King Saud University
College of Medicine
Second year – Endocrine Block

Thyroid Nodules and Neoplasms

Lecture - 2

430 Pathology Team

Seham AlArfaj

Aliya AlAwaji

Mohamed Bohlega

Mohanned AlEssa

Red: Doctors' and important notes.
Green: Team notes.

Introduction:

- Thyroid tumors can be benign (adenomas) or malignant.
- Benign tumors or adenomas of the thyroid:
    1. These tumors are most often solitary.
    2. Can be presented clinically as nodules and can occur in different histological patterns (e.g. Hürthle cell = enlarged epithelial cells in the thyroid that are often associated with Hashimoto's thyroiditis as well as follicular thyroid cancer).
    3. Most of the times they're nonfunctional, but can sometimes cause hyperthyroidism.

Solitary thyroid nodule

Definition: palpably discrete swelling within an otherwise apparently normal thyroid gland.

Incidence:

- The estimated incidence 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*

Thyroid Neoplasms:

Clues to the nature of a given thyroid nodule:

- If solitary nodules, then it is more likely → neoplastic
- Nodules in younger patients → neoplastic
- Nodules in males → neoplastic
- A history of radiation → neoplastic
- Nodules uptakeing radioactive iodine (hot nodules) → benign

The radioactive iodine uptake test, or RAIU test, is a type of scan used in the diagnosis of thyroid problems, particularly hyperthyroidism. It is entirely different from radioactive iodine therapy (RAI therapy), which uses much higher doses to destroy cancerous cells. The patient swallows radioactive iodine (131I sodium iodide) in the form of capsule or fluid, and its absorption by the thyroid is studied after 6 hours and after 24 hours. The normal uptake is between 15 and 25 percent. While increased and decreased uptake have different indications, unevenness in uptake suggests the presence of a nodule.

Adenomas

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

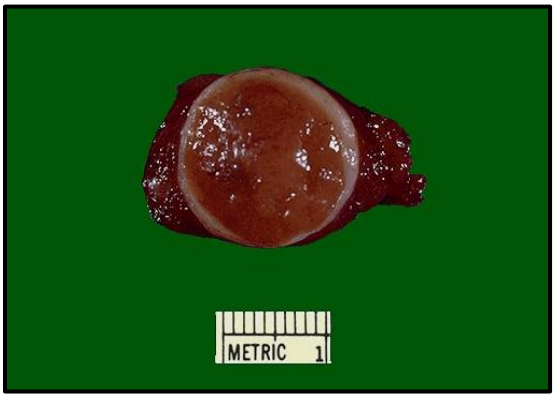
Depending on the degree of follicle formation and the colloid content of the follicles, follicular adenomas can be classified as:

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

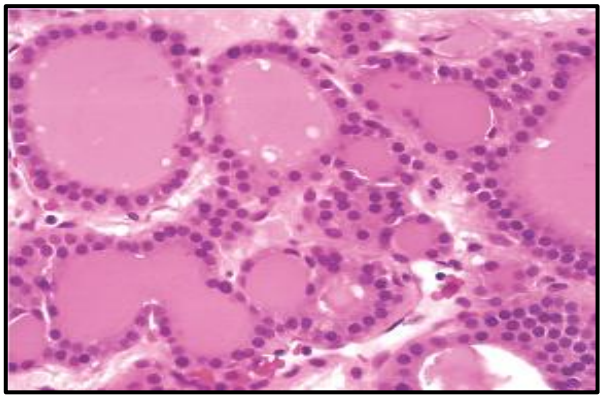
Note: These classifications are not important because mixed patterns are common, and most of these benign tumors are nonfunctional.

Careful evaluation of the integrity of the capsule is critical in distinguishing follicular adenomas from follicular carcinomas, which demonstrate capsular and/or vascular invasion. Histopathology does not help in diagnosis of the slide. Thyroid carcinomas are only differentiated from adenomas when there is invasion outside the capsule, without the need of other signs of malignancy (pleomorphism, mitosis, etc.).

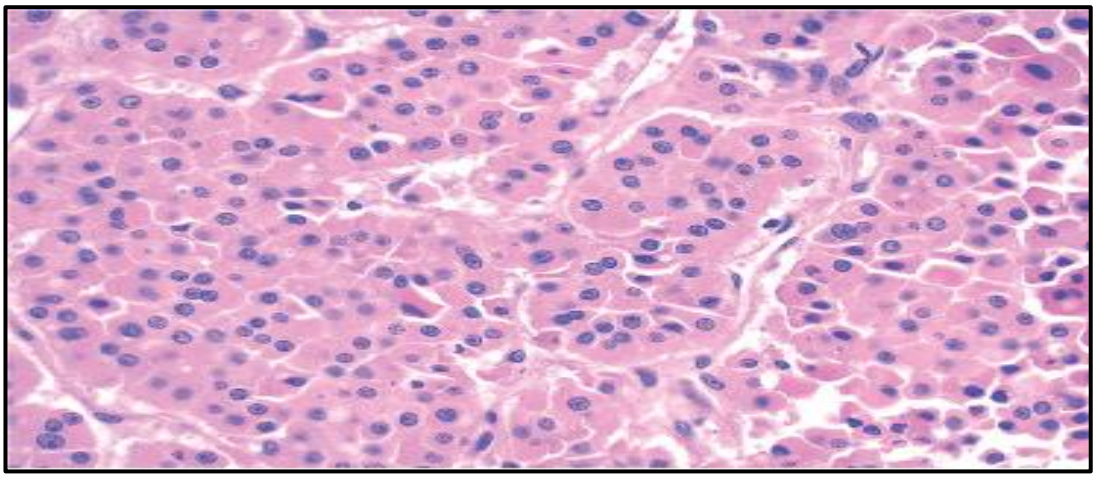
So multiple samples are taken from the area surrounding the capsule to see if there is invasion (capsular and/or vascular invasion) outside the capsule (indicating carcinoma) or if there is no invasion (indicating adenoma).



Well-circumscribed adenoma



Follicular adenoma showing well-differentiated follicles resemble normal thyroid parenchyma.



Hürthle cell adenoma (a variant of adenoma) A high-power view showing that the tumor is composed of cells with abundant eosinophilic cytoplasm and small regular nuclei.

Carcinomas:

Incidence and pathogenesis:

- Carcinomas of the thyroid account for 1.5% of all cancers
- The different types of thyroid carcinomas with their genetic abnormalities are:
  1. **Papillary carcinoma (> 85% of cases):** rearrangements of the tyrosine kinase receptors gene RET or NTRK1 or activating point mutations in BRAF oncogene.
  2. **Follicular carcinoma (05% to 15% of cases):** mutations in the RAS family of oncogenes.
  3. **Medullary carcinoma (5% of cases):** Familial medullary thyroid carcinomas occur in multiple endocrine neoplasia type 2 (MEN-2) RET protooncogene mutation.
  4. **Anaplastic carcinoma (<5% of cases):** 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, and will most likely cause papillary carcinoma.

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)

1. Papillary Thyroid Carcinoma:

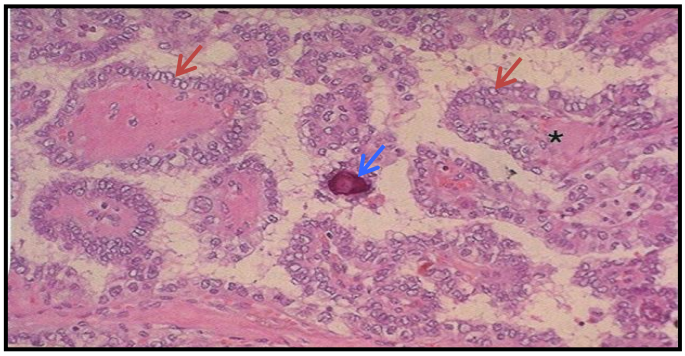
Incidence:

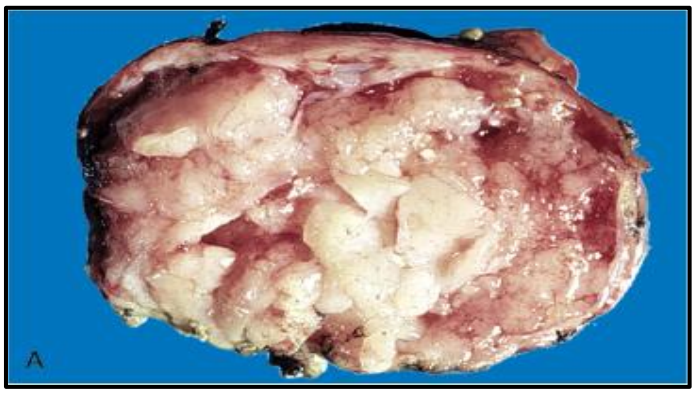
- Can be seen in all age groups, but most often between the ages of 25 and 50
- Majority of thyroid carcinomas associated with previous exposure to ionizing radiation to the neck or the breast (e.g: breast cancer)
- The incidence of papillary carcinoma has increased markedly in the last 30 years

Morphology:

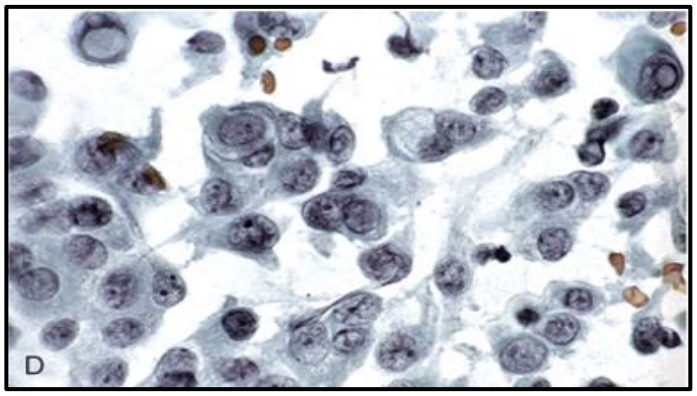
Papillary carcinomas may present as solitary or multifocal lesions within the thyroid. In some cases, they may be well circumscribed and even encapsulated; in other instances, they infiltrate the adjacent parenchyma with ill-defined margins.

1. Papillary structures (*)
2. Orphan Annie nuclei ("ground-glass") (red arrows)
3. Psammoma bodies (calcified spheres) (blue arrow)
4. Pseudoinclusions
5. Grooved nuclei (indented nuclei)





A) Papillary carcinoma with grossly discernible papillary structures



D) Characteristic intranuclear inclusions are visible in some of the aspirated cells.

Variants:

- Tall cell variant (long, tall columnar epithelium cells lining the papillary structures)
- Hyalinizing trabecular tumors (ret/PTC gene rearrangement) (rare with a trabecular pattern of growth and marked intratrabecular hyalinization.)
- Follicular (with the same nuclear features, but looks like follicles instead of papillae)
- Encapsulated (papillary carcinoma with a fully encircling capsule)
- Diffuse sclerosing (shows diffuse fibrosis throughout the thyroid gland)

Note: the diagnosis of papillary carcinoma is based on nuclear features even in the absence of papillary architecture.

Clinical features:

- Most present as asymptomatic thyroid nodules.
- The first manifestation may be a mass in a cervical lymph node.

Prognosis:

- Papillary thyroid cancers have an excellent prognosis (better prognosis than other thyroid cancers)
- Prognosis of PTC is dependent on several factors including:
  1. Age (in general, the prognosis is less favorable among patients older than 40 years)
  2. Presence of extra-thyroidal extension
  3. Presence of distant metastases (stage)

2. Follicular Carcinomas: is a follicular neoplasm with either capsular or vascular or both.

Incidence:

- 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

Types:

- Minimally invasive (well encapsulated)
- Widely invasive

Histologically:

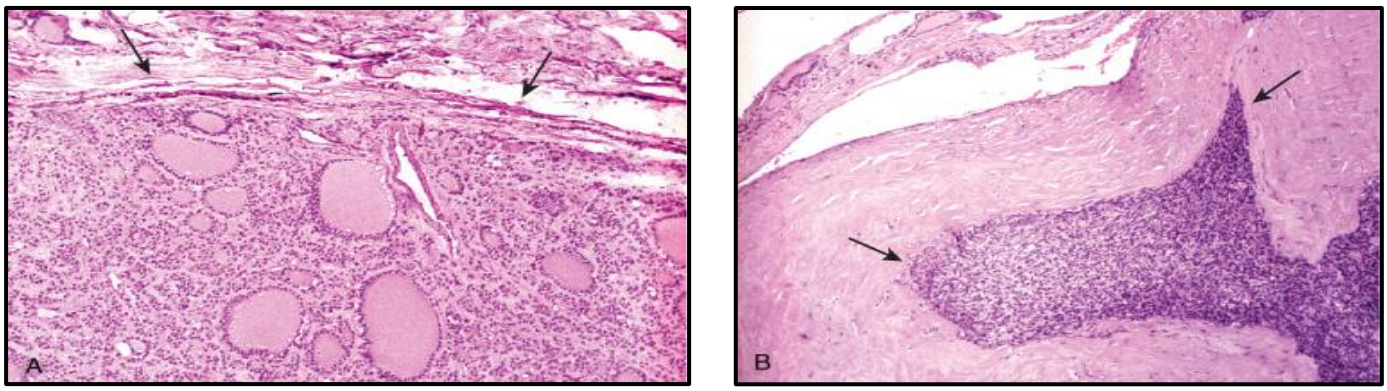
1. Uniform follicles.
2. Follicular proliferation with or without atypia(abnormality), showing invasion to the surrounding parenchyma.

Prognosis:

It has poorer prognosis than papillary carcinoma

How to differentiate between follicular adenomas, follicular carcinomas, and papillary carcinomas with follicular variant?

1. Follicular Adenomas show neoplastic cells confined with an intact capsule, and no vascular invasion.
2. Follicular carcinomas show neoplastic cells that infiltrate their capsule and invade adjacent parenchyma and/or the vasculature.
3. Papillary carcinomas of follicular variant are diagnosed depending on their nuclear features, regardless of being confined to a capsule or infiltrating.



(**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 (*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.

3. Medullary Carcinomas:

- Medullary carcinomas of the thyroid are neuroendocrine neoplasms derived from the parafollicular cells or C cells of the thyroid.
- Medullary carcinomas, similar to normal C cells, secrete calcitonin (a calcium-lowering hormone. And opposes parathyroid hormone.), the measurement of which in peripheral blood plays an important role in the diagnosis and postoperative follow-up of patients.

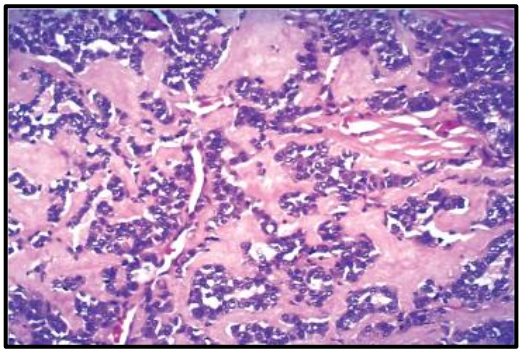
Note: although there is excess calcitonin secretion, the development of hypocalcemia is rare. Ca2+ levels are of almost no diagnostic value.

Incidence:

- About 70% of tumors arise sporadically.
- The remainder is familial cases occurring in the setting of MEN syndromes 2A or 2B or as familial tumors without an associated MEN syndrome (familial medullary thyroid carcinoma, or FMTC).

Morphology:

1. Polygonal to spindle cells
2. Amyloid deposition (containing stroma) (derived from the calcitonin secreation)
3. Bilaterality
4. Multicentricity
5. Necrosis
6. Hemorrhage



4. Anaplastic Carcinomas:

Definition: anaplastic carcinomas of the thyroid are undifferentiated tumors of the thyroid follicular epithelium. This neoplasm takes few weeks to grow.

Incidence:

- Can be either de novo (starting from the beginning as anaplastic carcinoma) or arising from a more differentiated carcinoma (papillary carcinoma)
- Lethal (deadly)(100%) (Metastases to distant sites are common, but 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)
- Older age group > 65 year

Morphology:

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