Best estmate of initial uptae, sub-organ localization, P in kidneys

Monday 26th August 2022 – 11:00

^{177}Lu-PRRT - Dosimetry overview

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IEO
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^{177}Lu-DOTATATE: some dose-effect correlations

Therapy	No. of Patients	Clinical Endpoint	Correlation Found	Reference
^{177}Lu-DOTATATE	14	Hematological toxicity (PLT [1] and WBC [2] variation)	Cumulative bone marrow absorbed dose	Bergsma 2016
^{177}Lu-DOTATATE	52	Hematological toxicity (PLT variation)	Per-cycle bone marrow absorbed dose	Del Prete 2019
^{177}Lu-DOTATATE	24	Tumor response (RECIST [3] criteria)	Tumor absorbed dose	Ilan 2015
^{177}Lu-DOTATATE	48	Tumor response (CT)	Tumor absorbed dose	Jahn 2021

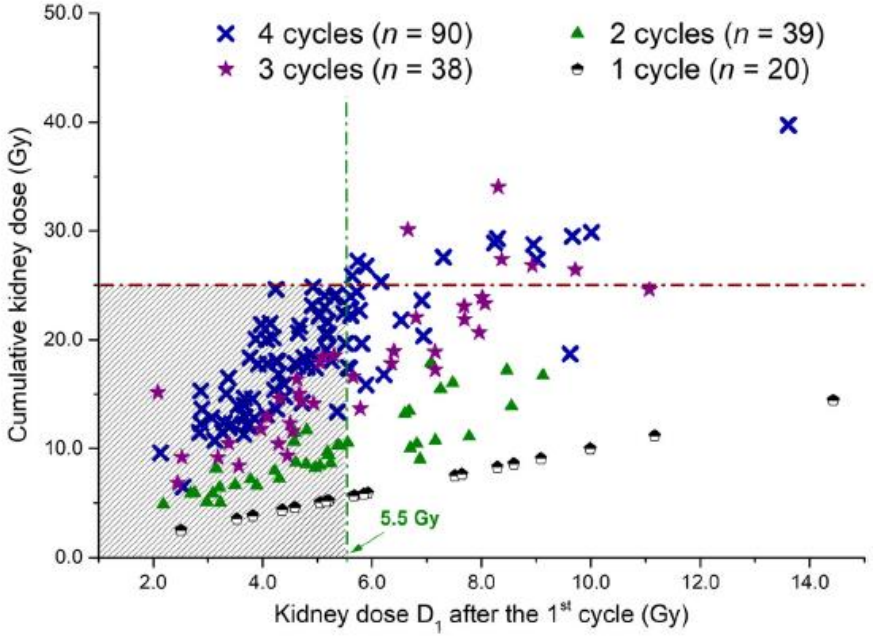
Danieli R, et al. Review. J Pers Med 2022. 12, 205

Absorbed doses in the kidneys

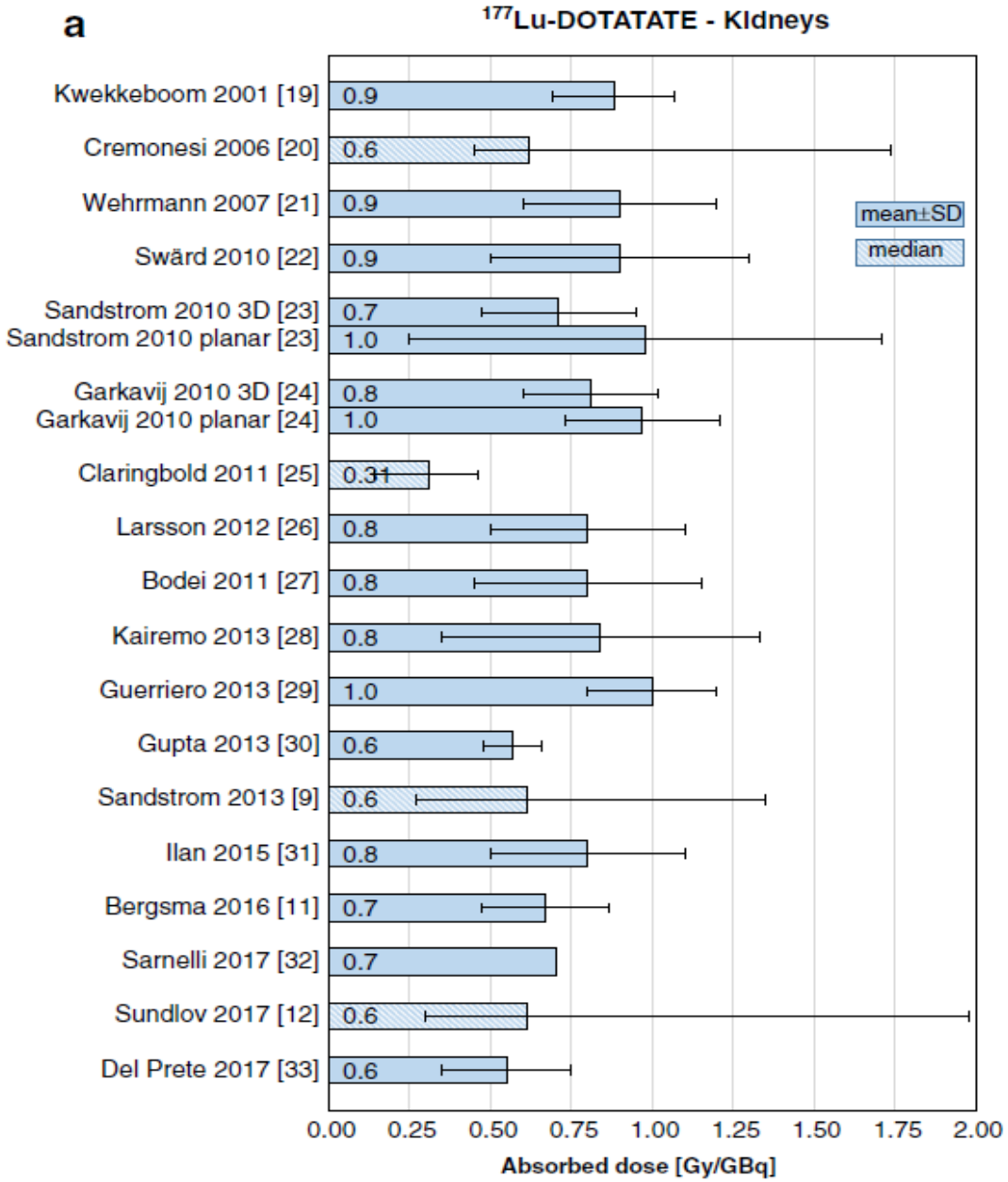
- Mean absorbed doses range: **0.54 - 1.00 Gy/GBq**

  Large inter-patient variabilities have been reported, e.g. 0.3–1.98 Gy/GBq - up to a factor of 3, also up to 6-7

- For 7,4 GBq x 4 cycles, cumulatively ~ **16 – 30 Gy**



Cremonesi, EJNMMI 2018; Sundlöv A, EJNMMI 2017; Marian Phys Med 2018; Chicheportiche, 2018



update: Santoro, 2018: 0,43 ± 0,13
Hou, 2019: 0,32 ± 0,17; 0,55 ± 0,32

KIDNEYS

The ranges of variability can be associated with different patient characteristics (e.g. renal function, tumour burden), the use of different renal protectors, and methodological aspects

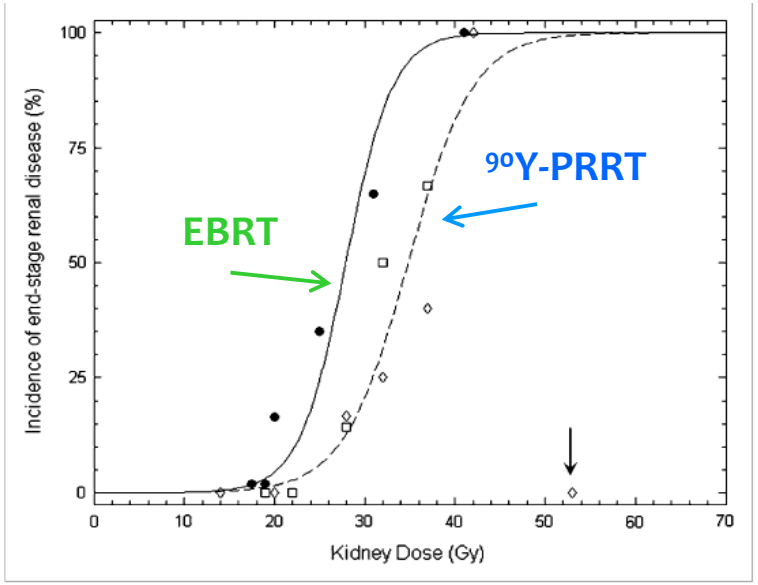
Owing to the inter- and intra-patient variability of kidney AD / GBq, a fixed activity and fixed number of cycles results in a highly variable cumulative AD.

From the clinical experience, the mean absorbed dose threshold to the kidneys seems to be

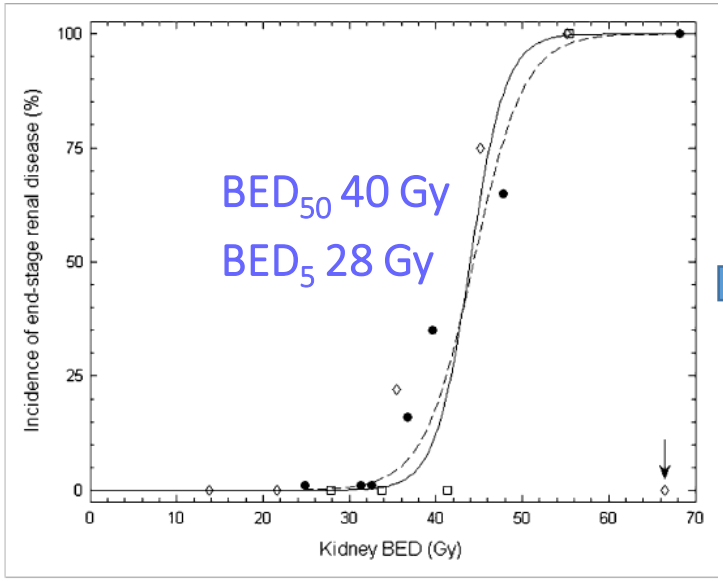
- for ^{90}Y-PRRT: identified in 3 or more cycles ($\rightarrow$ 40 BED)
- for ^{177}Lu-PRRT: not found yet, but > 23 Gy in 4 or more cycles, and with a BED > 40 Gy, possibly due to more non-uniform irradiation

- **Dose-toxicity correlations found for kidneys in ^{90}Y-PRRT**
- **The LQ model (BED) offers further improvement**

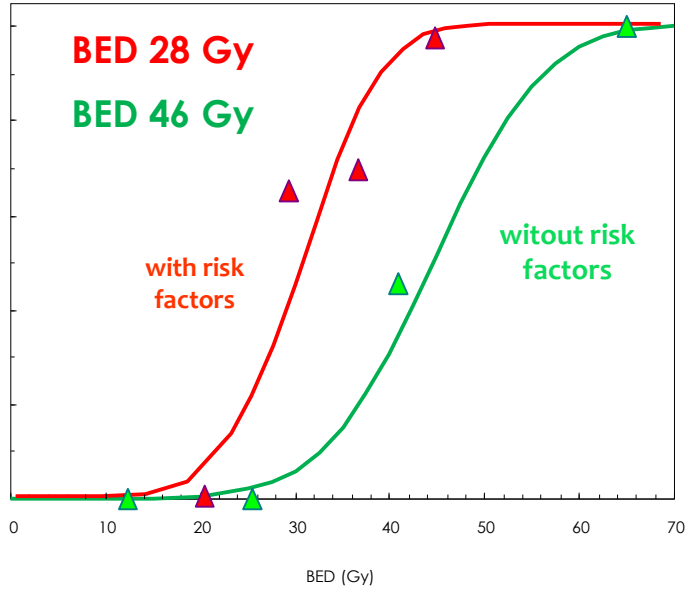
Absorbed dose vs. renal toxicity



BED (Biological Effective Dose)



moreover,



Patients could be stratified

Wessels B, MIRD 20 JNM 2008, 1884-99

Bodei L, EJNMMI 2008

• Models indicate different impact for ^{90}Y vs ^{177}Lu due to different dose distribution in renal cortex

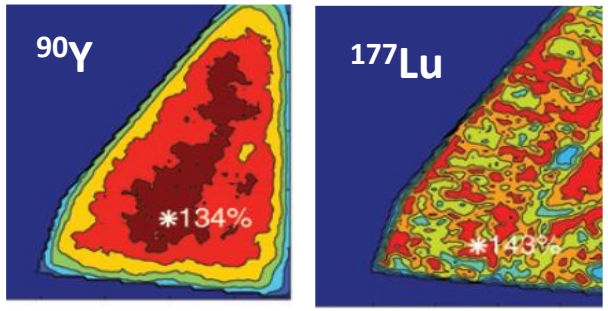
Do the same BED values apply also for ^{177}Lu, i.e. is it possible to extrapolate mean dose constraints for toxicity?

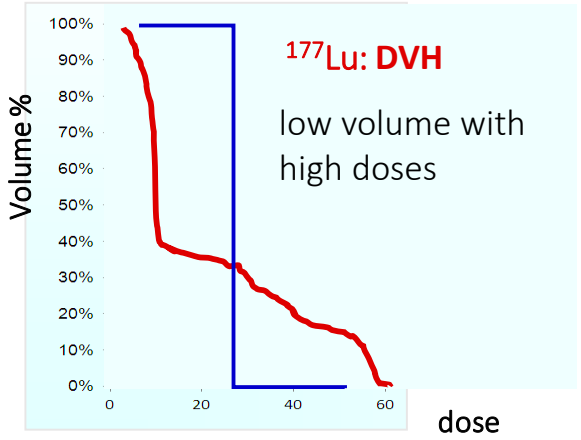
BED NTCP for ^{90}Y-PRRT → BED_{50} 40 Gy, BED_5 28 Gy → **D_{50} Lu 36 Gy, D_5 Lu 26 Gy** ?

NO TOXICITY HAS BEEN FOUND
even in the rare cases of this AD

The previous model applies in the assumption of dose uniformity…"acceptable" for ^{90}Y, but not for ^{177}Lu

Dose distribution in renal cortex from autoradiography





The higer non-uniformity of ^{177}Lu should mitigate the renal burden

→ **higher tolerability of ^{177}Lu vs.^{90}Y for a same mean dose**

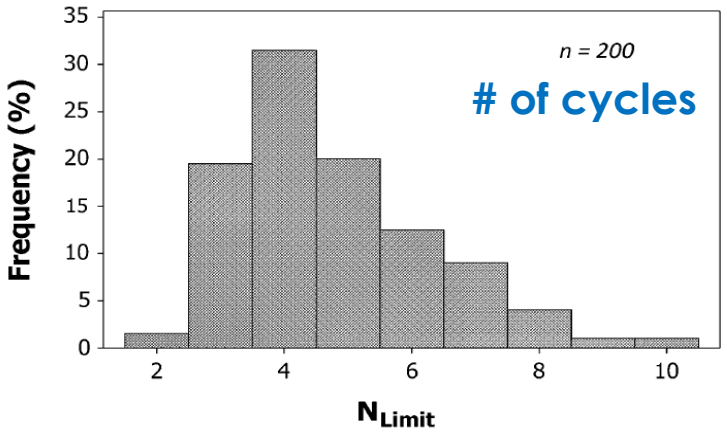
Subsequently confirmed by clinical data.

Konijnenmerg M et al, JNM 2007

dosimetry based ^{177}Lu-PRRT: increasing the activity by the # of cycles

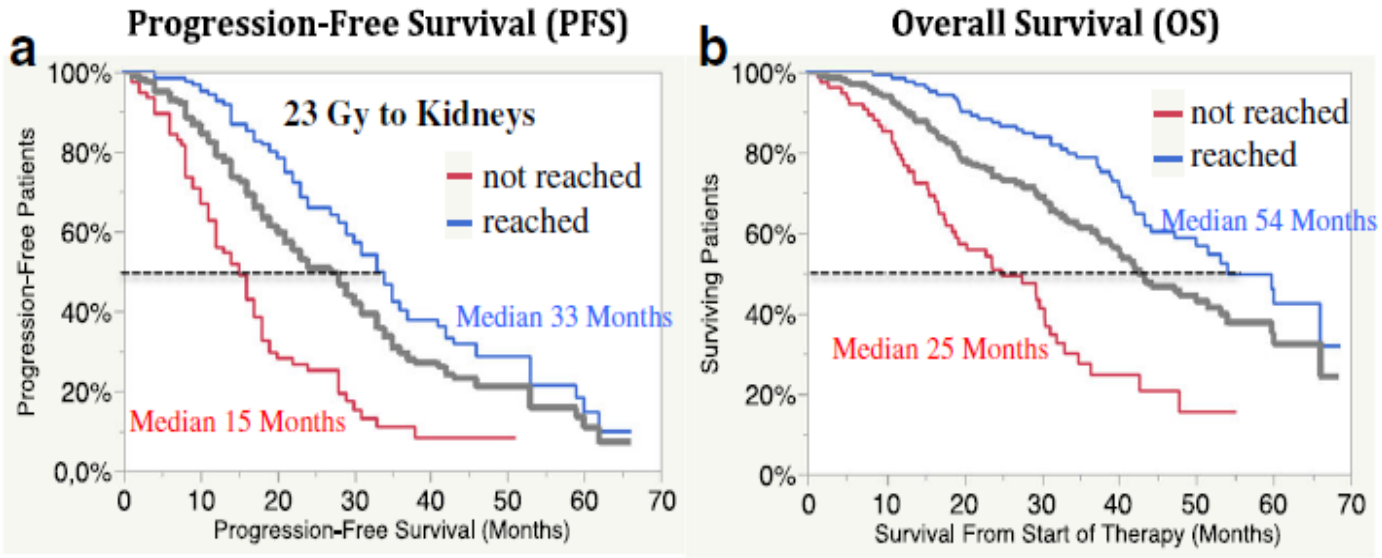
Sandstrom M, et al. J Nucl Med 2013; 54:33–41

7.4 GBq/cycle, # of cycles to give
Dose < 23 Gy to kidneys or 2 Gy to RM



> 4 cycles in 50% of pts, up to 10 cycles

Garske-Román U, et al. EJNMMI 2018;45(6):970-988.

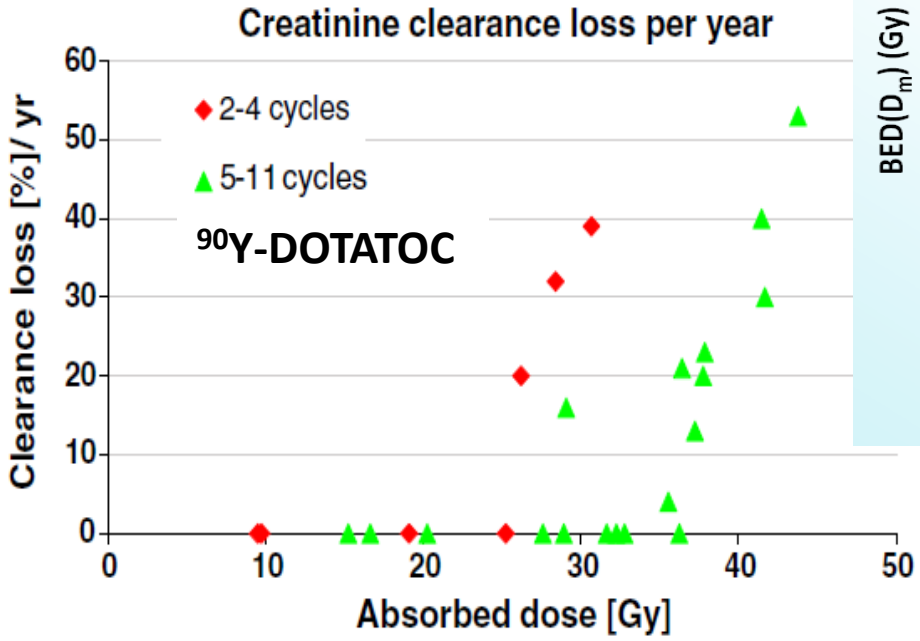


Pts with 23 Gy to kidneys → higher activity → higher PFS and OS
No toxicity

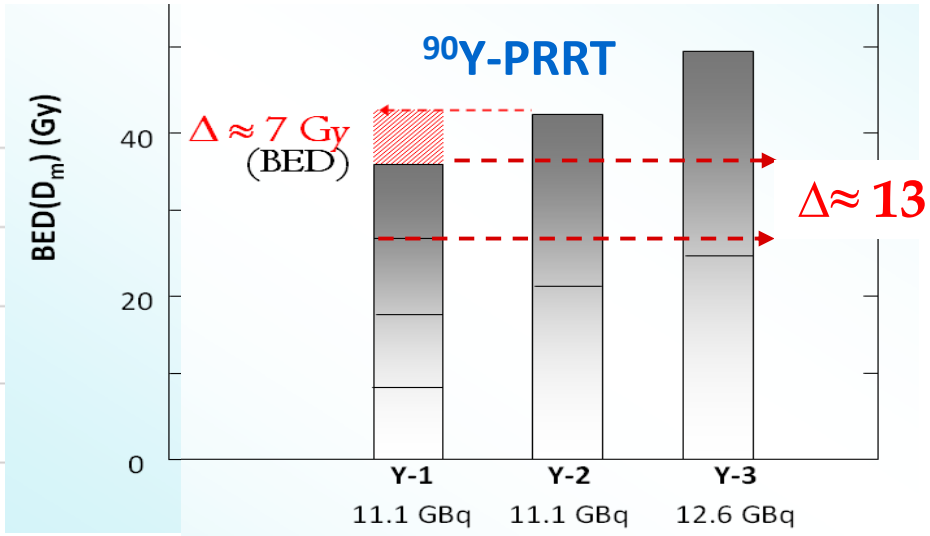
Dosimetry tailoring the # of cycles improves PFS and OS without toxicity

BUT DO WE NEED SO MANY CYCLES?

• The number of cycles impacts on renal impairment in ^{90}Y-PRRT…



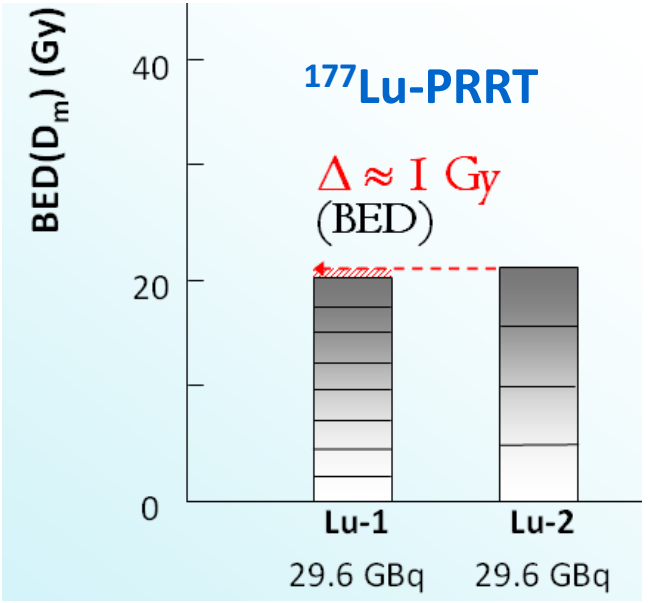
patients treated with a low numer of cycles of ^{90}Y-PRRT undergo toxicity at lower absorbed doses



The BED concept clearly explains

- why for ^{90}Y-PRRT
- why not for ^{177}Lu-PRRT

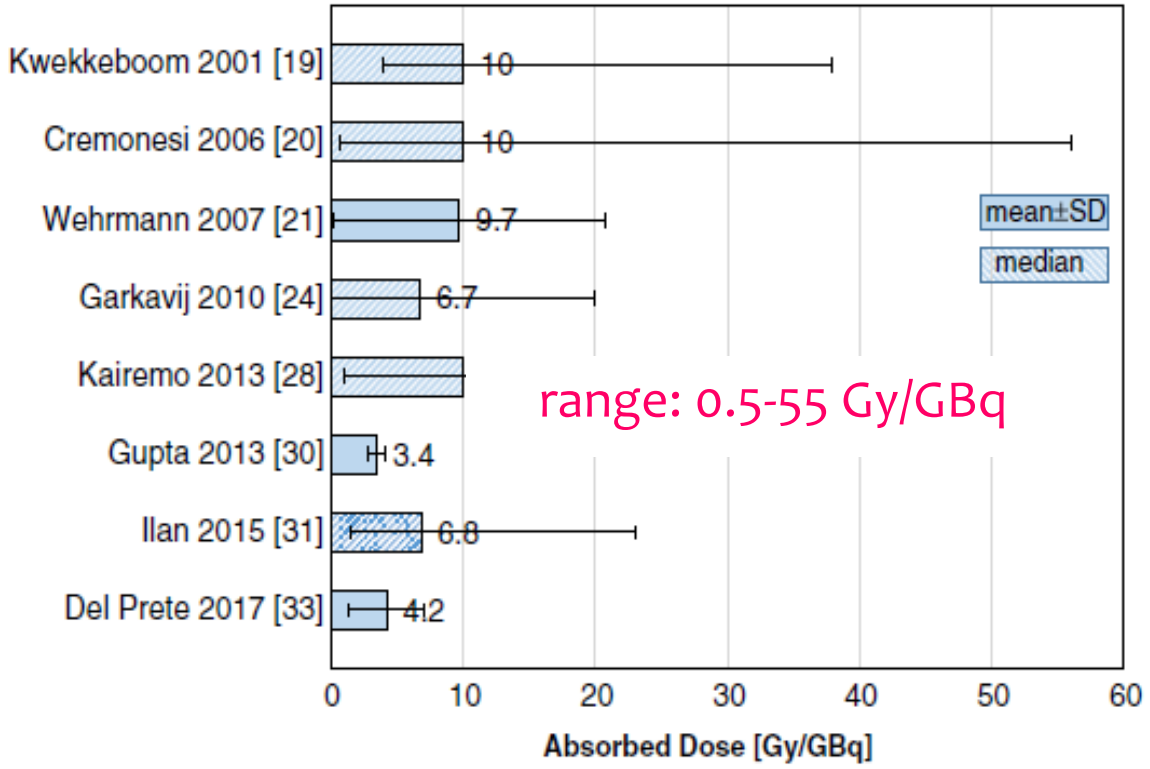
at the activities used



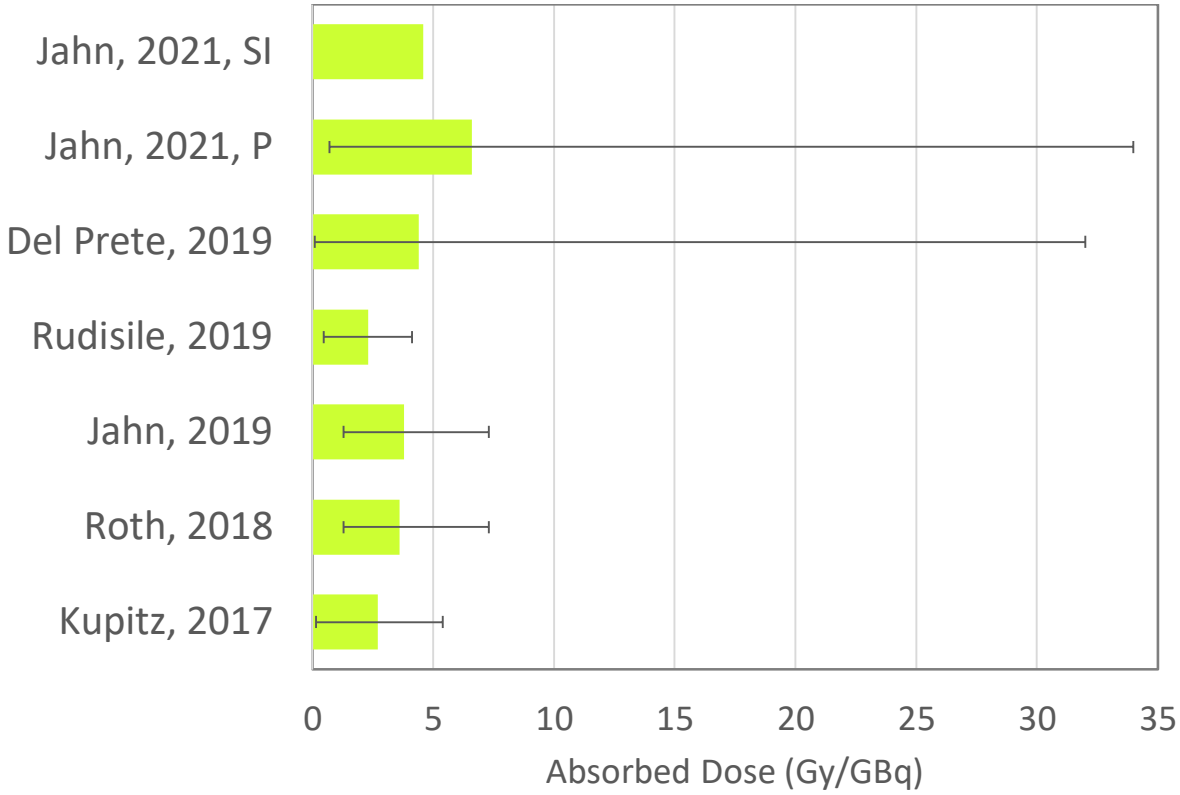
Bodei L, 2008; Sarnelli A, Q JNMMI 2017

Absorbed doses in tumors – (1rst cycle)

Up to 2017



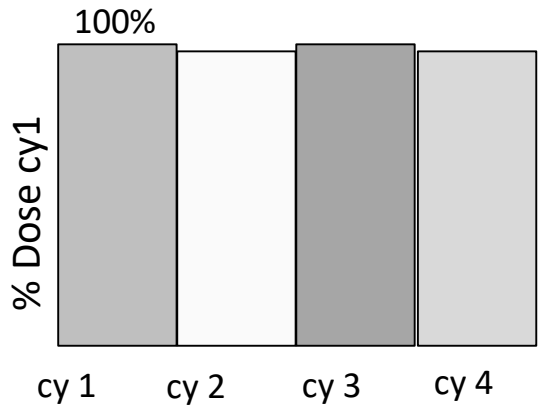
Update from 2018 (all SPECT / CT)



Cremonesi et al, EJNMMI 2018

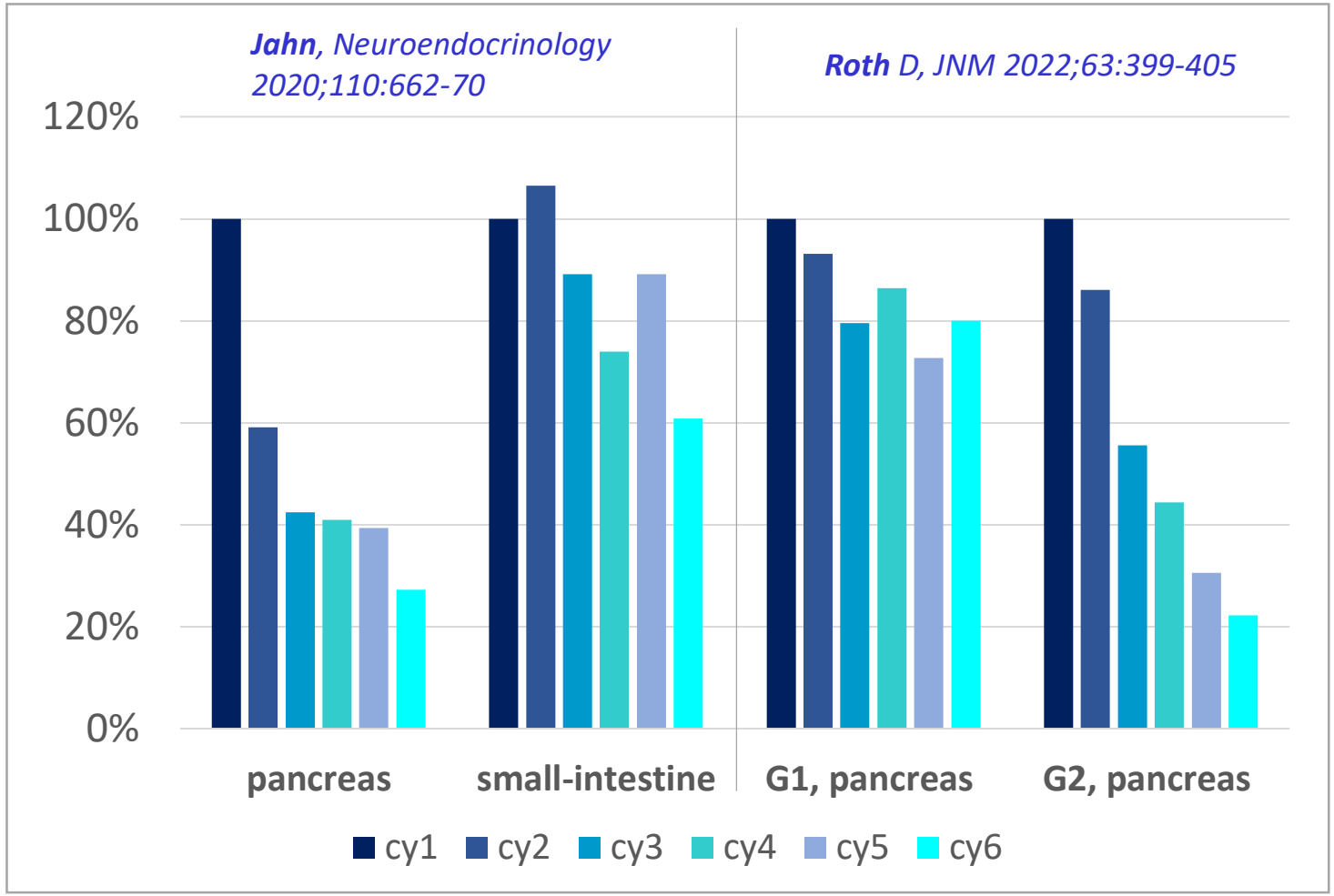
the # of cycles impacts on tumor and tumor/kidney balance - ^{177}Lu-DOTATATE

Kidney AD is almost stable over cycles (majority of cases)



However, differences of up to a factor of 2 - 3 have been reported (due to tumour response during the cycles or changes in renal function)

Tumor AD variation over cycles



Garkavij M, Cancer 2010;116(S):1084-92
Sundlov A, EJNMMI. 2017;44:1480-89
Santoro L, EJNMMI Res. 2018;8(1):103.

dosimetry based ^{177}Lu-PRRT in 4 cycles: increasing activity/cycle

Eur J Nucl Med Mol Imaging (2017) 44:1490–1500

Personalized ^{177}Lu-octreotate peptide receptor radionuclide therapy of neuroendocrine tumours: a simulation study

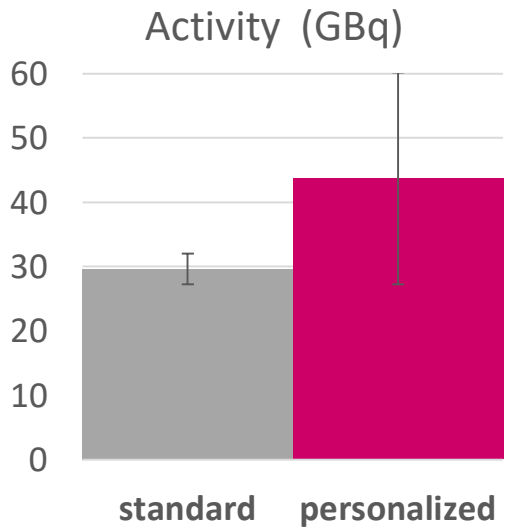
Michela Del Prete[1,2] · François-Alexandre Buteau[1,2] · Jean-Mathieu Beauregard[1,2]

Clinical Trial > Eur J Nucl Med Mol Imaging. 2019 Mar;46(3):728-742.
doi: 10.1007/s00259-018-4209-7. Epub 2018 Nov 30.

Personalized ^{177}Lu-octreotate peptide receptor radionuclide therapy of neuroendocrine tumours: initial results from the P-PRRT trial

Michela Del Prete[1 2 3 4], François-Alexandre Buteau[1 2], Frédéric Arsenault[1 2 3 4],

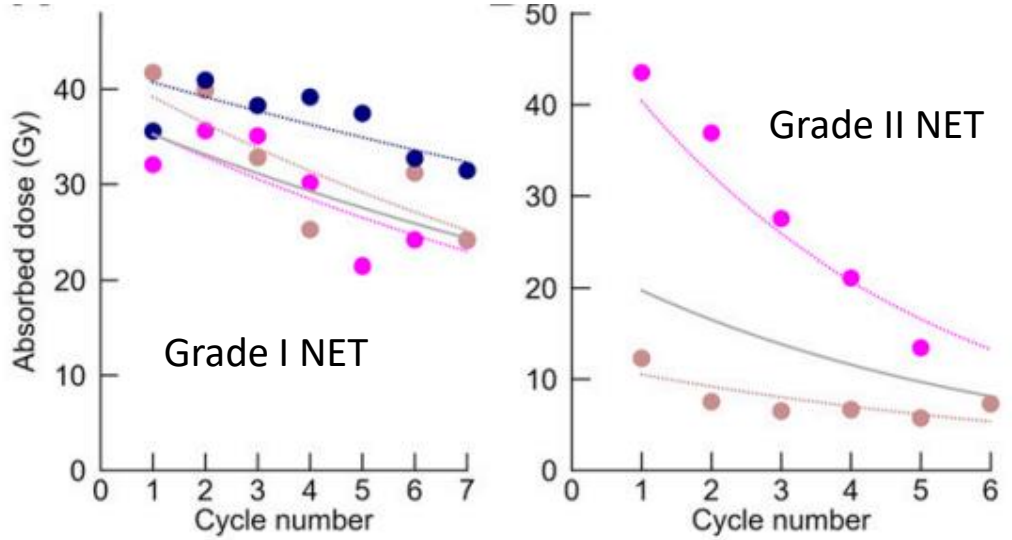
dose prescription: **23 Gy to kidneys in 4 cy**



~ 1.5-fold increased activity vs. standard
7.4 GBq x 4 cy

Roth D, et al. J Nucl Med 2022;63(3):399-405.

Tumour Dose descreases over cycles

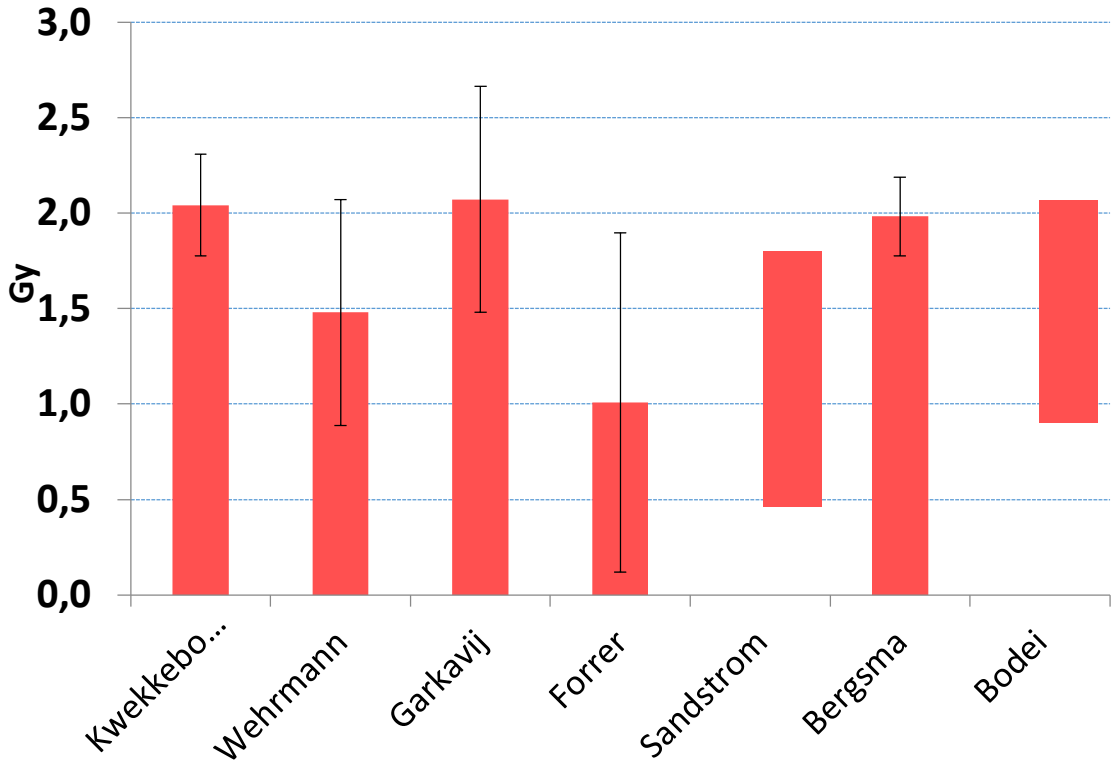


- **Low number of cycles are feasible without toxicity: more favorable rationale**

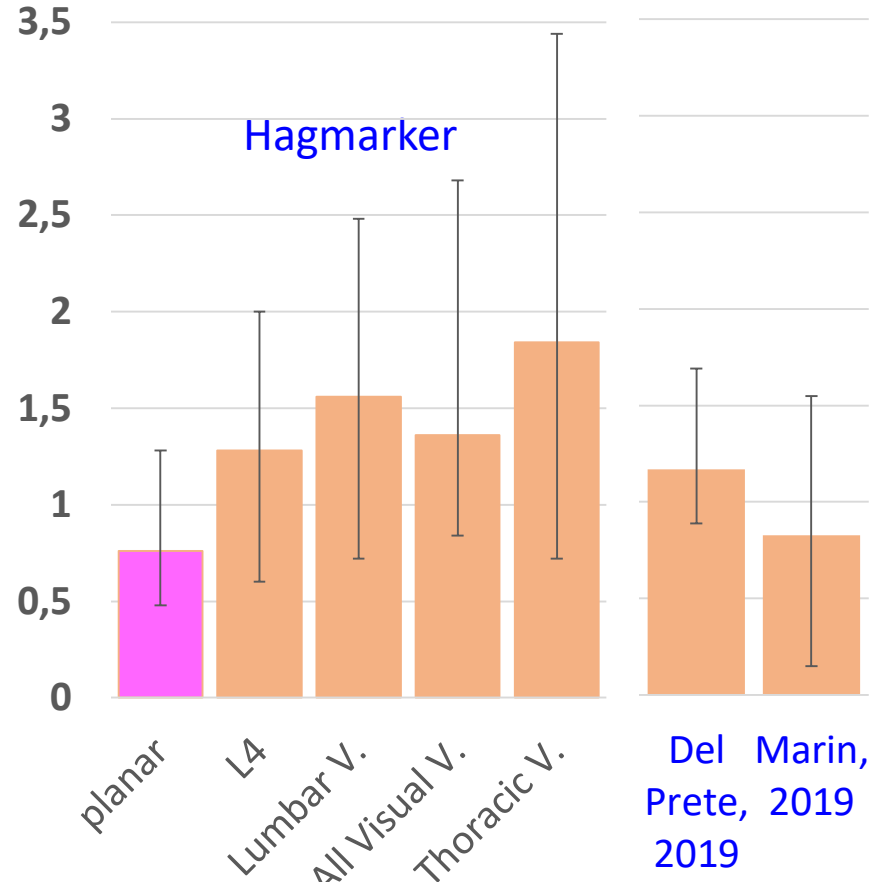
Red Marrow absorbed doses

Typically, for ^{177}Lu-PRRT **AD < 2 Gy, cumulatively**

blood based method

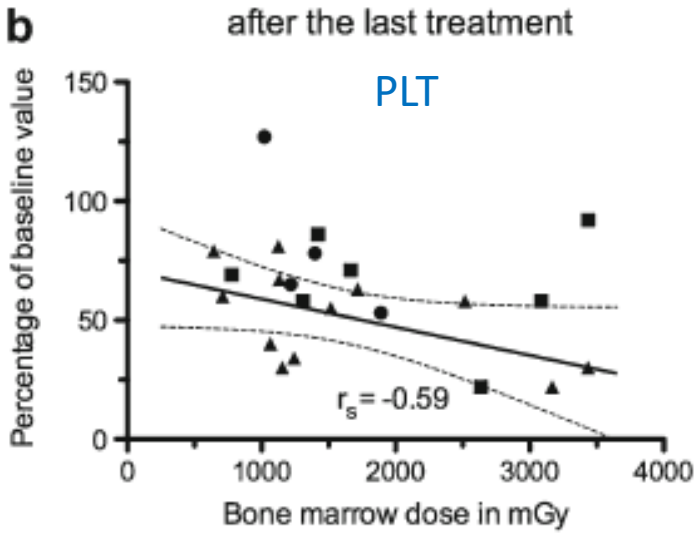


imaging method

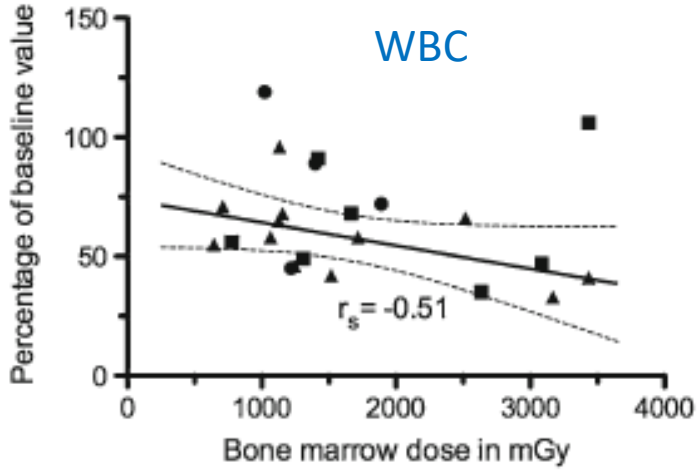


RM Absorbed Dose-toxicity correlations – imaging based

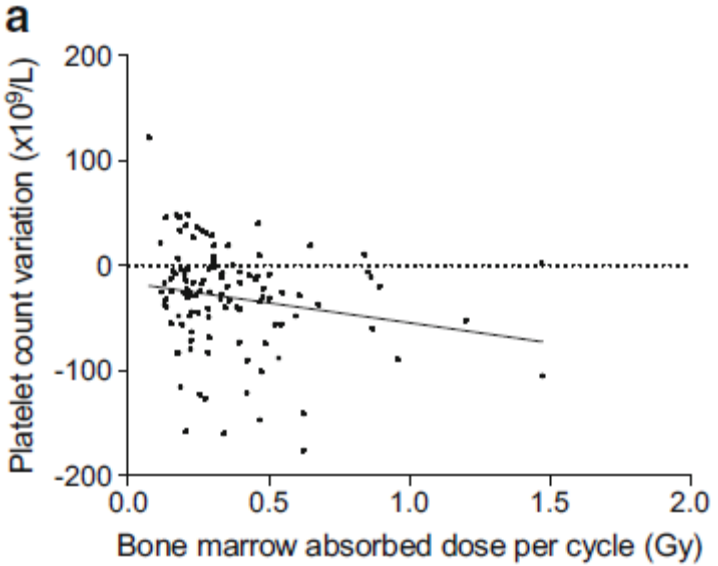
Bergsma, 2016 – blood, 12/23 pts

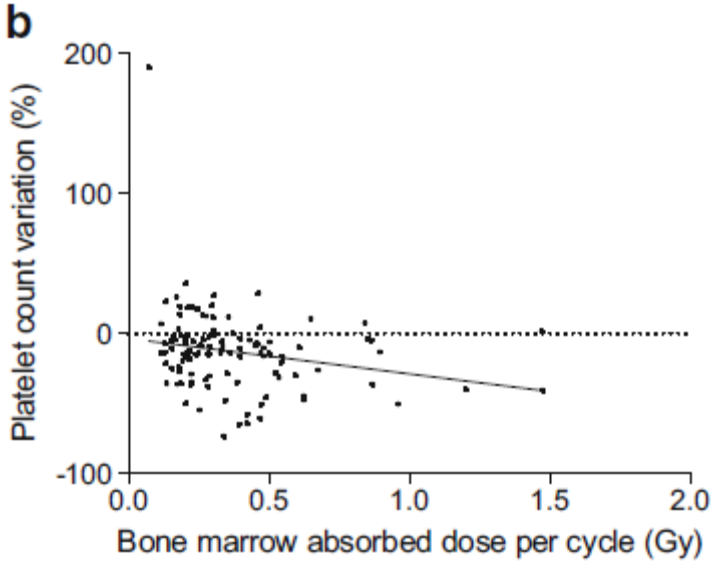


Only in triangles (group 7.40 GBq, n=12)
Significant Spearman's rank correlation

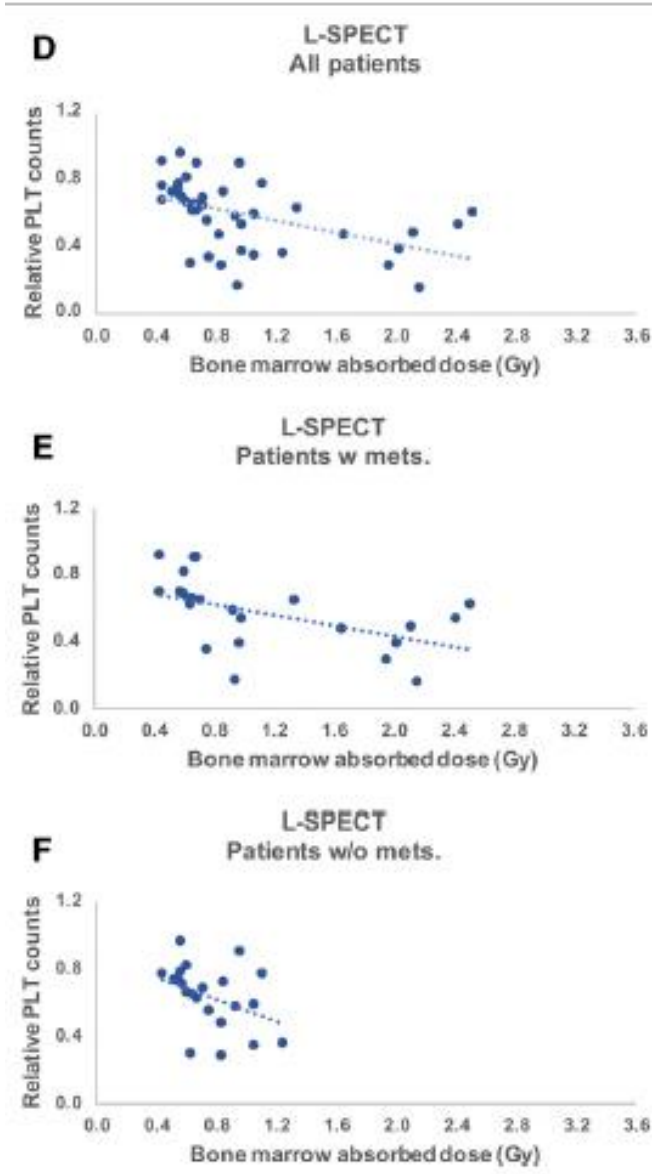


Del Prete, 2019





Hagmarker, 2019



Acute RM toxicity

	Bergsma, 2016	Del Prete, 2019	Hagmarker, 2019	Garske-Roman, 2018
n. of pts	320	52	46	200
grade	3/4	3/4		3/4
frequency	11% (35 pts)	< 10%		15%
Activity / cycle GBq	7.4	8.8 (0.7–32.4), to reach AD = 23 Gy to kidneys in 4 cycles		7.4
n. of cycles	4	4		To reach AD=23 Gy to kidneys
Dosimetry method	blood	SPECT, L4-L5	Planar, SPECT (different lumbar volumes)	blood
AD/activity Gy/GBq	In 23 evaluable patients 67 ± 7 mGy/GBq	0.29 (0.04–1.47) cumulative	Planar 0,026 (0,016-0,043) L4 spect 0,043 (0,020-0,068) L spetc 0,053 (0,024 -0,084) V spect 0,046 (0,028-0,091) T spect 0,062 (0,024-0,116)	0,16
Cumulative AD		1.17 (0.52–4.25)		(0.12 Gy/7.4 GBq)…
AD vs toxicity Correlation?	”in a selected group of patients			
Previous possibly hematotoxic treatments				
notes	15 pts required > 6 months or blood transfusions to recover			The treatment was stopped in 44 patients (22%) for RM-related reasons

to be completed….

Late effects ….

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	^{177}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%)

to be updated….

2003

Breitz H et al.
CaBioth Radopp. 2003;18(2):225-30.
83 myeloma pts for BM transplantation

^{166}Ho-DOTMP:
First case of severe renal toxicity at AD not very high, apparently

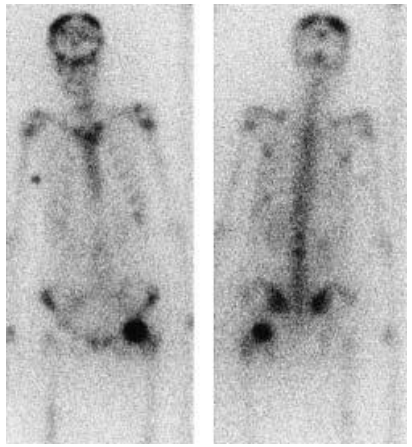
MIRD 14 u- bladder: 45-155 Gy

ICRP 53 kidney: 0.5-8 Gy

35% G3-G4 renal tox

33% G1–G3 u. bladder tox

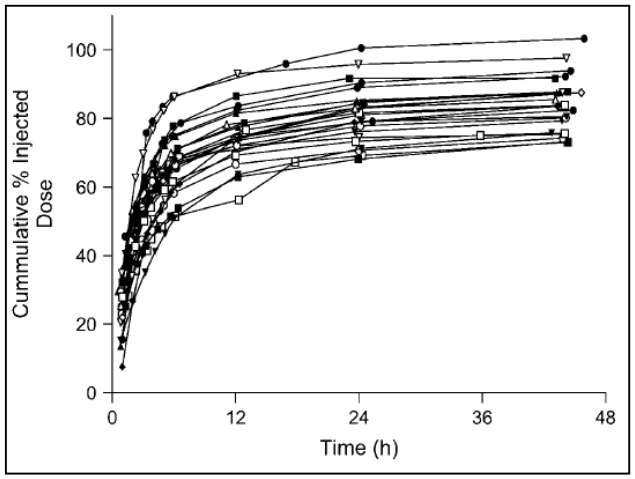
OARs



17-166 GBq

imaging @ 3 h show no kidney uptake

Very rapid transit tim through kidnys: 2,6 min



AD to the kidneys:

2-4 Gy with ICRP 53,

8-17 Gy from imaging

the severity was related to AD and probably to **dose rate**

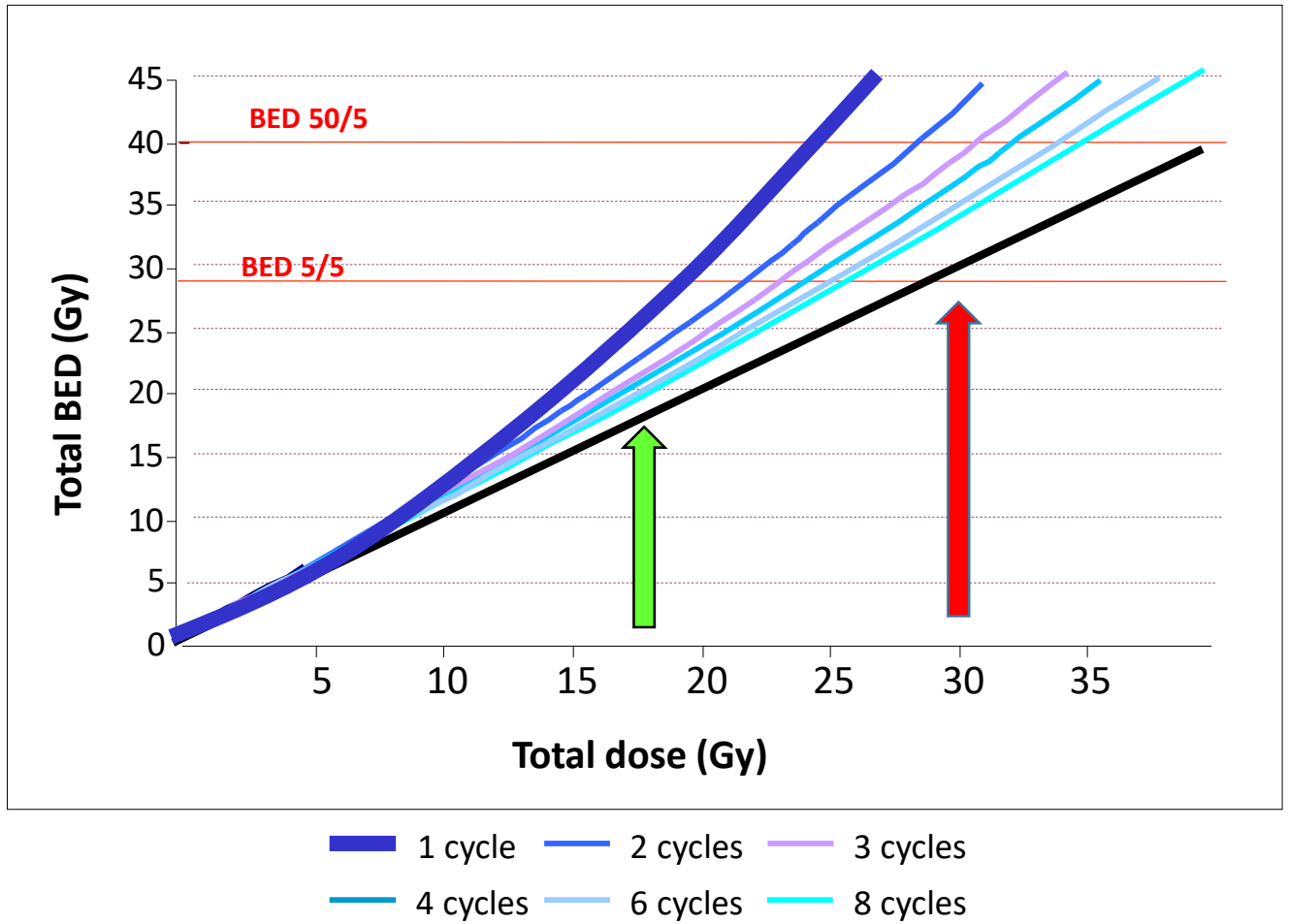
BED_{tot} = 20 - 44 Gy

Initial dose-rate to the kidney:
0.7 Gy/h, with rapid decrease

Breitz H et al.
JNM 2006;47(3):534-42.

BED as a bridge between NM and EBRT

Example: BED for kidneys in case of 90Y-PRRT



For mono-exp time-activity trends

$$BED = D + \beta/\alpha \cdot \frac{T_{1/2rep}}{T_{1/2rep} + T_{1/2eff}} \cdot D^2$$

RB parameters used for Kidneys

T_{repair}	2 h
α/β	2.5 Gy
$\alpha_{kidneys}$	0.03 Gy^{-1}

Wessels, MIRD20 JNM2008 1884-99

Red Marrow dosimetry

Limits

Blood based method	Imaging method
• not able to correlate with toxicity • not able and to consider the impact of infiltrating skeletal metastases	• low activity concentration in the vertebrae and possible scatter contribution from surrounding tissues → quantification? • dependence on the choice of the measured vertebrae; • impact by presence of infiltrating skeletal metastases

EANM Guide Lines on dosimetry in 177Lu- PRRT and RLT - Sjögreen Gleisner K, et al. EJNMMI 2022:
Illustrates the imaging method;
Indicates that RM dosimetry can be performed based on both methods

Clinical issues

How much should we be concernd to low RM toxicity (grade I-II)
How much should we be concernd to late effects for PRRT