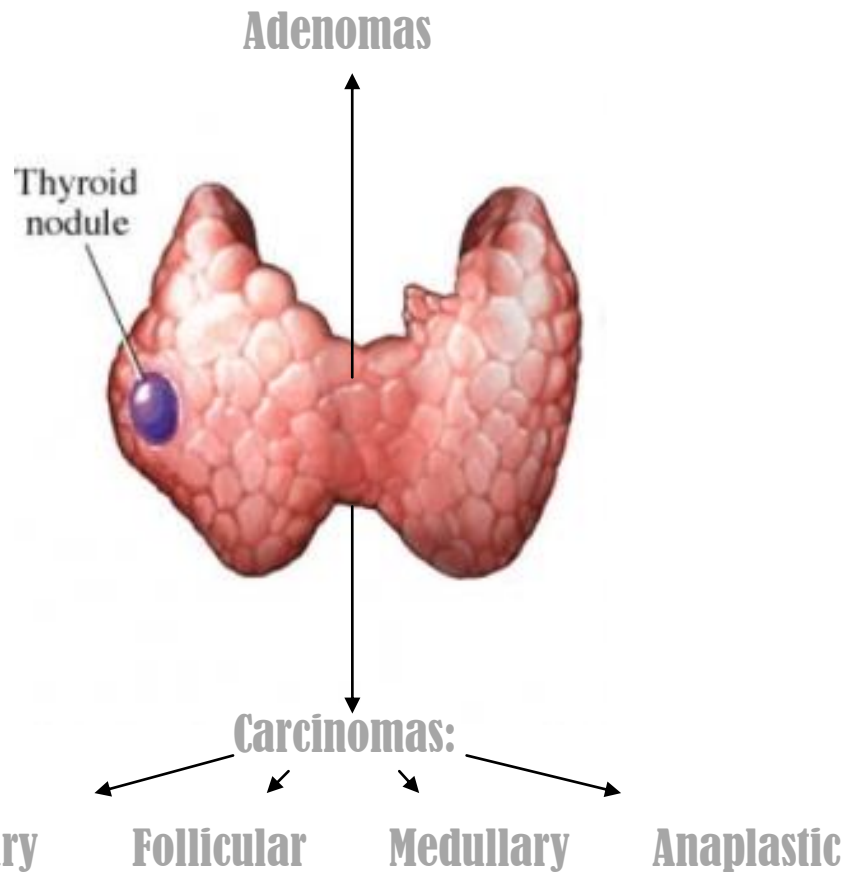
429's Pathology Team represents:

Thyroid pathology 2nd part – 2nd Edition

(fully revised with dr.Hala Kfouri)



Then a Table summarizing all !!

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THYROID NODULES:

A GROUND RULE:

When:
- ✓ Solitary nodules
- ✓ Nodules in younger patients
- ✓ Nodules in males
- ✓ A history of radiation

More likely to be **Neoplastic**

Nodules that take up radioactive iodine in imaging studies (hot nodules) are More likely to be benign than malignant.

TYPES:

1st] Follicular Adenomas: [confined to the follicle with ***NO*** invasion]

- **Origin :** Follicular cells.
- **Classification :**

According to its size:

1-Macro-follicular : ***Simple colloid adenomas*** .
Neoplastic follicles are **smaller** than normal gland cells.

2-Micro-follicular : ***Embryonal or Trabecular adenomas.***
Neoplastic follicles are **larger** than normal gland cells.

According to the manifestation:

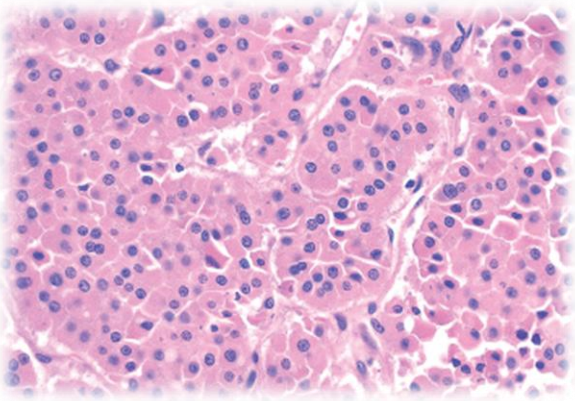
1-Asymptomatic – Hypo functional : ***Warm-Cold adenoma.***
2-Symptomatic : ***Hot adenoma.***

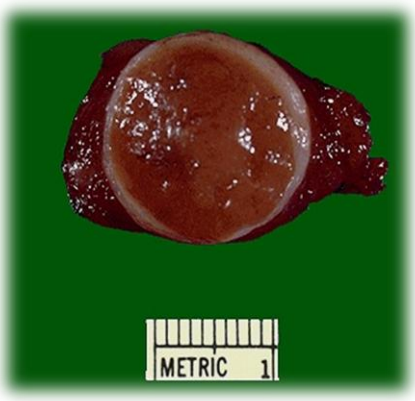
- **Characteristics :**

1- **Benign**.
2- Mostly non-functional (Does not produce hormones)
[small proportion are functional (produce thyroid hormones) and cause clinically apparent thyrotoxicosis]

- **Gross appearance :**

A **cystic** lesion that is:
1- Solitary.
2- Well-circumscribed nodule.
3- Encapsulated.
4- Discrete.





2nd] Papillary carcinoma :

(75% to 85% of cases) → most common

Etiology	**Arises by *multiple distinct, non-overlapping* molecular pathways such as:** - Rearrangements of the ***Tyrosine Kinase Receptors:*** ***RET*** or ***NTRK1*** -A ctivating mutations in the ***BRAF oncogene*** - ***RAS mutations*** (10% to 20% of papillary carcinomas) **(related to follicular carcinoma)**
Predisposing Factors	- Occurs in all ages - The major risk factor predisposing to thyroid cancer is exposure to *ionizing radiation*. -This type of carcinoma mostly filtrate to adjacent lymph nodes -Excellent prognosis
Origin	— ***Follicular cells***
Morphology	Papillary carcinoma can be diagnosed with the four nuclear features even if there is no **papillary formation. Nuclear features include:** 1- Pseudoinclusions (nuclear inclusions) 2- grooved nuclei **3- clear (ground-glass) (orphan annie) nuclei** **4- Psammoma bodies**
Subtypes (variants)	Different variants - related to **RET gene abnormality** - like: A) papillary carcinoma with nuclear features but looks like follicles so → follicular variant of papillary carcinoma B) Encapsulated with no invasion.

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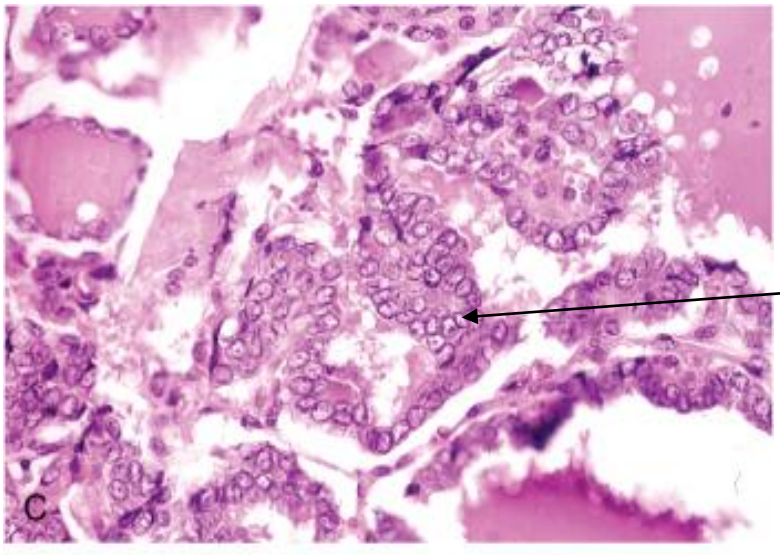

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Don’t forget to watch the movie ;)

3rd] Follicular carcinoma :

- Second most common form of thyroid cancer.
- Most commonly in middle adult years
- High frequency of ***RAS mutations*** ***(in the RAS family:*** KRAS, NRAS, HRAS ***)***
- It has a good prognosis

• Grossly:

❖ **Mainly** they are gray to tan to pink on cut section and, on occasion, are somewhat translucent when large, colloid-filled follicles are present.

❖ They are **single nodules** that may be:
well circumscribed (minimally invasive) or widely infiltrative.

- ➢ When a lesion is **sharply-demarcated** it would be *difficult to distinguish* it from **follicular adenomas**
- ➢ While larger lesions may penetrate the capsule and infiltrate well beyond the thyroid capsule into the adjacent neck.

(When a tumor is invading the thyroid tissue, it would be easily diagnosed as a carcinoma than a minimally invasive one.
The diagnosis of *Adenoma* versus *Minimally Invasive Carcinoma* → is based on **microscopic examination** to look for **Capsular** and/or **Vascular** invasion)

❖ **Degenerative changes**, such as central fibrosis and foci of calcification, are sometimes present

• Microscopically :

❖ **Most** of them are composed of :
fairly **uniform cells** forming small follicles
containing colloid, quite reminiscent of normal thyroid "resembling the normal tissue of the thyroid"

❖ **In other cases,** follicular differentiation may be less apparent, and there may be nests or sheets of cells without colloid

❖ **Occasional tumors** are dominated by **Hurthle cells** (cells with abundant granular, eosinophilic cytoplasm).

❖ **Widely infiltrative cancers** tend to have a greater proportion of solid or trabecular growth pattern, less evidence of follicular differentiation, and increased mitotic activity

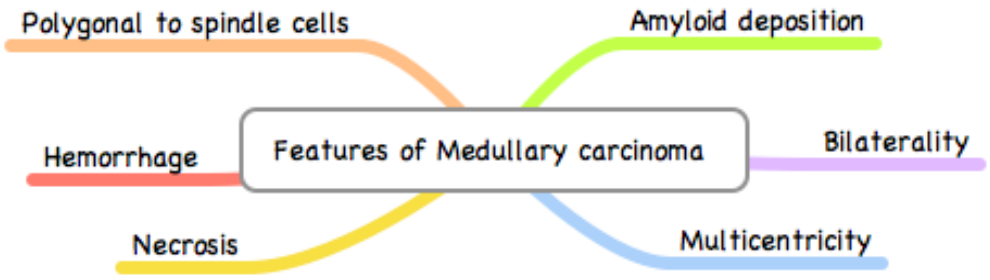
Between follicular and papillary carcinomas
Some papillary carcinomas may appear almost entirely follicular so it is important to know **the pattern of follicular carcinoma:**
- The nuclei lack the features typical of papillary carcinoma.
- Psammoma bodies are not present in follicular carcinomas.

Follicular lesions in which the nuclear features are typical of papillary carcinomas should be treated as papillary cancers

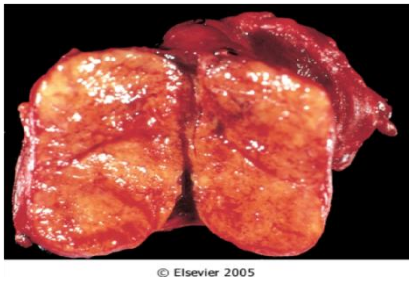
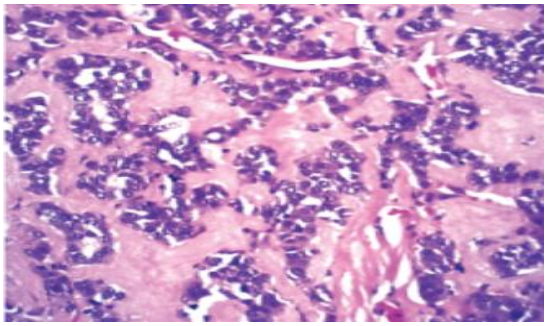
4th] Medullary carcinoma :

Are **Neuro-endocrine Neoplasms .Originate from** the parafollicular cells, or C cells (secrete calcitonin).

Related to **MEN2 gene** abnormality[(1)]



MORPHOLOGY:

GROSS	MICROSCOPE
Medullary carcinomas can arise as a solitary nodule or may present as multiple lesions involving both lobes of the thyroid. ***Sporadic neoplasms*** tend to **originate in one lobe** ***Familial Cases*** are more common to be **bilaterality** and **multicentricity.** ***Larger lesions*** often contain areas of necrosis and hemorrhage and may **extend** through the capsule of the thyroid. **The tumor tissue is** -firm -pale gray to tan -infiltrative They typically show a solid pattern of growth and **do not have connective tissue capsules**  	1) **Polygonal To Spindle-Shaped Cells** (may form nests, trabeculae, and even follicles) 2) **Acellular Amyloid Deposits,** due to ***altered calcitonin molecules*** in the adjacent stroma. ***[Calcitonin is demonstrable within the cytoplasm of the tumor cells as well as in the stromal amyloid by immunohistochemical methods]*** ***Electron microscopy*** reveals variable numbers of membrane-bound electron-dense **granules** within the cytoplasm of the neoplastic cells. **Familial medullary cancers show:** **multicentric C-cell hyperplasia** in the surrounding thyroid parenchyma. **Sporadic medullary cancers show:** **foci of C-cell hyperplasia** in surrounding thyroid parenchyma. 

(1): these tumors arise **sporadically** in about 80% of cases. The remainder occurs
a- in the setting of **MEN syndrome 2A or 2B**
b- or as a **familial tumor without an associated MEN syndrome.**

MEN (Multiple Endocrine Neoplasia): is an inherited autosomal dominant disorder of several distinct syndromes featuring tumors of endocrine glands. Some may benign and others may be malignant depending on the type of the MEN gene mutation (type 1 or 2A/2B)

5th]Anaplastic carcinoma

An aggressive undifferentiated tumor of the thyroid follicular epithelium.

- Less than 5% of thyroid carcinomas
- Most common in **elderly patients** and particularly in areas of **endemic goiter (multinodular goiter)**
- It seems to be believed that ***anaplastic carcinoma*** arises by a "dedifferentiation" from a "more differentiated" tumor as a result of one/more genetic changes
  (more frequently loss of function of the ***p53 tumor suppressor gene***)
  - ➔ 20% of the patients with these tumors have a history of **differentiated carcinoma**
    (or maybe a cancer that is arising at the same time along with it.
    More frequently a ***Papillary Carcinoma)***
- Foci of papillary or follicular differentiation may be present in some tumors, suggesting origin from a better-differentiated carcinoma

• Morphology

Gross: Anaplastic carcinomas present as bulky masses that typically grow rapidly beyond the thyroid capsule into adjacent neck structures.

Microscopically: these neoplasms are composed of highly anaplastic cells, which may take on several histologic patterns, including

(1) large, pleomorphic **giant cells**

(2) **spindle cells** with a sarcomatous appearance

(3) **mixed** spindle and giant-cell lesion

(4) **small cells,** resembling those seen in small-cell carcinomas at other sites.

• Clinical Features

- Anaplastic carcinomas grow with wild abandon despite therapy.
- Metastases to distant sites are common
- In most cases death occurs in less than 1 year as a result of aggressive local growth and compromise of vital structures in the neck. (it is believed to be a **Death sentence)**

	Follicular Adenoma	Papillary Carcinoma	Follicular Carcinoma	Medullary Carcinoma	Anaplastic Carcinoma
Origin	Follicular cells	Follicular cells		Parafollicular/C-cells	
Etiology		• All ages • Rearrangements of RET or NTRK1 tyrosine kinase receptos •BRAF oncogene mutation •10-20% have follicular features (RAS mutations) • Exposure to ionizing radiation • Most common	• Middle age • RAS mutation • 2nd most common	• All ages with a higher incidence in old age groups • MEN2 gene abnormality	• Old ages (65 years) • Loss of function of the p53 tumor suppressor gene • Multinodular goiter • Differentiated carcinoma
Morpho-logy	Grossly: Its a cystic capsule that is: 1. Solitary. 2.Well-circumscribed nodule. 3.Encapsulated. 4.Discrete.	Grossly: 1- papillary formation	Grossly: 1.Mainly they are gray to tan to pink, occasionally translucent. 2.Colloid-filled follicles 3.Well circumscribed or widely infiltrative single nodules 4.Degenerative changes (fibrosis and calcification)	Grossly: 1.Solitary nodule or may present as multiple lesions 2.involving both lobes of the thyroid. 3.Tumor tissue is firm, pale, gray to tan, infiltrative. 4.Show a solid pattern of growth and do not have connective tissue capsules 5.Hemorrhage and necrosis (large lesions)	Grossly: Bulky masses that typically grow rapidly beyond the thyroid capsule into adjacent neck structures.
		Microscopically: 2- Pseudoinclusions (nuclear inclusions) 3- grooved nuclei 4- clear (ground-glass)(orphan annie) nuclei 5- psammoma bodies	Microscopically: •Mostly, fairly uniform cells containing colloid. •In other cases there may be nests or sheets of cells without colloid •Occasional tumors are dominated by Hürthle cells •Widely infiltrative cancers have solid or trabecular growth pattern, less evidence of follicular differentiation, and increased mitotic activity	Microscopically: •Polygonal to spindle-shaped anaplastic cells •Acellular Amyloid Deposits •Variable numbers of membrane-bound electron-dense granules within the cytoplasm of the neoplastic cells • Multicentric C-cell (absent in sporadic lesions)	Microscopically: •Highly anaplastic cells take on several histologic patterns: (1) pleomorphic giant cells (2) spindle cells with a sarcomatous appearance (3) mixed spindle and giant-cell lesion (4) small cells, •Foci of papillary or follicular differentiation may be present in some tumors

SUMMARY From The Book

Thyroid Neoplasms

Most thyroid neoplasms present as solitary thyroid nodules; only 1% of all thyroid nodules are neoplastic. Follicular adenomas are the most common benign neoplasms, while papillary carcinoma is the most common malignancy.

Multiple genetic pathways are involved in thyroid carcinogenesis. Some of the genetic abnormalities that are fairly unique to thyroid cancers include :

- PAX8-PPARγ1 fusion (in follicular carcinoma) **<<< a new finding in molecular pathology.**
- RAS mutation (follicular cancers)
- Chromosomal rearrangements involving the *RET* oncogene (papillary cancers)

1. ***Follicular adenomas and carcinomas***
are both composed of well-differentiated follicular epithelial cells, and are distinguished by evidence of capsular and/or vascular invasion in the latter.

2. ***Papillary carcinomas***
are recognized based on nuclear features (ground-glass nuclei, pseudo-inclusions) even in the absence of papillae. Psammoma bodies are a characteristic feature of papillary cancers; these neoplasms typically metastasize via lymphatics but their prognosis is excellent.

3. ***Medullary cancers***
are nonepithelial neoplasms arising from the parafollicular C cells and can occur in either sporadic (80%) or familial (20%) settings. Multicentricity and C-cell hyperplasia are features of familial cases. Amyloid deposits are a characteristic histologic finding.

4. ***Anaplastic carcinomas*** are thought to arise by dedifferentiation of more differentiated neoplasms. They are highly aggressive, uniformly lethal cancers.