Operative Management of Differentiated Thyroid Cancer:
The Importance of Routine Central Neck Dissection

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Overview

- Background and epidemiology

- Level of evidence available on differentiated thyroid cancer

- Evidence clearly supporting central node dissection for differentiated thyroid cancer
Thyroid Cancer

- Most common endocrine malignancy

  - American Cancer Society estimates 33,550 people in U.S. will be diagnosed in 2007, 1530 will die of thyroid cancer
  
  - Lifetime risk of being diagnosed is about 1%
  
  - Between 1950 and 2000 the incidence increased 240%
  
  - Mortality during this same time decreased more than 44%

Thyroid Cancer

- **Well-differentiated thyroid cancer (90%)**
  - Papillary thyroid cancer (60-80%)
  - Follicular thyroid cancer (10-25%)
  - “Intermediate Differentiation” (10-15%)
    - Variants of PTC
    - Insular Carcinoma
    - Hurthle Cell

- **Medullary thyroid carcinoma (5-9%)**

- **Poorly differentiated (1-2%)**

Carling et al. World J. Surg; 2007
Differentiated Thyroid Cancer (DTC)

- **Papillary Thyroid Cancer (PTC)**
  - 60-80%
  - Lymphatic metastasis
    - 30-80% prophylactic neck dissections node positive
    - 70-90% of patients with PTC may have micrometastasis to adjacent lymph nodes at time of diagnosis.

- **Follicular Thyroid Cancer (FTC)**
  - 10-25%
  - Primarily hematogenous metastasis
    - Bone, Lung

Lymphatic Spread of DTC

- Lymphatic spread occurs in a sequential fashion
- Thyroid to:

1. Central compartment
2. Ipsilateral lateral compartment
3. Contralateral lateral compartment and mediastinum

Central (Level VI) Lymph Nodes

- **Neck Dissection Classification**
  - Originally published in 1991, revised in 2002
  - Neck is divided into 6 distinct anatomic levels.

- **Level VI Anatomic boundaries**
  - Superior: hyoid bone
  - Inferior: suprasternal notch
  - Lateral: Right and left common carotid arteries.

Evidence Based Recommendations

- The majority of evidence based literature exists as retrospective cohort studies or case series.
- Many authors assign levels of evidence based on a modification of Sackett’s classification as proposed by Heinrich et al.

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### Table 1.
Sackett’s classification of the level of evidence\(^{19}\) with Heinrich’s Modification\(^{27}\)

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Type of trial</th>
<th>Criteria for classification</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Large randomized trials with clear-cut results (and low risk of error)</td>
<td>Sample size calculation provided and fulfilled, study endpoint provided</td>
<td>A</td>
</tr>
<tr>
<td>II</td>
<td>Small randomized trials with uncertain results (and moderate to high risk of errors)</td>
<td>Matched analysis, sample size calculation not given or not fulfilled; study endpoint not provided, convincing comparative studies</td>
<td>B</td>
</tr>
<tr>
<td>III</td>
<td>Nonrandomized, contemporaneous controls</td>
<td>Noncomparative, prospective</td>
<td>C</td>
</tr>
<tr>
<td>IV</td>
<td>Nonrandomized, historical controls</td>
<td>Retrospective analysis, cohort studies</td>
<td>–</td>
</tr>
<tr>
<td>V</td>
<td>No control, case series only; opinion of experts</td>
<td>Small series, review articles</td>
<td>–</td>
</tr>
</tbody>
</table>
Evidence Based Recommendations

- No prospective randomized trials of trials to date.

Why?
- “None have yet been done and it is unlikely that any will be...”
- DTC has a “long natural history”
- “The indolent nature of PTC”
- “Prospective randomized trials assessing the impact of surgical management on PTC outcomes are impractical and have not been performed...”
“Wong et al estimated that a clinical trial to address the issue of ablative radioactive iodine therapy would require nearly 4,000 patients in each arm... to detect a 10% reduction in mortality after 25 years.” “The results would be available after 35 years.”

Patient with Differentiated Thyroid Cancer

- Total Thyroidectomy
  - Central Lymph Node Dissection at Time of Initial Operation
  - Thyroid Hormone Suppression
  - Prevent Disease Recurrence
  - Reduce Disease Related Mortality
  - Facilitate Ongoing Surveillance

- Minimize Morbidity: Nerve Injury and Hypoparathyroidism

- ¹³¹I Ablation of Remnant

- Prevent Disease Recurrence
- Reduce Disease Related Mortality
- Facilitate Ongoing Surveillance
Prevent Disease Recurrence

Central Lymph Node Dissection in Differentiated Thyroid Cancer

Matthew L. White, MD,1,2 Paul G. Gauger, MD,1 Gerard M. Doherty, MD1

- Systematic review of the literature using evidence-based criteria.

- “Does central lymph node dissection decrease recurrence or disease-specific mortality in PTC?”
## Level IV and V data showing decreased recurrence.

<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</td>
<td>195</td>
<td>195a</td>
<td>Not reported</td>
<td>NA</td>
<td>CLND compared with</td>
<td>NA</td>
</tr>
<tr>
<td>IV</td>
<td>14</td>
<td>342</td>
<td>60a</td>
<td>Increased with node metastases, decreased with compartment-oriented dissection</td>
<td>All &lt; 0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Compartment-oriented dissection</td>
<td>All &gt; 0.20</td>
<td>No analysis; only 1 death</td>
<td>NA</td>
</tr>
<tr>
<td>IV</td>
<td>29</td>
<td>103</td>
<td>27a</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>30</td>
<td>139</td>
<td>53a</td>
<td>Not reported</td>
<td>NA</td>
<td>Distant metastases, age, extrathyroidal growth, central lymph node dissection</td>
<td>All ≤ 0.04</td>
</tr>
<tr>
<td>V</td>
<td>11</td>
<td>43</td>
<td>43a</td>
<td>Increased in lateral compartments with more positive central nodes, decreased with CLND</td>
<td>0.003</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>37</td>
<td>447</td>
<td>56</td>
<td>Thyroglobulin level decreased with CLND, more patients athyroglobulinemic with CLND</td>
<td>P = 0.02</td>
<td>P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>32</td>
<td>252b</td>
<td>252a</td>
<td>Increased with greater tumor size; decreased with central neck dissection</td>
<td>All &lt; 0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>33</td>
<td>148</td>
<td>148a</td>
<td>Increased with more node metastases and elevated postoperative thyroglobulin</td>
<td>All ≤ 0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>35</td>
<td>139b</td>
<td>139a</td>
<td>Not reported</td>
<td>NA</td>
<td>Distant metastases, age, and TNM stage</td>
<td>All ≤ 0.012</td>
</tr>
<tr>
<td>V</td>
<td>36</td>
<td>759</td>
<td>759a</td>
<td>Increased with positive central nodes, age, and extrathyroidal extension</td>
<td>All ≤ 0.0259</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 (FTC) instead of PTC.*
Prevent Disease Recurrence

“Does central lymph node dissection decrease recurrence or disease-specific mortality in PTC?”

Conclusion:

“Systematic compartment-oriented central lymph node dissection (CLND) may decrease recurrence of PTC (Levels IV and V data, no recommendation) and likely improves disease-specific survival (grade C recommendation).”

Patient with Differentiated Thyroid Cancer

- Thyroid Hormone Suppression
- Total Thyroidectomy
- Central Lymph Node Dissection at Time of Initial Operation
- ¹³¹I Ablation of Remnant
- Prevent Disease Recurrence
- Minimize Morbidity: Nerve Injury and Hypoparathyroidism
- Reduce Disease Related Mortality
- Facilitate Ongoing Surveillance

Cure Found
Reduce Disease Related Mortality

“Does central lymph node dissection decrease recurrence or disease-specific mortality in PTC?”

Conclusion:

“Systematic compartment-oriented central lymph node dissection (CLND) may decrease recurrence of PTC (Levels IV and V data, no recommendation) and likely improves disease-specific survival (grade C recommendation).”

Death due to thyroid cancer occurred in 1.6% of the Goteborg cohort.

Death due to thyroid cancer in the comparison group was 8.4 – 11.1%
Patient with Differentiated Thyroid Cancer

Total Thyroidectomy

Central Lymph Node Dissection at Time of Initial Operation

1\textsuperscript{31}I Ablation of Remnant

Prevent Disease Recurrence

Minimize Morbidity: Nerve Injury and Hypoparathyroidism

Reduce Disease Related Mortality

Facilitate Ongoing Surveillance

Thyroid Hormone Suppression
Facilitate Ongoing Surveillance

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. Mazzaferri,⁷ Bryan McIver,⁸ Steven I. Sherman,⁹ and R. Michael Tuttle¹⁰

R43. Serum thyroglobulin should be measured every 6–12 months by an immunometric assay, ideally in the same laboratory and using the same assay, during follow-up of patients with differentiated thyroid carcinoma who have undergone total or near-total thyroidectomy and thyroid remnant ablation. Thyroglobulin antibodies should be quantitatively assessed with every measurement of serum thyroglobulin.---Recommendation A
Facilitate Ongoing Surveillance

- Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer
  - Sywak et al. Surgery 2006

- Retrospective cohort; 447 patients
- Patients with clinically node negative PTC >1cm
- Group A: Total thyroidectomy + Ipsilateral CLND
- Group B: Total thyroidectomy alone
Facilitate Ongoing Surveillance

- Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer
  - Sywak et al. Surgery 2006

Results:
- Serum postablative TG levels were lower with ipsilateral CLND
  - Group A (0.4 µg/L) vs. Group B (9.3 µg/L) \( p = 0.02 \)
  - More group A patients had undetectable TG levels
    - Group A 72% vs Group B 43% \( p < 0.001 \)
Patient with Differentiated Thyroid Cancer

Thyroid Hormone Suppression

Total Thyroidectomy

Central Lymph Node Dissection at Time of Initial Operation

\(^{131}\text{I} \text{ Ablation of Remnant}

Prevent Disease Recurrence

Reduce Disease Related Mortality

Facilitate Ongoing Surveillance

Minimize Morbidity: Nerve Injury and Hypoparathyroidism

Prevent Disease Recurrence

Reduce Disease Related Mortality

Facilitate Ongoing Surveillance
**Minimize Morbidity**

- Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer
  - Sywak et al. Surgery 2006

### Table III. Postoperative surgical complications

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>56</td>
<td>391</td>
<td></td>
</tr>
<tr>
<td>Mean no. of parathyroid glands autotransplanted (95% CI)</td>
<td>1.6 (1.4-1.9)</td>
<td>0.9 (0.7-1.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Postoperative infection* (%)</td>
<td>1 (1.8)</td>
<td>5 (1.3)</td>
<td>.76</td>
</tr>
<tr>
<td>Postoperative hemorrhage (%)</td>
<td>1 (1.8)</td>
<td>1 (1)</td>
<td>.6</td>
</tr>
<tr>
<td>Temporary hypocalcemia† (%)</td>
<td>10 (18)</td>
<td>32 (8)</td>
<td>.02</td>
</tr>
<tr>
<td>Permanent hypoparathyroidism‡ (%)</td>
<td>1 (1.8)</td>
<td>2 (0.5)</td>
<td>.27</td>
</tr>
<tr>
<td>Temporary RLN dysfunction (%)</td>
<td>1 (1.8)</td>
<td>4 (1.0)</td>
<td>.62</td>
</tr>
<tr>
<td>Permanent RLN injury (%)</td>
<td>0</td>
<td>4 (1.0)</td>
<td>.45</td>
</tr>
</tbody>
</table>
Minimize Morbidity

- Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer
  - Sywak et al. Surgery 2006

- No statistical difference in rate of permanent hypoparathyroidism or recurrent laryngeal nerve injury.
Minimize Morbidity

- White et al. Central Lymph Node Dissection in DTC
  
  “Does central lymph node dissection increase the risk of permanent hypoparathyroidism and permanent nerve injury?”

<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)</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>
</tbody>
</table>

Minimize Morbidity

- Gramatica et al. (aka Marseilles Study)
  - Prospective cohort series, 100 patients

<table>
<thead>
<tr>
<th></th>
<th>Recurrent laryngeal nerve palsy</th>
<th>Hypoparathyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transient</td>
<td>Permanent</td>
</tr>
<tr>
<td>Group 1</td>
<td>3 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Group 2</td>
<td>2 (4%)</td>
<td>0</td>
</tr>
</tbody>
</table>

- Conclusion: No increased risk of nerve injury
  Increased rate of hypoparathyroidism

- Thyroidectomy without CLND: 1-2% permanent hypoparathyroidism
  1-2% permanent nerve injury
Minimize Morbidity

- **White et al. Central Lymph Node Dissection in DTC**
  - Does reoperation in the central neck for recurrence increase risk of hypoparathyroidism and nerve injury?

<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>77&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (3.9)</td>
<td>2 (2.6)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Not reported</td>
</tr>
<tr>
<td>IV</td>
<td>45</td>
<td>48</td>
<td>4 (8.3)</td>
<td>12 (25)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Not reported</td>
</tr>
<tr>
<td>V</td>
<td>46</td>
<td>100&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Not reported</td>
<td>4 (4.0)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>47</td>
<td>20</td>
<td>1 (5.6)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (15)&lt;sup&gt;d&lt;/sup&gt;</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>

- Conclusion: Reoperation in the central neck for recurrent PTC may increase the risk of hypoparathyroidism and nerve injury when compared with thyroidectomy with or without CLND. (Grade C Recommendation)

*White et al. World J Surg 2007*
Patient with Differentiated Thyroid Cancer

Thyroid Hormone Suppression

Total Thyroidectomy

Central Lymph Node Dissection at Time of Initial Operation

131I Ablation of Remnant

Prevent Disease Recurrence

Minimize Morbidity: Nerve Injury and Hypoparathyroidism

Reduce Disease Related Mortality

Facilitate Ongoing Surveillance
“One third of patients who develop recurrent cancer will die from the disease.”

“Up to 90% have evidence for micrometastases. However, only 10% of patients with microscopic lymph node metastases are believed to develop clinically significant disease.”

- Sosa and Udelsman, J. Surg Onc 2006

R27. Routine central-compartment (level VI) neck dissection should be considered for patients with papillary thyroid carcinoma and suspected Hürthle 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 Hürthle cell cancers—Recommendation B