Applications of Radionuclide Therapy Dosimetry- Worked Examples

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Disclosures

- Yuni Dewaraja is a consultant for MIM Software, Inc.

Internal Therapy Dosimetry: Main Steps

- Image Acquisition - usually at multi time points
  - 2D Planar, 3D SPECT or PET, Hybrid Planar/SPECT
- Image Reconstruction
  - Iterative with corrections
- Segmentation (on functional or anatomical images)
- Quantification (conversion of reconstructed counts to activity)
  - Calibration factor/camera sensitivity (cps per unit activity)
  - Partial volume Ccrrection
- Time - activity fitting, time integrated activity
- Absorbed dose (AD) estimation
  - Time-integrated activity to AD or activity maps to dose-maps

Patient AD calculation in 2 therapies will be presented

1. ^{90}Y microsphere radioembolization (RE) in hepatic malignancies
   - Current treatment: minimally patient specific
   - Motivation for dosimetry based treatment approach: despite promising response rate survival is poor
   - Examples: Pre-therapy for planning, post for verification
2. ^{177}Lu DOTATATE peptide receptor radionuclide therapy (PRRT) in metastatic neuroendocrine tumor (NET)
   - Current treatment: fixed activity/cycles (4 x 7.4 GBq)
   - Motivation for dosimetry based treatment approach: despite promising progression free survival, poor complete response
   - Example: During therapy (after first cycle) dosimetry

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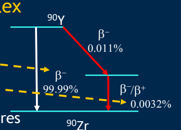
Patient specific dosimetry in Y-90 radioembolization

- Quantitative imaging for dosimetry is complex
  - Y-90 ‘pure’ β emitter
    - SPECT via bremsstrahlung photons
    - PET via low yield positron
  - Need imaging surrogate for planning
    - Differences between MAA particles vs. microspheres



But

- Practical to implement clinical dosimetry
  - Microspheres do not re-distribute
    - Need only a single imaging time point. Liver relative calibration
  - No γ-rays and short β range relative to resolution
    - Voxel-level dosimetry assuming local energy deposition

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Y-90 radioembolization dosimetry

$$MIRD\ schema\ for\ AD:\quad \bar{D}(r_T) = \sum_{r_S} \tilde{A}(r_S) S(r_T \leftarrow r_S)$$

$\tilde{A}(r_S) = A(r_S,0)\int_0^\infty e^{-\lambda t} = A(r_S,0)/\lambda$
Assuming physical decay only

$S(r_T \leftarrow r_S)$: AD to target per transformation in source
= Beta energy per decay/mass
= 49.38 J/GBq
Assuming all energy abs. in mass

$$\bar{D}_{VOI}(Gy) = 49.38\ \text{J/GBq} \cdot \frac{A_{VOI,0}[\text{GBq}]}{m\ [\text{kg}]}$$

$$A_{VOI,0} = \frac{C_{VOI,0}\ (cps)}{CF\ (cps/MBq)} = C_{VOI,0}\frac{A_{liv,0}}{C_{liv,0}} = C_{VOI,0}\frac{A_{admin}*(1-LSF)}{C_{liv,0}}$$

$CF = \frac{C_{liv}}{A_{liv}}$
Liver relative calibration

$A_{liv,0} = A_{admin}$ * (1-LSF)
Assuming all admin. activity is in liver and lung

Dezarn et al. Recommendations of the AAPM ...Med Phys , 38(8) 2011

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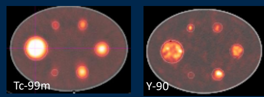
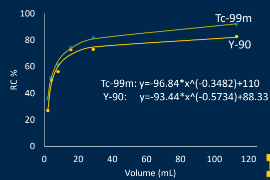
Partial volume correction

- Even with resolution modeling in iterative reconstruction, counts are not fully recovered in ‘small’ objects
  - Need PVC for quantification
  - Most practical is to use recovery coefficients (RC)
  - Phantom under similar conditions as in patient study
  - RC vs. volume curve

$$A_{VOI}(corrected) = \frac{A_{VOI}}{RC(v)}$$





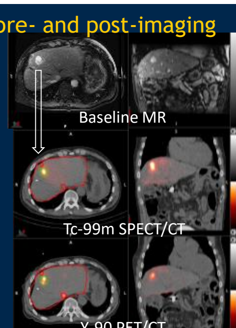
Dewaraja et al, MIRD 23 J Nucl Med 2012

Y-90 radioembolization example: study details

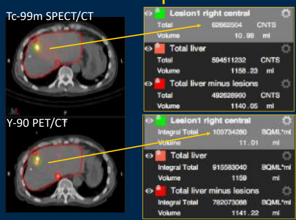
- Patient with metastatic adrenal cancer treated with 1.3 GBq Y-90 glass microspheres (Theraspheres) to the right lobe (700 cc)
- Pre-treatment (4 weeks prior) Tc-99m MAA (185 GBq)
  - Imaging ~ 2h post-admin
  - Planar: to determine lung shunt (2%)
  - SPECT/CT: to evaluate extra hepatic deposition
    - 4 iterations 8 subsets of OSEM with post-filter
- Post-therapy Y-90 time-of-flight PET/CT imaging as part of a research study
  - Imaging at ~ 2 h post RE (before discharge)
    - 1 iteration 21 subsets of OSEM with post-filter

Y-90 RE patient example: pre- and post-imaging

- Diagnostic quality MR used to segment
  - Lesions (> 2 mL) manually by radiologist
  - Liver by technologist using semi-automatic software
  - Non-tumoral liver = liver minus lesions
- Applied to co-registered SPECT/CT and PET/CT
  - Some fine tuning of contours to account for mis-registration



Y-90 RE patient example: AD estimation



Tc-99m MAA: $A_{tum} = C_{tum} \frac{A_{liver}}{C_{liv}}$

$= 62662504 * \frac{1.3}{594511232} = 137 \text{ MBq}$

$= 137/0.7 = 202 \text{ MBq (with PVC)}$

$\bar{D}(Gy) = 49.38 \cdot \frac{202\ MBq}{11cc*1.03\ g/cc}$ = 880 Gy

Y-90 PET can use act. directly from image:

$A_{tum} = 110\ MBq$

$= 110/0.6 = 170 \text{ MBq (with PVC)}$

$\bar{D}(Gy) = 49.38 \cdot \frac{170\ MBq}{11cc*1.03\ g/cc}$ = 742 Gy

		Predicted (from Tc-99m)		Delivered (from Y90-PET)	
	Volume (cc)	Act. (MBq)	Dose (Gy)	Act. (MBq)	Dose (Gy)
Lesion 1	11	202	880	170	742
NT Liver	1140	1060	45	902	38

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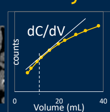
Y-90 RE patient dosimetry example: uncertainty

- Law of propagation of uncertainties
  - *Joint Committee for Guides in Metrology. Evaluation of measurement data - Guide to the expression of uncertainty in measurement (GUM). BIPM 2008*
- Application to internal dosimetry

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-018-4136-7
GUIDELINES
EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations



$$A_{VOI} = \frac{C_{VOI}}{R_{VOI} * CF} \qquad \frac{u(A_{VOI})}{A_{VOI}} = \sqrt{\left(\frac{u(CF)}{CF}\right)^2 + \left(\frac{u(R_{VOI})}{R_{VOI}}\right)^2 + \left(\frac{u(C_{VOI})}{C_{VOI}}\right)^2 - 2\frac{u(R_{VOI}, C_{VOI})}{R_{VOI}C_{VOI}}}$$

$$D_{VOI} = k * \frac{A_{VOI}}{M_{VOI}} \qquad \frac{u(D_{VOI})}{D_{VOI}} = \sqrt{\left(\frac{u(A_{VOI})}{A_{VOI}}\right)^2 + \left(\frac{u(M_{VOI})}{M_{VOI}}\right)^2 - 2\frac{u(A_{VOI}, M_{VOI})}{A_{VOI}M_{VOI}}}$$

	Volume (mL)	RC (Y-90 PET)	AD (Gy)	STD Uncert.
Lesion	11	0.6	742	10%
Normal liver	1140	0.9	38	5%

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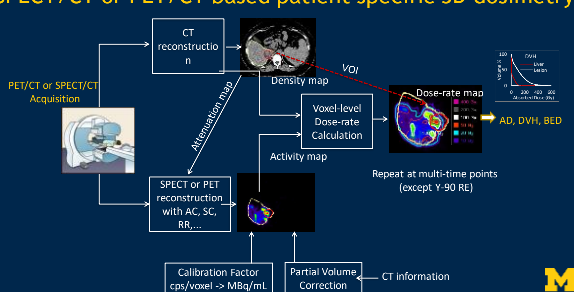
SPECT/CT or PET/CT based patient specific 3D dosimetry



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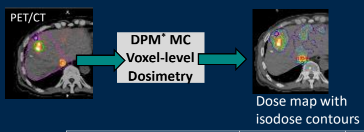
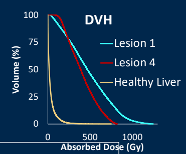
Y90 RE patient example: 3D Monte Carlo dosimetry





	Volume (cc)	Mean Dose (Gy)
Lesion 1	11	735
Lesion 4	5	779
Non-tumor liver	1140	38

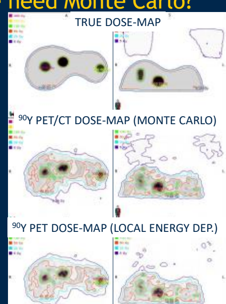
** Wilderman and Dewaraja. IEEE Trans Nucl Sci 2007;54:146.*

Y-90 RE dosimetry: Do we need Monte Carlo?

- Comparison of estimates from MC with estimates from local energy deposition assumption

	DPM* Monte Carlo Absorbed Dose (Gy)	Difference compared with Local Energy Deposition
8 mL sphere	191	2.5%
16 mL sphere	246	1.6%
29 mL ovoid	249	0.8%
Healthy liver	59	-1.6%
L Lung	4.5	-144% (-10%)
R Lung	4.8	-144% (-6%)

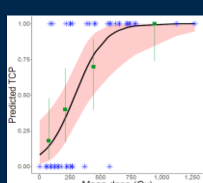
with density correction



Y90 PET-CT study at Univ Mich: Dose - outcome

- TCP models showed a strong association between dose metrics and the probability of response (for AD, AUC = 0.87 sensitivity = 0.75 and specificity = 0.83)

	Mean [Range] Responding* lesions	Mean [Range] Nonresponding* lesions	p-value
AD (Gy)	559 [90 - 1271]	183 [2 - 574]	<0.0001
BED (Gy)	1129 [102 - 4337]	255 [2 - 809]	<0.0001

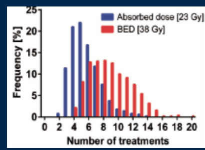


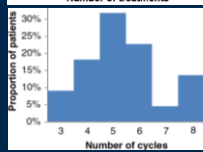
- No statistically significant correlation between non-tumoral liver AD and liver toxicity

Dewaraja et al. JNM 2019 (in press)

^{177}Lu DOTATATE PRRT of NETs: Benefit of individualized treatment

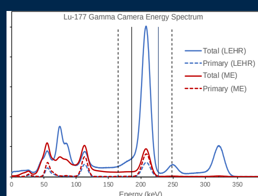
- Studies where number of cycles were adapted based on SPECT/CT based dosimetry after each cycle
  - *Sandstrom et al, ACTA ONCOL. 2018*
    - BED < 38 Gy to kidney and AD < 2 Gy to marrow
  - Sundlov et al, EJNMMI 2017
    - BED < 27 Gy to kidney
- # of cycles increased in most patients without reaching toxicity 'limits'





Lu-177 PRRT dosimetry: quantitative SPECT/CT imaging

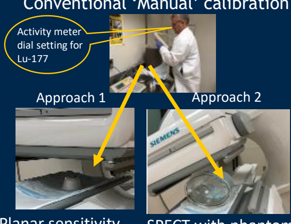
- Image acquisition: ME collimator, typically using 208 keV peak (10%). Also 113 keV peak (6%) available
- Quantification:
  - Can use OS-EM reconstruction with TEW scatter correction
  - Planar point source or SPECT phantom based calibration
    - Some new systems have 'in-built' Lu-177 calibration
      - Image in units of Bq/mL
  - RCs still needed



Ljungberg et al, MIRD 26, JNM 2017.

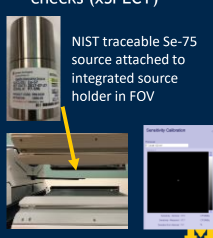
SPECT camera calibration procedure

Conventional 'Manual' calibration



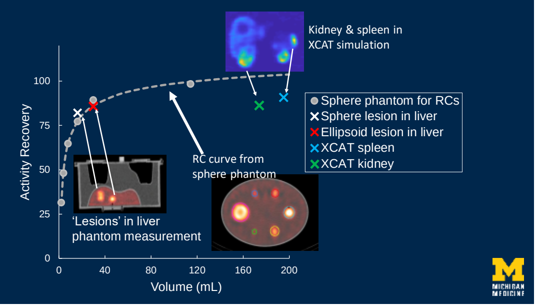
$S = C_{ref}/A_{ref}$ (cps per MBq)

'Built in' with monthly checks (xSPECT)



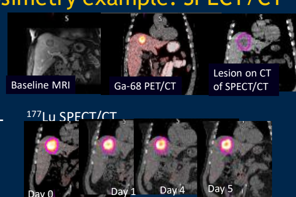
Bergeron & Cessna. Nuc Med Comm. 39: 500 - 504

RCs for Lu-177: demonstrating impact of object shape



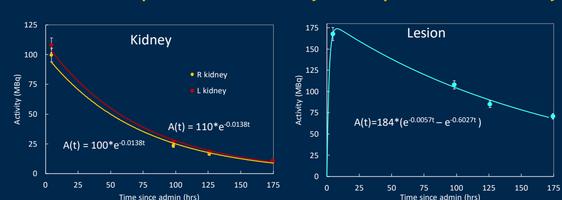
Lu-177 PRRT patient dosimetry example: SPECT/CT

- Quantitative SPECT/CT
  - day 0,1,4,5 after cycle 1
  - 80 mAs, 130 kVp CT on day 0, day1-5, 15 mAs CT for AC only
  - SPECT image directly in Bq/mL
- Segmented on day 0 CT
  - lesions > 4 mL by radiologist kidney by technologist
  - Co-register time points
- RCs for PVC
- Mono- or bi-exponential fit



	Vol mL	RC	Activity (STD) MBq			
			Day 0	Day 4	Day 5	Day 7
Lesion	111	0.94	168 ±8	108 ±5	85 ±4	71 ±3
R kidney	261	0.86	100 ±6	23±1	16 ±1	10 ±1
L kidney	277	0.86	108 ±6	27 ±2	18 ±1	11 ±1

Lu-177 PRRT patient dosimetry example: time-activity



R Kidney $\tilde{A} = 100 * \int_0^\infty e^{-0.0138t} = \frac{100}{0.0138} = 7225\ \mathrm{MBq-h}$

L Kidney $\tilde{A} = 110 * \int_0^\infty e^{-0.0138t} = \frac{110}{0.0138} = 7964\ \mathrm{MBq-h}$

Lesion $\tilde{A} = 184 * \int_0^\infty (e^{-0.0057t} - e^{-0.6027t})$
= 184* (1/0.0057 - 1/0.6027)
= 32111 MBq-h

Lu-177 PRRT example: kidney absorbed dose

MIRD schema for AD : $\bar{D}(r_T) = \sum_{r_S} \tilde{A}(r_S) S(r_T \leftarrow r_S)$ — AD to target per transformation in source

$$\bar{D}(r_{kid}) = \tilde{A}(r_{kid}) S(r_{kid} \leftarrow r_{kid}) + \tilde{A}(r_{rb}) S(r_{kid} \leftarrow r_{rb})$$

$$5.70 \cdot 10^{-5} \frac{\mathrm{mGy}}{\mathrm{MBq \cdot s}}$$

$$= S(r_{kid} \leftarrow wb) \cdot \frac{m(wb)}{m(rb)} - S(r_{kid} \leftarrow r_{kid}) \cdot \frac{m(r_{kid})}{m(rb)}$$

$$= 3.53 \cdot 10^{-7} \cdot \frac{7300}{(7300 - 422)} - 5.70 \cdot 10^{-5} \cdot \frac{422}{(7300 - 422)} = 2.36 \cdot 10^{-8} \frac{\mathrm{mGy}}{\mathrm{MBq \cdot s}}$$

$$\bar{D}(r_{kid}) = (7225 + 7964) * 3600\, MBq.s * 5.70 \cdot 10^{-5} \frac{\mathrm{mGy}}{\mathrm{MBq \cdot s}} + 205686 * 3600\, MBq.s * 2.36 \cdot 10^{-8} \frac{\mathrm{mGy}}{\mathrm{MBq \cdot s}} = 3.1\ \mathrm{Gy}$$

With mass scaling, $S(r_{kid} \leftarrow r_{kid}) = S(r_{kid} \leftarrow r_{kid}) * \frac{m(ref)}{m(pat)}$

then $\bar{D}(r_{kid}) = 2.4\ Gy$

MIRD Primer for Absorbed Dose Calculation 1991

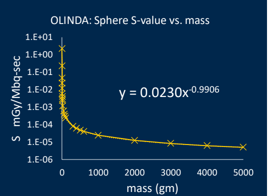
Lu-177 PRRT example: lesion absorbed dose

- OLINDA unit density sphere model (self-dose only) for 111 mL lesion:
  S = 2.2 x 10^{-4} mGy/MBq.s
- Tumor AD

$$\bar{D}(r_{tum}) = \tilde{A}(r_{tum}) S(r_{tum} \leftarrow r_{tum})$$

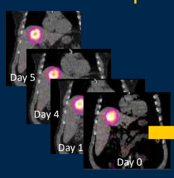
= *32111* 3600 MBq.s * 2.2x 10^{-4} mGy/MBq.s * 0.001*

= *25 Gy*

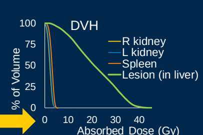


Stabin MG et al. OLINDA/EXM: the second-generation personal computer software … J Nucl Med. 2005 Jun;46(6):1023-7

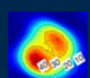
Lu-177 PRRT patient example: 3D Monte Carlo dosimetry



DPM MC Voxel-level Dosimetry



MC based mean AD
Tumor: 24 Gy
R Kidney: 2.4 Gy
L Kidney: 2.4 Gy



Lesion dose map with Iso dose contours(Gy)

Thank You
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Questions

1. Which of the following is the major contributor to self absorbed dose in therapies involving Lu-177 or Y-90

a. Bremsstrahlung photons
b. Gamma-rays
c. Beta-particles
d. Both gamma-rays and beta particles contribute equally

Reference: Sandström M, Garske-Román U, Johansson S, Granberg D, Sundin A, Freedman N. Kidney dosimetry during (177)Lu-DOTATATE therapy in patients with neuroendocrine tumors: aspects on calculation and tolerance. Acta Oncol. 2018 Apr;57(4):516-521.

Questions

2. Source region time-integrated activity for post-therapy imaging based absorbed dose estimation in Y-90 microsphere radioembolization typically

a. requires Y-90 imaging at multiple time points
b. requires Y-90 imaging at a single time point
c. can be obtained by PET imaging only
d. cannot be determined as Y-90 has no associated gamma-rays

Reference: Elschot M, Vermolen BJ, Lam MG, de Keizer B, van den Bosch MA, de Jong HW.
Quantitative comparison of PET and Bremsstrahlung SPECT for imaging the in vivo yttrium-90 microsphere distribution after liver radioembolization. PLoS One. 2013;8(2):e55742.