Follow-up del carcinoma tiroideo a rischio intermedio-alto
Tg ultrasensibile o stimolo con rhTSH?

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IRCCS Casa Sollievo della Sofferenza
San Giovanni Rotondo
Summary

- Differentiated thyroid tumors follow-up (current guidelines)
- Recombinant human TSH (Thyrogen®)
- Ultra-sensitive thyroglobulin
- The next future
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• Differentiated thyroid tumors follow-up (current guidelines)
• Recombinant human TSH (Thyrogen®)
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Current guidelines

Revised ATA guidelines 2009:

• No specific paragraphs regarding intermediate/high risk patients follow-up
• Recommended initial TSH suppression in all pts. to below 0.1 mU/l until Tg stimulation is performed (6-12 months later)
Current guidelines

Criteria for absence or residual disease:

- No clinical evidence of tumor
- No imaging evidence of tumor (post-treatment WBS and neck US)
- Undetectable Tg levels during TSH suppression and stimulation, in the absence of Tg antibodies
What we know for sure

The other two thirds will show undetectable or decreasing or stable Tg levels without any signs of residual disease.
Total thyroideectomy + $^{131}$I

6 months: (LT4) TSH, Tg, TgAb

12 months: (LT4) rhTSH-Tg + US (if neg. TgAb)

- Negative Tg, no other abnormalities
  - Substitutive LT4 dose
  - Yearly controls: TSH, Tg, US

- Low positive Tg: 1-5 ng/ml, no other abnormalities
  - Repeat rhTSH-Tg 1-2 yrs later

- Tg > 5 ng/ml, negative US
  - Morphology (CT, PET/CT, etc.)
  - Eventually $^{131}$I

- Stable/decreasing Tg: no disease
  - Negative Tg
  - Eventually repeat rhTSH-Tg 1-2 yrs later

- Increasing Tg: presence of disease
  - ETA 2006, modified
Summary

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rhTSH

Rosario 2012:
Retrospective study:
318 intermediate/high-risk pts, negative for all parameters 8-12 months after ablation (including post-dose WBS, LT4-Tg <1 ng/ml, TgAb, neck US)

WBS and stimulated Tg (withdrawal or rhTSH)

Rosario et al, Thyroid 2012
### Tg measured after L-T4 withdrawal (number of patients)

<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&lt;sup&gt;a&lt;/sup&gt;</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>Total</td>
<td>171</td>
<td>39</td>
<td>8</td>
<td>218</td>
</tr>
</tbody>
</table>

### Tg measured after rhTSH (number of patients)

<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&lt;sup&gt;a&lt;/sup&gt;</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>Total</td>
<td>82</td>
<td>16</td>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>

Rosario et al, Thyroid 2012
rhTSH

Long term recurrence rate (24-96 months)

- s-Tg <1 ng/ml: 2% (5/253)
- s-Tg 1-10 or 1-5 ng/ml: 10.9% (6/55)
- s-Tg >10 or >5 ng/ml: 42.8% (3/7)

NPV of sTg<1 ng/ml: 98%

Rosario et al, Thyroid 2012
## rhTSH

<table>
<thead>
<tr>
<th>Patients</th>
<th>Persistent disease (%)</th>
<th>NPV of rhTSH1 US- and Tg- (%)</th>
<th>PPV of rhTSH1 US- and Tg+ (%)</th>
<th>Increased Tg at rhTSH2 (%)</th>
<th>Tg+ Tg- (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castagna et al 2008</td>
<td>77 (67 Tg- 10 Tg+)</td>
<td>1/77 (1.3)</td>
<td>98.5</td>
<td>0</td>
<td>4/77 (5.2) (1 with disease)</td>
</tr>
<tr>
<td>Crocetti et al 2009</td>
<td>101 (89 Tg- 12 Tg+)</td>
<td>2/101 (2.0)</td>
<td>98.9</td>
<td>16.7</td>
<td>2/101 (2.0) (1 with disease)</td>
</tr>
</tbody>
</table>

Castagna et al, JCEM 2008  
Crocetti et al, Thyroid 2009
<table>
<thead>
<tr>
<th>rhTSH2 Tg-</th>
<th>rhTSH2 Tg+</th>
<th>Increased Tg</th>
<th>Confirmed residual disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**NPV: 99%**

**PPV: 0-16.7%: undetectable**

Tg at II rhTSH in 40-50% of Tg+

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Castagna et al, JCEM 2008
Crocetti et al, Thyroid 2009
Summary

• Differentiated thyroid tumors follow-up (current guidelines)
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• Ultra-sensitive thyroglobulin
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Comparison of Seven Serum Thyroglobulin Assays in the Follow-Up of Papillary and Follicular Thyroid Cancer Patients


Tg1 (at 3 months):
Traditional assays (cut-off 0.9 g/ml):
sensitivity 19-40% (very low)

Ultra-sensitive assays (cut-off 0.2-0.3 ng/ml):
sensitivity 54-63%, specificity 89%
84% of pts: Tg on Lt4 3 months after ablation (Tg1) <0.27 pg/ml, with a NPV of 99%

Conclusions: Tg stimulation can be avoided in the great majority of patients
Retrospective study: 1029 rhTSH tests in 849 TgAb-negative pts
rhTSH-Tg >2 ng/ml in only 2/655 tests with basal Tg <0.10 ng/ml: (NPV 99.7%)

Conclusions: rhTSH test could be avoided if basal Tg <0.10 ng/ml

Similar results:
Smallridge et al 2007  Malandrino et al 2011
Chindris et al 2012  Trimboli et al 2013
Pre-ablation Tg

Meta-analysis: 15 studies including 3947 pts.

<table>
<thead>
<tr>
<th>Author, year (Ref.)</th>
<th>Country</th>
<th>Number of patients reported (included)</th>
<th>Mean age (yr)</th>
<th>Timing of preablation Tg (d)</th>
<th>Outcome type (A, B, C)</th>
<th>Follow-up (yr) (mean or range)</th>
<th>Tg cutoff (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernier, 2005 (6)</td>
<td>Germany</td>
<td>407</td>
<td>46.0</td>
<td>30</td>
<td>B</td>
<td>0.61</td>
<td>5.0</td>
</tr>
<tr>
<td>Familiar, 2009 (7)</td>
<td>Spain</td>
<td>63</td>
<td>41.0</td>
<td>NS</td>
<td>B, C</td>
<td>5.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Giovanella, 2005 (8)</td>
<td>Switzerland</td>
<td>140</td>
<td>46.0</td>
<td>28</td>
<td>A, B, C</td>
<td>1.0</td>
<td>3.2</td>
</tr>
<tr>
<td>Heemstra, 2007 (9)</td>
<td>Netherlands</td>
<td>222</td>
<td>48.0</td>
<td>NS</td>
<td>C</td>
<td>8.3</td>
<td>27.5</td>
</tr>
<tr>
<td>Kim, 2005 (10)</td>
<td>South Korea</td>
<td>268</td>
<td>44.4</td>
<td>35</td>
<td>B, C</td>
<td>5.7</td>
<td>10.0</td>
</tr>
<tr>
<td>Lin, 2002 (11)</td>
<td>China</td>
<td>847 (654)</td>
<td>40.8</td>
<td>30</td>
<td>B, C</td>
<td>3.5–6.3</td>
<td>10.0</td>
</tr>
<tr>
<td>Oyen, 2000 (12)</td>
<td>Netherlands</td>
<td>206</td>
<td>45.0</td>
<td>28</td>
<td>C</td>
<td>2.7</td>
<td>6.6</td>
</tr>
<tr>
<td>Pelttari, 2010 (13)</td>
<td>Finland</td>
<td>495 (391)</td>
<td>40.6</td>
<td>28</td>
<td>B, C</td>
<td>10–24</td>
<td>10.0</td>
</tr>
<tr>
<td>Polachek, 2011 (14)</td>
<td>Israel</td>
<td>420</td>
<td>49.2</td>
<td>28</td>
<td>B, C</td>
<td>5.1</td>
<td>10.0</td>
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<tr>
<td>Ronga, 1999 (15)</td>
<td>Italy</td>
<td>334</td>
<td>41.6</td>
<td>40</td>
<td>C</td>
<td>4.0–16.0</td>
<td>11.1</td>
</tr>
<tr>
<td>Rosario, 2011 (16)</td>
<td>Brazil</td>
<td>237</td>
<td>43.0</td>
<td>90</td>
<td>A, B, C</td>
<td>0.7–1.0</td>
<td>10.0</td>
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<tr>
<td>Sawka, 2008 (17)</td>
<td>Canada</td>
<td>141</td>
<td>43.7</td>
<td>84</td>
<td>B</td>
<td>1.2–7.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Tamilia, 2011 (18)</td>
<td>Canada</td>
<td>193</td>
<td>45.5</td>
<td>63</td>
<td>B</td>
<td>1.0–1.5</td>
<td>10.0</td>
</tr>
<tr>
<td>Toubeau, 2004 (19)</td>
<td>France</td>
<td>212 (208)</td>
<td>47.0</td>
<td>28</td>
<td>B, C</td>
<td>1.0–12</td>
<td>30.0</td>
</tr>
<tr>
<td>Webb, 2011 (20)</td>
<td>United States</td>
<td>75 (63)</td>
<td>40.7</td>
<td>28</td>
<td>B, C</td>
<td>6.6</td>
<td>10.0</td>
</tr>
</tbody>
</table>

*a* Included patients were those with sufficient data for meta-analysis. Total patients = 4260 (included 3947). NS, not stated.

*b* A, Metastatic activity on posttreatment whole-body scan; B, surveillance stimulated Tg testing; C, recurrent structural disease.

Webb et al, JCEM 2012
Pre-ablation Tg

In most studies Tg cut-off 10 ng/ml

Cut-off 10 ng/ml: NPV 94%

Webb et al, JCEM 2012
Pre-ablation Tg

Bari, 7-10 novembre 2013

1/3 of patients at intermediate-high risk

Undetectable s-Tg at 6-18 months: 99%

Nascimento et al, Endocr Relat Cancer 2011
Pre-ablation Tg

If s-Tg at ablation <1 ng/ml and negative TgAb: Tg stimulation 1 year later is useless

Nascimento et al, Endocr Relat Cancer 2011
Prognostic Impact of Serum Thyroglobulin Doubling-Time Under Thyrotropin Suppression in Patients with Papillary Thyroid Carcinoma Who Underwent Total Thyroidectomy

Akira Miyauchi, Takumi Kudo, Akihiro Miya, Kaoru Kobayashi, Yasuhiro Ito, Yuuki Takamura, Takuya Higashiyama, Mitsuhiro Fukushima, Minoru Kihara, Hiroyuki Inoue, Chisato Tomoda, Tomonori Yabuta, and Hiroo Masuoka

426 DTC patients
4 or more Tg determinations (1 at 1-3 months, than twice or once a year) with TSH <0.1 mUI/L
Median follow-up 87 months
Tg doubling time

426 pts

137: detect. Tg
≥4 measur.: Tg DT

201: undetect. Tg

69 pts: Tg

17 pts: <1 year

21 pts: 1-3 years

30 pts: >3 years

10-yrs Cause Spec. Surv.: 50%

10-yrs Cause Spec. Surv.: 95%

10-yrs Cause Spec. Surv.: 100%

Miyauchi et al, Thyroid 2011
Multivariate analysis
Tg DT only independent predictor of:
- Disease-specific mortality
- Loco-regional recurrence
- New distant metastases

DT < 1 yr: 12% (17/137) of TG+ pts: 10 yr survival 50%

Miyauchi et al, Thyroid 2011
102 Tg+ pts: Tg DT < 1 year predicts positive $^{18}$FDG-PET/CT scan

Important: $^{18}$FDG-PET/CT scan accuracy significantly improves also when basal Tg > 5.5 ng/ml

Giovanella et al, EJNM Mol Imag 2013
Summary

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Total thyroidectomy + $^{131}$I

**Ablation-Tg ≤ 1 ng/ml**
- 12 months: T4-Tg ≤ 0.1 ng/ml
- Negative Tg, no abnormalities
  - Continue substitutive LT4 dose. Yearly controls: TSH, Tg, US

**Ablation-Tg > 1 ng/ml**
- 12 months: T4-Tg > 0.1 ng/ml
- Low positive Tg: 1-5 ng/ml, no other abnormalities
  - Repeat rhTSH-Tg 1-2 yrs later
- Tg > 5 ng/ml, negative US
  - Tg DT PET/CT, $^{131}$I
- Stable/decreasing Tg: no disease
  - Eventually repeat rhTSH-Tg 1-2 yrs later
- Increasing Tg: residual disease
  - Negative Tg