Management of Thyroid Goiter

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I have no conflict of interest to declare in regards to the contents of this lecture material.

The views put forth in this presentation do not reflect the views of the US Army or the Department of Defense.
Objectives

• To put forward an evidence-based approach to the treatment of…
  – Graves disease
  – Toxic multinodular goiter (Plummer’s disease)
  – Nontoxic MNG
  – Substernal goiter

Levels of Evidence

• Level I – Large well designed PRCT or meta-analyses
• Level II – Small PRCT with potential errors
• Level III – Non-randomized prospective studies and case-control studies
• Level IV – Retrospective studies with historic controls
• Level V – Expert opinion of consensus statements
Grading of Recommendations

- Grade A – Supported by Level I evidence
- Grade B – Supported by Level II evidence
- Grade C – Supported by Level III, IV, or V evidence

Graves’ Disease
Graves’ Disease

- Autoimmune disorder
- Annual incidence of 40 / 100,000 in US
- 4 – 6 times more common in ♀
- Mostly occurs between 20 – 50
- Treatments include
  - $^{131}$I (RAI) – Preferred in the US
  - Antithyroid drugs (ATD) – Preferred in Europe and Asia
  - Surgery
    - Indications include:
      - Suspicion for / known malignancy
      - Pregnancy not controlled with ATD
      - Desire for pregnancy
      - Local compressive symptoms
      - Recurrence after / failure of medical management

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Graves’ Disease

- PubMed search of English-language literature for 1980 – present
- Focused on PRCT, meta-analyses, & case series
- Four issues:
  1. Is surgery better than RAI or ATD?
  2. What is the recommended surgical approach?
  3. How does Graves ophthalmopathy (GO) influence the role of surgery?
  4. What is the role of surgery in GD in children?

Graves’ Disease

1. Is surgery better than RAI or ATD?
   - Only one PRCT attempted to study the issue
   - No difference was noted
   - Most other studies address the issue of GO
   - NO RECOMMENDATIONS REACHING ANY GRADE OF EVIDENCE FOR TOC FOR ADULTS WITH GD!


2. What is the recommended surgical approach?

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Evidence level</th>
<th>No. (m)</th>
<th>Treatment follow-up</th>
<th>Recurrent disease (%)</th>
<th>Permanent RLN palsy (%)</th>
<th>Permanent HPT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pole [29]</td>
<td>Meta-analysis</td>
<td>I</td>
<td>7241 538</td>
<td>TT vs. ST 5.6 years</td>
<td>7.9 0 0.7 0.9 1.0 0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Witz [30]</td>
<td>PRCT</td>
<td>II</td>
<td>150 50</td>
<td>TT vs. ST 18-38 months NA NA 1.9 2.1 2.9 10.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Witz [43]</td>
<td>RCS</td>
<td>IV</td>
<td>173 19</td>
<td>TT vs. ST 0.15-23.0 years</td>
<td>2.0 0 1.3 2.0 6.6 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miccoli [44]</td>
<td>RCS</td>
<td>IV</td>
<td>140 60</td>
<td>TT vs. ST 6-45 months</td>
<td>5.0 0 2.5 1.6 3.8 3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baskol [14]</td>
<td>RCS</td>
<td>IV</td>
<td>1360 119</td>
<td>TT vs. ST NA</td>
<td>NA NA 0.4 0.8 0.1 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ku [32]</td>
<td>RCS</td>
<td>IV</td>
<td>217 98</td>
<td>TT vs. ST 64 months</td>
<td>5.9 0 0 0 0.8 3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganzaro [45]</td>
<td>RCS</td>
<td>IV</td>
<td>714</td>
<td>TT and NT 6.7 years</td>
<td>0 2.0 1.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PRCT: prospective randomized clinical trial; RCS: retrospective case series; TT: total thyroidectomy; ST: subtotal thyroidectomy; NT: near-total thyroidectomy; RLN: recurrent laryngeal nerve.
Graves’ Disease

2. What is the recommended surgical approach?
   - Grade A recommendation that Total Thyroidectomy is the surgery of choice due to:
     - Complications rates equal to lesser resections
     - Higher cure rates
     - Negligible recurrence rates


Graves’ Disease

3. How does Graves ophthalmopathy (GO) influence the role of surgery?

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Evidence level</th>
<th>No. with GO</th>
<th>Treatment</th>
<th>Effect on GO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tallstedt [36]</td>
<td>PROCT II</td>
<td>II</td>
<td>44</td>
<td>STHVSATD</td>
<td>Progression in 32% of RA patients; no difference in progression between RA (12%) and AITD (10%)</td>
</tr>
<tr>
<td>Barbaria [39]</td>
<td>PROCT I</td>
<td>I</td>
<td>224</td>
<td>RRRAapredominantly ATD</td>
<td>11% in RA1 and progression in 69% in RA2 and progression in 11% in ATD</td>
</tr>
<tr>
<td>Melci [50]</td>
<td>PROCT I</td>
<td>I</td>
<td>60</td>
<td>TT vs. TT+RAT (IV glucocorticoids)</td>
<td>25% with TT alone had progression of GO at 9 months; none with RRRA had progression at 9 months</td>
</tr>
<tr>
<td>Vils [36]</td>
<td>PROCT II</td>
<td>II</td>
<td>29</td>
<td>TT vs. ST</td>
<td>No difference</td>
</tr>
<tr>
<td>Julliart [36]</td>
<td>PROCT II</td>
<td>II</td>
<td>44</td>
<td>TT vs. ST</td>
<td>No difference</td>
</tr>
<tr>
<td>McLeod [46]</td>
<td>PCC II</td>
<td>II</td>
<td>90</td>
<td>NT vs. ATD</td>
<td>17% (3/3) with GO progressed with NT; 25% (7/3) without GO developed GO vs ATD</td>
</tr>
<tr>
<td>Lenz [45]</td>
<td>PCS IV</td>
<td>I</td>
<td>19</td>
<td>SF</td>
<td>Improvement 60% exchanged at 19% progression 8/9</td>
</tr>
<tr>
<td>Abu [37]</td>
<td>PCS IV</td>
<td>I</td>
<td>65</td>
<td>ST vs. RA</td>
<td>75% (10/4) with RA had progression; 15% (1/4) with ST had progression</td>
</tr>
<tr>
<td>Vilsa [40]</td>
<td>RCS V</td>
<td>V</td>
<td>75</td>
<td>TT vs. ST</td>
<td>90% (10/10) with GO progressed on ST; 17% (4/8) with GO progressed on TT</td>
</tr>
<tr>
<td>Mocci [44]</td>
<td>RCS V</td>
<td>V</td>
<td>40</td>
<td>TT vs. ST</td>
<td>35% (15/4) with ST had progression; 98% (39/4) with TT had progression</td>
</tr>
<tr>
<td>Ageno [46]</td>
<td>RCS V</td>
<td>V</td>
<td>72</td>
<td>TT vs. ST</td>
<td>No difference</td>
</tr>
</tbody>
</table>

GO: Graves’ ophthalmopathy; PCC: prospective case-control study; PCS: prospective case series
Graves’ Disease

3. How does Graves ophthalmopathy (GO) influence the role of surgery?
   – Grade B recommendation for surgery
     – Effect may be negated by glucocorticoids
     – Especially in severe GO


Graves’ Disease

4. Preferred treatment for children with GD?
   – No grade of recommendations
     – No PRCT
     – ADT is effective in only a fraction
     – RAI effective, but ? Induction of papillary thyroid CA
     – RAI more difficult to dose.

Toxic MNG (Plummer’s Disease)

Toxic MNG

1. Should STN and TMNG be treated differently?

   - There are no PRCT in the English literature investigating the treatments and outcomes of STN and TMNG.

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Toxic MNG

2. Does subclinical hyperthyroidism (Suppressed TSH and Normal T3/T4) affect treatment outcome?

- Prospective review of 2,007 patients
  - 32% of those ≥ 60 with ↓ TSH develop Afib within 10 years (Level III data)
- Prospective observational study of 3,121 patients with stable cardiac disease
  - Significant ↑ in cardiac mortality in those with subclinical hyperthyroidism (Level III data)
- No PRCT to determine if treatment helps asymptomatic patients.

Toxic MNG

3. Do patients with a large goiter gain greater benefit from thyroidectomy?
   – Nonrandomized prospective study of the effect of RAI on STN size in 39 patients
     • 54% decrease in size (Level III data)
   – Nonrandomized prospective study of RAI on large goiters in 35 patients
     • 89% of the large goiters remained large (Level V data)
   – Level IV evidence supports thyroidectomy over RAI for large TMNG


Toxic MNG

4. Are compressive symptoms an indication for surgery?
   – No PRCT trials on the subject
   – Mayo data on 581 patients
     • 76 (13%) had compressive symptoms
     • 75% had thyroidectomy, 25% RAI
     • Only 46% were smaller after RAI
   – Level IV data supporting surgery over RAI for compressive symptoms

Toxic MNG

5. What is the risk of malignancy in TMNG?

- 2 – 3.3% rate of papillary thyroid carcinoma in TMNG
- 2.9% rate in STN
- 1.1% in Graves’ disease


Toxic MNG

6. Is there an optimal treatment dose for RAI?

- No randomized dose-controlled trials of RAI in Plummer’s disease
- No formula/regimen has been shown to universally produce an euthyroid state

7. Is percutaneous ethanol ablation (US-PEA) useful?

- Large prospective multi-center study of 429 solitary nodules (240 / 56% toxic)
  - At one year 67% of STN were successfully treated.
  - No recurrences
- US-PEA as a third-line treatment


8. What is the most cost-effective treatment?

- Only Level V data
- One study in 2004 showed:
  - Lifetime cost of RAI exceeded thyroidectomy by $3,264 for base case of 42 year-old female

Nontoxic MNG

- Affects 5 – 7% of the world’s population
- Second most common endocrinopathy
- Up to 60% of Americans develop nodules
- 10 – 15% of goiters ultimately get surgery
- Recurrence of MNG accounts for up to 12% of operations

Nontoxic MNG


- Two broad question:
  1. Best initial treatment with respect to recurrence risk?
  2. Frequency of surgical complications as a function of extent of surgery?
  3. Comparison of initial and “redo” operations?


Nontoxic MNG

Does thyroid hormone suppression effectively reduce nodule size?

- Two meta-analyses
- Castro in 2002
  - 13 studies
    - 6 RCT including 346 patients
      - T4 treatment – 22% (14 – 39%) had ≥ 50% reduction in size
      - No treatment – 10% (0 – 20%) decrease

Nontoxic MNG

*Does thyroid hormone suppression effectively reduce nodule size?*

- **Sdano in 2005**
  - 9 RCT – 609 patients
    - 310 patients got T4 with a 22% response rate of ≥ 50% decrease in size
    - 209 patients with no treatment had a 10% rate of decreased size


Nontoxic MNG

*Does thyroid hormone suppression effectively reduce nodule size?*

- **Koc study**
  - Two-arm crossover study regarding dose response
    - Equivalent volume reduction (35% vs. 40%) between doses
    - Volume reduction on T4 reversed with cross-over to placebo
    - Placebo-first group showed growth with significant decrease in size with crossover to T4 suppression.

Nontoxic MNG

Does extent of surgery influence the rate of recurrence?

- 15 publications
- 12/15 were retrospective
- 4 comparative
- One well-designed PRCT (Level I evidence) comparing TT to ST
  - Recurrence rate with mean 14 year follow up
    - 14% in ST group
    - 0% in the TT group


Nontoxic MNG

Is total thyroidectomy associated with a higher complication rate than ST?

- 13 studies
- 8 comparative
- 3 PRCT

Nontoxic MNG

*Is total thyroidectomy associated with a higher complication rate than ST?*

- Analysis of 8 comparative studies

<table>
<thead>
<tr>
<th></th>
<th>Total Thyroidectomy</th>
<th>Subtotal Thyroidectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary RLN Injury</td>
<td>1 – 10%</td>
<td>0.9 – 6%</td>
</tr>
<tr>
<td>Permanent RLN Injury</td>
<td>0 – 1.4%</td>
<td>0 – 1.4%</td>
</tr>
<tr>
<td>Transient Hypocalcemia</td>
<td>9 – 35%</td>
<td>0 – 18%</td>
</tr>
<tr>
<td>Permanent Hypocalcemia</td>
<td>0 – 4%</td>
<td>0 – 1.4%</td>
</tr>
</tbody>
</table>


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Nontoxic MNG

*Is reoperation associated with a higher complication rate?*

- 10 studies
- 9 comparative

<table>
<thead>
<tr>
<th></th>
<th>Redo Surgery</th>
<th>Initial Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary RLN Injury</td>
<td>0 – 22%</td>
<td>0.5 – 18%</td>
</tr>
<tr>
<td>Permanent RLN Injury</td>
<td>0 – 13%</td>
<td>0 – 4%</td>
</tr>
<tr>
<td>Transient Hypocalcemia</td>
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<td>1 – 27%</td>
</tr>
<tr>
<td>Permanent Hypocalcemia</td>
<td>0 – 22%</td>
<td>0.5 – 18%</td>
</tr>
</tbody>
</table>

Nontoxic MNG - 2

Further Validation

- Retrospective cohort study of 6,223 patients (Level IV data)
- Total thyroidectomy (TT) – 3,834
- Subtotal thyroidectomy (ST) – 2,238
- Near-total Thyroidectomy (NT) – 151
- Mean follow up > 7 years


<table>
<thead>
<tr>
<th></th>
<th>TT</th>
<th>ST</th>
<th>NT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary RLN</td>
<td>2.8%</td>
<td>1.2%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent RLN</td>
<td>1.4%</td>
<td>1.2%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporary</td>
<td>24%</td>
<td>22%</td>
<td>24%</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent</td>
<td>3.5%</td>
<td>2.5%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant Neoplasm in Remaining Thyroid</td>
<td>---</td>
<td>1.2%</td>
<td>0.66%</td>
</tr>
</tbody>
</table>

Substernal Goiter

- Multiple definitions
- MEDLINE search of the English Language
- 5 Questions
  1. Is there an increased risk of cancer and what are the risk factors?
  2. How often is an extracervical approach needed?
  3. Is there an increased risk of hypoparathyroidism and nerve injury?
  4. What is the incidence of tracheomalacia and tracheotomy?
  5. What percent are recurrent disease?


Substernal Goiter

1. Is there an increased risk of cancer, and what are the risk factors?
   - Limited Level III/IV data - no higher incidence of cancer
   - Risk factors:
     - Family history
     - Cervical radiation
     - Recurrent goiter
     - Cervical adenopathy
   - Grade C recommendation

Substernal Goiter

2. What percent of the time is an extracervical approach needed and what are the associated factors?
   • Level V data
   • 0 – 5.3% rate of extracervical approach (mean of 2%)
   • Risk factors:
     – Primary substernal goiter
     – Mass larger than the thoracic inlet.


Substernal Goiter

3. Is there an increased risk of permanent RLN injury and ↓PTH?

Substernal Goiter

4. What is the rate of tracheomalacia and tracheotomy? What factors are associated with these?
   • Tracheomalacia: 0 – 10.3%
   • Tracheotomy: 0 – 8.6%
   • Risk factors:
     – Substernal goiter > 5 years and significant tracheal compression (Grade C recommendation)


Substernal Goiter

5. What percent of substernal goiters are a result of recurrent or persistent disease? What were the initial operations?
   • Limited Level V data
   • Reoperation rate 6 – 11.2% (as high as 37% in one study)
   • Most common initial surgery
     – Subtotal thyroidectomy
     – Hemithyroidectomy

Summary

• Total thyroidectomy is superior to ST
  – No difference in complication rates
  – No recurrences of disease
• Total thyroidectomy for GO (±)
• General lack of Level I data

Thank you

Questions?