Thyroid Papillary Carcinoma (TPC) Outline

• Pathologic diagnostic features:
  – Usual type
  – Subtypes:
    • Follicular variant of TPC
      - Ancillary Testing
    • Aggressive Variants
• Prognostic Factors
Thyroid Papillary Carcinoma (TPC) Outline Continued

- Extrathyroidal Extension
- College of American Pathologists (CAP) Thyroid Protocol
- Intraoperative consultation
Thyroid Papillary Carcinoma
Definition

- Malignant thyroid follicular epithelial cell neoplasm characterized by distinctive nuclear features
Thyroid Papillary Carcinoma
Clinical Features

• Most common malignant thyroid neoplasm in iodine sufficient/excess diets
• Most common in 3rd-5th decades; F > M
• Asymptomatic palpable mass or lateral neck mass
• Thyroid scan - “cold” nodule
• Etiology: radiation, familial
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<tr>
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<th>Follicular adenoma or carcinoma (%)</th>
<th>Conventional papillary carcinoma (%)</th>
<th>Follicular variant of papillary carcinoma (%)</th>
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</table>
Thyroid Papillary Carcinoma
Pathologic Features

• Gross features:
  – majority are solid and solitary; may be cystic
  – encapsulated or overtly infiltrative
  – papillae may be seen
  – fibrosis and calcification
  – variable sizes:
    • Small = < 1-1.5 cm (microscopic; occult)
    • Intrathyroidal
    • Extrathyroidal
Thyroid Papillary Carcinoma Pathologic Features

- Histologic findings:
  A. Architectural features:
  - Growth patterns: papillary, follicular, solid, insular
  - Elongated and/or twisted appearing follicles
  - Calciospherites (psammoma bodies)
  - Intratumoral fibrosis
  - Color of colloid
Thyroid Papillary Carcinoma
Pathologic Features

• Histologic findings:
  B. Cytopathologic (Nuclear) features:
  – Nuclear enlargement with irregularities in size and shape
  – Dispersed to optically clear appearing chromatin; margination of chromatin along nuclear membrane
  – Crowding and overlapping
  – Grooves
  – Cytoplasmic invagination into nucleus (inclusions)
Thyroid Papillary Carcinoma
Histologic Types/Variants

- Usual or conventional
- Papillary microcarcinoma
- Encapsulated
- Follicular
- Macrofollicular
- Oncocytic or oxyphilic
- Clear cell
Thyroid Papillary Carcinoma
Histologic Types/Variants Cont’d

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

• Solid and Radiation-Induced
• Cribriform-Morular
• “Hobnail” (AJSP 2010;34:44-52)
• Aggressive variants
Papillary Microcarcinoma

• Measure $\leq 1.0$ cm in size
• Most common form of papillary carcinoma
• Usually incidental finding in a thyroid removed for other reasons or at autopsy
• May present as an occult primary tumor with cervical lymph node metastasis
• Encapsulated or nonencapsulated, papillary or follicular, ± sclerosis with typical nuclear features
• Commonly located at periphery of the gland
• May be multifocal in the same lobe or in the opposite lobe
• LOH mutational profiles not different from larger TPCs
Thyroid Papillary Microcarcinoma

- May metastasize to regional lymph nodes
- Distant metastasis are rare
- Excellent prognosis; generally of limited to no biologic import
- Diagnosis of papillary microcarcinoma is not, in and of itself, an indication for additional surgery
Papillary Microcarcinoma Terminology

- Latent papillary carcinoma
- Occult papillary carcinoma
- Chernobyl Pathologists Group (Int J Surg Pathol 2000;8:181-3) – exception in children and adolescents under 19 years of age due to significant number with extrathyroidal extension and distant metastases
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
Thyroid Lesions with Oncocytic Cells

- **Nonneoplastic Lesions:**
  - Lymphocytic thyroiditis
  - Adenomatoid nodules
  - Graves’ disease (Diffuse toxic goiter)
  - Post-radiation
  - Aging

- **Neoplasms:**
  - Follicular adenoma/carcinoma (Hürthle cell adenoma/carcinoma)
  - Thyroid Papillary Carcinoma
Solid Variant

- Papillary carcinoma > 50% solid growth
- Common in children including those with exposure to radiation (adults, too)
- Solid sheets of tumor cells with fibrovascular stroma (insular pattern) and typical nuclear features:
  - lack increased mitotic activity, necrosis
  - TGB, TTF1 +; CAL, NE markers negative
- Lymph-vascular invasion, extrathyroidal extension and nodal metastases
Cribriform-Morular Variant

- Characterized by prominent cribriform pattern with interspersed squamoid morules
- Circumscribed to encapsulated with or without invasion
- Follicles, papillae, and trabeculae
- Luminal spaces often devoid of colloid
- Varying nuclear features (columnar, cuboidal) but nuclear features typical for papillary carcinoma are present
- IHC:
  - TGB, TTF-1, cytokeratins, EMA
  - β-catenin (nuclear and cytoplasmic)
Cribriform-Morular Variant

• Sporadically occurring (solitary) neoplasm or familial adenomatous polyposis (FAP) related:
  – striking female predominance (17:1)
  – 28 years mean age at diagnosis
  – may pre-date diagnosis of FAP
  – often multifocal
  – APC germline mutation
  – Somatic RET/PTC rearrangements
Follicular Variant of Thyroid Papillary Carcinoma

• 4-14% of all TPCs
• Patients tend to be younger
• Often encapsulated without invasion
• Difference in molecular markers
• May metastasize in the absence of invasion; nodal metastasis less frequent compared to “conventional” TPC
• Excellent prognosis
Consensus

• 1) General agreement and 2) Solidarity of belief or sentiment
• Origin in a Latin word meaning literally to *feel together*
• The formal process of achieving consensus ideally requires serious treatment of the considered opinion of each group member:
  – those advocating the adoption of a particular course of action genuinely wish to hear those who may be against the proposal, since discussion, it is supposed, can only enhance ultimate consensus
  – the hope is that in such circumstances action, or the adoption of group opinion, without resolution of dissent will be rare
• A consensus rather than a voting process is often employed with this intention, as well as to minimize any possible damage to interpersonal relationships
Follicular Variant of TPC
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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Follicular Variant of TPC

Observer Variation

• Concordant diagnosis with a cumulative frequency of 39%
• Metastatic disease in 24.1% affirming need to differentiate follicular variant of TPC from benign thyroid lesions:
  – 10 reviewers dx of FVTPC cumulative frequency of 66.7%
  – 7 reviewers dx of FVTPC cumulative frequency of 100%
Thyroid Papillary Carcinoma
Most Important Criteria

1. Cytoplasmic invaginations in nucleus (25%)
2. Abundant nuclear grooves (100%)
3. Ground glass nuclei (98%)
4. Psammoma bodies (16%)
5. Enlarged overlapping nuclei (99%)
6. Irregularly shaped nuclei (100%)
Thyroid Papillary Carcinoma
Less Important Criteria

- Dark staining colloid (86%)
- Irregular contours of follicles (64%)
- Scalloping of colloid (59%)
- Elongated follicles (80%)
- Multinucleated macrophages in lumen of follicles (14%)
Follicular Variant of Papillary Carcinoma (FVPC) 
Observer Variation*

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

FVPC
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

“The pathologist with the highest CQ (credibility quotient) often carries the day”

Taylor and Kledziak, 1981
Thyroid Papillary Carcinoma
Issues

• Isolated or limited foci of TPC in an otherwise nondescript follicular lesion:
  – Is there a percentage of the lesion below which not TPC but beyond which is TPC?
  – Does IHC assist in the diagnosis and differential diagnosis?
  – What is the role of cytogenetics and/or molecular markers in the diagnosis?
  – Is this purely an H&E diagnosis?
  – What diagnostic term(s) should be used if not TPC?
  – How to treat?
Encapsulated Follicular Neoplasms

• Equivocal nuclear features but definitely invasive diagnose as carcinoma
• In such circumstances the specific designation of the type of carcinoma (i.e., papillary versus follicular) is academic since treatment should be the same
• For a neoplasm with invasive growth but equivocal cytomorphologic features:
  • carcinoma, favor thyroid papillary carcinoma, (follicular variant);
  • carcinoma, favor follicular carcinoma, minimally invasive;
  • well-differentiated carcinoma, NOS
Thyroid Papillary Carcinoma Issues

• Isolated or limited foci of TPC in an otherwise nondescript follicular lesion:
  – is there a percentage of the lesion below which not TPC but beyond which is TPC?
• varying thresholds
• there are no set criteria defining a minimum percentage that equates to a diagnosis of TPC
Thyroid Papillary Carcinoma
Does IHC Help?

• Thyroglobulin, TTF-1, cytokeratin positive
• Calcitonin, neuroendocrine markers negative
• Markers purportedly valuable in the diagnosis and DDX of TPC:
  – HMWCK, CK19, galectin-3, HBME-1, CITED-1, fibronectin-1, CD15, CD44, platelet-derive growth factor:
    • not specific;
    • staining can be patchy and weak even in classic TPC;
    • may be positive in normal follicles, nonneoplastic thyroid lesions and benign lesions/neoplasms
Thyroid Papillary Carcinoma
Cytogenetics and Molecular Biology

• Classic TPC:
  – RET/PTC fusion in 8-60% of cases (RET/PTC1 most common > RET/PTC3):
    • 30-40% in adults;
    • 50-60% in young children and young adults;
    • 60-80% in Chernobyl accident associated TPC;
    • 60-70% in external rads therapy in childhood
  – RET/PTC1 – TPC with prominent papillary architecture and papillary microcarcinoma
  – RET/PTC3 – tall cell and solid variants
  – Not found in follicular neoplasms
Thyroid Papillary Carcinoma
Cytogenetics and Molecular Biology

• BRAF mutation:
  – Occurs in 29-69% of TPC:
    • less common (0-13%) in TPC of children and young adults;
    • more prevalent in classic TPC, tall cell variant, oncocytic variant, Warthin tumor-like variant;
    • rare in follicular variant of TPC;
    • 33-50% of undifferentiated carcinomas;
    • 0-13% of poorly-differentiated carcinomas;
    • absent in follicular neoplasms and TMC
  – Equivocal whether of prognostic significance
Thyroid Papillary Carcinoma
Cytogenetics and Molecular Biology

• *ras* mutation:
  – 15% of TPC:
    • majority occurring in follicular variant of TPC
Thyroid Papillary Carcinoma, Follicular Variant
Cytogenetics and Molecular Biology

• Virtual absence of RET translocation
• Low frequency (3%) of BRAF mutation
• Presence of ras mutation (25-47%):
  – correlated to TPC with less characteristic nuclear features;
  – lack of extrathyroidal extension;
  – low rate of nodal metastasis
• Presence of PAX8/PPARγ translocation (38%):
  – also present in follicular adenoma (4-33%) and follicular carcinoma (45-63%)
Thyroid Papillary Carcinoma
Cytogenetics and Molecular Biology

• microRNA (miRNA) analysis as a potential diagnostic tool for papillary thyroid carcinoma:

• miRNAs over-expressed in TPC but not in FA and hyperplasia

• miRNAs are most promising and may potentially be an adjunct marker for TPC
Thyroid Papillary Carcinoma

- Does IHC and/or molecular markers assist in the diagnosis?
  - at present there are no IHC or molecular markers that can reliably differentiate TPC from other follicular lesions (e.g., adenoma, carcinoma, adenomatomoid nodules)
Thyroid Papillary Carcinoma

- Is this purely an H&E diagnosis?
  - at present, YES!
“The best research tool is a hematoxylin and eosin stained slide connected to the brain”

Hans Popper, M.D., Ph.D.
Isolated foci of TPC in an otherwise nondescript follicular lesion

• What diagnostic term should be used if is TPC?
  – Encapsulated follicular variant of TPC

• Treatment:
  – Total thyroidectomy and postoperative radioactive iodine
Isolated foci of TPC in an otherwise nondescript follicular lesion

- What diagnostic term(s) should be used if not TPC?
  - Atypical follicular adenoma
  - Follicular neoplasm of uncertain malignant potential
  - Well-differentiated follicular neoplasm of uncertain malignant potential

- Treatment:
  - Subtotal thyroidectomy
Isolated foci of TPC in an otherwise nondescript follicular lesion

- What diagnostic term should be used if you are unsure of the diagnosis? Benign, equivocal or malignant?
  - tendency to overdiagnose (encapsulated) follicular variant of TPC
  - err on the side of benignancy (follicular adenoma or atypical follicular adenoma)
  - Treat conservatively
Thyroid Papillary Carcinoma
Biologically Aggressive Variants

• Diffuse Sclerosing Type
• Columnar Cell Type
• Tall Cell Type
• Papillary carcinoma with prominent hobnail features – Asioli S, et al. AJSP 2010;34:44-52
Thyroid Papillary Carcinoma
Biologically Aggressive Variants

• Tendency to occur in older people
• Larger tumors
• Extrathyroidal invasion
• Early dissemination (nodal; visceral)
• Aggressive management
Diffuse Sclerosing Type, TPC
Clinical Features

• F>>M; adolescent – mid-thirties
• Presents as diffusely enlarged thyroid gland and/or lateral neck mass; may present as a dominant mass
• No known risk factors
Diffuse Sclerosing Type, TPC
Treatment and Prognosis

• Total thyroidectomy; post-operative radiiodine therapy
• High incidence of cervical lymph node metastasis
• Greater incidence of distant metastasis (i.e., lungs)
• Less probability of disease-free survival
• Tumor death rate is low
Tall Cell

• “Tall” cell is defined as a cell that is:
  – twice as tall as it is wide
  – eosinophilic cytoplasm
  – distinct cell margins
Tall Cell Type, TPC
Clinical Features

- Uncommon tumor type
- F > M; older age groups
- Presentation is usually that of a dominant large mass (> 6 cm) that may be associated with evidence of extension into adjacent structures
Tall Cell Type, TPC
Treatment and Prognosis

• Aggressive management:
  – Total thyroidectomy
  – Post-operative radioiodine therapy

• High incidence of both lymphatic and hematogenous dissemination

• Tendency to local recurrence and invasion into adjacent structures

• Poor prognosis
Columnar Cell

- “Tall” cell characterized by the presence of nuclear stratification
Columnar Cell Type, TPC
Clinical Features

- **Uncommon tumor type**
- **F > M; occurs over a wide age range**
- **Asymptomatic neck mass**
- **May present as a dominant (large) mass with evidence of extrathyroidal invasion**
Columnar Cell Type, TPC
Treatment and Prognosis

- Surgery and post-operative radioactive iodine
- Prognosis (biologic behavior) dependent on extent of invasion:
  - intrathyroidal – good (>80%) 5-year survival
  - extrathyroidal - poor (13%) 5-year survival

Thyroid Papillary Carcinoma
Treatment and Prognosis

• Surgery is the treatment of choice:
  – Extent of surgery dependent on:
    • Pathologic parameters
    • Comfort level of surgeon
• Indolent malignancy overall associated with excellent prognosis even in the presence of metastatic disease
• Overall mortality is 0.2%
Thyroid Papillary Carcinoma
Prognostic Factors

• Age and Gender:
  – Low Risk: F < 50 years; M < 40 years
  – High Risk: F > 51 years; M > 41 years
• Tumor size
• Histology
• Presence of metastatic disease
• Extrathyroidal Extension
Extrathyroidal Extension (ETE) Definition

• Direct involvement of the perithyroidal soft tissues by a primary thyroid cancer
• Applies to differentiated thyroid cancers (follicular-epithelial cell derived cancers and C-cell derived cancer)
Extrathyroidal Extension Criteria

• Extrathyroidal extension includes minimal extension and extensive extension
• Minimal extrathyroid extension includes the presence of cancer extending into perithyroidal soft tissues, including infiltration of adipose tissue and skeletal muscle, as well as around (and into) sizable vascular structures and nerves.
Extrathyroidal Extension Criteria

• Extensive extrathyroidal extension includes the presence of carcinoma well beyond the thyroid gland proper with direct invasion (i.e., not metastasis) into one or more of the following structures:
  – subcutaneous soft tissues;
  – adjacent viscera, including the larynx, trachea and/or esophagus;
  – the recurrent laryngeal nerve, carotid artery or mediastinal blood vessels
Extrathyroidal Extension
Significance

• AJCC Staging for Thyroid Cancers (7th ed)
  – applicable for differentiated thyroid cancers
• ETE “upstages” thyroid cancer in patients > 45 years:
  – T1, T2 carcinomas confined to the thyroid gland;
  – T3 carcinomas - minimal ETE (e.g., extension to
    sternothyroid muscle or perithyroid soft tissues)
  – T4 carcinomas – extensive ETE:
    • T4a invades subcutaneous soft tissues or adjacent
      structures
    • T4b invades prevertebral fascia or encases carotid artery
      or mediastinal vessels
• Stage III - T3N0M0 and T1-T3N1aM0
• Stage IV - Stage IVA: T4aN0M0, T4aN1aM0, T1-T4aN1bM0
  Stage IVB: T4b Any N M
  Stage IVC: any T Any N M1
Protocol for the Examination of Specimens from Patients with Carcinomas of the Thyroid Gland

- Protocol applies to all carcinomas of the thyroid
- Lymphomas, sarcomas and metastases are not included
- Based on AJCC/UICC TNM, 7th edition

Ronald Ghossein; Sylvia L. Asa; Leon Barnes; John Chan; Clara S. Heffess; Louis B. Harrison; Jennifer Leigh Hunt; Mary S. Richardson; Jatin Shah; Lester D. R. Thompson; Bruce M. Wenig
CAP Protocol for Thyroid Carcinomas

- Expanded procedure check list
- Specimen integrity and size
- Tumor focality:
  - Unifocal
  - Multifocal specifying locations
- Report all carcinomas of all sizes:
  - Dominant carcinoma
  - Secondary carcinoma(s) - microcarcinomas
CAP Protocol for Thyroid Carcinomas

• Histologic type:
  – WHO Classification
  – Papillary carcinoma
    • Architecture: Classical (papillary); Cribriform-morular; Diffuse sclerosing; Follicular; Macrofollicular; Solid
    • Cytomorphology: Classical; Clear cell; Columnar cell; Oncocytic or oxyphilic; Tall cell
CAP Protocol for Thyroid Carcinomas

- Margins
- Tumor Capsule Invasion:
  - Present
    - Extent:
      - Minimal
      - Widely invasive
      - Indeterminate
- Lymph-Vascular Invasion:
  - Present
    - Extent:
      - Less than 4 vessels
      - 4 or more vessels
CAP Protocol for Thyroid Carcinomas

• Extrathyroidal Extension
  – Present
  • Extent:
    – Minimal
    – Extensive
Thyroid Gland
To Freeze or Not to Freeze?
Intraoperative Consultation (IOC) Thyroid Gland

Indications

- Most effective in cases where FNAB is suspicious for thyroid papillary carcinoma
- Render a histologic diagnosis
- Differentiate benign from malignant that may require additional surgery
- Identification of nodal metastasis
- Incisional biopsy with intraoperative consultation:
  - unresectable disease
  - assure adequacy for diagnosis
IOC – Thyroid Gland
Surgeon’s Expectations

• Establish a correct diagnosis:
  – differentiate benign from malignant
• If nodes resected and sent for IOC
  identification of nodal metastasis
• Identify additional findings that may impact on treatment
IOC – Thyroid Gland
Specimen Handling

• Lobectomy specimen:
  – ink exterior of specimen
  – cut section through the center of lesion and measure it
  – single section to include capsule-to-tumor interface
  – no need to weigh gland
IOC – Thyroid Gland
Specimen Handling

- Subtotal or Total Thyroidectomy specimen:
  - if removed for malignancy ink exterior of specimen
  - gross examination usually suffices
  - no need to weigh gland
IOC – Thyroid Gland
Specimen Handling

• Follicular adenoma versus follicular carcinoma:
  – at least 4 blocks from tumor-to-capsule-to thyroid interface be examined
Thyroid Gland Intraoperative Cytology

- Cytologic preparations (touch preps, scrap preps, needle aspiration):
  - use in conjunction with frozen sections is complimentary and increases diagnostic accuracy
- Should be performed in all cases
# IOC – Thyroid Gland
## Diagnostic Categories

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<th>Diagnostic Consideration</th>
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<td>Encapsulated cellular follicular lesion with no invasion</td>
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<td>Follicular neoplasm suspicious for malignancy</td>
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IOC – Thyroid Gland
Diagnostic Considerations (“Pitfalls”)

- Thyroid papillary carcinoma (TPC)
- Follicular adenoma
- Follicular carcinoma
- Adenomatoid nodules
- Lymphocytic thyroiditis
- Thyroid Medullary Carcinoma
IOC – Thyroid Gland
FNAB Induced Changes

- Hemorrhage
- Infarction
- Nuclear atypia
- Capsular pseudoinvasion
- LVI pseudoinvasion
IOC – Thyroid Gland
Diagnostic Accuracy

• 98% correlation between IOC including FS and cytologic preparation and final histologic diagnosis

• Average deferral rate of 11% (compared to avg. deferral rate of 3% for other sites)

• Reoperation rate 1.4%
IOC – Thyroid
Contraindications/Limitations

• Not indicated in cases diagnosed as definitive for malignancy by FNAB

• Diagnosis of follicular carcinoma
IOC – Thyroid Gland

• Most effective where FNAB is suspicious for thyroid papillary carcinoma:
  – histology + cytology
• Not indicated in cases diagnosed as definitive for malignancy by FNAB
• Is of limited or no value in the diagnosis of follicular carcinoma
Thyroid Papillary Carcinoma
Conclusions

• Diagnosis based on constellation of histologic features
• Adjunctive testing of questionable utility in the diagnosis and differential diagnosis
• 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