Fundamentals of RNT dosimetry

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Outline

WHY ?

MIRD formalism – old

New

- MC-based personalized dosimetry
- Guidelines
- Activity quantification
- Uncertainty (EANM guidelines)
- Radiobiology
- Targeted Alpha-Particle Radiotherapy

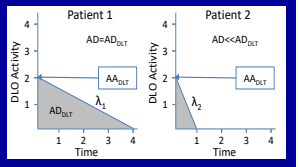
NO AD-based Treatment planning for RPT

Standard is the chemotherapy paradigm of dose escalation

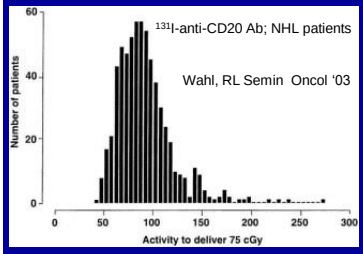
AA limit is set by patients with maximum retention

BUT great inter-patient variability – Xbeam is limited by NO toxicity

RPT is radiation just as Xbeam



Admin Activity (AA) vs Abs Dose



Example of patient variability

Previously demonstrated that 75 cGy to WB increases RM toxicity

Growing body of evidence, differences of up to an **order of magnitude** in NO dose with fixed activity

RPT standard treatments

- 100 mCi radioiodine for thyroid ablation
- 200 mCi radioiodine for thyroid therapy
- 200 mCi I-131 mIBG for neuroendocrine tumours
- 200 mCi x 4 for Y-90 DOTATATE of neuroendocrine tumours
- 200 mCi x 4 for Lu-177 DOTATATE for neuroendocrine tumours
- 200 mCi x 4 for Lu-177 PSMA for bone metastases
- 50 kBq/kg x 6 for Ra-223 for bone metastases

Credit: G. Flux Royal Marsden. EANM '18
J. Capala NCI Theranostics '18

Reasons for optimism for dosimetry

MIRD, AAPM (Ad Hoc Committee to become RPTSC), ASTRO, SNMMI, NCI, ICRU, IAEA goal of patient-specific dosimetry

NIST supportive

Collaboration between ASTRO and SNMMI

Billing, Education, Standardization

Need to engage Pharma, NRC, FDA

Dosimetry with fixed activity

- Retrospective
- Measure NO doses to establish data showing need for treatment planning
- Tumor dosimetry for dose-response
- Tumor dosimetry folded into treatment planning

RPT Dosimetry Basics

2 methods

1. Activity-based with phantom derived S values - **MIRD**
2. Dose rate-based using Monte Carlo and patient-specific anatomy (gold standard)

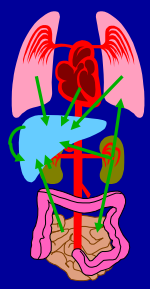
Both 'require' multiple time point 3D in vivo emission and transmission images (SPECT/CT or PET/CT)

Dosimetry – Absorbed Fraction

Absorbed Dose: Energy (damage) absorbed per unit mass. Unit: Gy

$$\frac{\text{Number of disintegrations} \times \text{Energy released per dis.} \times \text{Fraction that is absorbed}}{M_t}$$

Sources are internal, constraint is normal organ toxicity

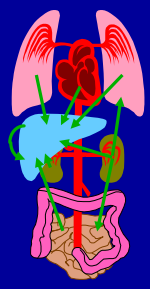


Dosimetry – Absorbed Fraction

Absorbed Dose: Energy (damage) absorbed per unit mass. Unit: Gy

$$\frac{\tilde{A}_S \times \text{Energy released per dis.} \times \text{Fraction that is absorbed}}{M_t}$$

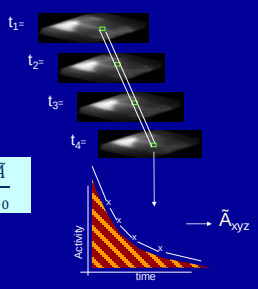
Sources are internal, constraint is normal organ toxicity



Time-Integrated Activity*

Activity images

$$\tilde{A} = \int_0^\infty A(t)dt$$



TIA coefficient (Residence time)

$$\tilde{a} = \frac{\tilde{A}}{A_0}$$

*(Cumulated activity)

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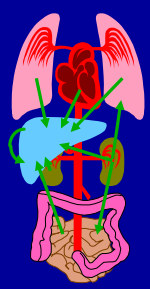
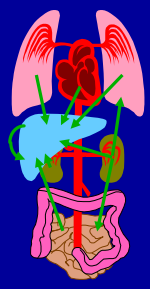


Dosimetry – Absorbed Fraction

Absorbed Dose: Energy (damage) absorbed per unit mass. Unit: Gy

$$\frac{\tilde{A}_S \times \Delta \times \text{Fraction that is absorbed}}{M_t}$$

Sources are internal, constraint is normal organ toxicity



Energy released per decay

MIRD: Radionuclide Data and Decay Schemes

53-IODINE-131

HALF-LIFE = 8.04 DAYS 21-JAN-76
DECAY MODE(S): β^-

RADIATION	PARTICLES/ TRANSITION n(i)	ENERGY/ PARTICLE E(i) MeV	ENERGY/TRANSITION Δ(i) rad g/μCi h	Δ(i) Gy kg/Bq s
β^- 1	2.13E-02	6.935E-02†	3.15E-03	2.37E-16
β^- 2	6.20E-03	8.693E-02†	1.15E-03	8.63E-17
β^- 3	7.36E-02	9.660E-02†	1.52E-02	1.14E-15
β^- 4	8.94E-01	1.915E-01†	3.65E-01	2.74E-14
β^- 6	4.20E-03	2.832E-01†	2.53E-03	1.91E-16
γ 1	2.62E-02	8.018E-02	4.48E-03	3.36E-16
Listed x,y and y± radiations			8.10E-01	6.09E-14
Omitted x,y and y± radiations‡			2.32E-03	1.75E-16
Listed β,ce and Auger radiations			4.05E-01	3.04E-14
Omitted β,ce and Auger radiations‡			3.96E-03	2.98E-16
Listed radiations			1.21E+00	9.13E-14
Omitted radiations‡			6.29E-03	4.73E-16

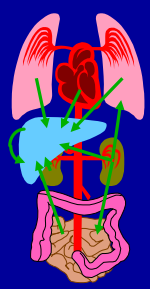
$\Delta_{photons}$
$\Delta_{electrons}$
Δ_{total}

Dosimetry – Absorbed Fraction

Absorbed Dose: Energy (damage) absorbed per unit mass. Unit: Gy

$$\frac{\tilde{A}_S \times \Delta \times \text{Fraction that is absorbed}}{M_t}$$

Sources are internal, constraint is normal organ toxicity

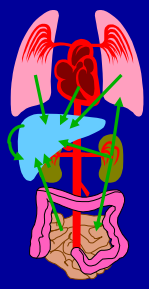


Dosimetry – Absorbed Fraction

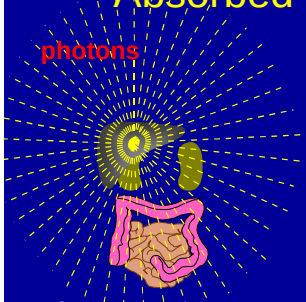
Absorbed Dose: Energy (damage) absorbed per unit mass. Unit: Gy

$$\frac{\tilde{A}_S \times \Delta \times \phi_{t \leftarrow s}}{M_t}$$

Sources are internal, constraint is normal organ toxicity



Absorbed Fraction



$0 \leq \phi_{t \leftarrow s} < 1$
$0 < \phi_{s \leftarrow s} \leq 1$

$\phi_{t \leftarrow s} = 0$
$\phi_{s \leftarrow s} = 1$

S-values

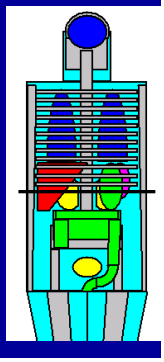
Absorbed fraction methodology uses MIRD S-values[a] determined from idealized geometrical model (no tumors) and Monte Carlo

$$\frac{\tilde{A}_S \times \boxed{\Delta \times \phi_{t \leftarrow s}}}{M_t}$$

S-value

OLINDA/EXM[b] is a widely used software which uses MIRD S-values, requires only CA

[a] MIRD Pamphlet #11
[b] Stabin *et al.* JNM '05



Time-Integrated Activity*

Registered Activity images

1. planar, use anterior – posterior methodology [a]

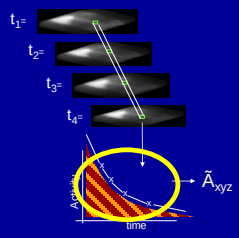
Involves background subtraction (artistic), technical problems of scatter and attenuation only poorly corrected - **very high uncertainty**, whole organ only.

2. **SPECT or PET**, enables voxelized results. 3 – dimensional images enable better reconstruction [b]

3. **Choice of time points !**

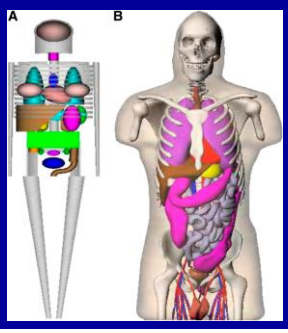
*Cumulated activity [c]

[a] MIRD #16 Siegel *et al*. JNM '99
[b] He *et al*. Phys Med Biol '05
[c] MIRD #21 Bolch *et al*. JNM '08



$$\tilde{A}(x,y,z) = \int_0^\infty A(x,y,z,t)dt$$

Evolution of phantoms



New ICRP phantoms

MIRD to publish S values and missing therapeutic source/target organs

NO TUMORS – use spherical models

B. Marine et al. J Nucl Med 2010;51:806-811 (not ICRP)

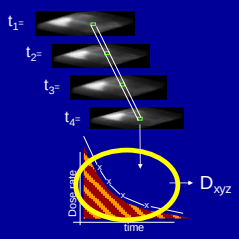
MC-based Dose Rate Integration

3-D dose rate images

$$D(x,y,z) = \int_0^\infty \dot{D}(x,y,z,t)dt$$

Advantages?

- No dependency on modelized anatomy – higher level of accuracy
- (Voxelized results)
- Tumor dosimetry
- (Radiobiology)



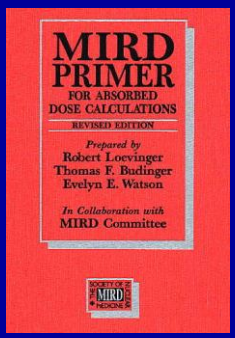
Sgouros *et al*. JNM '04

New Guidelines

New version MIRD Primer to be published this calendar year – old, new material, examples

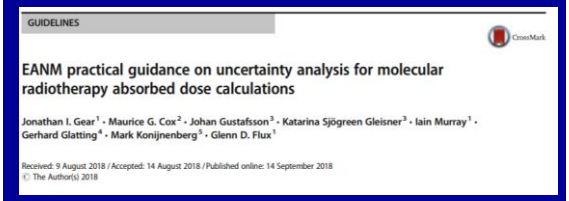
ICRU Report 31 by June 2020 includes MC

IAEA Dosimetry Guidelines



Activity Quantification (NMSC, MIRD)

- Imaging Energy Spectra
- Dead Time Corrections
- Acquisition parameters
- Collimator choices
- Reconstruction methods – iterations
- Response functions
- Calibrations
- Partial Volume Effect
- SPECT vs. Hybrid


GUIDELINES

EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations

Jonathan I. Gear[1] · Maurice G. Cox[2] · Johan Gustafsson[3] · Katarina Sjögreen Gleisner[3] · Iain Murray[1] · Gerhard Glatting[4] · Mark Konijnenberg[5] · Glenn D. Flux[1]

Received: 9 August 2018 / Accepted: 14 August 2018 / Published online: 14 September 2018

European Journal of Nuclear Medicine and Molecular Imaging , 45:2456-2474, 2018

EANM Uncertainty

The Joint Committee for Guides in Metrology (JCGM) Guide to the Expression of Uncertainty in Measurement (GUM)

Law of propagation of Uncertainty

Salient results

Error bars should be calculated for published results – long-standing argument and need

Clinically seek to reduce sources of error, need QA and standards

Activity quantification is not, in theory, the greatest source of uncertainty, but Volume of interest delineation – error bars blow up for tumors less than 8 ml.

MIRD Primer discussed practical sources of error

Bio-effect Modeling

- LQ formalism
- **BED and EQD2**
- **RBE and targeted alpha therapy** (MIRD 22)
- Sub-Organ (MIRD 19) and **Micro-scale modeling (MIRD formalism)**
- EUD
- NTCP
- Cellular-level (MIRD 25)

Biological Effective Dose (BED)

- Equivalent linear dose compared to the linear-quadratic absorbed dose with a repair term [a]
- Effectively Accounts for dose rate variations
- Correlates to toxicity (kidneys) [b]
- For exponential decay, G is given by:

$$e^{-\alpha BED} = e^{-\alpha D - G\beta D^2}$$

$$BED = D\left(1 + \frac{G(\infty)}{\alpha/\beta} D\right)$$

$$G(\infty) = \frac{\lambda}{\lambda + \mu}$$

$$G(\infty) = \frac{2}{D^2}\int_0^{\infty} \dot{D}(t)dt \int_0^{t} \dot{D}(w)e^{-\mu(t-w)}dw$$

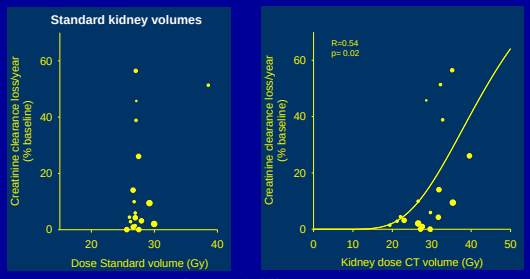
BED extensions enable wider range of applications [c]

α and β are the tissue specific coefficients for radiation damage from the linear-quadratic model; μ is repair constant

[a] Dale *et al*. Phys Med Biol '96
[b] Barone *et al*. JNM '05
[b] MIRD pamphlet 20 JNM '08
[c] Baechler *et al*. Med Phys '08
[c] Hobbs *et al*. Med Phys '09

Importance of organ volume in self irradiation

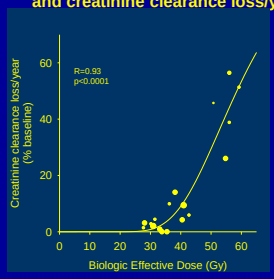
Correlation between kidney dose (Gy) and creatinine clearance loss/year (% baseline) N=18



Barone, et al. JNM '05

UNIVERSITE CATHOLIQUE DE LOUVAIN

Correlation between BED and creatinine clearance loss/year



Barone R, Borson-Chazot F, Valkema R, et al. J Nucl Med. 2005 Jan;46 Suppl 1:99S-106S

UNIVERSITE CATHOLIQUE DE LOUVAIN

MIRD Pamphlet No. 20: The Effect of Model Assumptions on Kidney Dosimetry and Response—Implications for Radionuclide Therapy*

Barry W. Wessels[1], Mark W. Konijnenberg[2], Roger G. Dale[3], Hazel B. Breitz[4], Marta Cremonesi[5], Ruby F. Meredith[6], Alan J. Green[7], Lionel G. Bouchet[8], A. Bertrand Brill[9], Wesley E. Bolch[10], George Sgouros[11], and Stephen R. Thomas[12]

*In collaboration with the MIRD Committee of the SNM: Stephen R. Thomas (Chair), Wesley E. Bolch, A. Bertrand Brill, Darrell R. Fisher, Ruby F. Meredith, George Sgouros, Barry W. Wessels (Task Group Leader), and Pat B. Zanzonico

[1]*Department of Radiation Oncology, Case Western Reserve University School of Medicine, Cleveland, Ohio;* [2]*Research and Development, Mallinckrodt Medical BV, Covidien, Petten, The Netherlands;* [3]*Radiation Physics and Radiobiology, Imperial Healthcare NHS Trust, London, United Kingdom;* [4]*Poniard Pharmaceuticals, Seattle, Washington;* [5]*Medical Physics Division, European Institute of Oncology, Milan, Italy;* [6]*University of Alabama at Birmingham, Birmingham, Alabama;* [7]*CRC Targeting and Imaging Group, Department of Oncology, Royal Free and University College Medical School, University College London, London, United Kingdom;* [8]*Still Rivers Systems, Inc., Littleton, Massachusetts;* [9]*Department of Radiology, Vanderbilt University, Nashville, Tennessee;* [10]*Department of Nuclear and Radiological Engineering, University of Florida, Gainesville, Florida;* [11]*Department of Radiology and Radiological Sciences, School of Medicine, Johns Hopkins University, Baltimore, Maryland; and* [12]*Department of Radiology, University of Cincinnati, Cincinnati, Ohio*

Journal of Nuclear Medicine, 49:1884-99, 2008 MIRD Committee

MIRD 20

Results from Barone et al.

Compares to external beam response data translated to BED

Agreement

$$EQD2 = \frac{D_{RPT}\left(\alpha/\beta + D_{RPT}\cdot G_i(\infty)\right)}{\alpha/\beta + 2}$$

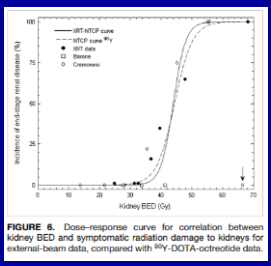


FIGURE 6. Dose–response curve for correlation between kidney BED and symptomatic radiation damage to kidneys for external-beam data, compared with ^{90}Y-DOTA-octreotide data.

Progression of Quantities

- Volume – why not give standard volumes of product
- Activity
- Dose – still very little biology, using patient pharmacokinetics. No genetics, no immune response assessment, physical quantitiy
- Standardized Dose – BED or EQD2 – Doses vary from one patient to another within the same modality; for comparison to external beam, EQD2 is needed
- Variations between modalities…

Radiobiology and Dose differences

- EBRT (and BT) voxel dose is uniform
- Anatomical distribution is driven by beam geometry
- Tumor doses are uniform
- NO doses are non-uniform, but visible
- RPT voxel dose is potentially non-uniform
- Anatomical distribution is driven by physiology – cell types or FSU uptake
- Current technologies based on imaging resolution – limitations
- Dose is not dose

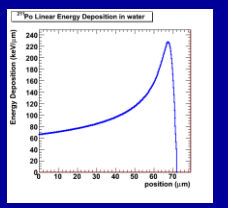
^{225}Ac: α-particle RPT

Massive particles (~ 8000 times electron), deposit greater energy - high Linear Energy Transfer (LET)

Short range, < 80 μm, localized toxicity, scale smaller than most organs and tumors, only a few cell widths. Localized activity leads to localized dose

2-3 hits for cell kill as opposed to thousands of EM tracks

BUT greater lethality means greater potential for toxicity.



α-particle dosimetry

Can we apply RPT paradigms to αRPT?

Challenges:

1. RBE – greater biological effect per unit dose
2. sub-organ localization of dose – short range means higher dose concentration
3. re-localization of daughters (^{225}Ac chain has 4 α-emissions, with ^{213}Bi 45 min HL)
4. low count rate for imaging (typical therapeutic activity is 100 μCi)

THANK YOU FOR YOUR ATTENTION!