Nodular Thyroid Disease and Thyroid Cancer: Management Scope

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Disclosures

- No relevant disclosures

Objectives:

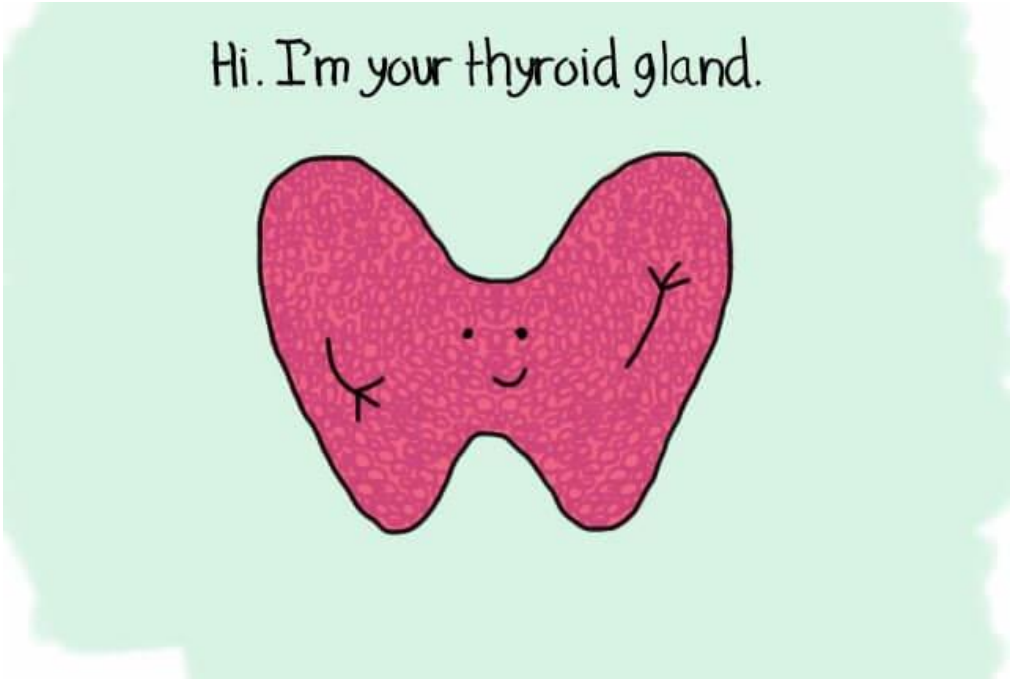
1. Describe the significance of thyroid nodule in clinical practice
2. Discuss risks of thyroid cancer in thyroid nodules
3. Review management options of thyroid nodules
4. Outline the management options of thyroid cancer

Background

- Thyroid nodules are very common in clinical practice
- Neck ultrasound can identify additional nodules up to 50% when able to feel one by physical exam
- High-resolution ultrasound (US) can detect thyroid nodules in up to 70% with higher frequencies in women and the elderly
- Only <15 % are malignant

Guth S et al. Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination. Eur J Clin Invest 39:699–706.
Tan GH, Gharib H et al. Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Ann Intern Med 126:226–231.

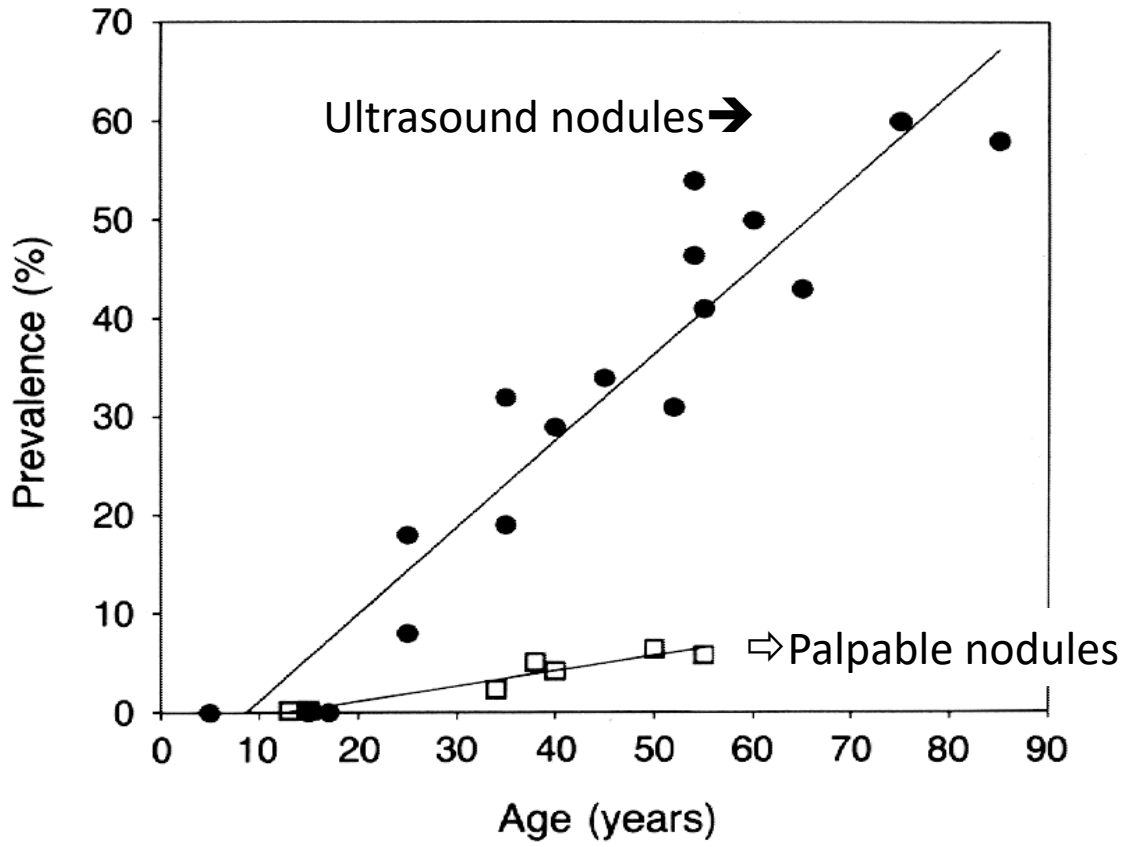
Thyroid nodules and pattern recognition



Why do we care:
1. is it cancer?
2. Does it cause symptoms?
3. Is it affecting thyroid function?

Thyroid nodules: A clinical problem

- **1% of all cancers, 0.5% of all cancer deaths**
- **Risk of nodule malignancy 10%**
- **Prevalence:**



Should the general population have thyroid ultrasounds?

Mazzaferri, NEJM, 1993

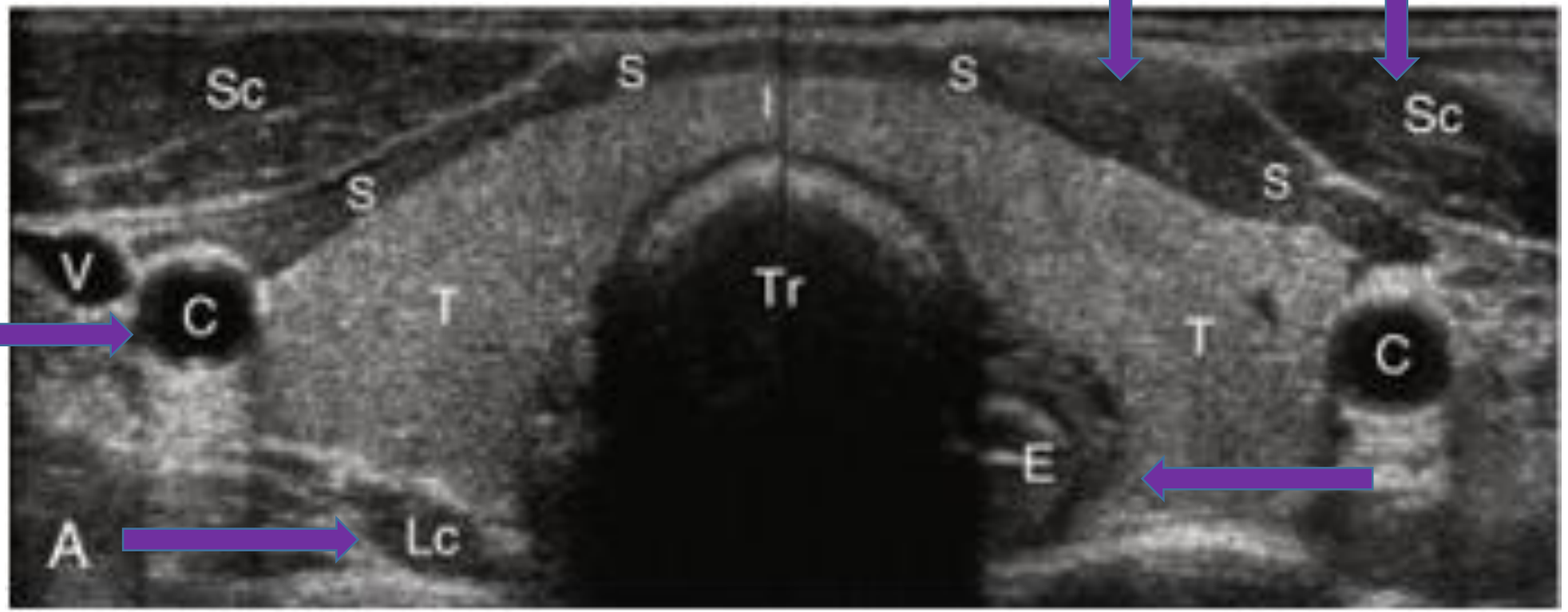
Evaluation of thyroid nodule:

- Complete history and physical examination
- Serum TSH
- If the serum TSH is subnormal, a radionuclide (preferably ^{123}I) thyroid scan should be performed
- If the serum TSH is normal or elevated, a radionuclide scan should not be performed as the initial imaging evaluation

Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26(1):1-133. doi:10.1089/thy.2015.0020

Normal Thyroid

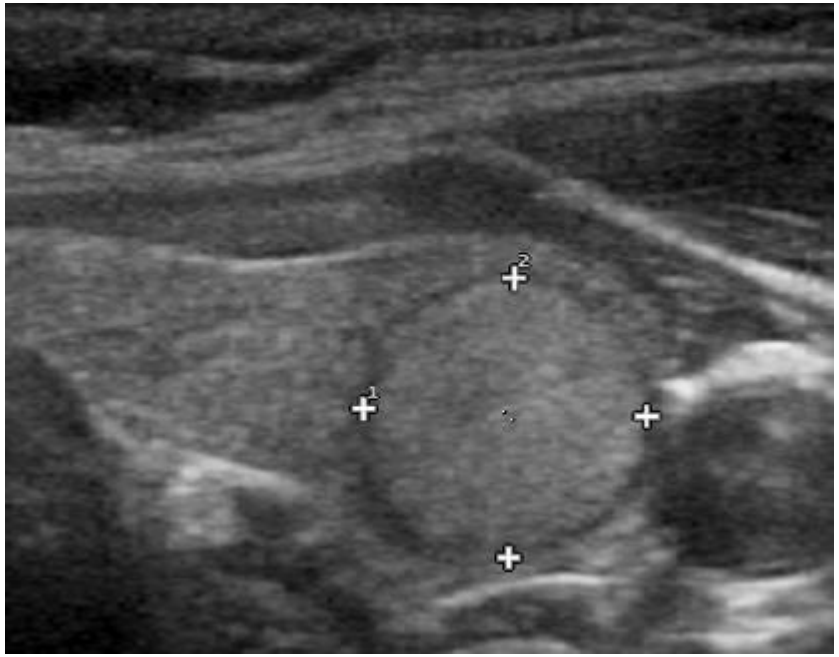
- Hyperechoic to adjacent muscles
- Homogeneous
- Scattered readily detectable internal vessels
- Diameter of lobes less than 2 cm in AP and transverse views
- Isthmus less than 4 mm



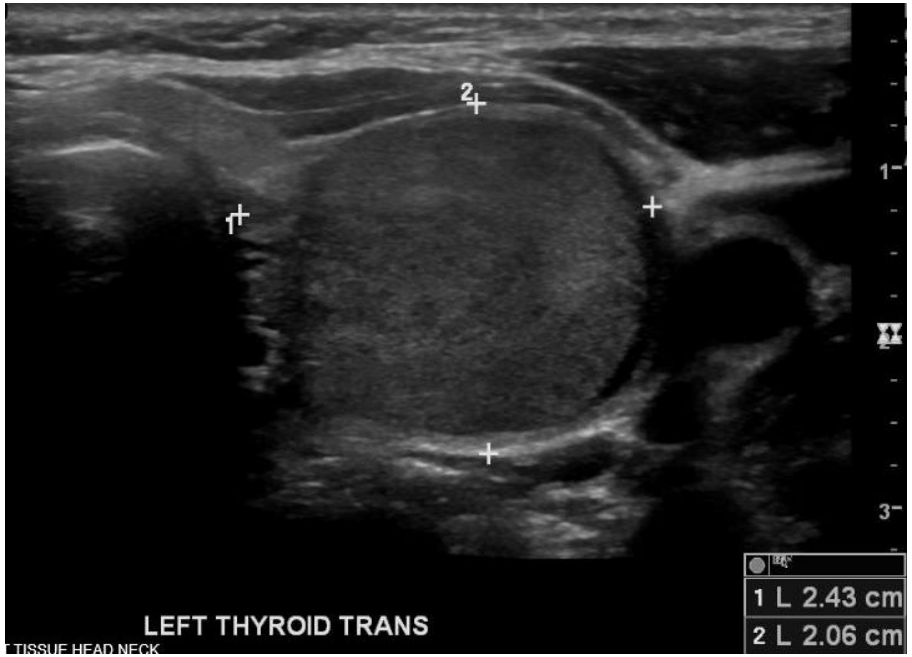
Barbara S. Hertzberg, and William D. Middleton: Ultrasound: The Requisites. Chapter 10, 229-262

Sonographic features suggesting benign nodules

Hyperechoic/ Isoechoic

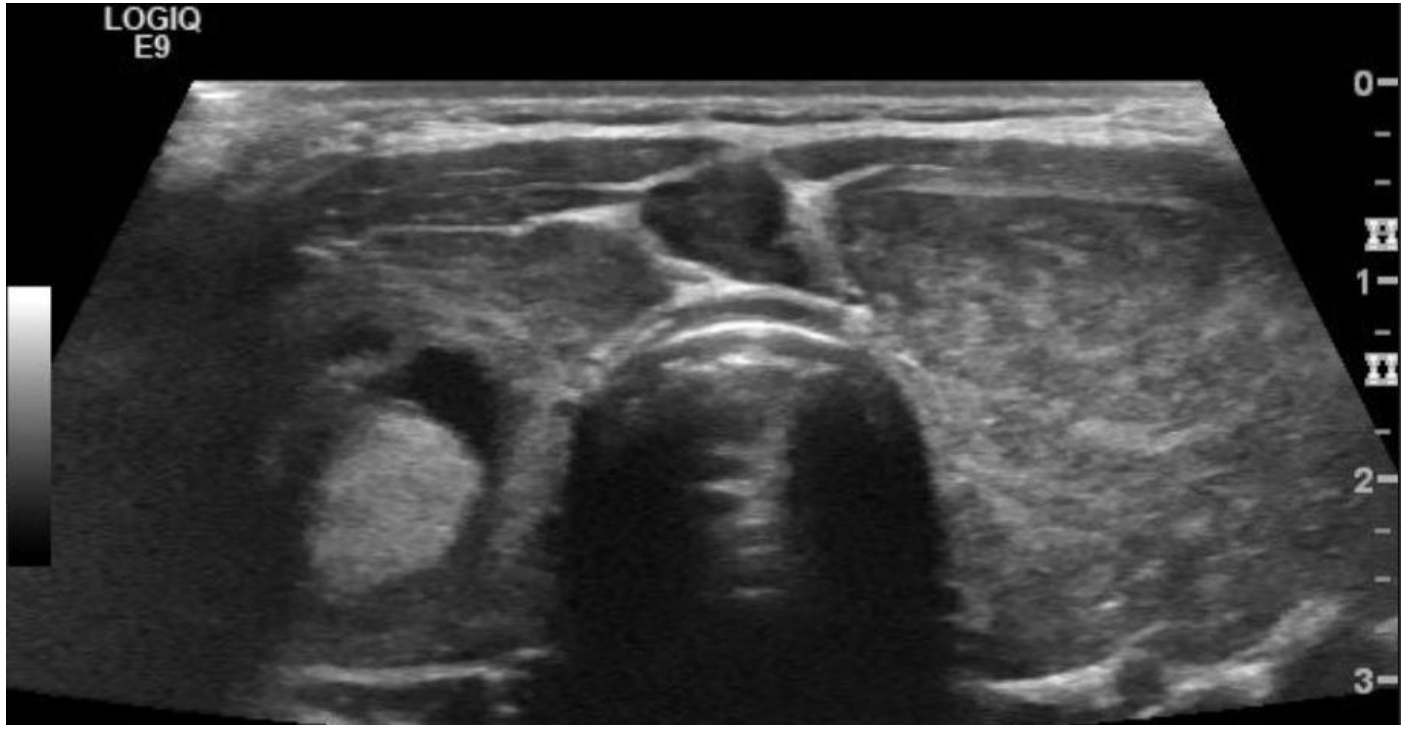


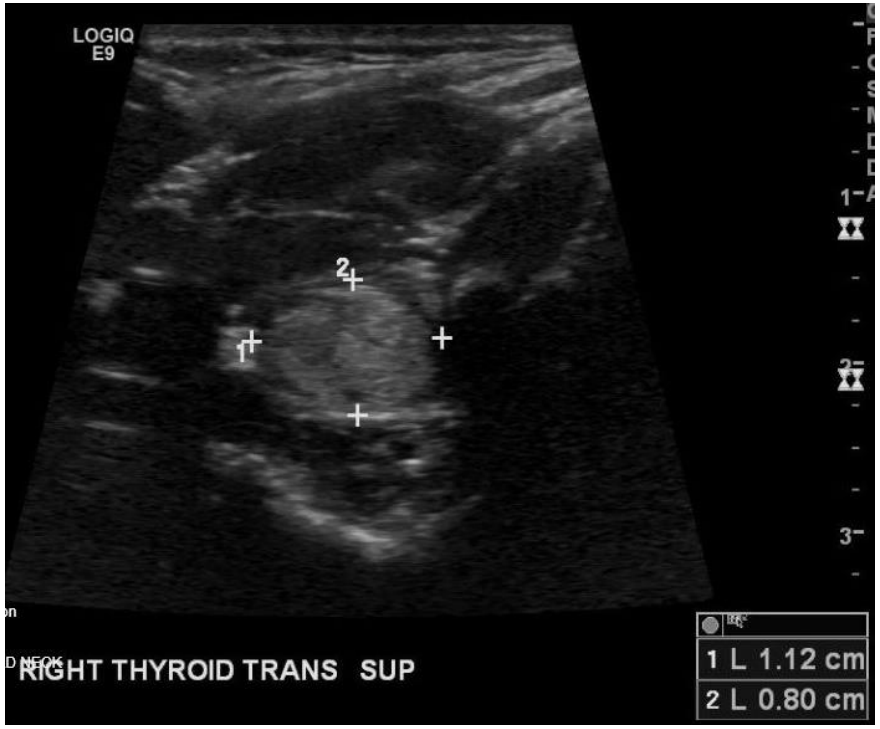
Halo sign and smooth margin



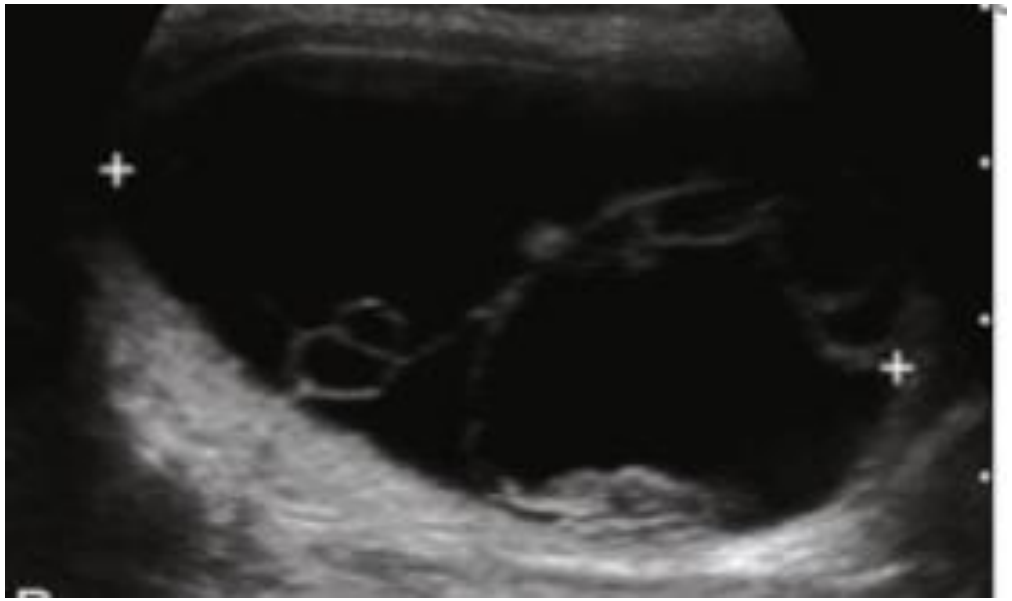
US Prediction of Thyroid Cancer Halo. Cerbone et al, Hormone Res 1999

Hashimoto’s thyroid disease with hyperechoic nodules



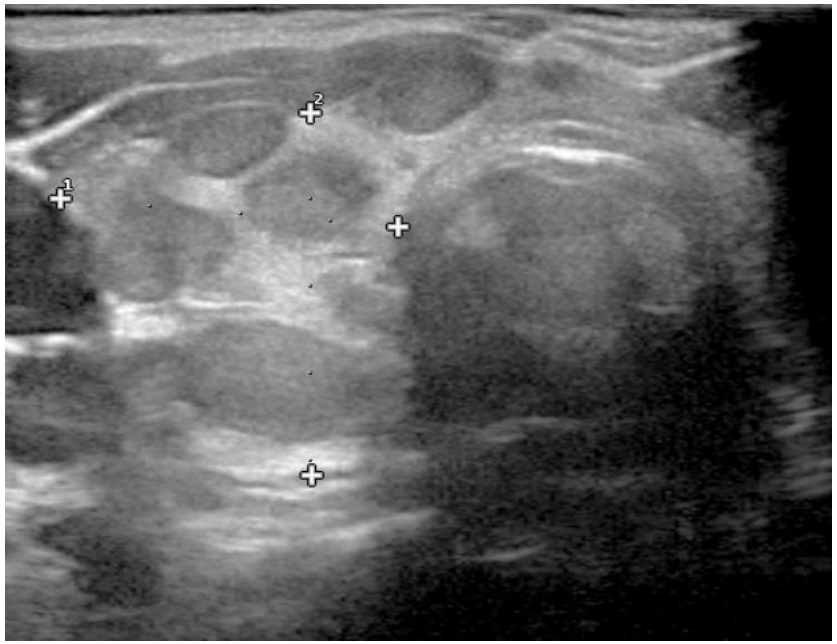


Thin-walled cyst with/without comet tail

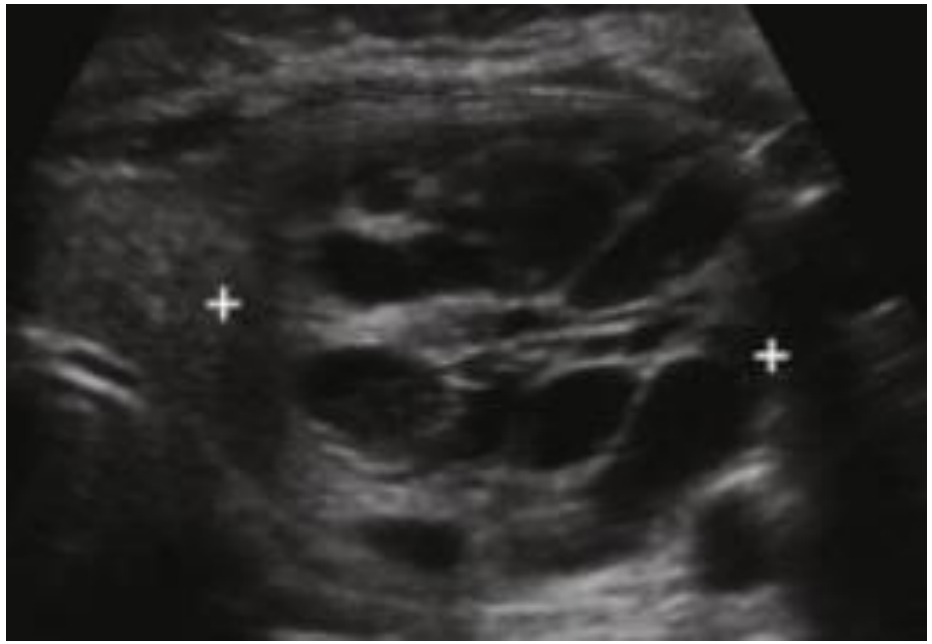


Sonographic features suggesting benign nodules

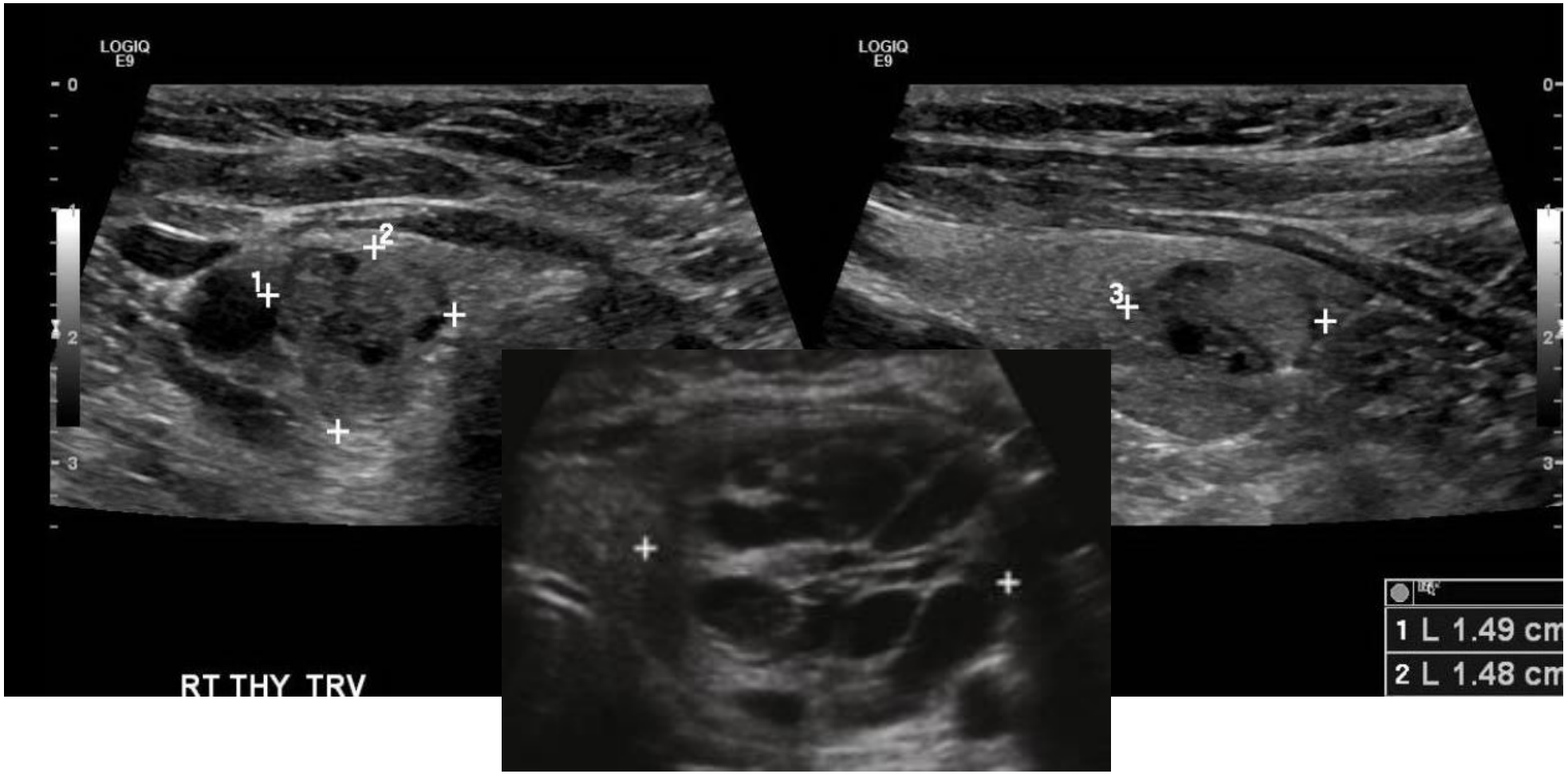
Multiplicity



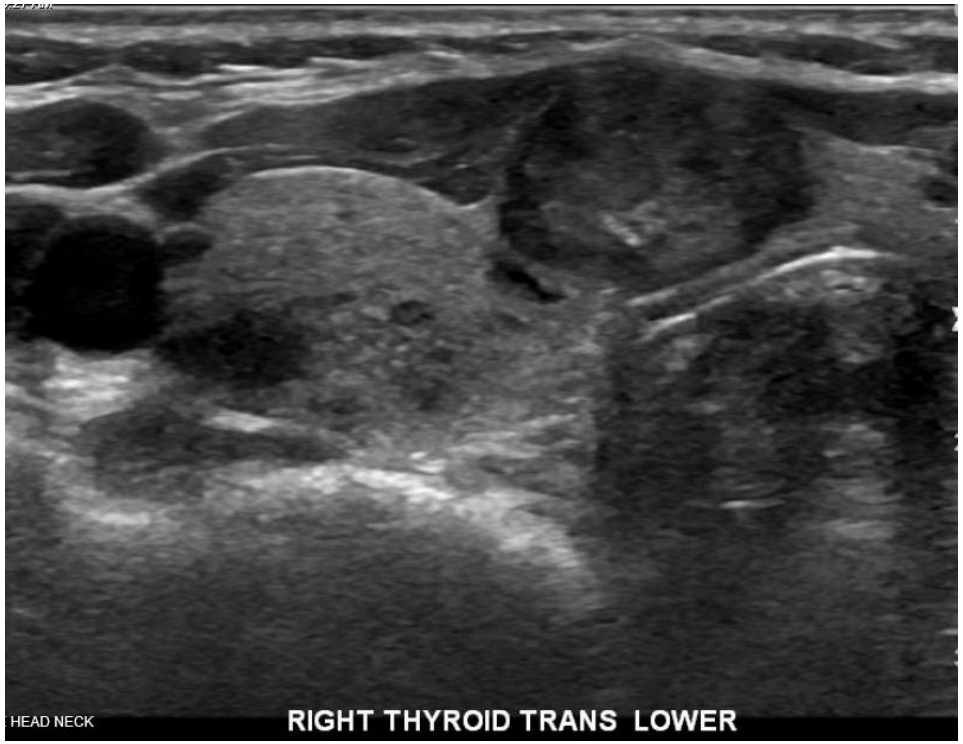
Spongiform Echotexture

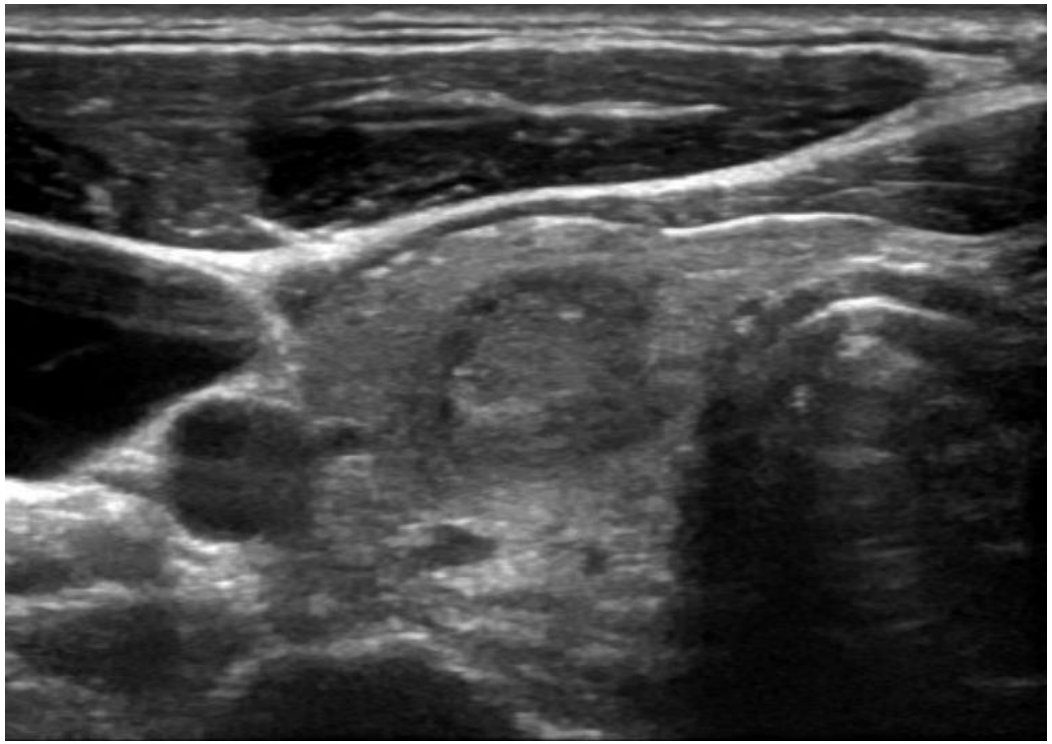


Benign thyroid nodules



Suspicious sonographic features for malignancy

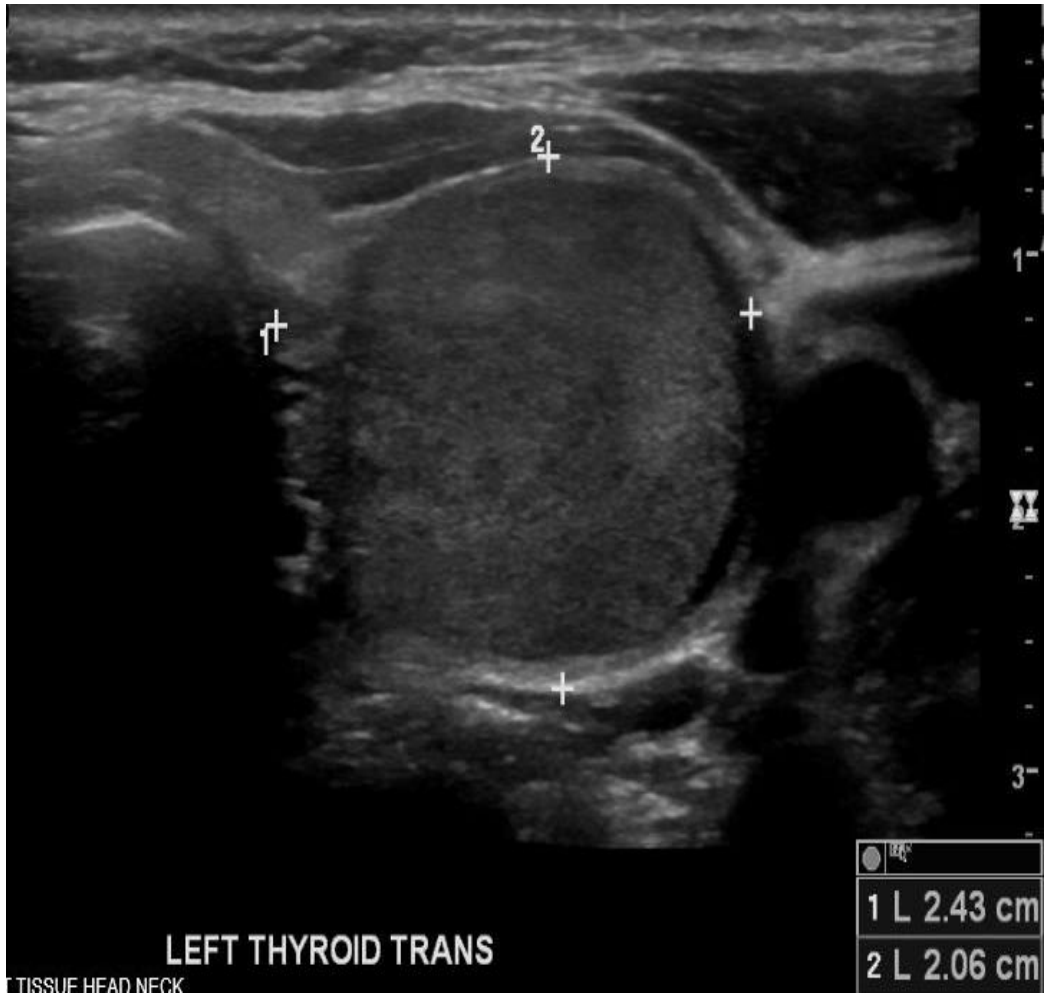




- (VERY)Hypoechoic
- Margins

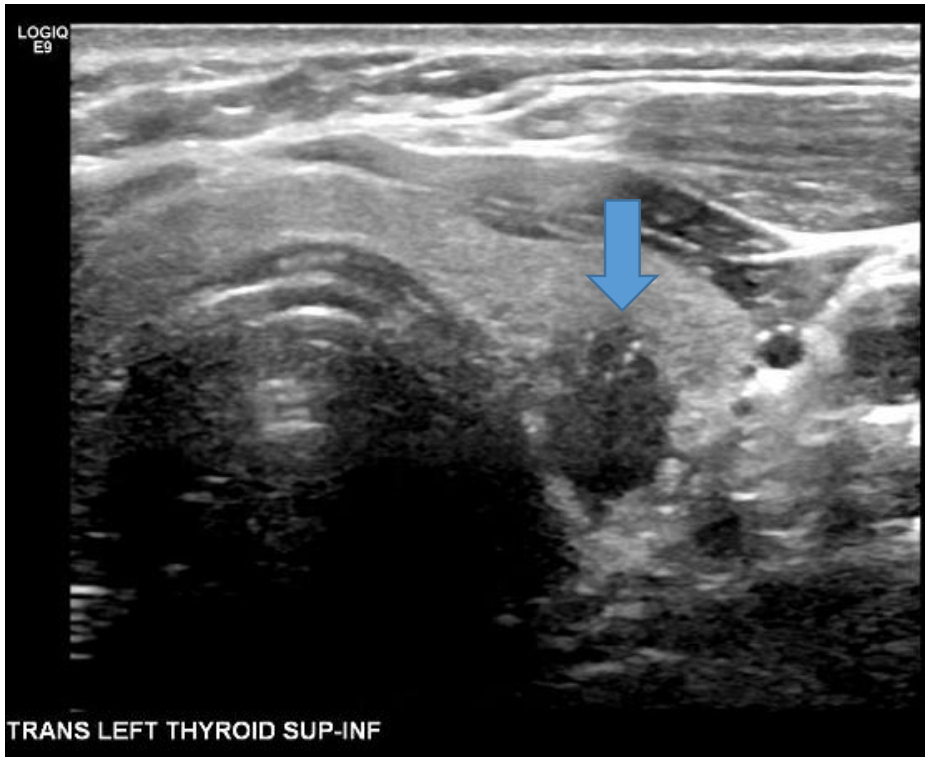
Most PTC are hypoechoic, but many hypoechoic nodules are benign!

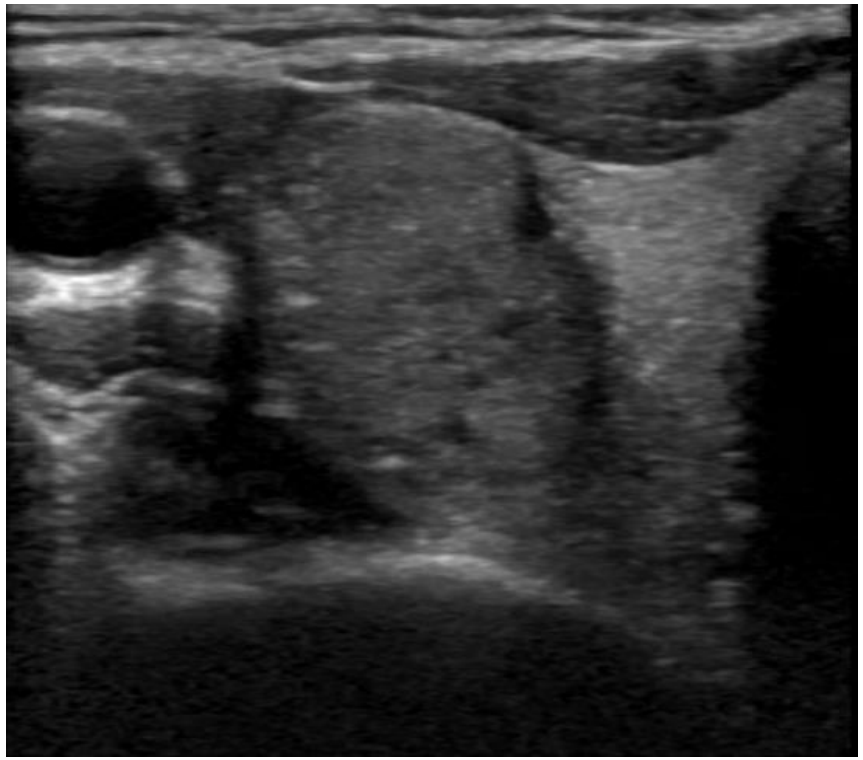
- ***Sensitivity 81%, Specificity 53%***
- **Associated features:**
  Solid, calcifications, nodular flow?



“Taller than wide”

- Suspicious of malignancy.
- Decreased compressibility.
- Seen in 12% of thyroid nodules.
- Sensitivity 40% -68%, specificity 82%- 93%, PPV 0.58-0.73, and NPV 0.77-0.88

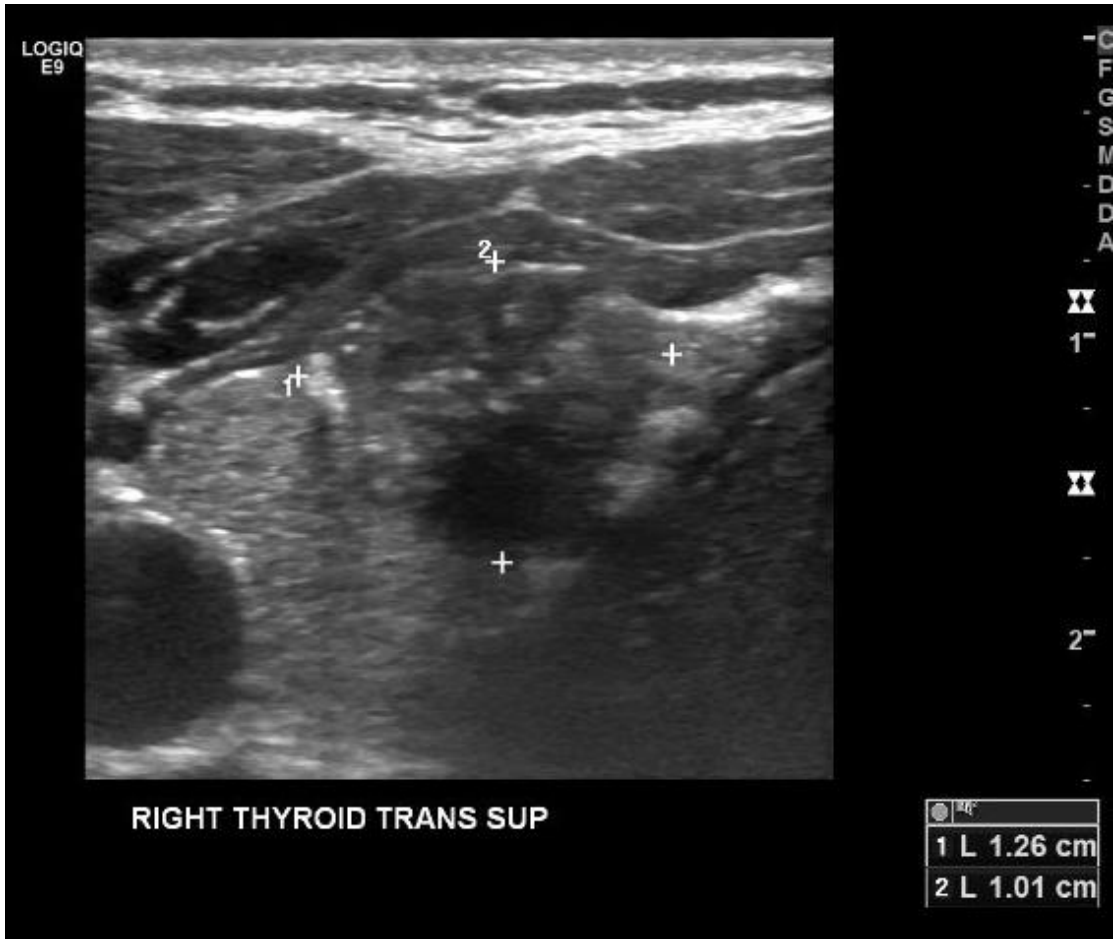




AP-to-transverse ratio > 1 is independent factor (OR, 2.698; *P* < .001) for PTC in small thyroid nodules (≤1 cm).

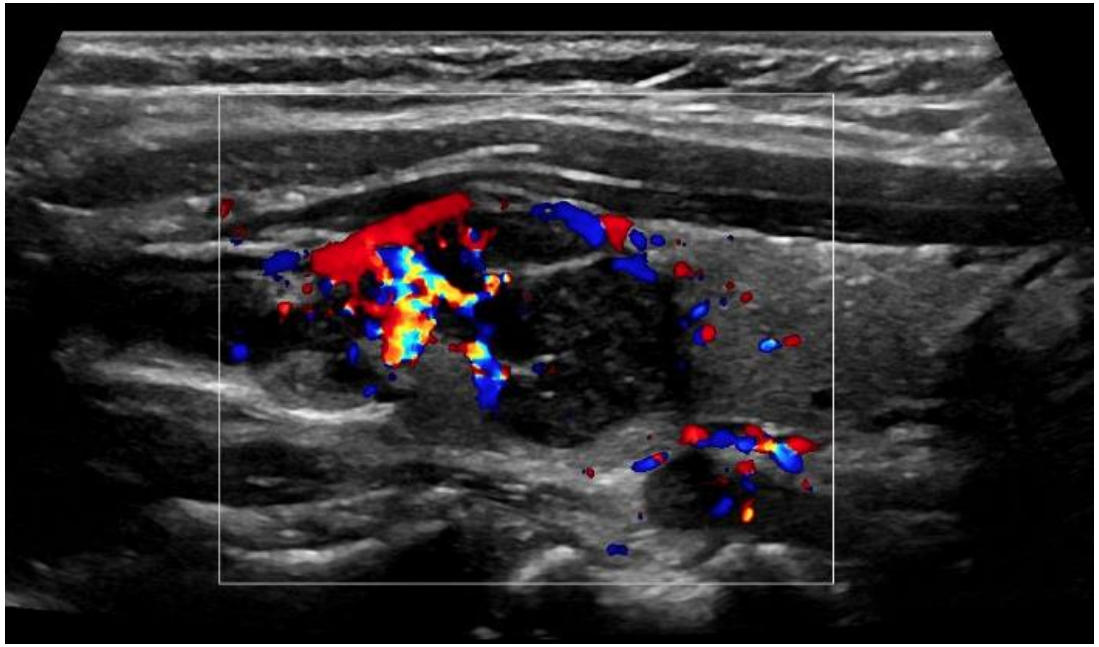
Kim GR et al. *Ann Surg Oncol* 2013; **20**:906–913.

Micro-calcifications (PEFs) and macrocalcifications



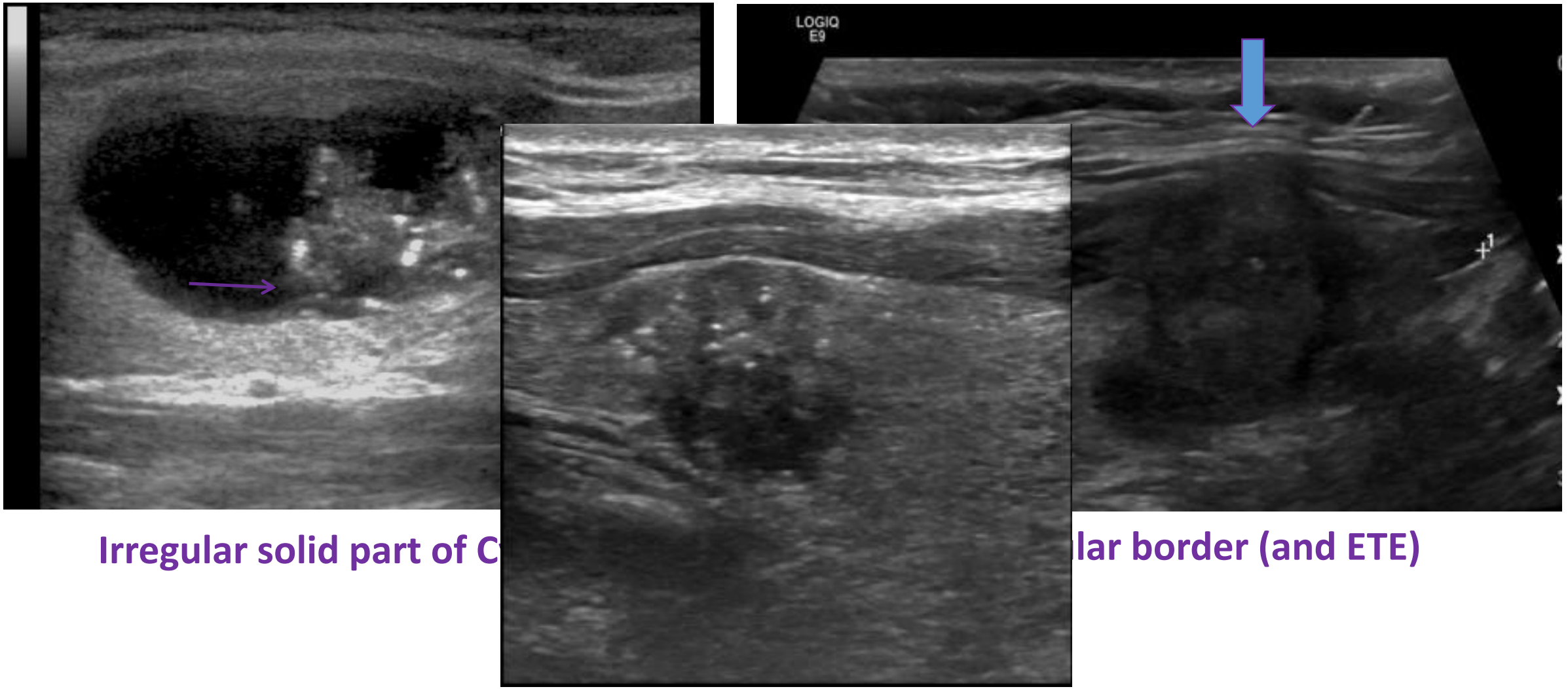
- Micro-calcifications: hyperechoic spots without acoustic shadowing (psammoma bodies) (<2mm) *Sensitivity 50%, Specificity 85%*
- Macro-calcifications : Solitary calcification (linear or round hyperechoic structure >2 mm usually with acoustic shadowing in the middle of a nodule
- Eggshell calcification/ Higher risk if interrupted rim calcifications
- More worrisome when associated with other suspicious features.

Irregular or “infiltrative” border



- *Sensitivity 55%*
- *Specificity 79%*
- High inter-observer variability

Irregular border PLUS



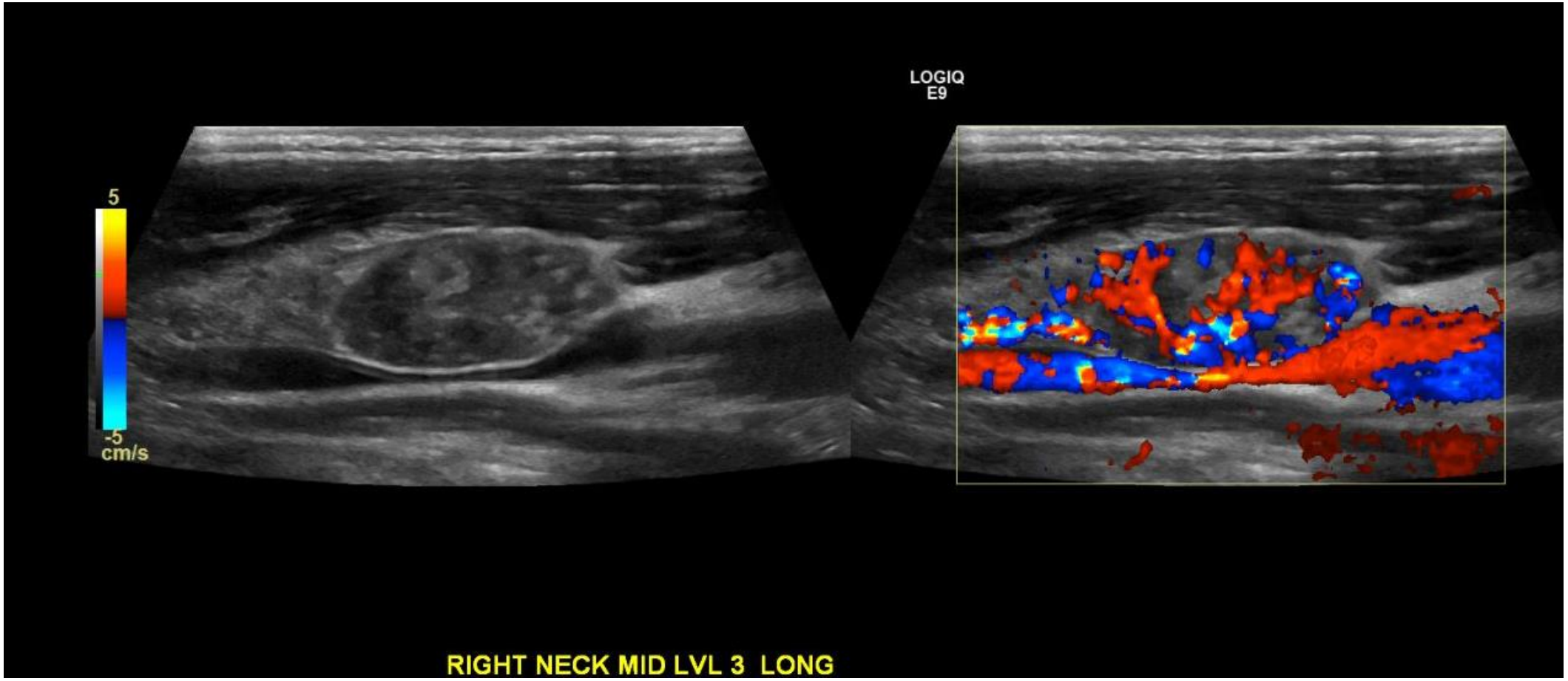
Irregular solid part of C

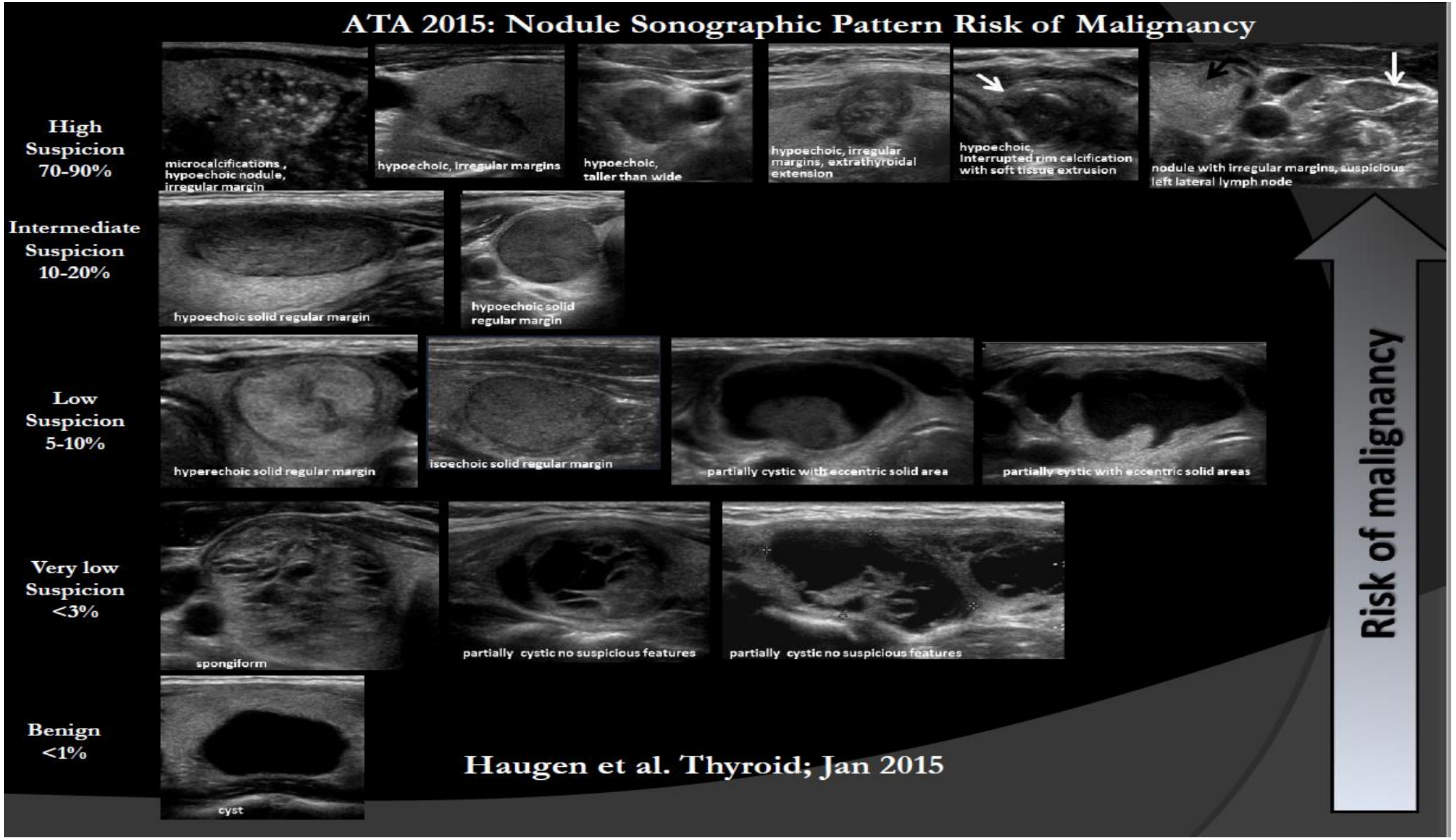
lar border (and ETE)

Korean J Radiol. 2012 Sep-Oct; 13(5): 530–535


LOGIQ
S8
LEFT THYROID LONG

Suspicious LN





Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26(1):1-133. doi:10.1089/thy.2015.0020

US suspicion	Risk %	Size- cm	Recs	
High	70-90	≥ 1 cm	Strong	
intermediate	10-20	≥1 cm	Strong	
Low	5-10	≥1.5 cm	Weak	
Very low	<3	≥2 cm	Weak	Surveillance
Benign	<1	No FNA		Cystic only

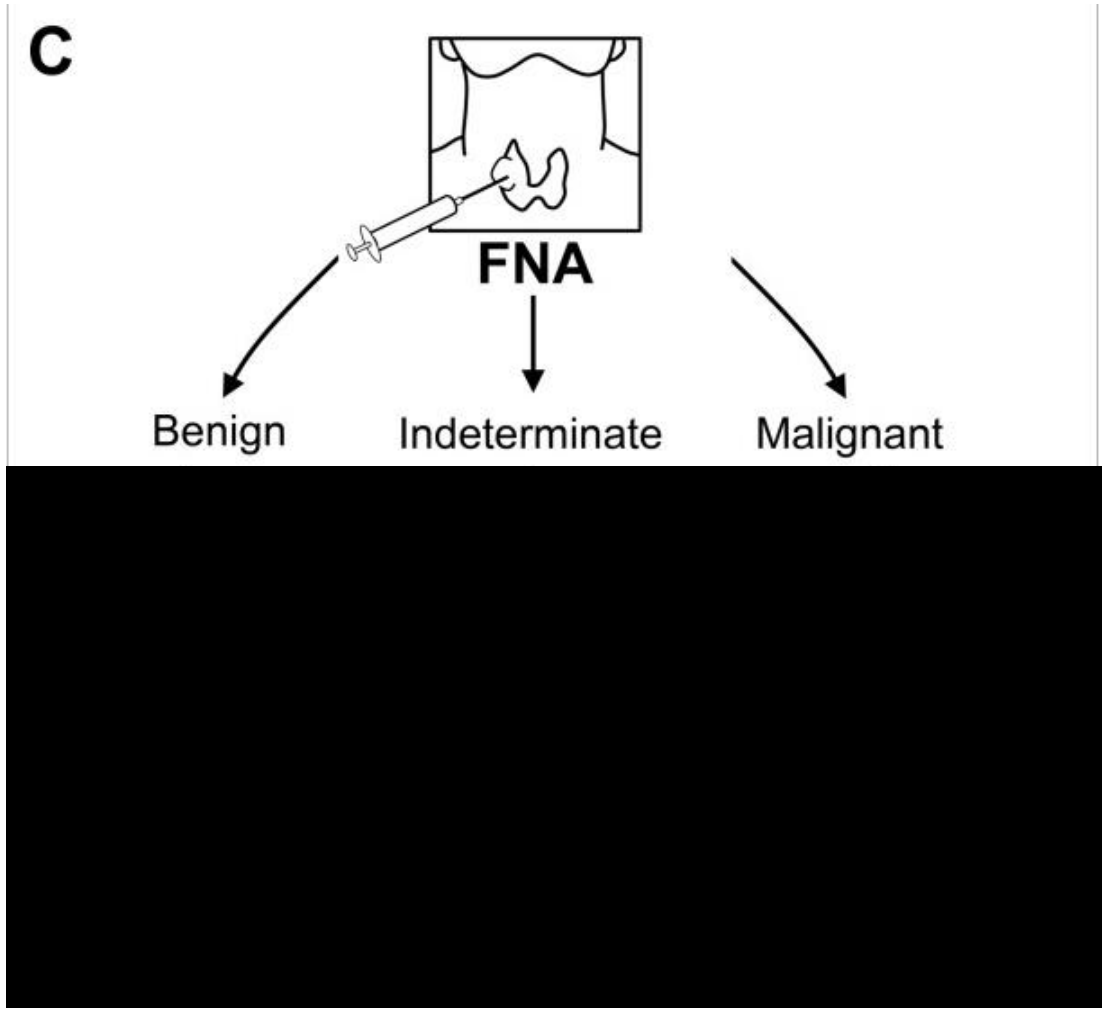
US Pattern and suggested FNA cutoffs

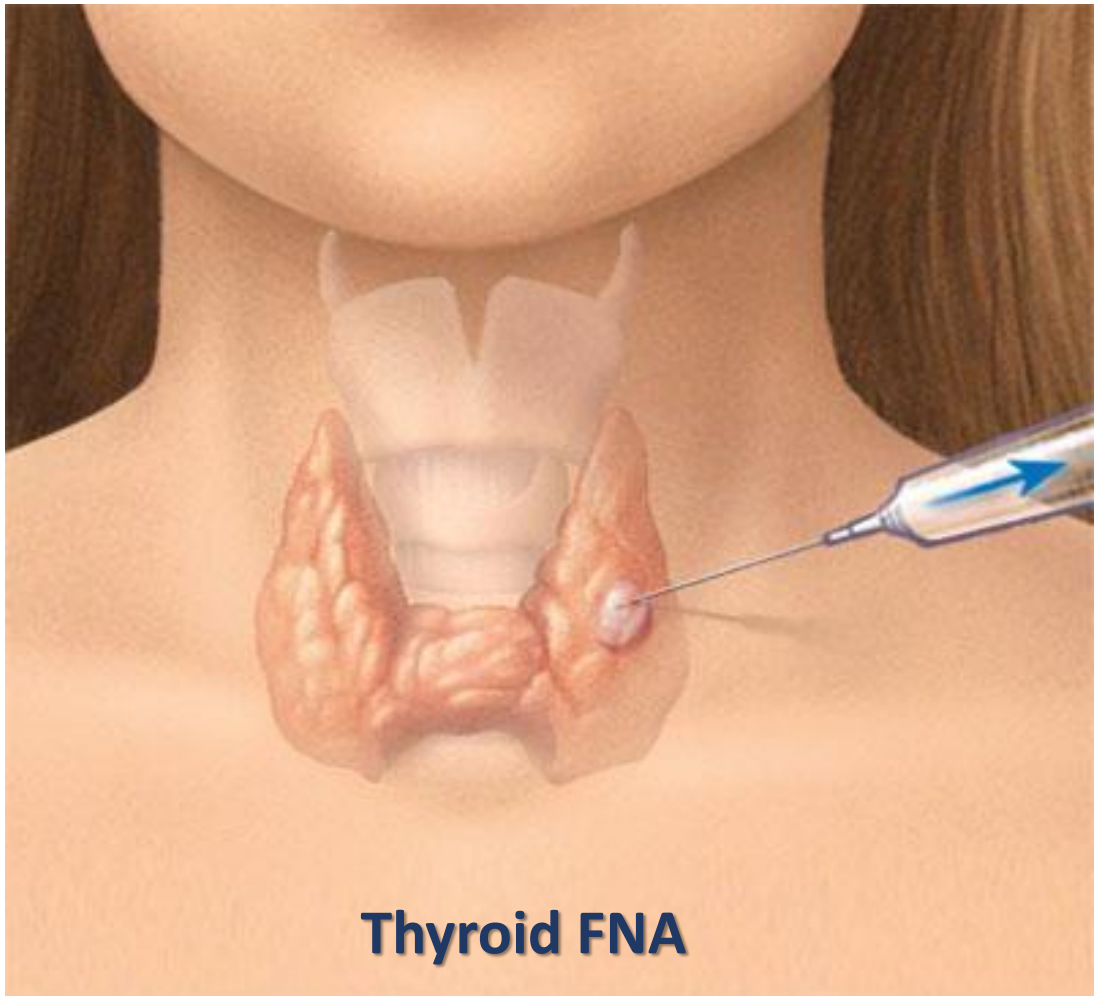
Haugen et al. Thyroid; January 2016

Comparison of ACR TI-RADS, ATA Guidelines, EU-TIRADS, and K-TIRADS

ACR TI-RADS Level	ATA	FNA Threshold (cm)	EU-TIRADS	FNA Threshold (cm)	K-TIRADS	FNA Threshold (cm)
High (TR5)	Solid hypoechoic nodule with any of five suspicious features[a]; solid hypoechoic component of partial cystic nodule with any suspicious features (both TR4–TR5)	≥ 1.0	At least one of four suspicious features[b] (TR4–TR5)	≥ 1.0	Solid hypoechoic nodule with any of three suspicious features[c] (TR4–TR5)	≥ 1.0
Intermediate (TR4)	Solid hypoechoic nodule with no suspicious features (TR4)	≥ 1.0	No suspicious features, but mildly hypoechoic (TR4)	≥ 1.5	Solid hypoechoic nodule with no suspicious features (TR4); partially cystic or isohypere-choic solid nodule with any of three suspicious features[c] (TR4–TR5)	≥ 1.0
Low (TR3)	Solid isoechoic or hyperechoic nodule with no suspicious features, only macrocalcifications (TR3–TR4); partial cystic nodule with eccentric solid areas with no suspicious features, only macrocalcifications (TR3); partial cystic nodule with eccentric solid areas with no suspicious features or echogenic foci (TR2)	≥ 1.5	No suspicious features, iso- or hyperechoic (TR2–TR3)	≥ 2.0	Partially cystic or isohyperechoic solid nodule with no suspicious features (TR2–TR3)	≥ 1.5
Very low (TR2)	Partially cystic nodule without high, intermediate or low suspicion features, or spongiform (TR1–TR2)	≥ 2.0	Anechoic or spongiform (TR1)	No FNA	Spongiform, partially cystic nodule with comet tail, pure cyst (TR1)	≥ 2.0 spongiform
Benign or normal (TR1)	Purely cystic (TR1)	No FNA	No nodule		No nodule	

Hoang JK, Middleton WD, Tessler FN. AJR Am J Roentgenol. 2021 Mar;216(3):570-578.





Molecular cytopathology for thyroid nodules:
A review of methodology and test performance

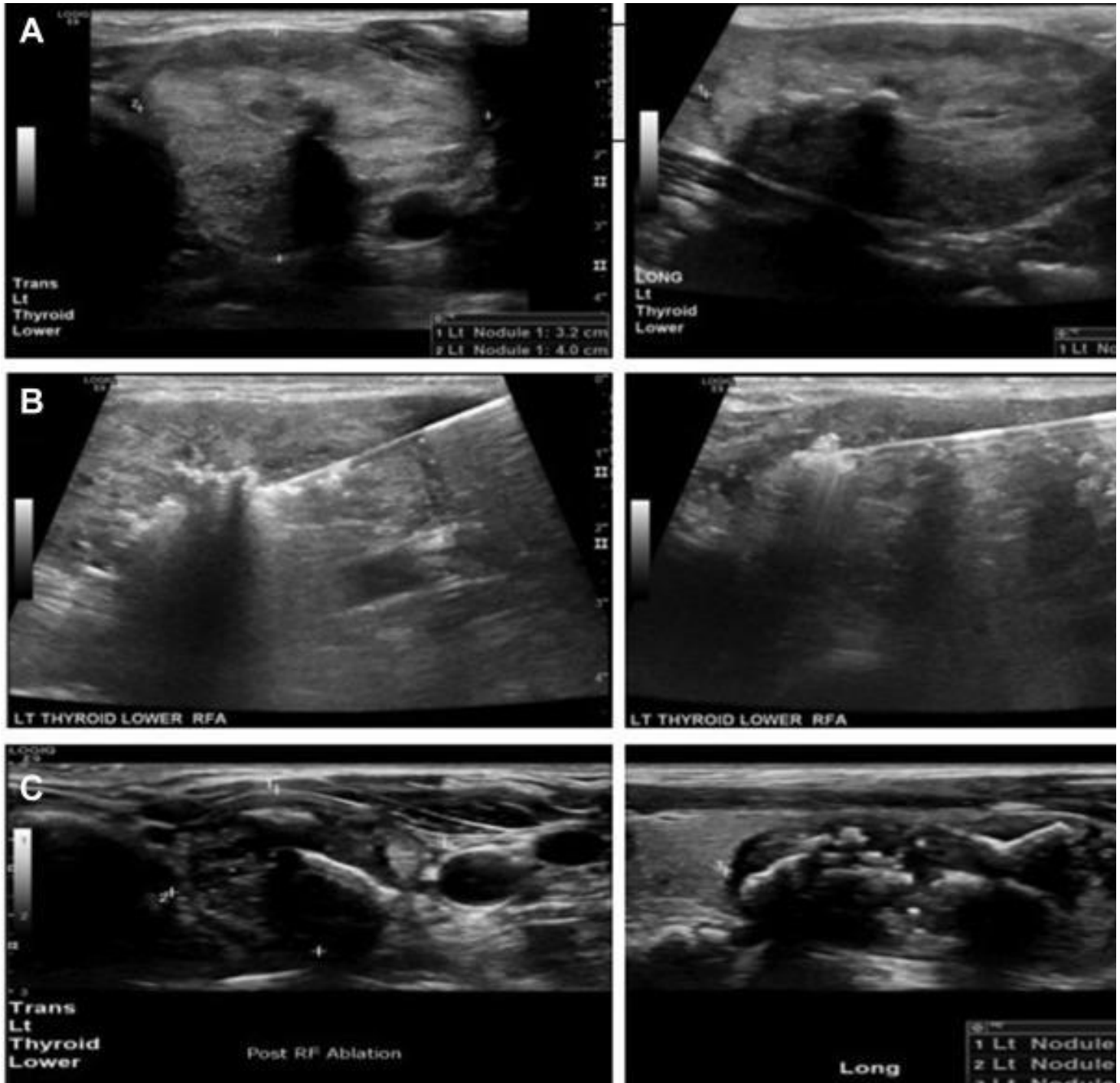
Molecular cytopathology for thyroid nodules: A review of methodology and test performance, Volume: 124, Issue: 1, Pages: 14-27, First published: 08 September 2015.

Management of benign thyroid nodules

- Surveillance
- Surgery – indications
- Minimally invasive procedures

Minimally invasive procedures

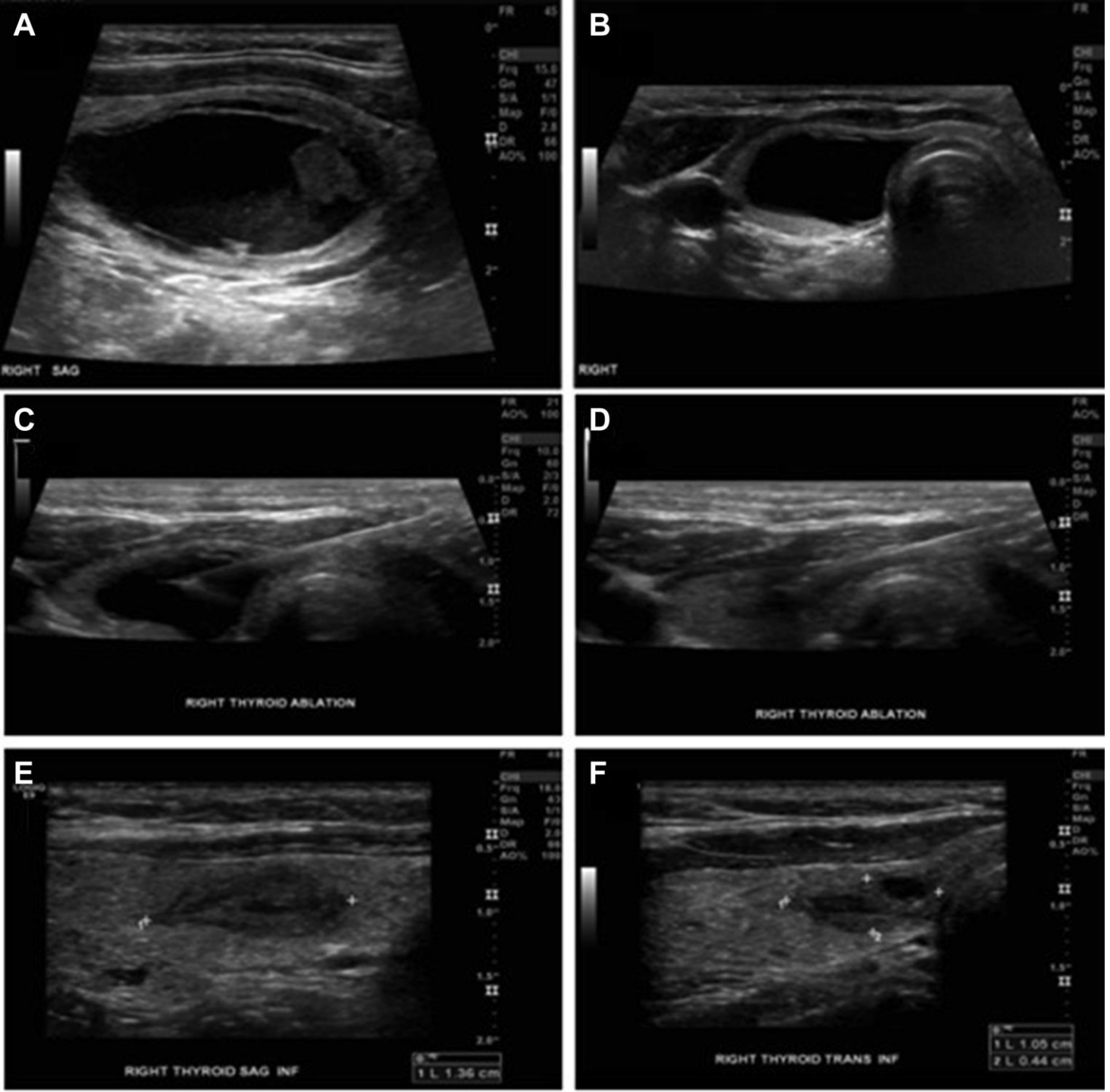
- Alcohol ablation
- Thermal ablation (RFA, Laser ..etc)
- HIFU



RFA

- A 51-year-old woman with a benign left thyroid nodule with neck obstructive symptoms
- She was treated with RFA
- Euthyroid
- VRR = 76%

Jasim S, Patel KN, Randolph G et al. Endocr Pract. 2022 Apr;28(4):433-448.



Ethanol Sclerotherapy

- A 62-year-old woman with a 3.3 x 2.6 x 1.6 cm right thyroid predominantly cystic nodule
- Diagnostic ultrasound performed 6 months after ablation shows persistent complete collapse of the nodule as seen on, (*E)*, sagittal and, (*F)*, transverse images.

Jasim S, Patel KN, Randolph G et al. Endocr Pract. 2022 Apr;28(4):433-448.

Differentiated Thyroid Cancer (DTC)

Thyroid cancer risk assessment

- ❑ The prevalence of thyroid nodules in the general population is high (≈60%)
- ❑ The prevalence of thyroid malignancy ≈ 7% - 15%
- ❑ The estimated new cases of thyroid cancer in USA is 43,800 new cases in 2022
- ❑ The cost of thyroid cancer care in the United States is estimated to reach $18-$21 billion
- ❑Thyroid nodule evaluation is no longer a 1-size-fits-all proposition:
  - ▪Known “clinical” risk factors for thyroid malignancy:
    Ionizing radiation, family history, thyroid autoimmunity, obesity, …etc
  - ▪ Sonographic features
  - ▪ Molecular testing
  - ▪ Modified therapeutic approach

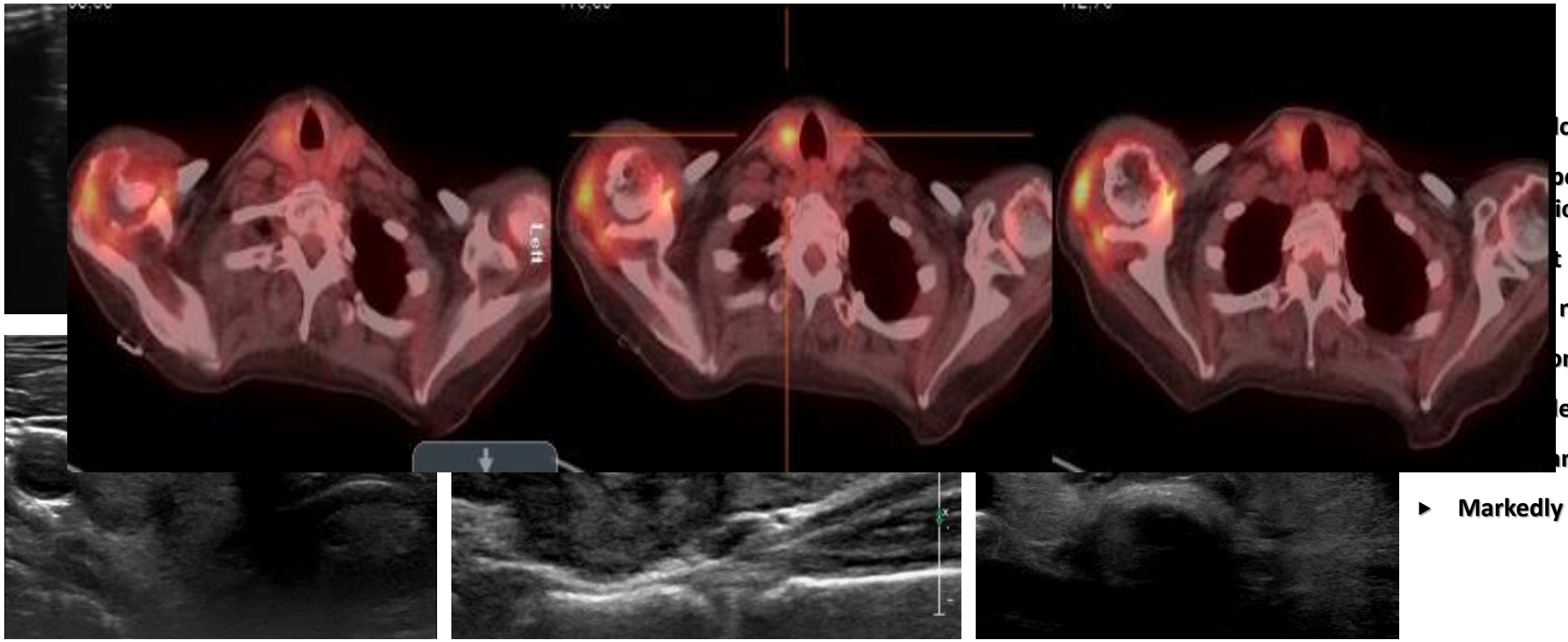
Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7-30
https://cancerstatisticscenter.cancer.org/#!/cancer-site/Thyroid

Differentiated thyroid cancer "DTC"	Medullary thyroid cancer "MTC"	Anaplastic thyroid cancer "ATC"
PTC: 80-85% FTC 5-10% >90% survival if managed early	2-4% of all TC Worse prognosis Familial/genetic- RET	1-2% Usually diagnosed at stage IV Mean survival <6 m

"Differentiated" malignant tumor that has the histologic appearance of cell types normally found in thyroid

US pattern recognition

Buzz words in US reports that suggest high suspicion of malignancy



cification

peripheral
ion (interrupted)

t border

margins

on/invasion

lenopathy

n wide

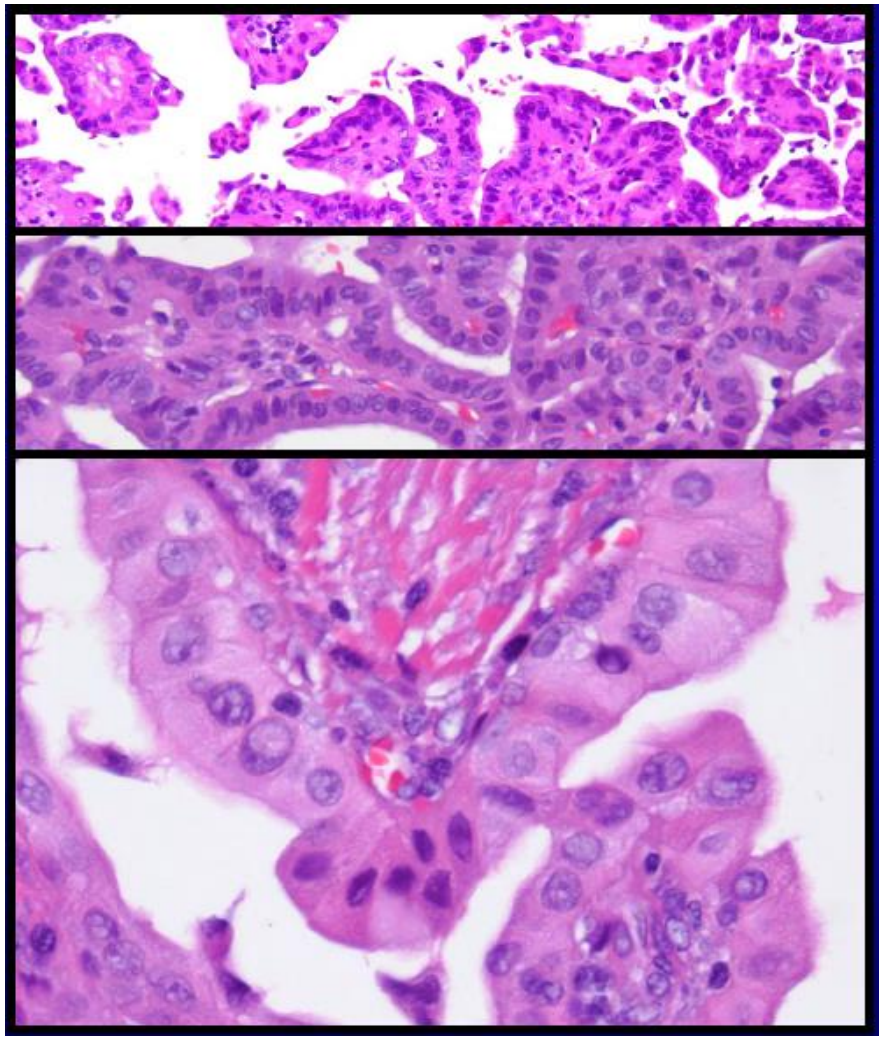
- **Markedly hypoechoic**

Papillary thyroid carcinoma

1. Low risk thyroid cancer and Micro-tumors: avoid overdiagnosis/treatment
2. New WHO terminology
3. Clinical DTC: risk based initial treatment and FU

Papillary thyroid carcinoma

- >80% of all thyroid carcinomas
- More in Females 2:1
- Median age at Dx: 30-40 yrs
- Nodal metastasis



40 y/o Female, incidental right 0.8 cm nodule. Cytology: PTC
Pathology: classic 0.6 cm PTC, No LNs

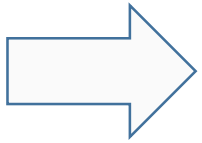
36 y/o Female, incidental right 1.3 cm nodule
Cytology: PTC Pathology: classic PTC, stage I, T1N1M0

36 y/o Female, incidental right 1.3 cm nodule
Cytology: PTC Pathology: non invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)

A 53 female with PTC, s/p Total thyroidectomy. Pathology: 4 cm Papillary thyroid cancer, tall cell variant, Extra-thyroidal extension, LN II- IV involvement with extra-nodal extension.

MOVING TOWARDS MORE INDIVIDUALIZED MANAGEMENT APPROACH

"Traditional Paradigm"
One Size Fits All
Total thyroidectomy
RAI remnant ablation
All with same follow up



"Risk Adapted Paradigm"
Management recommendations based individualized risk assessment

MARKED SHIFT TO DIAGNOSIS OF SMALL VOLUME THYROID CANCER WITH/WITHOUT MICROSCOPIC LN METS

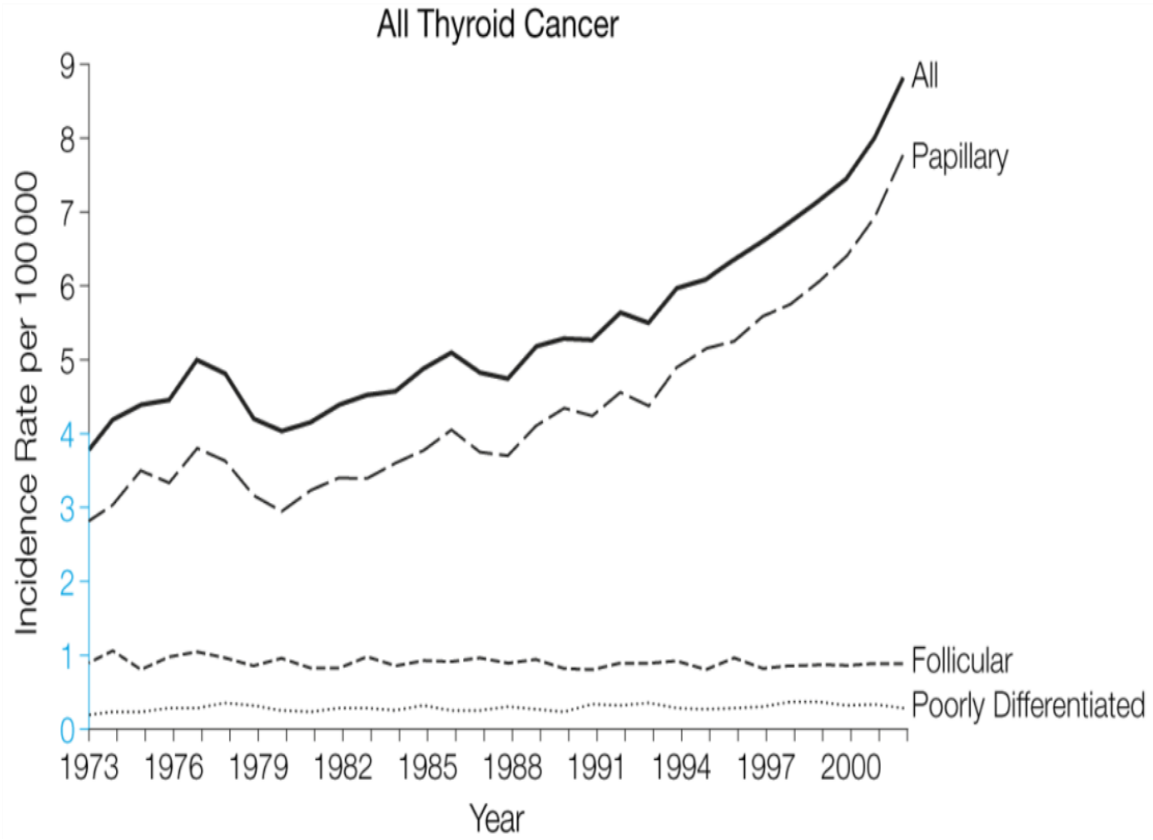
Rod Stewart

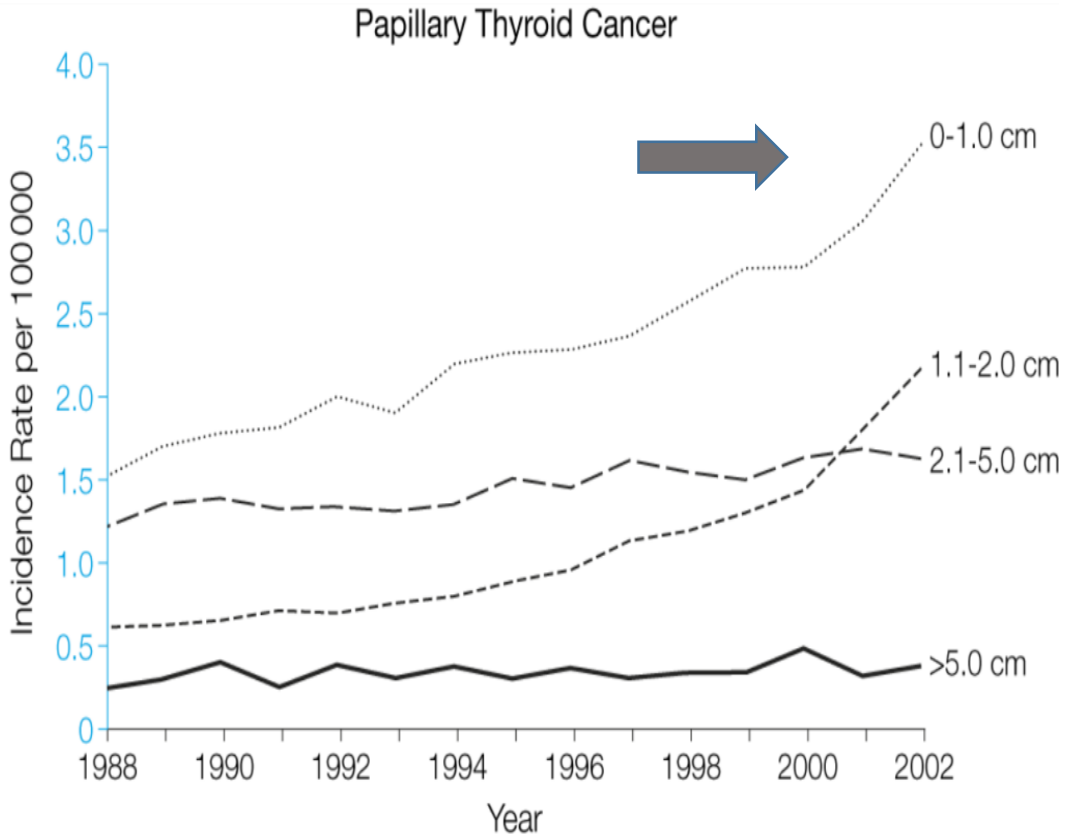
Sofia Vergara

Catherine bell

40 y/o Female, incidental right 0.8 cm nodule. Asymptomatic, no risk factors
Non-palpable on exam. Thyroid function tests normal
Cytology: PTC Pathology: 0.6 cm classic PTC , no ETE, no capsular invasion, no LNs

- **Microscopic Papillary thyroid cancer**
- **PTC < 1 cm**

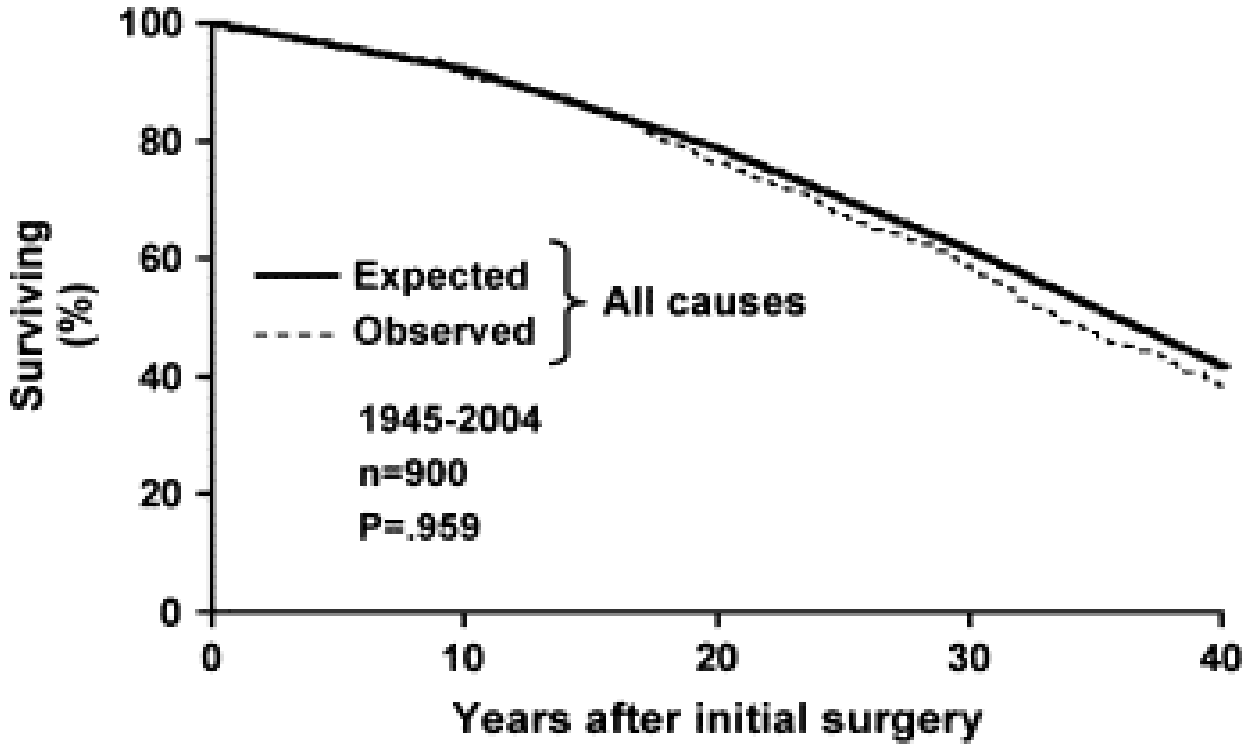




87% of the increase is due to primary tumors < 2 cm
49% of the increase is due to primary tumors < 1 cm

Davies, Louise and Welch, Gilbert. Increasing incidence of thyroid cancer in the United States, 1973-2002. *JAMA*. 2006;295(18):2164-2167.

Excellent Outcomes in Operated PTM: The Mayo Clinic Data



Observed all-cause survival for 900 patients with PTM treated at Mayo during 1945 through 2004. Expected survival (all causes) of persons of like age and sex based on 1982 Minnesota life-tables.

Hay ID et al. Papillary thyroid microcarcinoma: A study of 900 cases observed in a 60-year period. 2008 Surgery 144(6):980-988.

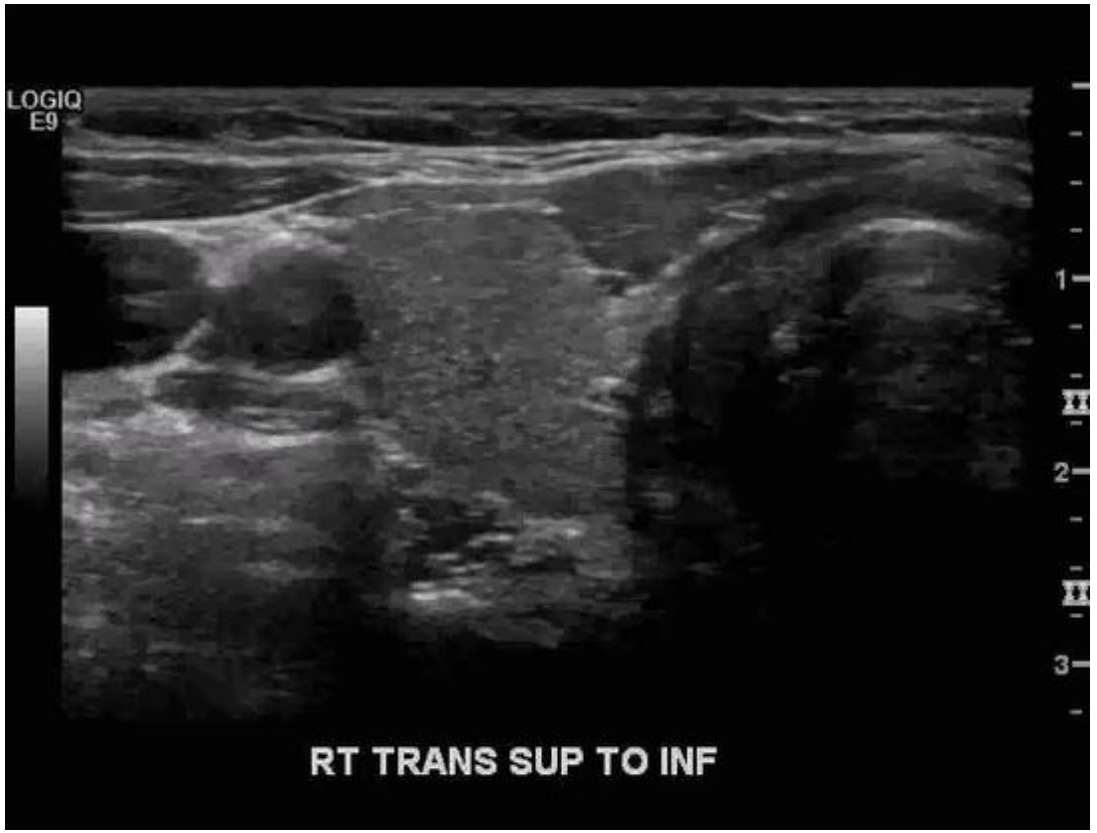
To avoid over diagnosis – The ATA recommends:

1. Do not perform neck US in asymptomatic subjects
2. Do not perform thyroid FNA on solid nodules < 10 mm unless there is evidence of extrathyroidal extension or of lymph node or distant metastases
3. Restrict surgery to lobectomy and avoid RAI in those with low risk features
4. Conduct further research to define the role of active surveillance instead of immediate surgery for patients with low risk tumors.

Therapeutic Strategies for Indolent Micro-PTC: The Present/Future

- **Active surveillance**
- **Lobectomy**

Observation **not** for everyone!



US VIDEOS: COURTESY OF DR. WILLIAM MIDDLETON

DEPARTMENT OF RADIOLOGY

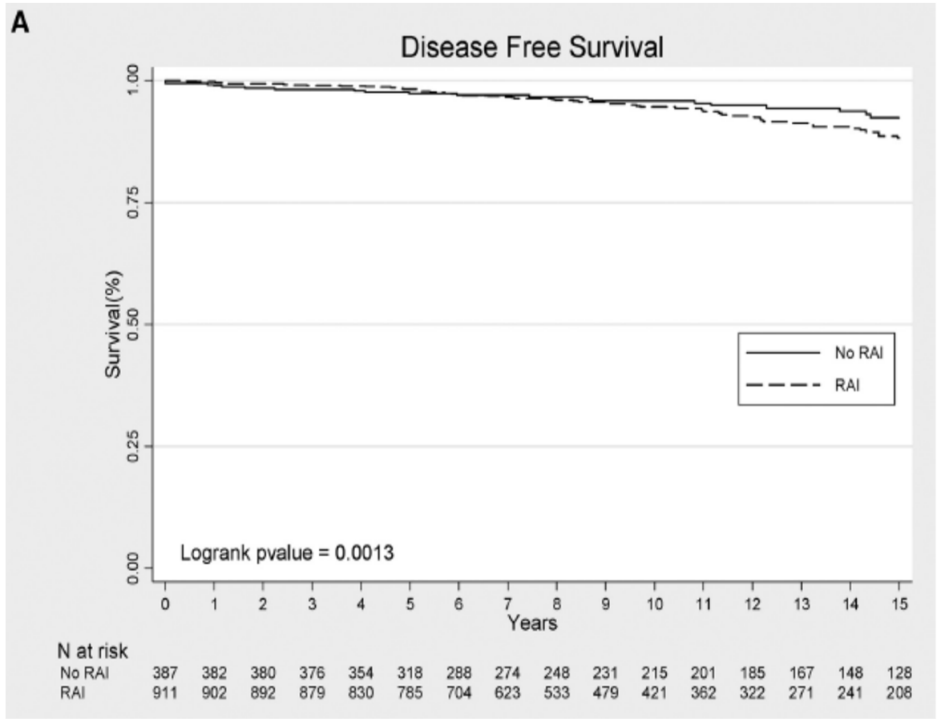
36 y/o Female, incidental right 1.3 cm nodule
Asymptomatic, no risk factors . Non-palpable on exam
Thyroid function tests normal
Cytology: PTC Pathology: classic PTC, stage I, T1N1M0

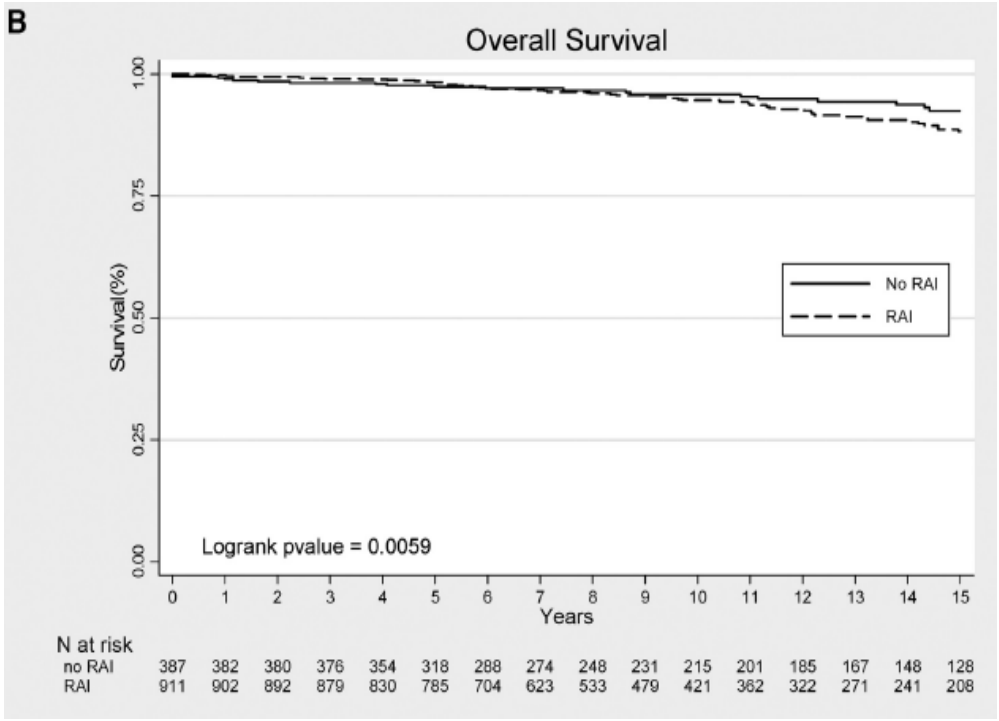
- **<u>What is low risk PTC</u>**
- Variable definitions
  - Absence of cN1a, cN1b
  - Absence of gross ETE and/or distant metastases
  - Absence of high risk pathology (TCV, widely invasive FTC)

Extent of surgery:
avoid morbidity in low risk thyroid cancer patients

- Optimal surgery may be a total thyroidectomy, when performed with a minimal risk of morbidity
- **Total thyroidectomy does not improve overall survival in low-risk thyroid cancer patients**
- When the risk of morbidity is high, a lobectomy is an alternative for many patients (T1-T2)
- Many low risk patients do not need post-op RAI
- Same debate need for prophylactic lymph node dissection: not needed in T1-T2 patients?
- Randomized trial (ESTIMABL3) in T2cN0 patients

Impact on Overall Survival of Radioactive Iodine in Low-Risk Differentiated Thyroid Cancer Patients





1298 low risk DTC patients
Bicentric retrospective
Median follow-up: 10 years

J Clin Endocrinol Metab. 2012;97(5):1526-1535.

The NEW ENGLAND JOURNAL of MEDICINE

Table 4. Adverse Events, According to Thyrotropin-Stimulation Method and ^{131}I Dose.*

Adverse Event	Recombinant Human Thyrotropin		Thyroid Hormone Withdrawal	
	1.1 GBq (N=186)	3.7 GBq (N=183)	1.1 GBq (N=179)	3.7 GBq (N=181)
Lacrimal dysfunction at time of ablation — no. (%)	18 (10)	19 (10)	35 (20)	43 (24)
Salivary dysfunction at time of ablation — no. (%)	19 (10)	26 (14)	24 (13)	29 (16)
Serious adverse events†	One hysterectomy	None	One renal stone related to hypercalcemia, one urinary infection, and one case of hypocalcemia	One case of cardiac insufficiency leading to death

Martin Schlumberger,n engl j med 366;18

Post-operative RAI: patient selection (ATA guidelines)

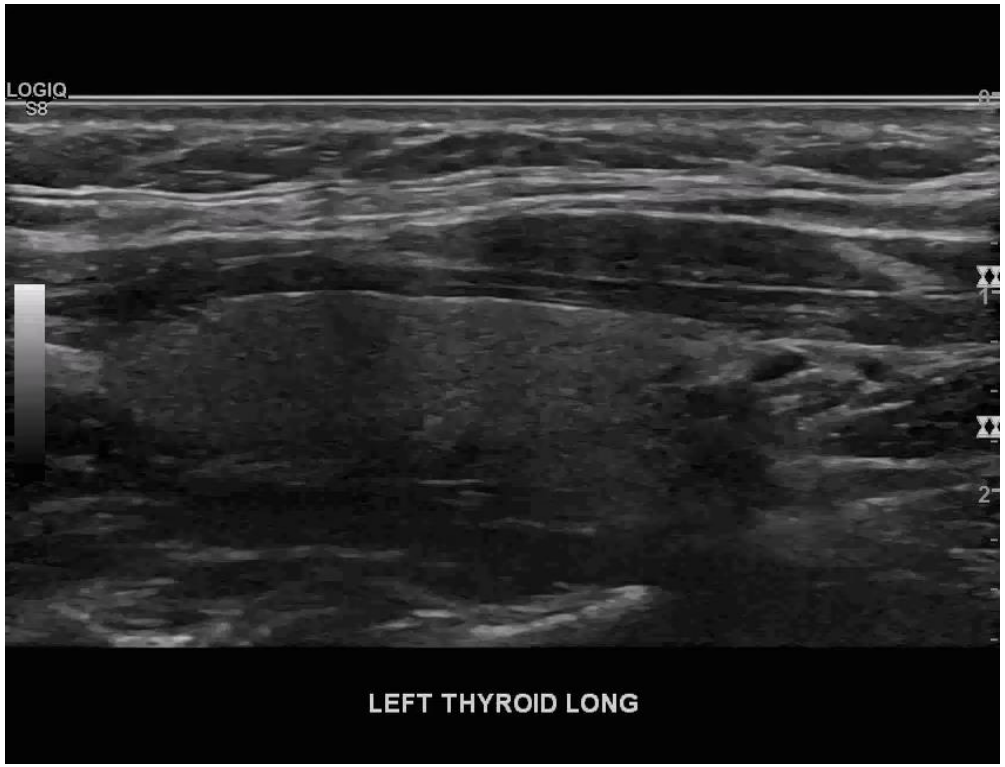
- After total thyroidectomy, RAI remnant ablation:
  - is not routinely recommended for ATA low risk.
  - should be considered for ATA intermediate risk .
  - is routinely recommended for ATA high risk patients.

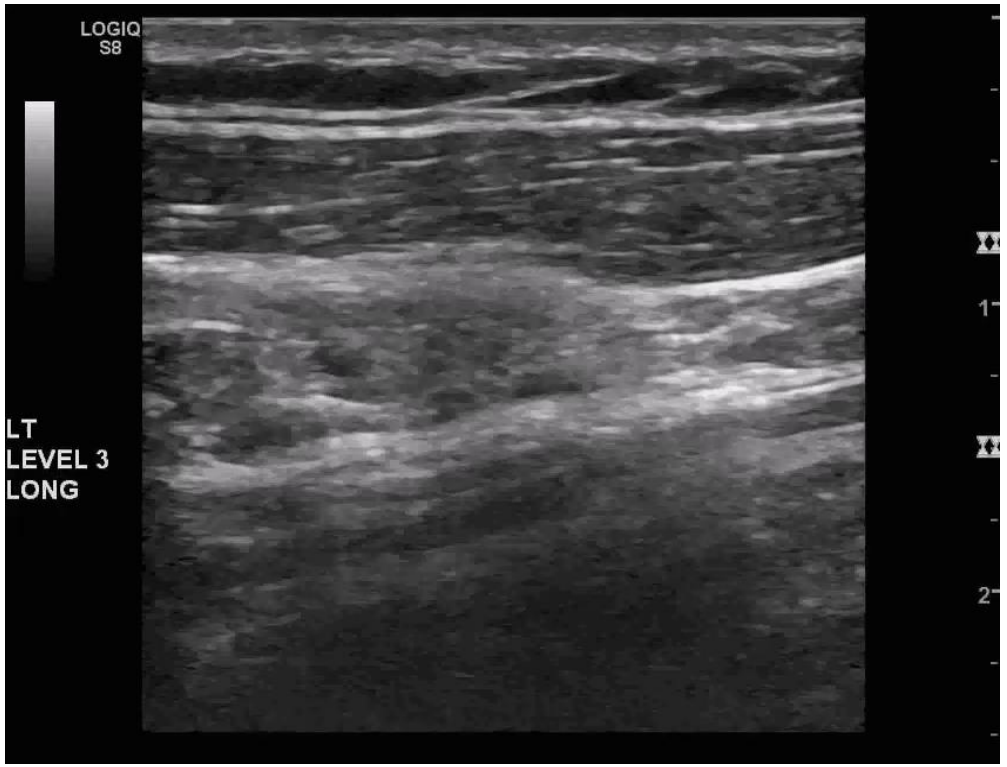
36 y/o Female, incidental right 1.3 cm nodule
Asymptomatic, no risk factors . Non-palpable on exam
Thyroid function tests normal
Cytology: PTC Pathology: classic PTC, stage I, T1N1aM0

- **<u>What is low risk PTC</u>**
- **Variable definitions**
  - **Absence of cN1a, cN1b**
  - **Absence of gross ETE and/or distant metastases**
  - **Absence of high risk pathology (TCV, widely invasive FTC)**

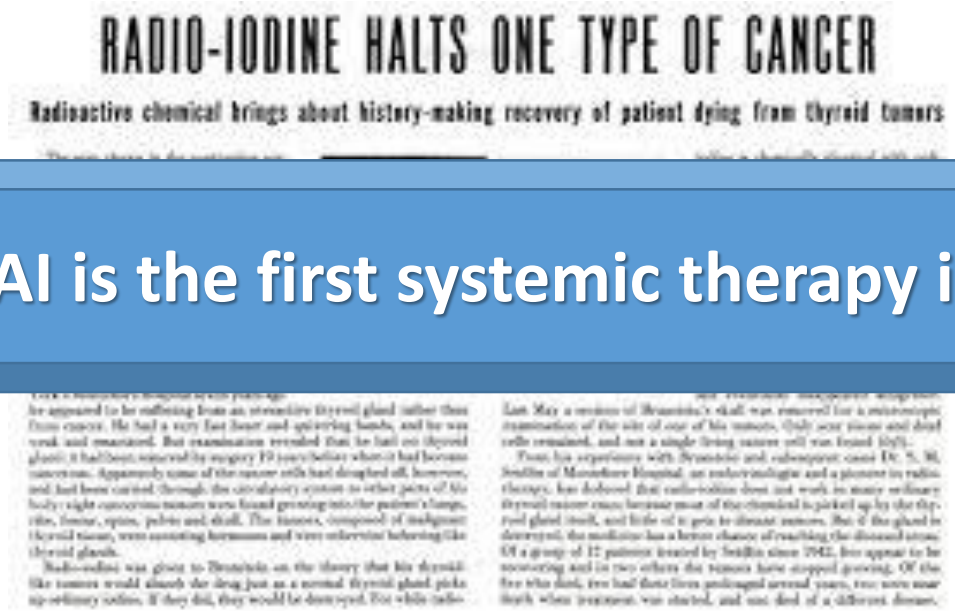
- **<u>Management Strategies for Low Risk PTC:</u>**
  - **Lobectomy vs near total/total thyroidectomy +/- lymph node dissection**
  - **Mild TSH suppression therapy (TSH = 0.1-0.5)**
  - **Selective use of TSH-stimulated radioactive iodine (RAI) [I^{131}] ablation (30 mCi)**

A 53 female with PTC, s/p Total thyroidectomy. Pathology: 4 cm Papillary thyroid cancer, tall cell variant, Extra-thyroidal extension, LN II- IV involvement with extra-nodal extension.





Management of Intermediate to High Risk Locally Confined PTC

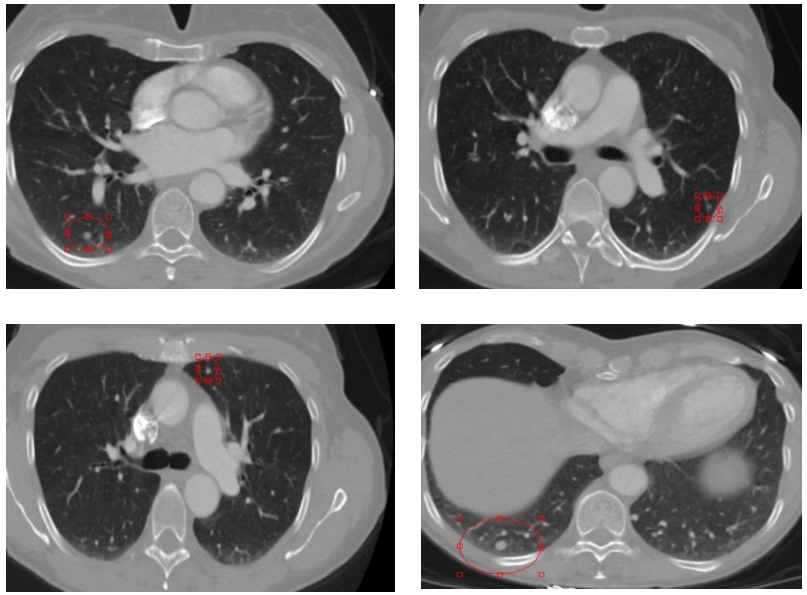


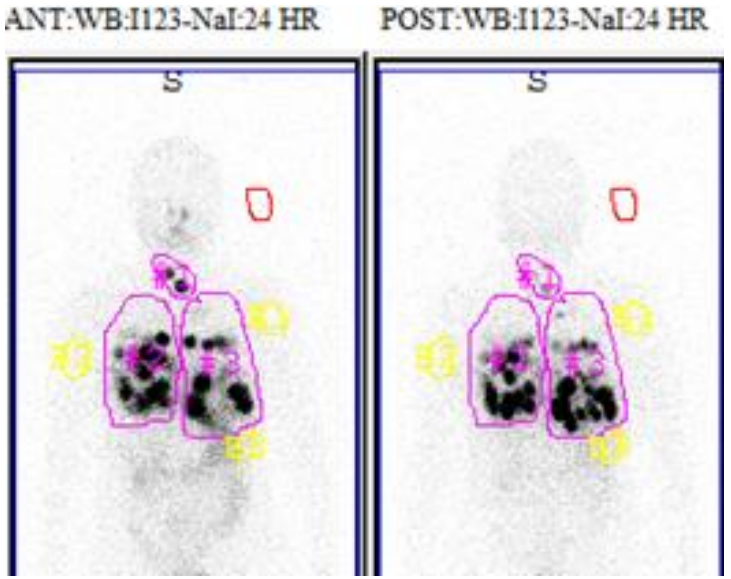
RADIO-IODINE HALTS ONE TYPE OF CANCER

Radioactive chemical brings about history-making recovery of patient dying from thyroid tumors

RAI is the first systemic therapy in DTC

- **Total thyroidectomy with lymph node dissection**
- **TSH suppression therapy : TSH <0.1**
- **Post op, adjuvant (RAI) [I^{131}] therapy (75-200 mCi)**

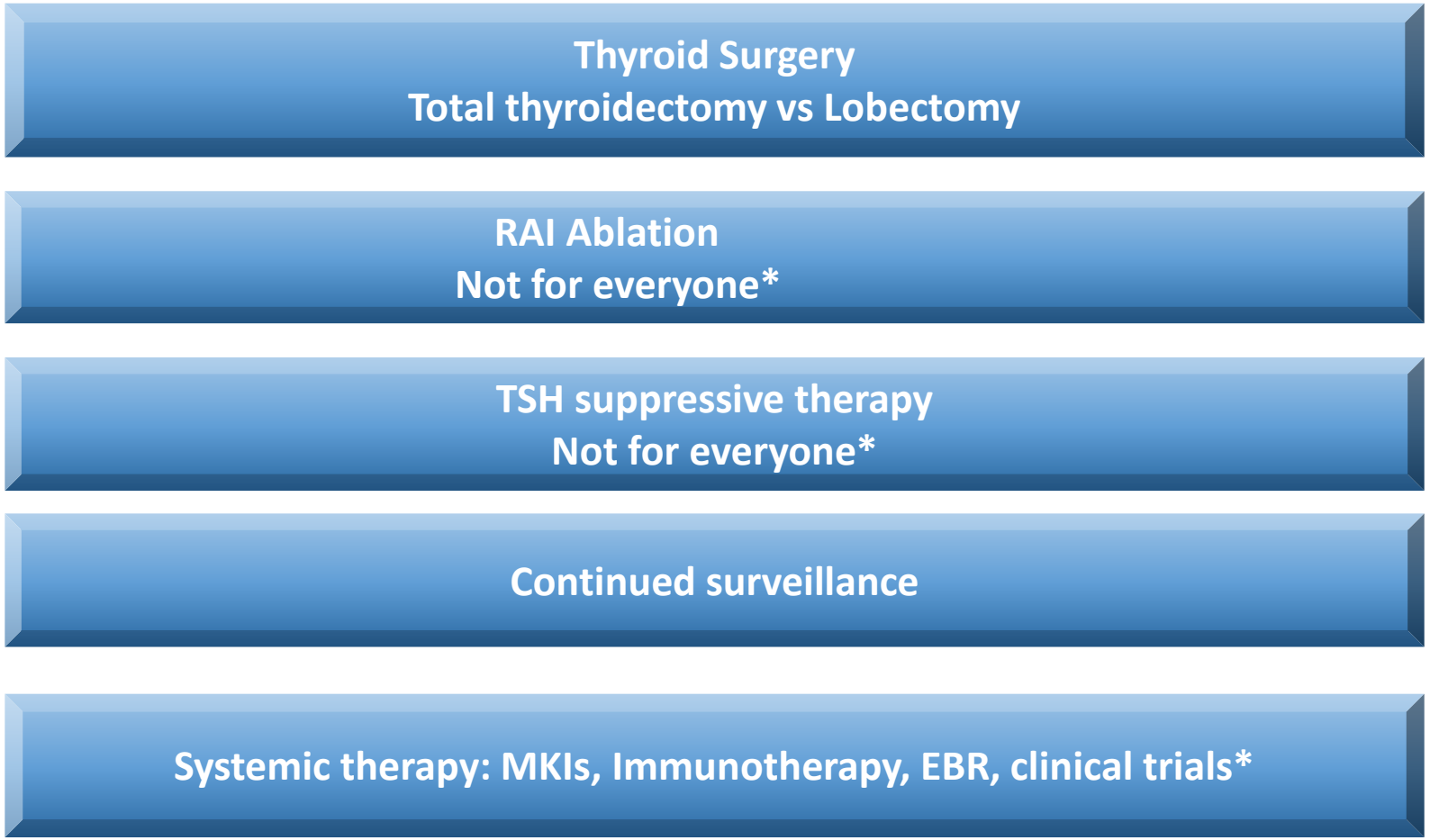




Tg: 21 (TSH 2)

- **<u>What is 'high risk' disease?</u>**
- Tumors > 4cm
- Gross extrathyroidal extension
- High risk pathology (TCV, PDTC)
- Incomplete resection
- High post op Tg

PAPILLARY THYROID CANCER: MANAGEMENT OPTIONS

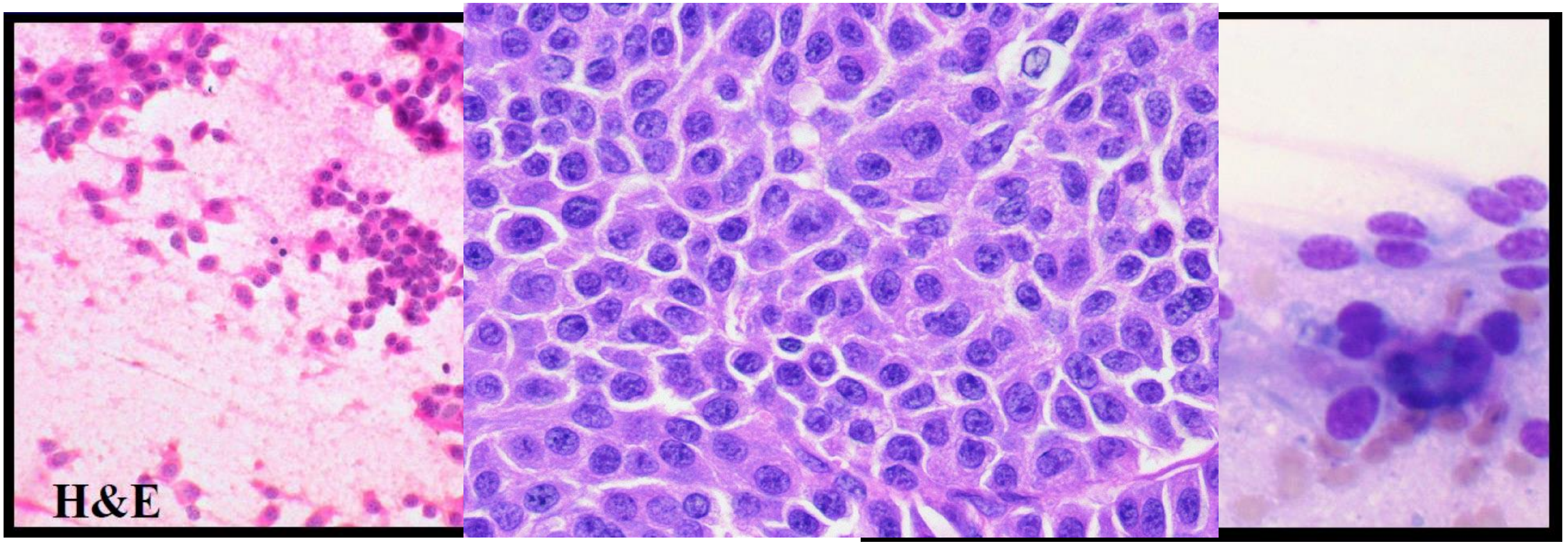


*Not for NIFTP, micro-PTC, low risk PTC

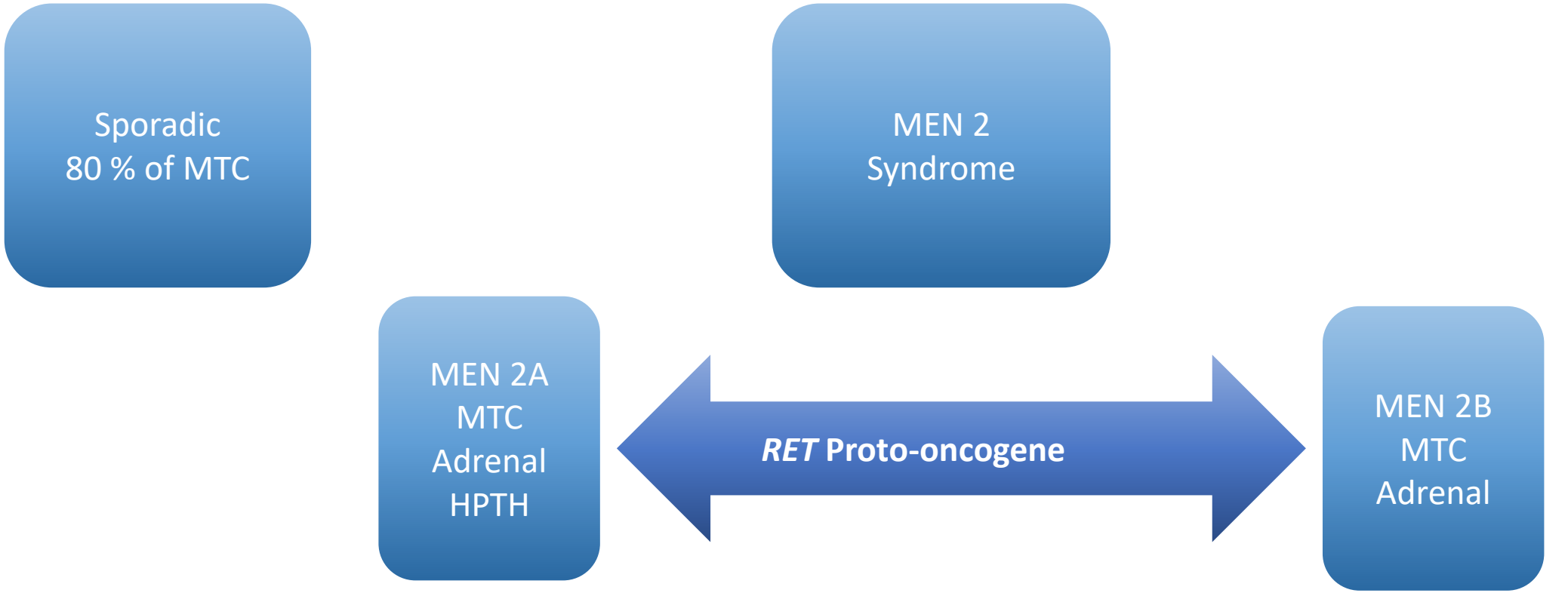
Medullary Thyroid Cancer

56 Y/O male, elevated Calcitonin, diarrhea

5 cm thyroid nodule, Family history of HyperCalcemia



Medullary Thyroid Cancer

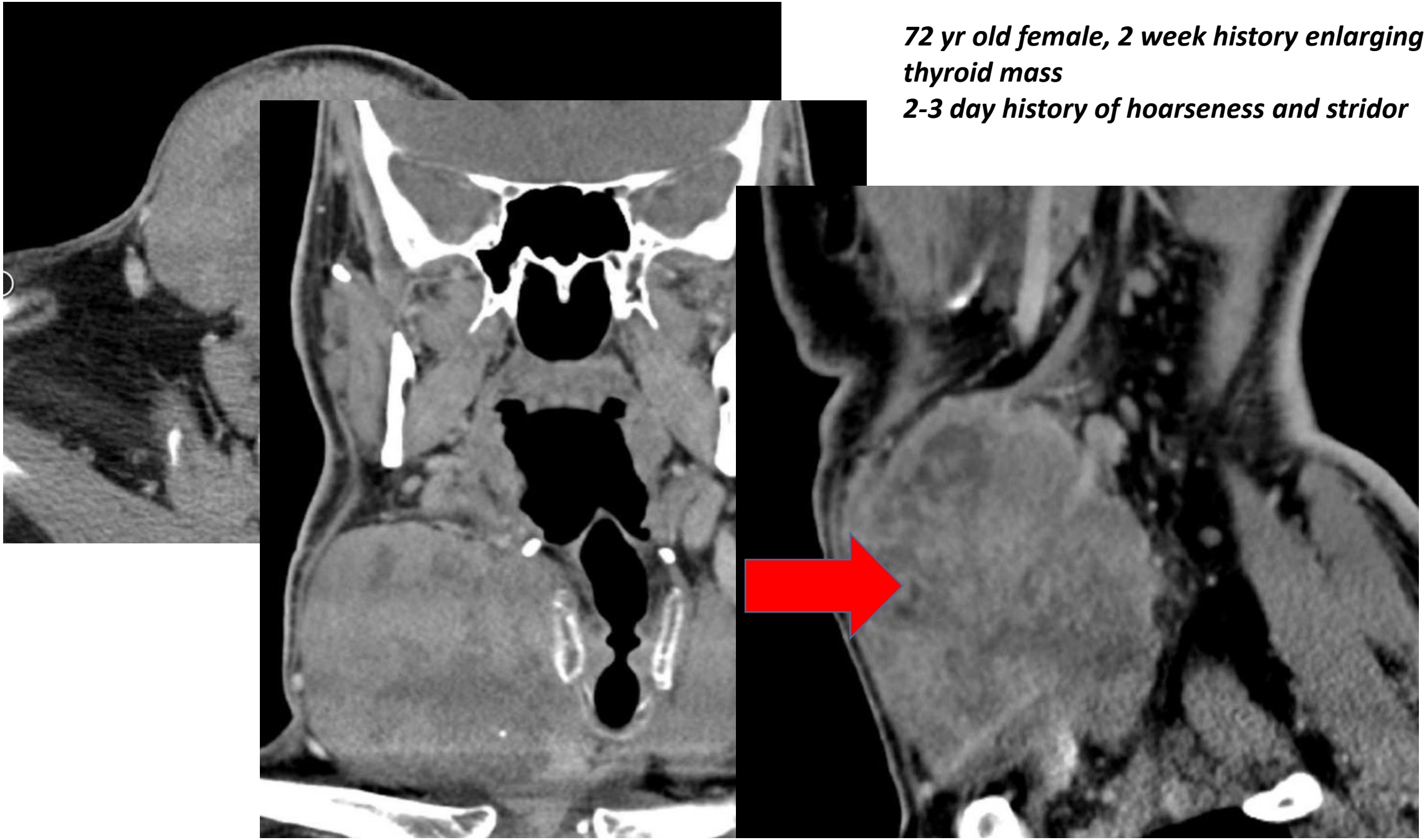


- **Classical MEN2A**
- **MEN2A with cutaneous lichen amyloidosis(634)**
- **MEN2A with Hirschsprung's disease (609,611,618,620)**
- **Familial MTC (804)**

Ganglioneuromas (Oral mucosa & GI tract)
Marfanoid

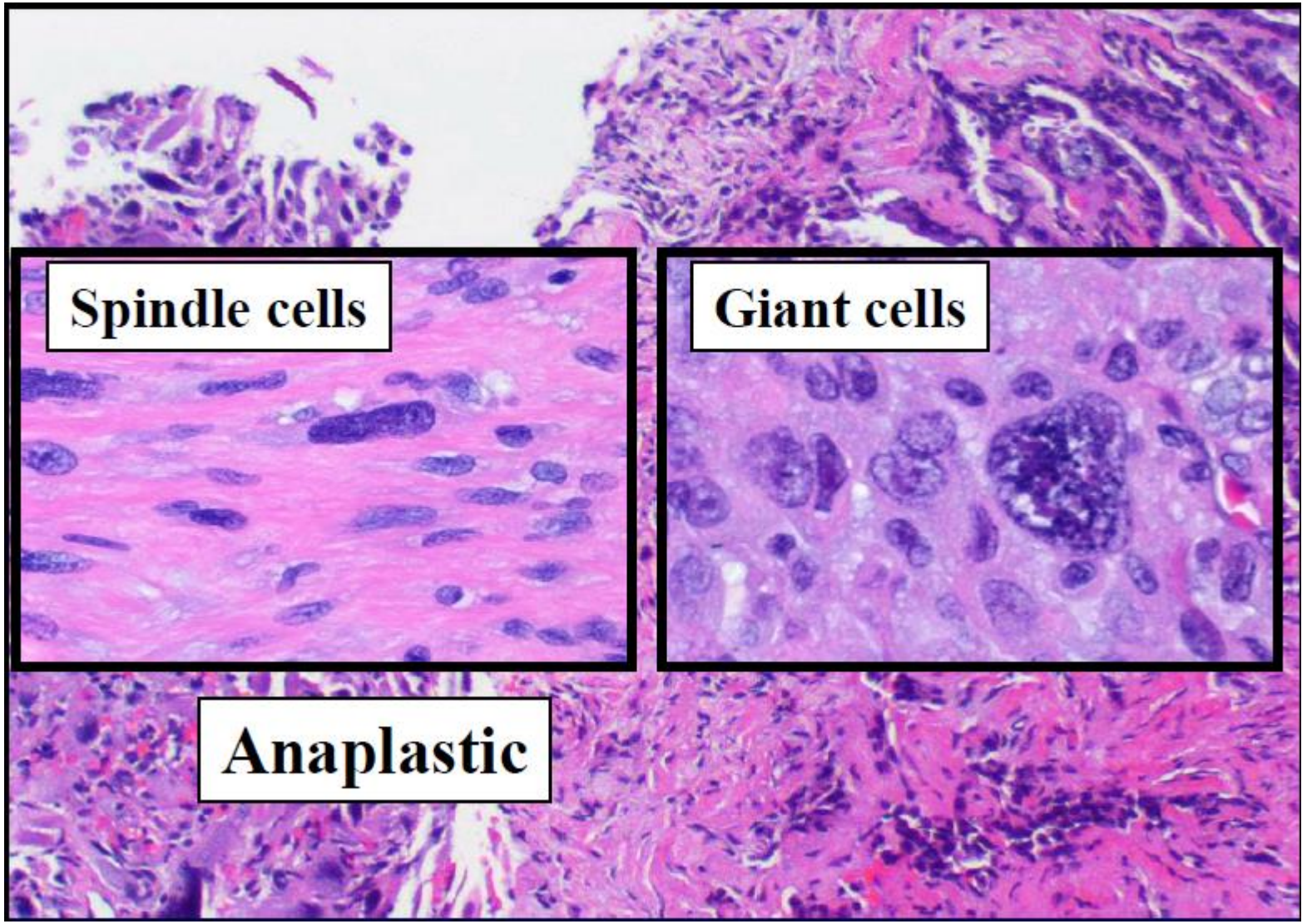
Thyroid lymphoma

J Clin Endocrinol Metab. 2006;91(10):3711-3712. doi:10.1210/jc.2006-0786

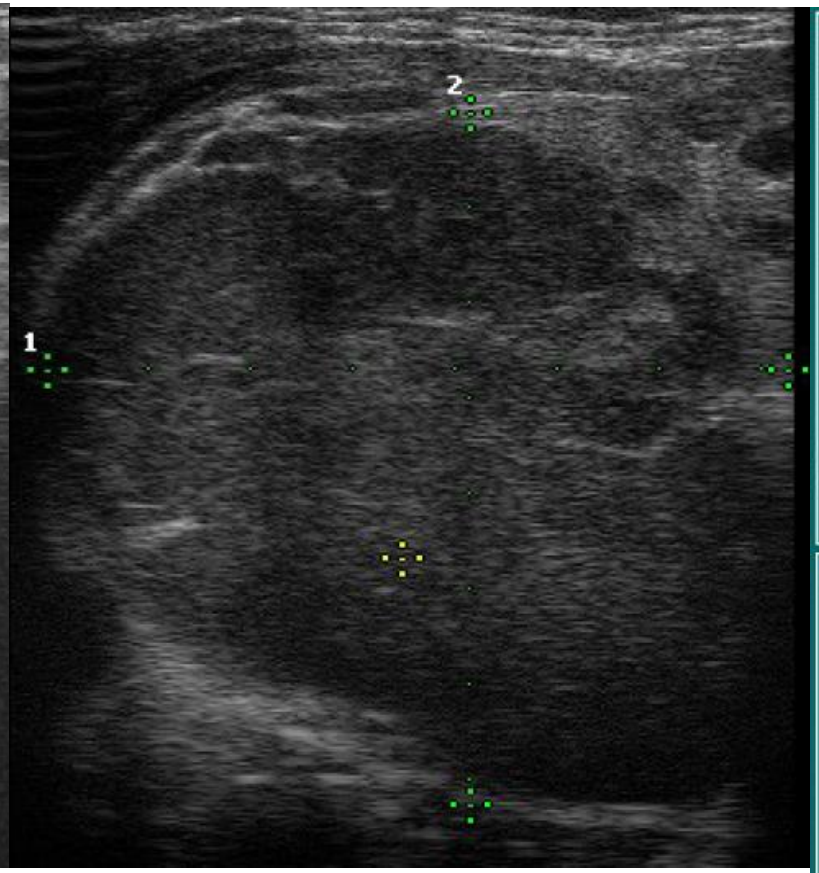


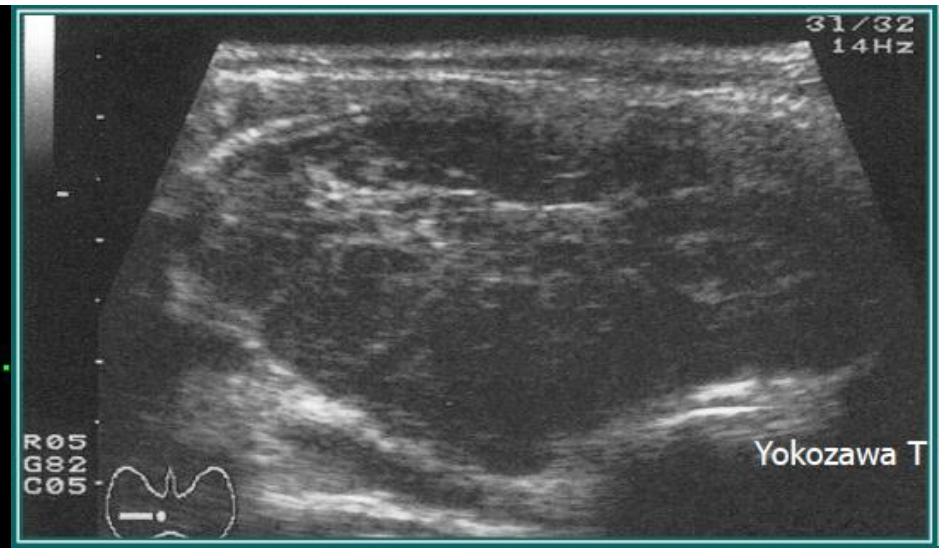
72 yr old female, 2 week history enlarging thyroid mass
2-3 day history of hoarseness and stridor

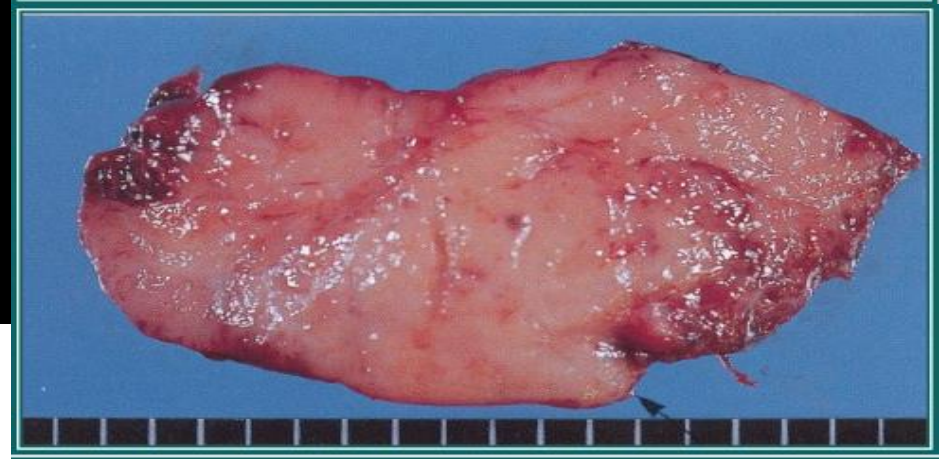
Anaplastic Thyroid Cancer



Hypoechoic Nodules

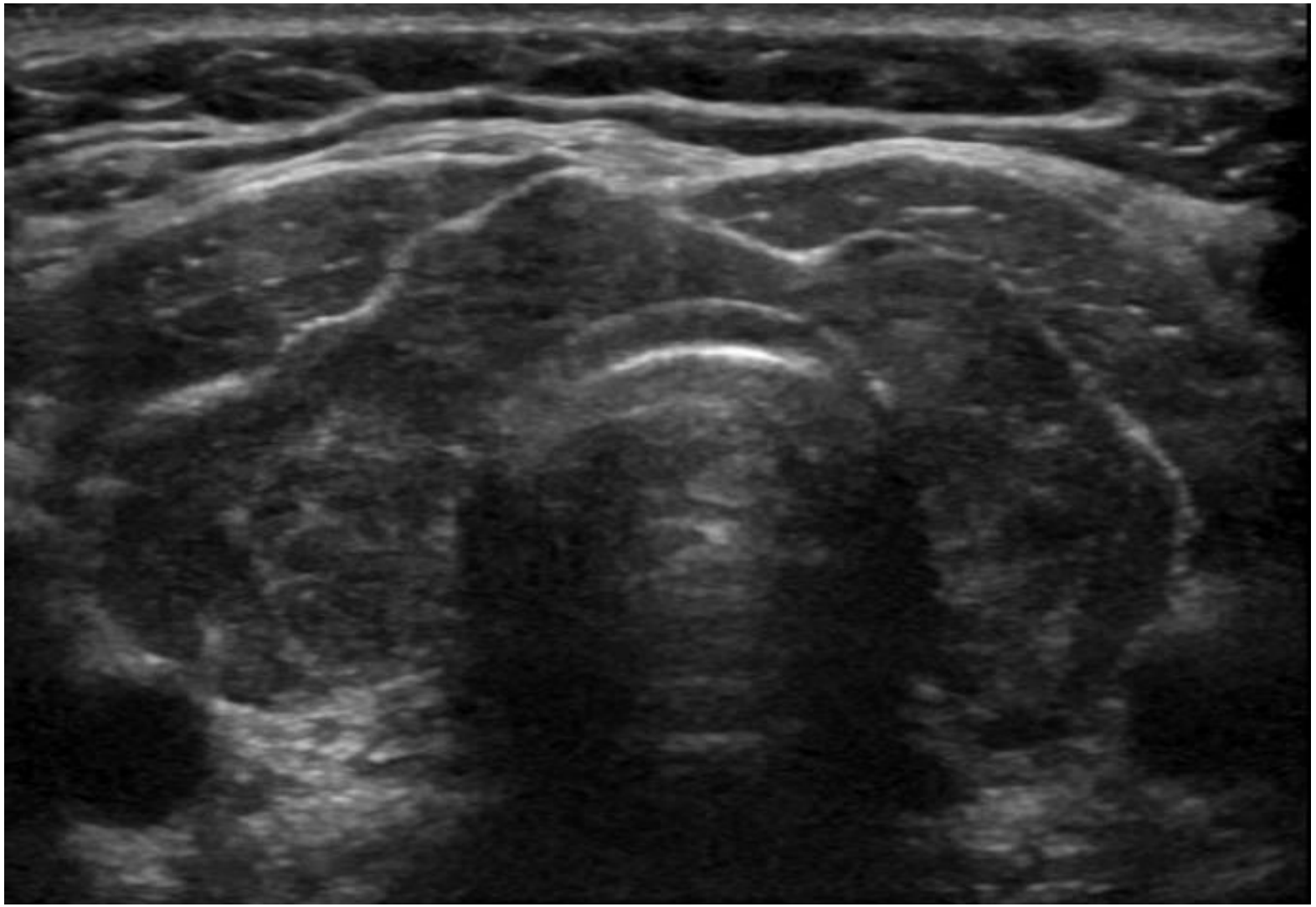






Most Common Mets to Thyroid: Renal, Breast, Lung, Melanoma

What is the Diagnosis?



Hashimoto's Thyroid disease

Take home points

- **Thyroid nodules are common in general practice**
- **Only about 10% of thyroid nodules are malignant**
- **Rapidly growing neck mass –Think anaplastic/lymphoma**
- **Spectrum of thyroid cancer is changing–Increasing incidence of very low risk papillary thyroid cancer**
  - **Proper role of minimal intervention and active surveillance**
- **Risk stratification is the cornerstone of initial and ongoing management**
- **RAI still the best systemic therapy for DTC**
- **Effective FDA approved drugs are now available for aggressive and RAI refractory disease**

Thank you!

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