Management of thyroid nodules and well-differentiated thyroid cancer

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Outline

- Epidemiology
- Discussion of 2015 ATA guidelines
- Role of ultrasound
- Role of cytology
- Management of non-diagnostic fna
- Long term management of benign nodules
- Management of indeterminate cytology
- Management of malignant cytology

Epidemiology of Nodular Thyroid Disease

- Prevalence of nodular thyroid disease
  - Palpable
    - 5% of population
  - Non-palpable
    - 50%
    - Increasingly detected as thyroid incidentalomas
      - Ultrasound
      - CT
      - MRI

Epidemiology of Thyroid Cancer

- Prevalence of cancer in non-palpable nodules < 1cm is similar to that in palpable nodules: 5--8%
- 63,000 new cases of thyroid ca in 2014, compared to 37,000 in 2009
- Incidence 14.3/100K compared to 4.9 in 1975
  - All PTC
  - ~ 40% of new diagnoses are < 1 cm
  - Expected to become 3rd most common cancer in women
- 1500 deaths due to thyroid ca/yr

2015 ATA Thyroid Nodule Guideline Aims

- Minimize potential harm from overtreatment in a majority of patients at low risk for disease-specific mortality and morbidity,

- while appropriately treating and monitoring those patients at higher risk.

Overriding principle

- Most nodules are low risk, and many thyroid cancers pose minimal risk to human health and can be effectively treated
- Only nodules > 1 cm should be biopsied unless there are significant risk factors, lymphadenopathy, or suspicious ultrasound features
- Biopsying subcentimeter nodules has the potential for leading to more harm than good

22: Importance of TSH

- Mandatory for ruling out hyperfunctioning nodules
- A suppressed TSH should lead to radioiodine uptake scan
- Patients with normal or elevated TSH do not benefit from scanning
- Hyperfunctioning nodules should not be biopsied

Ultrasound should be obtained in all patients with thyroid nodules.

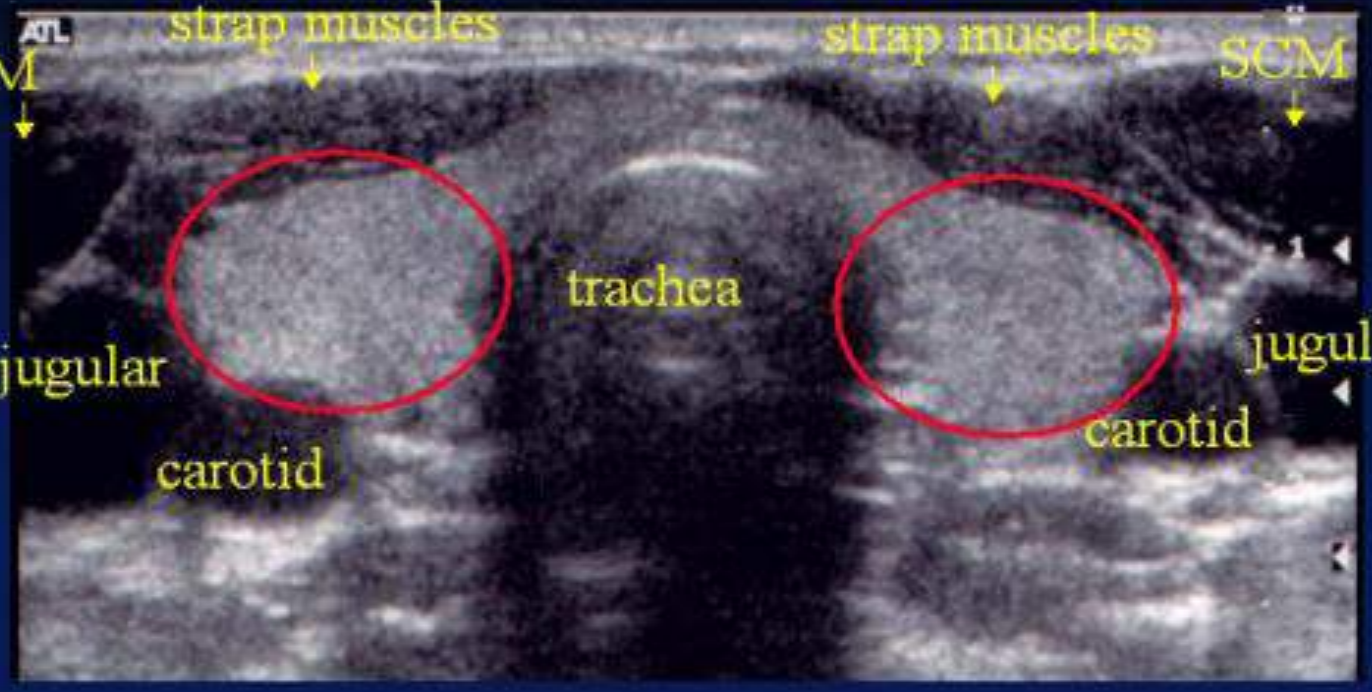
- Ultrasound as an Extension of the Physical Exam
- 15% of “palpable nodules” are without abnormality on US eval*
- 45% of patients have additional nodules

Brander et al. J Clin Ultrasound 1992; Marqusee et al. Ann Int. Med. 2000.

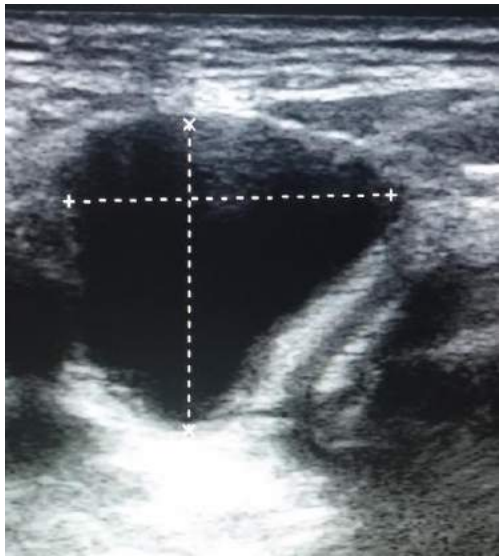
Ultrasound Characteristics of Thyroid Nodules

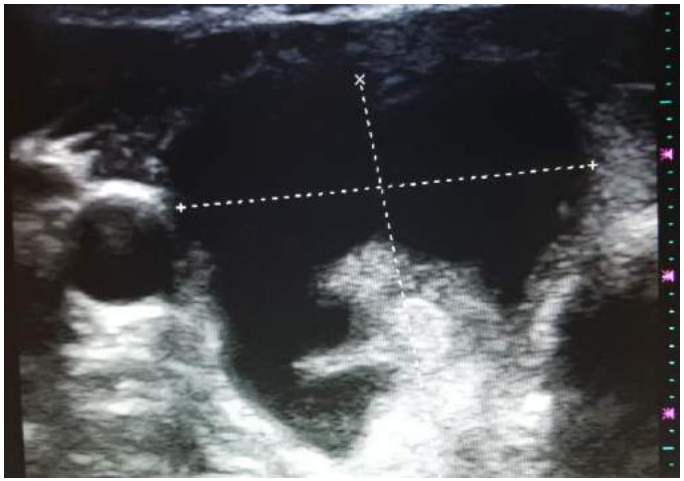
- Size
- Echogenicity
- Cystic vs. Complex
- Border: Regular vs. Irregular
- Calcification (micro vs. macro)
- Vascularity
- Shape
- Elastography
  - has not proven to be reliable predictor of malignancy

Normal thyroid



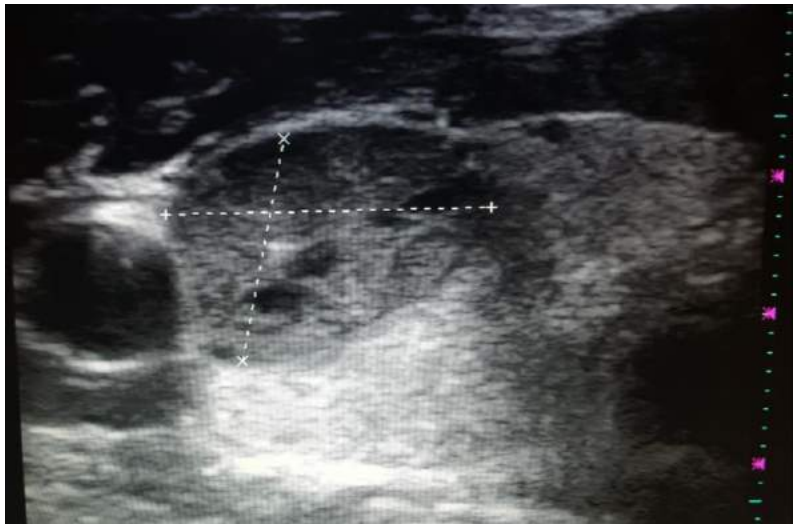
Cystic nodules

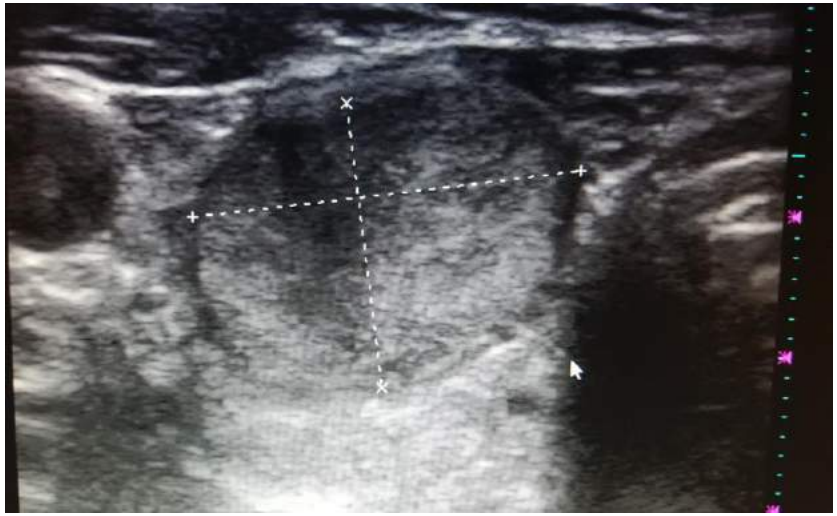




- Smooth borders
- Fluid is anechoic
- ? Solid component versus sludge/sediment
  - Check vascularity
- Simple cysts do not require biopsy

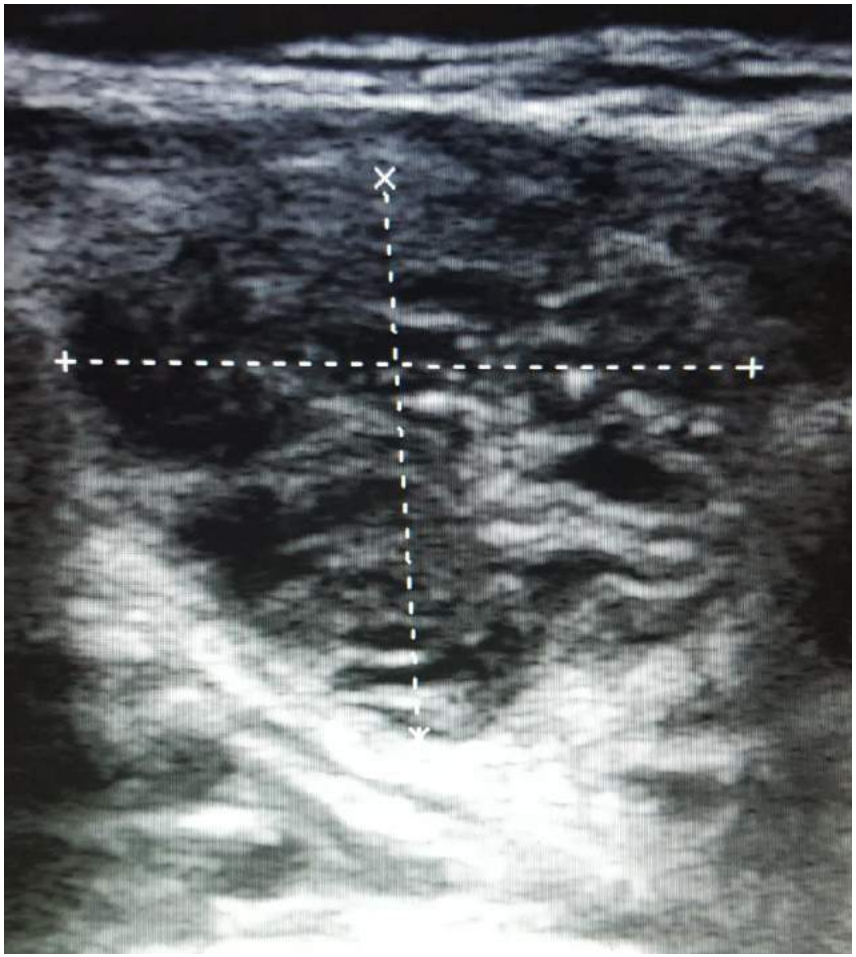
Intermediate and low suspicion nodules





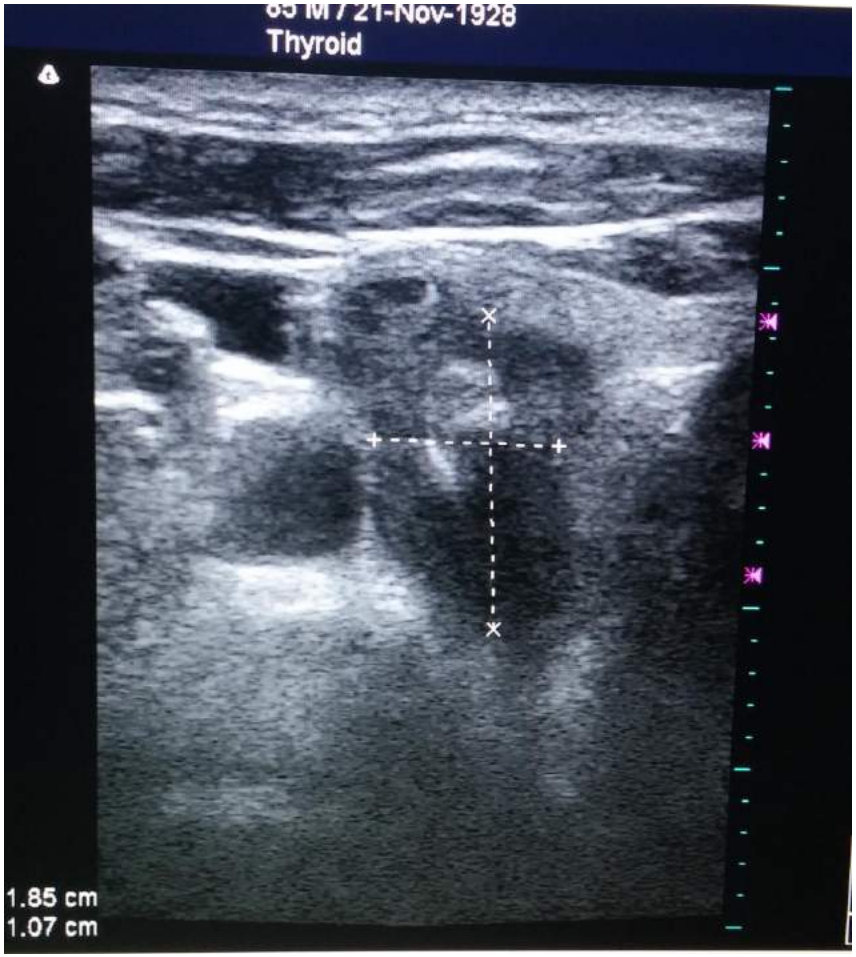
- Isoechoic or hyperechoic
- Smooth borders
- No calcifications
- Halo
- Cystic areas

Spongiform nodule



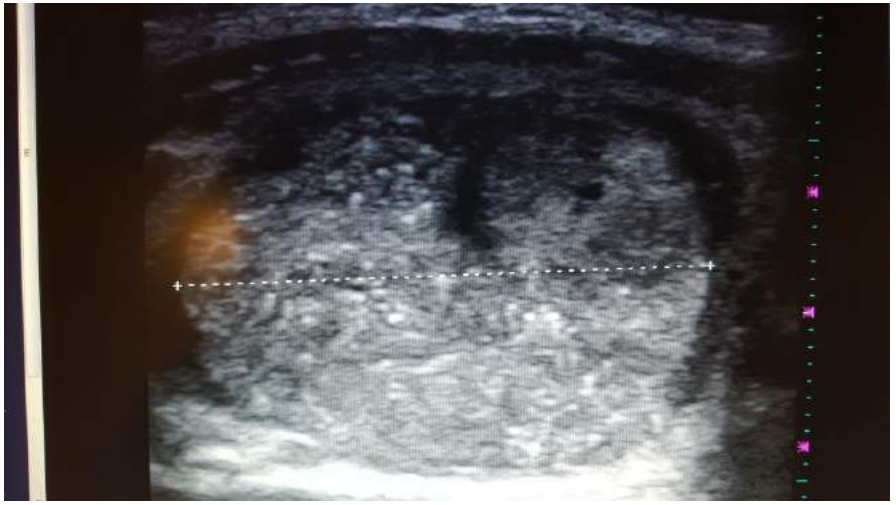
- Thought to be benign
- ATA guidelines suggest avoiding biopsy unless over 2 cm

Highly suspicious nodules



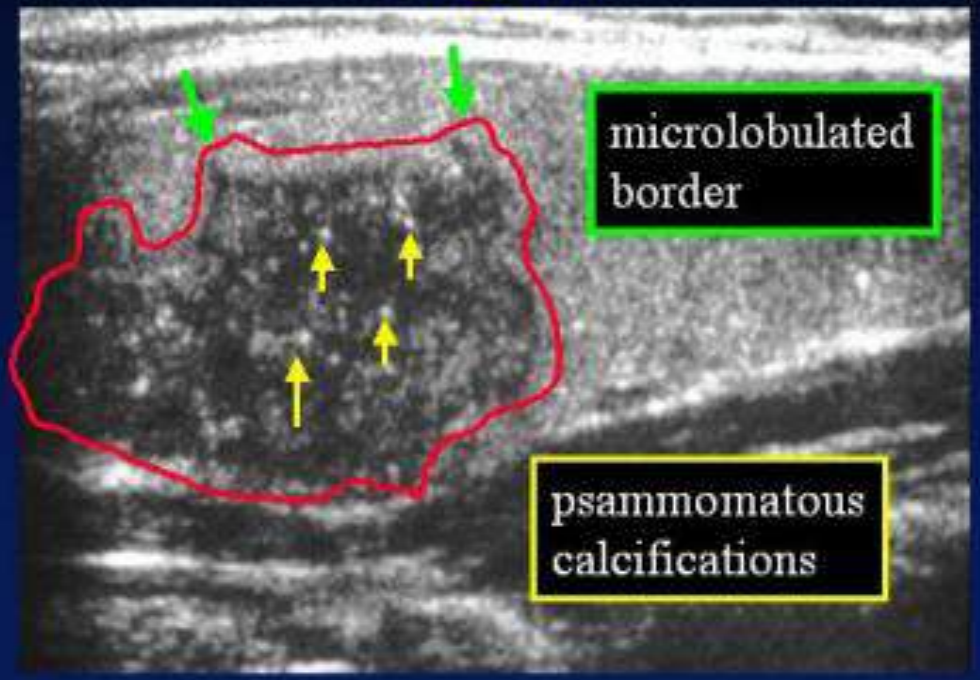
- Hypoechoic nodule
- Irregular border
- Shape: taller than wide
- Calcification

Classic microcalcifications

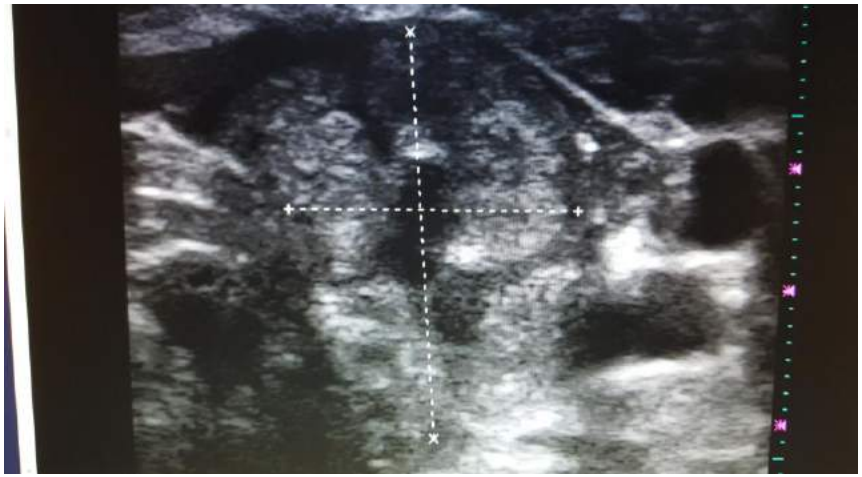


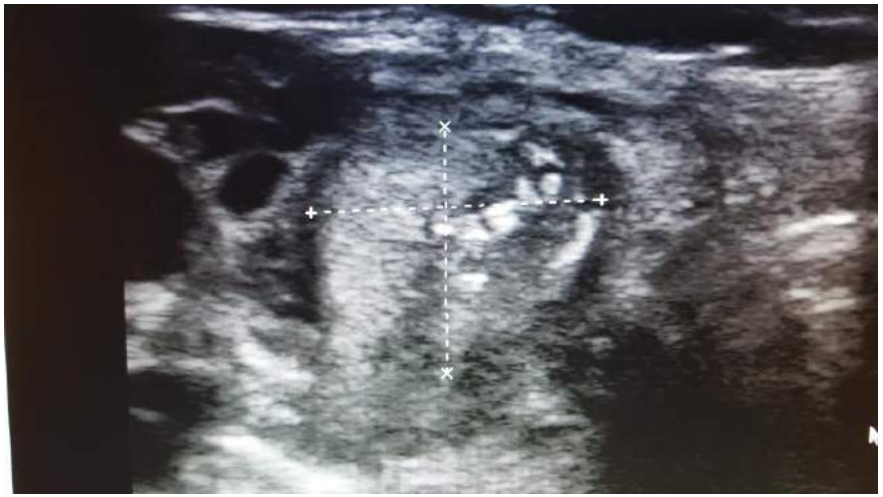
Infiltrating margins

Sagittal

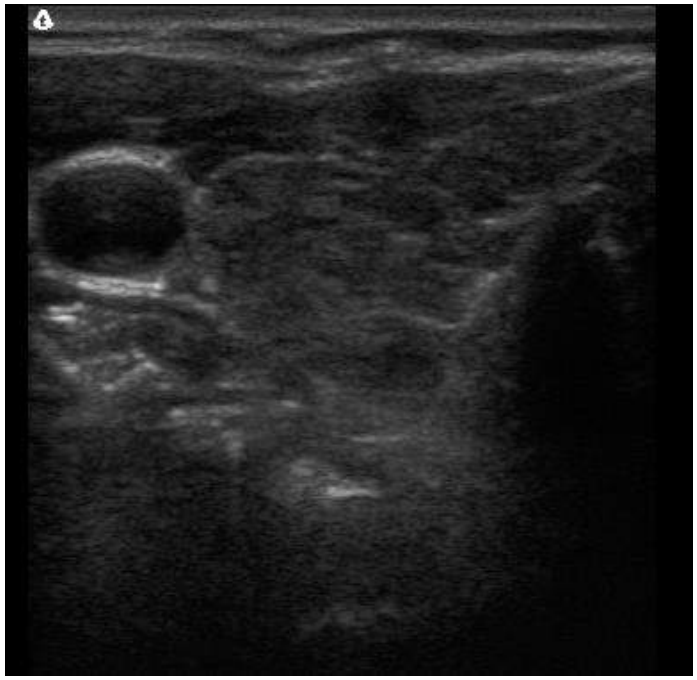


Malignant nodules





Hashimoto's glands in cross section



Appear very hypoechoic and heterogeneous. Can be confused for thyroid nodules

To Biopsy or Not to Biopsy

Can Ultrasound Improve the Odds?

Significance of Ultrasound Features for Distinguishing Benign from Malignant Nodules

	Malignant	Benign	P value	RR	Sens (%)	Spec (%)	PPV* (%)
Solid hypoechoic	87%	56%	.009	ns	87	43	
Irregular	77%	14%	.0001	16.8	77	85	39
Hyper vascularity	74%	19%	.0001	14.3	74	81	26
Micro calcification	29%	4%	.0001	4.9	29	95	36

Papini et al. Risk of Malignancy in Nonpalpable Thyroid Nodules: Predictive Value of Ultrasound and Color-Doppler Features. JCEM 87:1941-1946, 2002.

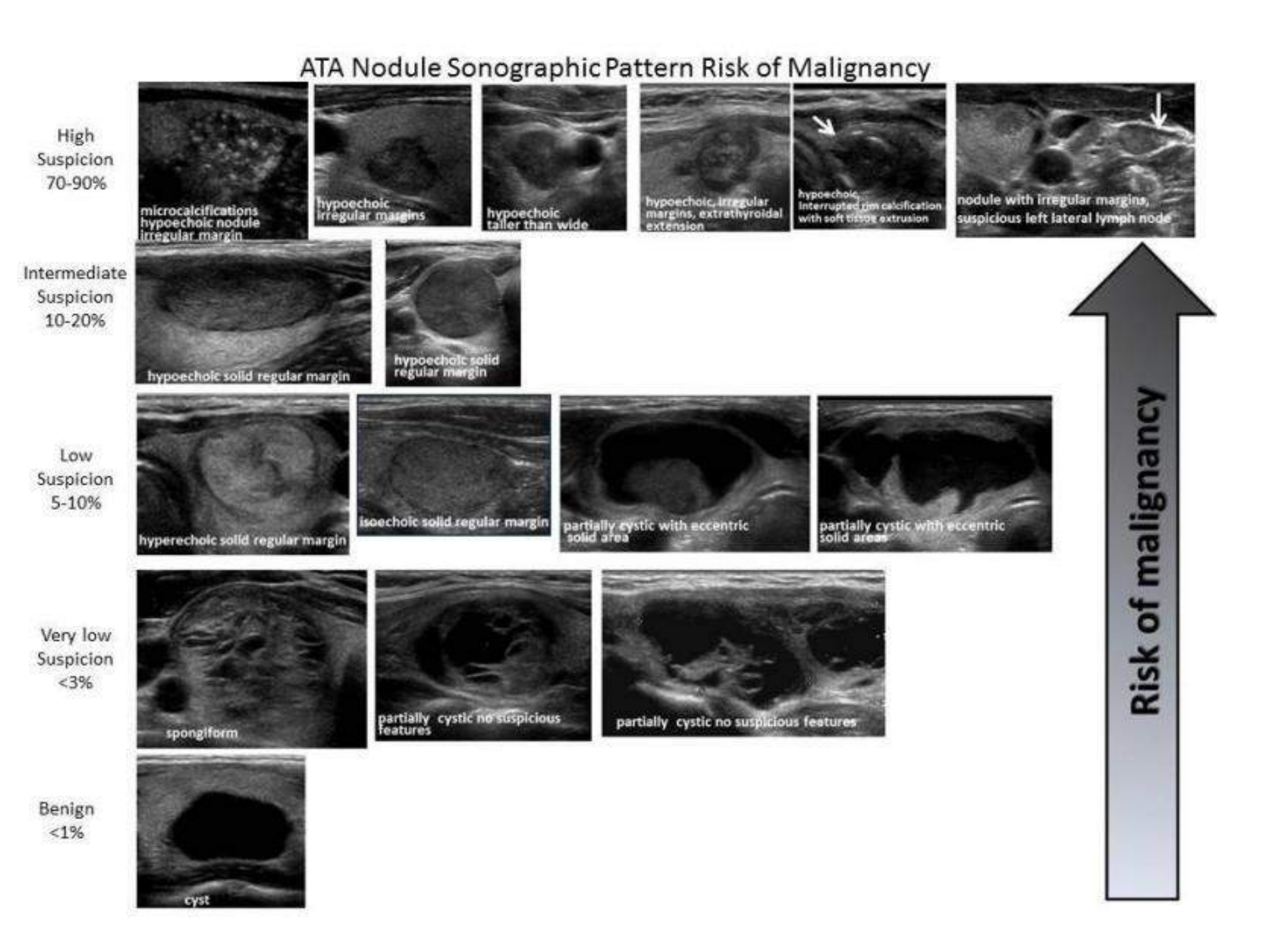
* Combined with hypoechogenicity

2015 American Thyroid Association Predictors of malignancy:

- Microcalcifications, irregular borders, taller than wide.
- Hypervascularity NOT correlated with malignancy
- Follicular thyroid cancer and follicular variant of papillary thyroid cancer (NIFTP) were less likely to exhibit suspicious ultrasound features
  - More likely to be hyper or isoechoic, round, non-calcified, with smooth margins

Sonographic pattern	US features	Risk of malignancy	Consider bx FNA size cutoff
High suspicion	Solid, hypoechoic with 1 or more: irregular margins, microcalc, taller than wide, rim calc with small extrusive soft tissue component, extrathyroidal extension	> 70—90%	> 1 cm
Intermediate	Hypoechoic, smooth margins w/o microcalc, extrathyroidal ext or taller than wide	10—20%	> 1 cm
Low	Iso or hyperechoic w/o susp features	5—10%	> 1.5 cm
Very low	Spongiform w/o	< 3%	> 2 cm or observe
Benign	Purely cystic	< 1%	No biopsy

ATA Nodule Sonographic Pattern Risk of Malignancy



2015 American Thyroid Association guidelines for who to biopsy

- > 1 cm with intermediate or high suspicion on US
- > 1.5 cm with low suspicion US
- > 2 cm with very low suspicion US
- Do not biopsy purely cystic nodules

Approach to multinodular goiter

- Assess each nodule individually, using same criteria as for solitary nodules
- Use sonographic pattern to assign preference
- If all nodules have low suspicion pattern and there is no normal thyroid parenchyma, it is reasonable to aspirate only largest nodules > 2 cm or continue surveillance with US

Subcentimeter nodules

- Reasonable to observe even if highly suspicious
- Study of 1235 Japanese patients observed with biopsy proven PTC
  - No distant mets or deaths
  - Tumor growth in 5.9% of pts < 40, 2.2% if > 60
  - Lymph node mets in 5.3% vs 0.4%

Ito Y et al. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid 24:27-34 2014

Fine Needle Aspiration: Logistics

- Office based
- Reliant on Expert Cytopathology
- Reliant on Sample Adequacy
- Potential Results: Benign, Malignant, Indeterminate/suspicious, Non-diagnostic

Cytology

- Recommend uniform reporting using Bethesda system
  1. Non-diagnostic
  2. Benign
  3. Atypia of undetermined significance (AUS) or Follicular lesion of undetermined signifance (FLUS)
  4. Follicular Neoplasm
  5. suspicious for PTC
  6. PTC

Cibas et al. A prospective assessment defining the limitations of thyroid nodule pathologic evaluation. 2013 Ann Intern Med 159:325-332

Bethesda classification

Diagnostic category	Risk of malignancy	Actual risk*
Non-diagnostic	1—4	20 (9—32)
Benign	1—3	2.5 (1—10)
AUS/FLUS	5—15	14 (6—48)
Follicular neoplasm	15—30	25 (14—34)
Suspicious	60--75	70 (53—97)
Malignant	97—99	99 (94—100)

Based on meta-analysis of 8 studies of surgical resection

Bongiovanni M et al. The Bethesda System for Reporting Thyroid Cytopath: a meta-analysis. 2012 Acta Cytol 56:333-339
Cibas ES, Ali SZ 2009 The Bethesda System for reporting thyroid cytopath. Am J Clin Pathol 132:658-665

What to with non-diagnostics

- Repeat FNA with US guidance
  - Will yield result 60—80% of the time except for cystic
  - If repeat is non-diagnostic, can observe or remove depending on US features
- Frequency of malignancy in all non-diagnostic FNA biopsies estimated at 2—4%

Follow-up of benign nodules

- If a second FNA is benign, NO further US surveillance is indicated—Strong recommendation
  - Up to 50% of benign nodules will continue to slowly increase in size
  - Sonographic pattern much more important as predictor of malignancy than growth

Kwak et al. Value of US correlation of a thyroid nodule with initially benign cytologic results. 2010 Radiology 254:292-300

Additional Recommendations for benign nodules from 2015 guidelines

- 25: no role for TSH suppression
- 26: obtain adequate iodine intake
- 27: consider surgery for growing, compressive nodules, especially if > 4 cm. Follow growing nodules

Nodules with indeterminate cytology

Atypia of undetermined significance

- AUS/FLUS
  - Cells with architectural and/or nuclear atypia but insufficient to be placed in higher risk category
  - Expected to make up 7% of FNA results, but in actuality seen in 1—27%
  - Mean risk of malignancy 16%
- Management strategies
  - Get expert cytopath review
  - Repeat FNA (helpful in most) and/or molecular testing
    - If inconclusive, either surveillance or excise, depending on risk factors, US appearance, and pt. preference

Ohori NP et al. Variability in the AUS/FLUS dgx in the Bethesda System. 2011 Acta Cytol 55:492

Follicular Neoplasms

- Cytologic definition: cellular aspirate comprised of follicular cells arranged in an altered architectural pattern characterized by cell crowding and/or microfollicles, lacking nuclear features of PTC
- 15—30% risk of malignancy
- #16: Gold standard: excision, but after consideration of clinical and sonographic features, molecular testing may be used to supplement malignancy risk

Factors considered when planning lobectomy versus total thyroidectomy for indeterminate nodules

- Estimated pre-surgical likelihood of ca
  - Family history or radiation hx
  - ? Size
  - Sonographic pattern
  - Cytologic category
  - Molecular test findings

Additional factors considered when planning lobectomy versus total thyroidectomy for indeterminate nodules

- Patient preference
- Presence of contralateral nodules
- Pre-existing hypo or hyper thyroidism
- Medical co-morbidities
- Surgical risks increased for total tx versus lobectomy
- Occupation
- Need for thyroid hormone replacement

IN AFRICA

DOES THE PATIENT HAVE THE ABILITY TO ALWAYS TAKE THYROID HORMONE REPLACEMENT?

Surgery for indeterminate nodules

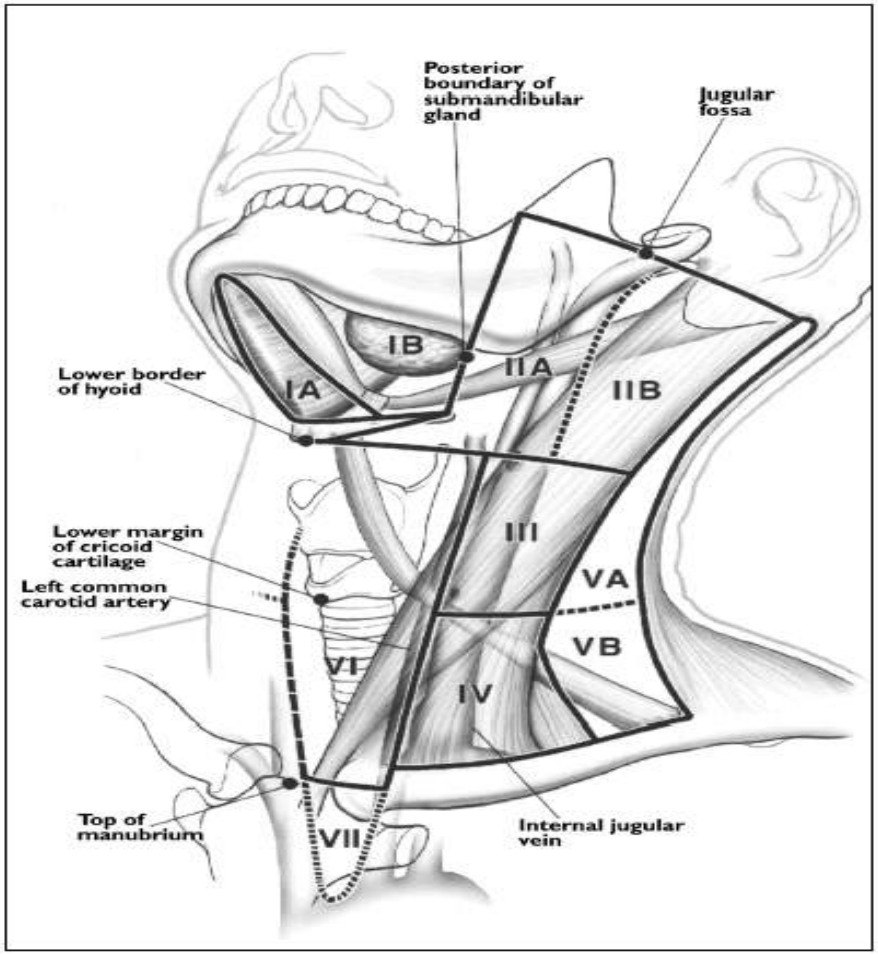
- #19: Lobectomy
  - No role for frozen section
  - May modify approach based on clinical or sonographic characteristics, patient preference and/or molecular testing
- #20: Total thyroidectomy is reasonable for suspicious cytology, presence of mutations specific for ca, sonographically suspicious, > 4 cm, or presence of risk factors for ca
  - Also for people with contralateral nodules and pts who prefer to avoid a possible second operation

US Applications in Patients with Established Thyroid Cancer

Cervical LN Assessment

- Anatomy--surgeon performed
- ~18%--25% of DTC will recur, usually in 1st 10 yrs
- Majority of recurrences in central or ipsilateral neck
- US twice as sensitive at detecting LN mets than nuclear medicine scanning

Lymph Node Compartments



Lymph node characteristics

Trait	Benign	Malignant
Shape	Oval	Round
Width/Length	< .5	> .5
Echogenicity (relative to strap muscle)	Central hypo (fatty hilus)	hyper
Vascularity	Hilar	Increased subcapsular

Lymph node metastases

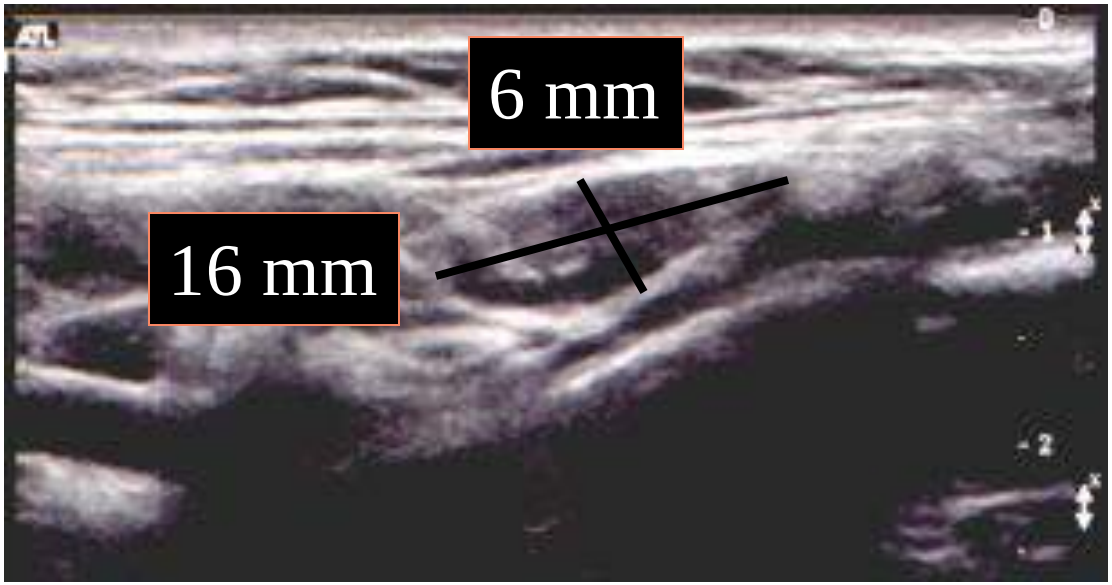
- Highly prevalent in PTC
  - Likely present in > 50% of cases
- Logical progression
  - Begin in Ipsilateral central compartment
  - Spread to lateral compartment and contralateral neck

Prognostic significance of lymph node metastases

- Minimal impact on long term survival
- Remember that in the new TNM guidelines if you are under 55, maximum tumor stage is II
  - Stage I:
    - covers everything from microcarcinoma to a patient presenting with bilateral lateral compartment metastases
  - Stage II: only if distant mets are present

Normal lymph node

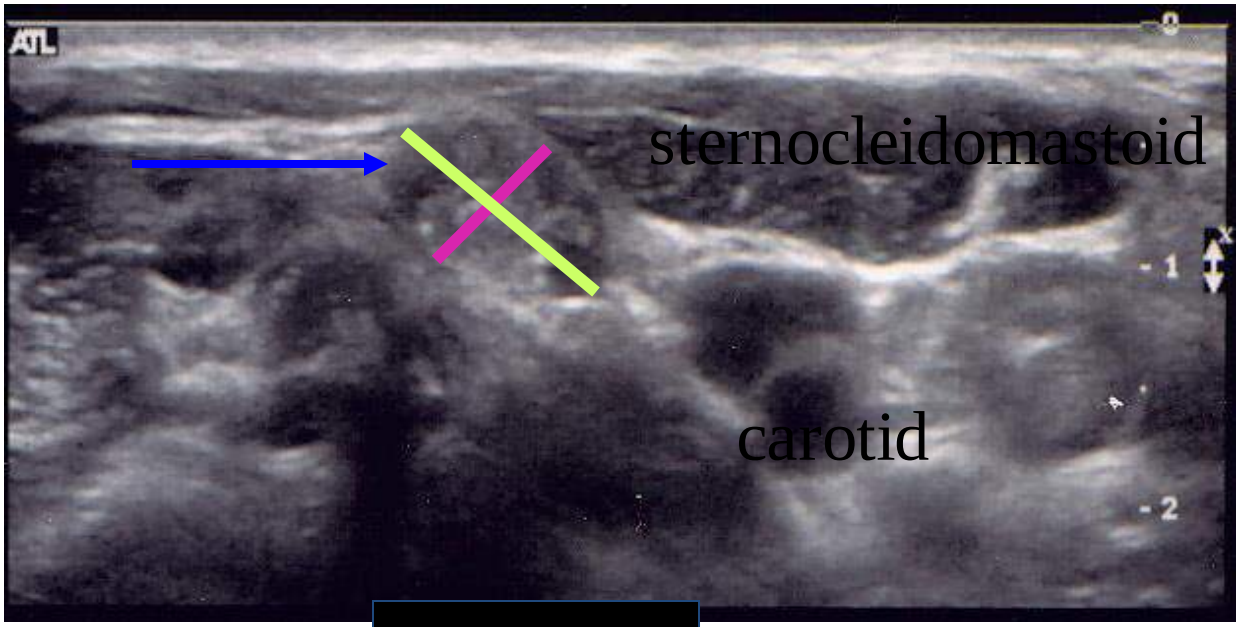
Sagittal



short:long 0.375

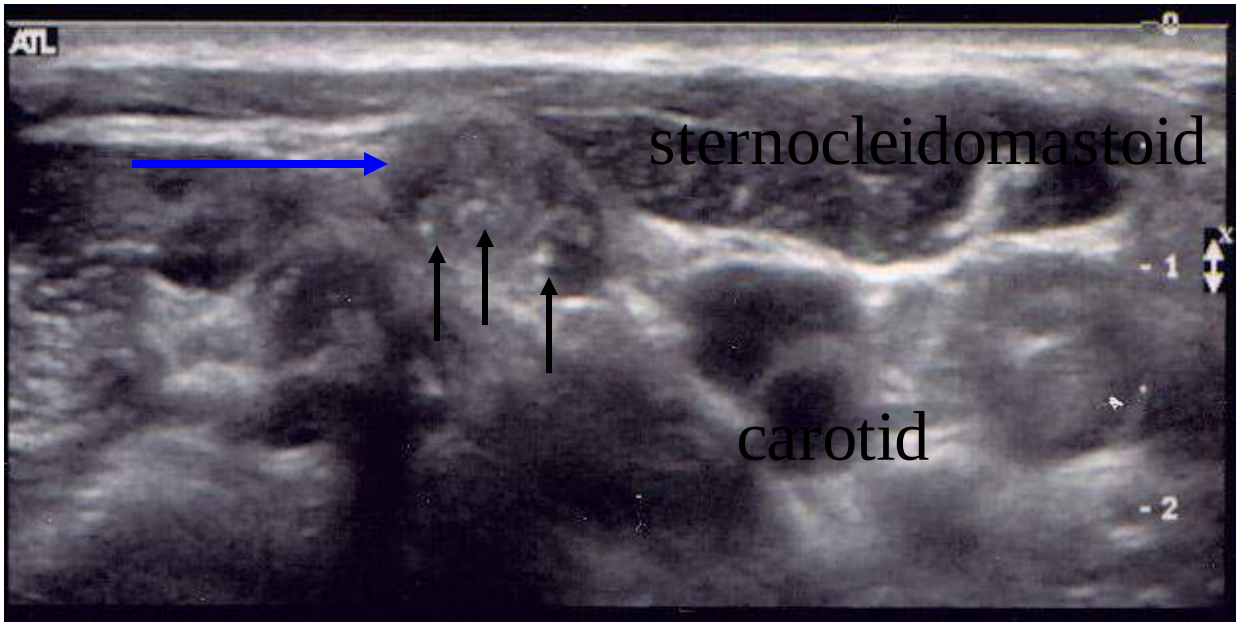
Malignant 9 mm right lateral cervical LN

hyperechoic, rounded shape,

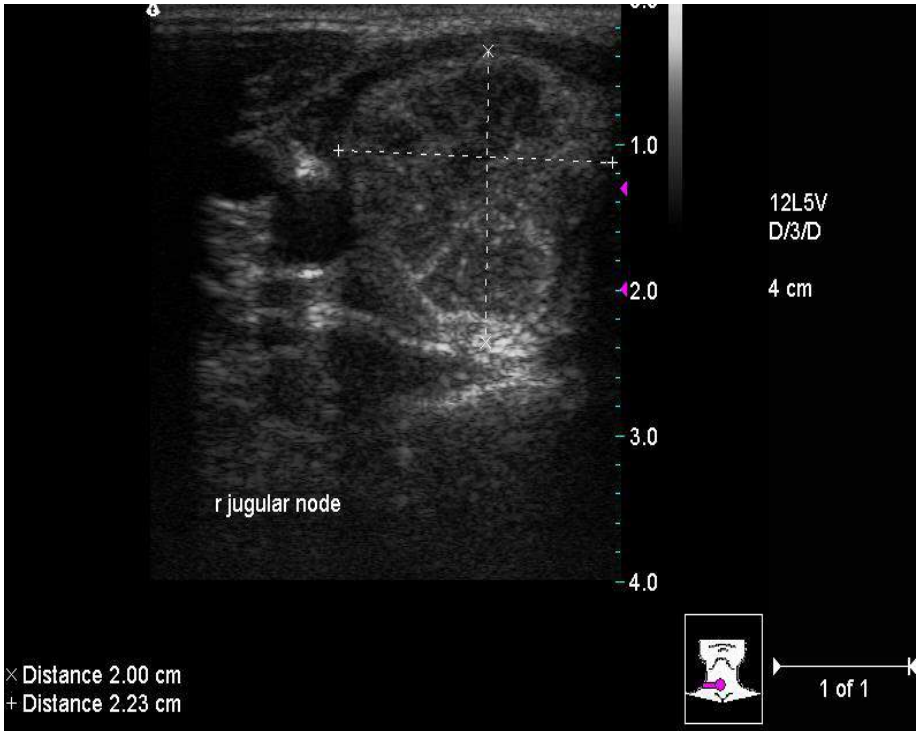


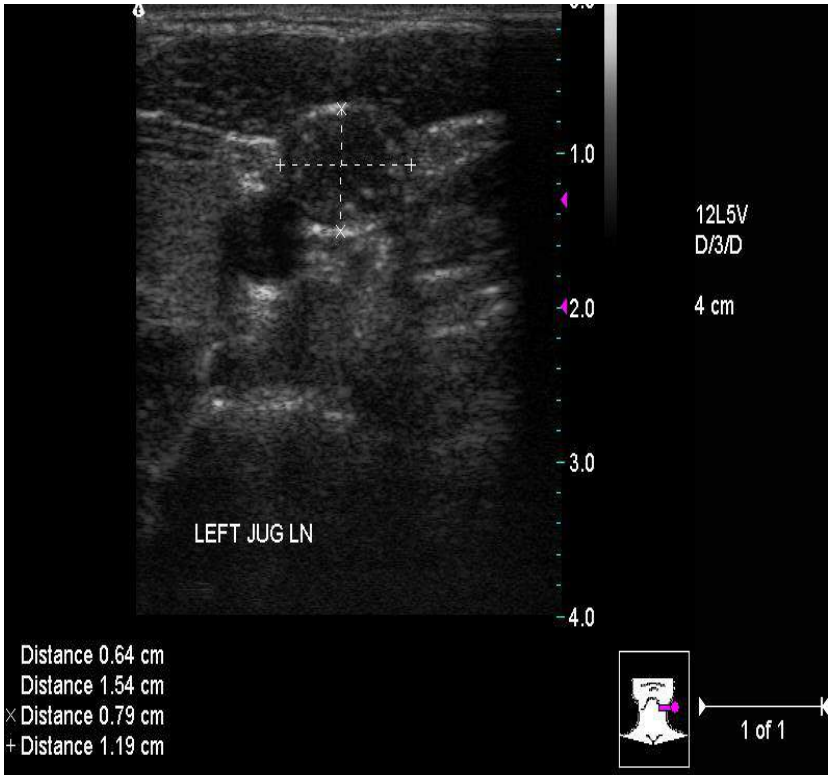
Malignant 9 mm right lateral cervical LN

micro Ca^{2+}



Examples of lymph node mets





Management of patients with thyroid cancer

- Ability to detect non-palpable local-regional metastases and change surgical management
- Retrospective review of 212 patients

Group	# of pts	# with dz on US, not on PE	Percent
Primary operation	107	21	20%
Reoperation for persistent disease	28	9	32%
Reoperation for recurrent thyroid ca	77	52	68%
Total	212	82	**39%**

Kouvaraki et al. Role of preop ultrasonography in the surgical management of patients with thyroid cancer. Surgery 2003;134:946-55.

When to use US for LN detection in thyroid cancer patients

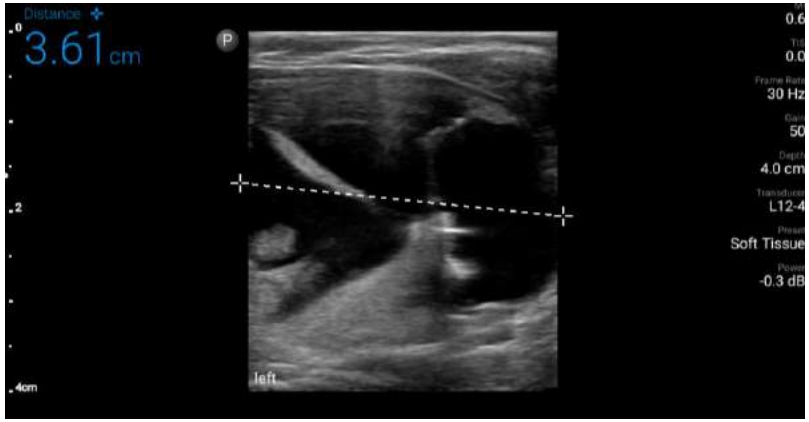
- Medullary CA—surveillance in calcitonin + pts
- Prior to thyroidectomy for pap CA (LN+ changes extent of surgery)
- As surveillance after I-131 therapy in DTC

When should ultrasound be used to follow thyroid cancer patients post-operatively?

American Thyroid Association recommends pre-op and annual post-op neck ultrasound for all thyroid cancer patients.

Rwanda Military Hospital Experience

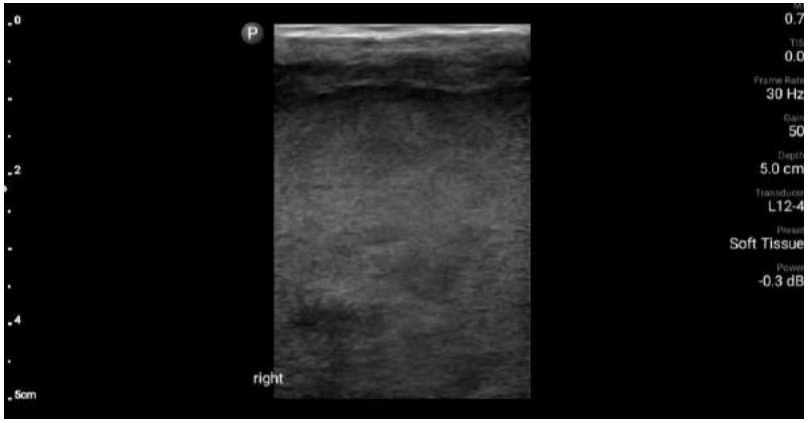
Cystic Nodules



Role for ultrasound illustrating laterality in patients with large symmetric goiters

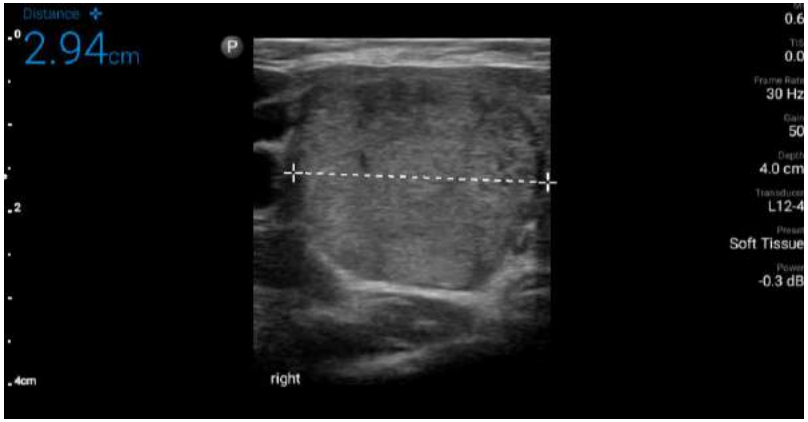
Left

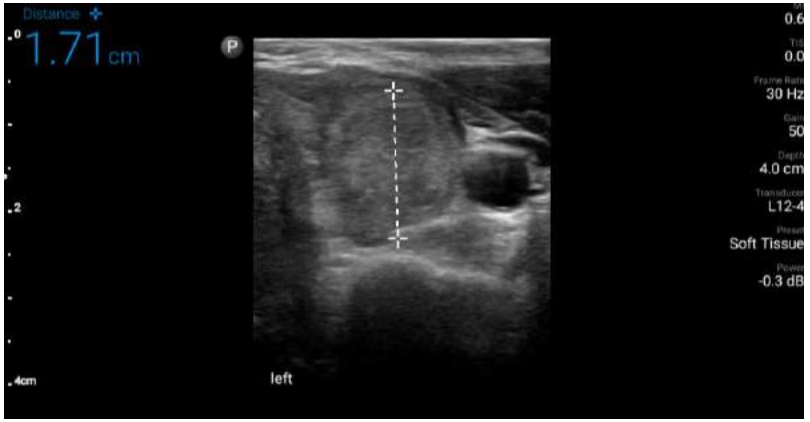
right



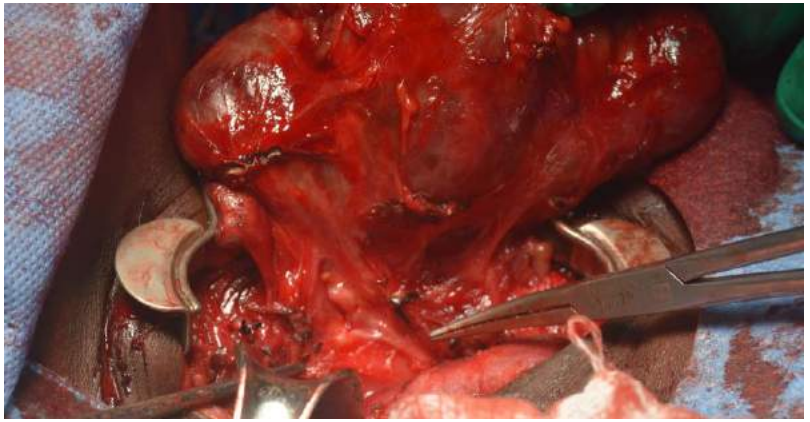
Ultrasound images of Vocal Cords

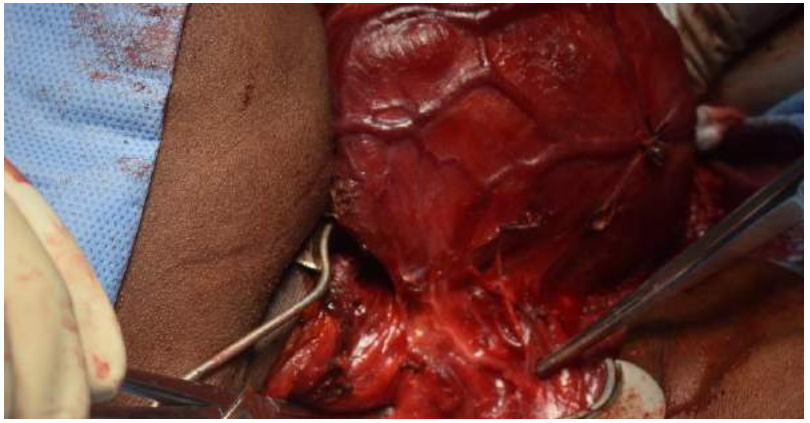
Multinodular goiter
nodules are solid and isoechoic



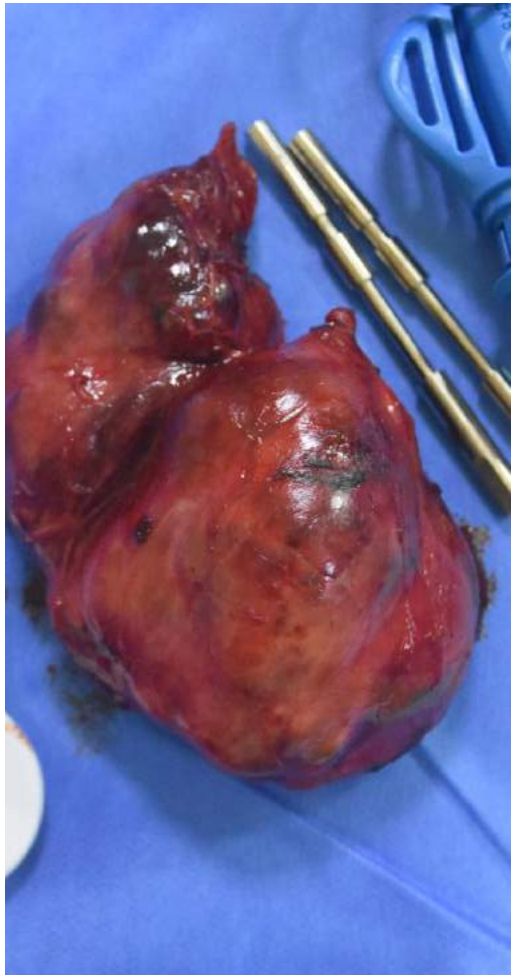


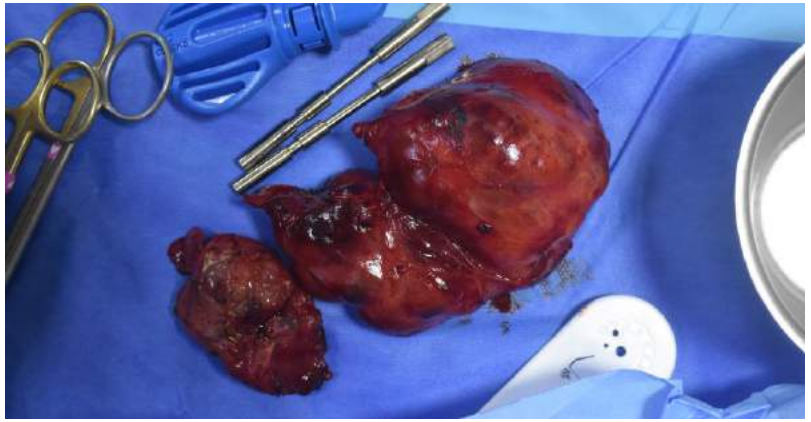
RLN Dissection in large goiter cases





Resected specimens





Post Neck Dissection US