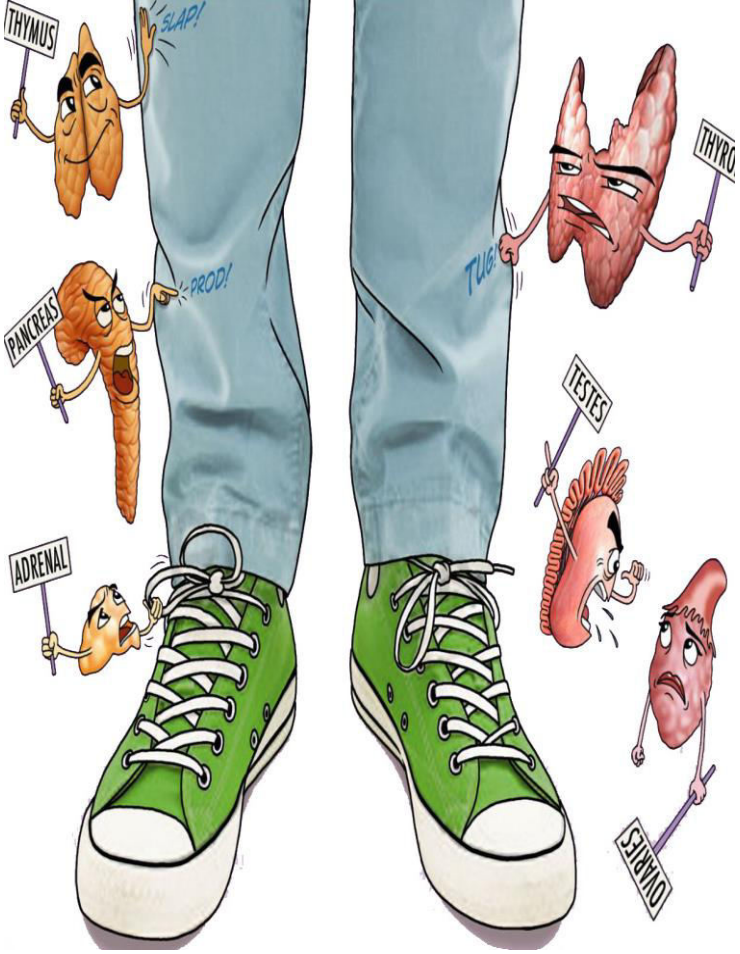
PATHOLOGY TEAM 436

MEDICINE
KING SAUD UNIVERSITY



Thyroid Nodules and Neoplasms

تمت المراجعة
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Objectives:

- Know the definition of a solitary nodule in the thyroid
- Recognize the differential diagnosis of a solitary thyroid nodule
- Understand the classification , pathology and behaviour of thyroid carcinoma

● Black: Doctors' slides. ● Red: Important! ● Light Green: Doctors' notes ● Grey: Extra.
● *Italic black: New terminology.*

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. (Solitary nodules are the opposite of multiple nodules, they are more suspicious whether benign or malignant)
- Nodules in males are more likely to be neoplastic than are those in females.(Because females have other thyroid conditions)
- Nodules in younger patients are more likely to be neoplastic than are those in older patients. (Not for sure just to help you think in a way for diagnosis)
- A history of radiation treatment to the head and neck region is associated with an increased incidence of thyroid malignancy. (People with history of radiation have a higher risk to develop malignancy)
- Nodules that take up radioactive iodine in imaging studies (hot nodules-active, takes up iodine) are more likely to be benign than malignant. (Malignancies are usually not functioning-cold nodules)
- Ultimately, it is the morphologic evaluation of a given thyroid nodule by fine needle aspiration(FNA-to distinguish between benign and malignant but doesn't distinguish between malignancies "Adenoma and carcinoma), combined with histologic study of surgically resected thyroid parenchyma, that provides the most definitive information about its nature.(The first steps of thyroid mass evaluation is examination, radioactive iodine, ultrasound. When a mass is detected, we move to FNA then finally surgery depending on clinical situation and diagnosis of FNA)

Classification:

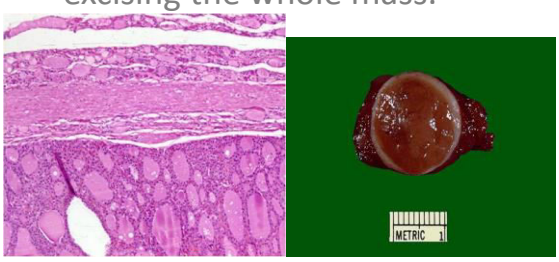
Non-Neoplastic	Neoplastic
• Dominant nodule in multinodular goiter (Some follicles are distended forming colloidal cysts) • Simple cysts • Foci of thyroiditis	• Adenoma • Carcinoma

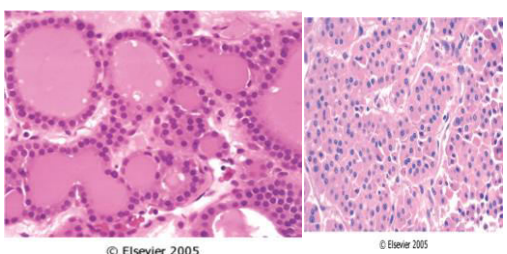
Adenoma:

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

- Follicular adenomas usually are solitary (single/one).
- On clinical and morphologic grounds, they may be difficult to distinguish from a dominant nodule in multinodular goiter, or from follicular carcinomas. The definitive diagnosis of thyroid adenoma can be made only by histological examination of excising the whole mass because we need the capsule to differentiate. (In FNA, we can only differentiate between adenoma and hyperplastic nodule in multinodular goiter)
- In general, follicular adenomas are not forerunners يتحولto carcinomas. (We cannot tell if its adenoma or carcinoma unless the thyroid gland is excised)
- The typical thyroid adenoma is a solitary, spherical lesion that compresses the adjacent non-neoplastic thyroid.
- 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.
- On microscopic examination, the constituent cells are arranged in uniform follicles that contain colloid . (Protrusion of follicular epithelium out of the capsule indicate carcinoma-invasion)
- Occasionally, the neoplastic cells acquire brightly eosinophilic granular cytoplasm (Hürthle / oxyphil cell change). ITS JUST A MORPHOLOGICAL VARIANT THAT HELPS IN DIAGNOSING .

- The clinical presentation and behavior of a Hürthle cell adenoma are no different from those of a conventional adenoma.
- Careful evaluation of the integrity of the capsule is critical in distinguishing follicular adenomas from follicular carcinomas, which demonstrate capsular and/or vascular invasion (The main criteria of differentiation) . Again, The definitive diagnosis of thyroid adenoma can be made only by histological examination of excising the whole mass.





- On radionuclide scanning, adenomas appear as **Cold** nodules (usually not functioning) relative to the adjacent normal thyroid gland.
- Essential techniques used in the preoperative evaluation of suspected adenomas are ultrasonography and fine needle aspiration biopsy.
- Suspected adenomas of the thyroid are removed surgically to exclude malignancy. (Adenomas can either be hot or cold nodules)
- Thyroid adenomas carry an excellent prognosis and do not recur or metastasize.

Carcinomas : (Are always cold nodules)

- Carcinomas of the thyroid : 1.5% of all cancers.
- The major risk factor predisposing to thyroid cancer is exposure to ionizing radiation(Environmental Factors).
- Majority of thyroid carcinomas associated with previous exposure to ionizing radiation.
- Most often between the ages of 25 and 50.
- **Solitary or multifocal lesions.**

Carcinomas[1]	Incidence	Gene mutation (pathogenisis)
Papillary Thyroid Carcinomas (If papillae is seen, we have to exclude the possibility of papillary carcinoma so if its not a carcinoma, its obviously an adenoma)	**> 85% of cases**	Rearrangements of the tyrosine kinase receptors **RET or NTRK1** or activating point mutations in BRAF. The incidence of papillary carcinoma has increased markedly in the last 30 years.
Follicular Thyroid Carcinomas	05% to 15% of cases	Mutations in the RAS family of oncogenes.
Medullary Thyroid Carcinomas	5% of cases	**Familial** medullary thyroid carcinomas occur in multiple endocrine neoplasia type 2 (MEN-2). RET protooncogene mutation.
Anaplastic Carcinomas	< 5% of cases	Inactivating point mutations in the p53 tumor suppressor gene are rare in well-differentiated thyroid carcinomas but common in anaplastic tumors.

(1) Other tumors of the thyroid are lymphoma, metastases and sarcoma

Papillary thyroid carcinomas (PTC):

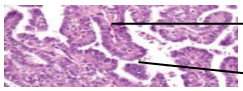
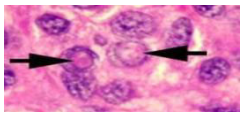
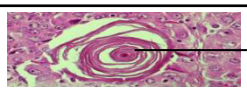
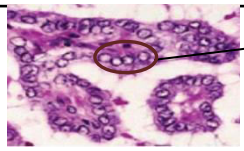
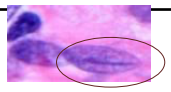
Usually metastasize and the most common site are lymph nodes. Oftenly, the first presentation is cervical lymphadenopathy. So we must suspect PTC. By FNA we can detect it and this type is called metastatic papillary thyroid carcinoma .

General features

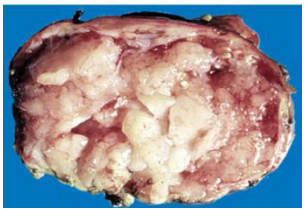
* The most **common** form of thyroid cancer(%85) .
* May occur at **any age**. (even in children)
* Associated with previous exposure to ionizing **radiation** .
* **Nonfunctional** (no hormones production = cold nodules =they do not take up radioactive iodine)

Indolent course = slow growing))* They are **indolent** lesions

Histopathology

* **Papillary architecture** (finger like projections.(this case with fibrovascular cores	 fibrovascular papillary stricture
(pseudoinclusion): Invagination of the cytoplasm may give the appearance of intranuclear inclusion • كأن السايتوبلازم داخل جوا النيوكليس. بس مو حقيقة داخل بس مع transverse cut طلع كذا	 pink spot : invagination of eosinophilic cytoplasm
* **psammoma bodies :**Concentrically calcified structures (often present)	 psammoma
* The nuclei of papillary carcinoma cells: (they have unique features of nuclei, which make the NFA sufficient for diagnosis)	
* **(Orphan Annie eye nucleus)** : very finely dispersed chromatin, with an optically clear appearance, giving rise to the designation ground glass	  carton character
* **Grooves** : grooved nuclei	 

Metastasis	Unlike follicular carcinoma which disseminates hematogenously , papillary carcinomas are metastasizing into **cervical lymph node** (lymphatic metastasis).
manifestations	they manifest most often as a **painless** mass in the neck, either within the thyroid or as metastasis in a cervical lymph node.
Diagnosis	*the diagnosis of papillary carcinoma is **based on nuclear features** even in the absence of a papillary architecture. * So, preoperative diagnosis usually can be established by **fine-needle aspiration.**

Variation	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** " absence of papillary structures , but presence of unique nuclear features" **).**
Prognosis associated with 10-year survival rates in excess of 95%.	:Prognosis of PTC is dependent on several factors including * **Age :** (in general, the prognosis is less favorable among patients older than 40 years). ***stage :** the presence of extra-thyroidal extension, and presence of distant metastases
Gross appearance	 un-encapsulated , infiltrative and may be multifocal .

It is true that it metastasize but its not an aggressive tumor so it has a good prognosis depending on age and stage (it depends more on the stage).

Treatment: patient undergo thyroidectomy and remove lymph nodes if there was metastases. But if not, the lymph nodes will not be removed.

There are two variants:

Classical: papillary variant depend on papillary structures

Follicular variants: exclusive follicles depend on the presence of nuclear features such as(orphan annie eye nucleus, psammoma bodies, pseudo-inclusions and grooves). So it is called follicular variant of papillary thyroid carcinoma

Not all PTC have the same histopathology(nuclear features), we must look at it at a higher magnification.

Follicular carcinoma

- 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
- Follicular carcinomas manifest most frequently as solitary cold thyroid nodules.
- These neoplasms tend to metastasize through the bloodstream to the lungs, bone, and liver.
- Minimally invasive(well encapsulated: only focal break-through or focal vascular invasion), 10 year survival rate 90%.
- Widely invasive carcinoma (scattered capsule and tumor), 10 year survival rate less than 50%.

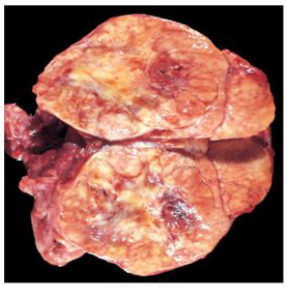
Morphology

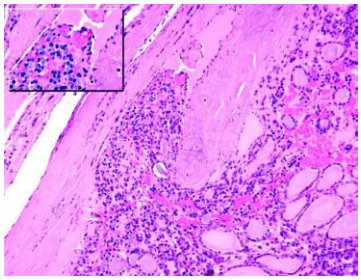
On microscopic examination, most follicular carcinomas are composed of fairly uniform cells forming small follicles, reminiscent of normal thyroid.(Depend on capsular and/or vascular invasion) (Here it is more crowded with absence of nuclear features looks like the normal thyroid gland)

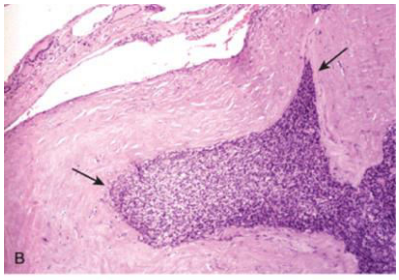
Follicular carcinomas may be:

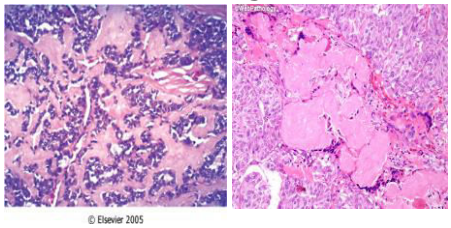
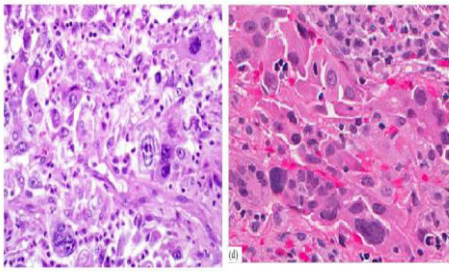
1- Widely invasive, infiltrating the thyroid parenchyma and extrathyroidal soft tissues.

2- Minimally invasive, 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







	General info	Morphology
Medullary carcinoma MEN syndrome has two types: Type 1: associated with pituitary, para-thyroid and pancreas Type 2: associated with medullary carcinoma	Medullary carcinomas of the thyroid are *neuroendocrine neoplasms* *made up of cells that are a combination of hormone-producing endocrine cells and nerve cells* *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. 1 About 70% of tumors arise sporadically No family history. 2 The remainder occurs in the setting of MEN syndrome 2A or 2B (30%) or as 3 Familial tumors without an associated MEN syndrome (familial medullary thyroid carcinoma, or FMTC).	• Polygonal to spindle cells • Amyloid deposition (congo-red stain) aggregates of proteins that become folded into a shape that allows many copies of that protein to stick together forming fibrils • Bilaterality. Both loops • Multicentricity (multifocal) having multiple centers of origin • Necrosis • Hemorrhage  © Elsevier 2005 EM: Neuro-secretory granules are also an important feature for diagnosis
Anaplastic Carcinomas	• Anaplastic carcinomas of the thyroid are undifferentiated tumors of the thyroid follicular epithelium. • Can be arising from a more differentiated carcinoma (papillary) These tumors starts differentiated then becomes undifferentiated resulting in anaplastic carcinomas (Cells are highly pleomorphic) • Lethal (100%) (Poor prognosis) • Older age group > 65 year	Highly anaplastic cells: (1) large, pleomorphic giant cells, including occasional osteoclast-like multinucleated giant cells (2) spindle cells with a sarcomatous appearance neoplastic cells resembling embryonic connective tissue. (3) mixed spindle and giant cells (4) small cells 

Robbin's Corner :

THYROID NEOPLASIA

t BASIC PRINCIPLES

A. Usually presents as a distinct, solitary nodule

1. Thyroid nodules are more likely to be benign than malignant,

B. ^{01}I radioactive uptake studies are useful to further characterize nodules.

1. Increased uptake ('hot' nodule) is seen in Graves disease or nodular goiter.
2. Decreased uptake ('cold' nodule) is seen in adenoma and carcinoma; often warrants biopsy

C. Biopsy is performed by fine needle aspiration (FNA).

n. FOLLICULAR ADENOMA

A. Benign proliferation of follicles surrounded by a fibrous capsule (Fig. 15,4)

B, Usually nonfunctional; less commonly, may secrete thyroid hormone

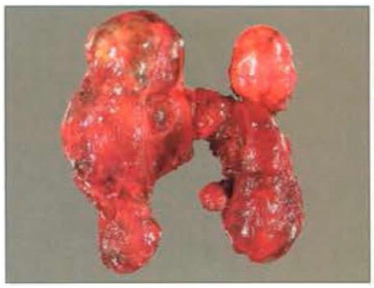


Fig. 15.2 Multinodular goiter. (Courtesy of Jamie Steinmetz, MO)

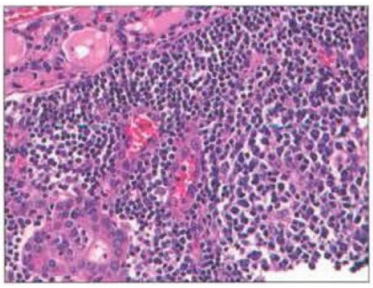


Fig. 15.3 Hashimoto thyroiditis.

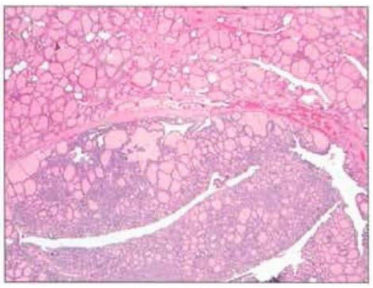
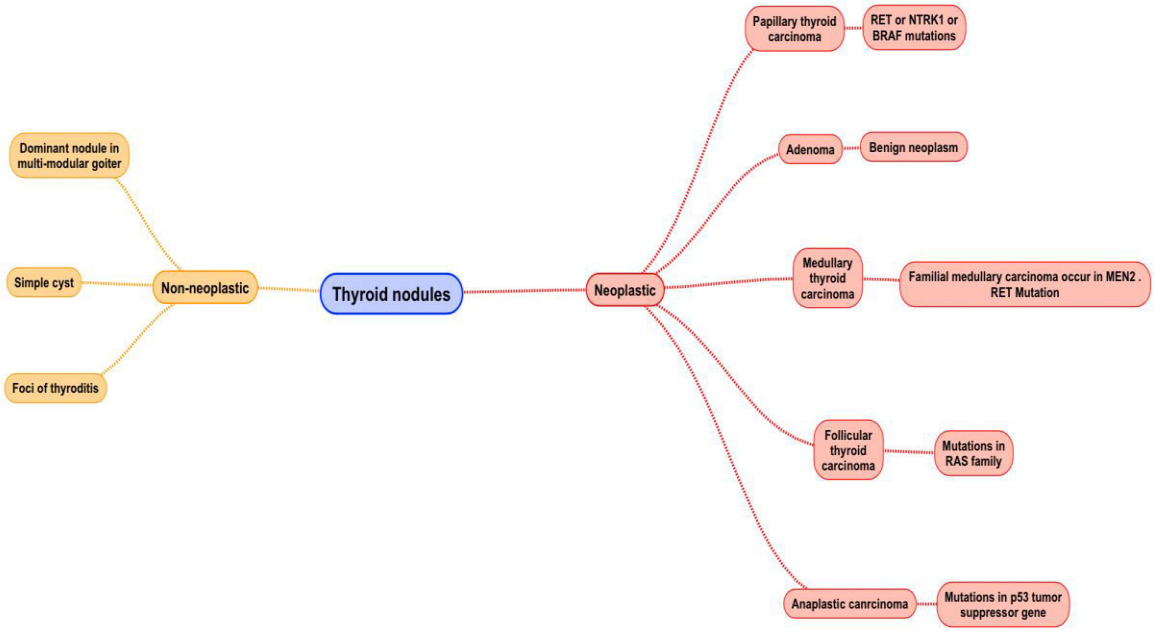


Fig. 15.4 Follicular adenoma.



III. PAPILLARY CARCINOMA

A. Most common type of thyroid carcinoma (80% of cases)
B. Exposure to ionizing radiation in childhood is a major risk factor.
C. Comprised of papillae lined by cells with clear, 'Orphan Annie eye' nuclei and nuclear grooves (Fig. 15.5A); papillae are often associated with psammoma bodies (Fig. 15.5B).
D. Often spreads to cervical (neck) lymph nodes, but prognosis is excellent (10-year survival > 95%)

IV. FOLLICULAR CARCINOMA

A. Malignant proliferation of follicles surrounded by a fibrous capsule with invasion Through the capsule (Fig. 15.6)
   1. Invasion through the capsule helps distinguish follicular carcinoma from follicular adenoma.
   2. Entire capsule must be examined microscopically.
   3. FNA only examines cells and not the capsule; hence, a distinction between follicular adenoma and follicular carcinoma cannot be made by FNA.
B. Metastasis generally occurs hematogenously.

V. MEDULI.ARY CARCINOMA

A. Malignant proliferation of parafollicular C cells; comprises 5% of thyroid carcinomas
   1. C cells are neuroendocrine cells that secrete calcitonin.
   2. Calcitonin lowers serum calcium by increasing renal calcium excretion but is inactive at normal physiologic levels.
   3- High levels of calcitonin produced by tumor may lead to hypocalcemia.
   4. Calcitonin often deposits within the tumor as amyloid.
B. Biopsy reveals sheets of malignant cells in an amyloid stroma (Fig. 15.7),
C. Familial cases are often due to multiple endocrine neoplasia (MEN) 2A and 2B, which are associated with mutations in the RET oncogene.
   1. MEN *2* results in medullary carcinoma, pheochromocyloma, and parathyroid adenomas (2A) or ganglioneuromas of the oral mucosa (2B).
   2, Detection of the RET mutation warrants prophylactic thyroidectomy.

VI. ANAPLASTIC CARCINOMA

A. Undifferentiated malignant tumor of the thyroid (Fig. 15,8); usually seen in elderly
B. Often invades local structures, leading to dysphagia or respiratory compromise
C. Poor prognosis

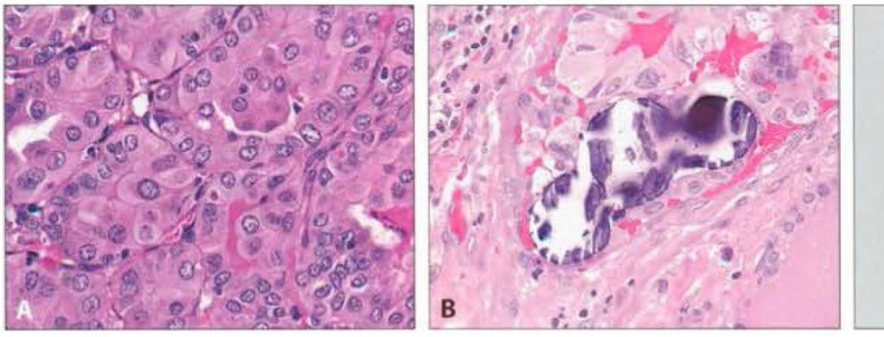


Fig. 15.S Papillary carcinoma, ft, Nuclear features. B. Psammoma bodies.

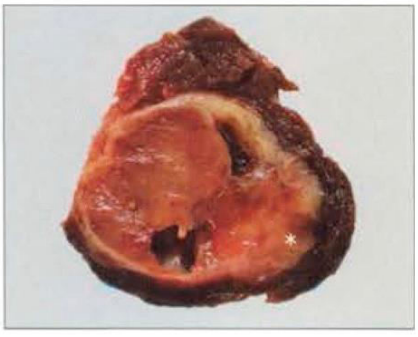


Fig. IS.6 Follicular carcinoma. (Courtesy of BulentCelasun, MD)

Questions

Q1: the measurement of calcitonin plays an important role in the diagnosis and postoperative follow-up of patients in which kind of tumors?

A. MC
B. Anaplastic carcinomas
C. Follicular carcinoma
D. PTC

Ans: A

Q2: Amyloid is stained by?

A. H&E
B. Indian ink
C. Congo red
D. Kinyouns-cold stain

Ans: C

Q3: Anaplastic cells can have?

A. pleomorphicgiant cells, sarcomatous appearance, larg cells.
B. sarcomatous appearance , giant cells and amyloid.
C. spindle cells with a sarcomatous appearance and small cells
D. Polygonal to spindle cells, , pleomorphicgiant cells and small cells

Ans: C

Q4:"Multiple nodules" are more likely to be neoplastic.

a) True
b) False

Ans :B

Q5:Hot nodules are more likely to be benign than malignant.

a) True
b) False

Ans:A

Q6:Foci of thyroiditis are considered as:

a) Neoplastic Nodules
b) Non-neoplastic Nodules
c) Adenoma
d) None of the above

Ans:B

Q7:Examination of a mass taken from a patient's thyroid showed multiple nodules, they are NOT compressing adjacent thyroid parenchyma, capsule is not well-formed. What is the most likely diagnosis?

a)Thyroid adenoma
b)Multinodular goiter
c)Thyroid follicular carcinoma

Ans:b

Q8:What it's the type of carcinoma that has RAS gene mutation?

a) Papillary thyroid carcinoma.
b) Follicular thyroid carcinoma.
c) Medullary thyroid carcinomas
d) Anaplastic carcinoma.

Ans:B

Q9: which one of the flowing consider as one of nuclear feature in PTU ?

a) psammoma bodies
b) Hurthle cell
c) Grooved nuclei

Ans:c

حسبي الله لا إله إلَّا هو عليه توكلت وهو رب العرش العظيم.

القادة

- حنين السبكي
- عبدالله أبو عمارة

الأعضاء

- لمى التميمي
- فاطمة الطاسان
- دعاء وليد
- رنيم الغامدي
- ابتسام المطيري
- مها الغامدي
- ريما الشايع
- بشرى قوقندي
- جواهر الخيال

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References: Doctor's slides + notes, Robbins basic pathology 10th edition.