Thyroid Remnant Ablation:  
if YES, how much radioiodine?  
If NO, then what?

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Disclosures  
Dr. Kloos is an employee and stockholder of Veracyte, Inc.
Clarifying the goals of RAI

- **Remnant Ablation**
  - To eliminate normal tissue to facilitate detection of recurrent disease and initial staging

- **Adjuvant Therapy**
  - To decrease the risk of recurrence and disease specific mortality by destroying suspected, but unproved metastatic disease

- **RAI Therapy**
  - To treat known persistent disease

Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Cooper et al. Thyroid 2009;19:1167

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**Hay, I – Mayo Clinic**
(N=1163, MACIS< 6, no distant metastases, All had TT or NTT, 1970 to 2000)

<table>
<thead>
<tr>
<th>Patients</th>
<th>20-Year Mortality</th>
<th></th>
<th>20-Year Recurrence</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No RAI</td>
<td>RAI</td>
<td>P-value</td>
<td>No RAI</td>
</tr>
<tr>
<td>All</td>
<td>0.4%</td>
<td>0.6%</td>
<td>0.64</td>
<td>8.7%</td>
</tr>
<tr>
<td>Node Negative</td>
<td>0%</td>
<td>0%</td>
<td>N/A</td>
<td>3.4%</td>
</tr>
<tr>
<td>Node Positive</td>
<td>1.2%</td>
<td>0.9%</td>
<td>0.99</td>
<td>19.5%</td>
</tr>
</tbody>
</table>

J Surg Oncol 2006;94:692-700
Systematic review and meta-analysis of the effectiveness of $^{131}I$ remnant ablation after bilateral thyroidectomy for DTC.

Pooled analysis of 18 cohort studies.

Updated unadjusted pooled analyses

- Any recurrence & loco-regional recurrence
  - Heterogeneity of RRA treatment effect precluded meaningful estimation of an overall treatment effect.
- Distant metastases
  - Statistically significant reduction in risk of distant metastatic recurrence -2% (95% CI -4%, -1%).
<table>
<thead>
<tr>
<th>Factors</th>
<th>Description</th>
<th>Decrease risk of death</th>
<th>Decrease risk of recurrence</th>
<th>May facilitate initial staging and follow up</th>
<th>RAI ablation usually recommended</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>1cm or less, intrathyroidal or microscopic multifocal</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>1-2 cm, intrathyroidal</td>
<td>No</td>
<td>Conflicting Data</td>
<td>Yes</td>
<td>Selective use*</td>
<td>I</td>
</tr>
<tr>
<td>T2</td>
<td>&gt; 2 to 4 cm, intrathyroidal</td>
<td>No</td>
<td>Conflicting Data</td>
<td>Yes</td>
<td>Selective use*</td>
<td>C</td>
</tr>
<tr>
<td>T3</td>
<td>&gt; 4 cm&lt;br&gt;&lt; 45 yrs old&lt;br&gt;≥ 45 yrs old&lt;br&gt;Any size, any age, minimal extrathyroidal extension</td>
<td>No&lt;br&gt;No&lt;br&gt;Yes&lt;br&gt;Yes</td>
<td>Conflicting Data&lt;br&gt;Yes&lt;br&gt;Yes&lt;br&gt;Yes</td>
<td>Yes&lt;br&gt;Yes&lt;br&gt;Yes&lt;br&gt;Yes</td>
<td>Yes&lt;br&gt;Yes&lt;br&gt;Yes&lt;br&gt;Yes</td>
<td>B&lt;br&gt;B&lt;br&gt;B&lt;br&gt;B</td>
</tr>
<tr>
<td>T4</td>
<td>Any size with gross extrathyroidal extension</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>B</td>
</tr>
<tr>
<td>Nx, N0</td>
<td>No clinical or pathologic LN documented</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>I</td>
</tr>
<tr>
<td>N1</td>
<td>&lt; 45 yrs old&lt;br&gt;≥ 45 yrs old&lt;br&gt;Any size, any age, minimal extrathyroidal extension</td>
<td>No&lt;br&gt;No&lt;br&gt;Yes&lt;br&gt;Yes</td>
<td>Conflicting Data&lt;br&gt;Yes&lt;br&gt;Yes&lt;br&gt;Yes</td>
<td>Yes&lt;br&gt;Yes&lt;br&gt;Yes&lt;br&gt;Yes</td>
<td>Yes&lt;br&gt;Yes&lt;br&gt;Yes&lt;br&gt;Yes</td>
<td>C&lt;br&gt;C&lt;br&gt;C&lt;br&gt;C</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis present</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>A</td>
</tr>
</tbody>
</table>
Current concepts

Risk Stratification
- Provide RAI to those who benefit by decreasing recurrence or mortality.
- Avoid RAI, its risks and costs, in those not benefited.

Low dose remnant ablation
- Minimize side effects
- Minimize risk of second primary malignancy

Risk Stratification
- Tools being applied to risk stratify
  - Clinicopathology features: TNM, MACIS
  - Serum Tg: basal, TSH stimulated
  - TSH stimulated SPECT/CT diagnostic WBS
Patients with low-risk well-differentiated thyroid carcinoma (WDTC) with undetectable anti-Tg antibodies were prospectively followed after total thyroidectomy and therapeutic central compartment neck dissection, when indicated.

Stim-Tg was performed 3 months postoperatively and used to base RRA selection.

mostly T1 and T2, N0M0

Results

Table 3. Breakdown of postsurgical Stim-Tg measurements and corresponding RRA administration rates.

<table>
<thead>
<tr>
<th>Stim-Tg subgroup</th>
<th>n (%)</th>
<th>Received RRA</th>
<th>n</th>
<th>% of subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 μg/L</td>
<td>59 (56.7)</td>
<td>1</td>
<td>1</td>
<td>1.7%</td>
</tr>
<tr>
<td>1–5 μg/L</td>
<td>35 (33.7)</td>
<td>6</td>
<td>6</td>
<td>17.1%</td>
</tr>
<tr>
<td>&gt;5 μg/L</td>
<td>10 (9.6)</td>
<td>9</td>
<td>9</td>
<td>90.0%</td>
</tr>
<tr>
<td>Total</td>
<td>104 (100)</td>
<td>16</td>
<td>16</td>
<td>15.4%</td>
</tr>
</tbody>
</table>

Abbreviations: Stim-Tg, stimulated thyroglobulin; RRA, radioiodine remnant ablation.
Follow-Up on Patients Not Receiving Radioiodine Remnant Ablation

- no patient with initial undetectable Stim-Tg had evidence of residual/recurrent disease based on repeat Stim-Tg tests and neck US at 6–12 mos intervals (mean, 3.3 yrs).
- Of patients in the 1–5 ug/L subgroup not initially given RRA (followed an average of 3.0 yrs), only 1/29 (3.5%) subsequently received RRA for “suspected clinical risk for residual disease”.


67%-85% ablation rate
Treatment and follow-up of low-risk patients with thyroid cancer

Criteria of low risk in thyroid cancer
- Well-differentiated papillary or follicular thyroid cancer
- Patient age <45 years
- Thyroid tumor size ranging from 1 cm to <4 cm in diameter
- No extension of the tumor beyond the thyroid capsule
- No lymph-node involvement
- No distant metastases

Risk Stratification

Diagnostic SPECT/CT
57 pts were studied using SPECT/CT 3–4 d after 131I ablation.  
- Planar WBS and SPECT/CT of the neck was performed.  
- 28/143 (19.6%) neck foci were reclassified.

20/57 pts (35%) were reclassified: 12 downstaged, 8 upstaged, resulting in risk category change in 25%.

Ohio State rhTSH-DxWBS + SPECT/CT: pre-therapy data to inform the decision of RAI

- Monday: Baseline labs (TSH, Tg, HCG, urine iodine, CMP, CBC) + rhTSH
- Tuesday: rhTSH + 123I or 131I Dx dose
- Wednesday:  
  - Stimulated labs (TSH + Tg)  
  - DxWBS + SPECT/CT  
  - Optional FDG-PET/CT  
  - Review labs & images: decide on 131I indication and dose
Thyrogen vs Thyroid Hormone Withdrawal Remnant Ablation

I-131 Ablation: choosing the activity

- **Ablation**
  - ESTIMABL and HiLo (RCT)
  - 30 mCi THW = 100 mCi THW in low-risk pts (RCT. PLoS ONE. 2008 Apr 2;3(4):e1885)
  - 30 mCi rhTSH = 30 mCi THW in low-risk pts (RCT)
  - 54 mCi rhTSH = 54 mCi THW in low-risk pts (RCT)
  - 50 mCi rhTSH = 100 mCi rhTSH in low-risk pts (RCT)
  - 100 mCi rhTSH = 100 mCi THW in low-risk pts (2 RCT)

- **Clinical Recurrence**
  - 100 mCi rhTSH = 100 mCi THW in low-risk pts (RCT)
HiLo: radioiodine ablation (1.1 vs 3.7 GBq), with or without Thyrogen, for Thyroid Cancer. Mallick et al. NEJM 2012

- Randomized non-inferiority trial of pT1-T3, N0-1, M0.
- Endpoints: ablation success after 6-9 months using scan and stimulated Tg <2.0 ng/ml.
- Statistics: non-inferiority if difference not >10%.
- 421 patients with analyzable data.
- Power: 1.1 vs 3.7 GBq, or rhTSH vs THW. No inferiority.
- 1.1 GBq+rhTSH (84%), 3.7 GBq+THW (88%), 3.7 GBq+rhTSH (90%) were comparable.
- Adverse events 1.1 GBq 21% vs 3.7 GBq 33% (p=0.007).


- Randomized: pT1aN1 or Nx, pT1b(any N), T2N0. All M0
- Endpoints: ablation success after 8 months using neck US and stimulated Tg ≤ 1ng/mL (or WBS if TbAB present).
- Statistics: equivalence within 10%.
- 684 patients with analyzable data.
- Power: 1.1 vs 3.7 GBq, or rhTSH vs THW. Were equivalent.
- 1.1 GBq+rhTSH (90%), 3.7 GBq+rhTSH (93%), 1.1 GBq+THW (92%), 3.7 GBq+rhTSH (94%) were comparable.
Randomized comparison of post-RAI recurrence: 100 mCi I-131 rhTSH vs THW

- Follow-up study to Pacini et al. JCEM 2006;91:926-932.
- After a median 3.7 yrs, comparable rates of tumor recurrence and persistence.

Elisei et al. JCEM 2009 Nov;94(11):4171-9

Retrospective non-randomized study of I-131 Rx for incidental small volume metastatic disease at ablation: rhTSH = THW

- 84 DTC pts in whom RAI-avid lesions outside the thyroid bed were 1st identified at remnant ablation (64 rhTSH, 20 THW) on either the DxWBS (63/84, 75%) or RxWBS (21/84, 25%).

- 76 with locoregional mets only, and 8 with pulmonary mets.

- Results: 70% of rhTSH-assisted patients and 55% of the THW group had no evidence of disease at a median of 2.7 years following the initial RAI ablation (P=0.159).

Tuttle et al. THYROID 2010;20(3):257
Advantages of rhTSH compared to THW when equivalent I-131 activities are given

- Lower side effects
- Lower radiation dose to the bone marrow
- Faster whole body radioiodine clearance

Radiotoxicity: rhTSH vs THW

- 94 consecutive non-randomized patients received 100 mCi for remnant ablation.

Radiotoxicity: rhTSH vs THW


<table>
<thead>
<tr>
<th>Parameter evaluated for damage</th>
<th>Test</th>
<th>Time of evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salivary glands</td>
<td>Serum amylase</td>
<td>Immediately before and 48 h after $^{131}I$</td>
</tr>
<tr>
<td>Ovaries</td>
<td>Serum FSH</td>
<td>2 and 7 d after $^{131}I$</td>
</tr>
<tr>
<td>Testes</td>
<td>Serum FSH</td>
<td>Immediately before and 6 mo after $^{131}I$</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Blood count</td>
<td>Immediately before and 30, 45, and 60 d after $^{131}I$</td>
</tr>
<tr>
<td>Oxidative</td>
<td>Plasma 8-epi-PGF$_{2α}$</td>
<td>Immediately before and 4 d after $^{131}I$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group A (rhTSH)</th>
<th>Group B (hypothyroid)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated FSH 6 mo after $^{131}I$</td>
<td>Men</td>
<td>4/6 (44.4%)</td>
<td>16/18 (89%)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>1/13 (7.7%)</td>
<td>8/30 (20%)</td>
</tr>
<tr>
<td>Mean increase of FSH</td>
<td>Men</td>
<td>105%</td>
<td>238%</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>65%</td>
<td>125%</td>
</tr>
<tr>
<td>Hyperamalgasaemia 48 h after $^{131}I$</td>
<td>Men</td>
<td>11/30 (36.6%)</td>
<td>48/60 (80%)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>8/40 (20%)</td>
<td>60/70 (86%)</td>
</tr>
<tr>
<td>Symptoms of acute salivadema due to $^{131}I$</td>
<td>Men</td>
<td>9/30 (30%)</td>
<td>65/63 (50%)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>1/20 (5%)</td>
<td>20/33 (60%)</td>
</tr>
<tr>
<td>Mean decrease of neutrophils (considering lowest count)</td>
<td>Men</td>
<td>20%</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>25%</td>
<td>52%</td>
</tr>
<tr>
<td>Mean decrease of platelets (considering lowest count)</td>
<td>Men</td>
<td>25%</td>
<td>52%</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>60%</td>
<td>125%</td>
</tr>
<tr>
<td>Mean increase of 8-epi-PGF$_{2α}$</td>
<td>Men</td>
<td>14/26 (54%)</td>
<td>45/45 (100%)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>10/26 (38%)</td>
<td>40/70 (57%)</td>
</tr>
</tbody>
</table>

Radiotoxicity: rhTSH vs THW

Dosimetry: rhTSH vs THW

Pacini et al. JCEM 2006;91:926-932.

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<th>Group A (rhTSH)</th>
<th>Group B (hypothyroid)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residence time in remnant (hour) *</td>
<td>Mean (SD)</td>
<td>1.4 (1.51)</td>
<td>0.9 (1.27)</td>
</tr>
<tr>
<td>Effective half-life in remnant (hour) **</td>
<td>Mean (SD)</td>
<td>48.0 (52.64)</td>
<td>67.6 (48.85)</td>
</tr>
<tr>
<td>Uptake in remnant (%) ***</td>
<td>Mean (SD)</td>
<td>0.9 (1.05)</td>
<td>0.5 (0.70)</td>
</tr>
<tr>
<td>Mean dose to blood (mGy/MBq)</td>
<td>Mean (SD)</td>
<td>0.17 (0.06)</td>
<td>0.11 (0.03)</td>
</tr>
</tbody>
</table>

* Residence time: Integral of the time-activity curve divided by the injected activity, unit: hours.
** Effective Halflife: For a mono-exponential decay: time after which the activity drops by 50%, a combination of biological excretion and physical decay, unit: hours.
*** Uptake: Percentage of activity retained in tissue.

- At fixed activities rhTSH delivers 35% less radiation to the blood
Radiotoxicity: rhTSH vs THW

- 20 DTC pts randomly assigned to THW group A, or rhTSH injections group B, before 131I ablation (3.7 GBq).
- The frequency of translocations in peripheral lymphocytes was analyzed with whole-chromosome-specific probes for chromosomes 1, 4, and 8.

**Results:** 45 d after 131I, the total chromosomal translocation rate was lower in group B than group A (P=0.02). The frequency of translocations increased in group A only (P=0.01 vs. baseline). Rearrangement involved chromosomes 4 & 8 (P =0.02 vs. baseline).


Randomized quality of life trial: rhTSH vs THW

- FACIT-F allows for 3 scores: FACT-G, FACIT-F, & FACIT-TOI
- All 3 scores for THW significantly lower than baseline and rhTSH at time of ablation.
- QOL preserved for rhTSH.

Taieb et al. Clinical Endocrinology (oxf) 2008;Sept 17 epub
Side effects of low dose remnant ablation

Minimal salivary side effects to low dose ablation

- **Retrospective** review of clinical records.
- Side effects within the 1st year are common, and the majority resolve.

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Developed side effect</th>
<th>Side effect resolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any symptom</td>
<td>101/262 (38%)</td>
<td>249/262 (95%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>45/262 (17%)</td>
<td>36/45 (87%)</td>
</tr>
<tr>
<td>Altered taste (&gt;2 mo)</td>
<td>35/262 (13%)</td>
<td>32/35 (91%)</td>
</tr>
<tr>
<td>Salivary swelling</td>
<td>41/262 (16%)</td>
<td>39/41 (95%)</td>
</tr>
<tr>
<td>Salivary pain</td>
<td>16/262 (6%)</td>
<td>15/16 (94%)</td>
</tr>
<tr>
<td>Tearing</td>
<td>2/262 (1%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Increased risk of SPM and leukemia with RAI

Table 2. Pooled Relative Risk of Second Primary Malignancy in Thyroid Carcinoma Patients Treated with Radioactive Iodine Relative to Those Not Treated with Radioactive Iodine

<table>
<thead>
<tr>
<th>Type of SPM</th>
<th>Relative risk</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SPM</td>
<td>1.19</td>
<td>1.04, 1.36</td>
<td>0.010</td>
</tr>
<tr>
<td>Bladder</td>
<td>1.19</td>
<td>0.51, 2.78</td>
<td>0.690</td>
</tr>
<tr>
<td>Breast</td>
<td>0.86</td>
<td>0.64, 1.16</td>
<td>0.324</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>1.74</td>
<td>0.73, 4.17</td>
<td>0.213</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>1.16</td>
<td>0.77, 1.75</td>
<td>0.472</td>
</tr>
<tr>
<td>Digestive tract</td>
<td>1.17</td>
<td>0.88, 1.54</td>
<td>0.28</td>
</tr>
<tr>
<td>Kidney and renal pelvis</td>
<td>1.39</td>
<td>0.71, 2.72</td>
<td>0.338</td>
</tr>
<tr>
<td>Leukemia</td>
<td>2.50</td>
<td>1.13, 5.53</td>
<td>0.024</td>
</tr>
<tr>
<td>Lung</td>
<td>1.50</td>
<td>0.86, 2.60</td>
<td>0.151</td>
</tr>
<tr>
<td>Melanoma (skin)</td>
<td>0.86</td>
<td>0.43, 1.70</td>
<td>0.655</td>
</tr>
<tr>
<td>Stomach</td>
<td>1.66</td>
<td>0.74, 3.72</td>
<td>0.220</td>
</tr>
</tbody>
</table>

The data pooled are from the SEER study by Brown et al. (18) and the European study by Rubino et al. (19). The total number of thyroid cancer survivors included in the pooled analysis is 16,502.

SPM, second primary malignancy.
Rising incidence of WDTC over time


Rising use of RAI over time without improved survival for low-risk WDTC


Proportion of patients receiving RAI for all patients, and for patients <45 years with low-risk WDTC (left; y-axis), and overall survival is illustrated (right; y-axis) for 1973-2006. Tumor size was recorded after 1983. Before 1983, low-risk disease was defined as intrathyroid N0M0 tumors; after 1983, low-risk was defined as T1N0M0 tumors.
Rising risk of SPM and leukemia over time of rising RAI use


SPMs and low dose RAI

- It is unknown if SPMs are increased with low dose RAI.
- The lower radiation dose to the blood with rhTSH suggests the possibility of greater safety.
Clarifying the goals of RAI: my practice

 GPI Remnant Ablation (30 mCi)
 • To eliminate normal tissue to facilitate detection of recurrent disease and initial staging
 • Consider no RAI if US + SPECT/CT negative for disease, and bTg <0.1 ng/ml or sTg <1.0 ng/ml

 GPI Adjuvant Therapy (100 mCi)
 • To decrease the risk of recurrence and disease specific mortality by destroying suspected, but unproved metastatic disease

 GPI RAI Therapy (>100 mCi for locoregional disease, ≥ 200 mCi for distant metastases, routine use of dosimetry)
 • To treat known persistent disease

![Graph showing tumor recurrence during follow-up](Kloos RT. JCEM. 2010 95:5241-8.)

- % Tumor Recurrence During Follow-up
- rhTSH-Tg value
- Enrollment
- Group 1: ≤0.5 ng/ml, 3% recurrence
- Group 2: 0.6-2.0 ng/ml, 11% recurrence
- Group 3: >2.0 ng/ml, 80-83% recurrence
IMA-1 correlation between b-Tg and rhTSH-Tg
(Access ICMA method, Beckman Coulter, functional sensitivity 0.05 ng/mL)

Together 2/655 (0.3%) with Tg >2 ng/ml

Limited benefit from stim-Tg when b-Tg <0.10 ng/mL

Limited benefit from stim-Tg when b-Tg >0.50 ng/mL

Spencer et al. Thyroid 6:587-595; 2010
**RTK:** Doesn’t this group benefit from stim-Tg testing?

b-Tg = 0.1-0.49 ng/mL in 183/849 (21.6%) of patients

![Graph showing serum Tg levels and rhTSH response](image)

Spencer et al. Thyroid 6:587-595; 2010

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**PTC follow-up paradigm**

- In PTC with basal Tg <0.1 ng/ml and negative neck US 9-12 months post-surgery/ablation:
  - Obtain annual basal Tg and periodic neck US.
- If Tg assay with functional sensitivity >0.1 ng/ml, consider stimulated Tg if basal Tg is undetectable and RAI was given.
**PTC follow-up paradigm**

- In PTC with bTg detectable but <0.5 ng/ml, or stimulated Tg 0.6 to 2.0 ng/ml
  - Mandatory **skilled** neck & superior mediastinum US.
  - If US negative, repeat bTg yearly (if sTg then repeat in 1-2 years).
    - If Tg is the same or falling then observe. (If sTg then repeat in 2-5 years).
    - Consider repeat annual **skilled** US.
  - If Tg rising then mandatory skilled US, chest CT when bTg >0.5 ng/ml or sTg>2 ng/ml, and further evaluation (including possible PET +/- I-131 RxWBS if bTg >1 ng/ml or sTg >5-10 ng/ml).