Theranostic clinical trials outlook and the role of medical physics

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Radiation Research Program

Division of Cancer Treatment and Diagnosis

NCI/NIH/HHS

Outline

- FDA-approved therapeutic radiopharmaceuticals
- Radiation dosimetry as a biomarker
- Treatment planning process and software
- Recent initiatives at professional societies (AAPM,SNMMI)
- Conclusions

RPTs Approved before 2022

RPT agent	Company	Indication	Properties
Radium-223 chloride[a]	Bayer	Bone metastasis	Calcium analogue
^{90}Y-loaded glass microspheres	BTG	Hepatic malignancies	Radioembolization of liver microvasculature
^{90}Y-loaded resin microspheres	CDH Genetech/ Sirtex	Hepatic malignancies	Radioembolization of liver microvasculature
^{131}I radioiodine	Jubilant Draximage/ Malklincrodt	Thyroid cancer	Active uptake through Na–I symporter and storage in follicular cells
^{153}[Sm]lexidronam	Lantheus	Cancer bone pain	Binding to hydroxyapatite matrix
^{177}Lu-labelled DOTATATE	Novartis/AAA	Neuroendocrine tumours	SSR-mediated binding
[^{131}I]mIBG	Progenics	Adrenergic receptor^{+} tumours	Active uptake mechanism via the adrenaline transporter and storage in presynaptic neurosecretory granules

Sgouros et al. Nature Reviews/Drug Discovery, 2020

VISION

The NEW ENGLAND JOURNAL of MEDICINE

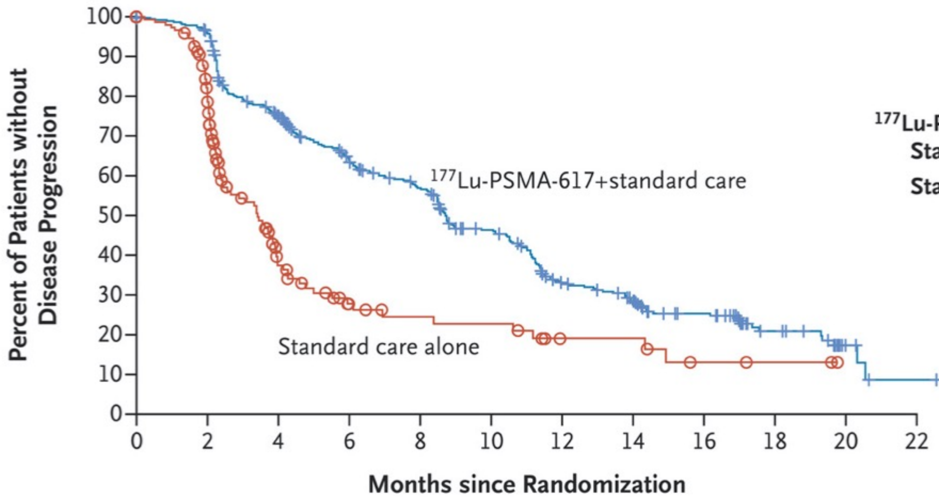
ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

Oliver Sartor, M.D., Johann de Bono, M.B., Ch.B., Ph.D., Kim N. Chi, M.D., Karim Fizazi, M.D., Ph.D., Ken Herrmann, M.D., Kambiz Rahbar, M.D., Scott T. Tagawa, M.D., Luke T. Nordquist, M.D., Nitin Vaishampayan, M.D., Ghassan El-Haddad, M.D., Chandler H. Park, M.D., Tomasz M. Beer, M.D., et al., for the VISION Investigators*

VISION

A Imaging-Based Progression-free Survival



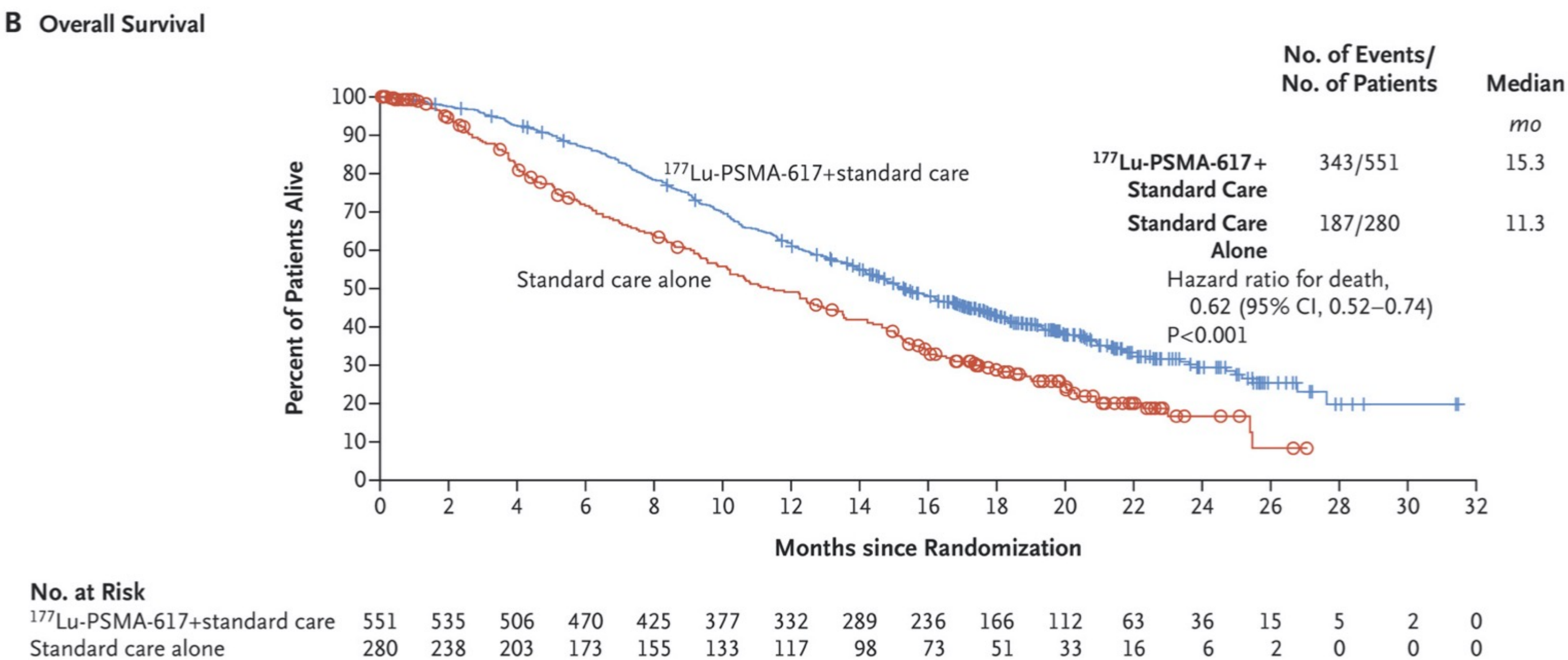
	No. of Events/ No. of Patients	Median
		mo
^{177}Lu-PSMA-617+ Standard Care	254/385	8.7
Standard Care Alone	93/196	3.4

Hazard ratio for progression or death, 0.40 (99.2% CI, 0.29–0.57)
P<0.001

No. at Risk

	0	2	4	6	8	10	12	14	16	18	20	22
^{177}Lu-PSMA-617+standard care	385	362	272	215	182	137	88	71	49	21	6	1
Standard care alone	196	119	36	19	14	13	7	7	3	2	0	0

VISION


B Overall Survival
No. of Events/ No. of Patients
Median
mo
^{177}Lu-PSMA-617+ Standard Care 343/551 15.3
Standard Care Alone 187/280 11.3
Hazard ratio for death, 0.62 (95% CI, 0.52–0.74)
P<0.001
^{177}Lu-PSMA-617+standard care
Standard care alone
Percent of Patients Alive
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32
Months since Randomization
No. at Risk
^{177}Lu-PSMA-617+standard care 551 535 506 470 425 377 332 289 236 166 112 63 36 15 5 2 0
Standard care alone 280 238 203 173 155 133 117 98 73 51 33 16 6 2 0 0 0

Current Approach

- 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 - 6 for Lu-177 PSMA for prostate cancers
- 50 kBq/kg x 6 for Ra-223 for bone metastases

Empirical chemotherapy paradigm – learning from observation and experience…

One Size Does Not Fit All

Absorbed Doses for Tumors and Organs at Risk in ^{177}Lu PRRT Studies

Organ or lesion	No. of patients	Absorbed dose (Gy/GBq) Median	Range	Mean ± SD	Method	Reference
Red marrow	6			0.07 ± 0.01	Blood	*9*
	61			0.04 ± 0.02	Blood	*10*
	15	0.02	0.01–0.13	0.034 ± 0.030	Blood	*11*
	12	0.03	0.02–0.06	0.04 ± 0.02	Blood	*13*
	200	0.02	0.01–0.05		Blood	*14*
	7	≤0.07* (≤0			SPECT	*16*
	10	0.04	0.02–0.06		Blood	*33*
Kidneys	6			0.88 ± 0.19	Planar	*9*
	61			0.90 ± 0.30	Planar	*10*
	16			0.97 ± 0.24	Planar	*12*
	16			0.90 ± 0.21	SPECT	*12*
	12	0.68	0.33–1.65	0.80 ± 0.35	Planar	*13*
	200	0.61	0.27–1.35		SPECT	*14*
	88		0.36–0.78	0.57 ± 0.09	Planar	*15*
	7	1.15* (0.6	0.54–2.16* (0.34–1.82†)	± 0.49* (0.84 ± 0.49†)	SPECT	*16*
	10	0.62	0.45–17.74		Planar	*33*
	33		[illegible]	0.8 ± 0.3	Planar	*42*
Tumors	6		3.9–37.9		Planar	*9*
	61			9.7 ± 11.1	Planar	*10*
	16	6.7	0.1–20		SPECT	*12*
	88		1.3–4.8	3.41 ± 0.68	Planar	*15*
	7		2–11* (1–11†)		SPECT	*16*
	10		0.6–56		Planar	*33*
	24	6.8	1.4–23		SPECT	*42*

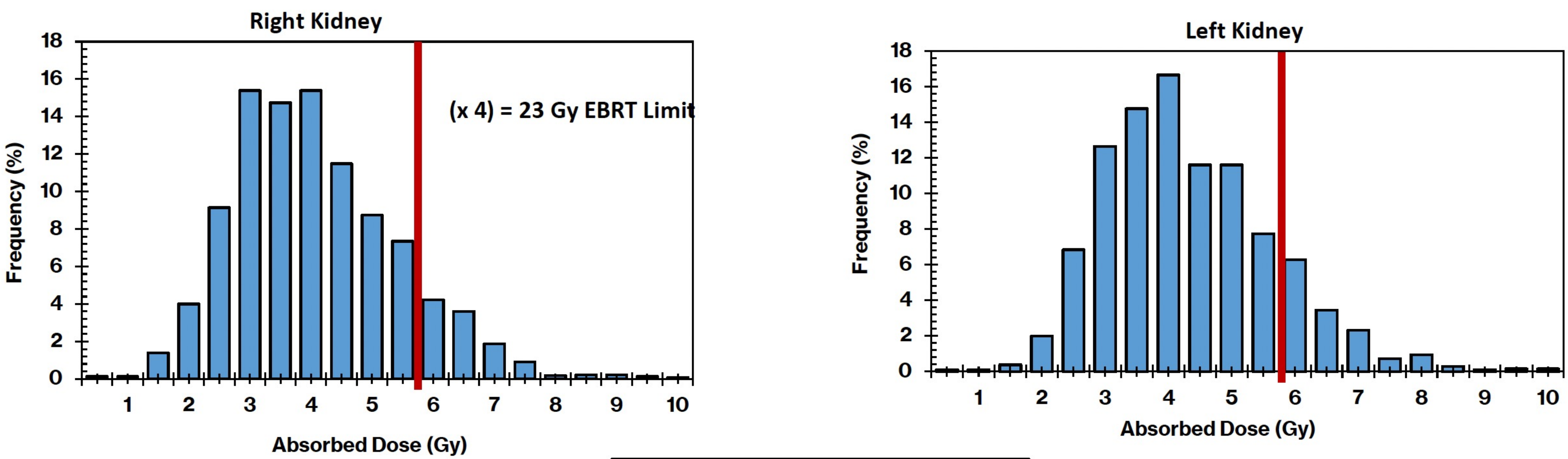
*Pretherapeutic.
†Posttherapeutic.

Eberlein Et al J Nucl Med 2017; 58:97S–103S

One Size Does Not Fit All

777 ^{177}Lu-DOTATATE Patients

SPECT/CT 1, 4 and 7 days post injection



$$P\left(D_{kidney} \leq 23\ Gy\right) = 0.85$$

Sandström, et al **EJNMI Physics** (2020) 7:73.

Dose (Gy) Matters

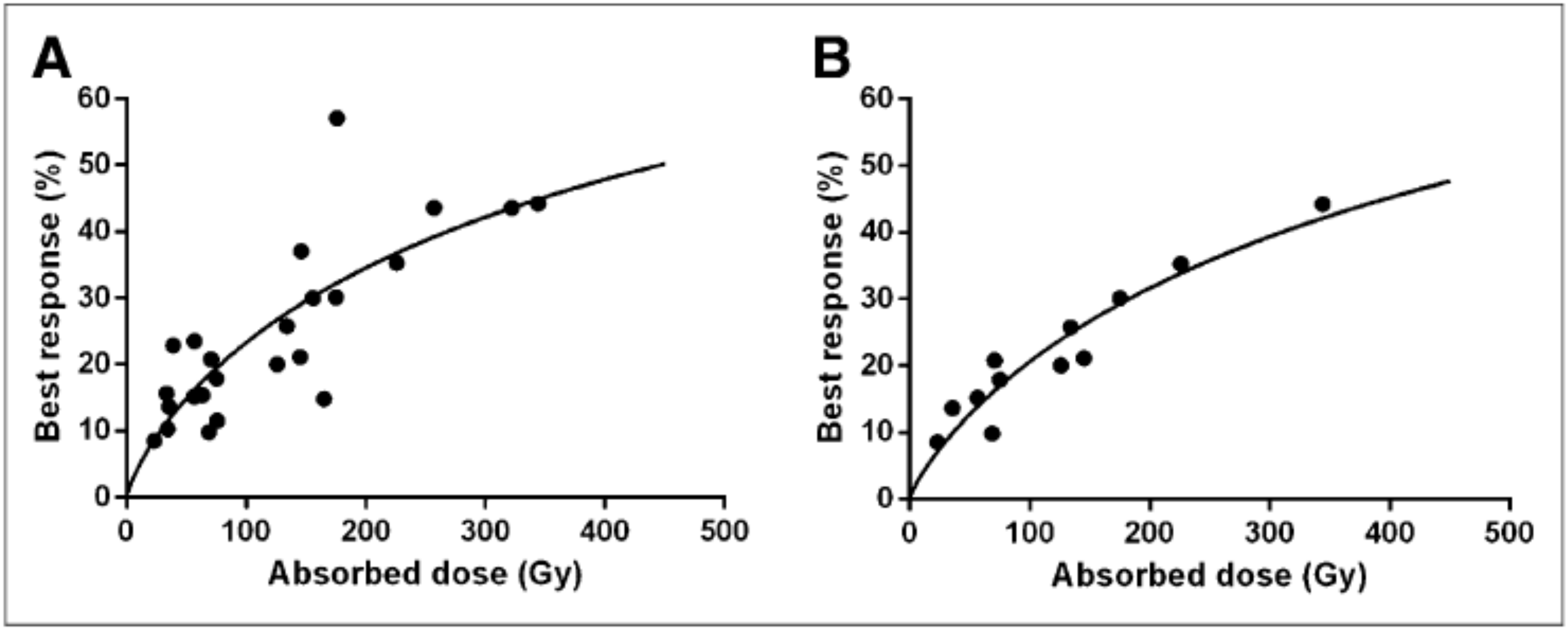
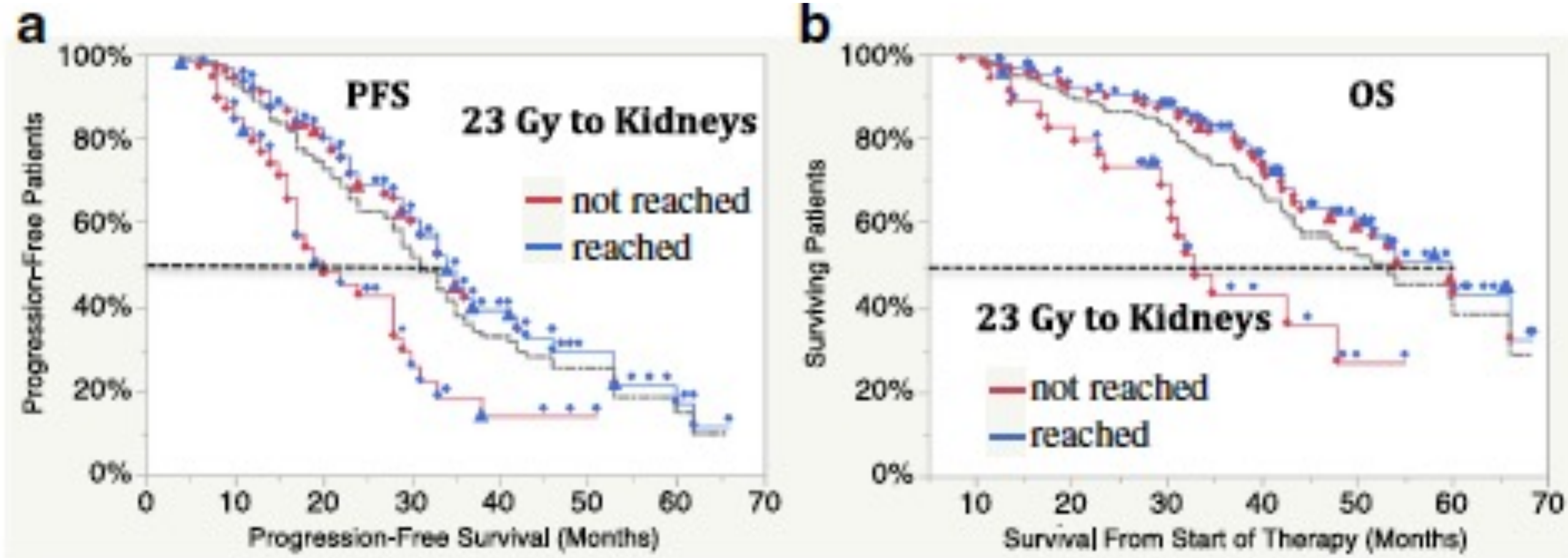


FIGURE 5. Tumor dose–response relationship for patients with PNETs treated with PRRT using ^{177}Lu-DOTATATE, including tumors larger than 2.2 cm (A) and only tumors larger than 4 cm (B).

J Nucl Med 2015; 56:177–182

Dose (Gy) Matters

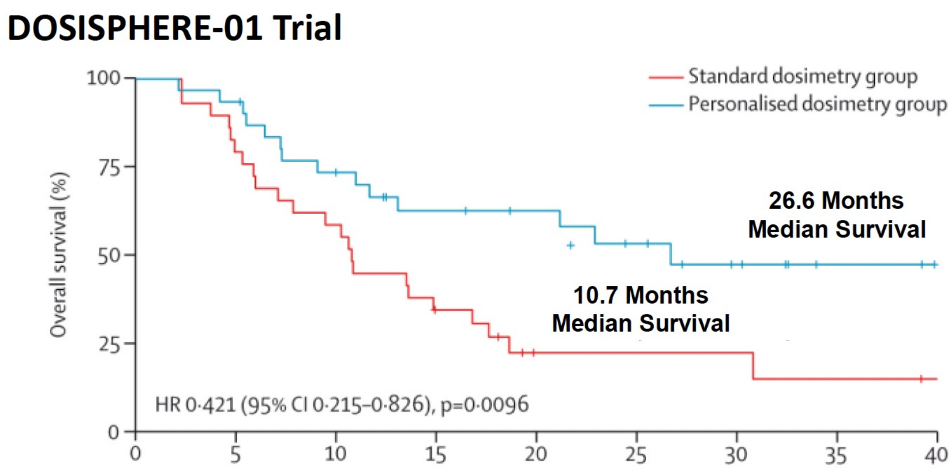
154 patients who stopped therapy for reasons other than progression or clinical deterioration



European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:970–988

Individual Treatment Planning Improves Survival

hepatocellular carcinoma that was not amenable to surgery or local ablative treatment



Personalised Dosimetry:
≥ 205 Gy to Index Lesion
Limit normal tissue ≤120 Gy
Hepatic reserve ≥30%

Standard Dosimetry:
120 Gy to Perfused Lobe

~ 16-month median survival benefit

36% of patients down-staged to surgery in personalized dosimetry are versus 4% in standard

These results challenge the interpretation of the previously published negative phase 3 trials, comparing Y-90 microspheres with other treatments, in which personalized dosimetry was not used.

Garin et al. Lancet Gastroenterol Hepatol 2021

Biomarkers

- Select patients most likely to respond
- Avoid toxicity
- **Tumor biopsy**
- **Serum sampling**
- **Genetic and epigenetic marker analysis**
- Methodology/Results 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 radioactivity counting**
- **Dose calculation**
- Methodology/Results must be rigorously qualified/validated retrospectively or in prospective studies
- Standardized
- Incorporated in the design of clinical trials

Radiopharmaceutical Therapy (RPT) Dosimetry: Main Steps

- Image Acquisition: usually at multi time points
  - Planar, Hybrid Planar/SPECT, SPECT, PET
  - Multi time point imaging – Can we reduce the burden to patient/clinic?
- Image Reconstruction
- Volume of interest segmentation
  - Manual segmentation is tedious/variable. Can we automate?
- Quantification
  - Calibration measurements – can we standardize?, incorporate this step into commercial systems?
- Time - activity fitting or dose-rate fitting
- Absorbed dose (AD) estimation

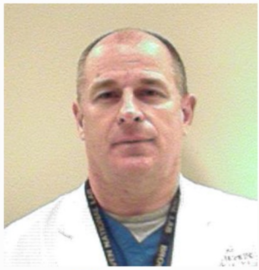
Courtesy: Yuni Dewaraja

MICHIGAN MEDICINE

Commercial and Open Source Dosimetry Software

- **Hermes Medical Solutions**: a suite of dosimetry tools for ^{67}Ga, ^{123}I, ^{131}I, ^{111}In, ^{81}Kr, ^{177}Lu, ^{99m}Tc, ^{201}Tl, ^{166}Ho, ^{90}Y, and ^{133}Ba (FDA cleared)
- **MIM Software**: image co-registration, automatic organ segmentation (using an FDA-cleared artificial-intelligence autosegmentation platform), dosimetry for several radionuclides, developing 2 methods of single-time-point dosimetry for ^{177}Lu DOTATATE
- **PLANET Dose** (DOSIsoft): image co-registration, automatic organ segmentation, FDA cleared for ^{90}Y-microsphere SIRT and CE-marked for other isotopes (^{90}Y, ^{177}Lu, ^{131}I [pending]).
- **Rapid:** quantitative imaging and dosimetry consulting and analysis services and the software, dosimetry calculations for a number of radionuclides, including ^{90}Y, ^{99m}Tc, ^{111}In, ^{123}I, ^{131}I, ^{201}Tl, ^{223}Ra, and ^{227}Th. A 510k application for FDA clearance in development.
- **QDOSE** (ABX-CRO): image co-registration, automatic organ segmentation, dose calculations for 27 commonly used radionuclides, including ^{90}Y-microsphere selective internal radiation therapy (SIRT).
- **The GE Dosimetry Toolkit** (GE Healthcare): image co-registration, automatic organ segmentation, dosimetry for ^{131}I-iodide thyroid cancer therapy, ^{90}Y-SIRT, and ^{177}Lu therapies.
- **PMOD** (PMOD Technologies): automatic organ segmentation generates dosimetry input data that may be directly imported into an OLINDA/EXM case file or an IDAC, version 2.1, file.
- **Simplicit90Y** (Mirada Medical) : software package developed for personalized ^{90}Y-SIRT planning, voxelwise techniques for pre- and posttreatment dosimetry.
- **RapidSphere:** software tools for ^{90}Y-microsphere dosimetry.
- **Voximetry Torch**: dose calculation algorithm in Torch has been benchmarked against the GEANT4 MC code, for multiple isotopes, including ^{90}Y, ^{177}Lu, ^{131}I, and ^{223}Ra**.** It is possible to generate a dosimetry report structured to meet the requirements for complex dosimetry billing codes in the US
- **Open Dose 3D:** full 3D dosimetry for molecular radiotherapy procedures using multiple time point 3D datasets, either SPECT/CT or PET/CT.
- **MIRD Software Tools (cell, fit, calc, mc):** a suite of free software applications designed and developed to support the medical radiation dose community.

AAPM RPT Subcommittee


Robert Hobbs
Subcommittee Chair

Charge

1. Consolidate, disseminate and maintain available information concerning RPT methodologies, dosimetry, science and practice.
2. Establish structures needed for providing guidelines and Standard Operating Procedures (SOPs) for new and existing RPTs such as Task Groups, Working Groups or MPPGs.
3. Take an active role in the education of the AAPM and general radiation oncology community regarding RPT methodologies and clinical practice.
4. Coordinate with stakeholder groups within AAPM, advising them of overlaps and seeking mutual solutions where needed.
5. Coordinate with stakeholder groups outside of AAPM to develop uniform and effective approaches to common problems with regard to RPT. These may include: SNMMI, EANM, ASTRO, ESTRO, ICRU, IAEA, ICRP, ABS, NIST, FDA, IROC, NRC, DOE.

Active Projects

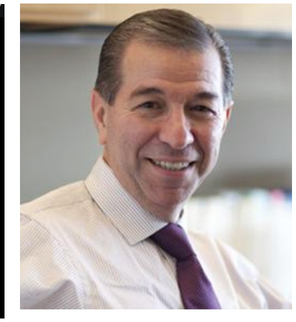
- WG on Radioactive Microspheres
- TG381 - AAPM Recommendations on imaging, dosimetry and quality assurance procedures for Lu-177-based radionuclide therapy
- TG 378 - Safety, treatment planning, and quantitative pre- and post-treatment imaging and dosimetry for hepatic yttrium-90 microsphere therapy
- MPPG 14 Y-90 microsphere radioembolization (TG356)
- AAPM Summer School 2023

Proposed Projects (pending final approval)

- WG on I-131
- WG on alpha-emitters
- TG on Release Criteria
- TG Calibration and Quality Assurance of SPECT/CT and Counting Systems used for Dosimetry-Guided Radiopharmaceutical Therapy
- TG on RPT traceability and dose calibration QA/QC

SNMMI RPT Dosimetry Task Force

co-chairs: George Sgouros and Pat Zanzonico



JNM Dosimetry Supplement Dec 2021

Radiopharmaceutical Dosimetry for Cancer Therapy: From Theory to Practice

Guest editors: Richard L. Wahl, MD, and John Sunderland, PhD

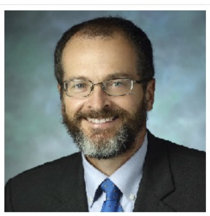
Can the tailoring of drug dosage improve the effectiveness of radiopharmaceutical therapy (RPT) for cancer patients? *The Journal of Nuclear Medicine* has issued a new supplement addressing both the rapid progress and the challenges in applying patient-specific radiation dosimetry to guide RPT.

Welcome to the SNMMI Lu-177 Dosimetry Challenge 2021

The SNMMI Dosimetry Task Force has the primary goal of advancing the use of **dosimetry in radiopharmaceutical therapy (RPT)**. It has identified the need for harmonization of dosimetry methods as an area of focus. Although efforts to harmonize and standardize internal dosimetry calculations have been made, there has been a lack of large-scale studies to on which to justify recommendations. **The Task Force is thus soliciting members of the nuclear medicine community to contribute to the 177Lu Dosimetry Challenge.**

Dosimetry Challenge Team

Yuni Dewaraja, PhD
University of Michigan



Eric Frey, PhD
Johns Hopkins University

John Sunderland, PhD
University of Iowa

Carlos Uribe, PhD, MCCPM
BC Cancer

Conclusions:

- RPT tsunami is on the way
- Current “one size fits all” approach is suboptimal
- Dosimetry could be considered as a biomarker of “safe” and “effective” treatment.
- Individualized dosimetry-based treatment planning has a potential to improve the outcome, avoid toxicity, and enable combination of RPT with other therapeutical modalities
- RPT dosimetry is gaining traction at relevant professional societies, but faces pushback
- The advantage of Individualized dosimetry-based treatment planning has to be proved in randomized clinical trails
- Involvement of medical physicist is necessary to improve the outcome of theranostics