Theranostics in a Dedicated Pediatric Hospital

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Conflicts of Interest: none

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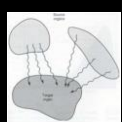
Cincinnati Children's

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
  - [I-131] Thyroid, [I-131] mIBG, [Y-90] SIR-Spheres, [Lu-177] Lutathera

Dosimetry: MIRD



- Medical Internal Radiation Dose (MIRD)
- Definitions:
  - Source organ (S)-time dependent localization of activity
  - Target organ (T)
  - For β^- emitting radionuclides, a source organ can be a target organ too
    - E.g. [I-131], the thyroid is both a source (γ irradiation of nearby organs) and a target from the short range β^-s
  - Absorbed fraction of energy emitted from source and deposited in target (φ_i)
    - $\Phi_i = 1$ for β^-s
    - $\Phi_i < 1$ for γ's
  - Cumulated activity ($\tilde{A}$)
    - This is a measure of decay rate in a source organ; represented by the area under the activity curve

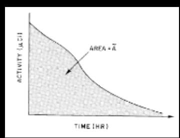
*Bloch et al. MIRD Pamphlet no. 21, J Nucl Med 2009; 50:477-484

Dosimetry: MIRD

- Cumulated activity: time-integrated activity of source (S) organ
  - Normalized by injected dose (A_0)

$$\tilde{A} = \frac{1}{A_0}\int_0^{T_D} A(r_S, t)dt$$

T_D=dose-integration period



Dosimetry: MIRD

- Residency time (τ_{res}): cumulated activity ($\tilde{A}$) normalized by administered activity (A_0)
  - If assume instantaneous uptake and biological clearance

$$\tau_{res} = 1.44 \cdot T_{eff} \cdot \frac{\tilde{A}}{A_0}$$

  - 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

$$\tau_{res} = 1.44 \cdot T_{eff} \cdot \left[1 - e^{-\frac{\ln(2)\cdot t}{T_{eff}}}\right] + \left[1.44 \cdot T_p \cdot e^{-\frac{\ln(2)\cdot t}{T_p}}\right]$$

Dosimetry: MIRD

- S-factor: mean absorbed dose per cumulated activity
  - Absorbed dose fraction (ϕ) to target (T)
  - Average energy of the (i^{th}) emission (E_i)
  - Yield (Y_i): number emitted by disintegration
  - Normalized by organ mass (M)

$$S = \frac{1}{M(r_T,t)} \sum_i E_i Y_i \phi(r_T \leftarrow r_S, E_i, t)$$

- 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

T_D=dose-integration period

$$\tilde{A} = \frac{1}{A_0}\int_0^{T_D} A(r_S,t)dt$$ ← Time-integrated activity of source (S) organ Normalized by injected dose (A_0)

$$S = \frac{1}{M(r_T,t)}\sum_i E_i Y_i \phi(r_T \leftarrow r_S, E_i, t)$$ ← Absorbed dose rate to target (T) Normalized by organ mass (M)

$$d(r_T, T_D) = \sum_{r_S}\left(\frac{1}{A_0}\int_0^{T_D} A(r_S,t)dt\right)\cdot\left(\frac{1}{M(r_S,t)}\sum_i E_i Y_i \phi(r_S \leftarrow r_S, E_i, t)\right)$$

Absorbed dose of target (T) organ May assumes time independency*

*Bloch et al. MIRD Pamphlet no. 21, J Nucl Med 2009; 50:477-484

[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

$$D_{RBM}\left(\frac{cGy}{mCi}\right) = 0.315 \cdot RMBLR \cdot C_{blood} + 0.456 \cdot \frac{\tilde{A}_{WB}}{m_{WB}}$$

*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

} ← Derived from adult studies

Patient Information

MRN		Age	10	Hematocrit (HCT)	39.3
Last Name		Gender	Female	RMECFF	
First Name		Height (cm)	147.4	Dosimetry Date:	
		Weight (kg)	47.9	Therapy Date:	

1) Calculate blood volume: enter patient demographical information marked in the red boxes.

Blood Vol (ml): 2602.45

*Retzlaff et al. Blood 1969, 33:649-667

$$BV(ml) = \alpha \cdot Ht(cm) + \beta \cdot Wt(kg) - C$$

Blood Volume (BV)	Male	Female
α	31.90	56.90
β	26.30	14.10
C	2402	6460

[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 (RMECFF)
  - If RMECFF is unavailable, use baseline value provided by Sgourous*
    - If RMECFF is in normal range use RMECFF = 0.19
    - Acceptable range of values provided by Sgourous: 0.15-0.25

$$RMBLR = \frac{RMECFF}{1 - HCT}$$

Hematocrit (B)[1]

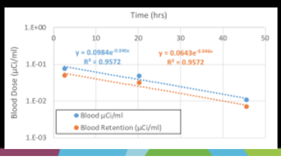
Age	Males (%)	Females (%)
Newborns	43.4–56.1	37.4–55.9
6 months–2 years	30.9–37.0	31.2–37.2
2–6 years	31.7–37.7	32.0–37.1
6–12 years	32.7–39.3	33.0–39.6
12–18 years	34.8–43.9	34.0–40.7
>18 years	33.4–46.2	33.0–41.0

* Sgouros JNM 1993, 34:689-694

[I-131] Thyroid Tx Dosimetry

- Calculate concentration of cumulated activity in blood (C_{blood})*
  - 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 (A_0)

$$y = A_0 \cdot e^{-\lambda_{eff} \cdot t} \qquad T_{eff} = \frac{\ln(2)}{\lambda_{eff}}$$

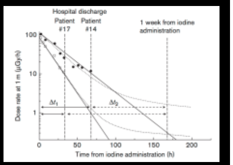


*Shen, et al. JNM 1999 40(12) 2102-2106

[I-131] Thyroid Tx Dosimetry

- Recommended to use a bi-exponential fitting model*
  - Clears as a mix of T_b and T_P
  - Rule of thumb, after 72 hrs, total decay is T_p

$$C_{blood} = \tau_{res} = 1.44 \cdot T_{eff} \cdot \left[1 - e^{-\frac{\ln(2) \cdot t}{T_{eff}}}\right] + \left[278.04 \cdot e^{-\frac{\ln(2) \cdot t}{T_p}}\right]$$



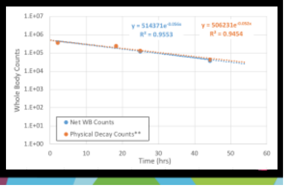
*Tenhunen et al. Nuc Med Com 2013 34 1208-1215

[I-131] Thyroid Tx Dosimetry

- Calculate residency time (τ_{res}) for body*
  - Measure whole body counts using gamma camera
  - 3-4 time points
  - Calculate whole body activity time ($\tilde{A}_{WB}$)

$$D_{RBM}\left(\frac{cGy}{mCi}\right) = 0.315 \cdot RMBLR \cdot C_{blood} + 0.456 \cdot \frac{\tilde{A}_{WB}}{m_{WB}}$$

$$Max\ D_{prescribe} = \frac{200}{D_{RBM}}$$



*Pruzan et al. Medicine 2016 95(11) e3154

[I-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

Urine Pb Shield

Urine pump

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

- [I-131] mIBG is placed in a laminar fume hood because liquid [I-131] 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 [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

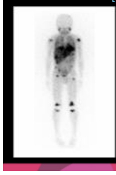
$$R = \frac{V_{[I-131]} + 2}{2}$$

- [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

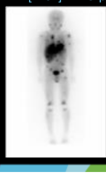
[I-123] mIBG pre-therapy scan



Whole Body protocol
Collimator
ELEGP- GE
ME-Siemens
12 cm/min
Scatter windows
159 keV ± 10%
Lat Skull
3 min static
256x256 matrix

SPECT protocol
LEHR collimators
30 sec/stop
6° rotation for 180°
60 views
Scatter windows
130 keV ± 10%
159 keV ± 7.5%
CT settings
weight based

[I-131] mIBG post-therapy scan



Whole Body protocol
HE Collimator
15 cm/min*
Lat Skull
5 min static
256x256 matrix
Scatter windows
364 keV ± 10%

Dose dependent

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)

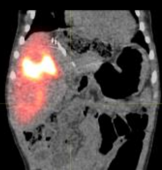
[Y-90] TARE Therapy

- 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

Particle	Sphere size (μm)
MAA	10-90
Sir-spheres	20-60
Thera-spheres	20-30



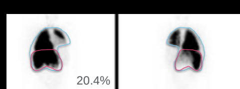
SPECT protocol
LEHR collimators
30 sec/stop
6° rotation for 180°
Number of views = 60
Scatter windows
140 keV ± 10%
120 keV ± 5%
CT settings
weight based

Pre-therapy [Tc-99m] MAA mapping

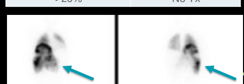
- Calculate percent of [Tc-99m MAA] dose is shunted to the lungs

$$Lung\ Shunt(\%) = \frac{C_{lung} \cdot 100}{C_{lung} + C_{liver}}$$

  - 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



Lung Shunt Fraction	Reduction Factor
< 10%	None
10-15%	20%
15-20%	40%
>20%	No Tx



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[m^2] – 0.2) + TI[%]/100 = 1.85 GBq (50.1 mCi)

Liver Dose [Gy] = A [GBq] x (1-LS) x 49.7 [Gy-kg/GBq] / M_{liver} [kg]
= 44.7 Gy (< 80 Gy)
Lung Dose [Gy] = A [GBq] x LS x 49.7 [Gy-kg/GBq] / M_{lung} [kg]
= 6.8 Gy (<25 Gy)

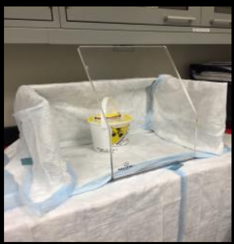
S. Cheenu Kappadath, PhD AAPM 2011 Annual Meeting

Hot Lab Set-up

- Use a ridiculous amount of chuxs
- 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

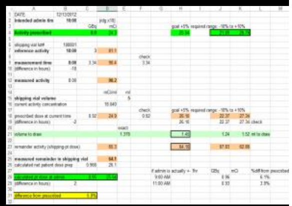
Hot Lab Set-up

- Cardboard box placed on table top
  - Provides protection from all sides and reduces air-flow
- Place chux in a shingle fashion to contain any spheres
- Acrylic L-block
  - Stops all β emission



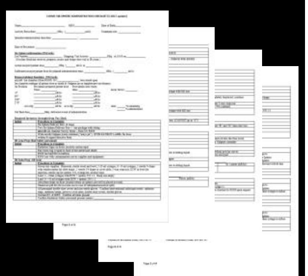
Y-90 TARE: Dose Draw

- 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

[Y-90] Sir-Spheres in suspension being delivered to the patient

Dose Delivery Box Set-up

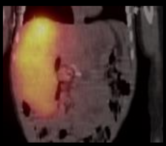
- NM tech positions the infusion cart
  - Close to patient, but away from high traffic area to minimize collision w/ staff
- Interventional Radiologist establishes connection with the Tx catheter

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:

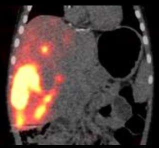
Bremsstrahlung SPECT-CT



MELP collimators
78 keV photo peak
w/ 30% window
Use patient to peak camera

Zoom = 1
128 x 128 matrix
180deg rotation
20 sec/stop

PET-CT



PET acq time (min) per bed	Y90 activity MBq	Y90 activity mCi
15	400	10.81
30	200	5.41
10.81	555	15
7.5	800	21.62

Goedicke A. IEEE *Transactions on Medical Imaging.* 2013;32:485-492

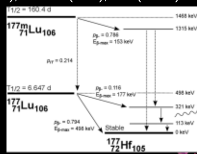
PET-CT protocol
- [Y-90] may need to be added to list of isotopes
- Time per bed position is variable with patient dose

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%)

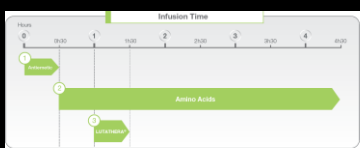


Gleisner KS, JNM 56(7) 2015; 976-984

[Lu-177] Lutathera Therapy

- Tx timeline

[Ga-68] PET



Advanced Accelerator Applications, white paper Feb 2018

Amino Acid infusion helps to protect the kidneys from radiation dose

Bailey et al. EJNMMI Physics (2015) 2:20

[Lu-177] Whole Body Post 4 hrs

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)

Delivered Dose

Modified pt delivery set-up

Dose Delivery Set-up

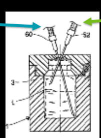
- Lutathera infusion ~30 mins
  - Check activity 5 min intervals
  - Disconnect vial when reading
    - Stable reading < 42 kcts/min
  - Flush tubing with 10 mL saline to complete dose delivery
- Patient dose
  - Pre infusion dose assay – post infusion assay
  - Common to leave behind ≤ 2 mCi

GM setup

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

Long needle → patient



Short needle → Saline

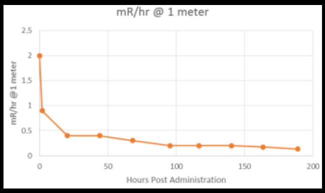
In-patient Experience

- 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

9 days

In-patient Experience

- Survey reading of patient

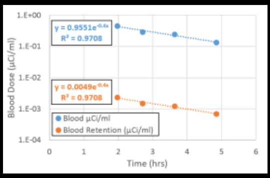


[Lu-177] Lutathera Dosimetry

- Dosimetry
  - Exists in literature for adults
  - One study for pediatric pts (no dosimetry provided)
- Calculated at our institution
  - 4 blood draws
    - T_b= 1.8 hrs
    - T_{eff}= 1.7 hrs
    - T_{res}= 2.4 µCi hrs
  - Blood/RBM not limiting factor

$$\frac{1}{T_{eff}} = \frac{1}{T_p} + \frac{1}{T_b}$$

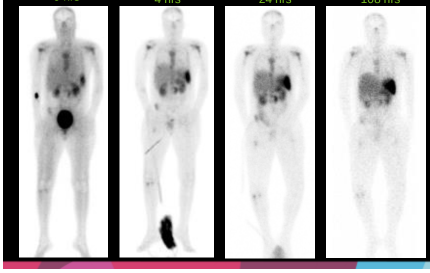
$$\tilde{A} = 1.44 \cdot T_{eff} \cdot A_0$$

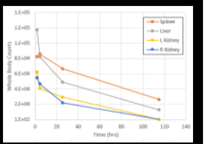


[Lu-177] Lutathera Dosimetry

Time since Tx completion

0 hrs | 4 hrs | ~24 hrs | ~108 hrs





- Organ doses

Lessons Learned-[Lu-177] Tx

- Keep long needle touching bottom of bottle to ensure better infusion of dose
- Sever nausea side effect 1-1.5 hrs post amino acid infusion
  - Carry meds w/ 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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