Surgical Management of Graves’ Disease

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Chief of Division of Endocrine Surgery
Vice Chair of Academic Affairs and Professional Development

Department of Surgery
University of Wisconsin
Graves' Disease

Background

• Most common cause of hyperthyroidism

• Autoimmune disorder

• Thyroid stimulating immunoglobulins which bind to the TSH receptor (TSHR Ab)
Diagnosis of Graves’ disease

- Graves’ diagnosis requires biochemical hyperthyroidism AND:
  
  1. Obvious extra-thyroidal manifestations such as ophthalmopathy or dermopathy (pre-tibial myxedema)

  OR

  2. Detectable serum TRAb

  OR

  3. Diffuse, increased uptake on thyroid uptake scan
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Treatment

Three main treatments:

1. Anti-thyroid medications
2. Radioactive iodine (RAI)
3. Surgery
American Thyroid Association Guidelines

Treatment of Graves’

Recommendation 4

Patients with overt Graves’ hyperthyroidism should be treated with any of the following modalities: RAI, anti-thyroid medications, or thyroidectomy.

- The patient and physician must choose between these three effective and relatively safe initial treatment options.
- Need to discuss the logistics, benefits, speed of recovery, drawbacks, potential side effects, and cost.
- Decision needs to incorporate the personal values and preferences of the patient.

Bahn et al. Thyroid 2011
Graves' Disease

Factors Influencing choice of treatment

- age of patient
- desire for children/pregnancy
- severity of disease
- size of gland
- coexistent pathology
- presence of ophthalmopathy
- access to surgeon and/or RAI
- patient preference
- contraindications to RAI or drugs

*physician preference/bias*  
*patient preference*  
NOT
Graves' Disease

Factors Influencing choice of treatment

<table>
<thead>
<tr>
<th></th>
<th>Medical Therapy</th>
<th>Surgery</th>
<th>RAI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all mean values normalized by 6 weeks, &quot;equally effective&quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recommend to a friend</strong></td>
<td>68%</td>
<td>74%</td>
<td>84%</td>
</tr>
<tr>
<td><strong>Risk of relapse</strong></td>
<td>37%</td>
<td>6%</td>
<td>21%</td>
</tr>
<tr>
<td><strong>TSHR Ab levels</strong></td>
<td>normalized by 18 mo</td>
<td>normalized by 15 mo</td>
<td>still elevated at 48 months</td>
</tr>
</tbody>
</table>

Toring JCEM 1996
Graves' Disease
*Treatment Recommendations Vary*

- Recommendation for “Uncomplicated Graves”

<table>
<thead>
<tr>
<th></th>
<th>RAI</th>
<th>Surgery</th>
<th>Anti-Thyroid Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>59%</td>
<td>1%</td>
<td>40%</td>
</tr>
<tr>
<td>Europe</td>
<td>13%</td>
<td>1%</td>
<td>86%</td>
</tr>
<tr>
<td>Asia</td>
<td>29%</td>
<td>1%</td>
<td>73%</td>
</tr>
</tbody>
</table>

Burch et al. JCEM 2012
Graves' Disease

*Radioactive Iodine*

- 1946: first RAI for the treatment of hyperthyroidism
- Has become the treatment of choice in the US

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inexpensive</td>
<td>Slow (4-6 months)</td>
</tr>
<tr>
<td>Non-invasive</td>
<td>Often requires multiple treatments</td>
</tr>
<tr>
<td>Minimal short term side effects</td>
<td>Unclear risk to women of childbearing age</td>
</tr>
<tr>
<td>Safer?</td>
<td>May worsen eye disease</td>
</tr>
<tr>
<td>Long term risks: nodular goiter,</td>
<td></td>
</tr>
<tr>
<td>thyroid cancer, secondary</td>
<td></td>
</tr>
<tr>
<td>malignancy, increased CV</td>
<td></td>
</tr>
<tr>
<td>mortality, hyperparathyroidism</td>
<td></td>
</tr>
</tbody>
</table>
Graves' Disease
Radioactive Iodine

Is there an increased risk of secondary malignancy?

- 2793 hyperthyroid patients in Finland treated with RAI vs. age and sex matched controls
  - Increased risk of Cancer (RR, 1.25, 95% CI:1.08-1.46)
  - Dose dependent, > 5 year latency

Graves' Disease
Failure Rate of Radioactive Iodine

Failure of Radioactive Iodine in the Treatment of Hyperthyroidism

David F. Schneider, MD, MS1, Philip E. Sonderman, BA1, Michaela F. Jones, BS1, Kristin A. Ojomo, MD1, Herbert Chen, MD1, Juan C. Jaume, MD2, Diane F. Elson, MD2, Scott B. Perlman, MD3, and Rebecca S. Sippel, MD1

1Section of Endocrine Surgery, Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI; 2Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI; 3Section of Nuclear Medicine, Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI

325 pts. treated with RAI between 2007-2010

22.8% failure rate

• 72% additional RAI
• 18% additional RAI and then surgery
• 10% surgery

Schneider ASO 2014
Graves' Disease
Time to Failure of Radioactive Iodine

75.7% 9.5% 14.9%

Schneider ASO 2014
Graves' Disease

Predictors of Failure of Radioactive Iodine

The lower the dose of RAI, the higher the failure

The higher the pre-op T3 level, the higher the failure

Schneider ASO 2014
Graves' Disease

Medical Therapy

- **Thionamides**
  - inhibit the synthesis of thyroid hormones
  - latent period of 2-6 weeks
  - recurrence after 6 months of therapy is 69%
  - side effects: rash, arthralgia, liver dysfunction, and agranulocytosis

**Methimazole**
- longer duration of action
- lower side effects

**Propylthiouracil**
- use in early pregnancy
- higher risk of liver dysfunction
Graves' Disease

Time required to become euthyroid

80% of patients euthyroid by 10 weeks

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Surgery

- Surgery is an immediate fix
- Top choice in Europe and Japan, underutilized in the US
- Rarely offered as a 1st line treatment, reserved as a “last resort”
- Due to increased vascularity and fibrosis, risks thought to be “too high”
**Graves' Disease**

*Indications for Surgery*

- Malignancy/Suspicious nodules
- Goiter with compressive symptoms
- Need for rapid control
- Pregnant/desire to become pregnant
- Children
- Graves opthalmopathy
- Allergies to or poor compliance with anti-thyroid medications
- Patient preference
Graves' Disease

Indications for Surgery

Patient preference is an important factor in decision-making

- One-third of patients choose surgery in the absence of a clear indication

- Satisfaction of patients who choose surgery is high (88%)

Grodski S, et al. Thyroid 2007, 17(2)
Complications of Thyroid Surgery

• Hypocalcemia due to hypoparathyroidism
  • Transient (5-20%)
  • permanent (<2%)
• Recurrent laryngeal nerve injury
  • Transient (5-10%)
  • permanent (<2%)
• Hematoma (<1 %)
ASSOCIATION FOR ACADEMIC SURGERY

Total Thyroidectomy: A Safe and Effective Treatment for Graves’ Disease

Jing Liu, B.S., Anna Bargren, B.S., Sarah Schaefer, N.P., Herbert Chen, M.D., and Rebecca S. Sippel, M.D.

Department of Surgery, Section of Endocrine Surgery, University of Wisconsin, Madison, Wisconsin

Submitted for publication October 11, 2010

TABLE 1
Operative Variables and Postoperative Complications

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Total</th>
<th>Subtotal</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>32 (59)</td>
<td>24 (44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated blood loss (mL)</td>
<td>83 ± 118</td>
<td>135 ± 152</td>
<td>0.045</td>
<td></td>
</tr>
<tr>
<td>Mean operative time (min)</td>
<td>140 ± 40</td>
<td>157 ± 36</td>
<td>0.023</td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient hypocalcemia</td>
<td>4 (7)</td>
<td>2 (4)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Permanent hypocalcemia</td>
<td>1 (2)</td>
<td>0</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Recurrent laryngeal nerve injury</td>
<td>0</td>
<td>0</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>0</td>
<td>4 (7)</td>
<td>0.008</td>
<td></td>
</tr>
</tbody>
</table>
Thyroidectomy is a First Line Treatment Option
Thyroidectomy for Graves 2003-2017

University of Wisconsin
The impact on the treatment of patients at our institution

>50% of patients choose surgery as 1st line therapy

Elfenbein et al ASO 2015
Graves' Disease

Does Timing of Treatment Matter?

Thyroidectomy as Primary Treatment Optimizes Body Mass Index in Patients with Hyperthyroidism

David F. Schneider, MD, MS¹, Ratnam Nookala, MBBS², Taylor J. Jaraczewski¹, Herbert Chen, MD¹, Carmen C. Solorzano, MD², and Rebecca S. Sippel, MD¹

¹Department of Surgery, University of Wisconsin, Madison, WI; ²Division of Surgical Oncology and Endocrine Surgery, Department of Surgery, Vanderbilt University Medical Center, Nashville, TN

Delayed surgery group had unhealthy weight gain

Schneider et al ASO 2014
Graves' Disease

Extent of Surgery

What is the optimal operation?

• Total vs. Subtotal thyroidectomy

1. What is the ideal remnant size?
   • Too big → recurrence
   • Too small → hypothyroidism

2. Risk of RLN injury and hypoparathyroidism
   • Are they less with subtotal thyroidectomy?
# Graves' Disease

## Surgery - Total vs. Subtotal

### Meta analysis - complications

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Total Thyroidectomy</th>
<th>Subtotal Thyroidectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>538</td>
<td>6703</td>
</tr>
<tr>
<td>Recurrence</td>
<td>0%</td>
<td>7.9%</td>
</tr>
<tr>
<td>transient RLN</td>
<td>7.7%</td>
<td>2.8%</td>
</tr>
<tr>
<td>permanent RLN</td>
<td>0.9%</td>
<td>0.7%</td>
</tr>
<tr>
<td>transient hypocalcemia</td>
<td>9.6%</td>
<td>7.4%</td>
</tr>
<tr>
<td>permanent hypoparathyroidism</td>
<td>0.9%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

Incidental CA in 4.5%, mortality 0%

Palit TK. JSR 2000
Graves' Disease
Extent of Surgery

- 119 total vs. 1246 subtotal thyroidectomy
  - Transient complications *higher* with total
  - Permanent complication rates *equal*
  - Incidence of euthyroid in subtotal thyroidectomy is low
    - 51% euthyroid at 6 months
    - only 27% euthyroid at 15 yrs

Barakate MS 2002. ANZ J Surg
Graves' Disease

Total vs. Subtotal Thyroidectomy

Reasons why Total thyroidectomy is preferred

1. Risks no greater with total over subtotal thyroidectomy
   • "in experienced hands"
   • exception is transient hypocalcemia

2. Difficult to predict remnant size
   • if too large of remnant is left, patients are at high risk for recurrence
   • If too little is left they are at high risk for hypothyroidism which can occur up to 15 years after surgery

3. More rapid and reliable cure

4. Treats potential cancer
Graves' Disease

*Pre-operative medical preparation*

1. Euthyroid by means of anti-thyroid medications
   - Important to monitor T3 and T4 levels as TSH often remains suppressed for months

2. B-blockers
   - Start at diagnosis - have an immediate effect
   - Given as a sole treatment if unable to tolerate anti-thyroid meds
   - Given to maintain a pulse rate below 80 bpm

3. Lugol's solution (SSKI)
   - Given to decrease the vascularity of the gland
   - Given 2-3 times a day beginning 10 days prior to operation
Graves' Disease
Pre-operative preparation

Does Lugol’s really do anything?

• Mechanism:
  • Blocks thyroid hormone release
  • Blocks iodine organification
  • Maximal effect at 10 days

• Randomized controlled trial 36 pts with Graves treated with/without Lugol's
  • Mean blood flow, microvessel density, CD-34 expression, and blood loss were all significantly reduced and correlated with Lugol's treatment
  • Lead to a decrease in intraoperative blood loss

Erbil Y. JCEM March 2007
Graves' Disease
Pre-operative preparation

Is Lugol’s Necessary?

• Maybe it reduced blood flow but made the gland more fibrotic
• Not sure it was really helping us

Impact of potassium iodide on thyroidectomy for Graves’ disease: Implications for safety and operative difficulty

Reese W. Randle, MD *, Maria F. Bates, MD, Kristin L. Long, MD, Susan C. Pitt, MD, MPH, David F. Schneider, MD, MS, and Rebecca S. Sippel, MD

Department of Surgery, University of Wisconsin, Madison, WI

Randle et al, SURGERY 2018
Graves' Disease

Pre-operative preparation

Does Lugol’s make surgery more difficult?

Randle et al, SURGERY 2018
Graves' Disease

Pre-operative preparation

Does Lugol’s decreases complications?

<table>
<thead>
<tr>
<th>Complications</th>
<th>No SSKI (n=34)</th>
<th>SSKI (n=25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient Hypoparathyroidism</td>
<td>9 (26%)</td>
<td>1 (7%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Transient Hoarseness</td>
<td>5 (16%)</td>
<td>0 (0%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Nerve Injury</td>
<td>1</td>
<td>0</td>
<td>0.29</td>
</tr>
<tr>
<td>ER Visit</td>
<td>2</td>
<td>0</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Randle et al, SURGERY 2018
Graves' Disease
Postoperative Medical Management

1. Thyroid Hormone
   • Half-life is 5-7 days
   • Start after resolution of hyperthyroid symptoms

2. Anti-thyroid meds
   • Stop PTU, Methimazole, and SSKI
   • Taper beta-blockers over 1-2 weeks

3. Hypocalemia
   • Dual mechanism: bone hunger and hypoparathyroidism
   • Post op Phosphate/PTH can help clarify the etiology
   • Treat aggressively with PO calcium and Vitamin D
Graves' Disease
Postoperative Care

Preventing Postoperative Hypocalcemia in Patients with Graves Disease: A Prospective Study
Sarah C. Oltmann, MD, Andrew V. Brekke, David F. Schneider, MD, MS, Sarah C. Schaefer, ANP-BC, Herbert Chen, MD, and Rebecca S. Sippel, MD
Department of Surgery, Section of Endocrine Surgery, University of Wisconsin, Madison, WI

- Pretreated 45 pts with 1 gm of Calcium Carbonate TID for 2 weeks prior to surgery

Reduced symptomatic hypocalcemia from 26% to 9%

Oltmann et al ASO 2015
Patient with Graves’ Disease

- Radioactive Iodine
  - Pros
  - Cons
- Surgery
  - Pros
  - Cons
- Anti-Thyroid Drugs
  - Pros
  - Cons

Medical Factors

Physician Preference/Bias

Patient Preference
Graves’ Disease
Conclusions

1. **Treatment options**: surgery, radioactive iodine, and long-term anti-thyroid drugs
2. **Surgery is increasingly being utilized**
3. **Surgery for Graves’** has significant advantages for some patients and should be offered as a first line treatment
4. **Surgery for Graves’** is more challenging, but in experienced hands surgery has excellent outcomes
Questions?

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