RADIOACTIVE IODINE THERAPY FOR HYERTHYROIDISM

Mark Tulchinsky, MD, FACNM, CCD
Professor of Radiology and Medicine
Division of Nuclear Medicine
Penn State University Hospital

Learning Objectives

• Treatment Options
  • Medications
  • Surgery
• ¹³¹I Treatment (RAIT)
  • Graves’ Disease w/o Orbitopathy
  • Graves’ Disease with Orbitopathy
  • Toxic Adenoma
  • Multinodular Toxic Goiter
  • Intermittent (recurrent) Thyroiditis
  • Amiodarone Thyrotoxicosis

Conditions Amenable to RAIT

<table>
<thead>
<tr>
<th>Condition</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves’ disease (~80%)</td>
<td>TSH-R-Ab stimulation of thyrocyte</td>
</tr>
<tr>
<td>Toxic Multinodular Goiter</td>
<td>mutation → TSH-R-Ab activation → autonomous function</td>
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<tr>
<td>Toxic Adenoma</td>
<td></td>
</tr>
<tr>
<td>Hashimoto’s Thyroiditis in productive phase (“Hashitoxosis”, overlaps Graves)</td>
<td>autoimmune disease · a variety of cell- and antibody-mediated immune processes</td>
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<tr>
<td>Intermittent/recurrent Thyroiditis</td>
<td>Unknown</td>
</tr>
<tr>
<td>Amiodarone Thyrotoxicosis</td>
<td>Multifactorial</td>
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</tbody>
</table>

*RAIT in recovery phase, prevents recurrences

Abbreviations: TSH-R-Ab = thyroid stimulating hormone receptor autoantibody, RAIT = RAI treatment

Therapeutic Options for Productive Hyperthyroidism

• Antithyroid Drug therapy (ATDT)
  ✓ Symptomatic control with beta blockers
  ✓ Thioureas, aka Thionamides, Anti-Thyroid Drugs (ATD’s)
  ✓ Corticosteroids
  ✓ Stable Iodine (SSKI, etc.)
  ✓ Rituximab

• Radioactive Iodine Treatment (RAIT)
  ✓ Alone or with adjuncts (steroids ± other DT)

• Surgery

I Love What I do, i.e.
Nuclear Medicine ...

No other relevant disclosures or conflicts of interest

Radioactive Iodine (RAI) Administration for Graves’ Disease: Birthplace of Radiotheranostics

Saul Hertz, M.D.

(April 20, 1905 – July 28, 1950)

• The first to study RAI in an animal model of hyperthyroidism
• March 31st, 1941, at the age of 35 y, administered the first RAI treatment (RAIT) to a patient with Grave’s disease
• The first to use RAI uptake to inform RAIT, i.e. radiotheranostic principle
Hyperthyroidism Drug Therapy
Thioureas: Propylthiouracil (PTU) & Methimazole (MZ)

ATD's divert oxidized iodide away from thyroglobulin, effectively ceasing thyroid hormone biosynthesis
- Inhibition of hormone synthesis depletes existing stores of iodinated thyroglobulin as the protein is hydrolyzed and hormone released, depleting thyroid hormone stores
- ATD's bind intrathyroidal iodide and facilitate its clearance from the thyroid, depleting thyroid iodine content

PTU inhibits peripheral T4 to T3 conversion
- X = the site of biochemical block by thioureas

Disadvantages of RAIT When Compared to Long-term ATDT: Realizations of 1990’s and 2000’s
- RAI may induce or worsen Graves’ Orbitopathy (GO) in 15-33%
- RAIT practice not standardized with erratic clinical & biochemical outcomes
  - Euthyroid goal (Eu-RAIT)
    - multiple, fixed or calculated SMALL activities
  - Hypothyroid goal (Ablation)
    - Fixed activity (15 mCi), over & under treat a lot
    - Radiation dose to thyroid, prolonged dosimetry
    - Activity per g of thyroid, simple & fewest failures

Cancer Mortality Following Treatment for Adult Hyperthyroidism

Typical Approach to GD in the USA: First Decade of 21st Century
- ATD + beta blocker for 1-2 years
- Stop therapy to check for remission
- If no remission or patient recurs after short remission → RAIT or Surgery
- Eu-RAIT used in early days, ablation became dominant after 2005 study that showed mortality advantage*
- No standardization of hypo-RAIT technique, approaches vary widely


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Optimal $^{131}$I Therapy of Thyrotoxicosis

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Comparison of Mortality in Hyperthyroidism During Periods of Treatment With Thionamides and After Radiodine

Kristen Boeart, Patrick Mahonoune, Barbara Torlina, and Jayne A. Franklin
Caine for Endocrinology, Diabetes, and Metabolism H.R. B. J.; U.A.L. School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, United Kingdom, and Disease of Endocrinology and Diabetes H.R. B. J. University of Health.

U Clin Endocrinol Metab 98: 1691-1881; 2013

What NM Docs Should Know?

- Be proactive in confronting GO concerns
  - Post RAIT Hypothyroidism – minimize
  - Practice RAIT that has predictable outcome
  - Guide referring about timing for TH replacement
  - Selective steroid prophylaxis
- Be proactive in improving symptoms before, during, and after RAIT
  - Pre-treat with ATDT, beta blockers
- Good practice – offer consultation service
  - Best practice – offer to consult and manage patients after RAIT

Pre-RAIT Work-Up:

99mTcO4\(^-\) Scan + 24-Hr $^{131}$I Uptake

Educate Patients (and Referring Doctors) About RAIT at Consultation

- Minimized dietary (LID) and medical Iodine
- Go over radiation precautions, pt. should come for RAIT unescorted, etc.
- Assure pts. – they will leave the facility generally feeling the same as on arrival
- Review meds, provide guidance (monitor HR for beta blocker adjustments, etc.)
- Explain RAIT comes as a capsule (pediatric cap. or liquid, if swallowing difficulties)
- It doesn’t cause nausea – but expectation and/or nervousness sure could!

Outcomes in Relapsed Graves’ Disease Patients Following Radioiodine or Prolonged Low Dose of Methimazole Treatment

RAIT n=102 pts

MMI n=114 pts

Reviewed

15 mCi

RAIT group

MZ group

Worsened

Unchanged

Improved

Between 1995 and 2013, Brazil (Campinas & São Paulo):

Villagelin, D et al. Outcomes in Relapsed Graves’ Disease Patients Following Radioiodine or Prolonged Low Dose of Methimazole Treatment. Thyroid 2015.

DOI: 10.1089/thy.2015.0195

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**Optimal $^{131}$I Therapy of Thyrotoxicosis**

**RAIT for Thyrotoxicosis**

**General Considerations**

- Absolute contraindication – Pregnancy and other*, document pregnancy test results
- Treating a very toxic patient may result in thyroid storm – pretreat with MZ (4-6 wks.)
- **Stop ATD’s for 2 d. (48 hrs.),** start uptake day 3, measure uptake, scan & RAIT day 4
- Beta-blocker can be continued, HR guided
- Re-starting ATD post-RAIT, optional
- Iodine (lithium) loading post-RAIT is optional, practiced rarely

*Contraindications: pregnancy, lactation, known or suspected thyroid cancer, individuals unable to comply with radiation safety guidelines.

**HYPERTHYROIDISM: TREATMENT GOAL**

- **RAIT Goals**
  - Euthyroidism – futile in Graves’ & hypothetically may increase carcinogenic risk – not recommended
  - Ablation – predictable, time-saver for pts & dead cells don’t turn cancerous – recommended (1)
- **Approach to Ablation**
  - Fixed dose (15 mCi) – simple, but not as predictable
  - Radiation dose (cGy) based – multiday dosimetry makes it impractical, simplified is same as below
  - Delivered activity per g of thyroid, normalized to 24 hr. uptake – simple, practical and rational


**Response to $^{131}$I Therapy in Graves’:**

0.24 mCi per gm of Thyroid

(PSU Experience)

**Grave’s Disease RAIT:**

mCi/g of Thyroid @ 24 hrs.

- Most give 0.12-0.20 mCi of $^{131}$I/g of thyroid, normalized to 24 hr. uptake
- Ablation activity (AA) coefficient at PSU is 0.24 mCi/g (developed empirically)
- AA = (gland weight in g x 0.24 mCi/g) / 24 hr. uptake fraction (i.e. 0.5 for 50% uptake)
- Gland weight: cannot palpate it for sure – 30 g; can palpate, but cannot see it – 40 g; can see it when pt. walks in – ≥ 60 g
- “Fudge Factor” – give more to pts. who are older, on anti-thyroid meds, MNG, severe HT, rapid $^{131}$I turnover, larger glands

**Relationship between thyroid radiation dose and hypothyroidism rate in patients who were <18 years old**


**Treatment Complications: Early**

- Typically None
- Thyroiditis (sore throat) is the most common 1:40
  - Occurs 1-3 days post therapy
  - Rarely needs medication
  - Responds well to NSAIDs
Optimal $^{131}$I Therapy of Thyrotoxicosis

### Treatment Complications: Early
- **Exacerbation of thyrotoxicosis (~1%)**
  - Rare in ATD-pretreated, self limited
  - Increase/start β-blockers and ± ATD’s
- **Thyroid storm (0.3%) – ATD pretreatment diminishes risk**
  - Key manifestation is fever
  - Mean time to onset 6 days
  - Treatment of the thyroid storm:
    - Thermoregulation, physiologic support
    - Iodine (30 drops of SSKI a day)
    - PTU (900-1200 mg a day)
    - β-adrenergic blockade (propranolol, atenolol, etc.)

### Late Complication of RAIT
- **Ageusia – water swish/swallow after RAI**
- **Very Rare complications – Sialadenitis/Xerostomia**
- **Hypoparathyroidism is extremely rare**
- **Hyperparathyroidism (parathyroid adenoma) – questionable relation to $^{131}$I**
- **There is no evidence of increased secondary primary malignancy incidence**
- **No evidence of congenital defects**
  - Avoid conception for 6-12 months

### Graves’ Orbitopathy (GO), aka
- Graves Ophthalmopathy, Thyroid-Associated Orbitopathy (TAO), Thyroid Eye Disease (TED)

#### Clinical Incidence:
- ~ 20% of GD

#### Imaging Reveals:
- > 60% of GD
- Severe in ≤ 5%

#### Predisposing factors:
- Smoking
- Older age
- Male sex
- Diabetes
- Hypothyroidism after RAIT

**Progression is the natural course of GO**

### What Do We Know About Risk of GO as Relevant to Therapy of GD?
- **Known risk factors = remove whichever possible, i.e. smoking, post RAIT TSH elevation/hypo (replace early)**
- **Higher the T3, the greater GO occurrence-progression probability for all treatments (especially for RAIT) = pretreat with ATD’s**
- **Higher the TSH-R-Ab & inflammation in thyroid, the greater GO risk => suppress autoimmune response with steroids**
- **GO progression after RAIT starts early => preventive measures must start early**

### Initial Experience: Basics

**RAI Group – 39 pts, initial dose 120 Gy → 13/39 worsening / de novo GO. 18/39 were given more than 1 dose, 12/18 developed worsening (10) or de novo (2) GO**

**Lesson 1:** “Gentle” RAIT is rough on the eye! Ablate with single administration! → RAIT, 67% → ↑GO

RAIT, 5% → ↑GO

### Choice of Primary Treatment in GD

**Case Presentation without GO**

**Case Presentation with mild GO**

**Abbreviations:** GD = Graves’ disease; CS = corticosteroids


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Grading Exophthalmos

- No signs of GO
- Mild GO (no proptosis, but has some inflammatory scleral redness, etc.
- Mod. GO: proptosis 21 - 24 mm
- Severe GO: proptosis > 24 mm

If any sign of GO – refer to ophthalmology for exophthalmometry

Prevention of Post-RAIT GO: Three-tier, Risk-adjusted Approach

- No GO findings, no risk factors → no prophylaxis
- No GO findings or Mild GO, + risk factor(s)
  - Prednisone 0.2 mg/kg/d, tapered over the 4-5 weeks, starting on the day of RAIT
- Mild to Moderate GO, + risk factor(s)
  - Prednisone 0.4-0.5 mg/kg/d, tapered over 3 months, starting on the day of RAIT
- Moderate to Severe GO → no RAIT

Autonomously Functioning Solitary Thyroid Nodules

- True adenoma, colloid nodules or local hyperplasia. Up to 4% may harbor occult cancer that is of doubtful clinical significance
- Nontoxic (euthyroid) or toxic (usually mild)
- Usually 1-3 cm in diameter, can enlarge quickly if internal hemorrhage occurs
  - ≤2 cm size usually doesn’t make enough TH to cause hyperthyroidism or suppress normal thyroid
  - At ~ 2.5 cm extra-nodular thyroid tissue function is suppressed, ± subclinical hyperthyroidism
  - At ~ 3 cm hyperthyroidism is expected

RAIT of Autonomous Solitary Toxic Nodules

- An ideal case for ¹³¹I treatment. The normal tissue is suppressed and endogenously protected
- Formerly, 30-60 mCi doses were used, which resulted in high incidence of needless hypothyroidism
- Usually, a 160-240 μCi/gm dose is administered (about 10 mCi on average)
- Expect euthyroidism in 91% by 6 months, and 93% by 1 year. 7% may need more than one dose. Hypothyroidism would be very unusual.
- If a nodule edema is a concern (compression), TU pre-treat and/or administer steroids and/or recommend surgery.

RAIT of Multiple Autonomous Toxic Nodules: Multinodular Goiter

- Somewhat more resistant to ¹³¹I treatment.
- The dose is greater than for Graves’, 30 mCi dose is usually given (fudge factors = thyroid weight & uptake)
- The hypothyroidism is less common following the treatment
  - Functioning nodules get ablative dose, then spared suppressed tissue becomes active, it may provide adequate euthyroid function
  - Poor iodine uptake is common and may require stimulation or higher ¹³¹I activities

Multiple Hyper-Functioning Nodules – Toxic Multinodular Goiter

- 24 hrs. ¹³¹I uptake = 38%
- Treated with 30 mCi, euthyroid 1 year later
Optimal $^{131}$I Therapy of Thyrotoxicosis

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SNMMI Annual Meeting, 6/26/2018
Aglaia Kyrilli et al. and Rodrigo Moreno Reyes. Thiamazole Pretreatment Lowers the $^{131}$I Activity Needed to Cure Hyperthyroidism in Patients With Nodular Goiter. J Clin Endocrinol Metab, June 2015, 100(6):2261–2267

• The most important finding should be this:

Stimulation with Recombinant Human Thyroid-Stimulating Hormone (rhTSH)

- Single dose of 0.01 – 0.03 mg IM
- Iodine is given 24 hours later
- Uptake improves by about 2 fold
- Pros
  - Quick prep
- Cons
  - High prevalence of HT CV side effects
  - High Cost
  - This is not an FDA approved use of rhTSH

Amiodarone-Induced Thyrotoxicosis (AIT): Type 2, Normalized off Amiodarone

- n = 15 pts, withdrawal period, 5-147 (33±34) mo., all had RAIU > 10% @24hrs
- Aim, prevent recurrent AIT All euthyroid before RAIT
- $I^{-131}$, 10-20 (15.6±5) mCi
- Outcome, 14 hypo- and 1 euthyroid
- Early, mild hyper in 2 pts
- Amiodarone reintroduced in 14 pts
- 12 pts had arrhythmia controlled

Amiodarone-Induced Thyrotoxicosis (AIT): Type 2, on Amiodarone

- n = 4 pts, only 1 was withdrawn, RAIU <4% @24hrs
- Aim – ablation. All thyrotoxic at RAIT
- Thyroid volume by Ultrasound, 1 g/mL → g
- RAI activity, 0.08 mCi/g/24hr-RAIU-ratio
- I-$^{131}$: 29, 35, 50, 80 mCi
- Outcome, 3 hypo- and 1 euthyroid

Conclusions:

- RAIT is safe and effective initial therapy for hyperthyroidism, including Graves’ disease, multi-nodular toxic goiter, etc.
- RAIT has lower mortality than ATD
- RAIT induced Graves’ Orbitopathy is preventable
- RAIT is effective and safe in reducing the size of toxic and substernal goiter, but it may require iodine uptake stimulation
- The most cost-effective and the safest stimulation maneuver to raise RAIU is thioureas pre-treatment

Thank you for your attention!