

Radiation Dosimetry for Theranostic Applications in Prostate Cancer

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Klinik und Poliklinik für Nuklearmedizin
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What is the aim of internal dosimetry in radionuclide therapy?

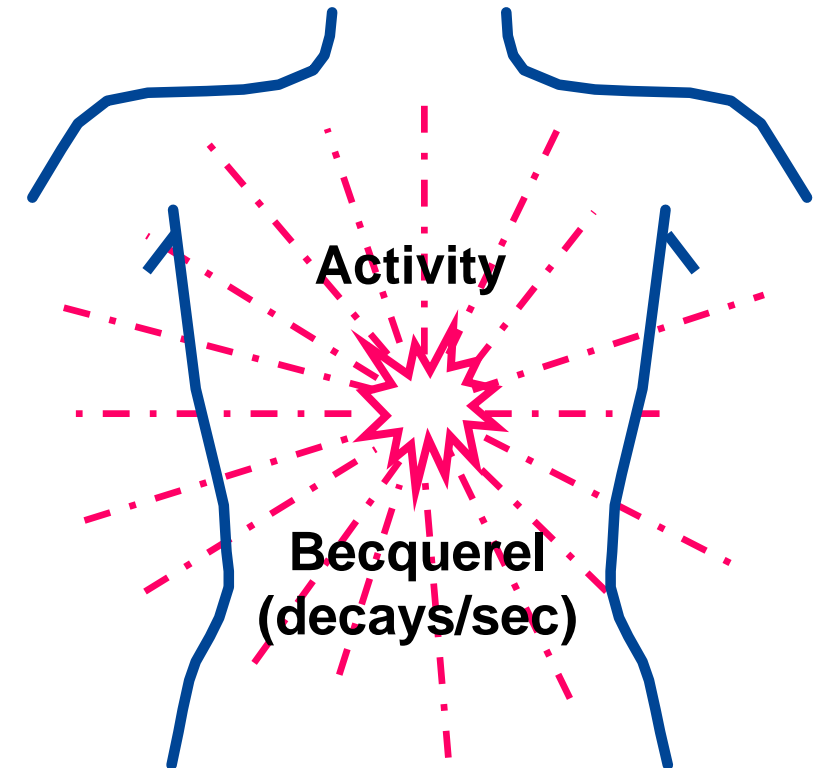
Define absorbed doses in critical organs and tumors

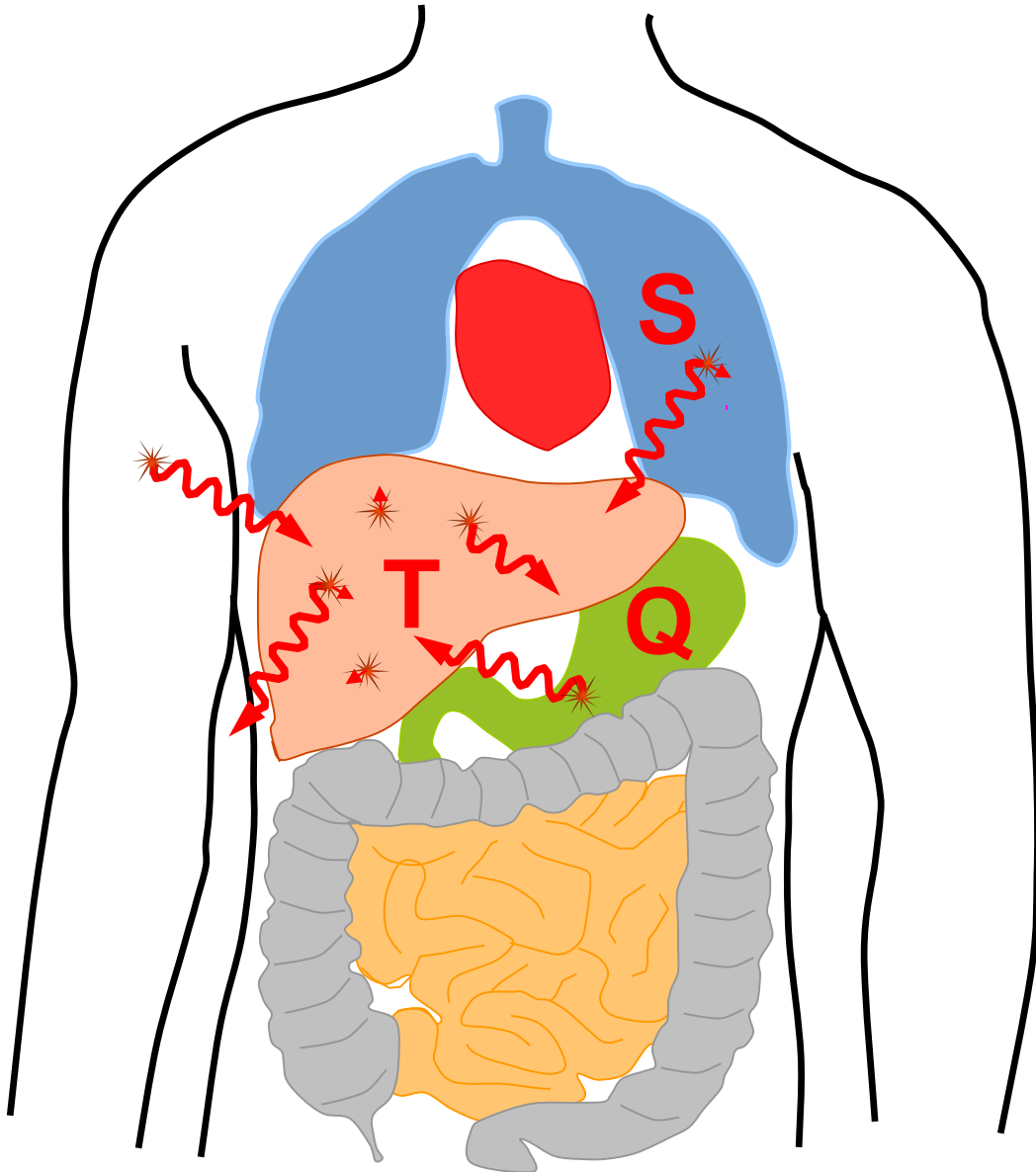
Absorbed Dose (Gy):

- ▶ Energy imparted to an organ or tumors divided by the corresponding mass, Unit: Gray [J/kg]

$$D = \frac{E}{M} = \frac{\text{energy}}{\text{mass}} \left[\text{Gy} = \frac{\text{J}}{\text{kg}} \right]$$

Absorbed Dose D





- ▶ Continuous irradiation with decreasing dose rate
 - in contrast to external irradiation
- ▶ Aspects that alter the absorbed dose:
 - Administered activity
 - Physical and chemical properties of the radiopharmaceutical
 - Sources that irradiate targets
 - Biokinetics and biodistribution
 - Biological uptake and excretion

Diagnostics

Low activities $\sim < 1 \text{ GBq}$,
Short lived radionuclides,
 γ/β^+ -emitter

Stochastic risk

Model-based dosimetry in a representative
group of volunteers or patients

Optimize image quality

Minimizing radiation-associated risk

Therapy

High activities:
Normally $> 1 \text{ GBq}$ for β^- -emitter,
5-10 MBq for α -emitter
Long lived radionuclides, α/β^- -emitter

Deterministic damage and stochastic risk

Patient-specific dosimetry

Maximize tumor absorbed doses

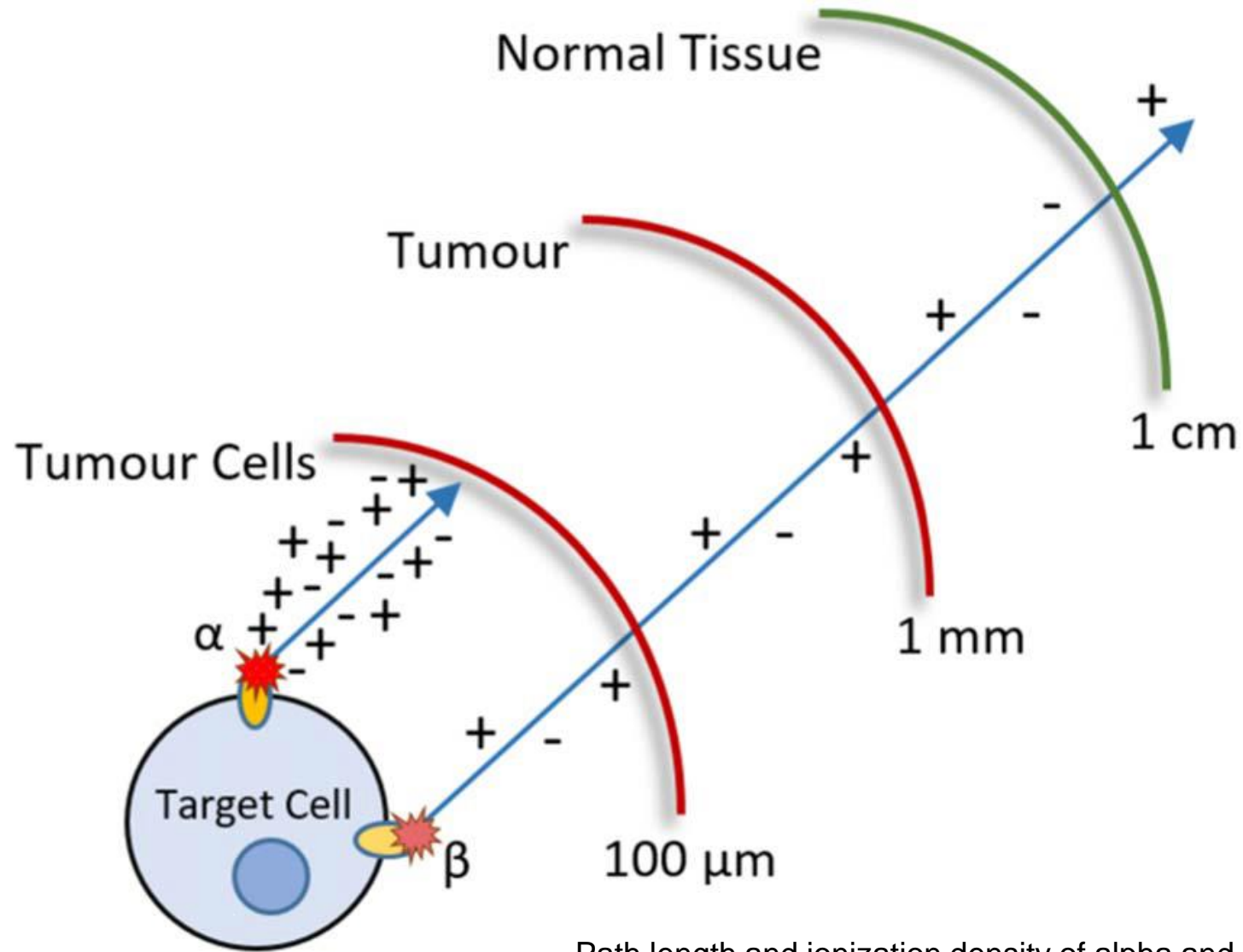
Minimize the absorbed doses to organs-at-risk

Most Important Radionuclides for Prostate Cancer Diagnostics and Treatment

Radionuclide	Halflife (h)	β_{\max} (MeV)	γ (keV)	Max. range (mm)	
F-18	1.83	0.63	511	2.3	diagnostic
Ga-68	1.13	1.90	511	8.9	
Lu-177	160	0.50	208	1.5	therapy
Ra-223	274	5.9 (α) ≈ 28 (α)*	81/84/95/144/15 4/269*	0.05	
Ac-225	240	5.8 (α) ≈ 28 (α)*	440/218*	0.05	

* incl. progeny

α versus β/γ -Emission



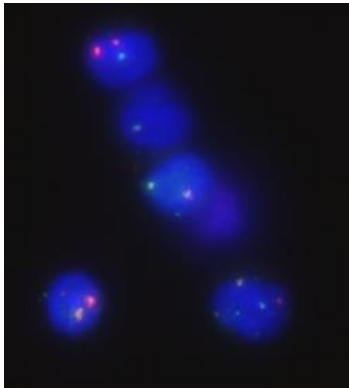
Path length and ionization density of alpha and beta radiation.

α versus β/γ -Emission

β/γ -emitters:

sparsely ionizing
(low LET)

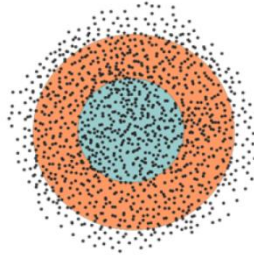
RBE: 1



γ -H2AX (green) and 53BP1 (red)
foci in a cell nucleus showing DNA
double strand breaks

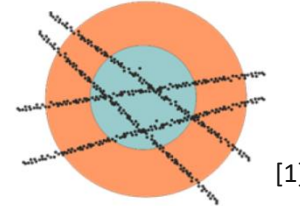
X-rays

1 Gy ~ 1000 hits/cell
~ 100 000 ionisations/cell



alpha particles

1 Gy ~ 4 hits/cell
~ 100 000 ionisations/cell



[1]

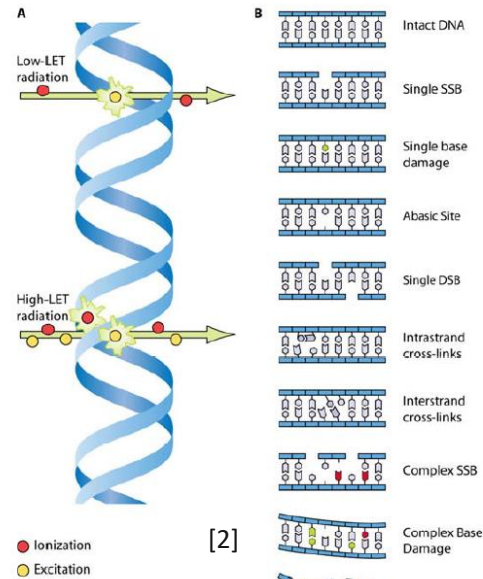
α -emitters:

densely ionizing
(high LET)

RBE: 5-20



α -tracks in a cell nucleus γ -H2AX
(green) and 53BP1 (red)



[2]

[1] <https://zfbweb.zfb.fuw.edu.pl/index.php/portfolio-item/monte-carlo-simulations-of-cell-response-to-dna-damage-of-various-complexities>

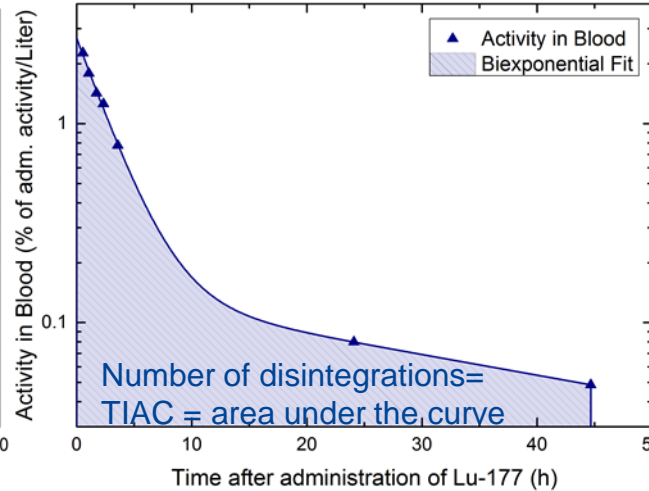
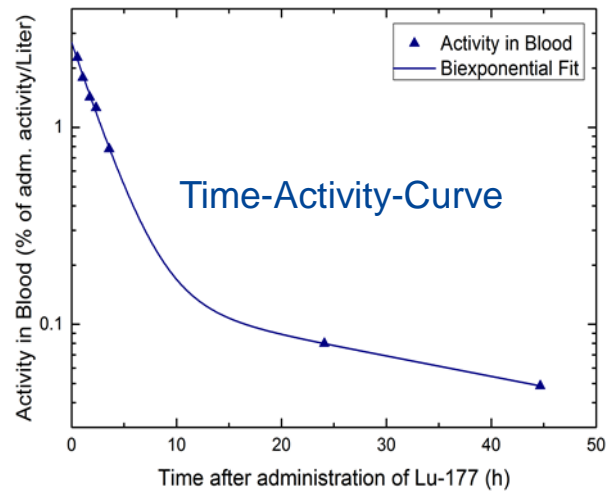
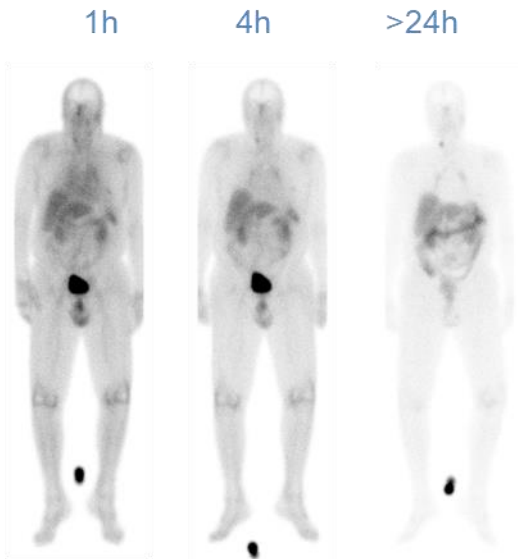
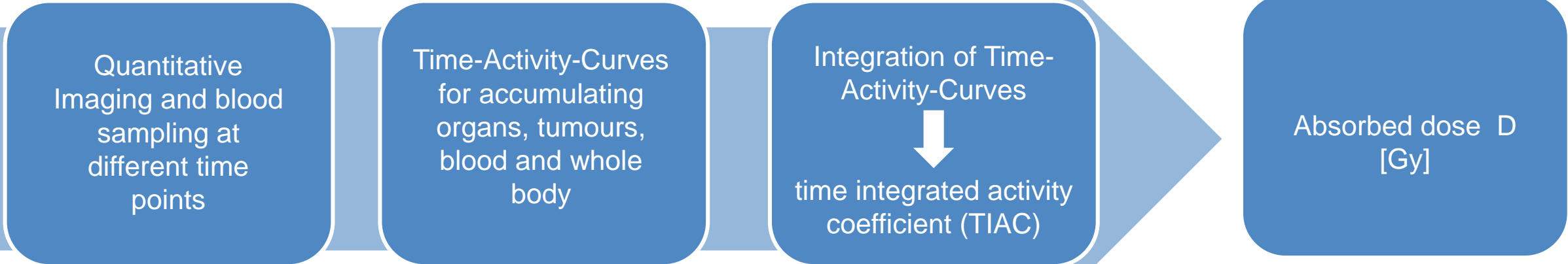
[2] © EPR-Biodosimetry 2011 IAEA, WHO

Absorbed Dose Limits for Organs-at-Risk

Organs-at-risk	Absorbed Dose (Gy)
Bone Marrow	2
Kidneys (Emami 1991)	23*
Salivary Glands (Buchali 1991)	20
Lacrimal Glands (Parsons 1996)	40

*Kidneys (threshold, MIRD 20): 33 Gy (BED) derived from therapies with ^{90}Y

Dosimetry Scheme



$$D_T(t) = A_0 \sum_S TIAC_S(t) \cdot S_{T \leftarrow S}$$

- A_0 : administered activity
- $S_{T \leftarrow S}$: mean absorbed dose per nuclear disintegration in the target organ

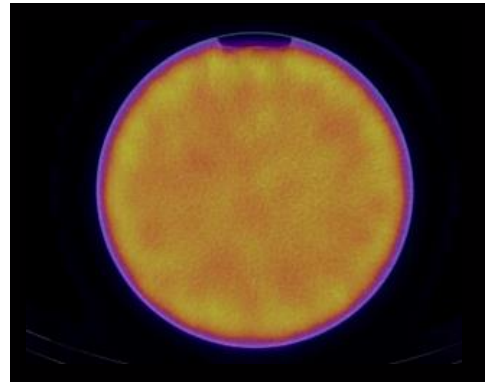
The EARL Quantitative ^{177}Lu -SPECT-CT Accreditation Programme

Radionuclide Calibrator Assessment

- ▶ Measurement of traceable sources

Quantitative Accuracy

- ▶ Requirement:
 - Scanner shall have an accurate activity concentration calibration



Characterisation of Spatial Resolution

- ▶ Requirement:
 - Resolution performance within appropriate limits

Open to data submission later this year!

Dickson J, et al. EJNMMI 2022:S187

OP-564

RESEARCH **LIFE**
EANM

The EARL Quantitative ^{177}Lu -SPECT-CT accreditation programme

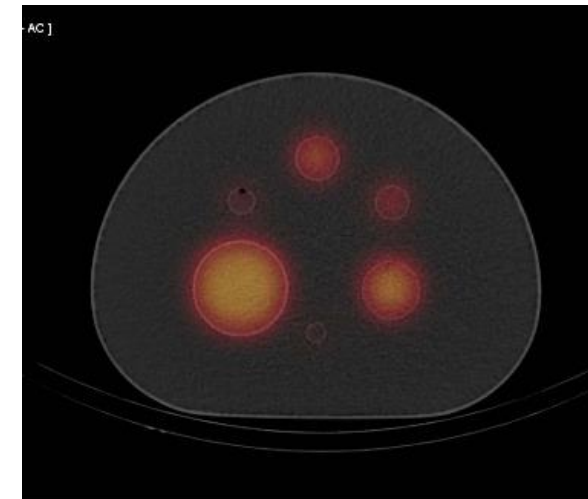
John Dickson, Marta Cremonesi, Ana M Denis-Bacelar, Ivalina Hristova, Michel Koole, Steffie Peters, Katarina Sjögren-Gleisner, Johannes Tran-Gia, Michael Laßmann

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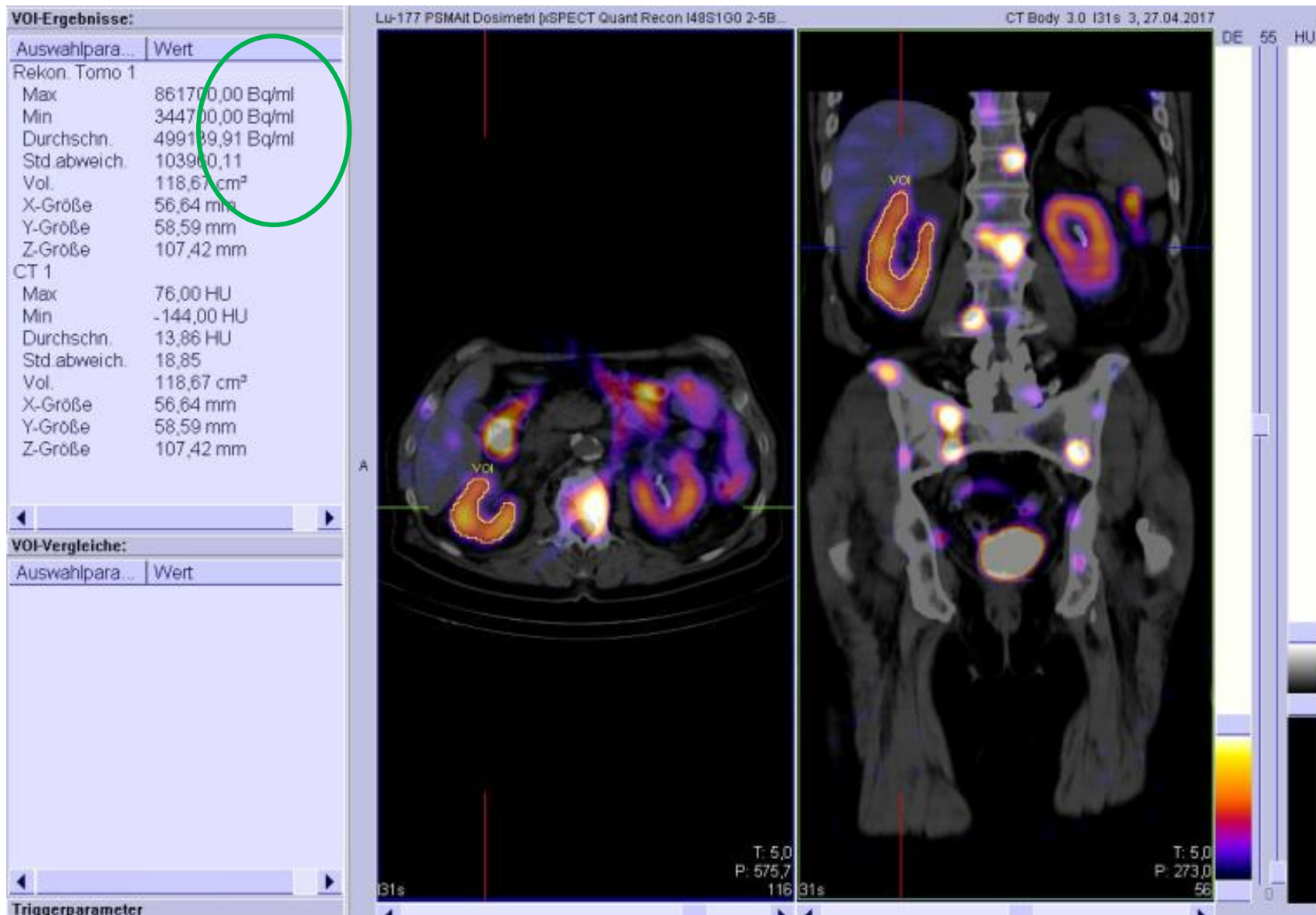
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NEMA phantom with Spheres filled with ^{177}Lu , no background (incl. 6 cm sphere)

Quantitative SPECT/CT with Lu-177-PSMA

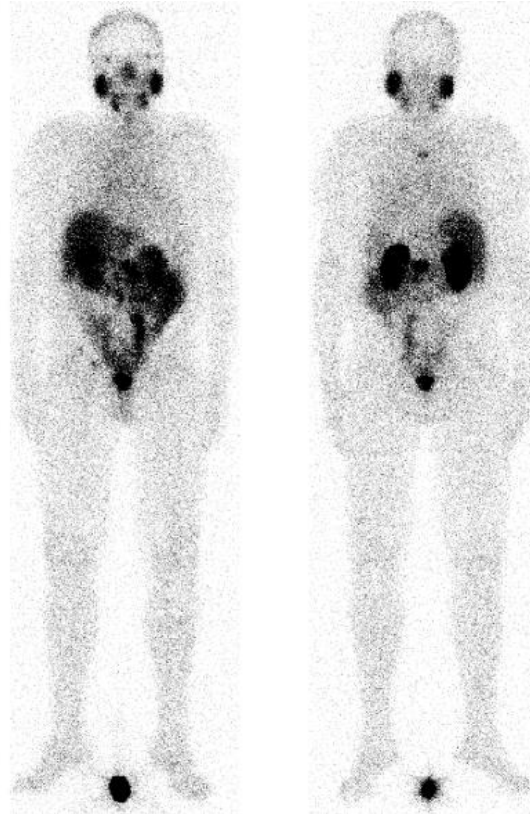


73y M with metastatic prostate cancer (bone, LN)

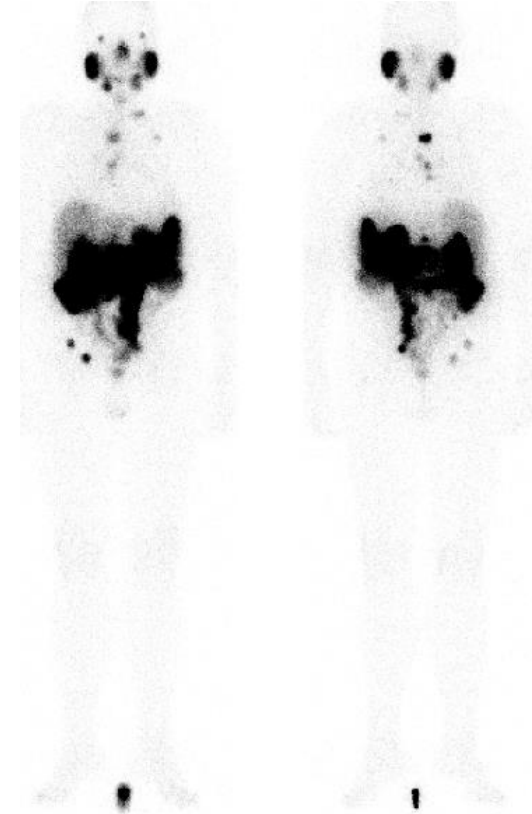
^{68}Ga -PSMA PET/CT



pre-therapeutic ^{177}Lu -PSMA



post-therapeutic ^{177}Lu -PSMA



Lu-177 PSMA: Absorbed Dose Coefficients

Authors	Method	Ligand	Absorbed Dose coefficient to Kidney (Gy/GBq)	Absorbed Dose coefficient Salivary Glands (Gy/GBq)
Fendler et al. 2017	qSPECT at 1, 24, 48 and 72 h	¹⁷⁷ Lu-PSMA-617	0.6 ± 0.2	1.0 ± 0.6
Kabasakal, 2017	Planar + 1 SPECT/CT at 4, 24, 48 and 120 h	¹⁷⁷ Lu-PSMA-617	0.8 ± 0.3	1.9 ± 1.2
Scarpa et al.2017	Planar at 0.5, 4, 24, 72 and 96 h	¹⁷⁷ Lu-PSMA-617	0.6 ± 0.4	0.56 ± 0.25
Okamoto et al. 2017	Planar at 0.5, 2, 24, 144 h	¹⁷⁷ Lu-PSMA-I&T	0.7 ± 0.2	0.6 ± 0.4
Violet et al. 2018	SPECT/CT at 4, 24 and 96 h	¹⁷⁷ Lu-PSMA-617	0.4 ± 0.2	0.6 ± 0.4
Herrmann et al. 2022 (dosimetry sub-study of the VISION trial)*	Planar and SPECT/CT at 2, 24, 48, and 168 h	¹⁷⁷Lu-PSMA-617	0.43 ± 0.16	0.63 ± 0.36

Kratochwil C, et al. EANM procedure guidelines for radionuclide therapy with ¹⁷⁷Lu-labelled PSMA-ligands (¹⁷⁷Lu-PSMA-RLT). EJNMMI. 2019, *Herrmann K, et al. Dosimetry of ¹⁷⁷Lu-PSMA-617 for the treatment of metastatic castration-resistant prostate cancer: results from the VISION trial sub-study. Journal of Clinical Oncology 2022; 40: 97-97

Lu-177 PSMA: Absorbed Doses

Authors	Method	Ligand	Absorbed Dose Kidney (Gy) (1 cycle)	Absorbed Dose Salivary Glands (Gy) (1 cycle)
Fendler et al. 2017	qSPECT at 1, 24, 48 and 72 h	¹⁷⁷ Lu-PSMA-617	4.4	7.4
Kabasakal, 2017	Planar + 1 SPECT/CT at 4, 24, 48 and 120 h	¹⁷⁷ Lu-PSMA-617	5.9	14.0
Scarpa et al.2017	Planar at 0.5, 4, 24, 72 and 96 h	¹⁷⁷ Lu-PSMA-617	4.4	4.1
Okamoto et al. 2017	Planar at 0.5, 2, 24, 144 h	¹⁷⁷ Lu-PSMA-I&T	5.2	4.4
Violet et al. 2018	SPECT/CT at 4, 24 and 96 h	¹⁷⁷ Lu-PSMA-617	3.0	4.4
Herrmann et al. 2022 (dosimetry sub-study of the VISION trial)*	Planar and SPECT/CT at 2, 24, 48, and 168 h	¹⁷⁷Lu-PSMA-617	3.2	4.7

Kratochwil C, et al. EANM procedure guidelines for radionuclide therapy with ¹⁷⁷Lu-labelled PSMA-ligands (¹⁷⁷Lu-PSMA-RLT). EJNMMI. 2019,
*Herrmann K, et al. Dosimetry of ¹⁷⁷Lu-PSMA-617 for the treatment of metastatic castration-resistant prostate cancer: results from the VISION
trial sub-study. Journal of Clinical Oncology 2022; 40: 97-97

- ▶ Patients with painful osseous metastases and reduced quality of life
- ▶ Increased uptake in places of augmented bone metabolism

Original article

Quantitative imaging of ^{223}Ra -chloride (Alpharadin) for targeted alpha-emitting radionuclide therapy of bone metastases

Cecilia Hindorf^{a,d}, Sarah Chittenden^a, Anne-Kirsti Aksnes^c, Chris Parker^b and Glenn D. Flux^a

**Nuclear
Medicine**
Communications

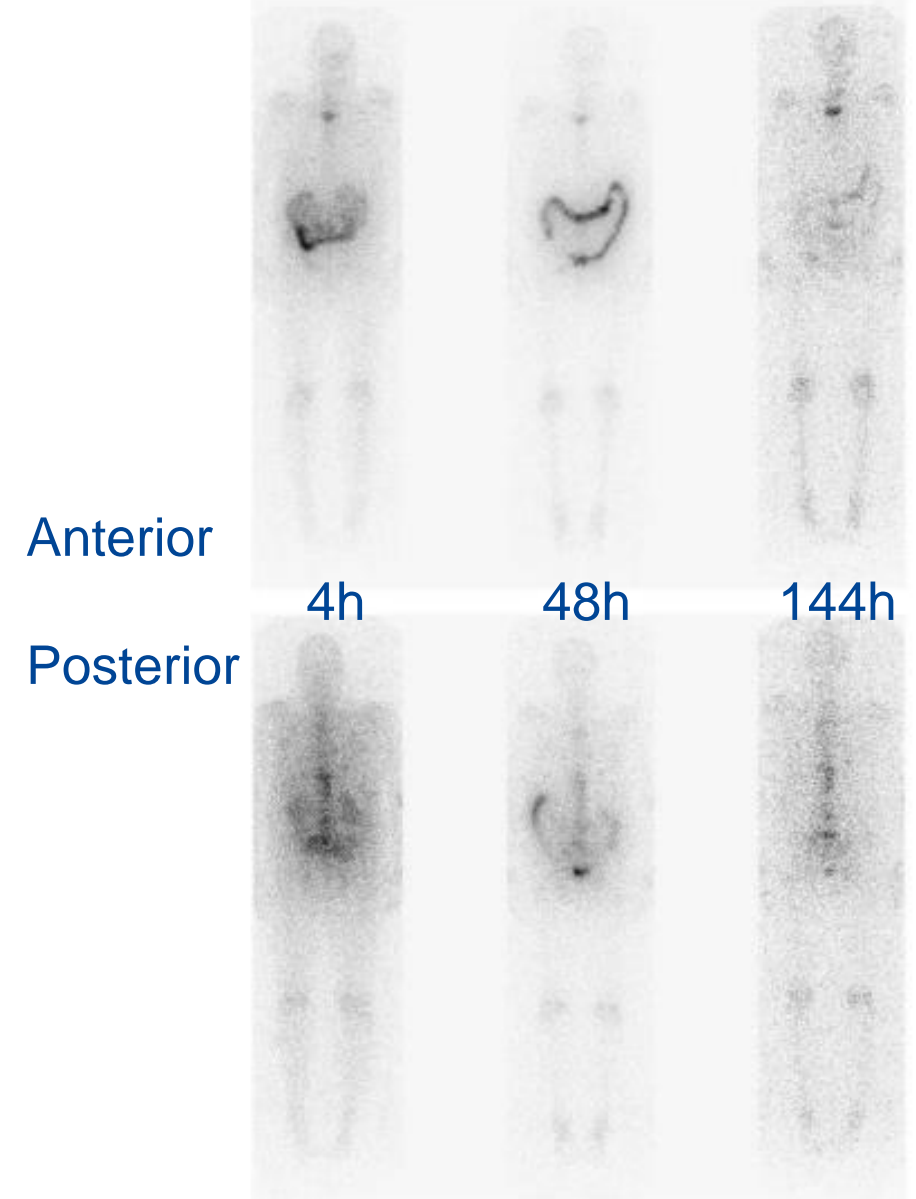


Table 1 Organ dose estimates after intravenous administration of ^{223}Ra -chloride

Organ	Absorbed dose for alpha particles (high LET)	Absorbed beta/gamma dose (low LET)	Dose coefficients	
	Gy/Bq	Gy/Bq	Gy/Bq ^a	Sv/Bq ^b
Adrenals	3.2E-09	2.4E-10	1.6E-08	6.5E-08
Bladder wall	3.3E-09	4.1E-10	1.7E-08	6.6E-08
Bone endosteum	7.5E-07	1.1E-08	3.8E-06	1.5E-05
Brain	3.2E-09	1.8E-10	1.6E-08	6.5E-08
Breast	3.2E-09	1.6E-10	1.6E-08	6.5E-08
GI tract				
Oesophagus	3.2E-09	1.7E-10	1.6E-08	6.5E-08
St wall	3.2E-09	2.1E-10	1.6E-08	6.5E-08
SI wall	3.2E-09	3.9E-10	1.7E-08	6.5E-08
ULI wall	6.8E-09	1.4E-08	4.8E-08	1.5E-07
LLI wall	1.3E-08	4.0E-08	1.1E-07	3.0E-07
Colon	9.5E-09	2.5E-08	7.3E-08	2.2E-07
Kidneys	3.4E-09	2.4E-10	1.7E-08	6.8E-08
Liver	3.6E-08	1.5E-09	1.8E-07	7.2E-07
Muscle	3.2E-09	2.0E-10	1.6E-08	6.5E-08
Ovaries	3.2E-09	4.3E-10	1.7E-08	6.5E-08
Pancreas	3.2E-09	2.2E-10	1.6E-08	6.5E-08
Red marrow	7.2E-08	5.5E-09	3.7E-07	1.5E-06
Respiratory tract				
ET airways	3.2E-09	1.7E-10	1.6E-08	6.5E-08
Lungs	3.2E-09	1.9E-10	1.6E-08	6.5E-08
Skin	3.2E-09	1.6E-10	1.6E-08	6.5E-08
Spleen	3.2E-09	1.9E-10	1.6E-08	6.5E-08
Testes	3.2E-09	1.8E-10	1.6E-08	6.5E-08
Thymus	3.2E-09	1.7E-10	1.6E-08	6.5E-08
Thyroid	3.2E-09	1.7E-10	1.6E-08	6.5E-08
Uterus	3.2E-09	2.8E-10	1.6E-08	6.5E-08

St stomach, *SI* small intestine, *LLI* lower large intestine, *ULI* upper large intestine, *ET* extrathoracic

^aRadiation weighting factor of 5 for α radiation, unit Gy as proposed by the ICRP in ICRP Publication 103 as the unit for an RBE-weighted absorbed dose for deterministic biological effects [16]

^bRadiation weighting factor of 20 for α radiation

6 treatments for a 70 kg person with an administered activity of 0.05 MBq/kg $^{223}\text{RaCl}_2$ each (overall: 21 MBq $^{223}\text{RaCl}_2$):

- Absorbed alpha dose to the bone endosteum: ~ 16 Gy
- Absorbed alpha dose to the red bone marrow: ~ 1.5 Gy

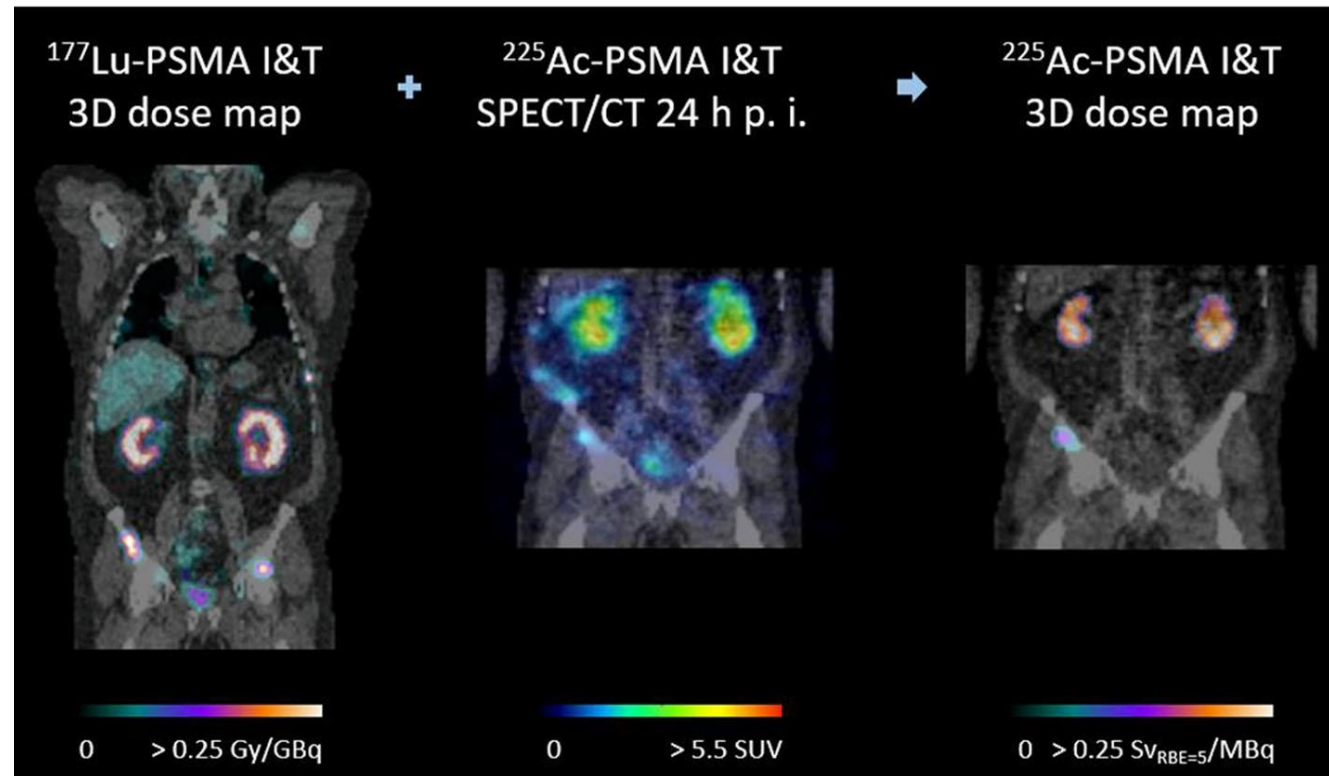
Eur J Nucl Med Mol Imaging (2013) 40:207–212
DOI 10.1007/s00259-012-2265-y

ORIGINAL ARTICLE

Dosimetry of ^{223}Ra -chloride: dose to normal organs and tissues

Michael Lassmann · Dietmar Nosske

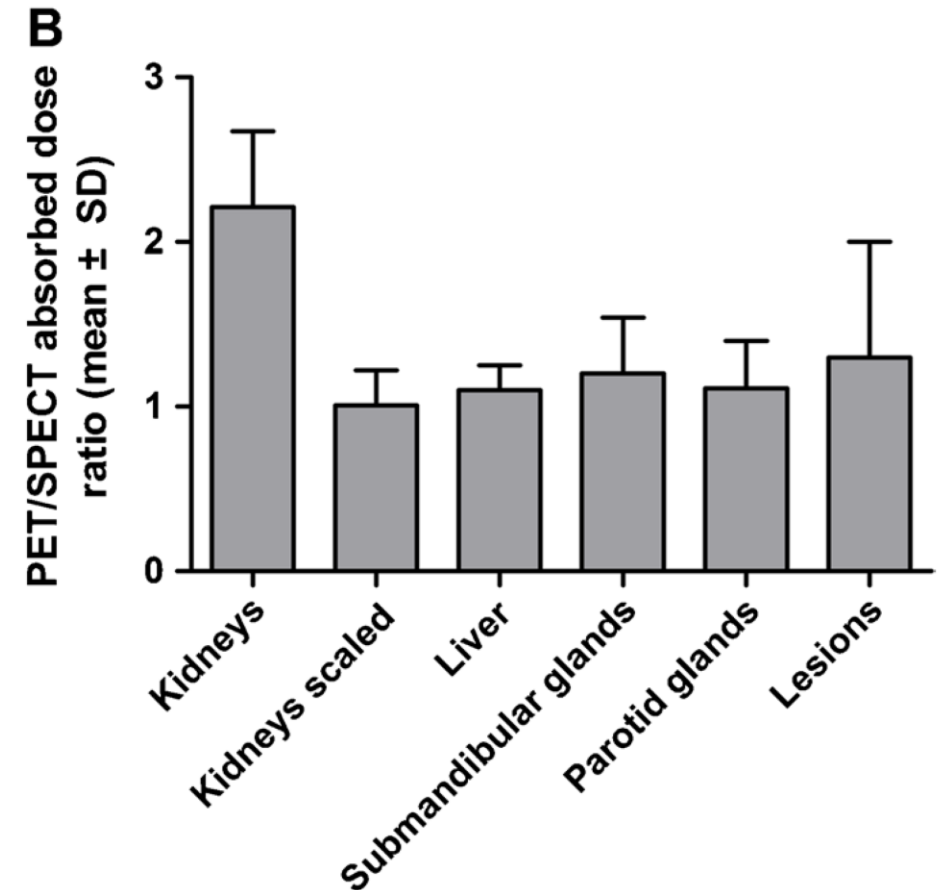
- ▶ Gamma emission at 440 keV, 25.9% and 218 keV, 11.4%
- ▶ Low therapeutic activities (4 - 8 MBq) limit the clinical applicability of SPECT and dosimetry
- ▶ **Theranostic pairs ^{177}Lu / ^{225}Ac :**
 - Dosimetry is performed using the effective half-life of a ^{177}Lu -PSMA sequence
- ▶ Kidney absorbed dose:
 - $0.18 \text{ Sv}_{\text{RBE}=5}/\text{MBq}$
- ▶ Versus for ^{177}Lu -PSMA
 - $0.27 \text{ Gy}/\text{GBq}$



Potentially different biokinetics!

Is PET able to predict therapeutic absorbed doses?

- ▶ Poor correlation between SUV_{max} and absorbed dose after therapy in PRRT [1] and PSMA therapy [2].
- ▶ Improved correlation when using $[^{68}Ga]Ga$ -PSMA-PET/CT tracer uptake at 1 h post-injection and the mean **tissue-specific effective half-life on SPECT** (shown in 10 patients) after 3 GBq $[^{177}Lu]Lu$ -PSMA [2].
- ▶ However, this approach only works with known data on biokinetics.
- ▶ Interesting approach: needs to be tested on more patients



Absorbed dose ratios per organs as determined from $[^{68}Ga]Ga$ -PSMA-PET/CT and $[^{177}Lu]Lu$ -PSMA-SPECT [1]

[1] Stenvall A. et al. EJNMMI Res 2022; 12

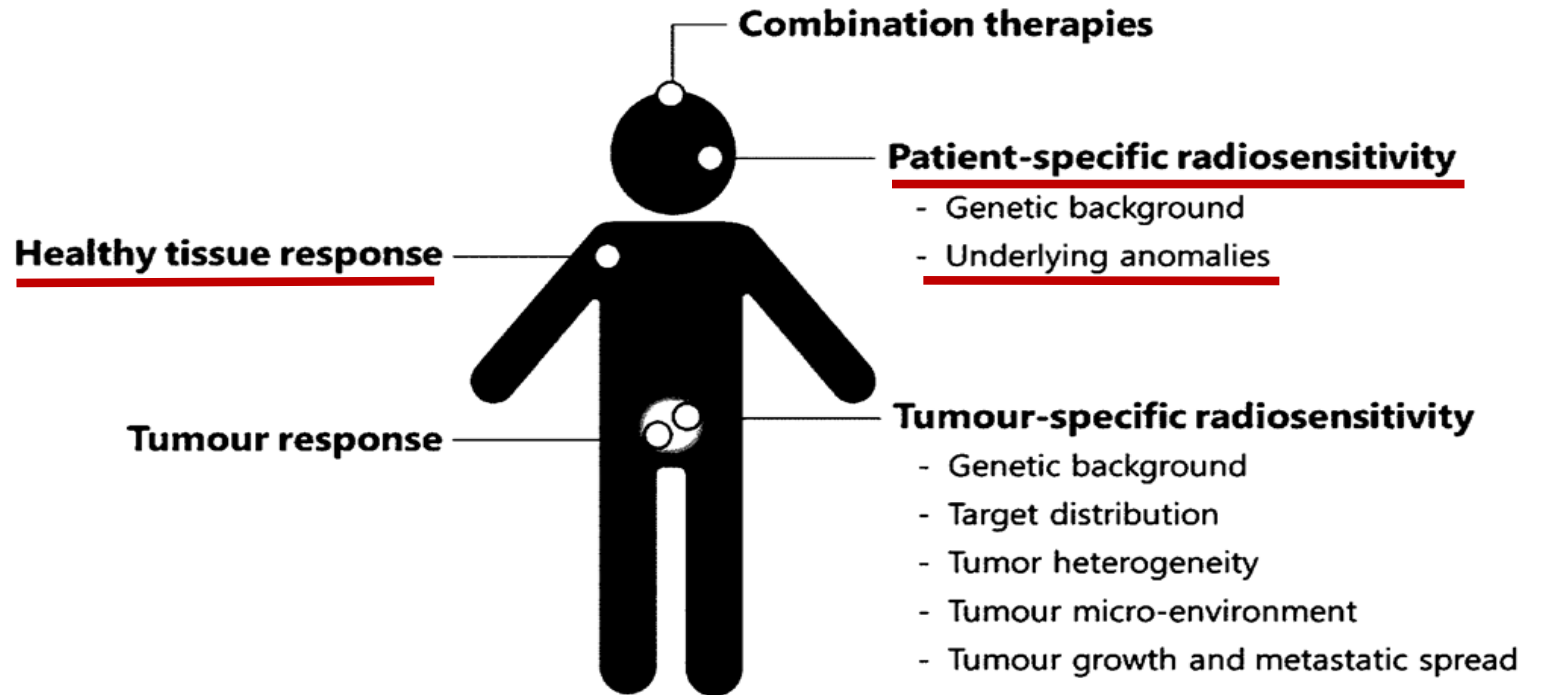
[2] Peters SMB, et al. EJNMMI,2022; 49

Physical parameters to be examined

- Radiation qualities
- Absorbed dose
- Dose rate
- Spatio-temporal dose (rate) distributions

Endpoints to be assessed

- DNA damage and repair
- Damage to other cell elements
- Death/survival pathways
- Senescence/oxidative stress/inflammation
- Effect on the immune/systemic reactions
- Repair capacities



European Journal of Nuclear Medicine and Molecular Imaging
<https://doi.org/10.1007/s00259-021-05345-9>

ORIGINAL ARTICLE

EANM position paper on the role of radiobiology in nuclear medicine

An Aerts¹ · Uta Eberlein²  · Sören Holm³ · Roland Hustinx⁴ · Mark Konijnenberg⁵ · Lidia Strigari⁶ ·
Fijis van Leeuwen⁷ · Gerhard Glatting⁸ · Michael Lassmann²

- ▶ There is a need to better define the dose-effect relationships of systemic ionizing radiation for tumors as well as for normal tissue.
- ▶ Absorbed dose rates and absorbed dose distributions in space and time are very different between external irradiation and systemic radionuclide exposure
 - ➔ **distinct radiation-induced biological responses to be explored in nuclear medicine**
- ▶ A strong link between radiochemists, radiopharmacists, radiobiologists, medical physicists, and physicians is warranted

European Journal of Nuclear Medicine and Molecular Imaging
<https://doi.org/10.1007/s00259-022-05934-2>

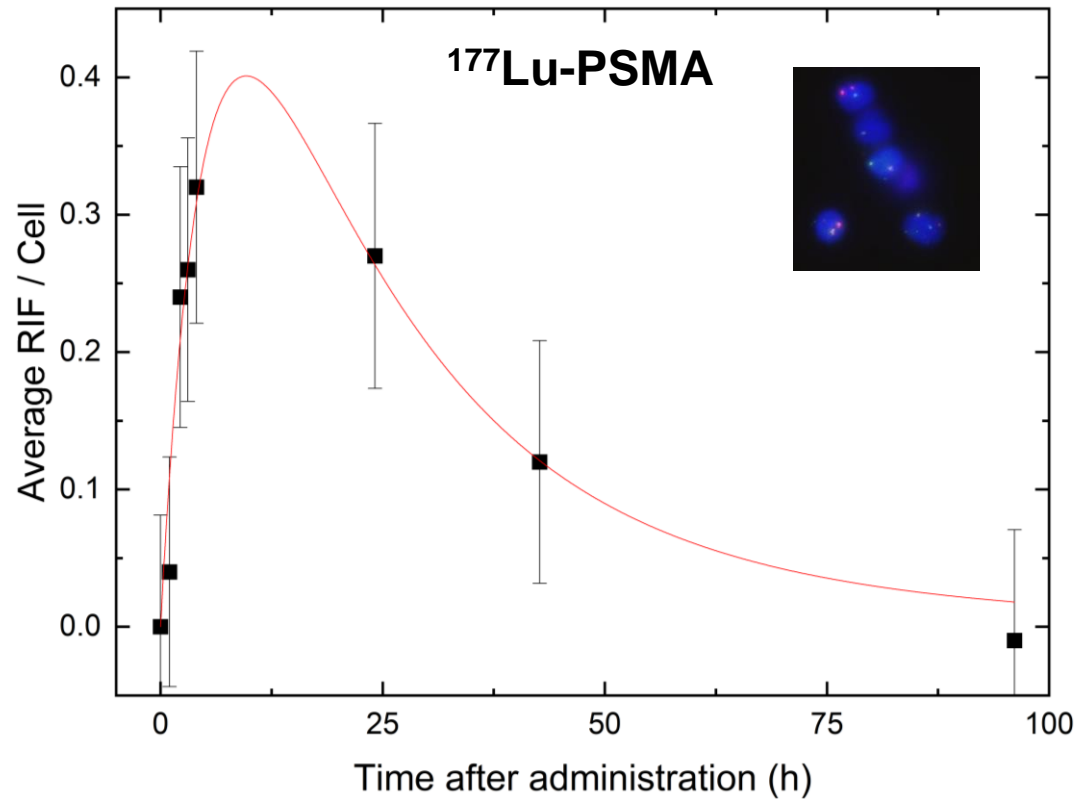
EDITORIAL



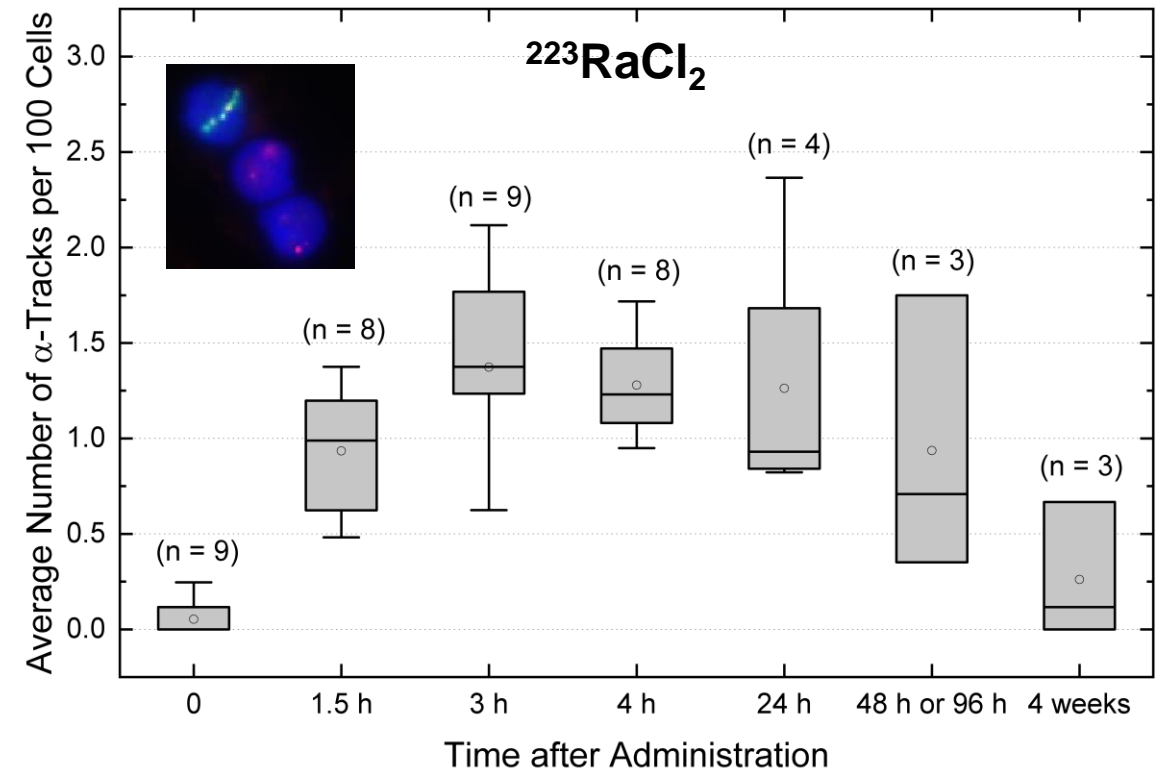
An EANM position paper on advancing radiobiology for shaping the future of nuclear medicine

EANM Radiobiology Working Group: · Jean-Pierre Pouget¹ · Mark Konijnenberg² · Uta Eberlein³ · Gerhard Glatting⁴ · Pablo Minguez Gabina⁵ · Ken Herrmann⁶ · Søren Holm⁷ · Lidia Strigari⁸ · Fijs W. B. van Leeuwen⁹ · Michael Lassmann³

- ▶ γ -H2AX + 53BP1 radiation induced foci (RIF) or α -tracks in PBMCs as a function of time after administration




Total absorbed dose to the blood: ≈ 100 mGy



At 4h absorbed dose to the blood: < 6 mGy

- ▶ Standardized image quantification for dosimetry across centers needs to be further promoted and supported e.g. by accreditation programs
- ▶ Efforts are made using theranostic pairs to predict absorbed doses
- ▶ Post-therapeutic analysis of patient-specific dosimetry could lead to an optimized activity prescription balancing safety and efficacy of a treatment
- ▶ Including dosimetry in clinical trials would be highly desirable
- ▶ Including radiobiology findings in nuclear medicine dosimetry could be beneficial for patient-specific treatment-planning



Thank you for your attention!