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

George Sgouros, Ph.D.
Russell H. Morgan Dept of Radiology & Radiological Science
Johns Hopkins University, School of Medicine
Baltimore MD

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
• Targeted Biologic Therapy (hormonal Tx)
  - Kill targeted by hormone and radiation delivery (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?

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**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:

\[ \text{number of dis.} \times \frac{\text{energy released per dis.}}{\text{mass of target tissue}} \times \frac{\text{fraction that is absorbed}}{\text{S} \times \text{D} \times \text{M}} \]

\[ D_t = \tilde{A}(r_s) \times \Delta \times \phi(r_{t} - r_s) \]

\[ D_t = \tilde{A}_{s1} \cdot S(t \leftarrow t_1) + \tilde{A}_{s2} \cdot S(t \leftarrow t_2) + \ldots \]
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

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**AA vs AD-based Dosing**

- **Admin Activity (AA) vs Abs Dose**
  - Wahl, RL Semin Oncol '03
**Nuclear Medicine Therapy**

“Radionuclide Therapy”

...and Dosimetry


Citations per year

0 200 400 600 800 1000 1200 1400 1600 1800 2000

**Iodine Metabolism in the Thyroid**

**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

- **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**

Thyroid Treatment Planning

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
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

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
Based on dosimetry analysis, patient was administered 5.1 GBq so as not to exceed 25-27 Gy to lungs.

Physician was thinking of 7.4 GBq.

Absorbed dose to T. lobe lesion $\approx$ 325 Gy.

Lung tumor dose 36 Gy.

Equivalent uniform dose (EUD) = 11.6 Gy.

PET-based thyroid dosimetry

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

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)
Methodological Comparison

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

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!

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