Minimal Criteria for Diagnosing Thyroid Carcinoma

• Diagnostic Criteria:
  – Invasion
  – Cytomorphologic findings
  – Mitoses and necrosis
  – Metastatic disease
Minimal Criteria for Diagnosing Thyroid Carcinoma

- Tumor types:
  - Follicular Carcinoma
  - Papillary Carcinoma
  - Poorly-Differentiated Thyroid Carcinoma
  - Anaplastic Thyroid Carcinoma
  - Medullary Carcinoma
  - Malignant Lymphoma

IHC in Differentiated Thyroid Neoplasms

- TGB
- PAX8
- TTF1
- CD56

Minimal Criteria for Diagnosing Thyroid Carcinoma

- Diagnostic Criteria:
  - Invasion:
    - Tumor capsular invasion
    - Angioinvasion or Vascular Invasion
    - Invasion into thyroid parenchyma
    - Extrathyroidal extension
Invasion = Carcinoma
Follicular Adenoma vs Follicular Carcinoma

• A diagnosis of follicular carcinoma is predicated on the presence of invasive growth:
  – capsular invasion
  – angioinvasion
  – invasion into adjacent thyroid parenchyma or beyond

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

*From Chan JKC. In: Fletcher CDM, ed. Diagnostic Histopathology of Tumors; 2013:1204.
**Post-FNAB Tract**

**Fibrous Capsule**

- 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 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 mass


**Fibrous Capsule**

- Histologic features:
  - Uniformity in thickness
  - Fibers run in parallel
Capsular Invasion

- Problematic features relative to diagnostic interpretation:
  - irregular contour(s) of the tumor
  - tangential sectioning
  - separate nodule(s) lying outside capsule of main nodule
  - serial sections to determine whether there is or is not connection
    - continuity between main nodule and nodule(s) outside the capsule = invasion (carcinoma)
    - absence of any connection does not exclude a diagnosis of carcinoma
    - may be indicative of multiple adenomatoid nodules
### 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

---

Adapted from: Meissner & Warren: Tumors of the Thyroid Gland. AFIP Fascicle 4; Second Series; 1969: 50.
Angioinvasion (AI) or Vascular Invasion (VI)

- More reliable than capsular invasion
- Tumor in vascular 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

Angioinvasion*

*From Chan JKC, In: Fletcher CDM, ed. Diagnostic Histopathology of Tumors. 2013:1202.

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

**** 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.

VI with fibrin thrombus
VI with fibrin thrombus

Angioinvasion*


VI without fibrin thrombus
VI without fibrin thrombus

Is this VI or not?

Follicular carcinoma with capsular invasion and foci worrisome for VI

Is this VI or not?

NOT!
Is this VI or not?

**NOT!**

Angioinvasion*

*This represents a common but controversial 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 Categorization
2017 CAP Protocol

• Angioinvasion (vascular invasion)
  ___ Not identified
  ___ Present
    + Extent:
      + ___ Focal (less than 4 vessels)
      + ___ Extensive (4 or more vessels)
  ___ Cannot be determined
• Lymphatic Invasion
  ___ Not identified
  ___ Present
  ___ Cannot be determined

Immunohistochemical staining using CD31 and podoplanin (D2-40) may be useful in differentiating capillary sized vascular spaces from lymphatic 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

Follicular Carcinoma
Histologic Types

- Oncocytic (Hürthle cell)
- Signet ring cell
- Clear cell
- Mucinous variant
- Hyalinizing trabecular carcinoma

2017 CAP Protocol - Histologic Type
Follicular Thyroid Carcinoma

- ___ Follicular carcinoma, minimally invasive
- ___ Follicular carcinoma, encapsulated angioinvasive
- ___ Follicular carcinoma, widely invasive
- ___ Follicular carcinoma, minimally invasive, oncocytic (Hürthle cell)
- ___ Follicular carcinoma, encapsulated angioinvasive, oncocytic (Hürthle cell)
- ___ Follicular carcinoma, widely invasive, oncocytic (Hürthle cell)
- ___ Follicular carcinoma, minimally invasive, other variant (specify)
- ___ Follicular carcinoma, encapsulated angioinvasive, other variant
- ___ Follicular carcinoma, widely invasive, other variant (specify)
- ___ Follicular carcinoma
**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

**Follicular Carcinoma, Oncocytic**

- Higher prevalence of aggressive behavior:
  - Older age group
  - Larger size
  - Greater tendency to ETE
  - Greater tendency to recur and/or metastasize (lung & bone):
    - may metastasize to lymph nodes
  - Less avidity to uptake RAI

**FNAB – Oncocytic Cells**
Thyroid Lesions with Oncocytic Cells

- Nonneoplastic Lesions:
  - Lymphocytic thyroiditis
  - Adenomatoid nodules
  - Graves disease
  - Post-radiation; aging

- Neoplasms:
  - Follicular adenoma/carcinoma (Hürthle cell adenoma/carcinoma); Papillary Thyroid Carcinoma

Minimal Criteria for Diagnosing 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
• Anaplastic Thyroid Carcinoma
• Malignant Lymphoma
• In general, follicular adenoma and follicular carcinoma cannot be differentiated based on cell type

Papillary Thyroid Carcinoma (PTC) Definition

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

PTC – Papillary Growth
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 – “Orphan Annie” Nuclei


PTC – Diagnostic Nuclei
PTC – Nuclear Inclusions

Inclusion in Follicular Adenoma

“Bubble artifact” ≠ Inclusions
PTC can be diagnosed by FNAB

Psammoma Bodies

Calcified/inspissated colloid – not psammoma body
Endocrine Atypia

Papillary Growth in Adenomatoid Nodule

Papillary Thyroid Carcinoma
Histologic Types/Variants
- Usual or conventional
- Papillary microcarcinoma
- Encapsulated
- Follicular
- Macrofollicular
- Oncocytic or oxyphilic
- Clear cell
PTC, Oncocytic Variant

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:
  - Diffuse sclerosing
  - Columnar cell
  - Tall cell
PTC, Tall Cell Variant

- WHO 2017 criteria:
  - Cells 2-3x tall as wide
  - Abundant eosinophilic (oncocytic-like) cytoplasm
  - Typical nuclear features for PTC
  - Account for ≥30% of all tumor cells

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

Circumscribed Follicular Pattern Lesion
Majority without 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

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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*
• 6 reviewers; 15 cases
• Interobserver and intraobserver variation
• Nuclear features of TPC not well developed or only focally developed


FVPTC
Observer Variation
• Unanimous agreement FVPTC 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 FVPTC

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/Circumscribed 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

Encapsulated/Circumscribed Follicular Neoplasms
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

Encapsulated/Circumscribed Follicular Neoplasms
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
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 is PTC?
  – Follicular variant of PTC (FVPTC)
• Treatment:
  – Total thyroidectomy and postoperative radioactive iodine

Isolated foci of PTC in an otherwise nondescript follicular lesion

• What diagnostic term(s) should be used if not PTC?
  – Follicular adenoma (atypical)
  – FT-UMP
  – WDT-UMP
• Treatment:
  – Subtotal thyroidectomy
Isolated foci of PTC in an otherwise nondescript follicular lesion

• What diagnostic term should be used if you are unsure of the diagnosis?
  – tendency to overdiagnose FVPTC
  – err on the side of benignancy (follicular adenoma or atypical follicular adenoma)
  – Treat conservatively

FVPTC
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

**Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma**

A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

JAMA Oncology April 2016
### Reclassification Noninvasive FVPTC

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

### NIFTP Inclusion Criteria

- Encapsulated or circumscribed
- Follicular pattern growth (<1% “true” papillae)
- No psammoma bodies
- Nuclear score 2-3
- < 30% solid, trabecular, insular growth
- No cellular features of other variants of PTC
- 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 Nuclear Score

- Enlargement, crowding/overlapping
- Elongation
- Irregular contours
- Grooves
- Chromatin clearing
- Inclusions
- 3-point scoring scheme with each class of nuclear features assigned score of 0 or 1 yielding a range of scores from 0-3
NIFTP

- Reclassification as a close entity to the follicular adenoma/carcinoma group:
  - No adverse events in 109 patients
  - 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 – WHO 2017

- Definition: NIFTP is a noninvasive neoplasm of thyroid follicular cells with a follicular growth pattern and nuclear features of PTC that has extremely low malignant potential
  - formerly referred to as non-invasive FVPTC
- 10-20% of all thyroid “cancers”
- F:M 3-4:1; wide age range most common in 4th-6th decades
- Cytology:
  - about 50% = Bethesda IV;
  - Most of remainder: Bethesda V or Bethesda III;
  - Rarely: Bethesda VI “reliable distinction between NIFTP & PTC cannot be made in cytological preparations”

NIFTP

- Since NIFTP initially reported:
  - Several patients with locoregional nodal (micro)metastasis reported in primary tumors meeting proposed diagnostic criteria for NIFTP
- Re-evaluation of criteria for NIFTP:
  - No well formed papillae
  - Presence of diffuse nuclear features of PTC → examination of entire tumor (not just the tumor-to-capsule/parenchymal interface)
  - NIFTPs typically show moderate expression of diagnostic nuclear features of PTC
  - Presence of BRAF V600E or other BRAF-like mutations (RET/PTC fusions) or high-risk mutations (TERT; TP53) → search for exclusionary features (e.g., true papillae; invasion)
NIFTP – Revised Diagnostic Criteria

• Primary:
  - Encapsulation of clear demarcation
  - Follicular growth pattern
  - Nuclear score 2-3
  - No vascular or capsular invasion
  - No tumor necrosis or high mitotic activity (≥3/10hpf)

• Secondary (helpful but not required for diagnosis of NIFTP):
  - Lack of \textit{BRAF} V600E mutation detected by molecular assays or immunohistochemistry
  - Lack of \textit{BRAF} V600E-like mutations or other high risk mutations (\textit{TERT, TP53})


• NIFTP or not? If not what diagnosis?
  • Narrowing definition = NIFTP
  • If not NIFTP = Follicular adenoma
  • NIFTP not meant to be a waste basket diagnosis

2017 CAP Protocol - Histologic Type
Papillary Thyroid Carcinoma

• Papillary carcinoma, classic (usual, conventional)
• Papillary carcinoma, follicular variant, encapsulated/well demarcated, with tumor capsular invasion
• Papillary carcinoma, follicular variant, encapsulated/well demarcated, noninvasive
• Papillary carcinoma, follicular variant, infiltrative
• Papillary carcinoma, tall cell variant
• Papillary carcinoma, cribriform-morular variant
• Papillary carcinoma, diffuse isthmus variant
• Papillary carcinoma, other variant (specify):
• Papillary carcinoma

#A subset of noninvasive tumors can now be reclassified as NIFTP.
+Noninvasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP)
## This category is not overtly malignant; reporting is optional and only size, laterality, and margin status are reported
Pre-invasive Stage of Invasive FVPTC

Hodak S, et al. Thyroid 2016;26:869-71

NIFTP
- Encapsulated, circumscribed (nonencapsulated)
- Low % intralesional sclerosis
- No psammoma bodies
- No ETE
- RAS mutation, PAX8/PPARγ translocation
- Low to no incidence of metastasis
- If invasive — Invasive FVPTC → behavior that of FTC

Invasive FVPTC
- Usually nonencapsulated
- ↑ % marked intralesional sclerosis
- Psammoma bodies may be present
- ↑ % ETE
- BRAF mutation, RET/PTC translocation
- Increased incidence of metastasis (nodal)
Invasive FVPTC

Follow-up Data for Noninvasive and Invasive FVPTC

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (Noninvasive FVPTC) (n = 120)</th>
<th>Group 2 (Invasive FVPTC) (n = 80)</th>
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<td>Adverse events during follow-up, No. (%)</td>
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NIFTP

Other Findings

- Multifocal lesions
- Subcentimeter lesions
- Lesions with oncocytic cytoplasm (Hürthle cells)
Minimum Diagnostic Criteria for Thyroid Cancer

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

Practical Genotype-Phenotype Correlations

<table>
<thead>
<tr>
<th>Variant Type</th>
<th>Genotype/Phenotype Characteristics</th>
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<tbody>
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<td>BRAF-V600E, Strong MAPK Output</td>
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<td>RAS-PPARG fusion</td>
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<td>Hobnail Variant</td>
<td>BRAF-V600E</td>
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<td>Diffuse Sclerosing Variant</td>
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<tr>
<td>Cribriform-Morular Variant</td>
<td>FAP associated, Nuclear B-catenin on IHC</td>
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Emerging view of thyroid cancer pathogenesis
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
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 – Insular, Trabecular and Solid
PDTC – Extrathyroidal Extension

- Positive:
  - Thyroglobulin, TTF1, PAX8
  - Cytokeratins
- Negative:
  - Calcitonin, synaptophysin and chromogranin
- Increased proliferation rate (MIB1)

PDTC
Immunohistochemistry

- Positive:
  - Thyroglobulin, TTF1, PAX8
  - Cytokeratins
- Negative:
  - Calcitonin, synaptophysin and chromogranin
- Increased proliferation rate (MIB1)
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

Follicular Adenoma

PDTC
Treatment and Prognosis
- Total thyroidectomy and radioactive iodine
- Extrathyroidal extension at presentation in >50%
- Nodal and distant metastasis at presentation in 40% and 30%, respectively
- Recurrence and metastasis occur after treatment in a high percentage of cases
- Poor prognosis: advanced age, large tumor size, extrathyroidal extension, metastasis
PDTC
Differential Diagnosis

• Papillary Thyroid Carcinoma, Solid Variant
• Undifferentiated (Anaplastic) Thyroid Carcinoma
• Medullary Thyroid Carcinoma

PTC, Solid Variant

• PTC > 50% solid growth
• Common in children including those with exposure to radiation (adults, too)
• Solid sheets of tumor cells insular pattern and diagnostic nuclear features for PTC:
  - lack increased mitotic activity, necrosis
  - TGB, TTF1 +; CAL, NE markers negative
• Lymph-vascular invasion, extrathyroidal extension and nodal metastases
Anaplastic Thyroid Carcinoma (ATC)

- Older patients
- Rapidly enlarging neck mass
- Long-standing history of thyroid-based mass
- Pathology:
  - Absence of follicular differentiation by light microscopy and IHC
- Rapid death due to locally uncontrollable disease:
  - Median survival 3 - 4 months
  - 5-year survival 3.6 - 10%
Medullary Thyroid Carcinoma (MTC)

- Malignant thyroid neuroendocrine tumor with C-cell differentiation
- Occurrence:
  - Sporadic: 70-80% of all cases
  - Hereditary: 20-30% of all cases:
    - Germline mutation of RET in 85% of families
    - MEN2A > Familial MEN > MEN2B
- Prognosis:
  - 5-yr survival: approximately 70-80%
  - 10-yr survival: approximately 50-78%
  - 15-yr survival: approximately 65%
Minimum Diagnostic Criteria for Thyroid Cancer

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

Thyroid Follicles in Lymph Nodes

• When is metastatic carcinoma and when is it something else?:
  – Thyroid inclusions
  – Lymphocytic thyroiditis

Benign Thyroid Inclusions in Lymph Nodes

• Diagnostic Criteria:
  – Midline or para-midline lymph nodes
  – Localized to capsule or subcapsular region
• Metastatic PTC:
  – Involvement of nodal parenchyma
  – Replacement of ≥1/3 of the node
  – Several nodes affected
  – Not identified in nodes lateral to great vessels
  – Diagnostic nuclei for PTC
  – Psammoma bodies
Thyroid Inclusions in Lymph Nodes

Chronic Lymphocytic (Hashimoto) Thyroiditis
Thyroid Carcinoma
Summary

• Diagnosis based on constellation of histologic criteria coupled by IHC and molecular genetics:
  - Despite established criteria interpretation can be contentious and subjective
  - Beware of potential pitfalls
• Specific types have distinct pathology but not necessarily distinct clinical features
• Histology (e.g., cell type, growth patterns) does not necessarily portend specific biology behavior
• Prognosis and treatment predicated on variety of parameters
• NIFTP replaces NI-FVPTC but still evolving category
• Molecular findings playing greater role in diagnosis of follicular neoplasms

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Questions?

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