Minimum Criteria for the Diagnosis of Thyroid Carcinoma

Arizona Society of Pathologists
October 1, 2016
Bruce M. Wenig, MD
Mount Sinai Health System
New York, NY

Thyroid Carcinoma Minimum Diagnostic Criteria

• Tumor types:
  – Follicular Carcinoma
  – Papillary Carcinoma
  – Poorly-Differentiated Thyroid Carcinoma
  – Undifferentiated (Anaplastic) Carcinoma
  – Medullary Carcinoma
  – Malignant Lymphoma

Minimum Diagnostic Criteria for Thyroid Carcinoma

• Diagnostic Criteria:
  – Invasion:
    • Tumor capsular invasion
    • Vascular Invasion (VI)
    • Invasion into thyroid parenchyma
Follicular Adenoma vs Follicular Carcinoma

- A diagnosis of follicular carcinoma is predicated on the presence of invasive growth:
  - capsular invasion
  - vascular invasion
  - invasion into adjacent thyroid parenchyma

Capsular Invasion

- Extent of capsular invasion is contentious:
  - any degree of invasion into the capsule qualifies categorization as minimally invasive follicular carcinoma
  - tumor has to penetrate the entire thickness of the capsule to be regarded as unequivocal evidence of capsular invasion
- Special stains of questionable utility
Capsular Invasion*

*From Chan JKC. In: Fletcher CDM, ed. Diagnostic Histopathology of Tumors; 2013:1204.
Benign tumors grow as cohesive expansile masses remaining localized to their site of origin and do not have capacity to infiltrate, invade, or metastasize.

- Benign tumors grow and expand slowly, develop a rim of compressed connective tissue—fibrous capsule:
  - separates tumor from host tissue
  - derived largely from extracellular matrix of native tissue due to atrophy of normal parenchymal cells under pressure of expanding tumor
  - encapsulation does not prevent tumor growth but keeps benign tumors as discrete masses.


**Histologic features:**
- Uniformity in thickness
- Fibers run in parallel
Fibrous Capsule

Capsular Invasion

Problematic features relative to diagnostic interpretation:

- irregular contour(s) of the tumor
- tangential sectioning
- separate nodule lying outside capsule of the main tumor:
  - serial sections to determine whether there is a connection present or not are indicated
  - presence of continuity between main mass and nodule outside the capsule would be indicative of a carcinoma
  - absence of any connection does not exclude a diagnosis of carcinoma
  - may be indicative of multiple adenomatoid nodules

Uniform Appearing Fibrous Capsule

Cellular Nodule – Tangential Section
Adenomatoid Nodule(s)
- Multiple nodules
- Poor encapsulation
- Variable structure
- Comparable growth pattern in adjacent gland
- No compression of adjacent gland
- Retrogressive changes common (post-FNAB)
- Polyclonal; reports of monoclonality

Follicular Adenoma
- Solitary nodule
- Good encapsulation
- Uniform structure
- Different growth pattern from adjacent gland
- Compression of adjacent gland
- Retrogressive changes less common (post-FNAB) (except oncocytic cell dominant)
- Monoclonal

Angioinvasion (AI) or Vascular Invasion (VI)
- More reliable than capsular invasion
- Tumor in vasc spaces within or beyond capsule
- Presence of tumor within an endothelial-lined space:
  - presence of tumor adherent to wall with associated thrombus formation
  - tumor cells protruding into a vascular space with an endothelial layer identified over the bulging tumor nests
- Tumor within fibrous capsule conforming to the contour of a blood vessel (rounded edges) suggests AI

Adapted from: Meissner & Warren: Tumors of the Thyroid Gland. AFIP Fascicle 4; Second Series; 1969: 50.
Angioinvasion (CAP Protocol)

- Minimal requirements for clinically meaningful vascular invasion are currently point of controversy
- Historically, presence of endothelialized tumor alone has been minimal criterion to identify vascular space invasion, a finding supported in the literature
- More recently, however, one group has raised the caveat that tumor cells within vascular lumina unassociated with thrombus, and tumor cells underlying intact endothelium could represent “pseudoinvasion” given the fenestrated endothelial network of endocrine organs

Angioinvasion (CAP Protocol)

- Using more rigorous criteria, namely invasion of tumor cells through a vessel wall as well as thrombus formation in association with tumor, this group demonstrated that over one-third of tumors that fulfilled these criteria had distant metastases
- It is acknowledged that the risk of metastasis when these criteria are not fulfilled by a focus in vessels is not entirely absent

Follicular Neoplasms

Angioinvasion

- Mete and Asa (Modern Pathology 2011;24:1545-52)
  - Strict criteria:
    - Tumor cells invade through vessel wall
    - Thrombus adherent to intravascular tumor
  - Found in 118 of 4000 lesions (3%)
  - Follow-up in 98 cases: 35% developed metastases
  - Application of rigid criteria for vascular invasion predicts distant metastasis in thyroid carcinoma especially well-differentiated thyroid carcinoma

**Angioinvasion**


Angioinvasion (CAP Protocol)

- Minimal requirements for clinically meaningful vascular invasion are currently point of controversy
- Historically, presence of endothelialized tumor alone has been minimal criterion to identify vascular space invasion, a finding supported in the literature
- More recently, however, one group has raised the caveat that tumor cells within vascular lumina unassociated with thrombus, and tumor cells underlying intact endothelium could represent “pseudoinvasion” given the fenestrated endothelial network of endocrine organs

Angioinvasion (CAP Protocol)

- Using more rigorous criteria, namely invasion of tumor cells through a vessel wall as well as thrombus formation in association with tumor, this group demonstrated that over one-third of tumors that fulfilled these criteria had distant metastases
- It is acknowledged that the risk of metastasis when these criteria are not fulfilled by a focus in vessels is not entirely absent

Follicular Neoplasms

Angioinvasion

- Mete and Asa (Modern Pathology 2011;24:1545-52)
  - Strict criteria:
    - Tumor cells invade through vessel wall
    - Thrombus adherent to intravascular tumor
  - Found in 118 of 4000 lesions (3%)
  - Follow-up in 98 cases: 35% developed metastases
  - Application of rigid criteria for vascular invasion predicts distant metastasis in thyroid carcinoma especially well-differentiated thyroid carcinoma

**Angioinvasion**

VI with fibrin thrombus

VI with fibrin thrombus

VI with fibrin thrombus

Angioinvasion*


VI without fibrin thrombus

VI without fibrin thrombus
VI without fibrin thrombus

IHC staining for VI

CD31

Is this VI or not?

Elastic stain of no help
Angioinvasion

* D represents a common but contentious scenario among experts, in light of these new proposed criteria for significant VI. This endothelialized tumor deposit is juxtaposed to the vessel wall. As this is somewhat similar to C, and there is no obvious thrombus, technically this would not count as significant VI. One counterargument is that the endothelialized appearance represents “organization” of a tumor thrombus and is thus still significant. While deeper levels may help, this scenario may still be considered a “JUDGMENT CALL” based on current level of evidence.

Follicular Carcinoma

• Based on the extent of the invasive component, follicular carcinoma divided into:
  – minimally invasive
  – widely invasive

Follicular Carcinoma

Minimal vs Widely Invasive

• Based on the extent of the invasive component:
  – minimally invasive follicular carcinoma, which in turn can be subdivided into:
    • with capsular invasion only
    • with VI < 4 vascular spaces
  – widely invasive follicular carcinoma:
    • ≥ 4 or more vascular spaces
Follicular Adenoma v Follicular Carcinoma

Tissue Sectioning

• Ideally submit entire lesion
• Not practical for larger tumors:
  – minimum of 10 blocks
  – International Workshop on Thyroid Pathology:
    • Encapsulated follicular neoplasm - at least 5:
      – Low cellularity, large follicles, edematous stroma and no invasion = FA
      – Increased cellularity and/or other suspicious features – at least 5 additional blocks

Follicular Tumor of Uncertain Malignant Potential (FT-UMP)

• Introduced for those tumors in which there is limited capsular invasion (absence of complete capsular transgression), absence of angioinvasion, absence of nuclear features of papillary thyroid carcinoma
• Follicular adenoma with atypical features

Well-Differentiated Tumor of Uncertain Malignant Potential (WDT-UMP)

• Introduced for those tumors in which there are questionable (incomplete) nuclear features of papillary thyroid carcinoma
• Follicular adenoma with atypical features
Minimum Diagnostic Criteria for Thyroid Carcinoma

• Diagnostic Criteria:
  – Invasion
  – Cytomorphologic findings
  – Mitoses and Necrosis
  – Metastatic disease

Diagnosis of Thyroid Carcinoma Based on Cell Type

• Papillary Thyroid Carcinoma
• Medullary Thyroid Carcinoma
• Poorly-differentiated Thyroid Carcinoma
• Undifferentiated (Anaplastic) Carcinoma
• Malignant Lymphoma
• In general, follicular adenoma and follicular carcinoma cannot be differentiated based on cell type

Papillary Thyroid Carcinoma Definition

• Malignant thyroid follicular epithelial cell neoplasm characterized by distinctive nuclear features

Papillary Thyroid Carcinoma Pathologic Features

• Cytopathologic (Nuclear) features:
  – Nuclear enlargement and/or elongation with irregularities in size and shape
  – Dispersed (very fine) to optically clear appearing chromatin
  – Crowding and overlapping
  – Nuclear grooves
  – Cytoplasmic invagination into nucleus (inclusions)
PTC – Diagnostic Nuclei

PTC – Diagnostic Nuclei

PTC – Nuclear Inclusions

Inclusion in Follicular Adenoma

“Bubble artifact” ≠ Inclusions

PTC can be diagnosed by FNAB
PTC can be diagnosed by FNAB

Psammoma Bodies

Inspissated Colloid

Endocrine Atypia

Endocrine Atypia

Papillary Growth in Adenomatoid Nodule
Oncocyte or Oxyphilic Cell

- A cell that is “swollen” due to increased mitochondrial content (by EM) resulting in a prominent granular eosinophilic cytoplasm (by light microscopy)
- Askanazy original described the oncocyte
- Hürthle described the parafollicular cell
Chronic Lymphocytic (Hashimoto) Thyroiditis

Thyroid Lesions with Oncocytic Cells
- Nonneoplastic Lesions:
  - Lymphocytic thyroiditis
  - Adenomatoid nodules
  - Graves disease
  - Post-radiation; aging
- Neoplasms:
  - Follicular adenoma/carcinoma (Hürthle cell adenoma/carcinoma); PTC

Papillary Thyroid Carcinoma
Histologic Types/Variants
- Usual or conventional
- Papillary microcarcinoma
- Encapsulated
- Follicular
- Macrocystic
- Oncocytic or oxyphilic
- Clear cell

Papillary Thyroid Carcinoma
Histologic Types/Variants Cont’d
- Warthin tumor-like
- Diffuse (Multinodular) Follicular
- PTC with nodular fasciitis-like stroma
- PTC with spindle cell metaplasia
- PTC with lipomatous stroma

Papillary Thyroid Carcinoma
Histologic Types/Variants Cont’d
- Solid and Radiation-Induced
- Cribriform-Morular
- “Hobnail” (AJSP 2010;34:44-52)
- Aggressive variants

Follicular Variant of Papillary Thyroid Carcinoma (FVPTC)
- Subset of papillary carcinoma entirely composed of follicular growth lacking papillary architecture lined by cells having the nuclear features of PTC
Encapsulated Follicular Pattern Lesion

Circumscribed Follicular Pattern Lesion

Majority without PTC Nuclei

Foci with PTC Nuclei

Foci with PTC Nuclei

Juxtaposition of Nuclear Changes
**FVPTC Observer Variation**

- 10 reviewers; 87 tumors
- Concordant Diagnosis
- Most important criteria for diagnosis
- Less important criteria for diagnosis

---

**Summary of Diagnoses**

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>FVPTC</th>
<th>FA</th>
<th>FCA</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>74.7</td>
<td>12.6</td>
<td>0</td>
<td>12.6</td>
</tr>
<tr>
<td>3</td>
<td>85.1</td>
<td>13.8</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>77</td>
<td>20.7</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>5</td>
<td>91.9</td>
<td>4.7</td>
<td>0</td>
<td>3.5</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>91.9</td>
<td>1.1</td>
<td>0</td>
<td>6.9</td>
</tr>
<tr>
<td>8</td>
<td>98.9</td>
<td>0</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>46.6</td>
<td>37.9</td>
<td>12.6</td>
<td>3.5</td>
</tr>
<tr>
<td>10</td>
<td>60.9</td>
<td>11.5</td>
<td>1.2</td>
<td>26.4</td>
</tr>
</tbody>
</table>

---

**FVPTC Observer Variation**

- Concordant diagnosis with a cumulative frequency of 39%
- Only 51% were diagnosed as follicular variant by all pathologists
- Metastatic disease in 24.1% affirming need to differentiate follicular variant of PTC from benign thyroid lesions

---

**FVPTC Observer Variation**

- Unanimous agreement FVPC in 13% (2 cases)
- Majority agreement on benign and malignant diagnoses in 27% (4 cases)
- Majority agreement on malignant diagnosis in 53% (8 cases)
- Intraobserver agreement ranged 17-100%
- Lack of agreement on minimal criteria needed to diagnose FVPC

---

**FVPTC Issues**

- Isolated or limited foci of PTC in an otherwise nondescript follicular lesion:
  - Is there a percentage of the lesion below which not PTC but beyond which it is PTC?
  - Does IHC assist in the diagnosis and DDX?
  - What diagnostic term(s) should be used if not PTC?
  - How to treat?
Encapsulated Follicular Neoplasms

- Equivocal nuclear features but definitely invasive diagnose as carcinoma
- In such circumstances specific designation type of carcinoma is academic as treatment is similar
- For a neoplasm with invasive growth but equivocal cytomorphologic features:
  - carcinoma, favor FVPTC
  - carcinoma, favor follicular carcinoma
  - well-differentiated carcinoma, NOS

Papillary Thyroid Carcinoma

Issues

- Isolated or limited foci of PTC in an otherwise nondescript follicular lesion:
  - is there a percentage of the lesion below which not PTC but beyond which is PTC?
  - varying thresholds
  - there are no set criteria defining a minimum percentage that equates to a diagnosis of PTC

Papillary Thyroid Carcinoma

Does IHC Help?

- Thyroglobulin, TTF-1, cytokeratin positive
- Calcitonin, neuroendocrine markers negative
- Markers purportedly valuable in diagnosis and DDX:
  - HBME1, CK19, galectin-3:
    - not specific
    - staining can be patchy and weak even in PTC
    - may be positive in normal follicles, nonneoplastic thyroid lesions and benign lesions/neoplasms

Adenomatoid Nodule

False positive HBME-1 Staining
Papillary Thyroid Carcinoma

- Does IHC assist in the diagnosis?
  - At present there are no IHC markers that can reliably differentiate PTC from other follicular lesions (e.g., adenoma, carcinoma, adenomatoid nodules)

Isolated foci of PTC in an otherwise nondescript follicular lesion

- What diagnostic term should be used if it is PTC?
  - Follicular variant of PTC (FVPTC)
- Treatment:
  - Total thyroidectomy and postoperative radioactive iodine

- What diagnostic term(s) should be used if not PTC?
  - Follicular adenoma (atypical)
  - FT-UMP
  - WDT-UMP
- Treatment:
  - Subtotal thyroidectomy

- What diagnostic term should be used if unsure of the diagnosis?
  - Tendency to overdiagnose FVPTC
  - Err on the side of benignancy (follicular adenoma or atypical follicular adenoma)
  - Treat conservatively

Molecular Biology

- Molecular profile much closer to follicular adenoma and follicular carcinoma than to classical papillary carcinoma
**Biologic Behavior of FVPTC**

  - No recurrence, lymph node metastasis
- Rivera M, et al. Mod Pathol 2010;23:1191-200:
  - Encapsulated/noninvasive tumors extremely low recurrence rate
  - Metastatic nodal pattern:
    - Noninvasive similar to follicular adenoma
    - Infiltrative similar to classical PTC

**Molecular Classification of PTC**

  - Noninvasive: among RAS-like tumors rather than BRAF V600E-like tumors
  - Invasive: among BRAF V600E-like tumors rather than RAS-like tumors

**Reclassification Noninvasive FVPTC**

- Recent recommendation to replace use of noninvasive FVPTC with “Noninvasive Follicular Tumor with Papillary-like Features (NIFTP)” reflecting:
  - Subjectivity among pathologists in diagnosis of FVPTC
  - RAS-like molecular profile
  - Exceedingly indolent biology not warranting the designation as “cancer”

**NIFTP Inclusion Criteria**

- Encapsulated or circumscribed
- Follicular pattern growth (<1% papillae)
- No psammoma bodies
- < 30% solid, trabecular, insular growth
- No tumor necrosis or high mitotic activity (≥ 3/10HPF)
- No invasion (vascular or capsular):
  - Entire tumor-capsule or tumor-parenchymal interface must be submitted
NIFTP Exclusion Criteria

- True papillae > 1%
- Psammoma bodies
- Infiltrative border (invasion similar to follicular ca.)
- High mitotic activity (≥ 3 mitoses/10 HPF)
- Cell/morphologic features of other variants of PTC (e.g., tall cell, columnar cell, hobnail, cribriform-morular variant, solid variant, others); no used for subcentimeter lesions

NIFTP

- Reclassification as a close entity to the follicular adenoma/carcinoma group:
  - Treatment by lobectomy alone even in the presence of adverse demographic prognostic factors (e.g., > 45 yrs, > 4 cm)
  - Countless number of patients with non-invasive follicular variant spared unnecessary therapy with associated morbidity, financial costs and the psychological impact of “cancer” diagnosis

NIFTP

- Encapsulated, circumscribed
- Low % marked intralilosical sclerosis
- No psammoma bodies or nuclear inclusions
- No ETE
- RAS mutation, PAX8/PPARγ translocation
- Low to no incidence of metastasis

INVASIVE FVPTC

- Nonencapsulated
- ↑ % marked interallosical sclerosis
- Psammoma bodies, nuclear inclusions may be present
- ↑ % ETE
- BRAF mutation, RET/PTC translocation
- Increased incidence of metastasis (nodal)
Invasive FVPTC

Minimum Diagnostic Criteria for Thyroid Cancer

- Diagnostic Criteria:
  - Invasion
  - Cytomorphologic findings
  - Mitoses and Necrosis
  - Metastatic disease

Poorly-Differentiated Thyroid Carcinoma (PDTC)

Definition

- Thyroid neoplasm with histologic and biologic features intermediate between those of differentiated thyroid carcinomas and undifferentiated (anaplastic) carcinoma
- Synonym: Insular Carcinoma

PDTC – Mitoses

PDTC – Necrosis
PDTC – Insular, Trabecular and Solid

PDTC – solid, convoluted nuclei, no colloid

PDTC – Invasion and Necrosis

PDTC – Angioinvasion

PDTC – Extrathyroidal Extension

PDTC

Immunohistochemistry

• Positive:
  – Thyroglobulin, TTF1, PAX8
  – Cytokeratins
• Negative:
  – Calcitonin, synaptophysin and chromogranin
• Increased proliferation rate (MIB1)
**PDTC Immunohistochemistry**

- **TGB**
- **TTF1**
- **CAM5.2**

**PDTC Turin Proposal***

- Presence of solid, trabecular or insular growth
- Absent nuclear features diagnostic for PTC
- Presence of at least one of the following:
  - Convoluted nuclei
  - Mitotic activity ≥3 mitoses per 10 HPF
  - Tumor necrosis
* Volante et al. AJSP 2007;31:1256-1264

**PDTC**

- PDTC not limited to tumors with insular/solid/trabecular growth:
    - PDTC defined on basis of ↑ mitotic activity and/or tumor necrosis
    - Necrosis and/or mitotic index (≥ 5 x 10HPF)

**Insular pattern ≠ Insular Carcinoma**

- Undifferentiated (Anaplastic) Thyroid Carcinoma (UTC)
Minimum Diagnostic Criteria for Thyroid Cancer

- Diagnostic Criteria:
  - Invasion
  - Cytomorphologic findings
  - Mitoses and Necrosis
  - Metastatic disease

Thyroid Follicles in Lymph Nodes

- When is metastatic carcinoma and when is it something else?:
  - Thyroid inclusions
  - Lymphocytic thyroiditis
Thyroid Inclusions in Lymph Nodes

- Midline or para-midline lymph nodes
- Not identified in nodes lateral to great vessels
- Follicles extremely limited in number and localized to capsule
Thyroid Inclusions in Lymph Nodes

Chronic Lymphocytic (Hashimoto) Thyroiditis

Minimal Diagnostic Criteria for the Diagnosis of Thyroid Carcinoma

- Invasion:
  - Capsular invasion
  - Vascular invasion

Conclusions

- Cytomorphology:
  - Papillary thyroid carcinoma
  - Medullary thyroid carcinoma
  - Poorly-Differentiated Thyroid Carcinoma
  - Undifferentiated (Anaplastic) Thyroid Ca.
  - Malignant lymphoma

Minimal Diagnostic Criteria for the Diagnosis of Thyroid Carcinoma

Conclusions
Minimal Diagnostic Criteria for the Diagnosis of Thyroid Carcinoma

Conclusions

• Necrosis and mitoses
• Metastatic disease