

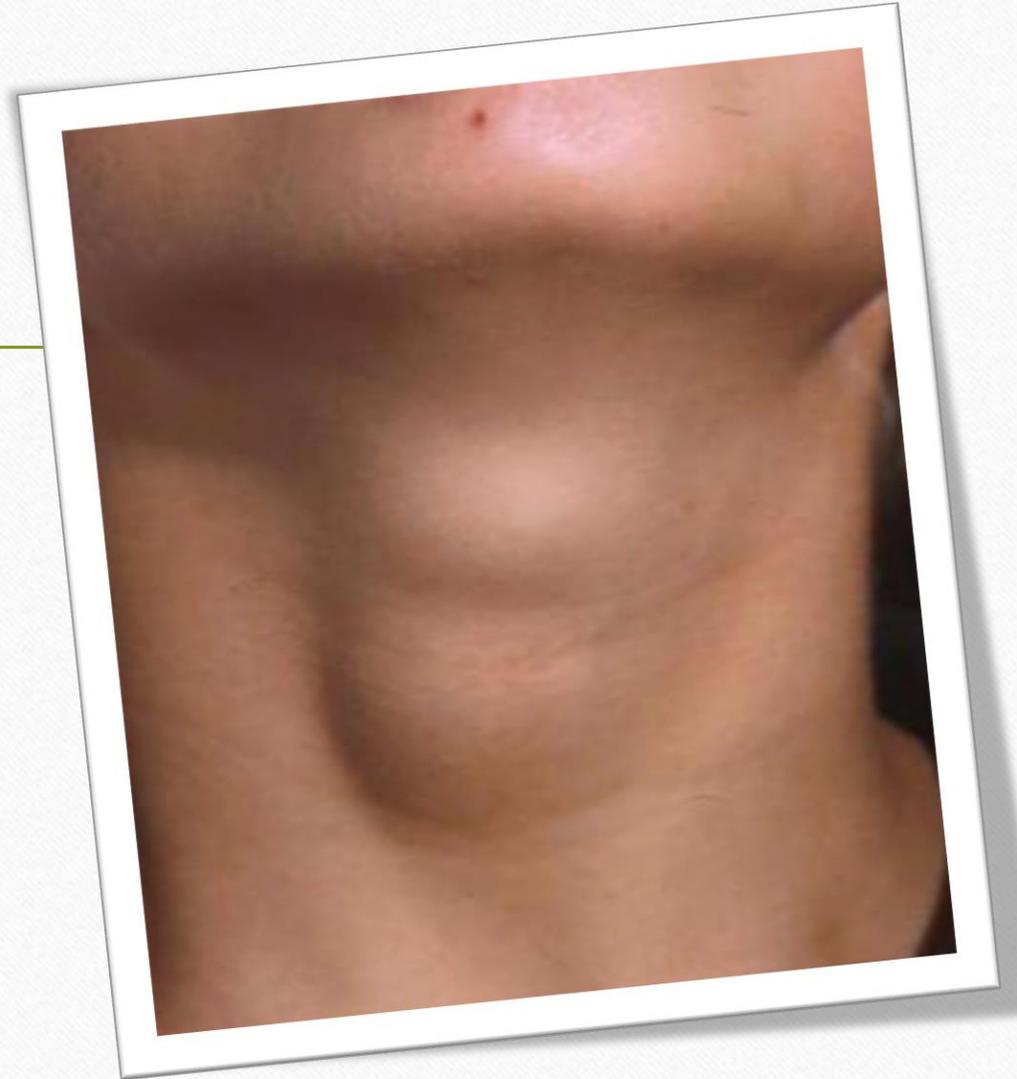
Thyroid Nodule

Dr.Davoud Mohammadi

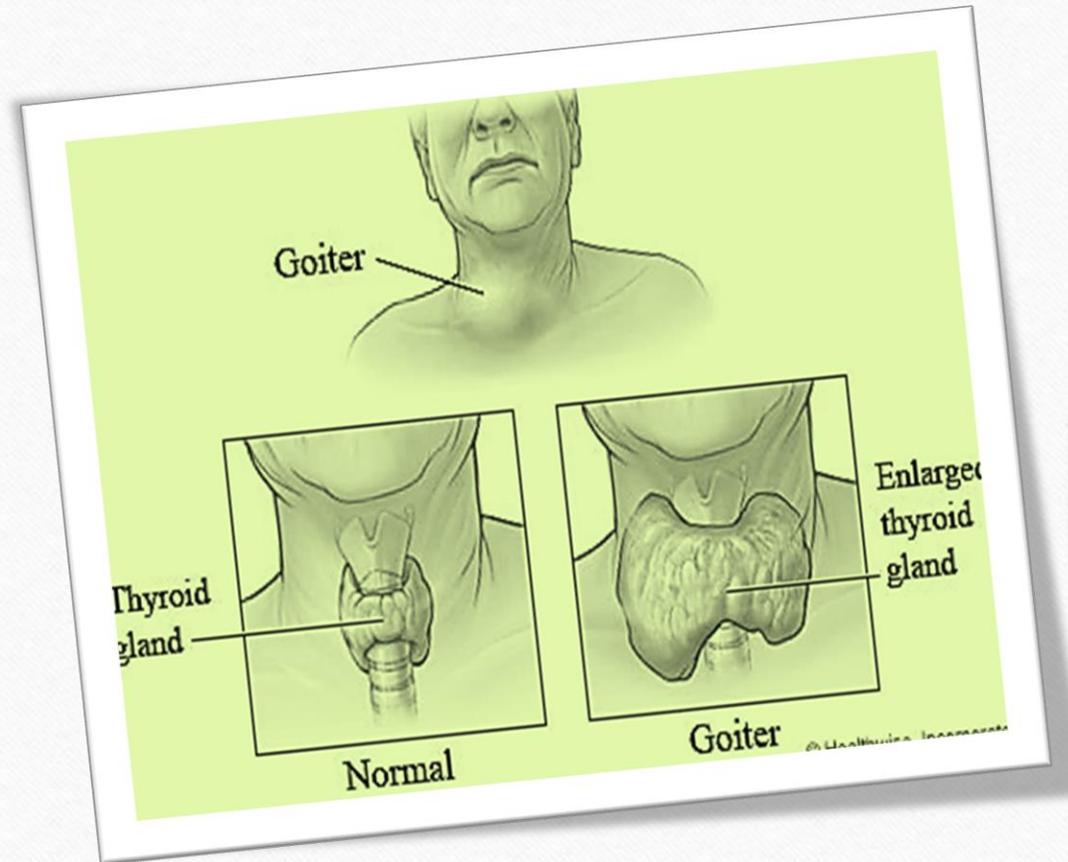
Thoracic Surgeon

Qazvin University of Medical Science

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- Introduction
 - Pathogenesis And Genetic Basis
 - Evaluation of Thyroid Nodule
 - Management of Thyroid Nodule



- **Goiter** refers to an **enlarged** thyroid gland...
- Due to by different mechanisms :
 - 1) Iodine deficiency,
 - 2) autoimmune disease,
 - 3) nodular diseases
- **Graves' disease** and **Hashimoto's thyroiditis** are also associated with goiter...



- A **thyroid nodule** is a discrete *lesion* within the thyroid gland that is *radiologically* distinct from the surrounding thyroid parenchyma...
- Nodules are **more common** :
 - ✓ in iodine-deficient areas,
 - ✓ in women,
 - ✓ with aging...
- prevalence of palpable thyroid nodules (in iodine-sufficient):
 - ✓ **5%** in women
 - ✓ **1%** in men



- Most *palpable nodules* are *>1 cm* in diameter, but the ability to feel a nodule is influenced by:
 - ✓ Its *location* within the gland,
 - ✓ The *anatomy* of the patient's neck, and
 - ✓ The *experience* of the examiner...
- Their *clinical importance* is primarily related to the need to exclude *thyroid cancer*, which accounts for 4 to 6.5 percent of all thyroid nodules in non-surgical series...
- Non-palpable nodules (*Incidentalomas*) have the same risk of malignancy as palpable nodules of the same size ...

PATHOGENESIS AND GENETIC BASIS

- Radiation
- TSH and Growth Factors...
- Oncogenes and Tumor-Suppressor Genes...

- Activation of the **RET-RAS-BRAF** signaling pathway is seen in up to **70%** of **PTCs**, although the types of mutations are heterogeneous.
- **RAS** mutations, are found in about **20–30%** of thyroid neoplasms, including both **PTC** and **FTC**...

- Most of the mutations seen in differentiated thyroid cancers have also been detected in ATCs...
- **BRAF** mutations are seen in up to **50%** of **ATCs**...
- Mutations of the **tumor-suppressor P53** also play an important role in the development of **ATC**...

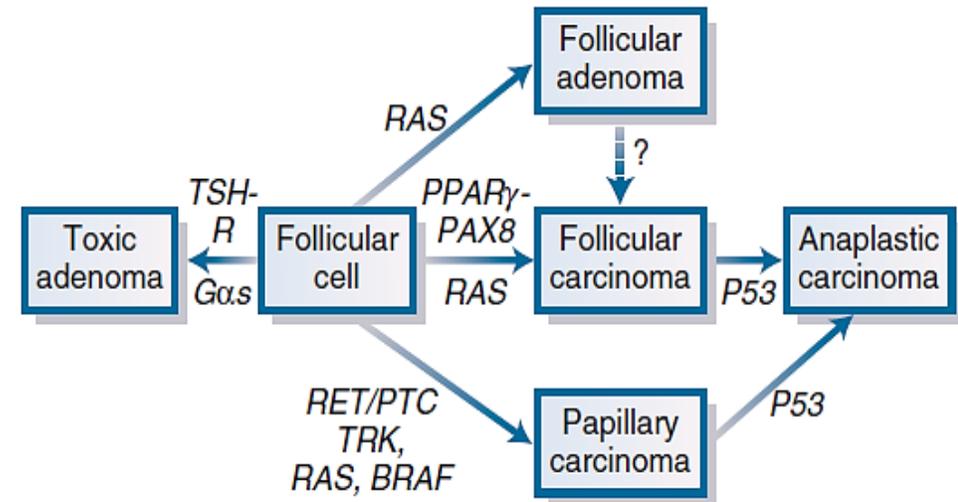


Figure 14-5 Genetic events in thyroid tumorigenesis. Activating point mutations of the *RAS* genes are found with a high frequency in both follicular adenomas and follicular carcinomas and are considered an early event in follicular tumorigenesis. The *PPAR γ -PAX8* rearrangement is found only in follicular tumors. Rearrangements of transmembrane receptors with tyrosine kinase activity (*RET/PTC*, *TRK* genes) and activating point mutation of the *BRAF* gene are found only in papillary thyroid carcinomas (PTCs). Inactivating point mutations of the *P53* gene are found only in poorly differentiated and anaplastic thyroid carcinomas. Activation of the cyclic adenosine monophosphate pathway, by point mutation of the thyrotropin receptor (TSH-R) or the α -subunit of the G protein genes, leads to the appearance of hyperfunctioning thyroid nodules. *G α s*, α -subunit of stimulatory guanyl nucleotide protein; PPAR, peroxisome proliferator-activated receptor.

Signs and symptoms

- **Benign** masses are usually **movable, soft, and non-tender...** and most patients are *asymptomatic...* Some exhibit signs and symptoms of altered levels of thyroid hormone...
- **Malignancy** is associated with a **hard nodule, fixation to surrounding tissue, and regional lymphadenopathy** and reported *rapid growth* or signs and symptoms of *local nerve involvement* (**dysphagia & hoarseness**) should trigger rapid investigation...

- Family members of patients with non-medullary differentiated thyroid cancer may be considered at risk based on epidemiological evidence showing that **5-10% of DTCs** have a *familial occurrence*...
- When only two family members are affected, the disease displays the features of “*genetic anticipation*” which is considered good evidence for a distinct clinical entity possibly representing true familial disease.
- **Screening** people with **familial** follicular cell–derived **DTC** may lead to an **earlier diagnosis** of thyroid cancer, but the panel *cannot* recommend for or against **US screening** since there is *no evidence* that this would lead to reduced morbidity or mortality...
- Patients with familial differentiated thyroid cancer should have a careful **history** and directed **neck examination** as a part of **routine health maintenance**...

Investigations of thyroid nodules :

- ✓ **LABORATORY STADIES**
- ✓ **ULTRASONOGRAPHY**
- ✓ **THYROID SCAN & OTHER IMAGINGS...**
- ✓ **FNA**

Laboratory studies

- **Serum TSH** is an independent risk factor for predicting malignancy in a thyroid nodule...
 - ✓ In a study of 1500 patients presenting to a thyroid practice, the prevalence of malignancy was 2.8, 3.7, 8.3, 12.3, and 29.7 percent for patients with serum TSH concentrations <0.4 mU/L, 0.4 to 0.9 mU/L, 1.0 to 1.7 mU/L, 1.8 to 5.5 mU/L, and >5.5 mU/L, respectively...
 - ✓ Some studies have shown that when **cancer** was diagnosed, a **higher TSH** was associated with a more **advanced stage** of cancer.
- **Antithyroid antibodies**... Complete blood count (**CBC**) ... calcitonin levels... &...

RECOMMENDATION ***for Serum calcitonin measurement***

- Data from a series of prospective, nonrandomized studies...suggest that the use of routine serum calcitonin for screening **may detect** C-cell hyperplasia and medullary thyroid cancer (**MTC**) at an **earlier stage** and overall survival consequently may be improved.
- The panel **can not** recommend either for or against routine measurement of serum calcitonin in patients with thyroid nodules...
(No recommendation, Insufficient evidence)

- If the unstimulated serum calcitonin determination has been obtained and the level is **greater than 50-100 pg/mL**, a **diagnosis of MTC is common**.

- There is emerging evidence that a **calcitonin measurement from a thyroid nodule FNA washout** may be **helpful** in the preoperative evaluation of patients with a **modestly elevated basal serum calcitonin (20-100 pg/ml)**...

Ultrasonography

- The most sensitive test to detect lesions in the thyroid and indicated in all patients who have a nodular thyroid...
- Diagnostic thyroid/neck US should be performed in all patients with a suspected **thyroid nodule, nodular goiter, or radiographic abnormality** suggesting a thyroid nodule incidentally detected on another imaging study... (e.g., CT or MRI or thyroidal uptake on 18FDG-PET scan...)

Clinical Utility of Neck Ultrasound

Map of the neck (thyroid and lymph node areas)

Thyroid gland: size, volume, characteristics

➤ Nodules: number and characteristics of each nodule: diameters, shape, echogenicity, composition, limits, presence of calcifications, vascularization.

➤ Lymph node compartments

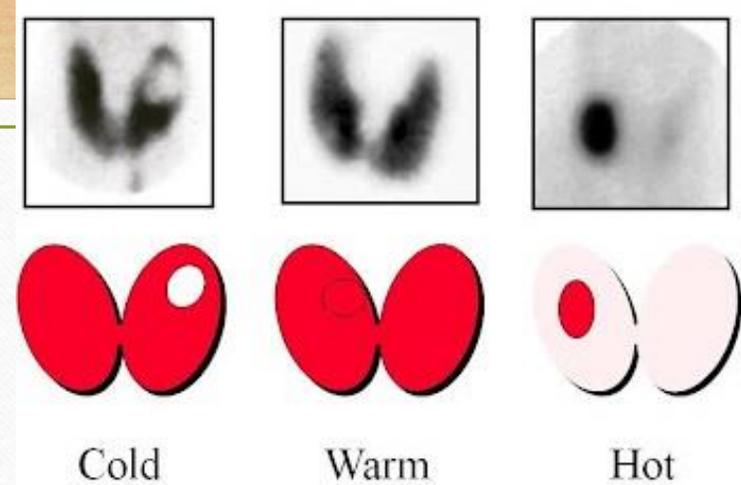
Follow-up: numbers and diameters of nodules

➤ Guidance for fine-needle aspiration biopsy

➤ Follow-up of thyroid cancer: thyroid bed and regional lymph nodes

Guidance for radiofrequency and ethanol ablation

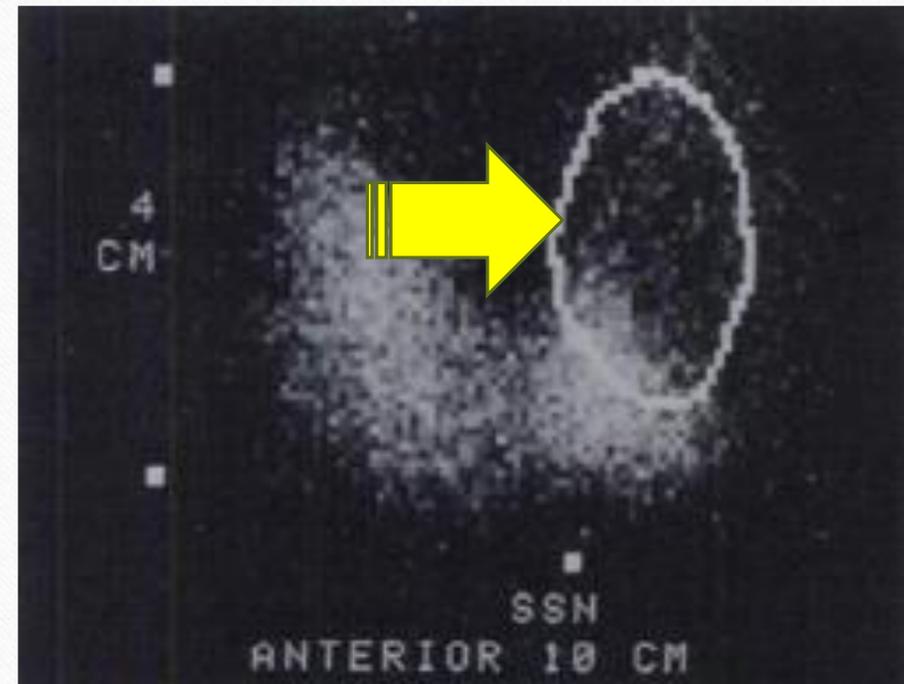
Radionuclide Scanning



- Usually either Technetium(Tc^{99}) or Radioiodine(I^{123}) used...
- Both benign and almost all malignant neoplastic tissue concentrate both radioisotopes less than normal thyroid tissue... **five percent** of **nonfunctioning** nodules are **malignant ...**
- A nodule that is **hyper-functioning** on radioiodine imaging does **not require FNA...**

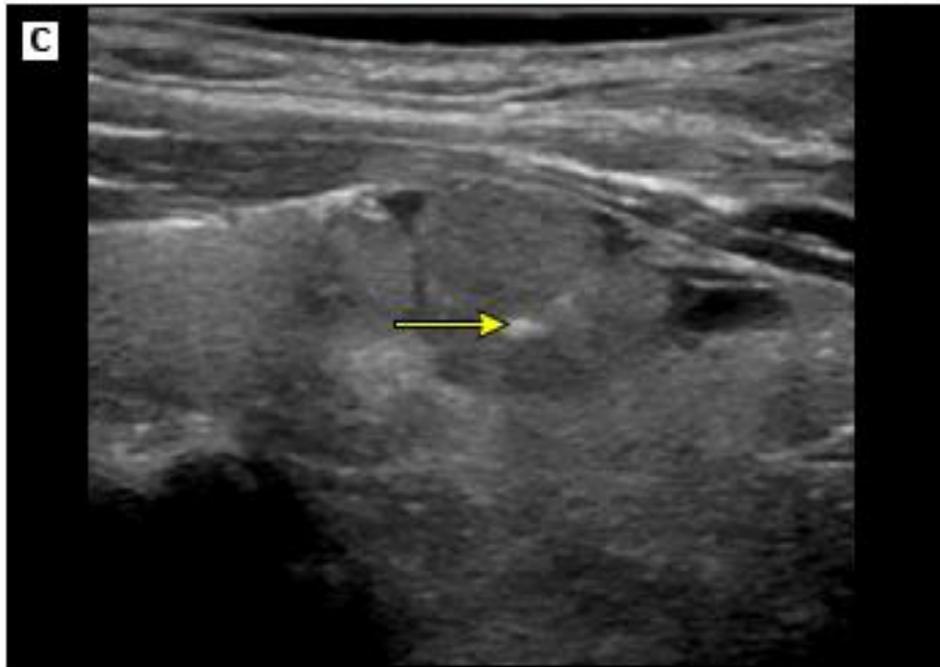
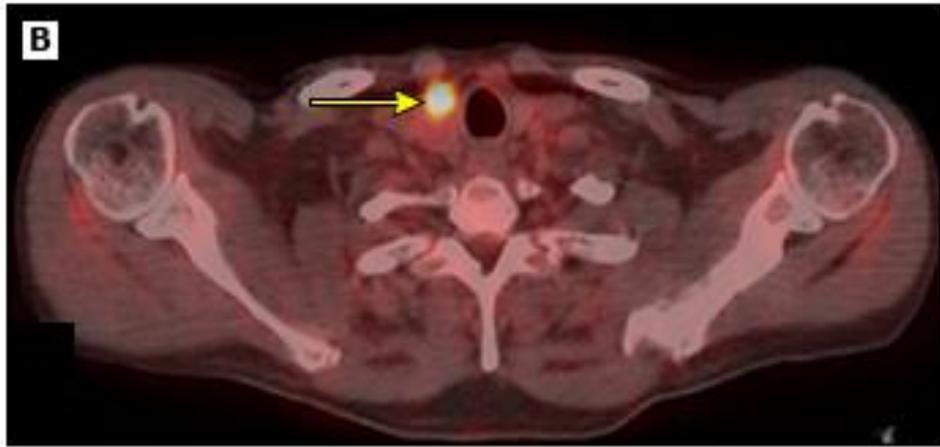
Cold Nodules

- Cyst...
- Non-functioning Adenoma...
- Malignancy...



RECOMMENDATION for *18FDG-PET Scan*

- **Focal 18FDG-PET uptake** within a **sonographically confirmed** thyroid nodule conveys an **increased risk of thyroid cancer**, and **FNA** is recommended for those **nodules > 1 cm**.
(Strong recommendation, Moderate-quality evidence)
- **Diffuse 18FDG-PET uptake**, in conjunction with sonographic and clinical evidence of **chronic lymphocytic thyroiditis**, **does not require further imaging or FNA...**
(Strong recommendation, Moderate-quality evidence)



FNA

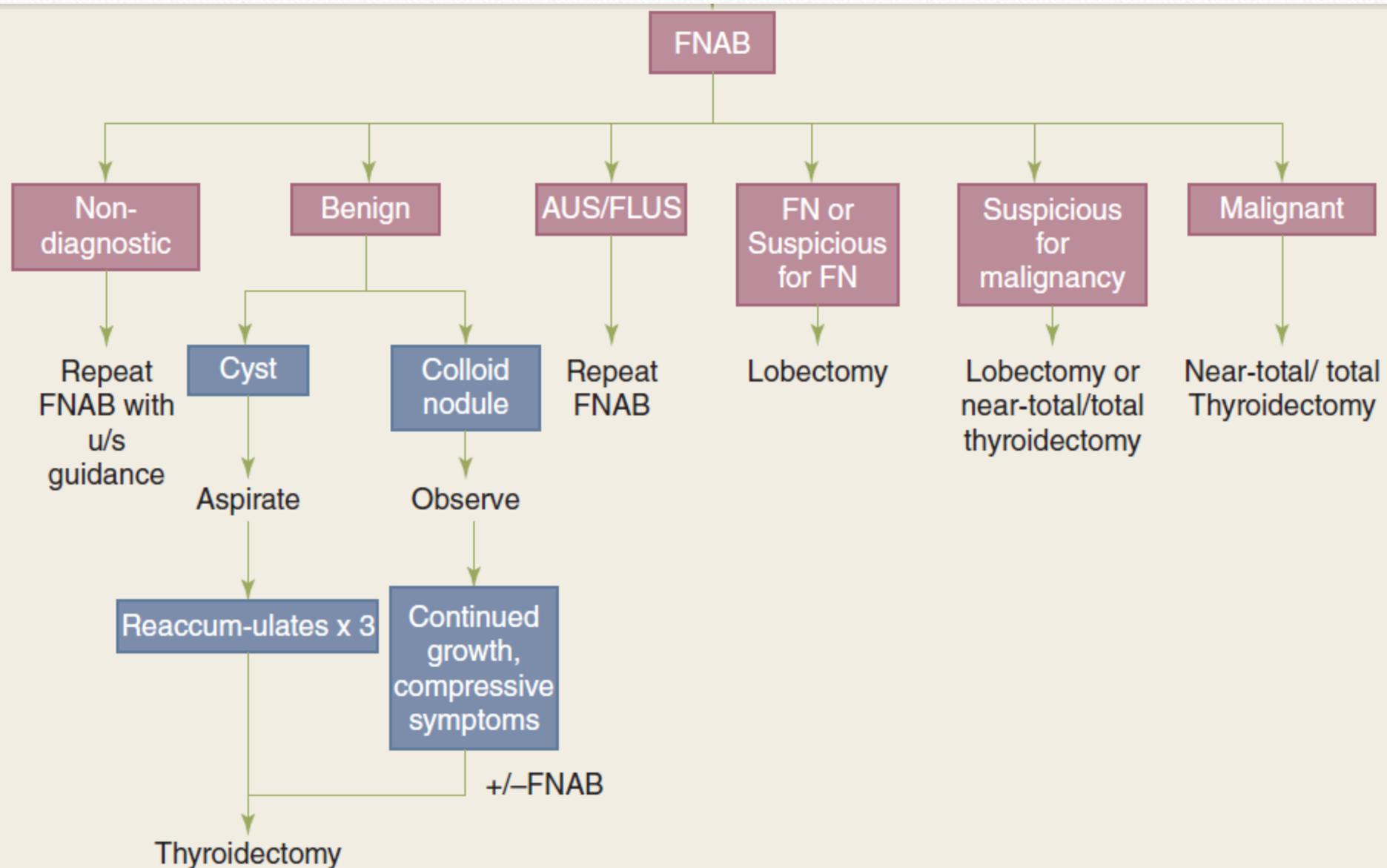
- Generally, only *nodules >1 cm* should be evaluated, since they have a greater potential to be clinically significant cancers...
- Occasionally, there may be *nodules <1 cm* that require evaluation because of :
 - 1) **suspicious US findings,...**
 - 2) **associated lymphadenopathy,**
 - 3) **history of childhood head and neck irradiation** or
 - 4) **history of thyroid cancer in one or more first degree relatives...**

USG guided FNAC



Indicated if :

- Palpation-guided FNAC **non-diagnostic**
- Complex (**solid/cystic**) nodule
- Impalpable nodule
- Abnormal cervical nodes



Primary Thyroid Malignancy

- Almost always leads to **thyroid surgery**... however, an active surveillance management approach can be considered as an alternative to immediate surgery in:

Nondiagnostic or unsatisfactory FNA

- Nondiagnostic or unsatisfactory FNA biopsies are those that fail to meet the established quantitative or qualitative criteria for **cytologic adequacy** (i.e. the presence of **at least six groups** of well-visualized **follicular cells**, **each group containing at least 10 well-preserved epithelial cells**, preferably **on a single slide**)
- **Surgery** should be considered; if nodule has a high suspicion sonographic pattern, growth of the nodule (greater than 20% in two dimensions) is detected during ultrasound surveillance, or clinical risk factors for malignancy are present.
(Weak recommendation, Low-quality evidence)

- It has been suggested that **repeat FNA** should be performed **no sooner than three months** after the initial FNA to prevent **false-positive** interpretation due to biopsy induced reactive/reparative changes...
- Repeat **FNA with ultrasound guidance** will yield a diagnostic cytology specimen in 60-80% of nodules, particularly when the cystic component is <50% .
- Nodules with **larger cystic portion** have a **higher chance** to yield **non-diagnostic** samples on the initial and repeated FNA...

Indeterminate cytology (AUS/FLUS, FN, SUSP)

- The largest studies of **preoperative molecular markers** in patients with indeterminate FNA cytology have respectively evaluated a 7-gene panel of genetic mutations and rearrangements (**BRAF, RAS, RET/PTC, PAX8/PPAR γ**), a gene expression classifier (**167 GEC; mRNA expression of 167 genes**), and **galectin-3** immunohistochemistry...
- Although **BRAF V600E** single mutation testing has been estimated to have a **specificity** of approximately **99%**.
- Furthermore, **long-term outcome data** from a strategy of using molecular markers in indeterminate FNA specimens to stratify surgical approach are **currently lacking**

RECOMMENDATION for AUS/FLUS Cytology

- For nodules with AUS/FLUS cytology, after consideration of worrisome clinical and sonographic features, investigations such as **repeat FNA** or **molecular testing** may be used to supplement malignancy risk assessment in lieu of proceeding directly with a strategy of either surveillance or diagnostic surgery...
- Informed **patient preference** and **feasibility** should be considered in clinical decision-making (Weak recommendation, Moderate-quality evidence).

Follicular Neoplasm/Suspicious for Follicular Neoplasm (FN/SFN) Cytology

- Diagnostic **surgical excision** is the long-established standard of care for the management of follicular neoplasm/suspicious for follicular neoplasm (FN/SFN) cytology nodules...
 - 1) After consideration of clinical and sonographic features, **molecular testing** may be used to supplement malignancy risk assessment data, in lieu of proceeding directly with surgery.
 - 2) Informed **patient preference** and feasibility should be considered in clinical decision making. (Weak recommendation, Moderate-quality evidence)

Suspicious for Malignancy (SUSP) Cytology

- Surgical management should be similar to that of malignant cytology, depending on clinical risk factors, sonographic features, patient preference, and possibly results of mutational testing (if performed). (Strong recommendation, Low-quality evidence)
- **Total thyroidectomy** may be preferred in patients with indeterminate nodules which are cytologically suspicious for malignancy, positive for known mutations specific for carcinoma, sonographically suspicious, large (>4 cm), or in patients with familial thyroid carcinoma or history of radiation exposure... (Strong recommendation, Moderate-quality evidence).

- Intraoperative evaluation, with or without **frozen section**, can occasionally confirm malignancy at the time of lobectomy allowing for conversion to total thyroidectomy if indicated.
- Frozen section is **most helpful** if the histopathologic diagnosis is **classic PTC**, where as its impact is low in follicular variant of PTC and FTC.

- **Nodules < 1 cm with very low suspicion US pattern** (including spongiform nodules) and **pure cysts do not require routine sonographic follow-up...**
(Weak recommendation, Low quality evidence)
- **Nodules < 5 mm without high suspicion US pattern** do not require routine sonographic FU and if repeated, the US should be performed at 24 months or later.
(Weak recommendation, Low quality evidence)

➤ *What is the role of medical or surgical therapy for **benign thyroid nodules...?***

- Routine **TSH suppression therapy** for benign thyroid nodules in iodine sufficient populations is **not recommended**...
(Strong recommendation, High-quality evidence)
- Individual patients with benign, solid or mostly solid nodules should have **adequate iodine intake**... If inadequate dietary intake is found or suspected, a daily supplement with containing **150 mcg iodine** is recommended...
(Strong recommendation, Moderate-quality evidence).

➤ RECOMMENDATION for GROWING NODULES

- **Surgery** may be considered for growing nodules that are benign after repeat FNA if :
 - 1) they are **large (>4 cm)**,
 - 2) causing **compressive or structural symptoms**, or
 - 3) based **upon clinical concern**.

(Weak recommendation, Low-quality evidence)

Thank You
