Theranostics: Nuclear Medicine's Beginnings and the Future

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No Conflicts of Interest to Declare
Learning Objectives

• Rapidly growing field of Theranostics/Radiotheranostics
• The beginnings: Radioactive Iodine Therapy (RAIT)
  . The birth of Theranostics - Benign thyroid conditions
  . Radiotheranostic approach to RAIT in benign diseases
  . Take-Home Messages from history of benign RAIT
• Differentiated Thyroid Cancer, history
  . Risk-based approach to RAI treatment
  . Preparation for RAI – Low Iodine Diet, Withdrawal vs. Thyrogen®
  . ATA “Cookbook” for radioactive potion
  . Effect of ATA Guidelines on practice and patients
  . Take-Home Messages of malignant RAIT
• The future ?
Theranostics or Radiotheranostics:

- Technique of sequential application of biosimilar radiopharmaceuticals – first, a diagnostic biosimilar agent (DBA), followed by a therapeutic agent (TA)

- The goal: Individualization of therapy
  - DBA objectives: establish disease (the target) presence, avidity, distribution & stage, radiation dosimetry, assess non-target localization to estimate TA’s adverse effects, monitor response to treatment and surveillance for recurrence
  - TA objective: deliver DBA-informed, patient-tailored radiation dose to the target
PubMed-derived number of publications including the term “theranostic” or “theragnostic” during each year from 2001 to 2017 (search performed July 16, 2017). Ken Herrmann et al. J Nucl Med 2017;58 (September 1, 2017):1S-2S
# Radiotheranostic Agents

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Target</th>
<th>DBA</th>
<th>TA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differentiated Thyroid Cancer</td>
<td>N-I symporter</td>
<td>$^{123}$I, $^{124}$I, $^{131}$I</td>
<td>$^{131}$I</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>PSMA GRPR</td>
<td>$^{67}$Ga-PSMA-617 $^{67}$Ga-NeoBOMB1</td>
<td>$^{177}$Lu-PSMA-617 $^{177}$Lu-NeoBOMB1</td>
</tr>
<tr>
<td>Lymphoma, myeloma</td>
<td>CXCR4</td>
<td>$^{68}$Ga-pentixafor</td>
<td>$^{177}$Lu-pentixafor</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>CD20</td>
<td>$^{111}$In-ibritumomab tiuxetan $^{131}$I-tositumomab</td>
<td>$^{90}$Y-ibritumomab tiuxetan $^{131}$I-tositumomab</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Monoamine transporter</td>
<td>$^{123}$I-MIBG</td>
<td>$^{131}$I-MIBG</td>
</tr>
<tr>
<td>Neuroendocrine Tumors</td>
<td>somatostatin receptor</td>
<td>$^{68}$Ga DOTATATE or DOTATOC, or DOTANOC</td>
<td>$^{177}$Lu or $^{90}$Y labeled versions</td>
</tr>
</tbody>
</table>

DOTATATE = DOTA-DPhe1,Tyr3-octreotate, DOTATOC = DOTA-d-Phe1-Tyr3-octreotide, DOTANOC = DOTA-1-Nal3-octreotide, GRPR = gastrin releasing peptide receptors, PSMA = prostate-specific membrane antigen, CXCR4 = C-X-C motif chemokine receptor 4, MIBG = metaiodobenzylguanidine
First $^{131}$I Treatment Given to Patient with Graves’ Disease: 

The Birth of Thrananostics

- Saul Hertz, M.D.
- (April 20, 1905 – July 28, 1950) laid the foundation of iodine physiology that made radioactive iodine therapy possible
- Performed (at age 35) the first RAI ($^{130}$I) treatment, administering on March 31st, 1941, 2.1 mCi to Ms. Elizabeth D. who suffered from Grave’s disease

Ms. Doris Darby who was Dr. Hertz’s laboratory assistant, arguably the first nuclear medicine technologist, demonstrating an uptake test using a “Multiscaler” counter that Dr. Hertz helped to develop at MIT.

Belated Congratulations on the 77th Anniversary!
### Benign Conditions Amenable to RAIT: From Graves’ to All These

<table>
<thead>
<tr>
<th>Condition</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Graves’ disease (GD) (~80%)</td>
<td>TSH-R-Ab stimulation of thyrocyte</td>
</tr>
<tr>
<td>2. Toxic Multinodular Goiter (NMNG)</td>
<td>mutation → TSH-R-Ab activation → autonomous function</td>
</tr>
<tr>
<td>3. Toxic Adenoma (TA)</td>
<td></td>
</tr>
<tr>
<td>4. Hashimoto’s Thyroiditis (HT) in productive phase (“Hashi-toxicosis”, overlaps Graves’)</td>
<td>autoimmune disease - a variety of cell- and antibody-mediated immune processes</td>
</tr>
<tr>
<td>5. Intermittent/recurrent Thyroiditis*</td>
<td>Unknown</td>
</tr>
<tr>
<td>6. Amiodarone thyroiditis, Type I</td>
<td>Multifactorial</td>
</tr>
</tbody>
</table>

*RAIT is given in the recovery phase, prevents recurrences

**Abbreviations:** TSH-R-Ab = thyroid stimulating hormone receptor autoantibody, RAIT = RAI treatment
Questions for the Audience: Raise your hand for “Yes”

• Have you been involved in I-131 therapy for GRAVES’ DISEASE for at least 10 years?
• Do you administer empirical activity (i.e. no-calculator-needed, e.g. 10, 15, etc. mCi ± “a fudge factor” for recent ATD, etc.) to majority of Graves’ Disease pts?
• Do you routinely see the pts before and after RAIT for clinical management?
• Have you experienced over the past 2 years any increase in numbers of pts referred for Graves’ disease RAIT?
131I Therapy of Hyperthyroidism: The Largest Study on its Radiation Effects

• The greatest concern of early NM physicians – risk of secondary leukemia
• Cooperative Thyrotoxicosis Therapy Follow-up Study (TTFUS) was initiated in 1961 (but in conception since 1957)
• Design – retrospective from 1961 to 1966 and prospective from 1961 to 1968
• In June 1968, the patient accrual ended
TTFUS – The Largest Hyperthy. Study: Done by Nuclear Medicine Doctors

- By June 1968, **35,606 patients** were enrolled from 23 centers, 98.8% complete follow-up
- **19,500** patients had been treated with $^{131}$I, **11,200** with surgery, **3,500** with surgery and $^{131}$I, and **1,300** with antithyroid drug treatment (ATDT) alone.
- In September 1968, 1st publication, mean follow-up 8-year, no increased incidence of leukemia with RAIT (~119,000 p-y.) when compared with surgery (~114,000 p-y.)
Incidence of Leukemia
Following Treatment of Hyperthyroidism

Preliminary Report of the Cooperative
Thyrotoxicosis Therapy Follow-Up Study

Eugene L. Saenger, MD; George E. Thoma, MD; and Edythalena A. Tompkins

This study was conducted to test for an increase in the incidence of leukemia in hyperthyroid patients treated by radioactive iodine $^{131}$I as compared to the incidence in patients treated differently. Of 36,000 patients from reported ten cases of leukemia in 32,000 treated patients followed up for 142,000 person-years; under these circumstances, 13.8 cases were expected. There were fewer chronic cases (three found, nine e
study of this size, as shown by a 96% follow-up of patients. The feasibility of utilizing such a large multicenter approach suggests that similar efforts are entirely possible in studying many other important disease states.

Detailed follow-up of many patients has confirmed that suspected increase in leukemia in hyperthyroid patients is not associated with treatment with radioactive iodine when these patients are compared to hyperthyroid patients treated surgically.

Assistance in analysis was given by Bruce P. Sherman, MD, and Paul A. Finkel of the National Center for Radiological Health, and Earl Diamond, PhD, of Johns Hopkins University. Review of pathological material was made by Clyde J. Dawe, MD, PhD, of the National Cancer Institute, Bethesda, Md, and Robert J. Hartsock, MD, of the Armed Forces Institute of Pathology, Washington, DC. Copies of the abstracts of the medical record of each patient used in this investigation may be obtained from the National Center for Radiological Health, 1901 Chapman Ave, Rockville, Md 20852.

References

1. Brill, A.B.; Tomanaga, M.; and Heyssel, R.M.: Leukemia in Man Following Exposure to Ionizing Radiation: A Summary of the Findings in Hiroshima and Nagasaki, and a Comparison With

Participants

Data were compiled and submitted by the following study center directors: David V. Becker, MD, New York Hospital-Cornell Medical Center; William H. Beierwaltes, MD, University of Michigan Medical Center, Ann Arbor; Earle M. Chapman, MD, Massachusetts General Hospital, Boston; Brown M. Dobyns, MD, Western Reserve University and Cleveland Metropolitan General Hospital, Cleveland; Thomas J. Fahey, Jr., MD, Memorial Hospital for Cancer and Allied Diseases, New York; A. Stone Freedberg, MD, Beth Israel Hospital, Boston; Lewis M. Hurxth, MD, Lahey Clinic Foundation, Boston; Henry L. Jaffe, MD, Cedars-Sinai Medical Center, Los Angeles; William M. McConahey, MD, Mayo Clinic, Rochester, Minn; Paul J. Murison, MD, Ochsner Clinic, New Orleans; Philip Rubin, MD, Strong Memorial Hospital, Rochester, NY; Bernard A. Sachs, MD, Montefiore Hospital and Medical Center, New York; Eugene L. Saenger, MD, University of Cincinnati College of Medicine; Glenn E. Sheline, MD, University of California, San Francisco Medical Center; Solomon Silver, MD, Mount Sinai Hospital, New York; Norman W. Spechl, MD, White Memorial Medical Center, Los Angeles; Paul Starr, MD, Los Angeles County Hospital; John P. Storaasli, MD, University Hospitals of Cleveland; George E. Thoma, MD, St. Louis University School of Medicine; Sidney C. Werner, MD, College of Physicians and Surgeons of Columbia University and Presbyterian Hospital, New York; G.M. Wilson, MD, United Sheffield Hospitals, Sheffield, England; Joseph B. Workman, MD, University of Maryland School of Medicine, Baltimore.
Conclusion
Patients with WDTC treated with RAI had an increased early risk of developing AML and CML but no other hematologic malignancies. AML that arises after RAI treatment has a poor prognosis. RAI use in patients with WDTC should be limited to patients with high-risk disease features, and patients with WDTC treated with adjuvant RAI should be monitored for myeloid malignancies as part of cancer surveillance.
<table>
<thead>
<tr>
<th>Comprehensive Diagnosis</th>
<th>ICD-O-3 Code</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Bladder CA</td>
<td>8050</td>
<td>Papillary carcinoma, NOS</td>
</tr>
<tr>
<td>8130</td>
<td>Papillary transitional cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>8260</td>
<td>Papillary adenocarcinoma, NOS</td>
<td></td>
</tr>
<tr>
<td>8290</td>
<td>Oxyphilic adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Breast CA</td>
<td>8330</td>
<td>Follicular adenocarcinoma, NOS</td>
</tr>
<tr>
<td>8331</td>
<td>Follicular adenocarcinoma well diff.</td>
<td></td>
</tr>
<tr>
<td>8332</td>
<td>Follicular adenocarcinoma trabecular</td>
<td></td>
</tr>
<tr>
<td>8335</td>
<td>Follicular carcinoma, minimally invasive</td>
<td></td>
</tr>
<tr>
<td>8340</td>
<td>Papillary carcinoma, follicular variant</td>
<td></td>
</tr>
<tr>
<td>8341</td>
<td>Papillary microcarcinoma</td>
<td></td>
</tr>
<tr>
<td>8342</td>
<td>Papillary carcinoma, oxyphilic cell</td>
<td></td>
</tr>
<tr>
<td>8343</td>
<td>Papillary carcinoma, encapsulated</td>
<td></td>
</tr>
<tr>
<td>8344</td>
<td>Papillary carcinoma, columnar cell</td>
<td></td>
</tr>
<tr>
<td>Fallopian tubes/testis CA</td>
<td>8450</td>
<td>Papillary cystadenocarcinoma, NOS</td>
</tr>
<tr>
<td>Pancreatic CA</td>
<td>8452</td>
<td>Solid pseudopapillary carcinoma</td>
</tr>
</tbody>
</table>
Extrapolated to 100,000 cases, RAIT would have added 66 excess cases of AML+CML while reducing solid cancers by 856 cases.
Exposure to ionizing radiation increases the risk of myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN), but such risks are not known in well-differentiated thyroid cancer (WDTC) patients treated with radioactive iodine (RAI). A total of 148,215 WDTC patients were identified from Surveillance, Epidemiology and End Results registries between 1973 and 2014, of whom 54% underwent definitive thyroidectomy and 46% received adjuvant RAI. With a median follow-up of 6.6 years, 77 and 66 WDTC patients developed MDS and MPN, respectively. Excess absolute risks for MDS and MPN from RAI treatment when compared to background rates in the US population were 6.6 and 8.1 cases per 100,000 person-years, respectively. Compared to background population rates, relative risks of developing MDS (3.85 [95% confidence interval, 1.7–7.6]; \( P = 0.0005 \)) and MPN (3.13 [1.1–6.8]; \( P = 0.012 \)) were significantly elevated in the second and third year following adjuvant RAI therapy, but not after thyroidectomy alone. The increased risk was significantly associated with WDTC size \( \geq 2 \) cm or regional disease. Development of MDS was associated with shorter median overall survival in WDTC survivors (10.3 vs 22.5 years; \( P < 0.001 \)). These data suggest that RAI treatment for WDTC is associated with increased risk of MDS with short latency and poor survival.
Supplementary Figure 3: Relative risks to develop MDS or Ph- MPN after WDTC treatment

Shown are the relative risks (RRs) ± 95% confidence intervals of developing MDS in the years following WDTC diagnosis for males (A) and females (B) and the RRs of developing Ph- MPN in the years following WDTC diagnosis for males (C) and females (D). Abbreviations: MDS, myelodysplastic syndrome; Ph- MPN, myeloproliferative neoplasm; RAI, radioactive iodine; WDTC, well-differentiated thyroid cancer.
Errors and Inconsistencies

- ICD codes for cohort selection – errors
- Numbers in the main figure and results do not add up – math errors (accepted “typos”)
- Counting latency time – diagnosis vs. exposure – inconsistency
- Latency time is too short (≤1 year)
- The two reports are product of the same project, split publication, questionable ethics
- Solid cancer benefit in RAI treated >> risk of (AML+CML) – “missing the forest for the trees”
Radioactive Iodine Therapy for Differentiated Thyroid Cancer: Lessons from Confronting Controversial Literature on Risks for Secondary Malignancy

Mark Tulchinsky¹, Ina Binse², Alfredo Campenni³, Sabina Dizdarevic⁴, Luca Giovanella⁵, Ian Jong⁶, Kalevi Kairemo⁷, and Chun K. Kim⁸

¹Section of Nuclear Medicine, Department of Radiology, Pennsylvania State University, Hershey, Pennsylvania; ²Department of Nuclear Medicine, University Hospital Essen, Essen, Germany; ³Nuclear Medicine Unit, Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy; ⁴Imaging and Nuclear Medicine Department, Brighton and Sussex University Hospitals, Brighton and Sussex Medical School, Brighton, United Kingdom; ⁵EOC Thyroid Diagnosis and Therapy Centre, Nuclear Medicine and PET/CT Centre, Oncology Institute of Southern Switzerland, Bellinzona and Lugano, Switzerland; ⁶Nuclear Medicine Department, Monash Health, Melbourne, Victoria, Australia; ⁷Docrates Cancer Center, Molecular Radiotherapy and Nuclear Medicine, Helsinki, Finland; and ⁸Department of Nuclear Medicine, Hanyang University College of Medicine, Seoul, Korea
Take-Home Message #1

If you want something done right, do it yourself!

Charles-Guillaume Etienne (5 January 1778 - 13 March 1845)

in Nuclear Medicine should be managing patients before, during and following our treatments, designing prospective studies to validate those therapies, build the big data repositories and analyze it.
131I Therapy of Hyperthyroidism: 20th Century Experience, Early Side-effects

- In 1956, Beierwaltes and Johnson reported U of Michigan 7-y experience with clinical f/u
  Beierwaltes recalled in 1979 review article that they “were widely criticized for reporting the highest incidence to date of hypothyroidism after treatment with 131I for Grave's disease (20%)”
- NM “Solution” – most turned to lower AAs
- In 1961, Beling and Einhora reported 3% per y. incidence of hypothyroidism no matter the 131I AA, i.e. preventing hypothyroidism is futile
- In general, 131I AAs stayed low, RAIT methods and responses varied, pts. f/u in NM dwindles ... stops

AA = administered activity; RAIT = radioactive iodine therapy
Typical Approach to GD in the USA: First Decade of 21st Century

- Anti-thyroid Drugs ± beta blocker for 1-2 years
- Stop ATD therapy to check for remission
- If no remission or patient recurs after short remission → RAIT or Surgery
- Euthyroid RAIT used in early days, hypothyroid RAIT (ablation) becoming more common around 2000, becomes dominant as 2005 study showed its mortality advantage*
- Still no standardization of hypo-RAIT technique, approaches still vary widely

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 methodology remained variable as did clinical & biochemical outcomes.
  - Euthyroid (Eu) goal
    - multiple, low, fixed activities (e.g. 2-5 mCi)
    - Multiple, 80 mCi/g calculated activity
  - Hypothyroid (hypo) goal (aka Ablation)
    - fixed activity (15 mCi)
    - Radiation dose to thyroid
    - Activity/g of thyroid, adjusted for iodine uptake
Grave’s Disease: mCi per Gram Method

- Most give 0.12-0.20 mCi of $^{131}$I/g of thyroid normalized to 24 hr. uptake ($\approx 15,000$ cGy)
- PSU Ablation activity (AA) factor, 0.24 mCi/g
- 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
- If scan confirms failed treatment by the 3rd month, consider dose ↑ by 25%.
Response to $^{131}$I Therapy in Graves’: 0.24 mCi per gm of Thyroid (PSU/HMC Experience)
Take-Home Message 2

- Accept inherent outcomes, optimize and standardize therapeutic techniques, follow your patients and determine the risk/benefit
- Calculate AA based on DBA (\(^{131}\)I or \(^{123}\)I uptake or dose to thyroid) → TA therapy standardization → predictable outcomes
- “All conventional wisdom has an element of truth to it, but good design requires more than an element of truth - it requires an ensemble of correct assumptions and valid calculations.” Henry Petroski
Graves’ Orbitopathy (GO), aka Graves Ophthalmopathy, Thyroid-Associated Orbitopathy (TAO), Thyroid Eye Disease (TED)

Progression is the natural course of GO

Clinical Incidence: ~ 20% of GD

CT&MR Incidence: > 60% of GD

Severe in ≤ 5%

Predisposing factors:
- Smoking
- Older age
- Male sex
- Diabetes
- Hypothyroidism after RAIT
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 earlier
Initial Experience: Basics

Iodine 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 or de novo GO, but only 1/21 after single treatment!

Take-Home Message #3: “Gentle” RAIT is rough on the eye! Ablate with a single administration!

>1 RAIT, 67% → ↑GO
1 RAIT, 5% → ↑GO

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

Differences in the selection of primary treatment modality for the index case of uncomplicated GD

RAIT as the primary treatment choice:
Changes between 1991 and 2011
Choice of Primary Treatment in GD

Case Presentation without GO

Case Presentation with mild GO

2011 Survey of Clinical Practice Patterns in the Management of Graves' Disease

Abbreviations: GD = Graves’ disease; CS = corticosteroids
Outcomes in Relapsed Graves’ Disease Patients Following Radioiodine or Prolonged Low Dose of Methimazole Treatment

RAIT n=102 pts    MMI n=114 pts

Danilo Villagelin,¹,² João H. Romaldini,¹,³ Roberto B. Santos,¹ Ana B.B.P. Milkos,³ and Laura S. Ward²

**Results:** The mean follow-up was 80.8 ± 35.3 months for the RAI group, and 71.3 ± 40.3 months for the low-dose MMI group. No notable side effects were observed in either group. Thyroid dysfunction was predominant in the RAI group ($p < 0.001$), and euthyroidism was more common in the MMI group ($p < 0.001$). GO deterioration was mainly evaluated by clinical activity score (CAS)—it was higher in the RAI group ($p < 0.0005$) over all periods of follow-up. Multivariate logistic analysis showed that RAI treatment was associated with no improvement in CAS during follow-up (24 months: OR = 3.51 [CI 1.02–12.03], $p < 0.05$; 36 months: OR = 8.46 [CI 1.47–48.58], $p < 0.05$; 48 months: OR = 19.52 [CI 1.70–223.10], $p < 0.05$; 60 months: OR = 21.1 [CI 1.5–298], $p < 0.05$). Kaplan–Meier survival analysis confirmed this finding ($p < 0.0003$). Assessment of QoL using the Short Form Health Survey’s 36 parameters in stable euthyroid patients (at least six months) was similar in both groups. The RAI group patients gained more weight ($p < 0.005$), particularly after 24 months of follow-up.

**Conclusions:** The use of low doses of MMI is efficient and safe, and offers better outcomes for GO than RAI treatment. Prolonged low doses of MMI may be an alternative choice for relapsed GD patients, particularly for GO patients or for patients who refuse a definitive treatment.

**Abbreviation:** MMI = Methimazole
Radioactive runaway sparked health scare

Patient who refused to remain in isolation put others at risk

By: Carol Sanders
Posted: 06/2/2017 4:00 AM | Comments:

In February 2015, a radioactive thyroid cancer patient in Winnipeg went rogue, leaving the hospital after undergoing radionuclide therapy — against medical advice and posing a public health hazard.
Realistic Expectations

- The RAIT of benign conditions has definitely declined for reasons that are not favorable for the patients
  - Endocrinologists – biased in favor of ATDT
  - Public – radiation phobia has increased
- The volumes of studies and therapy will continue declining, unless we – the US Nuclear Medicine community – own the responsibility to provide comprehensive care for patients with hyperthyroidism and manage them from start to finish, do state of the art research on small & the big data
The data now indicates that rising PTC incidence is not just due to better detection of microscopic disease.
If it ain't broke, don't fix it

2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer


*Authors are listed in alphabetical order and were appointed by ATA to independently formulate the content of this manuscript. None of the scientific or medical content of the manuscript was dictated by the ATA.

- 133 pages document, 1078 references, graded qualitatively for evidence strength: good, moderate, weak
- Made 101 recommendations (strong, weak, none): 21 were diametrically changed from 2009
Clinical Practice Guidelines We Can Trust

Standards for Developing Trustworthy Clinical Practice Guidelines (CPGs)

STANDARD 1
Establishing transparency
1.1 The processes by which a CPG is developed and funded should be detailed explicitly and publicly accessible.

STANDARD 2
Management of conflict of interest (COI)
2.1 Prior to selection of the Guideline Development Group (GDG), individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity, by written disclosure to those convening the GDG.
   • Disclosure should reflect all current and planned commercial (including services from which a clinician derives a substantial proportion of income), non-commercial, intellectual, institutional, and patient/public activities pertinent to the potential scope of the CPG.

2.2 Disclosure of COIs within GDG
   • All COI of each GDG member should be reported and discussed by the prospective development group prior to the onset of their work.
   • Each panel member should explain how their COI could influence the CPG development process or specific recommendations.

2.3 Divestment
   • Members of the GDG should divest themselves of financial investments they or their family members have in, and not participate in marketing activities or advisory boards of, entities whose interests could be affected by CPG recommendations.

2.4 Exclusions
   • Whenever possible GDG members should not have COI.
   • In some circumstances, a GDG may not be able to perform its work without members who have COIs, such as relevant clinical specialists who receive a substantial portion of their incomes from services pertinent to the CPG.
   • Members with COIs should represent not more than a minority of the GDG.
   • The chair or co-chairs should not be a person(s) with COI.
   • Funders should have no role in CPG development.

STANDARD 3
Guideline development group composition
3.1 The GDG should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG.

3.2 Patient and public involvement should be facilitated by including (at least at the time of clinical question formulation and draft CPG review) a current or former patient and a patient advocate or patient/consumer organization representative in the GDG.

3.3 Strategies to increase effective participation of patient and consumer representatives, including training in appraisal of evidence, should be adopted by GDGs.
Disclosure Statement

These guidelines were funded by the American Thyroid Association without support from any commercial sources.

KCB, GMD, YN, FP, GAR, AMS and KS have no significant financial or competing interests to disclose. **7 have no COI, 9 (>50%) with COI**

Chair BRH has received grant/research support from Veracyte and Genzyme. EKA has received research support from Asuragen. He has been a consultant for Genzyme and on Scientific Advisory Board Asuragen, and he holds stock options for Veracyte. SJM has received grant/research support from Veracyte and Asuragen. She has been on the scientific advisory committee for Asuragen, and has been a CME speaker for Genzyme. MS has received grant/research support from Genzyme, Bayer, AstraZeneca and Eisai. He has been a consultant for Genzyme, Bayer, AstraZeneca and Eisai. SIS has received grant/research support from Genzyme. He is a consultant for Veracyte, Exelixis, Bayer, AstraZeneca, Eisai, Novo Nordisk and Eli Lilly. JAS has received one-time speaker honorarium from Exelixis. DLS has received grant/research support from Astra-Zeneca. RMT is a consultant for Genzyme, Novo Nordisk, AstraZeneca and Veracyte. He holds stock options for Veracyte. LW has been a consultant for Asuragen and IBSA. He has received speaker honoraria from Genzyme.
2015 ATA Guidelines

- 133 pages document
- Reviewed 1078 references, grading of the evidence qualitatively
  - good, moderate, weak
- Made 101 recommendations, using modified ACP system
  - strong, weak, no recommendation
- There is a broad range of new or modified recommendations
  - 21 were *diametrically changed* from 2009

Abbreviations: ACP = American College of Physicians
The Goal: “A major goal of these guidelines is to minimize potential harm from overtreatment in a majority of patients at low risk for disease-specific mortality and morbidity, while appropriately treating and monitoring those patients at higher risk.” [AJCC/UICC staging?]

RECOMMENDATION 48: “The 2009 ATA Initial Risk Stratification System is recommended for DTC patients treated with thyroidectomy, based on its utility in predicting risk of disease recurrence and/or persistence.”
ATA’s Risk Stratification: Pathology-Centered Approach

• The tumor **size** is at the heart of ATA’s risk assessment, referral to RAI imaging, etc.

• Regional metastasis – important but not critical in risk assessment

• Distant metastasis are very important in risk assessment, but what ATA downplayed are
  - One has to look for mets to know whether or not they exist and, if so, iodine-avid or not
  - Based on pathology-centered approach many patients will never get imaged with RAI
56 year old woman
1.2 cm PTC, no extra thyroidal extension
+0/3 central lymph nodes
Tg 5.6, Tg Ab 1, TSH 48.6
pT1b, N0, M0. AJCC Stage I
ATA 2015 – “low risk”

Diagnostic Whole Body Scan (DxWBS)
After 1mCi of $^{131}$I, 24 hr. delay, Ant View

Slide Courtesy of Dr. Anca M. Avram
Restaging

Liver metastasis

T1b, N0, M1; Stage IV C
2015 ATA “High Risk”
Diagnostic (1 mCi) $^{131}$I scan at 6 mo. after 200 mCi RAI Rx:

Interval resolution of liver metastasis and of thyroid remnant tissue

**Theranostics principle** – risk
stratify based on surgical pathology,
withdrawal Tg + **I-131 scan** – treat
with commensurate I-131 activity

*Case 2*

Slide Courtesy of Dr. Anca M. Avram
2015 ATA vs. Theranostics

- 2015 ATA Guidelines - the “Magic bullet”?
  - Risk stratification for RAI Rx selection is based on surgical pathology + Tg => 60% ↓ in RAIT
  - Adm. activity / DTC response are ignored
  - DxRAIS is discounted, RxRAIS substituted

- Theranostics
  - Interrogate the target with a tracer
  - Determine adm. activity appropriate for the target
  - Deliver targeted radiation therapy to the lesion(s)

The Good
Target-Based RAIT Terms

Cooper DS et al. 2009 ATA guidelines. Thyroid
DOI: 10.1089/thy.2009.0110
Haugen BR et al. 2015 ATA guidelines. Thyroid
DOI: 10.1089/thy.2015.0020

- **Ablation** or **ablation therapy**: Eradicating remnant post-op **benign** thyroid tissue
- **Adjuvant therapy**: Eradicating **suspected** microscopic metastases
- **RAI therapy**: Eradicating **anatomically defined** (imaged) persistent/recurrent disease
  - We should commit to one of the specific terms above in our reports – avoid using general terms like “radioactive iodine treatment”, etc.

Abbreviations: RAIT = radioactive iodine treatment
2015 ATA Guidelines: Major Changes

- "2015 ATA Risk" stratification is based on "Recurrence Risk" (NOT mortality risk)
  - New approach, no direct data support
  - Extrapolated from studies where patients had been treated with RAI
  - Observation of good outcome led to classification of "low risk"; hence, those were Prospective clinical trial
  - Retrospective, observational, direct clinical evidence
  - No clinical evidence
  - Retrospective, observational, indirect clinical evidence
Thyrogen® ≠ Thyroid Hormone Withdrawal (THW)

3-3-99

10-11-99

48 hour uptake = 0.01%

72 hour uptake = 0.4%

Case 3

Fig. 1 $^{124}$I PET/CT images of the MHH patient at 24 h after $^{124}$I administration: iodine uptake in a cervical metastasis is substantially lower after rhTSH stimulation (a) than after THW (b). An iodine-avid adrenal gland metastasis is not visible after rhTSH (c) but visible after THW (d).

Thyrogen®

Thyroid Hormone Withdrawal (THW)
rhTSH versus THW

- The I-131 uptake is equal in remnant normal tissue with rhTSH versus THW stimulation\(^1\)
- The I-131 uptake and dose to metastatic tissue is GREATER with THW versus rhTSH stimulation. Uptake of I-131 was on average almost twice as high under THW as compared to rhTSH.\(^2\)

2015 ATA Guidelines: Recommendation 54

• rhTSH (Thyrogen®) preparation can be used as an alternative to thyroxine withdrawal (THW) for remnant ablation or adjuvant therapy

• The only category where THW gets some preference over rhTSH is distant metastatic disease

• Benefits of rhTSH are over-emphasized, but issues (poor DxWBS sensitivity for mets and poor RAI uptake in mets) are de-emphasized

Abbreviations: rhTSH = recombinant human Thyroid Stimulating Hormone
OBJECTIVE
To determine whether the use of imaging tests after primary treatment of differentiated thyroid cancer is associated with more treatment for recurrence and fewer deaths from the disease.

DESIGN
Population based retrospective cohort study.

SETTING
Surveillance Epidemiology and End Results-Medicare database in the United States.

PARTICIPANTS
28 220 patients diagnosed with differentiated thyroid cancer between 1998 and 2011. The study cohort was followed up to 2013, with a median follow-up of 69 months.

MAIN OUTCOME MEASURES
Treatment for recurrence of differentiated thyroid cancer (additional neck surgery, additional radioactive iodine treatment, or radiotherapy), and deaths due to differentiated thyroid cancer. We conducted propensity score analyses to assess the relation between imaging (neck ultrasound, radioiodine scanning, or positron emission tomography (PET) scanning) and treatment for recurrence (logistic model) and death (Cox proportional hazards model).

RESULTS
From 1998 until 2011, we saw an increase in incident cancer (rate ratio 1.05, 95% confidence interval 1.05 to 1.06), imaging (1.13, 1.12 to 1.13), and treatment for recurrence (1.01, 1.01 to 1.02), the change in death rate was not significant. In multivariable analysis, use of neck ultrasounds increased the likelihood of additional surgery (odds ratio 2.30, 95% confidence interval 2.05 to 2.58) and additional radioactive iodine treatment (1.45, 1.26 to 1.69). Radioiodine scans were associated with additional surgery (odds ratio 3.39, 95% confidence interval 3.06 to 3.76), additional radioactive iodine treatment (17.83, 14.49 to 22.16), and radiotherapy (1.89, 1.71 to 2.10). Use of PET scans was associated with additional surgery (odds ratio 2.31, 95% confidence interval 2.09 to 2.55), additional radioactive iodine treatment (2.13, 1.89 to 2.40), and radiotherapy (4.98, 4.52 to 5.49). Use of neck ultrasounds or PET scans did not significantly affect disease specific survival (hazard ratio 1.14, 95% confidence interval 0.98 to 1.27, and 0.91, 0.77 to 1.07, respectively). However, radioiodine scans were associated with an improved disease specific survival (hazard ratio 0.70, 95% confidence interval 0.60 to 0.82).

CONCLUSIONS
The marked rise in use of imaging tests after primary treatment of differentiated thyroid cancer has been associated with an increased treatment for recurrence. However, with the exception of radioiodine scans in presumed iodine avid disease, this association has shown no clear improvement in disease specific survival. These findings emphasize the importance of curbing unnecessary imaging and tailoring imaging after primary treatment to patient risk.
Second Opinion: Did thyroid imaging study miss the mark?

By Dr. Mark Tulchinsky, AuntMinnie.com contributing writer

October 27, 2016 -- In an article published July 21 in *BMJ*, researchers from the University of Michigan Comprehensive Cancer Center questioned whether the use of imaging after treatment for thyroid cancer improved patient outcomes.

Banerjee et al reported on statistical analysis of data spanning the years 1998 to 2011 that included more than 28,000 patients who had information available in the Surveillance, Epidemiology, and End Results (SEER) and Medicare databases.¹

The authors evaluated the rate of utilization of neck ultrasound (NUS), PET, and radioactive iodine whole-body scan (RAI WBS) in the surveillance (i.e., after initial treatment) of patients with differentiated thyroid cancer (DTC).

Their conclusion is rather disappointing for any physician practicing diagnostic imaging, as they state: "Imaging after primary treatment could lead to more treatment for recurrence; however, without an improvement in survival, except for radiiodine scans in presumably iodine-avid disease, it is not clear whether more imaging equals better care."

This conclusion clearly downplays the only test found to be positively associated with improved survival -- the radioactive iodine whole-body scan. It is unusual, if not unheard of, that a test showing positive association with survival is not the main focus of the article. But what this de-emphasis reveals is the researchers' conviction that all imaging is overused in surveillance of differentiated thyroid cancer.
Take-Home Message #4

Do Not Forget Take-Home Messages 1, 2 and 3!
Stand up to defend your field of practice – no one else will
• Drastic reductions in RAI pre-Rx scans & Rx
• Poor prep (rhTSH for stimulation, ±LID) = poor scan (if done) = poor RAI Rx
• Authorized users responsible mostly for dispensing RAI, if and when it’s ordered
• It might save $ for 3rd party payers … more f/u in endo, but at what (& whose) expense?
Are we ready to hang it up?

Is it “The End”?! Oh! But what about the future?

Thank You for Your Attention!?
“Doc”:

Future Is
Whatever You
Make It
1. Which type of therapy for Graves’ disease has beenshown to associate with development of new or progression of eye disease the most?

A. Methimazole high dose therapy
B. Propylthiouracil high dose therapy
C. Surgery
D. Radioactive iodine therapy
E. Methimazole low dose maintenance
2. What is the main goal of radioiodine therapy in Graves’ disease?

A. Rendering patients euthyroid for as long as possible
B. Rendering patients hypothyroid and instituting hormone replacement
C. Preventing Graves’ ophthalmopathy by eliminating thyroid tissue
D. Decreasing risk of thyroid cancer
3. What is the most rational and practical approach to radioactive iodine therapy of Graves' Disease?

A. Calculate the activity aimed at decreasing thyroid function to normal levels.

B. Calculate the activity based on thyroid dosimetry to deliver 15,000 cGy for ablation.

C. Calculate the activity to deliver 0.2-0.24 mCi per g of thyroid tissue adjusted for 24 hr. uptake with intent to ablate the gland.

D. Administer a standard fixed dose of 15 mCi to ablate the gland.
4. Which of the following best describes the scientific evidence for the proposed management of “low risk” differentiated thyroid cancer in the 2015 American Thyroid Association guidelines?

A. Prospective clinical trial

B. Retrospective, observational, direct clinical evidence

C. Retrospective, observational, indirect clinical evidence

D. No clinical evidence
5. Which of the following is true of recombinant human TSH stimulation as it compares to thyroid hormone withdrawal preparation for radioactive iodine (I-131) therapy?

A. It does not significantly change sensitivity of I-131 scan for detection of metastatic disease.
B. It results in uptake in the tumor similar to or better than that achieved with withdrawal prep.
C. It is beneficial for sparing salivary glands from I-131 side effects.
D. It significantly improves quality of life metrics during preparation.