Memorial Sloan Kettering Cancer Center

Workshop on Radiopharmaceutical Therapy (RPT)
Normal Tissue Effects in the Clinic (TEC)
RPT-TEC-2022

SEPTEMBER 24 - 29, 2022

Clinical Experience with Peptides

Sunday, September 25, 2022

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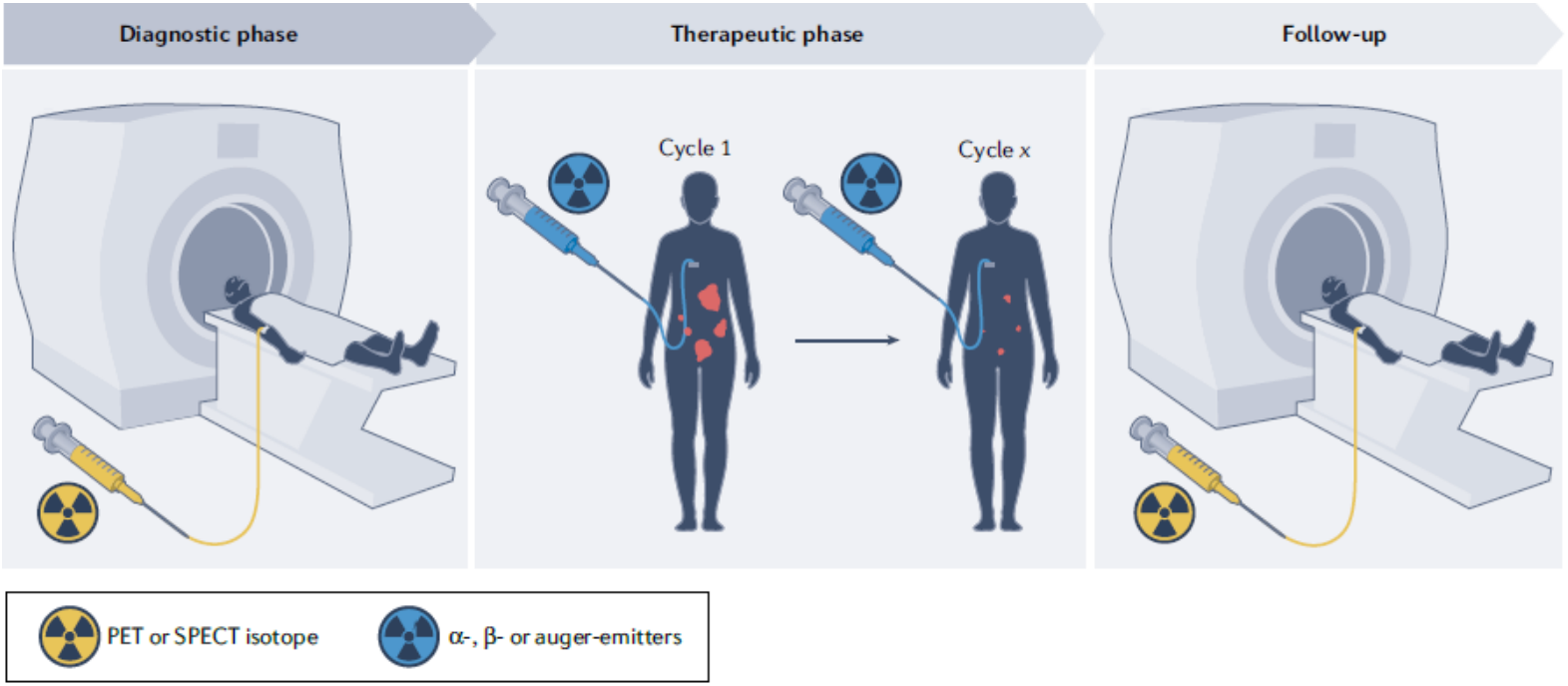
Disclosure

A) I hold a position as an employee, consultant, assessor or scientific advisory member for a pharmaceutical, device or biotechnology company (If so, please specify your title/project/company):	• *Nonremunerated Consultancies for Advanced Accelerator Applications, Ipsen, Clovis, ITM, Iba, Great Point Partners*
B) I work as an advisor for an industrial company	• NO
C) I am a member of the board of an industrial company	• NO
D) I receive support from a pharmaceutical, device or biotechnology company (If so, please specify which project and whether support is in kind or monetary):	• Advanced Accelerator Applications (IA PRRT)
E) I hold property rights/patents for pharmaceuticals, radiopharmaceuticals, medical devices or medical consulting firms:	• NO
F) I have written articles for pharmaceutical, radiopharmaceutical, medical device, biotechnology or consulting companies during the last 5 years (If so, please state article, journal and co-authors):	• NO

Theranostic Concept



Bodei L et al. Nature Rev Clin Oncol 2022

What is past is prologue… *The Tempest* of theranostics

1938 — **1992** — **2012-2021**

Arthur Roberts (*left*) and Saul Hertz (*right*) performing radioiodine biokinetic studies in rabbits

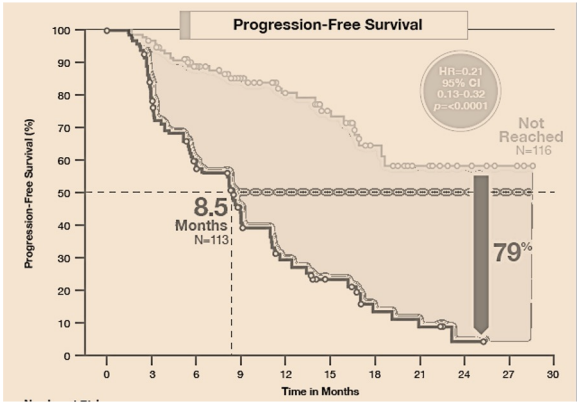
Fahey FH et al. EJNMMI Phys 2017

Radiotherapy with a Radiolabeled Somatostatin Analogue, [^{111}In-DTPA-D-Phe^1]-Octreotide

A Case History

E. P. KRENNING,[a,b,c] P. P. M. KOOIJ,[a] W. H. BAKKER,[a] W. A. P. BREEMAN,[a] P. T. E. POSTEMA,[b] D. J. KWEKKEBOOM,[a] H. Y. OEI,[a], M. DE JONG,[a] T. J. VISSER,[b] A. E. M. REIJS,[a] AND S. W. J. LAMBERTS[b]

NETTER-1



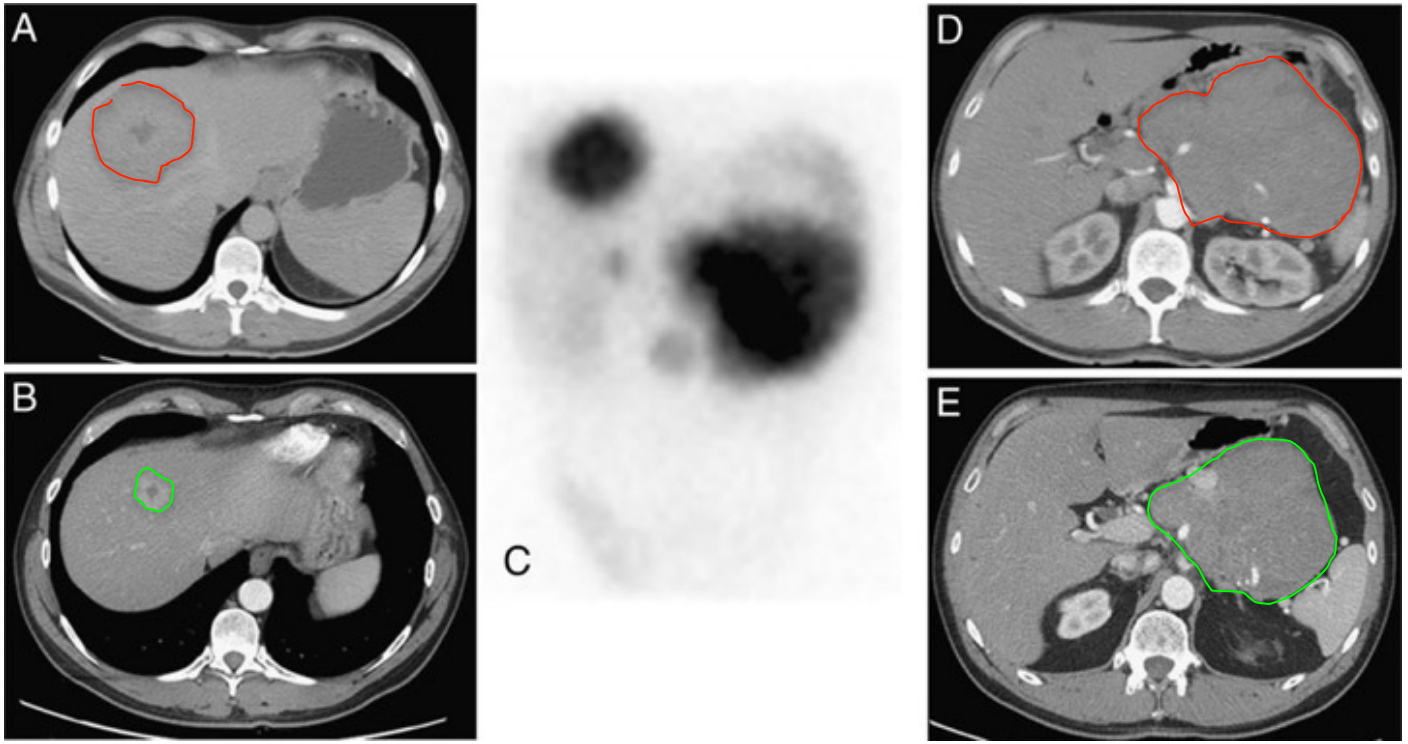
Strosberg J et al. NEJM 22017;

Somatostatin Receptor Targeted Radionuclide therapy (PRRT) for Neuroendocrine Tumors (NETs): ^{177}Lu-DOTATATE

G2 Pancreatic NET

Pre

Post



Bodei L et al. Eur J Nucl Med Mol Imaging 2011

Peptide Receptor Radionuclide Therapy of well-differentiated neuroendocrine tumors
Lessons Derived from 25 yrs of clinical trials

EFFICACY

- ✓ **Decrease in tumor size (18-60%)**
- ✓ **Symptom relief (60-70%)**
- ✓ **QoL improvement**
- ✓ **Impact on survival**

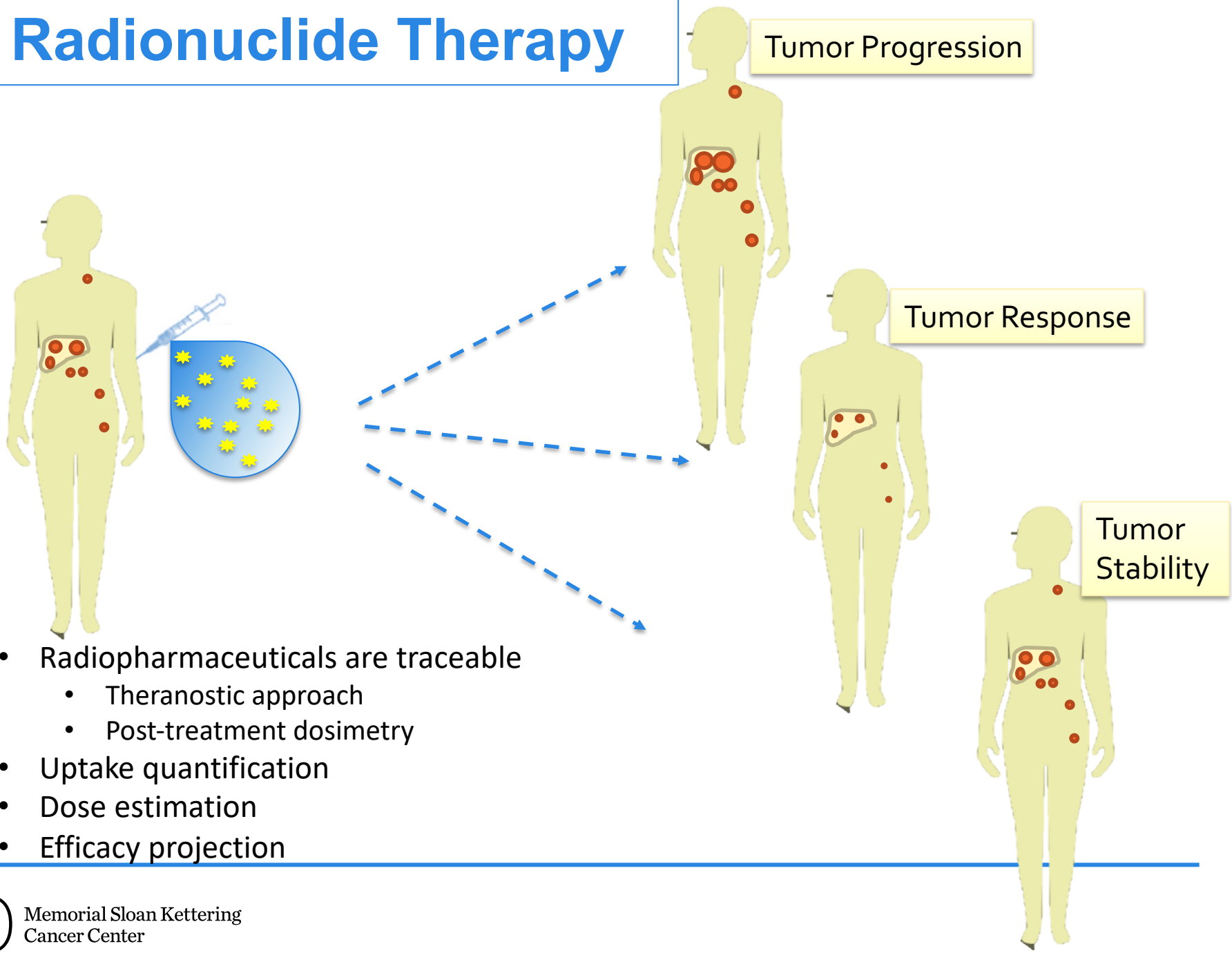
TOLERABILITY

- ✓ **Well tolerated**
- ✓ **Generally mild acute side effects:**
  - Amino Acid-related: nausea, vomiting
  - PRRT-related: fatigue, mild hair loss (Lu-tate),
  - Rarely: exacerbation of syndrome
- ✓ **Sub-acute hematological toxicity mild and reversible in ≥90%**
- ✓ **Chronic kidney and BM toxicity**
  - Generally mild if precautions undertaken

Kwekkeboom DJ et al. JNM 2005, 2008
Bodei L et al. Eur J Nucl Med Mol Imaging 2004, 2008, 2011
Kwekkeboom DJ et al. Endocrine Rel Cancer 2010
Brans B et al. Eur J Nucl Med 2007
Cremonesi M et al. Q J Nucl Med Mol Imaging 2011
Ezziddin S et al. EJNMMI 2014, JNM 2014
Sabet A et al. JNM 2013, EJNMMI 2014
Bodei et al. EJNMI 2015

Currently most used:
^{177}Lu-DOTATATE/TOC

Radionuclide Therapy

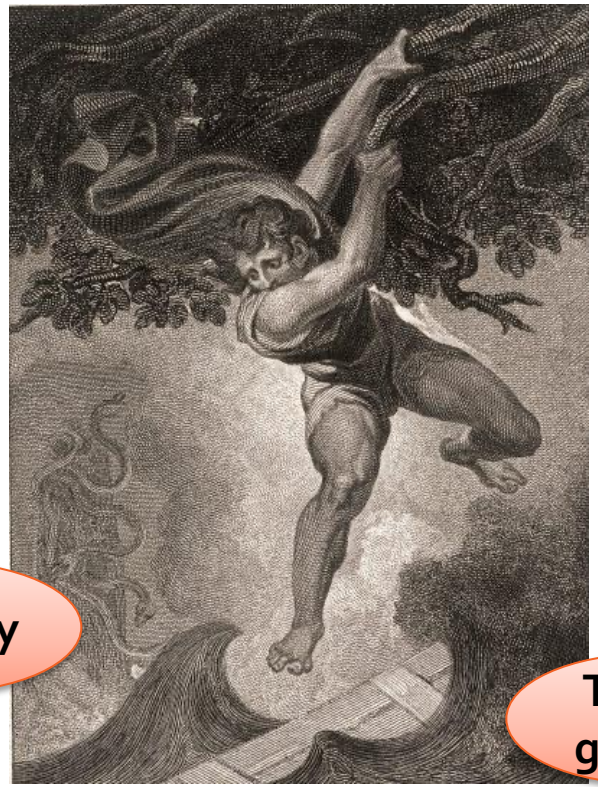


- Radiopharmaceuticals are traceable
  - Theranostic approach
  - Post-treatment dosimetry
- Uptake quantification
- Dose estimation
- Efficacy projection

Ethical Dilemma:
how to deliver adequate Tumor Doses without causing excessive Toxicity?

… How to measure what we're actually doing?

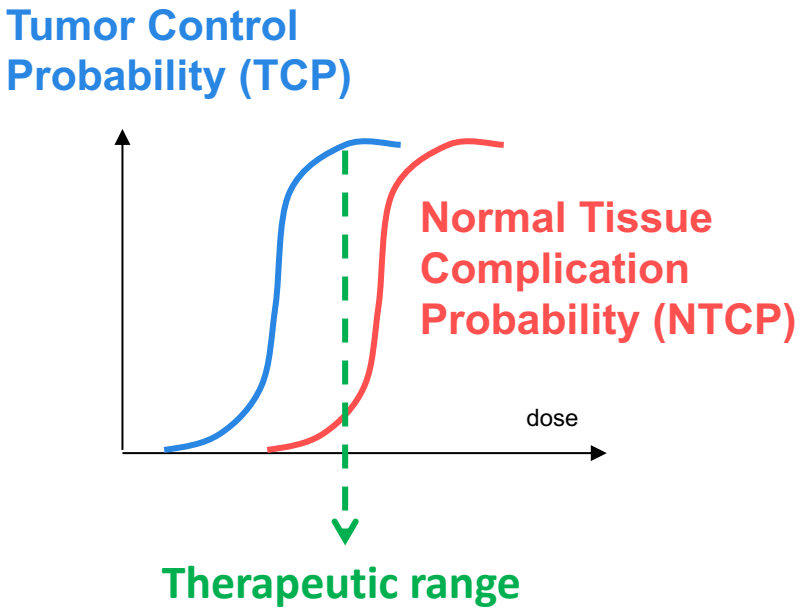
Targeted radiation is (relatively) safe



Toxicity

Tumor growth

Odysseus between Scylla and Charybdis
William Bromley, 1806

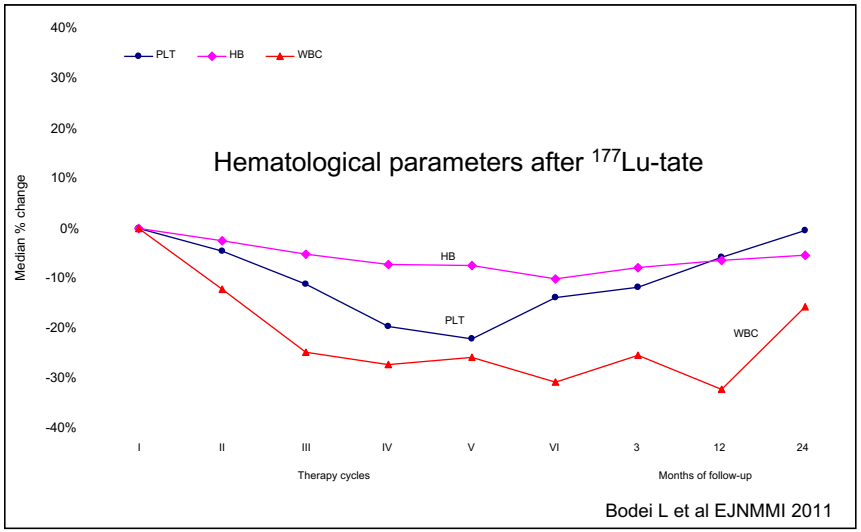


Radionuclide Therapy: where we are today

- **Currently, many prospective randomized studies and prospective trials are ongoing/planned**
- Most radionuclide therapies are **empirical** or based on the **DLT** concept
- **Individualization** is mainly obtained through empirical adaptation to clinical and laboratory parameters, frequently with suboptimal results
- Provisional **dosimetry** is regarded as time- and resource-consuming and not accurate ("*I don't believe in it*", "*It doesn't make a difference*")
- Issues to be addressed in **clinical dosimetry**:
  - Length and complexity of procedure
  - Inaccuracies in calculating the dose to the tumor (e.g. PVE, microenvironment)
  - Inaccuracies in calculating the dose to the normal organs (e.g. bone marrow)

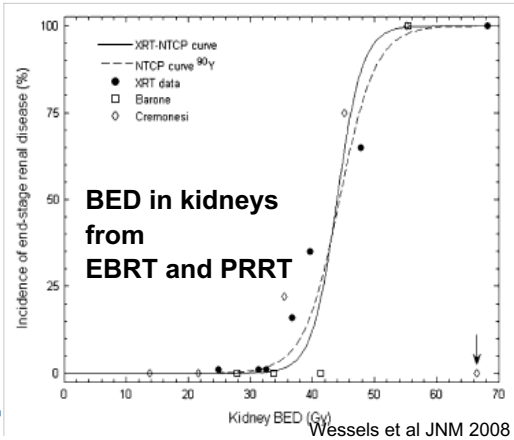
Biology of tissue damage

- Tissues with rapid turnover (mucosae, bone marrow, most tumors)
  - Damage after the lifespan of mature cells has elapsed→ **acute, may be reversible**



Bodei L et al EJNMMI 2011

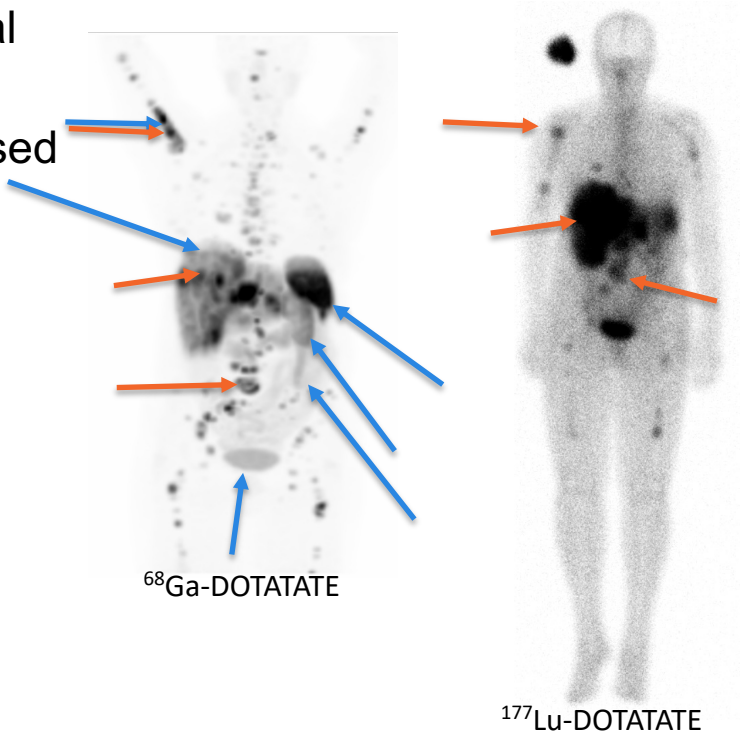
- Tissues with slow turnover (kidney, liver, lung, thyroid, SNC)
  - Cells mostly die of senescence→ damage is **delayed/chronic, irreversible**



Wessels et al JNM 2008

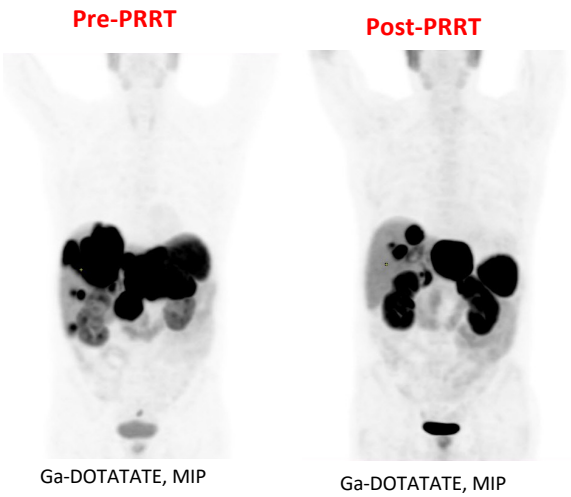
Side Effects of Radionuclide Therapies depend on

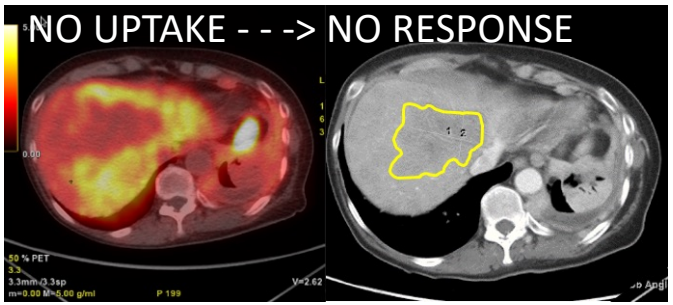
- **Normal distribution** of the radiopharmaceutical used
- Location of **tumor lesions**
- **Tolerance** of the organs involved to the radiation doses
  - –High: e.g. liver
  - –Low: e.g. bone marrow
- Patient's **conditions**
  - –KPS/ECOG
  - –Age
  - –Organ function
  - –Individual response
- Administered **activity**/delivered **dose to organ**

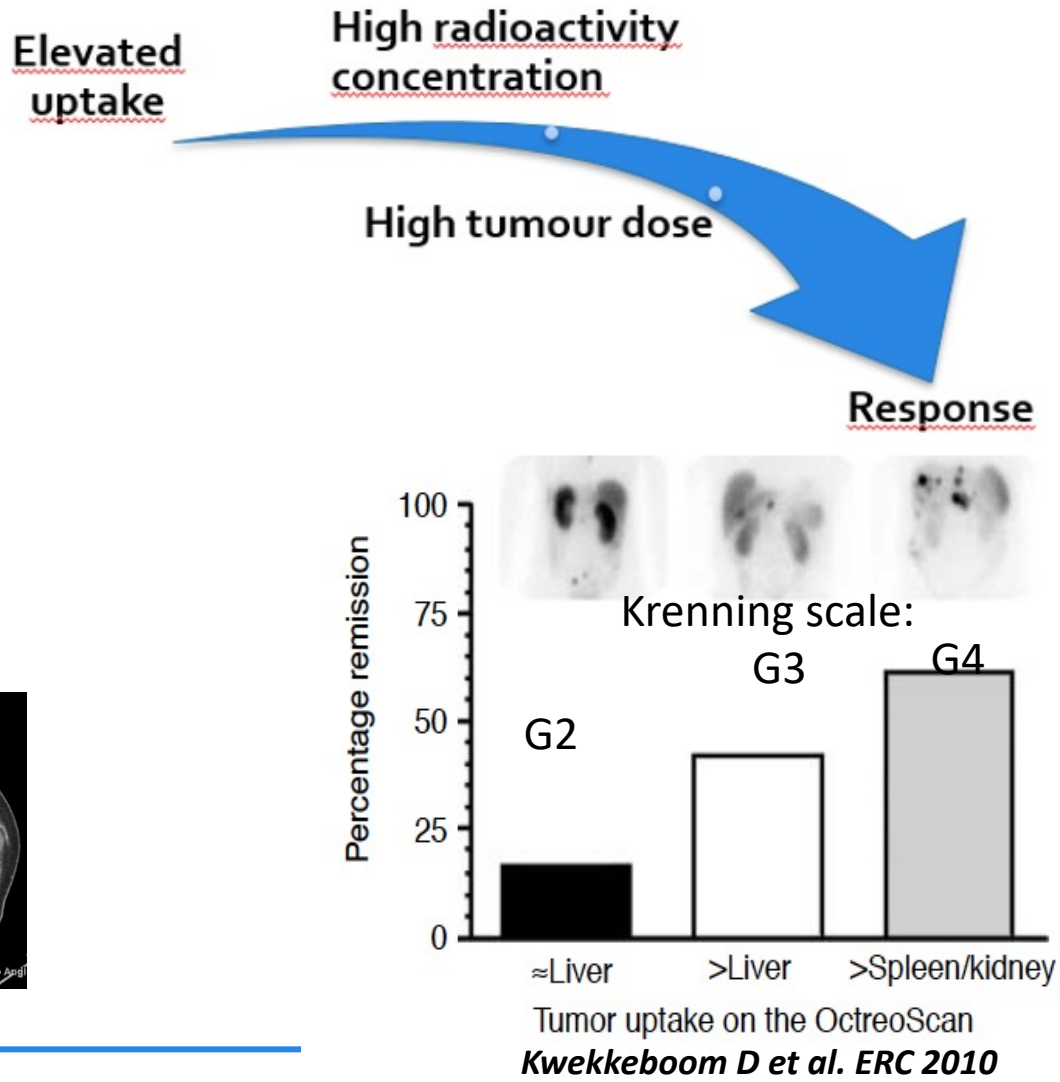


PRRT efficacy correlates with target expression

$^{68}Ga/^{64}Cu$-DOTATATE PET/CT

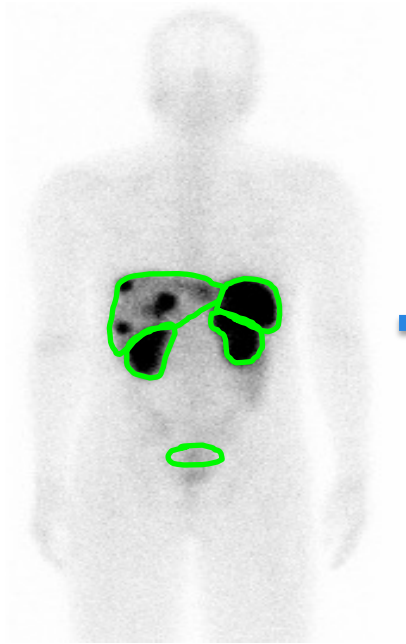


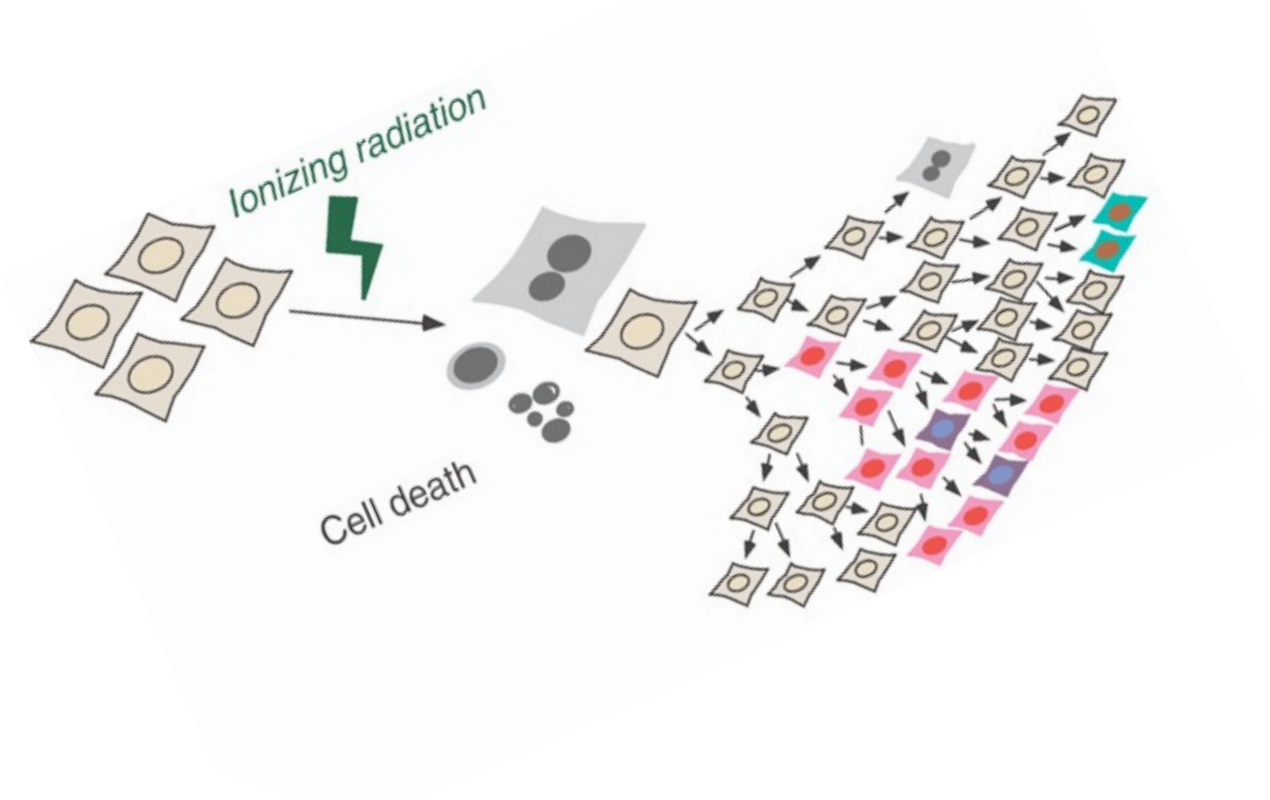




Kwekkeboom D et al. ERC 2010

The amount of drug reaching the target can be estimated: DOSIMETRY





There is no effect without the dose

Fixed Dosages: Advantages

- **Easy, rapid and economical (the "*oncologist's way*")**
- **Based on previous experiences (phase I DLT and phase II studies)**
- **Relatively efficient and safe in the majority of patients**
- **Removes the aura of complexity around RNT**

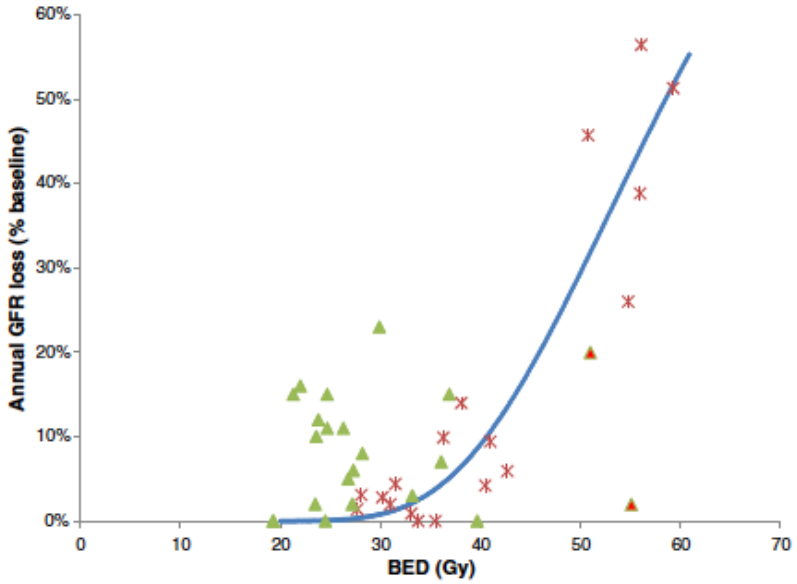
Dosimetry-Based Approach: Advantages

- Optimization of RNT
- Estimation of cost-benefit ratio of treatment in single pts
- Minimization of risks of toxicity
- Individualization according to clinical needs (eradication, palliation)

Normal organs…

Dosimetry-based ^{90}Y-PRRT reduces renal toxicity

37 Gy BED to kidneys

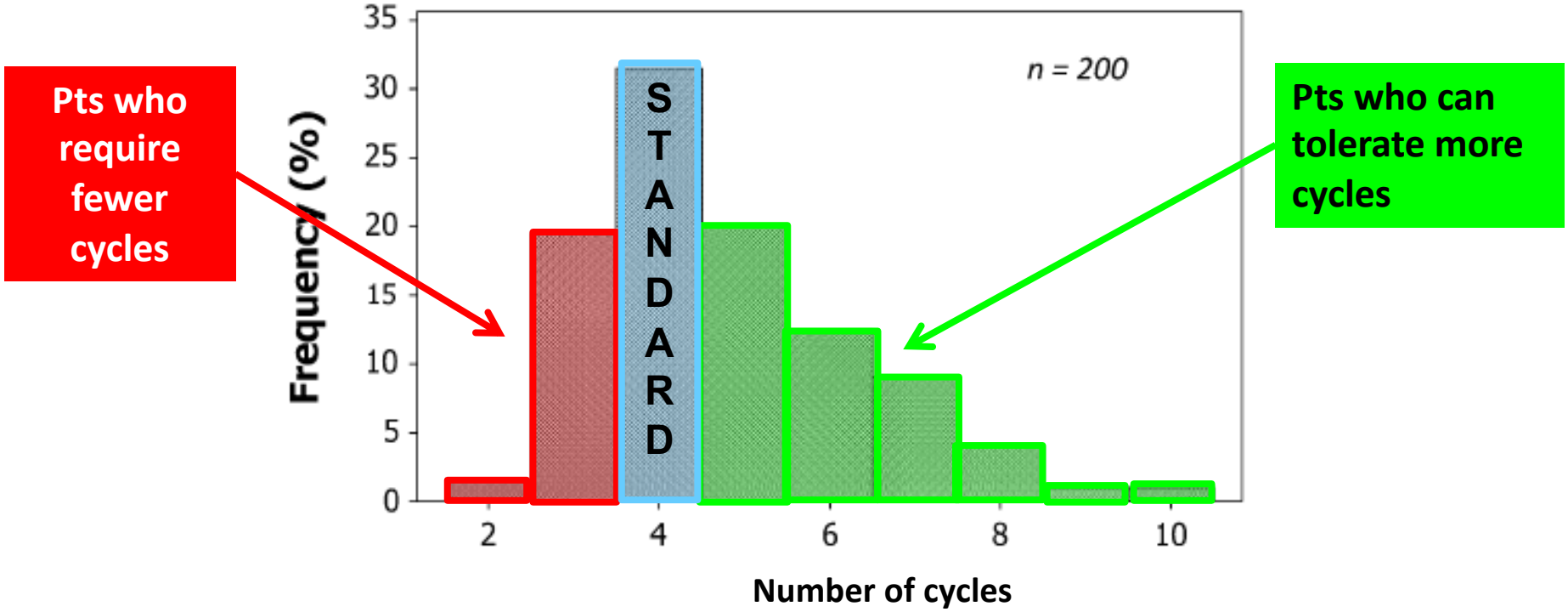


Van Binnebeek EJNMMI 2014

Prospective dosimetry is a good guide for PRRT and has a low risk of severe renal toxicity.

Dosimetry-based PRRT may guide optimized treatments

^{177}Lu-octreotate, standard 4 cycles, 23 Gy to kidneys, 2 Gy to BM



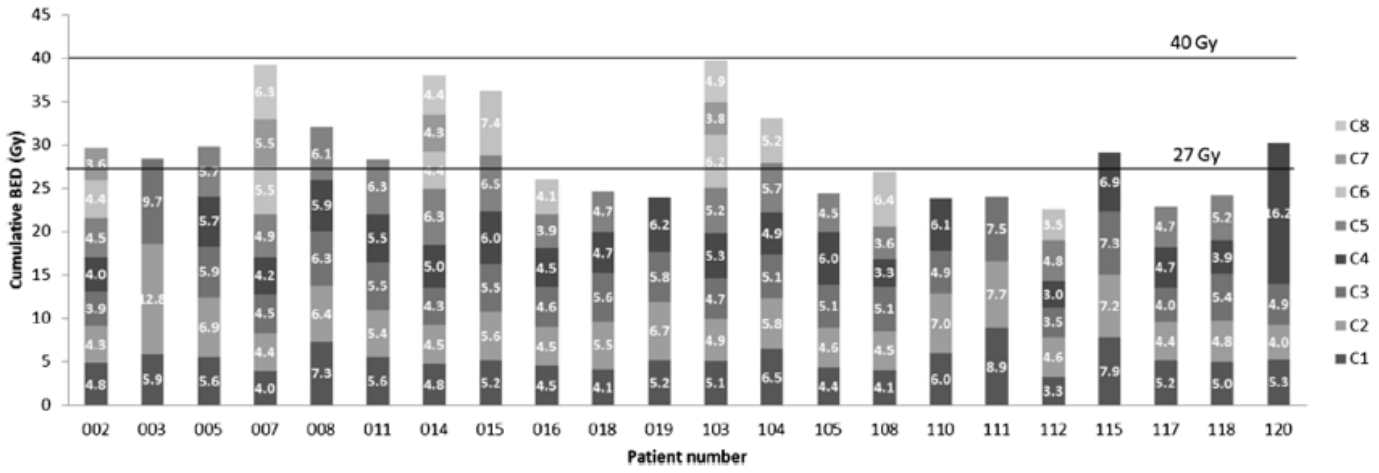
- Individualized absorbed dose essential for optimization

Sandström M JNM 2013

- Prospective dosimetry based on 23 Gy threshold is feasible

Gårske-Roman U et al. EJNMMI 2018

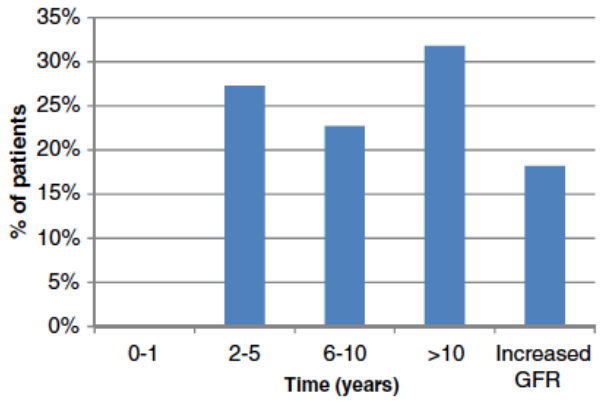
Dosimetry-based PRRT



Individualised dosimetry-based PRRT is feasible and safe, with the BED limits used in this protocol

Limitations:
- Short follow up/interim analysis
- Only kidney dosimetry
- *Bone marrow? Tumor?*

Projected time to significant reduction in GFR (<30 mL/min)



Anna Sundlöv et al. EJNMMI 2017

PRRT hematological toxicity is low but related to the dose

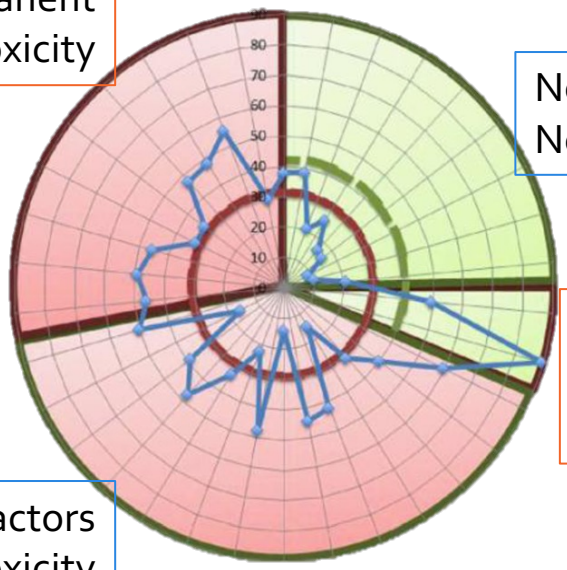
Organ	^{90}Y-DOTATOC		^{177}Lu-DOTATATE	
	Radiation dose	Reference	Radiation dose	Reference
Red marrow	0.03±0.01	[75, 76]	0.07±0.01	[85]
	0.17±0.02	[79]	0.04 (0.02–0.06)	[86]
	0.09 (0.03–0.18)	[80]	0.04±0.02	[65]
	0.05±0.00	[81]	0.02±0.03	[74]
	0.06±0.02	[82]		
	0.12±0.02	[67] (paediatric, ^{111}In)[a]		
Kidneys	6.05 (unprotected)	[83]	1.65±0.47 (unprotected); 0.88±0.19 (protected)	[85]
	3.7 (1.9–7.6) left; 4.3 (3.4–7.4) right	[84]	0.62 (0.45–17.74)	[86]
	3.84±2.02 (unprotected)	[74, 76]	0.9±0.3	[65]
	2.84±0.64	[79]	(0.32–1.67)	[87]
	2.44 (1.12–4.5)	[80]		
	2.73±1.41	[82]		
	1.71±0.89 (1.20–5.10)	[59]		
	2.24±0.84 (1.1–3.8)	[67][a]		
Liver	0.75±0.65	[74, 76]	0.18 (0.05–0.34)	[86]
	0.92±0.35	[79]	0.13–1.10	[87]
	0.86 (0.34–1.93)	[80]	0.21±0.08	[85]
	0.66±0.15	[81]		
	0.72±0.40	[82]		
	0.27	[83]		
	1.5±1.2 (0.3–3.0); 0.35 low burden, 2.67 high burden	[67][a]		

Bodei L et al. EJNMMI 2013

Dosimetry isn't all…

^{90}Y- and ^{177}Lu-PRRT

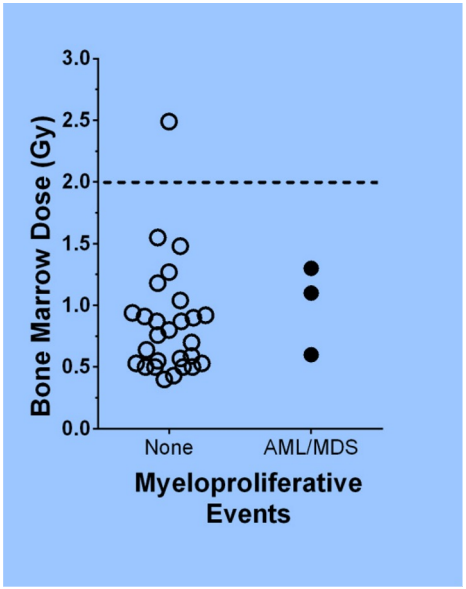
Risk factors
Permanent
toxicity



No risk factors
No toxicity

No risk factors
Permanent
toxicity

Risk factors
No toxicity

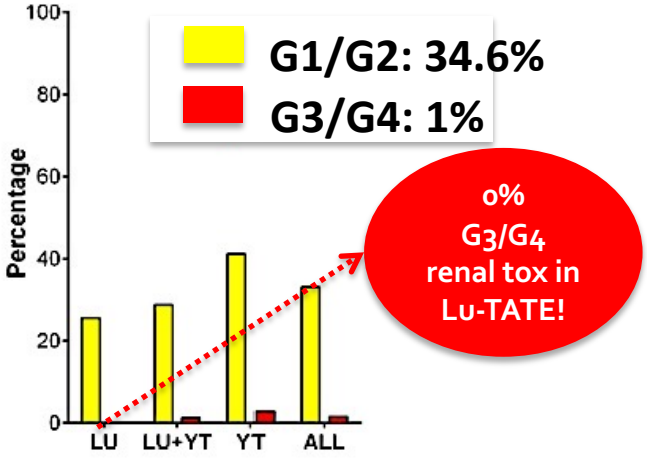


Unless very high doses are administered, there is a grey zone of unpredictable outcome around the thresholds

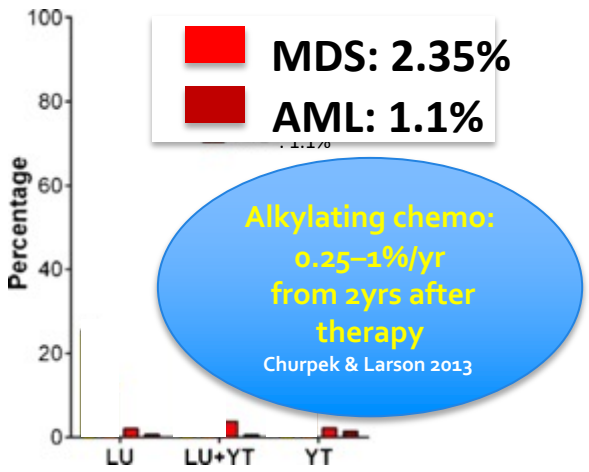
Individual susceptibility to adverse *sequelae* of PRRT is likely to have an individual genetic basis.

Permanent toxicity after PRRT is low and comparable to other treatments

Renal Toxicity



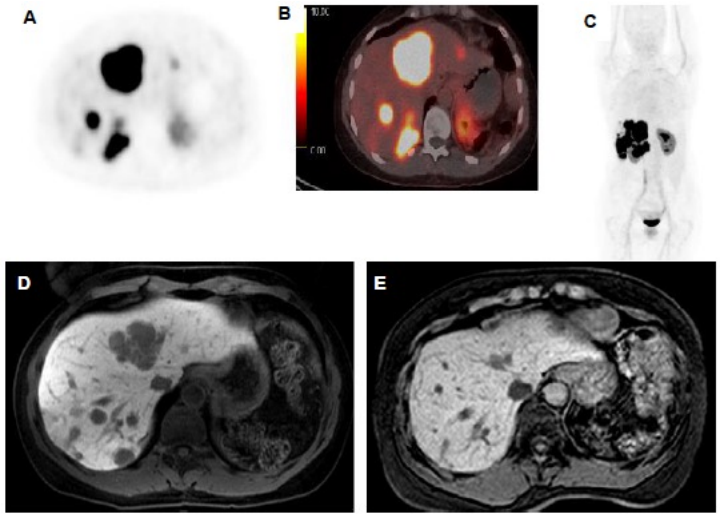
Bone Marrow Toxicity



- Severe nephrotoxicity was virtually absent after ^{177}Lu-peptides
- Bone marrow toxicity low and comparable with other anti neoplastic therapies

Bodei L et al. EJNMMI 2015

PRRT with ^{177}Lu-DOTA-JR11 (Satoreotide)



^{68}Ga-DOTA-JR11
60 min p.i. (MIP)

Liver MRI

- **20** heavily pretreated pts: **14** completed 2 cycles, **6** had 1 cycle
- **best ORR 45%** (5% CR, 40% PR); 40% SD and 15% PD.
- **mPFS 21.0 months**
- Prolonged but reversible G3/4 toxicity in first 4/8 (50%) treated with 2 cycles
- Promising data. Additional studies needed to determine optimal therapeutic dose/schedule

Reidy D et al. CCR 2019

Hematologic toxicity after ^{177}Lu-satoreotide

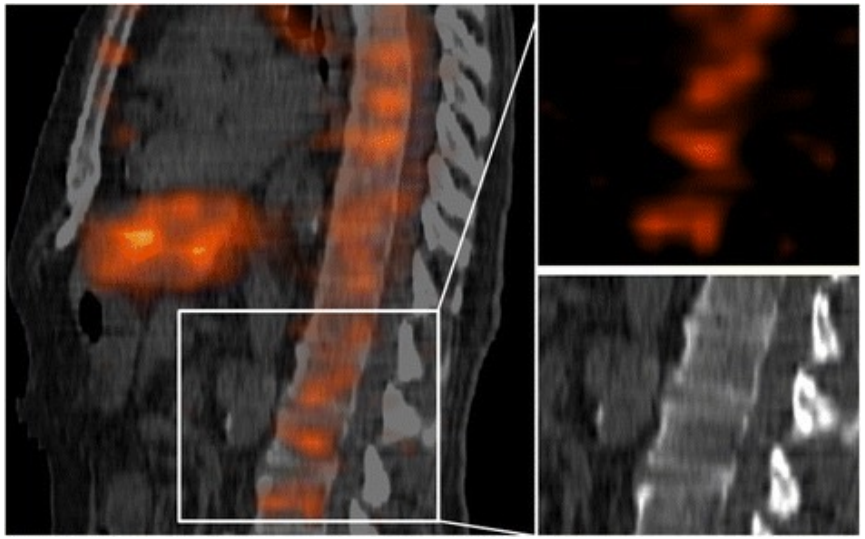
Patient	Cycles (No.)	Hb toxicity	WBC toxicity	PLT toxicity	ANC toxicity	Dosimetry (GBq)	D-T1 gap (days)	Therapy 1 (GBq)	T1-T2 gap (weeks)	Therapy 2 (GBq)	Total RMD (Gy)	Best response
1	2	1	0	0	0	1.81	58	7.12	13	7.29	1	SD
2	2	3	4	4	4	1.23	21	7.18	11	7.28	1.54	SD
3	2	1	2	1	1	0.81	7	7.85	10	7.15	0.99	PR
4	2	1	2	0	2	1.98	14	7.28	12	7.3	1.08	PR
5	2	2	3	4	3	1.82	13	6.6	13	7.24	1.5	CR
6	2	2	2	4	2	1.95	8	7.33	13	7.32	1.71	SD
7[a]	1	2	0	0	0	1.91	15	6.22	N/A	N/A	0.58	PD
8	2	3	3	4	3	1.99	28	5.65	12	4.86	1.44	PR
9[a]	1	2	2	2	2	1.92	28	7.37	N/A	N/A	0.69	PD
10[a]	1	0	0	1	0	1.93	20	7.37	N/A	N/A	0.78	PR
11	2	2	2	1	0	2.02	29	5.06	70	2.51	1.41	SD
12	2	2	2	1	2	1.88	21	6.16	74	3.62	1.42	SD
13	2	2	2	1	0	2.02	21	7.28	80	3.98	1.2	PR
14[a]	1	2	2	1	0	2.01	29	6.29	N/A	N/A	1	SD
15[a]	1	0	2	1	0	1.86	28	6.98	N/A	N/A	0.83	SD
16	2	1	0	0	0	2	29	7.28	84	4.02	0.74	SD
17	2	0	0	0	0	2.01	42	6.8	85	3.63	1.19	PR
18[a]	1	1	0	0	0	1.96	7	4.96	N/A	N/A	0.8	PD
19	2	0	1	2	1	2.01	20	6.17	80	3.16	1.35	PR
20	2	0	1	0	0	1.83	20	7.25	11	3.9	0.88	PR

Bone marrow doses were not considered unsafe and were similar to those observed in other patients who did not exhibit toxicity

Reidy-Lagunes D et al. CCR 2019

Improved Marrow Dosimetry is an unmet need

^{177}Lu-labeled di-HSG-peptide for anti-CEA/HSG RIT



3D-Red Marrow Dose correlates with toxicity, conventional 2D dosimetry was not informative

Woliner-van der Weg W et al. EJNMMI Physics 2014

Relevant skeletal populations:
- hematopoietic stem cells - risk of tMN
- osteoprogenitor cells – risk of bone cancer

} Millimetric, non-segmentable

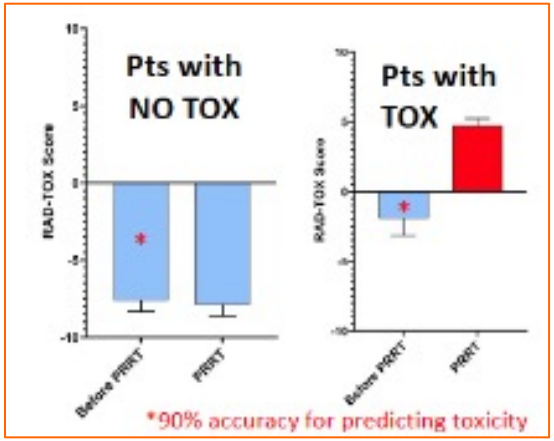
We need to develop microdosimetric modeling and specific toxicity biomarkers

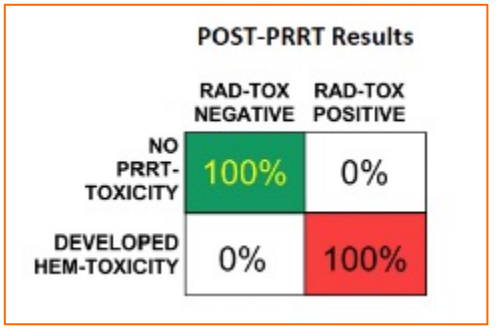
Transcriptomic signatures applied to PRRT: USA Validation

n=67

RADtox

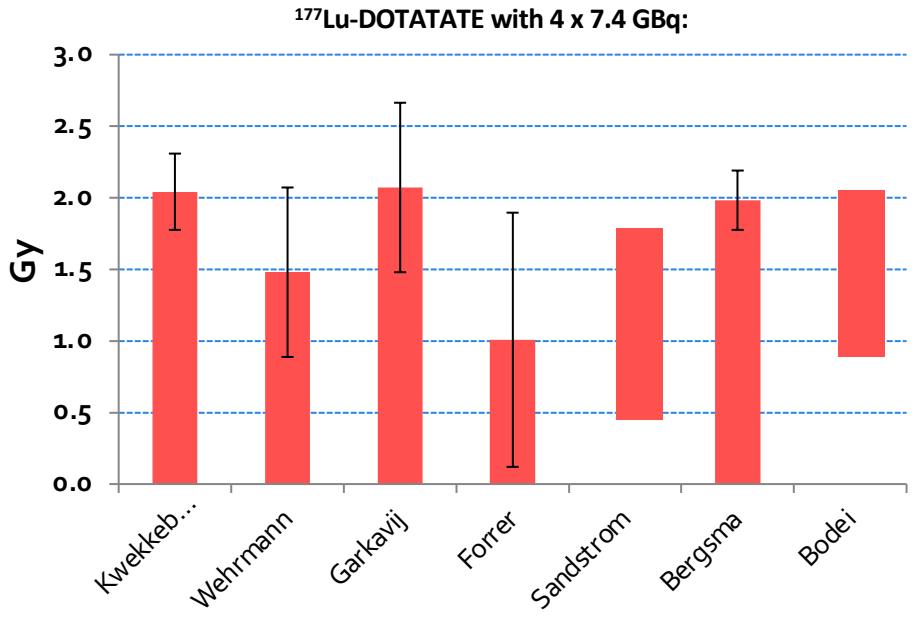
Hematological TOXICITY





Bodei L et al. 2019-2022

^{177}Lu-DOTATATE RM absorbed doses – blood based method



BM absorbed doses from the blood based method are low. Toxicity is mild. However, cumulative effects of depletion of BM resources can be observed

Typically, for ^{177}Lu-PRRT

AD < 2 Gy, cumulatively

Forrer F, EJNMMI 2009

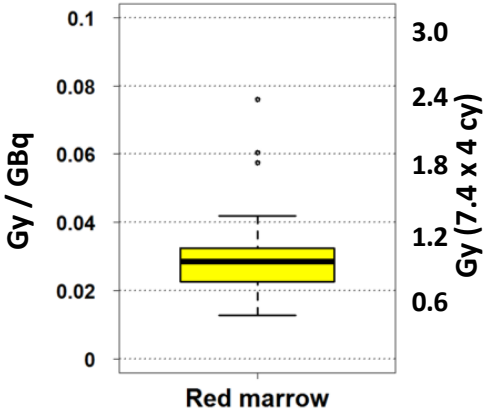
Linear correlation between Lu-TATE activity in blood and in BM aspirates (R^2 = 0.9, m= 1.35)
No significant binding of radiopeptides to RM stem cells.

However, from the blood model no correlation between BM doses and toxicity

^{177}Lu-DOTATATE RM absorbed doses – imaging based method

Similar results have been obtained from imaging (Lumbar vertaebre) and personalizd treatement

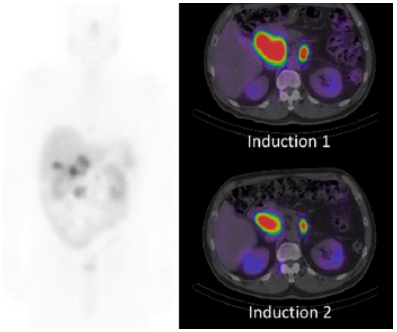
Marin, et al. Phys Med 2018



0.028 ± 0.010 Gy/GBq

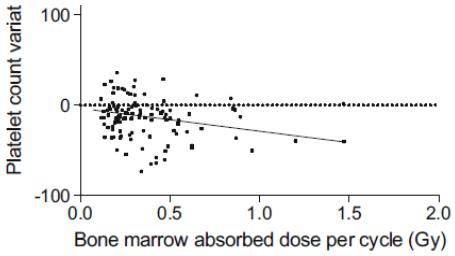
0,83 ± 0.30 Gy, 7.4 GBq x 4cy

Del Prete, et al. EJNMMI 2019

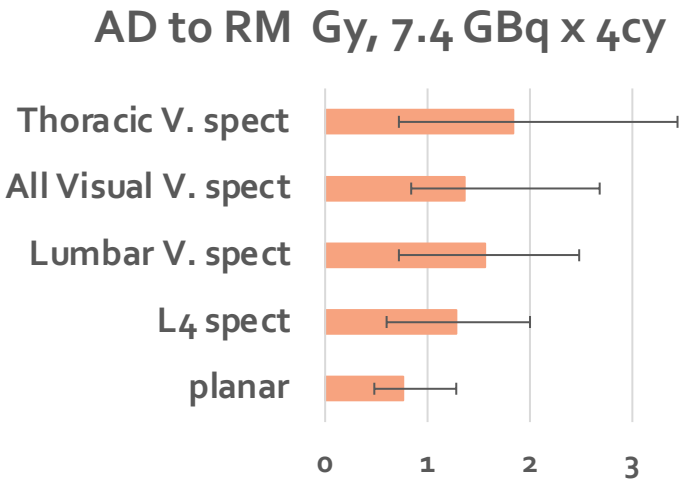


0.035 (0.004–0.216) Gy/GBq

1.17 (0.52–4.25) Gy, 7.4 GBq x 4cy



Hagmarker, et al. 2019



The blood based method is not able to consider the impact of infiltrating skeletal metastases

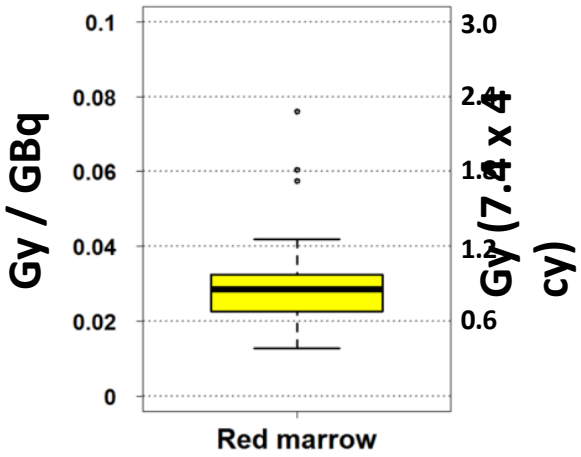
Limits of imaging method :

- low activity concentration in the vertebrae and possible scatter contribution from surrounding tissues (liver, spleen….);
- choice of the measured vertebrae;
- presence of infiltrating skeletal metastases

^{177}Lu-DOTATATE RM absorbed doses – imaging based method

Similar results have been obtained from imaging (Lumbar vertaebre) and personalizd treatement

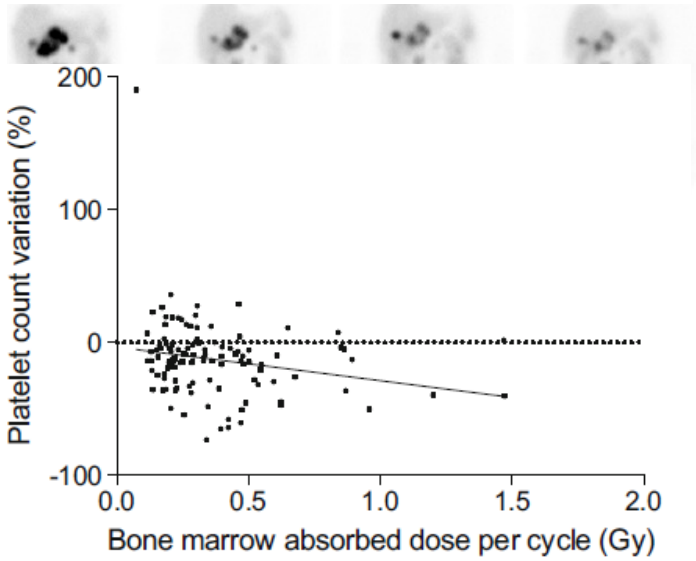
Marin, et al. Phys Med 2018

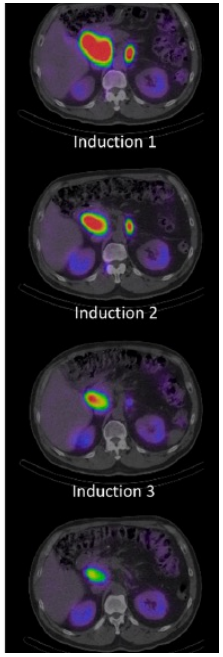


Del Prete, et al. EJNMMI 2019

1.17 (0.52–4.25) Gy cumulatively

0.035 (0.004–0.216) Gy/GBq





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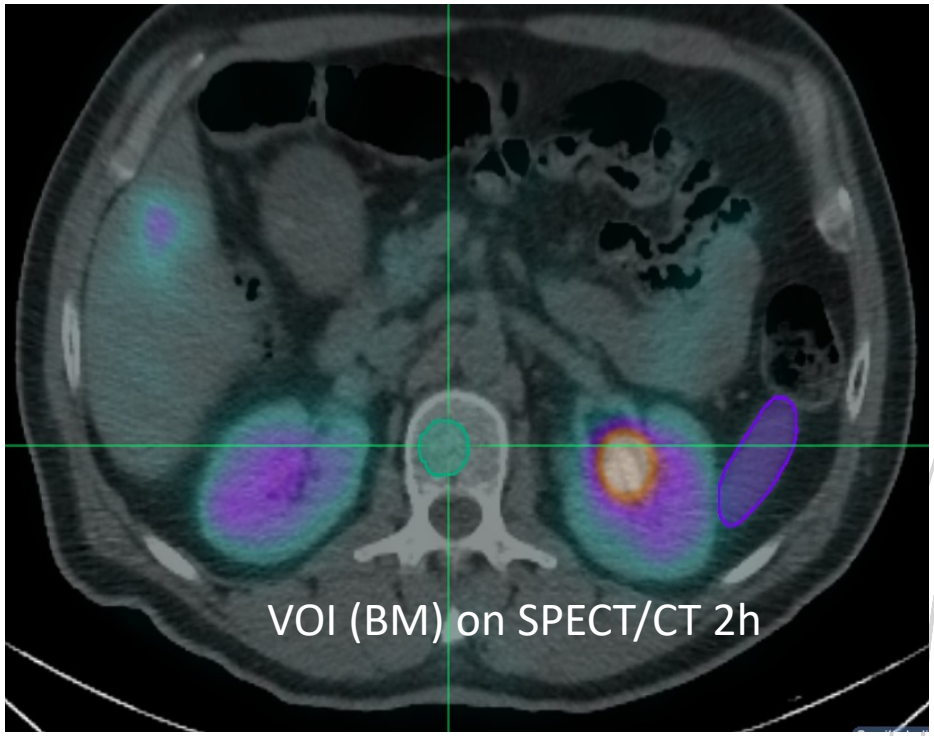
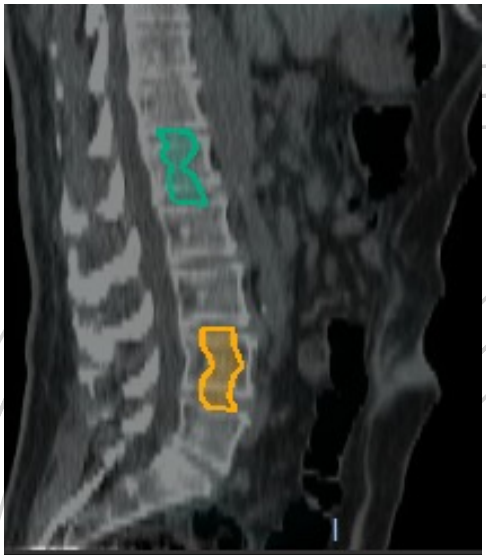
LUTATHERA

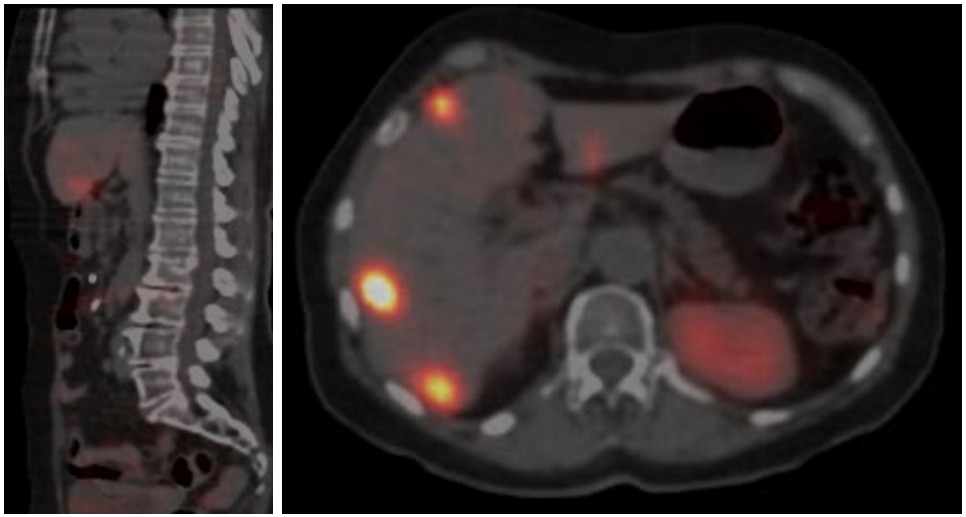




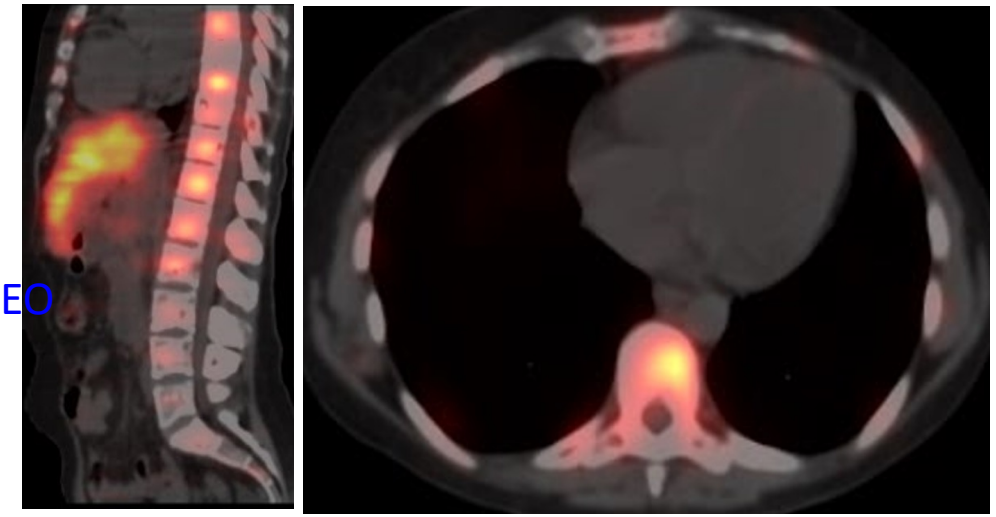
Courtesy of Elisa Grassi, AUSL-IRCCS Reggio Emilia, Italy

LUTATHERA

Patient 1, IEO



Patient 2, IEO



Courtesy of Mahila Ferrari, IEO, Italy

Long term effects – MSD and AL

Table 4 Myelodysplastic syndrome (MDS) and acute leukaemia (AL) associated with PRRT published in the literature

Reference	Radiopharmaceutical	Number pf patients	Patients with MDS	Patients with AL
Imhoff, 2011	^{90}Y-DOTATOC	1,109	1 (0.1%)	1 (0.1%)
Pfeifer, 2011	^{90}Y-DOTATOC	69	2 (2.9%)	–
Kwekkeboom, 2008	^{77}Lu-DOTATATE	504	3 (0.6%)	–
Sabet, 2013	^{177}Lu-DOTATATE	203	3 (1.5%)	–
Kesavan, 2014	^{177}Lu-DOTATATE + capecitabine and temozolomide	65	2 (3.1%)	–
Bodei, 2015	^{177}Lu-DOTATATE, ^{90}Y-DOTATOC	807	19 (2.4%)	9 (1.1%)
Brieau, 2016	^{177}Lu-DOTATATE + previous alkylating chemotherapy	20	3 (15%)	1 (5%)
Brabander, 2017	^{177}Lu-DOTATATE	610	9 (1.5%)	4 (0.7%)
Del Prete, 2017	^{177}Lu-DOTATATE + several previous chemotherapy regimens	36	–	1 (2.8%)

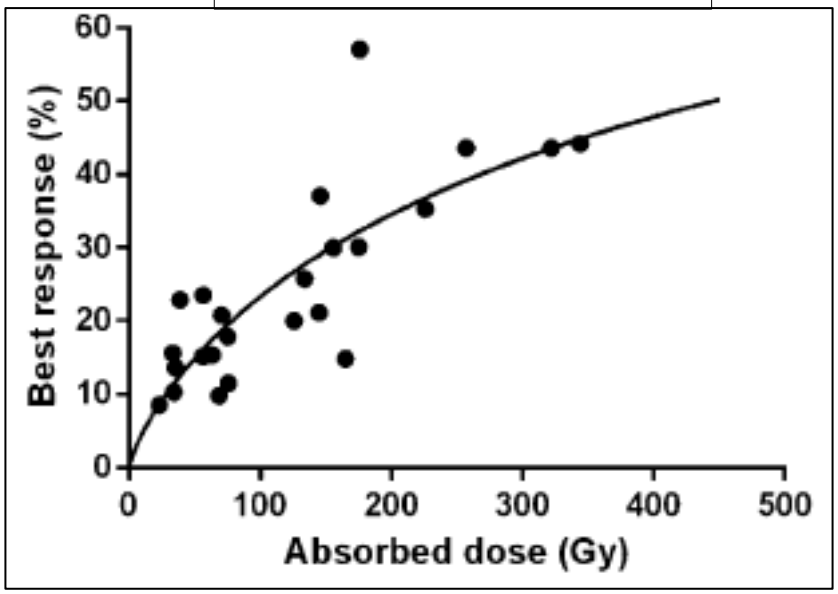
Cremonesi M, Ferrari M, Bodei L et al. EJNMMI 2018 - Review

The tumor…

Dose-Response Relationship

Lesion-generated curves based on real patients

^{177}Lu-DOTATATE in NETs

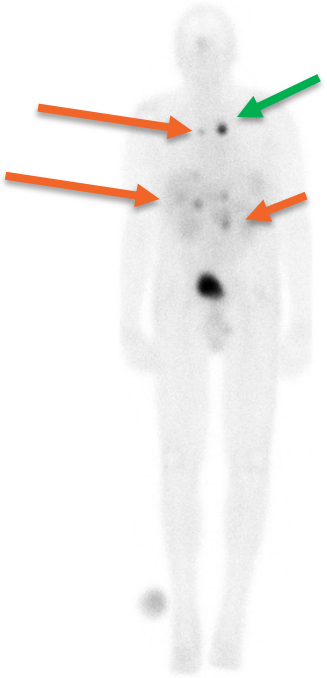


- **As the dose increases, the probability of tumor reduction increases**
- **However, intra- and inter-patient lesion doses may vary remarkably**

Ilan E et al. JNM 2015

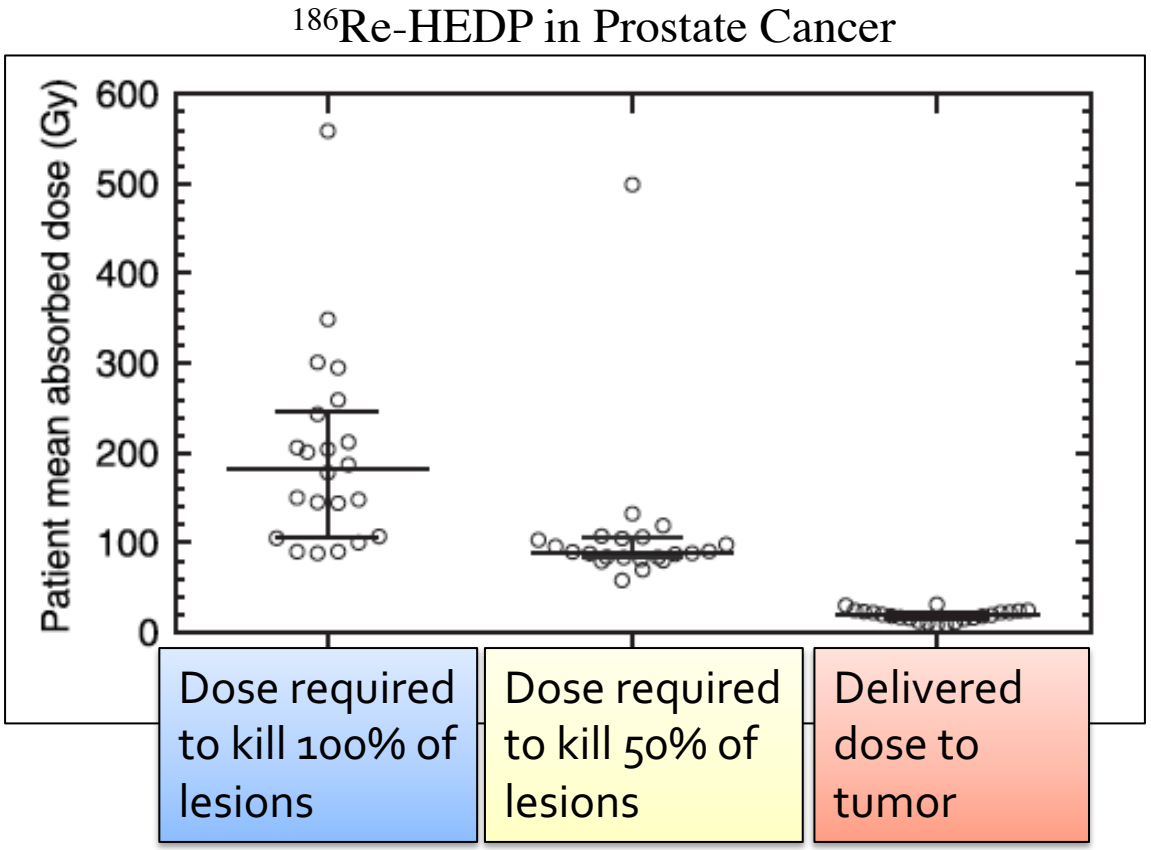
Why differences in lesion Absorbed Doses?

^{177}Lu-DOTATATE



- **Heterogeneity of uptake of radiopharmaceuticals**
- **Difficult to calculate the tumor volume**

Delivered and required Doses: Sometimes a significant Difference…..



Median: **183 Gy** **89 Gy** **19 Gy**

Denis-Bacelar et al. Phys Med Biol 2017

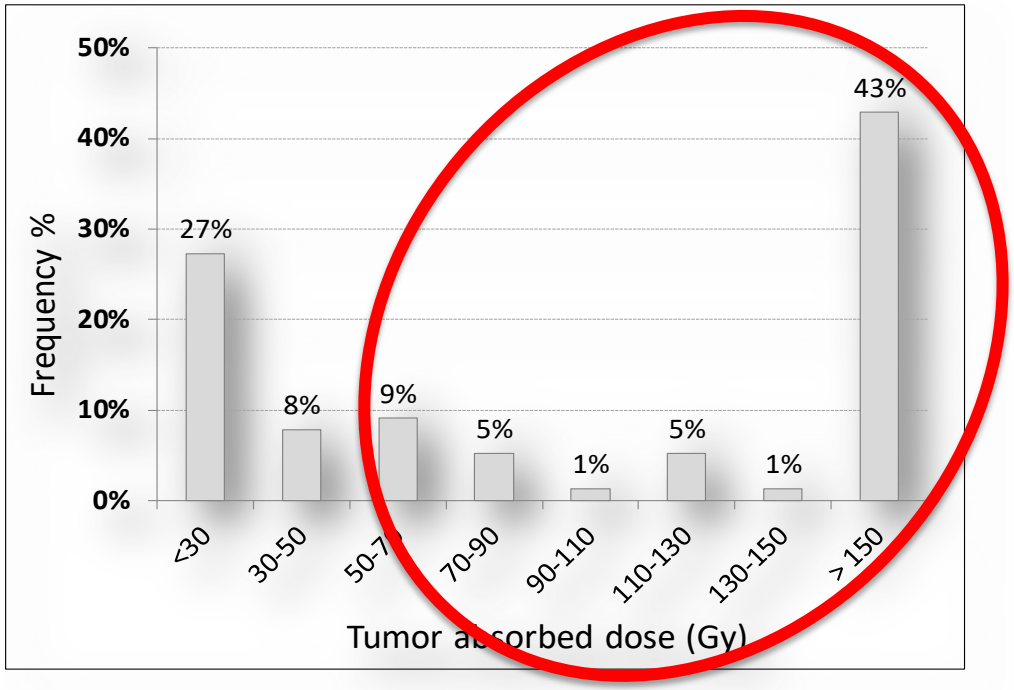
Is it desirable to have a Tumor Dose estimate?

To identify lesions/patients that would benefit from treatment

To exclude from treatment lesions which would not benefit or for which additional treatment should be integrated

NETTER-1 Sub-study (dosimetry)

Elevated tumor doses



Cumulative absorbed doses are high in the majority of lesions

Causes for inter/intra-patient variability include SSR expression level, specific shape, vascularization

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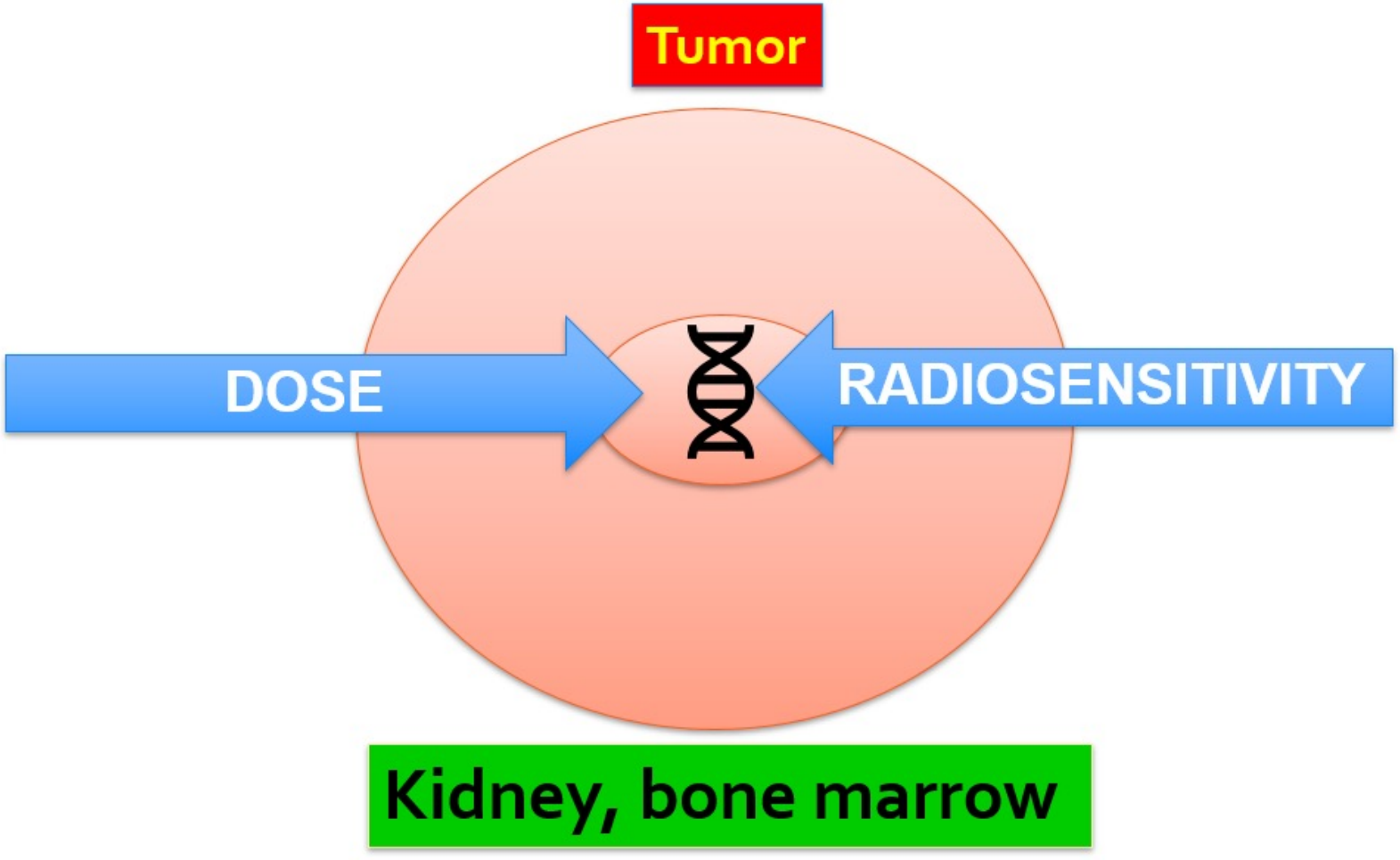
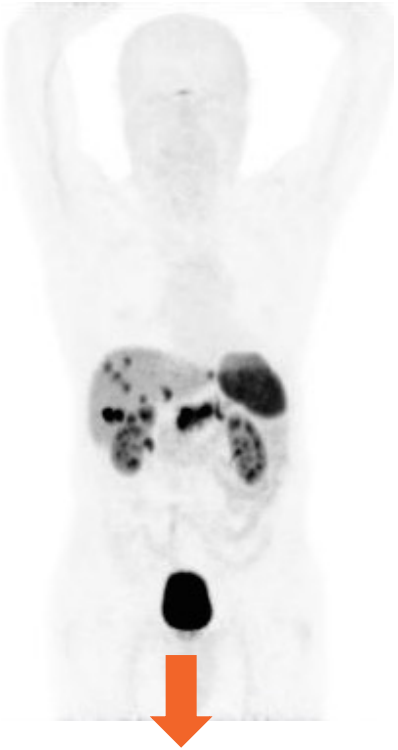
FDA report – Bodei et al. 2017
Manuscript in preparation

All things equal, not all tissues respond equally: RADIOSENSITIVITY



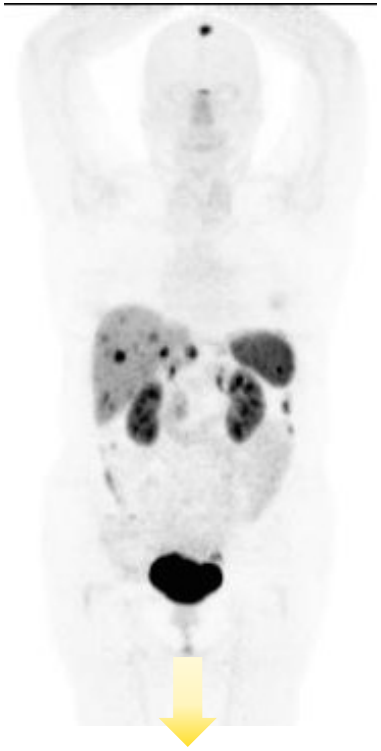
Same uptake does not guarantee a response

P-NET, G2 (Ki67 4%), FDG neg, ECOG 1, "Krenning" grade 4



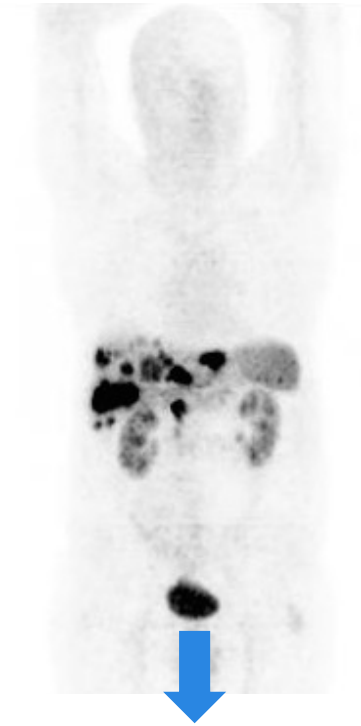
Progression

R-NET, G3 (Ki67 20%), FDG neg, ECOG 0, "Krenning" grade 4



Stability

SI-NET, G2 (Ki67 19%), FDG neg, ECOG 0, "Krenning" grade 4



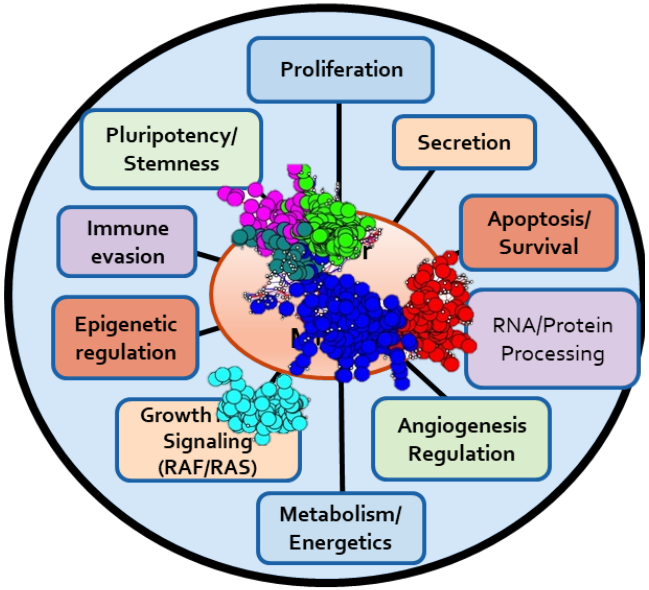
Response

Tumor genes quantifiable in blood: the example of neuroendocrine tumors

Artificial Intelligence mathematical modelling & algorithmic analyses

NEN Transcriptome

22,000 genes



BLOOD signatures

NETest

MONITORS PRRT RESPONSE

NETest functions as a liquid biopsy to identify NETs and MONITOR PRRT

PPQ

8 NETest genes + Ki67

PREDICTS PRRT RESPONSE

PPQ functions as a RADIOSENSITIVITY MARKER

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Kidd M, Modlin IM. Nature Genetics 2017
Bodei L et al. EJNMMI 2018, 2020

A True Predictive Tool for PRRT

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-018-3967-6

ORIGINAL ARTICLE

PRRT genomic signature in blood for prediction of ^{177}Lu-octreotate efficacy

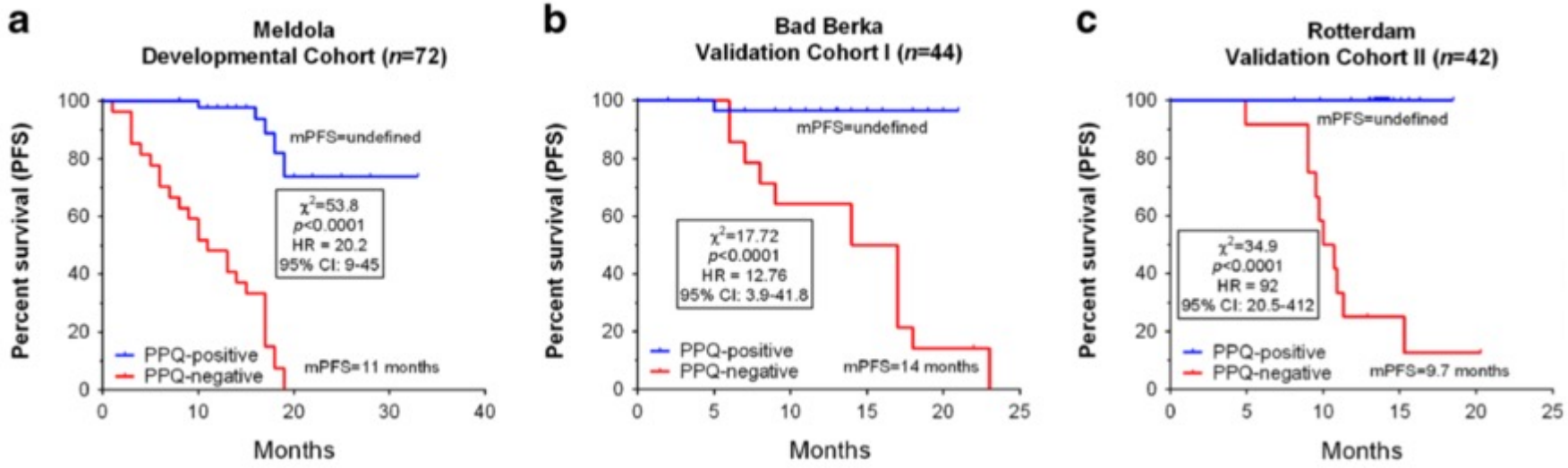
Lisa Bodei[1,2] · Mark S. Kidd[3] · Aviral Singh[4] · Wouter A. van der Zwan[5] · Stefano Severi[6] · Ignat A. Drozdov[3] · Jaroslaw Cwikla[7] · Richard P. Baum[2,4] · Dik J. Kwekkeboom[2,5] · Giovanni Paganelli[6] · Eric P. Krenning[2,8] · Irvin M. Modlin[2,9]

Received: 17 December 2017 / Accepted: 31 January 2018

Predictive accuracy: 95%

***n*=158**

PRRT



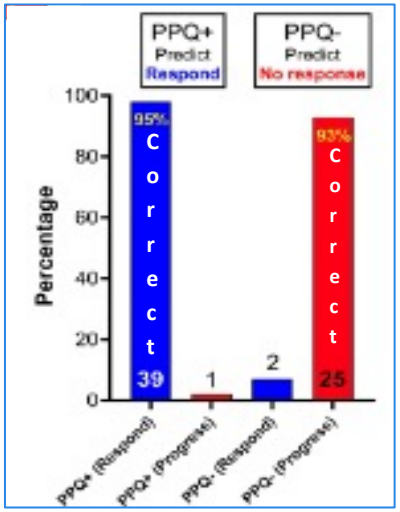
Multianalyte biomarkers capture tumor behavior as opposed to monoanalytes which only evaluate one feature (e.g. CgA, SSR)

USA Validation

n=67

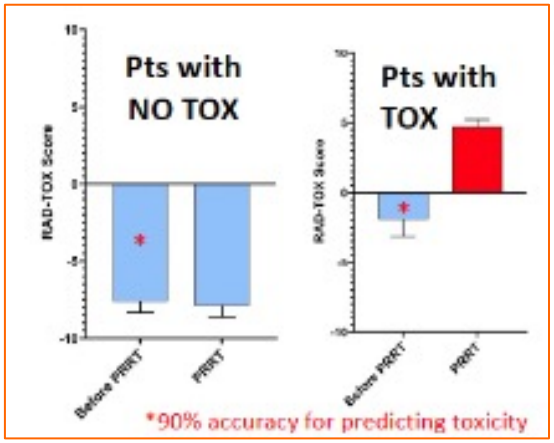
Predicting before PRRT

EFFICACY

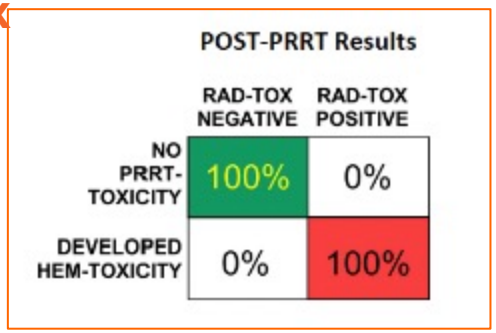


PPQ

Hematological TOXICITY



RADtox



Memorial Sloan Kettering Cancer Center

Bodei L et al. MSKCC 2019-2022
Submitted

Theranostic Radiopharmaceuticals:
Quo vadis..?
Lancet Oncology 2020

Molecular profiling of neuroendocrine tumours to predict response and toxicity to peptide receptor radionuclide therapy

Lisa Bodei, Heiko Schöder, Richard P Baum, Ken Herrmann, Jonathan Strosberg, Martyn Caplin, Kjell Öberg, Irvin M Modlin

Lancet Oncol 2020; 21: e431–43

Peptide receptor radionuclide therapy (PRRT) is a type of radiotherapy that targets peptide receptors and is typically used for neuroendocrine tumours (NETs). Some of the key challenges in its use are the prediction of efficacy and toxicity, patient selection, and response optimisation. In this Review, we assess current knowledge on the molecular profile of NETs and the strategies and tools used to predict, monitor, and assess the toxicity of PRRT. The few mutations in tumour genes that can be evaluated (eg, *ATM* and *DAXX*) are limited to pancreatic NETs and are most likely not informative. Assays that are transcriptomic or based on genes are effective in the prediction of radiotherapy response in other cancers. A blood-based assay for eight genes (the PRRT prediction quotient [PPQ]) has an overall accuracy of 95% for predicting responses to PRRT in NETs. No molecular markers exist that can predict the toxicity of PRRT. Candidate molecular targets include seven single nucleotide polymorphisms (SNPs) that are susceptible to radiation. Transcriptomic evaluations of blood and a combination of gene expression and specific SNPs, assessed by machine learning with algorithms that are tumour-specific, might yield molecular tools to enhance the efficacy and safety of PRRT.

The appropriate therapeutic to be selected needs calibration based on dosimetry and genomic analysis of individual genetically driven sensitivity of tumor and target organ

DISCUSSION

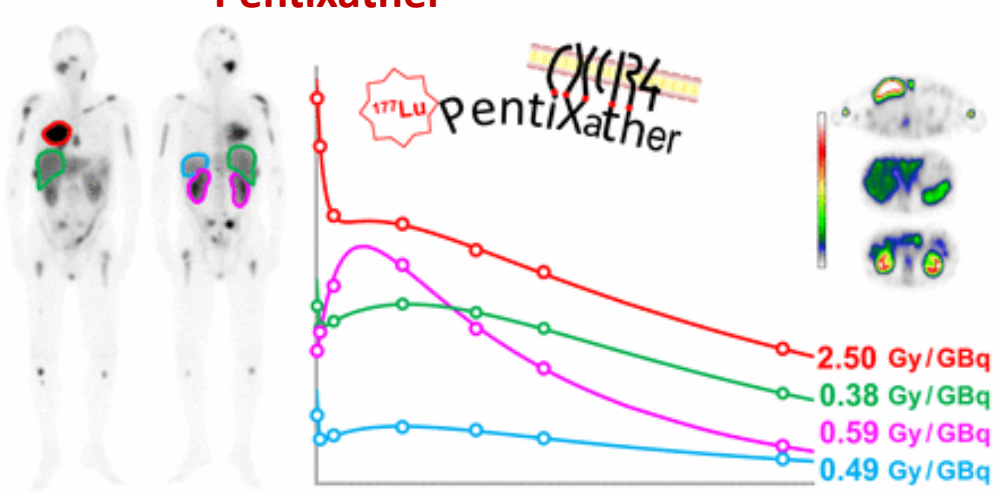
- Levels of toxicity
  - Bone Marrow
    - Acute: G3-4 in less than 1/3?
    - Chronic: stochastic, tMN – unacceptable? <3%?
  - Kidney
    - Acute: unrelated to PRRT
    - Chronic: which parameter? Grade 3 <5%?

- Tumor dose: 120 Gy? In at least 80% of lesions? PVE?

- NOTA
  - Need acceptable range
  - Need consideration of radiosensitivity: genomic signatures, radiomics?

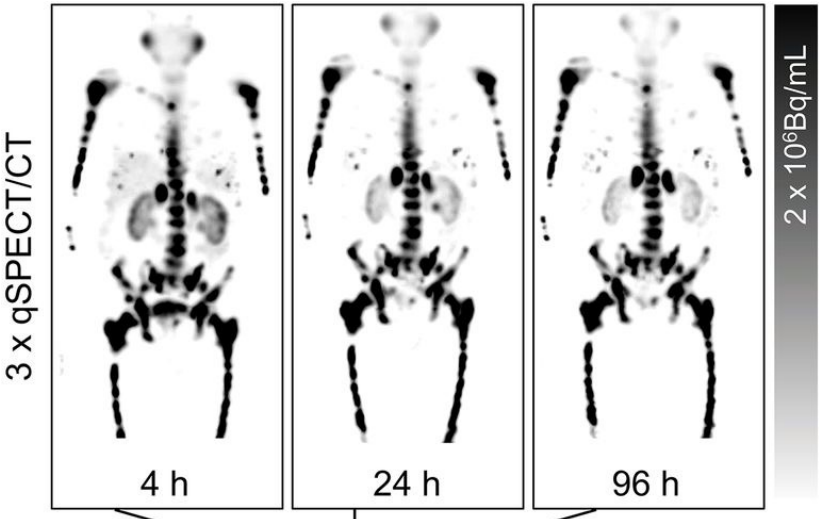
Different peptides, same issues

Pentixather

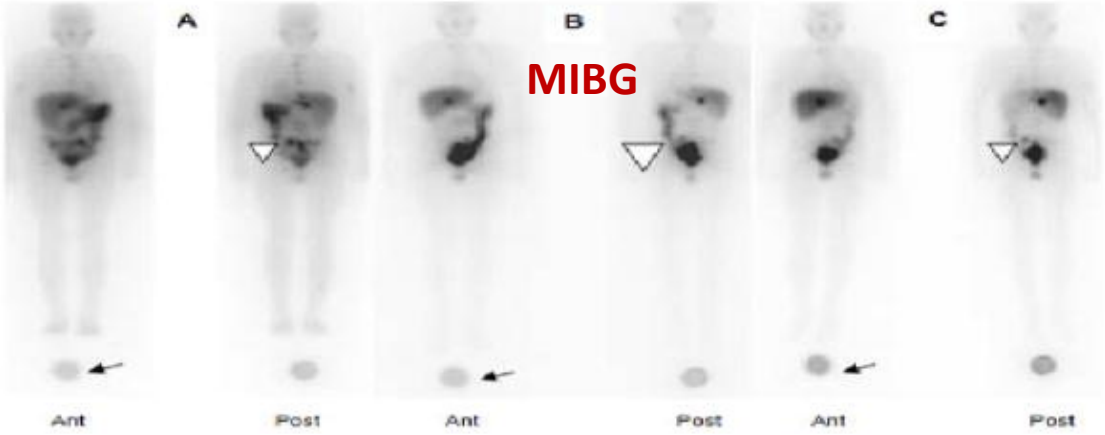


Hänscheid H et al. JNM 2022

PSMA



MIBG



Pandit-Taskar N et al. CNM 2017

Conclusions.

- *Treatment of tumors with radionuclide therapies confronts the nuclear medicine physician with the risk of reduced efficacy and increased toxicity*
- *Side effects and therapeutic efficacy depend on biodistribution, organ tolerance, patient comorbidities and delivered dose*
- *The challenge is to identify subjects at risk for excessive toxicity and to predict the response based on the integration of*
  - *risk factors/clinical characteristics*
  - *dosimetry, possibly refined / simplified (e.g. BM dose)*
  - *genomic biomarker predictors of efficacy and of toxicity in the individual patient*
  - *comprehensive self learning artificial intelligence algorithms*