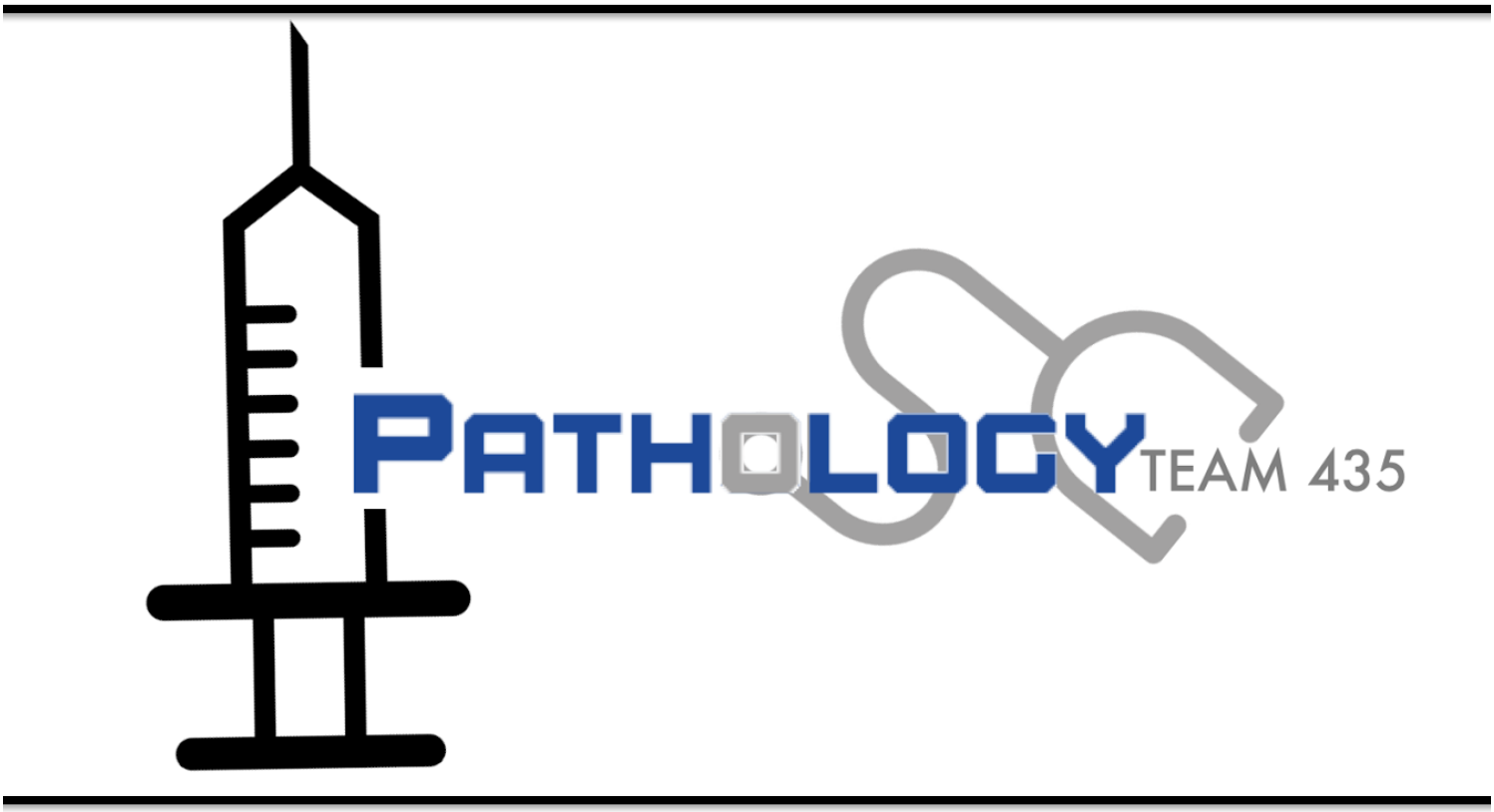
Lecture 2
Thyroid



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Revised by
خولة العماري & هشام الغفيلي

Red: Important. Grey: Extra Notes Doctors Notes will be in text boxes

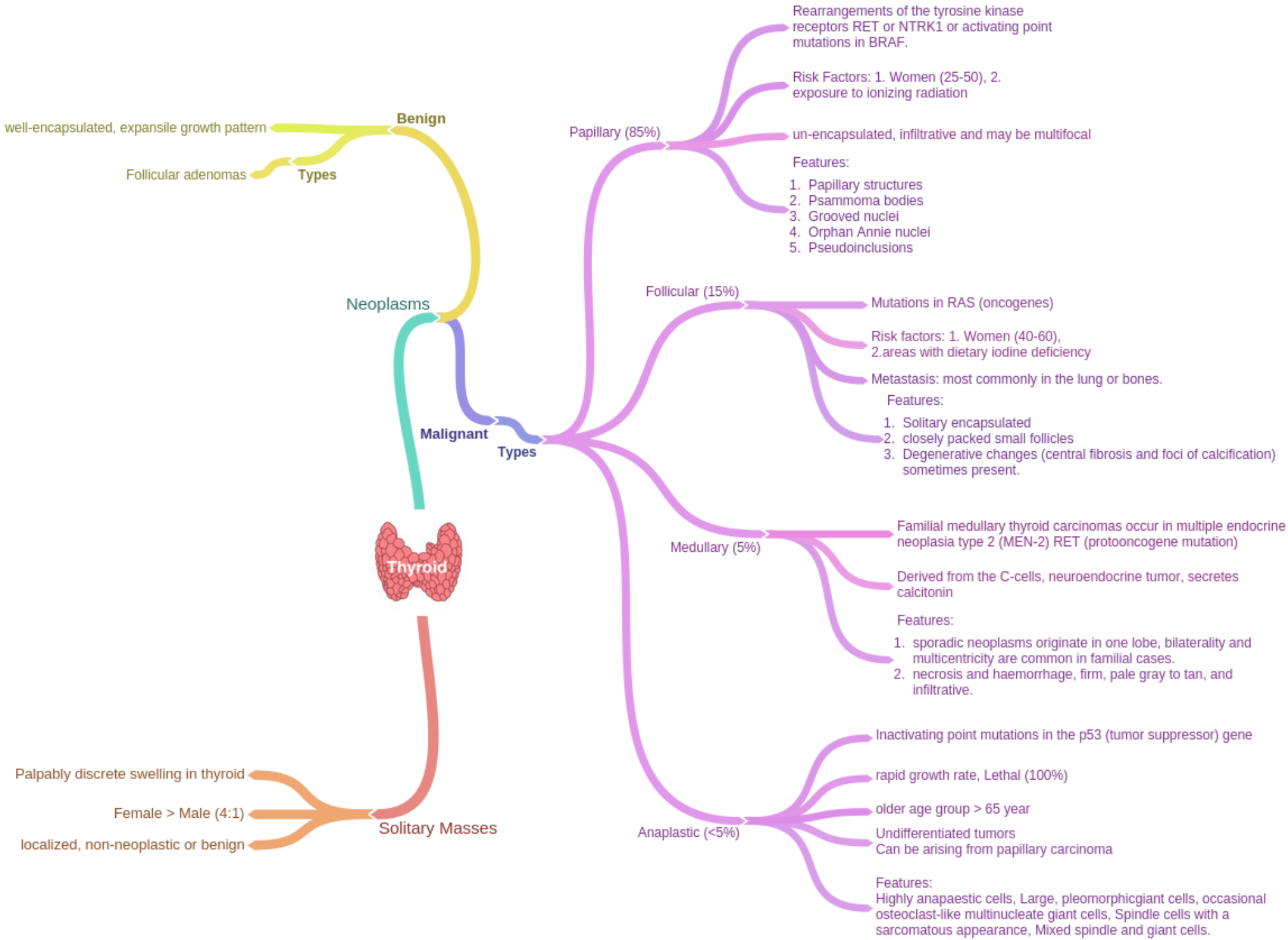
Objectives:

You should

- Know the causes of a solitary nodule in the thyroid (differential diagnosis & definition)
- Understand the classification and behavior of thyroid carcinoma

References: Lecture Slides, Robbins, Dr. Rikabbi & Dr. Hala's Notes.

** The actual lecture is only 7 pages**


Thyroid
Neoplasms
Benign
well-encapsulated, expansile growth pattern
Follicular adenomas
Types
Malignant
Types
Papillary (85%)
Rearrangements of the tyrosine kinase receptors RET or NTRK1 or activating point mutations in BRAF.
Risk Factors: 1. Women (25-50), 2. exposure to ionizing radiation
un-encapsulated, infiltrative and may be multifocal
Features:
1. Papillary structures
2. Psammoma bodies
3. Grooved nuclei
4. Orphan Annie nuclei
5. Pseudoinclusions
Follicular (15%)
Mutations in RAS (oncogenes)
Risk factors: 1. Women (40-60), 2.areas with dietary iodine deficiency
Metastasis: most commonly in the lung or bones.
Features:
1. Solitary encapsulated
2. closely packed small follicles
3. Degenerative changes (central fibrosis and foci of calcification) sometimes present.
Medullary (5%)
Familial medullary thyroid carcinomas occur in multiple endocrine neoplasia type 2 (MEN-2) RET (protooncogene mutation)
Derived from the C-cells, neuroendocrine tumor, secretes calcitonin
Features:
1. sporadic neoplasms originate in one lobe, bilaterality and multicentricity are common in familial cases.
2. necrosis and haemorrhage, firm, pale gray to tan, and infiltrative.
Anaplastic (<5%)
Inactivating point mutations in the p53 (tumor suppressor) gene
rapid growth rate, Lethal (100%)
older age group > 65 year
Undifferentiated tumors
Can be arising from papillary carcinoma
Features:
Highly anapaestic cells, Large, pleomorphicgiant cells, occasional osteoclast-like multinucleate giant cells, Spindle cells with a sarcomatous appearance, Mixed spindle and giant cells.
Solitary Masses
Palpably discrete swelling in thyroid
Female > Male (4:1)
localized, non-neoplastic or benign

Solitary masses:

Solitary thyroid nodule:

- Palpably discrete swelling within an otherwise apparently normal thyroid gland.
- Incidence: 1-10%, single nodules: Female/Male 4:1.
- Incidence ↑ throughout life.
- **Majority:** localized, non-neoplastic conditions or benign neoplasms such as follicular adenomas.
- Benign neoplasms outnumber thyroid carcinomas by a ratio of nearly 10:1.

The differential diagnoses of solitary thyroid masses are as follows:

- One dominant nodule in a multinodular goiter.
- Thyroid cysts.
- Thyroid neoplasm.
- Asymmetrical enlargement due to non-neoplastic disease (e.g. Hashimoto's thyroiditis).

The thyroid gland is very avid to iodine.
In some types the final aspiration will be the same so the surgical removal is essential (as in follicular adenoma and carcinoma)

Thyroid neoplasms:

Thyroid neoplasms can be **benign or malignant**. Most thyroid tumors are non-functioning and therefore appear **'cold' on scintigraphy** (i.e. they do not take up radioactive iodine). However, a minority are functioning, appearing **'warm' or 'hot' on scintigraphy** and possibly causing thyrotoxicosis.

- Morphologic evaluation of a nodule by **fine needle aspiration**, combined with histologic study of surgically **resected thyroid parenchyma** provide the most definitive information about its nature (whether it's benign or malignant).

Clues 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 uptaking radioactive **iodine** (hot nodules): benign

Benign	*Info*	▪ Almost all benign tumors of the thyroid gland are follicular adenomas. ▪ The tumors are well-encapsulated and have an expansile growth pattern, compressing the adjacent normal thyroid tissue. ▪ These features differentiate a follicular adenoma from a dominant nodule in a multinodular goiter.
	Histolo-gically	They may show a variety of appearances, the most common being a microfollicular architecture comprising multiple closely follicles with little colloid.
Malignant		Carcinoma of the thyroid is uncommon, and together with the fact that these tumors often have a good prognosis, they are responsible for less than 1% of all cancer deaths. Thyroid carcinoma is 2-3 times more common in females than males. Most thyroid carcinomas (except medullary carcinomas) are derived from the thyroid follicular epithelium.

Cold nodules (not functioning) → malignant

Pathogenesis: 2 factors are implicated in thyroid cancers.

1. Genetic Factors:

Distinct molecular events are involved in the pathogenesis of the four major variants of thyroid cancer. Genetic alterations in the three follicular cell–derived malignancies are clustered along **two oncogenic pathways:**

- The mitogen-activated protein (MAP) kinase pathway.
- The phosphatidylinositol-3-kinase (PI-3K)/AKT pathway.

Each type of thyroid carcinoma is associated with certain genetic mutation

The four main types of thyroid carcinoma are as follows[1]:

Papillary	(75%-85%)	**Activation of the MAP kinase pathway is a feature of most papillary carcinomas** and can occur by one of two major mechanisms (but not both at the same time): ▪ Rearrangements of the tyrosine kinase receptors **RET** or **NTRK1**[2], both of which encode transmembrane receptor tyrosine kinases. ▪ **Activating point mutations in BRAF** whose product is an intermediate signaling component in the MAP kinase pathway. Chromosomal rearrangements involving *RET*, such as the ***RET/PTC (fusion)*** translocations are seen here, but not in medullary carcinomas.
Follicular	(5-15%)	Chromosomes (2;3) translocation results in ***PAX8/PPARG* fusion genes.** Mutations in the RAS family of oncogenes, **the PI-3K/AKT signaling pathway.** ▪ Gain-of-function point mutations of ***RAS* and *PIK3CA*.** ▪ Loss-of-function mutations of ***PTEN***, a tumor suppressor gene and negative regulator of this pathway.
Anaplastic	(rare, <5%)	Can arise de novo or, more commonly, by **dedifferentiation** of a well-differentiated papillary or follicular carcinoma (RAS or PIK3CA mutations can change benign follicular adenomas to follicular carcinomas to anaplastic carcinomas). Inactivating point mutations in the p53 tumor suppressor gene are essentially restricted to anaplastic tumors (common).
Medullary	(5%)	Familial medullary thyroid carcinomas occur in **multiple endocrine neoplasia type 2 (MEN-2)** and are associated with RET proto-oncogene **mutation.** RET mutations are also seen nonfamilial cases.

Could be familial or sporadic

2. Environmental Factors:

- The major risk factor predisposing to thyroid cancer is exposure to **ionizing radiation,** particularly during the first 2 decades of life.
- **Deficiency of dietary iodine** (and by extension, an association with goiter) is linked with a higher frequency of follicular carcinomas.

[1] **Extra details under further reading.**

[2] Neurotrophic tyrosine kinase receptor 1

Cellular origin of thyroid malignancy			
Follicular Cell			Parafollicular Cell
Diffrentiated		Undiffrentiated	"C" Cell hyperplasia
Papillary	Follicular	Anaplastc	Medullary

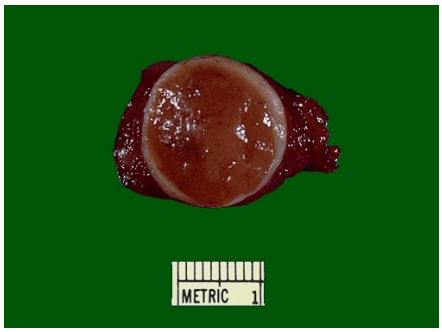
Follicular Adenoma of the Thyroid: (most common)

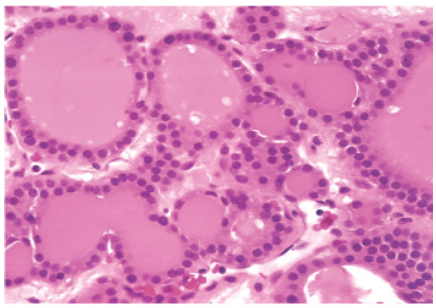
Benign masses derived from follicular epithelium (follicular adenomas).

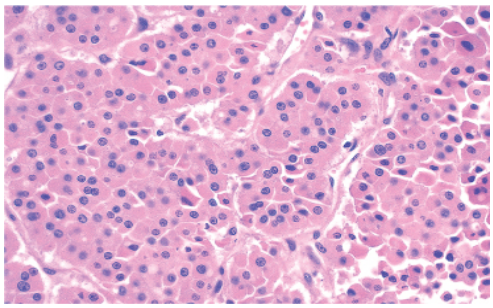
- **Degree of follicle formation and the colloid content of the follicles:**
  - Simple colloid adenomas (macrofollicular adenomas).
  - A common form recapitulate stages in the embryogenesis of the normal thyroid (fetal or microfollicular, embryonal or trabecular).
- Careful evaluation of the **integrity of the capsule** is critical in distinguishing follicular adenomas from follicular carcinomas.
- Although the vast majority are nonfunctional, a small proportion are toxic adenomas.

- Toxic adenoma: toxic indicates that the tumor is functioning (i.e., it secretes hormones). Those tumors which secrete hormones have hot nodules. (Hot since they uptake radioactive iodine unlike cold nodules).
- It is a benign tumor of the thyroid gland which is secreting thyroid hormones.
- Cold nodule, most probably tumor.
- Most hot nodules are benign.
- A nodule without explanation (hormonal profile is normal), being a male with thyroid enlargement, cold nodule = all these are features of malignancy.

Pathogenesis	▪ Somatic mutations in the genes encoding for TSH receptor or, to a lesser extent, the alpha subunit of Gs (GNAS) allow follicular cells to secrete thyroid hormone independent of TSH (known as thyroid autonomy). ▪ About 20% of nonfunctioning follicular adenomas present with mutations in RAS or phosphatidylinositol-3-kinase (PIK3CA).
Morpho-logy	▪ Solitary, typically discrete, spherical nodule that compresses adjacent nonneoplastic parenchyma with a **well-defined, intact capsule (the hallmark).** (unlike multi nodular goiters). → Lack of well-formed capsule ▪ Brightly eosinophilic granular cytoplasm **(Hürthle cell change).**

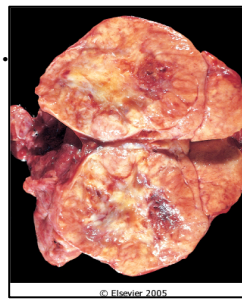






Follicular adenoma of the thyroid. A solitary, well-circumscribed nodule is seen.

Follicular carcinoma:



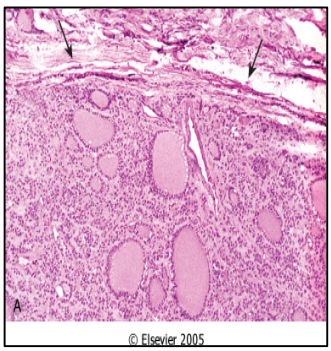
- Occurs in older age groups, peak incidence between 40 and 60 years.
- 5%-15% of primary thyroid cancers, more common in women (3:1).
- More frequent in areas with dietary iodine deficiency.
- Minimally invasive (well encapsulated), 10-year survival rate 90%.
- Widely invasive carcinoma, 10-year survival rate less than 50%.
- Prognosis: poorer than papillary carcinomas.

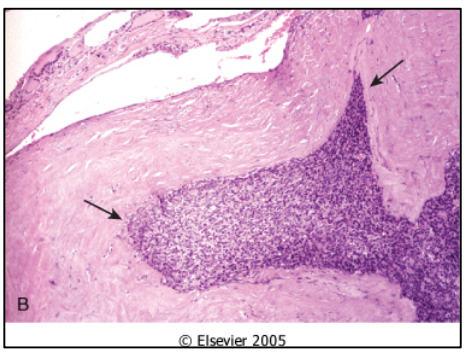
Metastasis (15%)

- Through the bloodstream ***(hematogenous dissemination)*** most commonly involving the lung, bones or liver.
- In contrast with papillary carcinomas, regional nodal metastases are uncommon.
- Larger lesions may penetrate the capsule and infiltrate well beyond the thyroid capsule into the adjacent neck. They are gray to tan to pink on cut section and, on occasion, are somewhat translucent when large, colloid-filled follicles are present.

Histologically

- **Solitary encapsulated** tumors most commonly consisting of closely packed small follicles containing colloid (cold thyroid nodules), and may therefore be difficult to distinguish from follicular adenomas by gross examination (Specially sharply demarcated lesions) **This distinction requires extensive histologic sampling (examination) of the tumor capsule–thyroid interface, to exclude capsular (microinvasive) and/or vascular (microvascular) invasion** (malignancy).
- In other cases, follicular differentiation may be less apparent, and could appear like papillary carcinoma, but whatever the pattern, the **nuclei** lack the features typical of papillary carcinoma, and psammoma bodies are **not present**. Some papillary carcinomas may appear almost **entirely** follicular, these details tell them apart.
- Hürthle cell variants of follicular carcinomas may be seen, like follicular adenoma.
- Degenerative changes, such as central fibrosis and foci of calcification, are sometimes present.
- **Widely invasive**: exhibits extensive invasion of adjacent thyroid parenchyma or extrathyroidal tissues. They tend to have a **greater proportion of solid or trabecular growth pattern, less** evidence of follicular differentiation, and ↑ mitotic activity.





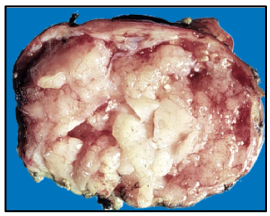
A, In adenomas, a fibrous capsule, usually thin but occasionally more prominent, surrounds the neoplastic follicles and no capsular invasion is seen (*arrows*); compressed normal thyroid parenchyma usually is present external to the capsule (*top*). **B,** By contrast, follicular carcinomas demonstrate capsular invasion (*arrows*).

- You can't tell whether it is benign or malignant from cytology (fine needle aspiration).
- Hürthle (oncocytic) cell change (if present, then more likely to be malignant, especially if male) (Hürthle cell-type follicular adenoma).
- Likes to invade through the blood, but not lymphatics.

Papillary carcinoma:

Most common malignant thyroid tumor (85%), forming finger-like projections.

- Typically occurs in women in the 3rd or 4th decade. These tumors may occur at any age.
- The tumors are un-encapsulated, infiltrative and may be multifocal.



Non-functional tumor , so it's not associated with hyperthyroidism

- The incidence has increased markedly in the last 30 years

Metastasis

Cervical **lymph node** metastases are present in as many as 50% of cases at presentation.

Histolo-gically

The lesions may contain areas of fibrosis and calcification and often are cystic Papillary carcinomas can exhibit a wide range of appearances.

- **Papillary structures:** common, with dense fibrovascular cores.
- **Psammoma bodies** (calcified glycoprotein bodies). Atypical cells: pleomorphism
- Foci of **lymphatic permeation** by tumor cells are often present, but invasion of blood vessels is uncommon.
- **Grooved nuclei.**
- **Orphan Annie nuclei (ground glass):** Hypochromatic nuclei, which imparts an **optically clear** appearance.

Usually multifocal, hence, it is treated by total thyroidectomy. (this will lead to post ablation hypothyroidism).

Optically clear means: white appearance nuclei (normally it's blue)

- **Pseudoinclusions:** invaginations of the cytoplasm may **give the appearance** of intranuclear inclusions.

Diagnosis

The diagnosis depends on the presence of certain cytological features:

- "Orphan Annie" nuclei.
- Eosinophilic cytoplasmic inclusions.
- Psammoma bodies.
- Nuclear grooves.

Variants (Can present in many ways including:)

- **Follicular (most common):** encapsulated and is associated with a lower incidence of lymph node metastases and extrathyroidal extension.
- Tall cell variant
- Encapsulated
- Diffuse sclerosing
- Hyalinizing trabecular tumors **(RET/PTC gene rearrangement)**

Clinical Course

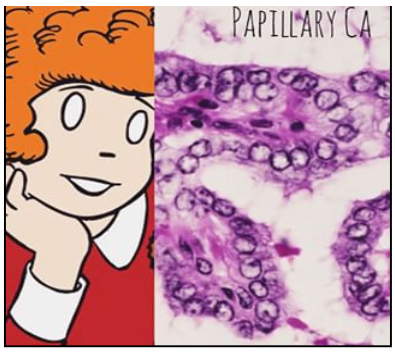
- Most present as asymptomatic thyroid nodules.
- The first manifestation may be a mass in a cervical lymph node.

Presented with painless mass in the neck (if it's painful that would be granulomatous thyroiditis)

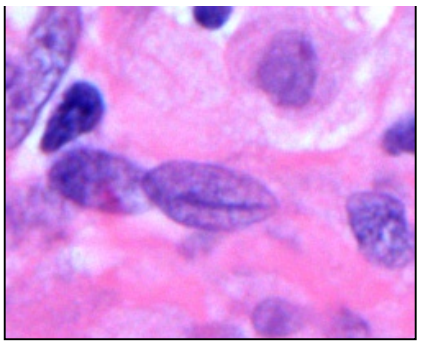
Prognosis

- Papillary thyroid cancers have an excellent prognosis.
- 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).

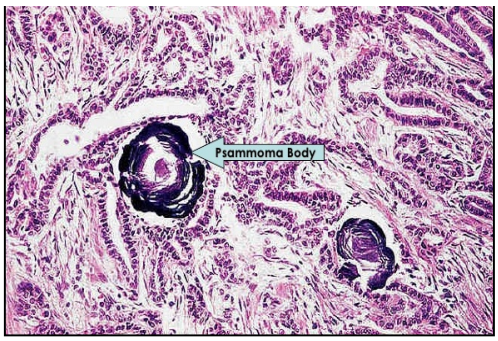
- It likes to invade lymph nodes. Hematogenous spread, unlike follicular carcinoma, is uncommon.
- It causes **morbidity** but not mortality. (recurrent lymphatics invasion), Indolent tumor (بطيء النمو) and not lethal. Lately may produce metastasis (eg lung). Less stage = better prognosis
- Fine needle aspiration cytology for the diagnosis of papillary carcinoma (nuclear features).



Orphan annie is strip cartoon character with empty circled eyes



Nuclear grooves



Psammoma bodies

Medullary carcinomas:

- Derived from the parafollicular cells **(the C-cells)** within the thyroid, and are therefore neuroendocrine tumors, **not** from follicular epithelium.
- Most secrete **calcitonin** (the measurement of which plays an important role in the diagnosis and postoperative follow-up of patients) but oversecretion of this hormone does **not** usually produce any clinical effects. High calcitonin level in blood
- Rarely, the tumor other secrete hormones (e.g. ACTH, or 5-hydroxytryptamine).
- About 70% of tumors arise sporadically. The remainder 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).

Grossly

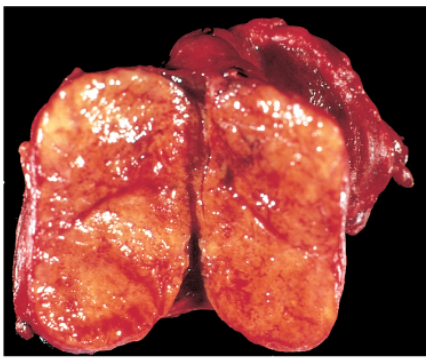
- Can arise as a solitary nodule or may present as multiple lesions involving both lobes of the thyroid.
- These tumors may pursue an indolent or aggressive course.
- The **sporadic neoplasms** tend to originate in one lobe.
- In contrast, **bilaterality and multicentric C-cell hyperplasia** are common in **familial cases.**
- **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, and infiltrative.

Microscopically

- Consists of nests or sheets of tumor cells (polygonal to spindle-shaped) in a characteristic **amyloid stroma.** Small, more anaplastic cells are present in some tumors and may be the predominant cell type.
- **Acellular amyloid deposits**, derived from altered calcitonin molecules.
- **Calcitonin** is found within the cytoplasm of the tumor cells as well as in the stromal amyloid and can be seen **by immunohistochemical methods.**
- Foci of C-cell hyperplasia are believed to represent the precursor lesions from which medullary carcinomas arise.

- Leads to hypocalcaemia. (parathyroid adenoma causes hypercalcemia), No RET/PTC fusion (no translocation), The RET gene is mutated. Can be associated with MEN syndrome (multiple endocrine neoplasia) (MEN type 2)
- **MEN:**
  - **Type 2A predisposes to:**
    1- medullary carcinoma of the thyroid. 2- pheochromocytoma. 3- Parathyroid adenoma
  - **Type 2B predisposes to:**
    1- medullary carcinoma of the thyroid. 2- pheochrompcytoma.3- oral ganglioneuroma)

Clinical Features		
	Sporadic cases	Manifests most often as a mass in the neck, sometimes associated with compression effects such as dysphagia or hoarseness. In some instances, the initial manifestations are caused by the secretion of a peptide hormone (e.g., diarrhea caused by the secretion of VIP).
	Familial cases	Screening of the patient's relatives for elevated calcitonin levels or RET mutations permits early detection of tumors <u>in familial cases</u>



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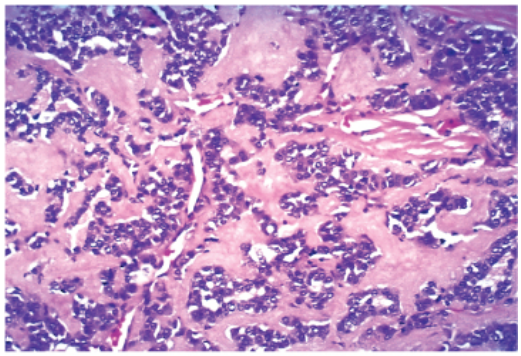

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Medullary carcinoma of thyroid. These tumors typically show a solid pattern of growth and do not have connective tissue capsules

- Immunohistochemistry: Anti-calcitonin antibodies
- Can be diagnosed by FNA cytology (not as accurate as papillary carcinoma)
- Secretes amyloid protein which accumulates around tumor cells.
- Special stain for amyloid: Congo red

Anaplastic carcinoma (Undifferentiated):

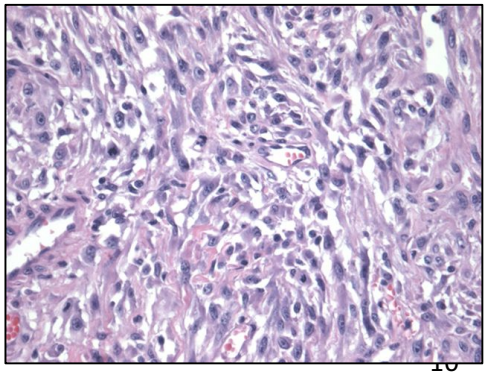
- Have a rapid growth rate, **lethal** (100%) and affects older age group > 65 year.
- Metastasizes widely and the prognosis is very poor. In most cases death occurs in < 1 year as a result of aggressive local growth and compromise of vital structures in the neck.

Histologically

- Un- or poorly differentiated tumors of the thyroid follicular epithelium.
- Can be arising from a more differentiated carcinoma (papillary)
- **Highly anaplastic cells:**
  - Large, pleomorphic giant cells, including occasional osteoclast-like multinucleate giant cells
  - Spindle cells with a sarcomatous appearance
  - Mixed spindle and giant cells
  - Small cells resembling those seen in small cell carcinomas arising at other sites.

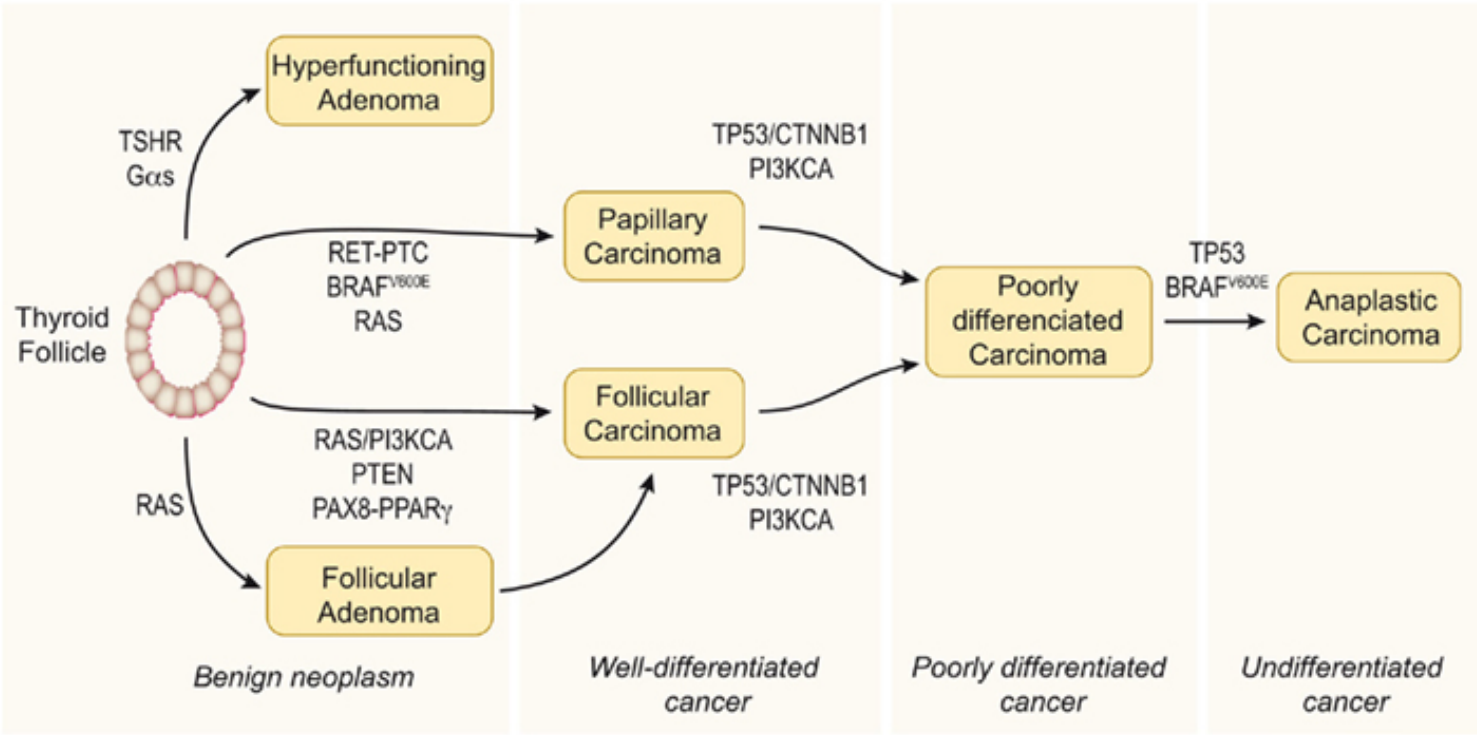
- Elderly patients, rare, pleomorphism (cells are variable in size and shape)
- Very **pleomorphic**, high grade and has a bad prognosis

It is unlikely that a true small cell carcinoma exists in the thyroid, and a significant number of such "small cell" tumors have ultimately proven to be medullary carcinomas or malignant lymphomas, which may also occur in the thyroid but have a much better prognosis. Foci of papillary or follicular differentiation may be present in some tumors, suggesting origin from a better differentiated carcinoma.



Notes about adenoma:

- There are three differential diagnosis which are clinically the same, so it is difficult to diagnosed based on clinical and morphologic ground:
  1. Follicular adenoma
  2. Follicular carcinoma
  3. Dominant (hyperplastic) nodule in multinodular goiter
- Dominant nodule in multinodular goiter mean: واحد من النوديولز ممكن يصير كبير جدًا وبارز ويمكن تحسسه بالبالبيتيشن ، فيصعب بمجرد الكلينيكال إكزامنيشن تفرقته عن الأدينوما أو الكارسينوما
- How to diagnose?
  1. Ultrasound (or final aspiration):
     - If it's multiple nodules → multinodular goiter
     - One nodule (solitary) → either follicular adenoma or follicular carcinoma
  2. Surgical (to see the **capsule** grossly): to differentiate between adenoma and carcinoma
     - Well-defined intact capsule → follicular adenoma
     - Invasion (capsular or vascular) → carcinoma
- So surgical removal of suspected adenoma is essential to exclude malignancy



Further reading: (Read it if you have spare time) *The graph before is very useful

Pathogenesis of Carcinoma: (We highly advise you to know all the Red-colored Genes)

In normal cells, these pathways are transiently activated by binding of soluble growth factor ligands to the extracellular domain of receptor tyrosine kinases, which results in autophosphorylation of the cytoplasmic domain of the receptor, permitting intracellular signal transduction. In thyroid carcinomas, as with many solid cancers, gain-of-function mutations along components of these pathways lead to constitutive activation even in the absence of ligand, thus promoting carcinogenesis.

- **Papillary thyroid carcinoma:**
  - The *RET* gene is not normally expressed in thyroid follicular cells. In papillary cancers, chromosomal rearrangements place the tyrosine kinase domain of *RET* under the transcriptional control of genes that are constitutively expressed in the thyroid epithelium. The novel fusion proteins that are so formed are known as **RET/PTC** (papillary thyroid carcinoma) and are present in approximately 20% to 40% of papillary thyroid cancers. The frequency of *RET*/*PTC* rearrangements is significantly higher in papillary cancers arising in the backdrop of radiation exposure. Similarly, rearrangements of *NTRK1* are present in 5% to 10% of papillary thyroid cancers, and the resultant fusion proteins are constitutively expressed in thyroid cells, leading to activation of MAP kinase pathways. And mutation in the **BRAF gene.**
- **Follicular Carcinoma:**
  - Approximately one third to one half of follicular thyroid carcinomas harbor **mutations in the PI-3K/AKT signaling pathway,** resulting in constitutive activation of this oncogenic pathway. The progressive increase in the prevalence of *RAS* and *PIK3CA* mutations from benign follicular adenomas to follicular carcinomas to anaplastic carcinomas suggests a shared histogenesis and molecular evolution among these follicular cell–derived tumors. A unique (2;3) (q13;p25) translocation has been described in one third to one half of follicular carcinomas. This translocation creates a fusion gene composed of portions of *PAX8*, a paired homeobox gene that is important in thyroid development, and the peroxisome proliferator– activated receptor gene (*PPARG*), whose gene product is a nuclear hormone receptor implicated in terminal differentiation of cells. Less than 10% of follicular adenomas harbor ***PAX8*/*PPARG*** **fusion genes,** and thus far these have not been documented in other thyroid neoplasms.
- **Anaplastic Carcinoma:**
  - Molecular alterations present in anaplastic carcinomas include those also seen in well-differentiated carcinomas (e.g., *RAS* or *PIK3CA* mutations), albeit at a significantly higher rate, suggesting that the presence of these mutations might predispose existing thyroid neoplasms to transform.
- **Medullary Carcinoma:**
  - *RET* mutations are also seen in approximately one half of nonfamilial (sporadic) medullary thyroid cancers.

(Not in our objectives, but in Dr.Rikkabi's notes)

Parathyroid Glands:

Learning objectives

You should:

- Know the structure and function of the parathyroid glands
- Know the various subtypes of hypothyroidism and their causes

Structure and function

Most individuals have four parathyroid glands. In the adult, the upper two glands almost always lie close to the upper posterior aspect of the thyroid gland, but the lower two may be found anywhere between the lower posterior aspect of the thyroid gland and the mediastinum. The glands are composed predominantly of chief cells, which secrete parathyroid hormone (PTH). PTH:

- Mobilizes calcium from bone
- Increases renal tubular resorption of calcium
- Promotes the production of 1, 25-dihydroxyvitamin D_1 (the active form of vitamin D) in the kidney
- Enhances phosphate excretion by the kidney

Overall, serum calcium levels are controlled by the actions of three hormones – PTH, calcitonin and vitamin D. PTH and vitamin D have a hypercalcaemic effect and calcitonin has a hypocalcaemic effect. The most important disorders of the parathyroids are hyperparathyroidism, hypoparathyroidism and tumors.

Hyperparathyroidism

Hyperparathyroidism can be divided into primary, secondary and tertiary types:

- Primary – hypersecretion of PTH by a parathyroid lesion
- Secondary – a physiological increase in PTH in response to hypocalcaemia
- Tertiary – development of a hypersecretory parathyroid adenoma in an individual with longstanding secondary hyperparathyroidism

Primary hyperparathyroidism

This condition can be caused by the following:

- An adenoma in one of the parathyroid glands (75-80%)
- Hyperplasia of all of the parathyroid glands (10-15%)
- Parathyroid carcinoma (<5%)

The clinical features, with the exception of the bone changes are due to hypercalcaemia and are commonly summed up as 'bones, stones, abdominal groans and psychic moans'.

Bone: Osteitis fibrosa cystica (brown tumor), due to excess PTH

Renal: Formation of calcium-containing renal stones *&* Nephrocalcinosis

Gastrointestinal: Peptic ulcer, Pancreatitis, Vomiting & Abdominal pain

Neuromuscular: Generalized weakness

Psychiatric: Depression, Impaired memory & Emotional lability

Secondary Hyperparathyroidism (and Renal Osteodystrophy)

This most commonly arises in the setting of renal failure or vitamin D deficiency. In renal failure, there is loss of calcium and reduced synthesis of 1, 25-dihydroxy vitamin D_1 leading to hypocalcaemia and secondary hyperparathyroidism and there is retention of phosphate, which also induces secondary hyperparathyroidism. The result is hyperplasia of the parathyroid glands and skeletal changes comprising a mixture of osteitis fibrosa cystica (due to increased PTH-dependent osteoclastic resorption of bone) and osteomalacia (due to lack of vitamin D). The skeletal changes are referred to as renal osteodystrophy.

Hypoparathyroidism

The most common causes of hypoparathyroidism are:

- Surgical removal or ablation of the parathyroid glands during thyroidectomy
- Congenital absence of all of the parathyroid glands (Di George syndrome)
- Autoimmune destruction of the glands

The clinical manifestations, which are due to hypocalcaemia are:

- Increased neuromuscular excitability – this is manifest by the Chvostek sign (tapping along, the course of the facial nerve causes the facial muscles to twitch), Trousseau sign (occlusion of the arteries in the forearm by inflating a blood pressure cuff induces carpal spasm), perioral paraesthesia, and if severely hypocalcaemic, overt tetany.

Check Your Understanding

MCQs:

1) **Least malignant thyroid cancer is:**
   A- Papillary carcinoma
   B- Follicular carcinoma
   C- Medullary carcinoma
   D- Anaplastic carcinoma

2) **Which of the following is the commonest tumor of thyroid?**
   A- Papillary carcinoma
   B- Follicular carcinoma
   C- Medullary carcinoma
   D- Anaplastic carcinoma

3) **What are the cells in the thyroid which produce the calcitonin?**
   A- G cells
   B- C cells (also called as the parafollicular cells)

4) **What is the screening method for medullary carcinoma of thyroid?**
   A- Serum ALP
   B- Serum calcium
   C- Serum calcitonin
   D- Serum acid phosphatase

5) **Medullary carcinoma of thyroid arises from?**
   A- Parafollicular cells
   B- Cells lining the acini
   C- Capsule of thyroid
   D- Stroma of the gland

6) **Which of the following gene defects is associated with development of the medullary carcinoma of the thyroid?**
   A- RET proto oncogene
   B- FAP gene
   C- RB gene
   D- BRCA 1 gene

1-A 2-A 3-B 4-C 5-A 6- A

7) **A 44-year-old male without previous illness presents with a 3-week history of progressive hoarseness, shortness of breath, and stridor. He is found to have a firm, large, tender thyroid mass that by CT scan extends posterior to the trachea and into the upper mediastinum. A fine-needle aspirate shows pleomorphic spindle cells. He is taken to surgery, and the mass is resected. The mass infiltrates into adjacent skeletal muscle. Four of seven cervical lymph nodes have metastasis. Pulmonary metastases are also identified by a chest radiograph. Which of the following neoplasms is most likely?**

A- Papillary carcinoma
B- Follicular carcinoma
C- Medullary carcinoma
D- Anaplastic carcinoma

8) **Thyroid carcinomas are common accounting for 30% of all cancers.**

A- T
B- F

9) **Which one of the following doesn't arise from follicular epithelium? or which one of the following types is derived from the C-cells within the thyroid?**

A- Papillary
B- Follicular
C- Anaplastic
D- Medullary

10) **Highly aggressive and lethal tumors that can arise de novo or by dedifferentiation of a well-differentiated papillary or follicular carcinoma are?**

A- Papillary
B- Follicular
C- Anaplastic
D- Medullary

11) **One of the following is not correct in papillary carcinoma of thyroid:**

A- Can be reliably diagnosed using fine needle aspiration cytology
B- Always unifocal
C- Typically spreads to the cervical lymph nodes
D- Requires a total thyroidectomy for large tumors

7- D 8- B 9-D 10-C 11-B

11: Answer is B, why? Papillary carcinoma is usually mulitifocal. Lymphatic spread occurs to cervical lymph nodes. (Hematogenous spread occurs in case of follicular carcinoma.)

12) The most precise diagnostic screening procedure for differentiating benign thyroid nodules from malignant ones is:

A- Thyroid ultrasonography.
B- Thyroid scintiscan.
C- Fine-needle-aspiration biopsy(FNAB).
D- Thyroid hormone suppression.

13) Which of the following statements about follicular carcinoma <u>is/are</u> true?

A- It presents at a later age than papillary carcinoma.
B- It disseminates via hematogenous routes.
C- It is the most common type of well-differentiated thyroid carcinoma.
D- Extensive angioinvasion portends a poor prognosis.
E- Follicular carcinomas are frequently multicentric.

14) The malignancy which is common on long standing goiter?

A- PCT
B- MCT
C- FCT
D- Anaplastic

15) Cancer that develops after irradiation?

A- PCT
B- MCT
C- FCT
D- Anaplastic

12-C 13-A,B,D 14-C 15-A

12: Answer is C, why? Analysis of multiple series in which patients with thyroid nodules have undergone FNAB has demonstrated a false-negative rate of 2.4% and a false-positive rate of 3.3%.Sensitivity for this method is 92%; specificity 74% .This surpasses the other methods for accurate selection of patients who require surgical resection.
13: Answer is A,B,D, why? Follicular carcinoma is more common in older patients (peak incidence in the fifth decade). The tumor has a marked propensity for vascular invasion and spreads hematogenously to bone, lung, liver,and central nervous system sites.Local nodal metastases are less common than in papillarycarcinoma.Extensive angioinvasion indicates a less favorable prognosis. Papillary carcinoma is the most common type of well-differentiated thyroid carcinomas. Follicular carcinomas are rarely multicentric.
14: Answer is C, why? FCT= Follicular carcinoma of the thyroid
15: Answer is A, why? PCT= Papillary carcinoma of the thyroid

16) How can you distinguish between follicular adenoma and thyroid carcinoma?

A- Radionuclide scanning
B- Histological examination
C- Ultrasonography
D- Clinical manifestations

17) Which of the following is a feature of follicular adenomas?

A- Psamomma bodies
B- Orphan Annie Eye nuclei
C- Intact capsule
D- Amyloid deposits

18) Which of the following is indicative of a benign thyroid nodule?

A- Solitary nodule
B- Frequent exposure to radiation
C- Hot nodules
D- Cold nodules

16-B 17-C 18-C

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قال صلى الله عليه وسلم: {من سلك طريقًا يلتمس فيه علمًا سهَّل الله له بهِ طريقًا إلى الجنة}

دعواتنا لكم بالتوفيق
