Radiation Dosimetry as a Biomarker

RF Hobbs (Johns Hopkins University)

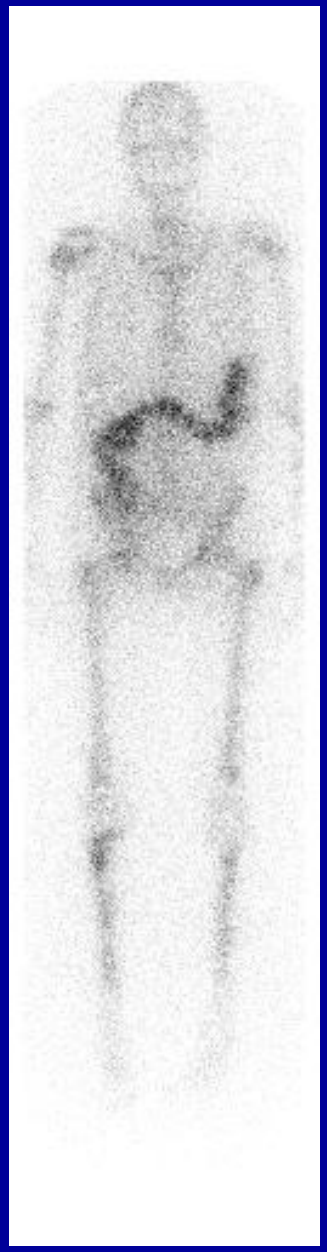
Radiopharmaceutical therapy

Oldest radiation modality, enjoying renewed interest

Other radiation modalities have machines to aim beam or applicators to guide source or discrete source – targets macroscopic disease, controlled radiation. Dose is quantity of administration.

$$D[Gy] = \frac{E[J]}{m[kg]}$$

Radioactive drug given IV – systemic therapy. Presents like chemo somewhat controlled distribution. Administered activity.

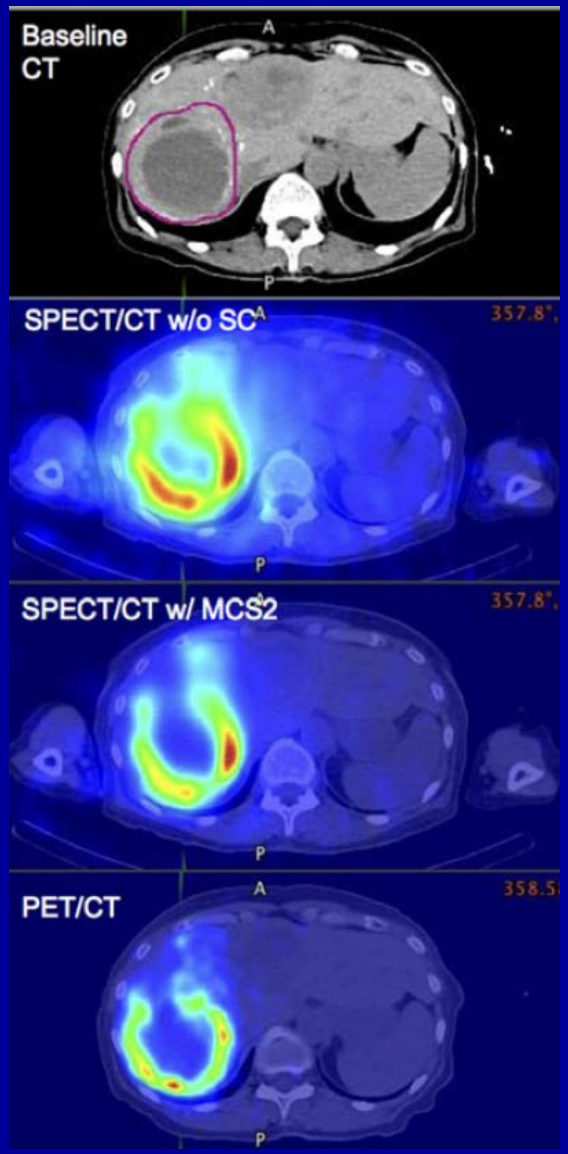


Uncontrolled, but not unknown.

The poorest nuclear medicine image provides an infinite amount of information over that available for ‘cold chemotherapeutics’

Imaging therapeutic drugs *in vivo* in real time

Continual research into quantifying SPECT and planar data for all radionuclides

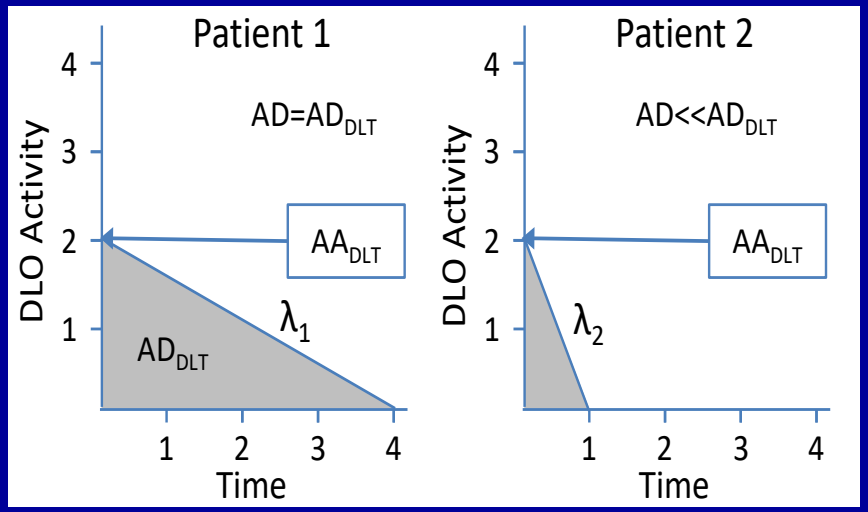


Ra-223 imaging
Hindorf Nucl Med Comun 2012

Bremstrahlung imaging
Dewaraja Med Phys 2017

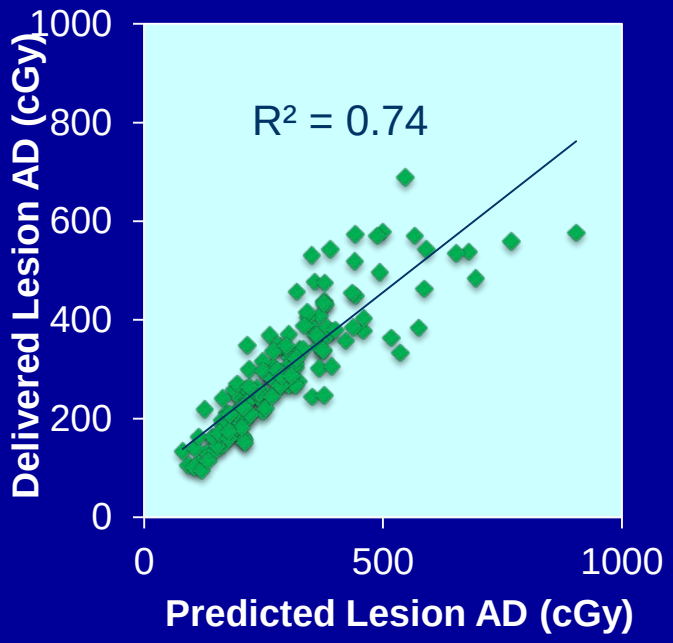
NO AD-based Treatment planning for RPT

- 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
- Can we use pre-therapeutics (theranostics) to predict and plan

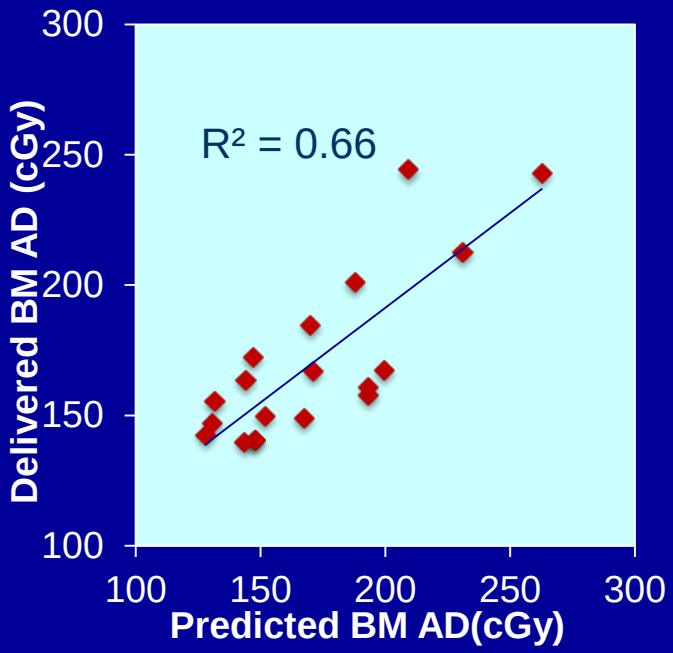


I-131 RIT: demonstrating potential for treatment planning

Predicted vs. Delivered Lesion Absorbed Dose



Predicted vs. Delivered BM Absorbed Dose



Dewaraja et al, JNM 2014

Dosimetry Basics

2 methods

1. Activity-based with phantom derived S values

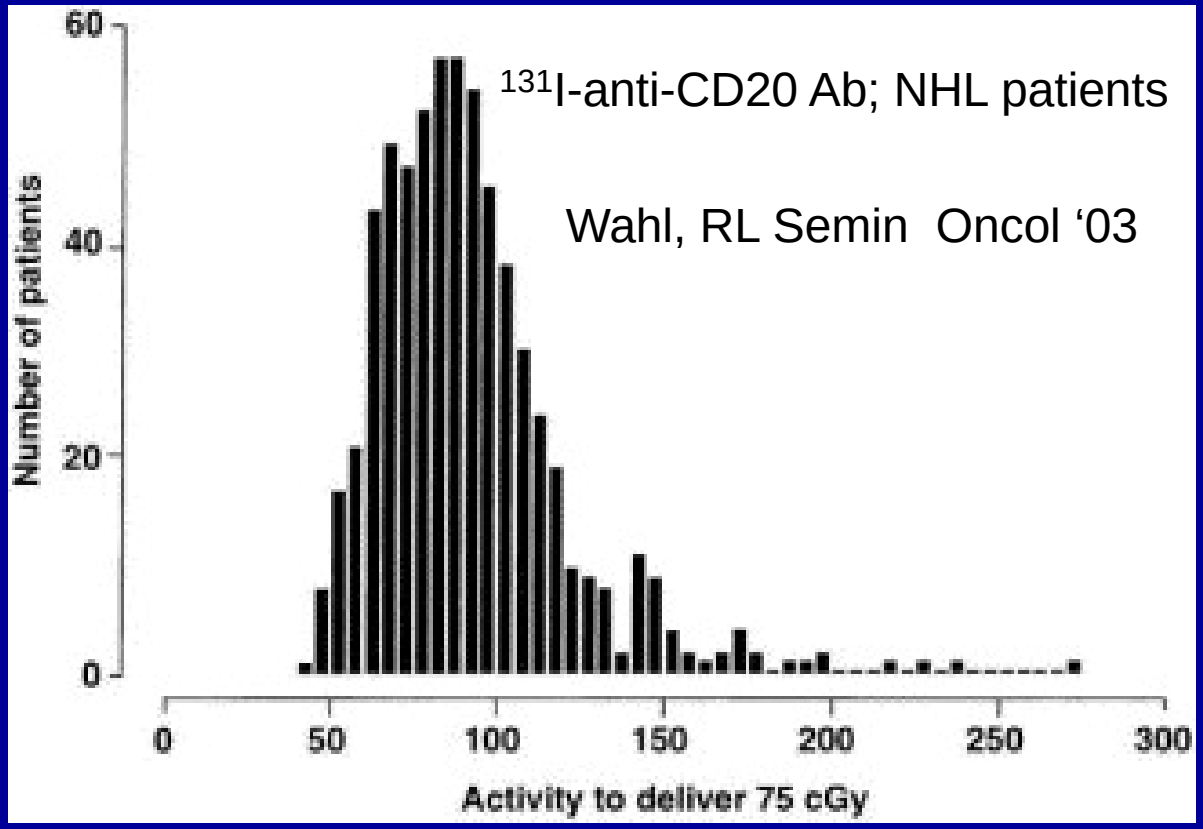
2. Dose rate-based using Monte Carlo and patient-specific anatomy (gold standard)

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

Dosimetry as Biomarker

- Do we need Dosimetry or is administered activity a valid surrogate ?
- Do we have dose-response relationships?
- NCI, AAPM, ASTRO, SNMMI, IAEA state that dose is the common language of radiation
- Current dosimetry technology is limited
- No widespread common methodology

Admin Activity (AA) vs Abs Dose



Example of patient variability

Previously demonstrated that 75 cGy to WB increases RM toxicity

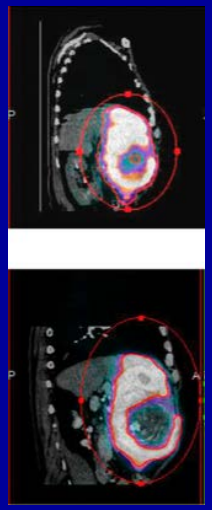
Biokinetics vary from patient to patient affecting uptake and retention
Radiosensitivities vary affecting response to treatment

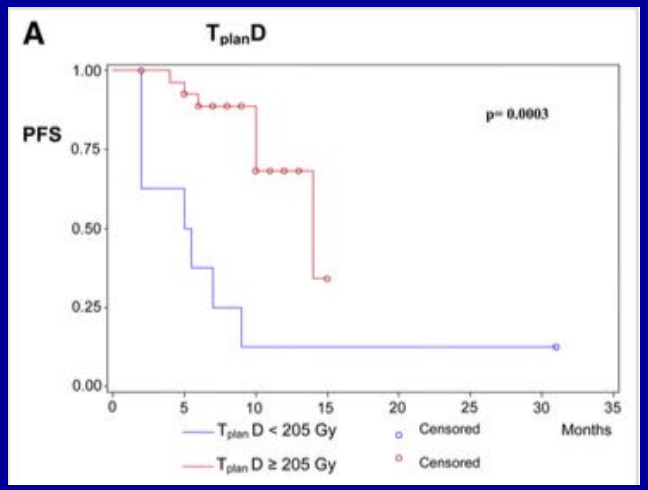
Absorbed doses from fixed activities of I-131 NaI and Ra-223 vary by ~1 order of magnitude for organs at risk and 2 orders of magnitude for target volumes

I-131 NaI for DTC (mGy / MBq)	**Ra-223 for bone metastases (mGy / MBq)**
Red marrow: Bianchi (2012) 0.04 – 0.4	Red marrow: Chittenden (2015) 177-994
Metastatic lesions: Kolbert (2007) 0.03 – 2.6	Lesions: Pacilio (2016) 0.9 – 8.9
Salivary glands: Jentzen (2006) 0.2 - 1.2	Kidneys: Chittenden (2015) 2-15
Thyroid remnants: Minguez (2016) 0.2 - 160	Bone surfaces Chittenden (2015) 2331 – 13118

Benefit of pre-treatment dosimetry: example from ^{90}Y RE

- Initial study (n=36):Tc-MAA SPECT/CT based tumor dosimetry, standard therapy (liver 120 Gy, lung < 30 Gy)
  - Established 205 Gy to tumor as threshold for response





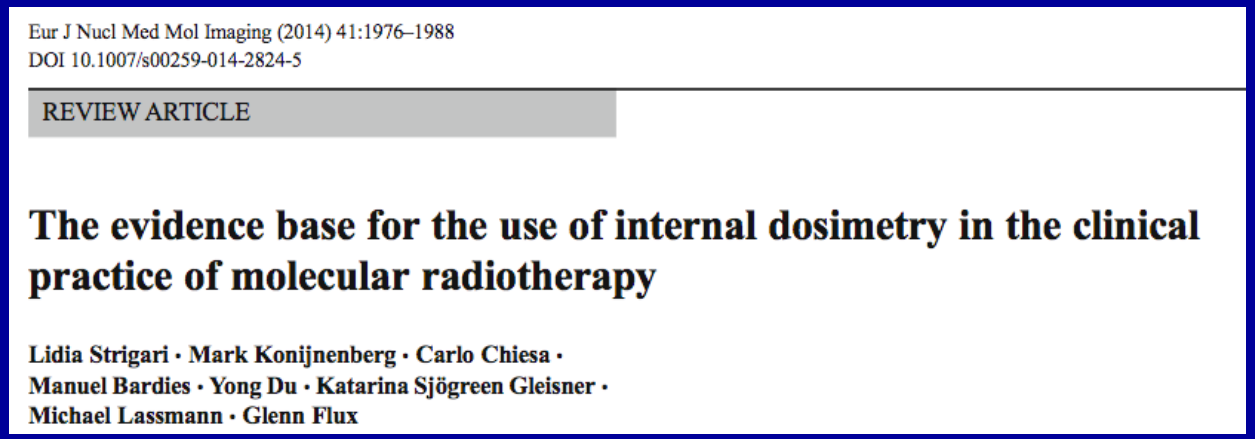
Garin el at, JNM 2012

- Intensification study (n=41): Activity based on MAA dosimetry. Tumor >205 Gy, normal liver<120 Gy,lung<30 Gy
  - 37% received higher activity
  - Improved Survival: TD < 205 Gy, 4 mo (3–5 mo)

  TD > 205 Gy, 18 mo (8–29 mo) (P = 0.005).
  - No increase in toxicity

Why post-therapy dosimetry: dose – effect studies

- Absorbed dose – effect relationships seldom investigated



Eur J Nucl Med Mol Imaging (2014) 41:1976–1988
DOI 10.1007/s00259-014-2824-5

REVIEW ARTICLE

The evidence base for the use of internal dosimetry in the clinical practice of molecular radiotherapy

Lidia Strigari · Mark Konijnenberg · Carlo Chiesa · Manuel Bardies · Yong Du · Katarina Sjögreen Gleisner · Michael Lassmann · Glenn Flux

- Pub Med search: dose-effect correlation in 48 out of 79 studies
- Evidence that dosimetry based treatment will improve outcome
- However, small sample sizes and different dosimetry methods
- Post-therapy imaging should be used for dose - effect

Biomarkers

- Select patients most likely to respond
- Avoid toxicity
- Tumor biopsy
- Serum sampling
- Genetic and epigenetic marker analysis
- Must be rigorously qualified/validated retrospectively or in prospective studies
- Standardized
- Incorporated in the design of clinical trials

Dosimetry

- Select patients most likely to respond
- Avoid toxicity
- **Quantitative Imaging**
- **Blood Counting**
- **Dose calculation**
- Methodology/Results must be rigorously qualified/validated retrospectively or in prospective studies ?
- Standardized
- Incorporated in the design of clinical trials

Dose – effect for ^{131}I therapy in DTC

Study	n	Endpoint	Threshold dose
Maxon	50	Ablation	300 Gy (remnant)
Maxon	26	Response	80 Gy (metastases)
Flux	23	Ablation	49 Gy (remnant)
Verburg	449	Ablation	0.35 Gy (blood)
Benua	122	Complications	2 Gy blood
Hartung	198	Toxicity > grade 3	2 Gy blood
Bianchi	17	Toxicity > grade 3	1.7 Gy blood

Strigari *et al*, Eur J Nuc Med Mol Imag (2014)

Dose – effect for ^{90}Y microsphere RE of liver cancer

Study	n	Imaging	Endpoint	Threshold dose
Garin	36	TcMAA SPECT	PFS, EASL (PR+CR)	205 Gy (lesion)
Mazzaferro	52	TcMAA SPECT	EASL (PR+CR)	500 Gy (tumor)
Chiesa	52	TcMAA SPECT	EASL (PR+CR) liver decomp 50% TCP 15% NTCP	250,1000 Gy(small, large tumor) 75 Gy (liver)
Chansanti	15	TcMAA SPECT	mRECIST (PR+CR)	191 Gy (tumor)
Chang	35	90Y PET/CT	mRECIST (PR+CR)	225 Gy (tumor)
Strigari	73	90Y SPECT	50% TCP (PR+CR) 5% > G2 toxicity	150 Gy (tumor), 50 Gy BED (liver)
Sangro	45		REILD	40 Gy (liver)
Campbell	12	TcMAA SPECT	FDG res. > 50%	260 Gy (tumor)
Flamen	8	TcMAA SPECT	FDG res. > 50%	46 Gy (tumor)
Song	23	90Y PET/CT	PFS, RECIST	200 Gy (tumor)

Strigari *et al*, Eur J Nuc Med Mol Imag (2014)

- 100 mCi radioiodine for thyroid ablation
- 200 mCi radioiodine for thyroid therapy
- 200 mCi Y-90 microspheres for treatment of liver metastases
- 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

Empirical chemotherapy paradigm – learning from observation and experience…

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

Biomarkers vs. Dosimetry

- Regulatory agencies provide considerable guidance on the biomarker qualification process. Biomarkers not institution specific.
- Dosimetry not currently used for treatment planning, developed and regulated for stochastic cancer risk
- Dosimetric methodologies lack completion /standardization and cross-institution validation. Need QA.

Beta vs Alpha

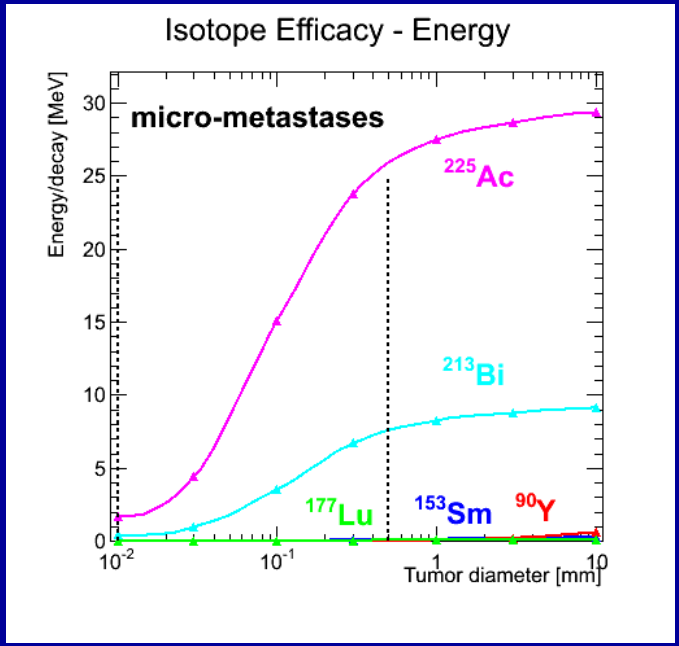
Short range, < 80 µm

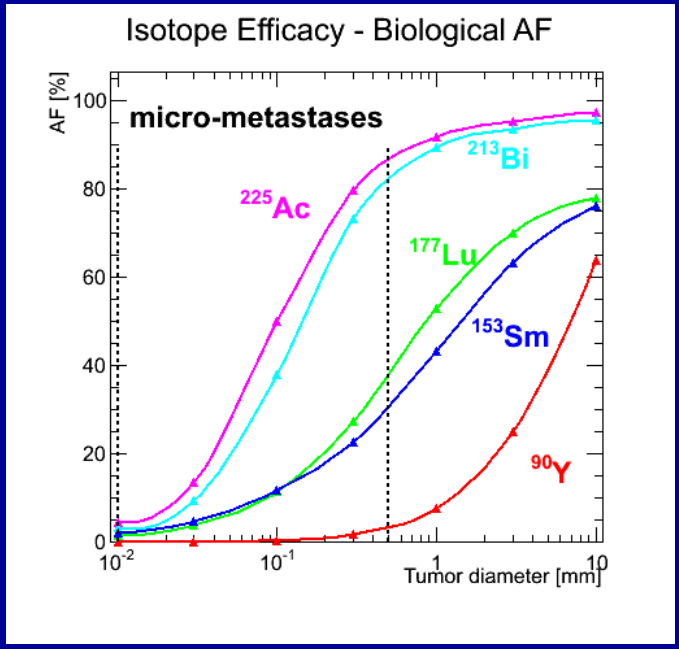
Higher LET – higher damage

BUT damage to both NO and tumors

AF is higher for micromets

Lower AAs (~ 100 µCi)





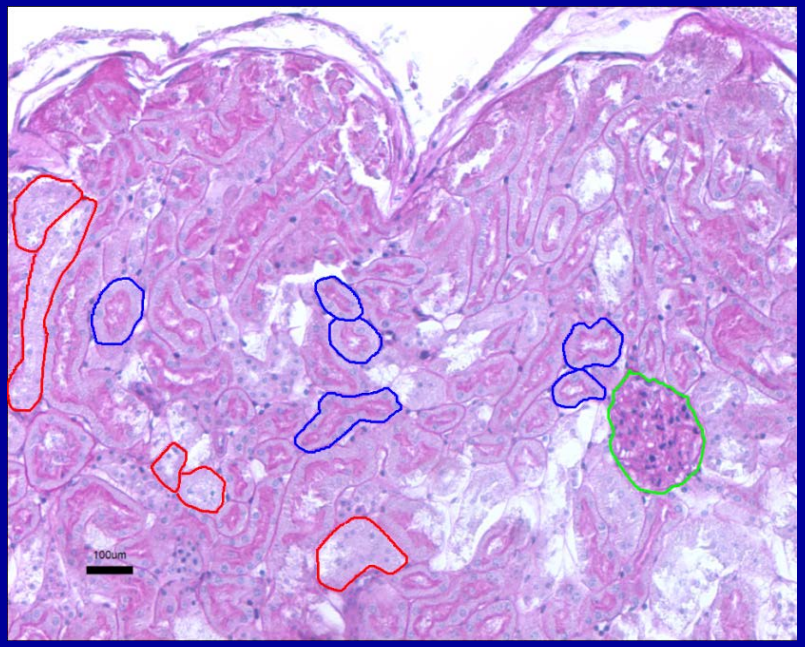
Alpha Dosimetry

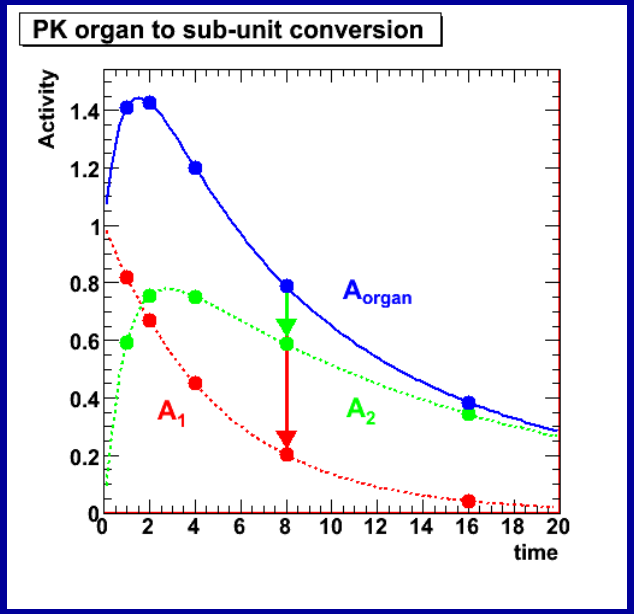
Small scale dosimetry – physiological localized uptake

Murine ex vivo quantification for apportionment to sub-structures

Low count rate imaging

Re-localization of daughter radionuclides





Methodology/QA dev

MIRD Primer – absorbed fraction methodology using time-integrated activity

New software – DosiSOFT FDA approved

ICRU Report 31

IAEA Report

AAPM

QA/reproducibility

Standards for both image and activity quantification and dosimetry consistency

NIST – B. Zimmerman

MetroMRT

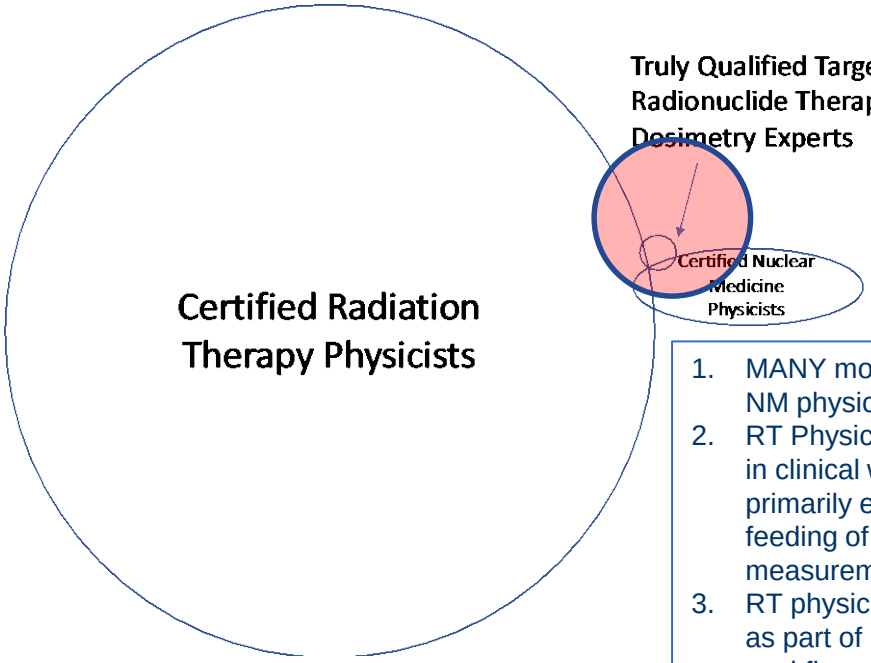
IAEA

AAPM

IROC/NCI

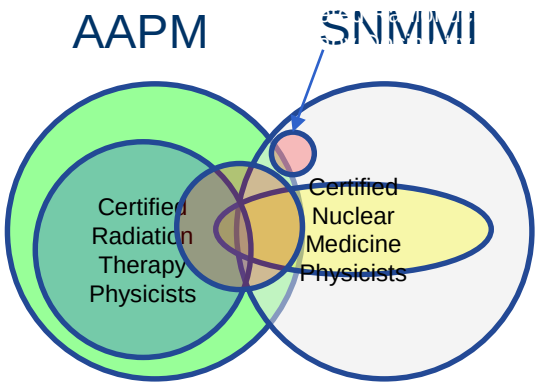
Dosimetry expertise

Distribution and Overlap of Specialty Certified Medical Physicists ***AND*** Actually Qualified TRT Dosimetry Physicists



1. MANY more RT physicists than NM physicists.
2. RT Physicists are engaged daily in clinical workflow, NM primarily engaged in care and feeding of imaging and NM measurement equipment
3. RT physicist work **reimbursed** as part of routine clinical workflow.
4. TRT experienced physicists are currently operating in a niche specialty.

Professional Society Home for Physicists



1. AAPM is primary home to RT Physicists
2. SNMMI is primary home to NM Physicists.
3. TRT Dosimetry physicists primarily (not exclusively) are SNMMI members (MIRD, RADAR).

Credit: J. Sunderland U Iowa. SNMMI/NCI Theranostics ‘18

Physician expertise

ASTRO and SNMMI working together.

Theranostics Center of Excellence

CE sessions

Symposia

Certificate

Reimbursement work

Trial designs

Data collection for dosimetric analysis during Phase I evaluation will likely save money and time in later stage trials. This is from the perspective of being able to better assess the factors that lead to toxicity or to a favorable treatment outcome.

Including a data collection effort in phase II or III trials that could lead to a sub-group analysis (similar to what is currently done w/ all of the trial result papers published in NEJM) that would examine whether there is evidence that **current** dosimetry-driven treatment would have reduced toxicity and improved tumor control. Such sub-group analyses are considered hypothesis generating and are typically evaluated in subsequent trials.

Credit: G. Sgouros

Dosimetry is more than AD

Dosimetry doesn't explain everything!

Other correlates exist!

Dosimetry is more than calculation of absorbed dose, but whatever correlates exist, including the absorbed dose will only improve personalization of TP.

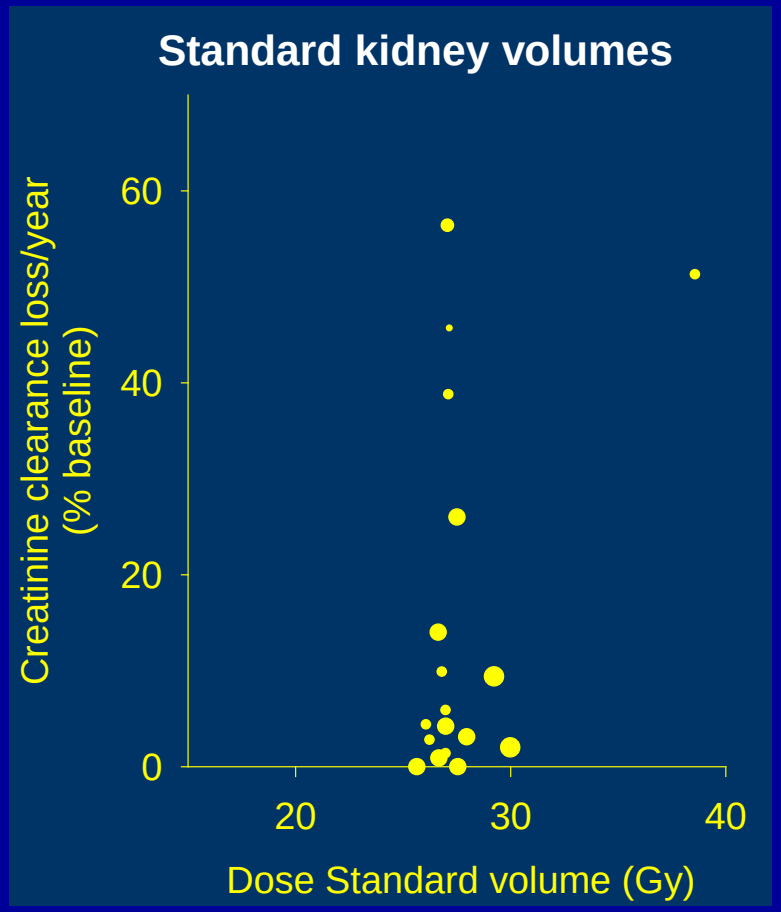
Dosimetry constantly becoming more sophisticated: PK models, small scale dosimetry, e.g.

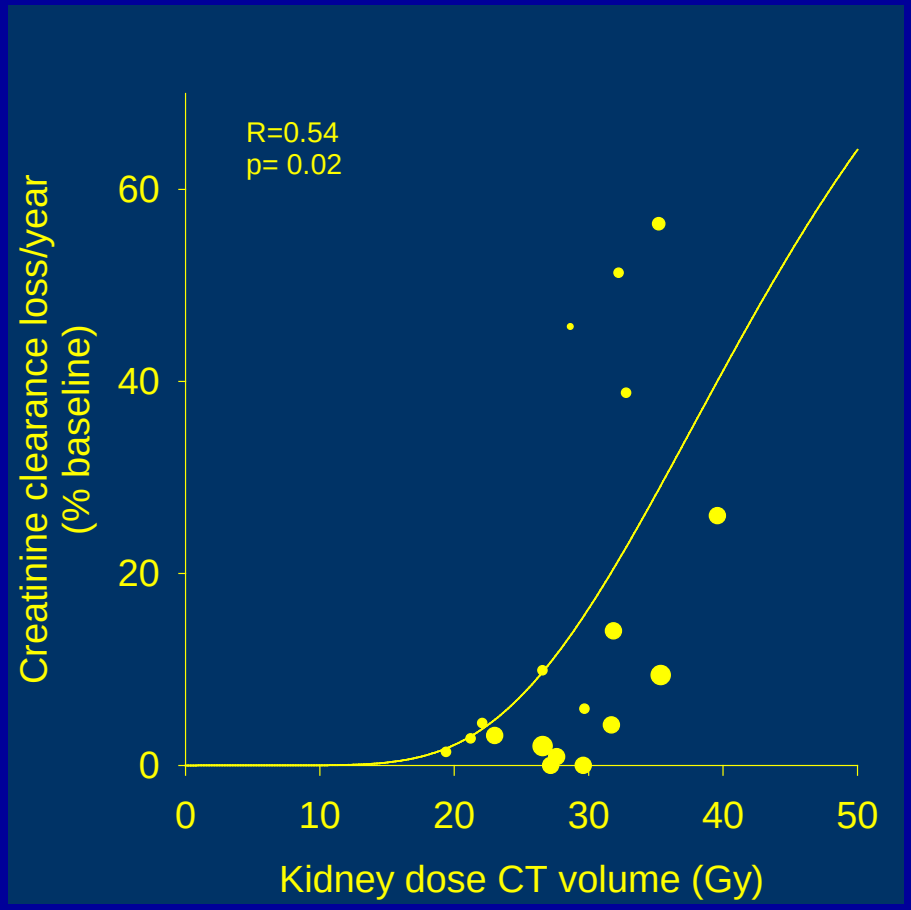
Radiobiology -> bioeffect modeling (BED, EUD), absocapal, bystander effects *

*J. Buchsbaum talk

Importance of organ volume in self irradiation

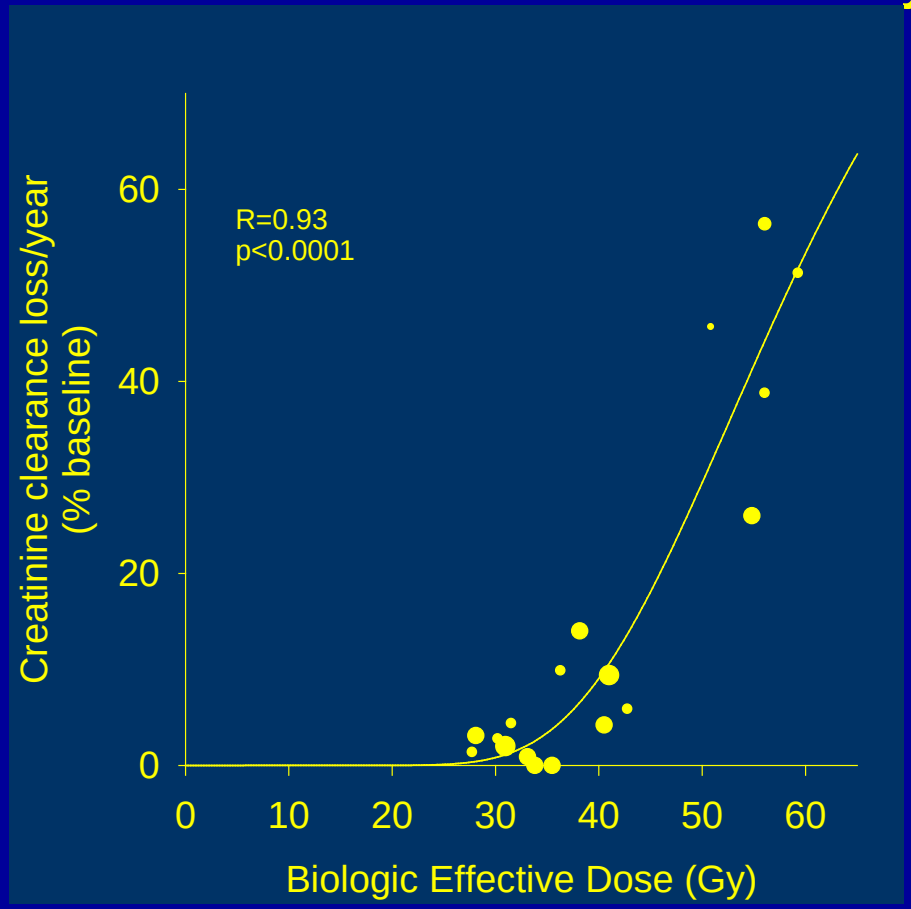
Correlation between kidney dose (Gy)
and creatinine clearance loss/year (% baseline) N=18





Barone, et al. JNM '05

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

Dosimetry as Biomarker ?

Dose is cause for damage not effect

Large number of correlative studies

Useful to consider as biomarker for QA/rigor comparisons

Methodologies depend on modality, affects value

Systematic application needs expertise, rigorous methodology, qa, reproducibility

THANK YOU FOR YOUR ATTENTION!