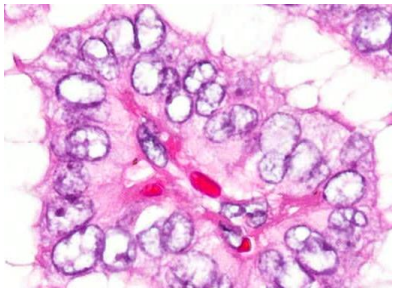
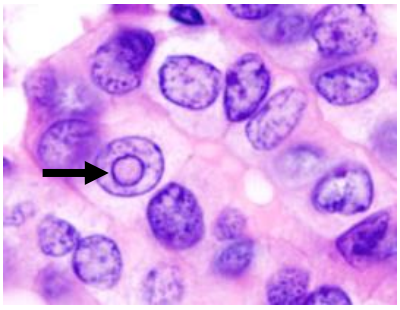
Thyroid & Parathyroid Lesions

Thyroid Tumors

Papillary Thyroid Carcinoma *"PTC"*

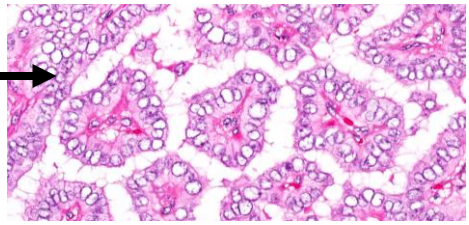
Malignant tumor with follicular epithelial cell differentiation and **distinct nuclear features**.
Most common form of thyroid cancer in both adults and children. More common in women.
Risk factor: Ionizing radiation. Often **relatively indolent** cancer.
Often presents with a painless thyroid mass.





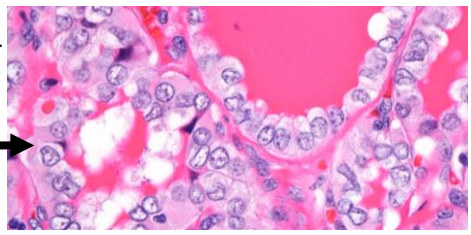
Nuclear Features: *(Definitional)*
- Nuclear **enlargement** and elongation
- Nuclear **overlapping**
- **Irregular nuclear contours**
- Intranuclear **pseudoinclusions (→)**
- Longitudinal nuclear **grooves**
- Nuclear **chromatin clearing**

Conventional (classic) PTC: Papillary architecture (hence the name!). May have mixed in other architectures like follicles. Frequent psammoma bodies. Occasional squamous metaplasia. Often cystic degeneration. Densely eosinophilic colloid.



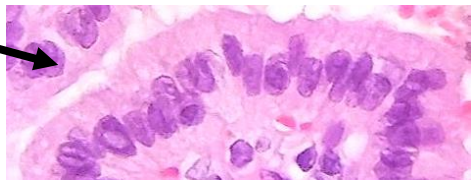
Papillary microcarcinoma: Tumor variant ≤ 1 cm. Often missed grossly/incidental. Malignant, but excellent prognosis.

Encapsulated variant: Totally surrounded by a fibrous capsule (intact or focally infiltrated). Excellent prognosis.

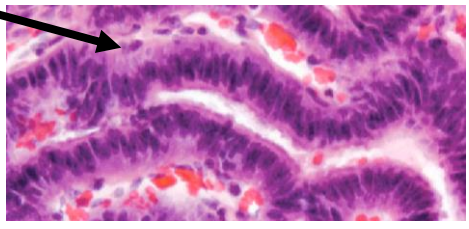


Follicular variant: Exclusively (or almost exclusively) follicular architecture. Can be infiltrative or encapsulated with invasion.

Tall Cell variant: Cells 2-3x as tall as they are wide with abundant eosinophilic cytoplasm. Must account for ≥30% of tumor. More aggressive behavior.

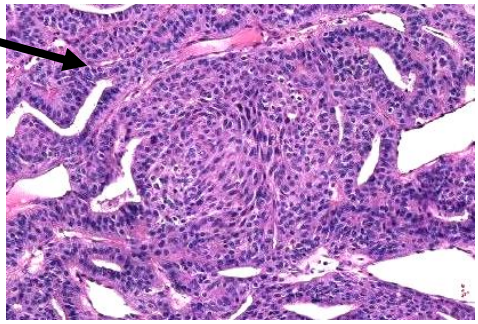


Columnar cell variant: Rare. Columnar cells with prominent pseudostratification. Lack conventional nuclear features. Resembles endometrioid/intestinal adenocarcinoma morphologically. IHC: CDX2+!



Diffuse sclerosing variant: Rare. Diffuse involvement with sclerosis and solid nests of tumor cells. Also background lymphocytic inflammation and psammoma bodies.

Cribriform-morular variant: Mixture of cribriform, follicular, papillary, trabecular, and solid growth with round squamoid structures (morules). Frequent vascular invasion. Almost exclusively in females. Association with FAP→ nuclear β-catenin. IHC: LEF-1 positive.

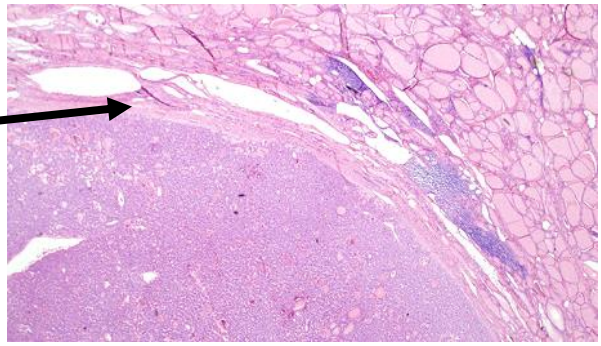


Other variants: Hobnail, solid/trabecular, oncocytic, spindle cell, clear cell, Warthin-like, and PTC with fibromatosis/fasciitis-like stroma

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

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

Follicular Adenoma

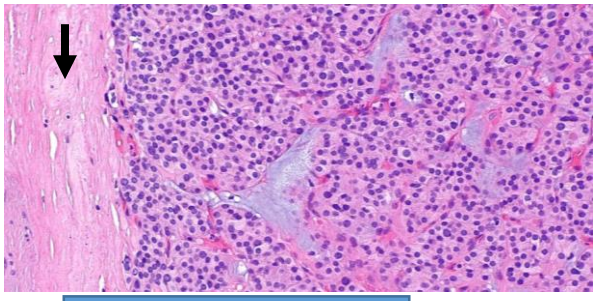


Benign neoplasm with thyroid epithelial differentiation

***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**.



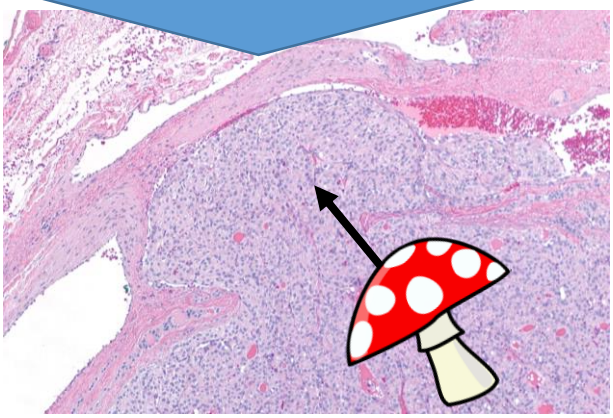
ABSENT: capsular/vascular invasion, PTC-like nuclei
(Must submit entire capsule to exclude invasion)

Molecular: Most frequently **RAS mutations**.
Associated with Cowden syndrome and Carney complex

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

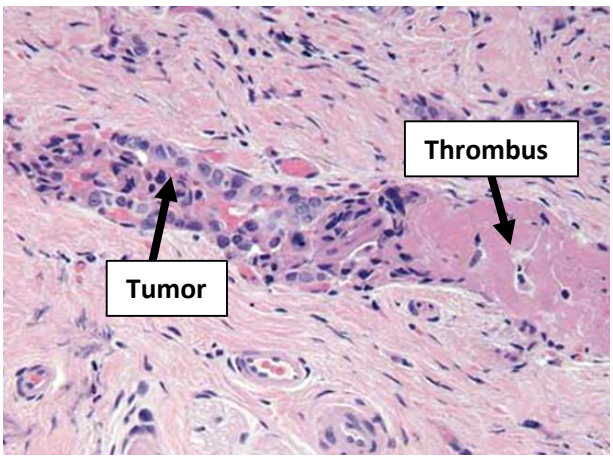


Malignant. Nuclear features of PTC are absent.

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

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: **RAS point mutations and PAX8-PPARγ gene fusions** most common.

Associated with Cowden syndrome

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

(More on next page!)

Is that "good enough" for capsular invasion?

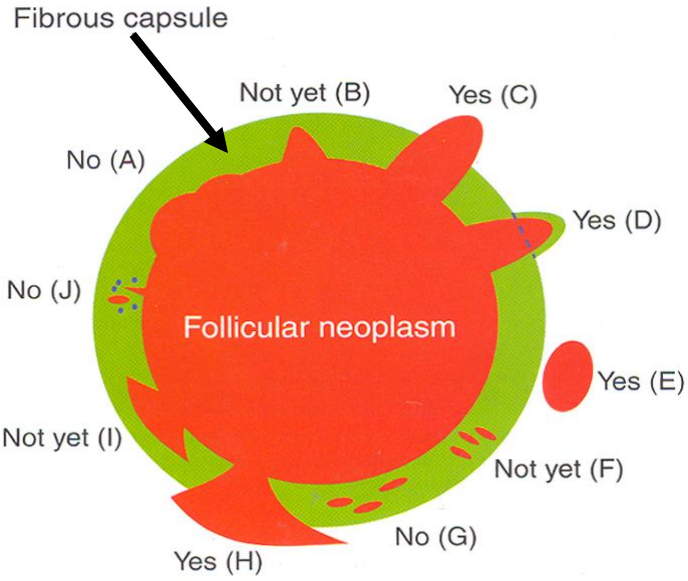
Most require complete ***transgression*** of the capsule (labeled "Yes"→)

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?

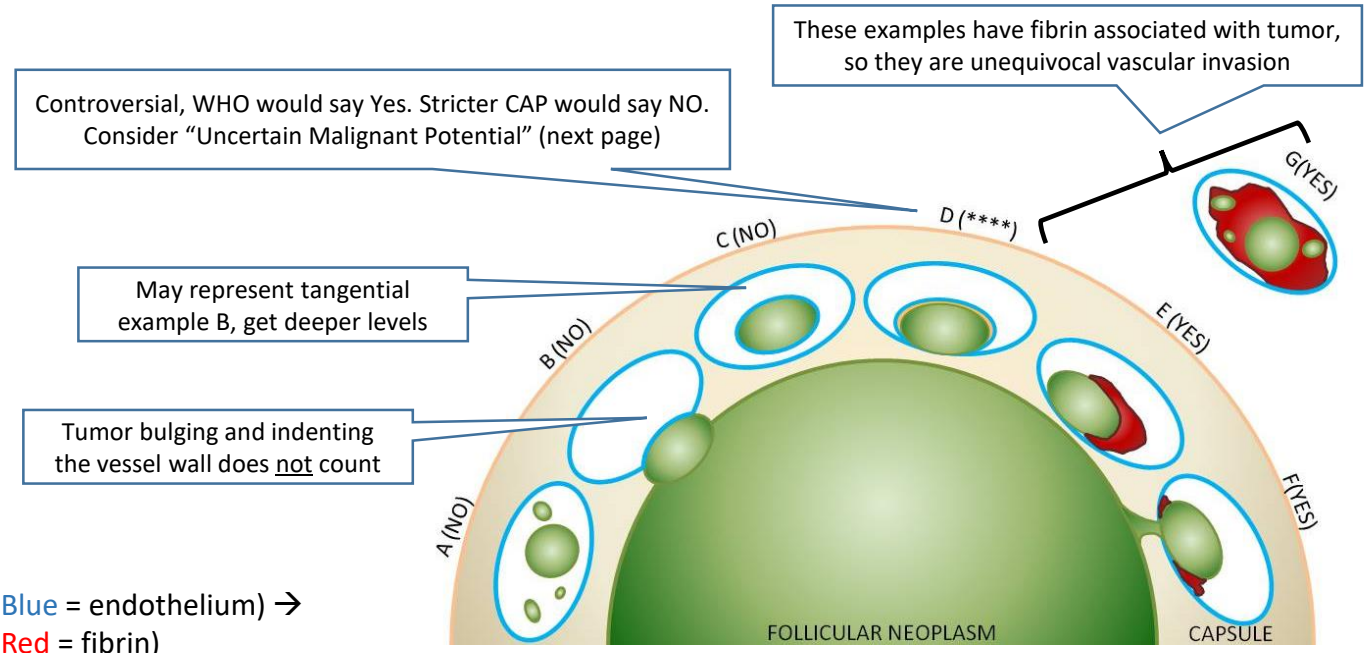
PTC→ usually spreads via lymphatics (no RBCs, stain with D2-40) to lymph nodes.
Follicular Carcinoma→ spreads via veins (luminal RBCs, stain with CD31) hematogenously to lungs/bones

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.

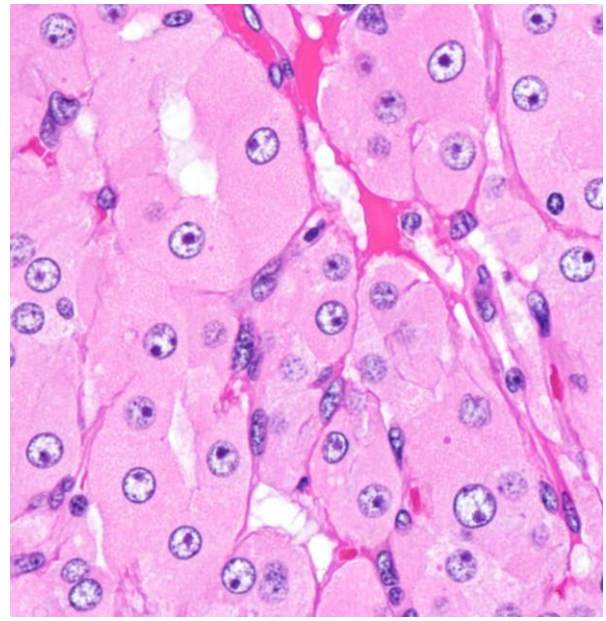
Stricter CAP unequivocal definition: **<u>invasion of tumor through a vessel wall accompanied by fibrin thrombus</u>**→ correlates more closely with aggressive disease.



(Blue = endothelium) →
(Red = fibrin)

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

Hürthle (Oncocytic) Cell Tumors



Neoplasms composed of **oncocytic cells with abundant eosinophilic granular cytoplasm**.

Hürthle cell adenoma→ essentially a follicular adenoma composed of Hürthle cells. Encapsulated. Benign.

Hürthle cell carcinoma→ contains vascular and/or capsular invasion (essentially a follicular carcinoma with Hürthle cells)

Most use term only if "majority" (greater than 75%) of tumor has this morphology (otherwise use term "Hürthle cell features")

Hürthle cells are large with abundant eosinophilic granular cytoplasm and large central nuclei with prominent nucleoli. Full of mitochondria.

Variable architecture: follicular, trabecular, or solid

Larger tumors are more likely to be malignant.

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 papillary thyroid carcinoma→ In such diagnostically uncertain cases, one can use the diagnosis of "*Uncertain Malignant Potential*" (UMP)

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.

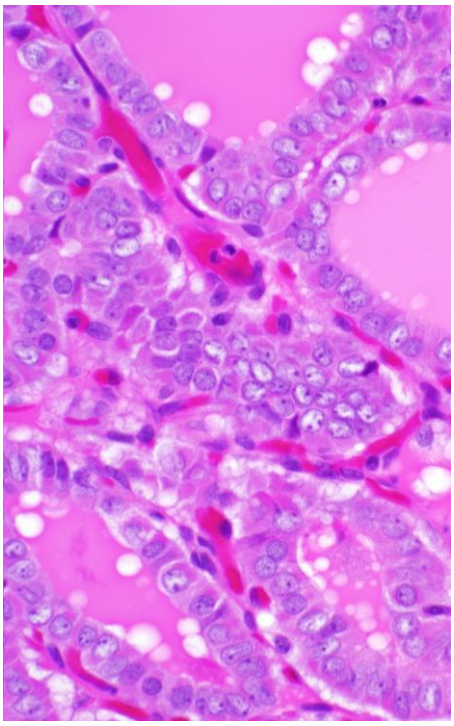
Follicular Tumor of Uncertain Malignant Potential→ encapsulated or well-circumscribed follicular-patterned tumor lacking nuclear features of PTC with equivocal vascular or capsular invasion (and no PTC-like nuclear features). Essentially between follicular adenoma and carcinoma.

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

		Capsular or Vascular Invasion		
		Present	**Questionable**	**Absent**
Nuclear features of PTC	**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 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:
   - No 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)

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)

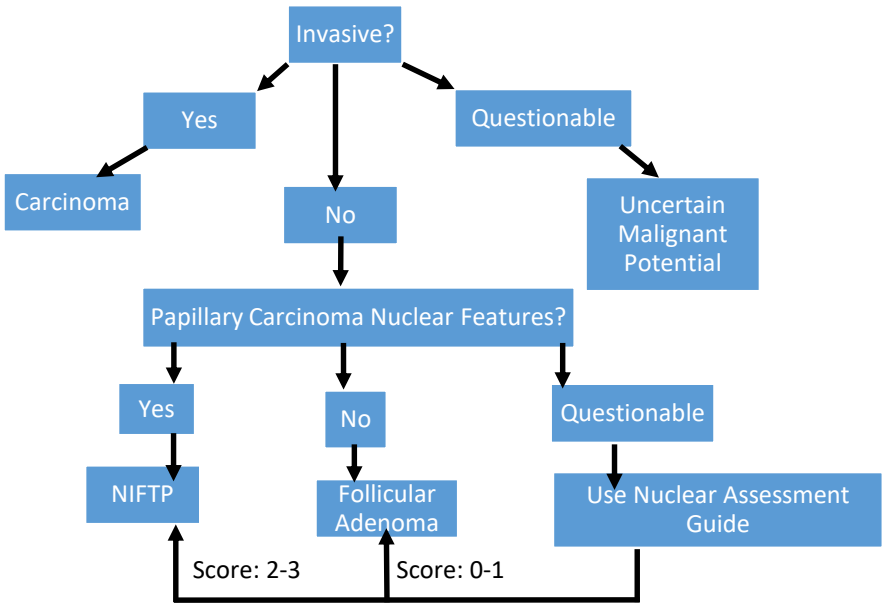
The entire tumor (or at least the entire capsule) should be submitted for histologic evaluation

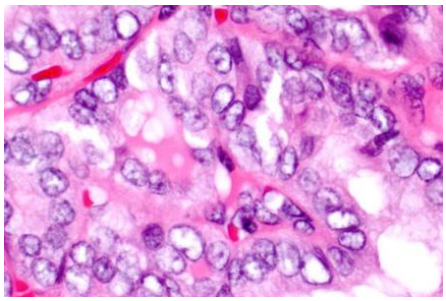
Molecular: **RAS mutations** (like follicular adenomas/carcinomas). BRAF mutations (like in PTC) are notably absent, which can be useful diagnostically with challenging cases.

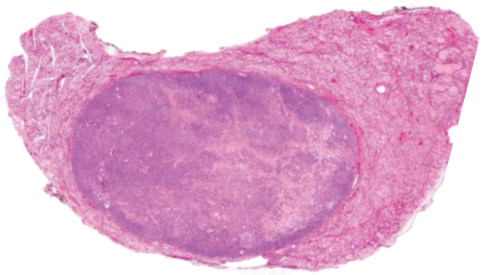
Prognosis: **Very low risk** of progressive disease. Can be treated with lobectomy alone.

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

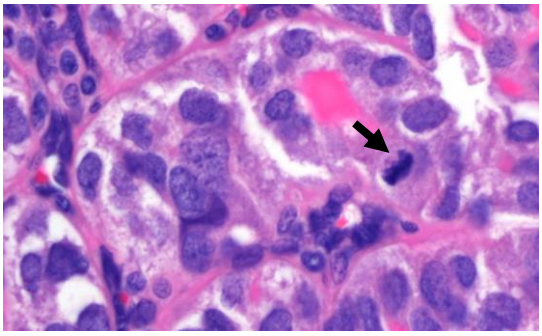


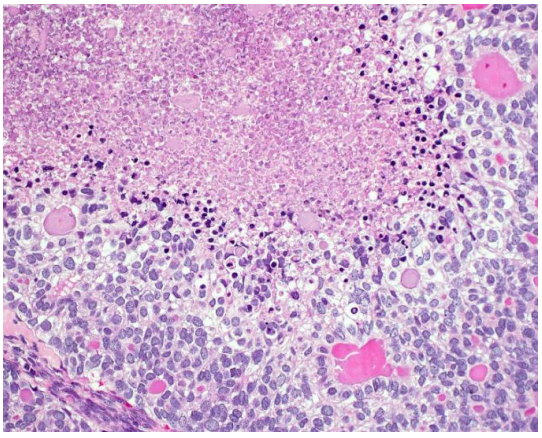


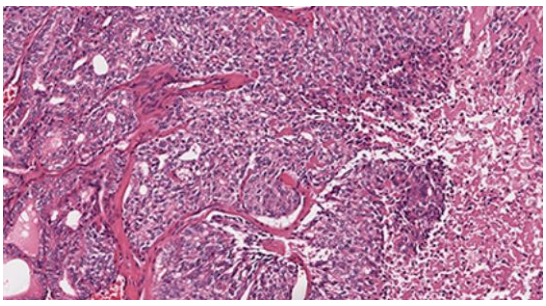


Modified from: WHO Classification of Tumors of the Endocrine Organs. 2017.

Poorly-Differentiated Thyroid Carcinoma







Thyroid carcinoma with **morphology, genetics, and behavior between differentiated carcinomas** (i.e., papillary and follicular) **and anaplastic carcinoma**. Applies to Hürthle cell tumors also.

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**

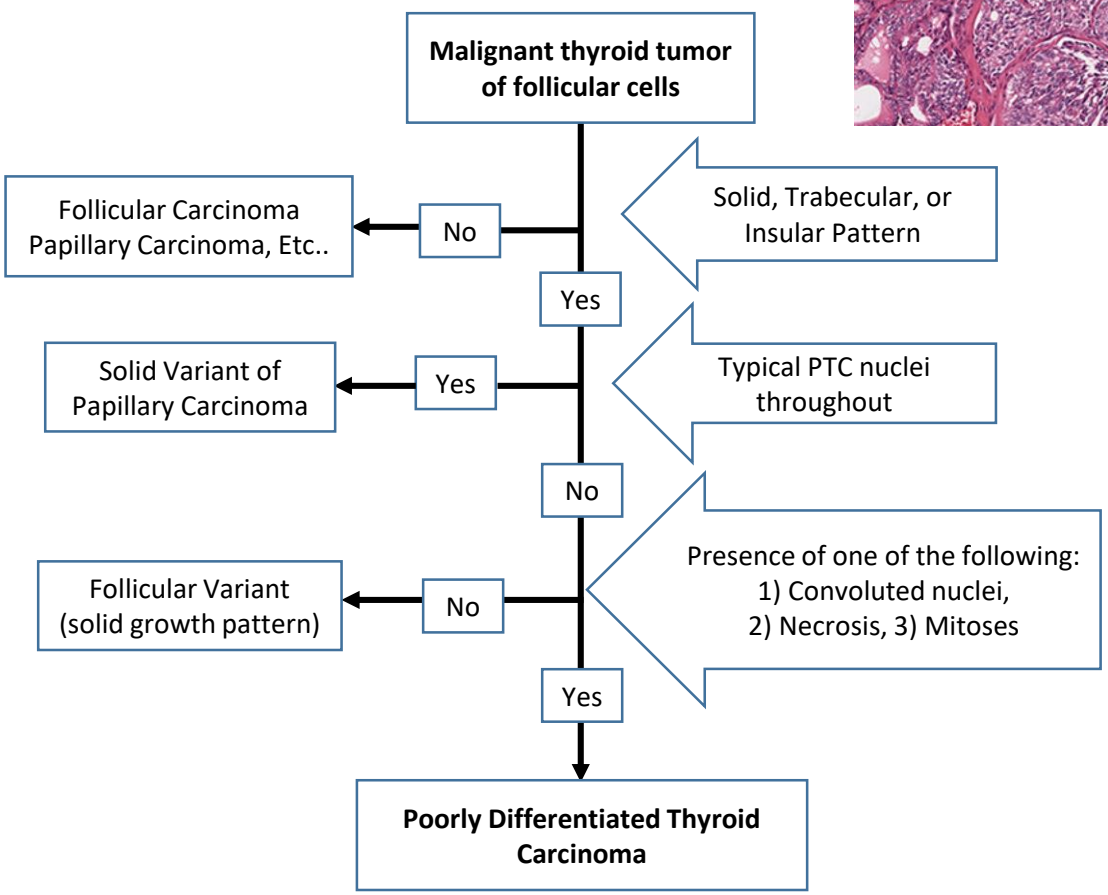
Tumor cells are small and uniform with round hyperchromatic nuclei or convoluted nuclei. Mitoses are common. Extensive tumor necrosis can give a peritheliomatous pattern.

Some arise from via dedifferentiation of PTC or follicular carcinoma (which may be visible in the lesion), while others appear to be de novo.

Often widely invasive into soft tissue and vessels

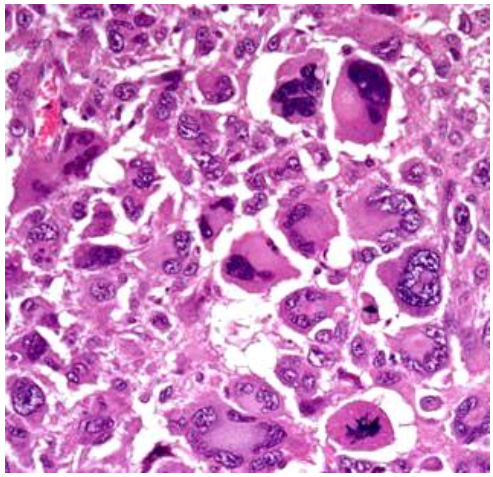
IHC: (+)TTF1, PAX8, Thyroglobulin, often express HMW-CKs

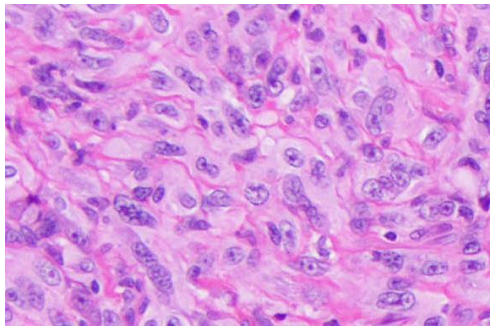
Prognosis: **Intermediate prognosis**



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, fixed, highly infiltrative neck mass → Pain, hoarseness, dysphagia
Can occlude airway!

Many cases seem to arise from dedifferentiation of a pre-existing thyroid tumor (may have history of long-standing nodule)

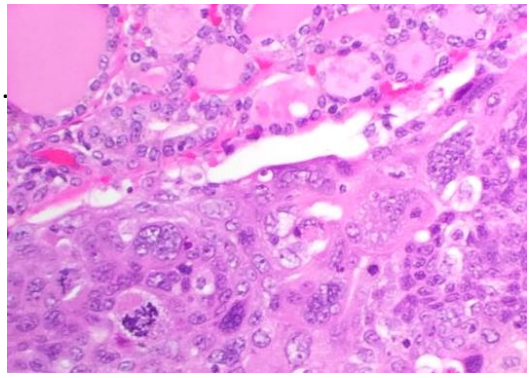
Variable morphology with 3 main patterns:
Sarcomatoid → spindled cells resembling pleomorphic sarcoma,
Giant cell → highly pleomorphic cells some of which have multiple nuclei, ***Epithelial*** → Squamoid nests

Common findings: **Necrosis, mitoses, invasive growth**.
Often inflammatory cells.

IHC: PAX8 often maintained. Frequent loss of TTF1, CK
Molecular: Frequent TP53 mutations. Also, BRAF, RAS, PTEN

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

Squamous Cell Carcinoma



Malignant epithelial tumor with **entirely squamous differentiation**.
Clinical features and prognosis similar to anaplastic carcinoma

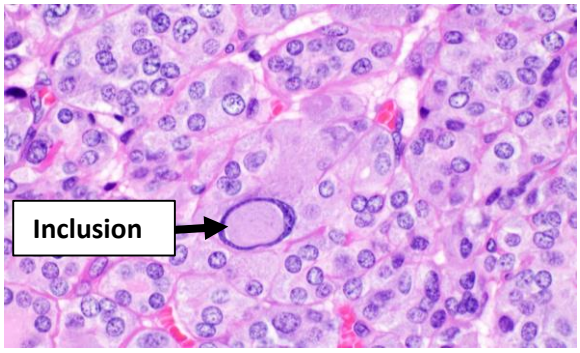
Notably, both PTC and Anaplastic carcinoma can have squamous areas, so the tumor should be sampled well to exclude squamous differentiation of another tumor.
Often extensive infiltration of soft tissue/vessels.

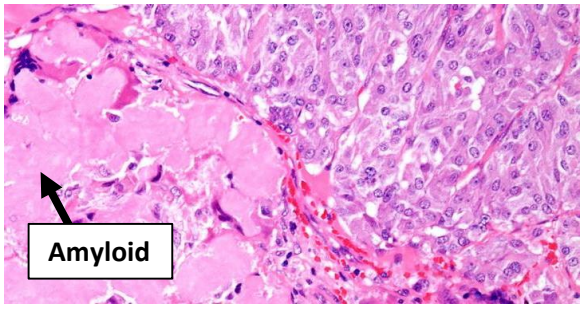
Thyroid Carcinoma Immunohistochemistry

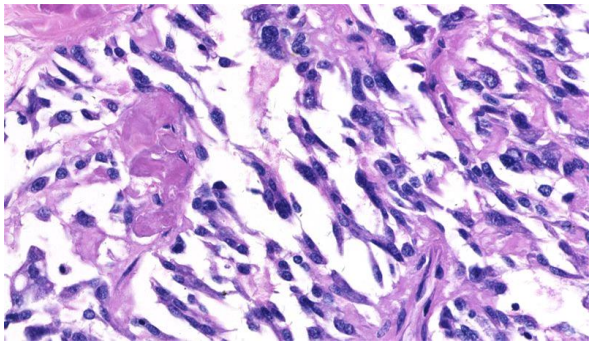
	CK	Thyroglobulin	TTF1	PAX8	Ki67	P53	Calcitonin, synaptophysin
Normal Thyroid Follicular cells	+	+	+	+	<3%	Wt	-
Well-differentiated thyroid carcinoma	+	+	+	+	<10%	Wt	-
Poorly-differentiated thyroid carcinoma	+	-/+	+	+	10-30%	+	-
Anaplastic thyroid carcinoma	+/-	-	-/+	+/-	>30%	+	-
Medullary carcinoma	+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

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

Medullary Thyroid Carcinoma







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

Uncommon. Although mostly sporadic, associated with Multiple Endocrine Neoplasia **(MEN) type 2** (germline RET mutations).

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.

In familial tumors (e.g., MEN 2b) → more frequently multifocal with C-cell hyperplasia.

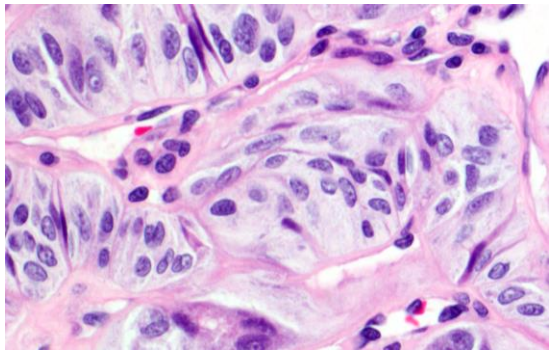
IHC: **(+) Calcitonin (most specific), Neuroendocrine markers** (synaptophysin, chromogranin), TTF-1. (+/-) PAX8. (-) thyroglobulin.

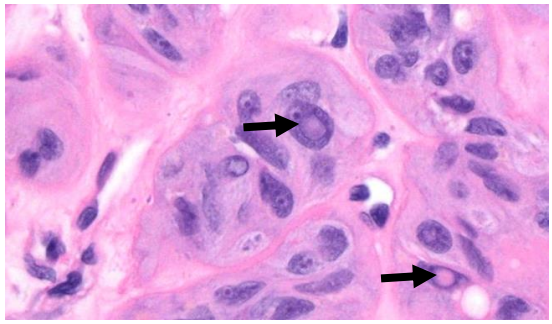
Molecular: **Frequent RET mutations**. Occasional RAS mutations.

Prognosis: **Intermediate aggressive behavior.**

Rare variant: "Mixed medullary and follicular thyroid carcinoma"

Hyalinizing Trabecular Tumor





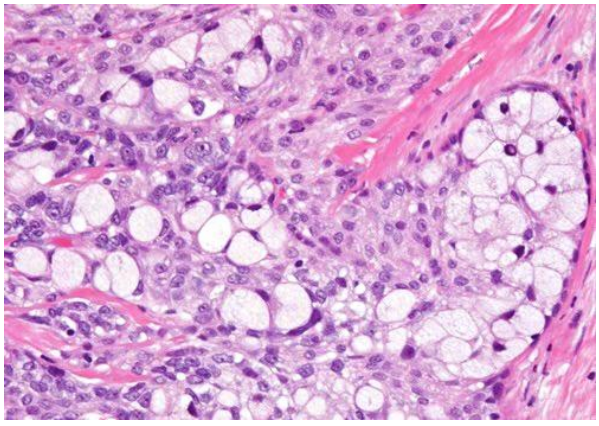
Extremely good prognosis. Follicular-derived neoplasm. Rare.
Solid, well-circumscribed nodule.
NO capsular, vascular, or thyroid parenchymal invasion.

Wide trabeculae and nests separated into **bundles** by stroma. Cells may be enveloped by hyalinized PAS-d positive basement membrane material.
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)

Mucoepidermoid Carcinoma

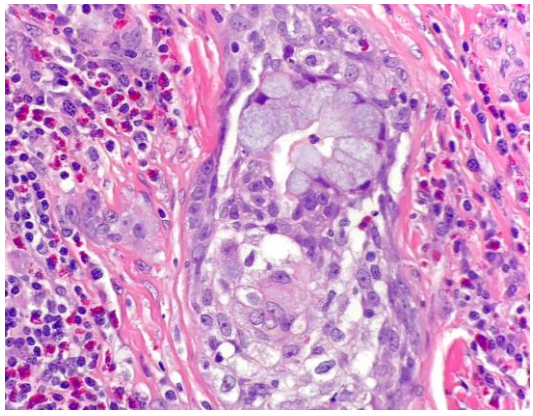


Low-grade malignant/indolent. **Very rare.**
Unclear origin, but favored to represent metaplastic differentiation of follicular derived carcinoma in most cases. Associated with PTC in ~1/2 of cases

Two required cell types: **1) Squamoid cells ,**
2) Mucin-producing goblet cells.

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

Sclerosing Mucoepidermoid Carcinoma with Eosinophilia

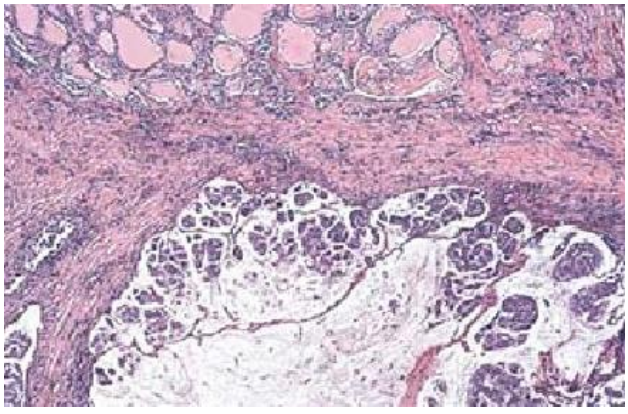


Malignant with sometimes aggressive behavior.
Rare. Strong female predominance.
Consistently associated with fibrosing Hashimoto's thyroiditis.

Small nests and strands of epidermoid cells infiltrating sclerotic stroma. With **interspersed mucous-secreting cells**.
Rich inflammatory infiltrate with lymphocytes, plasma cells, and **prominent eosinophils**.

Frequent PNI and LVI.
IHC: (+/-)TTF1, (-/+) Thyroglobulin.

Mucinous Carcinoma



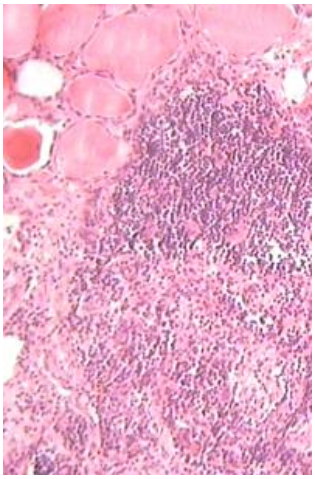
Malignant. Extremely Rare.

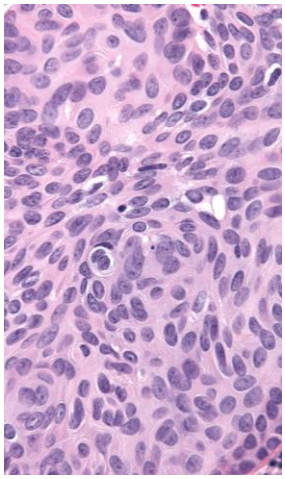
Unknown origin/etiology.

Abundant pools of mucin with floating trabeculae/ tumor clusters. Cells have large nuclei with nucleoli.
Other typical carcinomas should be absent.
Must clinically exclude a metastasis.

IHC: Focal staining with thyroglobulin, TTF-1, PAX8

Ectopic Thymoma



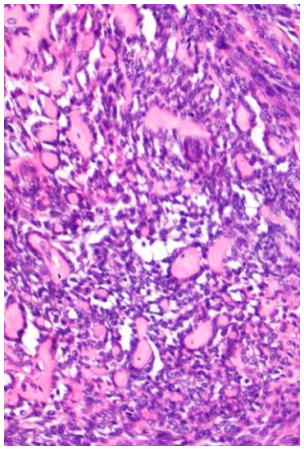


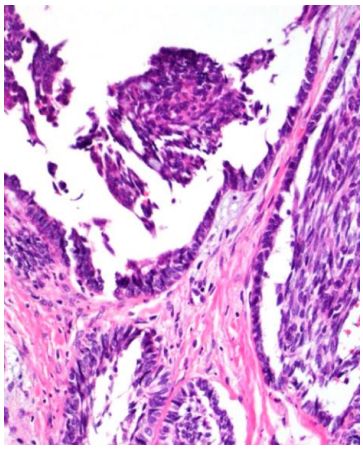
Very Rare. **Typical mediastinal thymoma histology**, but located ectopically within the thyroid gland.
Arises from ectopic thymus tissue.

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 Differentiation ("SETTLE")



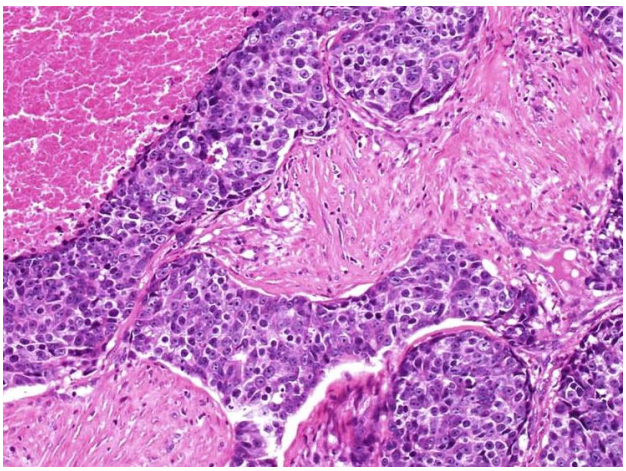


Malignant. Intermediate behavior. Rare.

Highly cellular. Lobulated architecture.
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 rarely show myoepithelial staining.

Intrathyroid 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%

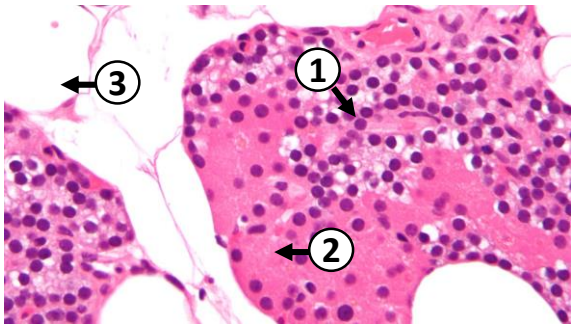
Other Thyroid Tumors

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

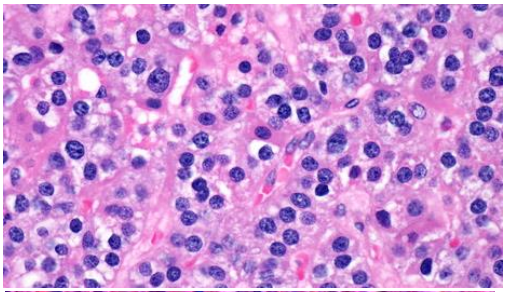
Normal Parathyroid

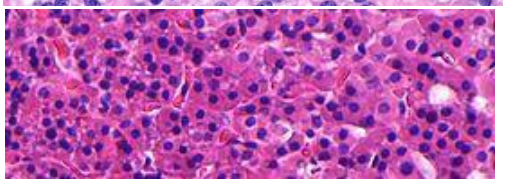


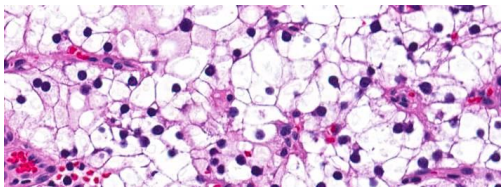
Regulates calcium levels with parathyroid hormone PTH

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.)

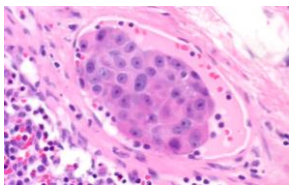
Can arise in any of the 4 glands, or be ectopic.
A minority of cases are associated with MEN1/2A

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)

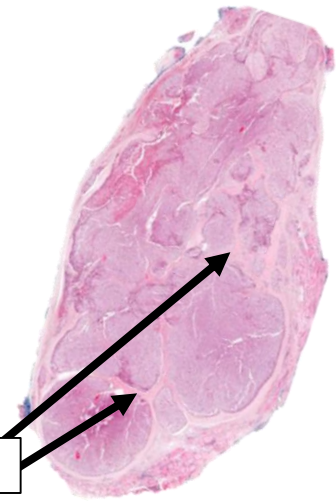
Remember, the surgeon often wants a weight!

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)
- **Metastases**



Usually subdivided by **broad fibrous bands.** Variable pleomorphism/mitoses.
Ki67 usually 6-8% (vs <4% in adenomas)

"Atypical Parathyroid Adenoma"
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.