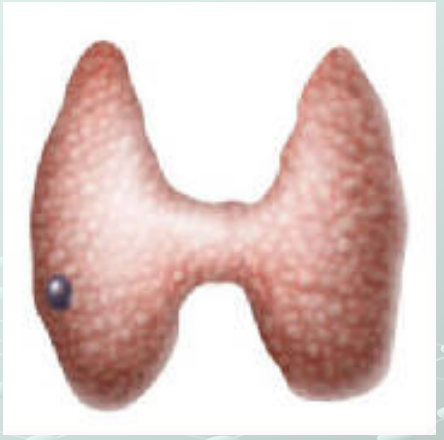

Thyroid Nodules and Thyroid Cancer

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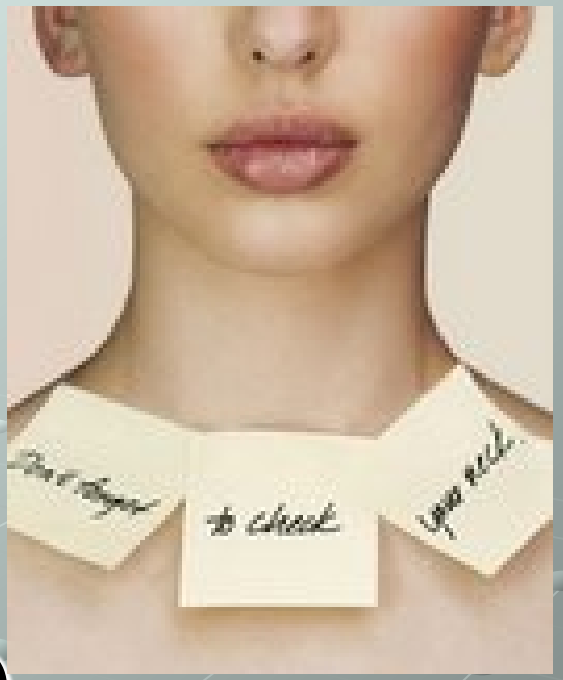
Epidemiology

- Thyroid nodules are very common.
- Most thyroid nodules are not clinically recognized.
- The prevalence of palpable nodules is 3-7%
- The prevalence based on US or autopsy data is as high as 50%. (up to 67% based on US)

Why do we care?

- Some thyroid nodules can cause obstruction or can be cosmetically disturbing to the pt.
- Nodules may cause thyroid dysfunction.
- Nodules may be cancer.

Discovery of nodules



- Sometimes discovered by the pt.
- Can be discovered in routine

physical examination (be sure

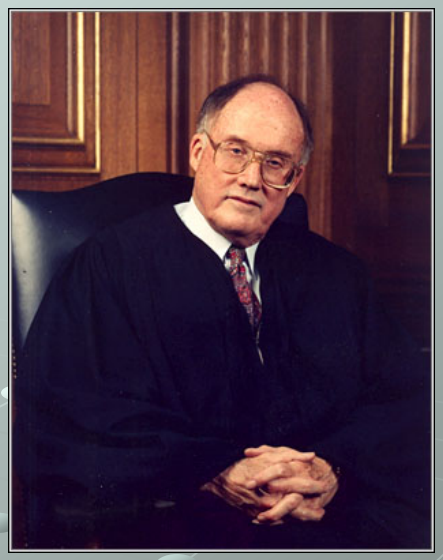
to do a thyroid exam in your patients!)

- Often found during a radiologic procedure performed for another reason (e.g. carotid US or CT scan of chest).

What are the causes of thyroid nodules?

- Multinodular goiter
- Hashimoto's (chronic lymphocytic) thyroiditis
- Cysts (simple, colloid, or hemorrhagic)
- Follicular adenomas
- Hurthle cell adenomas
- Papillary thyroid carcinoma
- Follicular carcinoma
- Medullary carcinoma
- Anaplastic carcinoma
- Primary thyroid lymphoma
- Metastatic carcinoma (breast, renal cell)

Rate of cancer



- Most thyroid nodules are benign.
- Cancers represent only about 5% of all nodules.

Epidemiology of thyroid cancer

- The American Cancer Society estimates that 60,220 new cases of thyroid cancer will be diagnosed in the US in 2013– 45,310 in women and 14,910 in men.
- During this same year, approximately 1040 women and 810 men will die from thyroid cancer.
- The chance of being diagnosed is more than twice what it was in 1990.
- Most thyroid nodules are benign, but 1 in 20 is cancerous.

An incidental nodule

- A 50 yr old female pt was admitted to hospital with L sided weakness concerning for a TIA. As part of the workup, a carotid doppler was performed with an incidental finding of a R sided thyroid nodule. The patient is requesting that the everything “be fixed” during her hospital stay, so you were consulted.
- What is the first thing you need to do?

Take a history. Certain pt characteristics are associated with an increased cancer risk.

- Children– a thyroid nodule in a child is twice as likely to be cancer than in an adult.
- Men– the rate of cancer is twice as high in men than women.
- Age– rate of cancer is higher in adults >60 and <30.
- History of radiation to the head and neck– used to be done to treat acne, tonsillar enlargement, thymic enlargement.
- Hematopoietic stem cell transplantation– increased relative risk of cancer.

Other risk factors

- Family history of thyroid cancer or multiple endocrine neoplasia.
- Nodule >4cm in diameter or partially cystic.
- Symptoms of compression including dysphagia, dysphonia, hoarseness, dyspnea, and cough.
- Rapid growth of a nodule.

Other factors associated with increased risk of thyroid nodules

- Smoking
- Iodine deficiency
- Alcohol consumption
- Elevated IGF-1 levels
- Uterine fibroids
- Possible decreased risk with OCP and statin use

Physical exam

- Palpate the thyroid looking for size, consistency, symmetry. You will need to watch the pt swallow from the front and side and will need to use water to have the pt swallow several times.
- Try to palpate nodules and note number, size, location, tenderness, mobility.
- Check for cervical lymph nodes.
- Check for tracheal deviation or substernal extension.
- Note voice quality and volume.

Concerning physical exam findings

- Nodule is very firm or hard
- Nodule seems fixed to adjacent structures
- Vocal cord paralysis
- Regional lymphadenopathy
- Physical exam has a low accuracy for finding nodules and for predicting cancer

What labs would you like to order for your patient?

- A. TSH, Thyroglobulin, TPO antibodies.
- B. TSH, total T4, TPO antibodies.
- C. TSH, total T4 and T3
- D. TSH, free T4, TPO antibodies, TSI
- E. TSH with reflex free T4
- F. TSH with reflex free T4, TPO antibodies, TSI.
- G. TSH with reflex free T4, calcitonin.

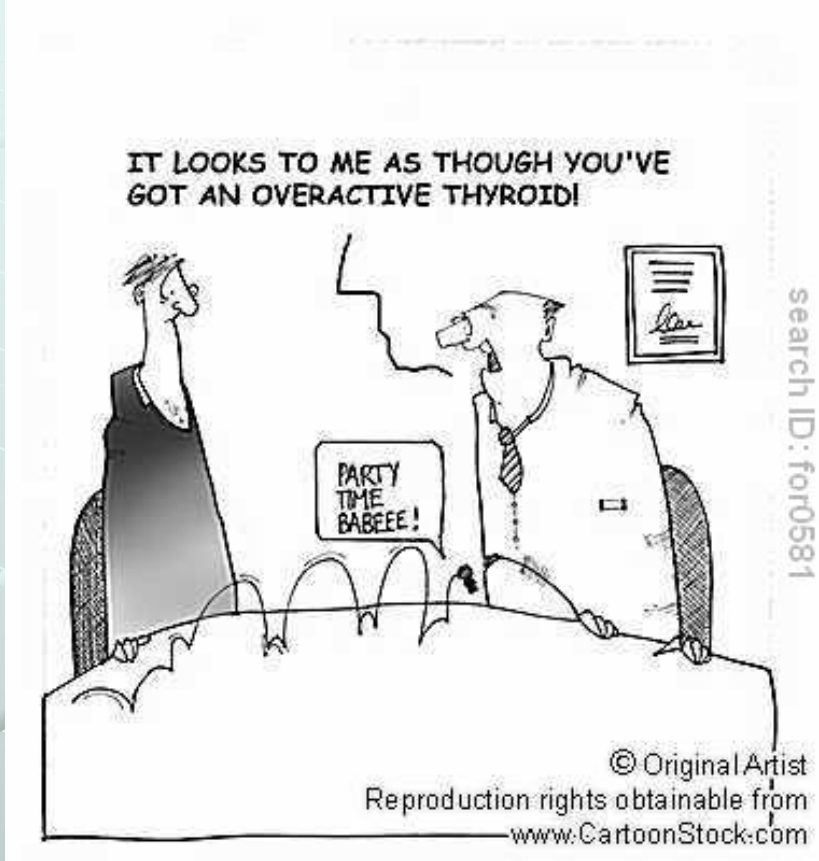
Answer E

- The only biochemical test usually needed is a TSH, and if this is abnormal, a FT4 should be measured.
- If TSH is elevated, TPO antibodies could be obtained to confirm Hashimoto's thyroiditis.
- Nearly all patients with thyroid cancer are euthyroid.
- If a pt has a family history of medullary thyroid cancer or MEN type 2, then a serum calcitonin level should be ordered.

TSH is low at 0.1 and FT4 is mildly elevated. What is the next step?

- A. Thyroid US
- B. US guided thyroid biopsy.
- C. Start methimazole and check US in 6 months to see if the nodule shrinks.
- D. Thyroid uptake and scan.
- E. Nodule is not cancer. Just follow thyroid function tests and treat pt's hyperthyroidism if symptomatic.
- F. Treat pt with levothyroxine.

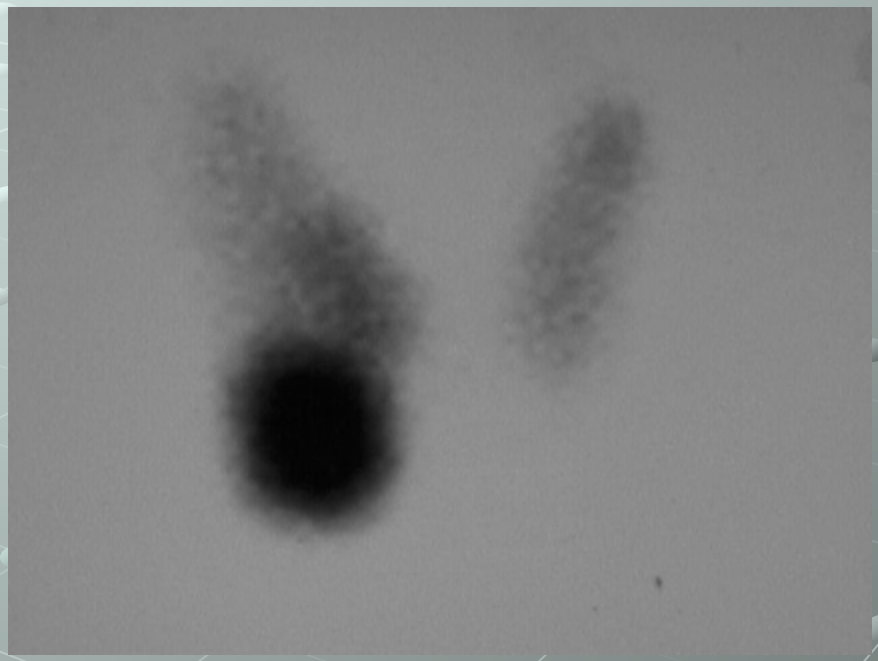
Answer D.



- A low TSH indicates overt or subclinical hyperthyroidism.
- Thyroid scintigraphy (thyroid uptake and scan) is the next step.

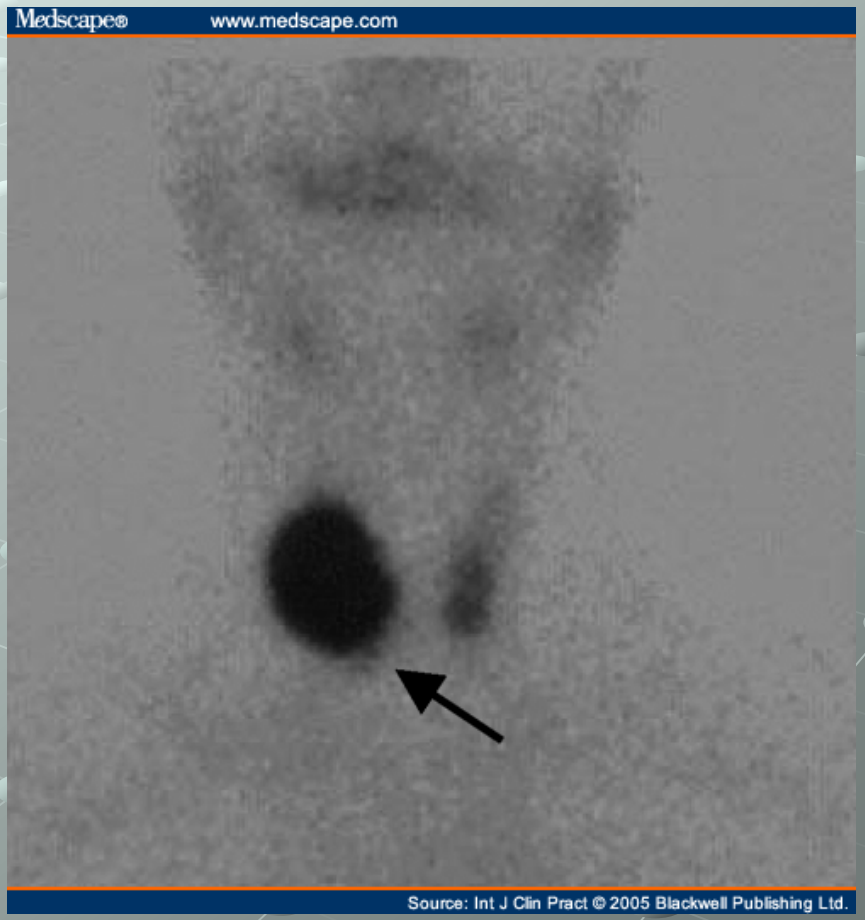
Autonomously functioning nodules

- May appear “hot” on scan.
- Account for only 5-10% of palpable nodules.
- These nodules are not likely to have thyroid cancer.



Treatment

- Pts can be treated with radioiodine, surgery, or antithyroid drugs.
- Consider treatment of subclinical hyperthyroidism (Low TSH with nl FT4) in older pts as they are at increased risk for atrial fibrillation and decreased bone density.



Cold nodules

- Most benign and virtually all malignant thyroid nodules concentrate radioiodine less avidly than adjacent normal thyroid tissue.
- Not cost effective to do scans to look for cold nodules prior to FNA.

TSH is normal. What is the next step?

- A. Thyroid US with possible biopsy.
- B. Surgical excision of thyroid nodule.
- C. Thyroid uptake and scan.
- D. CT scan of the soft tissue of the neck.
- E. PET scan to see if nodule hyperfunctioning.
- F. No further treatment necessary.

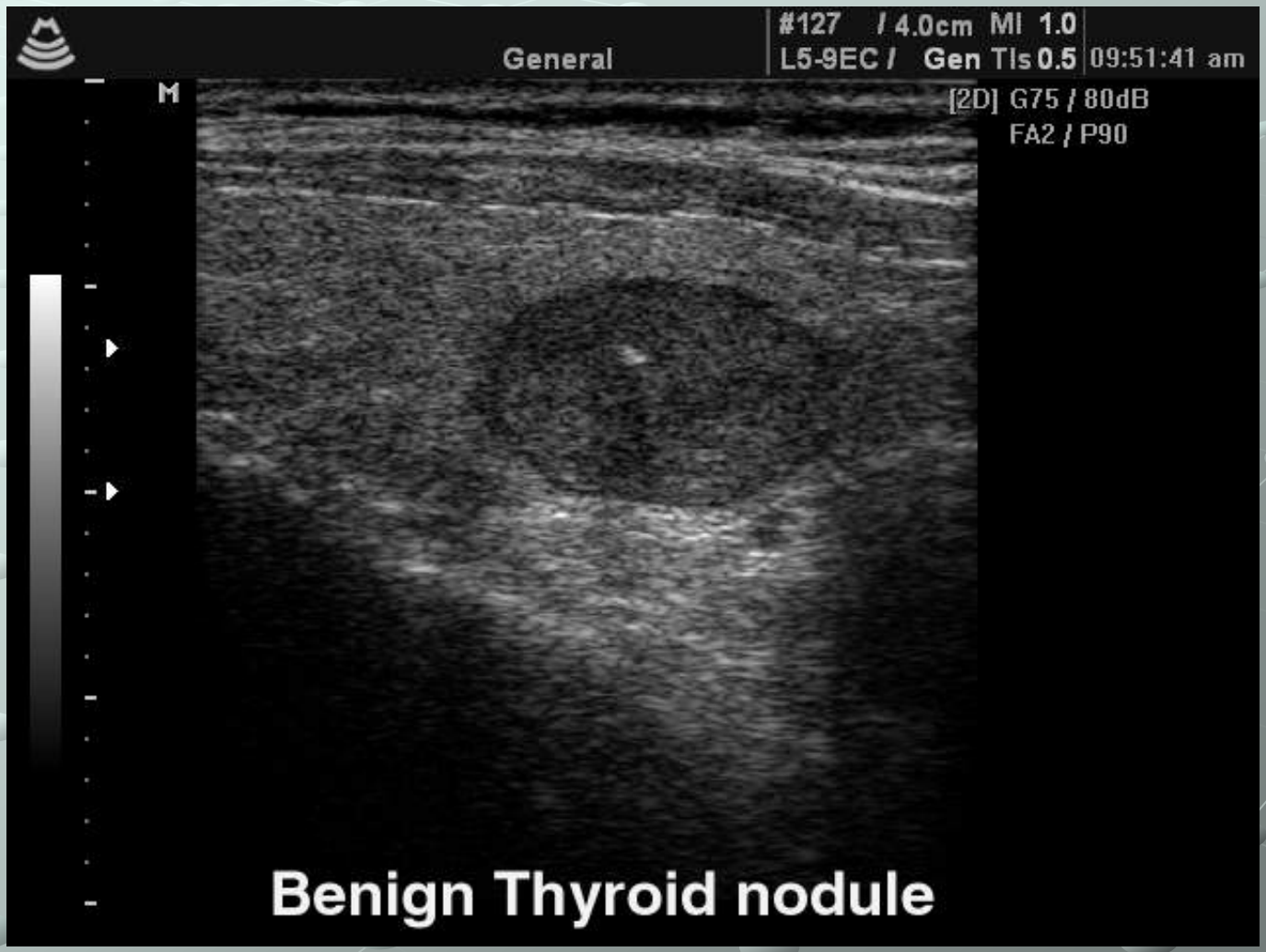
Answer A. Thyroid US

- Can accurately detect non-palpable nodules, estimate the size of the nodule and the volume of the goiter, and differentiate simple cysts from solid or mixed nodules.
- Cannot reliably distinguish benign from cancerous lesions, however.

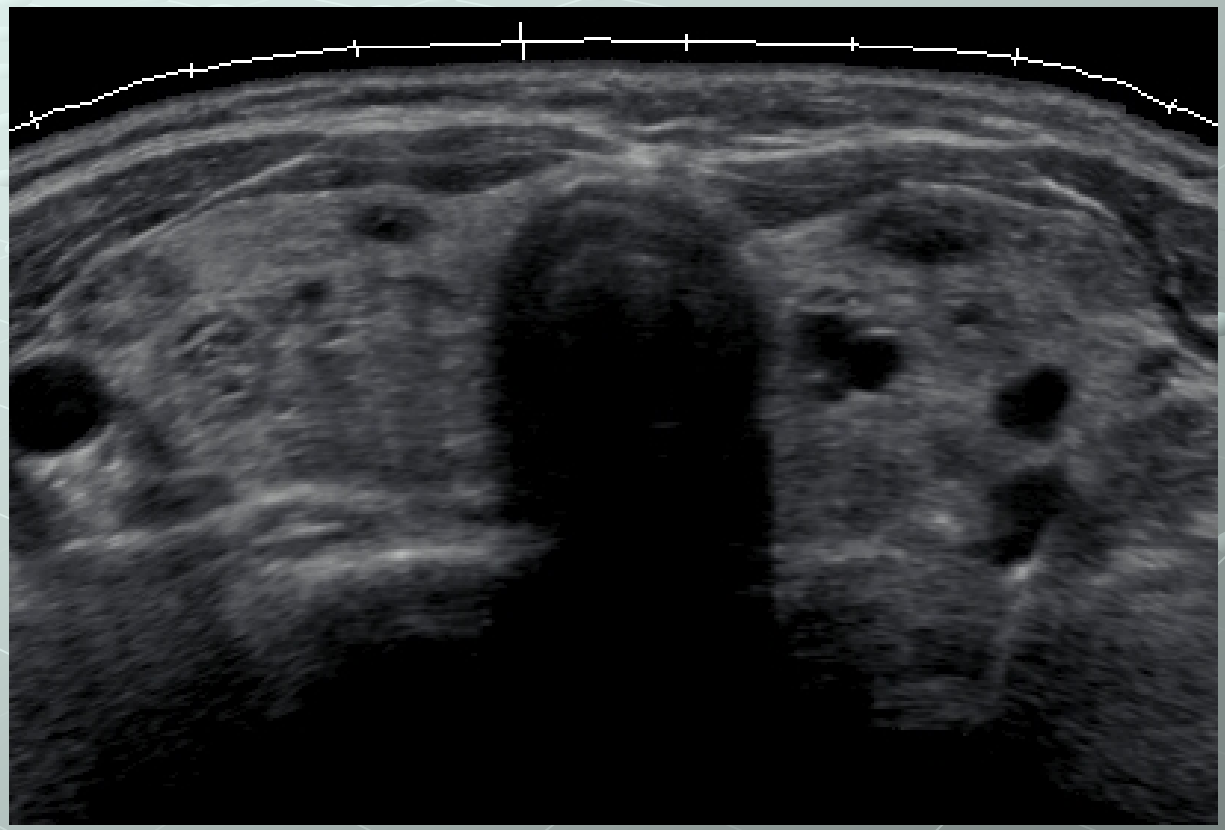
Benign nodules

- Usually round, homogenous in appearance.
- Often slightly hypoechoic.
- Can have “comet tail” artifact.

Benign nodule



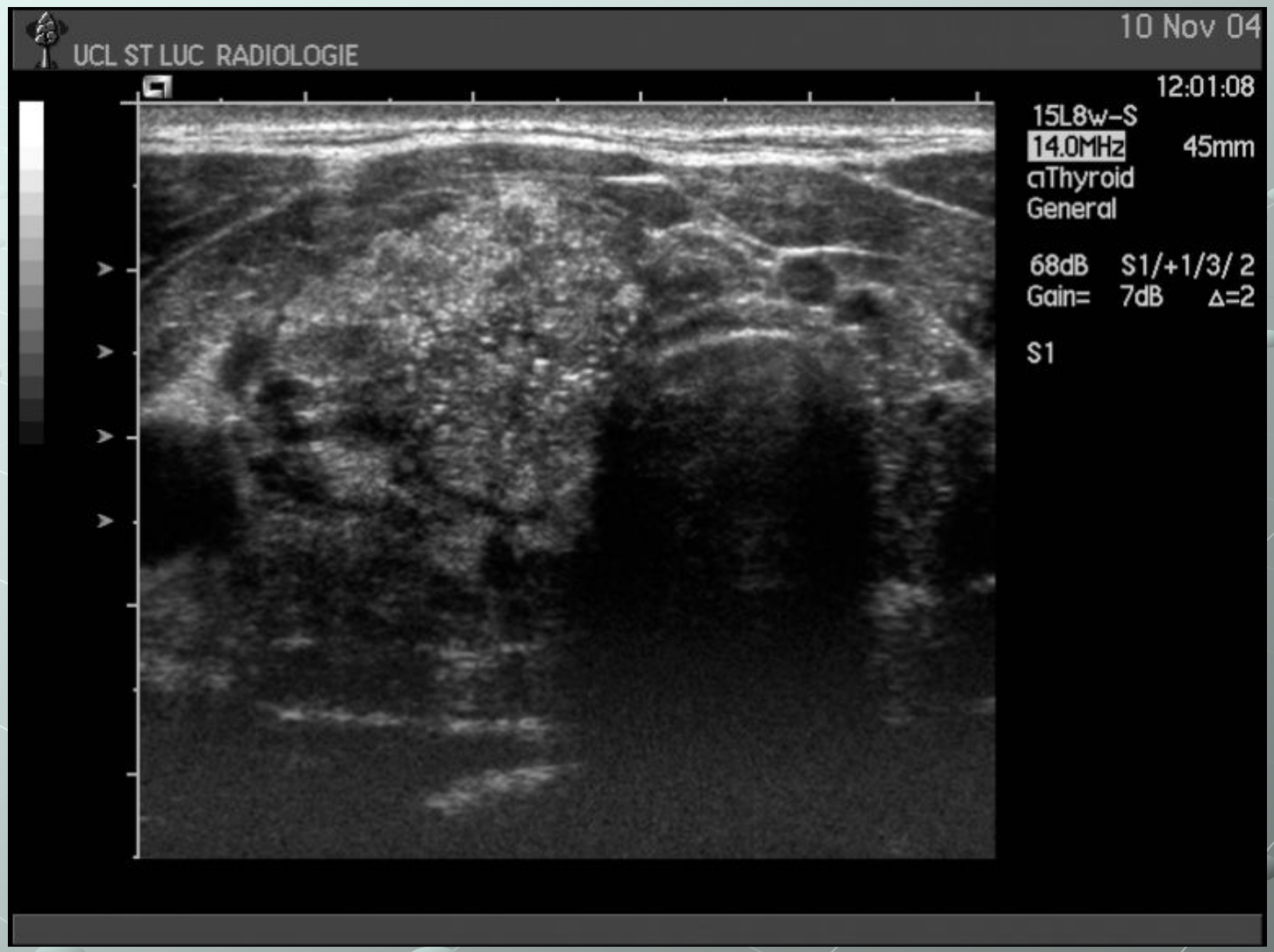
Multinodular goiter

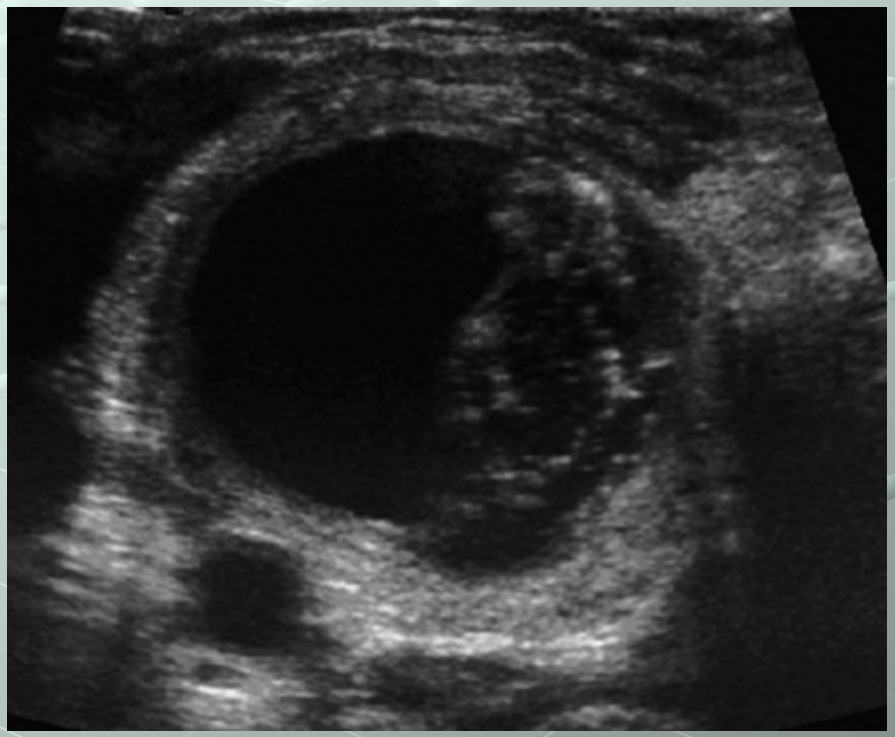


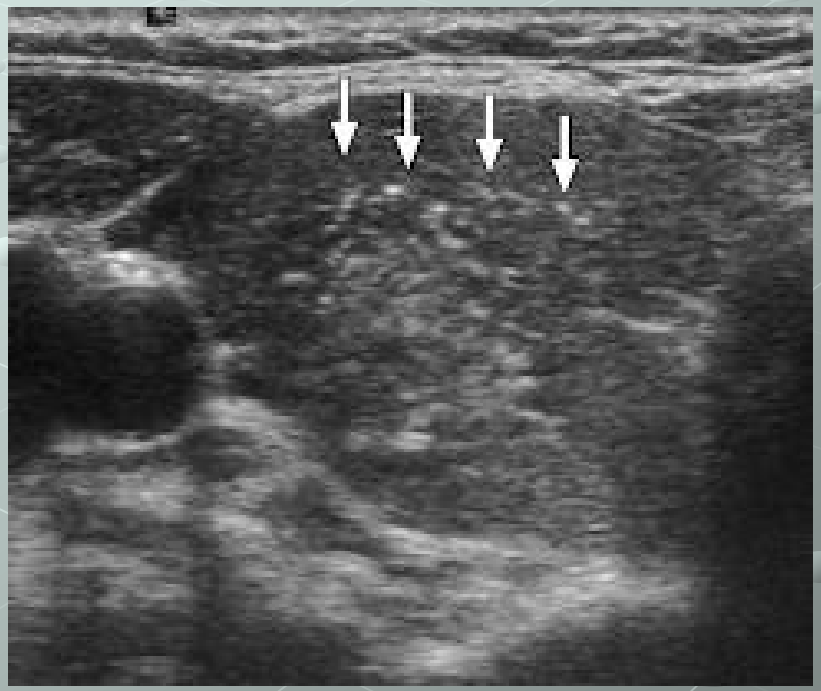
Concerning US characteristics

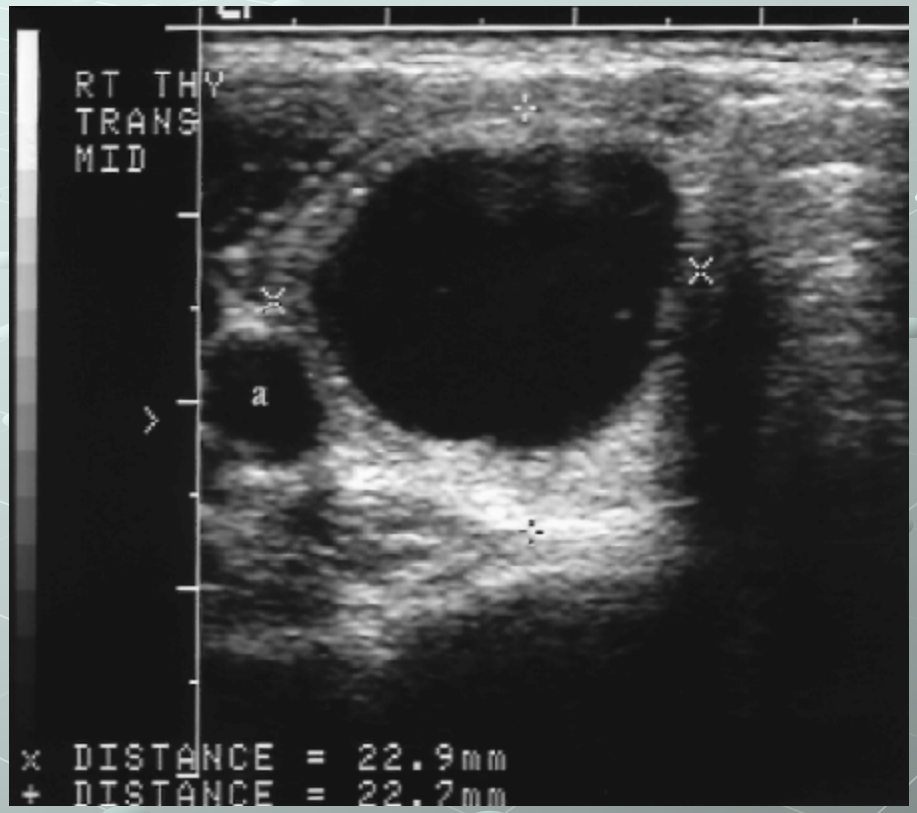
- Irregularly shaped nodules, irregular margins
- Poorly demarcated
- Usually hypoechoic
- Contain fine internal microcalcifications. Like a “starry night.”
- Increased internal vascularity on Doppler exam.
- Regional lymphadenopathy.
- Taller than it is wide.

Thyroid cancer





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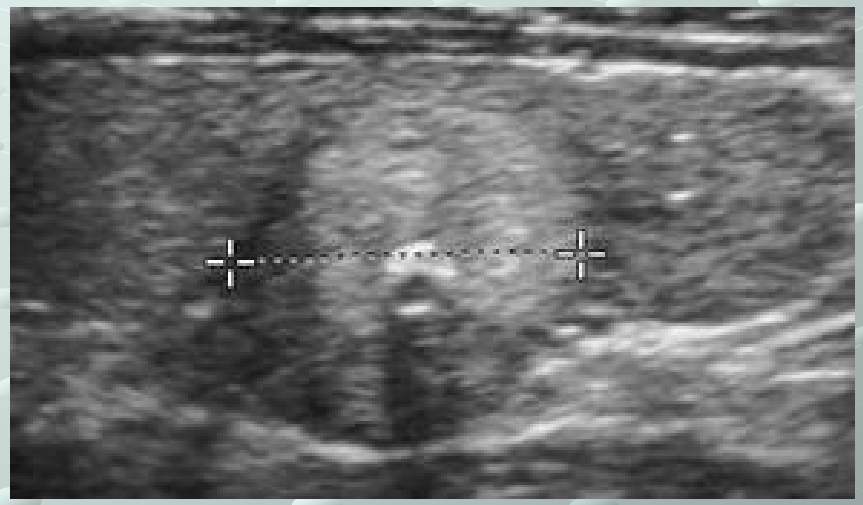
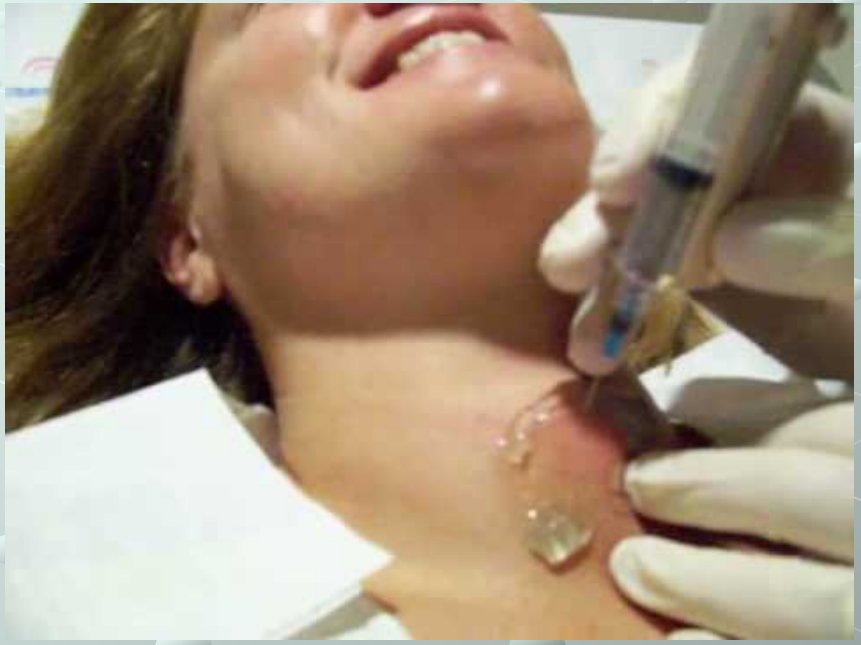


Other imaging modalities

- CT and MRI cannot reliably differentiate between malignant and benign nodules.
- These tests are rarely indicated in the evaluation of a nodule, but can be useful if there is a substernal goiter.
- PET can help distinguish benign from malignant nodules (and often thyroid cancers are detected on PET incidentally) but it is limited by cost and accessibility and biopsy still has to be done.

Fine needle aspiration biopsy



- Inexpensive outpt office procedure.
- Tissue samples obtained using a 23 to 27 gauge needle with or without local anesthesia.
- Often US guided.
- Diagnostically useful info obtained in 80% of cases.

FNA

- Nodules are usually considered for biopsy if they are greater than 1 cm in size.
- Solid lesions less than 1cm in size may be biopsied in high risk situations (PET positive, history with risk factors for cancer, concerning US characteristics).

FNA results (Bethesda criteria)

- Benign. Includes macrofollicular or adenomatoid/hyperplastic nodules, colloid adenomas, nodular goiter, and Hashimoto's thyroiditis.
- Follicular lesion of undetermined significance
- Suspicious for malignancy
- Malignant
- Atypia of undetermined significance
- Non-diagnostic

Non-diagnostic

- About 10-15% of aspirates.
- Usually inadequate sampling, or only cystic component was sampled.
- Less than 5% of these are malignant.
- Usually will repeat biopsy up to 3 times. If persistently insufficient, then would consider lobectomy.

Benign

- About 70% of aspirates.
- No surgical intervention is required unless the pt has cosmetic concerns or compressive symptoms.
- Pt will need continued surveillance– usually annual exam, US and thyroid function testing. If the nodules demonstrates growth, then FNA would be repeated.

AUS/FLUS

- About 5-15% prove to be malignant.
- FNA is usually repeated (often 3-6mos later).
- Lobectomy considered if results still indeterminate.

Suspicious for malignancy

- About 60-75% are cancer.
- Lobectomy or preferably total thyroidectomy is the management.

Malignant

- Represents about 5% of biopsies
- Positive predictive value for cancer is 97 to 99%.
- Total thyroidectomy is the preferred treatment.

Follicular lesion

- 15-30% are malignant, but diagnosis cannot be made by FNA because pathologists must evaluate for capsular and lymphovascular invasion, so lobectomy is often performed for definitive diagnosis.
- Intraoperative frozen section usually done, but diagnosis often cannot be made until final pathology analysis and the pt must return for completion thyroidectomy if follicular carcinoma or follicular variant of papillary carcinoma is found.

New diagnostic testing-- Afirma

- A new gene expression test called the Afirma biopsy by Veracyte has been available since early 2011.
- Test is designed to identify benign thyroid nodules that were originally diagnosed inconclusive and may spare unneccessary invasive surgery.

The procedure

- Sample undergoes a cytopathology review.
- If results are inconclusive, RNA is extracted from the sample.
- The RNA is then affixed to a microarray embedded with 142 genes known to be specifically expressed in either benign or malignant thyroid tissue.
- The gene chip also includes another 25 genes expressed in rare cancers.
- A computer scan of the microarray shows which genes the sample RNA binds to.
- An algorithm then classifies the sample as benign or suspicious for cancer.
- A benign gene expression test allows the physician to consider recommending against surgery.

Cysts

- There is disagreement regarding the risk of cancer in a cystic nodule.
- Aspiration of cyst fluid for cytologic analysis is almost always indicated (also FNA of the solid portion).
- Larger nodules, nodules with bloody aspirates, or cysts that re-accumulate after repeated aspiration are more likely to contain cancer (consider surgery).

Large nodules

- Nodules greater than 4 cm are more likely to be malignant and should therefore be excised.
- US guided FNA directed at several areas within the nodule can decrease the risk of a false negative biopsy, but there can still be sampling error.
- Most endocrinologists do not endorse an absolute size threshold for recommending surgery.

Treatment

- If there is a strong clinical suspicion for cancer, or FNA with malignant or suspicious pathology, then pt should go directly to surgery.
- Radioiodine is the preferred treatment for functioning nodules.
- Meta-analysis showed no difference in the size of nodules of patients who received levothyroxine suppressive therapy. There is no clear recommendation for its use, and it is contraindicated if TSH is already low.

Treatment

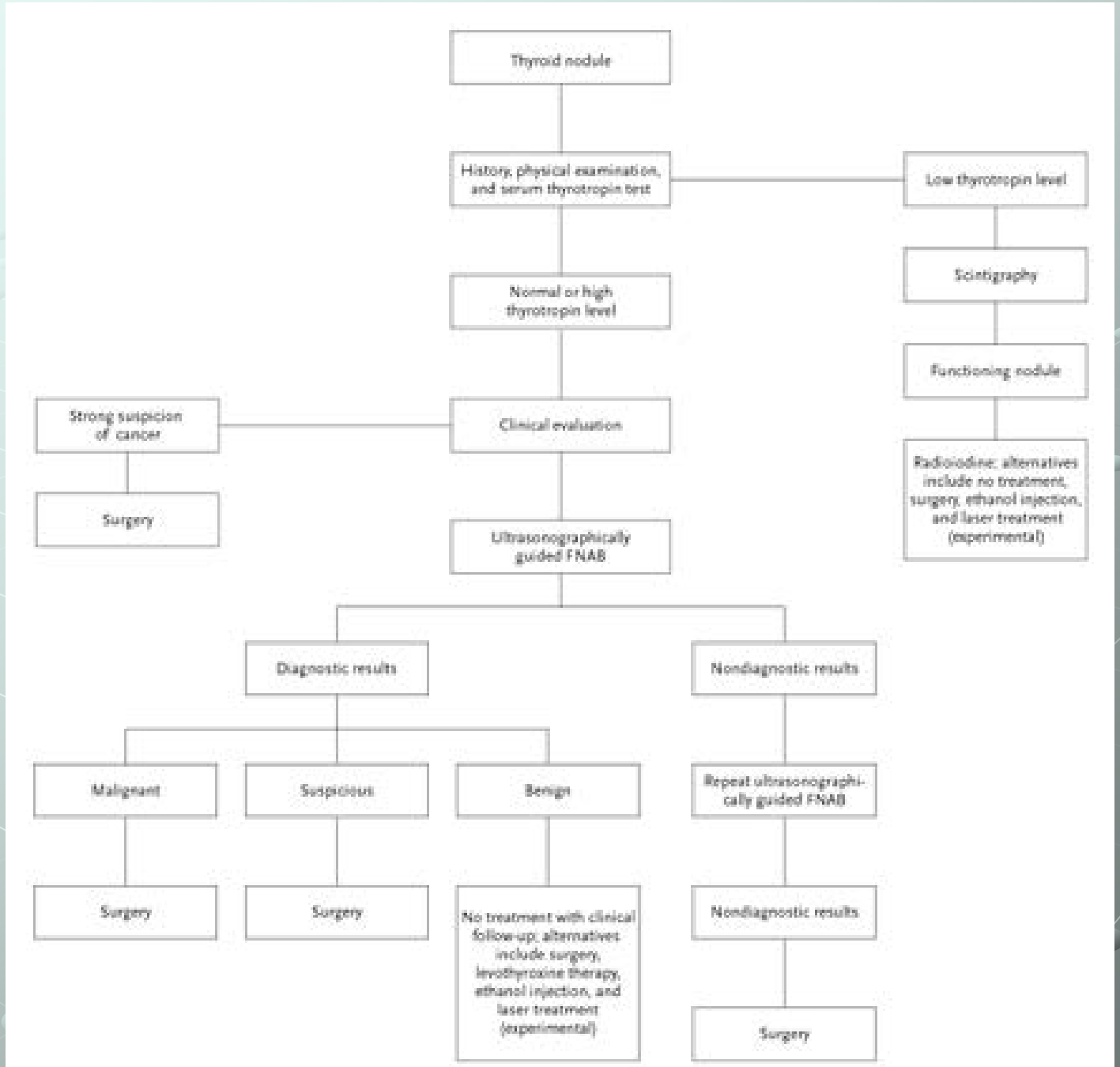
- Percutaneous ethanol injection and laser therapy have been used for nonfunctioning cystic nodules and some solid nodules, but data to support their use is limited.

Question

- You suspect that your pt may have medullary thyroid carcinoma of the thyroid. You have referred them for thyroidectomy, but what testing should you do first?

Follow-up

- In a nodule with benign cytology, periodic life-long follow-up every 6 to 24 months is recommended.
- A common approach is to perform annual palpation, TSH measurement, and US.
- FNA should be repeated if there is evidence of growth of the nodule.


Thyroid nodule
History, physical examination, and serum thyrotropin test
Low thyrotropin level
Scintigraphy
Functioning nodule
Radioiodine; alternatives include no treatment, surgery, ethanol injection, and laser treatment (experimental)
Normal or high thyrotropin level
Strong suspicion of cancer
Clinical evaluation
Surgery
Ultrasonographically guided FNAB
Diagnostic results
Nondiagnostic results
Malignant
Suspicious
Benign
Repeat ultrasonographically guided FNAB
Surgery
Surgery
No treatment with clinical follow-up; alternatives include surgery, levothyroxine therapy, ethanol injection, and laser treatment (experimental)
Nondiagnostic results
Surgery

A little bit about thyroid cancer

Thyroid carcinoma

- Most are differentiated carcinomas, arising from follicular cells.
- These cancers retain the properties of normal thyroid cells (which is useful for treating and following these cancers).
  - Take up iodine (and thus radioactive iodine)
  - They synthesize thyroglobulin
  - Their growth and function is stimulated by TSH

What is the most common type of thyroid cancer?

Chocolate Hills in the Phillippines

Papillary thyroid cancer

- Accounts for about 80% of thyroid cancers.
- Slow growing. Can remain localized for yrs.
- Most common place for metastasis is the cervical lymph nodes.
- Microscopic foci can be found incidentally when thyroidectomy performed for other reasons.

Papillary thyroid carcinoma

- One quarter are multicentric
- Lymph nodes are involved at initial presentation in about one third.
- Distant metastases are usually to the lung, and are present initially in about 5% of cases.

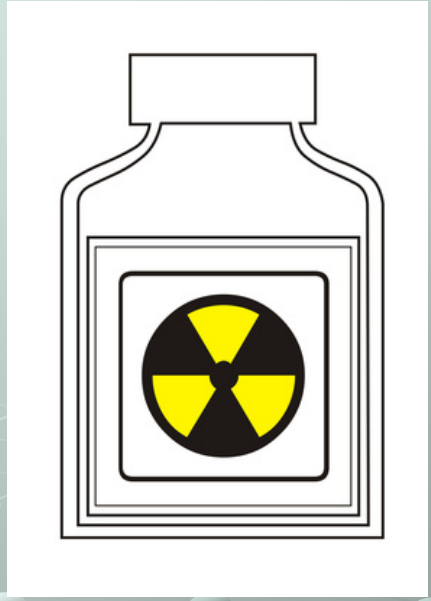
Follicular thyroid carcinoma

- Can be more aggressive.
- Accounts for about 15% of cancers.
- Can metastasize to lung and bone.
- Many cancers have mixed papillary and follicular features, but behave like papillary.
- Hurthle cell carcinoma is a subset of follicular neoplasms and may be more aggressive.

Treatment

- The initial treatment is thyroidectomy (although sometimes lobectomy is performed for papillary carcinomas <1cm).
- Pts considered to have increased risk for recurrence are treated with radioactive iodine.
- Levothyroxine therapy is withheld prior to this so that TSH rises to >30.

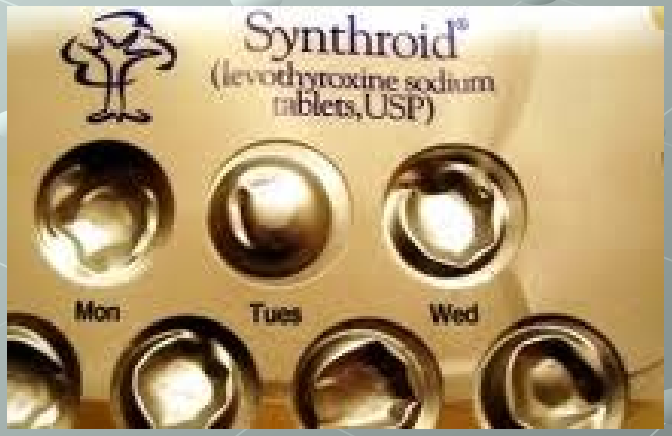
RAI Treatment



- This destroys any remaining normal or malignant thyroid tissue and decreases risk of recurrence and facilitates monitoring.
- A whole body scan is performed after the RAI ablation.

Treatment

- Pts are given levothyroxine at a dose that suppresses the TSH to below the normal range in order to inhibit growth of any remaining thyroid cells.



Thyroglobulin

- Usually measured at the time of whole body scan when TSH is high and secretion by tumor cells is stimulated.
- Repeated at 6-12 month intervals while on suppressive levothyroxine therapy.
- A rising level indicates tumor recurrence.

Other follow-up

- Neck palpation.
- US of thyroid bed and neck to look for lymphadenopathy.
- ***Thyroid cancer can recur even after many years, so patients require lifelong monitoring***

Medullary carcinoma of the thyroid

- Arises from parafollicular C cells.
- Accounts for about 5% of thyroid cancers.
- Plasma calcitonin can be elevated and thus used for diagnosis.
- Most cases are sporadic, but it can be associated with MEN2A and 2B, as well as familial MCT syndrome, which are all caused by mutations of the RET proto-oncogene.

Treatment of medullary carcinoma

- Total thyroidectomy is primary therapy.
- Genetic testing for the RET mutation can be helpful for early detection in family members with familial MCT and MEN2A and 2B.
- Levothyroxine is given to keep TSH within the normal range.
- Calcitonin is used for monitoring for recurrence.
- RAI therapy is not useful.

Metastases

- Occurs only rarely
- Renal and breast cancers are the more common tumors that can metastasize to the thyroid.
- Thyroidectomy may be performed if this is the only site of metastasis, but otherwise treatment is related to the site of origin.

Question

- You told your patient that most thyroid cancers are slow growing, but she comes to you worried because one of her nodules has exhibited sudden rapid growth. She can now feel and see a R sided nodule that she could not even a few weeks before.
- She has a multinodular goiter and a history of Hashimoto's thyroiditis on levothyroxine.
- What two rare malignancies are you concerned about?

Anaplastic thyroid cancer

- Rare
- Rapidly progressive form that has a poor prognosis.
- Surgery is often palliative, and often performed just to maintain an airway.

Primary thyroid lymphoma

- Accounts for about 1% of thyroid cancers.
- Risk is increased in patients with Hashimoto's thyroiditis.
- Treatment is chemotherapy and external beam radiation, although surgery alone may be used for early stage mucosa-associated lymphoid tissue lymphomas.

The End!


MASTERSHIP HONOR LOYALTY KNOWLEDGE VISION RESPECT HUMILITY GRATITUDE
The Way of