



**Minimum Criteria for the Diagnosis of
Thyroid Carcinoma**

**Arizona Society of Pathologists
October 1, 2016**

**Bruce M. Wenig, MD
Mount Sinai Health System
New York, NY**

**Minimum Diagnostic Criteria for
Thyroid Carcinoma**

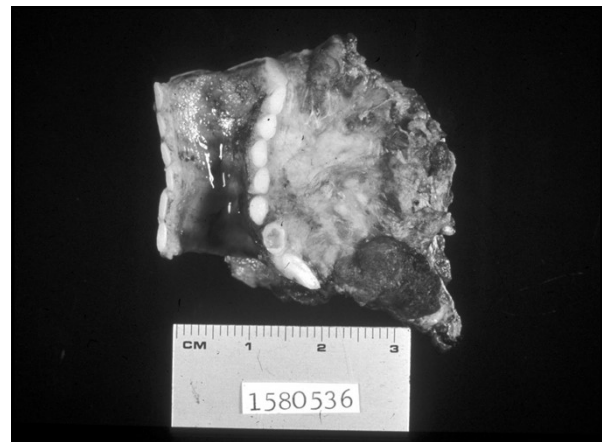
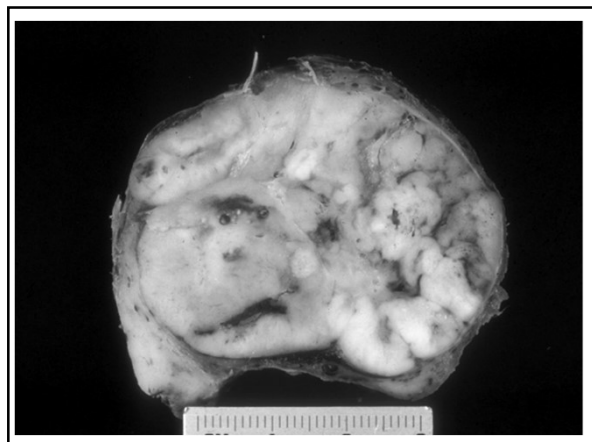
- **Diagnostic Criteria:**
 - **Invasion**
 - **Cytomorphologic findings**
 - **Mitoses and necrosis**
 - **Metastatic disease**

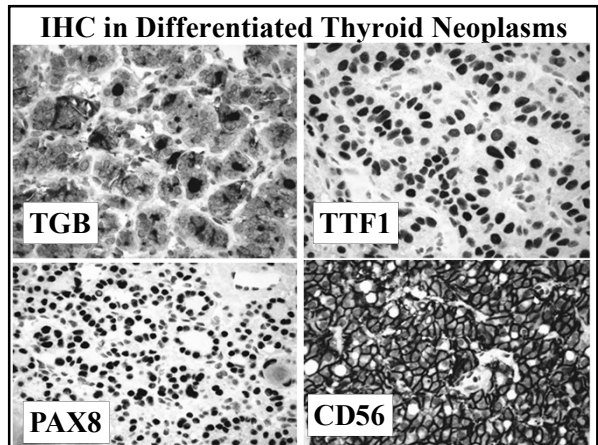
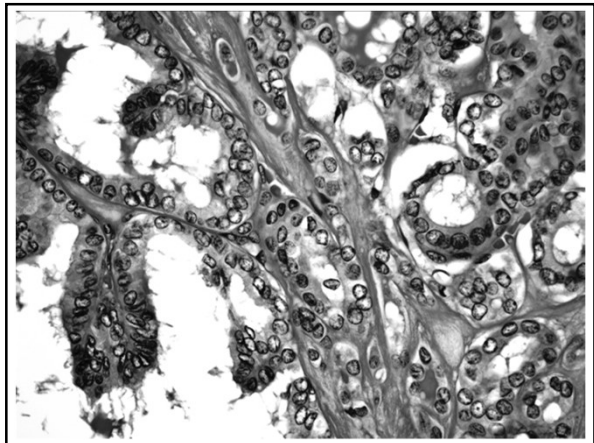
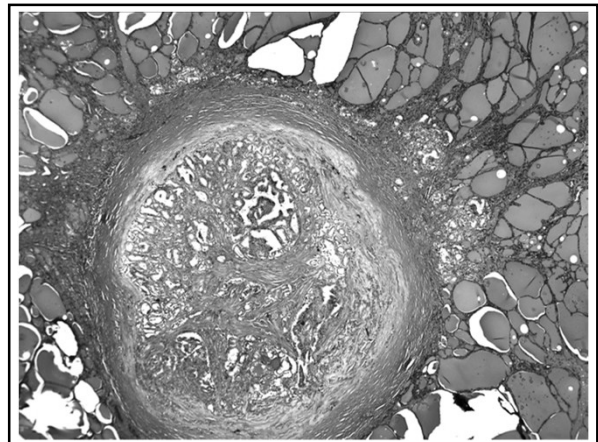
**Thyroid Carcinoma Minimum
Diagnostic Criteria**

- **Tumor types:**
 - **Follicular Carcinoma**
 - **Papillary Carcinoma**
 - **Poorly-Differentiated Thyroid Carcinoma**
 - **Undifferentiated (Anaplastic) Carcinoma**
 - **Medullary Carcinoma**
 - **Malignant Lymphoma**

**Minimum Diagnostic Criteria
for Thyroid Carcinoma**

- **Diagnostic Criteria:**
 - **Invasion:**
 - **Tumor capsular invasion**
 - **Vascular Invasion (VI)**
 - **Invasion into thyroid parenchyma**



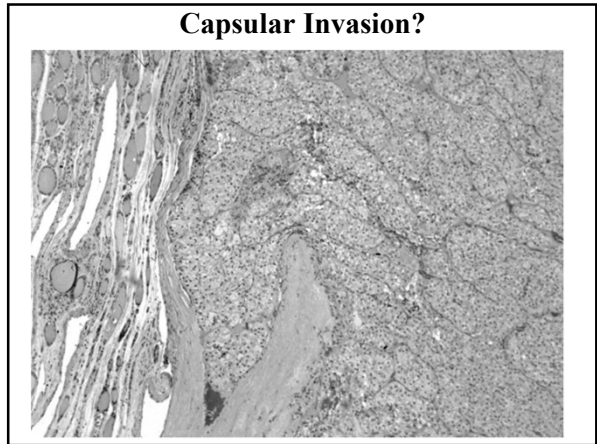
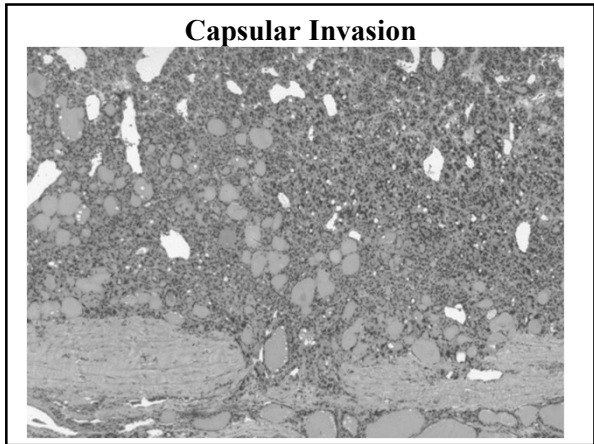
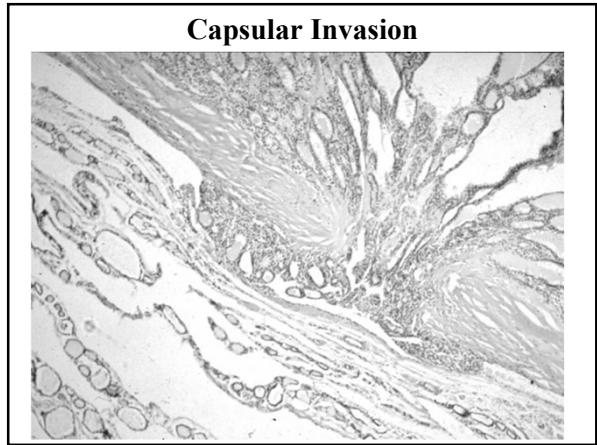
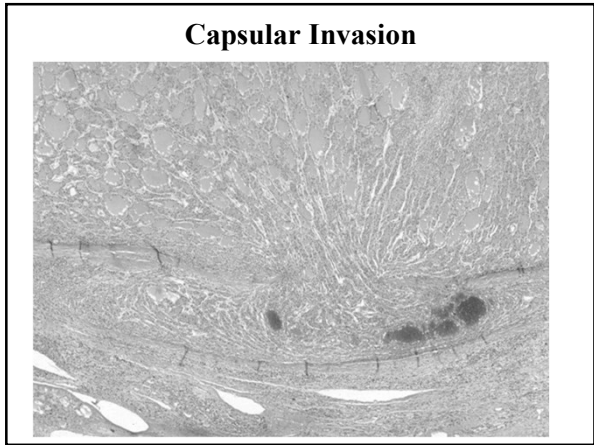
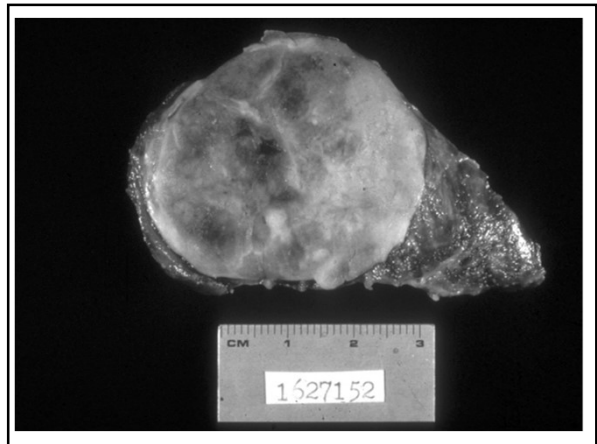
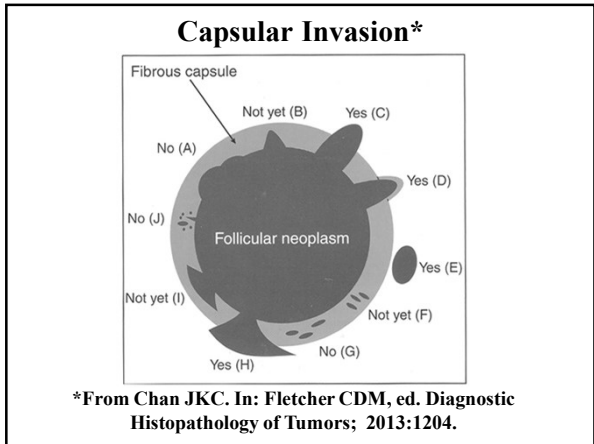


Follicular Adenoma vs Follicular Carcinoma

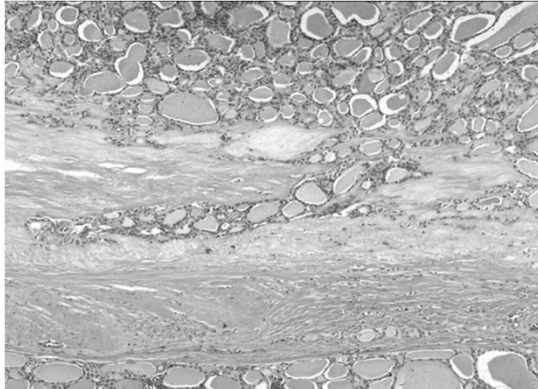
- A diagnosis of follicular carcinoma is predicated on the presence of invasive growth:
 - capsular invasion
 - vascular invasion
 - invasion into adjacent thyroid parenchyma

Capsular Invasion

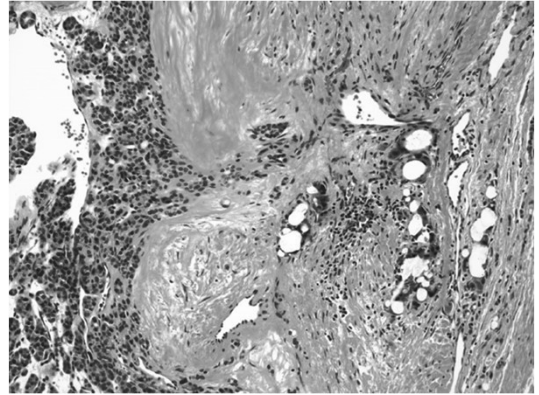
- Extent of capsular invasion is contentious:
 - any degree of invasion into the capsule qualifies categorization as minimally invasive follicular carcinoma
 - tumor has to penetrate the entire thickness of the capsule to be regarded as unequivocal evidence of capsular invasion
- Special stains of questionable utility



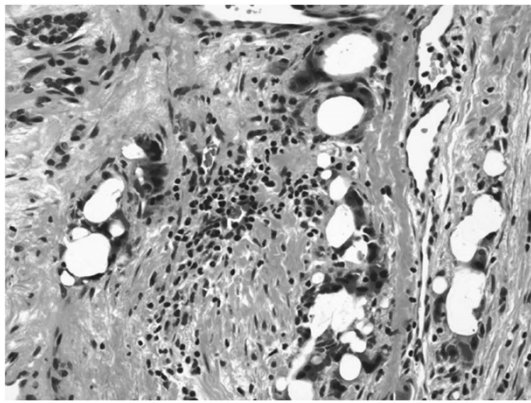
Capsular Invasion?



Post-FNAB Tract



Post-FNAB Tract



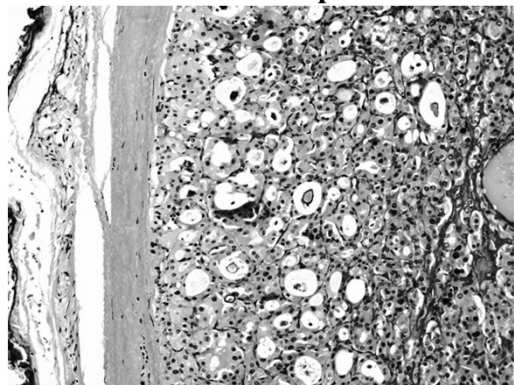
Fibrous Capsule

- *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
- *Robbins & Cotran. Pathologic Basis of Disease. 2010:268

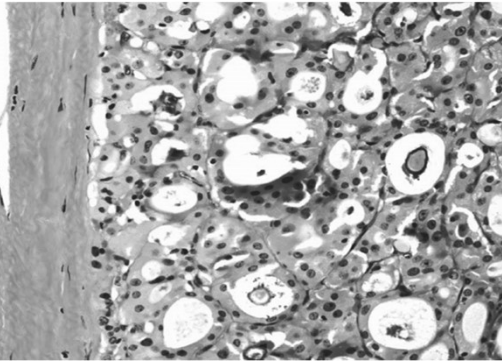
Fibrous Capsule

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

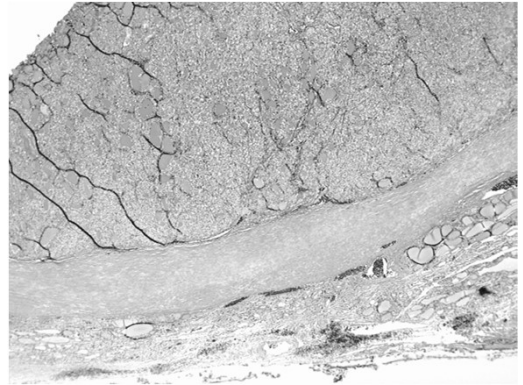
Fibrous Capsule



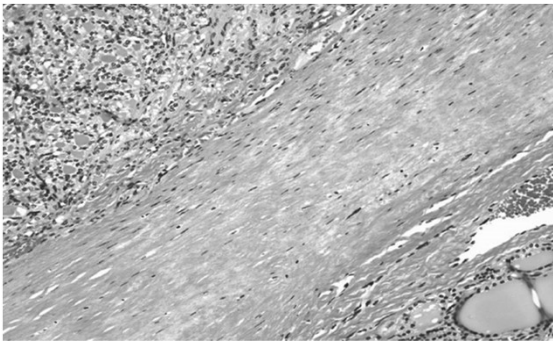
Fibrous Capsule



Fibrous Capsule



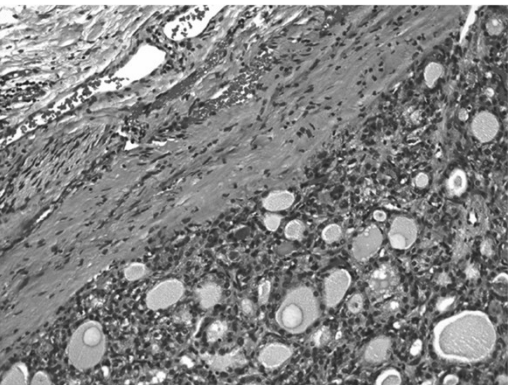
Fibrous Capsule



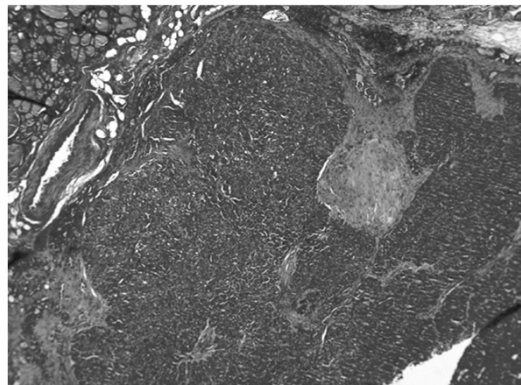
Capsular Invasion

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

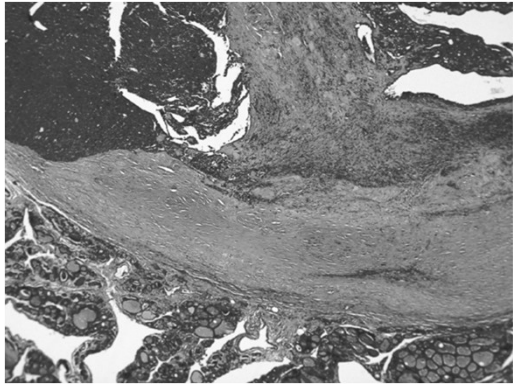
Uniform Appearing Fibrous Capsule



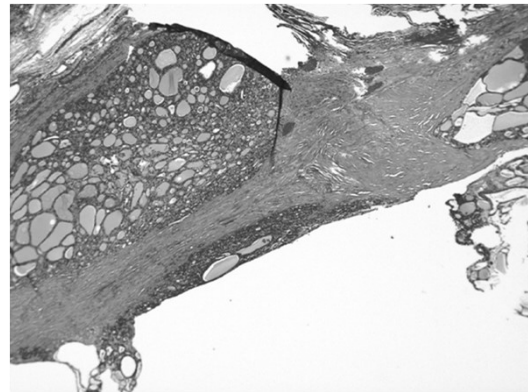
Cellular Nodule – Tangential Section



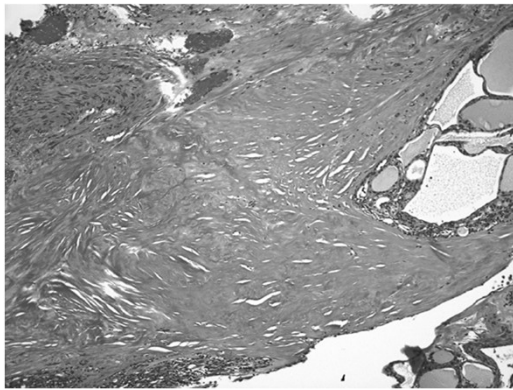
Nodule with irregular fibrosis



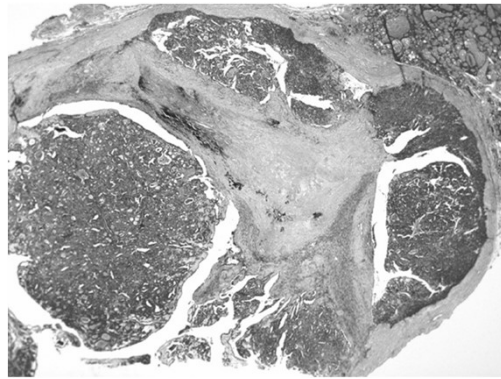
Nodule with irregular fibrosis



Nodule with irregular fibrosis



Nodule with retrogressive changes



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

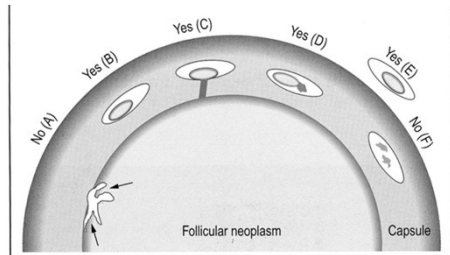
- Solitary nodule
- Good encapsulation
- Uniform structure
- Different growth pattern from adjacent gland
- Compression of adjacent gland
- Retrogressive changes less common (post-FNAB) (except oncocyctic cell dominant)
- Monoclonal

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 vasc 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

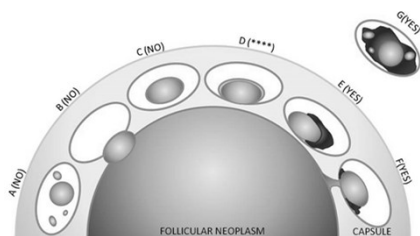
Angioinvasion (CAP Protocol)

- 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

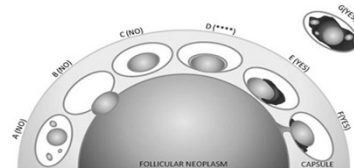
- Mete and Asa (Modern Pathology 2011;24:1545-52)
 - Strict criteria:
 - Tumor cells invade through vessel wall
 - Thrombus adherent to intravascular tumor
- Found in 118 of 4000 lesions (3%)
- Follow-up in 98 cases: 35% developed metastases
- Application of rigid criteria for vascular invasion predicts distant metastasis in thyroid carcinoma especially well-differentiated thyroid carcinoma

Angioinvasion*

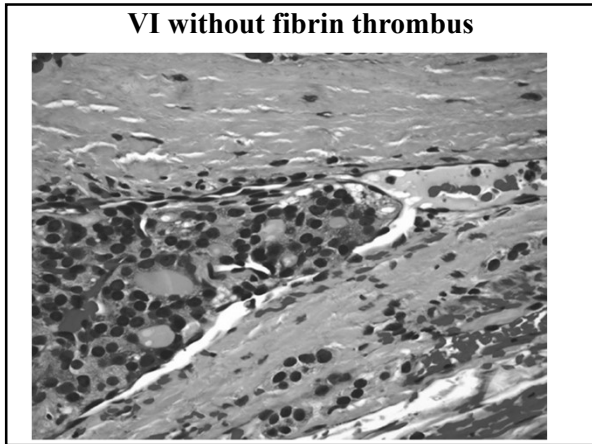
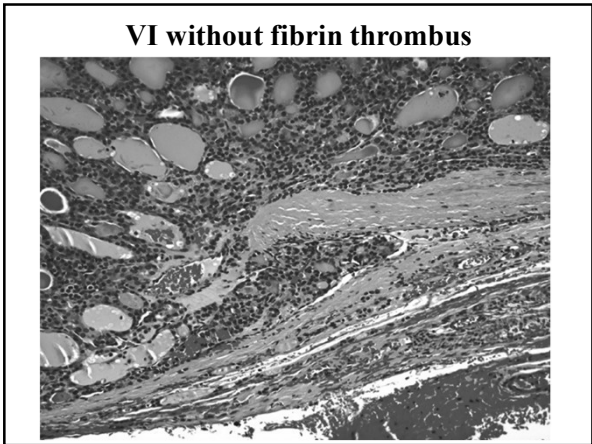
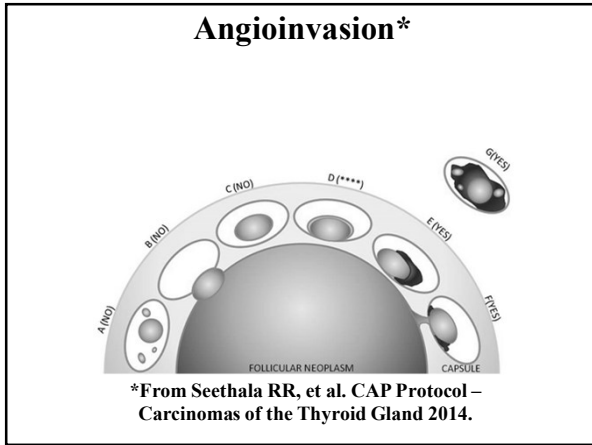
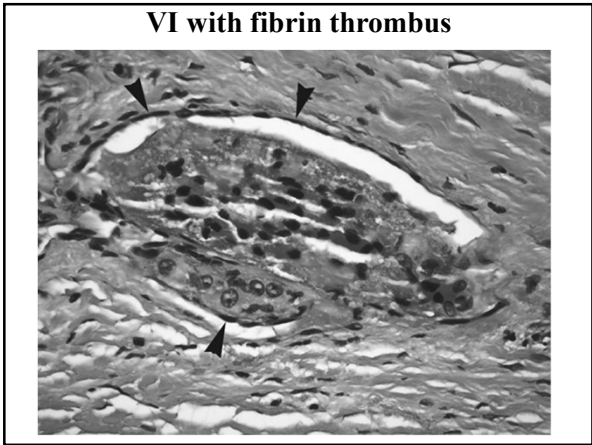
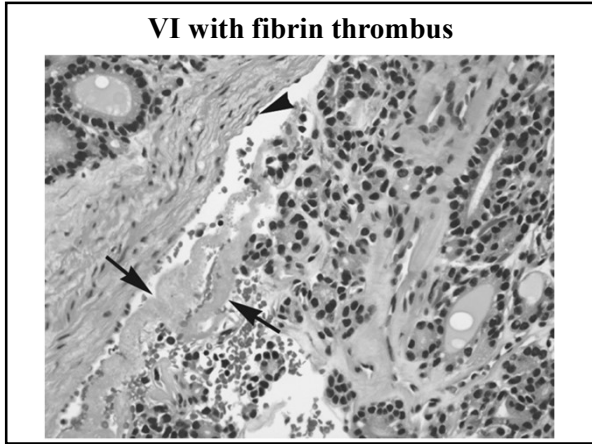
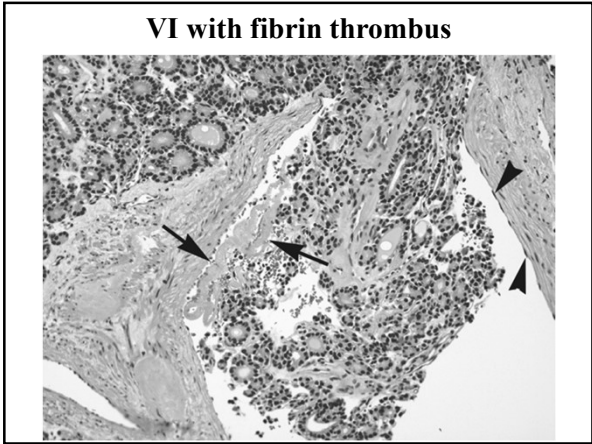


*From Seethala RR, et al. CAP Protocol – Carcinomas of the Thyroid Gland 2014.

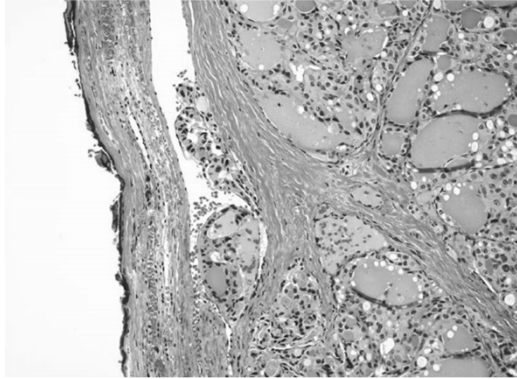
Angioinvasion*



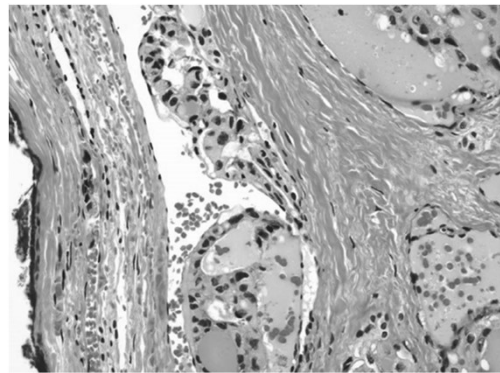
**** D represents a common but contentious scenario among experts, in light of these new proposed criteria for significant VI. This endothelialized tumor deposit is juxtaposed to the vessel wall. As this is somewhat similar to C, and there is no obvious thrombus, technically this would not count as significant 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



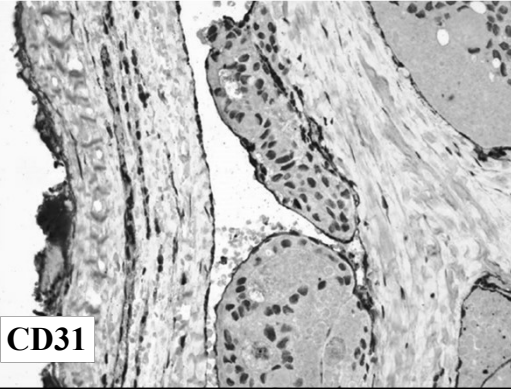
VI without fibrin thrombus



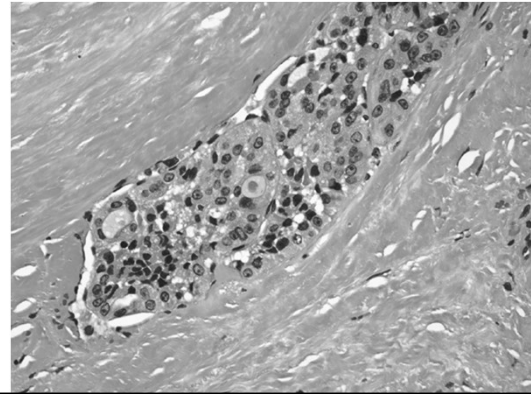
VI without fibrin thrombus



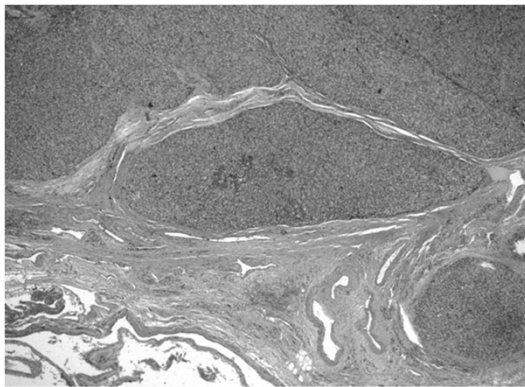
IHC staining for VI



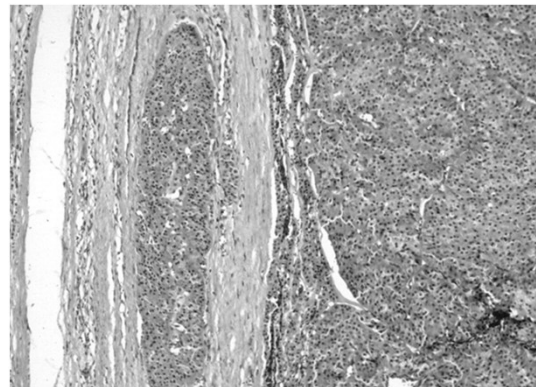
VI without fibrin thrombus

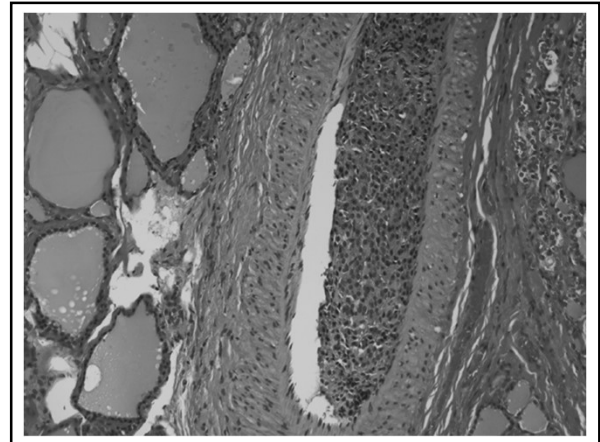
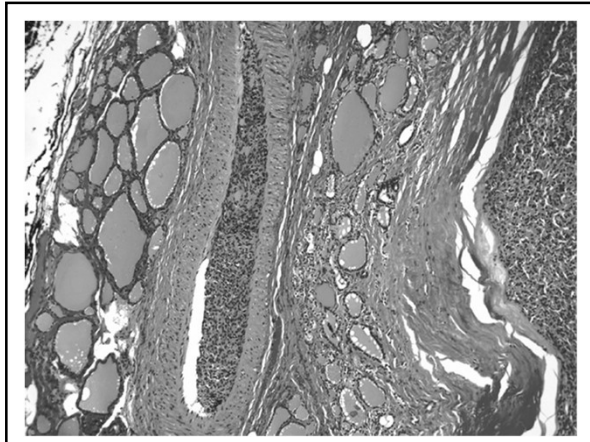


Is this VI or not?

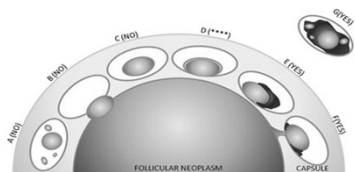


Elastic stain of no help





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

Follicular Carcinoma

- Based on the extent of the invasive component, follicular carcinoma divided into:
 - minimally invasive
 - widely invasive

Follicular Carcinoma Minimal vs Widely Invasive

- Based on the extent of the invasive component:
 - minimally invasive follicular carcinoma, which in turn can be subdivided into:
 - with capsular invasion only
 - with VI < 4 vascular spaces
 - widely invasive follicular carcinoma:
 - ≥ 4 or more vascular spaces

Categories of Follicular Carcinoma

	Minimally Invasive			Widely Invasive (Frankly Invasive)
	With Capsular Invasion Only	With Limited (<4) Vascular Invasion	With Extensive (≥4) Vascular Invasion	
Diagnostic criteria	Encapsulated tumor with capsular invasion only, no vascular invasion	Minimal invasion identified on histologic examination: Invasion of <4 blood vessels, with or without capsular invasion	Invasion of ≥4 blood vessels, with or without capsular invasion	Tumor with widespread invasion of adjacent thyroid tissue or blood vessels
Mean age at diagnosis	Younger (47-50 yr)	Younger (47-50 yr)	Younger (47-50 yr)	Older (53-59 yr)
Local recurrence	No	Rare	Rare	Yes
Regional lymph node metastasis	No	Rare	Rare	More common (1.3%-2.4%)
Distant metastasis	~0%	Rare (5%), and often delayed	Sometimes	Common (2.9%-6.9%), especially to lung, bone, brain, liver
Mortality rate	~0%	3%-5%	18%	30%-50%

Follicular Adenoma v Follicular Carcinoma Tissue Sectioning

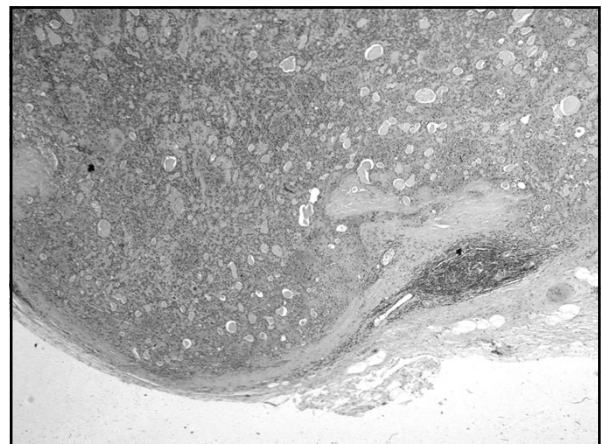
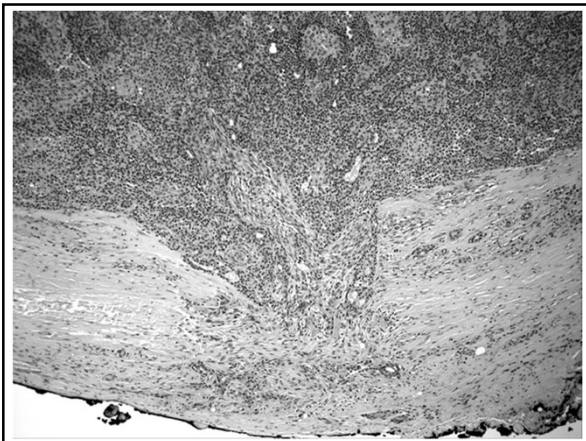
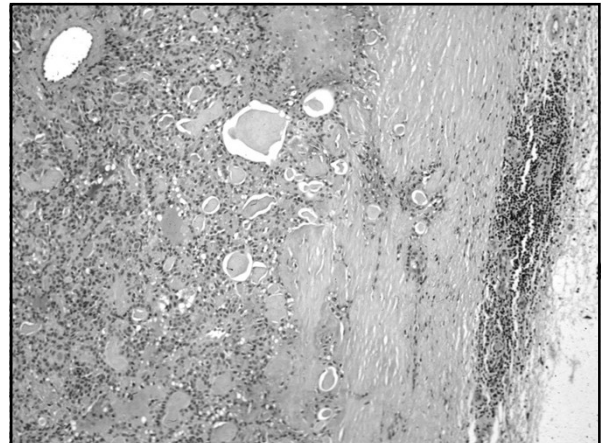
- Ideally submit entire lesion
- Not practical for larger tumors:
 - minimum of 10 blocks
 - International Workshop on Thyroid Pathology:
 - Encapsulated follicular neoplasm - at least 5:
 - Low cellularity, large follicles, edematous stroma and no invasion = FA
 - Increased cellularity and/or other 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



Minimum Diagnostic Criteria for 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
- Undifferentiated (Anaplastic) Carcinoma
- Malignant Lymphoma
- In general, follicular adenoma and follicular carcinoma cannot be differentiated based on cell type

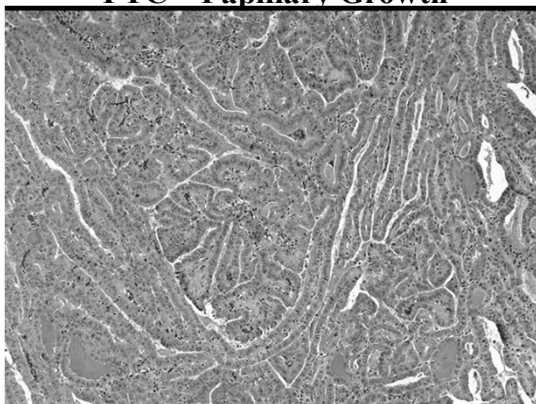
Papillary Thyroid Carcinoma Definition

- **Malignant thyroid follicular epithelial cell neoplasm characterized by distinctive nuclear features**

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)

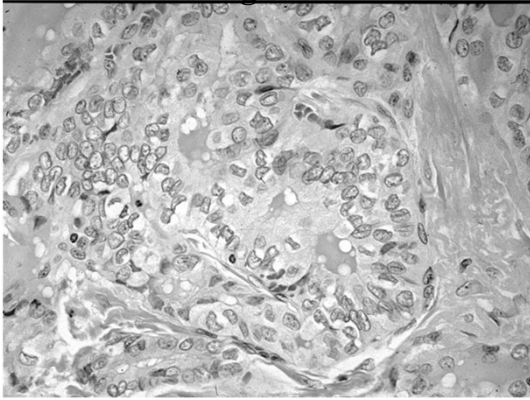
PTC – Papillary Growth



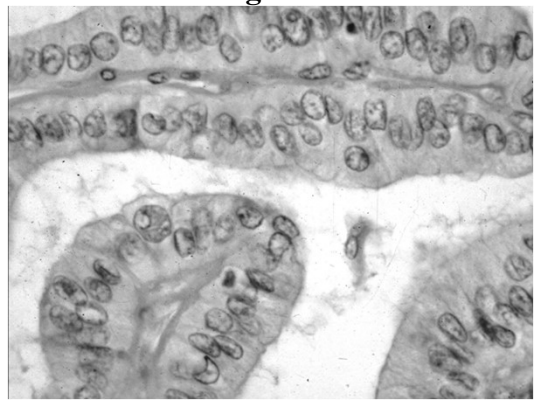
PTC – “Orphan Annie” Nuclei



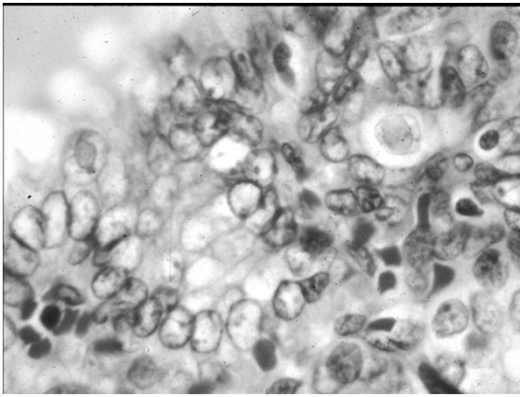
PTC – Diagnostic Nuclei



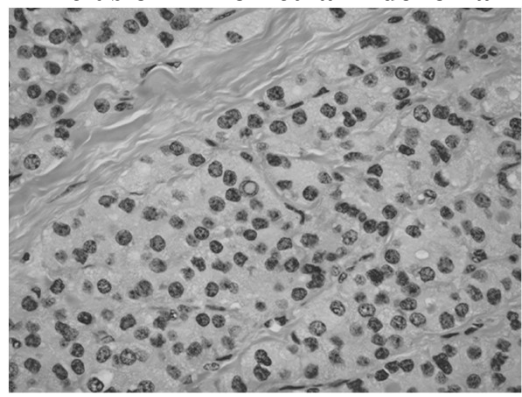
PTC – Diagnostic Nuclei



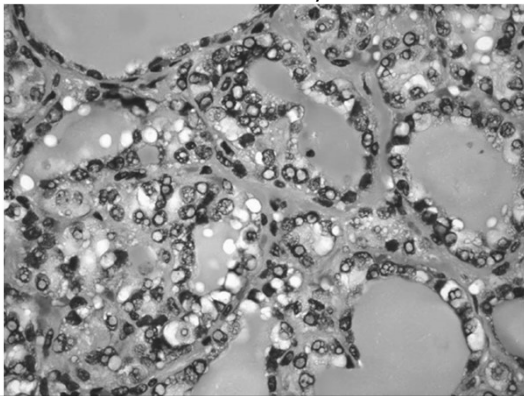
PTC – Nuclear Inclusions



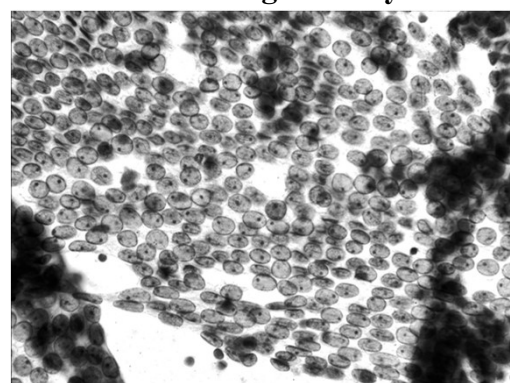
Inclusion in Follicular Adenoma



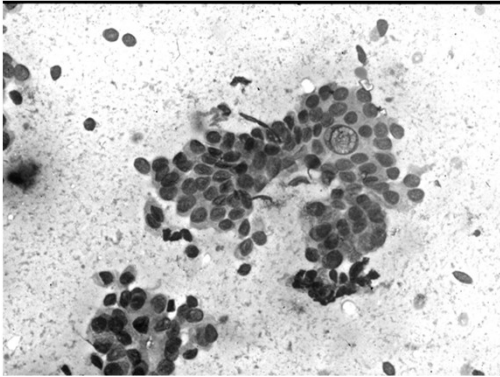
“Bubble artifact” ≠ Inclusions



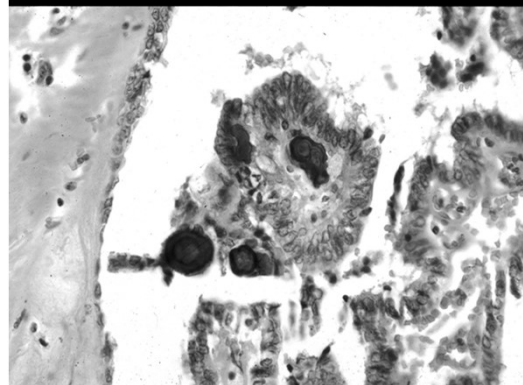
PTC can be diagnosed by FNAB



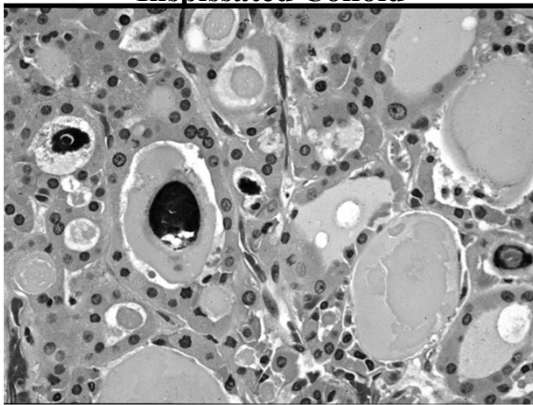
PTC can be diagnosed by FNAB



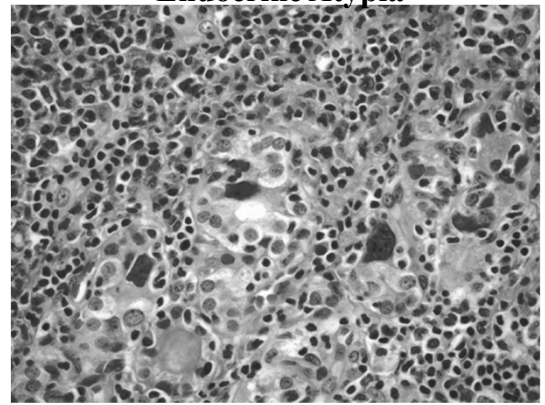
Psammoma Bodies



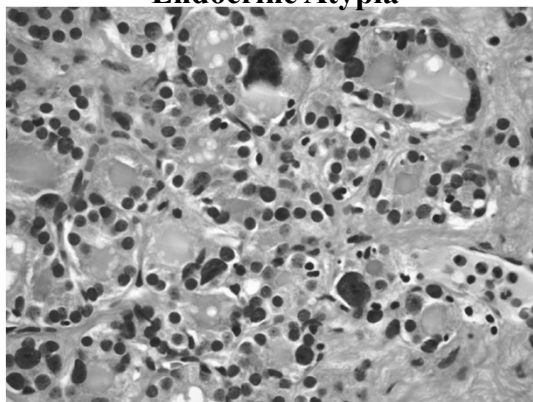
Inspissated Colloid



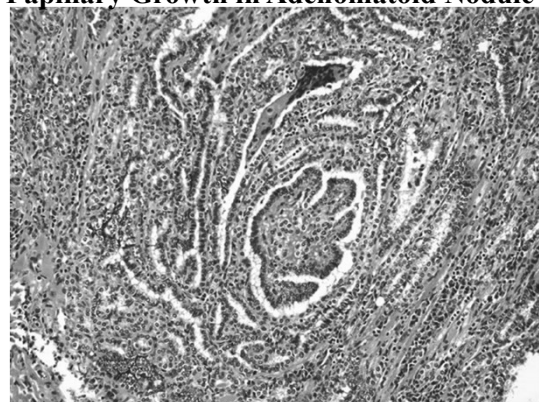
Endocrine Atypia



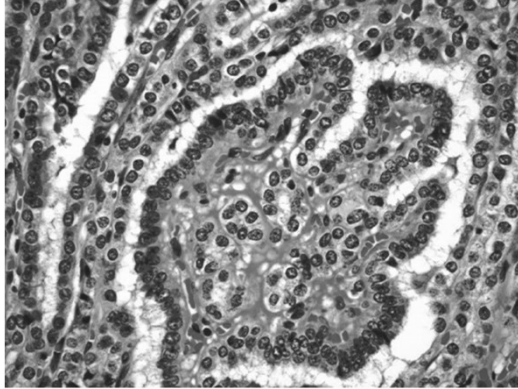
Endocrine Atypia



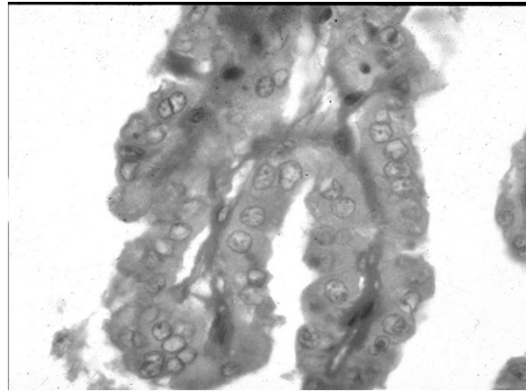
Papillary Growth in Adenomatoid Nodule



Papillary Growth in Adenomatoid Nodule



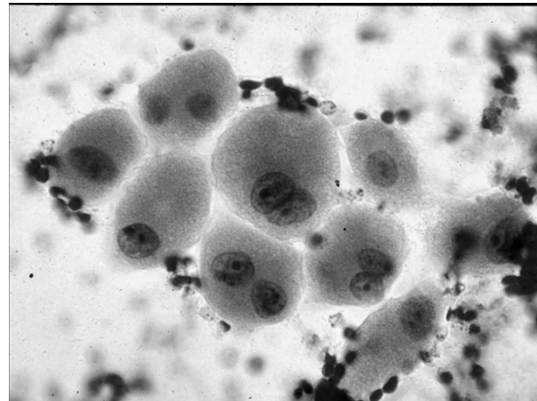
PTC, Oncocytic Variant



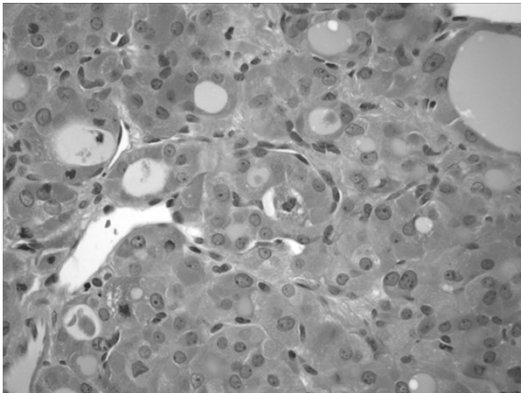
Oncocyte or Oxyphilic Cell

- 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

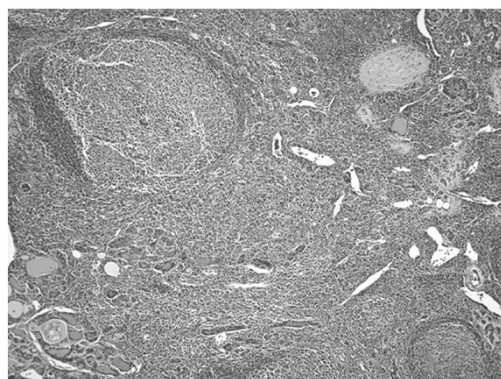
FNAB – Oncocytic Cells



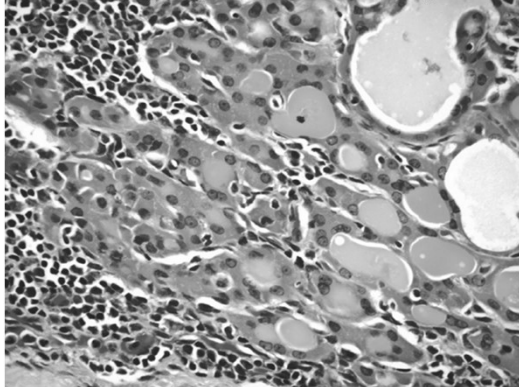
Follicular Neoplasm with Oncocytic Cells



Chronic Lymphocytic (Hashimoto) Thyroiditis



Chronic Lymphocytic (Hashimoto) Thyroiditis



Thyroid Lesions with Oncocytic Cells

- **Nonneoplastic Lesions:**
 - Lymphocytic thyroiditis
 - Adenomatoid nodules
 - Graves disease
 - Post-radiation; aging
- **Neoplasms:**
 - Follicular adenoma/carcinoma (Hürthle cell adenoma/carcinoma); PTC

Papillary Thyroid Carcinoma Histologic Types/Variants

- Usual or conventional
- Papillary microcarcinoma
- Encapsulated
- Follicular
- Macrofollicular
- Oncocytic or oxyphilic
- Clear cell

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

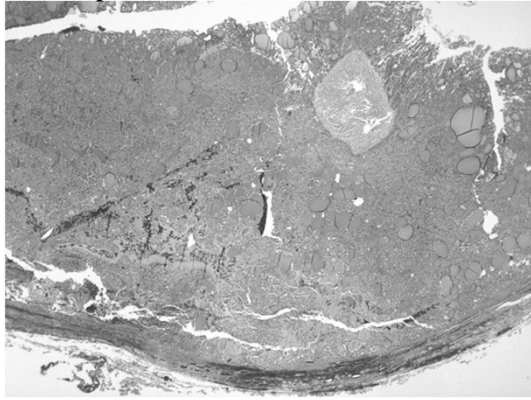
Papillary Thyroid Carcinoma Histologic Types/Variants Cont' d

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

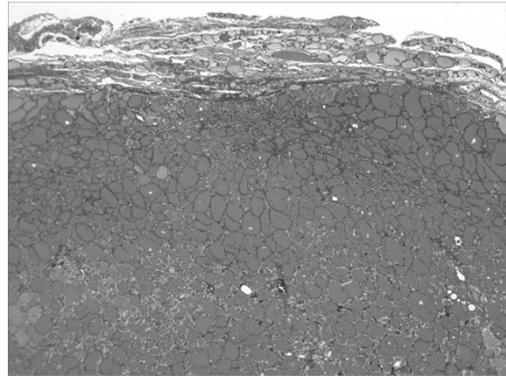
Follicular Variant of Papillary Thyroid Carcinoma (FVPTC)

- Subset of papillary carcinoma entirely composed of follicular growth lacking papillary architecture lined by cells having the nuclear features of PTC

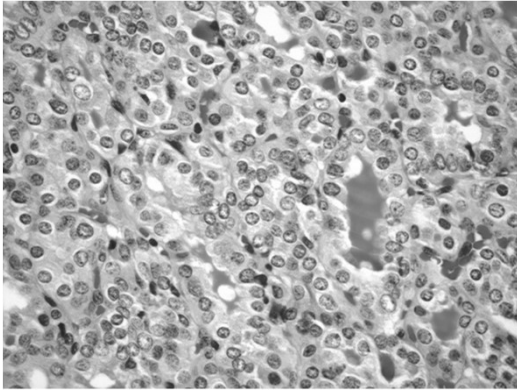
Encapsulated Follicular Pattern Lesion



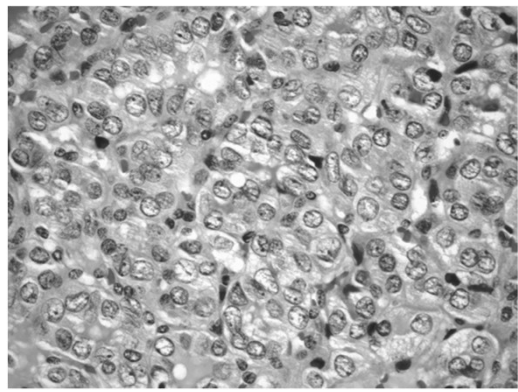
Circumscribed Follicular Pattern Lesion



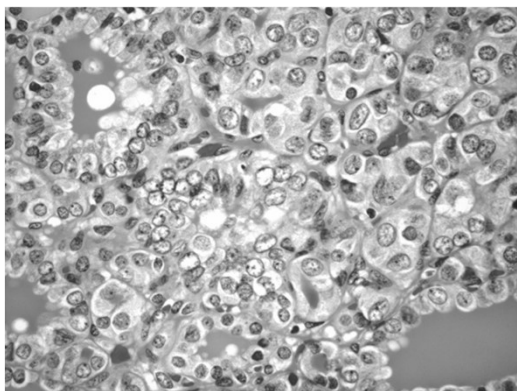
Majority without PTC Nuclei



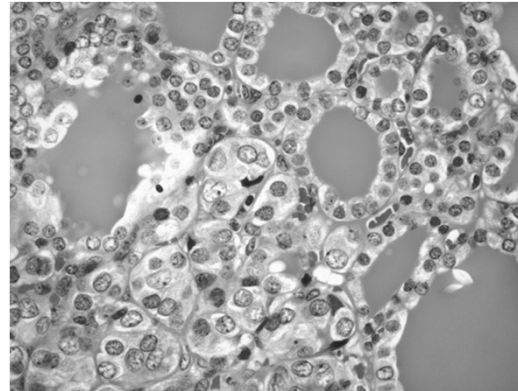
Foci with PTC Nuclei



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
- * Lloyd et al: AJSP 2004;28:1336-40

Summary of Diagnoses

Reviewer	FVPTC	FA	FCA	Other
1	100	0	0	0
2	74.7	12.6	0	12.6
3	85.1	13.8	1.1	0
4	77	20.7	1.1	1.1
5	91.9	4.7	0	3.5
6	100	0	0	0
7	91.9	1.1	0	6.9
8	98.9	0	1.1	0
9	46.6	37.9	12.6	3.5
10	60.9	11.5	1.2	26.4

**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

* Elsheikh TM, et al: AJCP 2008;130:736-744

**FVPTC
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

**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 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

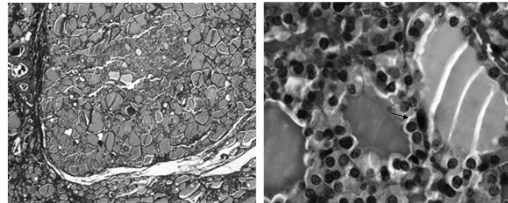
Papillary Thyroid Carcinoma Issues

- 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

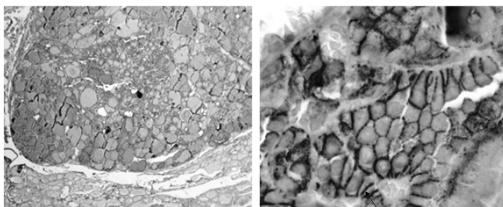
Papillary Thyroid Carcinoma Does IHC Help?

- 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

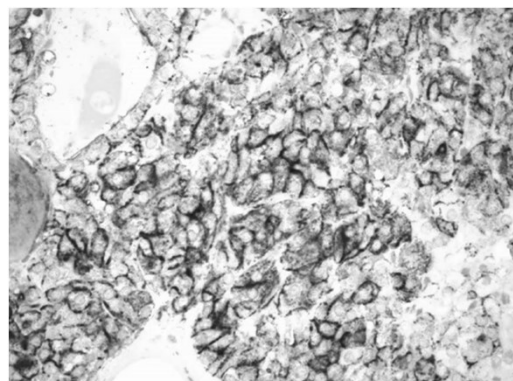
Adenomatoid Nodule



Adenomatoid Nodule False positive HBME-1 Staining



HBME-1 IHC in Follicular Adenoma



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

Frequency of various molecular alterations in papillary carcinoma and follicular neoplasms

	Follicular adenoma or carcinoma (%)	Conventional papillary carcinoma (%)	Follicular variant of papillary carcinoma (%)
RET/PTC translocation	0	26-28	3
BRAF mutation	0	53-75 (M600E)	0-7 (K601E)
RAS mutation	18-53	0	25-47
PAX8/PPAR γ translocation	Follicular adenoma: 4-33 Follicular carcinoma: 45-63	0	38

FVPTC Molecular Biology

- Molecular profile much closer to follicular adenoma and follicular carcinoma than to classical papillary carcinoma

Biologic Behavior of FVPTC

- Liu J, et al. Cancer. 2006;107:1255-64:
 - 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

- Giordano T, et al. Integrated genomic characterization of papillary thyroid carcinoma - Cancer Genome Atlas Research Network. Cell 2014;159:676-690
- 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

Yuri E. Nikiforov, MD, PhD; Raja R. Seethala, MD; Giovanni Tallini, MD; Zubair W. Baloch, MD, PhD; Fulvio Basolo, MD; Lester D. R. Thompson, MD; Justine A. Barletta, MD; Bruce M. Wenig, MD; Abir Al Ghuzlan, MD; Hiromichi Kakuho, MD, PhD; Thomas J. Giordano, MD, PhD; Venancio A. Alves, MD, PhD; Elham Khandafkar, MD, MS; Sylvia L. Asa, MD, PhD; Adel K. El-Haggar, MD; William E. Gooding, MS; Steven P. Hodak, MD; Ricardo V. Lloyd, MD, PhD; Guy Maytal, MD; Ozgur Mete, MD; Marina N. Nikiforova, MD; Vania Nosé, MD, PhD; Mauro Papotti, MD; David N. Poller, MB, ChB, MD, FRCPath; Peter M. Sadow, MD, PhD; Arthur S. Tischler, MD; R. Michael Tuttle, MD; Kathryn B. Wall; Virginia A. Livolsi, MD; Gregory W. Randolph, MD; Ronald A. Gosselin, MD

JAMA Oncology April 2016

Reclassification Noninvasive FVPTC

- Recent recommendation to replace use of noninvasive FVPTC with “Noninvasive Follicular Tumor 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% papillae)
- No psammoma bodies
- < 30% solid, trabecular, insular growth
- No tumor necrosis or high mitotic activity (≥ 3/10HPF)
- No invasion (vascular or capsular):
 - entire tumor-capsule or tumor-parenchymal interface must be submitted

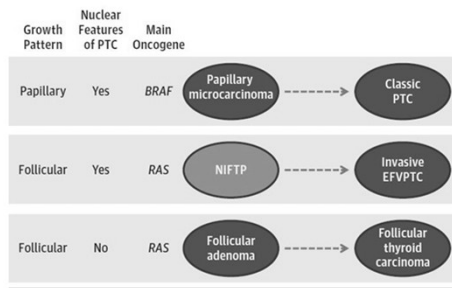
NIFTP Exclusion Criteria

- True papillae >1%
- Psammoma bodies
- Infiltrative border (invasion similar to follicular ca.)
- High mitotic activity (≥ 3 mitoses/10 HPF)
- Cell/morphologic features of other variants of PTC (e.g., tall cell, columnar cell, hobnail, cribriform-morular variant, solid variant, others); no used for subcentimeter lesions

NIFTP

- **Reclassification as a close entity to the follicular adenoma/carcinoma group:**
 - 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

Figure 2. Putative Scheme of Thyroid Carcinogenesis



EFVPTC indicates encapsulated follicular variant of PTC; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid carcinoma.

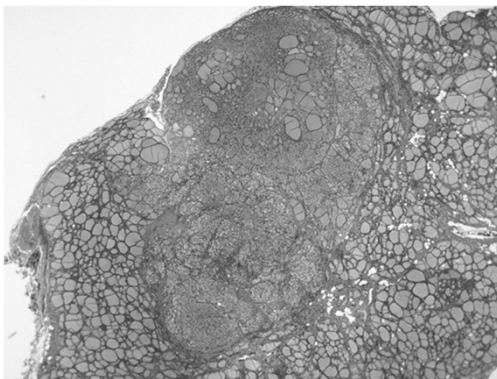
NIFTP

- Encapsulated, circumscribed
- Low % marked intralesional sclerosis
- No psammoma bodies or nuclear inclusions
- No ETE
- RAS mutation, PAX8/PPAR γ translocation
- Low to no incidence of metastasis

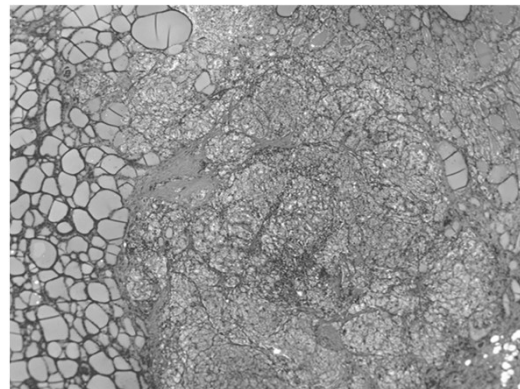
INVASIVE FVPTC

- Nonencapsulated
- \uparrow % marked intralesional sclerosis
- Psammoma bodies, nuclear inclusions may be present
- \uparrow % ETE
- BRAF mutation, RET/PTC translocation
- Increased incidence of metastasis (nodal)

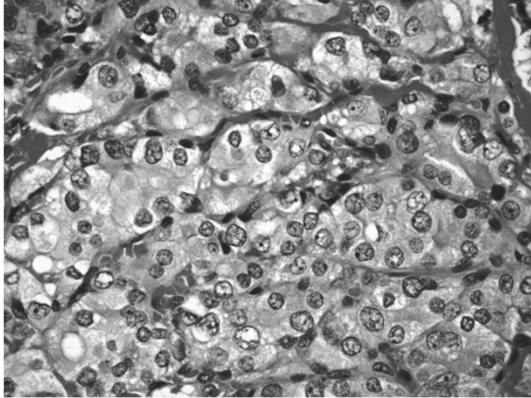
Invasive FVPTC



Invasive FVPTC



Invasive FVPTC



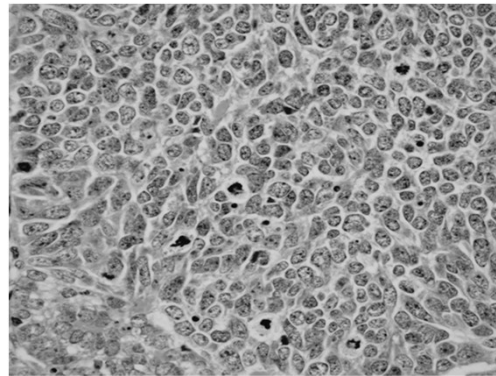
Minimum Diagnostic Criteria for Thyroid Cancer

- **Diagnostic Criteria:**
 - Invasion
 - Cytomorphologic findings
 - Mitoses and Necrosis
 - Metastatic disease

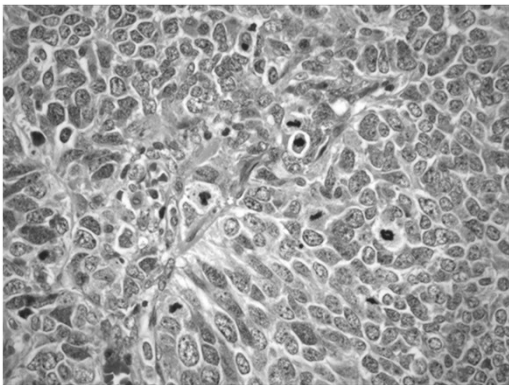
Poorly-Differentiated Thyroid Carcinoma (PDTC) Definition

- Thyroid neoplasm with histologic and biologic features intermediate between those of differentiated thyroid carcinomas and undifferentiated (anaplastic) carcinoma
- Synonym: Insular Carcinoma

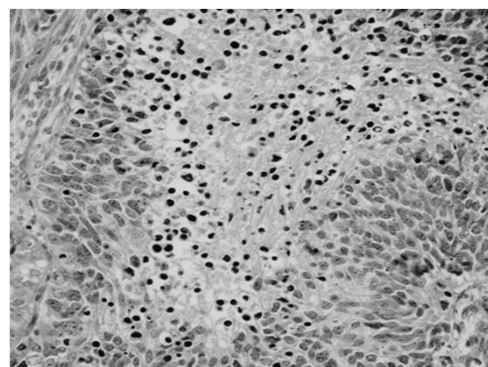
PDTC – Mitoses



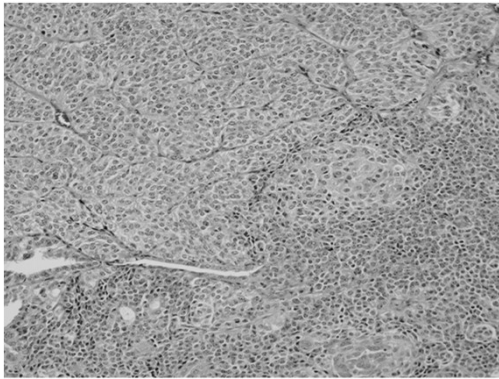
PDTC – Mitoses



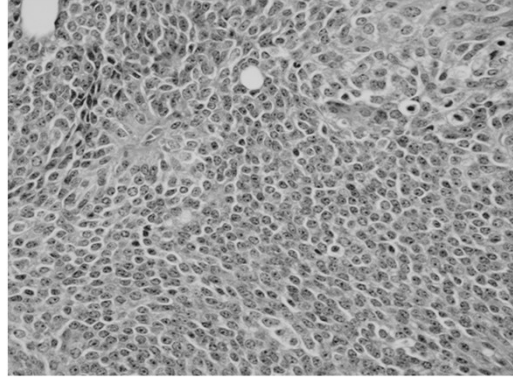
PDTC – Necrosis



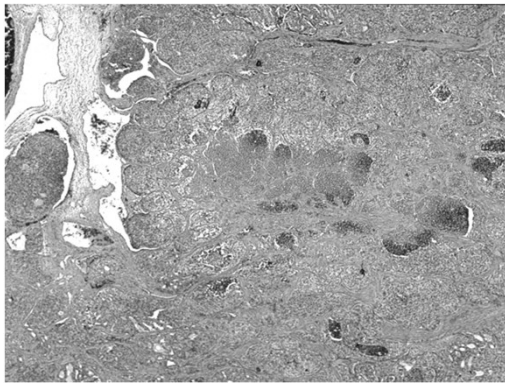
PDTC – Insular, Trabecular and Solid



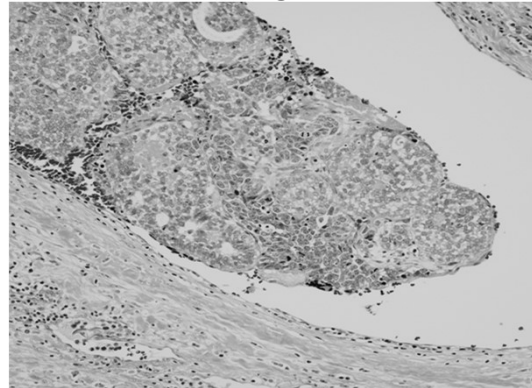
PDTC – solid, convoluted nuclei, no colloid



PDTC – Invasion and Necrosis



PDTC – Angioinvasion



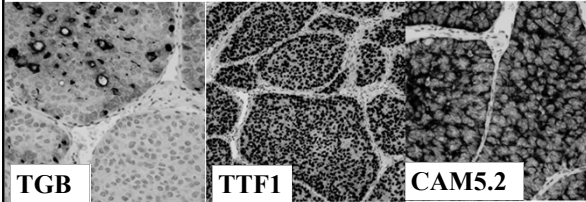
PDTC – Extrathyroidal Extension



**PDTC
Immunohistochemistry**

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

PDTC
Immunohistochemistry



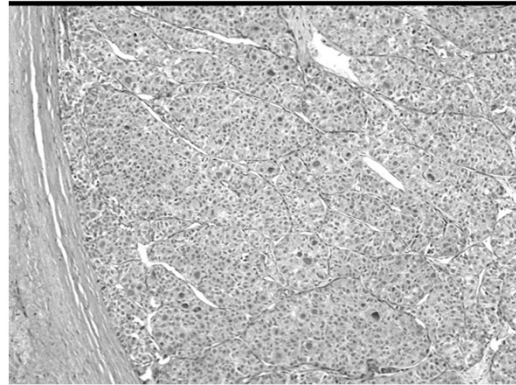
PDTC
Turin Proposal*

- 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

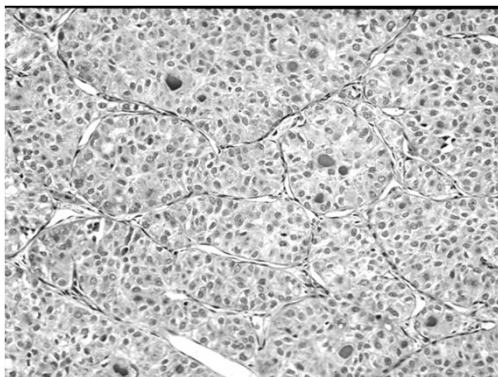
PDTC

- PDTC not limited to tumors with insular/solid/trabecular growth:
 - Hiltzik D, et al. Cancer 2006;106:1286-95:
 - PDTC defined on basis of \uparrow mitotic activity and/or tumor necrosis
 - Rivera M, et al. Cancer 2008;113:48-56:
 - Necrosis and/or mitotic index (≥ 5 x 10HPF)

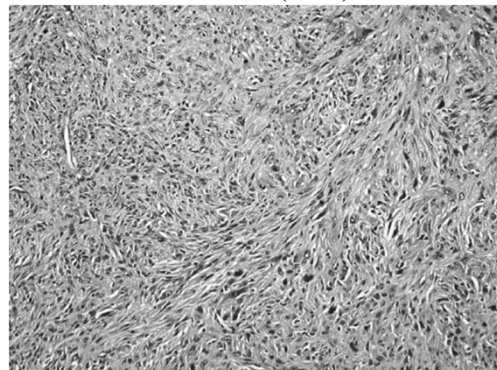
Insular pattern \neq Insular Carcinoma

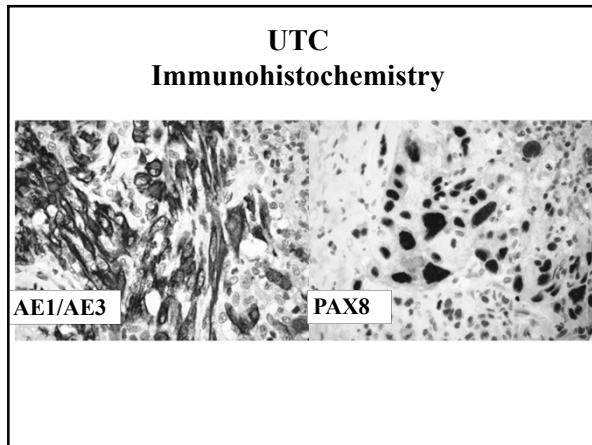
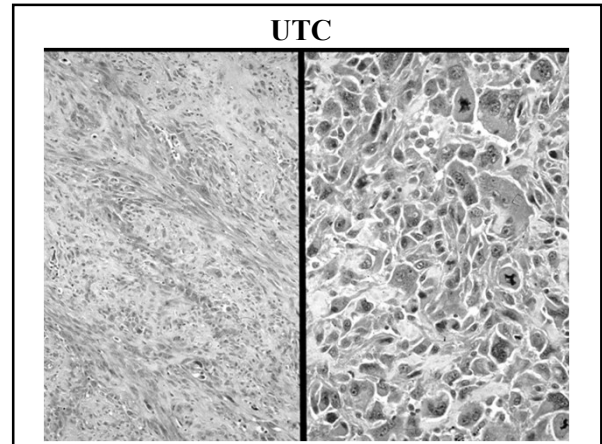
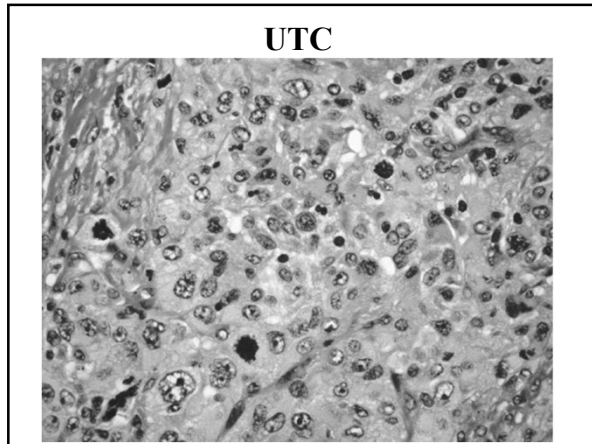


Insular pattern \neq Insular Carcinoma



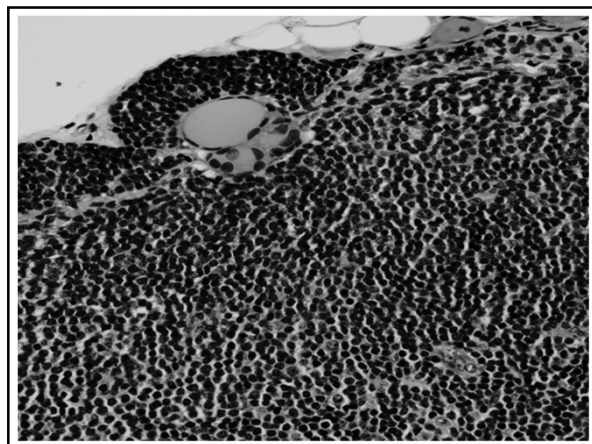
Undifferentiated (Anaplastic) Thyroid Carcinoma (UTC)





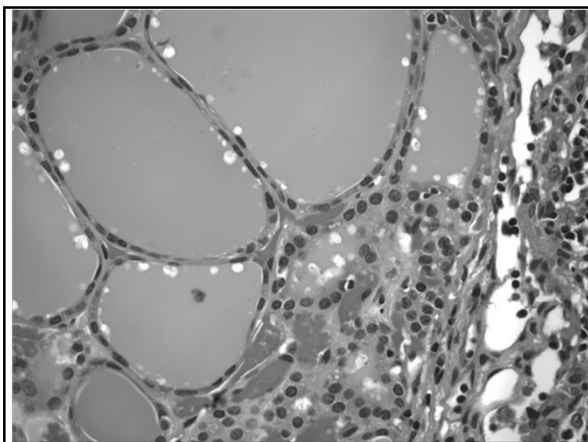
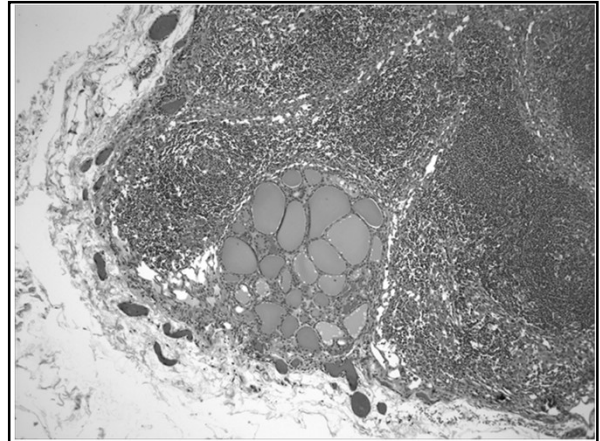
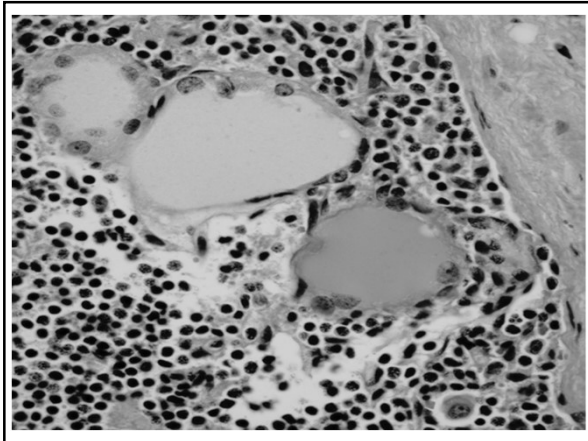
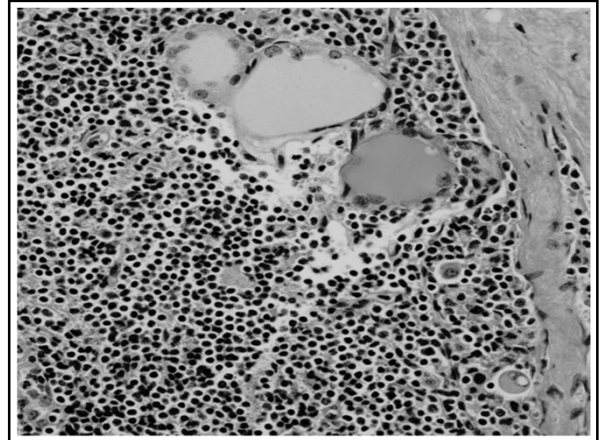
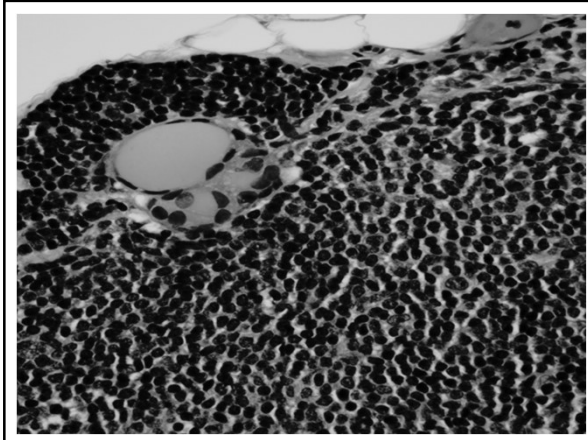
**Minimum Diagnostic Criteria
for Thyroid Cancer**

- **Diagnostic Criteria:**
 - Invasion
 - Cytomorphologic findings
 - Mitoses and Necrosis
 - Metastatic disease



Thyroid Follicles in Lymph Nodes

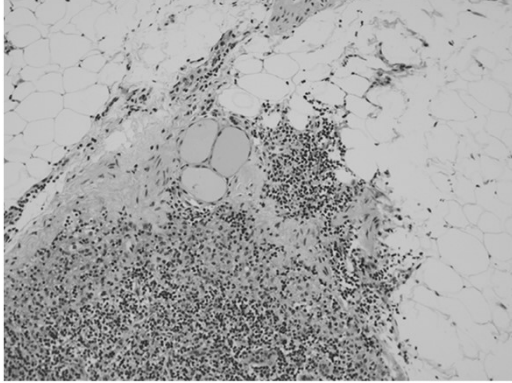
- **When is metastatic carcinoma and when is it something else?:**
 - Thyroid inclusions
 - Lymphocytic thyroiditis



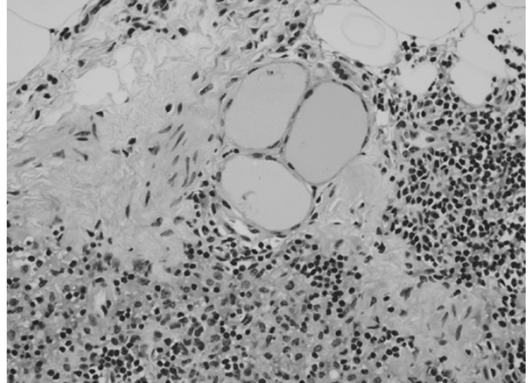
Thyroid Inclusions in Lymph Nodes

- **Midline or para-midline lymph nodes**
- **Not identified in nodes lateral to great vessels**
- **Follicles extremely limited in number and localized to capsule**

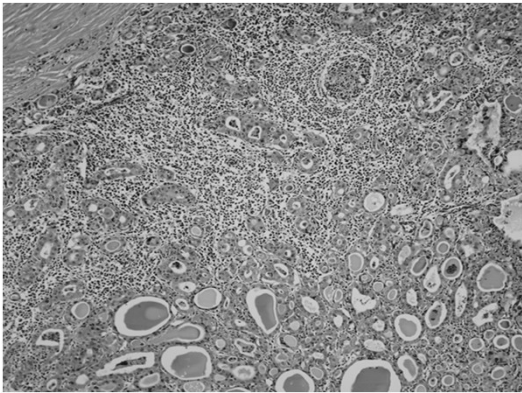
Thyroid Inclusions in Lymph Nodes



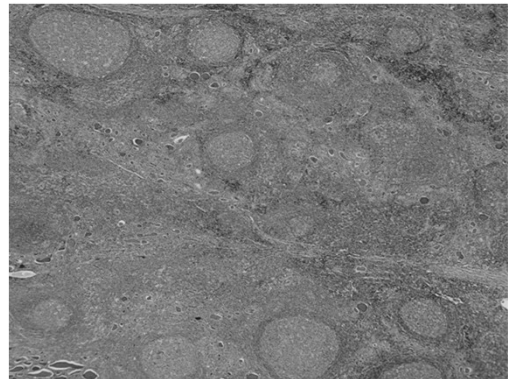
Thyroid Inclusions in Lymph Nodes



Chronic Lymphocytic (Hashimoto) Thyroiditis



Chronic Lymphocytic (Hashimoto) Thyroiditis



**Minimal Diagnostic Criteria for the
Diagnosis of Thyroid Carcinoma
Conclusions**

- **Invasion:**
 - Capsular invasion
 - Vascular invasion

**Minimal Diagnostic Criteria for the
Diagnosis of Thyroid Carcinoma
Conclusions**

- **Cytomorphology:**
 - Papillary thyroid carcinoma
 - Medullary thyroid carcinoma
 - Poorly-Differentiated Thyroid Carcinoma
 - Undifferentiated (Anaplastic) Thyroid Ca.
 - Malignant lymphoma

**Minimal Diagnostic Criteria for the
Diagnosis of Thyroid Carcinoma
Conclusions**

- **Necrosis and mitoses**
- **Metastatic disease**