AGGRESSIVE VARIANTS OF PAPILLARY THYROID CARCINOMA DIAGNOSIS AND PROGNOSIS
PAPILLARY THYROID CARCINOMA

○ Clinical
  ■ Any age
  ■ Microscopic to large
  ■ Female: Male = 2-4:1
  ■ Radiation history
  ■ Lymph nodes
  ■ Prognosis 95% at 25 years
PAPILLARY THYROID CARCINOMA

- **Gross**
  - Any size
  - Confined or extrathyroidal
  - May show capsule (especially follicular variant)
  - May be cystic
  - May note gross calcification or even bone
PAPILLARY THYROID CARCINOMA

- Pathology
  - Papillae and/or follicles
  - Can be totally follicular
  - Sclerosis
  - Calcification (psammoma bodies)
  - Nuclei
PAPILLARY THYROID CARCINOMA

● THE NUCLEI
  ○ Elongated
  ○ Enlarged
  ○ Cleared out center
  ○ Thick nuclear membrane
  ○ Grooves
  ○ Inclusions
  ○ Tiny nucleoli
PAPILLARY THYROID CARCINOMA

- **SUBTYPES**
  - Encapsulated
  - Cystic
  - Microcarcinoma

- **PROGNOSIS BETTER THAN USUAL PTC**
PAPILLARY THYROID CARCINOMA

- PATHOLOGY
  - Lymphatic invasion early on
  - May show vascular invasion also
  - Lymph nodes positive over 50% at diagnosis
  - May present as nodal metastasis in neck especially cystic (confused with branchial cleft cyst)

- CYTOLOGY FNA REALLY HELPS HERE. ALSO Tg ASSAY OF FLUID
PAPILLARY THYROID CARCINOMA

- **SUBTYPES**
  - TALL CELL
  - COLUMNAR
  - DIFFUSE SCLEROSIS VARIANT
  - SOLID VARIANT
  - HOBNAIL CELL VARIANT
  - MICROPAPILLARY VARIANT

- **PROGNOSIS** *WORSE THAN USUAL PTC*
PAPILLARY THYROID CARCINOMA

- **TALL CELL VARIANT**
  - Approximately 10-15% of PTC
  - Older patients
  - Large tumors
  - Extrathyroidal
  - Vascular invasion
  - 25% mortality at ten years
PAPILLARY THYROID CARCINOMA

● A TANGENT TO MOLECULAR BIOLOGY

● Braf mutation
  ○ Found in 40% of papillary carcinomas overall (depends on population and technique used)
  ○ Of those with mutations—
    ■ 30-40% are classic PTC
    ■ 75% are tall cell
PAPILLARY THYROID CARCINOMA

● A TANGENT TO MOLECULAR BIOLOGY

● DOES Braf mutation predict “bad” behavior?

● OR

● DOES HISTOLOGY DO SO?
PAPILLARY THYROID CARCINOMA

**TALL CELL VARIANT**

- Often underrecognized
- At least 40% of tall cell histology is not noted—especially those tumors with focal tall cell features
- These cases in recurrences or nodal mets often have a larger percentage of tall cell histology.
PAPILLARY THYROID CARCINOMA

● TALL CELL VARIANT

● Can be “overrecognized”:
  ○ Hurthle cell nodules (oncocytic nodules)
  ○ Graves disease
PAPILLARY THYROID CARCINOMA

● TALL CELL VARIANT

● Partial vs. total

● Meaning of recognizing small amounts of tall cell histology

● Recurrences

● Dedifferentiation
PAPILLARY THYROID CARCINOMA

- Tall cell and PTC with tall cell features (30-50%) when compared with classic PTC showed:
  - Older age at diagnosis
    - Larger tumors
    - More extrathyroidal spread
    - More positive margins
    - More nodal mets and ENE
    - Higher stage
    - Lower survival
PAPILLARY THYROID CARCINOMA

- Tall cell and PTC with tall cell features (30-50%) both behave similarly and so suggestion that tumor is diagnosed as tall cell PTC if 30% of it shows tall cell cytology

Ganly et al THYROID 2014 (MSKCC 453 cases)
PAPILLARY THYROID CARCINOMA

TALL CELL VARIANT (Hernandez-Prera et al Thyroid 2017.

Study of 39 cases reviewed by 14 expert pathologists. Correlation fair at best (kappa 0.39).

Most pathologists in this study defined TALL CELL PTC as cell 3 x tall as wide and that at least 30% of tumor shows tall cell cytology.

Compare to WHO definition (2017): TALL CELL PTC : tall cell is 2-3 x as tall as wide and at least 30% of tumor should show tall cell cytology.
PAPILLARY THYROID CARCINOMA

- COLUMNAR CELL VARIANT
  - Fewer than 5% of PTC
  - Extrathyroidal
  - Secretory look
  - Stratified nuclei
  - Bad prognosis if extrathyroidal
columnar cell variant
NOTE
STRATIFIED
NUCLEI

COLUMNAR CELL VARIANT
PAPILLARY THYROID CARCINOMA

- COLUMNAR CELL VARIANT
  - CDX2 is found in over 50% of this PTC type
  - In our study (2011) no other subtype on a thyroid tumor TMA showed this protein by IHC
  - One case reported by Sobrinho-Simoes et al of usual papillary carcinoma (over 75 cases)
  - Reason that this GI marker should be in this subtype is unknown.
PAPILLARY THYROID CARCINOMA

● COLUMNAR CELL VARIANT

○ In some of our cases diffuse nuclear staining throughout tumor; in others only in parts of the tumors.

○ No correlation known between presence or absence of CDX 2 staining and clinical behavior/prognosis.
PAPILLARY THYROID CARCINOMA

- DIFFUSE SCLEROSIS VARIANT
  - Teenagers, usually female
  - Goiter +/- mass
  - Hard, calcified
  - Lymphatics
  - Psammoma bodies
  - Lung mets 25%
  - Prognosis?
PAPILLARY THYROID CARCINOMA

- SOLID VARIANT (SOLID-FOLLICULAR VARIANT)
- Pediatric age group
- Radiation (Chernobyl)
- Ret/PTC 3
- Vascular invasion
- Prognosis?
PAPILLARY THYROID CARCINOMA

- SOLID VARIANT (SOLID-FOLLICULAR VARIANT)
- Can it occur in adults?  **YES**
- Relationship to autoimmunity?

Personal experience: Over 60% of solid variant PTC I have seen in adults have been associated with CLT and/or systemic autoimmune disease, eg RA, SLE.
PAPILLARY THYROID CARCINOMA

SOLID VARIANT: PROGNOSIS

Mayo Clinic series (2000): Survival 90% at 10 years (cf Classic PTC 100%) vs. 50% for poorly differentiated carcinoma

Italian series (Collini et al 2004): Solid variant in children similar survival to classic PTC (even in presence of necrosis).
PAPILLARY THYROID CARCINOMA

○ FOLLICULAR VARIANT
INFITRATIVE

PROGNOSIS--presumably similar to classic PTC of similar size and stage.
Arrow shows tumor invading normal thyroid (N)

Central sclerosis (F) is characteristic of this subtype

Note nuclei


FOLLICULAR VARIANT PTC, INFILTRATIVE
INFILTRATIVE FOLLICULAR VARIANT PTC

A tangent to molecular biology:

Many of these have similar molecular signatures to classic PTC--ret/PTC translocations; Braf V 600 E mutations.

Can show papillary growth in metastases.
PAPILLARY THYROID CARCINOMA

- FOLLICULAR VARIANT

ENCAPSULATED, INVASIVE
PAPILLARY THYROID CARCINOMA

○ FOLLICULAR VARIANT, ENCAPSULATED, INVASIVE
  ■ More vascular invasion
  ■ More distant metastases
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- ENCAPSULATED VARIANT
- INVASIVE LESIONS
  - Rare (<25% lymph node metastases)
  - Rarely “multifocal”
  - Hematogenous metastases (bone, lung)
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- ENCAPSULATED VARIANT
- INVASIVE LESIONS
- MOLECULAR CHANGES
- Ras mutations; Pax8/PPAR gamma translocations
- MOST RESEMBLE FTC
CASE STUDY

- 60 year old man with back pain.
- Noted by imaging to have vertebral fracture.
- Curetted
CASE STUDY

● Completion of physical exam showed thyroid nodule:
● Total thyroidectomy—left lobe 3 cm encapsulated nodule.
Sometimes

- There is history of thyroid tumor which may or may not have been diagnosed as a cancer. It is so on retrospective review.

The metastases in areas away from the neck and especially in bone, may not show the nuclear features and the diagnosis of “folliclar carcinoma” is given. Only examination of the primary shows the nuclei and these may be multifocal.
DIFFUSE FOLLICULAR VARIANT PAPILLARY THYROID CARCINOMA

- BLAND HISTOLOGICALLY BUT BAD ACTING TUMOR
- Presents in young women as goiter and 25% have HYPERTHYROIDISM
- Almost all have NODAL METS
- 25% have LUNG METASTASES at presentation

Rare case studied and suggest that tumor cells may be hyperfunctional—needs to be confirmed.
PAPILLARY THYROID CARCINOMA

- HOBNAIL SUBTYPE
  - Eight cases, predominantly women
  - Average age 57
  - Average size 2.5 cm
  - ETE (50%) cervical nodes (75%)
  - Braf mutated (57%)
  - DOD (50%) at 3.5 yrs
  - Additional 2 patients AWD.

- (Asioli et al AJSP 2010)
PAPILLARY CARCINOMA: HOBNAIL

- Additional reported cases show similar poor prognosis.
- Can be admixed with tall cell.
- Braf mutation in about half.
- Often have areas of micropapillary architecture.
PAPILLARY THYROID CARCINOMA

- MICROPAPILLARY TYPE

- VERY RARE BUT Similar to this histology in other organs—breast, ovary, bladder

- Do very poorly

- Over 50% mortality at 5 years

- Early access to lymphatics

- Then disseminate widely.
AGGRESSIVE PAPILLARY CARCINOMA

Common characteristics

1. Usually large size
2. Often extrathyroidal extension
3. Positive nodes with ENE
4. *Vascular* invasion often in extraglandular soft tissue.
5. Mitoses may be seen and Ki67 is elevated.
6. Necrosis and atypical mitoses should not be seen (this is *HIGH GRADE* carcinoma).
PAPILLARY:

- Most are grade 1 by pattern and nuclear morphology.
- Some however, have changes that suggest higher histologic grade.
RELATED TOPIC: HIGH GRADE PAPILLARY CARCINOMA

(Akslen & LiVolksi; Tallini)

MAINTAIN PAPILLARY GROWTH AND NUCLEI HAVE ALSO—

necrosis, mitotic activity, nuclear pleomorphism
HIGH GRADE PTC

- Extrathyroidal extension usually
- Prognosis worse than well differentiated PTC but probably not so bad as poorly differentiated thyroid carcinoma.

Not well studied as an entity but included in series of poorly differentiated carcinoma.
PROPOSED RELATIONSHIP SCHEME

Papillary carcinoma, low grade usually classic
Aggressive subtypes (tall cell, etc)
High Grade PTC
Poorly differentiated carcinoma

Anaplastic carcinoma.
Some physicians, especially endocrinologist, consider insular carcinoma a type of papillary carcinoma, probably because they can appear in one tumor.

I believe insular is a pattern seen in poorly differentiated carcinoma (along with trabecular and solid), is not its own entity and can occur meta-or asynchronously with PTC.
AGGRESSIVE VARIANTS OF PAPILLARY THYROID CARCINOMA DIAGNOSIS AND PROGNOSIS