PATHOLOGY TEAM

2

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RED: Important infos. | Orange box: for the extra infos. in the comments of lecturer slids and talks | Blue box: for the infos. quoted from Robbins.

What is Thyroid Nodules?

-They are solid or fluid filled lumps, which are abnormally formed within the thyroid gland.
-The possibility of neoplastic disease is **major concern** in individual who present with **thyroid nodule.**

Solitary thyroid nodule (one single nodule)

- Palpably discrete swelling within an otherwise apparently normal thyroid gland.
- The estimated incidence of solitary palpable nodules in the adult population of the United States varies between 1% and 10%.
- Single nodules are about four times more common in women than in men.
- The incidence of thyroid nodules increases throughout life.
- Majority of solitary nodules of the thyroid prove to be localized, non-neoplastic conditions or benign neoplasms such as follicular adenomas.
- Benign neoplasms outnumber thyroid carcinomas by a ratio of nearly 10 : 1.

- The most common clinical presentation of thyroid diseases is thyroid nodules.
- Fortunately, the overwhelming majority of solitary nodules of the thyroid prove to be benign lesions

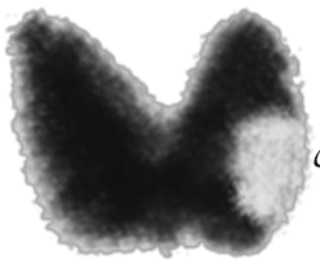
Thyroid Neoplasms

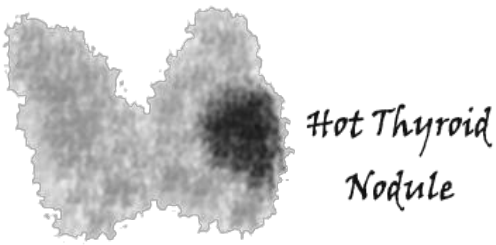
Several clinical criteria provide a clue to the nature of a given thyroid nodule :

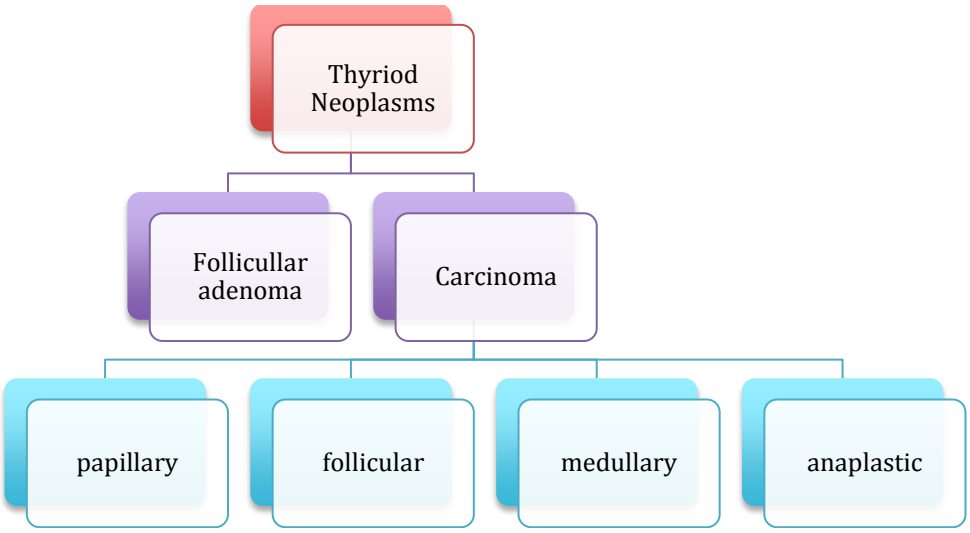
- Solitary nodules : neoplastic
- Nodules in younger patients : neoplastic
- Nodules in males : neoplastic
- A history of radiation : neoplastic
- Nodules uptakeing radioactive iodine **(hot nodules): benign**.

- Hot Nodule -excess uptake of I^{131},hyper-functioning thyroid tissue.
  Cold Nodule - no uptake of I^{131},hypo-functioning thvroid tissue.

The risk of malignancy will be high when the nodules are:
-Solitary.
-Presenting with young patient.
-Male.
-Cold nodule: that indicates nodules do not uptake radioactive iodine.







-Adenomas of the thyroid are benign neoplasms derived from follicular epithelium.

- Follicular adenomas are usually solitary.

Adenomas (follicular adenomas):

Adenomas of thyroid are typically discrete solitary masses.(follicular masses).

- **Degree of follicle formation and the colloid content of the follicles:**

(they call it depend on size of the follicle inside (macrofollicular adenoma or microfollicular).

The male doctor said the size of follicle is not important for prognosis because all of them benign)

- **Simple colloid adenomas (macrofollicular adenomas)(it resemble multinodulur**
- **A common form recapitulate stages in the embryogenesis of the normal thyroid (fetal or microfollicular, embryonal or trabecular).**

- Present as **painless nodules**.
- Larger masses may produce local symptoms such as **difficulty in swallowing**.
- Adenomas appear as "cold" nodules relative to the adjacent normal thyroid gland.
- Toxic adenomas, however, will appear as "warm" or "hot" nodules in the scan.
- As many as 10% of "cold" nodules eventually prove to be malignant.
- Definitive diagnosis of thyroid adenoma can only be made after careful **histologic examination** of the resected specimen
- Thyroid adenomas **have an excellent prognosis** and do not recur or metastasize.

Important note:

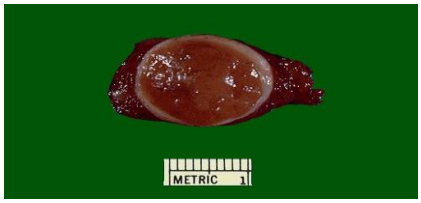
All the **hot nodules** are **BENIGN**

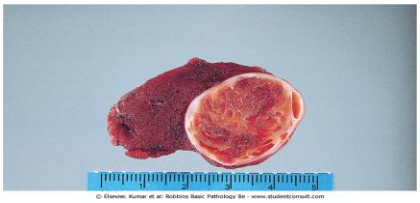
But the **cold nodule:**
90% BENIGN
10% Malignant

How to distinguish follicular adenomas from follicular carcinomas?

- Evaluation of the integrity of the capsule, which demonstrate capsular and/or vascular invasion.
  - Follicular adenoma: thyroid follicles, similar to each other and encapsulated.
  - Follicular carcinoma: invasion of capsule or blood vessels.

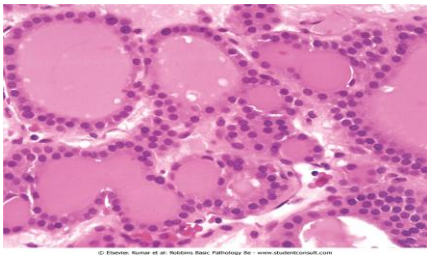
(If there is Capsular invasion or vascular = that indicates a Carcinoma)

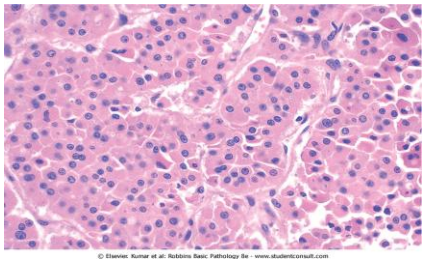




Remember:
No vascular and capsular invasion

Gross picture of the thyroid shows :
Follicular adenoma of the thyroid. A solitary, well-circumscribed nodule is seen.
Encapsulated and demarcated from surrounding thyroid parenchyma





The evaluation of capsule is very important from gross picture. It is indicator for the final diagnosis.

Photomicrograph of follicular adenoma shows:
Well-differentiated follicles resemble normal thyroid parenchyma.
So the gross picture is important for diagnosis.

Carcinomas

- Most cases of thyroid carcinoma occur in adults, although some forms, particularly papillary carcinomas, may present in childhood. (So it can be seen in all age groups).
- Carcinomas of the thyroid: 1.5% of all cancers
- **The major subtypes of thyroid carcinoma and their relative frequencies are as follows: (V.imp)**
- **Papillary carcinoma (> 85% of cases)**
- **Follicular carcinoma (05% to 15% of cases)**
- **Medullary carcinoma (5% of cases)**
- **Anaplastic carcinoma (<5% of cases)**

For easier memorizing:
- Follicular=round shape
رأس=round shaped =RAS
- Medullary = MEN-2

Carcinomas, Genetics

- **Follicular Thyroid Carcinomas**:

Mutations in the RAS family of oncogenes

- **Papillary Thyroid Carcinomas.**

a- Rearrangements of the tyrosine kinase receptors RET or NTRK1 ,
b-Activating point mutations in BRAF, or
c-RAS mutations (10% to 20% of papillary carcinomas).

- **Medullary Thyroid Carcinomas**: Familial medullary thyroid carcinomas occur in multiple endocrine neoplasia type 2 (MEN-2) RET proto-oncogene mutation

- **Anaplastic Carcinomas**: Inactivating point mutations in the p53 tumor suppressor gene are rare in well-differentiated thyroid carcinomas but common in anaplastic tumors.
- **Environmental Factors. The major risk factor predisposing to thyroid cancer is exposure to ionizing radiation**

Papillary Thyroid Carcinoma:

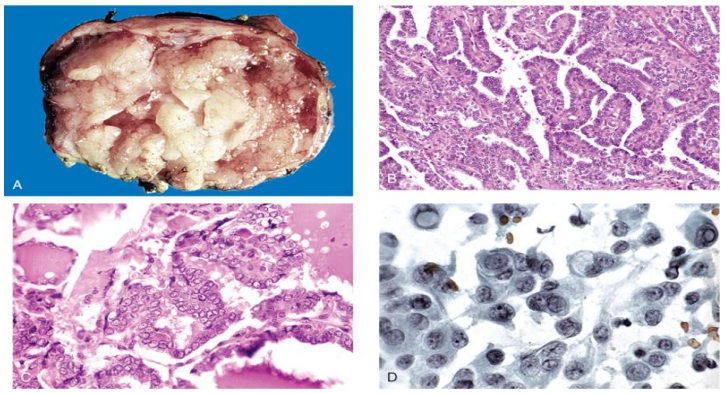
(Most common thyroid cancer)

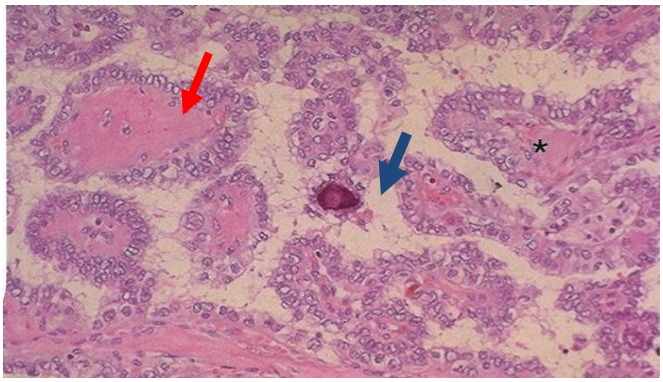
- Most often between the ages of 25 and 50
- Majority of thyroid carcinomas associated with **previous exposure to ionizing radiation.**
- The incidence of papillary carcinoma has increased markedly in the last 30 years
- solitary or multifocal lesions

- Patient comes with thyroid nodule and he/she has exposed to radiation of the neck you have to think about **Papillary Thyroid Carcinoma**

Papillary Carcinomas, Morphology: (V.imp)

- **Papillary structures**
- **Orphan Annie nuclei (Ground glass nuclei, clear cells)** (red arrow).
- **Psammoma bodies (Calcification)** (blue arrow)
- **Pseudoinclusions** (invaginations of the cytoplasm into the cell nuclei)
- **Grooved nuclei**(coffee beans)





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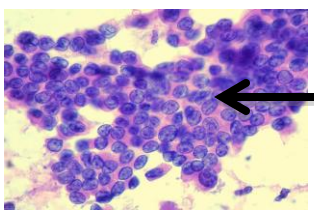
Papillary carcinoma of the thyroid.
(A) A papillary carcinoma with grossly discernible papillary structures.
(**B**), lined by cells with characteristic empty-appearing nuclei, sometimes termed "Orphan Annie eye" nuclei
(**C). D,** Cells obtained by fine-needle aspiration of a papillary carcinoma. Characteristic intranuclear inclusions are visible in some of the aspirated cells.

Papillary Carcinomas, Variants

- Tall cell variant
- Hyalinizingtrabecular tumors (ret/PTC gene rearrangement)
- Follicular
- Encapsulated
- Diffuse sclerosing

Grooved nuclei
(coffee beans)



Papillary Thyroid Carcinoma, Clinical Course:

- Most present as **asymptomatic thyroid nodules**,
- The first manifestation may be a mass in a **cervical lymph node**.
- Papillary thyroid cancers have **an excellent prognosis.**
- Prognosis of PTC is dependent on several factors including **age** (in general, the prognosis is less favorable among patients older than 40 years), the presence of **extra-thyroidal extension,** and presence of distant **metastases** (stage).

Follicular Carcinomas:

- 5% to 15% of primary thyroid cancers.
- More common in women (3 : 1)
- Peak incidence between 40 and 60 years.
- More frequent in areas with dietary iodine deficiency

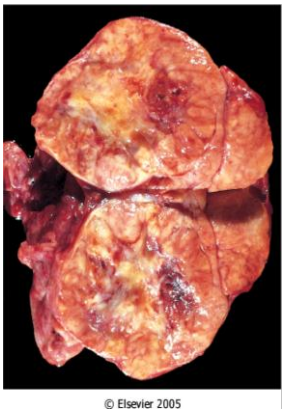
- **Minimally invasive(well encapsulated)**
- **Widely invasive (destructive cancer)**

It looks like FOLLICULAR ADENOMA but WITH the presence of EITHER:

1) Vascular invasion

2) Capsular invasion

Follicular carcinoma of the thyroid. A few of the glandular lumens contain recognizable colloid.



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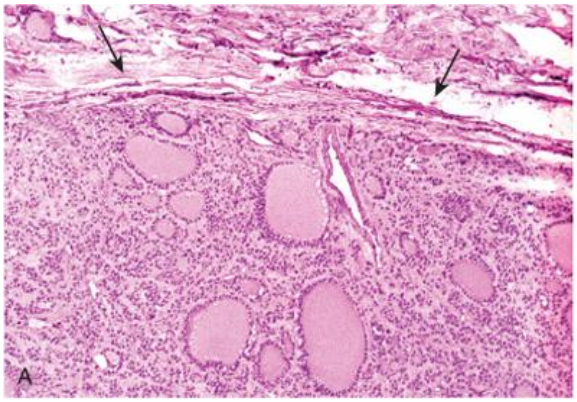

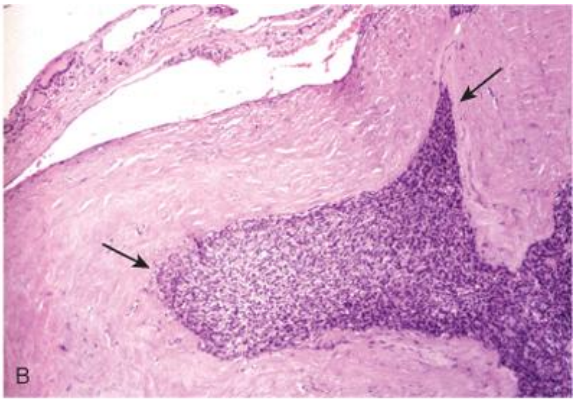

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Capsular invasion in follicular carcinoma. Evaluating the integrity of the capsule is critical in distinguishing follicular adenomas from follicular carcinomas.

In adenomas
(**A**), a fibrous capsule, usually thin but occasionally more prominent, surrounds the neoplastic follicles and no capsular invasion is seen *(arrows);* compressed normal thyroid parenchyma is usually present external to the capsule *(top)*
*(***B),** In contrast, follicular carcinomas demonstrate capsular invasion *(arrows)* that may be minimal, as in this case, or widespread with extension into local structures of the neck.

Medullary Carcinomas

- Medullary carcinomas of the thyroid are neuroendocrineneoplasms derived from the parafollicular cells, or C cells, of the thyroid.

- **Medullary carcinomas, similar to normal C cells, secrete calcitonin**, the measurement of which plays an important role in the diagnosis and postoperative follow-up of patients.
- About 70% of tumors arise sporadically.
- The remainder (30% familial) occurs in the setting **of MEN syndrome 2A or 2B or as**
- Familial tumors without an associated MEN syndrome (familial medullary thyroid carcinoma, or FMTC).

Medullary Carcinomas, Morphology

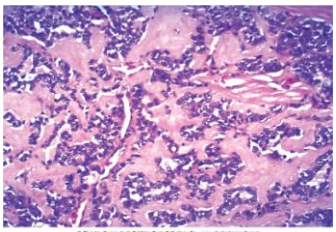
- Polygonal to spindle cells
- **Amyloid deposition** detected by Congo red stain

(Comparing with other types of thyroid carcinomas we only find this morphology feature in thyroid medullary carcinoma)

- Bilaterality
- Multicentricity
- Necrosis
- Hemorrhage

SO we use two stains for MEDULLARY CARCINOMA:

1) **IHC stain for Calcitonin(immunohistochemistry).**
2) **CONGO RED stain for Amyloid.**



Positive Congo red stain

Anaplastic Carcinomas (RARE, the least common and most dangerous)

- **Anaplastic carcinomas of the thyroid are undifferentiated tumors of the thyroid follicular epithelium.**
- **Can be arising from a more differentiated carcinoma (papillary)**
- **Lethal (100%)**
- **Older age group > 65 year**

Morphology : (shows all type of morphologic anaplasia)

- **Highly anaplastic cells:**
- **(1) large, pleomorphicgiant cells, including occasional osteoclast-like multinucleate giant cells**
- **(2) spindle cells with a sarcomatous appearance**
- **(3) mixed spindle and giant cells**
- **(4) small cells**

Questions:

- A 35 year old man came to the doctor with difficulty in swelling and he complained of loosing weight. He gave a history of exposure to radiation. The histological examination showed clear cells with calcification. The most likely diagnosis is:
  A. Papillary thyroid carcinoma.
  B. Follicular adenoma.
  C. Medullary carcinoma.

- A patient with medullary carcinoma, what do you expect to see in his histological examination?

  A. Orphan annie nuclei.
  B. Psammoma bosies.
  C. Amyloid deposition.

- The most common thyroid carcinoma is :
  A. Follicular carcinoma.
  B. Papillary carcinoma.
  C. Anaplastic carcinoma.

Summary:

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), chromosomal rearrangements involving the RET oncogene (papillary cancers), and mutations of RET (medullary carcinomas).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.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.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.Anaplastic carcinomas are thought to arise by dedifferentiation of more differentiated neoplasms. They are highly aggressive, uniformly lethal cancers