No conflict of Interests
TSH suppression increases the risk of osteoporosis without changing recurrence in non-high risk patients with differentiated thyroid carcinoma

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Memorial Sloan-Kettering Cancer Center
• Traditional treatment for WDTC
  • Total thyroidectomy +/- I-131 treatment + TSH suppression

• TSH stimulates thyroid cell proliferation

• Removing this stimulus is believed to inhibit growth of residual neoplastic tissue

• No evidence-based consensus on the optimal TSH level
  • reduce tumor recurrences, while ensuring minimal adverse effects

1 Cooper DS, et al. Thyroid. 2009; 19:1167-214
To determine the effect of TSH suppression:

1. Benefit on recurrence

2. Risk of harm
   - Composite outcome of harm
   - Risk of Atrial Fibrillation
   - Risk of Osteoporosis
Methods

• Total thyroidectomy at MSKCC
  • 2000 - 2006
  • Institutional database
  • Median follow-up: 6.5 years.

• Exclusion
  • ATA High Risk
  • Primary hyperparathyroidism
  • Less than 3 postoperative TSH lab results
  • Pre-operative atrial fibrillation
  • Pre-operative osteoporosis
1100 patients
Total Thyroidectomy
2000-2006

Inclusion
n = 771

Exclusion (n= 329)
ATA High Risk
Primary
hyperparathyroidism
Less than 3 TSH labs

Recurrence Analysis
n=771

Atrial Fibrillation Analysis
n=756

Exclusion

• Preop Atrial Fibrillation (n=15)

Osteoporosis Analysis
n=537

Exclusion

• Men (n=202)
• Women with preop osteoporosis (n=32)
Definitions

• Recurrence
  • Locoregional – biopsy proven
  • Distant – imaging or biopsy proven

• Atrial Fibrillation
  • EKG proof of persistent arrhythmia OR
  • New documentation

• Osteoporosis
  • DEXA scan T-score \( \leq -2.5 \) OR
  • New documentation OR
  • Bisphosphonate therapy in absence of another indication
Methods

• **TSH Suppressed group**
  median TSH ≤0.4 mU/L

• **TSH Not suppressed group**
  median TSH >0.4 mU/L

• TSH labs were analyzed up to the date of
  • event OR
  • last follow-up

• Excluded TSH labs within 7 days of RAI
Kaplan-Meier survival estimates were employed to assess risk of:
- Recurrence (n=771)
- Composite outcome of harm
- Atrial Fibrillation (n=756)
- Osteoporosis in women (n=537)

Cox Proportional Hazards Models were built to allow for multivariate adjustment by:
- Age
- Gender
- ATA risk of recurrence
- Administration of RAI

Propensity Scores to adjust for indication bias
## Patient and Tumor Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Suppressed TSH ≤0.4mU/L (n=449)</th>
<th>Not Suppressed TSH&gt;0.4mU/L(n=322)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y (mean±SD)</strong></td>
<td>46.3±13.8</td>
<td>50.1 ± 14.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Sex, females n (%)</strong></td>
<td>342 (76%)</td>
<td>226 (70%)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microcarcinomas</td>
<td>51 (11%)</td>
<td>58 (13%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Classical Type</td>
<td>150 (33%)</td>
<td>86 (27%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Follicular variant</td>
<td>127 (28%)</td>
<td>87 (27%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Tall cell variant</td>
<td>72 (16%)</td>
<td>44 (14%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Other</td>
<td>49 (11%)</td>
<td>47 (14%)</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Extrathyroidal extension</strong></td>
<td>162 (36%)</td>
<td>92 (29%)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Vascular invasion</strong></td>
<td>11 (2.5%)</td>
<td>15 (4.6%)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>N stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>169 (38%)</td>
<td>134 (42%)</td>
<td>0.26</td>
</tr>
<tr>
<td>N1a</td>
<td>100 (22%)</td>
<td>55 (17%)</td>
<td>0.09</td>
</tr>
<tr>
<td>N1b</td>
<td>76 (17%)</td>
<td>40 (13%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Nx</td>
<td>104 (23%)</td>
<td>93 (28%)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>RAI therapy</strong></td>
<td>335 (74%)</td>
<td>197 (61%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>ATA Risk</strong></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Low</td>
<td>179 (40%)</td>
<td>162 (50%)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>270 (60%)</td>
<td>160 (50%)</td>
<td></td>
</tr>
</tbody>
</table>

**Presentation from the 83rd Annual Meeting of the American Thyroid Association, October 16-20, 2013 (Laura Y. Wang)**
Disease Free Survival

Kaplan-Meier disease-free survival estimates

- 43/771 (5.6%) patients recurred
- HR: 1.02, p=0.956, 95%CI: 0.54-1.91
## Multivariate analysis for Recurrence

<table>
<thead>
<tr>
<th>Multivariate analysis</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH suppression</td>
<td>0.88</td>
<td>0.46-1.66</td>
<td>0.692</td>
</tr>
<tr>
<td>Age</td>
<td>0.99</td>
<td>0.97-1.02</td>
<td>0.862</td>
</tr>
<tr>
<td>Sex</td>
<td>0.53</td>
<td>0.29-0.96</td>
<td>0.038</td>
</tr>
<tr>
<td>RAI therapy</td>
<td>1.5</td>
<td>0.55-3.94</td>
<td>0.437</td>
</tr>
<tr>
<td>ATA risk</td>
<td>6.5</td>
<td>2.2-19.3</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Using Propensity Scores</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH suppression</td>
<td>1.08</td>
<td>0.45-2.63</td>
<td>0.856</td>
</tr>
</tbody>
</table>
Kaplan-Meier survival estimates of composite outcome

- HR: 2.1, p=0.05, 95%CI: 1.001-4.3

TSH>0.4mU/L

TSH≤0.4mU/L
Analysis time (months)

Kaplan-Meier survival estimates for Atrial fibrillation

- 17/756 (2.3%) developed post-operative AF
- HR: 0.78, p=0.63, 95%CI: 0.3-2.1

TSH≤0.4mU/L
TSH>0.4mU/L
Osteoporosis

Kaplan-Meier survival estimates for Osteoporosis

- 29/537 (5.4%) of women developed post-op osteoporosis
- HR: 3.5, p=0.023, 95%CI: 1.2-10.2

TSH>0.4mU/L

TSH≤0.4mU/L
## Multivariate analysis for Osteoporosis

<table>
<thead>
<tr>
<th>Multivariate analysis</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH suppression</td>
<td>4.32</td>
<td>1.45-12.85</td>
<td>0.009</td>
</tr>
<tr>
<td>Age</td>
<td>1.08</td>
<td>1.04-1.13</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Laura Y. Wang)**
What TSH level is optimal?

- Median TSH mU/L

- *p<0.05
- †p<0.08

HR

- Osteoporosis HR
- Tumor Recurrence HR

PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Laura Y. Wang)
Summary

- No recurrence benefit of TSH suppression
- TSH suppression increases the risk of a composite outcome of harm
- No effect of TSH suppression on risk of postoperative Atrial Fibrillation
- TSH suppression increases the risk of osteoporosis in women, especially in older women
Limitations

- **Retrospective study**

- **Indication bias**
  - Higher risk patients more likely to be TSH suppressed and treated with RAI
  - Patients at higher preoperative risk of Atrial Fibrillation or Osteoporosis may have received less TSH suppression
  - Patients on TSH suppression possibly more likely to be investigated for Atrial Fibrillation or Osteoporosis

- **Osteoporosis outcome measured in females only**
Conclusions

- TSH suppression $\leq 0.4$ mU/L increases the risk of osteoporosis without changing recurrence in thyroid cancer patients at low and intermediate-risk of recurrence

- Therapeutic efforts should focus on avoiding harm in indolent disease