Thyroid & Parathyroid Tumors

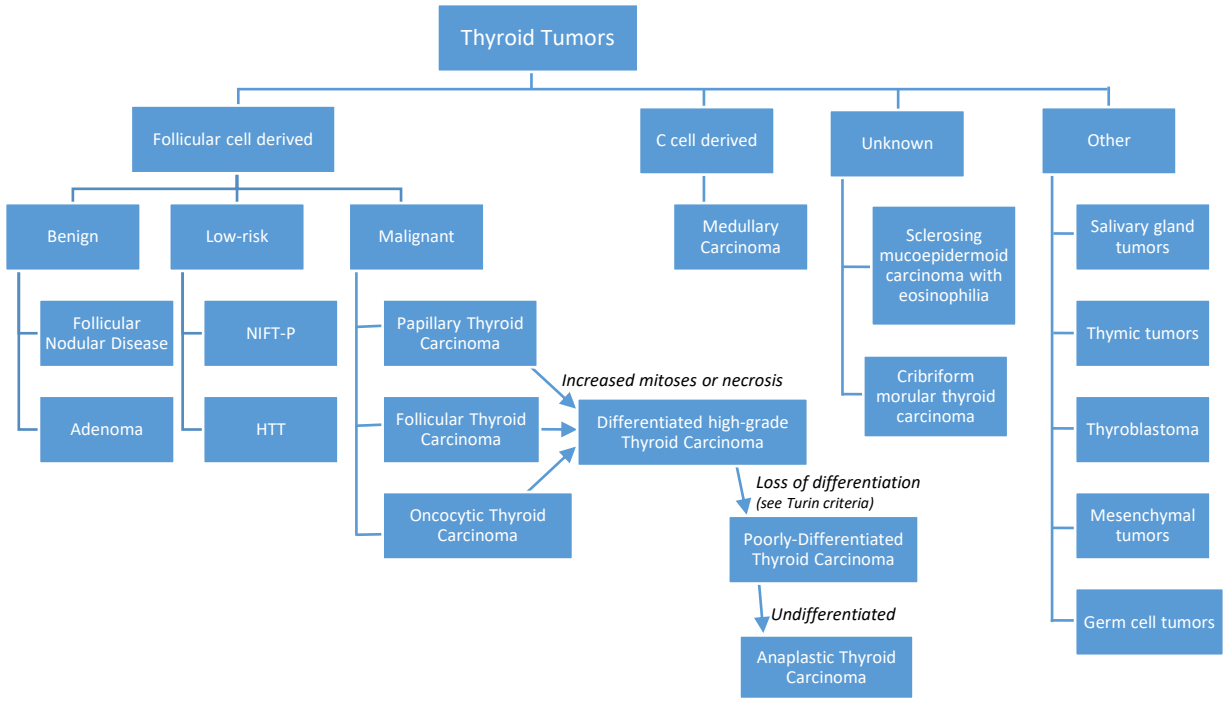
Thyroid Tumors

Thyroid tumors have 3 biologic potentials: Benign, Low-risk, Malignant

Benign = Adenoma. Usually have follicular architecture and RAS-like molecular profile.

Low-risk neoplasms = Tumor. Rarely give rise to metastases but the incidence of spread is extremely low. Called "tumor" to reduce overtreatment. Includes tumors that have cytologic features of malignancy but no evidence of invasive growth (NIFT-P) and tumors with uncertain invasiveness (UMP).

Malignant = Carcinoma. Well-differentiated tumors generally fall into two molecular categories:
RAS-like: Normal follicular architecture with expansile growth. Minimal/No nuclear atypia.
BRAF V600E-like: Abnormal architecture (papillary and/or invasive) with florid nuclear atypia.
Both can undergo additional genetic events (e.g., p53 mt) → Poorly-differentiated or Anaplastic carcinoma

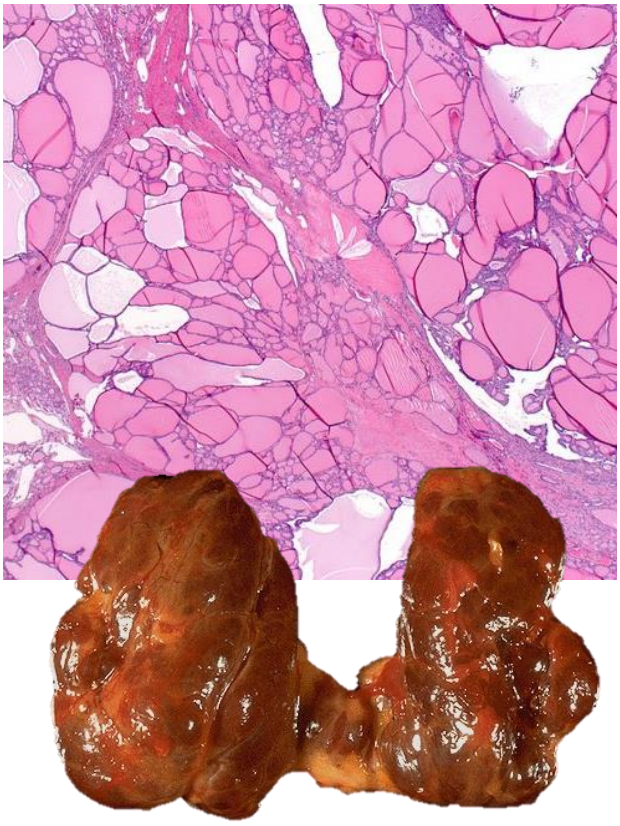


Thyroid Carcinoma Immunohistochemistry

	CK	Thyroglobulin	TTF1	PAX8	Ki67	P53	Calcitonin, synaptophysin
Normal Thyroid Follicular cells	+	+	+	+	<3%	Wt	-
Well-differentiated thyroid carcinoma	+	+	+	+	<10%	Wt	-
Poorly-differentiated thyroid carcinoma	+	-/+	+	+	10-30%	+	-
Anaplastic thyroid carcinoma	+/-	-	-/+	+/-	>30%	+	-
Medullary carcinoma	+	-	+	-/+		Wt	+

Modified from: WHO Classification of Tumors of the Endocrine Organs. 2017.

Follicular Nodular Disease



Formerly, "Adenomatous hyperplasia"
(and similar terms)

Multifocal, non-inflammatory, benign proliferation of thyroid follicular cells that results in multiple clonal and non-clonal nodules with highly variable architecture. Spans the hyperplasia-neoplasia sequence.
Very common. More common in females.

Bland nuclei. (No PTC-like nuclear changes)
Mostly **Unencapsulated nodules** with pushing borders
Mixture of large and small follicles.
Most nodules contain relatively **abundant colloid**
Variably sized nodules. Some may be dominant.
Frequent **degenerative changes** including: cystic degeneration, fibrosis, hemorrhage.

"Multinodular Goiter" is a *clinical* term for gland enlargement, *not* a surgical pathology diagnosis.

Total thyroidectomy for symptomatic disease (e.g., compressive symptoms like dysphagia)

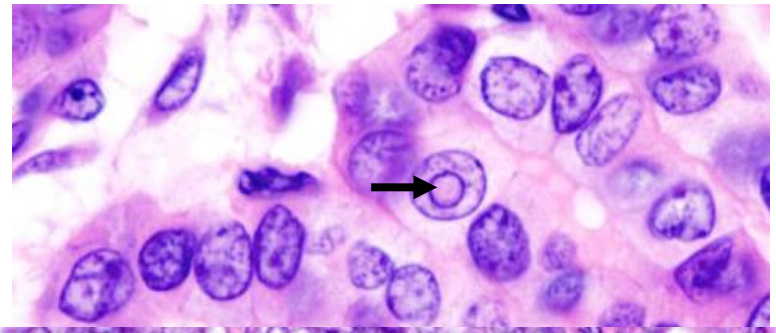
Papillary Thyroid Carcinoma *"PTC"*

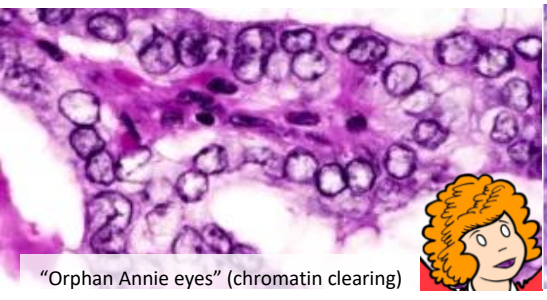
Malignant tumor with follicular epithelial cell differentiation.
Defined by: distinct nuclear features and either papillary or solid/trabecular architecture, or invasive growth in follicular-patterned tumors.

Most common form of thyroid cancer in both adults and children. More common in women.
Risk factor: Ionizing radiation. Often **relatively indolent** cancer. Often presents with a painless mass.
Often multifocal. Frequently invades lymphatics→ frequent lymph node metastases

Molecular alterations: BRAF (most common by far, V600E), RET, RAS, TERT promoter→ often mutually exclusive→ MAPK activation

Nuclear Features: *(Definitional)*
- Nuclear **enlargement** and elongation
- Nuclear **overlapping**
- **Irregular nuclear contours**
- Intranuclear **pseudoinclusions (→)**
- Longitudinal nuclear **grooves**
- Nuclear **chromatin clearing**





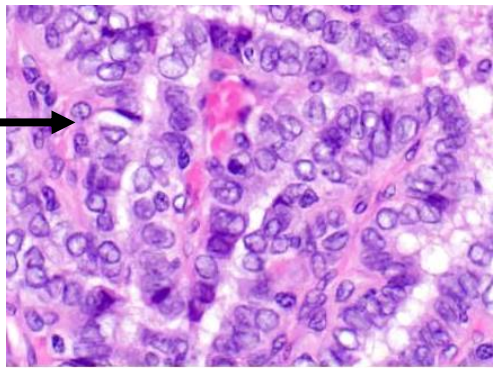
"Orphan Annie eyes" (chromatin clearing)

"Coffee bean nuclei" (Longitudinal nuclear grooves)

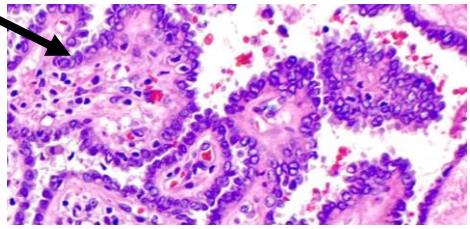
PTC Subtypes: *All have the same defining nuclear features!*

For the most part, all IHC: (+)TTF-1, PAX8, Thyroglobulin, CK7,

Conventional (classic): ***Most common***
Papillary architecture (hence the name!).
(May have mixed in other architectures, like follicles.)
Frequent psammoma bodies.
Often cystic degeneration.
Densely eosinophilic colloid.
May see focal solid growth or squamous metaplasia.



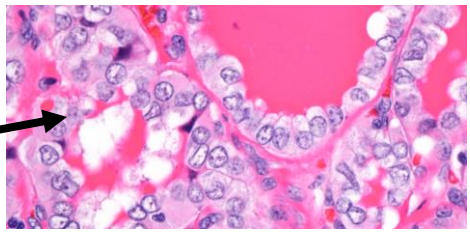
Encapsulated: Classic PTC enveloped by a thick fibrous capsule, which maybe intact or infiltrated by tumor with or without extension into surrounding thyroid parenchyma.



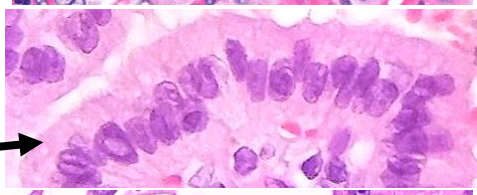
Microcarcinoma: Tumor variant ≤ 1 cm. Often missed grossly or incidental. Malignant, but excellent prognosis.
Still subtype as classical, follicular, etc..

Follicular: Exclusively (or almost exclusively) follicular architecture. Can be infiltrative or encapsulated with invasion. Second most common.
Two sub-subtypes

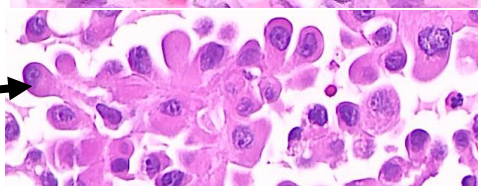
Invasive Encapsulated Follicular Variant PTC—Encapsulated, but capsular and/or vascular invasion. RAS-like
Infiltrative Follicular Variant PTC—Unencapsulated. Infiltrative advancing front.



Tall Cell: Cells 3x as tall as they are wide with abundant eosinophilic cytoplasm. Must account for ≥30% of tumor. More aggressive behavior. Prominent inclusions and cell membranes.

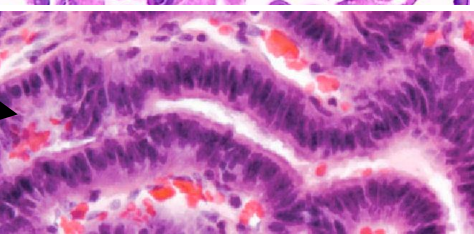


Hobnail: Aggressive, rare. Enlarged nuclei that bulge from the apical surface (hobnail appearance). Often associated poorly-differentiated or anaplastic carcinoma.



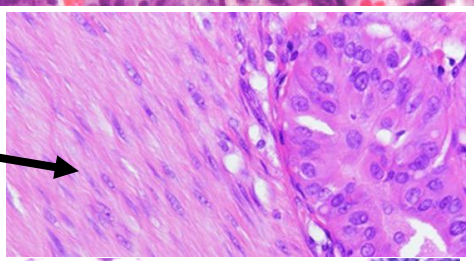
Columnar cell: Rare. Columnar cells with prominent pseudostratification. Lack conventional nuclear features (inclusions, clearing). Very cellular. Resembles endometrioid/intestinal adenocarcinoma morphologically. IHC: often CDX2+!

Diffuse sclerosing: Rare. Diffuse involvement with sclerosis and solid nests of tumor cells. Lots of LVI. Also background lymphocytic inflammation and psammoma bodies. Usu. Kids/young adults.

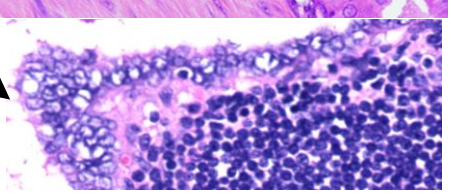


PTC with fibromatosis/fasciitis-like/desmoid-type stroma: Very rare. Abundant cellular stroma resembling nodular fasciitis, fibromatosis, desmoid or other myofibroblastic processes

Warthin-like: Resembles Warthin tumor of salivary gland. Papillae lined by oncocytic cells with the papillary cores a background of lymphocytes and plasma cells (Hashimoto's thyroiditis)



Other variants (where the name says it all): Clear cell, Oncocytic, Solid/Trabecular.

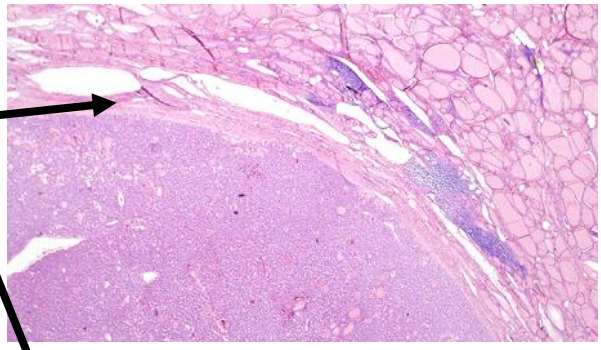


Follicular Adenoma

Benign

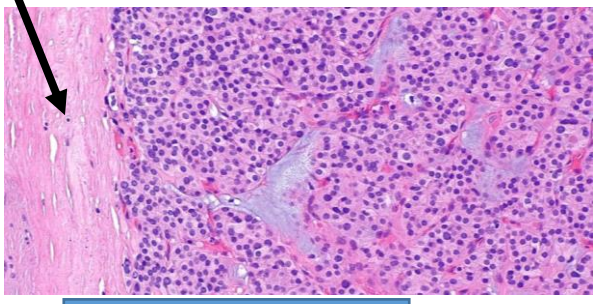
Non-invasive, encapsulated, follicular-patterned neoplasms

***Completely* surrounded by a fibrous capsule (→).**



Variety of architectural patterns: normo-, micro-, or macrofollicular, solid, and/or trabecular, but different than surrounding parenchyma

Cells are cuboidal with round, basally located nuclei. **Smooth nuclear contours and uniform chromatin**.



ABSENT: capsular/vascular invasion, PTC-like nuclei
(Must submit entire capsule to exclude invasion)

No Necrosis. Rare mitoses

Variants:
Hyperfunctioning—hyperthyroidism. Papillary projections.
Lipoadenoma—mature adipose tissue is sprinkled throughout
Signet-ring cell—cells with cytoplasmic vacuoles
Other variants: clear cell, spindle cell, black

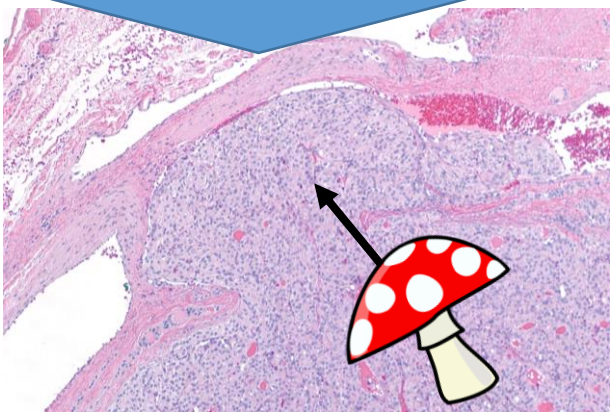
Capsular and/or Vascular Invasion

Follicular Carcinoma

Malignant.

"FTC"

Nuclear features of PTC are absent.

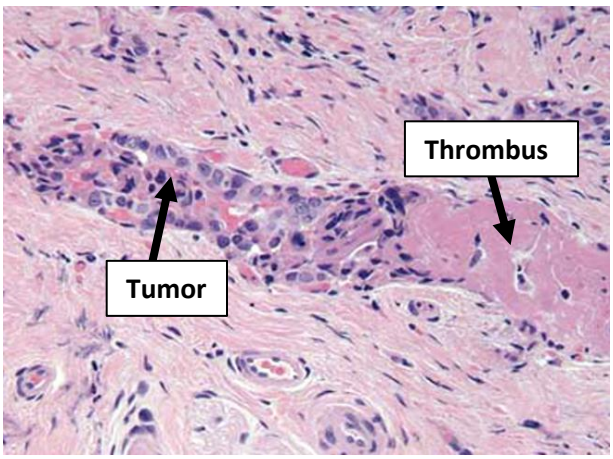


Risk factors: insufficient iodine, ionizing radiation
Often present with painless mass.

Requires either capsular or vascular invasion!
Otherwise, cytology and architecture is identical to follicular adenoma. No High-grade features.

Often surrounded by thick fibrous capsule.
Most require that tumor **penetrate the entire capsule**→
Classically has a "mushroom" appearance.

For vascular invasion, **tumor cells should be adherent to the vessel wall** either with covering endothelium or in a thrombus with fibrin (this is to distinguish from artifactual tumor "misplacement"). Controversial (see next page)
Invasion must occur in the capsule or beyond.



Subclassified into 3 groups:
1) **Minimally invasive** → capsular invasion only → excellent prognosis
2) **Encapsulated angioinvasive**→ risk of hematogenous metastasis (often bone/lung)
3) **Widely invasive** → extensive involvement of thyroid and soft tissues, often with prominent vascular invasion

Molecular (same for adenoma): **RAS point mutations and PAX8-PPARG gene fusions** most common.

Associated with Cowden syndrome, DICER1 syndrome, and Caney complex

IHC: (+)TTF-1, PAX8, Thyroglobulin, CK7,

(More on next page)

Is that "good enough" for capsular invasion?

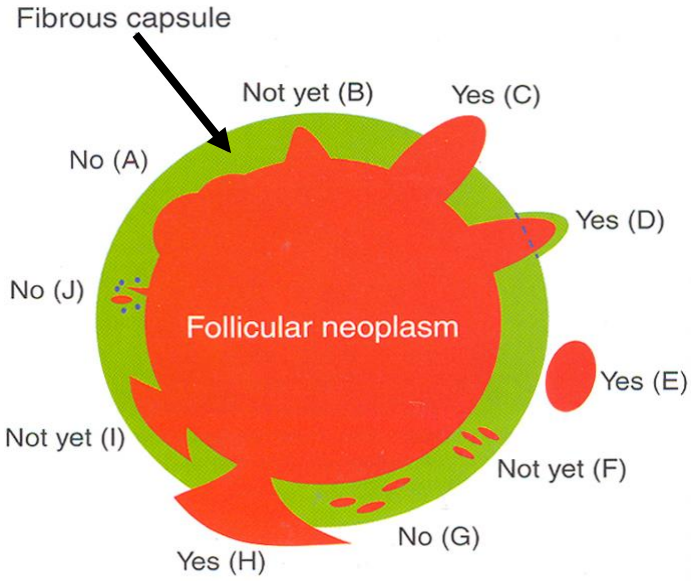
Most require complete ***transgression*** of the capsule (labeled "Yes"→)

Some pathologists are more lenient, and may accept those labeled "Not yet"

When in doubt, get multiple deeper histologic levels.

Remember, a prior FNA may disrupt the capsule.

Also, as the tumor grows and extends into the parenchyma, it can induce a ***new*** stromal reaction forming a *secondary* fibrous band (example D). So, instead of just the fibrous capsule itself, look at the gland ***contour***. If the invasive tongue of tumor extends outside of the usual contour (even if there is a thin capsule), many would consider this invasive.



From the CAP Protocol for the Examination of Specimens From Patients With Carcinomas of the Thyroid Gland

Is that "good enough" for vascular invasion?

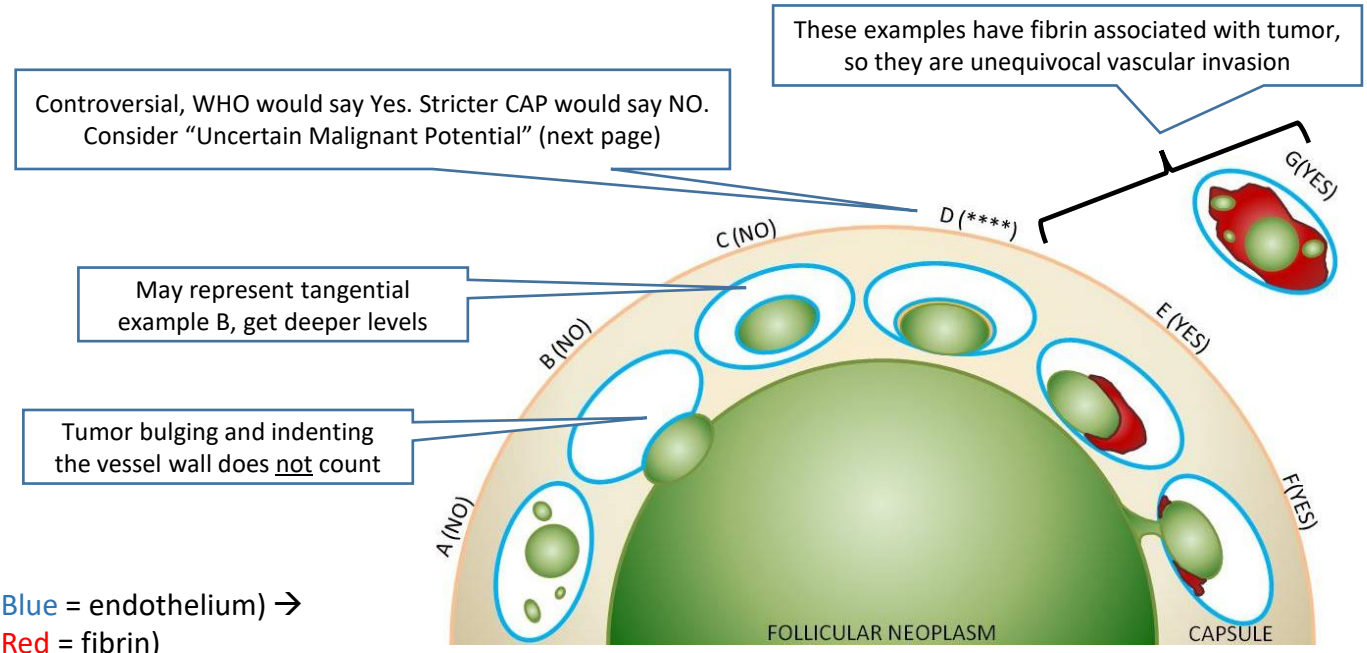
PTC→ usually spreads via lymphatics (no RBCs, stain with D2-40) to lymph nodes.
Follicular Carcinoma→ spreads via veins (luminal RBCs, stain with CD31) hematogenously to lungs/bones

Vascular invasion must be <u>outside of the tumor</u>—<u>either in the capsule or beyond</u>.

According to the WHO, tumor cells should be adherent to the vessel wall either with covering endothelium or in a thrombus with fibrin.

However, newer data suggests tumor cells within vascular lumina unassociated with thrombus and <u>tumor cells underlying intact endothelium could represent "pseudoinvasion</u>" given the fenestrated endothelial network of endocrine organs.

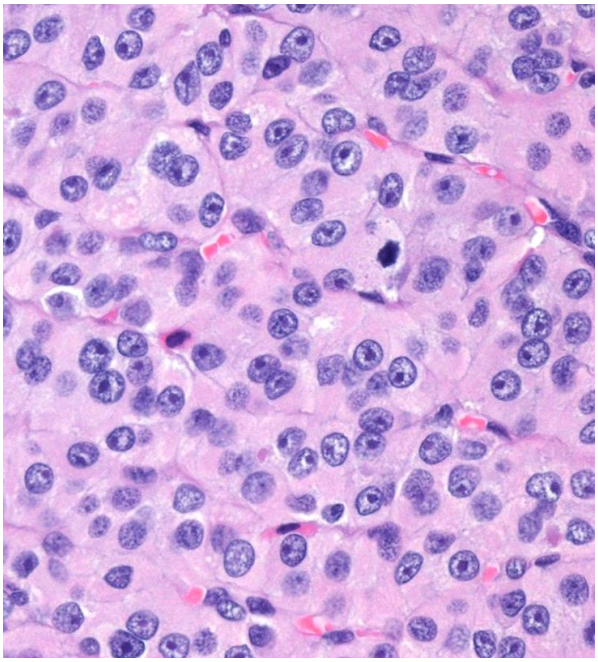
Stricter CAP unequivocal definition: **<u>invasion of tumor through a vessel wall accompanied by fibrin thrombus</u>**→ correlates more closely with aggressive disease.



(Blue = endothelium) →
(Red = fibrin)

From the CAP Protocol for the Examination of Specimens From Patients With Carcinomas of the Thyroid Gland

Oncocytic Tumors



Follicular-cell-derived neoplasms composed of >75% oncocytic (Hürthle) cells <u>with abundant eosinophilic granular cytoplasm</u>.
Large central round nucleus with prominent nucleolus.

<u>Oncocytic adenoma</u>→ follicular adenoma composed of Oncocytic cells. Encapsulated. Benign.

<u>Oncocytic carcinoma</u>→ contains vascular and/or capsular invasion (essentially a follicular carcinoma with oncocytes)

If less than 75%, could say "Oncocytic features"

Variable architecture: follicular, trabecular, or solid

Larger tumors are more likely to be malignant.

<u>Genetics</u>: **alterations in the mitochondrial genome** (mtDNA complex I subunit genes) → accumulate mitochondria → causes eosinophilic cytoplasm.

Tumors of *"Uncertain Malignant Potential"*

Some encapsulated neoplasms with a follicular architecture can have questionable capsular/vascular invasion or nuclear changes that are mild, where it is unclear if they are sufficient to justify a diagnosis of carcinoma→ In such diagnostically uncertain cases, one can use the diagnosis of "*<u>Uncertain Malignant Potential</u>*" (UMP) [However, still pretty good prognosis, luckily, with only rare metastases!]

For example: Tumor cells invade into, but not completely across the capsule, or, Tumor cells are in a blood vessel, but are not covered by endothelium or thrombus.

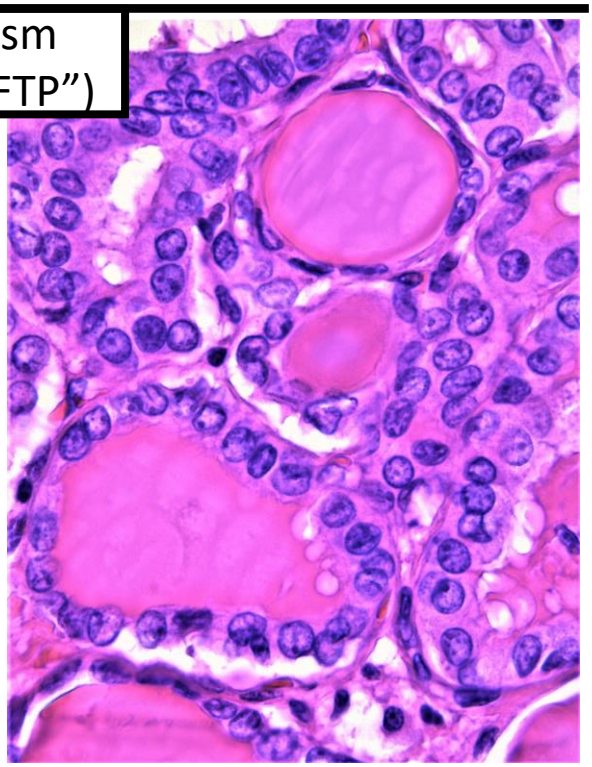
<u>Follicular Tumor of Uncertain Malignant Potential</u>→ encapsulated or well-circumscribed follicular-patterned tumor lacking nuclear features of PTC <u>with equivocal vascular or capsular invasion</u> (and no PTC-like nuclear features). Essentially between follicular adenoma and carcinoma.

<u>Well-differentiated Tumor of Uncertain Malignant Potential</u> → Encapsulated or well-circumscribed follicular-patterned tumor <u>well-developed or partially developed PTC-type nuclear changes and with questionable capsular or vascular invasion.</u> If invasion is totally excluded→ NIFTP (next page)

		Capsular or Vascular Invasion		
Nuclear features of PTC		**Present**	**Questionable**	**Absent**
	Present	Invasive Encapsulated Follicular Variant of PTC	Well-differentiated Tumor of Uncertain Malignant Potential	Non-invasive Follicular Thyroid Neoplasm with Papillary-like nuclear features (NIFTP)
	Questionable	Well-Differentiated Carcinoma, NOS		
	Absent	Follicular Thyroid Carcinoma	Follicular Tumor of Uncertain Malignant Potential	Follicular Adenoma

Modified from: WHO Classification of Tumors of the Endocrine Organs. 2017.

Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features ("NIFTP")



Diagnostic Requirements:

1) Encapsulated or Clear demarcation
2) Follicular pattern of growth with:
   - <1% true papillae
   - No psammoma bodies
   - <30% solid, trabecular, or insular growth pattern
3) Nuclear features of papillary carcinoma (nuclear score 2-3)
4) No lymphovascular or capsular invasion
5) No tumor necrosis
6) No significant mitotic activity (<3 mitoses/10 HPF or 2mm^2)
7) Lack of cytoarchitectural features of papillary carcinoma variants other than follicular variant (tall cell features, etc).

(BRAF p.V600E mutation detected by immunostaining or genotyping essentially excludes the diagnosis.)

Score nuclear features using table below. If present +1, if absent = 0. Need a score of 2-3 to qualify. May be patchy/focal.

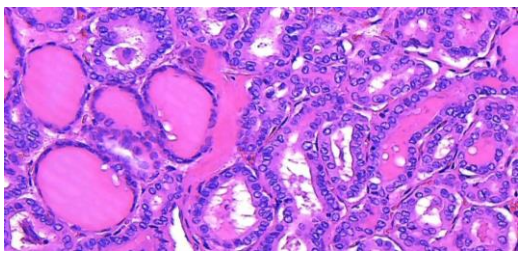
However, nuclear features of PTC are usually only partially developed in NIFTP. So, if they are *very* well-developed, reconsider the diagnosis and consider testing for BRAF mutations (present in PTC, not in NIFTP)

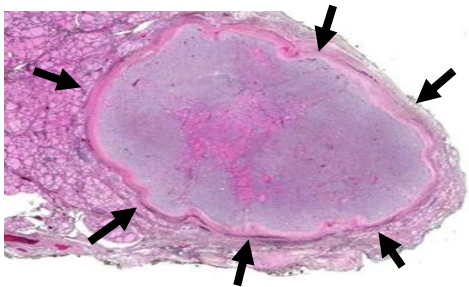
The entire tumor (or at least the entire capsule) should be submitted for histologic evaluation

Molecular: **<u>RAS mutations</u>** (like follicular adenomas/carcinomas). BRAF mutations (like in PTC) are notably absent, which can be useful diagnostically with challenging cases.

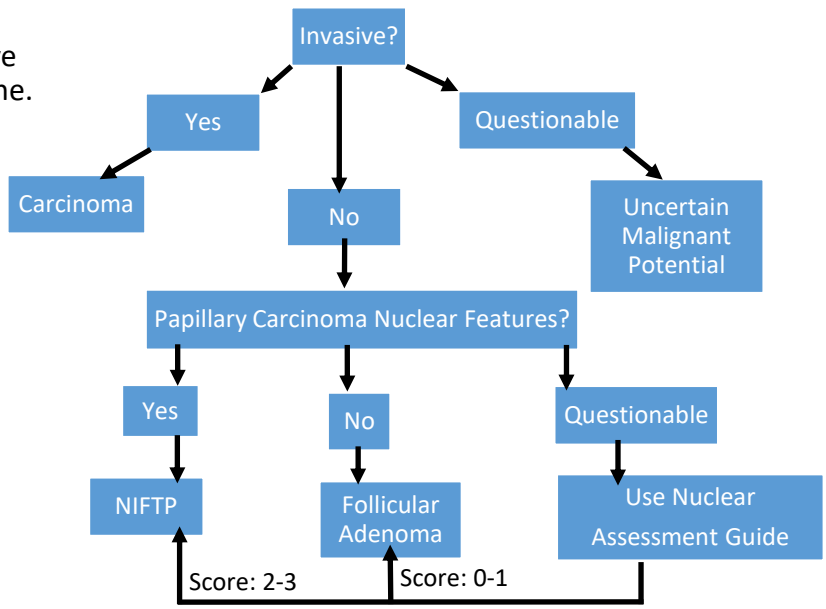
Prognosis: **<u>Very low risk</u>** (<1%) of progressive disease. Can be treated with lobectomy alone.

Nuclear Alteration	Findings
Size and Shape	Nuclear enlargement, overlapping, crowding, elongation
Nuclear membrane irregularities	Irregular contours, grooves, pseudoinclusions
Chromatin characteristics	Clearing with margination, glassy nuclei





Encapsulated Follicular Tumor Algorithm



Modified from: WHO Classification of Tumors of the Endocrine Organs. 2017.

High-grade follicular cell-derived non-anaplastic thyroid carcinoma

A **carcinoma of thyroid follicular cells** (papillary, follicular, or oncocytic carcinoma) **with high grade features as defined by *mitotic count* and *tumor necrosis*, without anaplastic histology**.

Essentially, the stepwise progression beyond PTC and FTC, but before Anaplastic carcinoma.
Similar "early" driver mutations to well-differentiated precursor (e.g., BRAF, RAS).
Additional "late" changes like TP53 and TERT promoter mutations

Retention of some (but not all) morphologic and immunohistochemical biomarkers of thyroid follicular epithelial cells.

Two types of tumors fall into this category:

Differentiated high grade thyroid carcinoma (DHGTC)

1) Retention of distinctive architectural and/or cytologic features of well-differentiated histotypes of carcinoma of follicular cells (e.g. papillary, follicular, or oncocytic);

2) Presence of ≥ 5 mitoses per 2 mm^2 and/or tumor necrosis, with invasion;

Necrosis is defined by karyorrhectic nuclear debris or ghost contours of dead tumor cells.
Must rule out post-FNA changes.
Can be obvious comedo-like or focal.

Most are high grade papillary thyroid carcinomas often belonging to aggressive subtypes such as tall cell, hobnail, or columnar cell.

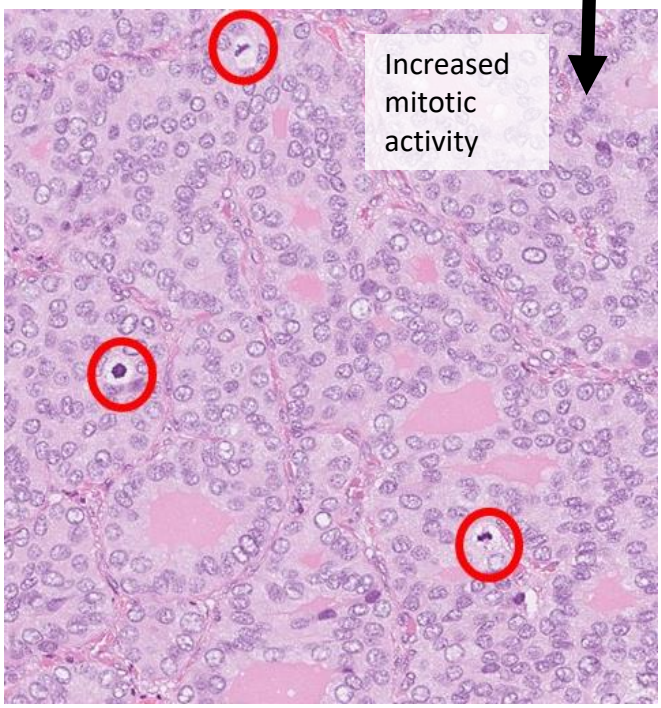
Poorly differentiated thyroid carcinoma (PDTC) *(More on next page)*

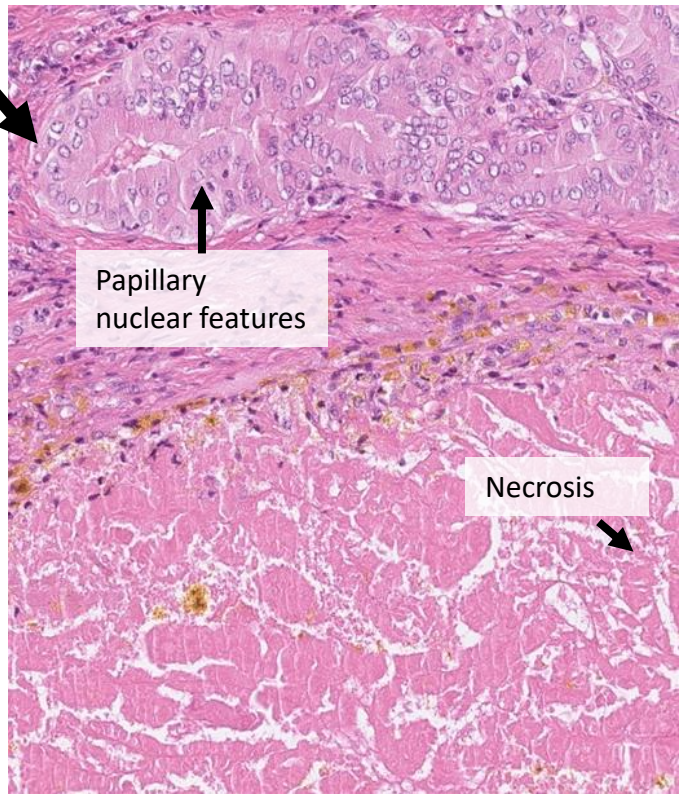
Lost *architectural and cytologic differentiation in the absence of anaplastic histology*

1) Solid/trabecular/insular pattern of growth in a tumor diagnosed as malignant based on the presence of invasion;

2) Absence of conventional papillary carcinoma nuclear alterations;

3) At least one of the following features: convoluted nuclei, mitotic count ≥ 3 per 2 mm^2, tumor necrosis;





Poorly-Differentiated Thyroid Carcinoma

Older name: Insular carcinoma

Subtype of "High-grade follicular cell-derived non-anaplastic thyroid carcinoma" (see prior page)

Turin Criteria:

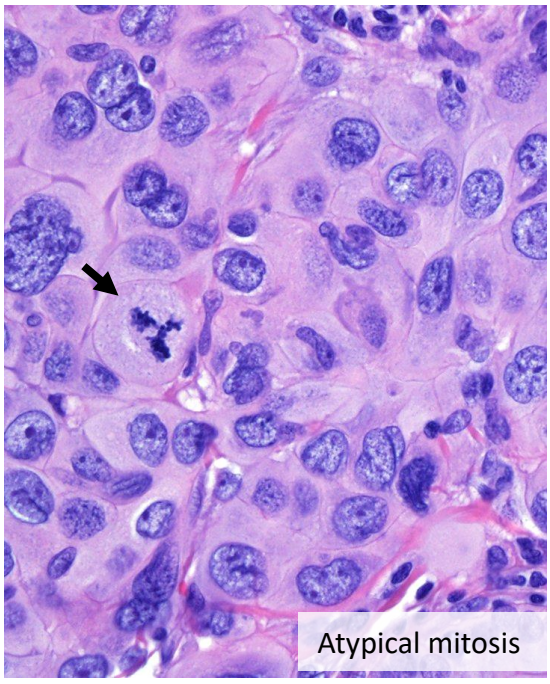
1) Carcinoma of follicular cell origin
2) **Solid, trabecular, or insular growth pattern**
3) Absence of conventional nuclear features of papillary thyroid carcinoma
4) **At least of <u>one</u> of the following:**
   - **Convoluted nuclei (dedifferentiated PTC nuclear features)**
   - **≥3 mitoses per 10 high-power fields**
   - **Tumor necrosis**

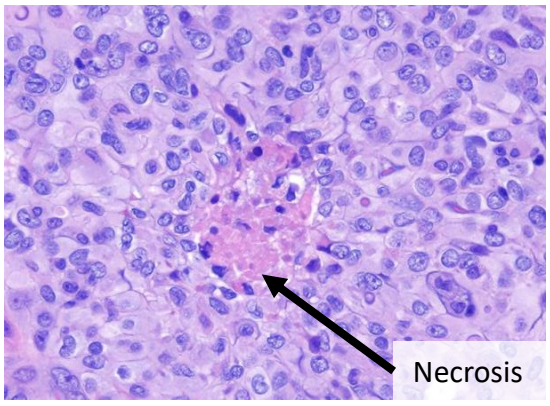
Tumor cells are small and uniform with round hyperchromatic nuclei or convoluted nuclei (raisins-like). Mitoses are common. Extensive tumor necrosis can give a peritheliomatous pattern.

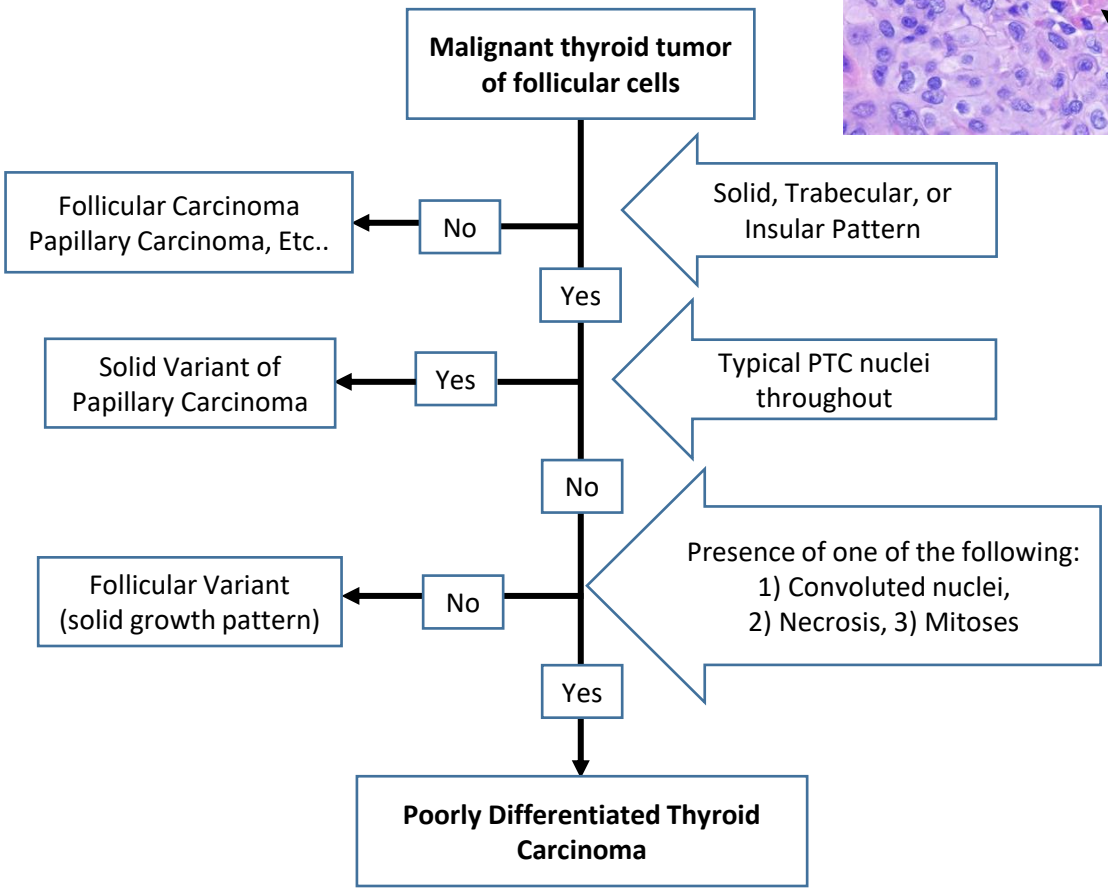
Often widely invasive into soft tissue and vessels

IHC: (+)TTF1, PAX8. often express HMW-CKs
Often reduced thyroglobulin with perinuclear dot-like staining.
Ki67 often 10-30%

Prognosis: **Intermediate prognosis**
(better than anaplastic, but worse than well-differentiated)

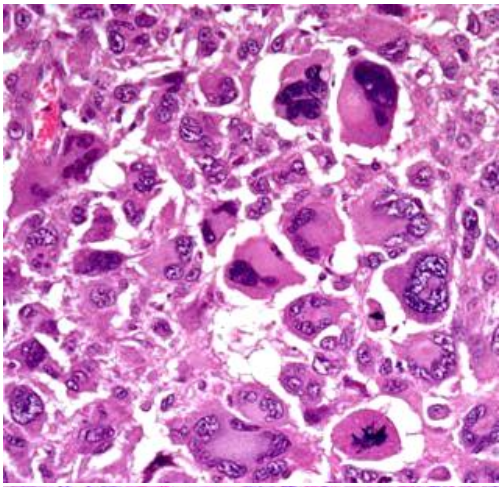


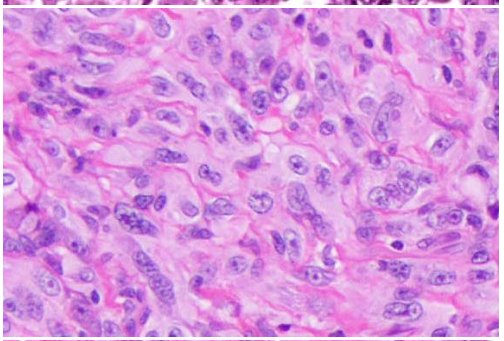


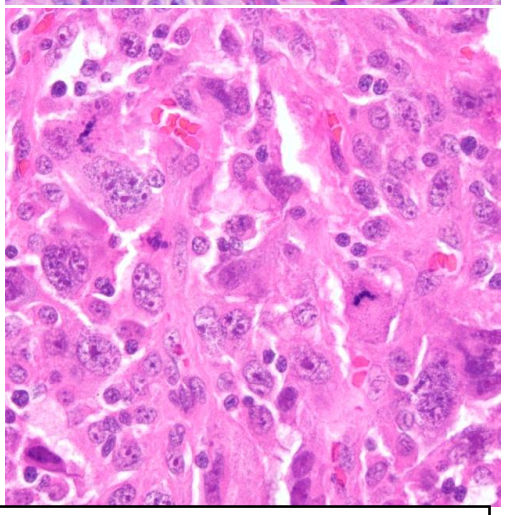


Modified from: WHO Classification of Tumors of the Endocrine Organs. 2017.

Anaplastic Thyroid Carcinoma







Highly aggressive thyroid malignancy composed of undifferentiated follicular epithelial cells.

Classically older women with rapidly growing, firm, large, fixed, highly infiltrative neck mass→ Pain, hoarseness, dysphagia
Can occlude airway! Frequent metastases.

Considered end-point of follicular cell-derived carcinoma progression. Preexisting better differentiated tumor may or may not be identifiable at time of diagnosis.
Accordingly, have both early driver mutations (BRAF or RAS) and late TP53 and TERT promoter mutations

***Undifferentiated tumor*→ to make the Dx you must**
1) Confirm thyroid origin with either focal features of thyroid follicular differentiation (e.g., retained PAX8 expression) and/or a previous differentiated thyroid carcinoma, *and*
2) Exclude other undifferentiated tumors

Common findings: **Necrosis**, **mitoses**, **invasive growth**.
Often inflammatory cells (often neutrophilic).

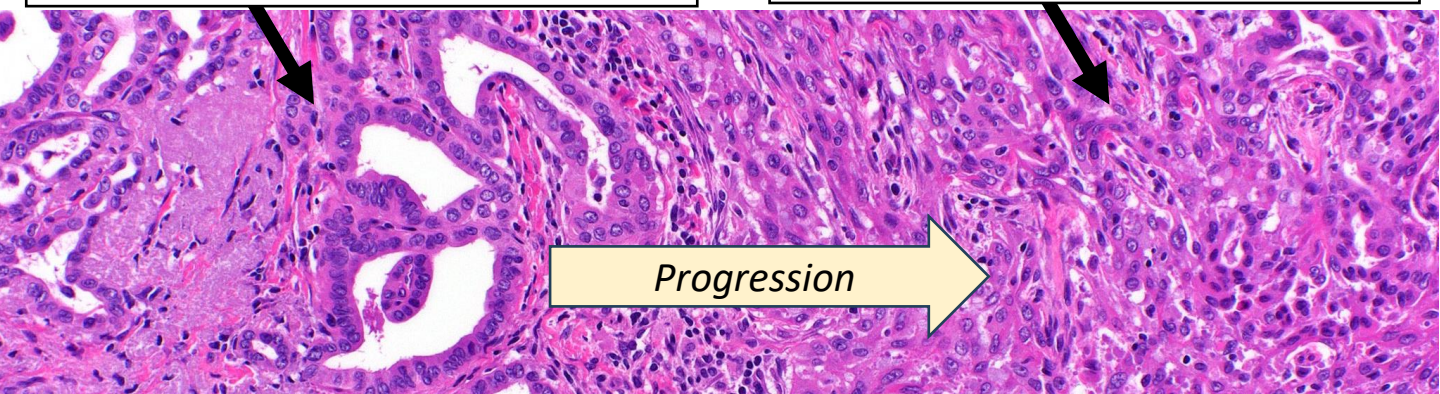
Variable morphology with 3 main patterns:
Sarcomatoid→ spindled cells resembling pleomorphic sarcoma,
Giant cell→ highly pleomorphic cells some of which have multiple nuclei,
Epithelial→ Squamoid nests
(pure SCC of the thyroid is now considered a subtype of anaplastic carcinoma as it has a similar outcome)

IHC: PAX8 often maintained. Frequent loss of TTF1, CK
Thyroglobulin almost always negative.

Prognosis: **Very aggressive with often <1 yr survival**

Papillary thyroid carcinoma (follicular variant)
RAS driver mutation
Differentiated morphology
IHC: (+) TTF1, PAX8, CK, Thyroglobulin

Anaplastic thyroid carcinoma
RAS + TP53 + TERT promoter mutations
"Undifferentiated" morphology
IHC: (+) PAX8; (+/-) CK; (-) TTF1, Thyroglobulin



Medullary Thyroid Carcinoma

Malignant tumor of the thyroid with **parafollicular C-cells** differentiation. Uncommon.

Although mostly sporadic, 25% associated with Multiple Endocrine Neoplasia **(MEN) type 2** (germline RET mutations) → frequently multifocal with C-cell hyperplasia.

Often present with painless mass. Frequent LN metastases at presentation with **elevated serum calcitonin**.

Wide morphologic spectrum! Common patterns of growth include: **solid, lobular, trabecular, and/or insular**.

Tumor cells can appear: round, polygonal, plasmacytoid, or spindled. **Nuclei are "Neuroendocrine" (round, speckled "salt and pepper") with occasional pseudoinclusions**. Cytoplasm is eosinophilic to amphophilic and granular.

Although scattered markedly atypical cells may be present ("Endocrine atypia"), generally not too pleomorphic.

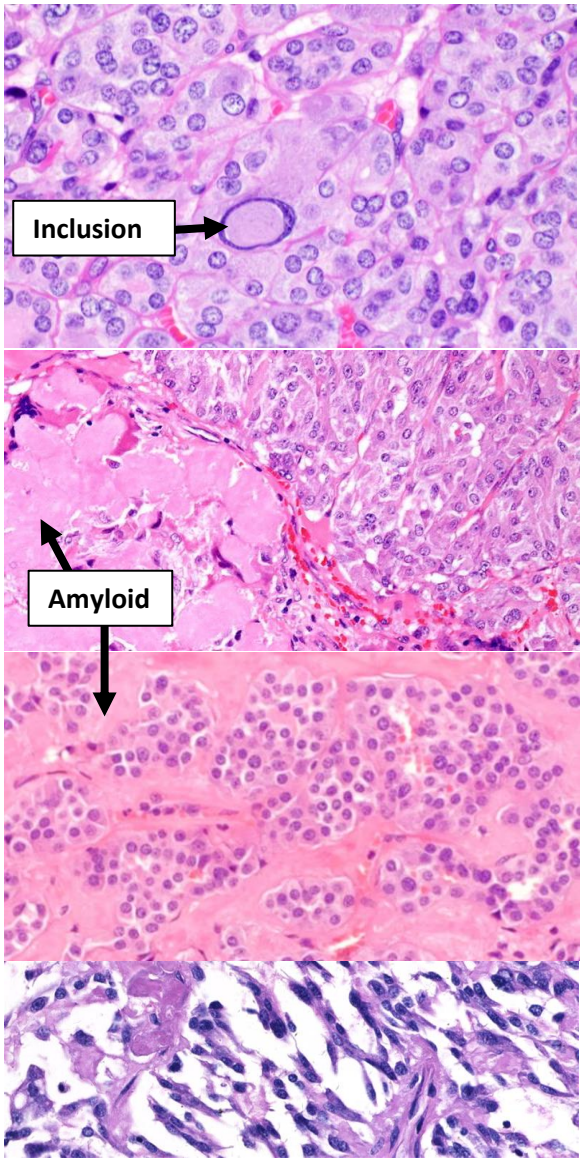
Frequent stromal amyloid.

IHC: **(+) Calcitonin (most specific), Neuroendocrine markers** (synaptophysin, chromogranin), TTF-1. (+/-) PAX8. (-) thyroglobulin.

Molecular: **Frequent RET mutations**. Rarer RAS mutations.

Prognosis: **Intermediate aggressive behavior.**

Rare variant: "Mixed medullary and follicular thyroid carcinoma" coexisting follicular and C cell–derived tumor cell populations within the same lesion.



Hyalinizing Trabecular Tumor

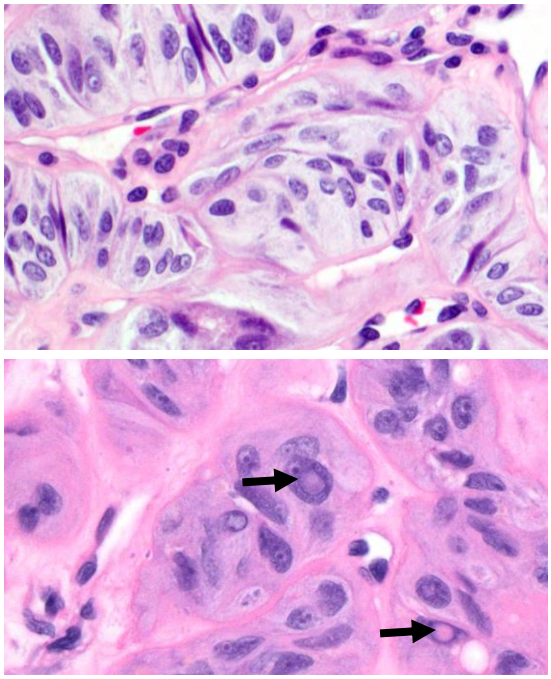
Extremely good prognosis. Follicular-derived neoplasm. Rare.

Well-circumscribed nodule. Wide trabeculae and nests.
Hyalinized basement membrane material (PAS-d positive) envelopes cells into bundles.
Large polygonal/elongated cells. Eosinophilic finely granular cytoplasm. Occasional perinuclear yellow bodies.

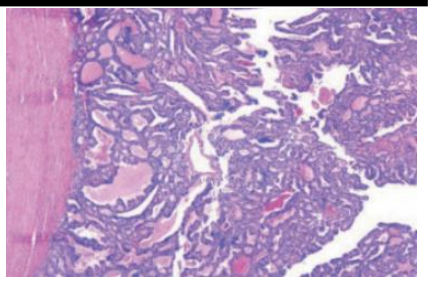
Nuclei are vesicular and mostly round, but with frequent grooves, inclusions (→), and membrane irregularities.
(Can be mistaken for PTC, particularly on FNA!!!)

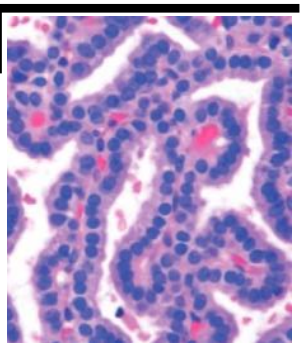
IHC: (+)TTF-1, thyroglobulin; (-) Calcitonin
Unique **membranous staining with MIB1** (Ki67 clone)
Molecular: GLIS fusions

Capsular, vascular, or thyroid parenchymal invasion? → small recurrence/metastasis risk



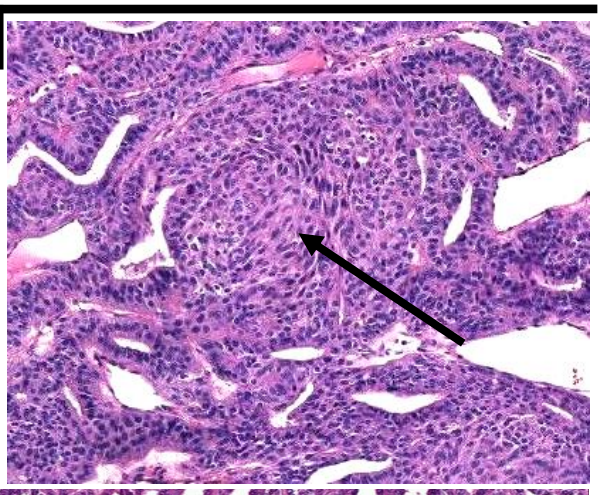
Follicular thyroid adenoma with papillary architecture





Benign.
Non-invasive encapsulated follicular-cell-derived neoplasm that is characterized by an intrafollicular papillary architecture. Also microfollicles.
No nuclear features of papillary thyroid carcinoma.
Often associated with autonomous hyperfunction.
Often young women.
Molecular: Activating TSHR mutations

Cribriform morular thyroid carcinoma



Previously considered "Cribriform-Morular variant" of PTC

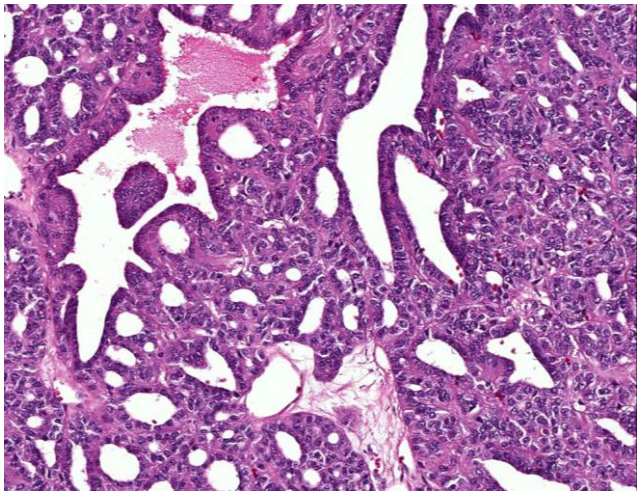
Rare. Almost exclusively in females. Usually young.
Well-circumscribed or locally invasive thyroid neoplasm.

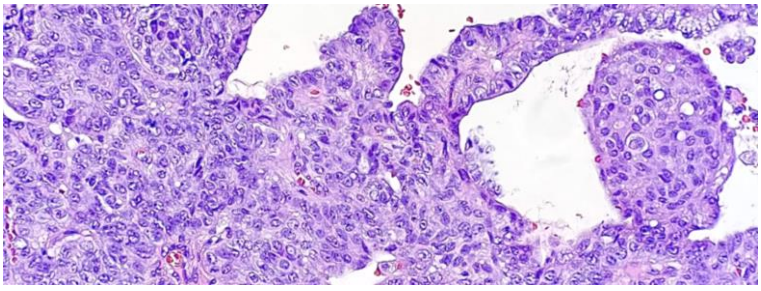
Predominant complex architecture including cribriform and squamoid morulae, with *no* colloid formation.

Constitutive **activation of the WNT/β-catenin pathway** that can occur with familial adenomatous polyposis (FAP, with germline APC mutations) or sporadically.

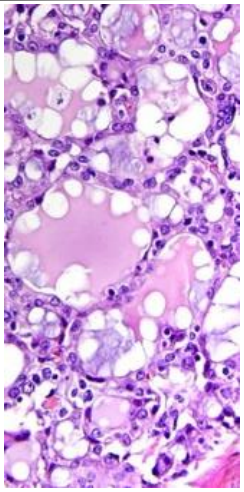
IHC: Diffuse nuclear beta-catenin expression;
(+) TTF1, CK, ER, PR, LEF-1.
(-/+)PAX8; (-)Thyroglobulin
(Morulae: Positive for CD10, CDX2, CD5 and CK5)

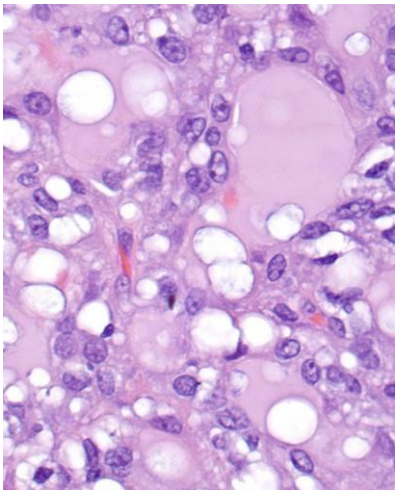
Malignant, but good prognosis usually.





Secretory carcinoma



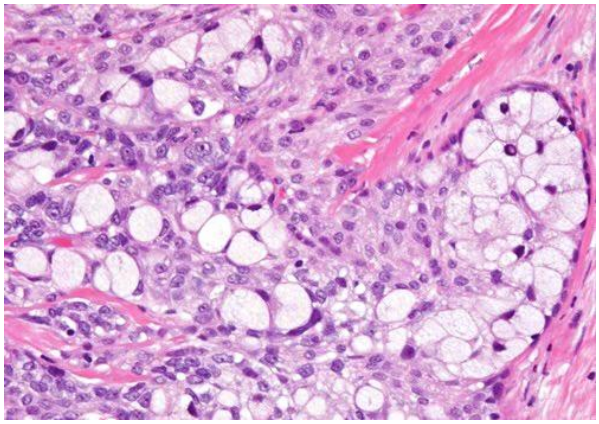


Very rare.
Salivary gland-type tumor of unclear origin in the thyroid.

Microcystic, tubular, and solid structures with abundant eosinophilic homogeneous or **bubbly secretions**.
Eosinophilic vacuolar cells

Molecular: ETV6 gene rearrangements
IHC: (+)S100, Mammaglobin, GATA3
(-) Thyroglobulin, TTF1; (-/+) PAX8.

Mucoepidermoid Carcinoma

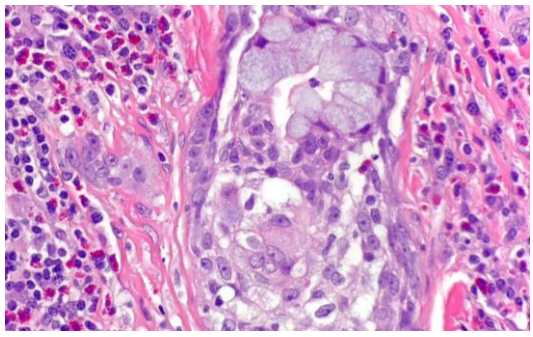


Very rare. Low-grade malignant/indolent. Unclear origin, but favored to represent metaplastic differentiation of follicular derived carcinoma in most cases. Associated with PTC in ~1/2 of cases

Required cell types: **1) Squamoid cells ,**
2) Mucin-producing goblet cells, and Intermediate cells

IHC: Can express PAX8, TTF-1, thyroglobulin
Molecular: Occasional MAML2 rearrangements.

Sclerosing Mucoepidermoid Carcinoma with Eosinophilia



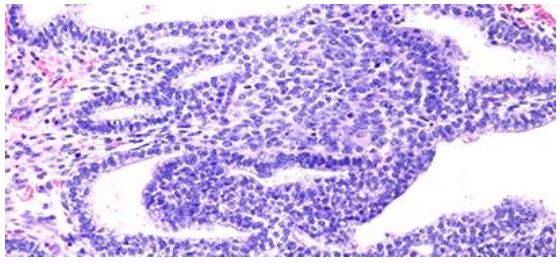
Rare. Strong female predominance.

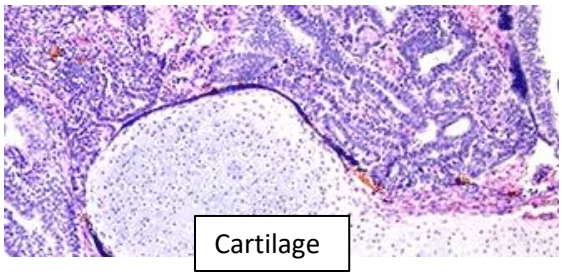
Primary thyroid carcinoma showing **epidermoid/squamoid and mucous cells in a background of stromal sclerosis with a rich inflammatory infiltrate containing eosinophils**.

Consistently associated with fibrosing Hashimoto's thyroiditis.

IHC: (+/-)TTF1, (-/+) Thyroglobulin, PAX8

Thyroblastoma



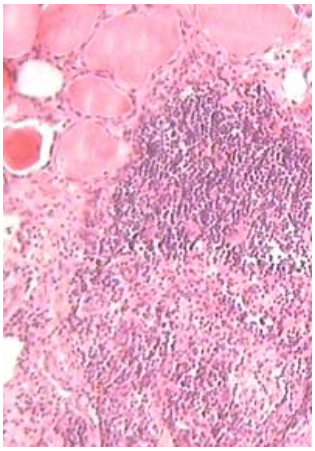


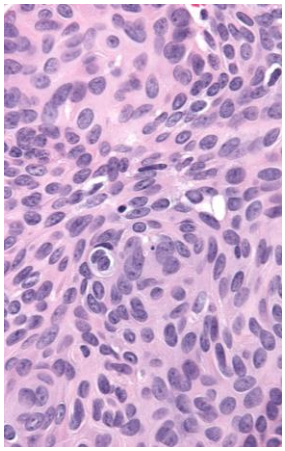
Embryonal high-grade thyroid tumor. **Very Aggressive!**
Usually middle-aged women with rapidly growing mass.

Primitive thyroid epithelium, small cell blastemal component, and mesenchymal stroma with or without rhabdomyoblasts and cartilage.
Absence of conventional thyroid carcinoma component, conventional germ cell component, expression of specific germ cell markers.

IHC: (+) TTF1, PAX8, Thyroglobulin within primitive follicles
Stroma often + Desmin and/or myogenin
Molecular: somatic **DICER1** mutations

Ectopic Thymoma



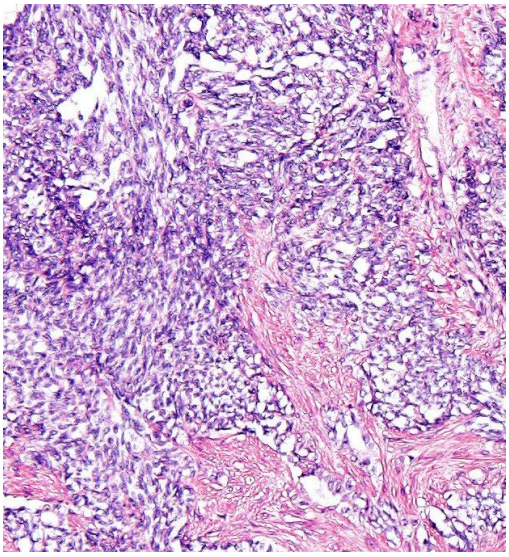


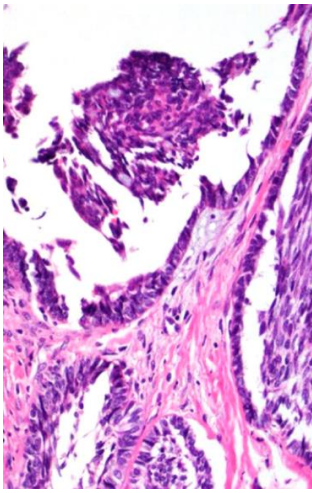
Very Rare. **<u>Typical mediastinal thymoma histology</u>**, but located ectopically within the thyroid gland.
Arises from ectopic thymus tissue.

Jigsaw puzzle-like lobules separated by sclerotic septae.
Intimate admixture of ovoid to spindled epithelial cells with a variable amount of small lymphocytes.

IHC: Epithelium—cytokeratins, p63, PAX8
Lymphocytes—immature T cells (TdT+, CD1a, CD99)

Spindle Epithelial Tumor with Thymus-like elements ("SETTLE")





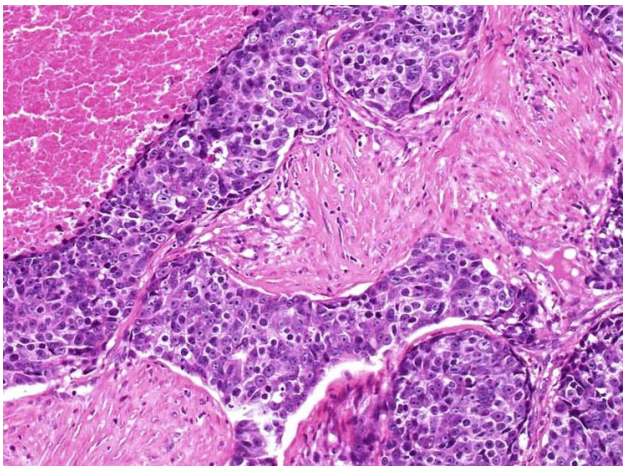
Rare. Malignant. Intermediate behavior.
Young.

Highly cellular.
Lobulated architecture. Fibrous septae.
Spindled epithelial cells that merge into glandular structures.
May have glomeruloid glands/papillae, reticulated fascicles, or be exclusively spindled.

IHC: Both cell types stain with HMWCK and CK7. Spindled cells may show myoepithelial staining.

Must exclude synovial sarcoma

Intrathyroidal Thymic Carcinoma



Old name: Carcinoma showing thymus-like differentiation ("CASTLE")

Very Rare. Malignant tumor with thymic epithelial differentiation (malignant counterpart of intrathyroidal thymoma).

Appears identical to thymic carcinoma of mediastinum: **essentially a squamous cell carcinoma with lymphocyte-rich stroma.**

IHC: (+) CD5, p63, CD117, Cytokeratins, PAX8, calretinin (-) TTF-1, Thyroglobulin; Ki67 10-30%

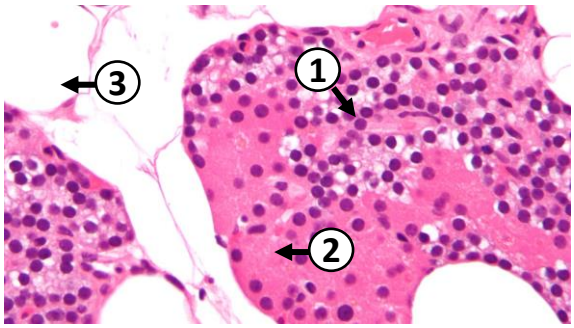
Other Thyroid Tumors

Paraganglioma
Peripheral Nerve Sheath Tumors
Hemangioma
Angiosarcoma
Smooth Muscle Tumors
Solitary Fibrous Tumors
Langerhans Cell Histiocytosis
Rosai-Dorfman Disease
Follicular Dendritic Cell Sarcoma
Diffuse Large B-cell Lymphoma
MALT lymphoma
Teratoma
Metastases

Parathyroid Tumors

IHC: These are **(+) PTH, GATA3, Synaptophysin, Chromogranin**
(-) TTF1, Thyroglobulin, Calcitonin; (+/-) PAX8

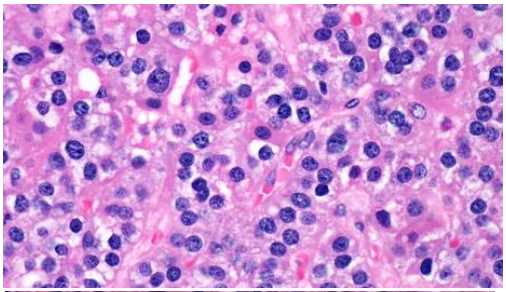
Normal Parathyroid

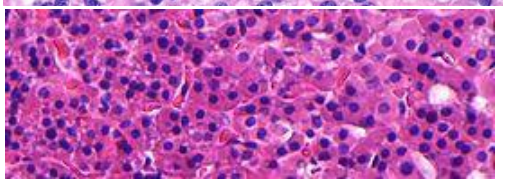


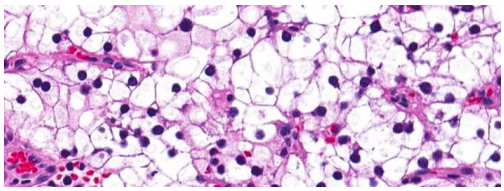
Regulates calcium levels with parathyroid hormone PTH

Three main components:
1- **Chief cells**: main cell type, round central nucleus, clear to amphophilic cytoplasm
2-**Oxyphil cells**: large cells with abundant pink cytoplasm
3-**Fat** (and fibrous tissue) dividing cells into lobules

Parathyroid Adenoma







Benign parathyroid neoplasm. Relatively **common**.

Often present with **primary hyperparathyroidism→ hypercalcemia** (metabolic bone disease, kidney stones, fatigue, etc.)

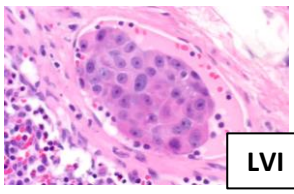
Can arise in any of the 4 glands, or be ectopic.
A minority of cases are associated with MEN1/2A

Well-circumscribed, often encapsulated
Composed of chief cells (most common), oncocytes, or a mixture.
Cells have round, central nuclei with dense chromatin.
Unlike normal parathyroid, there is **typically NO FAT**
Occasional mitoses acceptable. Sometimes follicular architecture.

Many variants: Oncocytic, water-clear cell, lipoadenomas (contain fat and other parenchymal elements)

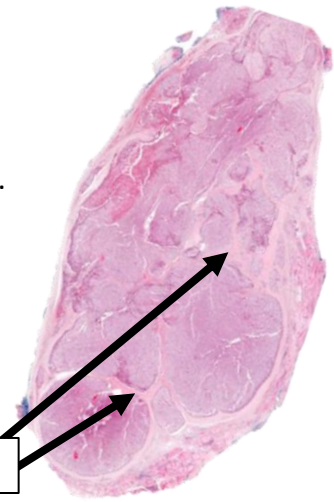
Remember, the surgeon often wants a weight!

Parathyroid Carcinoma



Rare. Malignant neoplasm derived from parathyroid cells.
Usually presents with hyperparathyroidism.

Requires evidence of one of the following:
- **Invasive growth** involving adjacent structures (e.g., thyroid or soft tissue)
- **Invasion of vessels** in capsule or beyond (attached to wall) or PNI
- **Metastases**



Usually subdivided by **broad fibrous bands.** Variable pleomorphism/mitoses.
Ki67 usually >5% (vs <4% in adenomas). Loss of nuclear parafibromin expression.

"Atypical Parathyroid Tumor"
Adenomas that exhibit *some* features of parathyroid carcinoma but lack unequivocal invasive growth→ essentially "Uncertain Malignant Potential."
Frequent findings: bands of fibrosis, adherence to other structures, tumor in capsule, solid/trabecular growth, nuclear atypia, increased mitotes.
Usually benign clinical course with close clinical follow-up.