Pathology of the Thyroid
Thyroid Carcinoma Arising from Follicular Cells

2015-01-19
Carcinomas Arising from Follicular Cells

• Differentiated Carcinoma
  – Papillary carcinoma
    • Conventional type
    • Many variants
  – Follicular carcinoma
    • Minimally invasive, encapsulated
    • Widely invasive
  – Differentiated carcinoma NOS
• Poorly differentiated carcinoma
• Anaplastic (undifferentiated) carcinoma
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<thead>
<tr>
<th></th>
<th>Papillary Carcinoma</th>
<th>Follicular Carcinoma</th>
<th>Poorly Diff. Carcinoma</th>
<th>Medullary Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>L/V</strong></td>
<td>L1</td>
<td>V1</td>
<td>L1, V1</td>
<td></td>
</tr>
<tr>
<td><strong>Cervical LN</strong></td>
<td>20-50% up to 90%</td>
<td></td>
<td>65% at initial presentation</td>
<td>33%</td>
</tr>
<tr>
<td><strong>Distant:</strong></td>
<td>&lt;5%</td>
<td>10-20%</td>
<td></td>
<td>10-15% initially +25% later</td>
</tr>
<tr>
<td>Lung, bone</td>
<td></td>
<td></td>
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</tbody>
</table>
Papillary Thyroid Carcinoma

- Epidemiology
- Diagnostic features
- Clinically relevant variants
- Immunohistochemistry
Epidemiology

Thyroid cancer: zealous imaging has increased detection and treatment of low risk tumours.


Revisiting overdiagnosis and fatality in thyroid cancer.

BMJ 2013;347: f4706 Too much medicine.
PTC: 95% survival at 25y!
Papillary Thyroid Carcinoma

- 80% of thyroid malignancies
- Radiation exposure as an etiologic agent
- PTC at autopsy: 5-35%
Pathology

• Lymphatic invasion early on
• May show vascular invasion
• Over 50% positive lymph nodes at diagnosis
• May present as nodal metastasis in neck LNs especially cystic (DD branchial cleft cyst)
PTC – Gross Features

- Firm solid tumor
- Cystic tumor
- LNs may be cystic
- Encapsulated vs infiltrative
Nuclear Features of PTC

- Enlarged, elongated overlapping nuclei
- Irregular nuclei
- Nuclear clearing (milk glass)
- Thick nuclear membrane
- Nuclear grooves (cave: oncocytes)
- Cytoplasmic invagination into nuclei
- Small nucleoli
Mimics of Nuclear Features of PTC

- Hashimoto thyroiditis
- Grave’s disease
- Some nodular goiters

→ Nuclear features should be present in a mass lesion, especially in Hashimoto’s thyroiditis.
Papillary Thyroid Carcinoma

Additional Features of PTC

- Papillae
- Psammoma bodies
- Dark colloid
- Colloid scalloping
- Multinucleated giant cells
- Elongated follicles
Variants of Papillary Carcinoma

- Conventional
- Follicular Variant
- Papillary microcarcinoma
- Tall cell
- Oncocytic
- Columnar cell
- Diffuse sclerosing
- Solid
- Clear cell
- Cribiform-morular
- Macrofollicular
- PTC with prominent hobnail features
- PTC with fasciitis-like stroma
- Combined papillary and medullary carcinoma
- PTC with dedifferentiation to anaplastic carcinoma

Mostly good prognosis
More aggressive subtypes
Papillary Carcinoma, Follicular Variant

- 9-22.5% of PTC
- Pattern must be (almost) entirely follicular
- Variably sized follicles
- Colloid darker or hypereosinophilic
- Difficult diagnosis on FNA

(Cancer 2003. 98:1997 LiVolsi V)
### Encapsulated Follicular Lesions

<table>
<thead>
<tr>
<th>Capsular and/or vascular invasion</th>
<th>Nuclear Features of PTC</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cap absent</td>
<td>Absent</td>
<td>Well-diff. follicular carcinoma</td>
</tr>
<tr>
<td>Imperfectly developed</td>
<td>Absent</td>
<td>Well-diff. Ca, NOS</td>
</tr>
<tr>
<td>Well-developed, diffuse</td>
<td>Absent</td>
<td>Follicular adenoma</td>
</tr>
<tr>
<td>Well-developed, focal, Rest of the nodule similar nuclear features</td>
<td>Well-developed, focal, Rest of the nodule benign</td>
<td>PTC, follicular variant (tumor diameter = whole nodule)</td>
</tr>
<tr>
<td>Well-developed, focal, Rest of the nodule benign</td>
<td>Well-developed, focal, Rest of the nodule benign</td>
<td>Follicular adenoma with papillary microcarcinoma</td>
</tr>
</tbody>
</table>

AFIP Fascicle 5 (3. series) Rosai et al.
Papillary Carcinoma, Follicular Variant

• Encapsulated (78%) FV-PTC behave like follicular tumors
  – Lack of adverse outcomes in noninvasive lesions
  – Rarity of lymph node metastases (5%)
  – RAS mutations 43%, BRAF mutations absent

• Infiltrative nonencapsulated (22%) FV-PTC behave like papillary cancers
  – Frequent lymph node metastases (65%)
  – RAS mut. 10%, RET/PTC rearr. 10%, BRAF mut. 26%

Papillary thyroid carcinoma (n=496)

- **BRAF-V600E-like**
  - Classic type
- **RAS-like**
  - Follicular variant
- Tall cell variant

**Frequent mutations**
- BRAF-V600E
- BRAF fusions
- RET fusions
- H/K/NRAS
- BRAF indels
- BRAF-K601E
- PAX8-PPARG fusions
- FGFR2 fusions
- THADA fusions

**Neutral mutations**
- NTRK1/3, ALK, MET, and LTK fusions

*Current Opinion in Oncology*  
*Volume 28(1) :1-4, January 2016*
Non-encapsulated (diffuse/infiltrative)  
FV-PTC  LN+ 65%

Encapsulated (capsular/vascular invasion)  
FV-PTC, invasive  LN+ 5%

Encapsulated (no invasion)  
FV-PTC, noninvasive  LN+ 0%  
Do not recur with lobectomy alone!
Encapsulated Noninvasive FV-PTC
Encapsulated FV-PTC with multifocal nuclear features of papillary carcinoma: Indicate the diameter of the whole nodule for staging and treatment purposes

Non-Encapsulated FV-PTC

TNM: pT3, pN1b (7/26), V1, L1, Pn1
Papillary Microcarcinoma

≤ 1cm:
28% LN metastases, 0.6% distant metastases, 3.3% disease recurrence, 0.3% die of disease

Risk factors:

> 45 J
Male
Non-Caucasian

Type I: follicular subtype
Type II: papillary subtype
Type III: desmoplastic stroma

Extrathyroidal extension
Non-encapsulated
Multifocality, bilateral tumors
L1, V1, R1
Subtype: tall cell, columnar, diffuse sclerosing, poorly differentiated
Lymph node and distant metastases
BRAF mutation
PTC Tall Cell Variant

- Most patients older, more males
- Bulkier, higher stage tumors
- Extrathyroidal extension, necrosis, V1
- Cytologic details:
  - Cells 2-3x as tall as they are wide (>30-70%)
  - Pink cytoplasm
  - Central nucleus with nuclear pseudoinclusions
  - Mitoses
PTC Tall Cell Variant

>3 : 1
• Common in younger patients
• Diffuse involvement of thyroid
• Squamous metaplasia and lymphocytes
• Abundant psammoma bodies
• May have lymph node and lung metastases
PTC Hobnail Variant

• Prominent hobnail features >30% tumor cells
• Prominent nuclei with atypia
• Increased mitotic activity
• Loss of cellular polarity
• p53 positive and BRAF mutations
• Only 54% disease specific survival at 20y
PTC Hobnail Variant

Immunohistochemistry in PTC

- **TTF-1**
- **Thyreoglobulin**
- **PAX8**
- **Cytokeratin 19**
- **HBME-1**
- **Galectin 3**
- **BRAF V600E**

Thyroid, follicular cells

Papillary carcinoma (but: much overlap, morphology more important)

50% PTC positive, FTC always negative
Immunohistochemistry in PDC

- Thyreoglobulin
- TTF-1
- Pan-cytokeratin
- CK19
- CD31, ERG
- S100, Melanoma cocktail

- Positive in poorly diff. carcinoma
- Negative in anaplastic carcinoma

- 25-30% anaplastic carcinomas are negative for cytokeratins.
- CK19 more sensitive!

- Exclude angiosarcoma, melanoma.
- May express cytokeratins!
Immunohistochemistry in MTD

- Thyreoglobulin -
- TTF-1 + (90%, focal)
- Low mol. CK +
- CEA + (most sensitive)
- Calcitonin + (variable quantities)
- CGA +, Synaptophysin +
- SSTR2a + (40-60%)
- S100 +/- sustentacular cells

- DD Parathyroid: GATA3 + PTH +
- DD Paraganglioma: S100+ sust. cells, CK -
101 Recommendations

Initial evaluation
Clinical and ultrasound criteria for FNA
Interpretation of FNA
Surgical management
Staging and risk assessment
Molecular markers
Radioiodine remnant ablation and therapy
TSH suppression therapy
Surveillance for recurrent disease
Management of recurrent and metastatic disease
Future research

*Thyroid 2015 Oct 14. [Epub ahead of print]*
ATA Guidelines, Thyroid 2015 Oct 14. [Epub ahead of print]
Risk of Structural Disease Recurrence
(In patients without structurally identifiable disease after initial therapy)

**High Risk**
- Gross extrathyroidal extension, incomplete tumor resection, distant metastases, or lymph node >3 cm

**Intermediate Risk**
- Aggressive histology, minor extrathyroidal extension, vascular invasion, or >5 involved lymph nodes (0.2-3 cm)

**Low Risk**
- Intrathyroidal DTC, ≤5 LN micrometastases (<0.2 cm)

- FTC, extensive vascular invasion (≈ 30-55%)
- pT4a gross ETE (≈ 30-40%)
- pN1 with extranodal extension, ≥3 LN involved (≈ 40%)
- PTC, ≥1 cm, TERT mutated ± BRAF mutated* (≈ 40%)
- pN1, any LN ≥3 cm (≈ 30%)
- PTC, extrathyroidal, BRAF mutated* (≈ 10-40%)
- PTC, vascular invasion (≈ 15-30%)
- Clinical N1 (≈ 20%)
- pN1, ≥5 LN involved (≈ 20%)
- Intrathyroidal PTC, <4 cm, BRAF mutated* (≈ 10%)
- pT3 minor ETE (≈ 3-8%)
- pN1, all LN <0.2 cm (≈ 5%)
- pN1, ≤5 LN involved (≈ 5%)
- Intrathyroidal PTC, 2-4 cm (≈ 5%)
- Multifocal PMC (≈ 4.6%)
- pN1 without extranodal extension, ≤3 LN involved (2%)
- Minimally invasive FTC (≈ 2-3%)
- Intrathyroidal, <4 cm, BRAF wild type* (≈ 1.2%)
- Intrathyroidal unifocal PMC, BRAF mutated* (≈ 1.2%)
- Intrathyroidal, encapsulated, FV-PTC (≈ 1.2%)
- Unifocal PMC (≈ 1.2%)

ATA Guidelines, Thyroid 2015 Oct 14. [Epub ahead of print]
Poorly Differentiated Carcinoma

Turin Criteria

- Malignant thyroid tumor of epithelial cells
- STI pattern?
  - NO: FTC, PTC, etc.
  - YES: Typical PTC nuclei throughout?
  - NO: Solid variant of PTC
  - YES: Presence of at least one of the following:
    - convoluted nuclei
    - necrosis
    - >3 mitoses / 10HPF
- FTC (solid growth pattern)
  - NO: PD carcinoma
  - YES: pure

*with coexistent PTC or FTC*
Convoluted Nuclei
>3 Mitoses/HPF
Necroses
V1
Thyreoglobulin