Variants and Mimickers of Papillary Thyroid Carcinoma

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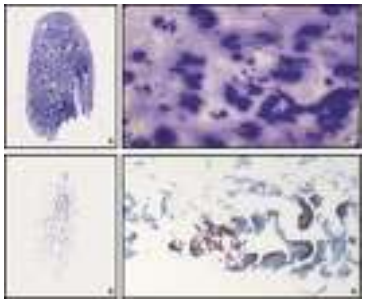
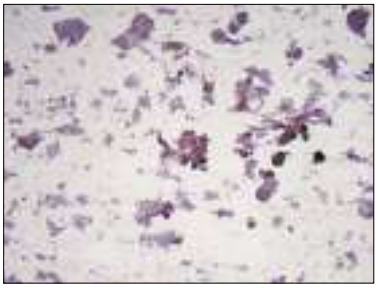
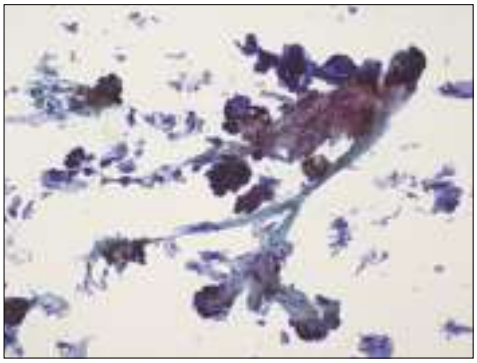
Gross features of classic PTC



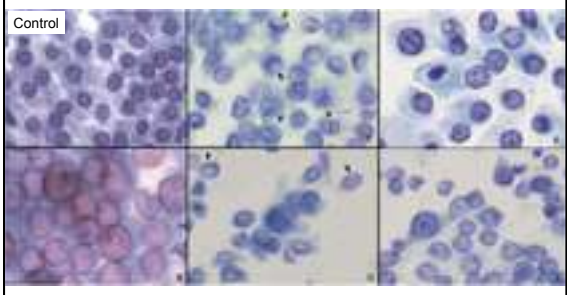
Cellularity of classic PTC



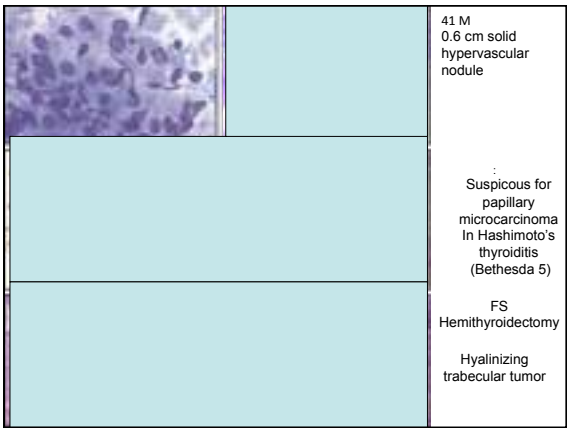
Architectural features of classic PTC



Nuclear features of PTC



Case examples



41 M
0.6 cm solid hypervascular nodule

:
Suspicous for papillary microcarcinoma In Hashimoto's thyroiditis (Bethesda 5)

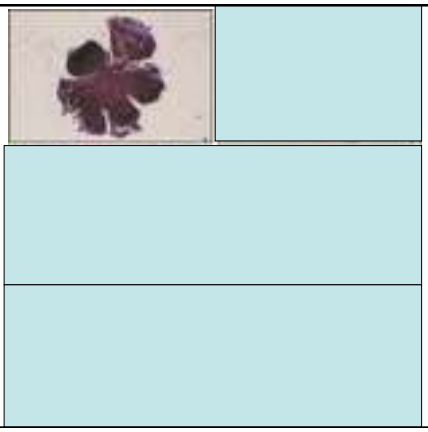
FS
Hemithyroidectomy

Hyalinizing trabecular tumor

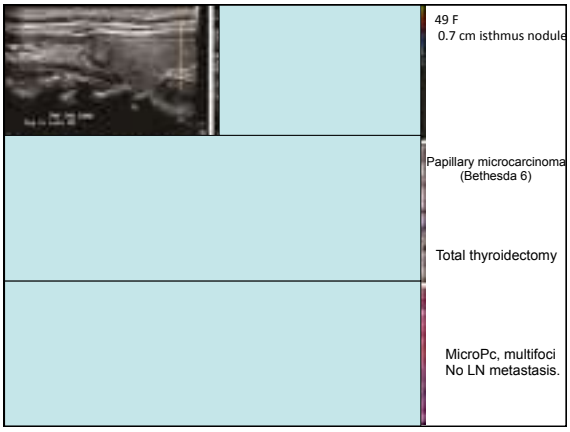
PTC,nuclear mimicker
Hyalinizing trabecular tumor

- Nuclear pseudoinclusions (Bethesda 5)
- Radially oriented cohesive cells with abundant cytoplasm around the central hyaline material.
- 99.2% benign (118/119 cases over a 20-years)
- Hemithyroidectomy
- RET/PTC rearrangement, but no BRAF (V600E) and RAS mutations.

PTC,architecture mimicker
Papillary hyperplasia

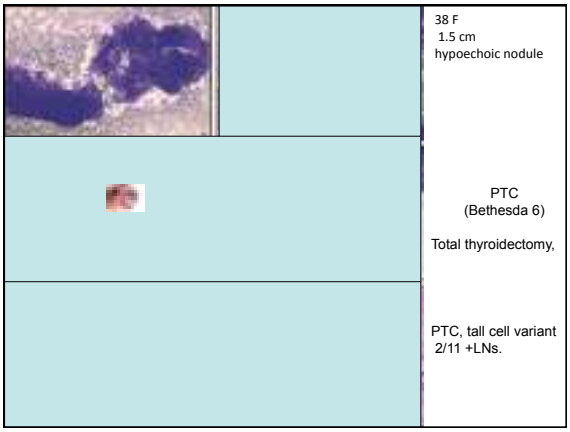


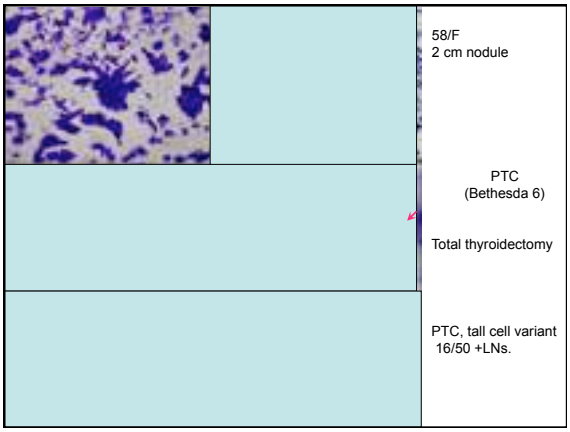
	Classic papillary carcinoma	Papillary hyperplasia
Circularity	4+	4+



Papillary microcarcinoma

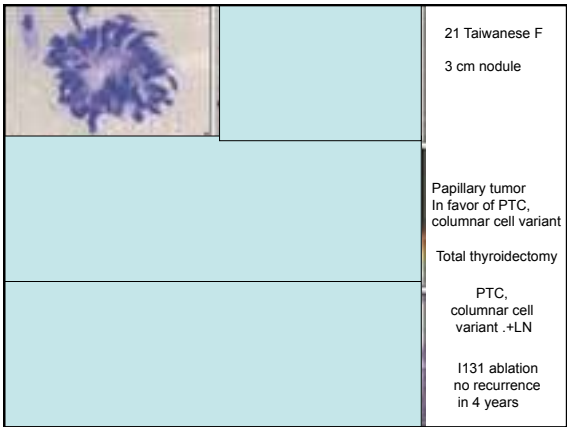
- Defined as ≤ 1 cm on final pathology , not the larger ultrasound size.(Increased from 14 to 105/664)
- 30-40% prevalence
- Due to the popularity of ultrasound guided thyroid FNA in the past decade, the rate of well-differentiated thyroid cancer has 2.4-fold increase between 1980 and 2005, half the overall increase in papillary carcinoma rates was due to increasing detection of papillary microcarcinoma.
- Most papillary microcarcinomas are indolent, except for the tall cell variant or familial form.
- *In a study of 119 cases, 7 were the familial form (5.9%) with aggressive behavior:*
  - *5 were multifocal,*
  - *3 were bilateral,*
  - *3 had angioinvasion,*
  - *4 had lymph node metastases.*
  - *3 patients had recurrence and 1 patient with pulmonary metastases died within 11 months.*





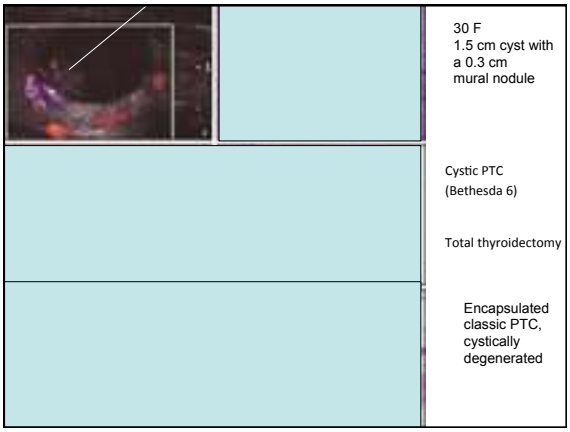
PTC, tall cell variant

- 4-17% prevalence (underdiagnosed by many general surgical pathologists)
- The most common of the aggressive variants of PTC
- Highest BRAF mutation (60-80%) in PTC
- More aggressive behavior than usual PTC, independent of tumor size, age, gender
- Less responsive to radioactive iodine therapy
- Tall cells: height/width ratio >2-3x, and ≥ 50% tall cells. (Ghossein and LiVolsi, 2008)
- LP growth pattern: Infiltrative parallel cords or tubules like rows of railroad tracks
- MP: Simple columnar epithelium resembling rows of vertically placed bricks with abundant eosinophilic oncocytic cytoplasm with high grade PTC nuclei (soap bubble-like)
- FNA smears: 18/20 cases were en face view of cohesive epithelium, like the first example.



PTC, columnar cell variant

- Extremely rare, <0.2 % prevalence
- 1988 Sobrinho-Simoes, et al: aggressive affecting elderly men with early dissemination and short survival periods
- 1998 Wenig et al. biologic behavior is predicated on clinical stage, with the status of extrathyroidal invasion being the single most important parameter.
- 2011 Harvard study reported that circumscribed or encapsulated tumors with a mean size of 2.1 cm behaved indolently in younger,predominantly female patients, whereas tumors with a mean size of 6.7 cm behaved aggressively, associated with regional and distant metastasis in older, predominantly male patients.



30 F
1.5 cm cyst with a 0.3 cm mural nodule

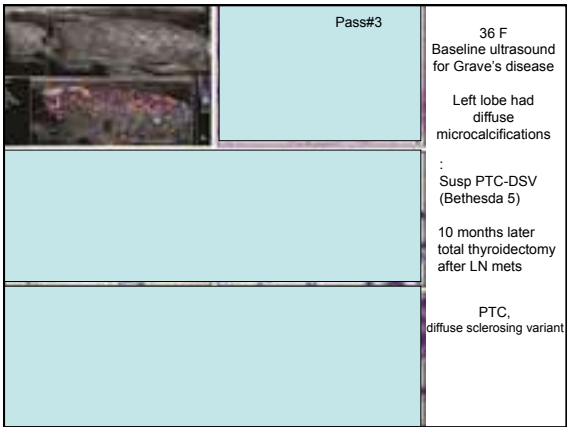
Cystic PTC (Bethesda 6)

Total thyroidectomy

Encapsulated classic PTC, cystically degenerated

PTC, cystic variant

- ~ 10% prevalence (4.4% in this series)
- Abundant thin colloid
- Low cellularity
- Small papillae with atypical nuclei
- 1970 Rosai ‘‘papillary cystadenocarcinoma”
- Encapsulated classic PTC (1988 WHO Histological Typing of Thyroid Tumours)
- Good prognostic category
- Thick encapsulated, cystic nodule containing papillae of various size in histology.



36 F
Baseline ultrasound for Grave’s disease

Left lobe had diffuse microcalcifications

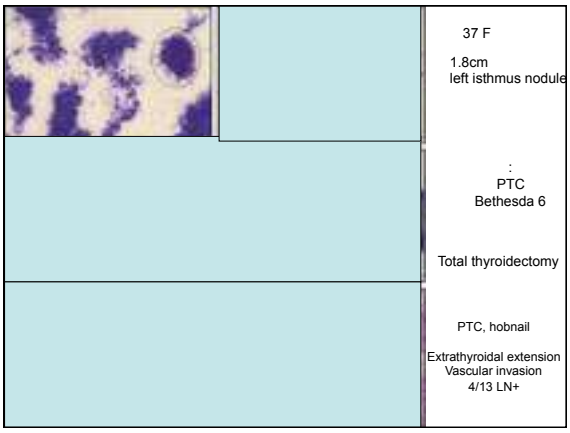
:
Susp PTC-DSV (Bethesda 5)

10 months later total thyroidectomy after LN mets

PTC,
diffuse sclerosing variant

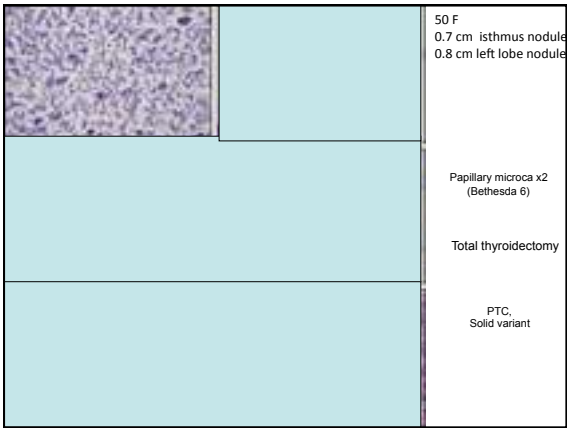
PTC, diffuse sclerosing variant

- 1-3% prevalence
- Associate with autoimmune lymphocytic thyroiditis
- Propensity for young women (4:1) with a mean age of 27
- Insidious and aggressive
- ~ 40% extrathyroidal extension,
- ~ 68% with lymph node metastases and
- ~19% with lung metastases at time of diagnosis.
- Diffusely enlarged, sometimes painful, thyroid, involving one or both lobes, simulating thyroiditis.
- Micropapillary formations within cleft like lymphatic spaces
- Psammoma bodies throughout thyroid parenchyma
- Intense lymphocytic infiltration,
- Squamous metaplasia of tumor cells
- Sclerotic fibrosis
- Result from diffuse lymphatic permeation within the thyroid parenchyma early.
- Degenerated tumor cells within lymphatics provide a nidus for psammoma body formation



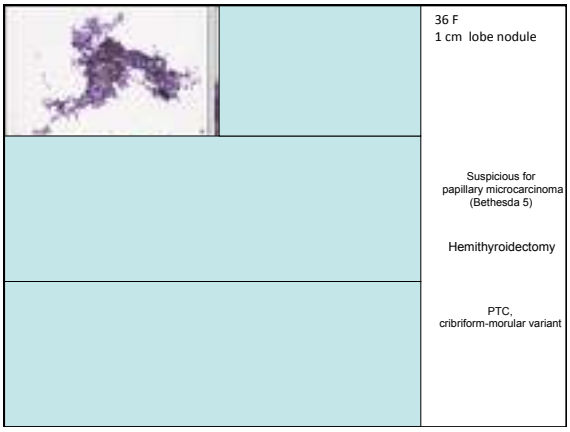
PTC, hobnail cell variant

- ~ 0.3% prevalence
- In 2011, Mayo Clinic reported 8 cases of aggressive variant of PTC characterized by
- Loss of polarity,
- Dyscohesiveness,
- Hobnail cells.
- Complex papillary structures (5), follicles (2) and in clusters (1).
- The % of hobnail cells ranged from 30% to 100%.



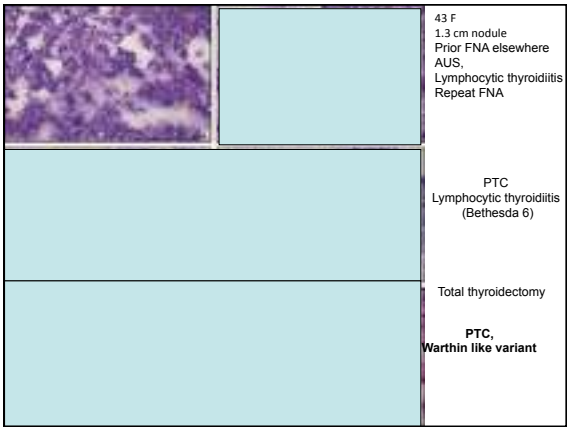
PTC, solid variant

- 1-3% prevalence in adults
- 30-35% in children with radiation exposure from Chernobyl nuclear incident
- Solid areas should occupy > 50% of the lesions that lack papillary growth pattern
- Associated with VK600-1E, a new BRAF gene mutation.



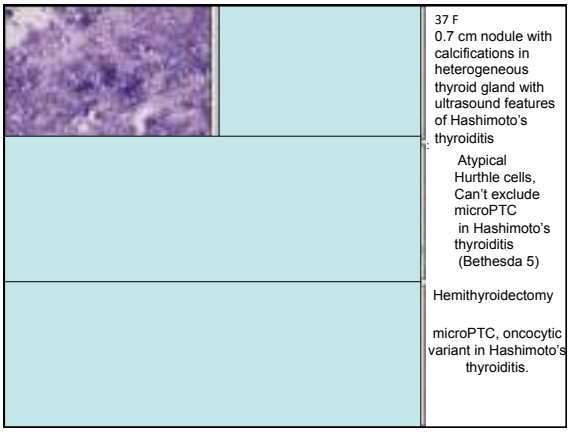
PTC, cribriform-morular variant

- 12% prevalence in familial adenomatous polyposis (germline mutation of the *APC* gene), 0.1–0.2% prevalence in sporadic form (somatic mutation of the *APC* gene)
- Young females (estrogen receptor +).
  - F/M ratio ≈ 17:1
  - Age 28 yrs (range 12 to 53 yrs).
- Encapsulated or locally advanced tumors without distant spread
- Cribriform, papillary, trabecular and solid patterns of growth
- Morules containing biotin-rich clear nuclei
- Hyperchromatic nuclei with grooves and pseudoinclusions.
- Aberrant β-catenin nuclear and cytoplasmic expression.
- RET/PTC-1 and RET-PTC-3 rearrangements. No BRAF mutations



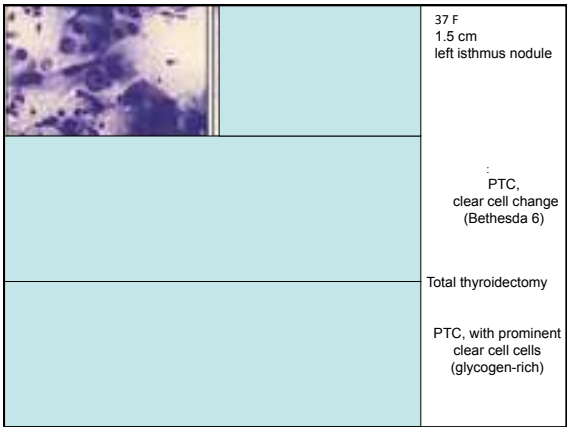
PTC, Warthin-like variant

- <1% prevalence
- In 1996, Apel et al reported in a 13 cases of a distinctive variant of PTC.
- The papillary stalks are distended by lymphocytes and plasma cells.
- Tumor epithelium became oncocytic to the point the low power histology bear a strong resemblance to Warthin's tumor of salivary gland.
- The intimate association of tumor cells with lymphoplasmacytic infiltration raised the question of host's immune defense against cancer cells,



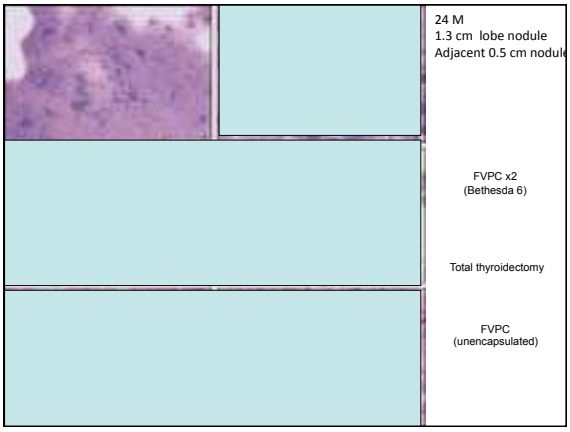
PTC, oncocytic variant

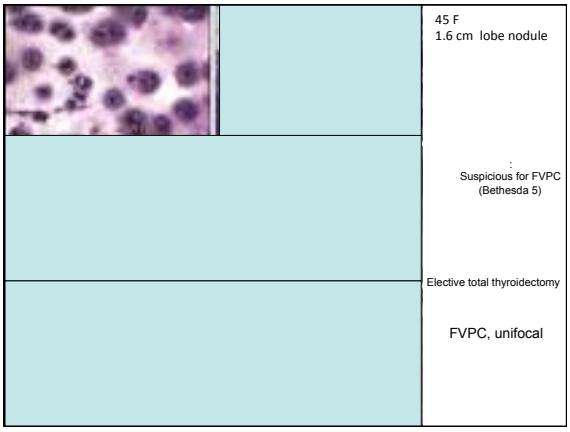
- <1% prevalence
- Oncocytes with abundant mitochondria-rich granular cytoplasm containing papillary nuclei with pseudoinclusions, grooves and clearing.
- Less responsive to radioactive iodine therapy.
- Papillae, microfollicles or macrofollicles.
- Most oncocytic variant of PTC can be distinguished from Hürthle cell lesions.
- A small group of tumors in which the distinction is not possible, due to papillary nuclei were camouflaged by pleomorphism and hyperchromasia associated with oncocytic change.

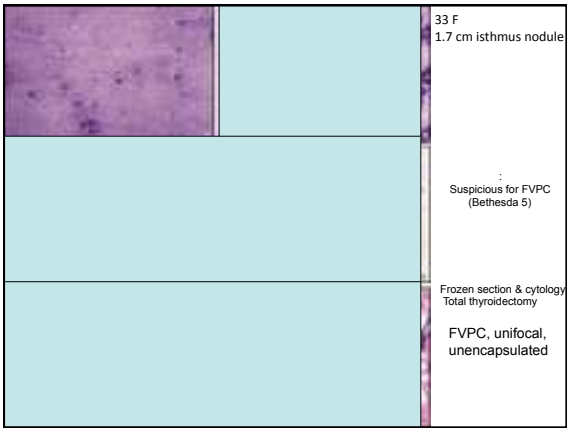


PTC, clear cell variant

- Extremely rare, ~0.06 % prevalence
- Older women
- Typical PTC nuclei except the cytoplasm is clear in >50% of the tumors.
- Accumulation of glycogen particles or empty mitochondria due to dilatation
- Papillary, follicular or nests growth patterns
- Biological behavior depends on the non-clear portion of the tumor.
- HBME1 and galectin-3 immunostains positive.







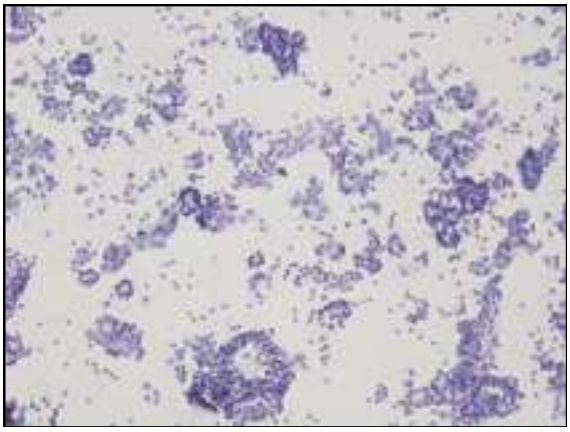
Follicular variant of PTC, (conventional, unencapsulated)

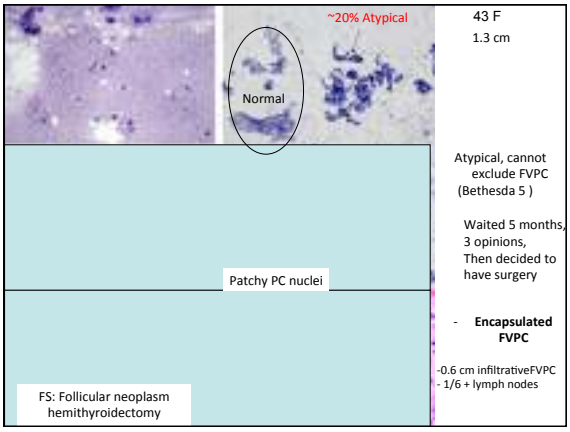
1977, Chem and Rosai, 6 cases

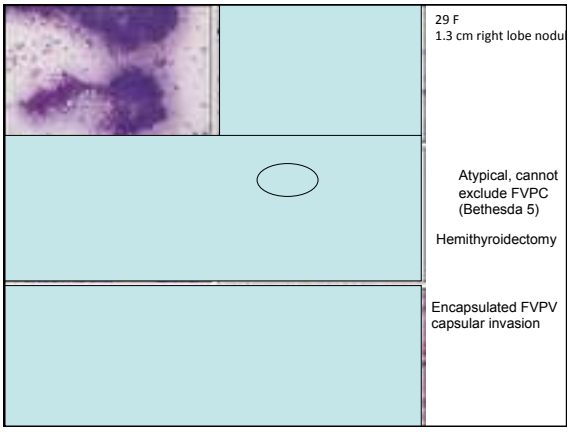
- ~12.6% prevalence
- Follicles with diffusely distributed, well-developed PTC nuclei
- Lymphatic metastasis similar to classic PTC
- RET/PTC1 rearrangement
- 26% have BRAF (V600E) mutation

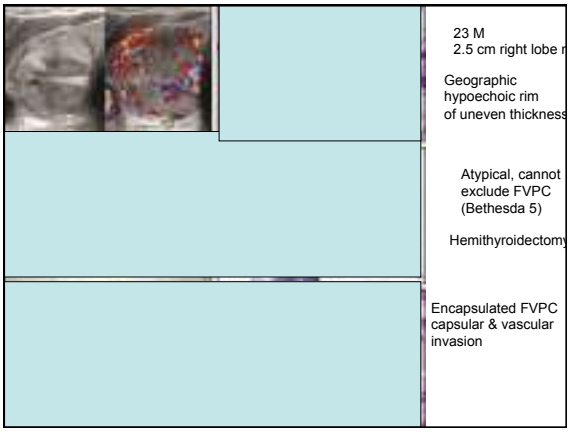
Encapsulated follicular variant of PTC

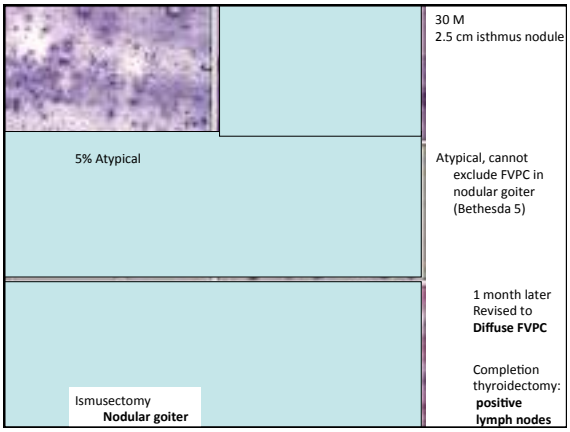
- 2006, Castro, et al
- ~10.2% prevalence
- PTC nuclear features are less developed and in more patchy distribution.
- Enigmatic tumor with immunohistochemical profile of papillary category with HBME-1 expression, but molecular profile of follicular category (PAX8-PPARγ rearrangements, RAS mutations,.BRAF mutations in this subset were K601E and G474R)
- Much lower frequency of extrathyroid extension, positive margins, and nodal metastases.
- More likely to have hematogeneous spread, if vascular invasion is present.
- If there is no vascular or capsular invasion found in the excised tumor,
  - Completion thyroidectomy may not been necessary
  - Difference in opinions among expert thyroid pathologists
    - Encapsulated FVPC
    - Follicular adenoma
    - Well-differentiated thyroid tumor with uncertain malignant potential .





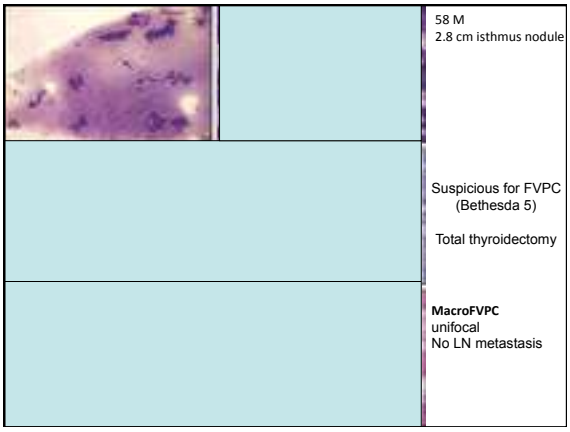






Diffuse follicular variant of PTC

- 1990 by Sobrinho-Simões et al, of 8 patients
- 1-3% prevalence,
- Predominantly young adult females, with 85% regional lymph node involvement and all developed distant metastasis to lung or bone within 10 years of thyroidectomy.
- Insidious and diffuse involvement of one or both lobes, resembling a multinodular goiter grossly and on frozen sections
- LP clue: the areas of tumor are characterized by the irregular shape of the follicles which are incompletely separated by fibrohyaline bands.
- HP: PTC nuclei with grooves and pseudoinclusions



43 F
4.6 cm right lobe
well-circumscribed
Solid, isoechoic nodule

:
Nodular goiter
(Bethesda 2)

Frozen section:
Follicular lesion

Hemithyroidectomy

PTC,
macrofollicular v.
.
Negative LN

Macrofollicular variant of PTC

- 1991 by Albores-Saavedra et al in 17 cases
- ~ 0.05% prevalence
- Indolent
- Also mimics nodular goiter at ultrasound, gross inspection and low power
- > 50% of the X-sectional area composed of macrofollicles mixed with foci of conventional follicular variant of PTC
- Tumor macrofollicles follicles with a diameter ≥ 200 μm
- Lined by 3 types of nuclei:
  - Large nuclei with clear chromatin (PTC nuclei),
  - Large nuclei with stippled chromatin,
  - Normal appearing small nuclei with dark chromatin.