Management and Radioiodine Therapy of Hyperthyroidism

Salil D Sarkar, MD, FACP
Chairman, Nuclear Medicine, North Bronx Healthcare Network
Associate Professor, Albert Einstein College of Medicine

Benign Thyroid Disorders

- **Autoimmune:** Hashimoto disease, Graves disease, Thyroiditis
- **Non-Autoimmune:** Nodular disease, Thyroiditis, Iodine excess, Trophoblastic tumor, Pituitary TSH excess
- **Developmental:** Dyshormonogenesis, Ectopic, Thyroid hormone resistance

Adapted from Sarkar, LLSAP, Soc Nucl Med

13-year-old F with ↑freeT4, ↓TSH

24-hour uptake = 60%

A) Parry’s disease?  B) Basedow’s disease?  C) Neither?

Description of Graves Disease

Caleb Parry: 1825
Robert Graves: 1835
Karl Basedow: 1840
Graves Disease

- Develops in setting of autoimmune thyroid disease
- Characterized by ↑TSH receptor antibody (TSHR-AB), which promotes thyroid hormone synthesis & release
- Thyroid peroxidase and thyroglobulin antibodies, markers of autoimmune thyroid disease, are also elevated in most patients

13-Year-Old F With Graves Disease

24-hour uptake = 60%

Primary Treatment?

Treatment of Graves

- Anti-thyroid drugs (ATD)
- Thyroidectomy
- Iodine-131

Methimazole, Propylthiouracil (PTU) in Graves Disease

- ‘Short-term’ treatment prior to I-131 therapy
- Primary treatment of Graves disease
**Short-Term Methimazole/PTU Treatment in Graves Disease**

A) Rapid control of hyperthyroidism – stabilizes high-risk cases, e.g., severe hyperthyroidism, co-existing cardiovascular/other disease

B) Depletion of stored thyroid hormone in risky patients – to prevent excessive hormone release after I-131 therapy

ATD stopped 2-5 days before I-131 therapy


---

**Methimazole/PTU as Primary Treatment of Graves Disease**

- ↓ T3/T4 synthesis, ↓ TSHR-AB; PTU reduces $T_4 \rightarrow T_3$
- After therapy for 1-2 years, remission in ~ 30%
- Remission more likely in mild disease, small goiter
- Possibly higher rate of relapse in patients with high TSHR-AB, severe eye disease

Adverse Effects: skin rash, GI upset, arthralgia, hepatic toxicity, lupus-like syndrome, marrow suppression

Cooper, NEJM 05; Nakamura, JCEM 07; Sosa, JCEM 08; Kaguelidou, JCEM 08

---

**Surgery for Childhood Graves Disease?**

Surgery for Graves in Childhood and Adolescence (Sherman, Surgery 2006)

- 78 patients had surgery at age < 18 yr, 1986-2003
- Complications: Transient hypoparathyroidism (6%) and recurrent laryngeal nerve palsy (1%)
- Hyperthyroidism cured in 75 patients, reoccurred in 3

Surgery for Graves uncommon in the United States
- Traditional indications for surgery in Graves: suspicious nodule, failure of PTU in Graves during pregnancy
Iodine-131 Therapy for Graves

“Radioactive iodine use in childhood Graves disease: Time to wake up and smell the I-131”

Rivkees, JCEM 2004

36-Year Followup of Young Patients with Graves Treated with I-131

Long-term safety of I-131 treatment in children

- 116 pts treated with I-131 at age < 20 yr, 1953-73
- 1990-91: No thyroid cancer or leukemia
- 2001-02: No thyroid cancer or leukemia, 1 hyperparathyroidism*

Read, JCEM 2004

---------------------------------------------------------------------

* Hyperparathyroidism is known to occur after childhood external head/neck radiation

I-131 Therapy of Graves Disease: General Considerations

- ‘Titration’ with small I-131 doses likely to prolong the hyperthyroid state
- Euthyroidism after I-131 therapy is temporary
- Certain factors associated with resistance to therapy
- Prolonged hyperthyroidism as well as prolonged hypothyroidism (after I-131 therapy) may have adverse clinical consequences
Adverse Effects of Prolonged Thyroid Dysfunction - Overt & Sub-clinical

- **Hyperthyroidism:** cardiac arrhythmia, embolic stroke, ↑ left ventricular mass, left ventricular dysfunction, angina; bone loss in elderly women, ↑ fractures?
- **Hypothyroidism:** diastolic hypertension, ↑ lipids, CAD

After I-131 therapy, sub-clinical thyroid dysfunction may be left untreated; optimal outcome, therefore, may well be near-term overt hypothyroidism, corrected with thyroxine.


---

Graves Disease: Retained I-131 Dose

(Alexander, JCEM 2002)

- Deliver 8 mCi (296 MBq) to thyroid based on 24h uptake
- 86% of patients hypothyroid or euthyroid at 1 year
- 14% failed: larger gland, higher T4, ATD > 4 mo, younger

Authors recommended 11 mCi delivered dose for gland size > 4x normal, ≥ 70% uptake, age < 20, ATD > 4 mo +

- Mean delivered = 173 µCi/g; administered = 14.6 mCi
- for shorter durations, radio-resistance may be more likely with PTU than with Methimazole

---

Graves in 13-yr-old: How much I-131?

(Thyroid Weight = 60g, Uptake = 60%)

1. Administer 5 mCi (185 MBq) empirically
2. Deliver 50 µCi (1.8 MBq) per gram to thyroid (based on thyroid weight and 24-hour uptake)
3. Administer 10 mCi (370 MBq) empirically
4. Deliver 150-200 µCi (5.5-7.4 MBq) per gram (based on thyroid weight and 24-hour uptake)

Graves in 13-Year-Old: How Much I-131?

(Thyroid Weight = 60g; uptake = 60%)

1. Administer 5 mCi (185 MBq)
2. Deliver 50 µCi (1.85 MBq/g)
3. Administer 10 mCi (370 MBq)
4. Deliver 150-200 µCi (5.5-7.4 MBq) per gram

*(150 x 60g) ÷ (0.60) = 15 mCi (555 MBq)*

Alexander, JCEM 2002; Rivkees, JCEM 1998
Graves: Absorbed Dose and % Cured

Peters, Euro J Clin Invest 1995
- 15,000 rads (150 Gy): 67%
- 25,000 rads (250 Gy): 84%

Reinhardt, EJNM 2002
- 15,000 rads (150 Gy): 27%
- 30,000 rads (300 Gy): 68%
≤ 42 ml goiter: 25,000 rads → 100%

I-131 Dose Determination

- Empirical
  - start with 15 mCi, add 5-10 mCi for radio-resistance

- Calculated
  - delivered dose: 8 mCi (296 MBq) or 175 µCi (6.4 MBq) per gram retained at 24h; adjust for radio-resistance
  - absorbed dose: 20,000 - 30,000 rads (200-300 Gy)

Hyperthyroidism in Pregnancy

28-year-old woman found to have Graves at 12 weeks of gestation. Which of the following management strategies is most appropriate?

1. Iodine-131 treatment
2. Propylthiouracil treatment
3. Neither

GTT (Gestational Transient Thyrotoxicosis)
- Not autoimmune; due to HCG; resolves in later pregnancy

Graves Disease
- Autoimmune, ↑TSH receptor antibody (TSHR-AB)
- TSHR-AB crosses placenta, may cause fetal Graves
- PTU/methimazole decrease TSHR-AB, but at high doses these drugs may cause fetal hypothyroidism/goiter

Endocrine Society Guideline, JCEM 07; Glinoer, Thyroid 98
**Graves in Pregnancy: Management**

- **PTU** - just enough PTU to maintain T4 at high-N levels (high PTU dose may → fetal hypothyroidism)
- **Surgery** - if large PTU doses needed, or non-compliance
- **Monitor** - maternal TSHR-AB (can cause fetal Graves)
  - fetal thyroid, heart rate, bone maturation
  - mother post partum for recurrence of Graves

Glinoer, Growth Horm IGF Res 03; Luton, JCEM 05; Tagami, Thyroid 07; Rotondi, JCEM 2008; Endocrine Soc Guideline, JCEM 07

**49-y-o hyperthyroid F with grittiness in eyes, photosensitivity, ↑tearing, retro-orbital pressure, diplopia**

Referred for I-131 therapy

**I-131 Therapy & Graves Orbitopathy**

- Progression/activation of orbitopathy in 15%, usually mild and temporary
- Higher risk in smokers, severe hyperthyroidism, high TSHR-AB, & prolonged hypothyroidism after I-131 therapy
- Prednisone may be beneficial in some patients

Tanda, Clin Endcor 08; Vannuchi, JCEM 09; Prabhakar, Endocr Rev 03

**Management of Graves: Key Points**

- **Iodine-131**
  - increasing preference for near-term hypothyroidism
  - ↑dose for large goiter, ATD, severe hyperthyroidism
  - may occasionally worsen eye disease, hyperthyroidism
- **Drug (Methimazole, PTU)**
  - to control hyperthyroidism before definitive treatment
  - may use as primary therapy of Graves, with limited success
  - preferred modality in pregnancy; prevents Graves in fetus
- **Surgery**
  - co-existing suspicious mass, ATD failure in pregnancy
9-year-old Heathcliff has become difficult to manage, and is losing weight despite a good appetite.

What is ailing Heathcliff?

Thyroid function testing reveals *hyperthyroidism*.

“Somatic mutations in the TSH receptor gene in feline hyperthyroidism: parallels with human hyperthyroidism”

_Watson, Endocrinol 2005_

**Multinodular Goiter (MNG)**

**Clinical Characteristics**
- Older patients
- Goiter frequently very large
- Tracheal compression
- Swallowing compromise
- Sub-clinical hyperthyroidism
- Normal or mildly ↑ 24h uptake

24h uptake = 35%

1) I-131 treatment?  2) Surgery?  3) Thyroxine?

**MNG With Hyperthyroidism: Treatment Goals**

-Reduce goiter volume
  - to decompress trachea
  - to relieve swallowing compromise

-Eliminate hyperthyroidism
  - to reduce potential cardiac complications
  - to decrease risk of bone loss in elderly

_Bauer, Ann Intern Med 01; Cooper, ICEM 07; Kang, Surgery 02_
**I-131 Therapy of Multinodular Goiter**

  - Mean dose of 70 mCi (2590 MBq); range 42-98 mCi
  - 40% ↓ in goiter volume, 36% ↑ in tracheal lumen
- Bonnema, JCEM 1999
  - Mean dose 61.6 mCi (2279 MBq); range 27-125 mCi
  - 34% ↓ in goiter volume, 18% ↑ in tracheal lumen

Limitations: large dose, modest volume reduction; rarely, may develop Graves disease after I-131 (Nygaard, JCEM 97)

**Surgery for Multinodular Goiter**

**Surgery in Nodular Goiter**

- Toxic Nodular (Kang, Surgery 2002)
  - vocal cord paralysis, permanent hypo-PTH in 2%
  - thyroid cancer in 3%
- Toxic Nodular & Graves (Senyurek, Surgery 2008)
  - thyroid cancer in 6% of MNG, 12% of adenoma,
    3% of Graves disease

- 35 year old actress with
  - weight loss, insomnia
  - 5 cm right lobe mass
- Free T4 = 2.4 ng/dl
- TSH = 0.01 mu/L

1) I-131 treatment? 2) Surgery?
Outcome of I-131 Treatment of Toxic Adenoma

- 39 patients, age 35-75 years, treated with 100 µCi/g
- Single dose in 30 patients, > 1 dose in others
- Volumes - **54% decrease** in nodule volume at 12 months
  - 18% decrease in non-nodular volume
- 10% became overtly hypothyroid *

* Hypothyroidism increases at long term follow-up

Erdogan, Nucl Med Commun, 2004

---

Single Toxic Nodule

- 35 year old actress, with weight loss, insomnia
- 5 cm right lobe mass
- Free T4 = 2.4, TSH = 0.01

24h uptake = 50%

Treat with either I-131 or surgery; no residual 'lump' after surgery

---

Toxic Nodular Goiter: Key Points

- For large MNG, surgery preferable but may not be feasible because of operative risk. High dose I-131 therapy is an alternative
- Surgery may help discover incidental cancer
- I-131 therapy of single toxic nodule may not eliminate the neck mass altogether
- Late hypothyroidism after I-131 therapy not uncommon

---

27-year-old female

- Nervousness, tachycardia, heat intolerance
- Thyroid moderately enlarged, firm, non-tender
- Free T4 = 2.8 ng/dL; TSH = 0.01 mu/L
- History of Graves disease in a sister
- Patient gave birth to healthy baby 4 months ago

Diagnosis?

A) Euthyroid goiter  B) Graves  C) Thyroiditis
27-year-old female

- Nervousness, tachycardia, heat intolerance
- Thyroid moderately enlarged, firm, non-tender
- Free T4 = 2.8 ng/dL; TSH = 0.01 mu/L
- History of Graves disease in a sister
- Patient gave birth to healthy baby 4 months ago

**Diagnosis: Postpartum thyroiditis or Graves**

(both ↑ in postpartum; but thyroiditis far more common)

Stagnaro-Green, JCEM 02; Lucas, Thyroid 05; Ando, JCEM 03

---

**Postpartum Thyroiditis (PPT)**

- Occurs in 1st yr after pregnancy
- History of prior PPT or Graves
- Attributed to ‘immune rebound’
- Increased hormone release, no increase in synthesis
- Self limited (hyper → hypo → eu)
- 50% hypothyroid over long term

Stagnaro-Green, JCEM 02; Lucas, Thyroid 05; Ando, JCEM 03; Azizi, Eur J Endocrinol 05

---

**Destructive (‘Subacute’) Thyroiditis**

- **Autoimmune** - postpartum, sporadic; painless
  - may reoccur, permanent hypo frequent
- **Post-Viral** - painful, flu-like syndrome
  - recurrence & permanent hypo infrequent
- **Amiodarone** - painless, may have protracted course
- **Other** - IFN-α, IL-2, denileukin diftitox, lithium
  - autoimmune and direct thyroid effects

Stagnaro-Green, JCEM 02; Fatsourechi, JCEM 03; Mandac, Hepatol 06; Kai-Hung, JCEM 09

---

Thank You