Thyroid Cancer & rhTSH: When and How?

8th Postgraduate Course in Endocrine Surgery
Capsis Beach, Crete, September 21, 2006

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Increasing Incidence of Thyroid Cancer

- 24,200 new cases of thyroid cancer in 2004
- 1,500 died of thyroid cancer in 2004
- 290,000 survivors of thyroid cancer in USA
- The incidence doubled from 1990
- 4% increase per year

(2004, SEER)
Paradigm Shift in Management and Follow up of Papillary Thyroid Cancer

“… most patients who eventually achieved freedom from disease do so by surgery with fewer patients cured by repetitive radiiodine treatments ….”

Management of Differentiated Thyroid Cancer at UCSF

- Total thyroidectomy, except small incidental tumor
  - Preop ultrasound. No nerve monitoring.
- Selective node dissection, large or palpable nodes
  - Re-resection for large or palpable recurrences
- RAI ablation & therapy (thyroxin w/d or rhTSH-stim)
- Thyroid hormone to suppress TSH
- Follow up: US and rhTSH-stim Tg & RAI
- Rarely external radiation and chemotherapy
  - in advance disease for palliation
- Experimental re-differentiation therapy
Post-Thyroidectomy Surveillance for Persistent or Recurrent Cancer (UCSF)

- Total thyroidectomy
- Hormone-withdrawal RAI scan and treatment
  - Optional rhTSH-stimulated RAI scan and treatment
- Initial 6-month then yearly rhTSH-stimulated Tg & RAI scan, and neck ultrasound
  - Less frequently after several years
  - Are all three tests necessary?
- PET scan if Tg-positive but RAI-negative
- Ultrasound guided FNA to confirm neck recurrence
TSH Stimulates Iodine Uptake & Thyroglobulin Production

Spitzweg & Morris: Clin Endocrinol 57:559, 2002

Fig. 1 Schematic illustration of a thyroid follicular cell showing the key aspects of thyroid iodine transport and thyroid hormone synthesis. TSHR, TSH-receptor; NIS, sodium iodide symporter; TPO, thyroid peroxidase; Tg, thyroglobulin.
Decrease Iodine Uptake by Thyroid Cancer

**Fig. 4** Sodium iodide symporter (NIS) and its potential role in malignant thyroid disease.

Spitzweg & Morris: Clin Endocrinol 57:559, 2002
Thyroid-Hormone-Withdrawal Protocol for Initial RAI-Tx after Thyroidectomy (UCSF)

- Levothyroxine (T4) for 4-6 weeks
- Cytomel (T3) for 2-3 week
- Stop T3 for 1-2 weeks, on low iodine diet (< 50 mcg/d) until serum TSH level > 30 mU/L
- 4 mCi (148 MBq) diagnostic scan (Dx-WBS)
- 30-50 mCi for ablation or 100-200 mCi for treatment followed by post-Tx-WBS
Recombinant Human TSH-Stimulation Protocol for Follow up after Thyroidectomy (UCSF)

- **Pre-study**
  - Low iodine diet (< 50 microgram/d) for 1 week
  - Continue levothyroxine (T4) therapy

- **Day 1**
  - Blood for serum levels of Tg and TSH
  - Urine pregnancy test if indicated
  - rhTSH 0.9 mg IM – first dose

- **Day 2**
  - rhTSH 0.9 mg IM – second dose
Recombinant Human TSH-stimulation Protocol for Follow up after Thyroidectomy (UCSF)

- **Day 3**
  - $^{131}$I 4 mCi PO
- **Day 5**
  - Blood for serum Tg
  - Neck and whole-body scan

- **Positive study: Tg > 2 ng/ml or + RAI scan**
  - indicate persistent or recurrent disease
Recombinant Human TSH-Stimulation Protocol for Follow up after Thyroidectomy (UCSF)

Low iodine diet

-7 1 2 3 4 5 Day

rhTSH 0.9 mg rhTSH 0.9 mg $^{131}$I 4 mCi

Check Tg, preg., TSH Tg.

Levothyroxine

Scan

Tg.
Recombinant Human TSH (rhTSH)

- Thyrogen (thyrotropin alfa for injection)
- Modified Chinese hamster ovary cell line
- Human alpha 92 aa, beta 118 aa, glycosylated, sialylated not sulfated
- 1.1 mg (4-12 IU/L) dissolved in 1.2 ml water, IM 1 cc gives 0.9 mg
Can high level of TSH be achieved?

- Standard regiment achieves high serum levels of TSH

<table>
<thead>
<tr>
<th>TSH</th>
<th>&gt;80mU/I</th>
<th>58–80mU/I</th>
<th>&lt;50mU/I</th>
</tr>
</thead>
<tbody>
<tr>
<td>303</td>
<td>253 (83.5%)</td>
<td>43 (14.2%)</td>
<td>7 (2.3%)</td>
</tr>
</tbody>
</table>

rhTSH Compared with Thyroid Hormone Withdrawal

- rhTSH is safe
- rhTSH-Tg similar to THW-Tg
- rhTSH-WBS similar to THW-WBS
- 10-15% discordance

Similar Diagnostic Accuracy (RAI-WBS & Stim-Tg) rhTSH vs. T4 Withdrawal


Table 3  Comparison of the diagnostic accuracy of hypothyroid and rhTSH stimulated DxWBS and Tg levels (Robbins et al., 2001a)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>DxWBS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HYPO (w/d)</td>
<td>80%</td>
<td>93%</td>
<td>96%</td>
<td>67%</td>
</tr>
<tr>
<td>rhTSH</td>
<td>69%</td>
<td>100%</td>
<td>100%</td>
<td>71%</td>
</tr>
<tr>
<td>Stimulated Tg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HYPO (w/d)</td>
<td>79%</td>
<td>89%</td>
<td>95%</td>
<td>62%</td>
</tr>
<tr>
<td>rhTSH</td>
<td>86%</td>
<td>82%</td>
<td>87%</td>
<td>80%</td>
</tr>
<tr>
<td>DxWBS + Tg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HYPO (w/d)</td>
<td>96%</td>
<td>81%</td>
<td>93%</td>
<td>88%</td>
</tr>
<tr>
<td>rhTSH</td>
<td>98%</td>
<td>82%</td>
<td>89%</td>
<td>97%</td>
</tr>
</tbody>
</table>

PPV, positive predictive value; NPV, negative predictive value.
Is rhTSH cost effective?

- Cost-utility decision-analysis
- Used the 6 comparative studies of rhTSH versus thyroid hormone withdrawal
- 11% discordance between studies
- $51,344 per QALY over a five year when use rhTSH compared to thyroxin-withdrawal

rh-TSH-stimulated Tg Predicts Persistent or Recurrent Differentiated Thyroid Cancer

<table>
<thead>
<tr>
<th>Tg</th>
<th>pers.rec/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5 ng/ml</td>
<td>1/68</td>
<td>1.6%</td>
</tr>
<tr>
<td>0.5-2 ng/ml*</td>
<td>1/19</td>
<td>5%</td>
</tr>
<tr>
<td>&gt;2 ng/ml</td>
<td>16/20</td>
<td>80%</td>
</tr>
</tbody>
</table>

(*50% became <0.5 ng/ml on f/u) Kloos RT, Mazzaferri EL.: JCEM 2005

<table>
<thead>
<tr>
<th>Tg</th>
<th>pers.rec/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.9 ng/ml</td>
<td>1/70</td>
<td>1.4%</td>
</tr>
<tr>
<td>0.9-5 ng/ml</td>
<td>2/7</td>
<td>29%</td>
</tr>
<tr>
<td>&gt;5 ng/ml</td>
<td>22/27</td>
<td>81%</td>
</tr>
</tbody>
</table>

How to interpret rhTSH-stimulated Tg level?

- **Undetectable Thyroglobulin**
  - very little risk for recurrence (1-2%)

- **Detectable but low Thyroglobulin**
  - Some become undetectable over time
  - 5-30% have pers/rec disease depending on the threshold (2 or 5 ng/mL)

- **Elevated Thyroglobulin**
  - 80% pers/rec disease
Add Ultrasound

- Postoperative surveillance of cervical recurrence by ultrasonography: Improves sensitivity
- Replaces RAI scan in low risk patients
TSH-stimulated Tg and Ultrasound are Sensitive in Detecting Persistent or Recurrent Disease

**TABLE 4. PPVs (positive predictive values) of THW-Tg >1–10, >10 ng/ml, and increasing THW-Tg level, respectively, and negative predictive value (NPV) of the combination of both negative THW-Tg and US at first follow-up**

<table>
<thead>
<tr>
<th></th>
<th>Tg(-)/US(-)</th>
<th>Tg &gt;1–10 ng/ml</th>
<th>Tg &gt;10 ng/ml</th>
<th>Increasing Tg</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV</td>
<td>18.8 (18/96)*</td>
<td>52.0 (13/25)</td>
<td>100 (8/8)</td>
<td></td>
</tr>
<tr>
<td>NPV</td>
<td>98.8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Percentage (ratio).

Off Label Use

- rhTSH-stimulated PET scan
- rhTSH-stimulated radioiodine ablation of thyroid remnant after thyroidectomy
- rhTSH-stimulated radioiodine treatment for thyroid cancer
- rhTSH-stimulated radioiodine treatment for multinodular goiter
rhTSH-stimulated Radioiodine Remnant Ablation or Treatment

◆ Indications
   – High risk from hypothyroidism
   – Insufficient TSH response from withdrawal
   – Patient preference

◆ Difference from withdrawal
   – No symptoms of hypothyroidism
   – RAI clearance is faster

rhTSH-stimulated Radioiodine Remnant Ablation or Treatment

◆ Review of 400 patients from 30 centers
◆ 65% of 115 late stage patients benefited
  – 2% complete remission
  – 36% partial response
  – 27% disease stabilization
◆ Tumor expansion and compression causing neurological or respiratory problem
  – Pretreatment with glucocorticoid needed in some
  – Less or more risk than thyroid hormone withdrawal?

Radioiodine Ablation of Thyroid Remnants after Preparation with Recombinant Human Thyrotropin in Differentiated Thyroid Carcinoma: Results of an International, Randomized, Controlled Study


TABLE 2. Results of thyroid remnant ablation at month 8 based on $^{131}$I thyroid bed uptake

<table>
<thead>
<tr>
<th>Uptake in thyroid bed</th>
<th>Hypothyroid (n = 28), n (%)</th>
<th>Euthyroid (n = 32), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No visible uptake or uptake &lt;0.1%</td>
<td>28 (100)</td>
<td>32 (100)</td>
</tr>
<tr>
<td>No visible uptake</td>
<td>24 (85.7)</td>
<td>24 (75.0)</td>
</tr>
<tr>
<td>Visible uptake &lt;0.1%</td>
<td>4 (14.3)</td>
<td>8 (25.0)</td>
</tr>
<tr>
<td>Visible uptake &gt;0.1%</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

RAI uptake same 8 months post tx

TABLE 3. Results of thyroid remnant ablation at month 8 based on rhTSH-stimulated serum thyroglobulin (ng/ml)

<table>
<thead>
<tr>
<th>rhTSH-stimulated serum thyroglobulin (ng/ml)</th>
<th>Hypothyroid (n = 21), n (%)</th>
<th>Euthyroid (n = 24), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>18 (85.7)</td>
<td>23 (95.8)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>3 (14.3)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>&lt;1</td>
<td>18 (85.7)</td>
<td>20 (83.3)</td>
</tr>
<tr>
<td>≤1</td>
<td>3 (14.3)</td>
<td>4 (16.7)</td>
</tr>
</tbody>
</table>

Tg levels same 8 months post tx

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**Table 4. Summary of $^{131}$I kinetics in remnant tissue (ITT population)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hypothyroid (n = 29)</th>
<th>Euthyroid (n = 33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>48-h uptake in remnant tissue (%)$^a$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.9 (1.1)</td>
<td>0.5 (0.7)</td>
<td>0.0969</td>
</tr>
<tr>
<td>Median</td>
<td>0.5</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.006–4.3</td>
<td>0.003–3.4</td>
<td></td>
</tr>
<tr>
<td>Residence time in remnant tissue (h)$^b$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.4 (1.5)</td>
<td>0.9 (1.3)</td>
<td>0.1098</td>
</tr>
<tr>
<td>Median</td>
<td>0.8</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.01–5.9</td>
<td>0.01–6.6</td>
<td></td>
</tr>
<tr>
<td>Effective half-life in the remnant (h)$^c$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>48.0 (52.6)</td>
<td>67.6 (48.9)</td>
<td>0.0116</td>
</tr>
<tr>
<td>Median</td>
<td>26.9</td>
<td>51.1</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>16.0–192.5</td>
<td>17.3–192.5</td>
<td></td>
</tr>
<tr>
<td>Dose to blood (mGy/MBq)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.167 (0.061)</td>
<td>0.109 (0.028)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

$^a$ Uptake, Percentage of activity retained in tissue.
$^b$ Residence time, Integral of the time-activity curve divided by the administered activity expressed in hours.
$^c$ Effective half-life, For a monoexponential decay, time after which the activity drops by 50%, a combination of biological excretion and physical decay, expressed in hours.

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<table>
<thead>
<tr>
<th>SF-36 domains</th>
<th>Euthyroid group (n = 83)</th>
<th>Hypothyroid group (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 4</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>82.0 ± 18.5</td>
<td>84.5 ± 18.3</td>
</tr>
<tr>
<td>Role-physical</td>
<td>43.0 ± 44.6</td>
<td>58.3 ± 38.9</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>57.8 ± 28.3</td>
<td>67.4 ± 23.6</td>
</tr>
<tr>
<td>General health</td>
<td>68.2 ± 18.4</td>
<td>66.1 ± 20.8</td>
</tr>
<tr>
<td>Vitality</td>
<td>46.6 ± 22.2</td>
<td>54.5 ± 22.5</td>
</tr>
<tr>
<td>Social functioning</td>
<td>62.1 ± 24.3</td>
<td>74.2 ± 21.4</td>
</tr>
<tr>
<td>Role emotional</td>
<td>46.9 ± 43.9</td>
<td>57.6 ± 44.3</td>
</tr>
<tr>
<td>Mental health</td>
<td>61.4 ± 18.8</td>
<td>71.0 ± 20.1</td>
</tr>
<tr>
<td>Mental component summary</td>
<td>40.0 ± 10.0</td>
<td>45.2 ± 11.9</td>
</tr>
<tr>
<td>Physical component summary</td>
<td>46.2 ± 7.5</td>
<td>47.6 ± 7.7</td>
</tr>
</tbody>
</table>

* The change from baseline in the euthyroid group is significantly different from that in the hypothyroid group in five of the eight domains: physical functioning, P = 0.016; role-physical, P = 0.018; vitality, P < 0.0001; social functioning, P < 0.0001; mental health, P = 0.002.
rhTSH-stimulated Radioiodine Remnant Ablation vs Thyroid Hormone Withdrawal: Randomized Study

- Used 100 mCi
- 8 months post treatment
  - Same Radioiodine uptake
  - Same thyroglobulin level
- Longer effective half-life of RAI in remnant
  - 68 h for rh-TSH vs 48 h for withdrawal
- Lower blood dose of radiation
  - 0.11 for rh-TSH vs 0.17 for withdrawal
- Better quality of life (SF-36)

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ATA guideline
*Thyroid*, 2006

- **6-12 months after remnant ablation**
- Ultrasound neck
  - Surgery if US +
- **rhTSH or THW**
  - if Tg + or scan +
  - CT (w/o contr)
  - I131 tx
rhTSH for Thyroid Cancer: Summary

- rhTSH is replacing thyroid hormone withdrawal for surveillance (RAI-Dx & Tg) for recurrence after thyroidectomy for differentiated thyroid cancer.
- rhTSH may replace thyroid hormone withdrawal for thyroid remnant ablation and RAI-Tx (currently off-label use).