Strategies for detection of recurrent disease in long-term follow-up of differentiated thyroid cancer

A rational approach to long-term follow-up based on dynamic risk assessment.
World Congress on Thyroid Cancer
July 12, 2013

• Douglas S Ross, Massachusetts General Hospital, Boston, MA USA
• Leonard Wartofsky, Washington Hospital Center, DC USA
• Mario Vaisman, Universidade de Federal do Rio de Janeiro, Brazil
Disclosures

- Douglas S Ross
  Genzyme consultant and research
- Leonard Wartofsky
  Genzyme consultant and speaker
  IBSA consultant
  Asurogen consultant
- Mario Vaisman
  None
Dynamic Risk Stratification
Risk Stratification

• Staging Predicts Mortality

• The majority of thyroid cancer patients are low-risk for dying and are being followed for recurrence
Papillary Thyroid Carcinoma - Age

Dying of pap ca. cumulative %

Years after initial Treatment

- < 50 (883)
- 50-59 (319)
- 60-69 (210)
- ≥ 70 (88)

Hay IA End and Metab
Clin NA 1990; 19: 545
Papillary Thyroid Carcinoma - Size

Dying of pap. ca. cumulative %

Years after initial treatment

> 7cm (40)

4.0-6.9cm (183)

2.0-3.9cm (485)

< 2 cm (792)

p < 0.0001

Hay IA End and Metab Clin NA 1990; 19: 545
Papillary Thyroid Carcinoma - Death

Dying of pap ca. cumulative %

Distant Metastases (32)

Extrathyroidal Only (191)

Intrathyroidal only (1277)

Years after initial treatment

Hay IA End and Metab Clin NA 1990; 19: 545
TNM Stage

UNDER AGE 45

STAGE 1
unless…

STAGE 2
DISTANT METS

AGE 45 OR OLDER

STAGE 1 : T1 < 2 cm
STAGE 2 : T2 < 4 cm
STAGE 3: T3 >4 cm,
MINOR
EXTRATHYROIDAL
CENTRAL NODAL METS

STAGE 4
LATERAL NODAL METS
EXTRATHYROIDAL
OR DISTANT METS
MACIS Score

M : 3.0 for distant metastases
A : 3.1 (≤ Age 39 )
0.08 x Age ≥ 40
C : 1.0 incomplete surgery
I : 1.0 locally invasive
S : 0.3 x size (cm.)
<table>
<thead>
<tr>
<th>MACIS Score</th>
<th>20 Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6.0</td>
<td>99 %</td>
</tr>
<tr>
<td>6.0 - 6.99</td>
<td>89 %</td>
</tr>
<tr>
<td>7.0 - 7.99</td>
<td>56 %</td>
</tr>
<tr>
<td>8.0 +</td>
<td>24 %</td>
</tr>
</tbody>
</table>

Hay IA et al.  Surgery 1993; 114, 1050
SEER INCIDENCE RATES FOR THYROID CANCER

- 1975  4.85 / 100,000
- 2007  11.99 / 100,000
- 2009  14.25 / 100,000
SEER DEATH RATES FOR THYROID CANCER

• 1975 0.55 / 100,000

• 2009 0.52 / 100,000
PERCENTAGE OF MICROCARCINOMAS

- 1960-1980: 5.1%
- 1981-1990: 16.1

QUEEN ELIZABETH HOSPITAL
HONG KONG
1348 PATIENTS

CHOW ET AL CLIN ONC 2003; 15:329
PERCENTAGE OF MICROCARCINOMAS

• UNIVERSITY WISCONSIN 42 %
• UNIVERSITY FERRARA 40 %
• JEWISH GENERAL, MONTREAL 49.9 %

CHEEMA ET AL ANN SURG ONC 2006;13:1524
ROTI ET AL JCEM 2006;91:2171
PAKDAMAN ET AL OTOLARYNGOLOGY 2008;139:218
Recurrence ≠ Mortality
Papillary Thyroid Carcinoma

Age at initial treatment

Rate per 1000 of post-op events

Post-Op Nodes

Local Recurrences
Distant Metastases

McConahey et al
Mayo Clin Proc
1986; 61:978
ATA Risk Stratification for Recurrence

<table>
<thead>
<tr>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastases - nodes    distant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete Resection - +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrathyroidal - micro    macro</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High grade - +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAIU other than bed - +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high Tg +</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Dynamic Risk Stratification

- “Restaging”
- “Reclassification” of risk based on initial response to therapy
Response to Initial Therapy

- Excellent
- Biochemical incomplete response
- Structural incomplete response
- Indeterminate response

Tuttle RM UpToDate 2013
Excellent response

No clinical, biochemical, or structural evidence of disease
Biochemical Incomplete Response

Abnormal thyroglobulin values in the absence of localizable disease
Structural Incomplete Response

Persistent or newly identified loco-regional or distant metastases
Indeterminate Response

Non-specific biochemical or structural findings which cannot be confidently classified as either benign or malignant
<table>
<thead>
<tr>
<th></th>
<th>low</th>
<th>intermediate</th>
<th>high</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial risk of recurrence</td>
<td>3%</td>
<td>18%</td>
<td>66%</td>
</tr>
<tr>
<td>Excellent response</td>
<td>2%</td>
<td>2%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Tuttle et al 2010
Dynamic Risk Stratification

- Case 1  TNM Stage 1  ATA low Risk
- Case 2  TNM Stage 1  ATA intermediate Risk

For each case we will discuss three different “responses to initial therapy.”
Case 1 A

• 28 year old woman
• 17 mm right intrathyroidal papillary cancer
• no nodes
• given 30 mCi radioiodine to ablate thyroid remnants
• Iodine scan shows uptake in thyroid bed only
Reassessment at 6 months

• Ultrasound: 2 mm nodule right bed benign appearing nodes

• Thyroglobulin <0.2
Clinical Questions

• Does this patient need a follow-up iodine scan?
• Should she have a rhTSH-stimulated Tg?
• When should the ultrasound be repeated?
Follow up of Patients at Low Risk of Recurrence

R45b
Low risk patients who have had remnant ablation, negative cervical ultrasound and undetectable TSH stimulated thyrogblobulin can be followed primarily with yearly clinical examination and suppressed Tg measurements.

R49c
In patients free of disease, especially those at low risk for recurrence, the serum TSH may be kept within the low normal range (0.3–2 mU/L).

Cooper et al, Thyroid 2009
Risk Estimates Using Response to Therapy Assessment
Total Thyroidectomy & RRA (n=506, Rio de Janeiro, Median F/U 10 yrs)

Outcome at final follow up (%)

- **Excellent** (n=213):
  - NED with additional treatments: 96%
  - NED following additional treatments: 3%

- **Acceptable** (n=41):
  - NED with additional treatments: 72%
  - NED following additional treatments: 5%

- **Biochemical Incomplete** (n=99):
  - NED with additional treatments: 34%
  - NED following additional treatments: 22%

- **Structural Incomplete** (n=153):
  - NED with additional treatments: 1%
  - NED following additional treatments: 9%

*p < 0.001

Median follow up 10 yrs

Vaisman, Vaisman, Tuttle, Clin Endo, 2012
Risk Based Recommendations

Early & Long term Follow-Up

RECOMMENDATION 45
(a) In low-risk patients who have had remnant ablation and negative cervical US and undetectable TSH-suppressed Tg within the first year after treatment, serum Tg should be measured after thyroxine withdrawal or rhTSH stimulation approximately 12 months after the ablation to verify absence of disease. Recommendation rating: A

(b) Low-risk patients who have had remnant ablation, negative cervical US, and undetectable TSH-stimulated Tg can be followed primarily with yearly clinical examination and Tg measurements on thyroid hormone replacement. Recommendation rating: B
Suppressed Thyroglobulin in patients who had an excellent response to therapy - follow-up

• "NPV of 100% with Tg-ICMA on T4 < or = 0.1 ng/ml combined with neck ultrasonography " (Rosário PW., Clin Endo 2008)

• "Sensitive methods for serum Tg can be used to avoid TSH stimulation 9-12 months after surgery in low-risk patients who have an undetectable serum Tg on L-T4 treatment" (Schlumberger M, Nat Rev Endocrinol 2011)

• “Monitoring low-risk differentiated thyroid carcinoma patients with neck US and T(4)-suppressed Tg appears to be safe” (Pelttari H, Clin Endo 2008)
The role of stim Tg

- Stimulated Tg of 2 μg/liter or less had a 91.7% NPV in low risk patients (Robbins RJ., JCEM 2002)

- Combined with the negative neck US, the NPV for disease-free survival was 98% after the first undetectable rhTSH-stimulated Tg and 100% after the second one or third. (Klubo-Gwiezdzinska J, Clin Endo 2011)

- First undetectable rhTSH-stimulated Tg NPV 98% (Rosário PW, Thyroid 2012)
# DxWBS in patients with suppressed Tg <1

<table>
<thead>
<tr>
<th>DxWBS</th>
<th>&lt;1 ng/mL</th>
<th>1–10 ng/mL</th>
<th>&gt;10 ng/mL</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>146</td>
<td>31</td>
<td>6</td>
<td>183</td>
</tr>
<tr>
<td>Uptake only in thyroid bed (^a)</td>
<td>25</td>
<td>8</td>
<td>2</td>
<td>35</td>
</tr>
<tr>
<td>Ectopic uptake</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>171</strong></td>
<td><strong>39</strong></td>
<td><strong>8</strong></td>
<td><strong>218</strong></td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>DxWBS</th>
<th>&lt;1 ng/mL</th>
<th>1–5 ng/mL</th>
<th>&gt;5 ng/mL</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>74</td>
<td>13</td>
<td>2</td>
<td>89</td>
</tr>
<tr>
<td>Uptake only in thyroid bed (^a)</td>
<td>8</td>
<td>3</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Ectopic uptake</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>82</strong></td>
<td><strong>16</strong></td>
<td><strong>2</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

Rosário PW et al, thyroid 2012
Case 1 A (continued)

• One year after presentation:
  Tg after rhTSH is <0.2

• When should repeat stimulation testing be performed?
LIMITED VALUE OF REPEATED rhTSH STIMULATION TESTS

• Basal & stimulated Tg undetectable in 68 pts (one of whom had lymph nodes)
• rhTSH-Tg retested 2-3 yrs later
• 66/67 (98.5%) negative (all except pt with LN’s on U/S)
• Conclusion: Probably no need for repeat testing

Castagna et al., J Clin Endocrinol Metab 2008; 93: 76-81
DOES AN UNDETECTABLE rhTSH-Tg ONE YR POST RX INDICATE CURE?

Clin Endo 2011; 74:111-117

- 278 pts (Stages I – IV) who had repeated rhTSH testing
- F/U 3-12 yrs; 2-7 rhTSH tests
- 11 pts (4%) had evidence of disease based on 2nd or 3rd stimulated Tg [5/11 false+]
- Together with a negative neck U/S, NPV for disease free survival was 98% after first rhTSH stim test and 100% after second
Are repeated rhTSH-stimulated Tg measurements necessary in follow up of WDTC patients?

<table>
<thead>
<tr>
<th></th>
<th>NPV</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{st} stim Tg</td>
<td>97.8%</td>
<td>-</td>
</tr>
<tr>
<td>2\textsuperscript{nd} stim Tg</td>
<td>99.6%</td>
<td>80%</td>
</tr>
<tr>
<td>2\textsuperscript{nd} stim Tg+ US</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Conclusions

1. Frequency & intensity of F/U should be adjusted to new risk estimates evolving with time.

2. A first rhTSH-stimulated Tg at 1 yr after initial Rx is an excellent predictor for remission and long-term disease-free survival independent of clinical stage at presentation, but is not infallible.

3. One additional rhTSH-Tg stimulation test at 3 years together with neck U/S provides a NPV of 100% and Sensitivity of 100%.

Klubo et al, Clin Endocrinol 74: 111, 2011
Case 1 B

- 28 year old woman
- 17 mm right intrathyroidal papillary cancer
- no nodes
- given 30 mCi radioiodine to ablate thyroid remnants
- Iodine scan shows uptake in thyroid bed only
Reassessment at 6 months

- Ultrasound: 6 mm indeterminate right node
  internal blood flow
  possible microcalcification

- Thyroglobulin 2.5
Clinical Questions

• Does this patient need a follow-up iodine scan?
• Should she have a rhTSH-stimulated Tg?
• Should the node be biopsied or followed?
• If followed, when should she have the next ultrasound?
• If biopsy is positive, role of surgery versus ethanol ablation?
**Neck Ultrasound**

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any suspicious feature in thyroid bed nodule*</td>
<td>0.80</td>
<td>0.52</td>
<td>0.12</td>
<td>0.97</td>
</tr>
<tr>
<td>Microcalcifications in thyroid bed nodule</td>
<td>0.74</td>
<td>0.56</td>
<td>0.28</td>
<td>0.90</td>
</tr>
<tr>
<td>Increased vascularity in thyroid bed nodule</td>
<td>0.75</td>
<td>0.54</td>
<td>0.21</td>
<td>0.93</td>
</tr>
<tr>
<td>Avascular thyroid bed nodule</td>
<td>0.19</td>
<td>0.47</td>
<td>0.30</td>
<td>0.87</td>
</tr>
<tr>
<td>Other abnormal cervical lymph nodes</td>
<td>0.74</td>
<td>0.53</td>
<td>0.17</td>
<td>0.94</td>
</tr>
<tr>
<td>Rising serum Tg</td>
<td>0.77</td>
<td>0.55</td>
<td>0.24</td>
<td>0.93</td>
</tr>
<tr>
<td>Combination of any suspicious features, other abnormal cervical lymph nodes and rising serum Tg</td>
<td>0.88</td>
<td>0.31</td>
<td>0.11</td>
<td>0.96</td>
</tr>
</tbody>
</table>

*Suspicious features defined as microcalcifications, hypoechogenicity, or increased vascularity in any thyroid bed nodule

Rondeau G, Thyroid 2011
Case 1 C

- 28 year old woman
- 17 mm right intrathyroidal papillary cancer
- no nodes
- given 30 mCi radioiodine to ablate thyroid remnants
- Iodine scan shows uptake in thyroid bed only
Reassessment at 6 months

• Ultrasound: nothing in the thyroid bed
  no lymphadenopathy

• Thyroglobulin 25
Clinical Questions

• Does this patient need a follow-up iodine scan? Withdrawal or rhTSH?
• Should she have a rhTSH-stimulated thyroglobulin?
• What other imaging should she have? Would you obtain this before or after an iodine scan?
Dx WBS

- In 75 pts with post-ablation WBS with uptake only in thyroid bed; Dx’tic WBS during follow up had sensitivity of 16% (Leboulleux S, thyroid 2012)

- Distant Mets + Neg Dx’tic WBS/ positive post therapy scan $\rightarrow$ no clinical benefit from empiric RAI treatment (Sabra MM, Thyroid 2012)

- May be useful for patients with positive TgAb (Rosário PW, Thyroid 2012)
High Tg only

Thyroidectomy + I-131

- Get neck US
- Get rhTSH or THW stimulated Tg if Tg undetectable on TH

Surgery

- YES

Get chest CT* w/o contrast if Tg detectable on TH, or >2 ng/mL after stimulation

- Is the neck US+, chest CT-, & the Tg level consistent with the volume of visualized disease?
- If distant disease present, is neck central compartment disease >1 cm present?

- NO

Get stimulated FDG PET/CT scan +/- simultaneous DxWBS if:
- Tg >2 ng/mL on TH, or
- >5 ng/mL after rhTSH, or
- >10 ng/mL after THW

- PET+

Consider surgery, EBRT, RFA, tumor embolization, or clinical trial

- PET-

Consider I-131 therapy and RxWBS

- NO

Consider additional I-131 therapy if RxWBS positive, and significant Tg or tumor volume reduction

Kloos R JCEM 2008
PET/CT in localizing Mets

<table>
<thead>
<tr>
<th>Author</th>
<th>Nr. of patients</th>
<th>TSH status</th>
<th>131-I-WBS</th>
<th>PET scan</th>
<th>Nr. of patients</th>
<th>PET sensitivity</th>
<th>PET specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grunwald (^{29})</td>
<td>222</td>
<td>Not stimulated</td>
<td>Negative</td>
<td>PET</td>
<td>40</td>
<td>94%</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive</td>
<td>PET</td>
<td>6</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stimulated</td>
<td>Negative</td>
<td>PET</td>
<td>101</td>
<td>77%</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive</td>
<td>PET</td>
<td>40</td>
<td>80%</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>Ching (^{30})</td>
<td>54</td>
<td>Not Stimulated</td>
<td>Negative and Positive</td>
<td>PET</td>
<td>54</td>
<td>94%</td>
<td>95%</td>
</tr>
<tr>
<td>Schluter (^{33})</td>
<td>64</td>
<td>Both</td>
<td>Negative and Positive</td>
<td>PET</td>
<td>64</td>
<td>69%</td>
<td>42%</td>
</tr>
<tr>
<td>Gabriel (^{35})</td>
<td>36</td>
<td>Not stimulated</td>
<td>Negative</td>
<td>PET</td>
<td>36</td>
<td>88%</td>
<td>50%</td>
</tr>
<tr>
<td>Iwata (^{36})</td>
<td>19</td>
<td>Stimulated</td>
<td>Negative and positive</td>
<td>PET</td>
<td>19</td>
<td>81%</td>
<td>NE</td>
</tr>
<tr>
<td>Palmedo (^{37})</td>
<td>40</td>
<td>Stimulated</td>
<td>Negative</td>
<td>PET</td>
<td>40</td>
<td>79%</td>
<td>76%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PET/CT</td>
<td>40</td>
<td>95%</td>
<td>91%</td>
</tr>
<tr>
<td>Mirallić (^{38})</td>
<td>45</td>
<td>Stimulated</td>
<td>Negative</td>
<td>PET/CT</td>
<td>45</td>
<td>63%</td>
<td>77%</td>
</tr>
<tr>
<td>Freudenberg (^{39})</td>
<td>36</td>
<td>Stimulated</td>
<td>Negative</td>
<td>PET/CT</td>
<td>36</td>
<td>82%</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PET/CT</td>
<td>36</td>
<td>96%</td>
<td>79%</td>
</tr>
<tr>
<td>Finkelstein (^{41})</td>
<td>65</td>
<td>NA</td>
<td>Negative</td>
<td>PET/CT</td>
<td>65</td>
<td>98%</td>
<td>81%</td>
</tr>
<tr>
<td>Kim (^{42})</td>
<td>20</td>
<td>Not stimulated</td>
<td>Negative (123-Iodine)</td>
<td>PET/CT</td>
<td>20</td>
<td>90%</td>
<td>NE</td>
</tr>
<tr>
<td>Esteva (^{43})</td>
<td>50</td>
<td>Stimulated</td>
<td>Negative</td>
<td>PET/CT</td>
<td>50</td>
<td>82%</td>
<td>64%</td>
</tr>
</tbody>
</table>

NE: not evaluable due to the small number of patients; NA: not available.

Pace et al., Q J Nucl Med Mol Imaging, 2009
Case 2 A

- 22 year old woman
- 12 mm right intrathyroidal papillary cancer
- 14 of 32 central and lateral nodes positive
- Given 100 mCi radioiodine
- Post-treatment scan shows uptake in the central neck
Reassessment at 6 months

• Ultrasound: nothing in the thyroid bed
  no lymphadenopathy

• Thyroglobulin <0.2
Clinical Questions

• Does this patient need a follow-up iodine scan?
• Should she have a rhTSH-stimulated Tg?
• When should an ultrasound be repeated?
# Risk Adapted Initial Follow Up

Follow up after Total Tx and RRA

*The first 2 years*

<table>
<thead>
<tr>
<th></th>
<th>6 mo</th>
<th>12 mo</th>
<th>18 mo</th>
<th>24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppressed Tg</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>US</td>
<td>-</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Stimulated Tg</td>
<td></td>
<td></td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Diagnostic WBS</td>
<td>High</td>
<td>yes</td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>CT/MRI</td>
<td>consider</td>
<td></td>
<td></td>
<td>consider</td>
</tr>
<tr>
<td>FDG PET</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Evaluate response to therapy and re-staging
Independently of the initial risk, once patients were categorized as excellent response they had NED in 99%
Case 2 B

- 22 year old woman
- 12 mm right intrathyroidal papillary cancer
- 14 of 32 central and lateral nodes positive
- Given 100 mCi radioiodine
- Post-treatment scan shows uptake in the central neck
Reassessment at 6 months

• Ultrasound: nothing in the thyroid bed
  3 indeterminate right nodes
  6, 8, and 12 mm

• Thyroglobulin 12
Clinical Questions

- Does this patient need a follow-up iodine scan?
- Should she have a rhTSH-stimulated Tg?
- Should she have a node biopsied?
- Should she have any other imaging?
- How should she be followed?
Small Lymph nodes in Follow-up

% Growth

166 pts
Size 0.5-1.2cm

Robenstok E, J Clin Endocrinol Metab. 2012
Case 2 C

- 22 year old woman
- 12 mm right intrathyroidal papillary cancer
- 14 of 32 central and lateral nodes positive
- Given 100 mCi radioiodine
- Post-treatment scan shows uptake in the central neck
Reassessment at 6 months

• Ultrasound: nothing in the thyroid bed
  no lymphadenopathy

• Thyroglobulin 6
Clinical Questions

• Does this patient need a follow-up iodine scan? Withdrawal or rhTSH?
• Should she have a rhTSH-stimulated Tg?
• Should she have other imaging? Would you order this before or after an iodine scan?
## Response to therapy (6–24 mo after initial therapy)

<table>
<thead>
<tr>
<th>Excellent response</th>
<th>Acceptable response</th>
<th>Biochemical incomplete response</th>
<th>Structural incomplete response</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the following:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Suppressed and stimulated Tg $&lt; 1$ ng/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No evidence of disease on neck US,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Additional cross-sectional and/or nuclear medicine imaging negative (if performed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any of the following:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Suppressed Tg $&lt; 1$ ng/mL with stimulated Tg $\geq 1$ and $&lt; 10$ ng/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Non-specific imaging findings without definite evidence of disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any of the following in the absence of structurally identifiable disease:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Suppressed Tg $\geq 1$ ng/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Stimulated Tg $\geq 10$ ng/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rising Tg values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any of the following regardless of Tg values:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Persistent or newly identified disease on cross-sectional imaging and/or nuclear medicine imaging</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Vaisman, Tuttle, thyroid 2011
Final Clinical Status of biochemical incomplete response group
Rio de Janeiro, Brazil

Outcome at final follow up (%)

- NED with additional treatments
- NED following additional treatments
- Persistent-Recurrent disease

Young women, low risk
AJCC/UICC and ATA and have low sup and stim Tg

p < 0.001

Median follow up 10 yrs

Vaisman, Vaisman, Tuttle, Clin Endo, 2012
Re-evaluating the Incomplete Response to Therapy

Cumulative Survival

Follow-up (yrs)

Biochemical Incomplete

Structural Incomplete
Only Loco-regional Disease

Structural Incomplete
Distant Metastases

P < 0.0001