Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

Graves Disease & I-131 Thyroid Ablation *in Pediatrics*

Hedieh Khalatbari, MD, MBA
Seattle Children's Hospital
University of Washington, NM CME Lecture
April 18, 2019

No Conflicts of Interest

Learning Objectives

- Describe the clinical manifestations and results of thyroid function studies in hyperthyroidism
- List the differential diagnosis of hyperthyroidism
  - Describe the role of NM in establishing the diagnosis
- Summarize treatment options for Graves disease
- Discuss the contraindications to I-131 ablation in Graves disease
- Calculate the I-131 ablation dose
- Manage concurrent thyroid nodules in patients with Graves disease

Overview: Thyroid Diseases

- Thyroid dysfunction
  - Hypothyroidism
  - Hyperthyroidism
    - *I-131 ablation in Graves disease*
- Thyroiditis
- Thyroid enlargement
- Thyroid nodules and carcinoma

Hyperthyroidism

- Graves disease
- Hashitoxisosis
- Thyroid nodules
  - autonomous thyroid nodule
  - multinodular goiter

Seattle Children's®
HOSPITAL • RESEARCH • FOUNDATION

Hyperthyroidism

Clinical manifestations
Physical examination
Laboratory tests
Etiologies

Overt Hyperthyroidism: Clinical Manifestations

- anxiety, emotional lability
- weakness, tremor
- palpitations, heat intolerance, increased perspiration
- weight loss despite a normal or increased appetite
  - some gain weight due to excessive increased appetite

http://tr-i-life.tumblr.com/post/32017595712/hyperthyroidism-mnemonic

Overt Hyperthyroidism: Physical Examination

- hyperactivity and rapid speech
- stare (lid retraction) and lid lag
- warm and moist skin
- thin and fine hair

http://josephwalrathmd.com/2013/06/17/thyroid-eye-disease-repair-of-lid-retraction/

http://www.odermatol.com/wp-content/uploads/image/20161/OURD-7-5-g006.jpg

Overt Hyperthyroidism: Physical Examination

- tachycardia, irregularly irregular pulse, systolic HTN
- tremor, proximal muscle weakness, and hyperreflexia

http://josephwalrathmd.com/2013/06/17/thyroid-eye-disease-repair-of-lid-retraction/

http://www.odermatol.com/wp-content/uploads/image/20161/OURD-7-5-g006.jpg

Physical Examination: Thyroid

- size: normal to enlarged
- palpable nodule, in autonomously functioning thyroid adenoma
- pain and tenderness, in subacute (granulomatous) thyroiditis

Physical Exam: Graves Disease

- exophthalmos
- periorbital and conjunctival edema
- limitation of eye movement
- infiltrative dermopathy (pretibial myxedema)

http://www.thyroidmanager.org/chapter/graves-disease-and-the-manifestations-of-thyrotoxicosis/

Laboratory Tests and Diagnosis: Primary Hyperthyroidism

- Overt hyperthyroidism
  - Low TSH
  - High free T4 and T3
- Subclinical hyperthyroidism
  - Low TSH
  - Free T4, T3, and free T3 are normal

- Diagnosis of hyperthyroidism is based upon thyroid function tests

Hyperthyroidism: Etiology

- Obvious: new onset ophthalmopathy, a large non-nodular thyroid, and moderate to severe hyperthyroidism has Graves' disease
- Other tests
  - Measurement of thyrotropin receptor antibodies (TRAb, TSI) → ↑ *in Graves*
  - Determination of the radioactive iodine uptake
  - *Measurement of thyroid blood flow on US*

Radioactive Iodine Uptake

- High or normal
  - de novo synthesis of hormone
- Low
  - inflammation and destruction of thyroid tissue
  - extrathyroidal source of thyroid hormone
    - factitious thyrotoxicosis
    - struma ovarii
  - exposure to large amounts of iodine
    - intravenous radiographic contrast
    - amiodarone

Seattle Children's®
HOSPITAL • RESEARCH • FOUNDATION

Case 2 (series)

Graves Disease

- Clinical photograph shows diffuse thyroid enlargement (black solid arrow) in a patient with Graves disease (GD). Diagnosis of GD is based on clinical features and laboratory tests. US is usually not indicated for patient management.
- *Obtain US when you suspect gland may weigh > 80 grams*

Case 1a

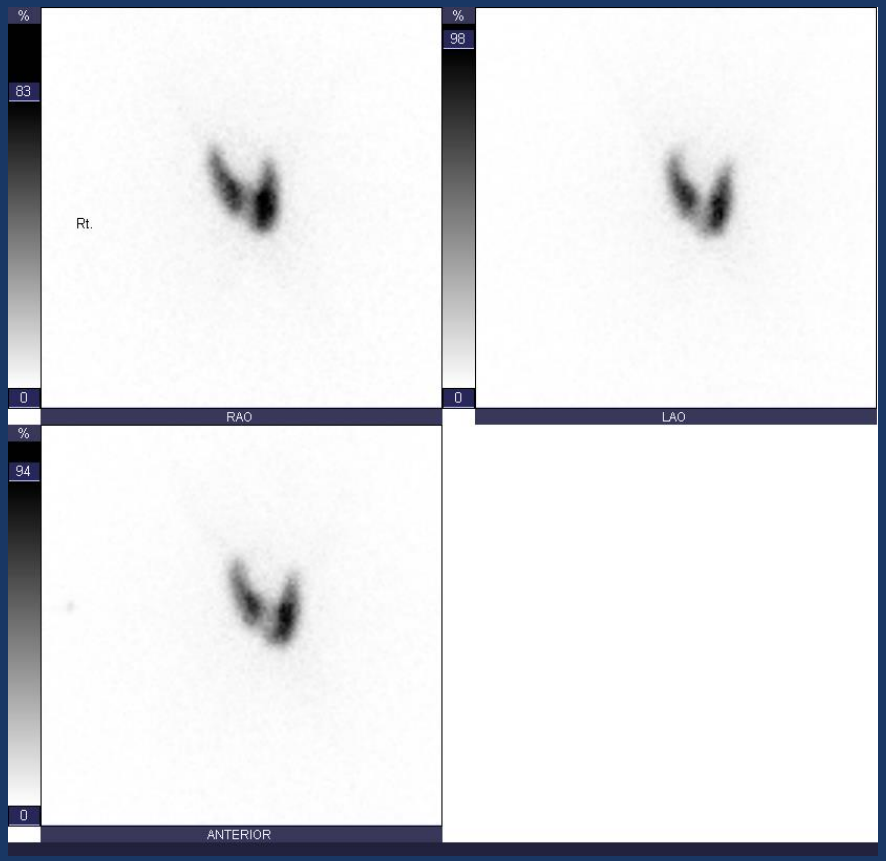
Lab							
Endocrine							
Thyroid Stimulating Hormone			<0.02 (L)	<0.02 (L)	<0.02 (L)	<0.02 (L)	
Thyroxine Free Test			2.4 (H)	1.9	2.6 (H)	4.1 (H)	
Triiodothyronine			1.81 *	1.93	2.89 (H)		
Free Triiodothyronine						15.00 (H)	
Thyroid Stimulating Immunoglobulin					1.3 *		
Thyrotropin Receptor Antibody						2.09 * (H)	
HCG, Urine Qualitative		Negative *					Negative *

16 year old female with menstrual irregularity.

TFT: low TSH, elevated free T3 and free T4

TSI: not increased

Case 1a

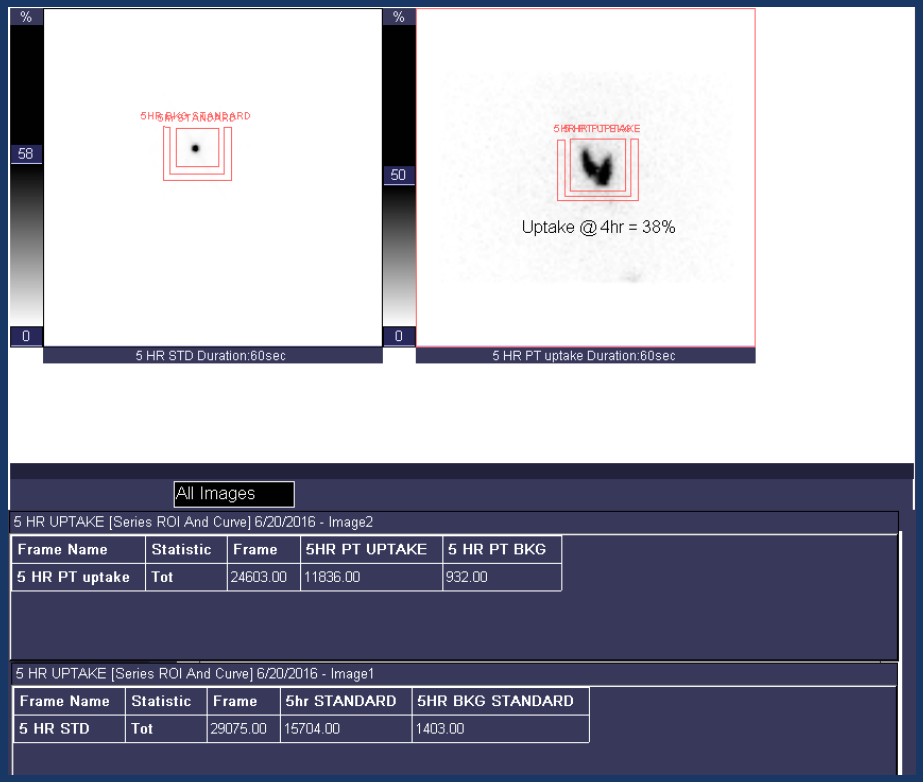


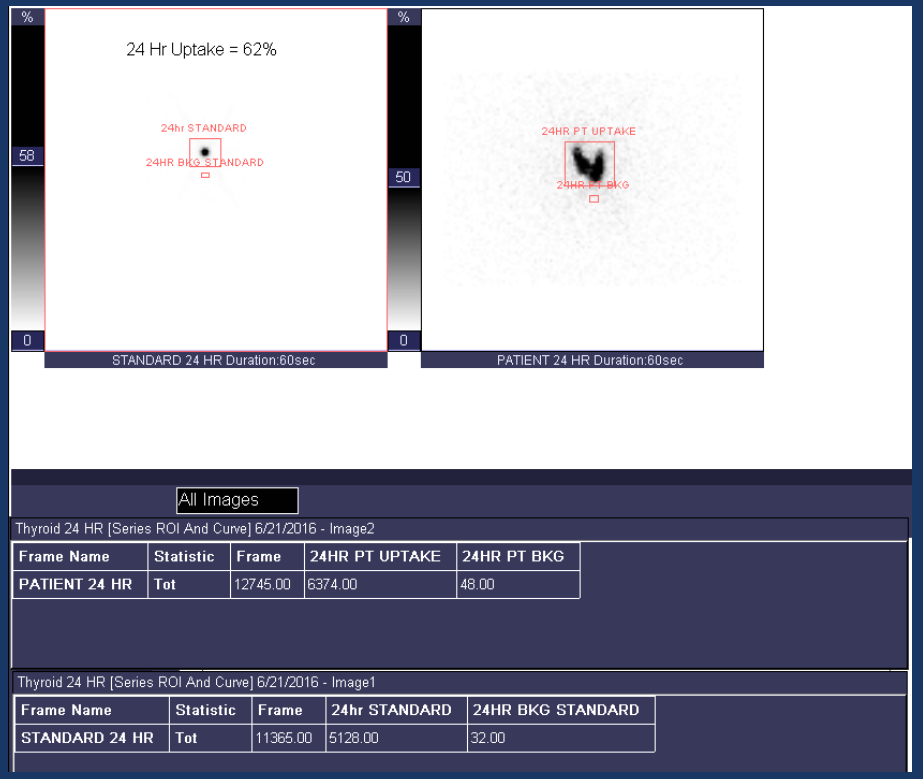
16 year old female with menstrual irregularity.

TFT: low TSH, elevated free T3 and free T4

TSI: not increased

Case 1a





4- hour uptake of 38%

24-hour uptake of 62%

- *Normal range of 5-hour uptake : 6-18 %*
- *Normal range of 24-hour uptake : 10-35 %*

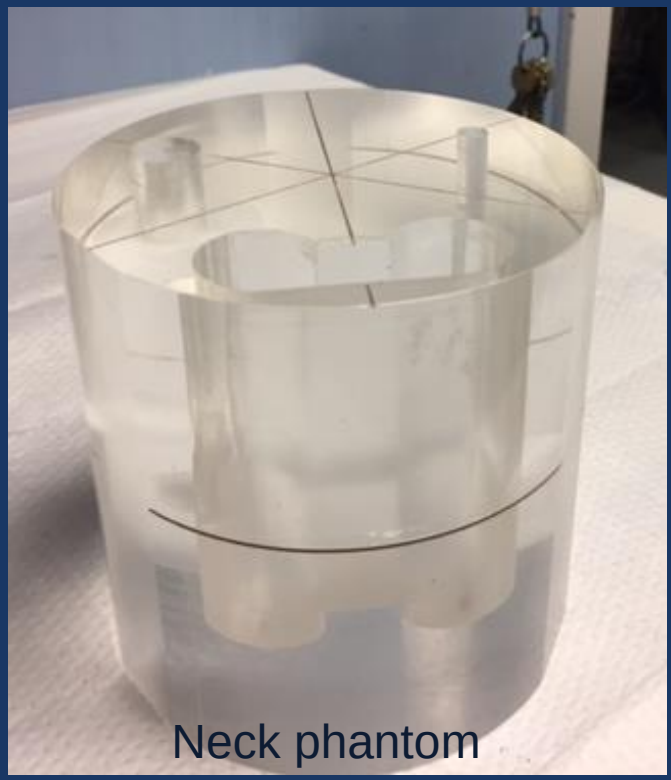
Case 1a

5 HR UPTAKE [Series ROI And Curve] 6/20/2016 - Image2

Frame Name	Statistic	Frame	5HR PT UPTAKE	5 HR PT BKG
5 HR PT uptake	Tot	24603.00	11836.00	932.00

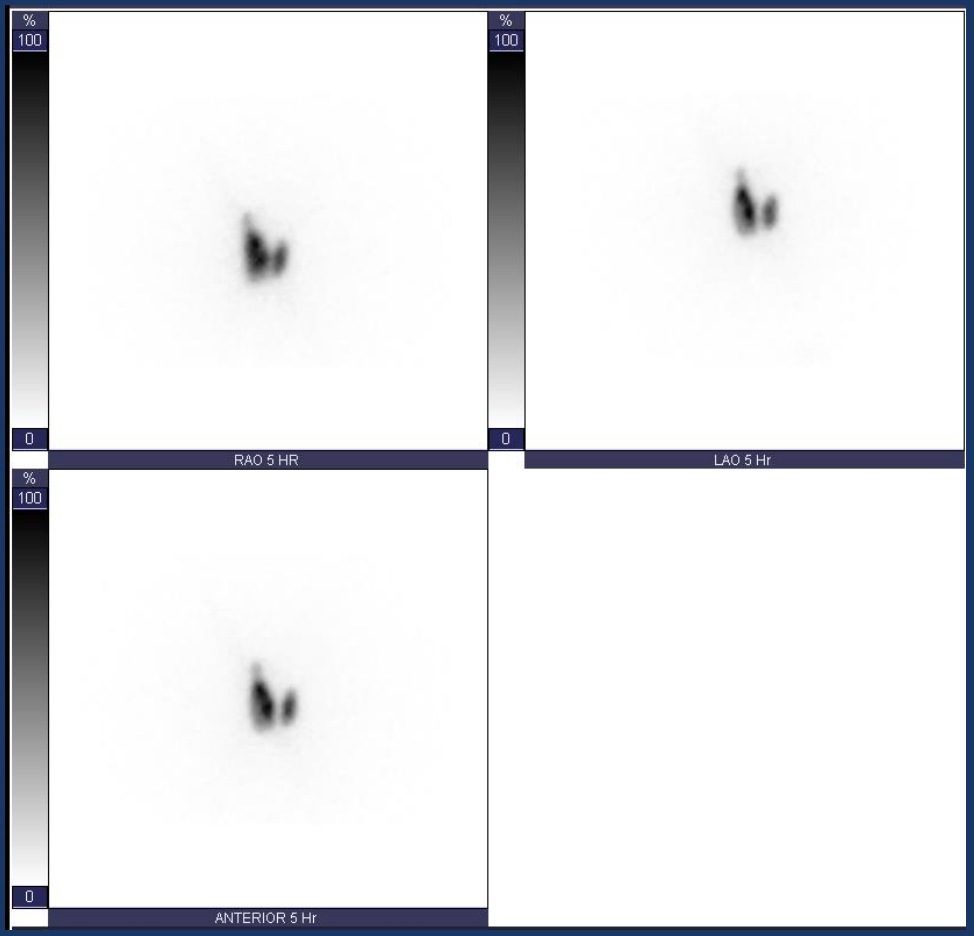
5 HR UPTAKE [Series ROI And Curve] 6/20/2016 - Image1

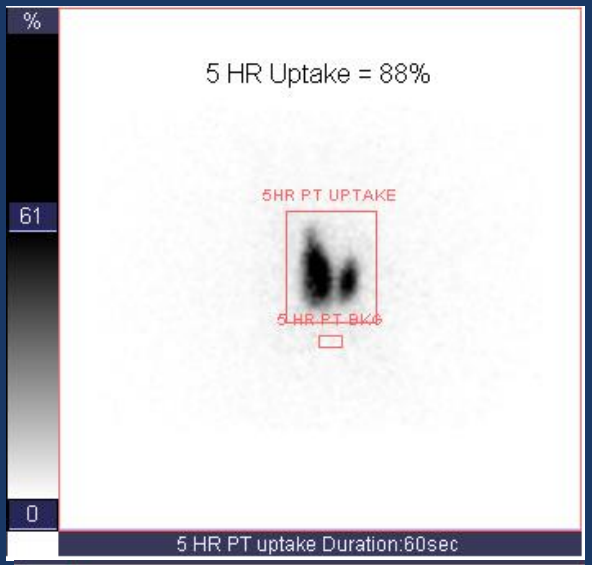
Frame Name	Statistic	Frame	5hr STANDARD	5HR BKG STANDARD
5 HR STD	Tot	29075.00	15704.00	1403.00

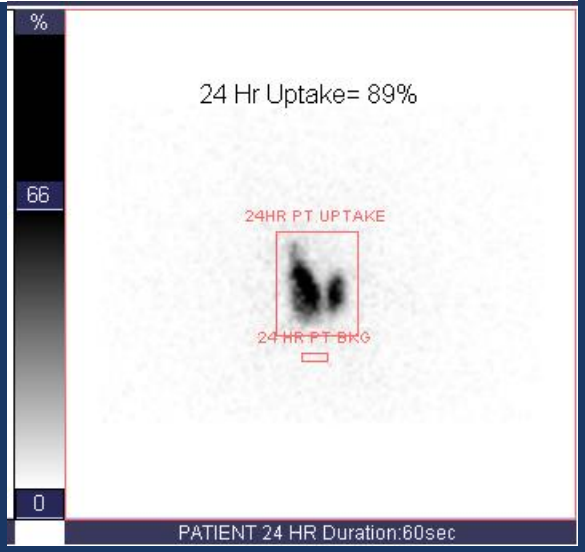

Neck phantom

$$\frac{\text{(Patient counts - patient BKG)}}{\text{(Standard counts – standard BKG)}}$$

Case 1b

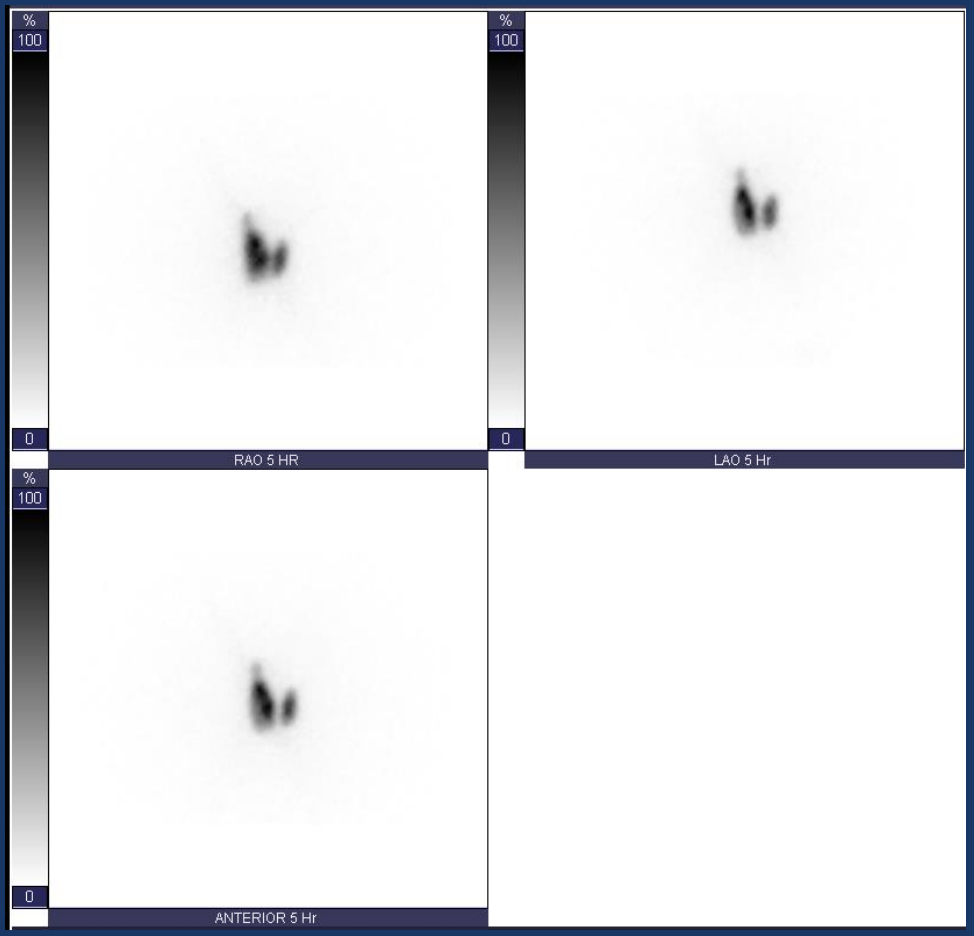


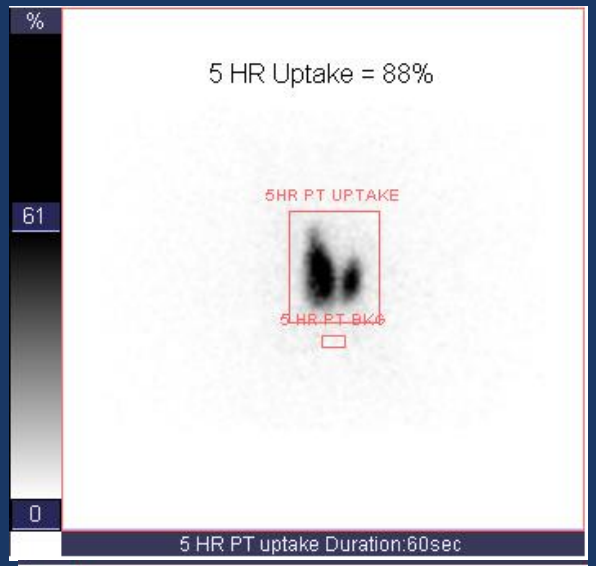


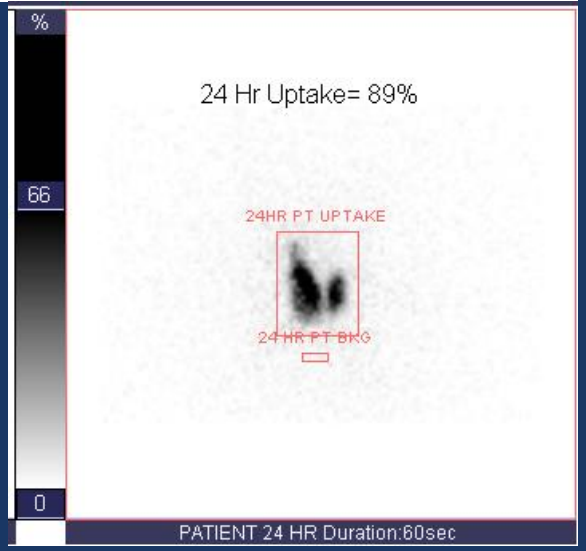


16 year old female with Graves disease diagnosed at another facility three years ago. Patient has an asymmetrically enlarged right lobe. NM thyroid scan and US were requested for further evaluation (rule out thyroid nodule).

Case 1b



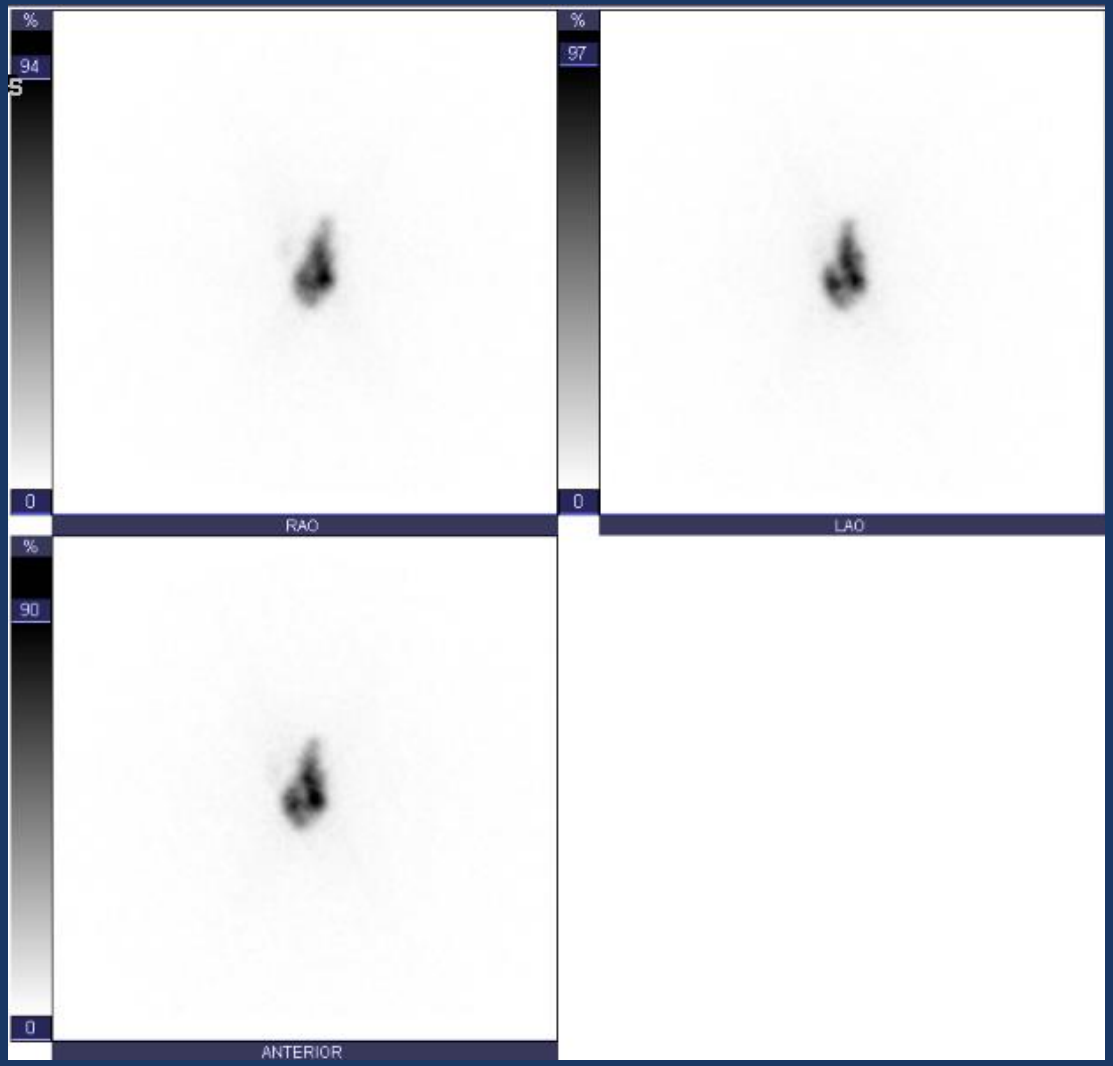


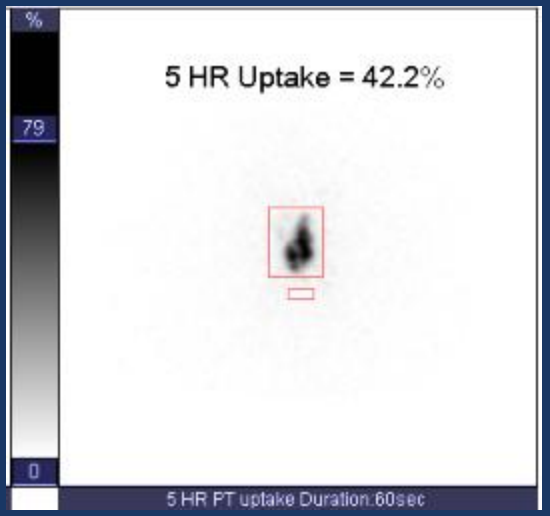


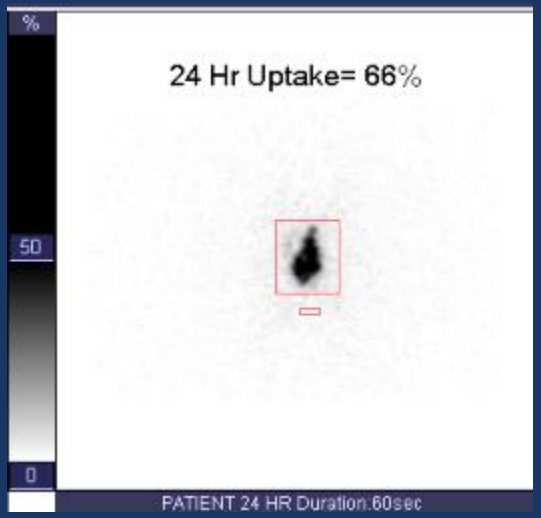
- Asymmetrically enlarged right lobe (55 vs 19 mL on US. No nodule on US)

- *Normal range of 5-hour uptake : 6-18 %*
- *Normal range of 24-hour uptake : 10-35 %*

Case 1c



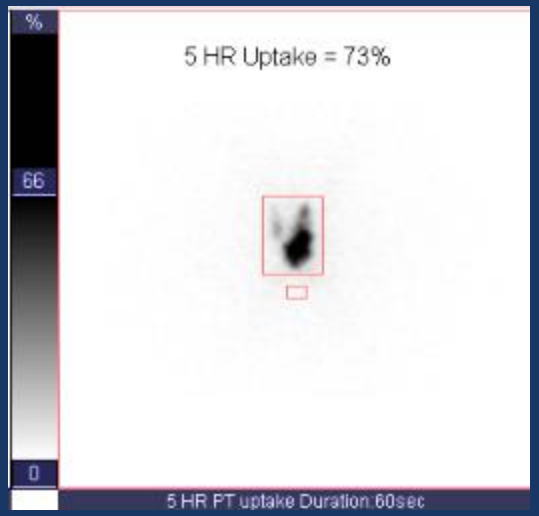


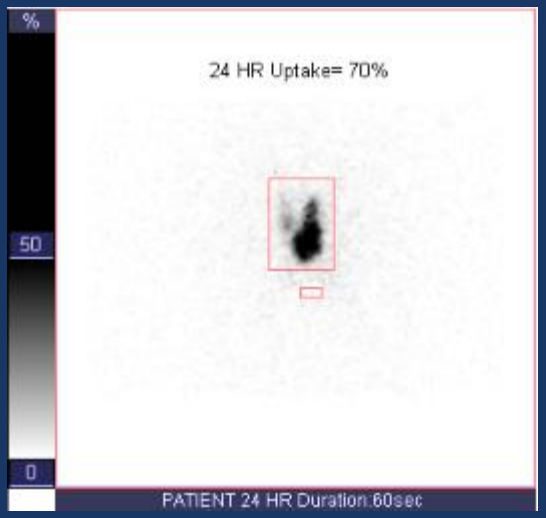


Hyperthyroidism with negative TSI

August 2013, I-123 scans and uptake were interpreted as Graves disease

Case 1c

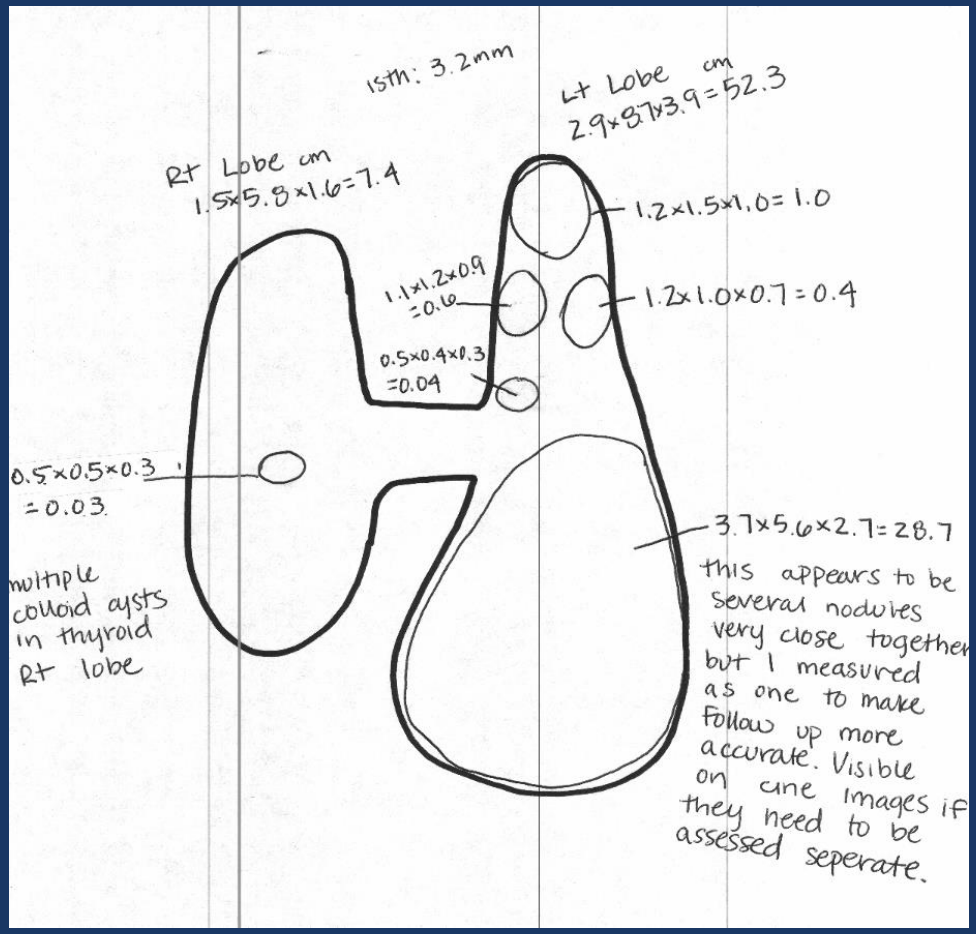




June 2015 ,I-123 scans and uptake, referred for I-131 ablation

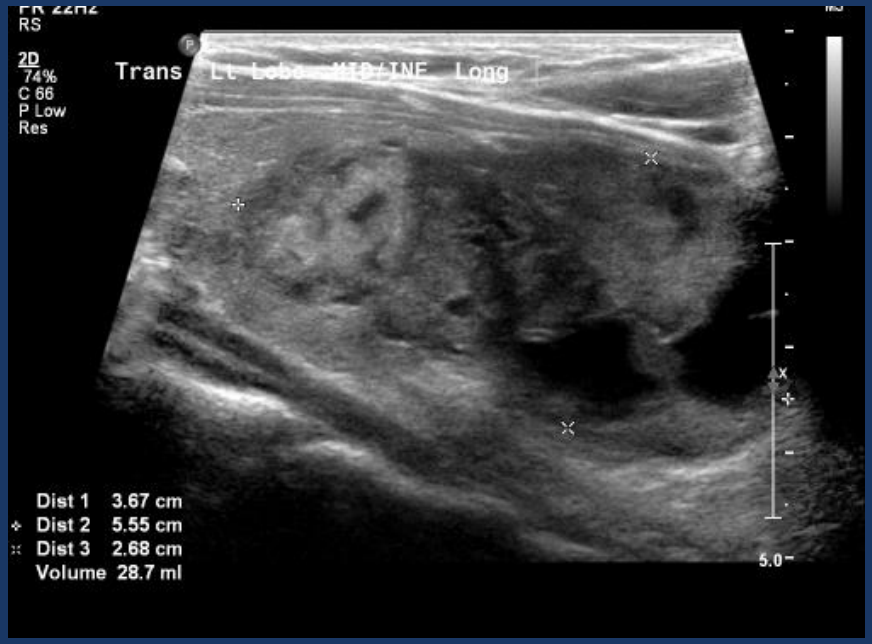
Dx.: Multinodular goiter

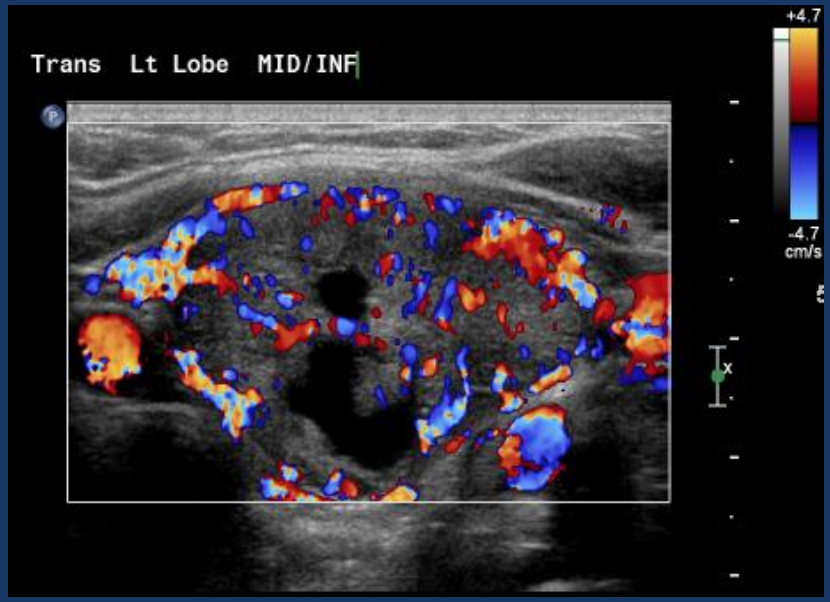
Case 2c

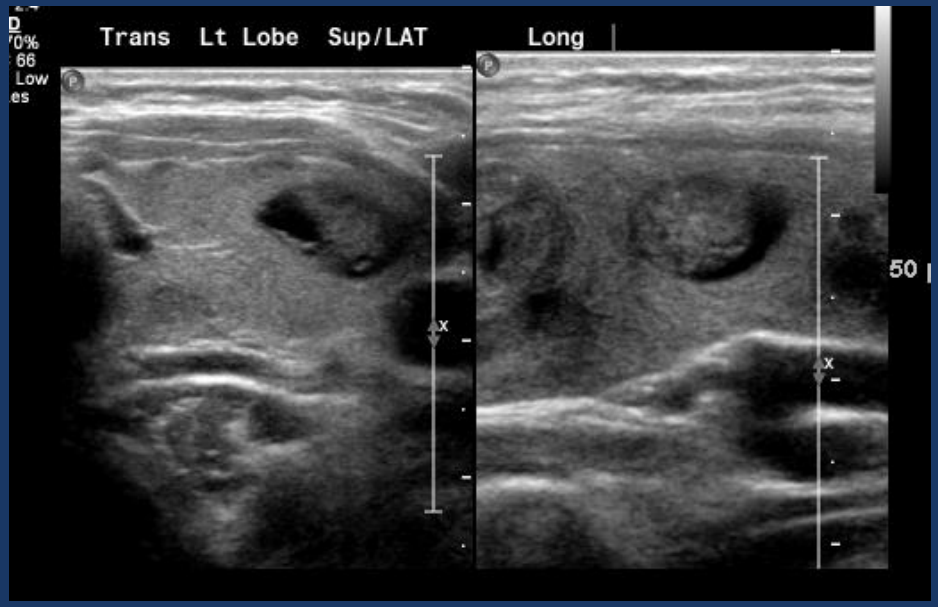


US June 2015


2D
71%
C 66
P Low
Res
Trans Lt Lobe MID/INF
Dist 1 3.67 cm


RS
2D
74%
C 66
P Low
Res
Trans Lt Lobe MID/INF Long
Dist 1 3.67 cm
Dist 2 5.55 cm
Dist 3 2.68 cm
Volume 28.7 ml
5.0

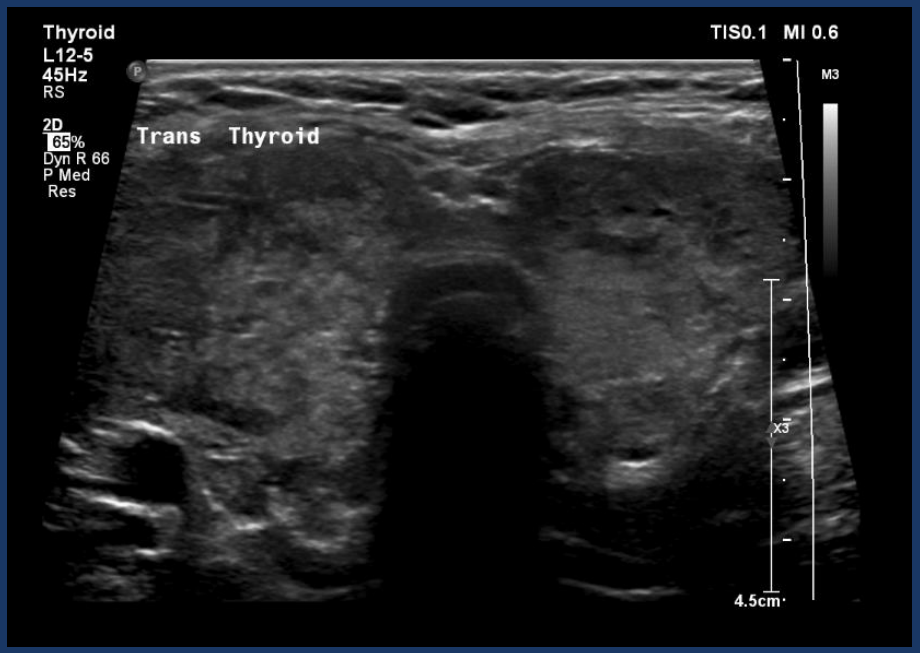

Trans Lt Lobe MID/INF
+4.7
-4.7
cm/s

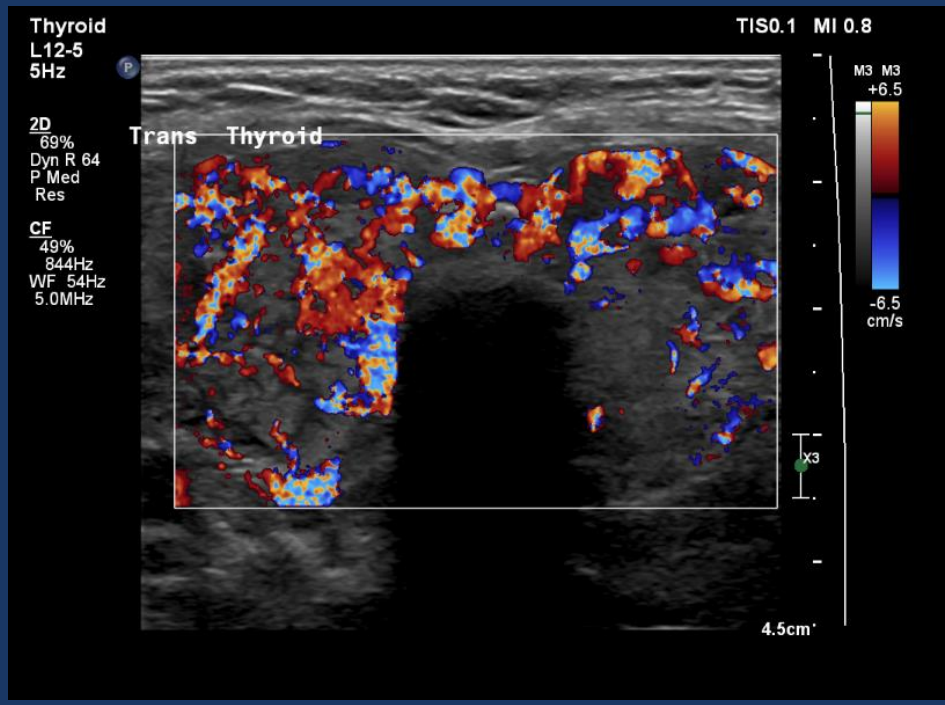

Trans Lt Lobe Sup/LAT
Long
50

Case 1c

- FNAs and biopsy: suggestive of benign follicular nodule
- Surgery: left hemithyroidectomy
- Pathology: nodular hyperplasia with dominant nodule

Case 2d

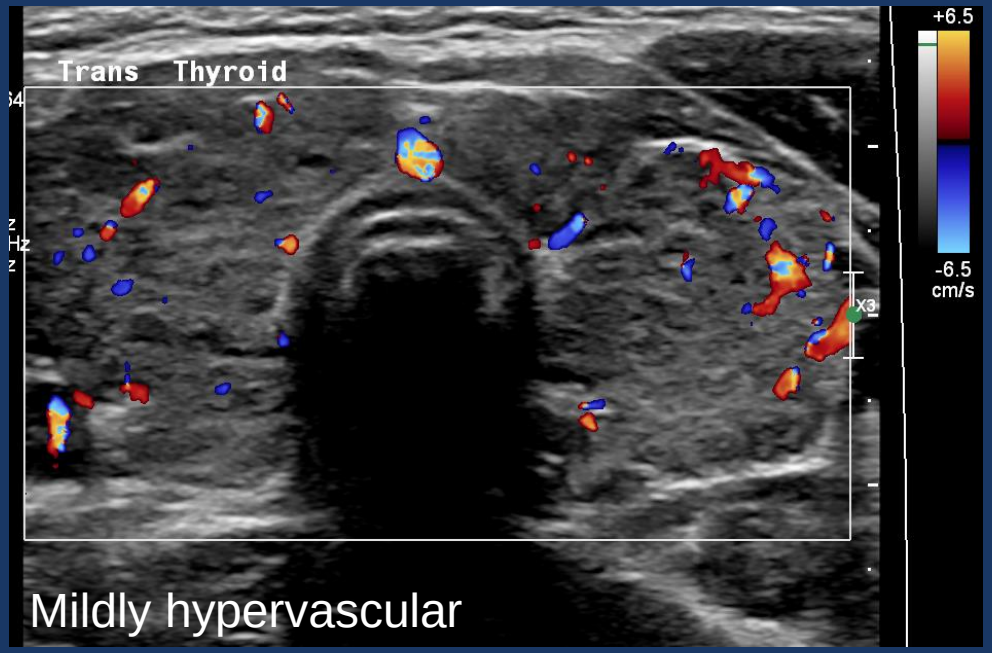




Graves' disease referred for I-131 ablation

- right lobe measures 4.3 x 7.0 x 2.5 cm (39 mL; previously 55.7 mL)
- left lobe measures 2.2 x 2.1 x 6.1 cm (15.1 mL; previously 18.9 mL)
- Interval decrease in size → candidate for I-131 ablation (weight should be < 80 grams)

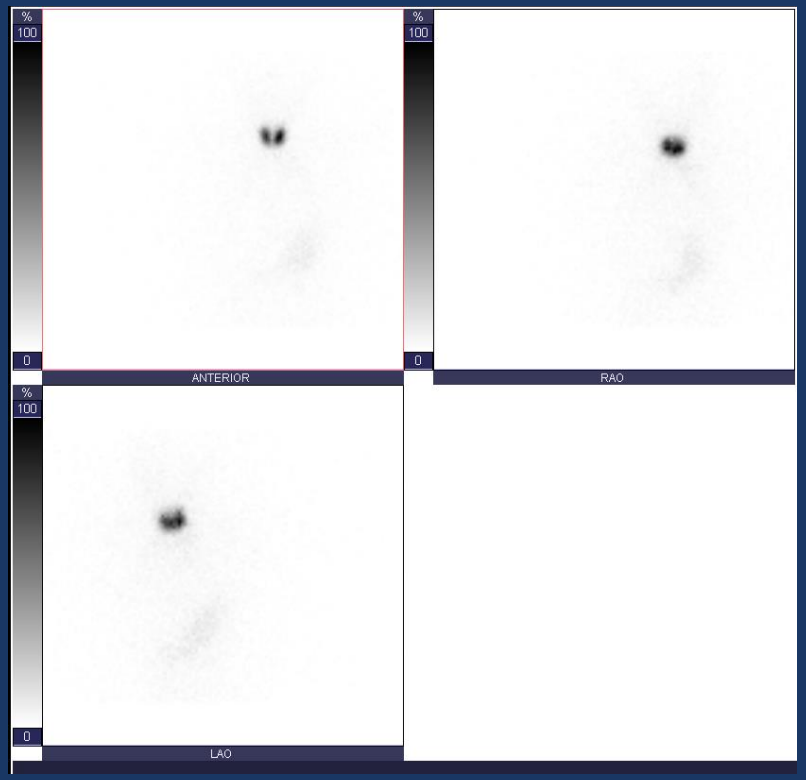
Case 2d- comparison

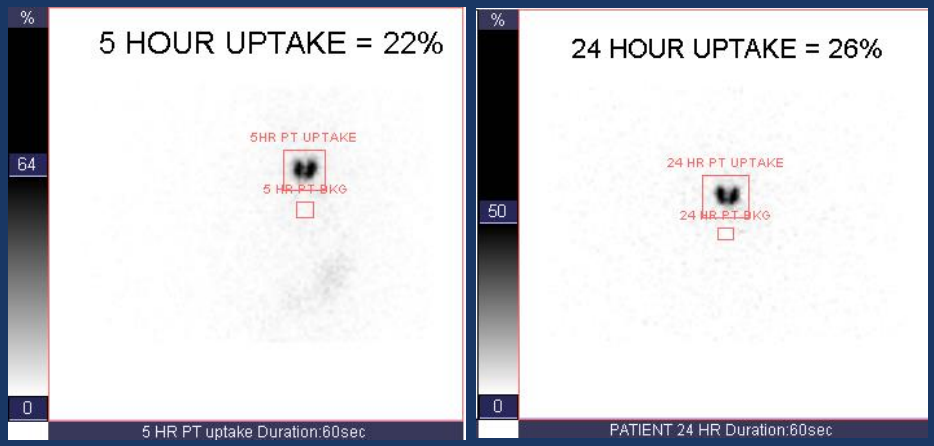


Hashimoto's thyroiditis, euthyroid

- 18-year old female with FH of thyroid diseases, normal TSH and T4, and positive thyroid autoantibodies (thyroid peroxidase and TG)

Case 2e





- *Normal range of 5-hour uptake : 6-18 %*
- *Normal range of 24-hour uptake : 10-35 %*

- 2 year old male with obstructive sleep apnea, s/p tonsillectomy. Tachycardic during sleep study.
- Abnormal TFTs. Diagnosed with Graves at 2 years of age. NM study at 2 years of age
- Orbitopathy. Referred to Oto for thyroidectomy at 8 years of age

Graves Disease: Treatment

- Antithyroid drug - methimazole
- I-131 ablation
  - May be used as first line treatment
- Total thyroidectomy

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

Case 2 (series)

Hyperthyroidism

I-131 thyroid ablation

THYROID
Volume 26, Number 10, 2016

DOI: 10.1089/thy.2016.0229

SPECIAL ARTICLE

2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis

Douglas S. Ross,[1*] Henry B. Burch,[2**] David S. Cooper,[3] M. Carol Greenlee,[4] Peter Laurberg,[5†] Ana Luiza Maia,[6] Scott A. Rivkees,[7] Mary Samuels,[8] Julie Ann Sosa,[9] Marius N. Stan,[10] and Martin A. Walter[11]

Background: Thyrotoxicosis has multiple etiologies, manifestations, and potential therapies. Appropriate treatment requires an accurate diagnosis and is influenced by coexisting medical conditions and patient preference. This document describes evidence-based clinical guidelines for the management of thyrotoxicosis that would be useful to generalist and subspecialty physicians and others providing care for patients with this condition.
Methods: The American Thyroid Association (ATA) previously cosponsored guidelines for the management of thyrotoxicosis that were published in 2011. Considerable new literature has been published since then, and the ATA felt updated evidence-based guidelines were needed. The association assembled a task force of expert clinicians who authored this report. They examined relevant literature using a systematic PubMed search supplemented with additional published materials. An evidence-based medicine approach that incorporated the knowledge and experience of the panel was used to update the 2011 text and recommendations. The strength of the recommendations and the quality of evidence supporting them were rated according to the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation Group.
Results: Clinical topics addressed include the initial evaluation and management of thyrotoxicosis; management

2016

■ **RECOMMENDATION 69**

If RAI therapy is chosen as treatment for GD in children, sufficient RAI should be administered in a single dose to render the patient hypothyroid.

Strong recommendation, moderate-quality evidence.

The goal of RAI therapy for GD is to induce hypothyroidism, rather than euthyroidism, because lower administered activities of RAI result in residual, partially irradiated thyroid tissue that is at increased risk for thyroid neoplasm development (351). Because of an increased risk of thyroid nodules and cancer associated with low-level thyroid irradiation in children (314,352–354) and poor remission rates [illegible] low-administered activities of RAI (88–90), it is [illegible] portant that RAI activities >150 μCi (>5.55 MBq/g) rather than smaller activities of RAI be administered to achieve hypothyroidism (312). With large glands (50–80 g), RAI activities of ^{131}I 200–300 μCi/g (7.4–11.1 MBq/g) may be needed (349). The administered activity of RAI to patients with very large goiters is high, and a tendency exists to underestimate the size of the gland (and thereby administer insufficient RAI activities to these patients) (90). Therefore, surgery may be preferable to RAI in children with goiters larger than 80 g.

Physicians at some centers administer a fixed dose of about 15 mCi RAI to all children (350), whereas others calculate the activity from estimation or direct measurement of gland size and ^{123}I uptake (349). To assess thyroid size, particularly in the setting of a large gland, ultrasonography is recommended (355). There are no data comparing outcomes of fixed versus calculated activities in children; in adults, similar outcomes have been reported with the two approaches (356). One potential advantage of calculated versus fixed dosing is that it may be possible to use lower administered activities of RAI, especially when uptake is high and the thyroid is small.

- > 150 microCi/gm
- 50 – 80: grams: 200-300 microCi/gm
- > 80 grams: surgery

OR

- Fixed dose of 15 mCi

At SCH we calculate using 300 microCi/gm and do not administer doses < 10 mCi

2016

[R] If thyroidectomy is chosen as treatment for GD in children, how should it be accomplished?

[R1] Preparation of children with GD for thyroidectomy

■ **RECOMMENDATION 70**

Children with GD undergoing thyroidectomy should be rendered euthyroid with the use of MMI. A KI-containing preparation should be given in the immediate preoperative period.

Strong recommendation, low-quality evidence.

Surgery is an acceptable form of therapy for GD in children. Thyroidectomy is the preferred treatment for GD in young children (<5 years) when definitive therapy is required, and the surgery can be performed by a high-volume thyroid surgeon. In individuals with large thyroid glands (>80 g), the response to RAI may be poor (88,90) and surgery also may be preferable for these patients. When performed, near-total or total thyroidectomy is the recommended procedure (363).

Technical remarks: MMI is typically given for 1–2 months in preparation for thyroidectomy. KI (50 mg iodide/drop) can be given as 1–2 drops (i.e., 0.05–0.1 mL) three times daily for 10 days before surgery. SSKI can be mixed in juice or milk.

■ **RECOMMENDATION 71**

If surgery is chosen as therapy for GD in children, total or near-total thyroidectomy should be performed.

Strong recommendation, moderate-quality evidence.

2016

When RAI activities >150 μCi/g (>5.55 MBq/g) are administered, hypothyroidism rates are about 95% (88,339, 349). While there are reports that hyperthyroidism can relapse in pediatric patients rendered hypothyroid with RAI, this is very infrequent.

Technical remarks: RAI is excreted by saliva, urine, perspiration, tears, and stool. Significant radioactivity is retained within the thyroid for several days. It is therefore important that patients and families be informed of and adhere to local radiation safety recommendations following RAI therapy. After RAI therapy, T_3, T_4, and/or free T_4 levels should be obtained every month. Because TSH levels may remain suppressed for several months after correction of the hyperthyroid state, TSH determinations may not be useful in this setting for assessing hypothyroidism. Hypothyroidism typically develops by 2–3 months posttreatment (333,349,350), at which time levothyroxine should be prescribed.

2016

Special Considerations

- Contraindications
  - Less than 5 years of age
  - Pregnant or breast feeding
  - Thyroid > 80 grams
- Special considerations
  - Inability to swallow capsule
  - 5 to 10 year old
  - Thyroid orbitopathy

consider treatment if the calculated I-131 administered activity is <10 mCi or there are particular concerns regarding a surgical thyroidectomy

[O] How should GD be managed in children and adolescents?

[O1] General approach

- **RECOMMENDATION 58**

  Children with GD should be treated with MMI, RAI therapy, or thyroidectomy. RAI therapy should be avoided in very young children (<5 years). RAI therapy in children is acceptable if the activity is >150 μCi/g (5.55 MBq/g) of thyroid tissue, and for children between 5 and 10 years of age if the calculated RAI administered activity is <10 mCi (<473 MBq). Thyroidectomy should be chosen when definitive therapy is required, the child is too young for RAI, and surgery can be performed by a high-volume thyroid surgeon.

  Strong recommendation, moderate-quality evidence.

2016

[Q] If RAI is chosen as treatment for GD in children, how should it be accomplished?

[Q1] Preparation of pediatric patients with GD for RAI therapy

- **RECOMMENDATION 68**
  We suggest that children with GD having total T_4 levels of >20 μg/dL (260 nmol/L) or free T_4 >5 ng/dL (60 pmol/L)

who are to receive RAI therapy be pretreated with MMI and β-adrenergic blockade until total T_4 and/or free T_4 normalize before proceeding with RAI treatment.

Weak recommendation, low-quality evidence.

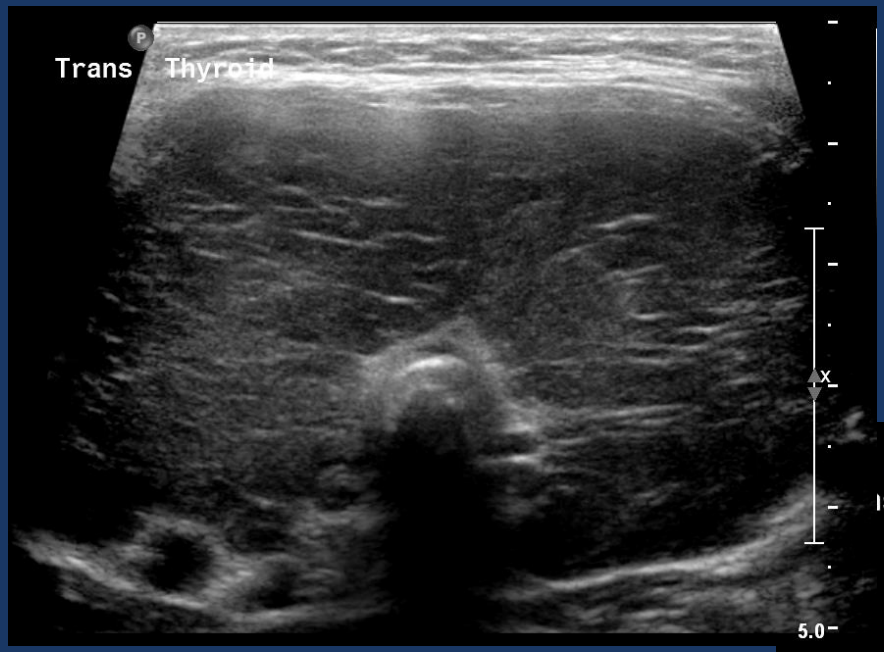
2016

Steps in Ordering I-131 Ablation

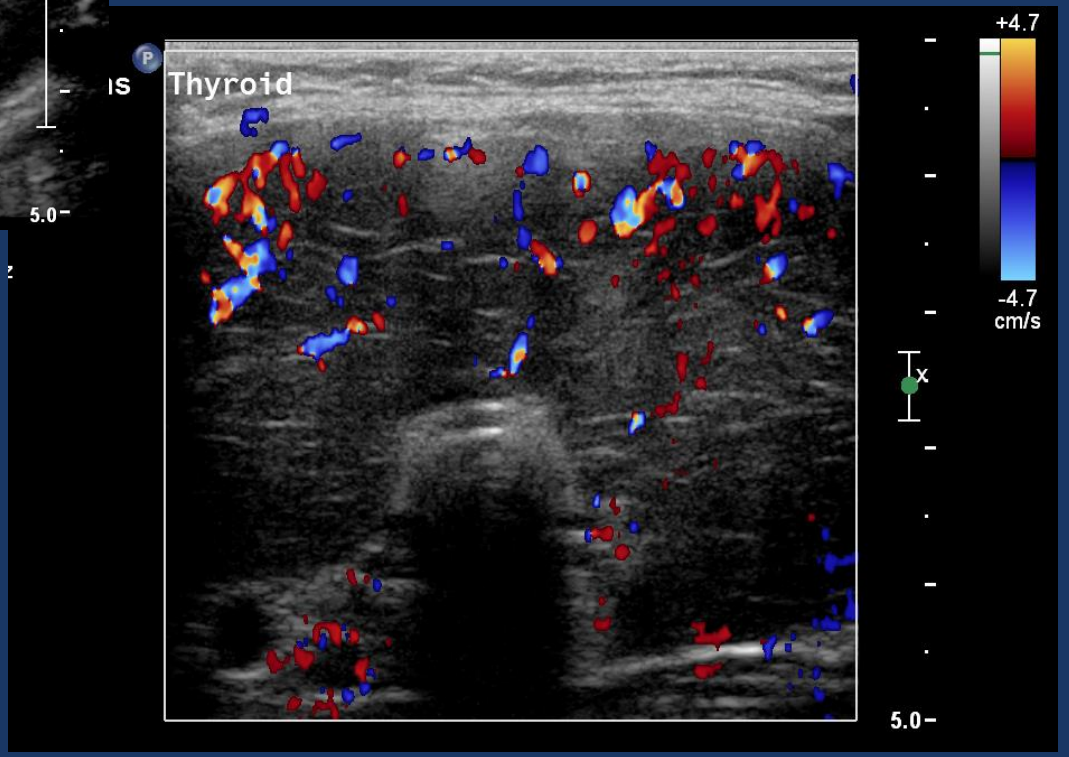
- Order set, “Radioiodine Treatment for Hyperthyroidism”
  - If thyroid deemed to be larger than 80 grams → confirm with thyroid US prior to ordering ablation
  - If thyroid orbitopathy is present → ophthalmology referral prior to ablation to determine need for steroids (IV methylprednisone 10-12 weeks, first one before ablation)

Component	Status	Details
Radioiodine Treatment for Hyperthyroidism Plan (Planned Pending)		
Ordersets		
Laboratory		
Please order HCG, Pregnancy test for female patient 12 years and older within 24 hours of Radioiodine Treatment for Hyperthyroidism		
HCG, Urine Pregnancy Test		Urine, Routine, Order for future visit, Within 24 hours of Radioiodine Treatment for Hyperthyroidism
Lab orders need to be scheduled at the same time as the Return to Clinic visit		
Thyroid Stimulating Hormone (TSH)		Blood, Routine, Order for future visit, 2-4 weeks after radioiodine treatment date
Free Triiodothyronine (Free T3)		Blood, Routine, Order for future visit, 2-4 weeks after radioiodine treatment date
Thyroxine Free (Free T4)		Blood, Routine, Order for future visit, 2-4 weeks after radioiodine treatment date
Radiology		
NM Thyroid Scan w I-123 w F/U		Reason: Radioiodine Treatment for Hyperthyroidism
NM Therapy by oral admin		Reason: Radioiodine Treatment for Hyperthyroidism
US Thyroid Sonogram		Reason: Radioiodine Treatment for Hyperthyroidism
Nursing		
Clinician radiology communication (Communication, Radiology)		Please request family to schedule safety preparation meeting 2 weeks before treatment, Requested date/time: T;N
Discharge Information		
Return to Clinic		Clinic: Endocrine, Requested return: 2 months, Schedule after diagnostic test(s), radioiodine treatment

Case 2a



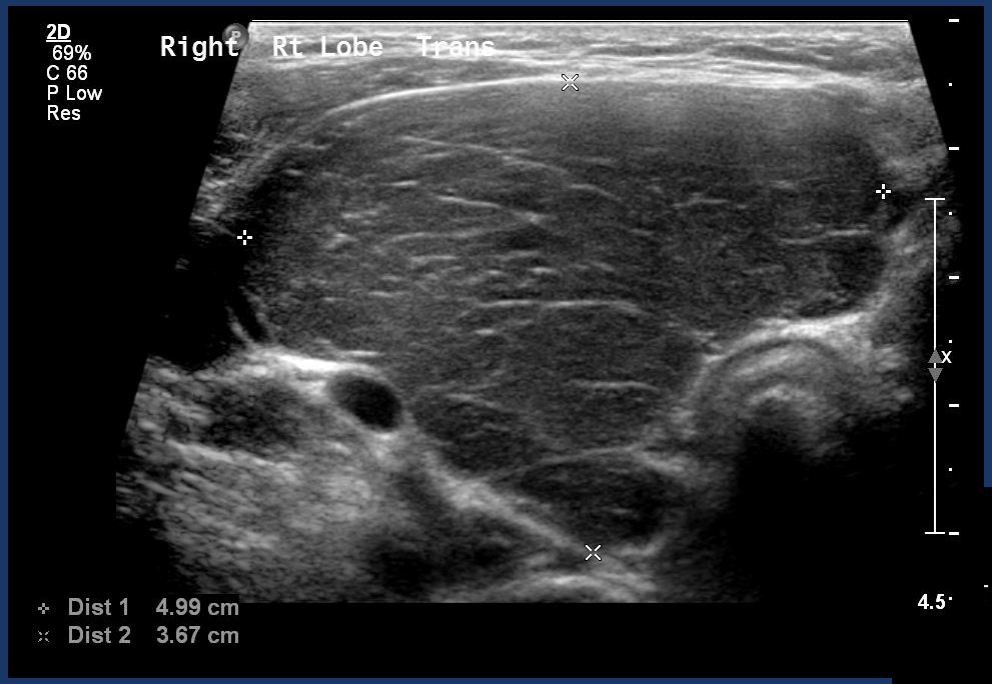
Normal volume: Neonate 0.4-1.4 mL,
↑ by 1.0-1.3 mL for each 10 kg weight up to normal volume of 10-11 (± 3-4) mL in adults



Graves' disease, 11-year old female

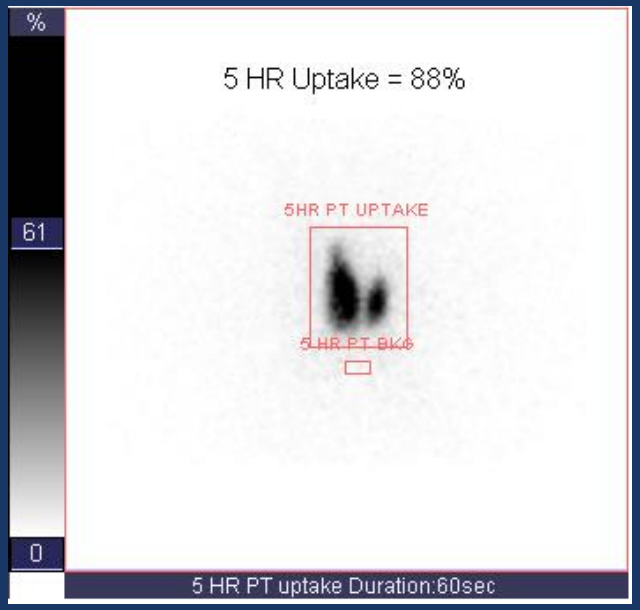
- Diffusely heterogeneous echogenicity
- Doppler: hypervascular ("thyroid inferno")

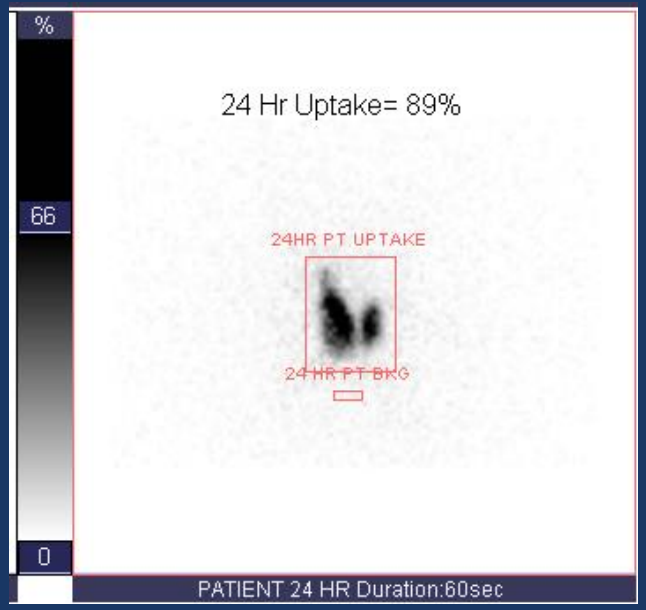
Case 2a



- Right lobe: 5.0 x 3.7 x 8.2 cm, 78.8 mL
- Left lobe: 3.9 x 3.5 x 8.5 cm, 61 mL
- Gland is too large for I-131 ablation → surgery

Case 2b





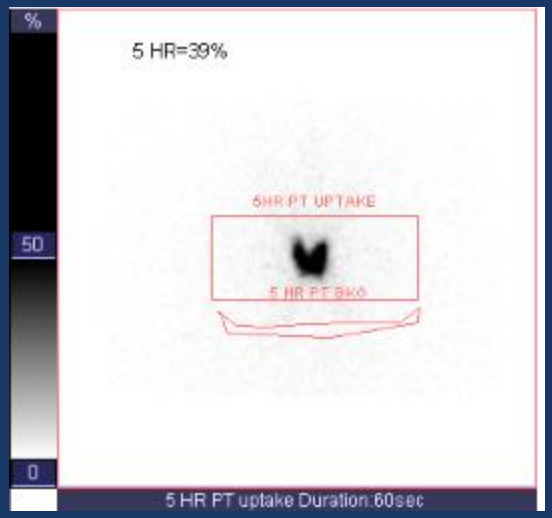
- Estimated thyroid gland volume of 54 mL and weight of 54 grams
- Target radiation of 300 microCi per gram of thyroid tissue
- Oral dose of I-131 of 18.2 milliCi was calculated

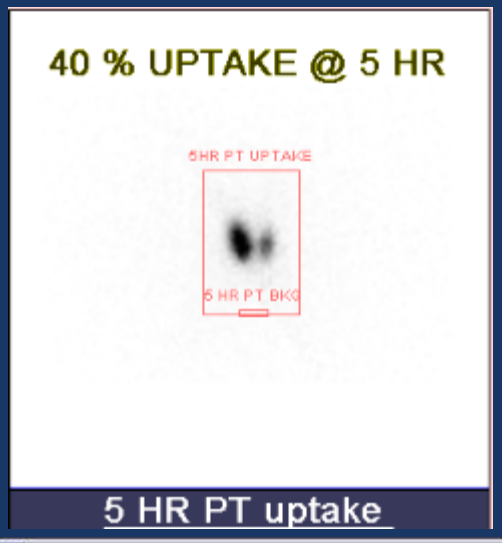
I-131 dose = (thyroid weight x 300) / (24-hr uptake x 1000)

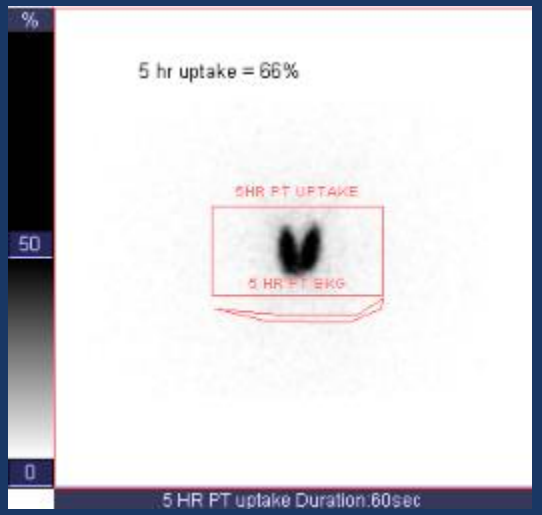
I-131 dose = (54 x 300) / (0.89 x 1000)

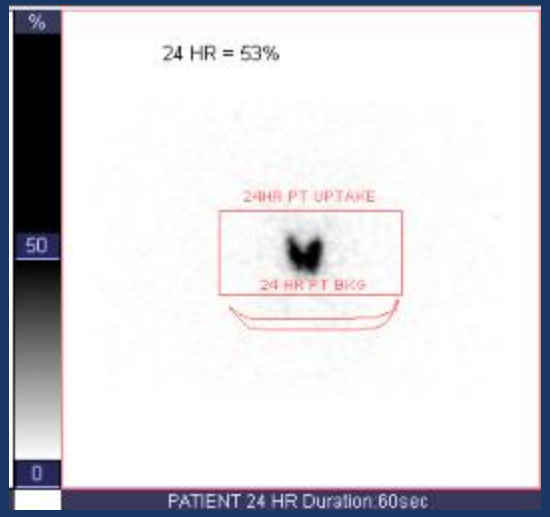
I-131 dose = 18.2 milliCi

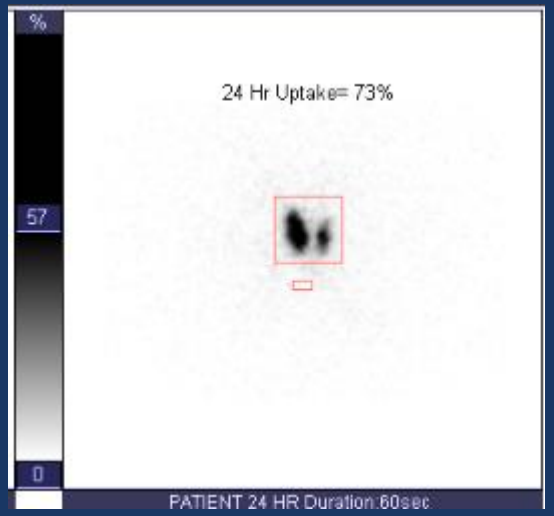
Cases 2c – 3 different cases

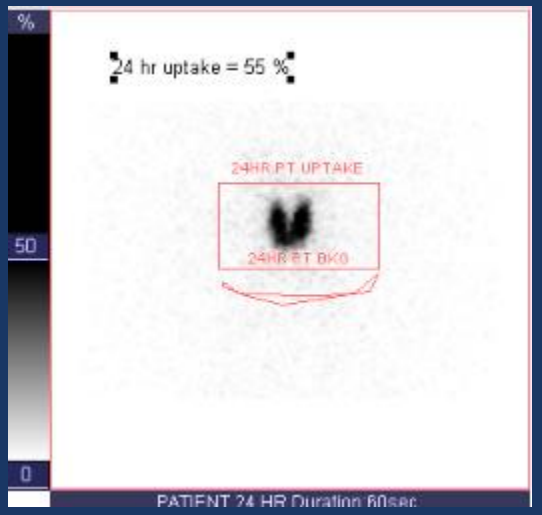












17.3 gm weight
Calculated at 9.8 milliCi
Administered 11.7 millici

35.1 gm weight
Calculated at 14.4 milliCi
Administered 15.1 millici

35 gm weight
Calculated at 19.1 milliCi
Administered 19.5 millici

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

Case 3 (series)

Graves disease with incidental thyroid nodules on US

- US performed prior to I-131 ablation to estimate thyroid weight

[G] How should thyroid nodules be managed in patients with GD?

■ **RECOMMENDATION 33**

If a thyroid nodule is discovered in a patient with GD, the nodule should be evaluated and managed according to recently published guidelines regarding thyroid nodules in euthyroid individuals.

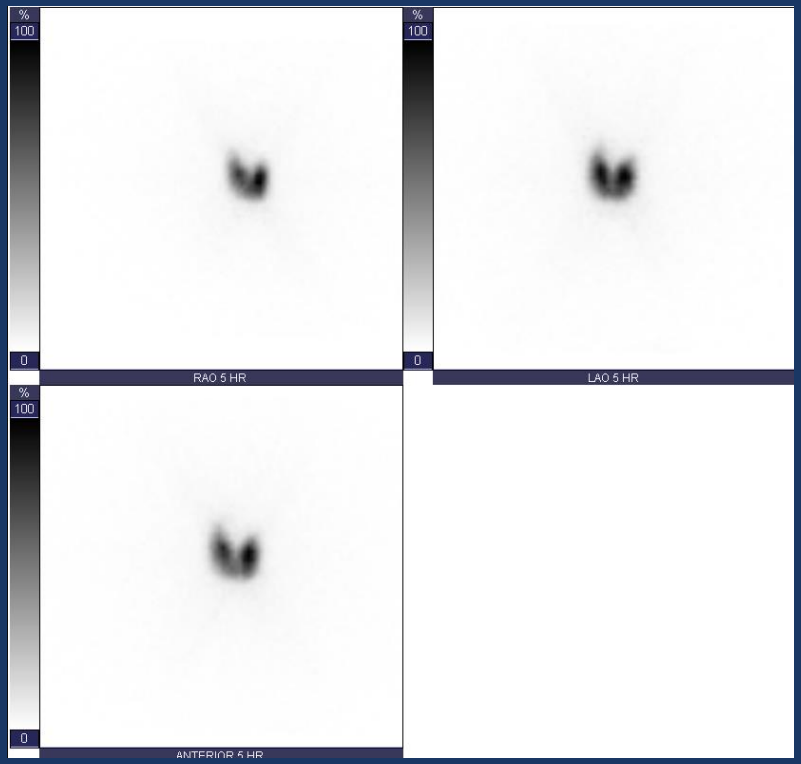
Strong recommendation, moderate-quality evidence.

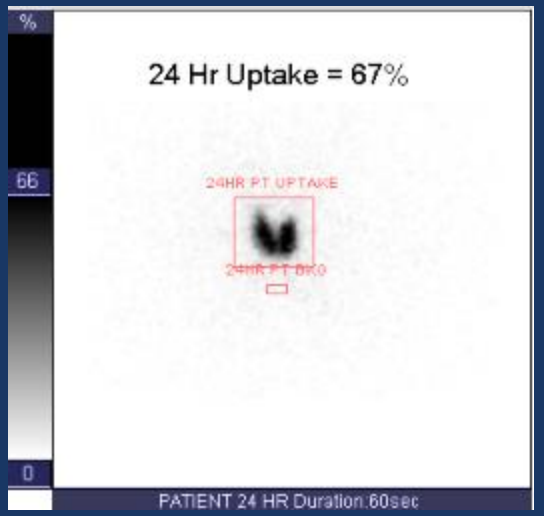
Thyroid cancer occurs in GD with a frequency of 2% or less (221). Thyroid nodules larger than 1–1.5 cm should be evaluated before RAI therapy. If a RAI scan is performed, any nonfunctioning or hypofunctioning nodules should be considered for fine-needle aspiration because they may have a higher probability of being malignant (62). If the cytopathology is suspicious or diagnostic of malignancy, surgery is advised after normalization of thyroid function with ATDs. Surgery should also be considered for indeterminate cytology. Disease-free survival at 20 years is reported to be 99% after thyroidectomy for GD in patients with small (≤1 cm) coexisting thyroid cancers (222).

The use of thyroid ultrasonography in all patients with GD has been shown to identify more nodules and cancer than does palpation and ^{123}I scintigraphy. However, since most of these cancers are papillary microcarcinomas with minimal clinical impact, further study is required before routine ultrasound (which may lead to surgery) can be recommended (223,224).

Technical remarks: The ATA recently published updated management guidelines for patients with thyroid nodules and differentiated thyroid cancer (225).

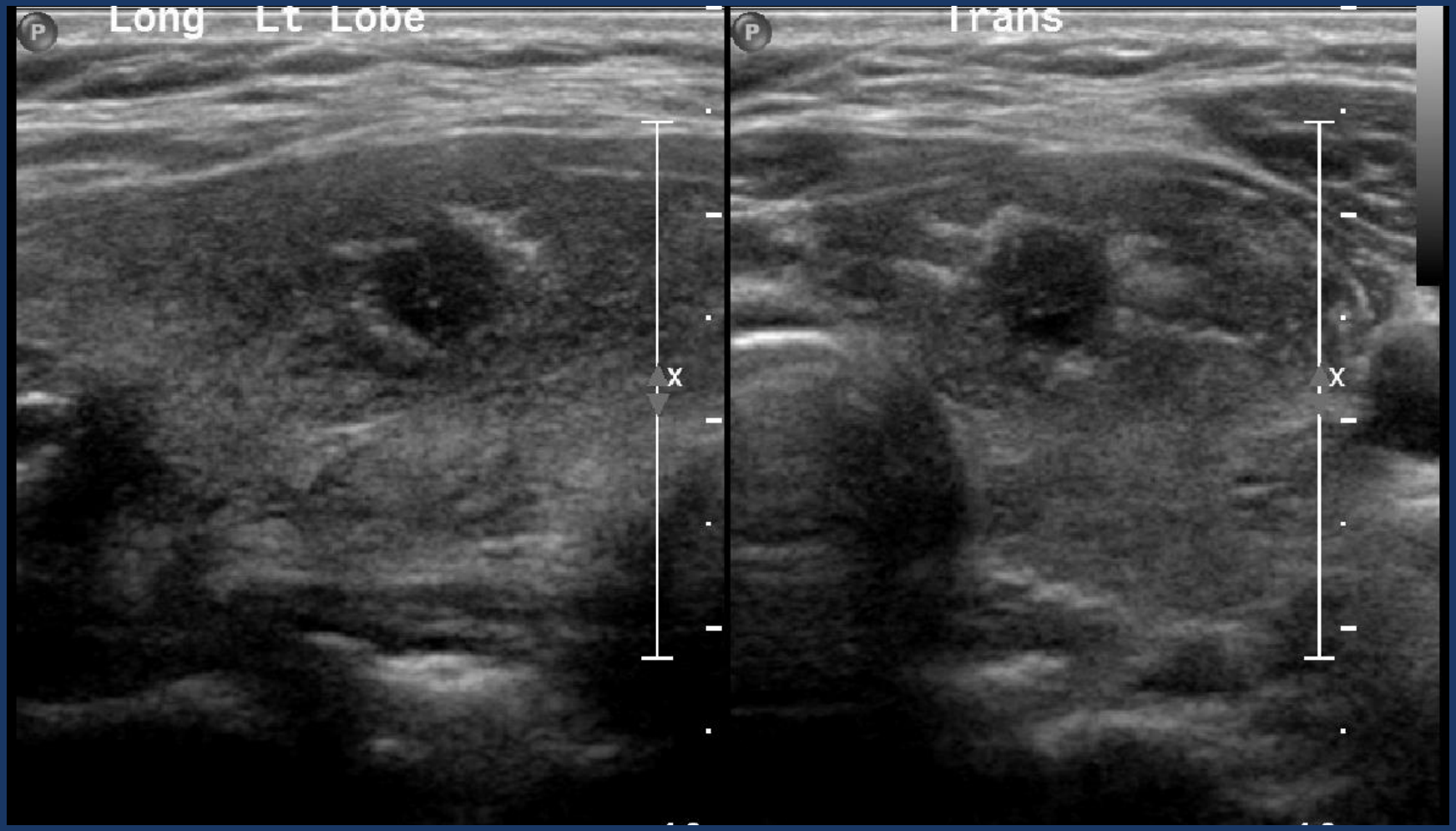
Case 3a





17-year old female with Graves' disease referred for I-131 ablation

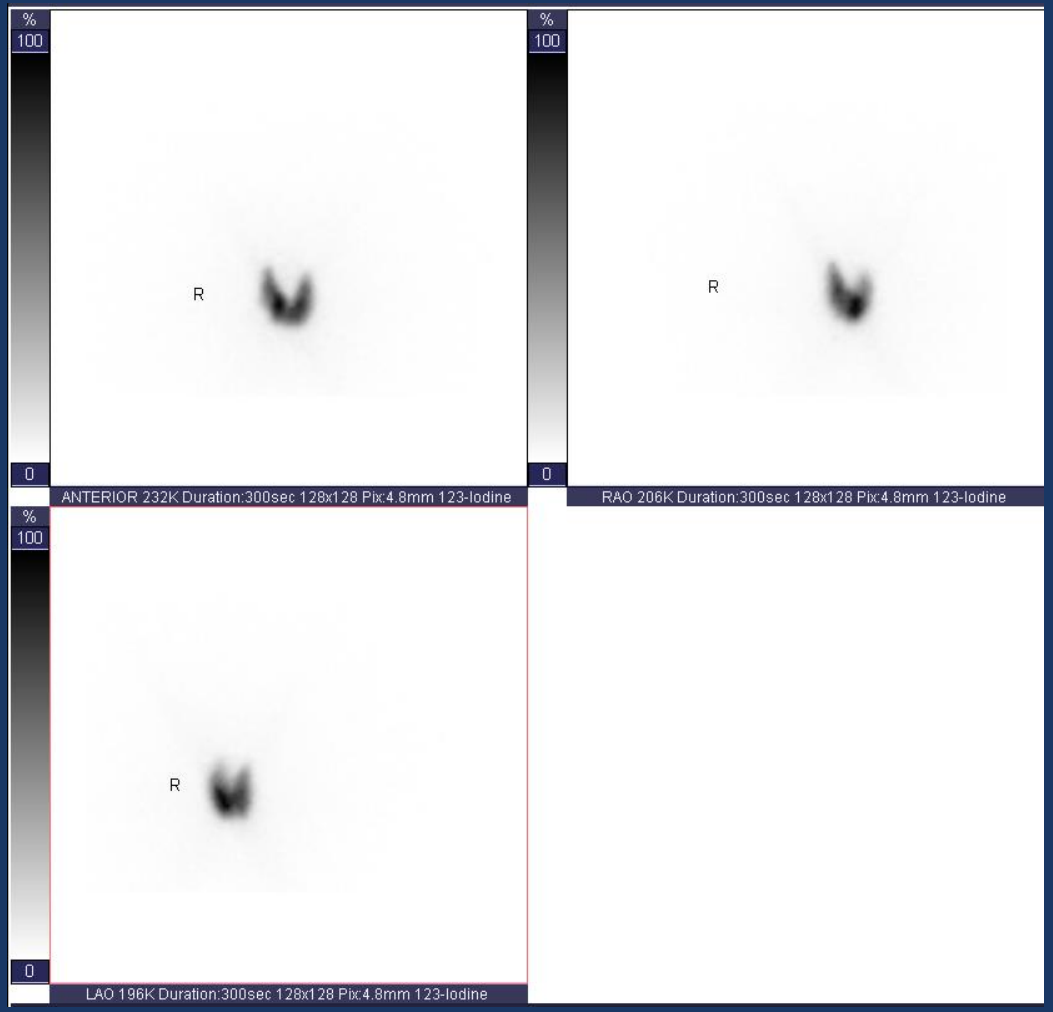
Case 3a, October 2013

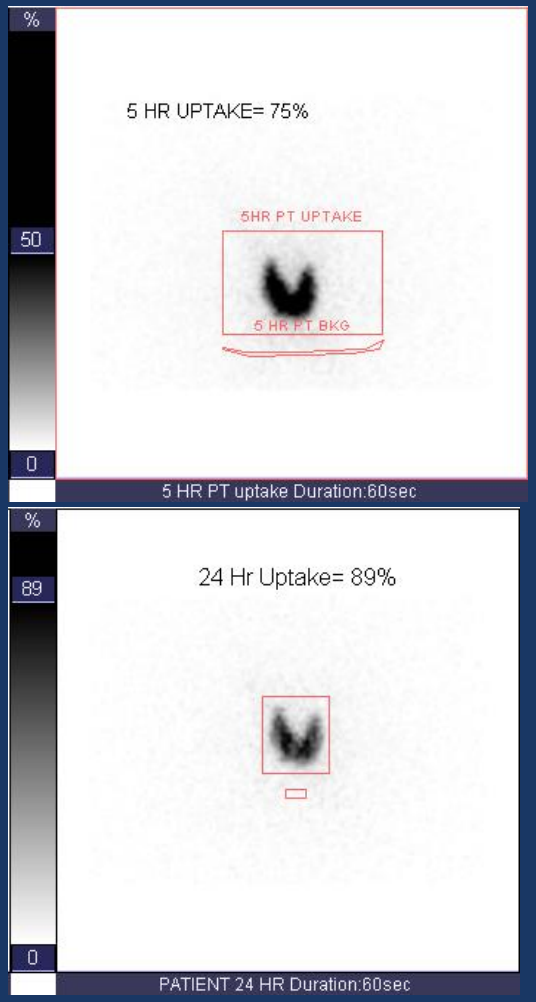


Incidental thyroid nodule in Graves' disease

Pathology: Papillary thyroid carcinoma, Stage 1 (T1, N1, M0)

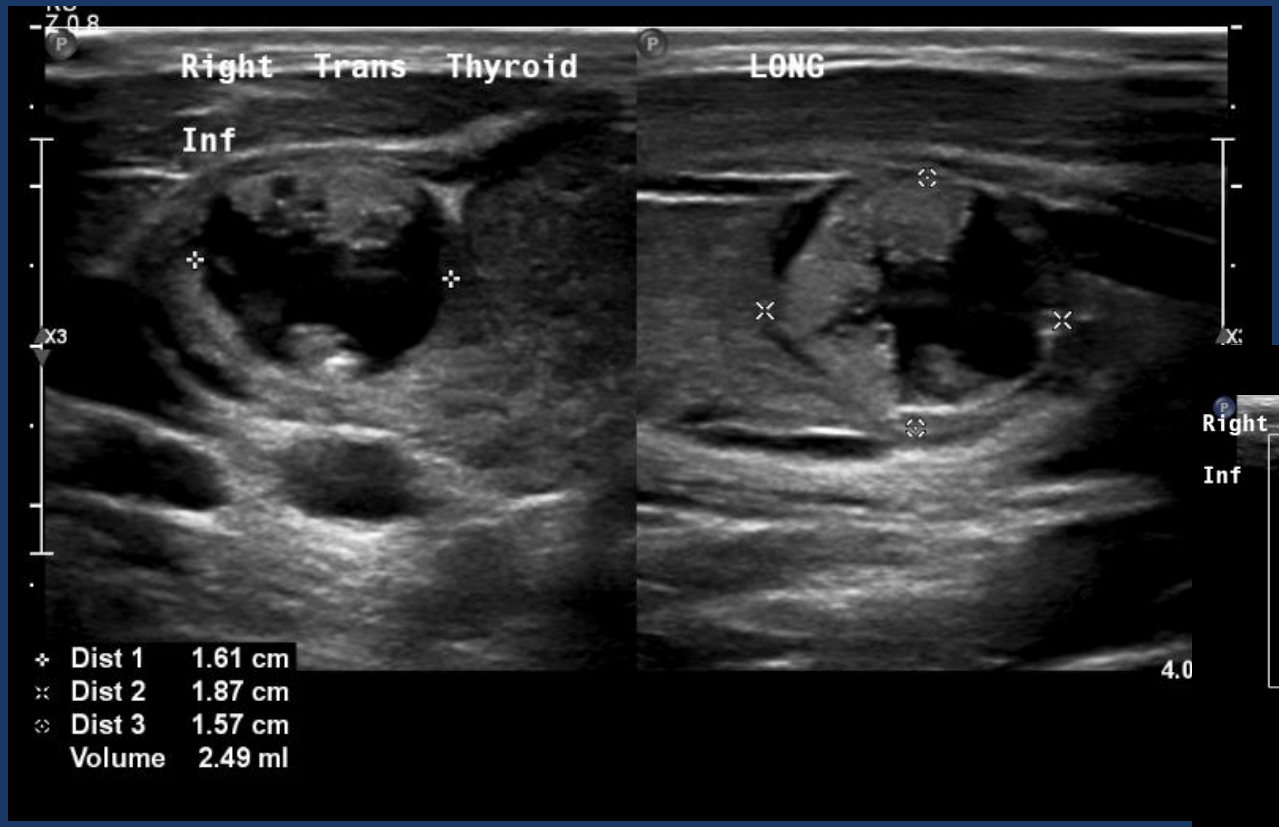
Case 3b, October 2015

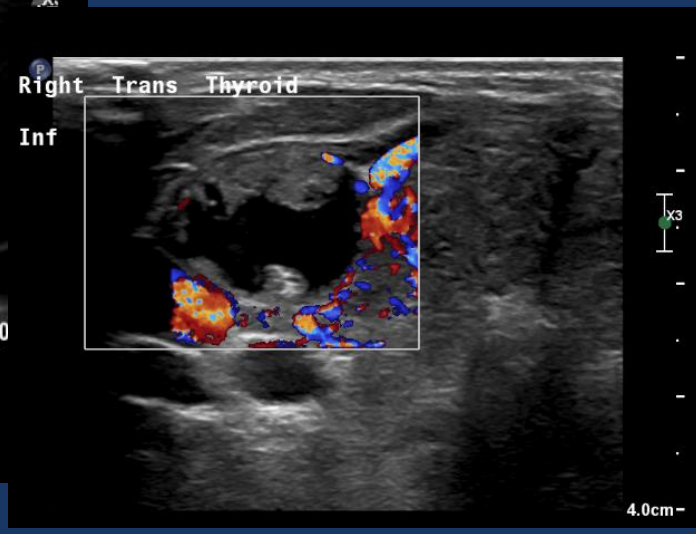




12-year-old male with medically managed Graves' disease referred for I-131 ablation

Case 3b





- Right inferior lobe mixed cystic and solid nodule with calcifications
- FNA non diagnostic
- Total thyroidectomy with pathology c/w Graves disease an 1.3 cm papillary thyroid carcinoma
- CT chest was negative → observation with no I-131 therapy

Radiation Safety Instructions

- Will be covered in a subsequent lecture

Seattle Children's®
HOSPITAL • RESEARCH • FOUNDATION

Thank you!