Radioactive Iodine Treatment for Differentiated Thyroid Cancer

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No Conflict of Interests to Declare
Learning Objectives

• History
• Treatment options terminology for Differentiated Thyroid Cancer (DTC)
  • Based on target tissue definition
  • Based on activity selection approach
• Determining the best administered activity (AA)
• Acceptable, logical practice today
• Evidence
• How to identify the “fake news” articles
RADIOACTIVEIODINE THERAPY

Effect on Functioning Metastases of Adenocarcinoma of the Thyroid

S. M. SEIDLIN, M.D.
L. D. MARINELLI, M.A.
and
ELEANOR OSHRY, B.S.
New York

Therapy of neoplastic disease usually consists of two phases: first, the treatment of the primary focus and, second, that of metastases. Specifically, in adenocarcinoma of the thyroid, the primary site together with its immediate extensions is conventionally treated by surgery, radiation or both. Distant metastases, if treated, are usually subjected to palliative external irradiation. This paper is a report of successful therapy of a case of metastatic adenocarcinoma of the thyroid treated by the principle of specific internal irradiation with radioactive iodine.
Samuel M. Seidlin, M.D.
First $^{131}$I Therapy for Thyroid CA
Montefiore Medical Center, Bronx, NY
Celebrated Patient BB

Case 1

1943
Prior to Radioiodine Tx

1949
After Radioiodine Tx

Siegel E. Cancer Biother Radiopharm 1999
BB was “...a Brooklyn shoe salesman ... destined to become one of the most famous patients in medical history ... is the first person known to be cured of metastatic cancer... Metastatic cancer has always been 100% fatal. But ... tumors were destroyed in a simple, almost miraculous way: by the drinking of four doses of radioactive iodine. ...he appeared to be suffering from an overactive thyroid gland ... he was weak and emaciated. ... his thyroid gland ... had been removed by surgery. ...Radioiodine was given on the theory that his thyroid tumors would absorb the drug. ...If they did, they would be destroyed. ...Three months after he drank his first glass of tasteless, colorless liquid ... he started to put on weight. ...After three additional doses the tumors ... eventually disappeared altogether.
Dr. Samuel Seidlin was a physiologist at McGill University during the late 1930’s. He was particularly interested in the field of hormone interaction. Just before the beginning of World War II, he moved to a private practice of endocrinology in New York City. His early hospital connections were with Montefiore Hospital and some of his research was done in their laboratories. However, he was one of the first to have a private practice of nuclear medicine.
Seidlin wanted to try radioiodine on his cancer patient—therapeutically (he already knew the diagnosis). Obviously, if radioiodine was made in a cyclotron, then telephone a cyclotron driver. A telephone call to California from New York City costs money, so Seidlin called Dr. Evans; it was cheaper to call Boston. He asked if the M.I.T. cyclotron made radioactive iodine. He was told that beyond any shadow of a doubt, M.I.T. could do anything that California could do, and probably do it better. After a long and detailed conversation about the condition of the neutron flampus decapitance and the problem of target fordumucle feedback, the Boston scientist remarked, “Of course, there is a small problem of cost.”

“How much does it cost?” asked Seidlin.

“Eighteen hundred dollars an hour,” said Evans.

After Seidlin picked himself up off the floor, he answered, “Well, send me some.”

“How many millicuries do you want?” asked Evans.

Not having the slightest idea of what a millicurie was, Seidlin replied, “Send me a whole hour’s worth, naturally.”

This was the beginning of the science of radioisotope dosimetry.
Seidlin’s patient did not have $1,800; he was a medical indigent. Neither did Seidlin have $1,800; he was also a medical indigent. But he figured it would take a week to deliver the drug, another week to get the bill for it, he would stall for a week, and in three weeks the radioiodine would be mostly gone anyway, so they could sue him. This was the beginning of the science of financing radioactive pharmaceuticals.
DTC is Insidious, Survival is Excellent: Who Should be Treated and How?

- The question is just as “excellent” today as it was in 1943, except that there’re many more diagnostic and treatment options …
- Today we “risk stratify” patients based on certain metrics, mostly labs (thyroglobulin, etc.) and surgical pathology:
  - Size of the primary tumor
  - Extra thyroidal extension (gross vs. micro.)
  - Regional lymph node mets
- “Risk comes from not knowing what you’re doing.” Warren Buffett
Evolution and State of the RAIT

• Initial phase of therapy is still total thyroidectomy, but hemi thyroidectomy and active surveillance are growing in popularity
• Eval. phase – Risk Stratification (RS) determines management, including RAIT
• RS - subjective & variable: AGES, AMES, EORTC, MACIS, MSKCC, ATA, TNM 7th Ed. …
# DTC Risk Stratification Systems

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<td>Extrathyroidal invasion</td>
<td>X</td>
<td>X</td>
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<td>Nodal metastatic lesion</td>
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<td>Distant metastatic lesion</td>
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<td><strong>Operative factors</strong></td>
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<td>Incomplete resection</td>
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</table>

X = variable used in defining risk group  
Y = schemes devised only for PTC  
– = variable not used  

EORTC = European Organization for Research on Treatment of Cancer  
AGES = patient age, histologic grade of the tumor, tumor extent (extrathyroidal invasion or distant metastases), and size of the primary tumor  
AMES = patient age, presence of distant metastases, extent and size of the primary tumor  
MACIS = metastasis, patient age, completeness of resection, local invasion, and tumor size  
OSU = Ohio State University  
MSKCC = Memorial Sloan-Kettering Cancer Center  
NTCTCS = National Thyroid Cancer Treatment Cooperative Study  
ATA = American Thyroid Association  
TNM = American Joint Committee on Cancer, Tumor, Node, Metastases, 7th Ed.  
QTNM = Quantitative TNM, symplified by Onitilo et al., JCO 2009
“Life is really simple, but we insist on making it complicated.” Confucius
**Table 11. ATA 2009 Risk Stratification System with Proposed Modifications**

**ATA low risk**  
Papillary thyroid cancer (with all of the following):
- No local or distant metastases;
- All macroscopic tumor has been resected
- No tumor invasion of loco-regional tissues or structures
- The tumor does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma)
- If $^{131}$I is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first posttreatment whole-body RAI scan
- No vascular invasion
- Clinical N0 or ≤5 pathologic N1 micrometastases (<0.2 cm in largest dimension)$^a$
  Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer$^a$
  Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion$^a$
  Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including $BRAF^{V600E}$ mutated (if known)$^a$

**ATA intermediate risk**  
Microscopic invasion of tumor into the perithyroidal soft tissues
- RAI-avid metastatic foci in the neck on the first posttreatment whole-body RAI scan
- Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma)
- Papillary thyroid cancer with vascular invasion
- Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension$^a$
- Multifocal papillary microcarcinoma with ETE and $BRAF^{V600E}$ mutated (if known)$^a$

**ATA high risk**  
Macroscopic invasion of tumor into the perithyroidal soft tissues (gross ETE)
- Incomplete tumor resection
- Distant metastases
- Postoperative serum thyroglobulin suggestive of distant metastases
- Pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension$^a$
- Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)$^a$

$^a$Proposed modifications, not present in the original 2009 initial risk stratification system. See sections [B19]–[B23] and Recommendation 48B.
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 RAI Scan (DxRAIS)
1mCi of $^{131}$I, 24 hr. delay, Ant View

Case 2

Case Courtesy of Dr. Anca M. Avram
“It ain't what you don't know that gets you into trouble (or your patient into trouble) . It's what you know for sure that just ain't so.”

Mark Twain
DxRAIS + SPECT/CT

Right thyroid remnant

Liver metastasis
Critical Role – Post-TT
Staging of DTC
T1b, N0, M1; Stage IV C
2015 ATA “High Risk”

Case 2

Case Courtesy of Dr. Anca M. Avram
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
“It's not the size of the *dog* in the fight, it's the size of the *fight* in the dog.”
Mark Twain

It’s **not** the size of the tumor inside the Thyroid, it’s the **spread** of the tumor outside the thyroid.

DxRAIS is the most direct and specific way of determining (1) I-131 avidity and (2) aggressiveness of IODINE-AVID DTC
Radioiodine Treatment Options

• Empiric, Fixed (“Standard”) vs. Severity-Scaled Activity

1. Give fixed amount, e.g., 100 mCi, to all for as long as post-treatment scan remains positive (Schlumberger et al.)

2. Give empirical activities, amounts scaled to the type of thyroid cancer, metastatic spread and location

• Maximum Tolerated Activity Therapy (MTAT), based on Whole Body Dosimetry

ü Determining the maximum activity the patient can tolerate, sparing pts fatal radiation induced side effects

• Lesion-Based (“Lesional”) Dosimetry

ü Administering activity that delivers a lethal dose to the lesion(s)


Preparing the Patients for RAIT:

ATA RECOMMENDATION 57

A low iodine diet (LID) for approximately 1–2 weeks should be considered for patients undergoing RAI remnant ablation or treatment. (Weak recommendation, Low-quality evidence)

“There are no studies examining whether the use of a LID in preparation for RAI remnant ablation or treatment impacts long-term disease-related recurrence or mortality rates.”

Should we do studies examining whether the use of a parachute improves mortality of paratroopers?


... drop a few “control subjects”?! Any volunteers... any ATA investigators?
Administered Dose Thresholds At ≥80% Response Rate

<table>
<thead>
<tr>
<th>Metastatic Sites</th>
<th>AD (Gy)</th>
<th>Ref.#</th>
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<tbody>
<tr>
<td>Lymph node</td>
<td>85</td>
<td>1, 2</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>85</td>
<td>2</td>
</tr>
<tr>
<td>Thyroid Remnant</td>
<td>300</td>
<td>1</td>
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<tr>
<td>Bone</td>
<td>350-650</td>
<td>3</td>
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Abbreviations: AD = Administered Dose or lesion-absorbed radiation dose
RECOMMENDATION 73

(A) Although there are theoretical advantages to dosimetric approaches to the treatment of loco-regional or metastatic disease, no recommendation can be made about the superiority of one method of RAI administration over another (empiric high activity versus blood and/or body dosimetry versus lesional dosimetry).

(No recommendation, Insufficient evidence)

(B) Empirically administered amounts of $^{131}$I exceeding 150 mCi that often potentially exceed the maximum tolerable tissue dose should be avoided in patients over age 70 years.

(Strong recommendation, Moderate-quality evidence)

• **Ablation** or **ablation therapy**, i.e., eradicating remnant, benign tissue post-TT, typically applies to 1st visit

• **Adjuvant therapy**, i.e., eradicating suspected microscopic metastases, usually at first post-TT visit, but also applies to later visits, e.g. –DxRAIS/+Tg

• **RAI therapy of metastatic DTC** RAIT of anatomically defined metastatic DTC

• **Missing** **SALVAGE THERAPY**, i.e., positive surgical margins, tumor not surgically removable, etc.

Abbreviations: –DxRAIS = negative radioactive iodine scan; +Tg = positive thyroglobulin; ATA = American Thyroid Association; DTC = differentiated thyroid cancer; RAIT = radioactive iodine treatment; TT = total thyroidectomy
ATA Definitions of Response to RAIT

- **Excellent response (Complete response?)**
  - no clinical, biochemical, or structural evidence of disease
- **Biochemical incomplete (partial) response**
  - abnormal Tg or rising anti-Tg antibody levels in the absence of localizable disease
- **Structural incomplete (partial) response**
  - persistent or newly identified loco-regional or distant metastases
- **Indeterminate response**
  - Other than any of the above
**Table 13. Clinical Implications of Response to Therapy Reclassification in Patients with Differentiated Thyroid Cancer Treated with Total Thyroidectomy and Radioiodine Remnant Ablation**

<table>
<thead>
<tr>
<th>Category</th>
<th>Definitions&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Clinical outcomes</th>
<th>Management implications</th>
</tr>
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<tbody>
<tr>
<td>Excellent response</td>
<td>Negative imaging &lt;br&gt;and either &lt;br&gt;Suppressed Tg &lt; 0.2 ng/mL&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;or &lt;br&gt;TSH-stimulated Tg &lt; 1 ng/mL&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1%–4% recurrence&lt;sup&gt;c&lt;/sup&gt;&lt;br&gt;&lt;1% disease specific death&lt;sup&gt;c&lt;/sup&gt;</td>
<td>An excellent response to therapy should lead to an early decrease in the intensity and frequency of follow up and the degree of TSH suppression</td>
</tr>
<tr>
<td>Biochemical incomplete response</td>
<td>Negative imaging &lt;br&gt;and &lt;br&gt;Suppressed Tg ≥ 1 ng/mL&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;or &lt;br&gt;Stimulated Tg ≥ 10 ng/mL&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;or &lt;br&gt;Rising anti-Tg antibody levels</td>
<td>At least 30% spontaneously evolve to NED&lt;sup&gt;d&lt;/sup&gt;&lt;br&gt;20% achieve NED after additional therapy&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;20% develop structural disease&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;&lt;1% disease specific death&lt;sup&gt;d&lt;/sup&gt;</td>
<td>If associated with stable or declining serum Tg values, a biochemical incomplete response should lead to continued observation with ongoing TSH suppression in most patients. Rising Tg or anti-Tg antibody values should prompt additional investigations and potentially additional therapies.</td>
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<tr>
<td>Structural incomplete response</td>
<td>Structural or functional evidence of disease &lt;br&gt;With any Tg level &lt;br&gt;With or without anti-Tg antibodies</td>
<td>50%–85% continue to have persistent disease despite additional therapy&lt;sup&gt;c&lt;/sup&gt;&lt;br&gt;Disease specific death rates as high as 11% with loco-regional metastases and 50% with structural distant metastases&lt;sup&gt;a&lt;/sup&gt;</td>
<td>A structural incomplete response may lead to additional treatments or ongoing observation depending on multiple clinico-pathologic factors including the size, location, rate of growth, RAI avidity, &lt;sup&gt;18&lt;/sup&gt;FDG avidity, and specific pathology of the structural lesions.</td>
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<tr>
<td>Indeterminate response</td>
<td>Nonspecific findings on imaging studies &lt;br&gt;Faint uptake in thyroid bed on RAI scanning &lt;br&gt;Nonstimulated Tg detectable, but &lt;1 ng/mL &lt;br&gt;Stimulated Tg detectable, but &lt;10 ng/mL &lt;br&gt;or &lt;br&gt;Anti-Tg antibodies stable or declining in the absence of structural or functional disease</td>
<td>15%–20% will have structural disease identified during follow-up&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;In the remainder, the nonspecific changes are either stable, or resolve&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;&lt;1% disease specific death&lt;sup&gt;a&lt;/sup&gt;</td>
<td>An indeterminate response should lead to continued observation with appropriate serial imaging of the nonspecific lesions and serum Tg monitoring. Nonspecific findings that become suspicious over time can be further evaluated with additional imaging or biopsy.</td>
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NED denotes a patient as having no evidence of disease at final follow-up.<br><sup>a</sup>References (538,539,542,586–593,595–601,1078).<br><sup>b</sup>In the absence of anti-Tg antibodies.<br><sup>c</sup>References (598,599,617–621).<br><sup>d</sup>References (328,607,626,627,898).
PI: “The THYROGEN scan failed to detect remnant and/or cancer localized to the thyroid bed in 17% (14/83) of patients in whom it was detected by a scan after thyroid hormone withdrawal. In addition, the THYROGEN scan failed to detect metastatic disease in 29% (7/24) of patients in whom it was detected by a scan after thyroid hormone withdrawal.”

- In patients with distant metastases you will miss one in every 3rd – 4th patients under rhTSH stimulation
- Initial FDA approval was only for “low-risk” DTC
- Others should be scanned on THW stimulation
- Soft evidence was generated by company-sponsored studies, allowing amendment of PI
Thyrogen®

3-3-99

48 hour uptake = 0.01 %

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)

Case 4

Thyrogen®

Thyroid Hormone Withdrawal (THW)
rhTSH versus THW

• The I-131 uptake is equal in remnant normal tissue with rhTSH versus THW stimulation¹

• 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 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
Disclosure Statement

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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**

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First, Post-Thyroidectomy, Evaluation: Tg Levels Attributable to Benign Thyroid Remnant under PSU Protocol

- DTC patients referred for ablation on hormone withdrawal stimulation protocol in the past 3 years were reviewed.

- Excluded: 1) positive regional metastatic disease at surgery, 2) positive scan or thyroglobulin at one year follow-up, 3) suspicious ultrasound findings or any other indication for residual disease at one year follow-up evaluation, and 4) abnormal Tg antibody titer.
First, Post-Thyroidectomy, Evaluation: Tg Levels Attributable to Benign Thyroid Remnant: Patients & Results

- 43 patients (30 females) were included. The patients’ data [mean ± standard deviation (range)] included:
  - age of 50.0±15.0 (21-88)
  - 24 hour iodine uptake (24HrIU) of 7.12±7.51 (0.1-32.7)
  - Tg of 5.87±8.43 (0.2-47.8)
  - TSH ranged from 6.58 to >100 (<35 in 6 pts, ≥35 to 100 in 19 pts, and >100 in 18 pts)
First Post-Thyroidectomy Evaluation

\[
[(24\text{Hr.}\%\text{IU} \times 2) + 1] \leq \text{Tg}
\]

TG values in withdrawal stimulated DTC patients who had no residual tumor

42/43 pts. excluded  
Specificity 97.7%

24 hour I-131 uptake probe results (%)

PSU Protocol

Tulchinsky M. 2014
First Post-Operative Presentation

- 57 y/o with follicular variant of papillary CA, 2.5 cm, +0/1 LN.
- The post-op 24 hour uptake, obtained with 7 μCi of I-131 on a probe, was 23.5% on 9/14/2001.
- 9/13/2001 labs: TSH = 34.2; Tg = 5.6; Tg Ab <0.3
- Would the chance of remnant tumor justify escalating the activity to adjuvant therapy?
Pre-Treatment Tc-99m Pertechnetate Scan

9/13/2001 labs:
TSH = 34.2; Tg = 5.6; Tg Ab <0.3

24 hr. uptake = 23.5%

(23.5 x 2) + 1 = 48. Tg of 5.6 is less than 48, i.e. no excess Tg, no evidence for residual tumor.

Evaluation prior to RAIT indicates Ablation is sufficient.
Post-Treatment I-131 Whole Body Scan – No Metastatic Disease

F/U:
NED at 15 years
38 y/o female with coughing, hoarseness and feeling of “pressure on esophagus”

- Fall 2015 the above complaints
- US showed 2 right pole nodules, 16 and 12 mm
- Bx not sufficient tissue, follicular morphology
- Dr. S performed hemi on 2/16, classical papillary 1.5 cm, positive posterior margin
- Dr. S gave the patient options, 1) observation with US versus 2) complete thyroidectomy
- Patient decided to do completion thyroidectomy
38 y/o female with coughing, hoarseness and feeling of “pressure on esophagus”

- 4/7/16 completion thyroidectomy, 2 and 1 mm papillary Ca., presumed Stage I
- Dr. S. recommends no RAI
- Dr. M. (Endo.) recommends no RAI
- Later that month, Tg is 19.2, Ab 1, TSH 0.08
- Post-op US, a suspicious LN, but bx was negative for PTC
- Patient elected to proceed with RAI evaluation and treatment according to DxRAIS/Tg findings
38 y/o female with path “Stage I”

- 24 hr. uptake in the neck = 1.5%
- Max Tg expected would be (1.5x2)+1=4
- 10/20/16 TSH 70.6, Tg 74, Ab 1
38 y/o female with “Stage I”

- 24 hr. uptake in the neck = 1.5%
- Max Tg expected would be \((1.5 \times 2) + 1 = 4\)
- 10/20/16 TSH 70.6, Tg 74, Ab 1
- RAI-WBS, remnant benign thyroid, no mets
- Conclusion: Tg out of proportion to remnant normal thyroid; hence, occult tumor present, too small to detect vs. NIA
- RAIT, ablative & adjuvant activity, 150 mCi
- Post-treatment RAI-WBS to follow

NIA = non-iodine avid
38 y/o female with “Stage I” POST-TREATMENT SPECT-CT Lung mets, Stage II
Empiric Activities Method: Implies Diagnostic RAI Scan

  - Cervical lymph nodes metastases: 150-175 mCi
  - Lung metastases: 175-200 mCi
  - Bone metastases: 200 mCi

- 2012 SNM Practice Guideline for Therapy of Thyroid Disease with I-131
  - Postoperative ablation: 30-100 mCi
  - Cervical or mediastinal lymph node metastases: 150-200 mCi
  - Distant metastases: 200 mCi or higher

Simple.
Convenient.
Long history of use.

- Cervical node mets
- Lung mets
I-131 Administered Activities (AA), PSU

- **Empirical**
  - No residual/metastatic DTC
    - $\geq 30 - 100$ mCi for Ablation
  - Regional lymph node (LN) or $\uparrow Tg>\text{remnant}$
    - $\geq 100 - 150$ mCi for Adjuvant (Salvage) Therapy
  - Distant metastatic disease (LN, lung, bone, etc.)
    - $\geq 200 - 250$ mCi for Therapy

- **Dosimetry-Guided Activity considered for:**
  - Suspected metastatic disease, Tg or Imaging
  - Renal insufficiency or failure
  - Age $\geq 70$ y/o
Empiric vs Dosimetry: Safety

• Kulkarni K. et al. (Van Nostrand D.) Thyroid. 2006;16(10):1019-1023.
  – 127 patients who had dosimetry data
  – Retrospectively calculated absorbed dose to the red marrow if empiric activities of 100, 150, 200, 250 or 300 mCi had been given
  – Majority of patients could have received higher activities of I-131 without exceeding 2Gy BM dose limit
  – Although 100 mCi activity dose rarely exceeded the 2Gy limit, activity doses >=200 mCi frequently exceeded the limit

  – 328 patients who had dosimetry data
  – Retrospectively calculated absorbed dose to the red marrow for empiric activities of 140, 200 and 250 mCi
  – Empiric activities of 200 and 250 mCi exceeded 2Gy limit, especially in the elderly >=70 y.o.
    • 200 mCi: Exceeded limit in 8-15% of patients < 70y; 22% of patients 70-79y; 38% of patients >=80y
    • 250 mCi: Exceeded limit in 22% of patients < 70y and 50% of patients >=70y
MTARAIT: Preselecting versus Routine

• Indications
  - Metastasis, lung or LN beyond regional
  - Regional lymph node involvement
  - Follicular CA or high-risk PTC Variants
  - Renal dysfunction
  - ≥70 y/o

• Variables prompting consideration
  - Tumor at the inked margins
  - Gross extrathyroidal invasion
  - PTC, size greater than 3.5 cm
I-131 Absorbed Dose to Red Bone Marrow

Blood is surrogate for red marrow.

Gamma radiation:
- Urine collection
- Gamma probe or camera

Beta radiation:
- Blood samples

BM Dose = β + γ
Treatment Activity Dose Calculation

Counts from gamma probe/gamma camera and blood samples converted to activity (uCi/MBq) using standards to create time activity curves.

1-10 mCi I-131
Day 1
Whole Body Dosimetry

- Administer the maximum activity of I-131 without causing life-threatening critical organ damage => red bone marrow or lung fibrosis
  - Originated from the work by Benua et al. in 1962; Benua and Leeper 1986
  - Absorbed dose limit to blood/red marrow -> 2 Gy
  - Whole body retention @48 hours:
    - $< 120 \text{ mCi}$ (no diffuse lung uptake)
    - $< 80 \text{ mCi}$ in the presence of diffuse lung metastases

**Rationale:**
- Higher I-131 treatment activities impart higher therapeutic effect.
- Lower non-tumoricidal doses to the tumor may lower the effectiveness of subsequent doses.

“It was observed that a series of some treatments resulted in a fatal marrow injury. This early experience also showed that metastases treated with either smaller repeated doses of I-131 or with external irradiation seemed to lose the ability to function but continued to grow.” Benua RS et al. 1962
Time Activity Curves
slower clearance $\dot{E}$ $\uparrow$ area under the curve $\dot{E}$ $\uparrow$ absorbed dose
Treatment Activity Dose Calculation

Absorbed Dose calculations

MIRD method classical dosimetry

Absorbed Dose (cGy)
Activity (MBq)

\[
\text{Treatment Activity Dose (Mbq)} = \frac{200 \text{ cGy}}{\beta(\text{cGy/MBq}) + \gamma(\text{cGy/MBq})}
\]

2 Gy blood absorbed dose limit
Case 7

1st Presentation
Post-TT

40.4% uptake
Case 7

1st Presentation
Post-TT
TREATMENT #1

Treated with a MTAT = 150 mCi dose.
4.6% uptake

2nd Presentation 1 year later

Case 7
TREATMENT #2

Treated with MTAT = 250 mCi dose.
Case 7

3rd Presentation
2 year later

0.15% uptake
2.44% Uptake

0.369 rads/mCi

Case 7
TREATMENT #3

1 year after, only 2 nodes remained in the neck, resected, remaining with stable low-abnormal Tg for the past 6 years (9 years since first visit)
“Simplified” Dosimetry Methods

→ No blood samples
→ Single time point

  - Correlation between pre-therapy and post-therapy I-131 scans whole body retention at 48 hours
  - Modify empiric activities using whole body retention at 48 hr

  - WBR at 48 hours with 2 Gy blood dose limit
  - Regression analysis of full dosimetry data from 142 patients

  - 14-17% of I-131 whole body residence time => blood
  - Approximate blood absorbed dose from whole body retention

  - Estimate blood absorbed dose from WBR at 24 or 48 hours using 14% of whole body residence time attributed to the blood
“Simplified” Dosimetry Methods

  – Retrospective study of 211 patients who received I-124 PET/CT lesion and blood dosimetry
  – Compared several shortened dosimetry MTA with full dosimetry MTA in 2 groups: pre I-131 tx (n=108) and post I-131 tx (n=103)
  – Blood and whole body residence times were better correlated in post I-131 tx vs pre I-131 tx group
    • Simplified dosimetry methods utilizing only whole body retention may be better suited in patients who have had prior I-131 tx.
  – Shortened dosimetry using both blood and whole body counts at 3 time points for both groups or blood counts only at 3 time points in post tx group were equivalent to full dosimetry MTA
    • Equivalent => Estimated MTA from shortened dosimetry △ 20% full dosimetry MTA in 95% of patients
  – Shortened dosimetry MTA using whole body counts not equivalent
“Simplified” Dosimetry Methods

• Simplified dosimetry methods do not replace full dosimetry
  – Full dosimetry method provides more accurate estimate of the maximum tolerated activity

• Simplified dosimetry may be helpful when full dosimetry method not available
Whole Body Dosimetry

“Pros”
- Individualized
- Long history of use
- Fewer # of therapies
- Safer than empiric activity in some patients
  - ↑ age, diffuse lung mets, ↓ GFR
- Preempting RAI resistance

“Cons”
- Complex & longer
  - Simpler & shorter methods available
- Improved response rates or outcomes not validated
- absorbed tumor dose unknown

Comparison of Empiric Versus Whole-Body/-Blood Clearance Dosimetry-Based Approach to Radioactive Iodine Treatment in Patients with Metastases from Differentiated Thyroid Cancer

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See a commentary on this article on page 697.

Radioactive iodine (RAI; ¹³¹I) has been used since the late 1940s for the treatment of patients with distant metastases from differentiated thyroid cancer (1). The optimal management in terms of administered ¹³¹I activity, number of treatment courses, and their frequency remains unclear.

For RAI to have a therapeutic effect, it is necessary to deliver a tumoricidal radiation dose to the metastatic foci (2–5). On the basis of the assumption that higher administered activities (>9.25 GBq) of RAI would be more likely to deliver therapeutic
Critique

- Overall Survival was compared
  - French women happen to overall live longer
- “Dosimetry” group was older than “One-size-fit-all” group
- “Dosimetry” was done in ALL pts with rhTSH stimulation
  - >99% of Dosimetry is done with THW
- COI (Genzyme) not fully declared
- Not a valid comparison study – result are not valid
REPLY: We agree that several confounding variables may be present in retrospective studies, but available data on thyroid cancer patients are mostly retrospective. Therefore, treatment strategies are based on low-level evidence and always open to challenge. The efficacy of radioactive iodine (RAI) treatment may be related to patient age, histology, lesion size and number, $^{18}$F-FDG uptake, treatment preparation (thyroid hormone withdrawal [THW] vs. recombinant human thyroid-stimulating hormone [rhTSH]), administered activity, number of treatments, cumulative activity, radiation dose to tumor foci, and assessment of response. Most of these factors were considered and discussed in our article (1).

Tulchinski et al. point out the difference in mortality rate between French and American
specific therapies or as re differentiation agents to improve the efficacy of RAI therapy).

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DISCLOSURE

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REFERENCES


Learning Objectives: RAI in Differentiated Thyroid Cancer (DTC)

- History
- Treatment options terminology for DTC
  - Based on target tissue definition
    - Ablation, Adjuvant, Metastatic Therapy
  - Based on activity selection approach
    - Fixed Activity, Risk-scaled Empirical, Max Tolerated Activity – marrow dose, Lesional dosimetry
- Defining the outcomes
- Incorporating thyroglobulin and diagnostic RAI scan
- Making decisions on which therapy is appropriate
- Treat to cure at the first therapeutic visit
1. Which is the correct definition of **excellent response** to therapy (remission or no evidence of disease) according to the ATA?

A. Negative imaging & suppressed TG < 0.2 ng/mL AND stimulated TG < 2 ng/mL

B. Negative imaging & suppressed TG < 0.2 ng/mL AND stimulated TG < 1 ng/mL

C. Non-specific imaging findings & suppressed TG < 0.2 ng/mL AND stimulated TG < 2 ng/mL

D. Negative imaging & suppressed TG < 0.2 ng/mL OR stimulated TG < 1 ng/mL
2. According to current guidelines, **biochemical incomplete response** to therapy is defined as:

A. Negative imaging & suppressed TG $\geq 1$ ng/mL OR stimulated TG $\geq 10$ ng/mL, OR rising anti-TG antibodies

B. Negative imaging & suppressed TG $< 0.2$ ng/mL OR stimulated TG $< 1$ ng/mL

C. Non-specific imaging findings & suppressed TG $\geq 1$ ng/mL OR stimulated TG $\geq 10$ ng/mL, OR rising anti-TG antibodies

D. Negative imaging & suppressed TG $\geq 0.2$ ng/mL OR stimulated TG $< 1$ ng/mL
3. What is the long-term clinical outcome in patients with biochemical incomplete response to therapy?

A. 60% patients develop structurally identifiable disease over 5–10 years follow-up
B. 20% patients develop structurally identifiable disease over 5–10 years follow-up
C. 50% patients continue to have persistently abnormal TG values without structural correlate
D. 80% patients have no evidence of disease over long-term follow-up
4. Diagnostic radioiodine scans with SPECT/CT are **MOST** useful for which of the following?

A. To complete post-operative thyroid cancer staging prior to 131-I therapy

B. To determine the dose of 131-I therapy

C. To alter the pre-operative management

D. To perform whole body dosimetry calculations
5. Which of the following, if found on scintigraphy to be iodine avid, require the highest administered dose to assure at least 80% response rate?

A. Remnant benign thyroid tissue
B. Lymph node metastases
C. Lung metastases
D. Bone metastases
Thank You For Your Attention!