Limited Resection in Thyroid Cancer

Joel Baumgartner
Surgery Grand Rounds
November 12, 2007
Papillary Thyroid Cancer

- 60-80% of all thyroid carcinomas
- 1:3 M:F
- Psammoma bodies & orphan Annie nuclei
- 80% multifocal
- Lymphatic spread
Central Lymph Node Dissection (CLND)

Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association Guidelines Taskforce*

Members: David S. Cooper,¹ (Chair), Gerard M. Doherty,² Bryan R. Haugen,³ Richard T. Kloos,⁴ Stephanie L. Lee,⁵ Susan J. Mandel,⁶ Ernest L. Mazzaferrì,⁷ Bryan McIver,⁸ Steven I. Sherman,⁹ and R. Michael Tuttle¹⁰

R27. Routine central-compartment (level VI) neck dissection should be considered for patients with papillary thyroid carcinoma and suspected Hurthle carcinoma. Near-total or total thyroidectomy without central node dissection may be appropriate for follicular cancer, and when followed by radioactive iodine therapy, may provide an alternative approach for papillary and Hurthle cell cancers—Recommendation B

Cooper DS, et al. Thyroid 2006;16(2):109-42
CLND Systematic Review

- 1 prospective, 5 retrospective/cohort, & 7 case series
- Asking these questions
  1) Does CLND decrease recurrence or disease-specific mortality?
  2) Does CLND increase risk of hypoparathyroidism and recurrent laryngeal nerve injury?
  3) Does reoperation in the central neck compartment for recurrent PTC increase the risk of hypoparathyroidism and recurrent laryngeal nerve injury?
CLND Systematic Review

- Weak evidence
  - “No prospective, randomized data exist to explain the impact of CLND on recurrence or disease-specific mortality in PTC”
  - Grade C recommendations
  - Conclusion: “these recommendations support the application of CLND at the initial operation for differentiated thyroid cancer in expert hands”

No Evidence Routine CLND Prevents Recurrence or Survival

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Reference</th>
<th>Total patients</th>
<th>CLND</th>
<th>Factors predictive of recurrence</th>
<th>P</th>
<th>Survival factors</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>28 Goteborg, 1996</td>
<td>195</td>
<td>195</td>
<td>Not reported</td>
<td>NA</td>
<td>CLND compared with contemporaneous series, distant metastases, age</td>
<td>Not reported</td>
</tr>
<tr>
<td>IV</td>
<td>14 Hannover, 1994</td>
<td>342</td>
<td>60</td>
<td>Increased with node metastases, decreased with compartment-oriented dissection</td>
<td>All &lt; 0.005</td>
<td>Node metastases, distant metastases, age, tumor invasion, compartment-oriented dissection</td>
<td>All &lt; 0.001</td>
</tr>
<tr>
<td>IV</td>
<td>29 Toronto, 2003</td>
<td>103</td>
<td>27</td>
<td>No correlation with dissected compartment, no increase in unoperated central compartment with microscopically positive nodes</td>
<td>All &gt; 0.20</td>
<td>No analysis; only 1 death</td>
<td>NA</td>
</tr>
<tr>
<td>IV</td>
<td>31 Oita, 1998</td>
<td>2,000</td>
<td>53</td>
<td>Not reported</td>
<td>NA</td>
<td>Distant metastases, age, extrathyroidal invasion; effect of CLND alone not reported</td>
<td>All ≤ 0.04</td>
</tr>
<tr>
<td>IV</td>
<td>Sydney, 2006</td>
<td>43</td>
<td>43</td>
<td>Increased in lateral compartment with more positive lymph nodes</td>
<td>All = 0.02</td>
<td>No deaths</td>
<td>All &lt; 0.04</td>
</tr>
<tr>
<td>V</td>
<td>Tokyo, 2003</td>
<td>252</td>
<td>252</td>
<td>Increased with greater tumor size; decreased with central neck dissection</td>
<td>All &lt; 0.0001</td>
<td>Not reported</td>
<td>NA</td>
</tr>
<tr>
<td>V</td>
<td>Dusseldorf, 1996</td>
<td>148</td>
<td>148</td>
<td>Increased with more node metastases and elevated postoperative thyroglobulin</td>
<td>All &lt; 0.03</td>
<td>Not reported</td>
<td>NA</td>
</tr>
<tr>
<td>V</td>
<td>Paris, 2005</td>
<td>281</td>
<td>63</td>
<td>Extent of thyroidectomy and number of tumor foci</td>
<td>All &lt; 0.01</td>
<td>Not reported</td>
<td>NA</td>
</tr>
<tr>
<td>V</td>
<td>Paris, 1998</td>
<td>139</td>
<td>139</td>
<td>Increased with positive central nodes, age, and extrathyroidal extension</td>
<td>All ≤ 0.025</td>
<td>Not reported</td>
<td>NA</td>
</tr>
</tbody>
</table>

CLND: central lymph node dissection
*Additional lateral compartments were dissected.
*Minority had follicular thyroid cancer (PTC) instead of PTC.

Routine CLND has morbidity

- Risk of permanent hypothyroidism as high as 14%
- Risk of unintentional recurrent laryngeal nerve injury as high as 5.7%
## Table 3.
Complications after CLND for PTC

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Reference</th>
<th>Total patients</th>
<th>Patients undergoing TT and CLND</th>
<th>Permanent hypoparathyroidism (%)</th>
<th>Permanent nerve injury (%)</th>
<th>Unintentional permanent nerve injury (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>10</td>
<td>100</td>
<td>50</td>
<td>2 (4.0) vs. 0%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>41</td>
<td>159</td>
<td>71&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (1.4)</td>
<td>4 (5.6)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>IV</td>
<td>37</td>
<td>447</td>
<td>56&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 (1.8) vs. 0.5% vs. 0%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>42</td>
<td>139</td>
<td>53&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1 (1.9)</td>
<td>1 (1.9)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>V</td>
<td>7</td>
<td>35</td>
<td>35&lt;sup&gt;f&lt;/sup&gt;</td>
<td>5 (14.3)</td>
<td>2 (5.7)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>V</td>
<td>11</td>
<td>43</td>
<td>43&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2 (4.6)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>4 (9.3)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>12</td>
<td>100</td>
<td>94&lt;sup&gt;h&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>28</td>
<td>195</td>
<td>195</td>
<td>6 (3.1)</td>
<td>6 (3.1)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>V</td>
<td>33</td>
<td>148</td>
<td>148&lt;sup&gt;h&lt;/sup&gt;</td>
<td>4 (2.7)</td>
<td>17 (11.5)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5 (3.4)</td>
</tr>
<tr>
<td>V</td>
<td>43</td>
<td>39</td>
<td>39&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0</td>
<td>1 (2.9)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>44</td>
<td>600</td>
<td>274&lt;sup&gt;f&lt;/sup&gt;</td>
<td>31 (11.3)</td>
<td>2 (0.7)</td>
<td>2 (0.7)</td>
</tr>
</tbody>
</table>

**Significant risk associated with routine CLND**

CLND Systematic Review

- Reoperative CLND has some morbidity
  - Only one prospective study
    - More permanent hypoparathyroidism in reoperative group (3.9% vs. 1.7%) but LESS permanent nerve injury (2.6% vs. 6.8%)
    - Some patients in primary surgery group had no CLND and some in reoperative group had CLND in primary operation

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Reference</th>
<th>Patients with recurrent thyroid carcinoma</th>
<th>Permanent hypoparathyroidism (%)</th>
<th>Permanent nerve injury</th>
<th>Unintentional permanent nerve injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>32</td>
<td>77a</td>
<td>3 (3.9) vs. 1.7%</td>
<td>2 (2.6) vs. 6.8%</td>
<td>Not reported</td>
</tr>
<tr>
<td>IV</td>
<td>45</td>
<td>48</td>
<td>4 (8.3)</td>
<td>12 (25)</td>
<td>Not reported</td>
</tr>
<tr>
<td>V</td>
<td>46</td>
<td>100c</td>
<td>Not reported</td>
<td>4 (4.0)</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>47</td>
<td>20</td>
<td>1 (5.6) vs. 0</td>
<td>3 (15)</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>48</td>
<td>45</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

CLND Systematic Review

- Reoperative CLND not conclusively with more risk than initial CLND

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Reference</th>
<th>Patients with recurrent thyroid carcinoma</th>
<th>Permanent hypoparathyroidism (%)</th>
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<tr>
<td>IV</td>
<td>45</td>
<td>48</td>
<td>4 (8.3)</td>
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<td>Not reported</td>
</tr>
<tr>
<td>V</td>
<td>46</td>
<td>100</td>
<td>Not reported</td>
<td>4 (4.0)%</td>
<td>0</td>
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</tr>
<tr>
<td>V</td>
<td>48</td>
<td>45</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Discordance of + CLNs, Recurrence and Mortality

- **High incidence of + CLNs**

- **Lower incidence of recurrence**
  - 9-30% (JACS 2007;205:239-247)

- **Even less mortality**
  - < 10% after 10yrs
Discordance of + CLNs, Recurrence and Mortality

- + CLNs do not predict survival
- Many micrometastatic + CLN treated with radioiodine
CLNs Do Not Predict Survival

- Retrospective series of 576 patients
  - + LNs correlated with recurrence but not survival (Mazzaferri EL, Young RL. Am J Med 1981;70(3):511-518)

- Retrospective study of 200 pts

- Retrospective series of 819 patients
CLNs Do Not Predict Survival

- Many scoring systems do not utilize LN status
  - AGES: age, grade, extent, size
  - MACIS: metastases, age, completeness of resection, invasion, size
  - AMES: age, metastases, extent, size
  - Only TNM uses N status
CLNs and Survival

- Swedish case-control study of 5123 patients with differentiated thyroid CA
  - Matched cases of death from thyroid CA to controls who did not die
  - Looked at prognostic factors for mortality

Lundgren CI, et al. Cancer 2006;106:524-531
+ CLNs and Survival

**TABLE 3**

Occurrence of Lymph Node and Distant Metastases in Patients with Differentiated Thyroid Carcinoma, Demonstrating Univariate and Multivariate ORs of Dying from Thyroid Carcinoma with 95% CIs

<table>
<thead>
<tr>
<th>Metastases</th>
<th>Cases</th>
<th>Controls</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>%</td>
<td>Total</td>
<td>%</td>
<td>OR</td>
</tr>
<tr>
<td>Lymph node metastases</td>
<td>196</td>
<td>33</td>
<td>127</td>
<td>21</td>
<td>2.5</td>
</tr>
<tr>
<td>No lymph node metastases</td>
<td>116</td>
<td>19</td>
<td>179</td>
<td>30</td>
<td>1.0</td>
</tr>
<tr>
<td>Initial distant metastases</td>
<td>146</td>
<td>25</td>
<td>29</td>
<td>5</td>
<td>6.6</td>
</tr>
<tr>
<td>No initial distant metastases</td>
<td>427</td>
<td>72</td>
<td>547</td>
<td>92</td>
<td>1.0</td>
</tr>
<tr>
<td>Late distant metastases</td>
<td>394</td>
<td>66</td>
<td>93</td>
<td>16</td>
<td>15.3</td>
</tr>
<tr>
<td>No late distant metastases</td>
<td>122</td>
<td>21</td>
<td>456</td>
<td>77</td>
<td>1.0</td>
</tr>
</tbody>
</table>

- LNs not differentiated as central or lateral
- Included follicular and papillary carcinoma
- CLND not routine
- Cannot conclude +CLNs influence survival

Lundgren CI, et al. Cancer 2006;106:524-531
+ CLNs and Survival

- Japanese series of 1740 papillary carcinoma patients
  - Looked at prognostic factors for recurrence and survival
  - Overall recurrence 10.9%
  - Overall cause-specific survival (CSS)
    99.4% at 10yr, 97.2% at 15yr
+ CLNs and Survival

- No difference in DFS or CSS in pN0 vs. pN1a (+ CLN)

N1a = + CLN  N1b = + LLN

+ CLNs and Survival

- On multivariate analysis
  - Central node metastasis was a prognostic factor for DFS
  - Central node metastasis was NOT a prognostic factor for CSS
Summary

- Recommendation for routine CLND based on poor evidence
- High incidence + CLN in routine CLND
- + CLNs do not predict worse survival
- Routine CLND increases surgical complications and cost
Conclusions

- Routine CLND not proven to improve survival
- Large RCT needed with at least 12 yr f/u
- Is it worth risking hypoparathyroidism and nerve injury in all patients for a small potential % of patients to benefit in 15 yr survival?
Conclusions

- Given intensive follow-up with thyroglobulin levels and US, perhaps the real issue is doing CLND to prevent recurrence of questionable significance.
- Does intensive follow-up improve survival?
Breast and Colon CA

Intensive vs. Clinical f/u in Breast CA

JAMA 1999;281(17):1586

Intensive vs. Clinical f/u in Colorectal CA

Gastroenterology 1998;114:4-14

p=0.2
Conclusion

Are we treating the patient or “malignant” thyroglobulinemia?