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Any future corrections will be in the editing file , Click

Pathology

Thyroid nodules and neoplasms

439

Color index

- Important
- Doctor's note
- Extra info
- Main text
- ★ Male's slide
- ★ Female's slide

" اللهم لا سهل الا ماجعلته سهلا و انت تجعل الحزن إذا شئت سهلا "

Objective

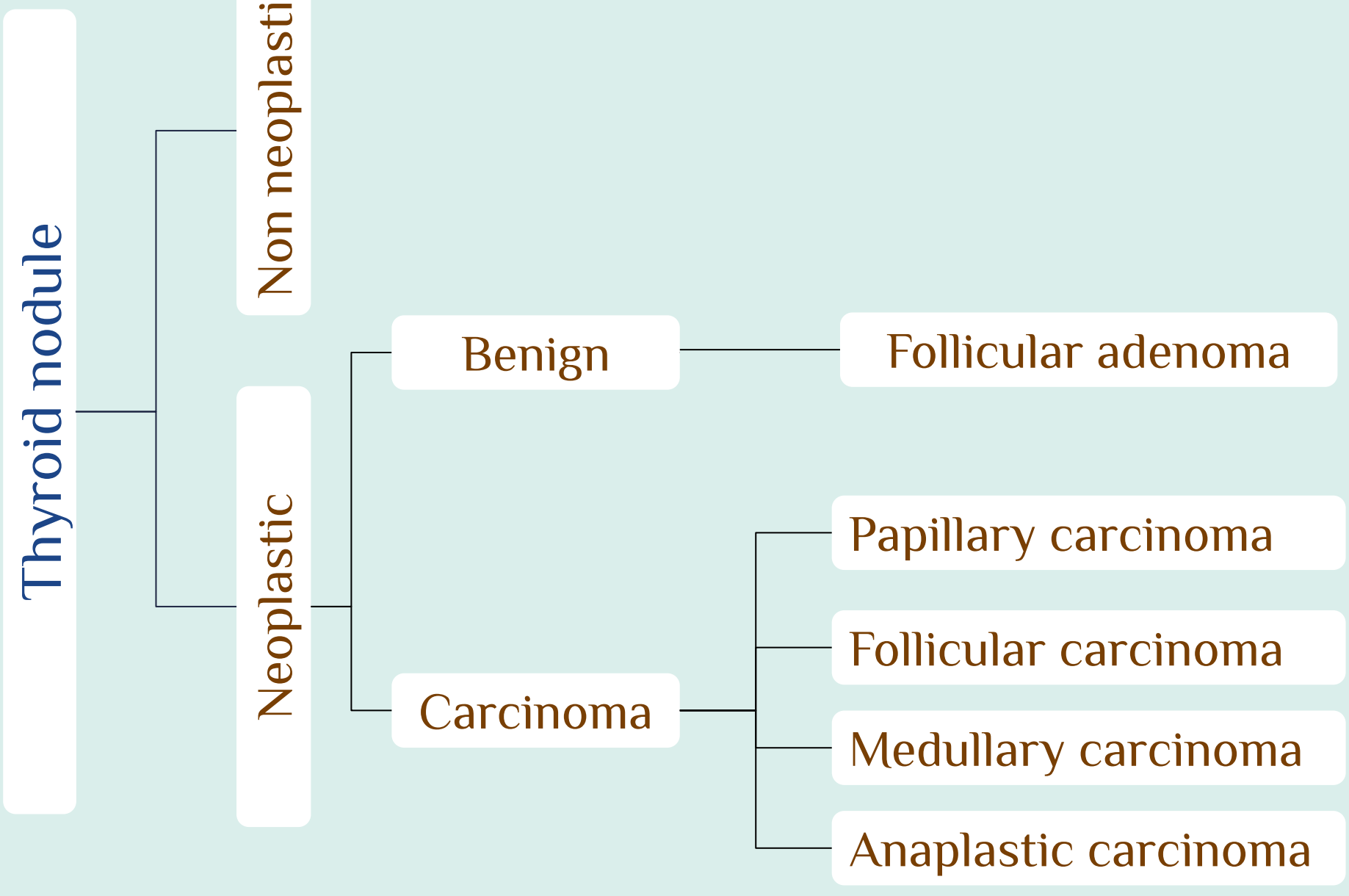
01 To Know the definition of a solitary nodule in the thyroid

02 To Recognize the differential diagnosis of a solitary thyroid nodule, neoplastic and non- neoplastic

03 To know the benign causes of thyroid nodules

04 To Understand the classification, pathology, gross and microscopic morphology and behavior of thyroid carcinoma (papillary, follicular, medullary and anaplastic)

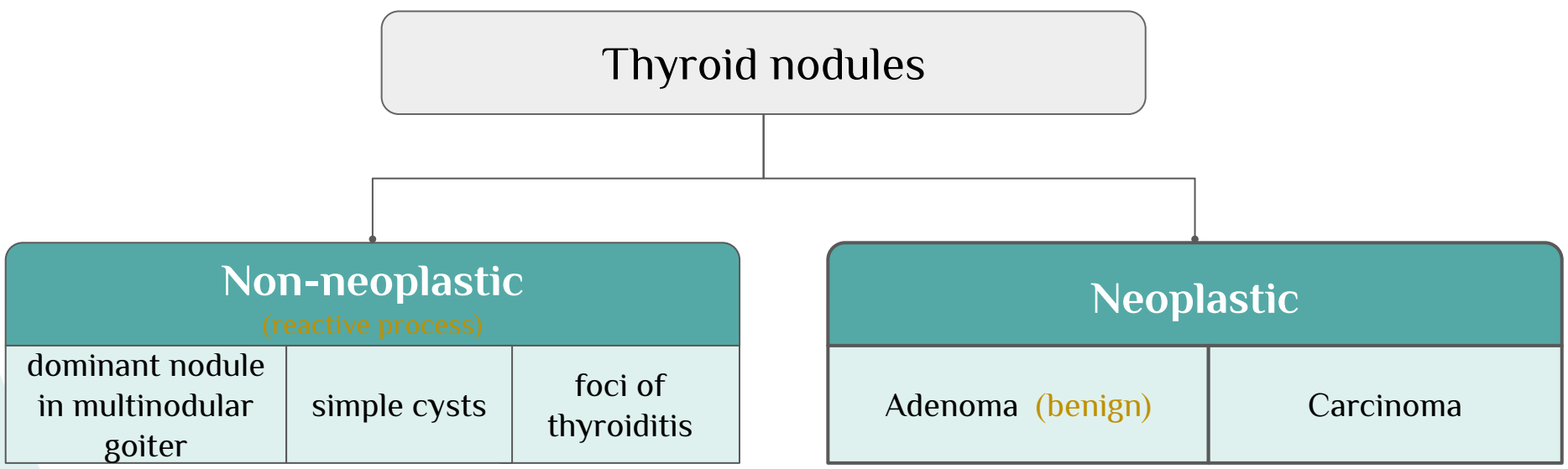
Overview



Thyroid nodules

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

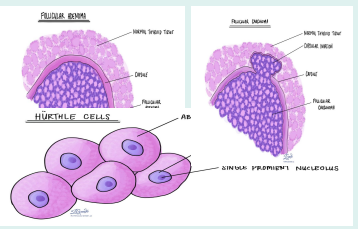
- Solitary nodules, in general, are more likely to be neoplastic than are multiple nodules , diffuse or multinodular are more toward a non neoplastic cause they're hyperplastic.
- Nodules in males are more likely to be neoplastic than are those in females
- Nodules in younger patients are more likely to be neoplastic than are those in older patients
- A history of radiation treatment to the head and neck region is associated with an increased incidence of thyroid malignancy
- Nodules that take up radioactive iodine in imaging studies (hot nodules) (cold nodules have worse prognosis) are more likely to be benign than malignant
- Ultimately, it is the morphologic evaluation of a given thyroid nodule by fine needle aspiration, combined with histologic study of surgically resected thyroid parenchyma, that provides the most definitive information about its nature
- A patient complains of an enlargement of the thyroid gland (euthyroid= no hyper or hypothyroidism), what are the investigations that can be done? Radioactive iodine uptake and ultrasound .
- If the solitary nodule appeared in the ultrasound (in rt. lobe or lt. lobe or isthmus) this is more likely to be neoplastic (tumor whether it's benign or malignant)., but if there were multiple nodules we should think of the non-neoplastic lesions .
- If there was a single nodule in a male patient and we are suspecting a neoplasm , after doing the ultrasound and radioactive-iodine uptake the 2nd step will be fine needle aspiration. Fine needle aspiration is cytology (dealing with cells)., we aspirate the cells by a needle and spread them on the slide and look at them under the microscope , we don't see intact tissue we see scattered cells.
- take up radioactive I = FUNCTIONAL (HOT NODULES)
- don't take = NON FUNCTIONAL (COLD NODULES)

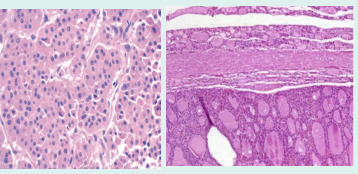


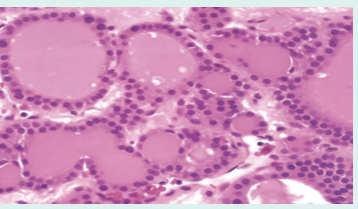
Adenoma

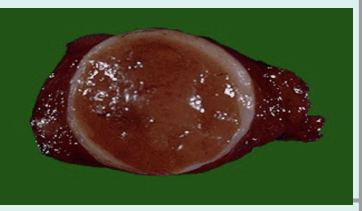
Follicular adenoma

Overview	-Adenomas of the thyroid are benign neoplasms derived from follicular epithelium -Follicular adenoma is a non-cancerous thyroid gland tumour -Follicular adenomas usually are solitary , round and firm and may be felt as a lump in the front of the neck
Clinical manifestation	Presents with long standing solitary thyroid nodule
Diagnosis	- **radionuclide scanning** : adenomas appear as **cold nodules** (non-functioning = not producing follicles or thyroid hormones) relative to the adjacent normal thyroid gland. -Essential techniques used in the preoperative evaluation of suspected adenomas are **ultrasonography** and **fine needle aspiration biopsy** [1]
Morphological changes	❖ The cells in a follicular adenoma are separated from the normal thyroid gland by a barrier called a capsule. the tumour is so well separated from the normal thyroid tissue, it usually forms a nodule that can be felt in the neck when the thyroid gland is examined ❖ Grossly : The typical thyroid adenoma is a **solitary**, spherical lesion that compresses the adjacent non-neoplastic thyroid , encapsulated ❖ Microscopically : 1) The neoplastic cells are demarcated from the adjacent parenchyma by a well-defined, intact **capsule** , These features are important in making the distinction from multinodular goiters, which contain multiple nodules on their cut surface , do not demonstrate compression of the adjacent thyroid parenchyma, and lack a well-formed capsule. 2) the constituent cells are arranged in uniform follicles that contain colloid (benign neoplasm: formed of the same component “thyroid follicles”) 3) Occasionally, the neoplastic cells acquire brightly eosinophilic granular cytoplasm (**oxyphil or Hürthle cell change**) , the clinical presentation and behavior of a Hürthle cell adenoma are no different from those of a conventional adenoma ❖ On clinical and morphologic grounds, they may be difficult to distinguish from a dominant nodule in multinodular goiter, or from follicular carcinomas (morphological changes only) ★ Careful evaluation of the integrity of **the capsule is critical in distinguishing follicular adenomas from follicular carcinomas, which demonstrate capsular and/or vascular invasion** , In other word , the cells in a follicular adenoma can look very similar to the cells in a type of thyroid cancer called follicular carcinoma. The only difference between a follicular adenoma and a follicular carcinoma is that all of the abnormal cells in a follicular adenoma are separated from the normal thyroid gland by the capsule. In contrast, in a follicular carcinoma, the tumour cells have broken through the capsule and have entered the surrounding normal thyroid gland. Pathologists describe this as capsular invasion. ❖ **Spectrum of differential diagnosis if a solitary nodule appears on the ultrasound scan of thyroid gland:** 1- Non-neoplastic : a dominant nodule in multinodular goiter 2- Adenoma : benign neoplasm 3- follicular carcinoma It is difficult to distinguish between them, but if the background shows multiple nodules → **multinodular goiter**. But if it is a single nodule → **neoplasm** . But there’s no way to tell if it was benign adenoma or follicular carcinoma neither on ultrasound nor clinically or even by the fine needle aspiration . We need surgery , excision of the thyroid lobe (thyroidectomy) to differentiate between them in histological slides
Prognosis	❖ Suspected adenomas of the thyroid are removed surgically to exclude malignancy ❖ Thyroid adenomas carry an excellent prognosis and do not recur or metastasize



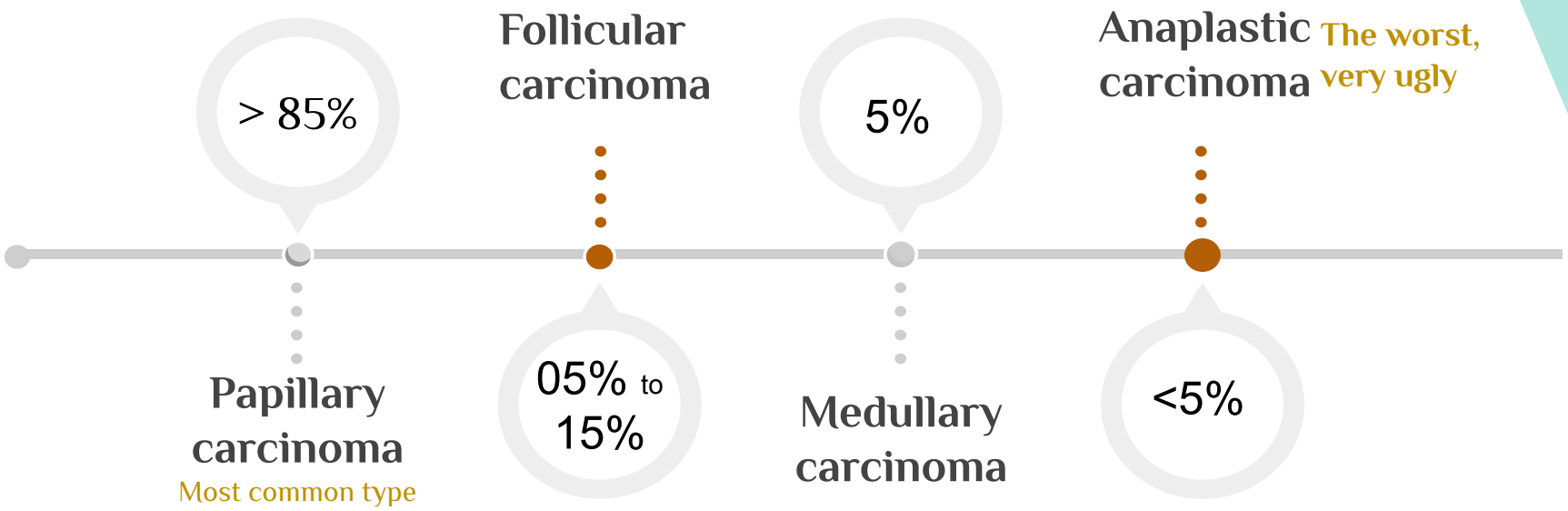






1-A fine needle aspiration (FNA) is a procedure which removes a small amount of thyroid tissue. This tissue is then examined by a pathologist under the microscope.
2-A Hurthle cell is thyroid tissue that has a distinct look under the microscope; it is bigger than a follicular cell and has pink-staining cellular material.

Carcinoma



- Carcinomas of the thyroid are relatively uncommon in the United States, accounting for about 1.5% of all cancers. A female predominance has been noted among patients who develop thyroid carcinoma in the early and middle adult years.
- Most thyroid carcinomas (except medullary carcinoma) are derived from the thyroid follicular epithelium, and of these, the vast majority are well-differentiated lesions

Risk factor for thyroid cancer include: :

- Environmental Factors :

1) The major risk factor predisposing to thyroid cancer is exposure to ionizing radiation particularly during the first 2 decades of life , there was a marked increase in the incidence of papillary carcinomas among children exposed to ionizing radiation . However Majority of thyroid carcinomas associated with previous exposure to ionizing radiation
2) Deficiency of dietary iodine (and by extension, an association with goiter) is linked with a higher frequency of follicular carcinomas

- Having a family history of thyroid disease or thyroid cancer.
- Having certain genetic conditions such as familial medullary thyroid cancer (FMTC), multiple endocrine neoplasia type 2A syndrome (MEN2A), or multiple endocrine neoplasia type 2B syndrome (MEN2B)
- Most often Being between between the ages of 25 and 50
- The incidence of papillary carcinoma has increased markedly in the last 30 years between the ages of 25 and 50
- Having a history of goiter (enlarged thyroid) , Thyroid cancer may not cause early signs or symptoms. It is sometimes found during a routine physical exam , Signs or symptoms may occur as the tumor gets bigger
- Solitary or multifocal lesions

different types of thyroid cancer:

- Well-differentiated tumors (papillary thyroid cancer and follicular thyroid cancer) can be treated and can usually be cured.
- Poorly differentiated and undifferentiated tumors (anaplastic thyroid cancer) are less common. These tumors grow and spread quickly and have a poorer chance of recovery. Patients with anaplastic thyroid cancer should have molecular testing for a mutation in the BRAF gene
- Medullary thyroid cancer is a neuroendocrine tumor that develops in C cells of the thyroid. The C cells make a hormone (calcitonin) that helps maintain a healthy level of calcium in the blood.

Papillary carcinoma (PTC)★

Focus on the genes, "الجينز هذي يحبونها في الاختبار"

Overview

- papillary carcinoma represent the most common form of thyroid cancer , and it is the most common form of well-differentiated thyroid cancer
- These tumors may occur at any age, and they account for the vast majority of thyroid carcinomas
- Risk factor : associated with previous exposure to ionizing radiation (head and neck radiotherapy)
  - spread to lymph nodes
  - There are different types of papillary thyroid carcinoma and each type is called a variant , The most common variants are classic and follicular
- There are over a dozen variants of papillary thyroid carcinoma, but the most common is one composed predominantly or exclusively of follicles (**follicular variant of papillary thyroid carcinoma**) in which the nuclear features are present but the architecture is more follicular than papillary

Pathogenesis

rearrangements of the tyrosine kinase receptors **RET** or **NTRK1** or activating point mutations in **BRAF**

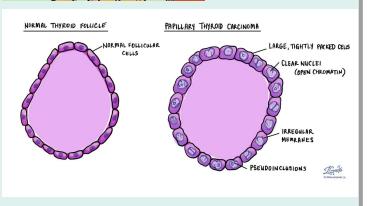
Clinical manifestations

- Papillary carcinomas are nonfunctional [1] tumors, so they manifest most often as a **painless mass in the neck**, either within the thyroid or as **metastasis in a cervical lymph node** (might be the first presentation)

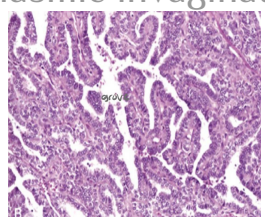
Diagnosis

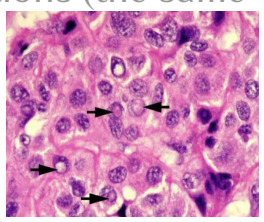
- A preoperative diagnosis usually can be established by fine-needle
- The diagnosis of papillary carcinoma is based on **nuclear features** even in the absence of a papillary architecture .
  - So in PTC we expect to see papillary architecture (classic type), but there are other variants without papillary architecture so we depend on nuclear features for the diagnosis

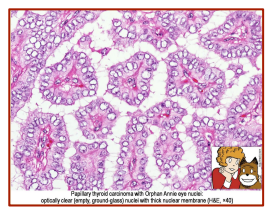
Morphological changes

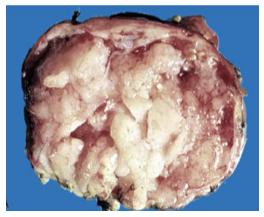


- The **nuclei feature** of papillary carcinoma cells show:
  1)Change of nuclear size and shape: nuclear enlargement, elongation and overlapping
  2)Chromatin characteristics : Very finely dispersed chromatin, with an **optically clear (grooved clear nucleus)** appearance, giving rise to the designation ground glass or , "Orphan Annie eye" nuclei is a significant feature , with thick nuclear membrane
  3)cytoplasmic invagination : may give the appearance of **intranuclear inclusions (pseudoinclusions)** Intranuclear pseudoinclusions are cytoplasmic invaginations (the same color as cytoplasm)
- Archateral pattern :
  1) Papillary architecture (in the classic type)
  2) Grooves (coffee bean like appearance)
- Other pathological features:
  1) Concentrically calcified (body) structures termed **psammoma bodies** often are present (not necessary for the diagnosis)







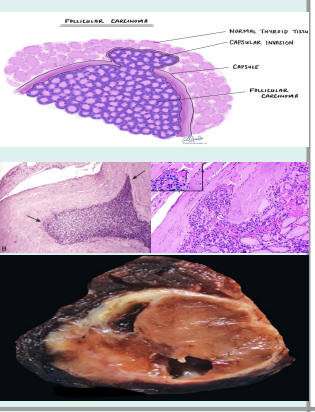


Prognosis

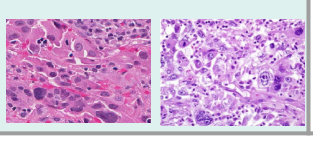
- Papillary carcinomas are indolent lesions, with 10-year survival rates in excess of 95%.
- Prognosis of PTC is dependent on several factors including 1) directly related to age Patients under 55 years of age do much better than patients who are over 55 years of age (in general, the prognosis is less favorable among patients older than 55 years), the presence of extrathyroidal extension, and presence of distant metastases (stage)
  - related to tumor size. Less than 1.5 cm [1/2 inch] is a good prognosis

1-Non functioning tumors usually do not cause symptoms until they grow large or spread to other parts of the body (no hormone secretion)

Follicular carcinoma

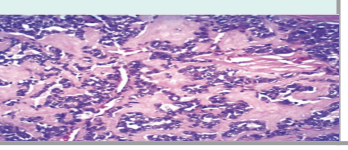
Prevalence :	❖ 5% to 15% of primary thyroid cancers , More common in women (3 : 1) ❖ Peak incidence between 40 and 60 years ,**More frequent in areas with dietary iodine deficiency** is a risk factor ❖ It develops from the follicular cells
Pathogenesis :	**Mutations in the RAS family** of oncogenes
Clinical manifestation :	manifest most frequently as solitary cold thyroid nodules
Morphology 	❖ On microscopic examination **most follicular carcinomas are composed of fairly uniform cells forming small follicles**, reminiscent of normal thyroid Follicular carcinomas may be show two patterns of invasion: - **widely invasive** [1] : infiltrating the thyroid parenchyma and extrathyroidal soft tissues. - **minimally invasive** [2] : are sharply demarcated lesions that may be impossible to distinguish from follicular adenomas on gross examination.This distinction requires extensive histologic sampling of the tumor capsule–thyroid interface, to exclude capsular and/or vascular invasion ❖ Follicular lesion with capsular or vascular invasion but without papillary nuclear features
Prognosis	These neoplasms tend to metastasize through the **bloodstream** [3] to the lungs, bone, and liver ❖ **Minimally invasive**(well encapsulated), 10 year survival rate 90% ❖ **Widely invasive carcinoma** [4] , 10 year survival rate less than 50% ❖ **We need to cut the whole capsule and examine it under the microscope:** 1- capsular invasion by the neoplastic cells 2- vascular invasion outside the capsule If we saw one of the previous two points → follicular carcinoma

Anaplastic carcinoma

Overview	-Anaplastic carcinomas of the thyroid are undifferentiated tumors -high grade tumor- of the thyroid follicular epithelium. Can be arising from a more differentiated carcinoma (papillary) -undifferentiated thyroid carcinoma, is a rare, highly aggressive malignant tumor
Prevalence	Older age group > 65 year
Pathogenesis	Anaplastic Carcinomas: **Inactivating point mutations in the p53 tumor suppressor gene** are rare in well-differentiated thyroid carcinomas but common in anaplastic tumors.
Prognosis	-Lethal (100%) = the prognosis is very bad -continues to be one of the most deadly diseases worldwide and carries a very poor prognosis
Manifestation	Anaplastic carcinomas manifest as **bulky masses** that typically grow rapidly beyond the thyroid capsule into adjacent neck structures ,painful, firm, low anterior neck mass usually fixed to the underlying structures Compressive symptoms including:Hoarseness, dysphagia, dyspnea, and cough
Morphology 	On microscopic examination, these neoplasms are composed of **highly anaplastic cells, which may be** **-large pleomorphic giant cell** occasional osteoclast-like multinucleated giant cells **-spindle shaped cell** with sarcomatous appearance -mixture spindle and gait cell -small cells

1-This means that the tumour is not surrounded by a capsule or that only a small area of capsule still remains. The cells in a widely invasive tumors have spread much further into the normal thyroid than the cells in a minimally invasive tumour. In some cases, the spread of tumour cells into the normal thyroid gland can be seen without a microscope during the gross examination (could be distinguished from adenoma)
2-This means that the tumour is surrounded by a capsule but tumour cells were found spreading past the capsule into the normal thyroid gland. The tumour cells that have spread past the capsule are usually only found after the tissue has been examined under the microscope.
3-Follicular carcinoma is more likely to show vascular invasion than other types of thyroid cancer.
4-Widely invasive tumours are more likely to spread to other parts of the body such as the lungs or bone. The spread of tumour cells to another body site is called metastasis.

Medullary carcinoma ★

Overview	-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, the measurement of which plays an important role in the diagnosis and postoperative follow-up of patients.**
Prevalence	- Sporadic : About 70% of tumors. The remainder occurs in the setting of MEN syndrome - Hereditary (familial : About 30%) : 1) Due to MEN 2A or 2B syndrome or as: 2) Familial medullary thyroid carcinoma (FMTC) Familial tumors **without** an associated MEN syndrome Caused by gain of function germline mutations in the RET gene.
Pathogenesis	-Medullary Thyroid Carcinomas: Familial medullary thyroid carcinomas occur in multiple endocrine neoplasia type 2 (MEN-2) **RET in proto oncogene mutation** -Medullary carcinoma can be sporadic (occurs in anyone) or within a syndrome (MEN-2) with other endocrine neoplasm RET proto oncogene mutation
Diagnosis	Usually discovered by screening test for serum calcitonin or peripheral blood RET oncogene mutational analysis
Morphology Microscopically 	- Medullary carcinomas may arise as a solitary nodule (if solitary, mainly its sporadic) or may manifest as multiple lesions involving both lobes of the thyroid. - Multicentricity is particularly common in familial cases - Larger lesions often contain areas of necrosis **On microscopic examination** : 1-composed of **polygonal to spindle-shaped cells**, which may form **nests**, trabeculae, and even follicles 2-**Amyloid deposits** [1] from calcitonin are present in the adjacent stroma in many cases and are a distinctive feature (congo and red stain) 3-One of the characteristic features of **familial medullary carcinomas** is the presence of multicentric/multiple C **cell hyperplasia** in the surrounding thyroid parenchyma, a feature usually absent in sporadic lesions

1-**Characteristic** as pink area. It's a protein we can see it by congo red stain

Summary

	Follicular adenoma	Papillary carcinoma	Follicular carcinoma	Medullary carcinoma	Anaplastic carcinoma
Neoplastic nodule	Benign	Malignant			
Overview		-the most common form of thyroid cancer -well-differentiated thyroid cancer		neuroendocrine neoplasms derived from the parafollicular cells	undifferentiated thyroid carcinoma, is a rare, highly aggressive malignant tumor
Risk factor		previous exposure to ionizing radiation	More frequent in areas with dietary iodine deficiency		
Spread		metastasis in a cervical lymph node	bloodstream		
Pathogenesis		rearrangements of the tyrosine kinase receptors RET or NTRK1 or activating point mutations in BRAF	Mutations in the RAS family of oncogenes	Medullary Thyroid Carcinomas: Familial medullary thyroid carcinomas occur in multiple endocrine neoplasia type 2 (MEN-2) RET in proto oncogene mutation	Inactivating point mutations in the p53 tumor suppressor gene
Morphological changes	Grossly : solitary, , encapsulated (covered by capsule)		solitary	solitary nodule or may manifest as multiple lesions	
	Microscopically : -well-defined, intact capsule -eosinophilic granular cytoplasm -Hürthle cell changes	-nuclear changes : Orphan Annie eye" nuclei = optically clear (grooved clear nucleus) , nuclear enlargement, and elongated , Very finely dispersed chromatin -intranuclear inclusions (pseudoinclusions) -calcified (body) structures =psammoma bodies	uniform cells forming small follicles,,it can be widely invasive that infiltrate the thyroid parenchyma or minimally invasive which are sharply demarcated lesions. -capsular and/or vascular invasion	-polygonal to spindle-shaped cells, that form nests -Amyloid deposits -C cell hyperplasia characteristic features of familial medullary carcinomas	-large pleomorphic giant cell occasional osteoclast-like multinucleated giant cells -spindle shaped cell with sarcomatous appearance -mixture spindle and gait cell -small cells
Diagnosis	-radionuclide scanning : cold nodule -ultrasonography -fine needle aspiration biopsy	-nonfunctional tumors (cold nodule) -fine needle aspiration biopsy (based on nuclear features)	-cold thyroid nodules	-congo and red stain -secrete calcitonin measured in diagnosis and postoperative follow-up of patients	
Prognosis	excellent prognosis and do not recur or metastasize	indolent lesions, with 10-year survival rates in excess of 95%	Minimally invasive (well encapsulated) will have 10 year survival rate 90%. If Widely invasive,10 year survival rate less than 50%.		-the prognosis is very bad Lethal (100%)

QUIZ!

MCQs

01 | 33-year-old woman presents with a swelling in her neck, which she first noticed 2 months ago. Physical examination reveals a solitary, nontender nodule of the thyroid gland measuring 2 cm in diameter. Thyroid function tests are within normal limits. The nodule does not accumulate 125 Iodine on thyroid scintiscan.A biopsy was taken showed intact capsule. Which of the following is the most likely diagnosis?			
A) Follicular adenoma	B) Metastatic carcinoma	C) Papillary thyroid carcinoma	D) Multinodular goiter
02 | 36-year-old woman presents with swelling in her neck that she first noticed 3 months ago. She also complains of intermittent watery diarrhea over the same time period. Physical examination reveals a nontender nodule in the left lobe of the thyroid. The patient's mother died of thyroid cancer 8 years ago. The thyroid nodule is found to be "cold" by radioiodine scintiscan. A needle biopsy of the nodule reveals malignant cells and homogeneous eosinophilic material and with multicentric C cells hyperplasia). Laboratory studies would likely show elevated blood levels of which of the following hormones in this patient?			
A) ca	B) PTH	C) T3	D) T4
03 | A 32-year-old woman presents with a solitary, nontender, firm nodule on the left side of her neck. Thyroid function tests are within normal limits. A fine-needle biopsy reveals malignant cells. The tumor is excised and examined by light microscopy (showed optically clear appearance with with calcification and intracellular inclusion). What is the appropriate pathologic diagnosis?			
A) Follicular adenoma	B) Metastatic carcinoma	C) Papillary thyroid carcinoma	D) Multinodular goiter
04 | The most important feature of follicular carcinoma is ?			
A) capsular invasion	B) vascular invasion	C) both	D) nuclear pleomorphism
05 | A 45-year-old man presents with swelling in the anterior portion of his neck. Physical examination reveals an enlarged nodular thyroid. Thyroid function tests are within normal limits. A thyroid scintiscan shows a dominant "hot" nodule. A biopsy of this nodule reveals neoplastic cells with evidence of vascular and capsular invasion. X-rays demonstrate distant bony metastases. What is the most likely diagnosis?			
A) Anaplastic Carcinoma	B) Follicular Carcinoma	C) Medullary Carcinoma	D) Metastatic Carcinoma
06 | oncologist performed fine needle aspiration on a 49 years old man , histopathology picture showed neoplasm arising from parafollicular cell and it is linked to familial mutation MEN-2 , what is the diagnosis ?			
A) Anaplastic Carcinoma	B) Follicular Carcinoma	C) Medullary Carcinoma	D) Metastatic Carcinoma

MCQs Answer key	01	02	03	04	05	06
	A	A	C	C	B	C

" اللهم علمنا ماينفعنا ، وانفعنا بما علمتنا وزدنا علما يارب العالمين "

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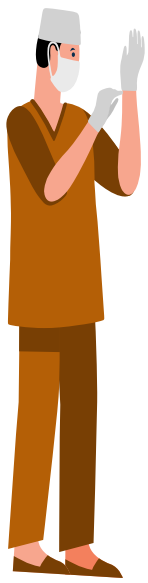

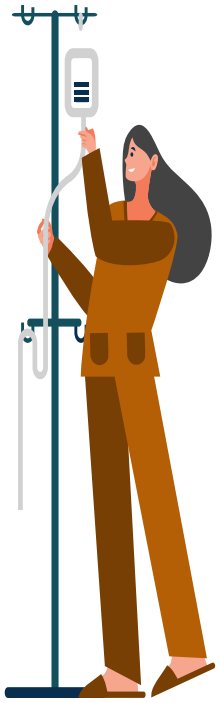

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