



Radiology
Team 438

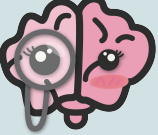
Imaging of thyroid and parathyroid disease

Lecture 18

Objectives

- ❖ Identify the anatomy, location of the thyroid gland & parathyroid gland.
- ❖ Understand the radiological sign and radiological investigations of thyroid Ophthalmopathy.
- ❖ Recognize renal osteodystrophy involving different skeletal images as well as radioiodine study.
- ❖ To know the thyroid nodules and how we can differentiate benign from malignant nodule.
- ❖ To explain the usage of scintigraphy for thyrotoxicosis.

Reviewed By



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Color Index:

♦ Important

♦ Doctor's Notes

♦ Extra

♦ Female slides

♦ male slides

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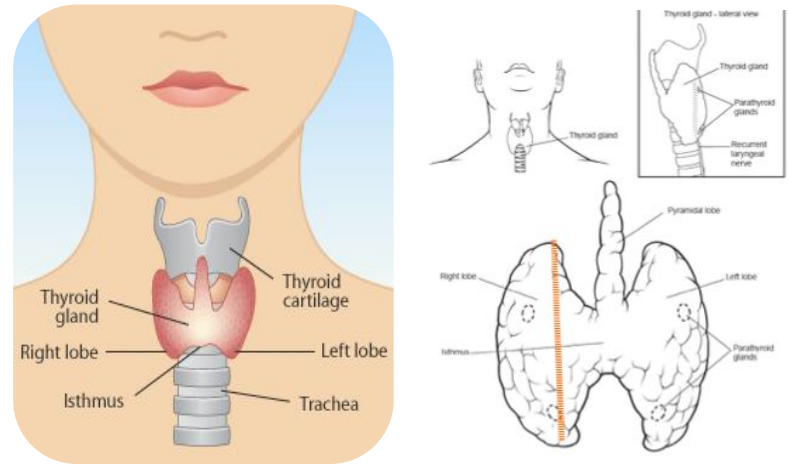
Fares Aldokhayel

Mohammed Aldajani

Anatomy of the Thyroid Gland

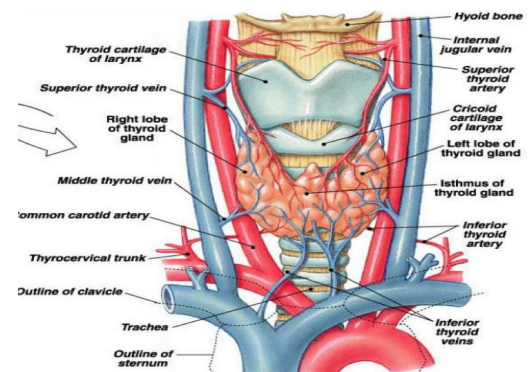
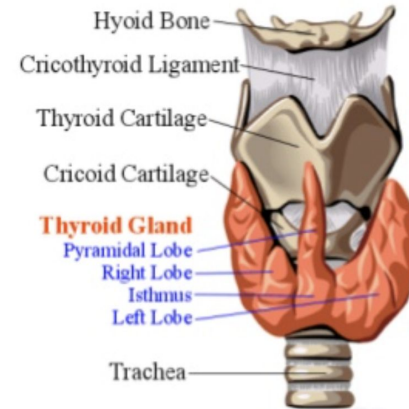
- Anterior neck, the lower part of the front and side of the neck.
- Overlays 2nd - 4th tracheal rings.
- Average width: 12-15 mm (each lobe).
- Average height: 40-60 mm long.
- Average weight: 25 g.

(Understand the numbers, **don't** memorize)



» Gross Anatomy

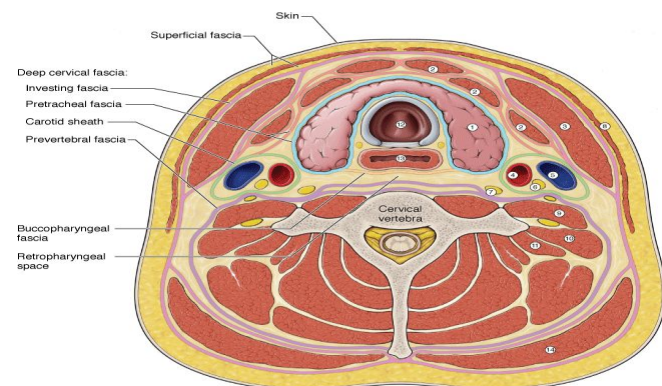
- The thyroid extends from **C5 to T1** and lies **anterior to the thyroid and cricoid cartilages** of the larynx and the first three tracheal rings.
- Each lateral lobe extends upwards to the oblique line of thyroid cartilage and below up to the 5th or 6th tracheal ring.
- The isthmus extends across the midline in front of the 2nd, 3rd and 4th tracheal ring.
- The thyroid is butterfly or "H"-shaped and is composed of two lobes, each with a superior and inferior pole, connected by an isthmus. Each lobe measures approximately 4-6 cm in length.



so in case of taking a biopsy you should introduce the needle in an oblique position. if you go medially you will injure the RLN, laterally=carotid space ect..

» Relations

- Anteriorly: strap muscles.
- Posteriorly: thyroid cartilage, cricoid cartilage, trachea.
- **Posteromedially**: trachea, esophagus, tracheoesophageal groove (containing lymph nodes, recurrent laryngeal nerve, parathyroid glands).
- **Posterolaterally**: carotid space (carotid artery, internal jugular vein, vagus nerve).



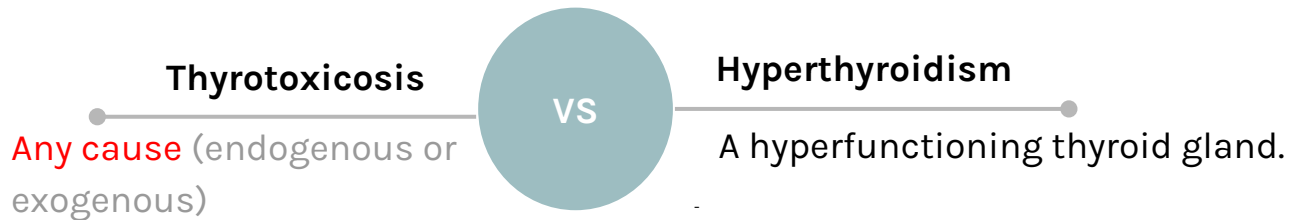
KEY	
1. Thyroid gland	8. Platysma m.
2. Infrahyoid mm.	9. Ant. scalene m.
3. Sternocleidomastoid m.	10. Mid. scalene m.
4. Common carotid a.	11. Post. scalene m.
5. Internal jugular v.	12. Trachea
6. Vagus n.	13. Esophagus
7. Sympathetic trunk	14. Trapezius m.

Sources: Morton DA, Foreman KB, Albertine KH: *The Big Picture: Gross Anatomy*. www.accessmedicine.com
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Thyrotoxicosis Vs Hyperthyroidism

A group of symptoms and signs due to increase production of thyroid hormones.

- typical sign and symptoms of Hyperthyroidism: Weight loss, diaphoresis, tremors, palpitation, exophthalmos (exophthalmos is mainly associated with graves disease)
- hypothyroidism is more common to females causing weight gain



Thyrotoxicosis:

❑ Hyperthyroidism causes:

- 1- Diffuse toxic goiter (Graves' disease¹).
- 2- Single toxic nodule.
- 3- Multinodular toxic goiter.

- ❑ Early phase subacute thyroiditis.
- ❑ Exogenous thyroid hormone intake.

TFT & Thyroid Scan:

- ❖ First modality to use when patient presents with hyperthyroidism symptoms and high T3/T4 but low TSH is **ultrasound**

Thyrotoxicosis → suppressed TSH and elevated T3/T4.

- Based on **thyroid function test**, the exact cause of thyrotoxicosis can't be Determined
- **Thyroid scan** is a very helpful tool in differentiating between various causes of thyrotoxicosis.

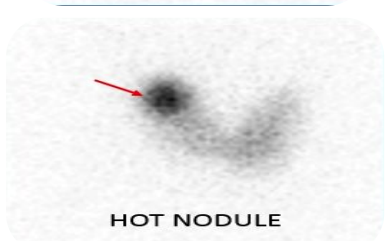
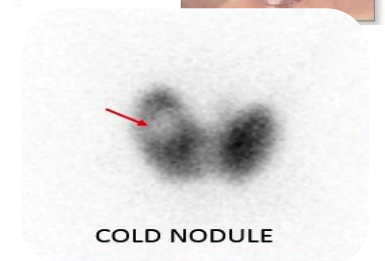
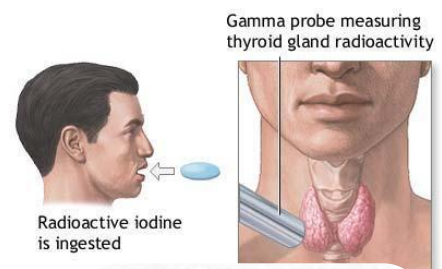
» Thyroid scan and uptake:

Radioactive Iodine (RAI) is used for thyroid **scan** and **uptake**

- it's given **orally**.
- Image and uptake are obtained **after 24 hours**
- This test determines how much of orally ingested iodine accumulated in the thyroid at 24 hours.

Imaging Findings:

- Symmetric or asymmetric uptake.
- Homogeneous or inhomogeneous uptake.
- Nodules: Cold(**decrease uptake**) or Hot(**increase uptake**).
 - If the active material was **trapped** in the nodules then its called **hot** nodules. If the material **isn't trapped** then it's called **cold** nodules.

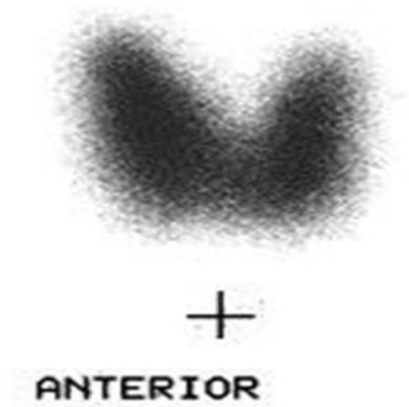


¹The main finding is multiple diffuse nodules

⇒ A) Hyperthyroidism:

I. Diffuse Toxic Goiter (Graves' Disease): associated with bilateral exophthalmos

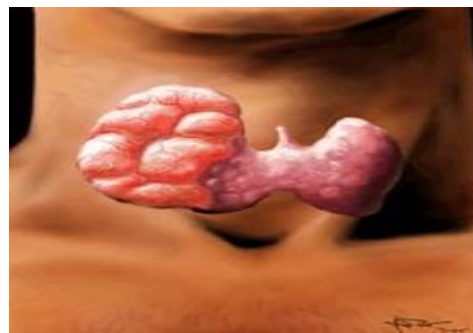
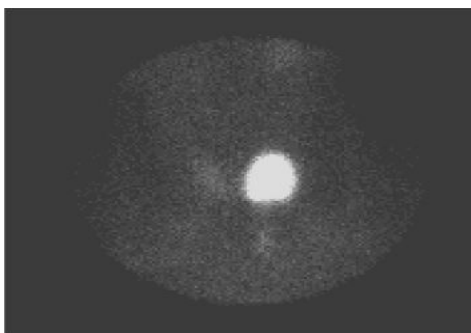
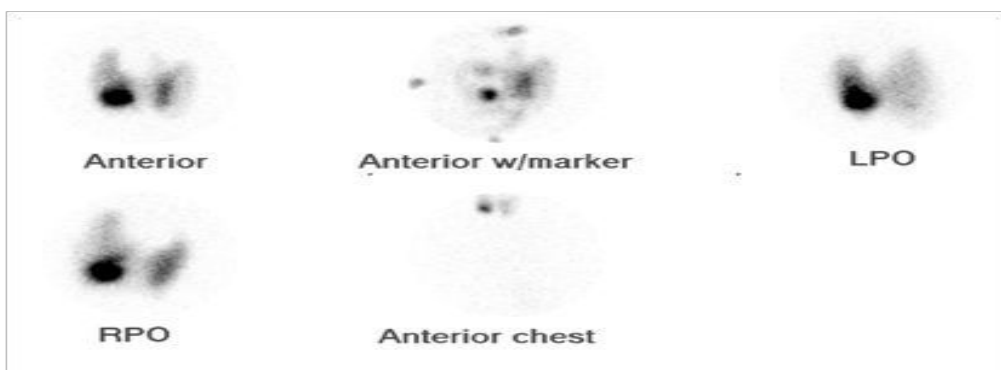
- Diffuse enlargement of thyroid gland.(usually symmetrical)
- Homogeneous increased uptake due to an increase in activity.
- No significant focal abnormalities (nodules).
- 24-hour RAI uptake is elevated, usually >35%.



II. Single Toxic Nodule:

(In graves disease the treatment will be medical while in toxic nodule the treatment might be medical or surgical)

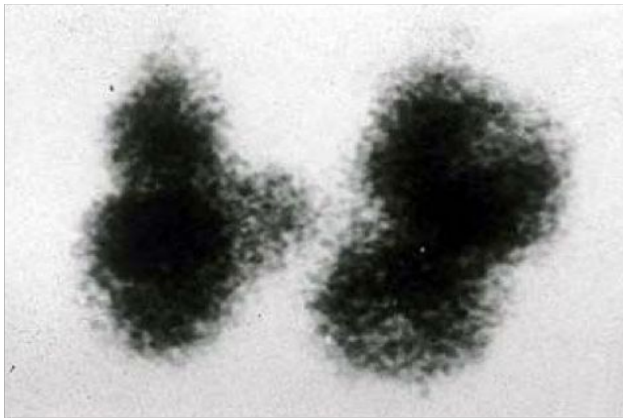
- Single hot nodule (independent of TSH or autonomous).
- Rest of thyroid gland is poorly visualized due to low TSH level (TSH dependent).
- 24-hour RAI uptake is slightly elevated, usually around 20%.



Toxic (hot) nodule

III. Toxic Multinodular Goiter

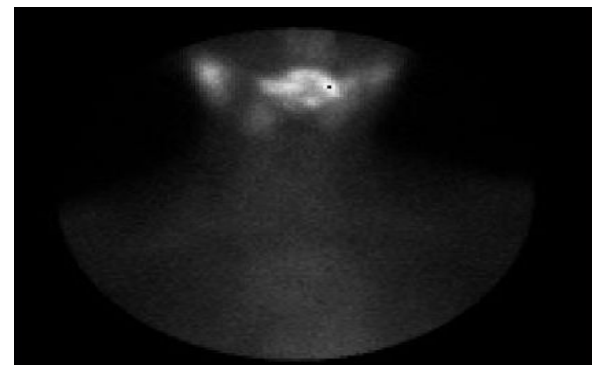
- Mild **inhomogeneous** uptake in thyroid gland.
- Multiple **cold (Malignant)** and **hot (Benign) nodules** in both thyroid lobes.
- 24-hour uptake is **mildly elevated**, usually between 20%-30%.



Multinodular goiter
with diffuse asymmetrical appearance of the gland with multiple areas of hyperfunction activity.

» Early Phase Subacute Thyroiditis :

- **Inhomogeneous uptake** could be mild or severe. In some cases thyroid gland is not visualized.
- No significant focal abnormalities (nodules).
- 24-hour RAI uptake is **low**, usually < 5%.

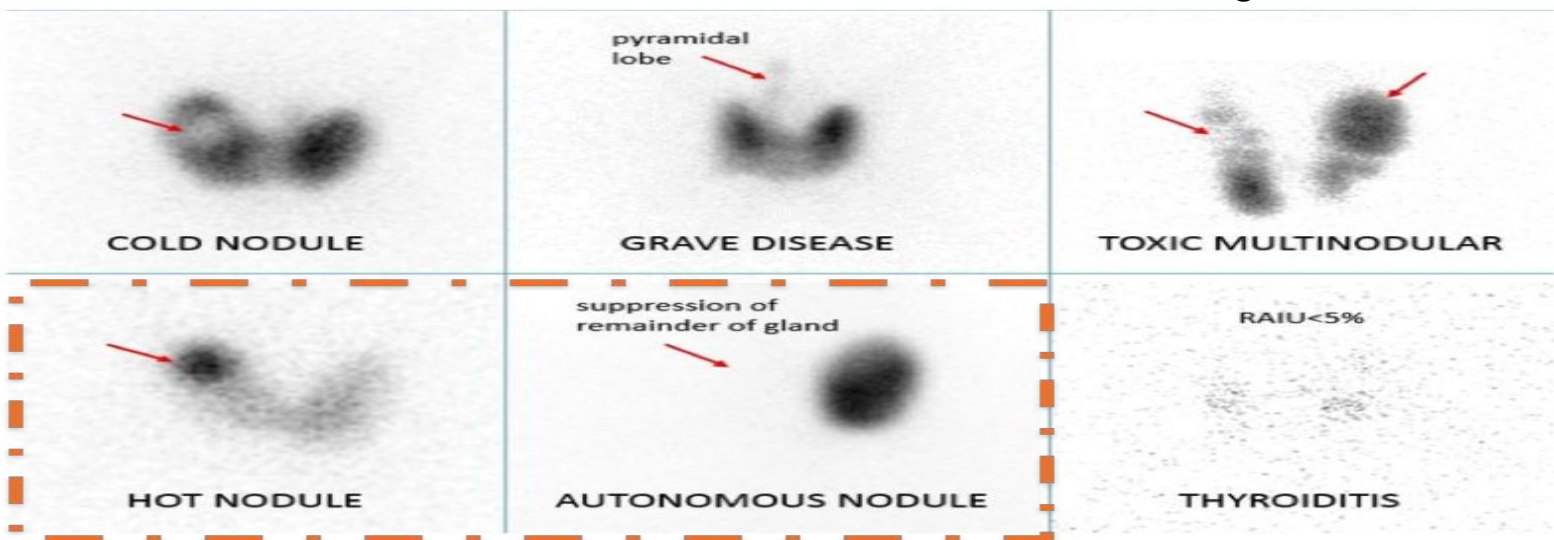


» In Summary

Malignancy (Cold nodule)

Bilateral symmetrical uptake (No nodule)¹

Cold & Hot nodules together



The outline of the thyroid gland is clear with hot nodule

We can't see the outline of the thyroid gland

Minimal uptake

¹ equal radioactive uptake with no size enlargement

⇒ Hypothyroidism

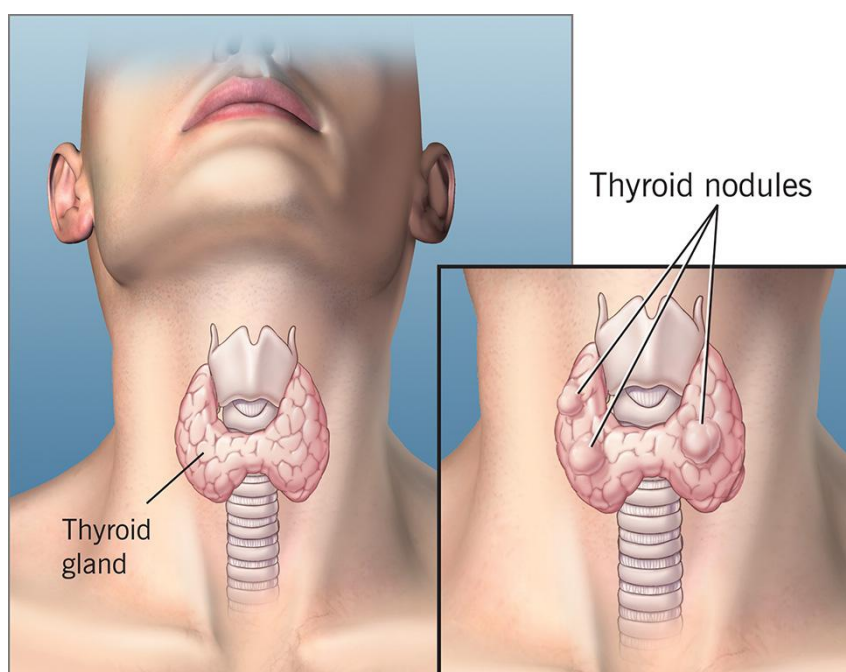
- The main cause is **chronic thyroiditis (Hashimoto's thyroiditis)**.
- TFT → **TSH is elevated** & Low T3/T4.
- Thyroid scan **does not** have significant diagnostic value in this entity. Unless, there is a nodule, thyroid scan may be helpful.
- For example, comparing it to hyperthyroidism it's important to differentiate between different causes because they have different treatments for example, Graves' disease is treated medically while both single and multiple nodules are treated surgically.

⇒ Thyroid nodules

why are we afraid of thyroid nodule? Because of malignancy

Common **more in Females than Males**, almost existing in half of the population.

- Usually found by **physical examination** or by **ultrasound**.
- **US is the first** modality used to investigate a palpable thyroid nodule¹.
- Scintigraphy (thyroid scan) is reserved for characterizing functioning nodules and for staging **follicular** and **papillary** (not aggressive, very common, good prognosis) **carcinomas**.
- The patient is usually **euthyroid**².
- If the patient is **hyperthyroid** do nuclear scan otherwise do FNA.
- FNA is the most **accurate** and **cost-effective** method for diagnostic evaluation of thyroid nodules.
- FNA have a sensitivity of 76%–98%, specificity of 71%–100%.



¹it is not definitive, if you see features of malignancy you have to do FNA to confirm diagnosis.

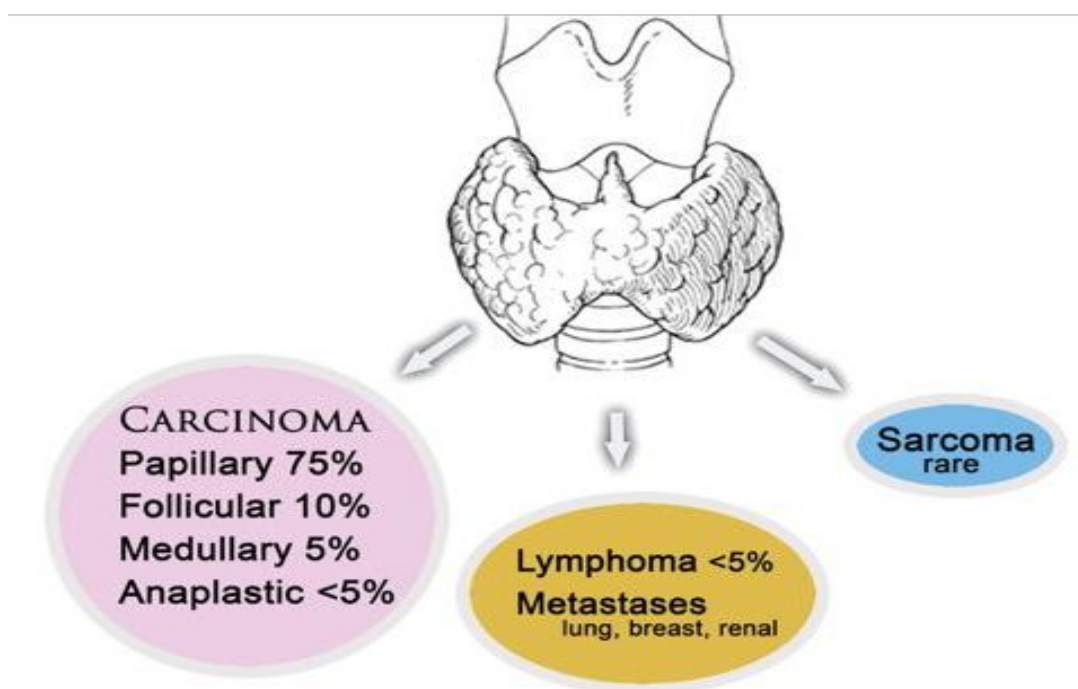
²the patient comes with neck swelling, no other symptoms, the lab is normal, so there is no signs suggesting hyper or hypothyroidism. You have to do US to roll out cancer.

» Risk Factors for thyroid Cancer

1. Family history of thyroid cancer.
2. History of head and neck irradiation.
3. **Male** Gender.
 - (It is more common in female so, If we find it in male then it is highly suspicious).
4. Age of less than 30 years or more than 60 years.
5. Previous diagnosis of type 2 Multiple Endocrine Neoplasia (**MEN-2**).

From 433:

- If you have a patient with multinodular goiter and lab shows euthyroid, what is the next step?
 - **US then FNA.**
- If you have a patient with multinodular goiter and lab shows hyperthyroidism, what is the next step?
 - **US then thyroid scan then +/- FNA if needed.**
 - **So, always after TFT do US.**
 - **Remember that if there is MICROCALCIFICATION or a solid lesion do FNA**

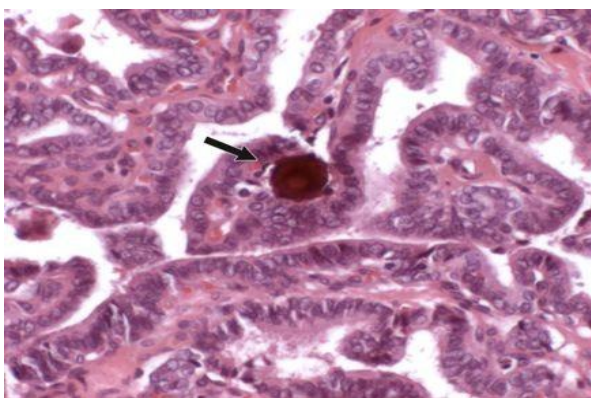


» US Features of Thyroid Nodules

- Certain US features are helpful in differentiating between the two.
- **Important: How to differentiate between benign and malignant nodules**
- **Malignant features are:**
 1. **Micro-calcifications.**
 2. Local invasion **To capsule, trachea, esophagus**
 3. A nodule that is taller than it is wider.
 4. **Markedly reduced echogenicity (hypoechoic=less white).**
 5. Lymph node metastases
- Other less specific features of malignant nodules which may be useful, such as:
 1. Absence of a halo.
 2. ill-defined irregular margins.
 3. Solid composition.
 4. **Increased Vascularity in **duppler US**** (Don't memorize the numbers)

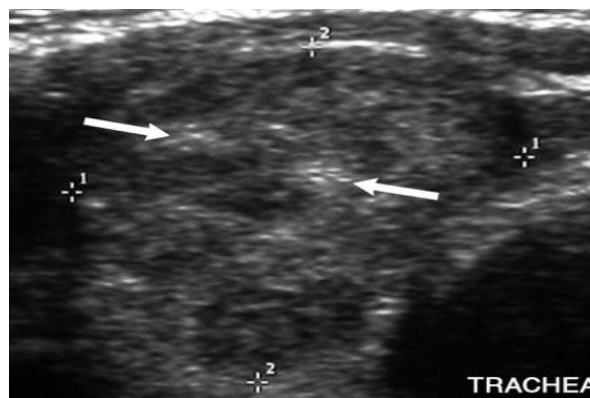
US Feature*	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Microcalcifications (1–5)	26.1–59.1	85.8–95.0	24.3–70.7	41.8–94.2
Hypoechoogenicity (2–5)	26.5–87.1	43.4–94.3	11.4–68.4	73.5–93.8
Irregular margins or no halo (2–5)	17.4–77.5	38.9–85.0	9.3–60.0	38.9–97.8
Solid (4–6)	69.0–75.0	52.5–55.9	15.6–27.0	88.0–92.1
Intranodule vascularity (3, 6)	54.3–74.2	78.6–80.8	24.0–41.9	85.7–97.4
More tall than wide (2)	32.7	92.5	66.7	74.8

» Thyroid microcalcifications



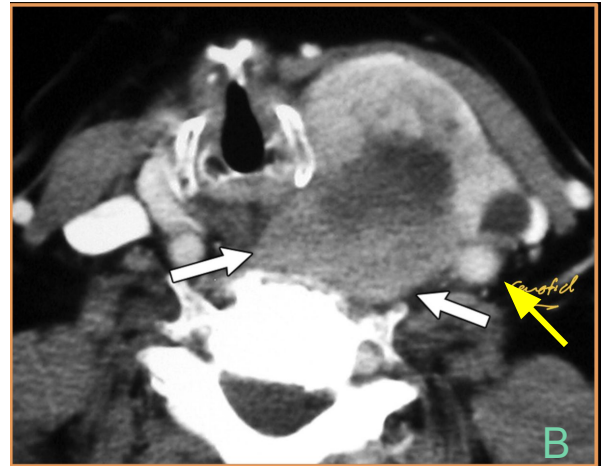
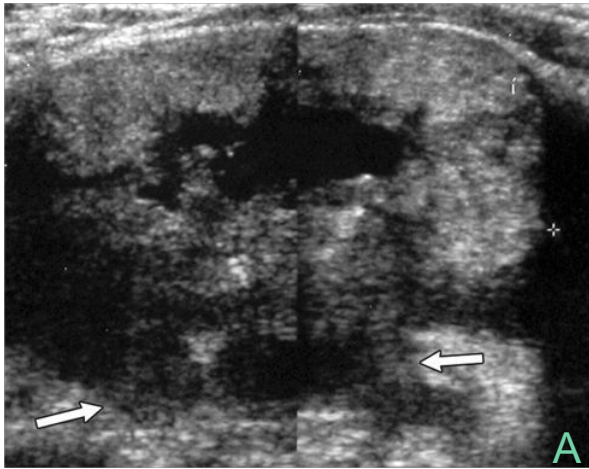
Psammoma bodies (arrow), which are 10–100 μm in diameter

° if you see it, you are handicap to send it to surgery, so you have to do FNA before sending the patient to surgery.



- Transverse sonogram of the right lobe of the **thyroid** demonstrates punctate echogenic foci **without** posterior acoustic shadowing.
- (Arrows) indicative of **microcalcifications** which suggest **malignancy**."

Anaplastic thyroid carcinoma in an 84-year-old woman.



Nodules invading the capsule and esophagus suggesting a very malignant tumor (e.g. medullary carcinoma):

(A) Transverse sonogram of the left lobe for the thyroid shows an advanced tumor with infiltrative posterior margins (arrows) and invasion of prevertebral muscle. Anaplastic type invading the capsule and prevertebral muscles.

B) Axial contrast-enhanced CT image shows a large tumor that has invaded the prevertebral muscle (white arrows).

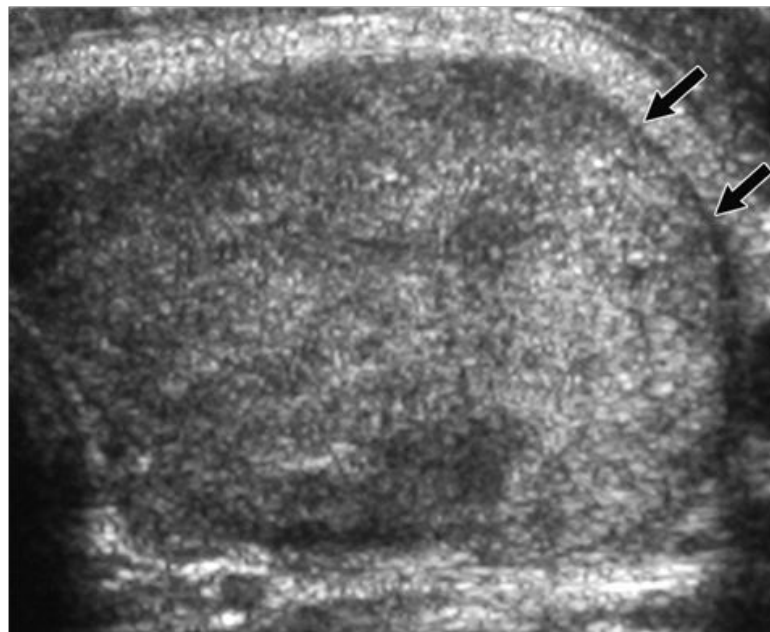
What is the name of the structure pointed at by the yellow arrow? **The carotid artery**

» Margin, Contour, and Shape:

A completely uniform halo around a nodule is highly suggestive of benignity, with a specificity of 95%.

Presence of halo = most likely benign.

Follicular adenoma in a 30-year-old woman:



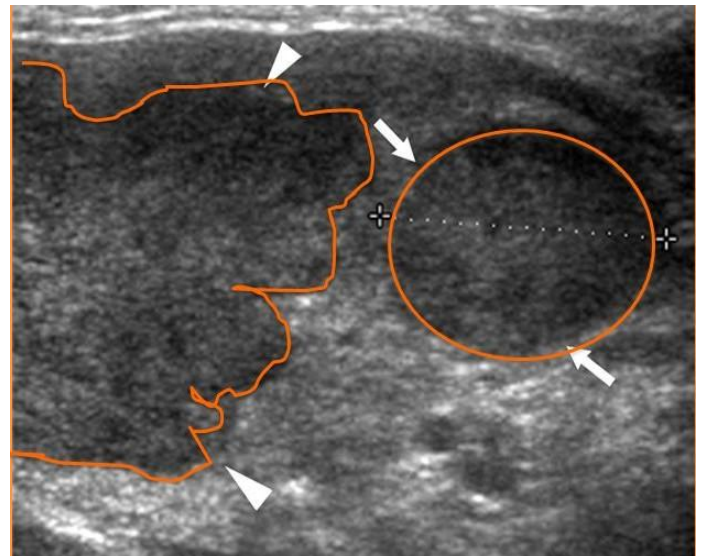
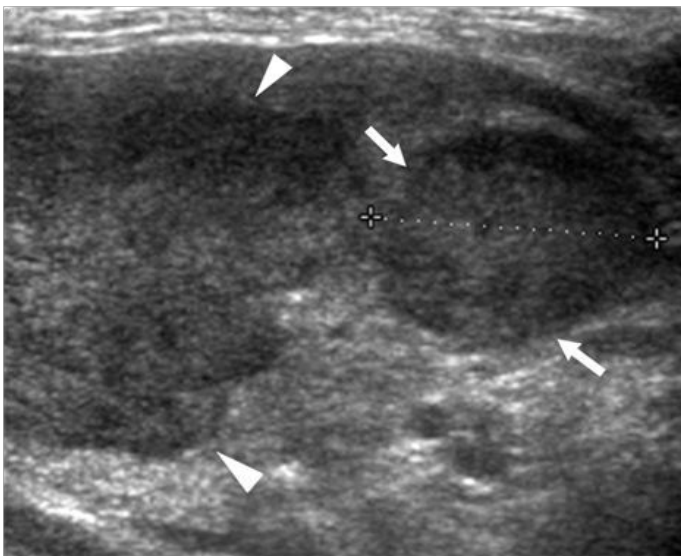
Halo (arrows) suggesting benign lesion (well encapsulated)

» Vascularity

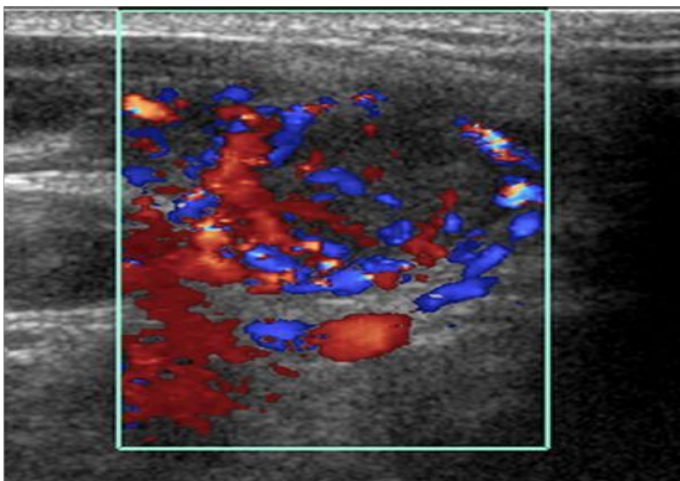
- Papillary thyroid carcinomas had some intrinsic blood flow
- Avascular nodule is very unlikely to be malignant.

When vascularity of the nodule is within the center it is usually considered malignant while if it is in the periphery it is considered benign.

Renal cell carcinoma metastases to the thyroid in a 69 year old women



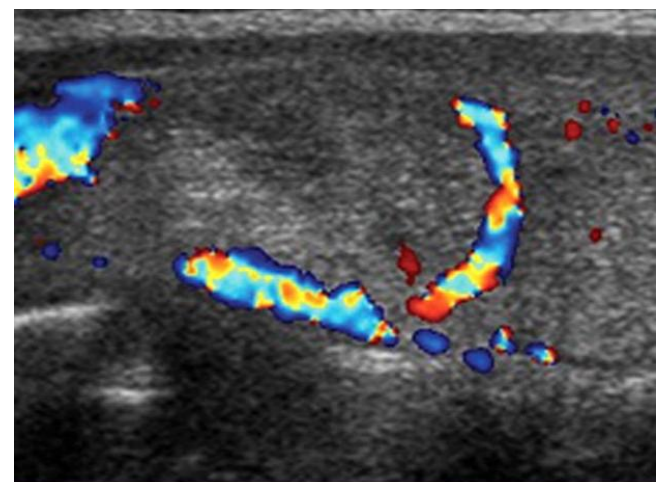
A Longitudinal sonogram of the right lobe of the thyroid shows a round hypoechoic nodule (arrows) and an irregular-shaped hypoechoic nodule (arrowheads)



Color Doppler sonogram of the round nodule shows increased internal vascularity.

Follicular adenoma in a 36 year old women:

There is not much increase in the vascularity so, it became to be an adenoma



» Hypoechoic Solid Nodule:

Marked **hypoechoogenicity** is very suggestive of **malignancy**.

- Benign → **Hyper-echoic**: Presence of halo → **Avascularity**.
- Malignant → **Hypo-echoogenicity**: Absence of halo → **Increase vascularity**.

B cell lymphoma of the thyroid in a 73-year-old woman with Hashimoto thyroiditis:



Diffused hypoechoogenicity suggests neoplastic changes:

Transverse sonogram of the left lobe of the thyroid shows a large heterogeneous mass (between calipers) with marked hypoechoogenicity when compared with the strap muscles (SM). A normal isthmus (arrow) also is visible.

What are the names of the structures pointed at?

- red arrow=internal jugular vein
- Yellow arrow=carotid artery

» Non Specific US Features

- The size of a nodule **is not helpful** for predicting or excluding malignancy. If the nodule grew over a day or a week it means there is **cystic degeneration or hemorrhage**
- There is a common but mistaken practice of selecting the largest nodule in a multinodular thyroid for FNA.

» Interval Growth of a Nodule

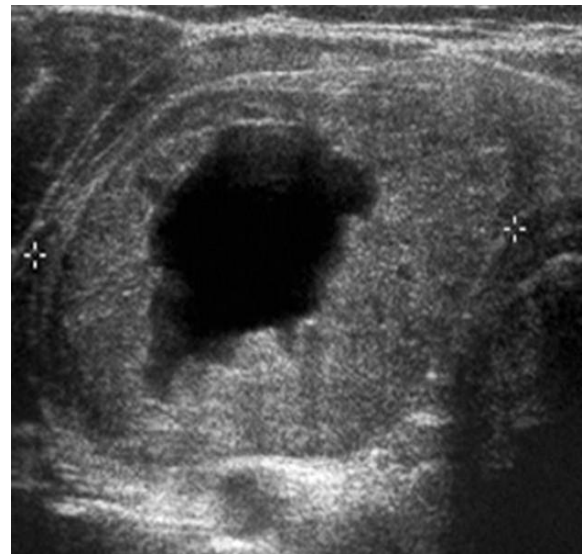
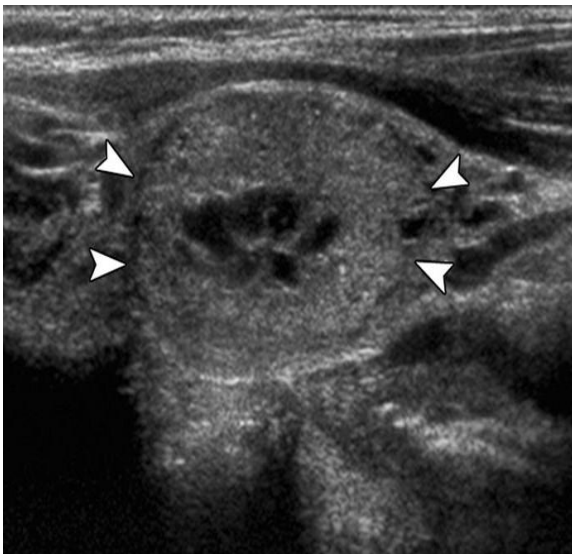
- In general, interval growth of a thyroid nodule is a **poor indicator of malignancy**. Benign thyroid nodules may change in size and appearance over time.
- The exception is clinically detectable **rapid interval growth**, which most commonly occurs in **anaplastic thyroid carcinoma** but also may occur in lymphoma, sarcoma, and, occasionally, high-grade carcinoma.

» Recommendations for Thyroid Nodules 1 cm or Larger in Maximum Diameter

US Feature	Recommendation
Solitary nodule	
Microcalcifications	Strongly consider US-guided FNA if ≥ 1 cm
Solid (or almost entirely solid) or coarse calcifications	Strongly consider US-guided FNA if ≥ 1.5 cm
Mixed solid and cystic or almost entirely cystic with solid mural component	Consider US-guided FNA if ≥ 2 cm
None of the above but substantial growth since prior US examination	Consider US-guided FNA
Almost entirely cystic and none of the above and no substantial growth (or no prior US)	US-guided FNA probably unnecessary
Multiple nodules	Consider US-guided FNA of one or more nodules, with selection prioritized on basis of criteria (in order listed) for solitary nodule*

(This table is for your information)

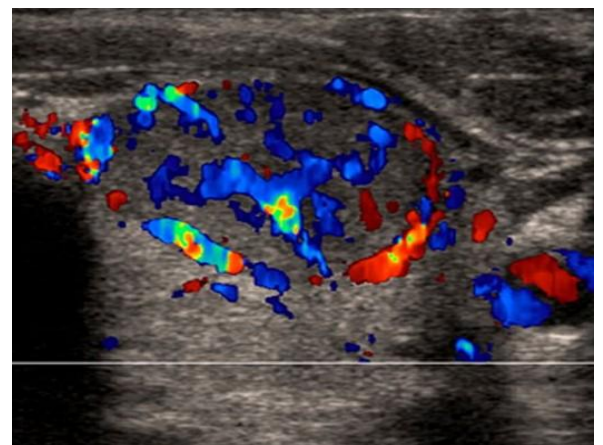
» Thyroid nodules of varying parenchymal composition (solid to cystic)US



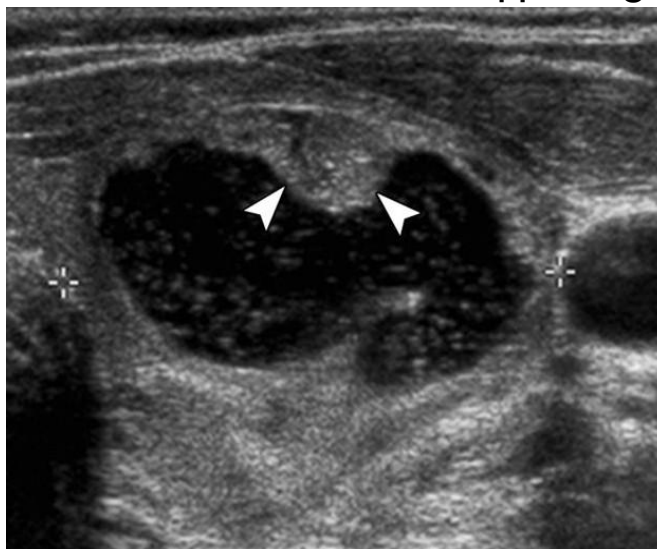
- **Left image:** Sagittal image of predominantly solid nodule (arrowheads), which proved to be benign at cytologic examination.
- **Right image:** Transverse image of mixed solid and cystic nodule (calipers), which proved to be benign at cytologic examination.
- **both images have halo = benign tumor.**

Predominantly solid thyroid nodule:

- increase vascularity suggests malignant nodule: . This was a papillary carcinoma.



Predominantly cystic nodule with small solid-appearing mural component:



Eccentric nodule with cystic degeneration and it was growing very fast

The lesion was benign at cytologic examination.

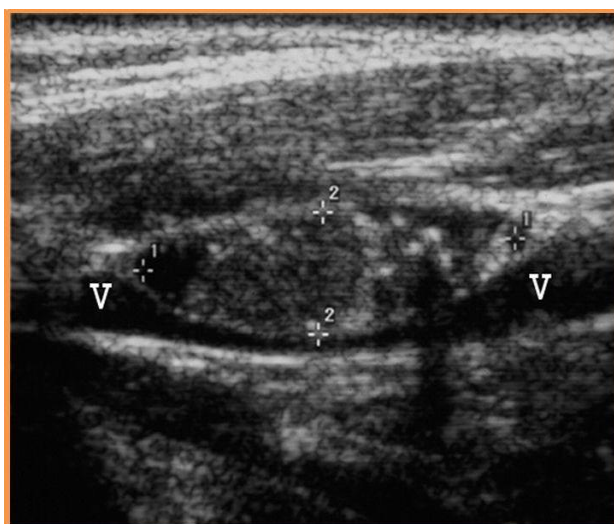
(There is still no imaging feature for us to prove that a lesion is 100% malignant or benign)

» US Features of Malignant Lymph Nodes

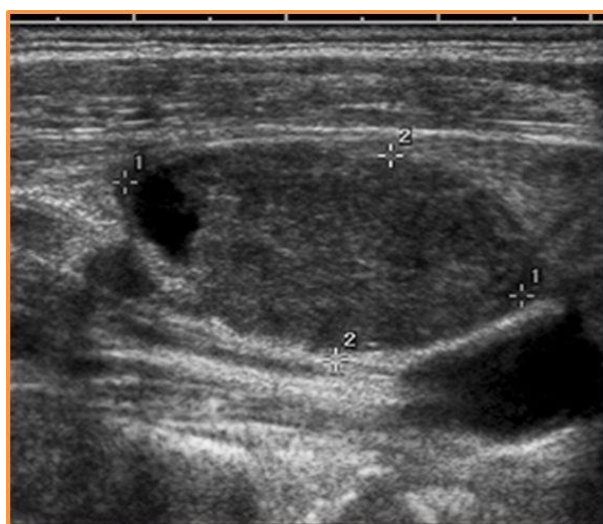
1. Rounded bulging shape.
2. **Increased size.**
3. Replaced fatty hilum.
4. Irregular margins.
5. Heterogeneous echotexture.
6. Calcifications.
7. Cystic areas.
8. Vascularity throughout the lymph node instead of normal central hilar vessels at Doppler imaging.

Keep in mind US is suggestive NOT diagnostic.

Abnormal cervical lymph nodes:



A) Lesion that is enlarged in size with cystic degeneration metastatic papillary carcinoma.

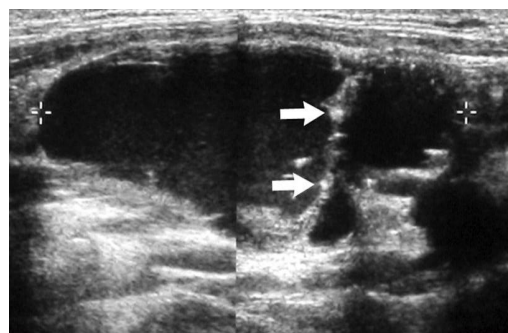


B) Replacement of the fat hilum and enlarged lymph node metastatic papillary carcinoma.

Papillary carcinoma and cystic lymph node metastasis in a 28Y woman:

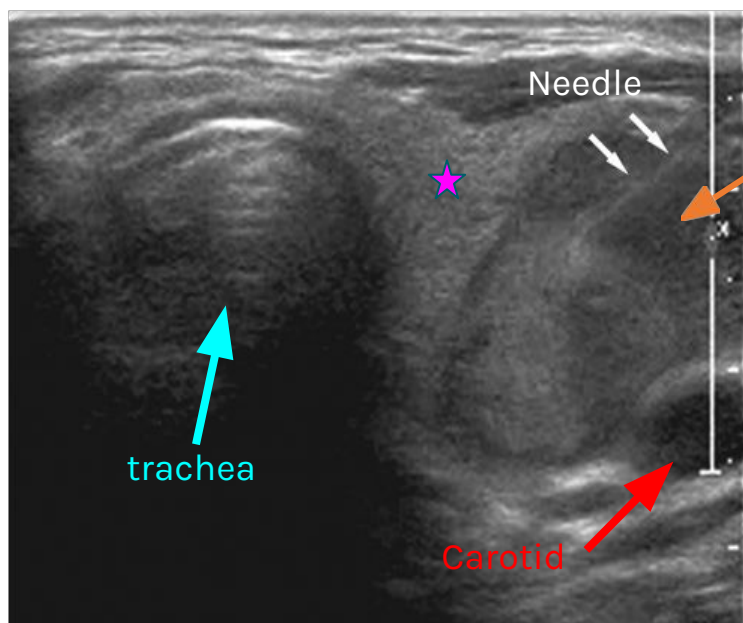
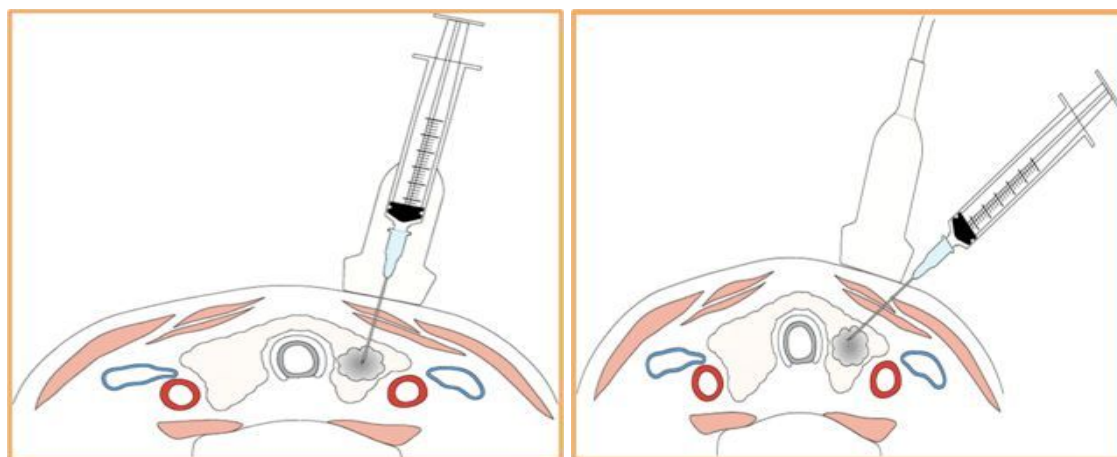
Cystic degeneration

(If you are suspicious and not sure; you have to do an FNA)



US-guided FNA Technique:

The needle may be introduced parallel or perpendicular to the transducer, and the needle tip should be carefully monitored during the procedure. Diagram shows insertion of the needle in a plane parallel to that of scanning.



You have to use US guidance:

- 1- To target the needle to go inside the nodule.
- 2- To not injure the carotid.
- 3- To not injure the trachea

the lesion is less echoic(hypoechoic) when compared with the echogenicity of the normal thyroid. Indicating a more malignant lesion

To summarize:

First you have to identify whether it is euthyroid or hyperthyroid → If it is hyper you have to assess if it's a solitary nodule or multiple or Grave's → You have to assess by US if it is neoplastic or not → If you suspect malignancy do FNA to confirm.

* If it is papillary carcinoma, it is hard to diagnose even by FNA.

If you were to insert the needle in the normal thyroid tissue you will get a normal false negative result.. that's why we need US :)

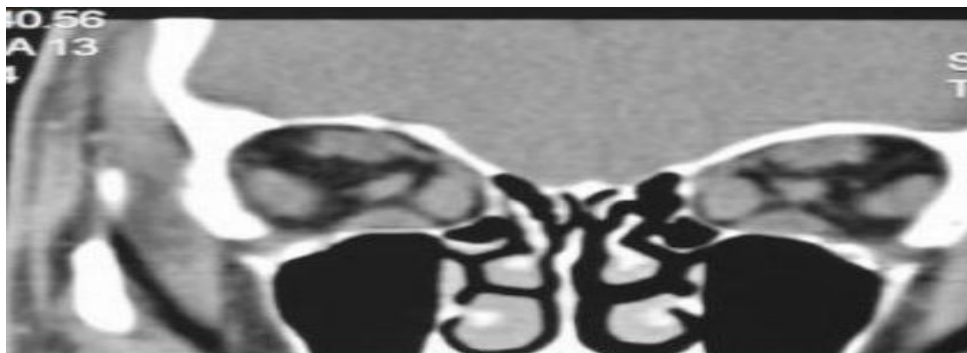
» Thyroid Ophthalmopathy (Graves' Disease):

Clinical history:

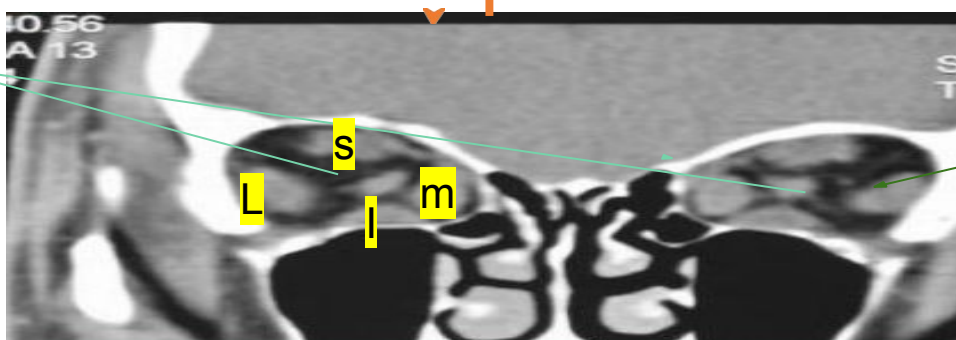
- **Slow onset** (months), **painless** exophthalmos. (Usually presented by **bilateral** proptosis)
- **disease causing painful exophthalmos** = infection, orbital pseudotumor

Patterns of muscle involvement in thyroid ophthalmopathy:

- **Bilateral (85%)** ex; graves disease
 - Unilateral (5%) ex:orbital pseudotumor
 - Normal muscles (10%)
 - Involvement of **All** muscles is **the most common scenario** of extraocular muscle enlargement.
 - If only individual muscles involved, commonly its **Inferior** then **Medial recti muscles**
 - **Lateral rectus muscle: last to become involved**; rarely/never the only muscle involved
- The first muscles get affected respectively are: **I'M SLOW** (**I**nferior, **M**edial, **S**uperior, **L**ateral)**IMP**
- Muscle enlargement characteristically involves the body of the muscle, sparing the tendinous attachment to the globe. (does not affect the tendon)
 - Patients should not be having hyperthyroid (some have euthyroid).
 - **CT Coronal imaging** is **the method of choice** for assessing muscle thickness.



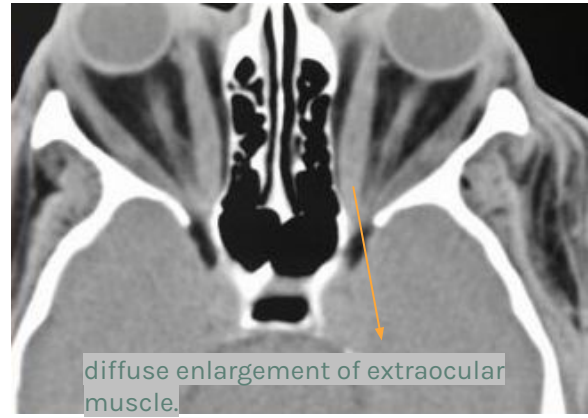
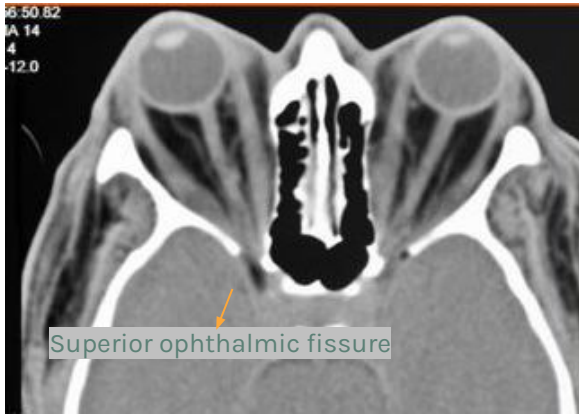
optic nerve
the circle in
the middle
between 4
rectus
muscles



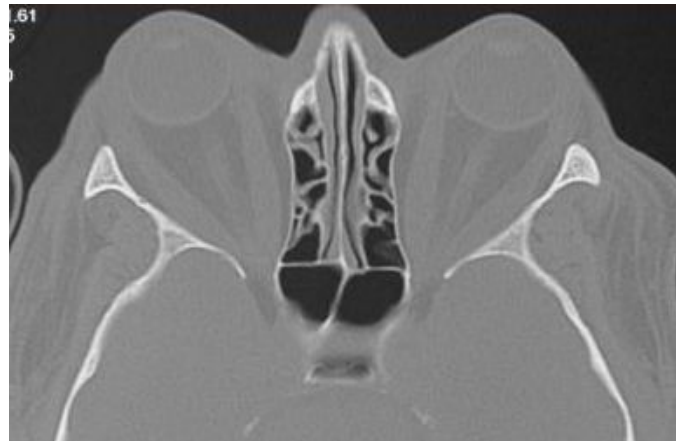
Lateral rectus
muscle

- Almost symmetrical and bilateral enlargement of the muscle belly
- Diffuse enlargement of the extraocular muscles, why are we afraid?
 - because there is bilateral ptosis and stretches of the optic nerve and we are afraid of the compression around the orbital apex

Thyroid Ophthalmopathy

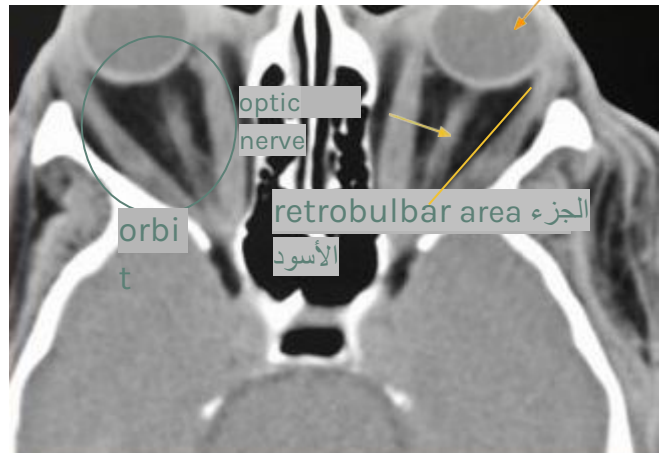
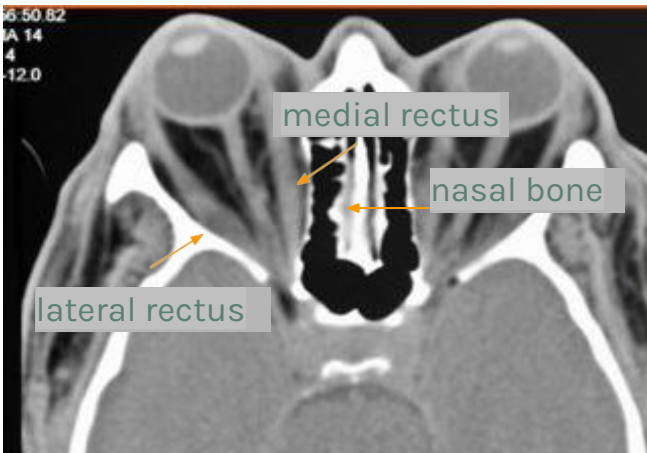


symmetrical and bilateral enlargement of muscle belly



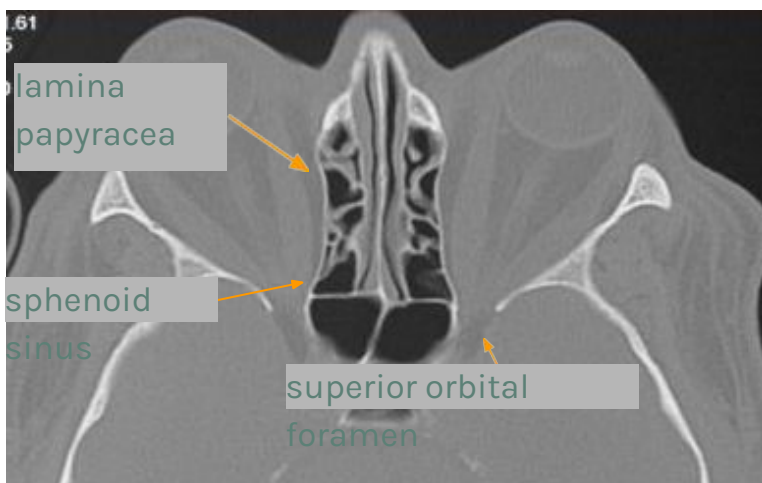
Bilateral; exophthalmos there is protrusion of the globe abundant of retrobulbar fat

CT axial image level of orbit:

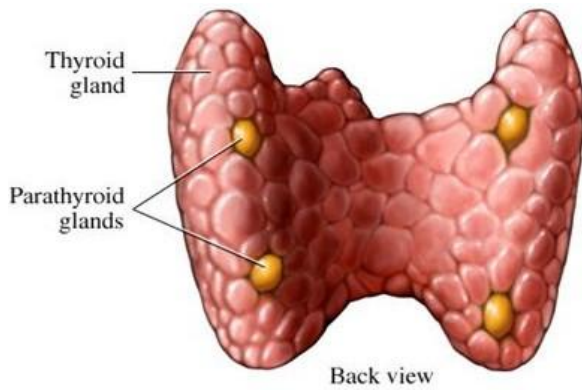


Soft tissue window

Bone window



- Radiological features:** The disease is bilateral
1. Exophthalmos protrusion (because the globe is outside the orbit).
 2. Enlargement of extraocular muscles.
 3. increased retrobulbar fat pad.
 4. herniation in the fat through superior orbital fissure.
 5. lamina papyracea (convex to outside concave inside) secondary to the compression of the medial rectus
 6. Stretching of optic nerve.



- Two pairs of glands usually positioned behind the left and right lobes of the thyroid.
- Typically 4 parathyroid glands (Superior and Inferior) parathyroid glands.

⇒ Renal Osteodystrophy

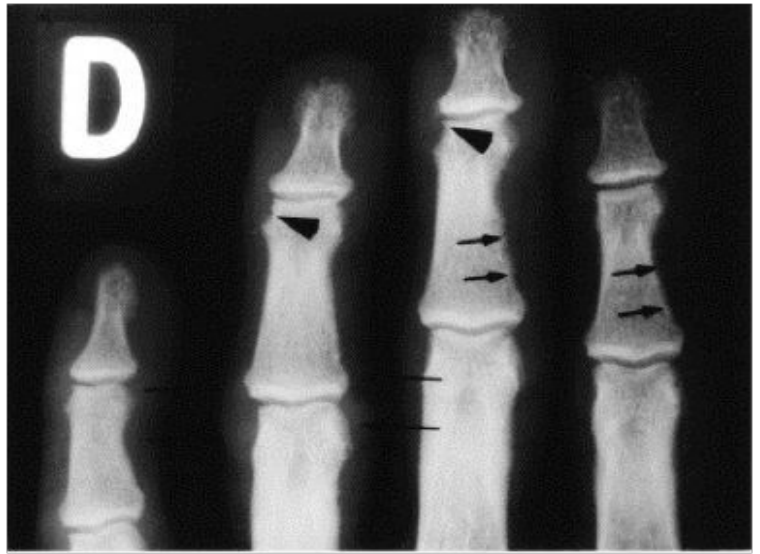
- ❖ Seen in setting of: chronic, **end-stage renal disease**.
- ❖ Related to combination of:
 - **Osteomalacia**.
 - **Secondary hyperparathyroidism** (in primary the patient will present with renal stones)
- ❖ **Radiological manifestation**
 - **Bone resorption** mainly (Sub-periosteal)
 - Cortical thinning.
 - **Soft tissue and vascular calcifications**
 - **Osteosclerosis**
 - Brown tumors (seen in primary rather in secondary).
- ❖ **Osteopenia** is the most common finding; however, **10-20%** of patients also exhibit osteosclerosis.
- ❖ Characteristic finding of osteosclerosis is "**Rugger jersey spine**", Bands of hazy sclerosis that parallels the vertebral body endplates. happens in ESRD
- ❖ Both axial and appendicular skeleton involved.
- ❖ Increased risk for **pathologic fracture**.



Osteodystrophy



Soft tissue calcification



Typical subperiosteal bone resorption at the “radial aspects of the middle phalanges” (small arrows) with bone resorption (subligament resorption) at the margins of the distal interphalangeal joints (short arrows).



Rugger jersey spine (diffuse osteopenia)



Cortical thinning with subperiosteal resorption



Subligamentum resorption + Brown tumors

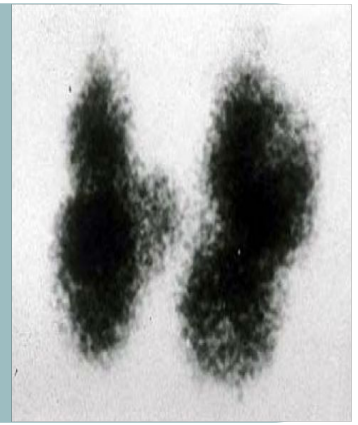
- **Structures relations to the thyroid gland;**
 - **Posteromedially:**
 - tracheoesophageal groove (containing lymph nodes, recurrent laryngeal nerve, parathyroid glands).
 - **Posterolaterally:**
 - carotid space (carotid artery, internal jugular vein, vagus nerve).
- **What is Rugger jersey spine?**
 - A Characteristic finding of osteosclerosis with Bands of hazy sclerosis that parallels the vertebral body endplates.
- **Causes of thyrotoxicosis?**
- **Hyperthyroidism causes:**
 - 1- Diffuse toxic goiter (Graves' disease¹). □ Early phase subacute thyroiditis.
 - 2- Single toxic nodule. □ Exogenous thyroid hormone intake.
 - 3- Multinodular toxic goiter.
- **What are the malignant features of thyroid nodule?**
 - **Micro-calcifications.**
 - Local invasion
 - **Markedly reduced echogenicity (hypoechoic=less white).**
 - **Increased Vascularity in duplex US**
- **What are the structures affected by Thyroid ophthalmopathy?**
 - The fist muscles get affected respectively are:
 - **I'M SLOW**
 - Inferior
 - Medial
 - Superior
 - Lateral
- **What is the location of subperiosteal resorption?**
 - Typical subperiosteal bone resorption location is at the “**radial aspects of the middle phalanges**”

Summary

- The first modality of choice in palpable thyroid nodule is **ULTRASOUND**
- A completely uniform halo around a nodule is highly suggestive of benignity, with a specificity of 95%.
- Signs of malignant nodules:
 - 1. **Micro-calcifications** 2. Local invasion 3. A nodule that is taller than it is wider 4. Markedly reduced echogenicity (hypoechoogenicity) 5. **Lymph node metastases** 6. **Absence of a halo** 7. Defined **irregular margins** 8. Solid composition.
- US Features of Malignant Lymph Nodes:
 - 1. Rounded bulging shape 2. Increased size 3. Replaced fatty hilum 4. Irregular margins 5. Heterogeneous echotexture 6. Calcifications 7. Cystic areas 8. Vascularity throughout the lymph node instead of normal central hilar vessels at Doppler imaging
- FNA:
 - **In case of malignant nodules features DO FNA ULTRASOUND GUIDING..** You have to use US guidance, why: 1- to target the needle to go inside the nodule. 2- To not injure the carotid. 3- To not injure the trachea.
- Radiological features of Grave's ophthalmology:
 - The disease is bilateral, 1. Exophthalmos protrusion (because the globe is outside the orbit) 2. Enlargement of extraocular muscles 3. increased retrobulbar fat pad 4. herniation in the fat through superior orbital fissure 5. Stretching of optic nerve.
- Renal Osteodystrophy (parathyroid disease):
 - **Seen in setting of chronic and end-stage renal disease.** Related to combination of Osteomalacia and Secondary hyperparathyroidism.
 - Radiological manifestations: 1. **Bone resorption mainly (Sub-periosteal)** 2. Cortical thinning 3. Soft tissue and vascular calcifications. 4. **Osteosclerosis (Rugger jersey spine)** 5. **Brown tumors**

1- patient presents with sign of thyrotoxicosis
After Perform RAI scan what is the most likely
the cause:

- a. Grave's disease
- b. Plummer disease
- c. Toxic autonomous nodule
- d. Hashimoto's Thyroiditis



2- which of the following is sign of benign nodule:

- a. Increase vascularity
- b. Microcalcification
- c. hypoechogenicity
- d. hyperechogenicity

3- In grave's disease what RAI
scan looks like:

- a. Homogenous uptake
- b. Mild inhomogeneous uptake
- c. No uptake
- d. Single uptake

4- when do we perform imaging of
RAI:

- a. After a day
- b. After 12 h
- c. After 2 days
- d. After 6 h

5- what is the most common
finding in renal osteodystrophy:

- a. Osteosclerosis
- b. osteopenia
- c. Pathological fracture
- d. Rugged jersey spine

6- while performing FNA the
physician should be careful not to
injure:

- a. Thyroid gland
- b. Common carotid Artery
- c. Vagus nerve
- d. Esophagus

Answers
1) b
2) d
3) a
4) a
5) b
6) b