# Radioiodine Therapy of Thyroid Cancer – the Prototypical Precision Medicine Approach to Cancer Treatment

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# Current cancer therapies

Before the cancer has spread/metastasized

- Surgery
  - Remove the tumor
- Radiotherapy
  - Deliver radiation beams focused on the tumor

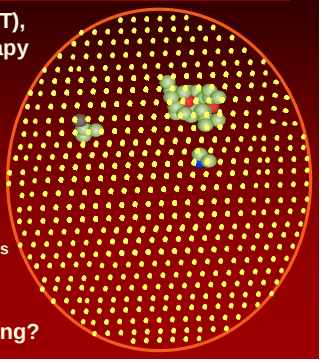
# Current cancer therapies

After the cancer has spread/metastasized

- Chemotherapy
  - Kill rapidly proliferating cells
- Radiopharmaceutical Therapy (hormonal Tx)
  - Kill targeted cells by targeted radionuclide delivery
  - Inhibit signaling pathways that cancer cells are addicted to (*i.e.*, rely on to maintain cancer phenotype)
- Immunotherapy
  - Overcome immune tolerance to cancer

# Radiopharmaceutical Therapy

**Molecular Radiotherapy (MRT), Targeted Radionuclide Therapy Radioimmunotherapy (RIT)**



**Agent distributes throughout body**

**Reacts with/binds to target cells**

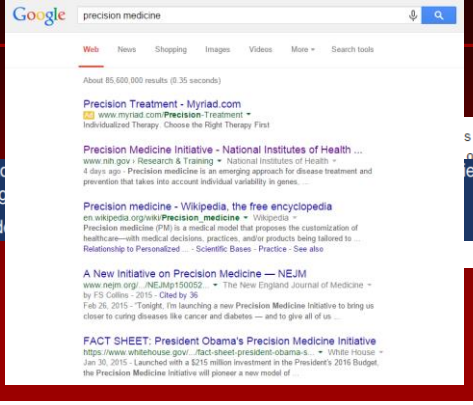
**Cleared from non-target cells**

**Prolonged exposure to target cells gives larger radiation dose to target cells than to normal cells**

**Where (else) does the drug concentrate, and for how long?**

# Radiopharmaceutical therapy

- **RPT provides targeted delivery of radiation**
- **Not susceptible to resistance mechanism seen in chemotherapy**
- **Kills target cells vs inhibiting growth/survival pathways; precludes adaptation**
- **Can measure delivery of the therapeutic agent to tumor targets and to normal organs**
- **Guide escalation protocols and plan treatment**



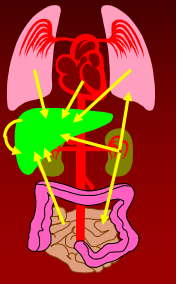
## What does "dose" mean?

- In chemotherapy/medicine, in general "dose" refers to the quantity of an agent that is administered to the patient.
- In RPT, the relevant quantity is "absorbed dose" – the amount of energy absorbed per unit mass.
- This is not equal to the amount of radioactivity administered.
- Absorbed dose is most closely related to biologic effect.

## Internal Dosimetry

Energy absorbed per unit mass:

$$\frac{\text{number of dis.} \times \text{energy released per dis.} \times \text{fraction that is absorbed}}{\text{mass of target tissue}}$$



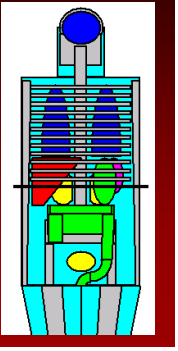
## MIRD S-Value Dosimetry

Energy absorbed per unit mass:

$$\frac{\tilde{A}(r_s) \times \Delta \times \phi(r_t \leftarrow r_s)}{M_t}$$

S, absorbed dose per unit time-integrated activity

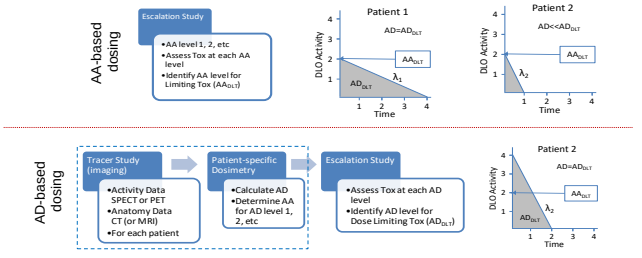
$D_t = \tilde{A}_{s1} \cdot S(t \leftarrow s1) + \tilde{A}_{s2} \cdot S(t \leftarrow s2) + \ldots.$



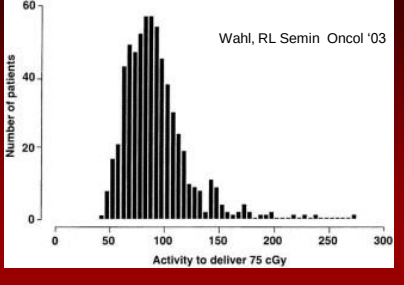
## Absorbed Dose → Biological Effects

- **Diagnostic Imaging: risk of cancer**
  - Stochastic (prob of effect occurring ↑ w/ ↑ dose)
  - Atomic bomb survivor epidemiological data
  - BEIR organ dose estimates → probability of cancer
  - Need whole organ doses to estimate risk of diag. imaging
- **Therapy: efficacy and toxicity**
  - Deterministic (effect ↑ w/ ↑ dose)
  - Radiotherapy, pre-clinical, phase 1 studies
  - Dose distribution, radiobiology → efficacy, toxicity

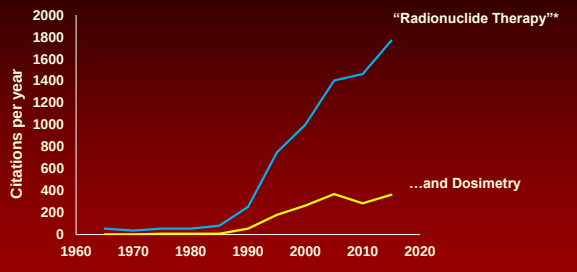
## *AA vs AD-based Dosing*




## Admin Activity (AA) vs Abs Dose

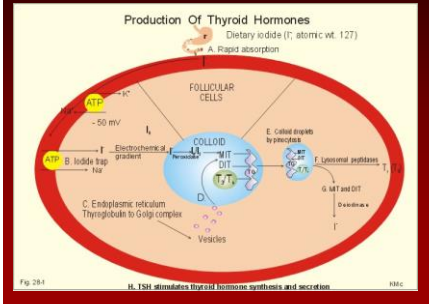


# Nuclear Medicine Therapy




*("radioiodine therapy" OR "radionuclide therapy" OR "isotope therapy" OR "radioimmunotherapy" OR "radiolabeled antibody therapy" OR "radioimmunoconjugate therapy") AND ("dosimetry" OR "absorbed dose")

# Iodine Metabolism in the Thyroid





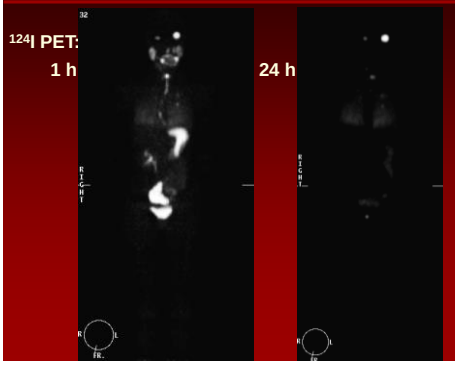
Triiodothyronine (T3)

## *The question*:
## Can iodine be made radioactive?

Saul Hertz, MD
(1905 – 1950)

1925: A.B. Michigan
1929: M.D. Harvard
1929-31: Mt. Sinai, Cleveland
1931-43: MGH Thyroid Unit
- Chief, Thyroid Clinic

# PET-based thyroid imaging




# Thyroid Treatment Planning

- How much I-131?
  - Fixed
  - Tumor absorbed dose (kill tumor)
  - Benua-Leeper dosimetry (avoid toxicity)
- Benua-Leeper dosimetry for Thyroid Tx
  - Blood dosimetry
  - Whole-body retention
- Lung Dose-Rate Method
- 3D-RD, patient-specific dosimetry

# Patient-specific, 3-D dosimetry

**3D-Internal Dosimetry (3D-ID)**

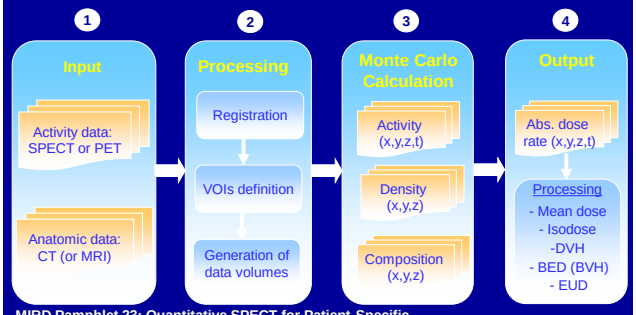
- Patient specific, using 3-D anatomy and activity data
- Calculates absorbed dose voxel by voxel
- Output dose as mean over chosen volume or DVH

**3D-Radiobiological Dosimetry (3D-RD)**

- Integrates Monte Carlo calculation
- Radiobiological modeling: absorbed dose →response
- Better predict tumor response and toxicity

Sgouros, et al. JNM '90.
Baldeaux, et al. JNM '07
Kolbert, et al. JNM '07

# 3D-RD Flowchart




**MIRD Pamphlet 23: Quantitative SPECT for Patient-Specific 3-D Dosimetry in Radionuclide Therapy, JNM 2012**

# 3D-RD Clinical Implementation

- Real time (1 week) $^{131}$I treatment planning for an 11 year-old girl with metastatic differentiated papillary thyroid cancer using patient specific 3-dimensional dosimetry (3D-RD).
- Heavy lung involvement meant concern about pulmonary toxicity and concern for overdosing
- Other considerations: tumor dose and brain toxicity
- Patient had prior $^{131}$I for diagnostic and still retained significant quantities especially in two brain tumors
- Use $^{124}$I and PET/CT for dosimetric assessment

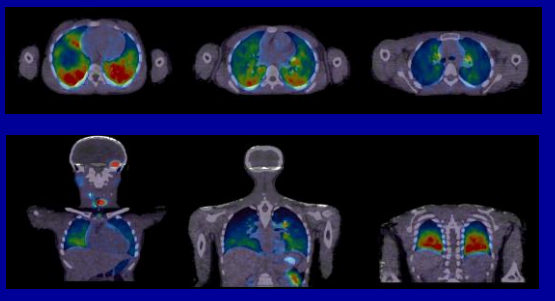
Hobbs, *et al* JNM '09

# Method

- The patient received 92 MBq (2.5 mCi) of $^{124}$I
- Whole body PET/CT scans were performed at 1, 24, 48, 72, and 96 h.
  - 2D mode with tungsten septa in place
  - Calibration with a standard measured in counting well
- 3D-RD calculation includes
  - longitudinal co-registration
  - compensation for different half-lives
  - EGS-based Monte Carlo simulation of $^{131}$I decay for each time point.
- The dose rate results were fitted and an estimated absorbed dose per administered ($^{131}$I) activity to lungs was obtained and scaled to MTD of 27 Gy to normal lung
- Other methods (absorbed fraction with OLINDA and Benua-Leeper) were used for comparison using PET activity maps

Hobbs, *et al* JNM '09

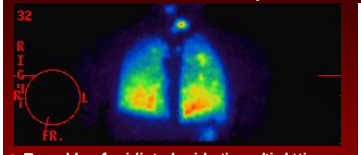
# PET/CT images



Hobbs, *et al* JNM

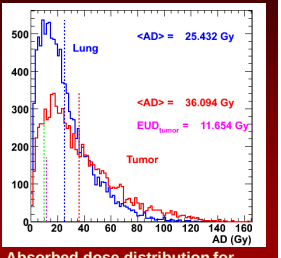
# PET-based thyroid dosimetry

**Absorbed Dose Map**




- Based on dosimetry analysis, patient was administered 5.1 GBq as not to exceed 25-27 Gy to lungs
- Calculation completed within 48 h of last time point
- Physician was thinking of 7.4 GBq
- Absorbed dose to T lobe lesion ~ 325 Gy
- Lung tumor dose 36 Gy
- Equivalent uniform dose (EUD) = 11.6 Gy

**Dose-Volume histograms**

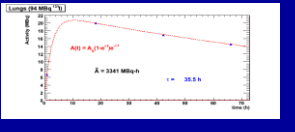


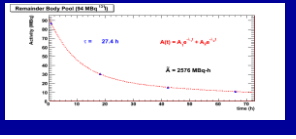

**Absorbed dose distribution for 5.1 GBq $^{131}$I administration**

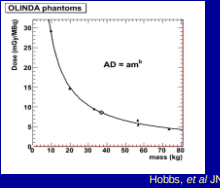
Hobbs, *et al* JNM '09

# OLINDA-absorbed fraction

- Residence times from lungs and rest of body pool
- Input into OLINDA for all phantoms
- Phantom results as a function of mass and fit
- Input patient mass
- Scale to 27 Gy MTD constraint
- **AA: 2.89 GBq (78 mCi)**








Hobbs, *et al* JNM '09

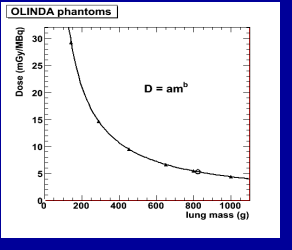
## Methodological Comparison

- What activity to administer?
- OLINDA: 2.9 GBq
- 3D-RD: 5.1 GBq
- Retrospective re-examination

Hobbs, *et al* JNM '09

## OLINDA reviewed

- Patient lung mass greater than typical
  - Tumor increases density
  - Higher mass means lower dose for same activity
  - Plot OLINDA phantom results as a function of lung mass
  - Input patient lung mass
  - Scale to 27 Gy MTD
  - **AA: 5.18 GBq (140 mCi)**
- Convergence of results!



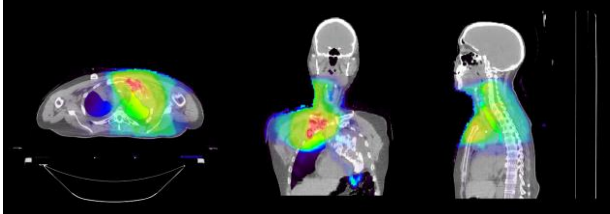

Hobbs, *et al* JNM '09

## 3D-RD for pediatric case

- Feasibility of real time treatment planning using 3D-RD, patient-specific dosimetry.
- A higher recommended AA than by an S-value based method (with a highly favorable clinical outcome) was obtained.
- Re-visitation of methods led to convergence (for this case).
- Further investigation of lung/tumor discrimination in future

Hobbs, *et al* JNM '09

# Combined RPT-XRT dose-map



Hobbs, *et al* IJROBP '10

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