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)
  - ü Based on target tissue definition
  - ü Based on activity selection approach
- Determining the best administered activity (AA)
- Acceptable, logical practice today
- Evidence
- How to identify the “fake news” articles

RADIOACTIVE IODINE THERAPY

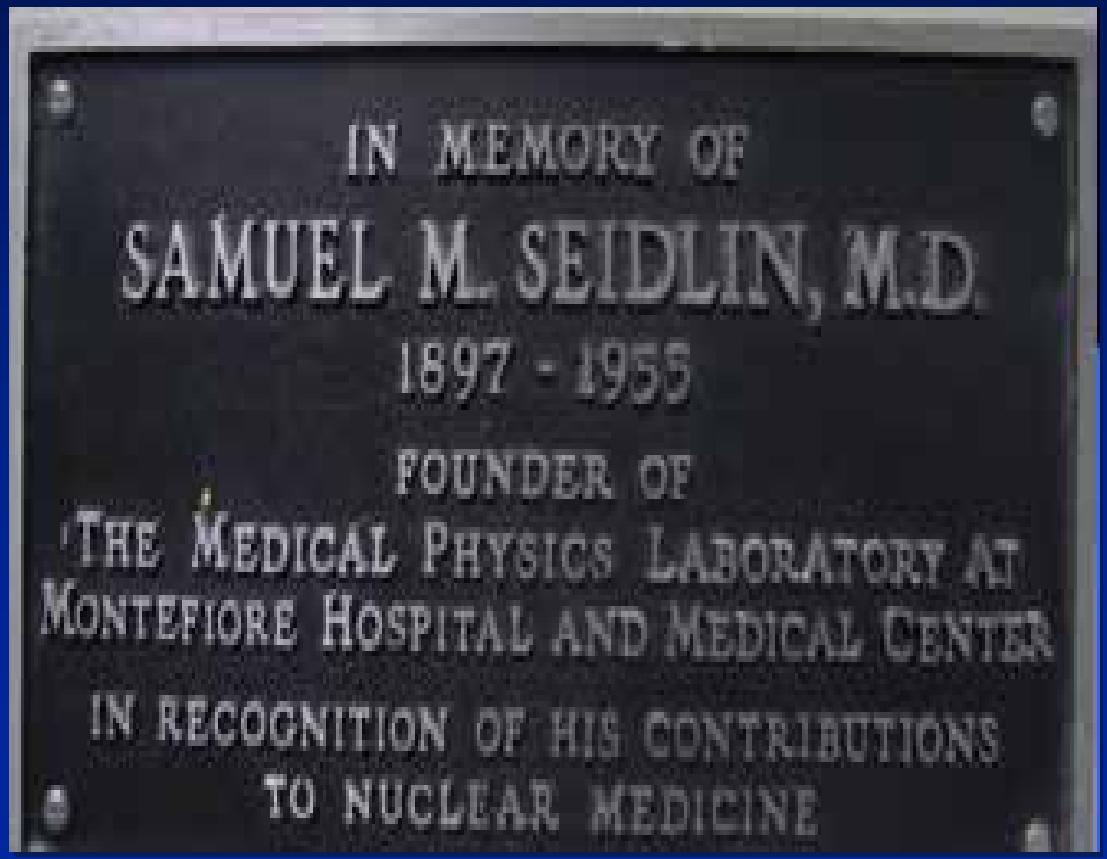
Effect on Functioning Metastases of Adenocarcinoma of the Thyroid

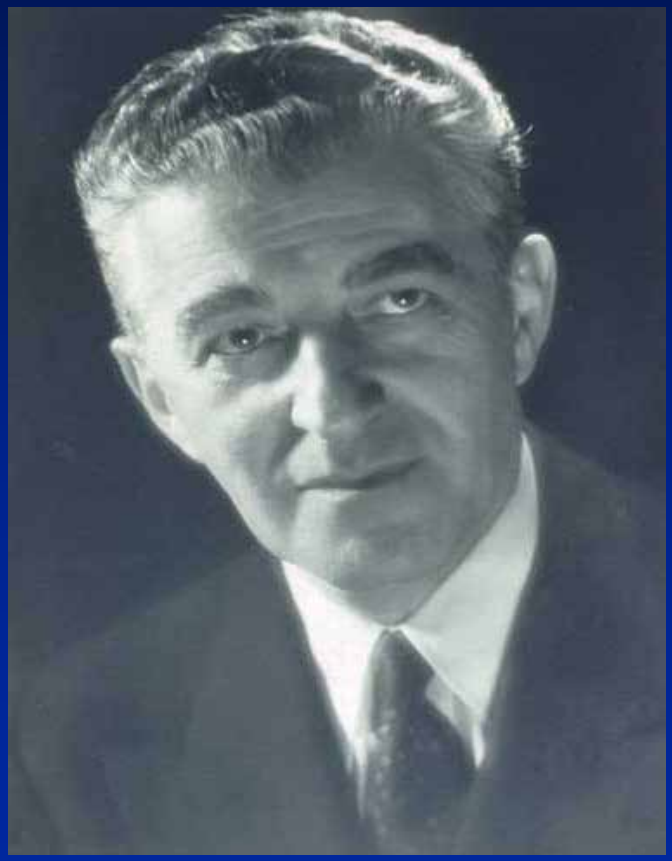
S. M. SEIDLIN, M.D.
L. D. MARINELLI, M.A.
and
ELEANOR OSHRY, B.S.
New York

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.

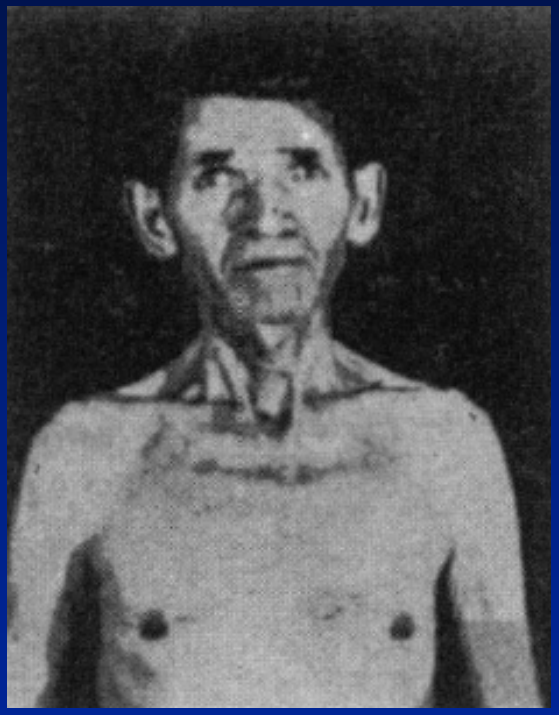
JAMA. 1946; 132(14):838-847. doi: 10.1001/jama.1946.02870490016004

Samuel M. Seidlin, M.D.
First ^{131}I Therapy for Thyroid CA
Montefiore Medical Center, Bronx, NY





Celebrated Patient BB



1943
Prior to Radioiodine Tx

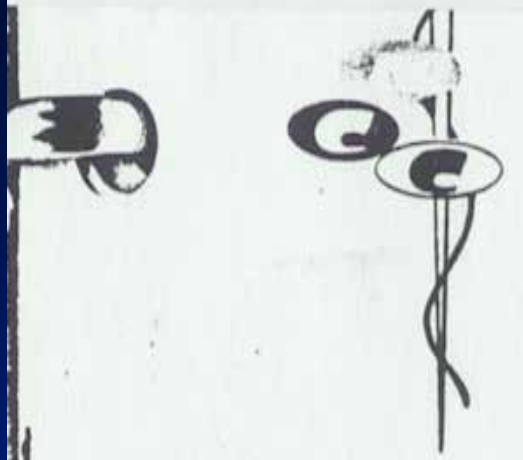
1949
After Radioiodine Tx

Case 1

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.

Life Magazine 1949



VIGNETTES in NUCLEAR MEDICINE

by MARSHALL BRUCER, M.D.

THE SEIDLIN BEGINNING

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.

Vignettes in Nuclear Medicine:
by Marshall Brucer

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 flamus 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.

Vignettes in Nuclear Medicine:
by Marshall Brucer

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:
  - ü Size of the primary tumor
  - ü Extra thyroidal extension (gross vs. micro.)
  - ü 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

Prognostic Variable	AGES (1987)	AMES (1988)	ATA (2015)	EORTC (1979)	MACIS (1993)	MSKCC (1995)	NTCTCS (1998)	OSU (1994)	QTNM (2009)	TNM (2010)
Patient factors										
Age	X	X	–	X	X	X	X	–	X	X
Sex	–	X	–	X	–	–	–	–	–	–
Tumor factors										
Size	X	X	X	–	X	X	X	X	X	X
Multicentricity	–	–	X	–	–	–	X	X	–	
Histologic grade	X	–	–	–	–	X	–	–	–	–
Histologic type	Y	X	X	X	Y	X	X	–	X	–
Extrathyroidal invasion	X	X	X	X	X	X	X	X	X	X
Nodal metastatic lesion	–	–	X	–	–	X	X	X	X	X
Distant metastatic lesion	X	X	X	X	X	X	X	X	–	X
Operative factors										
Incomplete resection	–	–	–	–	X	–	–	–	–	–

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

ATA 2015 Guidelines

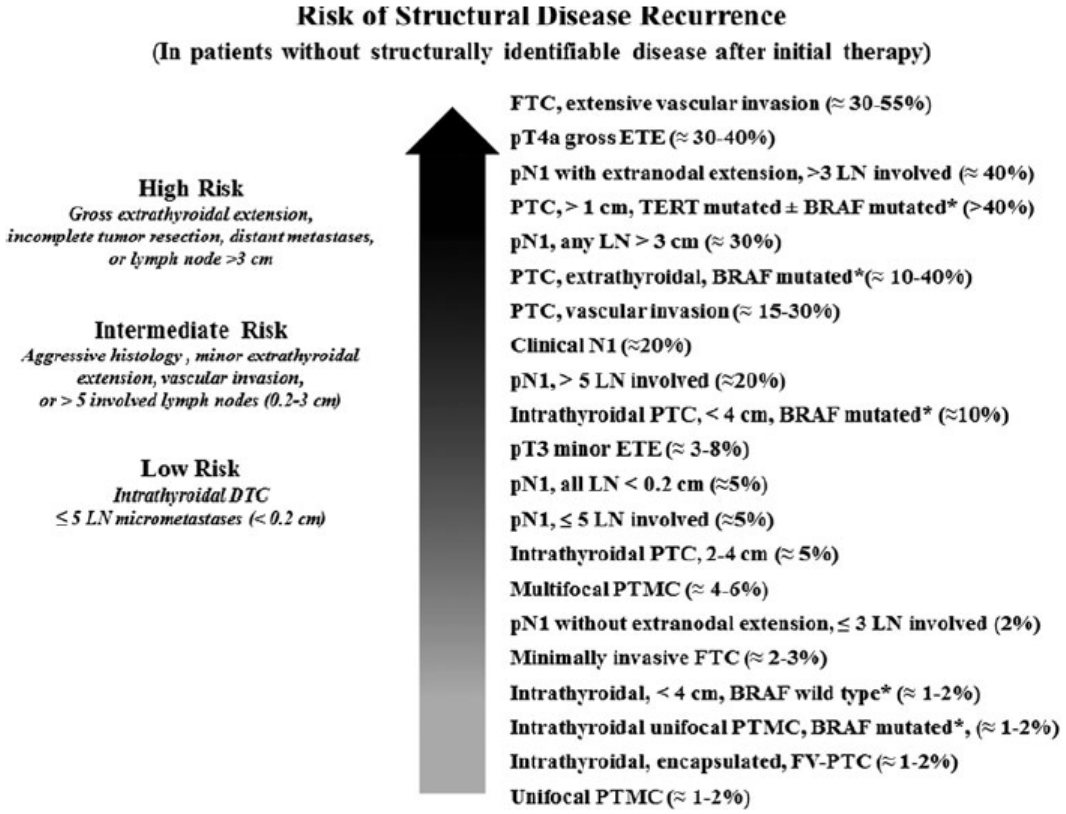


FIG. 4. Risk of structural disease recurrence in patients without structurally identifiable disease after initial therapy. The risk of structural disease recurrence associated with selected clinico-pathological features are shown as a continuum of risk with percentages (ranges, approximate values) presented to reflect our best estimates based on the published literature reviewed in the text. In the left hand column, the three-tiered risk system proposed as the Modified Initial Risk Stratification System is also presented to demonstrate how the continuum of risk estimates informed our modifications of the 2009 ATA Initial Risk System (see Recommendation 48). *While analysis of *BRAF* and/or *TERT* status is not routinely recommended for initial risk stratification, we have included these findings to assist clinicians in proper risk stratification in cases where this information is available. FTC, follicular thyroid cancer; FV, follicular variant; LN, lymph node; PTMC, papillary thyroid microcarcinoma; PTC, papillary thyroid cancer.

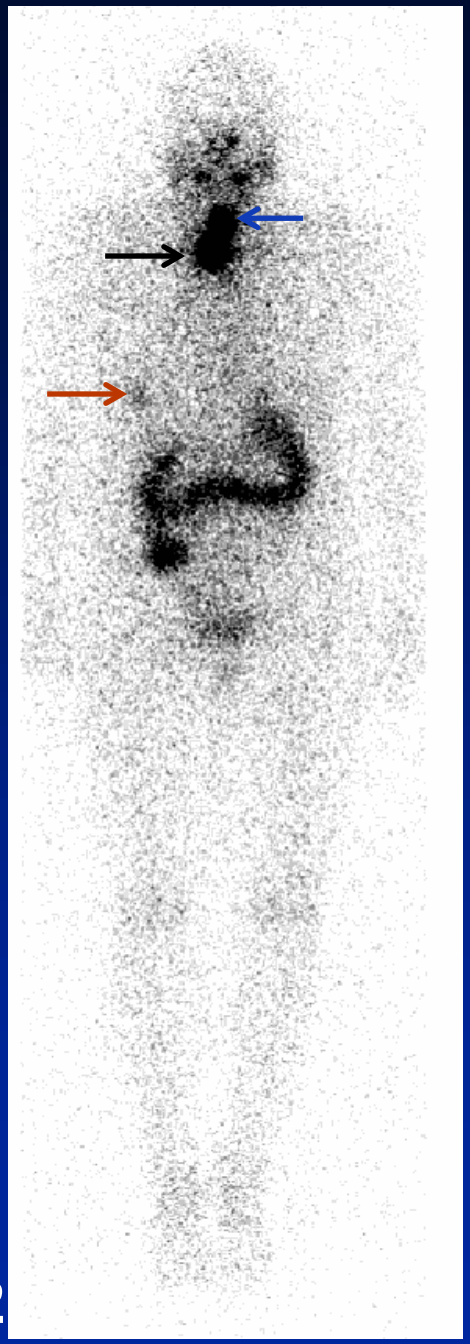
"Life is really simple, but we insist on making it complicated." Confucius

"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

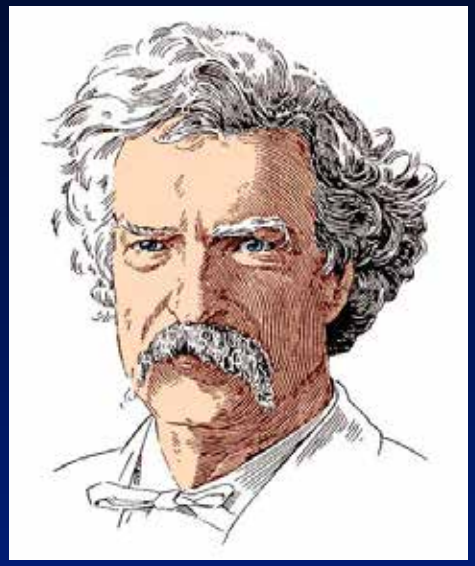
pT1b, N0, M0. AJCC Stage I

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

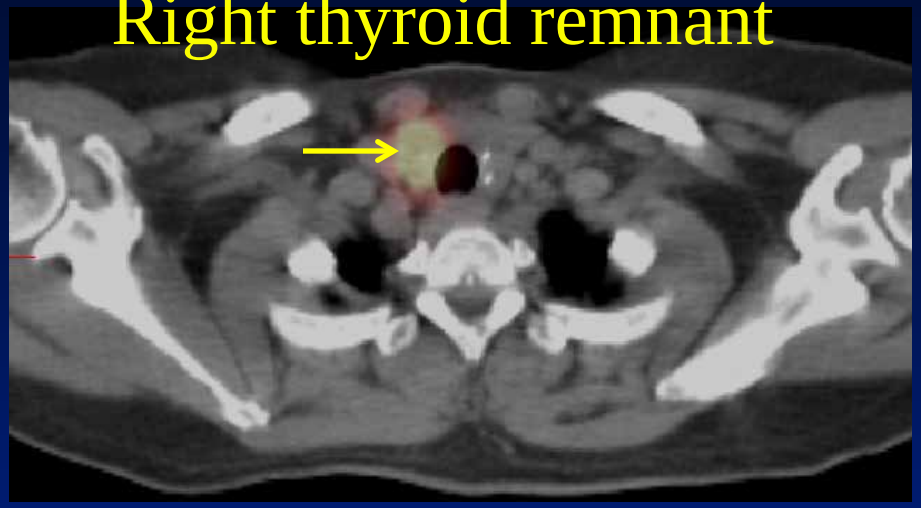


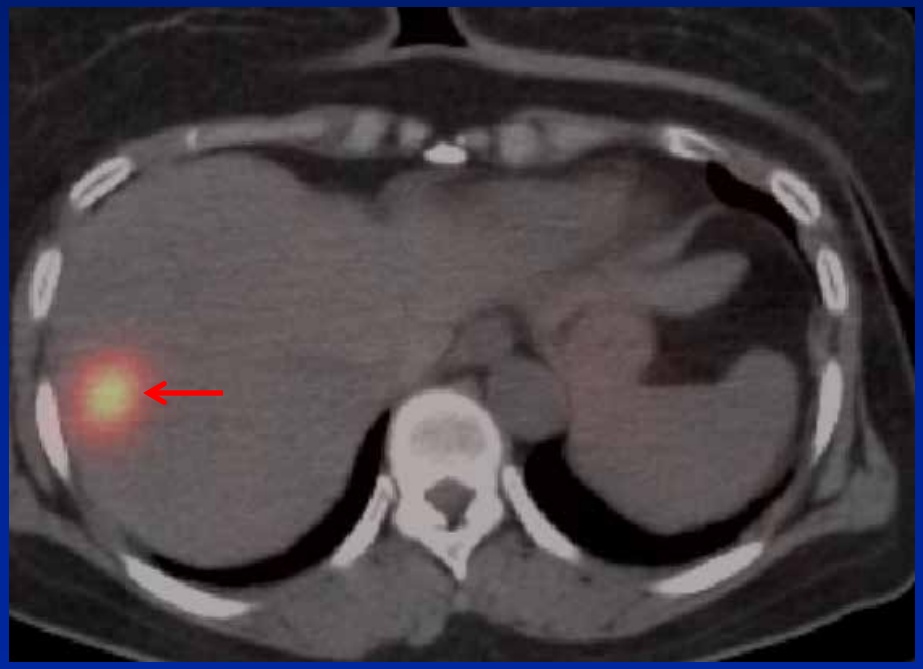
“It ain't what you don't know that **gets you into trouble** (*or **your patient into trouble***) **. It's what you know for sure that just ain't so**.”

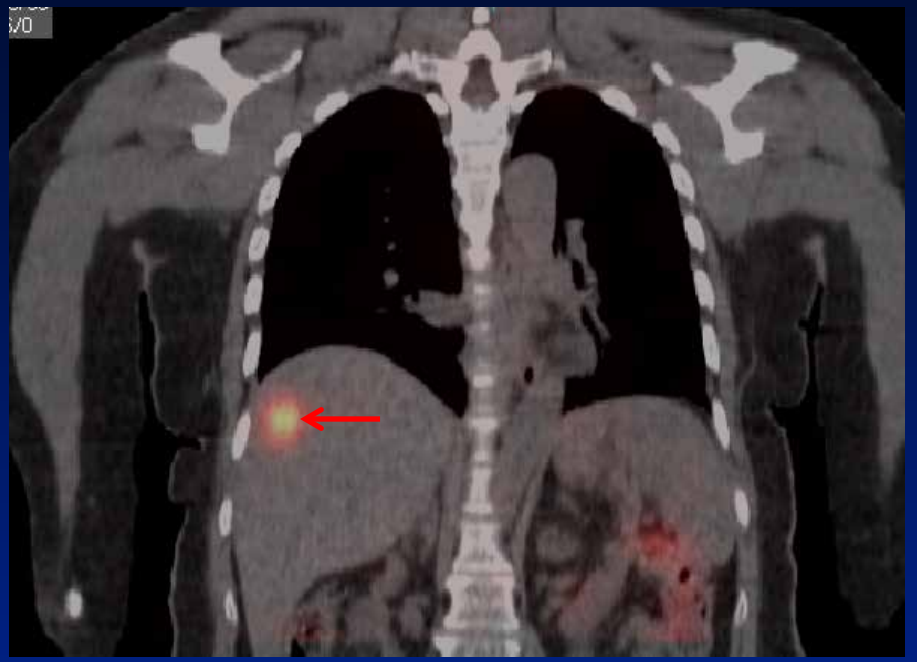
Mark Twain

DxRAIS + SPECT/CT

Right thyroid remnant







Liver metastasis

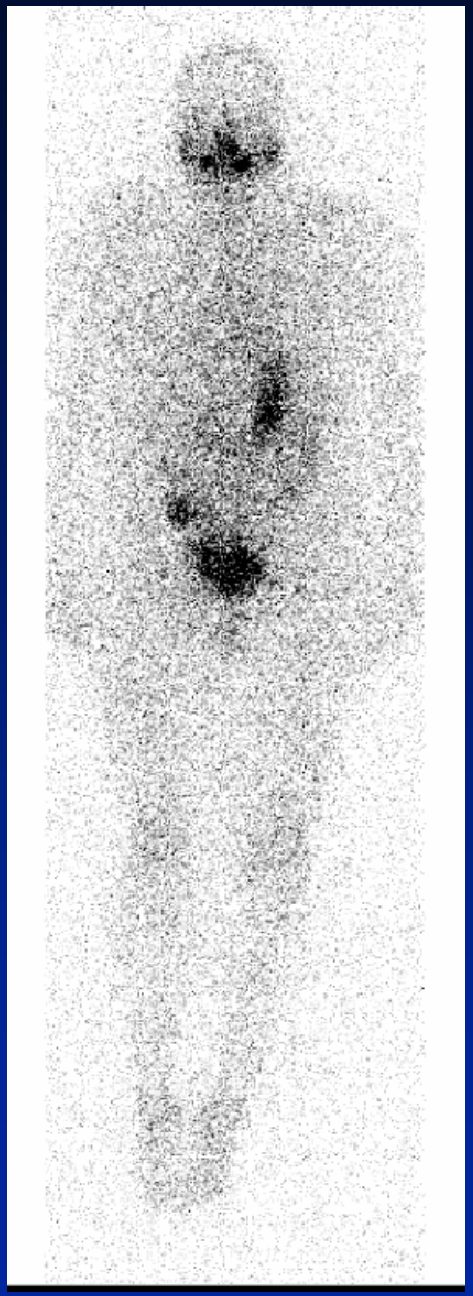
Critical Role – Post-TT Staging of DTC

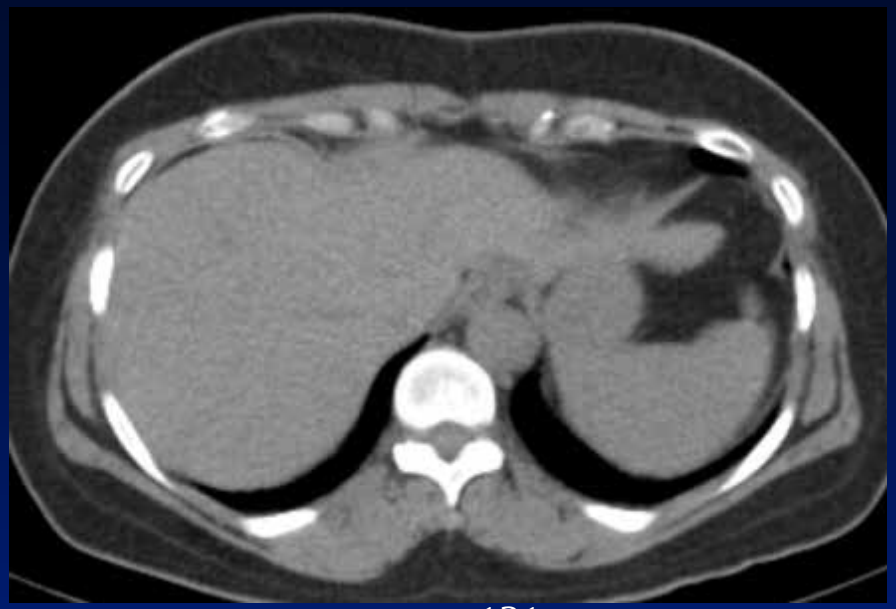
T1b, N0, M1; Stage IV C

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:

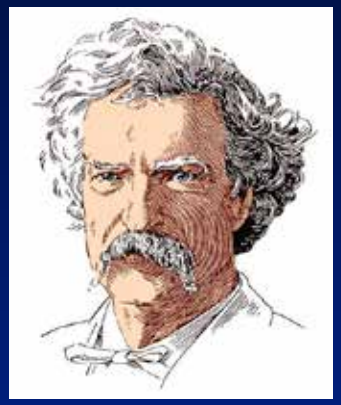
Interval resolution of liver metastasis and of thyroid remnant tissue

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

Case 2

Case Courtesy of Dr. Anca M. Avram

“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

Get it right every time

Preparing the Patients for RAIT:
ATA RECOMMENDATION 57

Administered Dose Thresholds At ≥80% Response Rate

Metastatic Sites	AD (Gy)	Ref.#
Lymph node	85	1, 2
Pulmonary	85	2
Thyroid Remnant	300	1
Bone	350-650	3

1. Maxon HR, 3rd, et al. Radioiodine-131 therapy for well-differentiated thyroid cancer--a quantitative radiation dosimetric approach: outcome and validation in 85 patients. J Nucl Med 1992;33(6):1132-6.
2. Jentzen W, et al. Assessment of lesion response in the initial radioiodine treatment of differentiated thyroid cancer using 124I PET imaging. J Nucl Med 2014;55(11):1759-65.
3. Jentzen W, et al. 124I PET Assessment of Response of Bone Metastases to Initial Radioiodine Treatment of Differentiated Thyroid Cancer. J Nucl Med 2016;57(10):1499-504.

Abbreviations: AD = Administered Dose or lesion-absorbed radiation dose

Haugen BR, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26(1):1-133.

■ **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)

Smith GCS, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. BMJ 2003;327:1459-1461.

RAIT: 2009/2015 ATA Terminology

Cooper, DS et al. 2009 ATA guidelines. Thyroid (DOI: 10.1089/thy.2009.0110)
Van Nostrand, D 2009 The benefits and risks … Thyroid (DOI: 10.1089/thy.2009.1611)
Haugen, BR et al. 2015 ATA guidelines. Thyroid (DOI: 10.1089/thy.2015.0020)

- **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?)
  - ü no clinical, biochemical, or structural evidence of disease
- Biochemical incomplete (partial) response
  - ü abnormal Tg or rising anti-Tg antibody levels in the absence of localizable disease
- Structural incomplete (partial) response
  - ü persistent or newly identified loco-regional or distant metastases
- Indeterminate response
  - ü Other than any of the above

Where is DISEASE PROGRESSION?

TABLE 13. CLINICAL IMPLICATIONS OF RESPONSE TO THERAPY RECLASSIFICATION IN PATIENTS WITH DIFFERENTIATED THYROID CANCER TREATED WITH TOTAL THYROIDECTOMY AND RADIOIODINE REMNANT ABLATION

Category	*Definitions*[a]	*Clinical outcomes*	*Management implications*
Excellent response	Negative imaging ***and either*** Suppressed Tg <0.2 ng/mL[b] ***or*** TSH-stimulated Tg <1 ng/mL[b]	1%–4% recurrence[c] <1% disease specific death[c]	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
Biochemical incomplete response	Negative imaging ***and*** Suppressed Tg ≥1 ng/mL[b] ***or*** Stimulated Tg ≥10 ng/mL[b] ***or*** Rising anti-Tg antibody levels	At least 30% spontaneously evolve to NED[d] 20% achieve NED after additional therapy[a] 20% develop structural disease[a] <1% disease specific death[a]	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.
Structural incomplete response	Structural or functional evidence of disease With any Tg level With or without anti-Tg antibodies	50%–85% continue to have persistent disease despite additional therapy[e] Disease specific death rates as high as 11% with loco-regional metastases and 50% with structural distant metastases[a]	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, ^{18}FDG avidity, and specific pathology of the structural lesions.
Indeterminate response	Nonspecific findings on imaging studies Faint uptake in thyroid bed on RAI scanning Nonstimulated Tg detectable, but <1 ng/mL Stimulated Tg detectable, but <10 ng/mL ***or*** Anti-Tg antibodies stable or declining in the absence of structural or functional disease	15%–20% will have structural disease identified during follow-up[a] In the remainder, the nonspecific changes are either stable, or resolve[a] <1% disease specific death[a]	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.

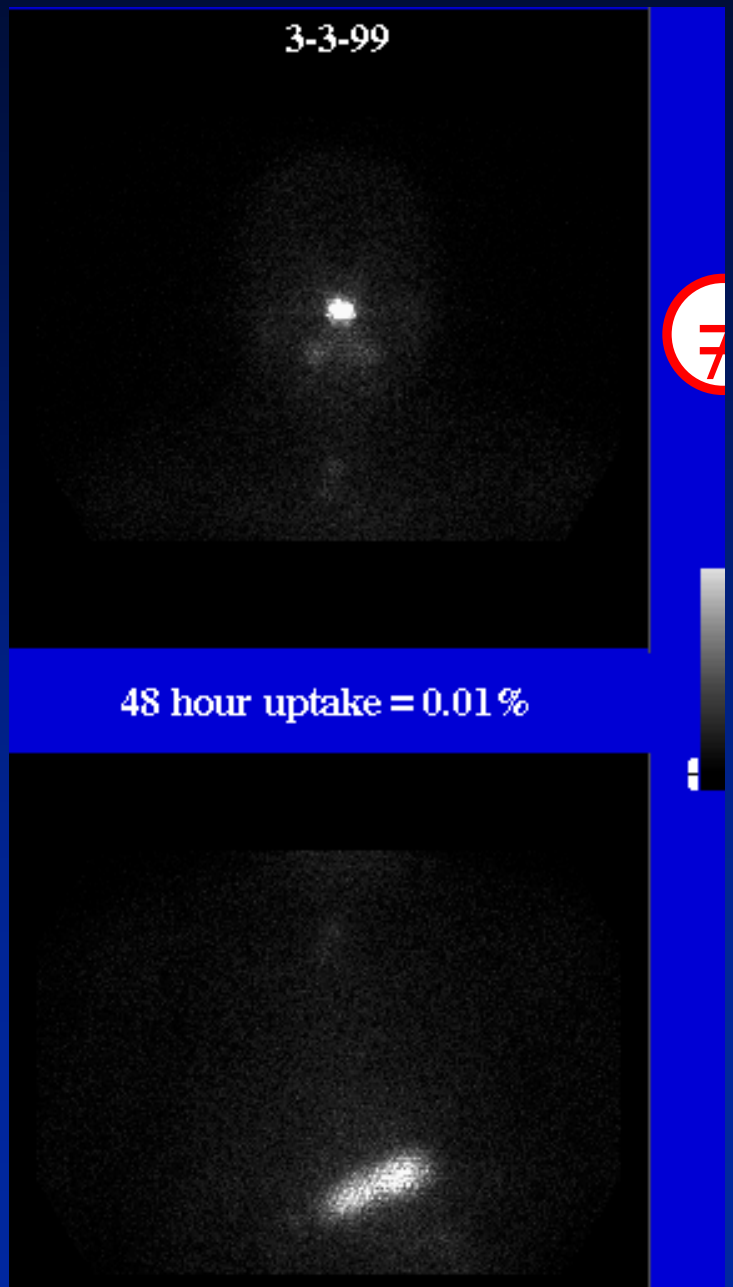
NED denotes a patient as having no evidence of disease at final follow-up.
[a]References (538,539).
[b]In the absence of anti-Tg antibodies.
[c]References (538,539,542,586–593,595–601,1078).
[d]References (598,599,617–621).
[e]References (328,607,626,627,898).

rhTSH versus THW

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®



Case 3

Freudenberg LS et al. Lesion dose in differentiated thyroid carcinoma metastases after rhTSH or thyroid hormone withdrawal: ^{124}I PET/CT dosimetric comparisons.

Eur J Nucl Med Mol Imaging (2010) 37:2267–2276

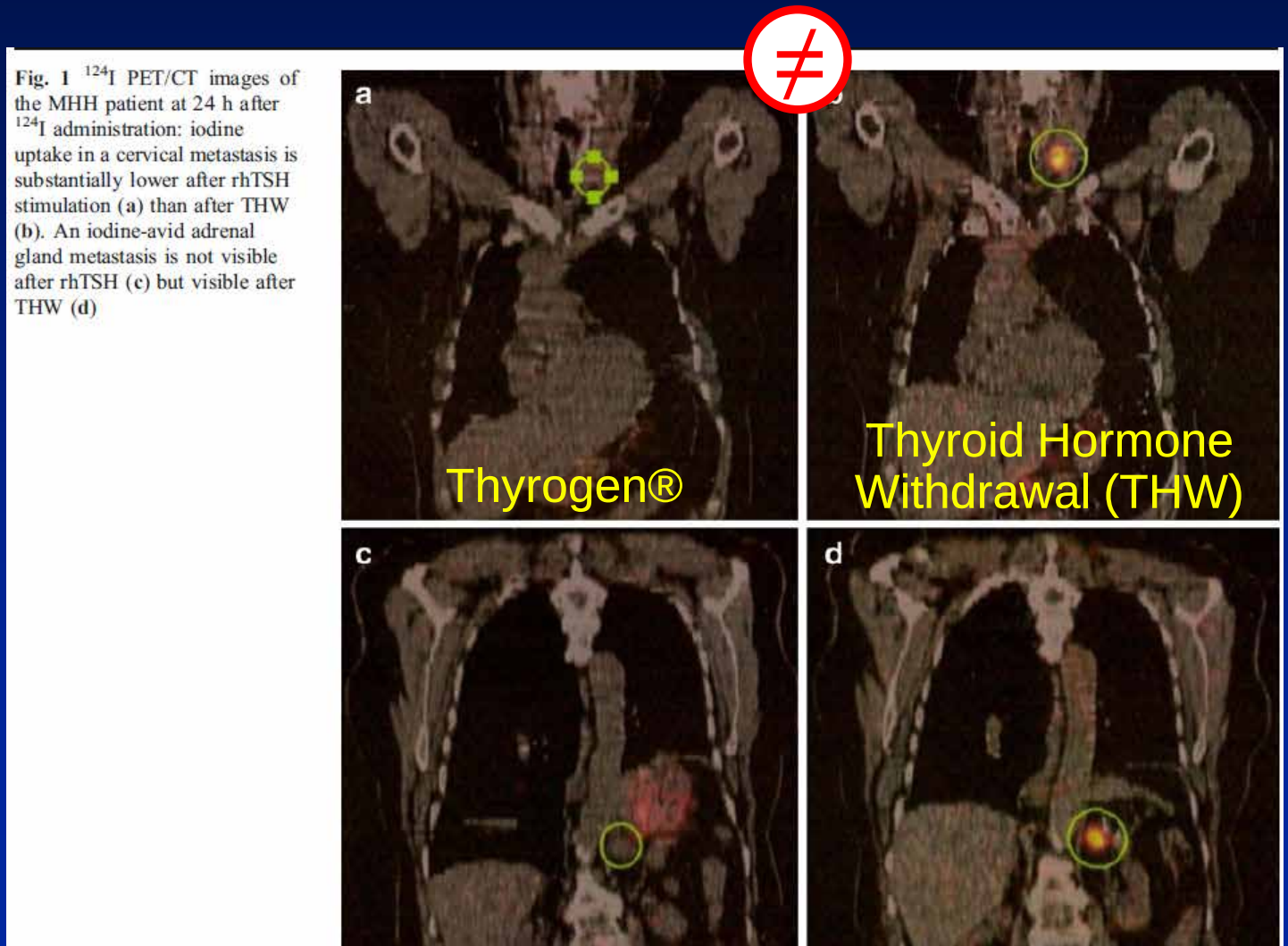


Fig. 1 ^{124}I PET/CT images of the MHH patient at 24 h after ^{124}I administration: iodine uptake in a cervical metastasis is substantially lower after rhTSH stimulation (a) than after THW (b). An iodine-avid adrenal gland metastasis is not visible after rhTSH (c) but visible after THW (d)

Case 4

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]

1. Zanotti-Fregonara P et al. On the effectiveness of recombinant human TSH as a stimulating agent for 131-I … Eur J Nucl Med Mol Imaging (2010) DOI: 10.1007/s00259-010-1608-9

2. Freudenberg LS et al. …Dosimetric Comparison of rhTSH versus Thyroid Hormone Withholding… Exp Clin Endocrinol Diabetes 2010 DOI: 10.1055/s-0029-1225350

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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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.

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

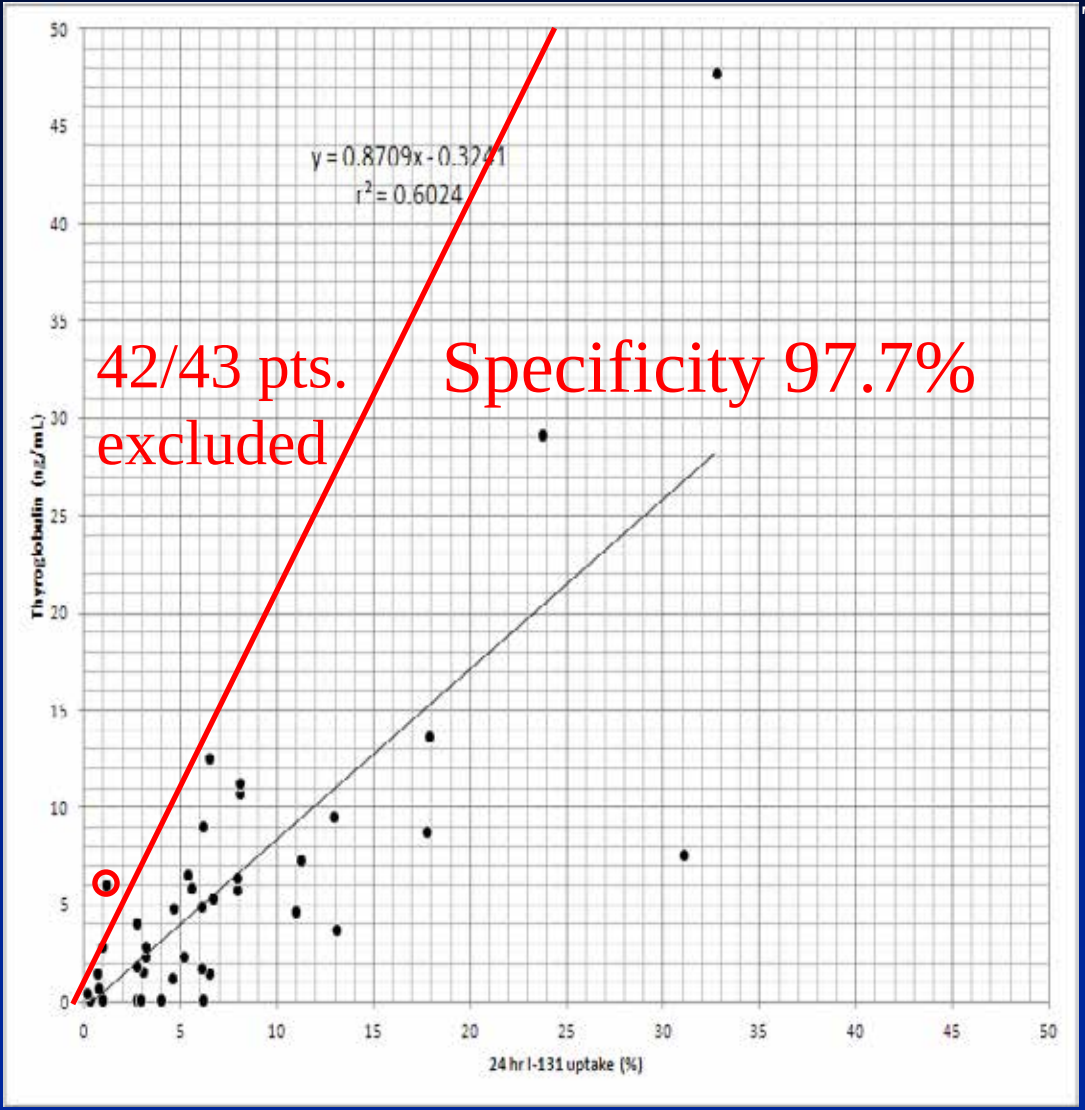
- 43 patients (30 females) were included. The patients' data [mean ± standard deviation (range)] included:
  - ü age of 50.0±15.0 (21-88)
  - ü 24 hour iodine uptake (24HrIU) of 7.12±7.51 (0.1-32.7)
  - ü Tg of 5.87±8.43 (0.2-47.8)
  - ü TSH ranged from 6.58 to >100 (<35 in 6 pts, ≥35 to 100 in 19 pts,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

First Post-Thyroidectomy Evaluation

[(24Hr.%IU x 2) +1] ≤ Tg

Tulchinsky M. 2014

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



24 hour I-131 uptake probe results (%)

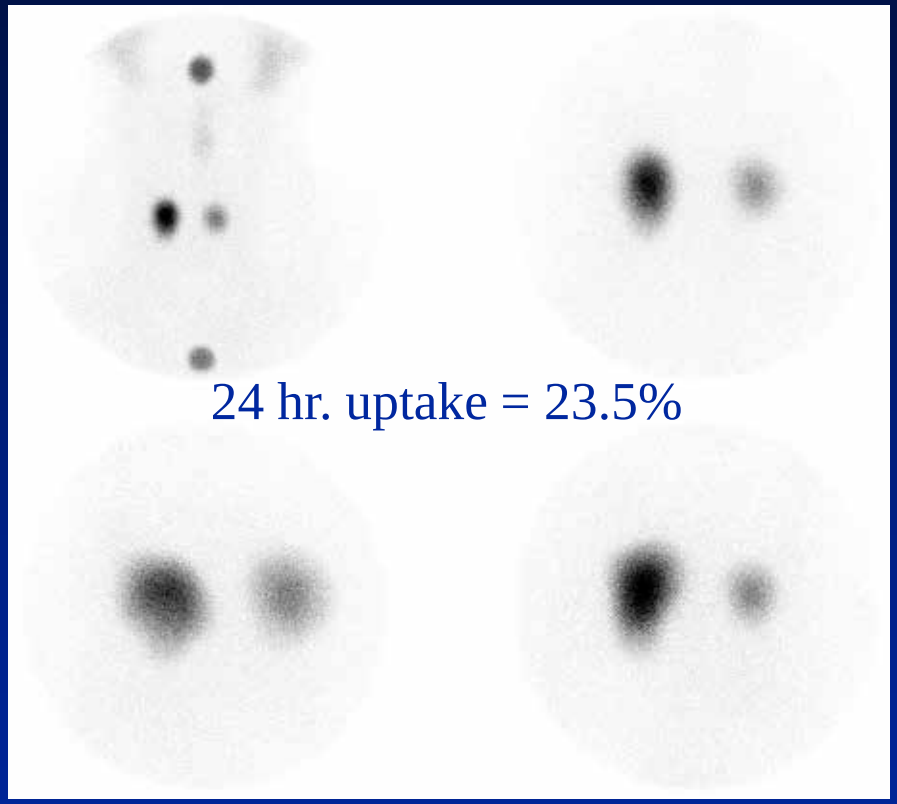
PSU Protocol

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

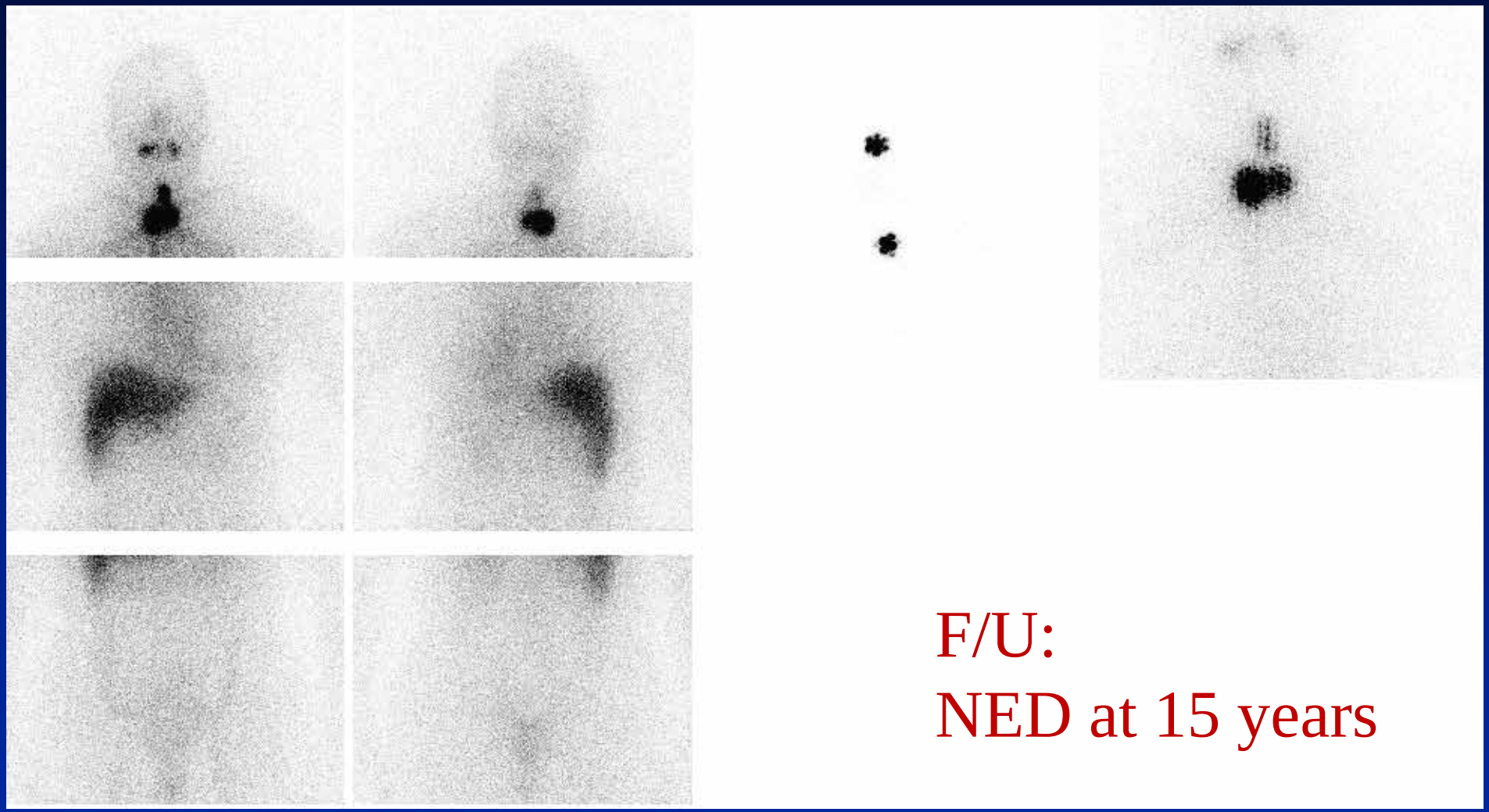
9/13/2001 labs: TSH = 34.2; Tg = 5.6; Tg Ab <0.3



(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

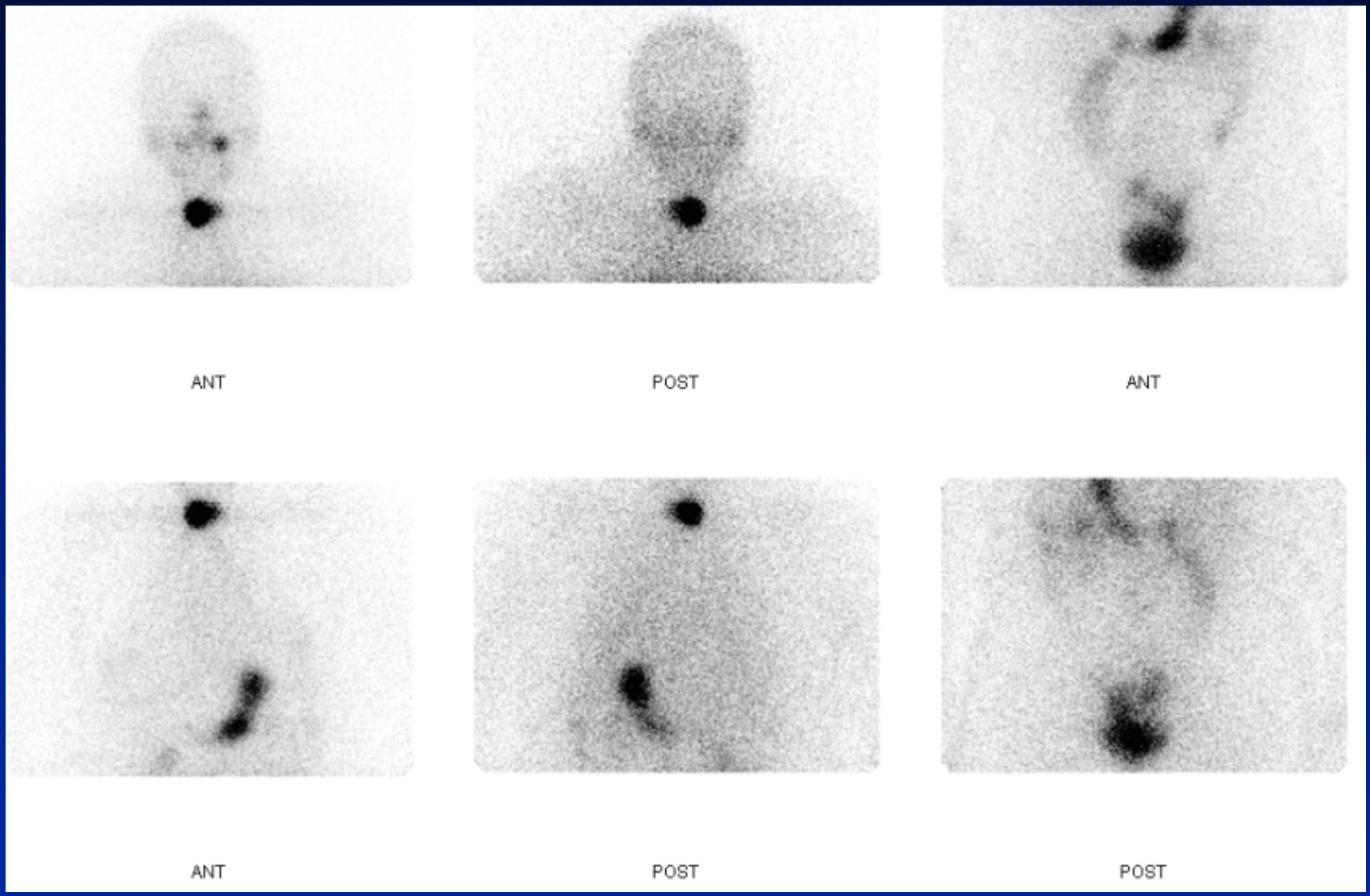
38 y/o female with coughing, hoarseness and feeling of “pressure on esophagus”

- 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

Pre-Treatment WBS 10/24/16

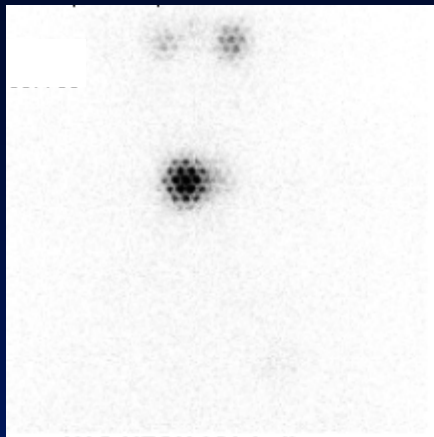


Case 6

38 y/o female with “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
- 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



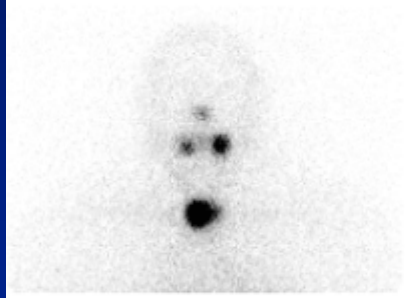
MAG NECK 131-Iodine

MAG NECK 57-Cobalt

=

MAG NECK

All Frames



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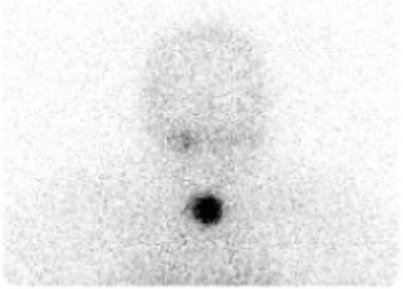

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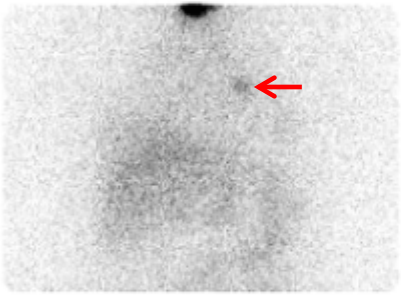

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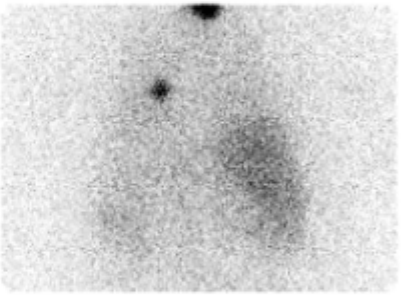
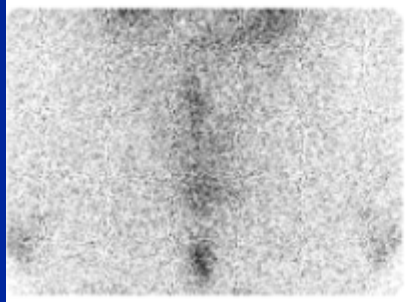
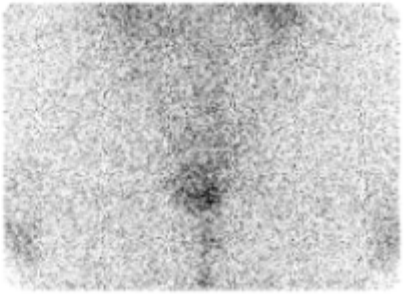


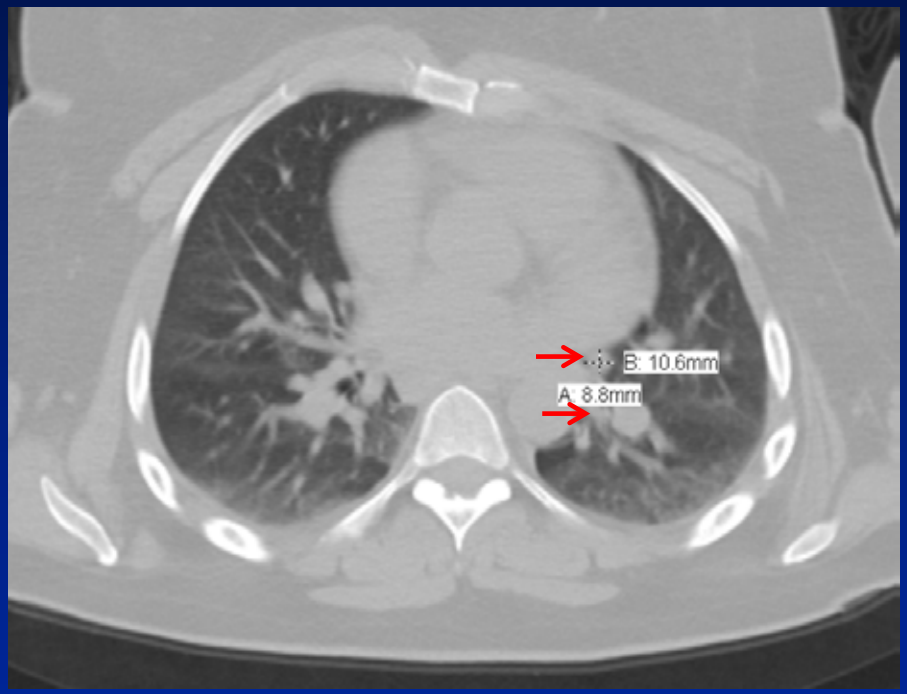
POST

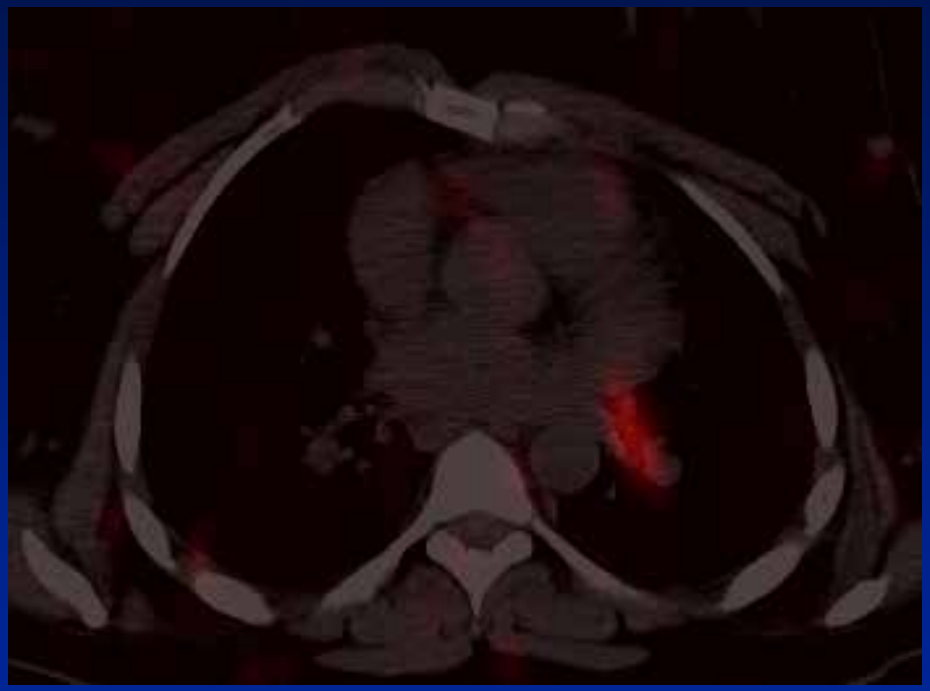




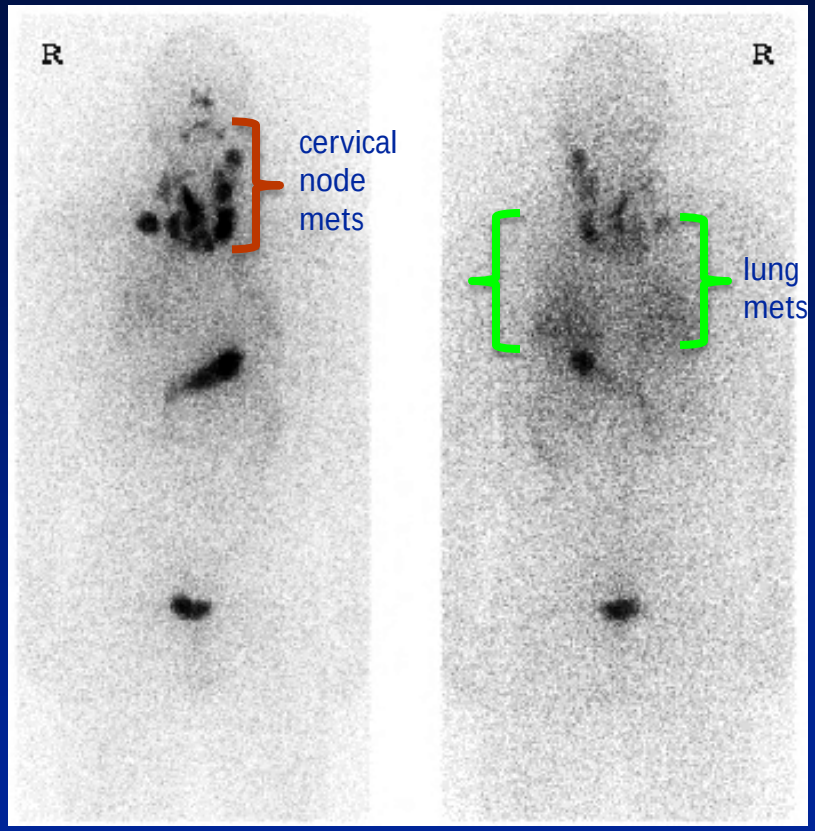
Case 6

38 y/o female with “Stage I”
POST-TREATMENT SPECT-CT
Lung mets, Stage II





Empiric Activities Method: Implies Diagnostic RAI Scan



- Beierwaltes WH. The treatment of thyroid carcinoma with radioactive iodine. Semin Nucl Med. 1978 Jan;8(1):79-94.
  - 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

ü Simple.
ü Convenient.
ü Long history of use.

I-131 Administered Activities (AA), PSU

- Empirical
  - ü No residual/metastatic DTC
    - ø 30 – 100 mCi for Ablation
  - ü Regional lymph node (LN) or ↑Tg>remnant
    - ø 100 – 150 mCi for Adjuvant (Salvage) Therapy
  - ü Distant metastatic disease (LN, lung, bone, etc.)
    - ø 200 – 250 mCi for Therapy
- Dosimetry-Guided Activity considered for:
  - ü Suspected metastatic disease, Tg or Imaging
  - ü Renal insufficiency or failure
  - ü Age ≥ 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

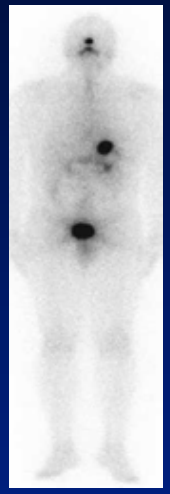
- Tuttle RM et al. J Nucl Med. 2006;47:1587-1591.
  - 328 patients who had dosimetry data
  - Retrospectively calculated absorbed dose to the red marrow for empiric activities of 140, 200 and 250 mCi
  - Empiric activities of 200 and 250 mCi exceeded 2Gy limit, especially in the elderly >=70 y.o.
    - 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

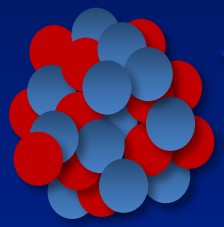
- Indications
  - ü Metastasis, lung or LN beyond regional
  - ü Regional lymph node involvement
  - ü Follicular CA or high-risk PTC Variants
  - ü Renal dysfunction
  - ü ≥70 y/o
- Variables prompting consideration
  - ü Tumor at the inked margins
  - ü Gross extrathyroidal invasion
  - ü PTC, size greater than 3.5 cm

I-131 Absorbed Dose to Re Marrow

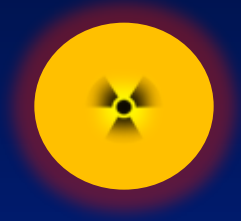
Blood is surrogate for red m



G :
-
- Gamma probe or camera



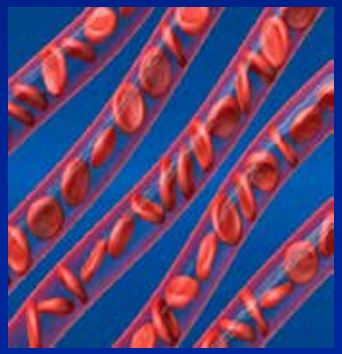
131
53 I
Radioactive I-131



Gamma Radiation

Beta Radiation

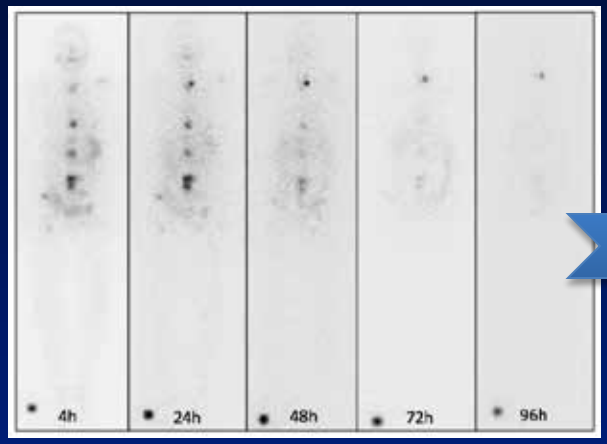
BM Dose= β + γ



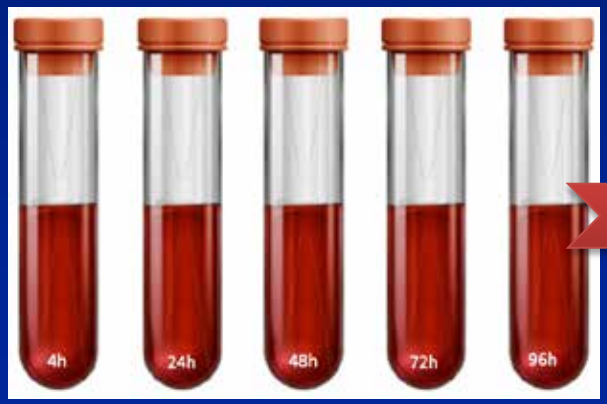
Beta radiation :
-Blood samples

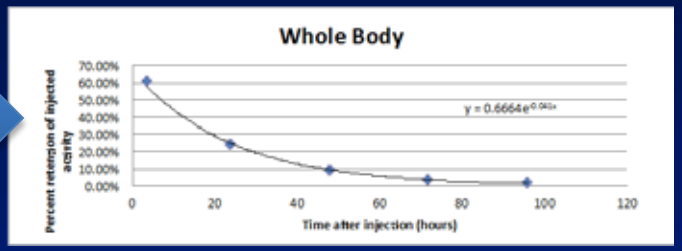
Treatment Activity Dose Calculation

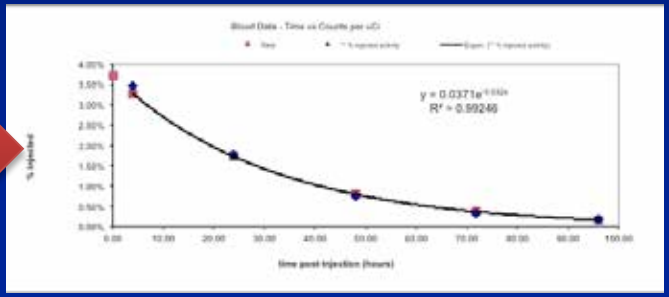
1-10 mCi I-131
Day 1



Days 1 - 5







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

Whole Body Dosimetry

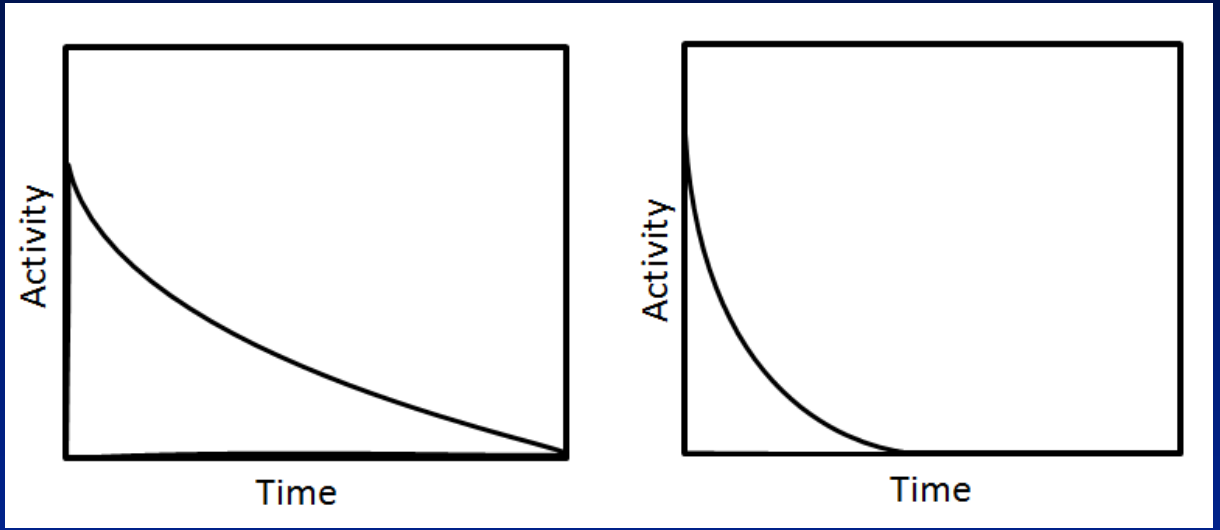
- Administer the maximum activity of I-131 without causing life-threatening critical organ damage => red bone marrow or lung fibrosis
  - ü Originated from the work by Benua et al. in 1962; Benua and Leeper 1986
  - ü Absorbed dose limit to **blood/red marrow -> 2 Gy**
  - ü **Whole body retention @48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

Rationale:

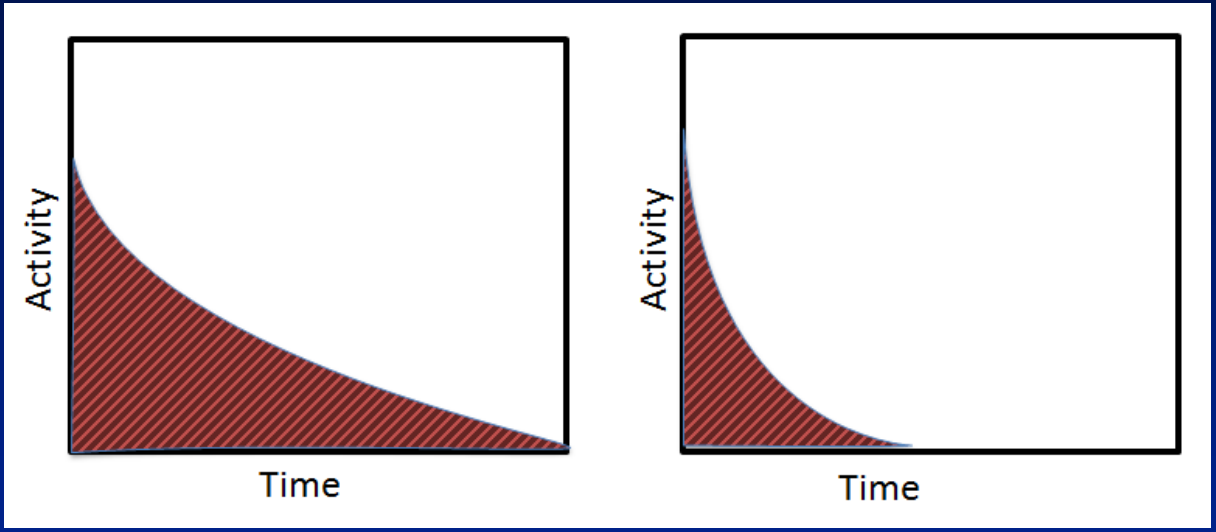
- Higher I-131 treatment activities impart higher therapeutic effect.
- Lower non-tumoricidal doses to the tumor may lower the effectiveness of subsequent doses.

"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

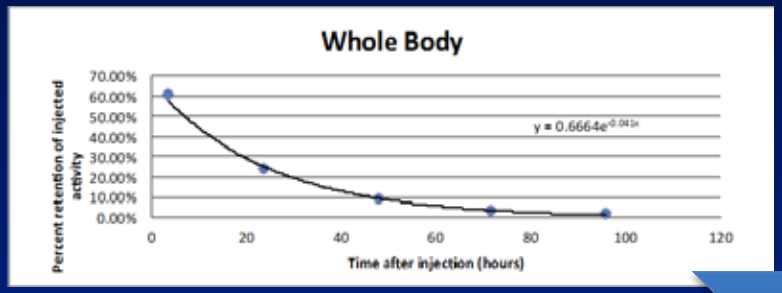


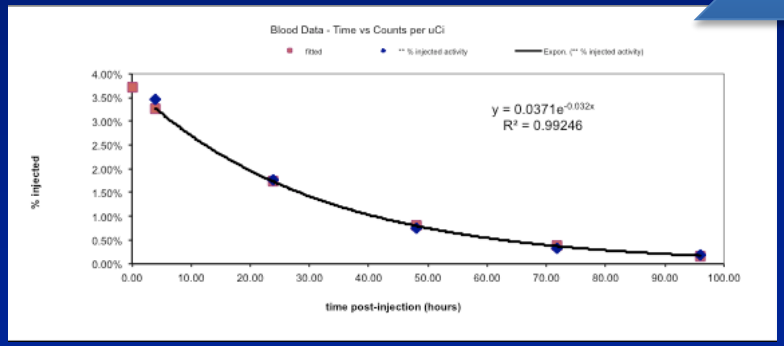
Time Activity Curves



slower clearance è ↑ area under the curve è ↑ absorbed dose

Treatment Activity Dose Calculation





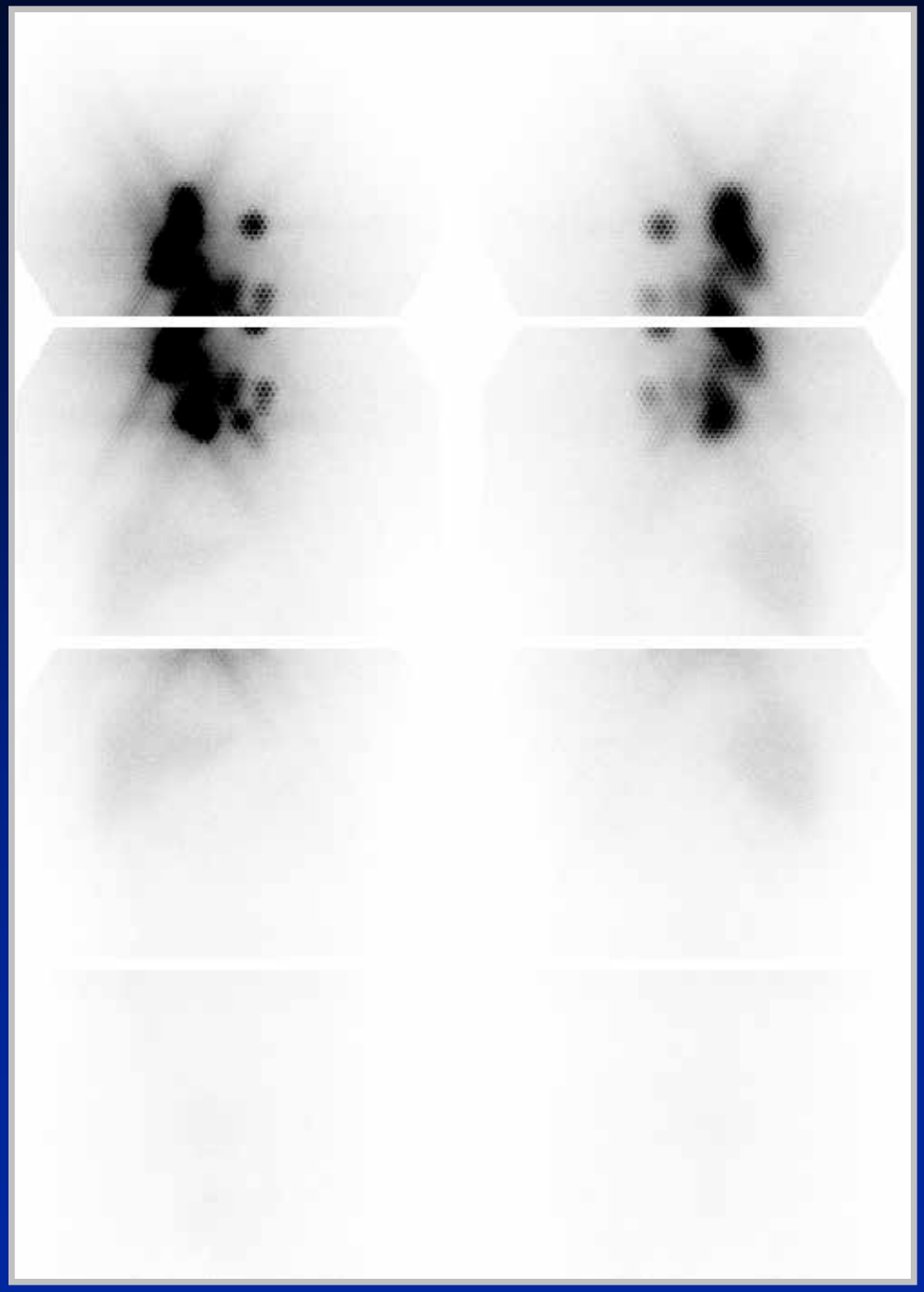
absorbed dose calculations

[MIRD method classical dosimetry]

Absorbed Dose (cGy)
Activity (MBq)

2 Gy blood absorbed dose limit

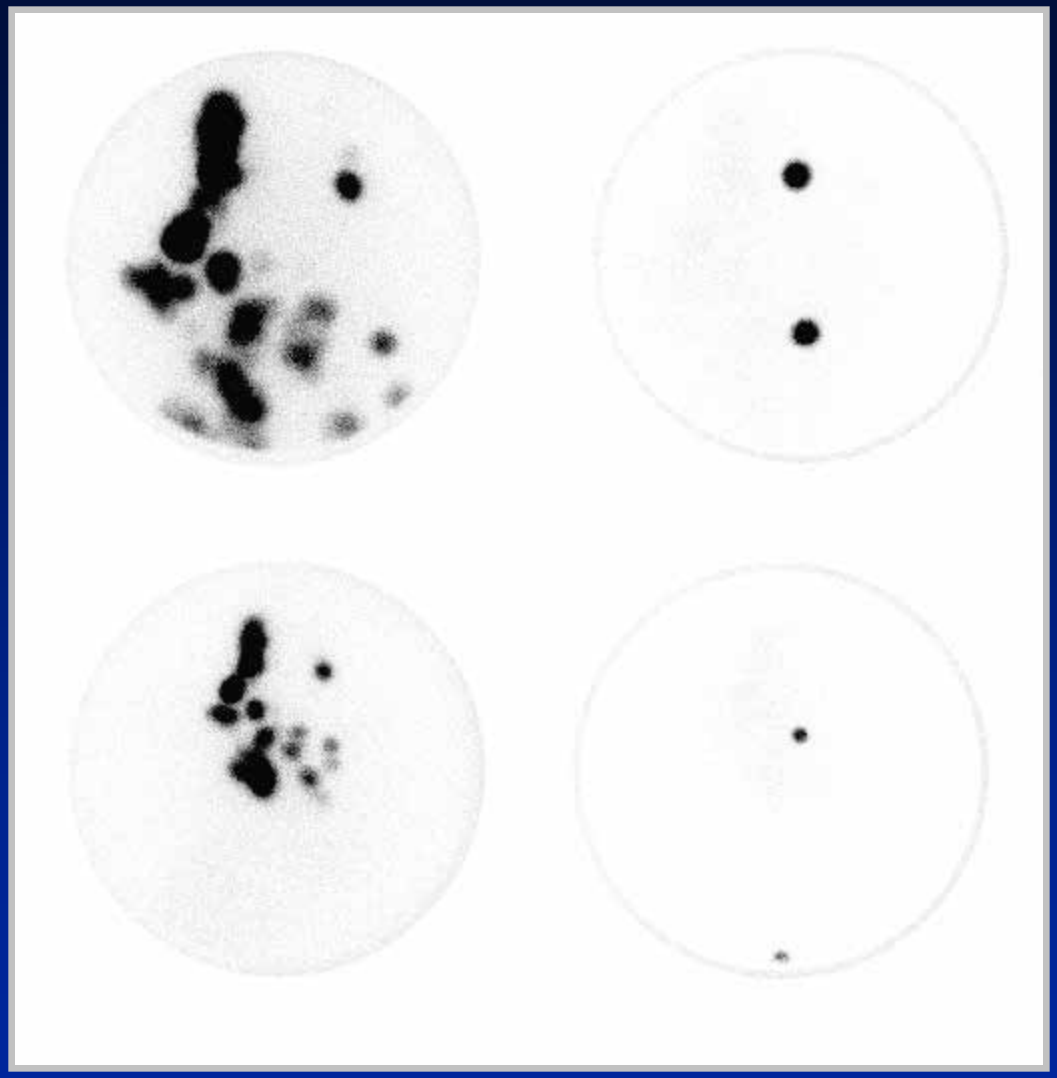
$$\text{Treatment Activity Dose (Mbq)} = \frac{200\ \text{cGy}}{\beta(\text{cGy/MBq}) + \gamma(\text{cGy/MBq})}$$



40.4% uptake

1st Presentation
Post-TT

Case 7

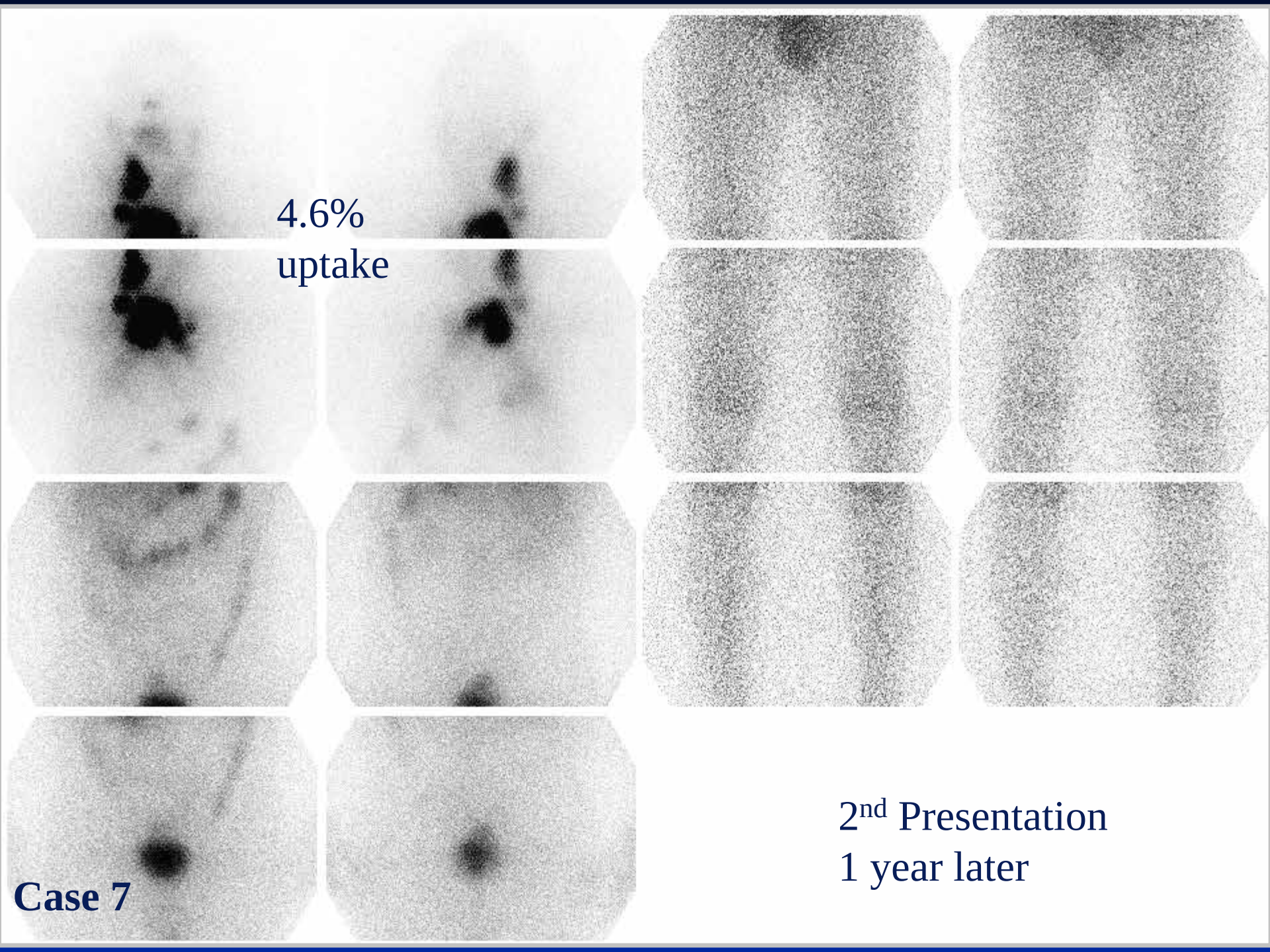


Case 7

1st Presentation
Post-TT

TREATMENT #1

Treated with a MTAT = 150 mCi dose.

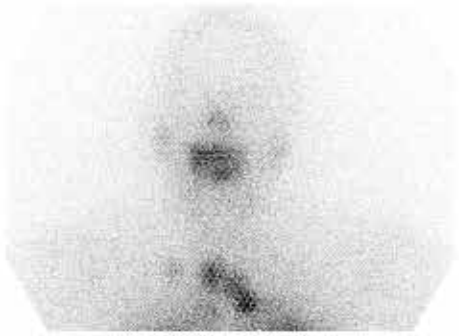


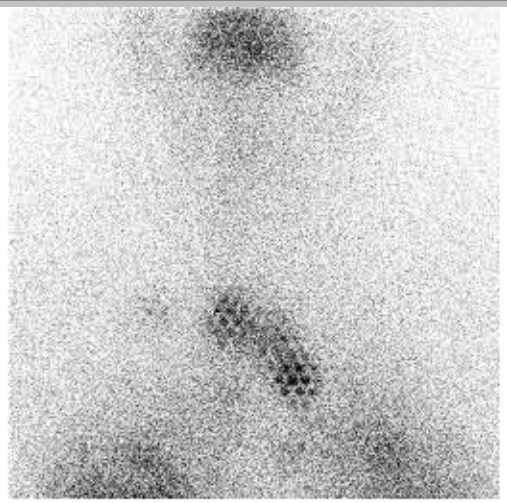
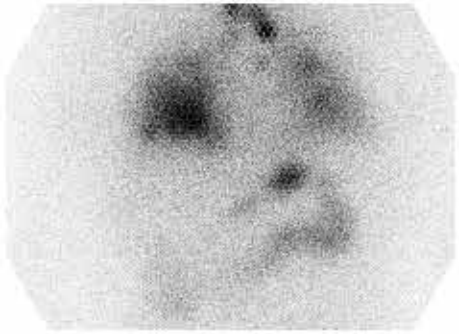
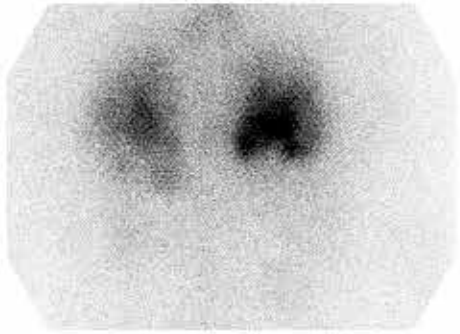
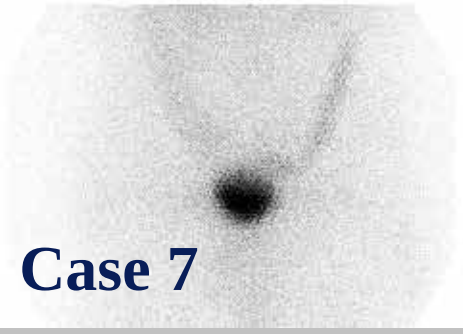
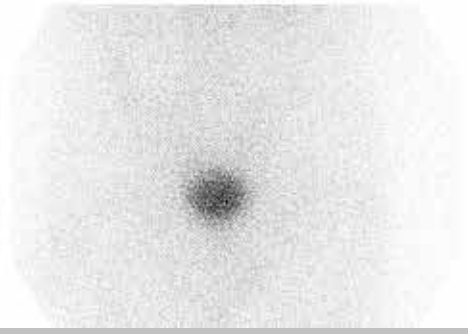
2nd Presentation
1 year later

Case 7

TREATMENT #2

Treated with MTAT = 250 mCi dose.

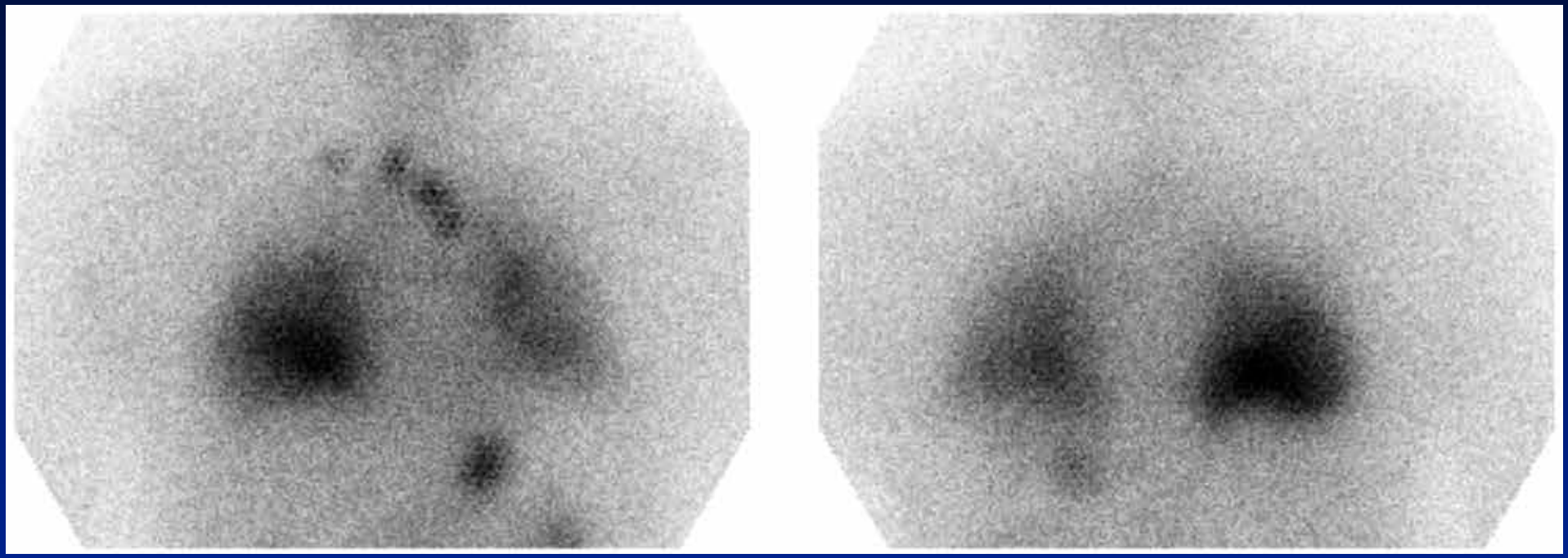


0.15%
uptake

3rd Presentation
2 year later

Case 7



Anterior View

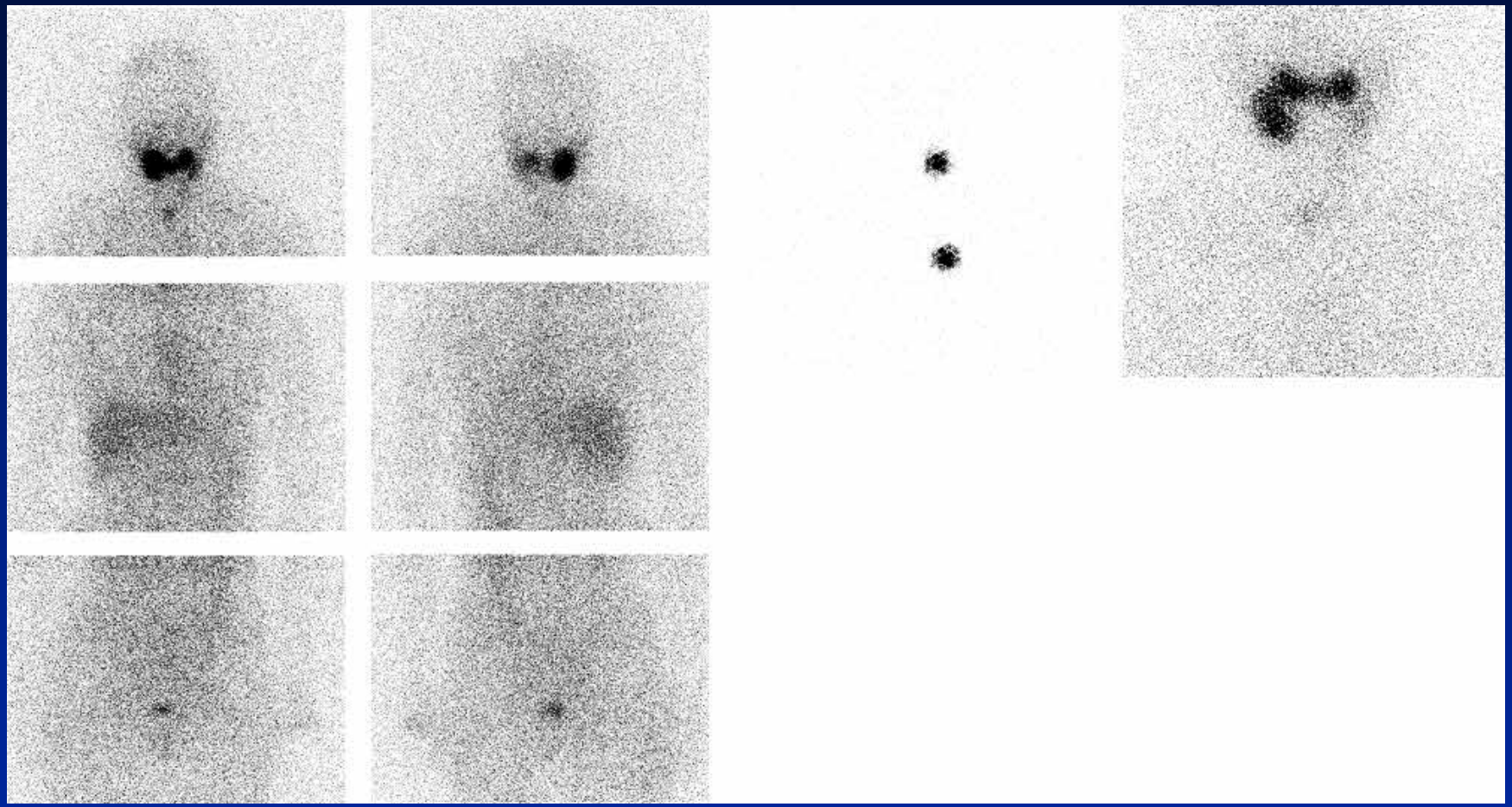
2.44%
Uptake

Posterior View

0.369 rads/mCi

Case 7

TREATMENT #3



Case 7

“Simplified” Dosimetry Methods

- → No blood samples
- → Single time point

Calculate MTA from whole body retention at a single time point

- Sisson JC et al. J Nucl Med. 2003;44(6):898-903.
  - 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
- Van Nostrand D et al. Thyroid. 2009;19(10):1093-1098.
  - WBR at 48 hours with 2 Gy blood dose limit
  - Regression analysis of full dosimetry data from 142 patients
  - Atkins F et al. Thyroid. 2015;25(12):1347-1350.

- Thomas SR et al. Nucl Med Biol 1993; 20:157-62.
  - 14-17% of I-131 whole body residence time => blood
  - Approximate blood absorbed dose from whole body retention
- Hanscheid H et al. Endocr Relat Cancer. 2009;16(4):1283-1289.
  - 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

- Jentzen W et al. J Nucl Med. 2015;56:832-838.
  - 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

Van Nostrand D et al. Thyroid. 2002; 12(2): 121-134.
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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.

The optimal management of radioactive iodine (RAI) treatment in patients with metastatic thyroid cancer (TC) is still a matter of debate. **Methods:** We retrospectively analyzed 352 patients with RAI-avid metastatic well-differentiated TC treated with ^{131}I by an empiric fixed activity of 3.7 GBq at Gustave Roussy (GR, n = 231) or by personalized activity (2.7–18.6 GBq) based on whole-body/-blood clearance (WB/BC) dosimetry at Memorial Sloan Kettering Cancer Center (MSKCC, n = 121). The primary endpoint was to com-

Radioactive iodine (RAI; ^{131}I) 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 ^{131}I 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
  - ü 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
  - ü >99% of Dosimetry is done with THW
- COI (Genzyme) not fully declared
- Not a valid comparison study – result are not valid

Reply: Comparison of Empiric Versus Dosimetry-Guided Radioiodine Therapy: The Devil Is in the Details

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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 redifferentiation agents to improve the efficacy of RAI therapy).

The authors declare that there is no conflict of interest regarding the publication of this paper.

DISCLOSURE

Martin Schumberger has received grant/research support from Genzyme, and R. Michael Tuttle is a consultant for Genzyme. No other potential conflict of interest relevant to this article was reported.

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Learning Objectives: RAI in Differentiated Thyroid Cancer (DTC)

- History
- Treatment options terminology for DTC
  - ü Based on target tissue definition
    - ø Ablation, Adjuvant, Metastatic Therapy
  - ü Based on activity selection approach
    - ø 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 ≥ 1 ng/mL OR stimulated TG ≥ 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 ≥ 1 ng/mL OR stimulated TG ≥ 10 ng/mL, OR rising anti-TG antibodies
D. Negative imaging & suppressed TG ≥ 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!