Recurrent Thyroid Cancer:
How to Detect & When to Treat

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Disclosures

• None

Thanks

• My special thanks for the invitation to participate at this meeting, and for the honor of speaking to your group today
Increasingly Sensitive Tools for Disease Detection

CXR

Supp Tg
Stim Tg

RAI

Ultrasound

FDG PET

The result
Much higher rates of persistent disease than previously known
Increasingly Sensitive Tools for Disease Detection

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

CXR
Supp Tg
Stim Tg
RAI
Ultrasound
FDG PET
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,1,2 Jaime L Wiebel,3 Cui Guo,1 Brittany Gay,4 Megan R Haymart2,4,5

Use of Imaging

- Disease-specific death
- Diagnosis
- Imaging tests
- Treatment for recurrence

Trends in Use of Specific Treatments

- Surgery
- Radiotherapy
- Radioactive iodine Rx
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
• Cause of increased pt anxiety & cost
Tools in Thyroid Cancer Surveillance

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

- Not all thyroid cancers secrete Tg
- Tumors may differentiate & cease making Tg or trap $^{131}$I
- Always use same assay for same pt
- Always obtain TgAb
- No Tg “normal” range after Tx
# Thyroglobulin (Tg) Assays

<table>
<thead>
<tr>
<th></th>
<th>Radioimmunoassay (RIA)</th>
<th>Immunometric (ICMA, IRMA)</th>
</tr>
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<tbody>
<tr>
<td><strong>Method</strong></td>
<td>Single Ab</td>
<td>Double Ab</td>
</tr>
<tr>
<td><strong>Functional sensitivity ng/mL</strong></td>
<td>0.7-2.0</td>
<td>0.1-0.6</td>
</tr>
<tr>
<td><strong>TgAb</strong></td>
<td>Resistant</td>
<td>Susceptible</td>
</tr>
<tr>
<td><strong>TgAb+</strong></td>
<td>Generally unaffected</td>
<td>False low value</td>
</tr>
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</table>
Anti-Thyroglobulin Antibodies (TgAb)

• Are present in 30% of thyroid cancer pt
• In 50% of pt initially (+), TgAbs become undetectable in 1-2 yrs
• Considered an alternative “tumor marker”
• 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

Percent evolving to a Tg <1 ng/mL with observation

- <1 ng/mL: 99% (n=181)
- 1-5 ng/mL: 54% (n=69)
- 5-10 ng/mL: 19% (n=21)
- >10 ng/mL: 7% (n=28)

Padovani, et al Thyroid 2012
Serum Tg Levels Continue to Decline For Years After TTX & RAI Remnant Ablation With Continued Observation

Cumulative percent achieving nadir suppressed Tg

- 58% at 6 months
- 75% at 12 months
- 81% at 18 months
- 85% at 24 months
- 89% at 36 months
- 94% at 48 months

Padovani, et al Thyroid 2012
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 ↑ 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 $^{131}$I Rx
### Parameters of Favorable Outcome After Initial Tx & RAI Rx

<table>
<thead>
<tr>
<th>Category</th>
<th>Definitions</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent Response</td>
<td>Suppressed Tg&lt;1</td>
<td>1-4% recurrence rates</td>
</tr>
<tr>
<td></td>
<td>Stimulated Tg&lt;1</td>
<td>&lt;1% Dz-specific death rate</td>
</tr>
<tr>
<td></td>
<td>Negative TgAb</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative imaging</td>
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</table>

Haugen et al: Thyroid. 2016;26:1-133
Follow-Up of DTC

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

- $^{131}$I Whole Body Scan  
  23 (45%)

- Tg > 2 ng/ml (off T4 therapy)  
  29 (57%)

- Tg detectable  
  34 (67%)

- Ultrasound  
  48 (94%)

Frasoldati, et al; Cancer 2003
Ultrasonographically Detected Small Thyroid Bed Nodules Identified After Total Thyroidectomy for Differentiated Thyroid Cancer Seldom Show Clinically Significant Structural Progression

Geneviève Rondeau, Stephanie Fish, Lucy E. Hann, James A. Fagin, and R. Michael Tuttle

9 Patients With Biopsy Proven Disease

Subcm thyroid bed nodules
191 patients
5 mm (2-11 mm)
9% increased in size over 5 yrs follow up
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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disordered vascularity</td>
<td>86%</td>
<td>82%</td>
</tr>
<tr>
<td>Microcalcifications</td>
<td>45%</td>
<td>100%</td>
</tr>
<tr>
<td>Cystic Degeneration</td>
<td>11%</td>
<td>100%</td>
</tr>
<tr>
<td>Absence of Hilar Line</td>
<td>95%</td>
<td>20%</td>
</tr>
<tr>
<td>Hypoechoic Echotexture</td>
<td>39%</td>
<td>18%</td>
</tr>
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</table>

Lebouleux: JCEM, 2007
Papillary Carcinoma
Small Round Nodes – Malignant
Papillary Carcinoma
Small Round Nodes – Malignant
Malignant Node  Cystic Necrosis
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 WBS avoids some
Diagnosis of Recurrent DTC in 51 of 494 Patients

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

Frasoldati, et al; Cancer 2003
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
- Post-op TTx for PTC
- $^{123}$I scan after THW
- Thyroid bed uptake 5.9%
- Rx 50 mCi
FTC with Lung Metastasis
• 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

- **Complete remission**
- **Tg positive, no evidence of disease**
- **Recurrence**

<table>
<thead>
<tr>
<th>Ablation-Tg (μg/liter)</th>
<th>Percentage of patients</th>
</tr>
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<tbody>
<tr>
<td>≤2 (n=125)</td>
<td>80%</td>
</tr>
<tr>
<td>&gt;2 &amp; ≤10 (n=79)</td>
<td>60%</td>
</tr>
<tr>
<td>&gt;10 (n=64)</td>
<td>40%</td>
</tr>
</tbody>
</table>

Kim et al: J Clin Endocrinol Metab 2005;90:1440-1445
Q: What level of post-op Tg should prompt RAI Rx?

A: Optimal cut-off value for post-op Tg (suppressed or stimulated) to guide RAI Rx is not known*

*ATA Guidelines, 2015
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 $^{99m}$Tc, $^{123}$I or $^{131}$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

![FDG structure](image.png)

**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

\[
\text{SUV} = \frac{\text{radioactivity concentration in a selected part of the body}}{\text{radioactivity concentration in the hypothetical case of an even distribution throughout the whole body}}
\]
\(^{18}\text{F-FDG PET/CT for Differentiated Thyroid Cancer}\)

- Useful in evaluation for recurrent disease in pt when Tg+, WBS–
- Less differentiated cancer causes ↑ glucose metabolism but ↓ 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%*

*Dong et al: Nuc Med Commun, 2009
Papillary Thyroid Cancer
Iodine Negative $^{18}$F-FDG PET/CT Positive
Metastatic Papillary Thyroid Cancer

F18-FDG PET/CT
High uptake of both $^{131}$I and FDG in a metastatic LN right lower neck

High uptake of both $^{131}$I and FDG in metastasis in the left kidney
18F-FDG PET/CT for DTC

High jugular chain LNs metastases are not seen well on US
18F-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
History of Hürthle cell cancer & complaints of diffuse aches.
CT indeterminate lung nodule with some mediastinal adenopathy; US and 131I scans negative. PET image showed widespread bone and lung metastases, confirmed with right hilar biopsy.
FDA Approved MKI Drugs

- DTC…Sorafenib; lenvatinib
- MTC…Vandetinib; cobazantinib
- ATC…Dabrafenib; trametinib
- PTC first choice: Lenvatinib
- MTC first choice: Vandetinib
Recurrent Thyroid Cancer
Considerations in Management: Rx or observe?

• 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

<table>
<thead>
<tr>
<th>1960-2000</th>
<th>Seek and destroy residual/recurrent thyroid cancer</th>
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<tbody>
<tr>
<td></td>
<td>Surgery/RAI/EBRT/Systemic therapy</td>
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<tr>
<td></td>
<td>To improve clinical outcomes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2010-</th>
<th>Identify clinical significant residual/recurrent disease</th>
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<tbody>
<tr>
<td></td>
<td>Observe clinically insignificant disease</td>
</tr>
<tr>
<td></td>
<td>Treat clinically significant disease</td>
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Thank you