



# Recurrent Thyroid Cancer: How to Detect & When to Treat

**Puerto Rico AACE Chapter  
Endocrine Meeting**

**San Juan**  
February 25, 2020

**Hossein Gharib, MD, MACP, MACE**

Professor, Mayo Clinic College of Medicine  
Past President, American Thyroid Association  
Past President, American Association of Clinical Endocrinologists

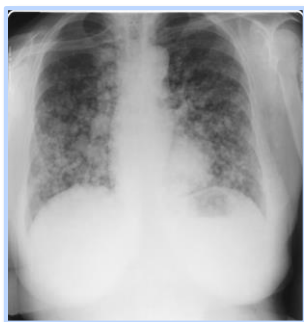
# Disclosures and Thanks

- None
- My special thanks to my good friend, Dr Myriam Allende, for the invitation to visit you and for the honor of speaking to your group today

# Facts

- Incidence of thyroid cancer is increasing in U.S. & worldwide
- PTC accounts for 90% of cancers
- Low- or intermediate-risk PTC accounts for 80-85% of DTC
- Trend to chose less aggressive therapy

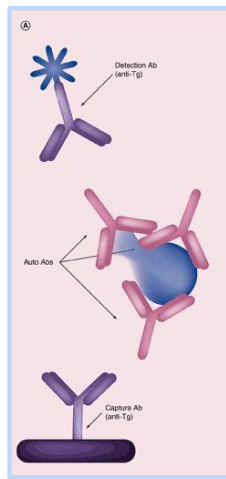
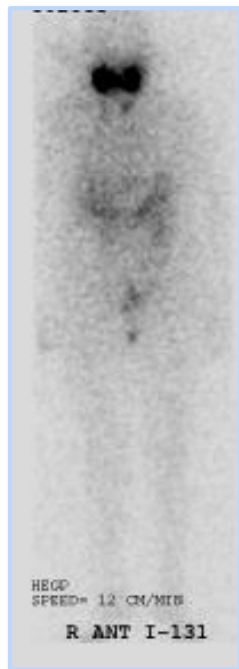
# Increasingly Sensitive Tools for Disease Detection



**CXR**



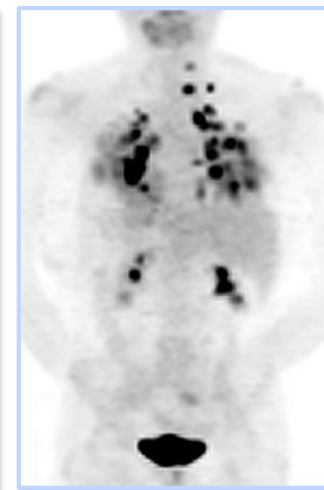
**RAI**



**Supp Tg  
Stim Tg**



**Ultrasound**



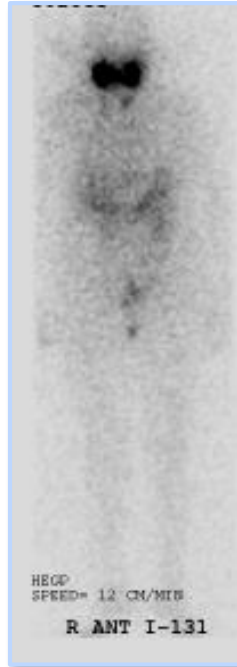
**FDG PET**

**The result**  
Much higher rates of  
persistent disease than  
previously known

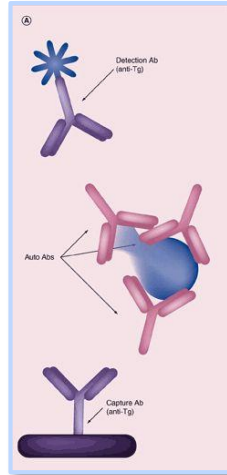
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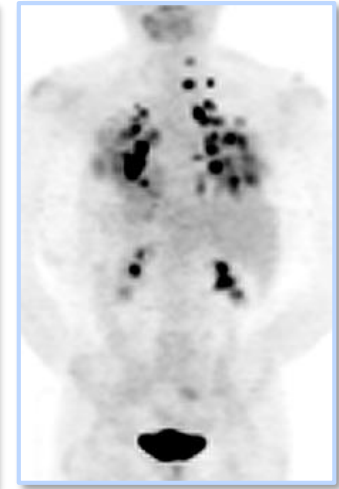
**RAI**



**Supp Tg  
Stim Tg**



**Ultrasound**



**FDG PET**

## Consequences of Occult Disease Detection

Repeated doses of RAI

More therapeutic neck dissections for recurrent disease

More therapeutic neck dissections as primary therapy

Prophylactic neck dissections for occult disease



AMERICAN THYROID ASSOCIATION  
ATA | Founded 1923

Clinical **THYROIDOLOGY**<sup>®</sup>

MARCH 2018 | VOLUME 30 | ISSUE 3

Clin Thyroidol 2018;30:108–111.

## Most “Recurrences” of Thyroid Cancer Represent Persistent Rather Than Recurrent Disease

Martin Biermann and Katrin Brauckhoff<sup>1</sup>

Bates MF, Lamas MR, Randle RW, Long KL, Pitt SC, Schneider DF, Sippel RS. Back so soon? Is early recurrence of papillary thyroid cancer really just persistent disease? *Surgery* 2018;163:118–123. Epub 2017 Nov 8. PMID 29128176.



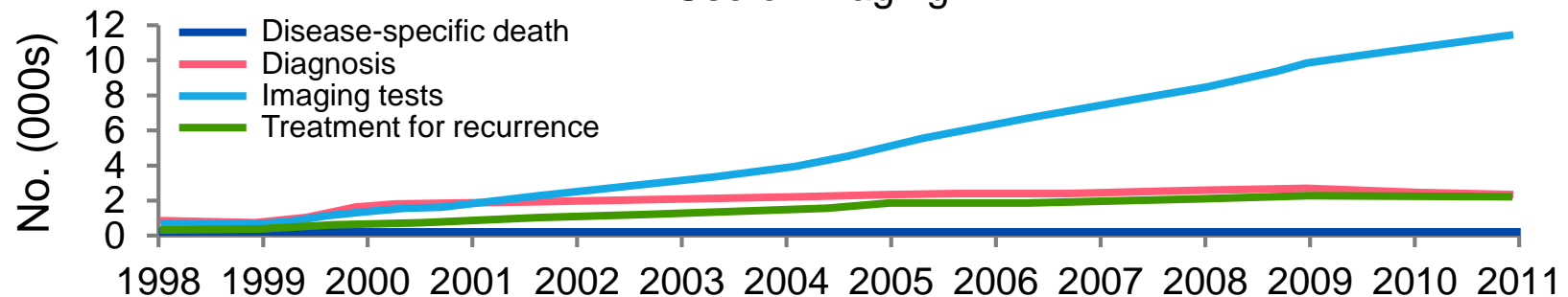
OPEN ACCESS

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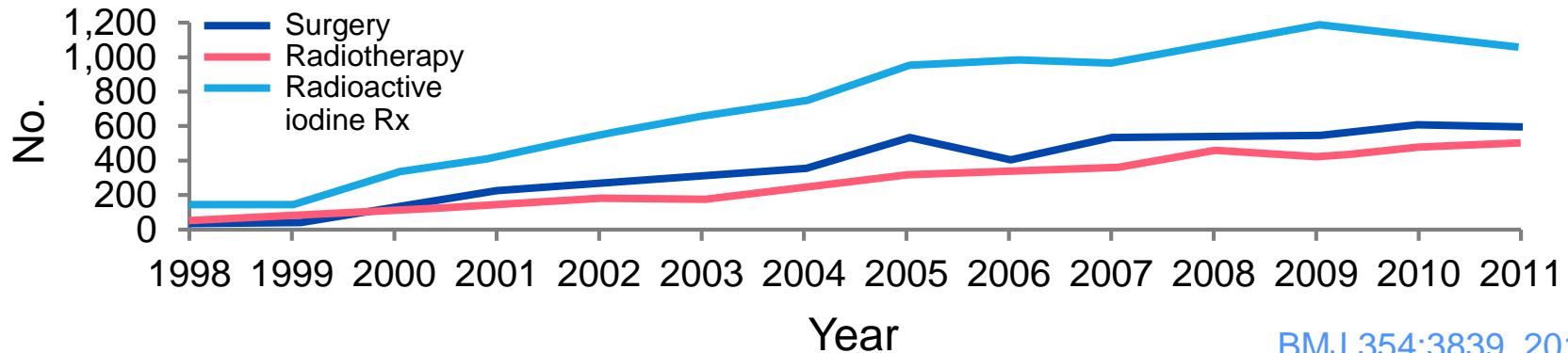
# Use of imaging tests after primary treatment of thyroid cancer in the United States: population based retrospective cohort study evaluating death and recurrence

Mousumi Banerjee,<sup>1,2</sup> Jaime L Wiebel,<sup>3</sup> Cui Guo,<sup>1</sup> Brittany Gay,<sup>4</sup> Megan R Haymart<sup>2,4,5</sup>

## Use of Imaging



## Trends in Use of Specific Treatments



BMJ 354:3839, 2017



# Lessons From Additional Treatments

- Sometimes beneficial
- Repeated doses of RAI seldom cured pt
- Most pt had persistent disease after repeated neck dissections
- No clear evidence of improved disease-free survival
- Small incidence of clinically significant side effects
- Increased pt anxiety & cost



# Tools in Thyroid Cancer Surveillance

- Thyroglobulin (Tg)
- Ultrasound (US)
- $^{131}\text{I}$  Whole Body Scan (WBS)
- PET/CT

# Thyroglobulin (Tg)

- Not all thyroid cancers secrete Tg
- Tumors may dedifferentiate & cease making Tg or trap  $^{131}\text{I}$
- Always use same assay for same pt
- Always obtain TgAb
- Tg assay sensitivity increased from 3 ng/dl in 1980s to 0.1 in 2020

# Thyroglobulin (Tg) Assays

	Radioimmunoassay (RIA)	Immunometric (ICMA, IRMA)
Method	Single Ab	Double Ab
Functional sensitivity ng/mL	0.7-2.0	0.1-0.6
TgAb	Resistant	Susceptible
TgAb+	Generally unaffected	False low value

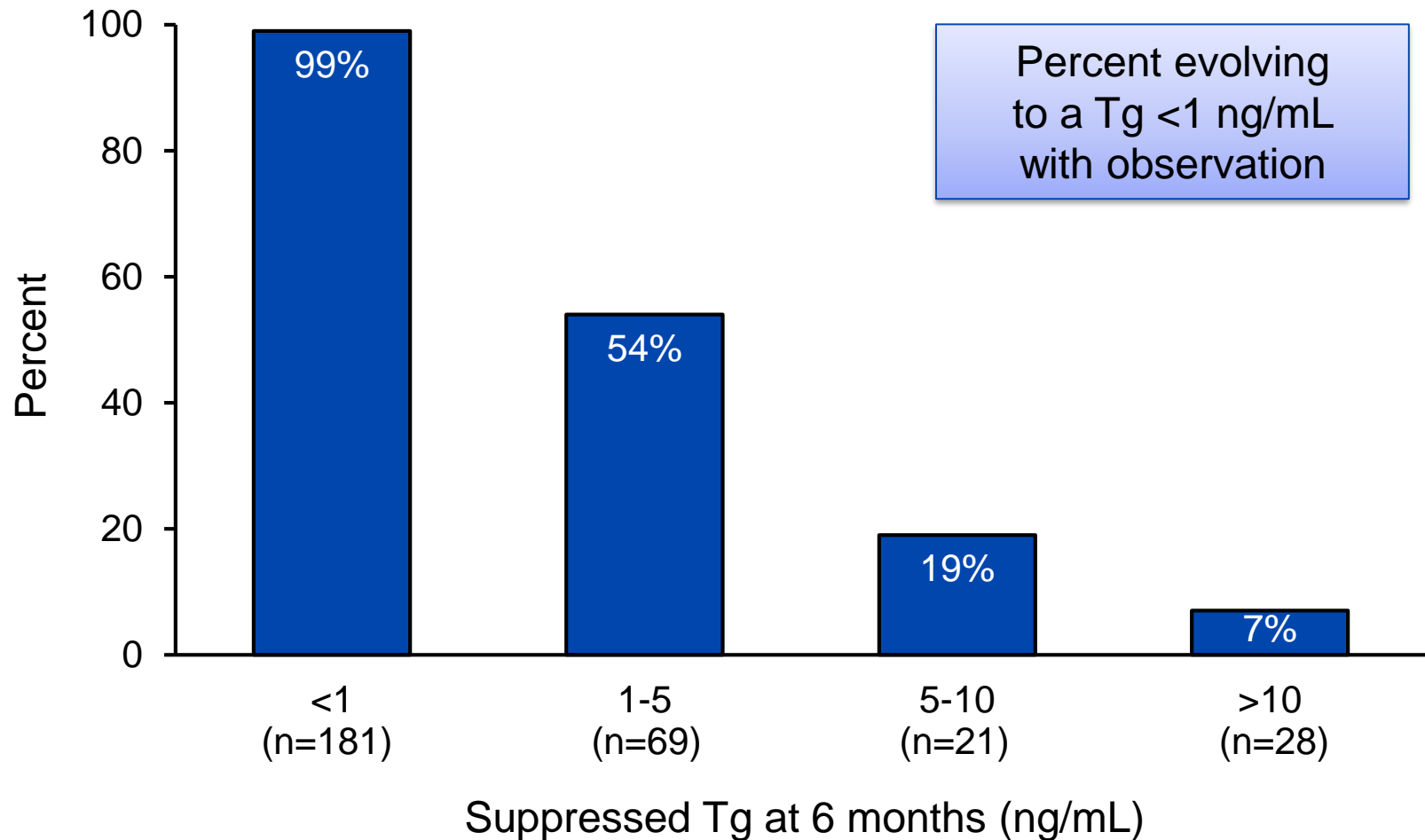
# Thyroglobulin Antibodies (TgAb)

- Are present in 30% of thyroid cancer pt
- In 50% of pt initially (+), TgAbs become undetectable in 1-2 yrs
- Tg is  $<1$  in 96% after only TTx
- Mass spectrometry digests TgAbs and eliminates interference
- However, mass spec has higher detection limit (0.4-2.5 ng/dL) and is less useful

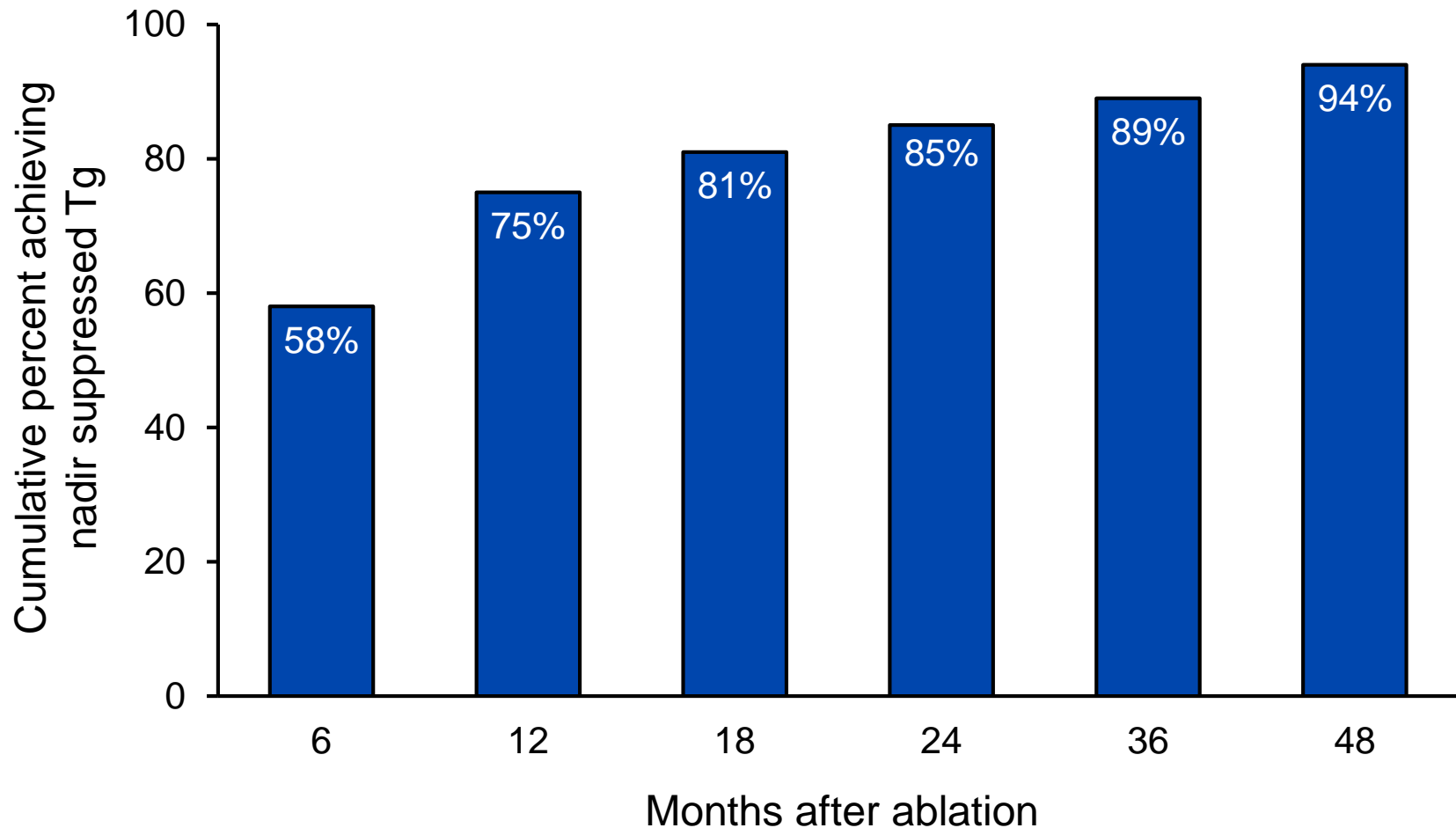
# Factors Influencing Predictive Value of Postop Tg

- Amount of residual cancer or normal thyroid tissue
- TSH level at Tg measurement
- Functional sensitivity of Tg assay
- Cut-off used in analysis (0.1, 0.5, 1.0, etc)
- Sensitivity of post-Rx imaging (US, WBS, PET, etc)

# 6 Month Suppressed Tg Values Predict Likelihood of Eventually Developing Suppressed Tg <1 With Continued Observation



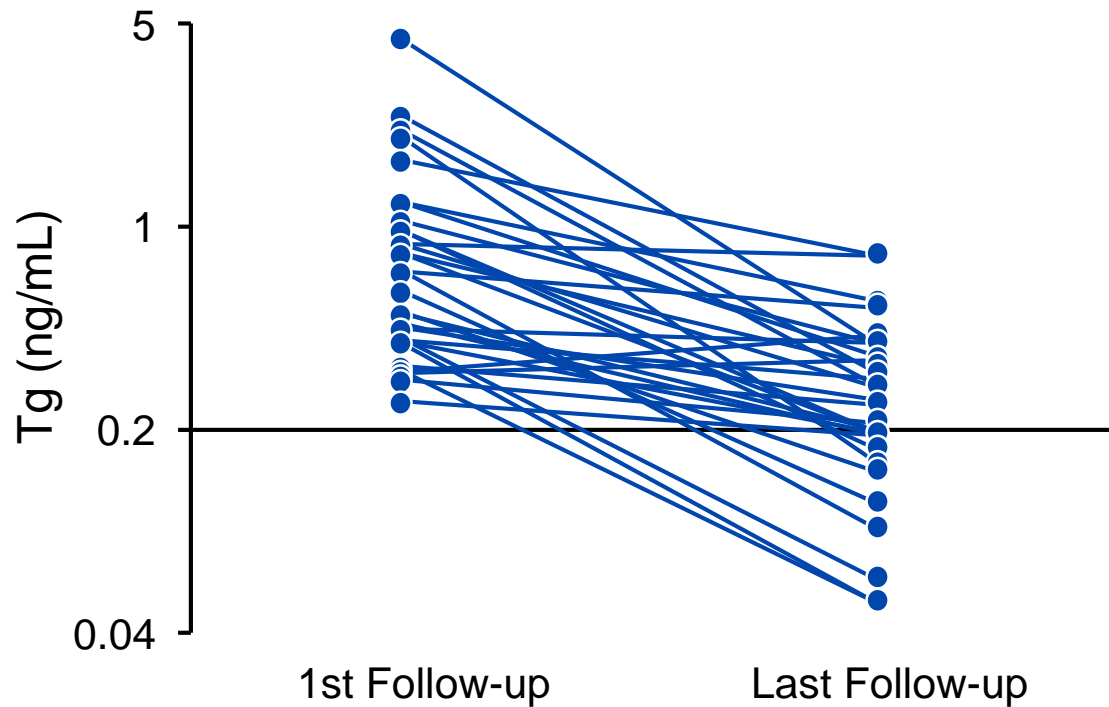
# Serum Tg Levels Continue to Decline For Years After TTX & RAI Remnant Ablation With Continued Observation





# Long-Term Surveillance of Papillary Thyroid Cancer Patients Who Do Not Undergo Postoperative Radioiodine Remnant Ablation: Is There a Role for Serum Thyroglobulin Measurement?

Cosimo Durante, Teresa Montesano, Marco Attard, Massimo Torlontano, Fabio Monzani, Giuseppe Costante, Domenico Meringolo, Marco Ferdeghini, Salvatore Tumino, Livia Lamartina, Alessandra Paciaroni, Michela Massa, Laura Giacomelli, Giuseppe Ronga, and Sebastiano Filetti on behalf of the PTC Study Group



# Clinical Utility of Postop Tg

- A suppressed postop Tg  $<1$  ng/mL is associated with excellent outcome & recurrence  $<1\%$  in low and intermediate PTC even absent RAI ablation
- Suppressed or stimulated postop Tg  $>10$  ng/mL  $\uparrow$  likelihood of persistent disease, distant mets and death
- In some pt postop serum Tg levels may decline even without further Rx
- In pt with detectable but stable Tg & negative imaging (WBS, US), follow up favored over  $^{131}\text{I}$  Rx

# Parameters of Favorable Outcome After Initial Tx & RAI Rx

Category	Definitions	Clinical Outcomes
Excellent Response	Suppressed Tg<1 Stimulated Tg<1 Negative TgAb Negative imaging	1-4% recurrence rates <1% Dz-specific death rate

# Follow-Up of DTC

- Monitor neck exam, TSH, FT4, Tg every 6-12 months
- Periodic neck US every 12 months
- $^{131}\text{I}$  WBS use selectively
- Chest CT with or without contrast in aggressive disease
- PET/CT for Tg<sup>+</sup>, WBS<sup>-</sup> pt

# Postop US

# Postop Imaging

- US evaluation is uniquely operator-dependent but in expert hands its accuracy is >90%
- US is widely available & affordable
- US is preferred over CT because of superior neck imaging, lower cost, less time and allows FNA
- Use WBS or PET only in selected cases

# Diagnosis of Recurrent DTC in 51 of 494 Patients

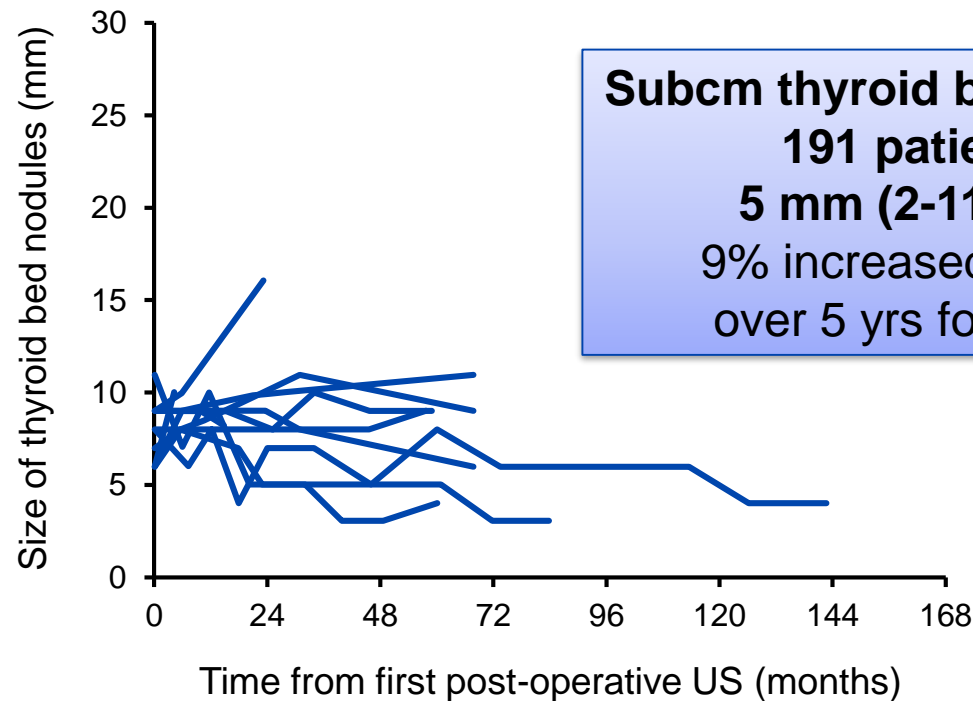
- $^{131}\text{I}$  Whole Body Scan 23 (45%)
- Tg > 2 ng/ml (off T4 therapy) 29 (57%)
- Tg detectable 34 (67%)
- Ultrasound 48 (94%)



## Ultrasonographically Detected Small Thyroid Bed Nodules Identified After Total Thyroidectomy for Differentiated Thyroid Cancer Seldom Show Clinically Significant Structural Progression

Geneviève Rondeau,<sup>1</sup> Stephanie Fish,<sup>1</sup> Lucy E. Hann,<sup>2</sup> James A. Fagin,<sup>1</sup> and R. Michael Tuttle<sup>1</sup>

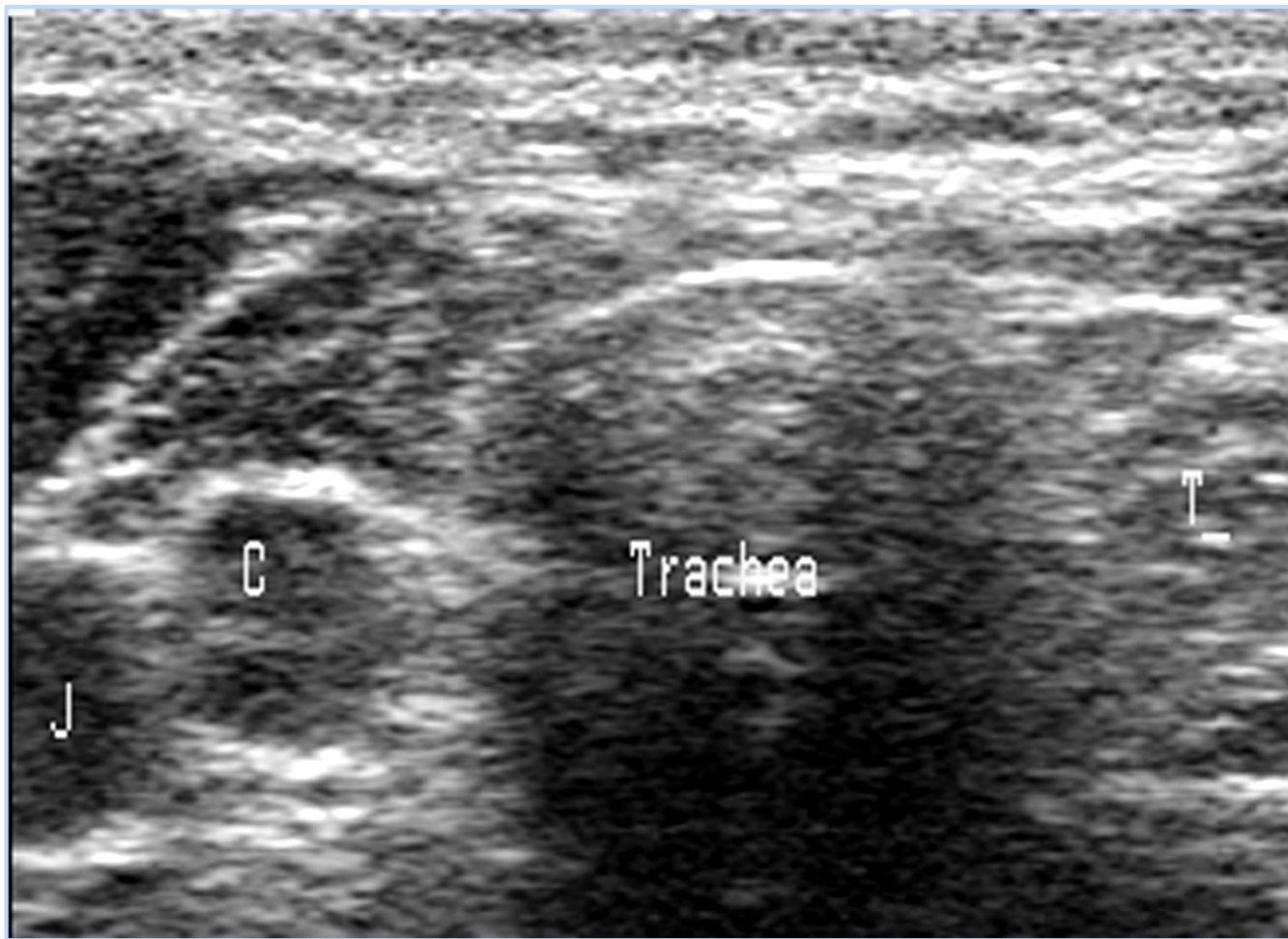
### 9 Patients With Biopsy Proven Disease



# Post-Op US Evaluation

- Both central and lateral compartments of the neck are easily surveyed with US in the post-op thyroid cancer patient
- FNA using US guidance allows both cytology and analysis for Tg without regard to Tg antibody

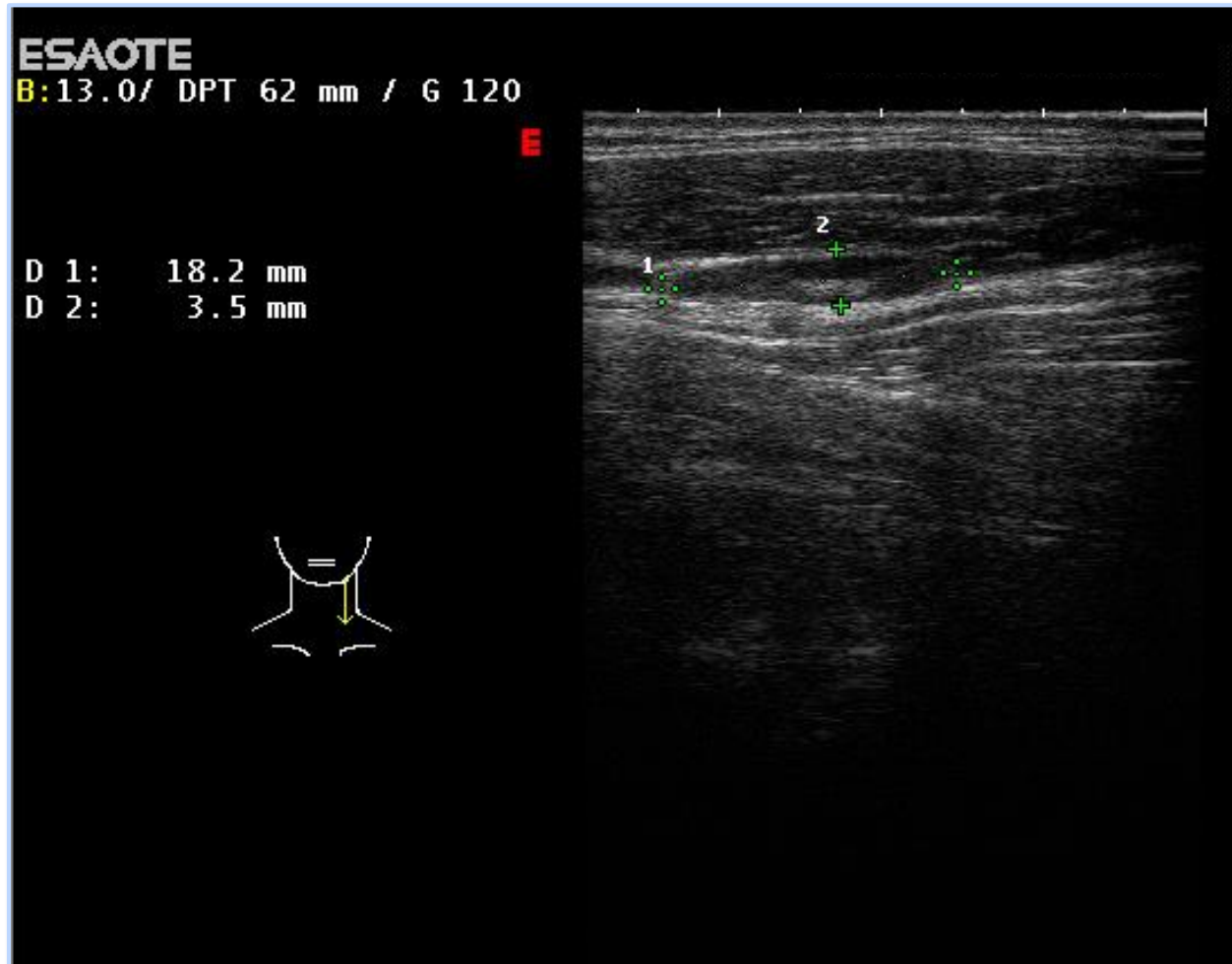
# Post-Operative Neck



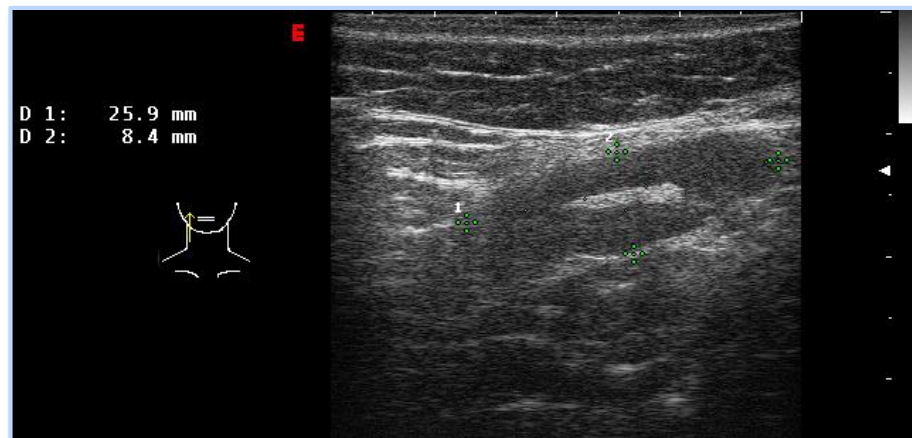
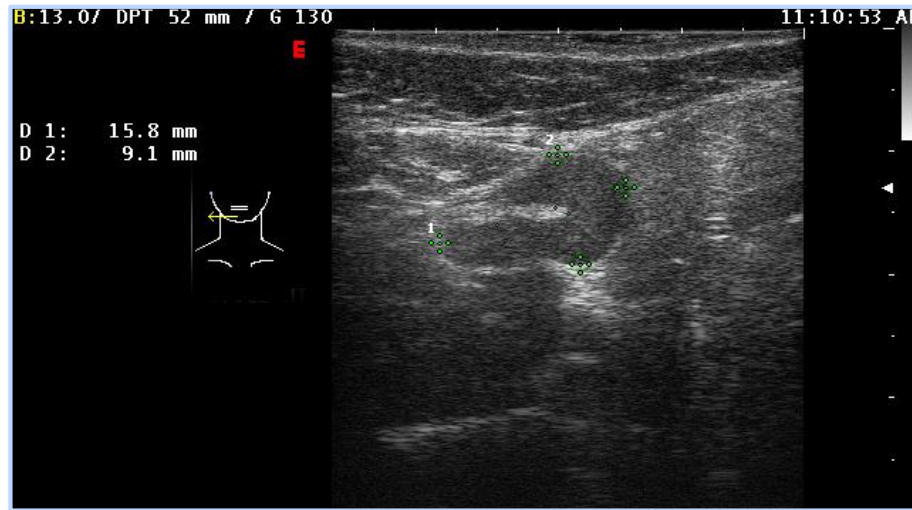
# Characteristics of Benign Lymph Nodes

- Flattened or oval shape ( $AP/T < 0.5$ )
- Echogenic (hilar) line
- Hilar vascular flow on Doppler
- Size varies with compartment and is less important than morphology
- Border definition also less important

# Normal Lymph Node

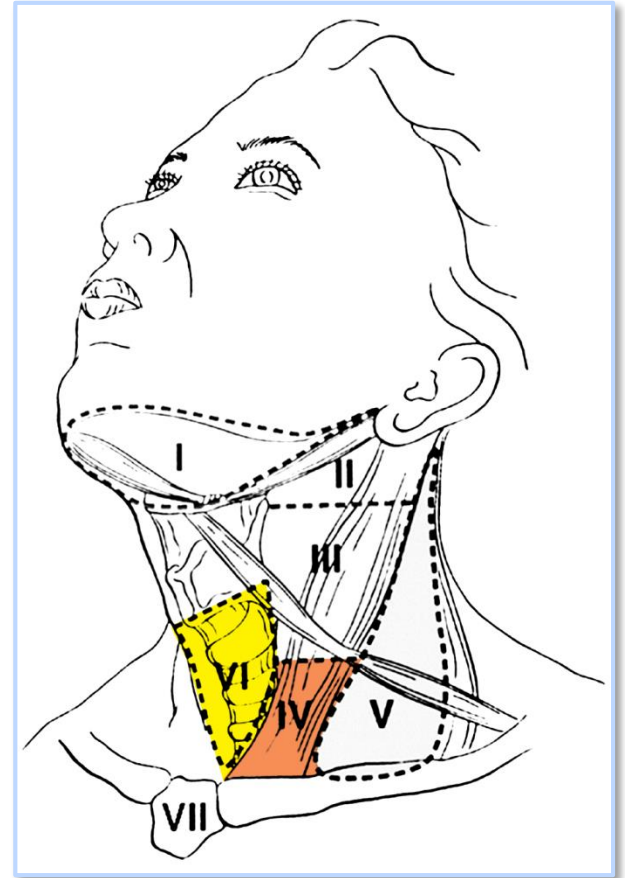


# Large Benign Node - Compartment 2



# Lymph Node Metastasis in PTC

- Most are ipsilateral
- Central before lateral (usually but not always)
- Levels III, IV, VI in 80% of pt
- Level VI nodes not identified by preop US



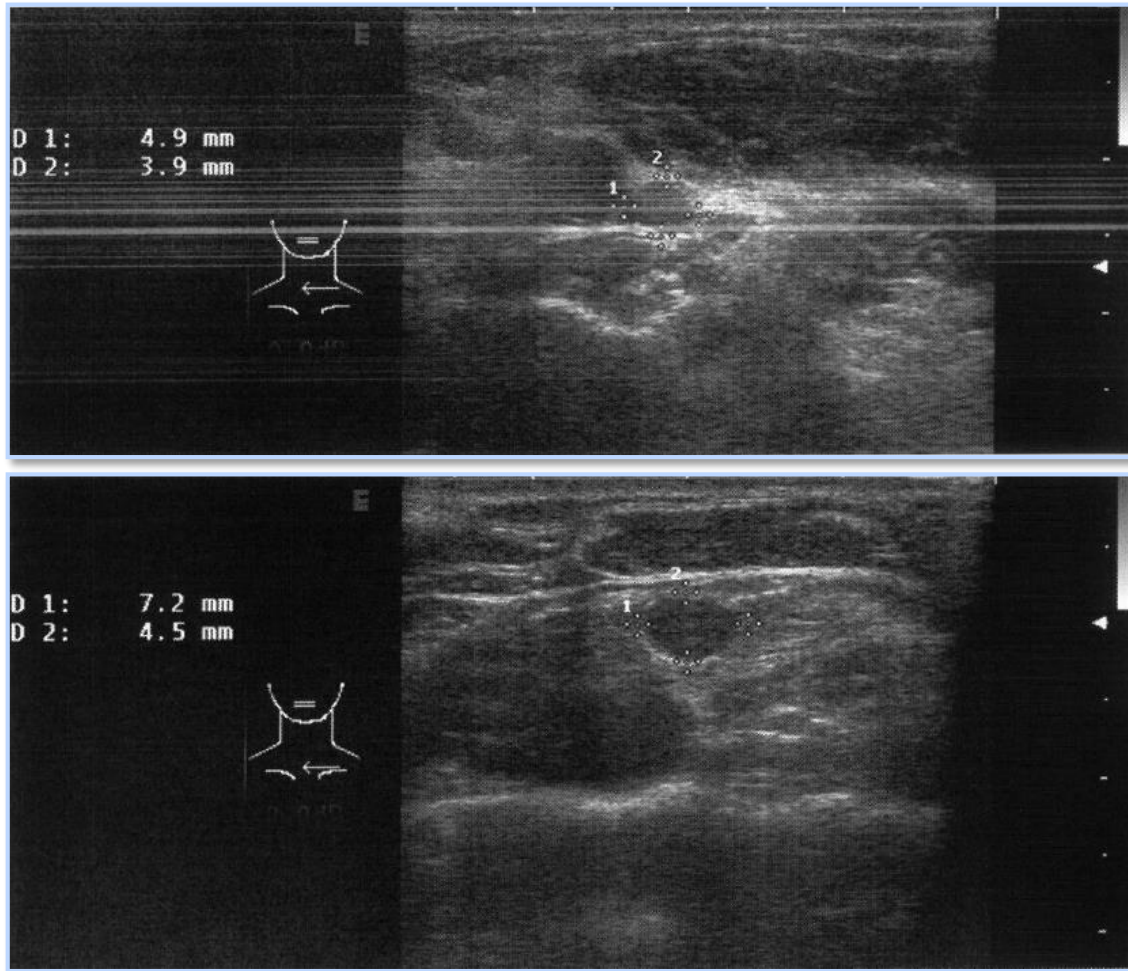


# Characteristics of Malignant Nodes

	Sensitivity	Specificity
Disordered vascularity	86%	82%
Microcalcifications	45%	100%
Cystic Degeneration	11%	100%
Absence of Hilar Line	95%	20%
Hypoechoic Echotexture	39%	18%

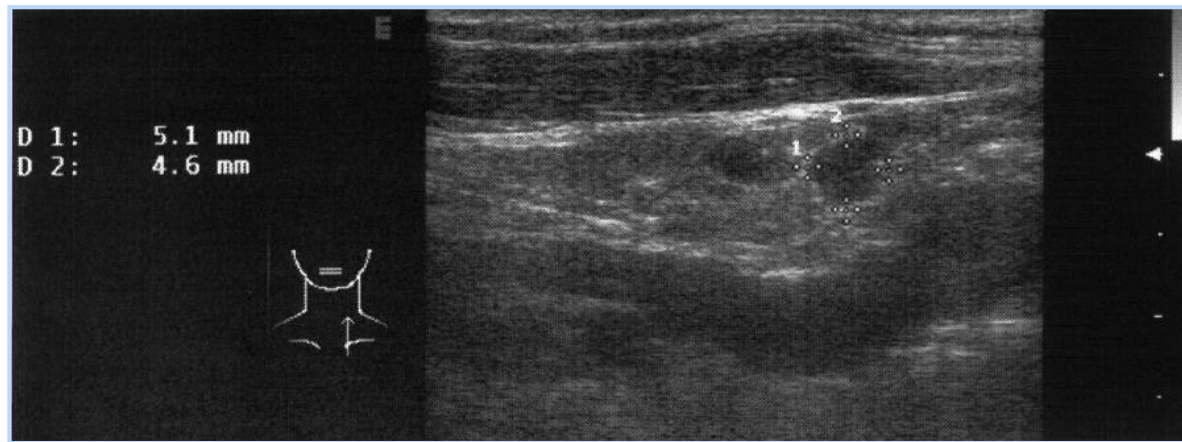
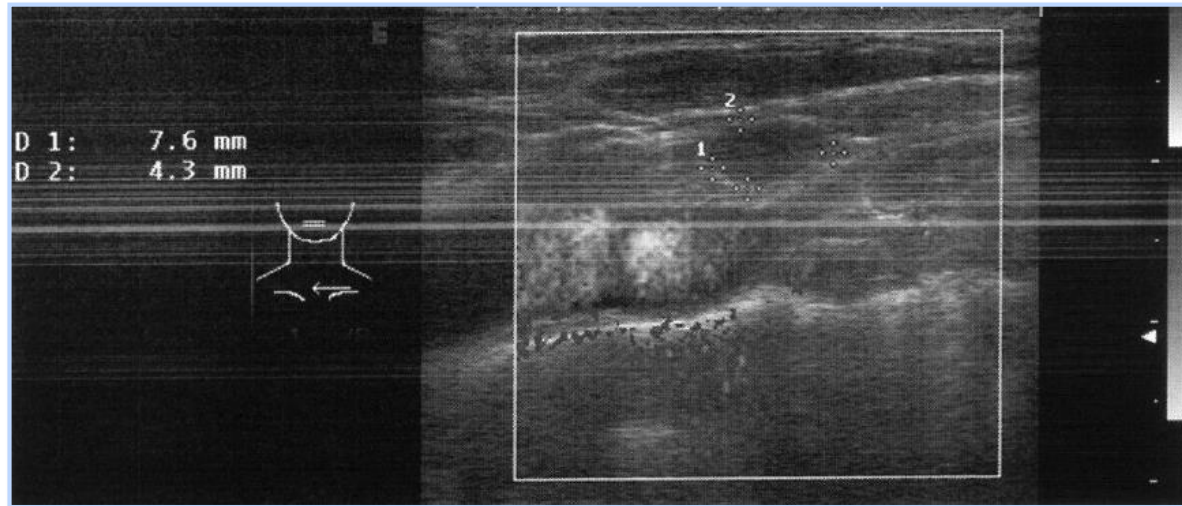
# Papillary Carcinoma

## Small Round Nodes – Malignant

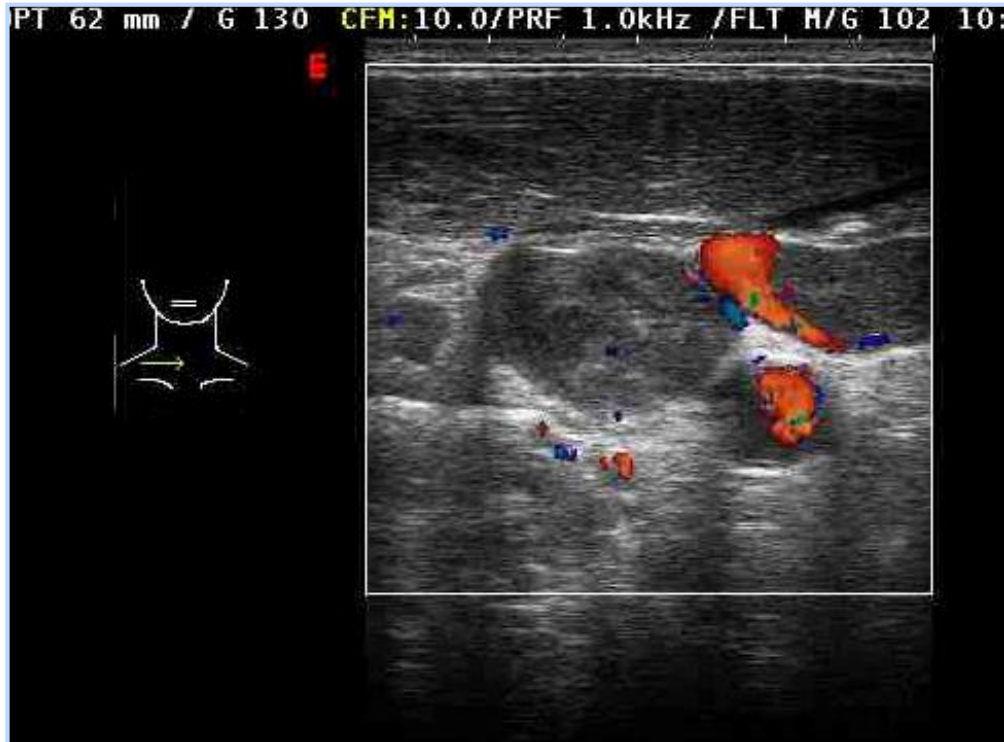


# Papillary Carcinoma

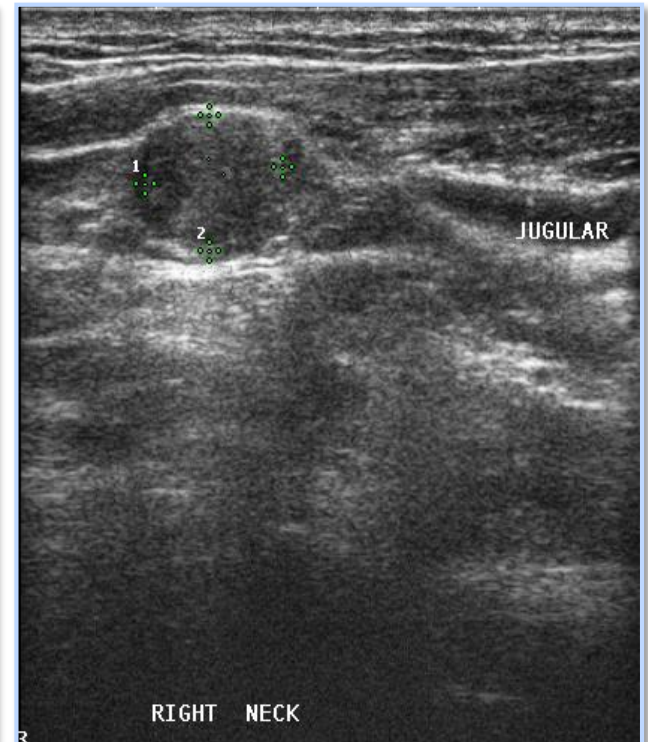
## Small Round Nodes – Malignant



## Malignant Node



## Cystic Necrosis



# **Suspicious Cervical Lymph Nodes Detected after Thyroidectomy for Papillary Thyroid Cancer Usually Remain Stable Over Years in Properly Selected Patients**

**JCEM 2012**

E. Robenshtok, S. Fish, A. Bach, Jose M. Domínguez, A. Shaha, and R. M. Tuttle

## **166 differentiated thyroid cancer patients**

With suspicious lateral neck LNs by US (1.3 cm)

Followed with serial US (median of 6)

Median of 3.5 yrs (range 1-13 yrs)

### **Growth of Suspicious LN**

≥3 mm 33/166 (20%)

≥5 mm 15/166 (9%)

### **Time to progression**

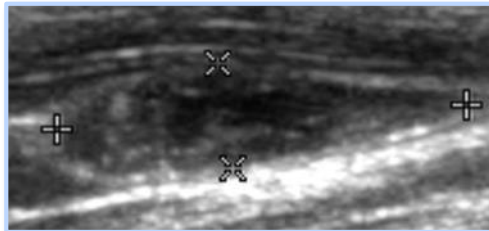
2 years



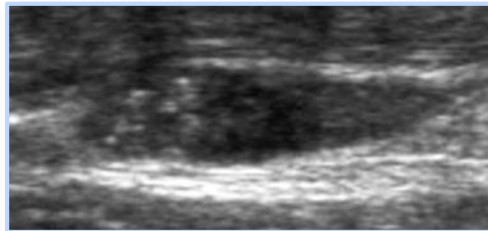
# FNA Proven Cervical LN Mets

**Case 1**

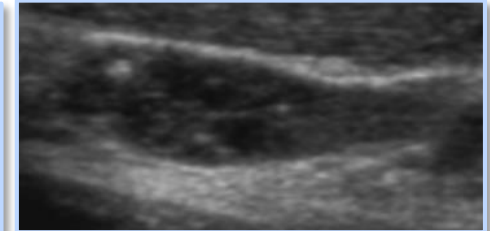
Baseline



3 years

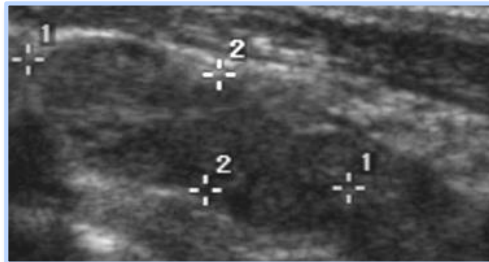


5 years

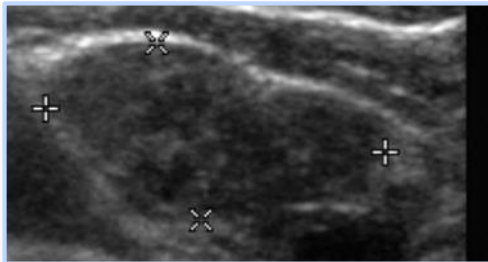


**Case 2**

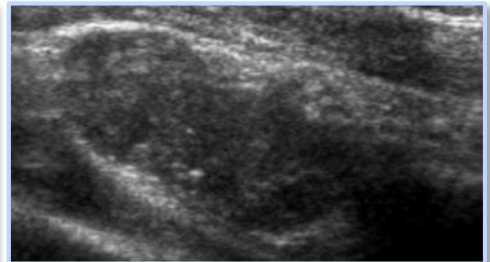
Baseline



3 years

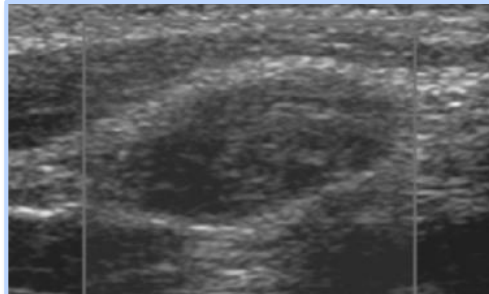


9 years

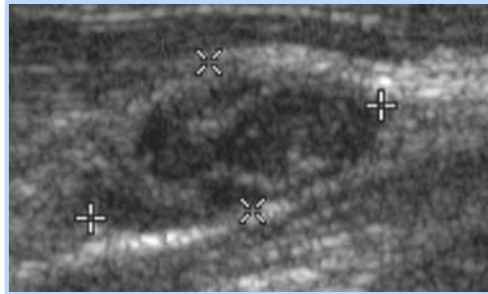


**Case 3**

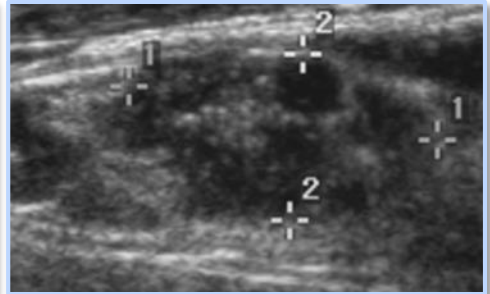
Baseline



3 years



10 years



E Robenshtok, JCEM 2012

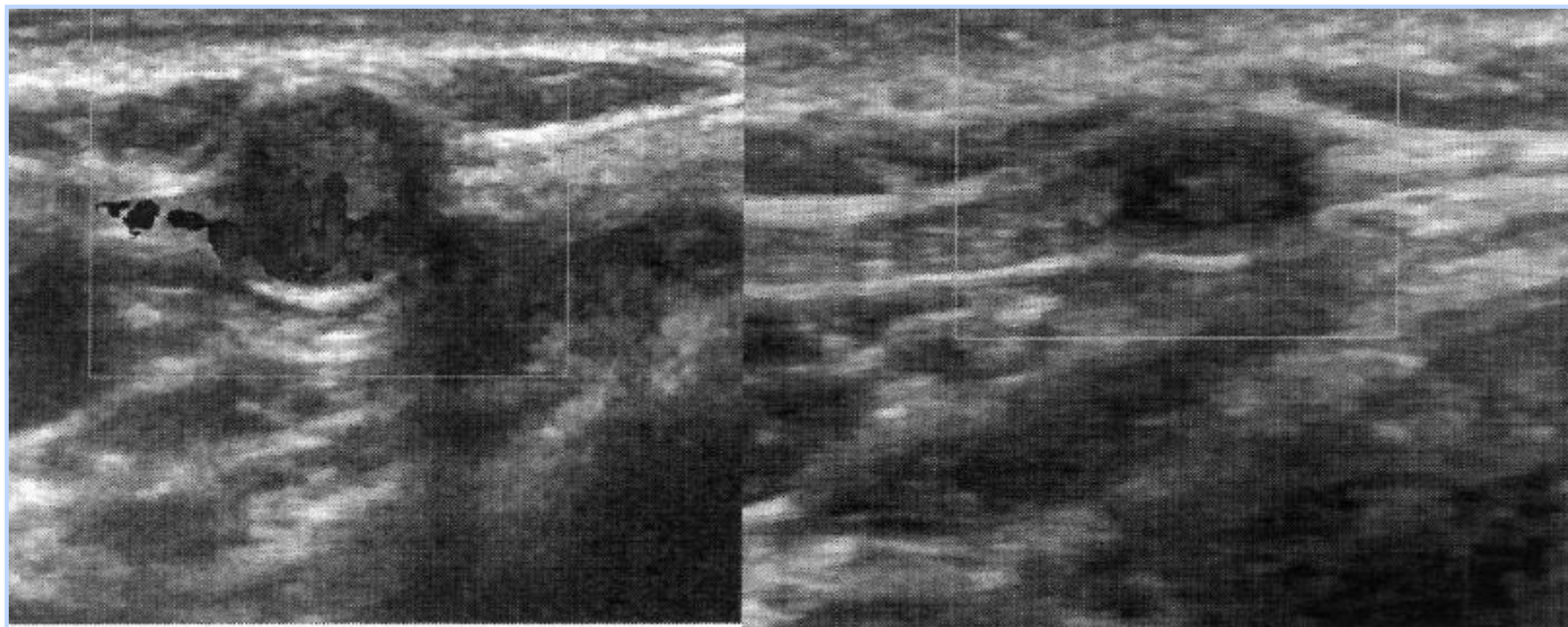
# Percutaneous Alcohol Injection Treatment (PEIT) For Recurrent Thyroid Cancer

- Alternative to conventional (surgery or RAI) Rx for limited cervical recurrence of thyroid cancer
- Image-guided, minimally invasive procedure injecting alcohol into metastatic node
- Appropriate for small volume disease and when pt not surgical candidate



# PEIT Treatment For Recurrent Thyroid Cancer Cont'd

- Most commonly employed for PTC with success
- May shrink or arrest growth of metastatic node for several years
- Requires training and special clinic
- Minimal discomfort; no serious complications; can be repeated; low cost



Three months after treatment the nodule is 75% smaller by volume and avascular on color Doppler

# Radioiodine (RAI) Whole Body Scan

# Limitations of Whole Body Scans

- Morbidity of thyroid hormone withdrawal (THW)
- Expense
- Poor sensitivity (60-75%)
- “Stunning”
- Potential for causing tumor growth?
- Use of rhTSH preferred

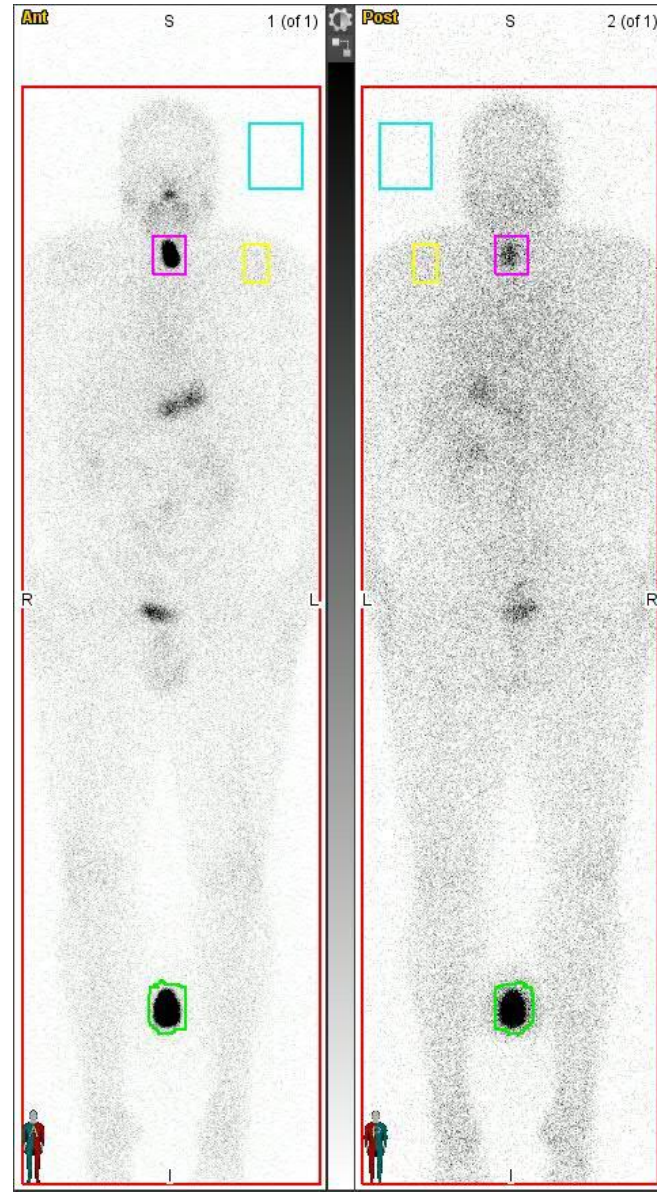
# Diagnosis of Recurrent DTC in 51 of 494 Patients

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# Remnant Ablation

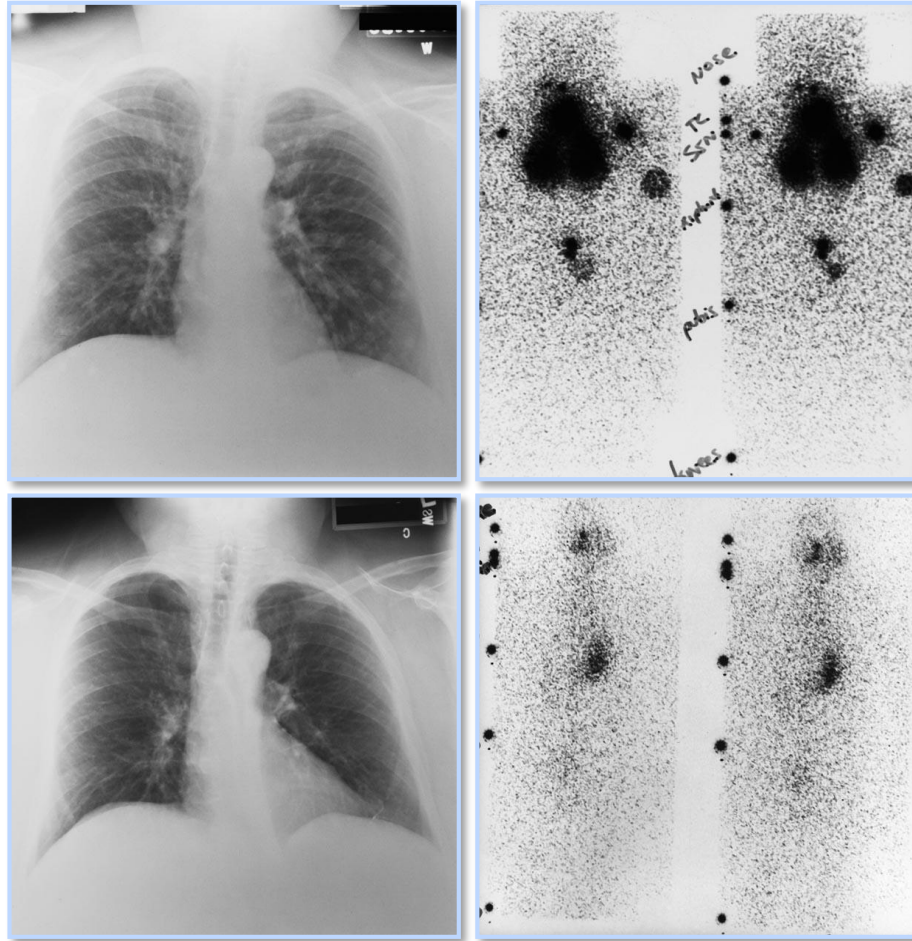
- RAI remnant ablation is not necessary for most pt with low-risk DTC
- RAI remnant ablation should be considered for some intermediate-risk and most high risk DTC pt
- Would ablate low- or intermediate-risk pt with postop Tg >5-10
- Conversely, a post-op Tg of <1 ng/mL should not preclude RAI ablation in a high-risk pt

- $^{123}\text{I}$  WBS
- Use rhTSH
- 1.6% neck uptake
- Note physiologic activity in gut & bladder & location of marker





# FTC with Lung Metastasis



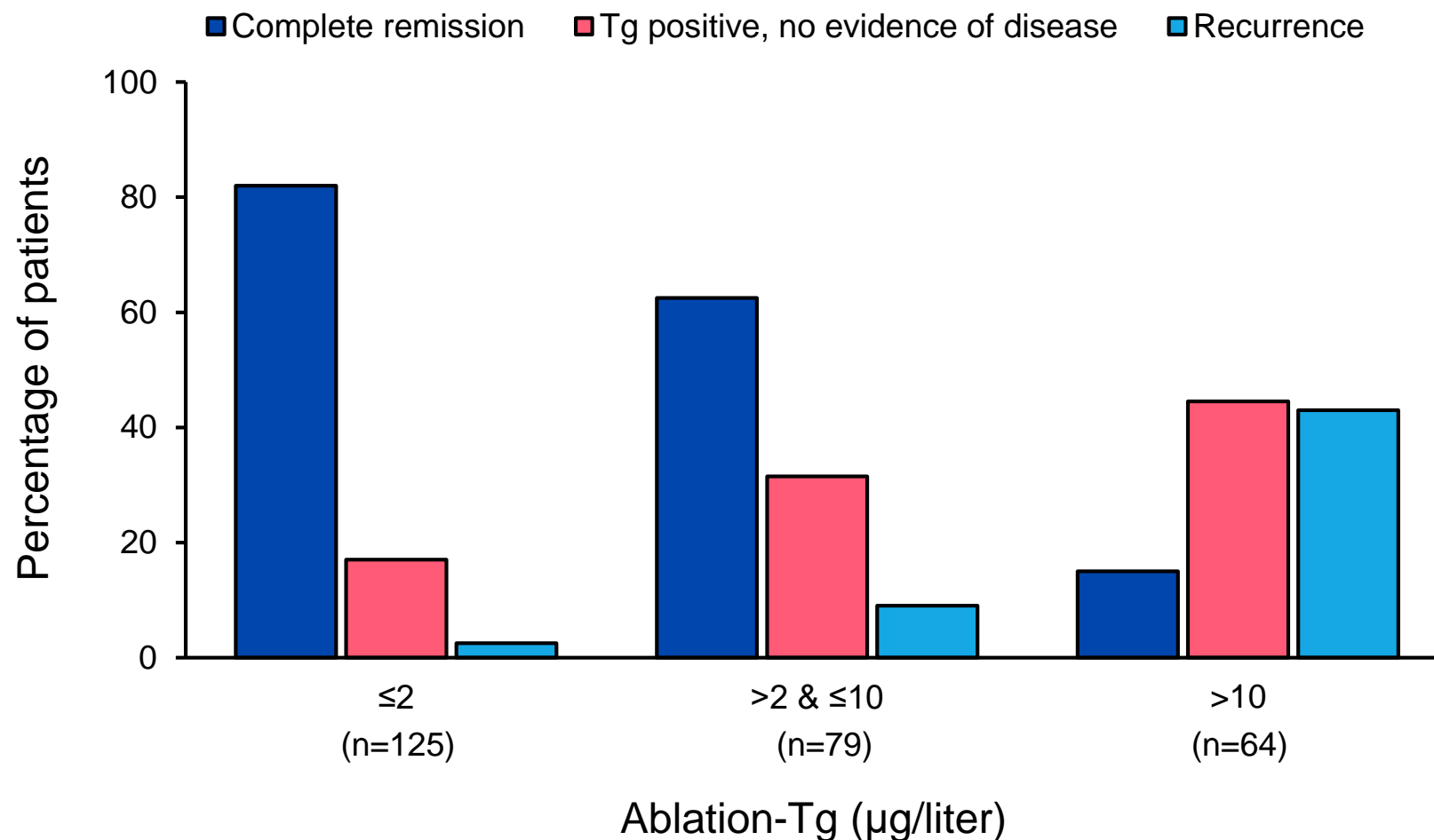


## Value of Diagnostic Radioiodine Whole-Body Scanning After Initial Therapy in Patients with Differentiated Thyroid Cancer at Intermediate and High Risk for Recurrence

Pedro Wesley Rosario,<sup>1,2</sup> Mariana de Souza Furtado,<sup>1,3</sup> Augusto Flávio Campos Mineiro Filho,<sup>1</sup>  
Rafaela Xavier Lacerda,<sup>1</sup> and Maria Regina Calsolari<sup>2</sup>

- 318 pt po Tx and RAI Rx for intermediate- and high-risk DTC (large tumor, node positive, & ETE)
- When post-Rx WBS & US negative, and Tg <1 with TgAb–, no need for another WBS

# Clinical Outcome According to Serum Tg at Time of Remnant Ablation



Kim et al: J Clin Endocrinol Metab 2005;90:1440-1445

# PET

# PET

- Positron emission tomography
- Uses 18-F FDG a glucose analogue
- Enters cells like glucose by not metabolized
- Picked up by malignant cells with ↑ glucose uptake
- Expensive

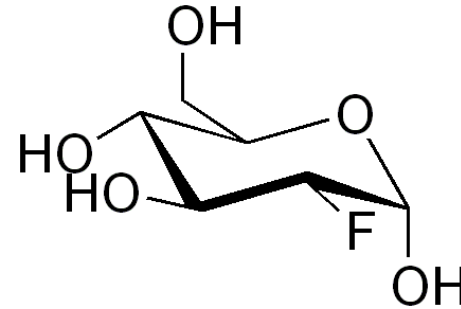
# SPECT/CT

- Single-photon emission CT (SPECT)
- Nuclear imaging using radioisotope to create 3-D images
- Isotopes are  $^{99m}\text{Tc}$ ,  $^{123}\text{I}$  or  $^{131}\text{I}$
- Resolution < PET
- Cost < PET

# F-18 Fluorodeoxyglucose

## F-18 - FDG

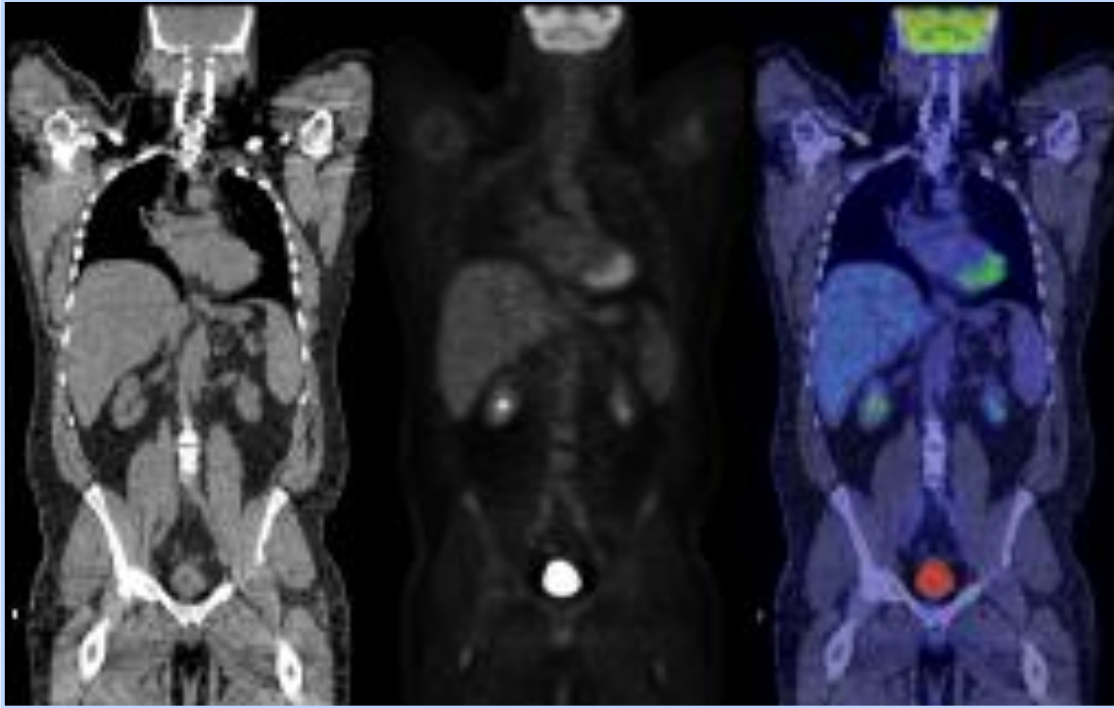
- Accumulates in areas of high glucose metabolism
  - Malignant tissues
  - Inflammation
- Phosphorylated in the cells, but not metabolized further
- Not re-absorbed in kidneys
- F-18 decays by positron emission (97% of the time) average range in tissue 0.6 mm



F18-FDG

- 2-Deoxy-2-fluoro-D-glucose

# FDG Normal Distribution



**Brain** - intense uptake

Thyroid – low uptake

Heart - variable uptake

Urinary tract - intense uptake

Liver SUV 3

Mediastinal blood pool 2.5

**SUV**  
standard uptake value

=

radioactivity concentration in a selected part of the body

radioactivity concentration in the hypothetical case of  
an even distribution throughout the whole body

# **$^{18}\text{F}$ -FDG PET/CT for**

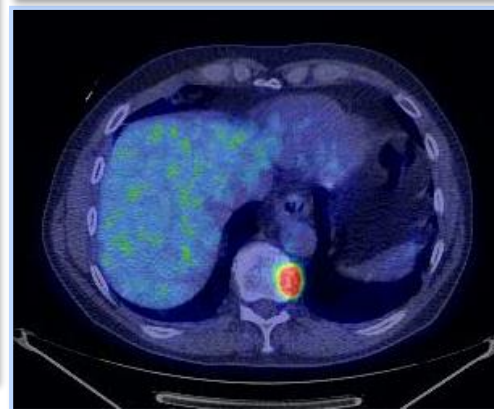
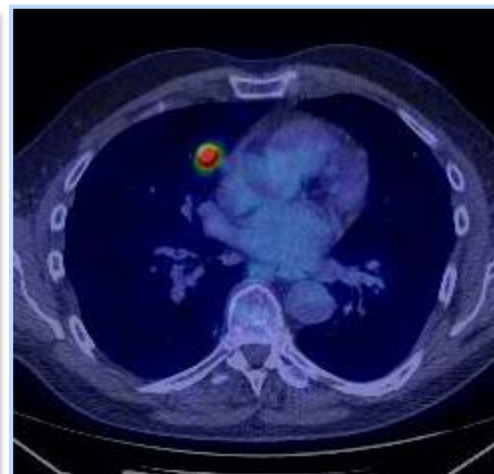
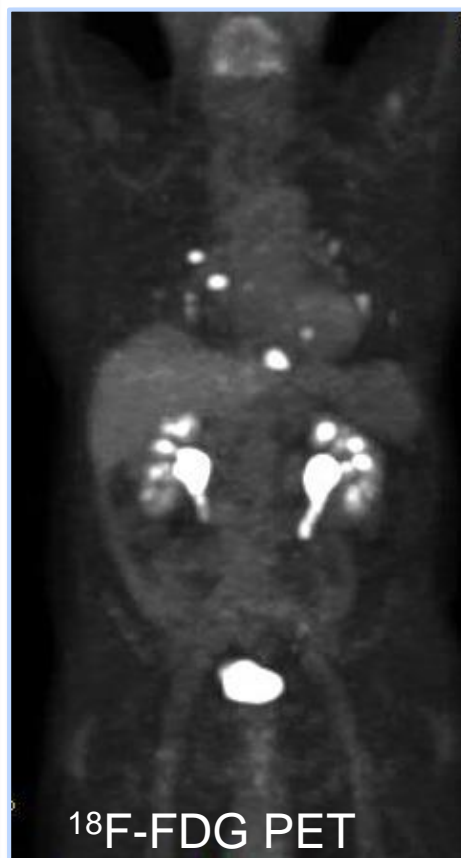
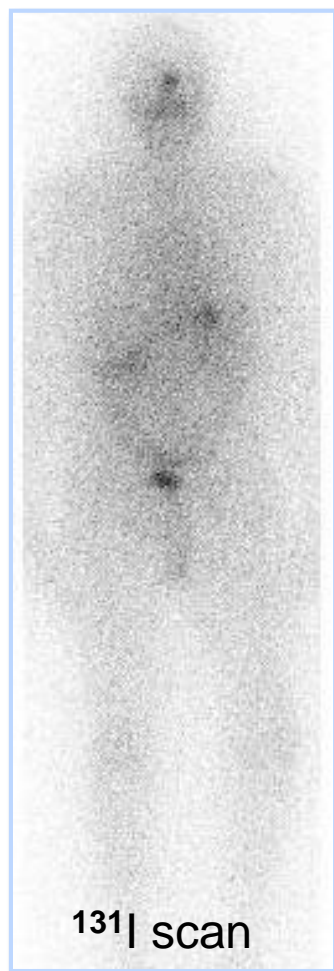
## **Differentiated Thyroid Cancer**

- Useful in evaluation for recurrent disease in pt when Tg+, WBS–
- Less differentiated cancer causes  $\uparrow$  glucose metabolism but  $\downarrow$  iodine uptake
- Resolution is better by PET/CT (4 mm) vs SPECT/CT (1 cm)
- Most useful when stim Tg  $>10$  ng/mL
- A meta-analysis of 17 studies including 571 pt with DTC and negative WBS showed FDG PET/CT had sensitivity 84% and specificity 84%\*



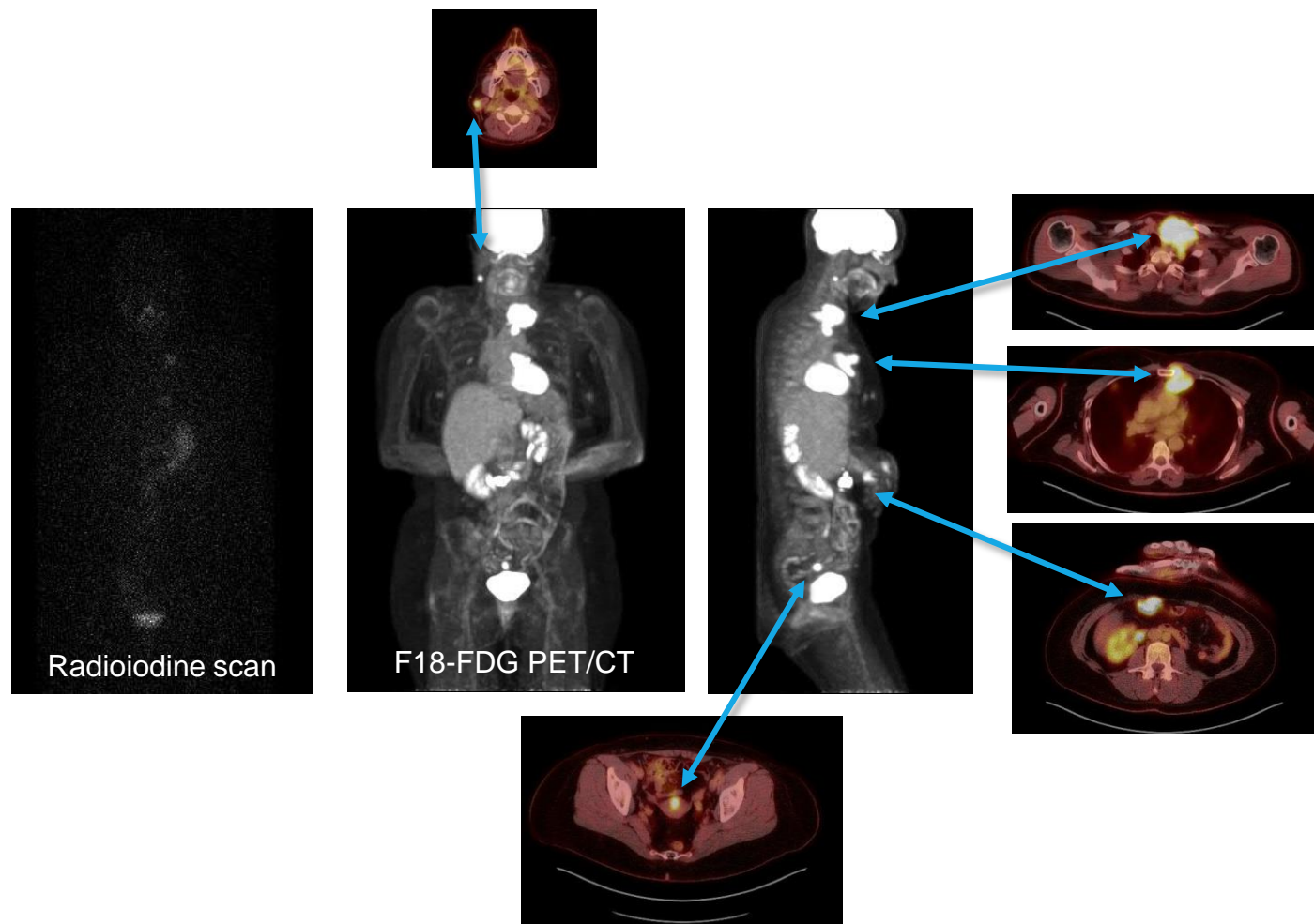
# Papillary Thyroid Cancer

Iodine Negative  $^{18}\text{F}$ -FDG PET/CT Positive



# Metastatic Papillary Thyroid Cancer

## F18-FDG PET/CT



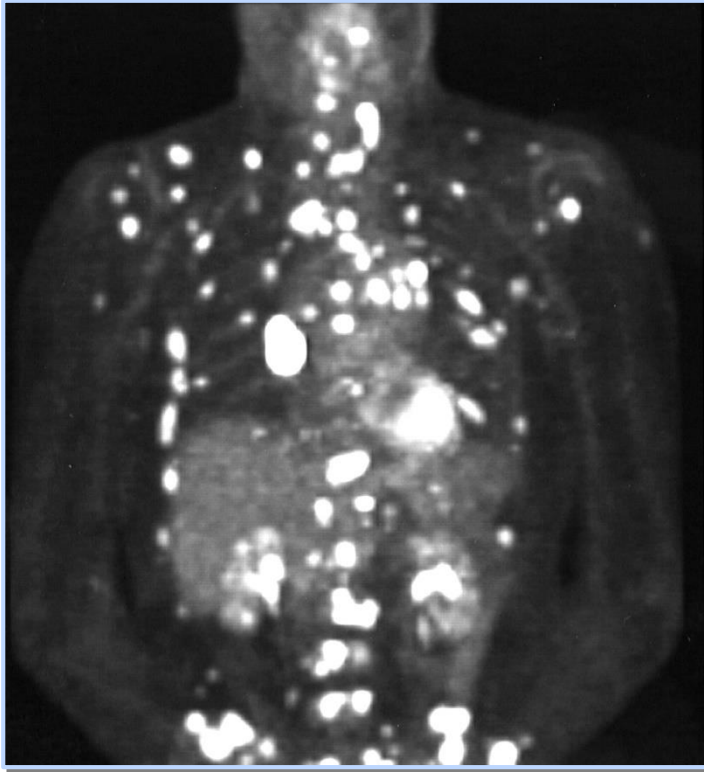
# **$^{18}\text{F}$ -FDG PET/CT for DTC**

## **Role of Recombinant TSH**

- More sensitive than non-stim PET
- Changes management in 9%
- Usually useful when Tg+, WBS–
- Most useful when Tg elevated but not very high
- Available in most nuclear medicine departments

# $^{18}\text{F}$ -FDG PET/CT

## Hurthle Cell Carcinoma



History of **Hürthle cell** cancer & complaints of diffuse aches. CT indeterminate lung nodule with some mediastinal adenopathy; US and  $^{131}\text{I}$  scans negative. PET image showed widespread bone and lung metastases, confirmed with right hilar biopsy.

**$^{18}\text{F}$ -FDG PET** of patients with Hürthle cell carcinoma.  
Lowe VJ, Mullan BP, Hay ID, McIver B, Kasperbauer JL.  
J Nucl Med. 2003



# Recurrent Thyroid Cancer

## Considerations in Management: Rx or observation?

- Risks associated with recurrent disease
- Impact of disease on mortality
- Risks of additional therapies
- Risks of observation

# Observation vs Intervention

- **Biochemical Incomplete Response**
  - Persistent abnormal Tg in absence of localizable disease
  - Trend in Tg
  - Tg doubling time
- **Structural Incomplete response**
  - Persistent or newly identified local or distant mets
  - Size
  - Location
  - Rate of change
  - FDG activity
  - Histology

# Goals of Follow-Up?

## Evolving Management Approach

**1960-2000**

**Seek and destroy residual/recurrent thyroid cancer**

Surgery/RAI/EBRT/Systemic therapy

To improve clinical outcomes

**2001-2020**

**Identify clinical significant residual/recurrent disease**

Observe clinically insignificant disease

Treat clinically significant disease

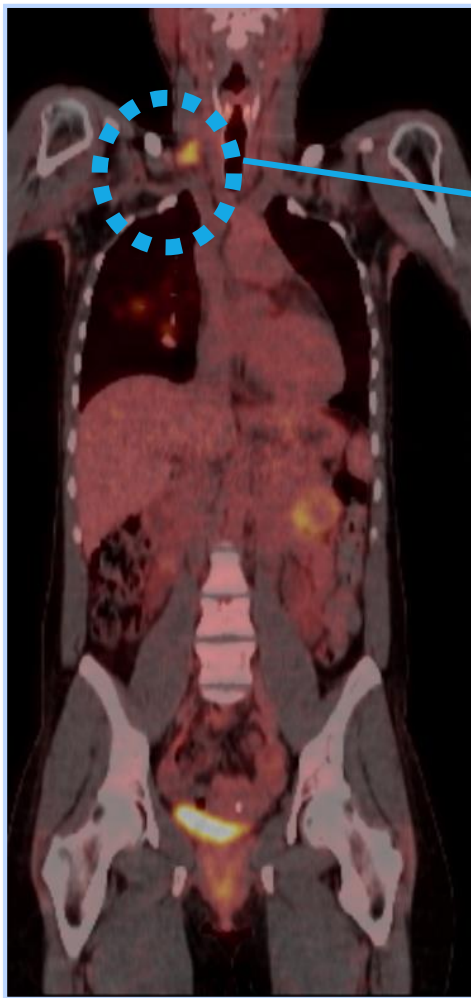




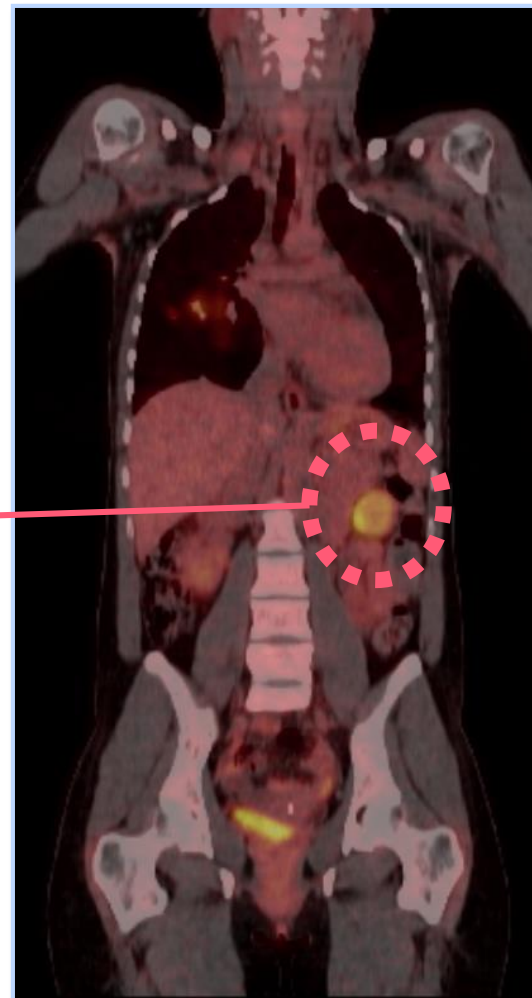
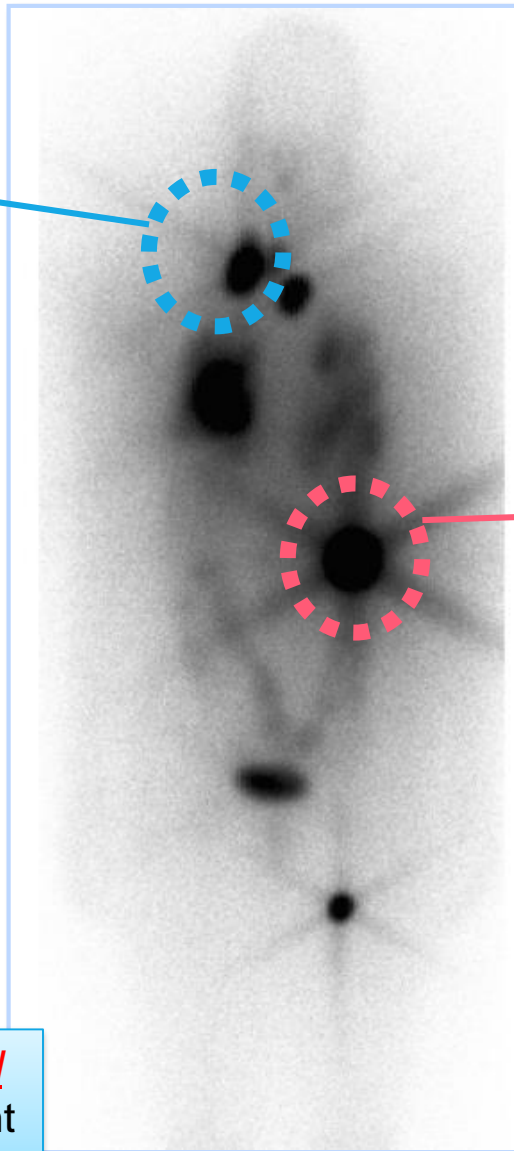
**Thank you**







High uptake of both  $^{131}\text{I}$  and FDG in a metastatic LN right lower neck



High uptake of both  $^{131}\text{I}$  and FDG in metastasis in the left kidney

# $^{18}\text{F}$ -FDG PET/CT for DTC

High jugular chain LNs metastases are not seen well on US

