Long Term Follow-up and Surveillance of Thyroid Cancer

Using response to therapy assessments to guide follow-up recommendations

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Disclosures

**Consultant**
- Genzyme/Sanofi
- Veracyte
- Bayer/Onyx
- Novo Nordisk

**Research Support**
- Genzyme/Sanofi
Evolving Management Approach

Born September 27, 1936
Passed away May 14, 2013
Married 55 yrs to Florence (Marolt)
4 children (Patricia, Mike, Sharon, Ernest Jr)
14 grandchildren

B.S. in Biology and M.D. at The Ohio State University in 1962
United States Air Force from 1964-72
University of Nevada-Reno, Chairman of Internal Medicine
Division Director of Endocrinology at OSU
Chairman of Internal Medicine, 1984-1999

Authored >160 peer reviewed articles, >150 editorials, case studies, and abstracts, and edited or co-authored 53 medical texts

Above all of his accomplishments in medicine, he was most proud of the thousands of students, interns, residents, and fellows that he mentored throughout his illustrious career; however, he always said that his marriage to his wife and the accomplishments of his children were his greatest achievements in life.

1990 returned to active duty during Desert Storm
Evolving Management Approach

Born an Endocrinologist, Raised by Surgeons

E. Mazzaferri

L. Wartofsky, K. Burman

A. Shaha

R. Robbins

J. Shah

M. Tuttle
Goals of Follow-up?

The answer depends on when you asked me

1990's
Seek and destroy residual/recurrent thyroid cancer
Surgery/RAI/EBRT/Systemic therapy
To improve clinical outcomes

How did seek and destroy become the holy grail of thyroid cancer therapy?

Major clinical trial result?
Major unmet need?
Driven by technology?
“Common Sense”? 
Goals of Follow-up?

It ain't what you don't know that gets you into trouble.

It's what you know for sure that just ain't so.

How did seek and destroy become the holy grail of thyroid cancer therapy?

Major clinical trial result?
Major unmet need?
Driven by technology?
“Common Sense”? 
Goals of Follow-up?

This was the prevailing paradigm at the time

1990's
Seek and destroy residual/recurrent thyroid cancer
Surgery/RAI/EBRT/Systemic therapy
To improve clinical outcomes

Voices of Concern

I Hay  K Heller  P Singer  A Shaha
"Establishing optimal follow-up paradigms for patients with DTC remains challenging. Yet it is important, because even modest increments in detecting occult tumor that is ameneable to treatment will benefit many patients."
Increasingly Sensitive Tools for Disease Detection

CXR

Supp Tg
Stim Tg

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
Increasingly Sensitive Tools for Disease Detection

Results of these additional treatments

Sometimes were beneficial

Repeated doses of RAI seldom cured the patient

Most patients had persistent disease after repeat neck dissections

Small incidence of clinically significant side effects
Ultrasonographically Detected Small Thyroid Bed Nodules Identified After Total Thyroidectomy for Differentiated Thyroid Cancer Seldom Show Clinically Significant Structural Progression

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
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
166 differentiated thyroid cancer patients
With suspicious lateral neck LN’s by US
Followed with serial US (median of 6)
Median of 3.5 yrs (range 1–13 yrs)

Median LN size: 1.3 cm (0.5 – 2.7 cm)
Abnormal features: 41% hypervascular,
40% microcalcifications, 24% cystic,
70% with multiple suspicious features
Active Surveillance

Growth of Suspicious LN

- ≥ 3 mm: 33/166 (20%)
- ≥ 5 mm: 15/166 (9%)

Time to progression: 2 years

E Robenshtok, JCEM 2012
FNA Proven Cervical LN Mets

22 patients with documented PTC in the abnormal LN's

Salvage therapy was effective at the time of progression

Expected selection bias: none with PDTC, 91% classical PTC

E Robenshtok, JCEM 2012
Observation of Abnormal Tg in the Absence of Structurally Identifiable Disease

25 yr old male, 3 cm PTC, 12/38 LN + 100 mCi RAI

<table>
<thead>
<tr>
<th>Year</th>
<th>Supp Tg</th>
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<tbody>
<tr>
<td>2001</td>
<td>5.3</td>
</tr>
<tr>
<td>2002</td>
<td>5.1</td>
</tr>
<tr>
<td>2003</td>
<td>5.0</td>
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<td>2004</td>
<td>4.8</td>
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<td>2010</td>
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<tr>
<td>2011</td>
<td>2.9</td>
</tr>
<tr>
<td>2012</td>
<td>2.5</td>
</tr>
<tr>
<td>2013</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Diagnostic RAI Scan
1 year later
US negative
Supp Tg 5.3
Stim Tg 26.9
Serum Tg levels continue to decline for years after total thyroidectomy and RAI remnant ablation with observation.
6 month suppressed Tg values predict the likelihood of eventually developing a suppressed Tg <1 ng/mL with continued observation.

<table>
<thead>
<tr>
<th>Suppressed Tg at 6 months (ng/mL)</th>
<th>Percent evolving to a Tg &lt;1 ng/mL with observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 (n=181)</td>
<td>99%</td>
</tr>
<tr>
<td>1-5 (n=69)</td>
<td>54%</td>
</tr>
<tr>
<td>&gt;5-10 (n=21)</td>
<td>19%</td>
</tr>
<tr>
<td>&gt;10 (n=28)</td>
<td>7%</td>
</tr>
</tbody>
</table>

Padovani, Tuttle Thyroid 2012
Favourable course of disease after incomplete remission on $^{131}$I therapy in children with pulmonary metastases of papillary thyroid carcinoma: 10 years follow-up

Johannes Biko • Christoph Reiners •
Michael C. Kreissl • Frederik A. Verburg •
Yuri Demidchik • Valentina Drozd

Course of Tg levels in 20 patient with pulmonary mets during and after cessation of RAI therapy
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 Tortalano, 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
Increasingly Sensitive Tools for Disease Detection

**Clinical Findings**
- Disease foci that require treatment
- Low level Tg abnormalities often stable or resolve spontaneously
- Structural disease that is often stable for years

**Which patients benefit from highly sensitive disease detection tools?**
Clinical Status During Follow-up

Excellent Response
No clinical, biochemical, or structural evidence of disease

Biochemical Incomplete Response
Persistent abnormal thyroglobulin values in the absence of localizable disease

Structural Incomplete Response
Persistent or newly identified loco-regional or distant metastases

Indeterminate Response (Acceptable)
Non-specific biochemical or structural findings which cannot be confidently classified as either benign or malignant

Excellent Response to Therapy (Remission)
No clinical, biochemical, or structural evidence of disease

19 retrospective studies
After total thyroidectomy and RAI ablation
Risk of recurrence 1-5% (median 1.8%)
Over 5-10 yrs of follow-up

Clinical Implications of Response to Therapy

Outcome Classes

Clinical Outcomes after 5-10 yrs of follow-up

- 34% evolve to NED with no additional therapy
- 35% are NED after additional treatments
- Only 8-17% develop structural disease (almost always with rising Tg or Tg Ab over time)

No disease specific deaths

Biochemical Incomplete
Persistent abnormal thyroglobulin values in the absence of localizable disease

Clinical Implications of Response to Therapy
Outcome Classes

**Structural Incomplete**

Persistent or newly identified loco-regional or distant metastases

**Clinical Outcomes after 5-10 yrs of follow-up**

Despite additional treatments, the majority have persistent structural disease at final follow-up

- 11% death rate with structural loco-regional disease
- 57% death rate with structural distant mets

Clinical Implications of Response to Therapy

Outcome Classes

Indeterminate (Acceptable)
Non-specific biochemical or structural findings which cannot be confidently classified as either benign or malignant

Clinical Outcomes after 5-10 yrs of follow-up

15-20% are diagnosed with persistent/recurrent disease

80-85% are stable or have the non-specific finding resolve

No deaths

Tuttle Thyroid 2010, Vaisman Clin Endo 2012
Modifying Management Recommendations Based on Response to Therapy

**Excellent Response**
No clinical, biochemical, or structural evidence of disease

**Biochemical Incomplete Response**
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**Structural Incomplete Response**
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*Tuttle. Thyroid 2010*  
*Vaisman. Clin Endo 2012*  
*Vaisman. Thyroid 2011*
Goals of Follow-up?

Evolving Management Approach

1990's
Seek and destroy residual/recurrent thyroid cancer
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To improve clinical outcomes

2013
Identify patients that are likely cured
Less aggressive monitoring and TSH suppression
Identify clinically significant residual/recurrent disease
Observe clinically insignificant disease
Treat clinically significant disease
Three Eras of the Management of Thyroid Cancer

Keith Heller, NYU

The Age of Palpation

The Age of Detection

The Age of Reason

Tg  US