Theranostics in a Dedicated Pediatric Hospital
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Conflicts of Interest: none

Educational Objectives
• Review dosimetry calculations
  – MIRD formulation
  – Example calculations
  – I-131 Tx: bone marrow dose & whole body lung retention
• Discuss how to setup a quantitative pediatric theranostics program
  – Lessons learned, pointers, and tips

Dosimetry: MIRD
• Medical Internal Radiation Dose (MIRD)
• Definitions:
  – Source organ – time dependent localization of activity
  – Target organ (T)
  – For β-emitting radionuclides, a source organ can be a target organ too
  – For γ-emitting radionuclides, the thyroid is both a source (yRadiation of nearby organs) and a target from the short range β-
• Absorbed fraction of energy emitted from source and deposited in target (φ)
  – φ = 1 for β
  – φ < 1 for γ
• Cumulative activity (A)
  – This is a measure of decay rate in a source organ; represented by the area under the activity curve
Dosimetry: MIRD

Cumulated activity (time-integrated activity of source (S) organ)
- Normalized by injected dose ($A_0$)
\[ A = \frac{1}{T_D} \int_0^{T_D} A(t) \, dt \]
- $T_D$: dose-integration period

Residency time ($\tau_{res}$): cumulated activity ($\mathcal{A}$) normalized by administered activity ($A_0$)
- If assume instantaneous uptake and biological clearance
\[ \tau_{res} = 1.44 \cdot T_{eff} \cdot \frac{1}{\lambda} \]
- If assume a two compartment model
  - Body (clears as a mix of $T_b$ and $T_p$)
  - Tumor/organ, e.g., $I_{-131}$ is trapped and clears by $T_p$
\[ \tau_{res} = 1.44 \cdot T_{eff} \left[ 1 - e^{-\frac{T_{eff}}{T_b}} \right] + 1.44 \cdot T_p \cdot e^{-\frac{T_{eff}}{T_p}} \]

S-factor: mean absorbed dose per cumulated activity
- Absorbed dose fraction ($\phi$) to target (T)
- Average energy of the ($i$) emission ($E_i$)
- Yield ($Y_i$): number emitted by disintegration
- Normalized by organ mass (M)
\[ S = \frac{1}{\Phi(T)} \sum_i E_i Y_i \phi(\gamma, c, E_i, T) \]
- Use tomographic imaging (e.g., CT) to measure organ mass
- Or use computational phantoms
Dosimetry: MIRD

- Medical Internal Radiation Dose (MIRD)
  - Pamphlet #21*: A generalized schema for radiopharmaceutical dosimetry-standardization of nomenclature

\[ A = \frac{1}{\lambda} \int_0^T d(s, t) \, dt \]

\[ S = \frac{1}{A(\text{inj})} \sum_i \sum_j E_i \phi_{ij}(s \leftarrow s_i, E_j) \]

\[ d(s, t) = \sum_i \left( \frac{1}{\lambda} A(s_i, E_i) \right) \left( \frac{1}{\Sigma E_j \phi_{ij}(s \leftarrow s_i, E_j)} \right) \]

Absorbed dose rate to target (T) organ
Normalized by organ mass (M)

\[ S = \frac{1}{M(s, t)} \sigma_i E_i Y_i \phi(s \leftarrow s_i, E_i) \]

\[ T_D = \text{dose-integration period} \]


[I-131] Thyroid Tx Dosimetry

- I-131 Tx same since 1950s
- Main difference between pediatric and adult:
  - Not all children can swallow capsules
  - Diagnostic I-131 capsules can be dissolved
    - (see Sammet talk AAPM 2017 for pediatric horror story)
  - Use of liquid I-131 for therapeutic dose
- Prior to Tx calculate, max Tx dose*
  - Use I-123 or I-131

\[ D_{\text{max}}(s) = 0.315 \cdot \text{AMBLR} \cdot C_{\text{blood}} + 0.456 \cdot \frac{A_{\text{inj}}}{M_{\text{org}}} \]

*Shen, et al. JNM 1999 40(12) 2102-2106

[I-131] Thyroid Tx Dosimetry

- Thyroid ablation dosimetry considerations:
  - 2 Gy to blood (RBM)
  - 80 mCi lung retention 48 hrs post Tx

\[ \text{Derived from adult studies} \]

<table>
<thead>
<tr>
<th>Patient Information</th>
<th>Age</th>
<th>Gender</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Hematocrit (Hct)</th>
<th>BMI (kg/m²)</th>
<th>Dosimetry Dose</th>
<th>Therapy Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>34</td>
<td>F</td>
<td>165</td>
<td>67</td>
<td>33.2</td>
<td>19.4</td>
<td>0.37</td>
<td></td>
</tr>
</tbody>
</table>

\[ \text{Blood Volume (L)} = 70 \times (\text{Height (cm)} - 152) / 100 \]

\[ \text{body surface area (BSA) } = \sqrt{\text{Weight (kg)} \times \text{Height (cm)} / 3600} \]
[I-131] Thyroid Tx Dosimetry

- Calculate an estimated red marrow to blood activity concentration (RMBLR):
  - Need patient Hematocrit (HCT)
  - The red marrow extracellular fluid fraction (RMECF)
  - If RMECF is unavailable, use baseline value provided by Sgourous*.
  - If RMECF is in normal range use RMECF = 0.19
  - Acceptable range of values provided by Sgourous: 0.15-0.25

  \[ RMBLR = \frac{RMECF}{1 - HCT} \]

<table>
<thead>
<tr>
<th>Monochrome (%)</th>
<th>Male (%)</th>
<th>Female (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>45.4-56.1</td>
<td>37.4-55.9</td>
</tr>
<tr>
<td>0-2 months</td>
<td>31.0-37.0</td>
<td>31.0-37.2</td>
</tr>
<tr>
<td>2-4 years</td>
<td>31.7-37.7</td>
<td>32.0-37.1</td>
</tr>
<tr>
<td>6-11 years</td>
<td>31.7-37.3</td>
<td>32.0-37.6</td>
</tr>
<tr>
<td>12-18 years</td>
<td>34.8-41.9</td>
<td>34.0-40.7</td>
</tr>
<tr>
<td>18+ years</td>
<td>32.6-40.7</td>
<td>33.0-40.0</td>
</tr>
</tbody>
</table>

*Shen, et al. JNM 1999 40(12) 2102

- Calculate concentration of cumulated activity in blood (Cblood)*
  - Calculate time activity curve
    - Draw 1 ml of blood
    - Using well counter
    - Need 3-4 time points
    - Blood retention: convert net counts to mCi/ml and normalize by (A0)

  \[ y = A_0 \cdot e^{-\lambda_{eff} \cdot t} \]

  \[ T_{eff} = \frac{\ln(2)}{\lambda_{eff}} \]

  \[ C_{blood} = \tau_{res} = 1.44 \cdot \frac{T_{eff}}{270.04} \cdot e^{\frac{-0.9033}{T_{eff}}} \]

*Tenhunen et al. Nuc Med Com 2013 34 1208-1215
[I-131] Thyroid Tx Dosimetry

- Calculate residency time ($\tau_{res}$) for body:
  - Measure whole body counts using gamma camera
  - 3-4 time points
  - Calculate whole body activity time ($A_{WB}$)

$$\tau_{res} = \frac{\text{Counts}}{\text{Time}} = 0.315 \cdot \text{RMUR} \cdot \text{Activity}$$

$$\text{Max} \frac{D_{prescript}}{D_{max}} = 200$$

Pruzan et al. Medicine 2016 95(11) e3154

[1-131] mIBG Tx-History

- Cincinnati Children’s opened MIBG therapy program in 2007
  - One of the first pediatric programs in the USA
- We have performed over 100 mIBG therapies
- We have 4 Tx rooms
  - Newly designed rooms allowed Tx of a patient with a dose up to 1.2 Ci

Room Preparation

- All surfaces must be covered in either paper or plastic
  - Radiation Safety Technicians perform a majority of the room preparation and shield placement
Room Preparation

- Nuclear Medicine technologists lay out the tubing for urine control
  - Tubing is taped to the floor using red tape
  - Urine pump is set up and tested
  - Fit urine tubing connectors

- Yellow tubing is covered by red tape
- Toilet covered in plastic

Room Preparation

- A real-time survey meter is attached over the bed/patient
- Mobile shields are placed around the patient’s bed
- Shields provide radiation safety protection to hospital staff and parents
  - Parents are trained to care for patient
    - Radiation dose monitored via personal dosimeters during Tx
  - Trained patients help minimize staff dose

Hot Lab Preparation

- $[^{131}I]$-mIBG is placed in a laminar fume hood because liquid $[^{131}I]$ is volatile
- Lead bricks are used in place of a shielded L-block
- Use a shielded dose drawing system
Hot Lab Preparation

- Transfer the dose into a shielded column and place lid on top
- Radiation Safety will get a dose rate reading from the surface of the shielded column
- Radiation Safety will escort the deliver of the \([\text{I-131}]\) mIBG dose to the patient’s room
  - Limit elevator access

Infusion Preparation

- mIBG infusion cart is brought into the patient room
- Remove the therapeutic dose from the Pb column and load it into the infusion pump
- All persons present in the room must have
  - a gown
  - double shoe covers
  - double gloves

Infusion Preparation

- Pump rate is
  \[ R = \frac{m_{\text{Th}} \cdot 131 + 2}{2} \]
- \([\text{I-131}]\) mIBG is delivered to the patient over the course of 90 minutes
- IV fluids are run into the 4-way stopcock and mixed with the mIBG dose for delivery
Post Therapy

• Release Criteria
  – Patient must be under 7 mR/hr at one meter
  – Patient must bathe before leaving the Tx room
  – Post Tx scan must be acquired to confirm therapeutic dose was delivered

[I-123] mIBG pre-therapy scan
[I-131] mIBG post-therapy scan

Lessons Learned-[I-131] mIBG Tx

• [I-131] mIBG is both sticky and sneaky
  – [I-131] mIBG will find a way out
  – Minimize or eliminate breaking any connections with the infusion set up
  – It is easy to cross-contaminate surfaces
  – Wear proper PPE!!
• Patient vomiting can increase potential for contamination
  – Anti-emetics are often given
• Some younger patients may require Versed (Midazolam)

Lessons Learned-[I-131] mIBG Tx

• Clean up
  – [I-131] mIBG was sticking to drainage pipes
  – Use liquid bleach to pour down toilet
  – Very hot water helps clean up stubborn [I-131] surface spills
    • Boil water in room w/ electric hot plate
    • Use appropriate gloves (don’t burn hand)
[Y-90] TARE Therapy

- Trans-Arterial-Radio-Embolization (TARE) therapy
  - Also known as Selective-Internal-Radiation-Therapy (SIRT)
  - Primary clinical indication → treat HCC
  - A way to deliver beta radiation to liver tumors
- First pediatric hospital in the U.S. to treat a pediatric patient
  - First patient treated (22.14 mCi) was a 5 yr old (Dec 2012)
  - Vendor (Sir-Tex)
  - Patient age range 3-18 yrs
  - Highest dose 45.5 mCi
  - Average dose (mCi) high teens low 20's

Pre-therapy [Tc-99m] MAA mapping

- Evaluate hepatic blood flow post coil embolization
- [Tc-99m MAA] is administered to the liver to mimic [Y-90] therapeutic spheres

<table>
<thead>
<tr>
<th>Particle</th>
<th>Sphere size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAA</td>
<td>10-90</td>
</tr>
<tr>
<td>Sir-spheres</td>
<td>20-60</td>
</tr>
<tr>
<td>Thera-spheres</td>
<td>20-30</td>
</tr>
</tbody>
</table>

Pre-therapy [Tc-99m] MAA mapping

- Calculate percent of [Tc-99m MAA] dose is shunted to the lungs
  \[ \text{Lung Shunt(%)} = \frac{C_{\text{lung}}}{C_{\text{lung}} + C_{\text{liver}}} \times 100 \]
  - Geo. metric mean lung/liver counts
  - Exclude patients w/ lung rad dose
    - > 25-30 Gy/Tx or
    - > 50 Gy cumulative
  - Ensure that [Tc-99m MAA] is not getting into the GI tract

<table>
<thead>
<tr>
<th>Lung Shunt Fraction</th>
<th>Reduction Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10%</td>
<td>None</td>
</tr>
<tr>
<td>10-15%</td>
<td>20%</td>
</tr>
<tr>
<td>15-20%</td>
<td>40%</td>
</tr>
<tr>
<td>&gt;20%</td>
<td>No Tx.</td>
</tr>
</tbody>
</table>

Lung Shunt (%)

20.4%
Pre-therapy [Tc-99m] MAA mapping

- Calculate percent of [Tc-99m MAA] dose is shunted to the lungs
  - AAPM Virtual library: Cheenu Kappadath, PhD

  Basic model: 2.5 GBq (67.5 mCi)
  BSA model: BSA(m²) = 0.2 + Tl[%]/100 = 1.85 GBq (50.1 mCi)

  Liver Dose [Gy] = A [GBq] × 1.5 × 40.7 [Gy·kg/GBq] / M_{liver} [kg]
  = 44.7 Gy (± 0.8 Gy)

  Lung Dose [Gy] = A [GBq] × 15 × 40.7 [Gy·kg/GBq] / M_{liver} [kg]
  = 6.8 Gy (± 2.5 Gy)

Hot Lab Set-up

- Use a ridiculous amount of chux
- Place dose calibrator as close to dose prep area as possible
  - Dose calibrator must be set up for [Y-90]
    - Calibration certificate is necessary to setup dose calibrator's cal setting
- PPE
  - Double shoe covers
  - Isolation gown
  - Sterile gloves to cover sleeves
  - Radioactive waste bucket close

Hot Lab Set-up

- Cardboard box placed on table top
  - Provides protection from all sides and reduces airflow
- Place chux in a shingle fashion to contain any spheres
- Acrylic L-block
  - Stops all β emission
Y-90 TARE: Dose Draw

- Nuclear Medicine Technologist will draw up the dose
- Medical Physicist will be near by to enter dose information into Excel
- Use subtraction method from the shipping vial

Check List

- Checklists help things move smoothly and orderly

Treatment Suite

- Items include:
  - Nalgene container with Y-90 Sir-Sphere dose
  - Check list
  - Survey meter
  - Delivery box
- Radiation Safety:
  - Waste bags
  - Step-off mats
  - Survey technician
Delivery Box Set-up

- Sterile drape is placed over the infusion cart
  - All supplies required for infusion are placed on the sterile drape
  - All syringes and bowls are labeled
- IR tech reads through check list to set up delivery box
- NM tech remains sterile and receives "next step" direction from the IR Tech

Delivery Box Set-up

- Syringes are filled and all tubing is primed to remove air bubbles
- NM tech places the needles into the dose delivery system

Dose Delivery Box Set-up

- NM tech positions the infusion cart
  - Close to patient, but away from high traffic area to minimize collision w/ staff
- Interventional Radiologist establishes connection with the Tx catheter
Radiation Safety

- Radiation Safety is present throughout the entire procedure from the dose draw to the completion of the infusion
  - A spill kit is available if needed
- Survey all personnel leaving the IR suite
- Room survey

Post Therapy Scanning Options:

Bremsstrahlung SPECT-CT

- MELP Collimators
- 78 keV photo peak
- 30% window
- Use patient to peak camera
- Zoom = 1
- 120 x 128 matrix
- 180° rotation
- 20 sec/step

PET-CT

- PET-CT protocol
  - [Y-90] may need to be added to list of isotopes
  - Time per bed position is variable with patient dose

Lessons Learned-[Y-90] TARE Tx

- Multidisciplinary team approach involving:
  - Interventional Radiology, Nuclear Medicine, Medical Physics, Radiation Safety, Anesthesia
  - Coordination/communication of services is a key factor
- Perform PET-CT imaging over Bremsstrahlung SPECT-CT
  - Block enough time in the camera rooms for post-therapy imaging
  - Make sure that Anesthesia equipment is set up for imaging
- Take time so that errors are eliminated
  - Don’t move forward without all members of the team
- Improve!
  - Revise check list as needed and eliminate any wasted steps
[Lu-177] Lutathera Therapy

- Dx [Ga-68] NETSPOT (Dotatate) based radiopharmaceutical
  - Used to image neuroendocrine tumors such as Neuroblastoma, select sarcomas, and nasopharyngeal carcinomas
  - Uptake similar to mIBG in adrenergically innervated tissues
    - Hot spot uptake: spleen (27%), kidneys (21%), liver (10%), bladder (14%), rem (~28%)

- [Lu-177]
  - Half life: 6.7 d
  - β: 497 keV (78%)
    - Mean range 0.67 mm (max range 2.2 mm)
  - γ: 113 keV (6%), 208 keV (11%), 321 keV (0.2%)

Dose Delivery Set-up

- Lutathera dose comes in Pb pig
- Modified shielding for delivery
  - Plastic for the β's (inside layer)
    - Max range is 14 mm, plastic shield 20 mm thick
  - Pb for the γ's (outside layer)

Amino Acid infusion helps to protect the kidneys from radiation dose
Dose Delivery Set-up

- Lutathera infusion ~30 mins
  - Check activity 5 min intervals
  - Disconnect vial when reading
  - Stable reading < 42 kcts/min
  - Flush tubing with 10 mL saline to complete dose delivery
- Patient dose
  - Pre infusion dose assay – post infusion assay
  - Common to leave behind ≤ 2 mCi

Dose Delivery Set-up

- Patient dose
  - Maximize infusion ensure long needle touches bottom of bottle
  - Heave Lutathera molecules sink to the bottom as the bottle fills with saline

In-patient Experience

- Typical adult experience with Lutathera is out-patient
- Our patient was in-patient (for other clinical reasons)
  - Patient was housed in mIBG suite
    - The nursing and support staff on the mIBG floor are comfortable working around radiation
    - 27 individuals entered the room over 9 days
      - Total stay time = 155.2 hrs.
      - Integrated dose for all visitors = 23.6 mR
      - Max individual dose (parent) = 7.5 mR
In-patient Experience

- Survey reading of patient

![Graph showing dose rate over time]

[Lu-177] Lutathera Dosimetry

- Dosimetry
  - Exists in literature for adults
  - One study for pediatric pts (no dosimetry provided)
- Calculated at our institution
  - 4 blood draws
    - $T_{1/2} = 1.8$ hrs
    - $T_{1/2} = 1.5$ hrs
    - $T_{1/2} = 2.4$ μCi/hr
    - Blood/RBM not limiting factor

$$T_{eff} = T_{pa} + T_{lb}$$

- Blood/RBM not limiting factor

![Graph showing time since Tx completion]

[Lu-177] Lutathera Dosimetry

- Organ doses

![Images of patient scans at different time points]
Lessons Learned-[Lu-177] Tx

• Keep long needle touching bottom of bottle to ensure better infusion of dose
• Severe nausea side effect 1-1.5 hrs post amino acid infusion
  – Carry meds with you while traveling around hospital for imaging
• More education for parents
  – How to operate urine pump
  – Language queue cards for when translator is not present
• Provide sedation for younger patients
  – Provide foley bag
• Don’t worry about badging nursing staff and parents

Thank you

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