li, MD PhD
10/28/2016

Department of Laboratory Medicine and Pathology

Objectives

• Recognize morphologic features of different follicular-patterned thyroid neoplasms
• Understand evidence-based classification of follicular-patterned thyroid neoplasms
• Explain the logics and rationale of new diagnostic concept of NIFTP

Thyroid lesions

• Thyroid nodules are common
  – Palpation: 4-7%
  – Ultrasonography: 19-67%
• Risk of malignancy 8 to 16%
  – 45,310 new cases of thyroid cancer in US (2013)
• Initial assessment based on clinical history, examination, serum TSH and ultrasonography
• Nodules of over 1 cm, PET positive or with suspicious features sampled by Fine Needle Aspiration (FNA)
Thyroid nodules

• Most are follicular origin and benign
  – Reactive
  – Neoplastic
    • Adenoma
    • Carcinoma
  • C-cell derived is malignant

Thyroid Carcinoma

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

WHO Classification of Thyroid Cancer

• Follicular derived
  – Papillary carcinoma
  – Follicular carcinoma
  – Poorly differentiated thyroid carcinomas including insular carcinoma
  – Undifferentiated (anaplastic) carcinoma
• Medullary carcinoma
• Carcinoma, type cannot be determined
C-cell derived neoplasm

- C-cell hyperplasia – precursor lesion
- Medullary microcarcinoma
- Medullary carcinoma

Follicular derived

- Architectural
  - Form follicles: Follicular-patterned:
  - Fibrovascular core: Papillary-patterned
- Nuclear features
  - Follicular: Round, smooth, granular chromatin, nucleoli
  - Papillary:
    - Elongated
    - Irregular/groove/nuclear pseudoinclusion
    - Enlargement/crowding/overlapping
    - Chromatin clearing

Follicular lesions

No papillary nuclei!!!!
Papillary lesions

Papillary nuclei are not specific

Hürthle cell change
How to classify follicular-derived lesions

- Traditionally, nuclear features have been considered critical to classify follicular-derived proliferation and determine benign vs. malignant
- Papillary nuclei = malignant, but clinical evidence does not support
- Growth patterns may be more important

Papillary neoplasms with papillary pattern and nuclei

- Papillary architecture with papillary nuclei features – Classic papillary thyroid carcinoma, no diagnostic problem
- Capsule
- Angiolympathic invasion
- Extrathyroidal extension
- Lymph node or distant metastasis

Papillary neoplasms with follicular pattern and papillary nuclei

- Follicular pattern with papillary nuclear features – Problematic
  - Has been called follicular variant of PTC
  - Highly debated over decades
- Infiltrative without capsule – malignant, no controversy
- Encapsulated with capsular and vascular invasion – malignant, not much controversy
- Non-invasive encapsulated - new concept
Follicular patterned neoplasm without PTC nuclei – What make it malignant

- Histologically bland morphology – Invasion separates follicular carcinoma from adenoma
  - Encapsulation
  - Capsular invasion
  - Vascular invasion
- Histologically malignant
  - Poorly differentiated carcinoma
  - Anaplastic carcinoma

Capsular invasion
Capsular invasion

Criteria for Capsular Invasion

Minimally vs widely
- Minimally invasive
  - Gross encapsulation
  - Capsule invasion only
  - Very rare if only capsule invasion to recur or metastasize
  - Lobectomy enough?
- Widely invasive
  - Multifocal beyond capsule
  - Into surrounding tissue, original capsule is gone
Angioinvasion

- Encapsulated
  - Extracapsular vessels
  - Capsular vessels
- No tumor capsule
  - Any vessel with tumor
- Less than 4 vessels
- More than 4 vessels

Extracapsular vascular invasion

Capsular vascular invasion
Tumor thrombus

Questionable angioinvasion

Criteria for angioinvasion

From CAP protocol
Hürthle cell (oncocytic) neoplasm

- Follicular neoplasm in which 75% or more of follicular cells have oncocytic features
  - Exclude oncocytic metaplasia or change
  - Hürthle cells/oncocytes by themselves are nonspecific, and are seen in Hashimoto’s thyroiditis and other neoplasms
- Tend to infarct after fine needle aspiration
- Size is predictive
  - 2 cm or less - almost always adenoma
  - 6 cm or more - almost always carcinoma
- Malignant if capsular or vascular invasion

Poorly differentiated carcinoma

- Insular, solid, trabecular growth patterns
- Convoluted nuclei
  - Should PTC excluded?
- Mitosis
- Necrosis

Poorly differentiated thyroid carcinomas

"Poorly Differentiated Carcinoma of the Thyroid"
A Clinico-pathologic Entity for a High-Risk Group of Papillary and Follicular Carcinomas

The relationship between histologic type and survival of 286 thyroid malignancies has been studied. A new classification system, poorly differentiated carcinoma, has been proposed. Papillary and follicular carcinomas of the thyroid showed no significant differences in survival rates. Both tumors were histologically similar to well-differentiated and poorly differentiated carcinomas, as are thyroid cancer. However, in the PTC group, which showed more aggressive behavior, the death rates were higher. Poorly differentiated carcinomas exhibited more aggressive behavior, and the prognosis was worse than that of well-differentiated carcinomas. The differences between well-differentiated and poorly differentiated thyroid malignancies were statistically significant. Progression data suggest that the clinicopathologic entity of poorly differentiated carcinomas is of value in determining management and survival of thyroid cancer patients.

Causer 93:161-99, 1984
Prognosis based on growth patterns
Prognosis based on scoring

Criteria for PDTC diagnosis
- Morphology gives hints of possible PDTC
- Criteria
  - Mitoses
    - Turin 3 or more per 10 high power fields
    - MSK 5 or more per 10 high power fields
  - Necrosis

MSK criteria
Growth pattern or nuclear feature not important
- Necrosis
- Mitosis 5 or more per 10 HPFs
Poorly Differentiated Thyroid Carcinoma: The Turin Proposal for the Use of Uniform Diagnostic Criteria and an Algorithmic Diagnostic Approach

Maurizio Valentini, MD,* Paola Cossio, MB, BS; Yael E. Nikielski, MD, PhD,* Andrea Salamon, MD†; Konrad Kodolinski, MD, PhD;† Kojase Kosek, MD*; Ricardo V. Loyola, MD; Virginia A. Lio, MD;‡,* Marion Peters, MD*; Manuel Valdés, Cancio, MD, PhD†;§; Gérald Beaudry, MD, JRC; Panzetta and Jean Renat, MD†;§

Abstract: Poorly differentiated (PD) thyroid carcinoma is characterized by both morphologically and behaviorally between well-differentiated and undifferentiated components. Following the original descriptions of this entity, different diagnostic criteria have been suggested, resulting in wide discrepancies and diagnostic delays. The authors present a proposal (the Turin proposal) to correct these situations in different scenarios and used the multi-parametric activity 23 x 10 BfT and tissue markers. An algorithmic approach has been derived for practical use in the diagnosis of this cancer.

Keywords: thyroid carcinoma, poorly differentiated, classification, immune programs.

Lynk J. Thyroid Pathol 2017;31(6): 1266.
Conclusions: As even slight amounts of PD areas (≥ 10%) in a thyroid carcinoma affect the prognosis significantly, the presence of such areas may be worth reporting in thyroid carcinomas.
PDTC

- Often has solid, insular, or trabecular pattern of growth, but this does not automatically qualify the diagnosis of PDTC
  - Mitoses 3 or 5 more per 10 HPFs
  - Necrosis
- Often has capsular or LVI, but this is not required

Anaplastic TC

- Undifferentiated (high grade) carcinoma
  - Cannot tell it is from thyroid gland morphologically
- 2% of thyroid cancers, but 40% of thyroid cancer deaths
- Rapidly enlarging, bulky neck mass
  - Widely invades adjacent structures
  - Causing hoarseness, dysphagia, dyspnea
- Any thyroid sarcoma or pleomorphic tumors are most likely anaplastic carcinomas unless proved otherwise
Tumor morphology

- Large, pleomorphic giant cells resembling osteoclasts
- Spindle cells resembling sarcoma
- Squamoid cells that are relatively undifferentiated but also appear epithelial with occasional focal keratinization
- Rarely has rhabdoid inclusions
- Diffuse necrosis
- Frequent vascular invasion
- Many mitotic figures

Pleomorphic and necrotic

Spindle
Squamoid

Follicular patterned neoplasm – What make it malignant

- Follicular carcinoma vs adenoma
  - Capsular invasion
  - Vascular invasion
- Poorly differentiated carcinoma
  - Morphology
    - Convoluted nuclei
    - Insular, solid, trabecular growth pattern
  - Criteria
    - Mitoses
      - Turin 3 or more per 10 high power fields
      - MSK 5 or more per 10 high power fields
    - Necrosis

Papillary neoplasm – What make it malignant

- Papillary architecture with papillary nuclear morphology so called classic
- Follicular pattern with papillary nuclei
  - Infiltrative without capsule – malignant, follicular variant of PTC
  - Encapsulated with invasive – malignant, follicular variant of PTC
  - Capsular invasion
  - Vascular invasion
- Psammoma body
- Poorly differentiated carcinoma
Follicular variant of thyroid papillary carcinoma: A clinicopathologic study of six cases. 
Chen, Karl K.C.; Rosai, Juan
ABSTRACT. The clinicopathologic features of six cases of a peculiar variant of differentiated carcinoma of the thyroid composed of follicles with or without solid areas and having a characteristic ground-glass appearance of the nuclei were studied and compared with those of conventional papillary and follicular carcinomas. This variant resembled papillary carcinoma in its biologic behavior and all morphologic features with the exception that papillae were not present. The term "papillary carcinoma, follicular variant" is proposed for this tumor type in order to emphasize its close biologic relationship with the conventional papillary carcinoma.

Comparison of Clinopathologic Features of Papillary Carcinoma, Follicular Carcinoma and Papillary Carcinoma, Follicular Variant

<table>
<thead>
<tr>
<th>Feature</th>
<th>Papillary carcinoma</th>
<th>Follicular carcinoma</th>
<th>Follicular variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>1965</td>
<td>1965</td>
<td>1965</td>
</tr>
<tr>
<td>Axillary lymph node</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>20-42%</td>
<td>20-42%</td>
<td>20-42%</td>
</tr>
<tr>
<td>Regional metastasis</td>
<td>30-35%</td>
<td>30-35%</td>
<td>30-35%</td>
</tr>
<tr>
<td>Recurrence</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Infiltrative FVPTC
Classic PTC nuclei

Invasive FVPTC
Classic PTC nuclei

Less than 1% papillary

Encapsulated Follicular Variant of Papillary Thyroid Carcinoma with Bone Metastases

Ezraei W. Beemer, M.D., Ph.D., and Virgilio A. J. Folci, M.D.
Department of Pathology & Laboratory Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania


Mets FVPTC in the bone.

Note: “It is interesting that in none of the bony metastasis were nuclear features of papillary carcinoma seen.”
Follicular patterned neoplasm with PTC nuclei – encapsulated non-invasive

- Well circumscribed or encapsulated without capsular invasion – debated over decades
- If PTC nuclear features well developed and everywhere, often no problem on diagnosis
- However nuclear features
  - Not specific
  - May be focal
  - May be less than perfect
  - No consensus and consistence even among world experts

Observer Variation in the Diagnosis of Follicular Variant of Papillary Thyroid Carcinoma

Ricardo V. Lloyd, MD,* Lori A. Erickson, MD,* Mary R. Casey, MD,* King F. Lee, MBBS, FRCPA,* Christina M. Lobato, MS,* Sofia L. Au, MD, PhD,* John K. C. Chan, MBBS, FRCPA,* Ronald A. DeLellis, MD,† H. Irwin Harsh, MD, PhD,‡ Konstantin Katsonis, MD, PhD,‡ Virginia A. DiFiore, MD,* Michael J. Roti, MD,‡ and Marc R. Lass, MD,‡

Abstract: The histopathologic diagnosis of follicular variant of papillary thyroid carcinoma (FVPTC) can be difficult. Recent reports have demonstrated that this variant may be histologically heterogeneous.

Histologic features of FVPTC are illustrated in Figure 1A–E. Capsular invasion was present in 67% of cases, while lymphovascular invasion was observed in 5.7% of cases (Fig. 1F). Metastatic disease was present in 21 cases.

TABLE 2. Concordant Diagnoses by Reviewers

<table>
<thead>
<tr>
<th>No. of Reviewers Who Diagnosed FVPTC</th>
<th>n (%)</th>
<th>Cumulative n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>34 (39.1)</td>
<td>34 (39.1)</td>
</tr>
<tr>
<td>9</td>
<td>15 (17.2)</td>
<td>49 (56.3)</td>
</tr>
<tr>
<td>8</td>
<td>9 (10.3)</td>
<td>58 (66.7)</td>
</tr>
<tr>
<td>7</td>
<td>14 (16.1)</td>
<td>72 (82.8)</td>
</tr>
<tr>
<td>6</td>
<td>6 (6.9)</td>
<td>78 (89.7)</td>
</tr>
<tr>
<td>5</td>
<td>3 (3.5)</td>
<td>81 (93.1)</td>
</tr>
<tr>
<td>4</td>
<td>4 (4.6)</td>
<td>85 (97.7)</td>
</tr>
<tr>
<td>3</td>
<td>2 (2.3)</td>
<td>87 (100)</td>
</tr>
<tr>
<td>2</td>
<td>0 (0)</td>
<td>87 (100)</td>
</tr>
<tr>
<td>1</td>
<td>0 (0)</td>
<td>87 (100)</td>
</tr>
</tbody>
</table>
pathologists were asked to choose from the following list of diagnoses: FA, FC, FVPC, or other benign lesion. Diagnoses
given as “follicular neoplasm with questionable invasion/
suspect (sic) for FC” or “well-differentiated thyroid tumor
of uncertain malignant potential” were categorized as FA
for statistical purposes. The experts were also instructed
to list, in descending order, the 4 most important observed
histologic and cytologic criteria that enabled them to reach
a diagnosis of FVPC in each case and document the presence
of capsular (partial or complete) and/or vascular invasion.

Results

A complete listing of diagnoses made by the 6 experts is
given in Table 3. The experts were assigned random num-
bers, which were unrelated to their listed alphabetical order as
col-league. There was complete agreement among all 6 in only
2 cases (13%). FVPC (case 7) and lymphocytic thyroiditis
(cases 5) were consistent with malignancy. In the only case
that demonstrated definite malignancy on follow-up: classic PTC
Image 21 in contralateral completion thyroidectomy (case 7, Table 1).

There was a majority agreement (among 4 or more
experts) on the diagnosis of FVPC in 6 (40%) of 15 cases.
When diagnoses were categorized as benign (FA, nodul-
ar goiter, or lymphocytic thyroiditis), all 4 cases and
malignant (FC or FVPC), agreement among all 6 experts was seen in 4 cases
(27% cases 2, 4, 7, and 15). Majority agreement on malig-
nant diagnosis was demonstrated in 8 cases (53%) (Table 3).

Diagnostic Criteria for Follicular Variant of Papillary
Carcinoma as Cited by Experts

<table>
<thead>
<tr>
<th>Histologic Criteria</th>
<th>Majority Agreement Cases (n = 6)</th>
<th>Nonmajority Agreement Cases (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleolar clearing</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nuclear grooves</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Nuclear overlapping</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Nuclear irregularity</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Nuclear enlargement</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Chromatin margination</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Desmoplastic fibrous architecture</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Nuclear elongation</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Intracytoplasmic pseudoinclusions</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Rhabdoid cells</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Scarce lymphocytes</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Multiple nuclei</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Increased cellularity</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

* Ranked as determining factor of importance
1 Majority agreement: ≥ 4 of 6 experts agreed.
2 Nonmajority agreement: ≥ 3 of 6 experts agreed.
Total 78 cases
- 65% of infiltrative FVPTCs had lymph node metastases.
- 5% of encapsulated FVPTCs had lymph node metastases.
- All encapsulated tumors with LN metastases had foci of LVI.
- No encapsulated tumors without invasion had LN metastases.
Encapsulated Papillary Thyroid Carcinoma: A Clinicopathologic Study of 106 Cases with Emphasis on Its Morphologic Subtypes (Histologic Growth Pattern)

Michael Rivers, M.D.¹, R. Michael Tuttle, M.D.², Snehal Patel, M.D.², Ayrool Shahe, M.D.², Jatin P. Shah, M.D.¹, and Ronald A. Ghossein, M.D.¹

Table 5. Outcome and Clinicopathologic Characteristics of 30 Noninvasive Encapsulated Papillary Thyroid Carcinoma with Adequate Follow-Up Treated Surgically by Lobectomy Only with No RAI Therapy

<table>
<thead>
<tr>
<th>Median follow-up</th>
<th>8.9 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median size</td>
<td>3 cm</td>
</tr>
<tr>
<td>Median age</td>
<td>38 years</td>
</tr>
<tr>
<td>Male:Female</td>
<td>1:2.7</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td>Classical: 10 patients; follicular variant: 20 patients</td>
</tr>
<tr>
<td>Lymph node metastases at presentation</td>
<td>3 encapsulated classical PTC*</td>
</tr>
<tr>
<td>Outcome</td>
<td>No recurrence</td>
</tr>
</tbody>
</table>

*These three patients with encapsulated classical PTC and lymph node metastases at presentation did not recur after 99, 13, and 23 years of follow-up.
Encapsulated non-invasive FVPTC

- No uniform diagnostic criteria
- Molecular profile is not the same as classic PTC
- Excellent clinical outcome
- Should be considered benign?
Box 1. Consensus Diagnostic Criteria for the Encapsulated Follicular Variant of Papillary Thyroid Carcinoma (EFVPTC)

**Major Features**
- Encapsulation or clear demarcation
- Follicular growth pattern
- Nuclear features of papillary thyroid carcinoma (PTC):
  - Enlargement, crowding/overlapping
  - Elongation
  - Irregular contours
  - Grooves
  - Pseudoinclusions
  - Chromatin clearing

**Minor Features**
- Dark colloid
- Irregularly shaped follicles
- Intratumoral fibrosis
- "Sprinkling" sign
- Follicles devoid of stroma
- Multinucleated giant cells within follicles

**Features Not Seen/Exclusion Criteria**
- "True" papillae
- Psammoma bodies
- Infiltrative border
- Tumor necrosis
- High mitotic activity
- Cell/morphologic characteristics of other variants of PTC

- [Image of histological slides showing various features of EFVPTC]
Table: Summary of Follow-up Information for Patients in the Study Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (Nomivax EVPTC) (n = 100)</th>
<th>Group 2 (Invasive EVPTC) (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>45.9 (21.8-81)</td>
<td>42.8 (8-78)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>91 (83)</td>
<td>71 (70)</td>
</tr>
<tr>
<td>Male</td>
<td>18 (17)</td>
<td>30 (30)</td>
</tr>
<tr>
<td>Tumor size, mean (range), cm</td>
<td>3.1 (1.1-9.5)</td>
<td>2.5 (0.3-5.3)</td>
</tr>
<tr>
<td>Extent of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobectomy</td>
<td>67</td>
<td>15</td>
</tr>
<tr>
<td>Total Thyroidectomy</td>
<td>42</td>
<td>86</td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>Mean (range)</td>
<td>14.4 (10-26)</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>
</tbody>
</table>

Box 2. Diagnostic Criteria for NIFTP

1. Encapsulation or clear demarcation
2. Follicular growth pattern with <1% Papillae
   - No psammoma bodies
   - 30% Solid/lobular/insular growth pattern
3. Nuclear score 2-3
4. No vascular or capsular invasion
5. No tumor necrosis
6. No high mitotic activity

* Thick, thin, or partial capsule or well circumscribed with a clear demarcation from adjacent thyroid tissue.
† Including microfollicular, nonfollicular, or nonfollicular architecture with abundant colloid.
‡ Requires adequate microscopic examination of the tumor capsule interface.
§ High mitotic activity defined as at least 3 mitoses per 10 high power fields (400x).

Figure 2. Putative Scheme of Thyroid Carcinogenesis

- Papillary microcarcinoma
- Classic PTC
- NIFTP
- Invasive EVPTC
- Follicular adenoma
- Follicular thyroid carcinomas
Conceptual evolution of follicular pattern PTC

- Old dogma - Any thyroid follicular-patterned tumor with PTC-like nuclei are malignant called FVPTC
  - Infiltrative
  - Encapsulated
    - With or without CI or VI
- New concept - Encapsulated without capsular or vascular invasion has no adverse outcome and therefore not malignant
  - Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP)
Morphologic assessment

- Border
  - Circumscribed vs infiltrative
  - Encapsulation
    - Capsular invasion
    - Vascular invasion
- Architecture - Papillary or follicular
- Nuclear morphology
  - PTC nuclei
  - Convoluted nuclei
- Psammoma body
- Growth patterns – Insular, solid, or cribiform
- Mitoses and necrosis

THANK YOU!
ANY QUESTIONS?