Targeted Radionuclide Therapy – Current Status and Trends

Jacek Capala and Jeff Buchsbaum

Radiation Research Program

Division of Cancer Treatment and Diagnosis

NCI/NIH/HHS

Outline

- FDA-Approved Therapeutic Radiopharmaceuticals
- One size does not fit all
- Dose (Gy) matters (efficacy)
- Dose (Gy) matters (safety)
- Dosimetry as a biomarker
- Treatment planning software
- Recent initiatives at professional societies (AAPM, ASTRO, 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 Diiscovery, 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*

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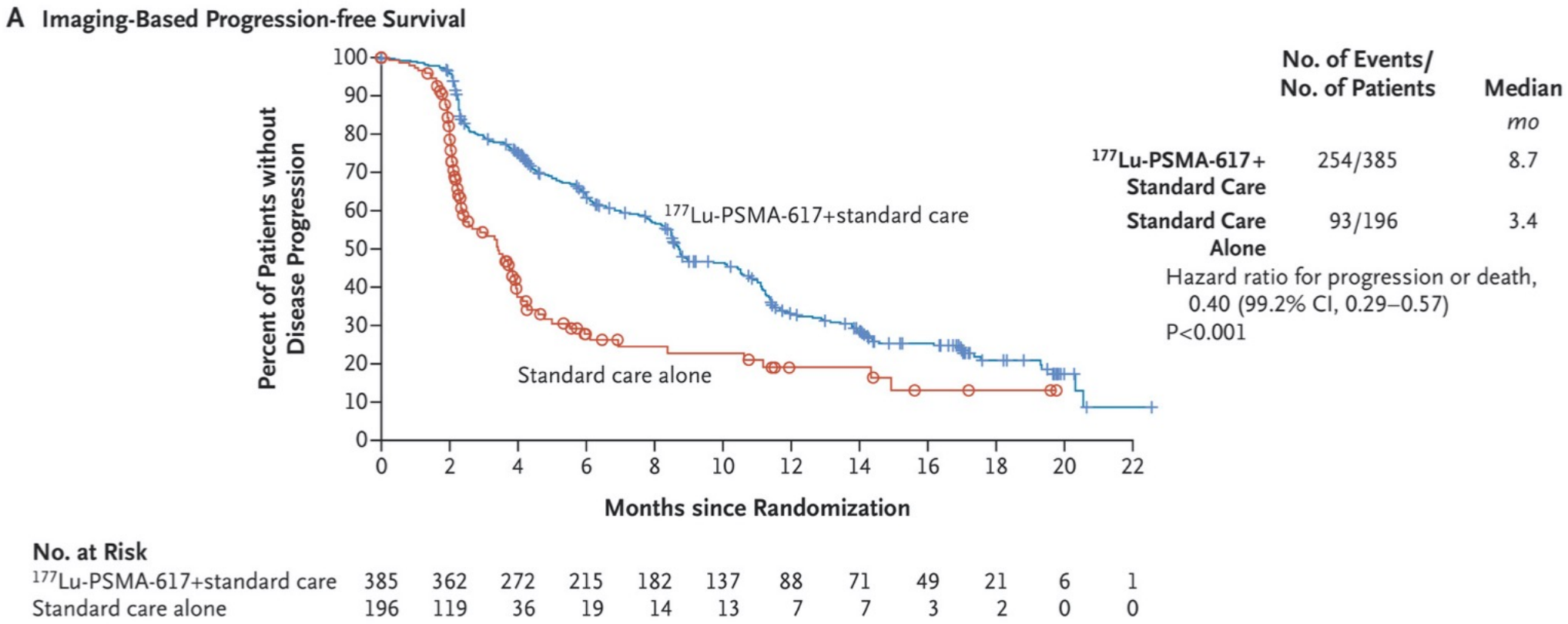
A Imaging-Based Progression-free Survival
Percent of Patients without Disease Progression
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
22
Months since Randomization
177Lu-PSMA-617+standard care
Standard care alone
No. of Events/ No. of Patients
Median
mo
177Lu-PSMA-617+ Standard Care
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
177Lu-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

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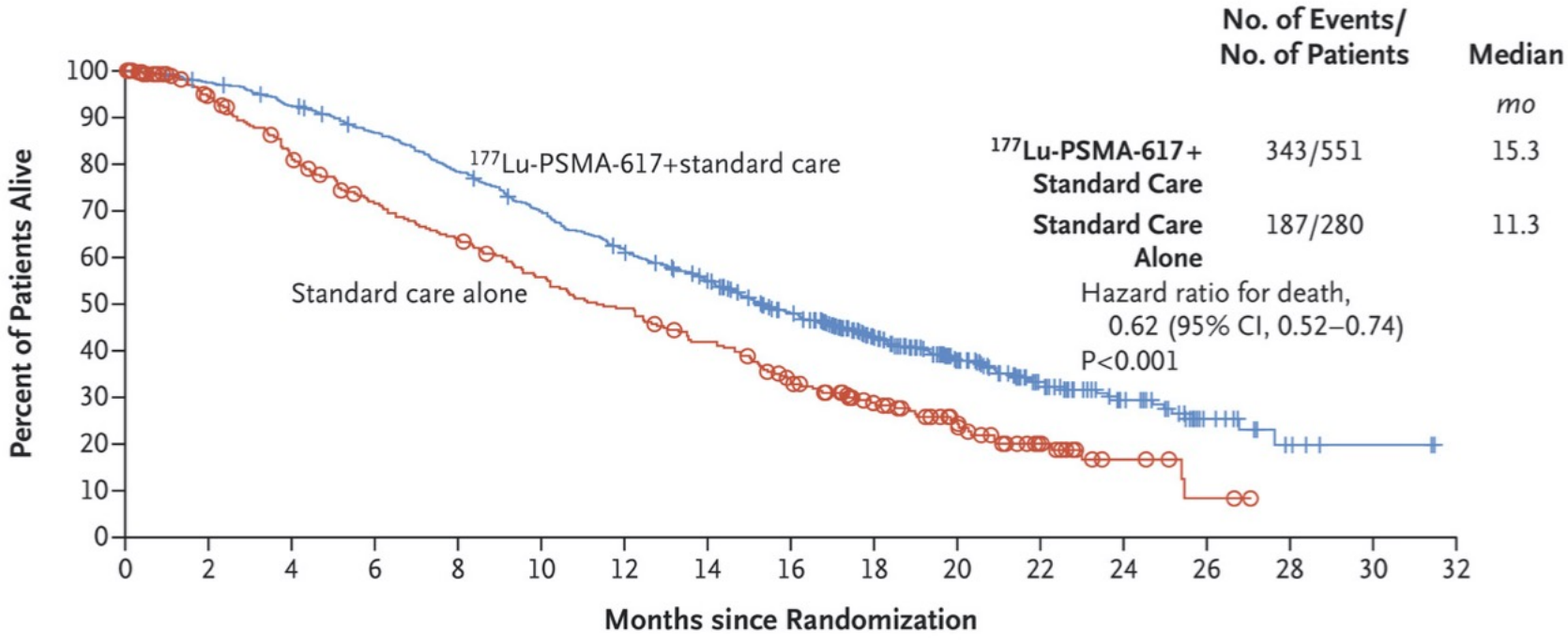
B **Overall Survival**



No. at Risk

177Lu-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

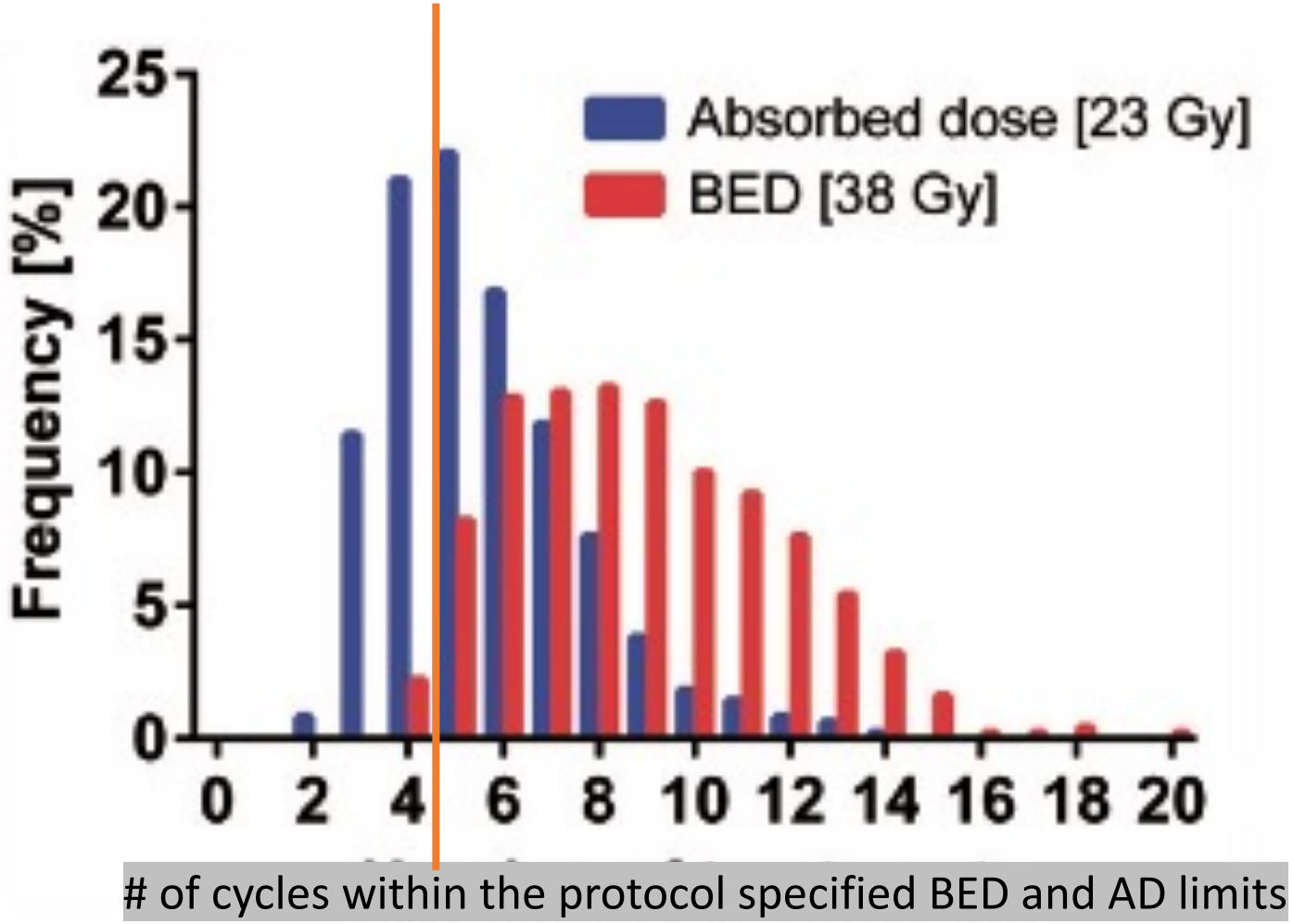
Absorbed Doses for Tumors and Organs at Risk in ^{177}Lu PRRT Studies

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			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				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



^{177}Lu-DOTATATET (7.4MBq)

With BED < 38 Gy to the kidneys and

AD < of 2 Gy to marrow

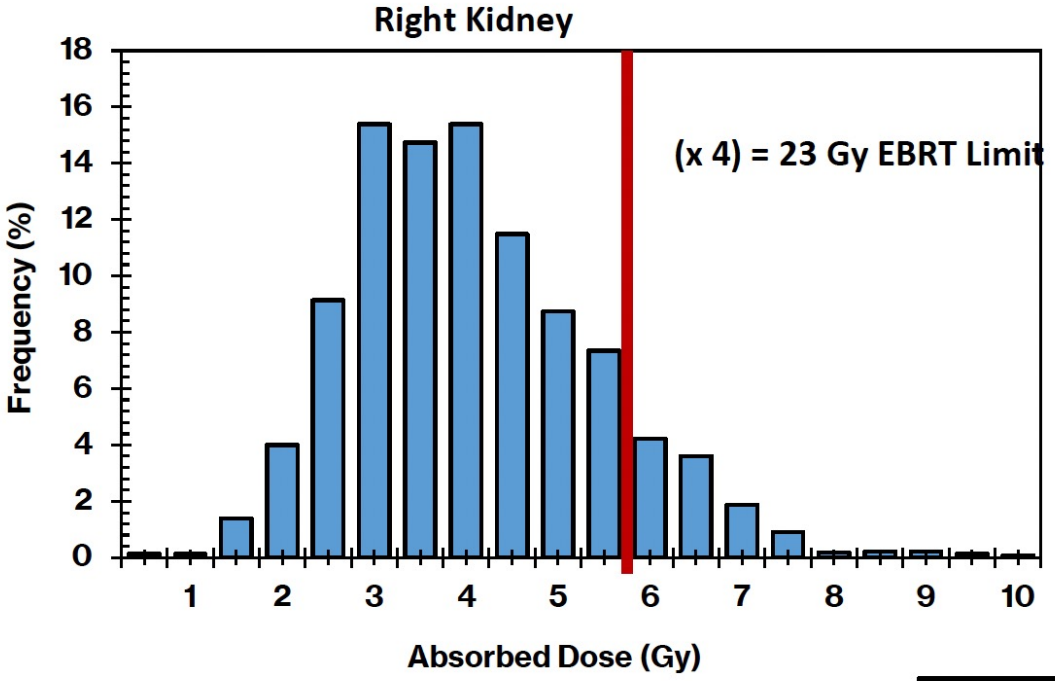
95% could get > 4 cycles

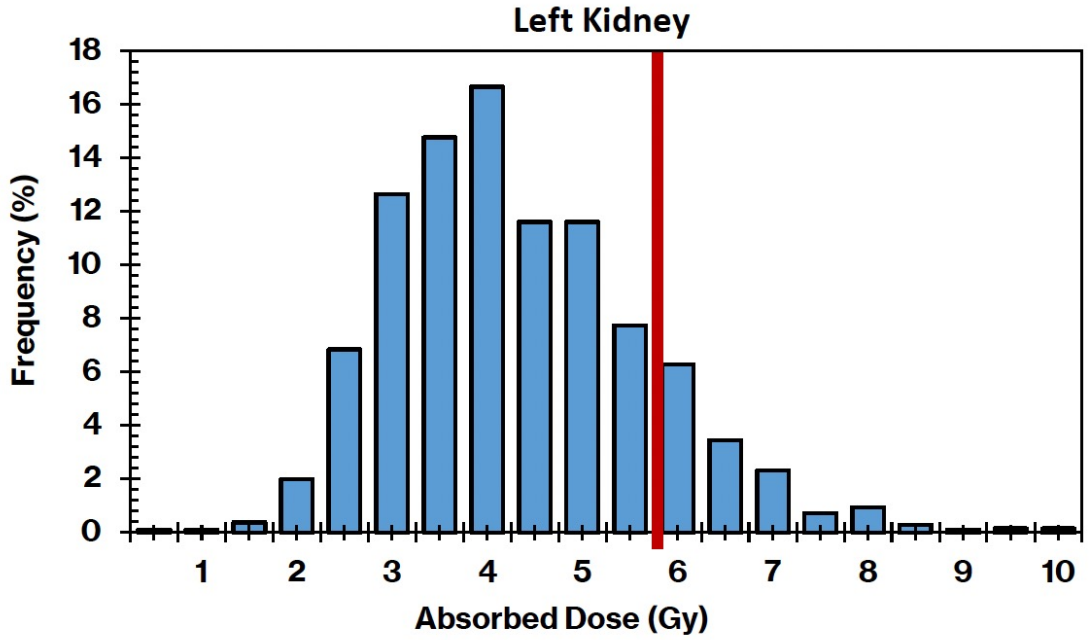
Sandstrom et al, ACTA ONCOL. 2018

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 (efficacy)

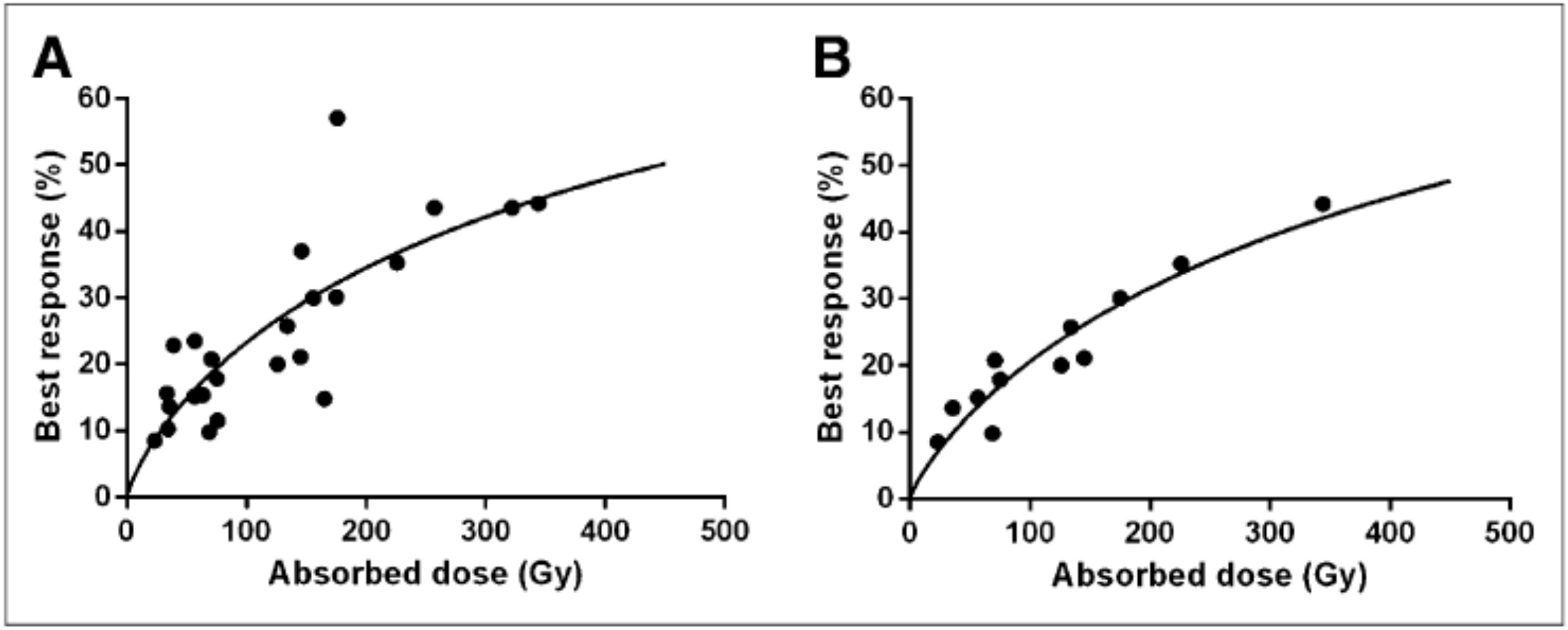
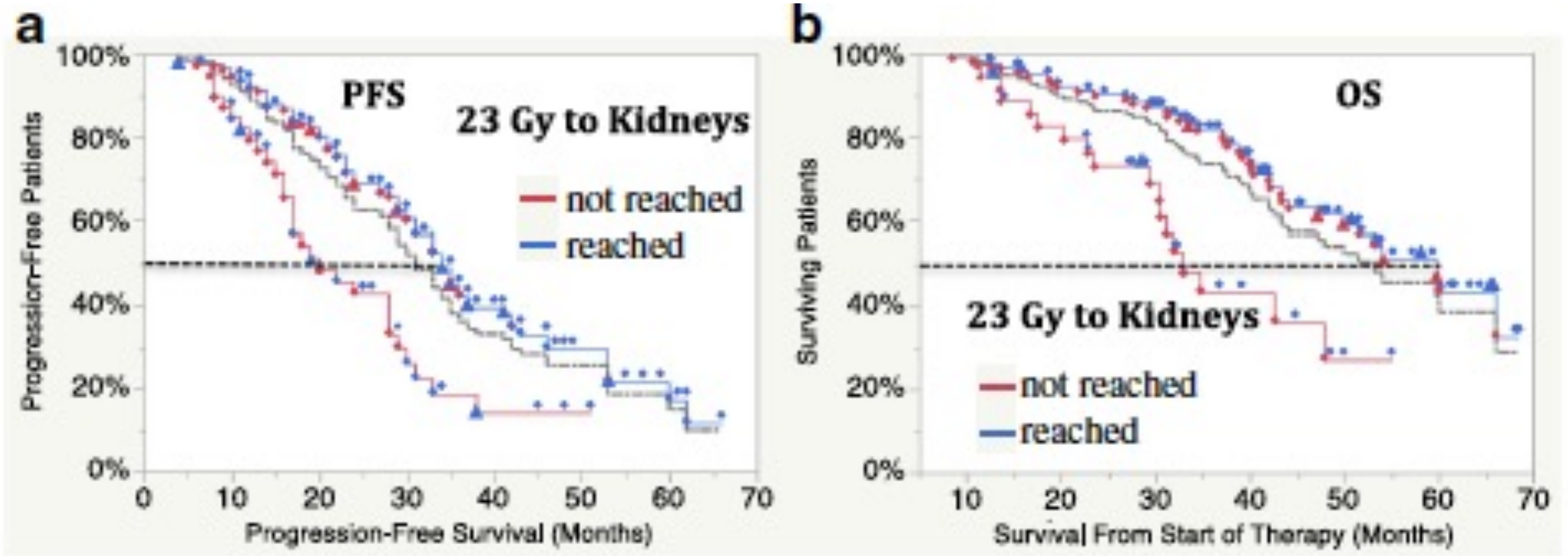


FIGURE 5. Tumor dose–response relationship for patients with PNETs treated with PRRT using ^{177}Lu-DOTATATE, including tumors larger than 2.2 cm (A) and only tumors larger than 4 cm (B).

J Nucl Med 2015; 56:177–182

Dose (Gy) Matters (efficacy)

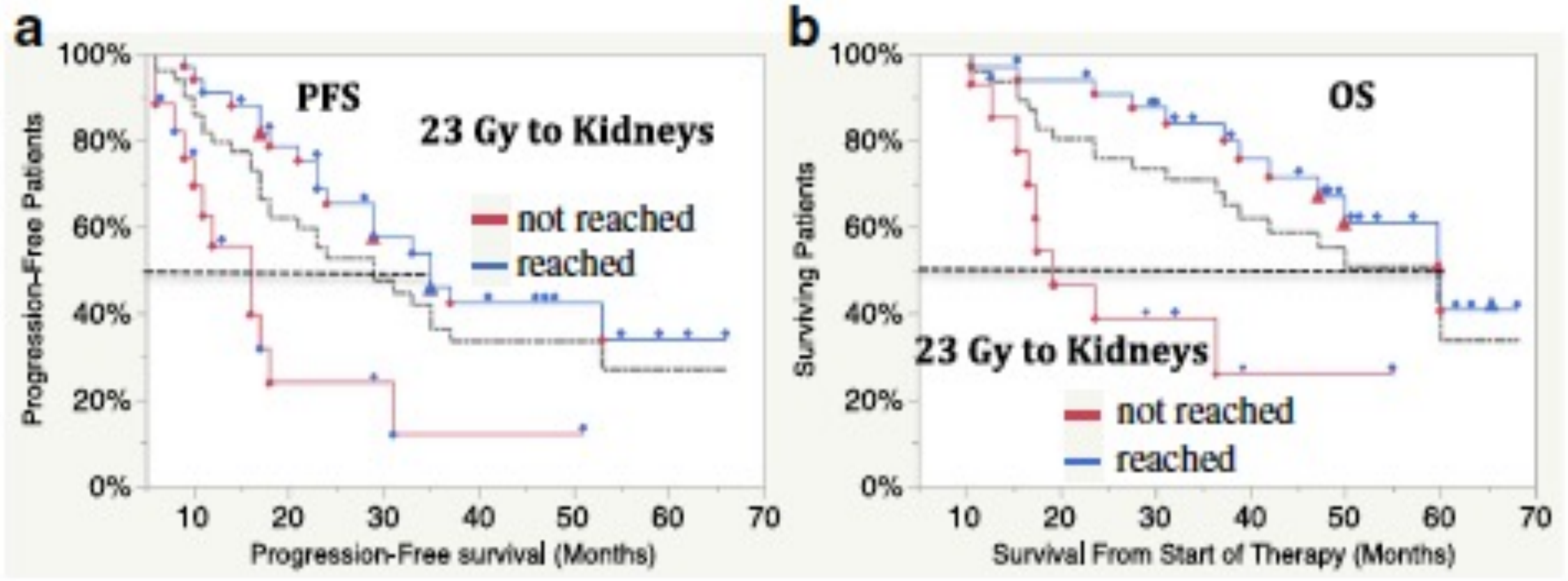
154 patients who stopped therapy for reasons other than progression or clinical deterioration



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

Dose (Gy) Matters (efficacy)

50 patients who received exactly four cycles of ^{177}Lu-DOTAoctreotate.



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

Netter-1 Disappointment

^{177}Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial

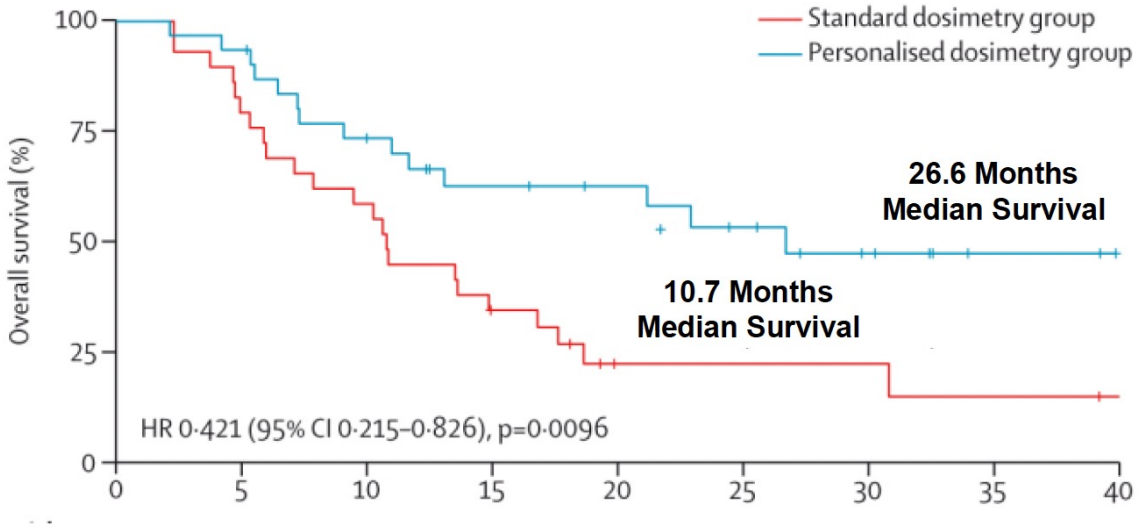
*Jonathan R Strosberg, Martyn E Caplin, Pamela L Kunz, Philippe B Ruszniewski, Lisa Bodei, Andrew Hendifar, Erik Mittra, Edward M Wolin, James C Yao, Marianne E Pavel, Enrique Grande, Eric Van Cutsem, Ettore Seregni, Hugo Duarte, Germo Gericke, Amy Bartalotta, Maurizio F Mariani, Arnaud Demange, Sakir Mutevelic, Eric P Krenning, on behalf of the NETTER-1 investigators**

Interpretation ^{177}Lu-Dotatate treatment did not significantly improve median overall survival versus high-dose long-acting octreotide. Despite final overall survival not reaching statistical significance, the 11·7 month difference in median overall survival with ^{177}Lu-Dotatate treatment versus high-dose long-acting octreotide alone might be considered clinically relevant. No new safety signals were reported during long-term follow-up.

Individual Treatment Planning Improves Survival

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

DOSISPHERE-01 Trial



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

Standard Dosimetry:
120 Gy to Perfused Lobe

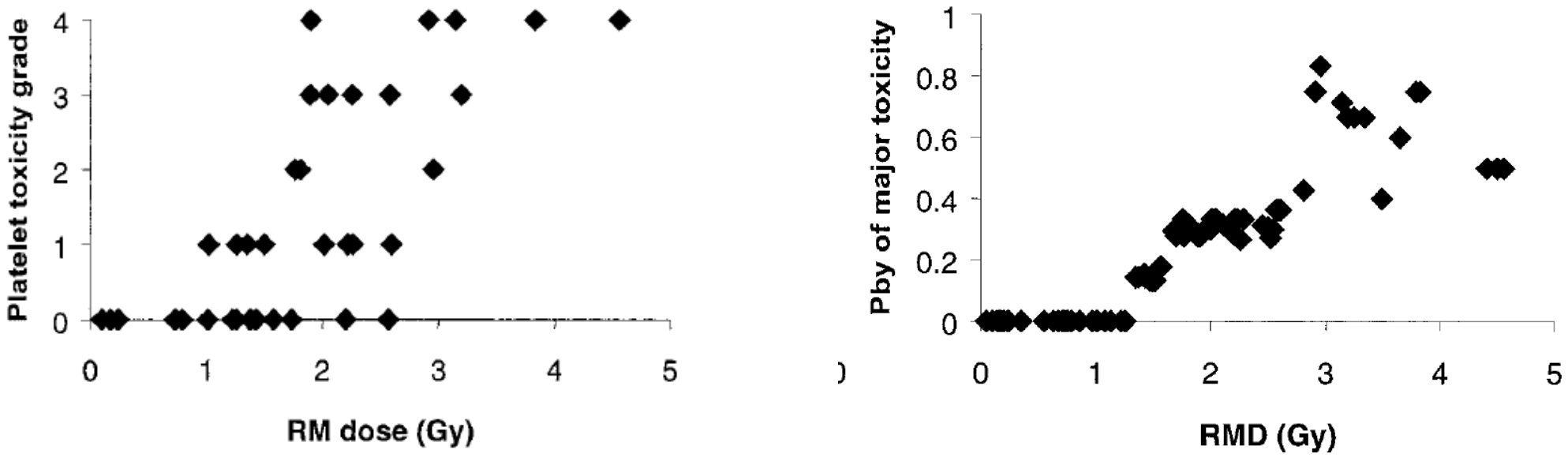
~ 16-month median survival benefit

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

Dose (Gy) Matters (safety)



Marrow Toxicity vs. Dose

**J. O'Donoghu et al., "Hematologic Toxicity in Radioimmunotherapy: Dose-Response Relationships for I-131 Labeled Antibody Therapy" Canc. Bio. Radiopharm., 2004*

No RPT safety data for the kidneys

Dose (Gy) Matters (safety)

- Combination with other therapies
  - radiotherapy
  - radiosensitizers
  - immunotherapy
- Retreatment

Mol Imaging Biol. 2015 Apr;17(2):284-94. doi: 10.1007/s11307-014-0783-7.

Patient-specific dosimetry using pretherapy [^{124}I]m-iodobenzylguanidine ([^{124}I]mIBG) dynamic PET/CT imaging before [^{131}I]mIBG targeted radionuclide therapy for neuroblastoma

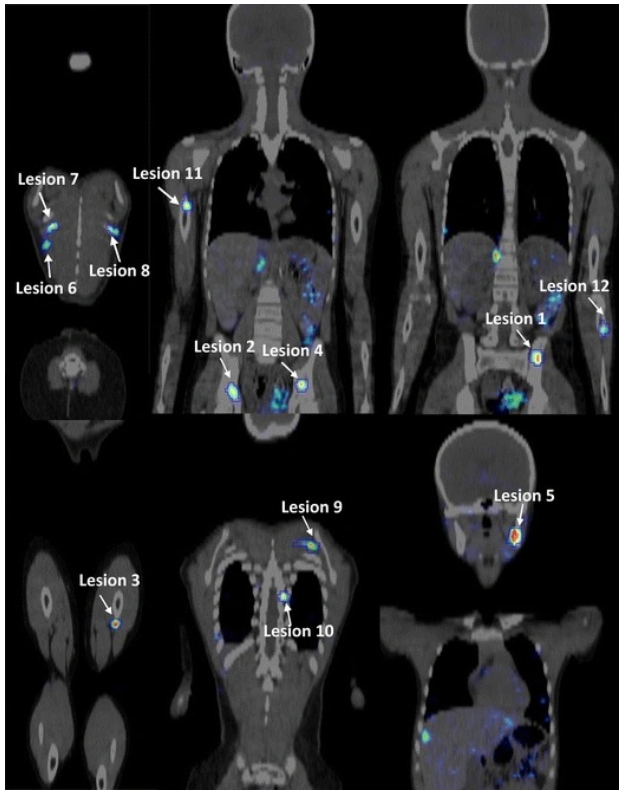
Shih-ying Huang [1], Wesley E Bolch, Choonsik Lee, Henry F Van Brocklin, Miguel H Pampaloni, Randall A Hawkins, Aimee Sznewajs, Steven G DuBois, Katherine K Matthay, Youngho Seo

Affiliations + expand

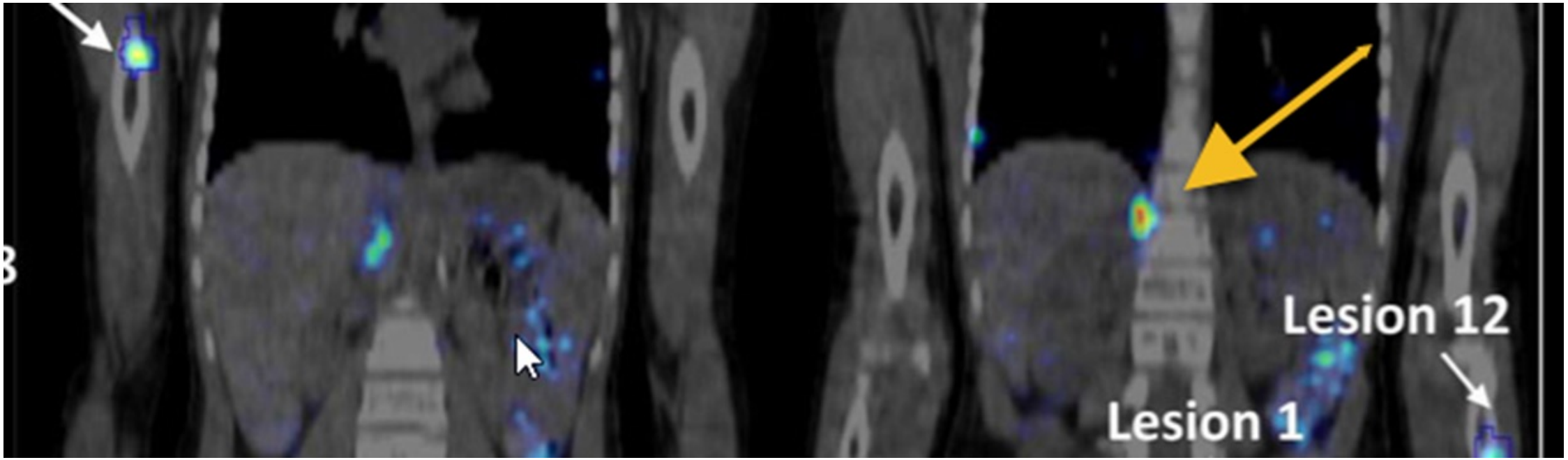
PMID: 25145966 PMCID: PMC4336853 DOI: 10.1007/s11307-014-0783-7

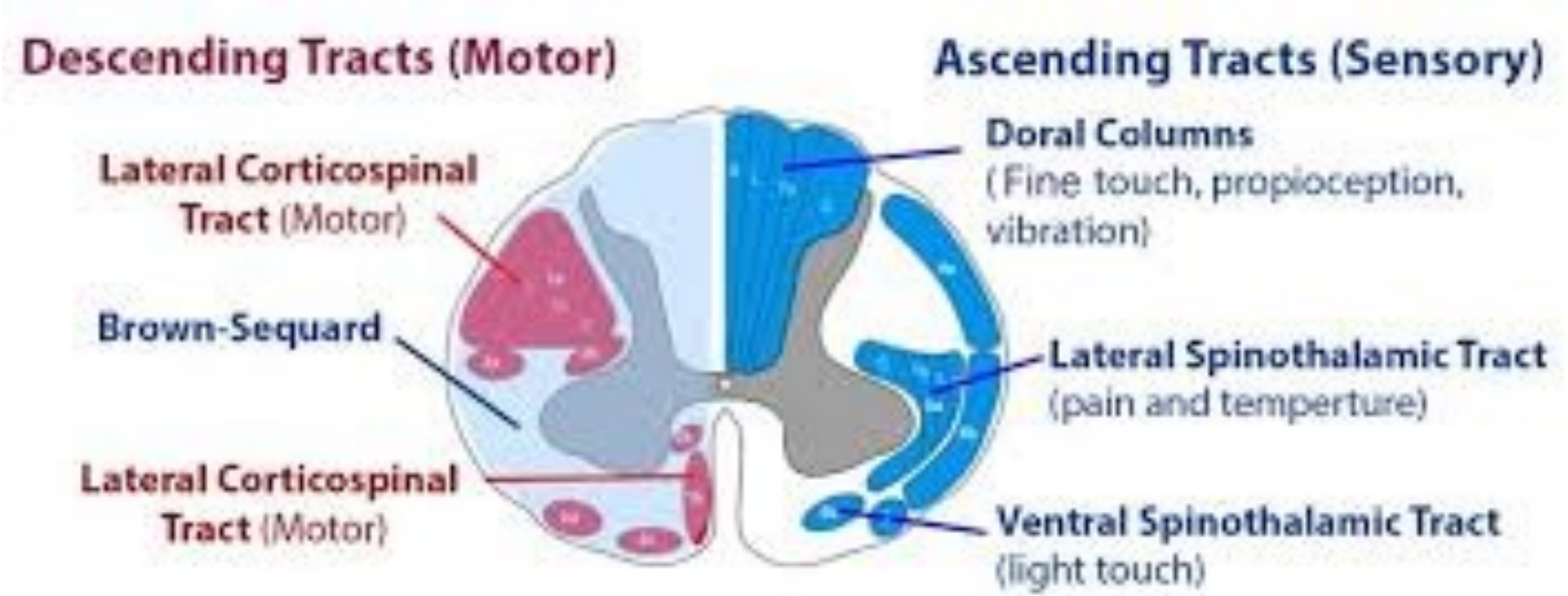
Free PMC article

Target organ	Absorbed dose (Gy)
Brain	1.46
Osteogenic cells	1.84
AM	2.25
Skin	2.72
Muscle	3.77
Colon wall	3.84
SI	3.99
Breasts	4.06
Kidneys	4.50
Total body	4.88
Thymus	4.93
Ovaries	4.94
Pancreas	4.96
Uterus	5.07
Stom wall	5.14
Right adrenal	5.91
UB wall	6.01
GB wall	7.63
Spleen	15.96
Lungs	21.16
Thyroid	22.56
Liver	34.27
Hrt wall	36.49
Salivary glands	98.02



Tumor no.	Metabolic tumor volume (cm^3)	[^{131}I]mIBG residence time (MBq-hr/MBq)	Absorbed dose (Gy)	% Self-dose	% Cross-dose
Lesion 1	0.87	0.461	946.27	99.80	0.20
Lesion 2	3.59	1.634	892.16	99.78	0.22
Lesion 3	0.37	0.317	1,331.61	99.90	0.10
Lesion 4	0.19	0.199	1,641.32	99.88	0.12
Lesion 5	0.57	0.312	886.88	99.08	0.92
Lesion 6	0.52	0.179	505.23	99.24	0.76
Lesion 7	0.36	0.116	522.29	99.23	0.77
Lesion 8	0.33	0.129	637.26	99.50	0.50
Lesion 9	1.36	0.219	253.94	91.17	8.83
Lesion 10	0.17	0.061	461.31	99.36	0.64
Lesion 11	0.50	0.099	312.26	99.31	0.69
Lesion 12	0.56	0.049	143.86	99.31	0.69





https://www.orthobullets.com/spine/2008/incomplete-spinal-cord-injuries

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

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 United States

AAPM

AAPM COMMITTEE TREE

Radiopharmaceutical Therapy Subcommittee (RPTSC)

- bookmark this page (bookmarks show under "My AAPM" in the menu to left)

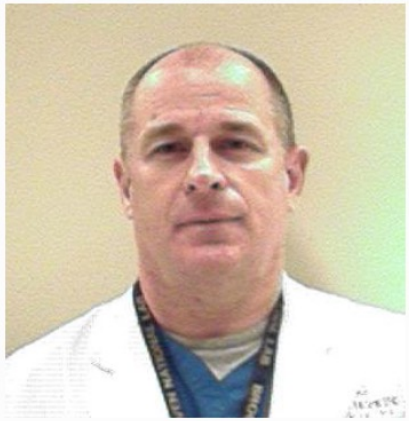
No Website on file. | **Directory:** Committee | Membership

Email You may send email to this group now using gmail or outlook.
- or -
You may save the address *2022.RPTSC@aapm.org*
to your local address book. This alias updates hourly from the AAPM Directory.

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.

Chair



Robert Hobbs
Subcommittee Chair

ASTRO

Radiopharmaceutical Therapy

The ASTRO Think Tank: Radiopharmaceutical Therapy (RPT) aims to:

1. Engage with RPT stakeholders
2. Explore the importance of personalized dosimetry for RPT

Activities of the Think Tank include:

- A series of online sessions (mostly invitation-only) for ASTRO experts to network, collaborate, and discuss with RPT stakeholders about the field of RPT
- Collaborative review article development
- Collaborative grant proposal development

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.

Recent SNMMI Meeting

8:30-11:00 am **Dosimetry**

Moderator: Stephen A. Graves, PhD, DABR – University of Iowa

Presentations include:

- **Dosimetry Infrastructure**

  Bryan P. Bednarz, PhD. – Wisconsin Institutes for Medical Research, University of Wisconsin Madison

- **Latest updates on Y-90 Dosimetry**

  Yuni K. Dewaraja, PhD – University of Michigan

- **Dosimetry in the Treatment of Neuroendocrine Malignancies**

  Stephen A. Graves, PhD, DABR – University of Iowa

- **Latest on Dosimetry in Thyroid Cancer**

  Douglas Van Nostrand, MD, FACP, FACNM, MedStar Research Institute and Washington Hospital Center

- **Optimizing Dosimetry Workflow in Nuclear Medicine**

  Stephen A. Graves, PhD, DABR – University of Iowa

- **Reimbursement for Dosimetry**

  Gary Dillehay, MD – Northwestern Memorial Hospital.

Recent SNMMI Meeting

There is a consensus in Nucl. Med. community leaders that individualized, dosimetry-based treatment planning is needed to improve the outcome of RPT, but they are getting pushback from medical oncologist and hospital administration based on the current standard procedures.

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