Erasmus MC
University Medical Center Rotterdam

Erasmus Experience

^{177}Lu-DOTA-octreotate PRRT

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METRO/MRT meeting
2015, NPL, Teddington

Leading questions ?

1. For which MRT procedure dosimetry is used?
2. Is the dosimetry for patient management, or for research?
3. Which scans, what times, activity-time integration, what method of dose calculation, how is the result presented? (mean, maximum, DVH, etc.)
4. How are the measurements calibrated ?
5. What accuracy validations have been done?
6. Estimate of the uncertainty in dose measurements?
7. Do you think that the dosimetry you are doing could be incorporated in MRT treatment planning on individual patients and be used for personalised treatments?

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Simple answers

1. We stopped doing dosimetry for ^{177}Lu-DOTA-octreotate therapy
2. Dosimetry was performed routinely for research on tox response
3. Planar, 3 time points (24, 96 and 168 h) leading to mean dose
4. Calibration is based on phantom acquisitions
5. No accuracy validations
6. Uncertainty in dosimetry in the order of 50%
7. We really have to better ….

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Dosimetry for 4 x 7.4 GBq ^{177}Lu-DOTA-octreotate

- Absorbed doses to critical organs:
  - Kidneys (N=408): **21 ± 7 Gy**
  - Bone marrow (N=27): **1.5 ± 1,1 Gy**
  - Spleen (N=36): **37 ± 17 Gy**
    - No organ volume correction
    - Planar conjugate view
- Absorbed dose to target volumes:
  - Tumours (N=7): **207 (17 – 387 Gy)**
    - Still only 40% of patients show complete or partial response
- Overall dosimetry question:
    - Is fixed activity optimal?

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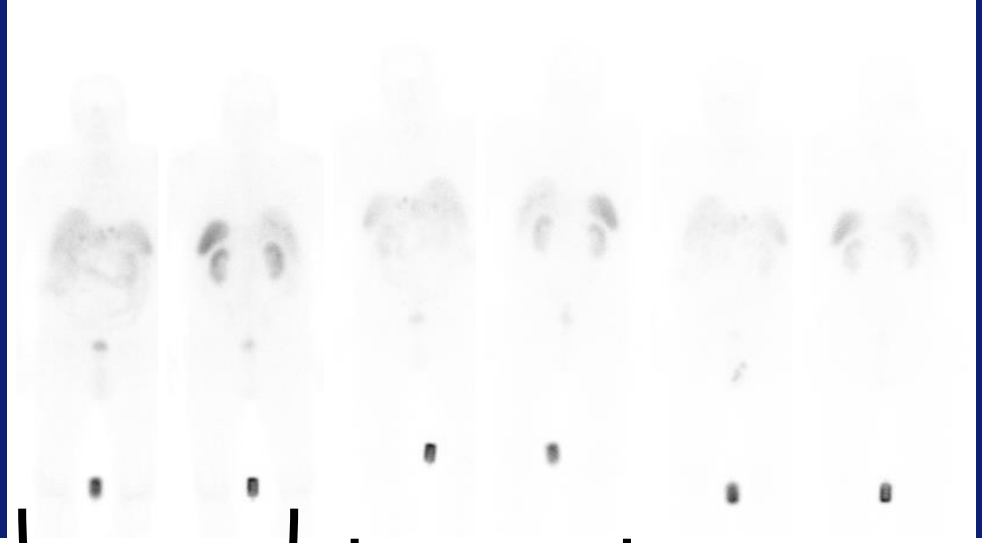
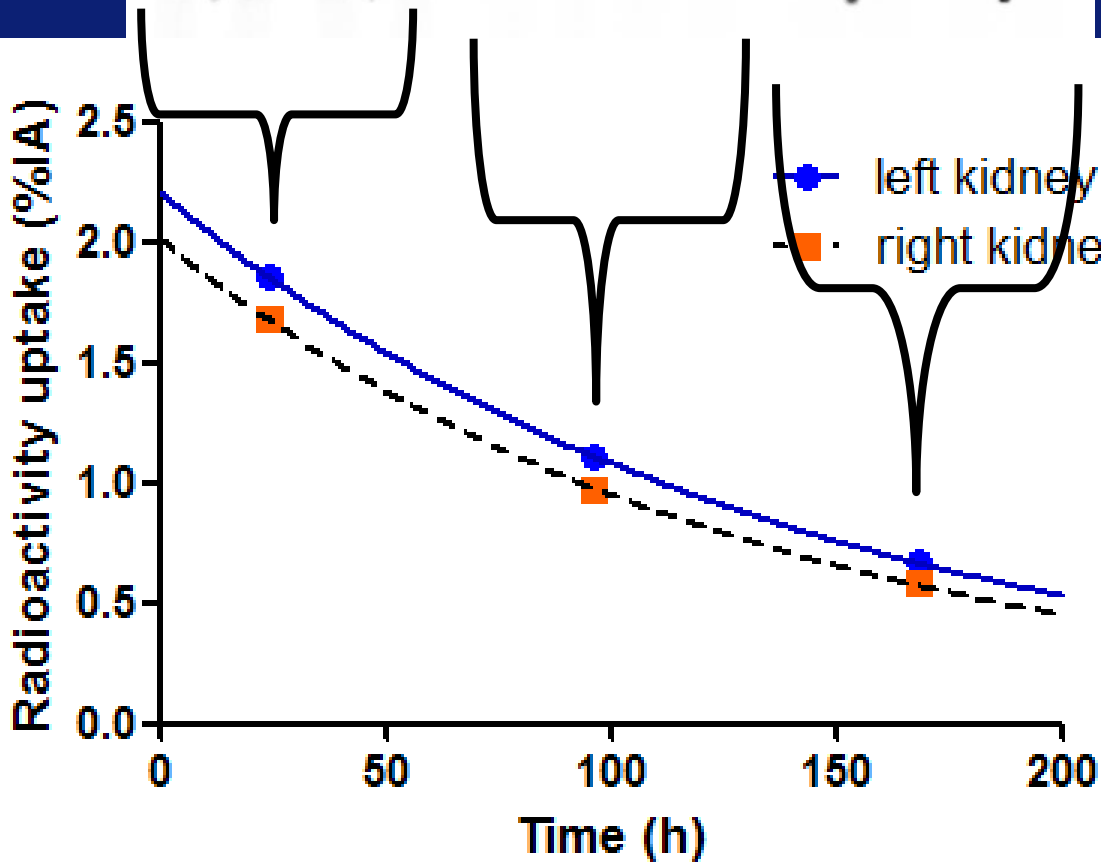
Planar-based dosimetry ^{177}Lu-DOTA-octreotate

- Planar imaging γ-camera
  - Geometric mean uptake $\sqrt{ant \times post}$
  - Kinetics:
    - 1, 3 en 7 days
    - Renal clearance:

      $T_{eff} = 61 \pm 12$ h
- Go/No Go 4th therapy cycle 7.4GBq based on
  - Total dose $\leq$ 23 Gy

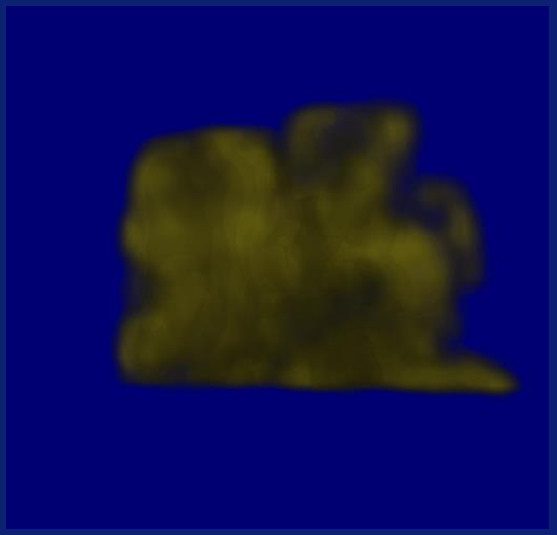


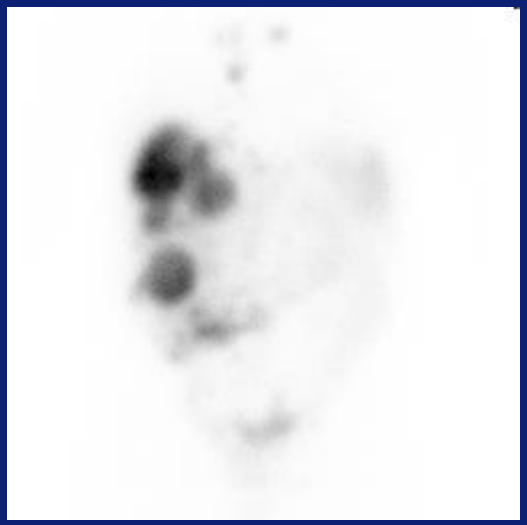


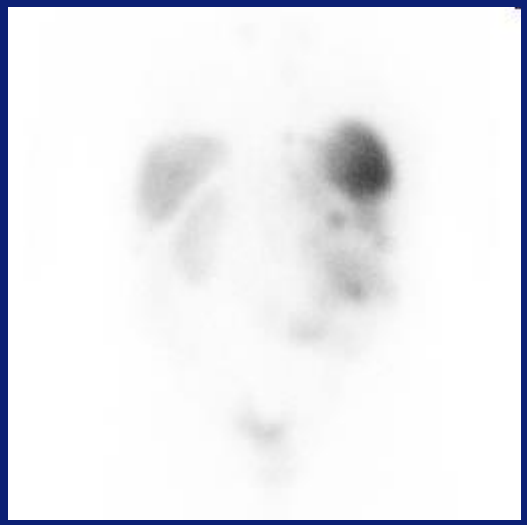
No dosimetry possible in 1/3 of the patient group

Search the kidneys

somewhere....







- Overlapping activity in tumour lesions
- High uptake in liver
- 207 / 615 (34%) patients without dosimetry

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Kidney dosimetry
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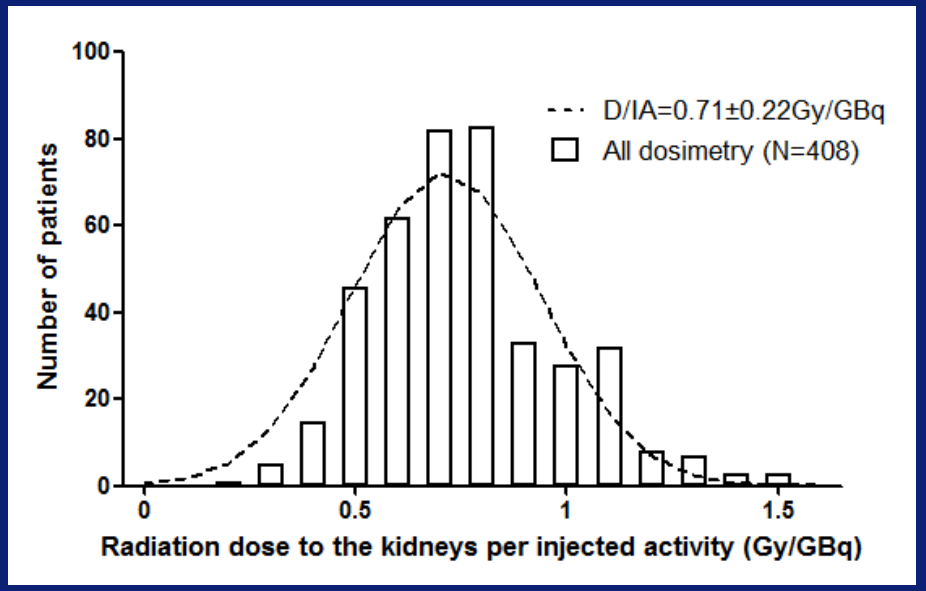
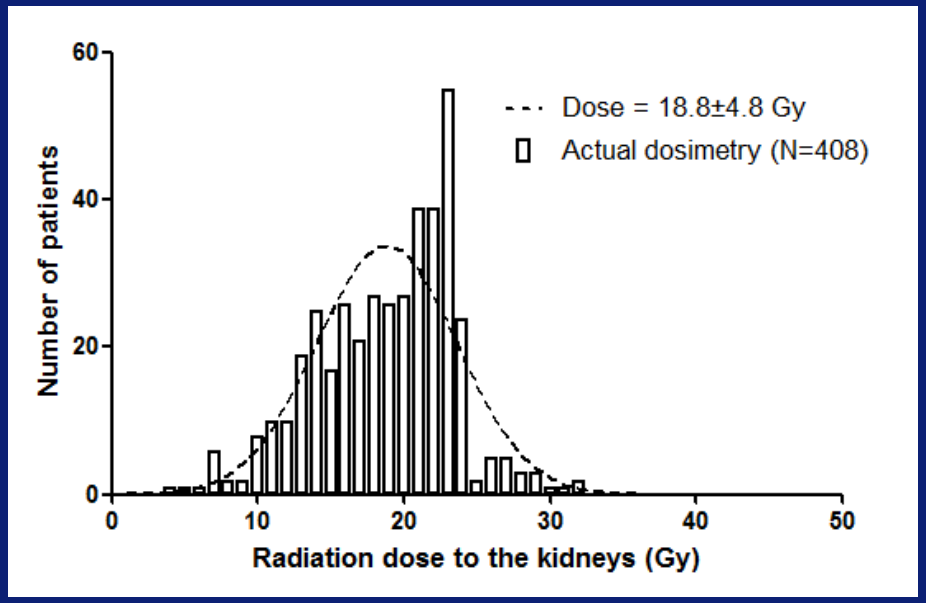
- Planar dosimetry in
  - 408 / 615 patients
  - 23 Gy dose limit
  - 99 stopped at 22 GBq
- Mean absorbed dose per administered activity
  - 0.71 ± 0.22 Gy/GBq
- Mean cumulative absorbed dose for complete therapy
  - **19 ± 5 Gy**





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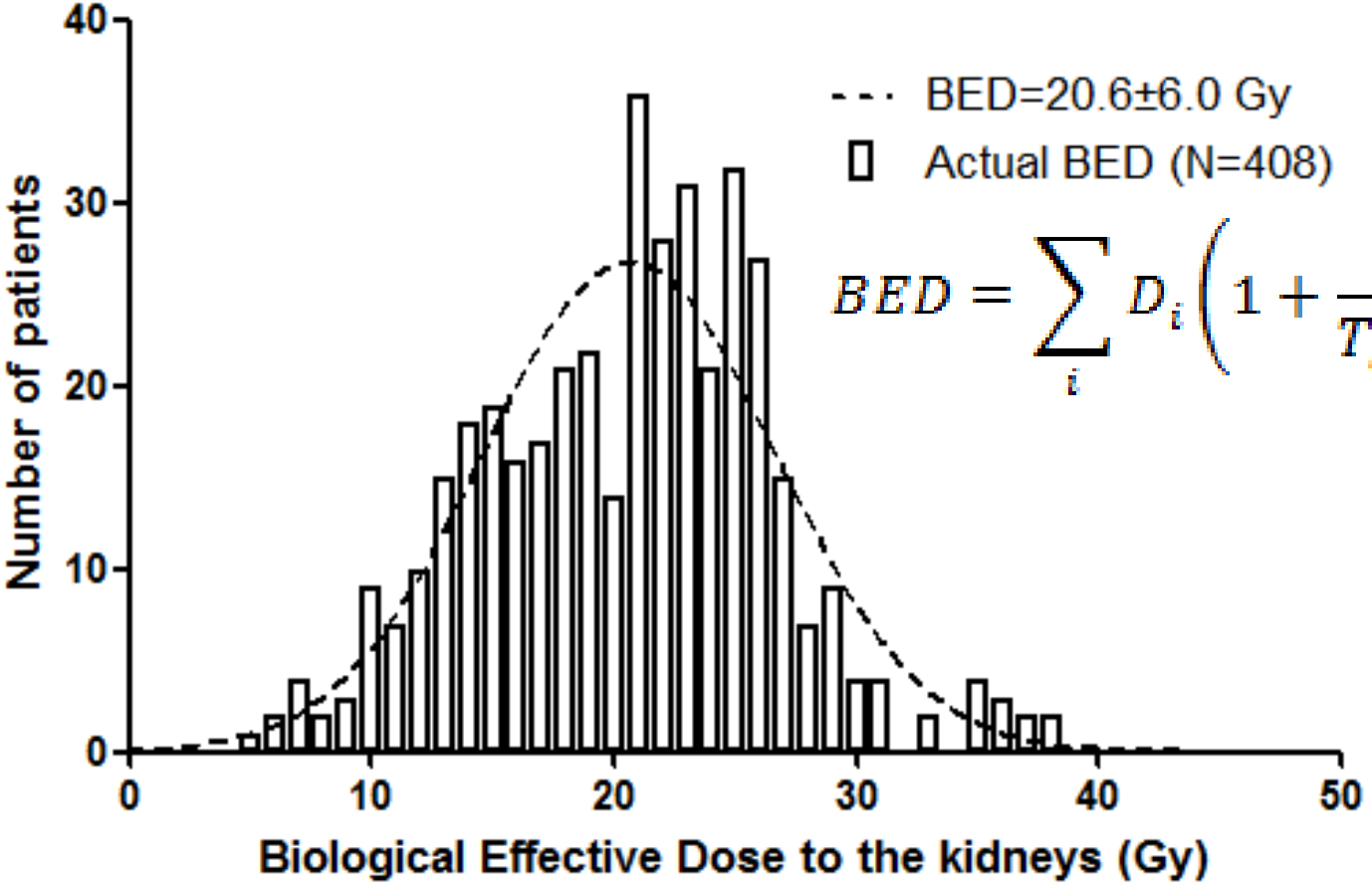
Biologic Effective Dose kidneys ^{177}Lu-DOTA-octreotate



- Mean BED: 21 ± 6 Gy (5 – 38 Gy)
- Mean effective half-life:T_{eff} = 61 ± 12 h

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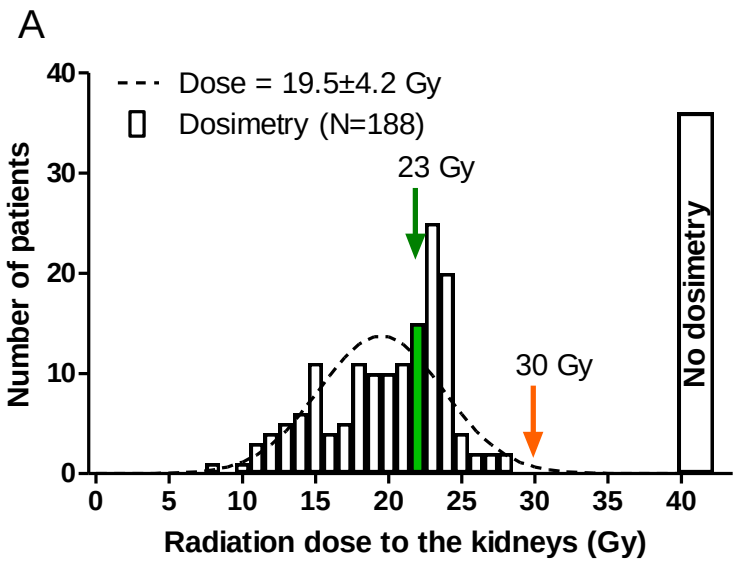
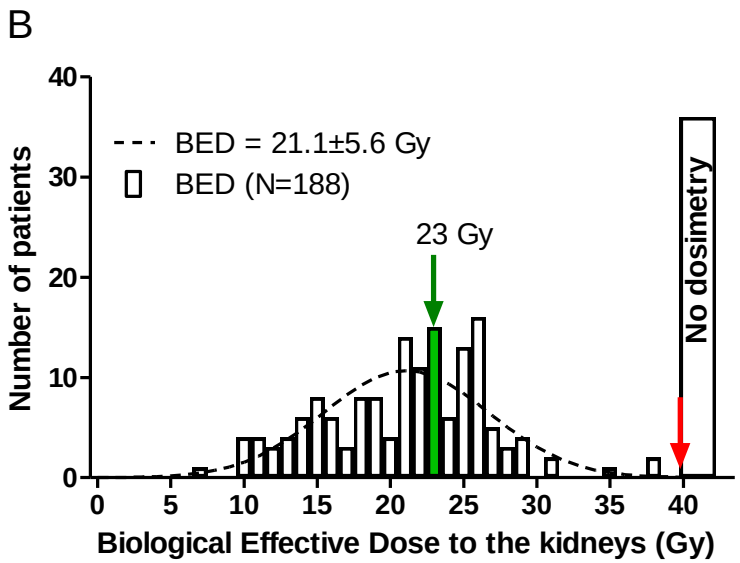
Absorbed doses in 188 patients with > 1 year follow-up





- 152 Patients with dosimetry
  - Follow-up: 2.5 year (1.1 – 7.5 year)
  - Mean absorbed dose to the kidneys: 20 ± 4 Gy
  - Mean BED to the kidneys: 21 ± 6 Gy
- 36 Patients without dosimetry:
  - Follow-up: 2.1 jaar (1.0 – 5.9 jaar)

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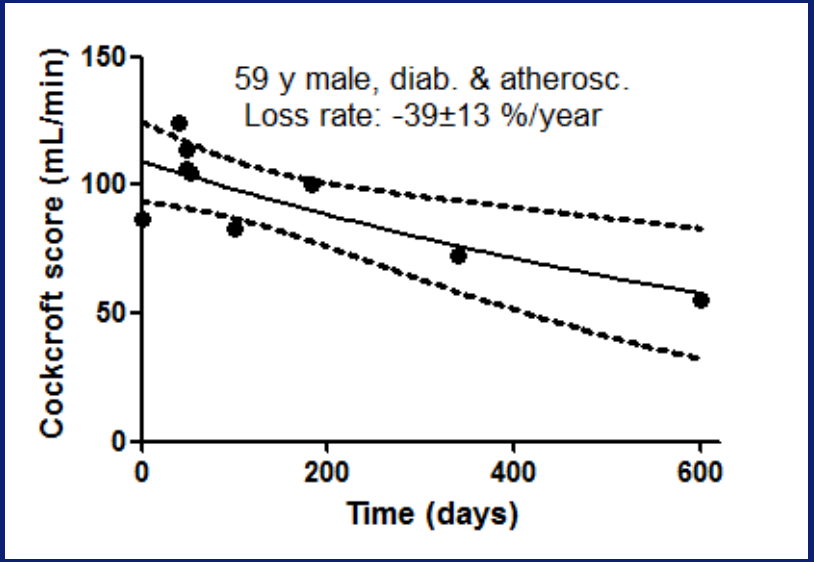
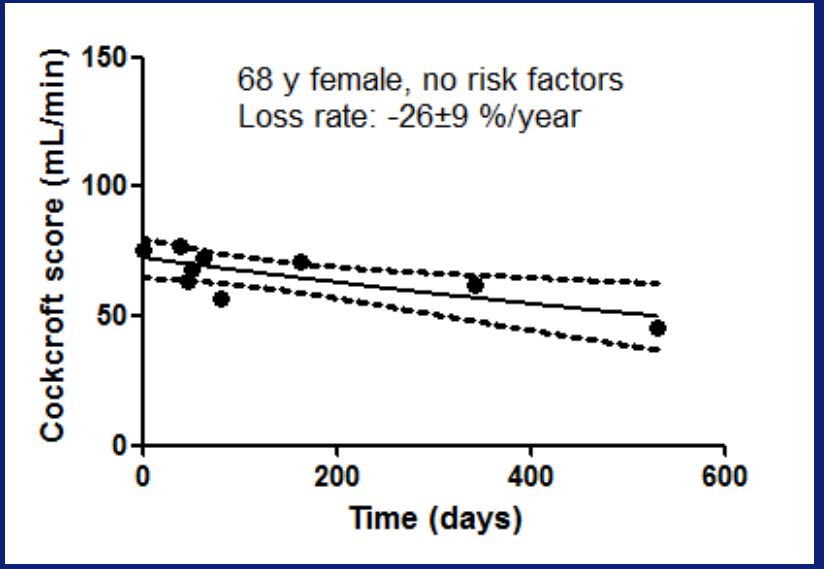
Late kidney toxicity after ^{177}Lu-DOTA-octreotate therapy

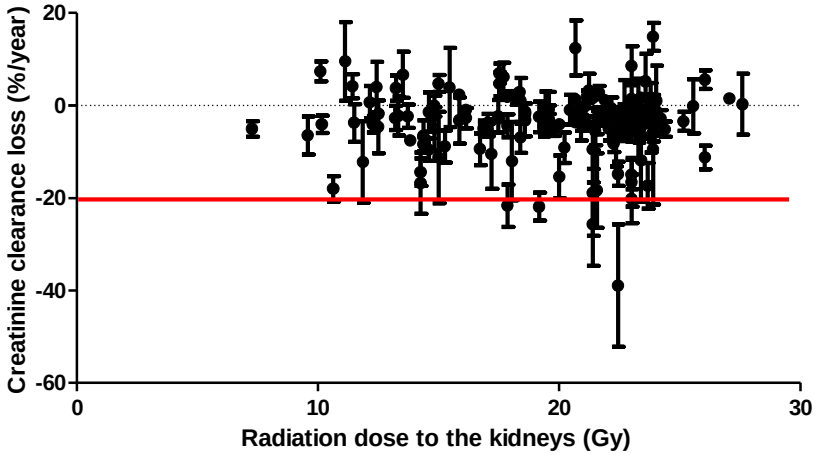
- Decrease in creatinine clearance
  - Limit > 20% / year
- 7 Patients in total (7/188 = 4%)
  - 5 / 152 in the dosimetry group
  - 2 / 36 without dosimetry
- 5/7 Patients with multiple risk factors for kidney problems
  - Age (58-79 y)
  - High blood pressure
  - Diabetes
  - Atherosclerosis
- All patients (still) do not show severe serum creatinine toxicity (< grade 3)





No evidence found for a dose-effect relation for renal toxicity

A



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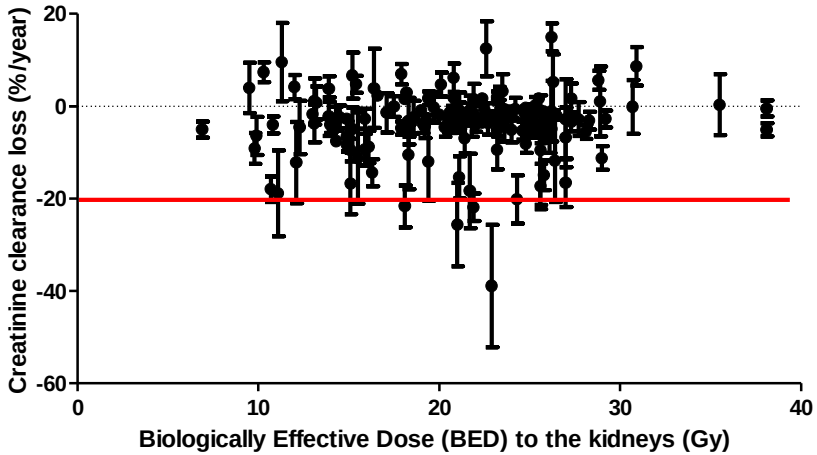

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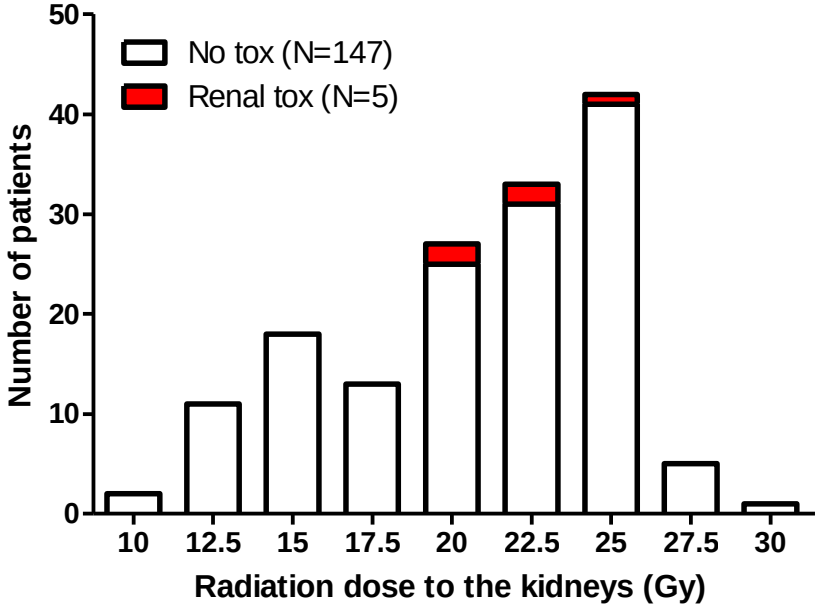

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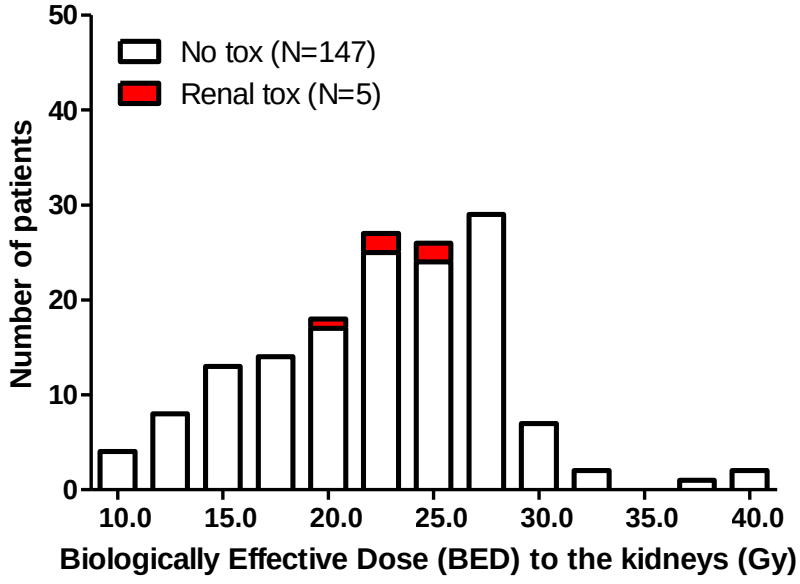
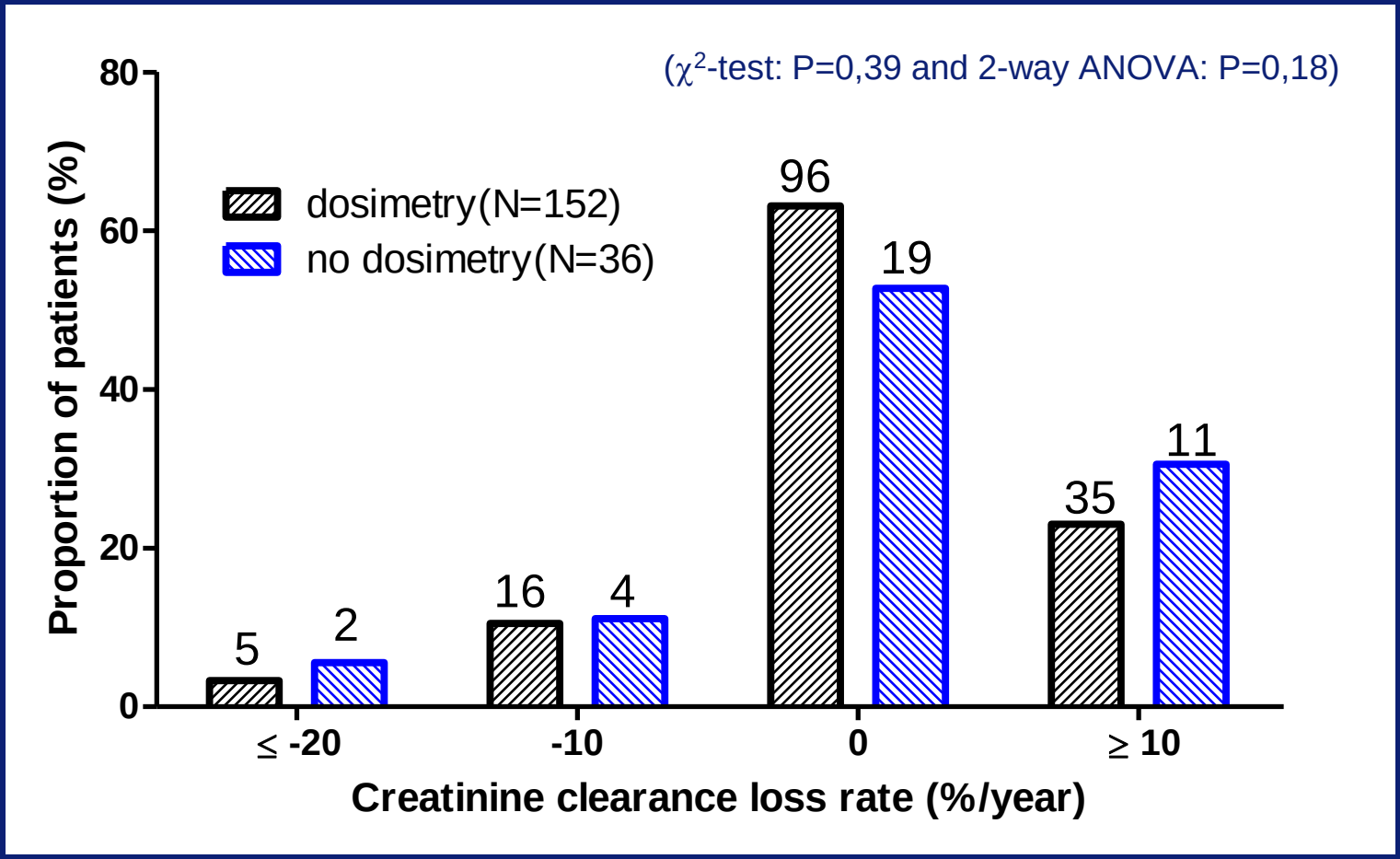


No evidence for different toxicity profile for patients restricted by dosimetry and those without dosimetry



- Kidney dosimetry for ^{177}Lu-DOTA-octreotate is not necessary in fixed dosing scheme of 4 x 7,4 GBq with amino-acids.

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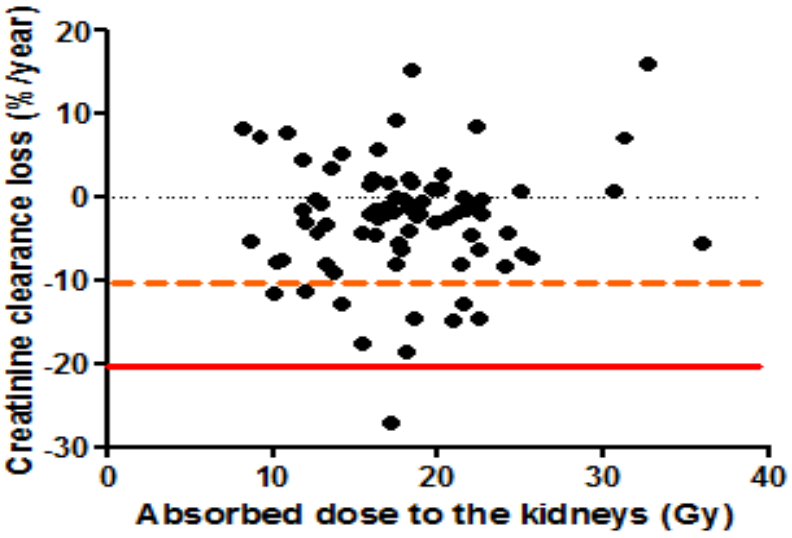
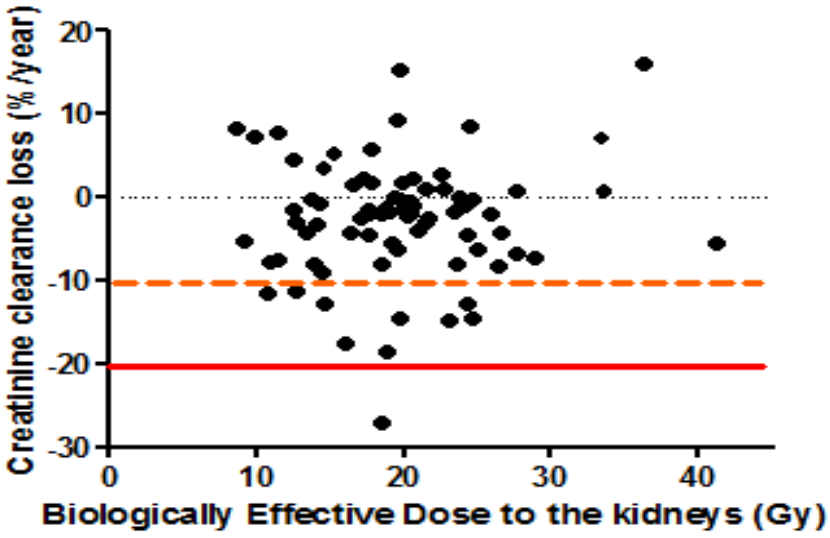
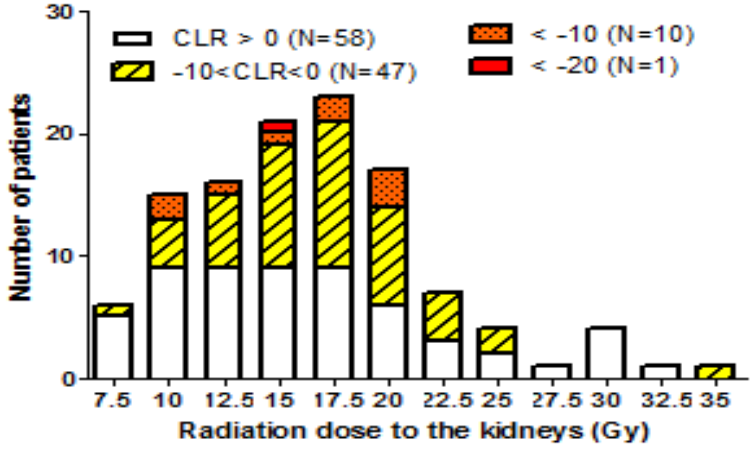
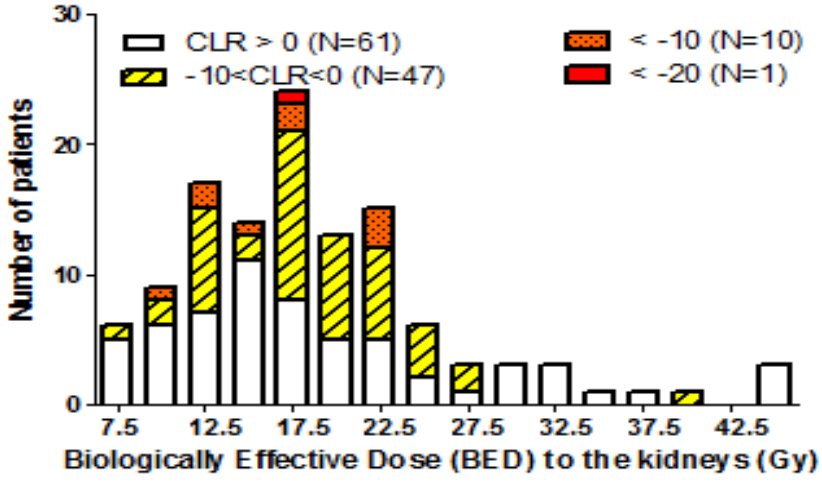
Or evidence for bad dosimetry (volume correction)



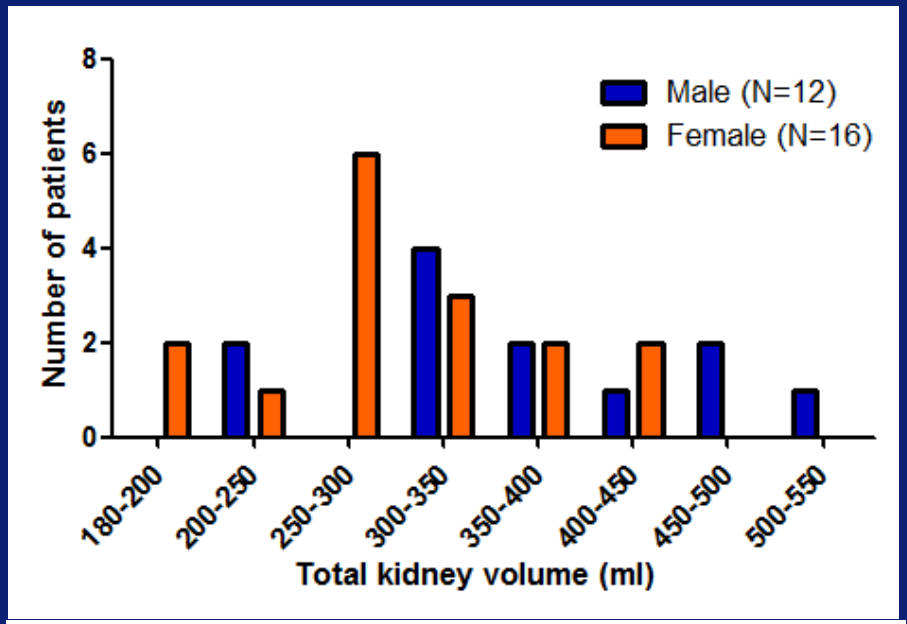


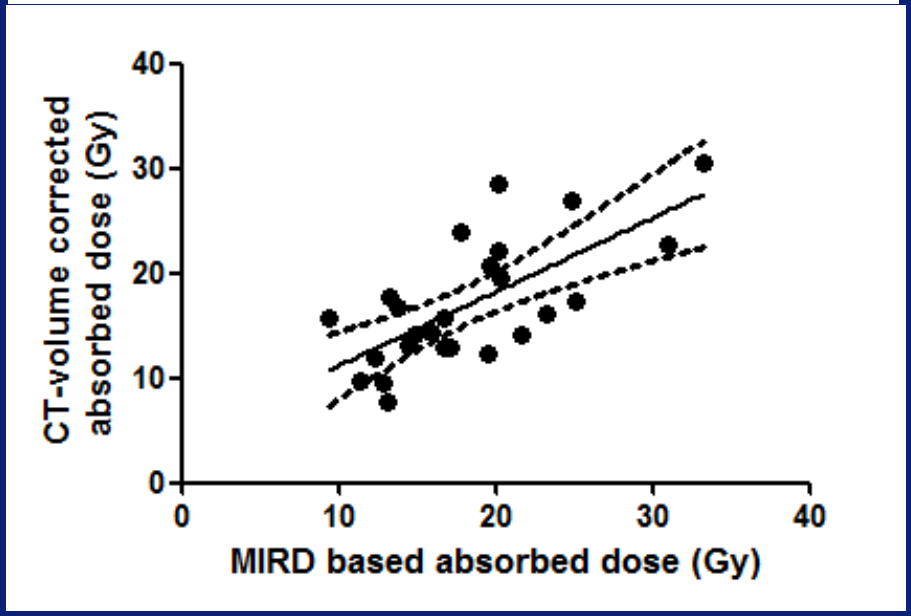




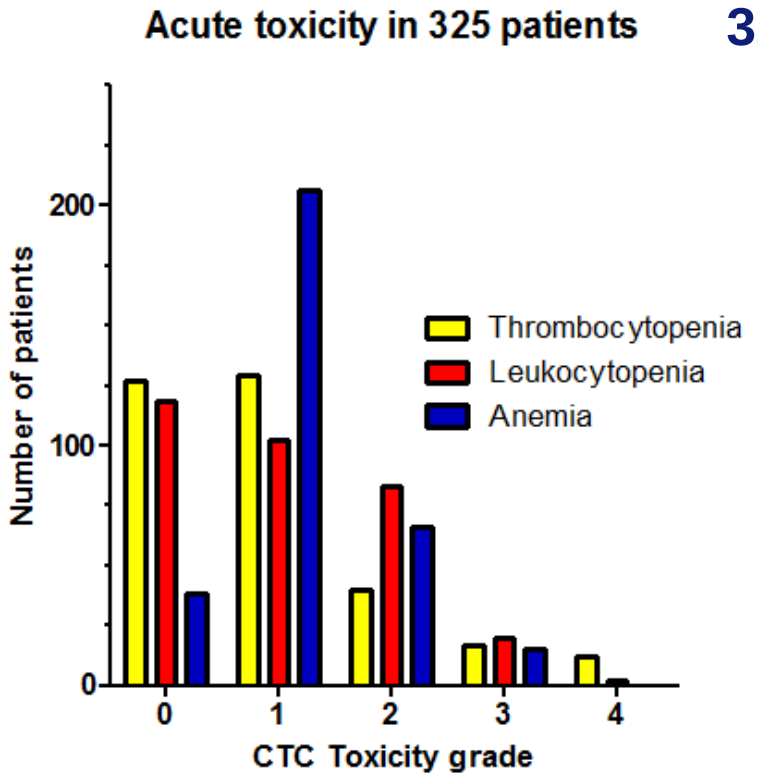
Kidney volumes determined in 28 retreated patients

- Female (N=16):
  - Mean volume 298 ± 70 ml
  - 5 volumes < 275 ml
  - Mean dose at 44.4 GBq:
    - MIRD: 27 ± 6 Gy
    - Vol Cor: 27 ± 6 Gy
- Male (N=12):
  - Mean volume 366 ± 89 ml
  - 2 volumes < 299 ml
  - Mean dose at 44.4 GBq:
    - MIRD: 27 ± 6 Gy
    - Vol Cor: 24 ± 6 Gy
- Mean volume correction factor:
  - 0.93 ± 0.26 (0.6 – 1.5)

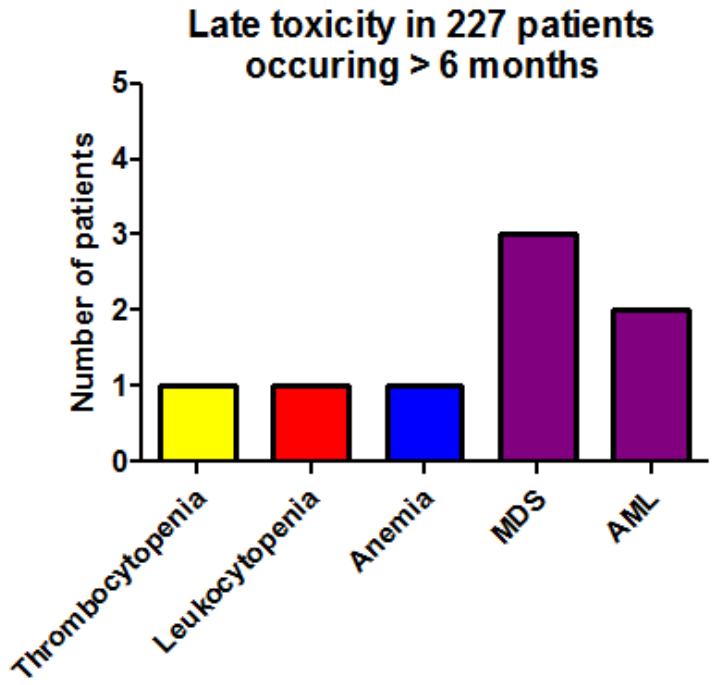




Hematological toxicity after ^{177}Lu-DOTA-octreotate PRRT



32 Patients (32/325 = 10%)



- 35 Acute toxicity
  - 24 Therapy related: 8%
  - Mostly thrombocytopenia
- 8 late toxicity (2%) after 0.5 – 5 year
  - MDS/Leukemia (N=5)
  - Cytopenia (N=3)

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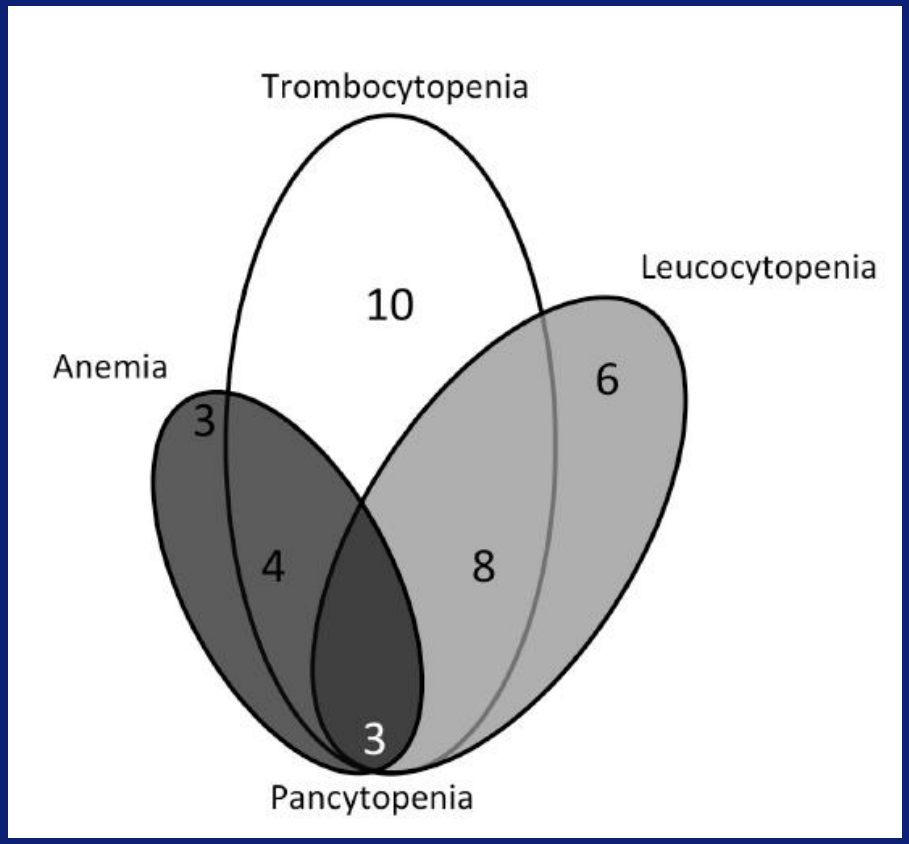
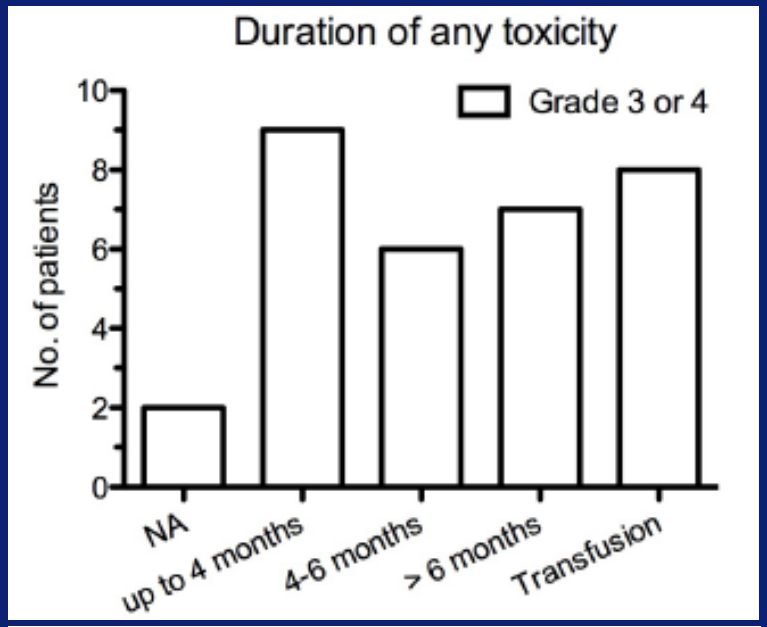
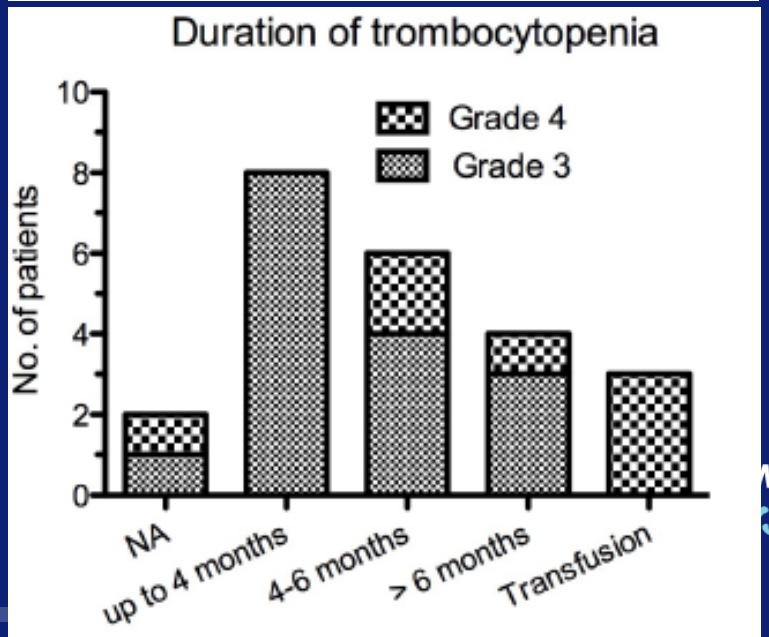
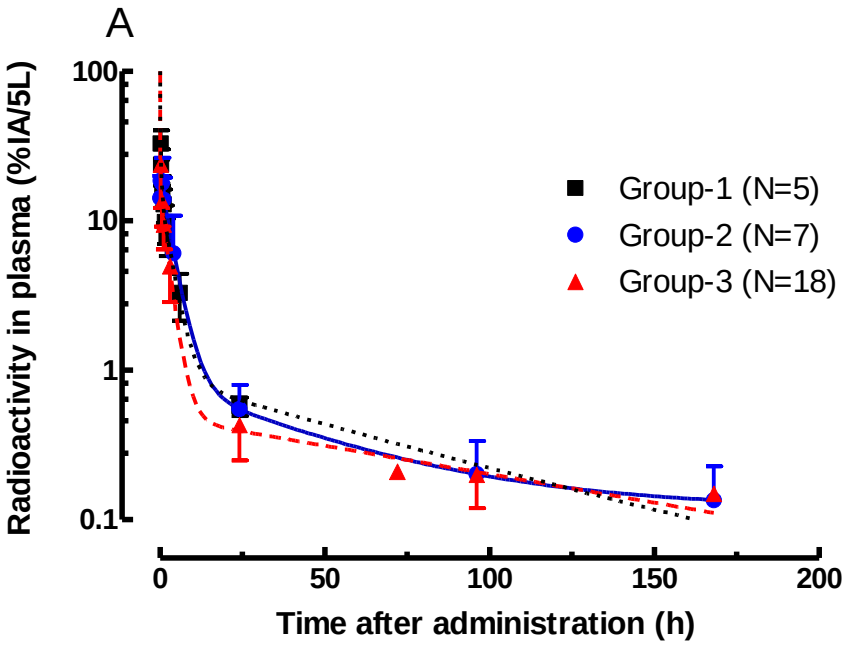
Multiple types of grade 3 and 4 bone marrow toxicity

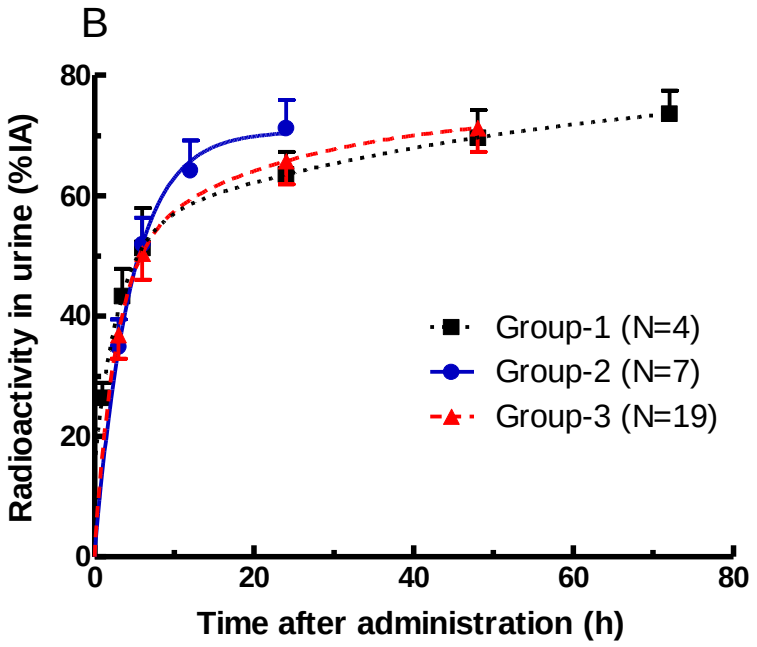






Plasma & urine clearance ^{177}Lu-DOTA-octreotate (N=30)





- Plasma clearance: 91% with $T_{1/2}$: 24 min and 8% with $T_{1/2}$: 5 h
- Urinary clearance: 69% with $T_{1/2}$: 3 uur
  - 2,6 GBq ^{177}Lu (35%IA) in urine at 3 h

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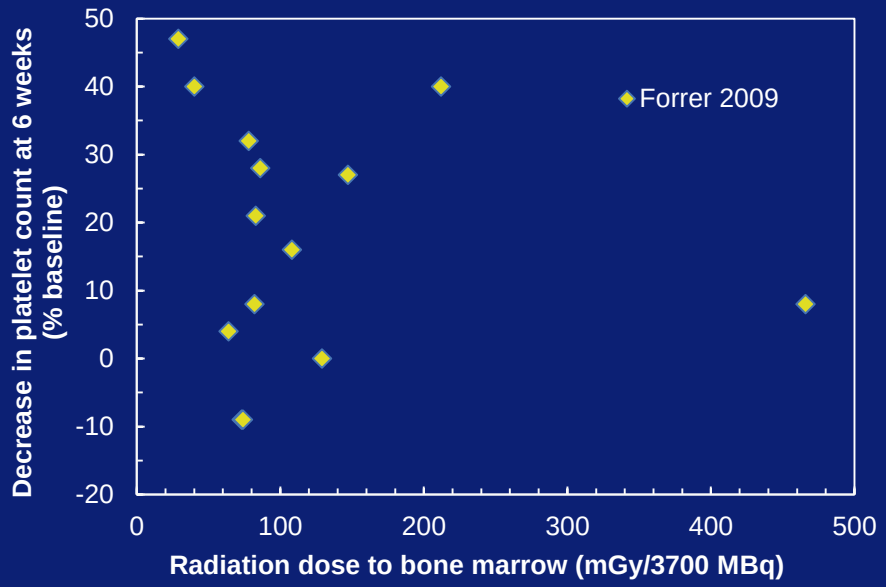
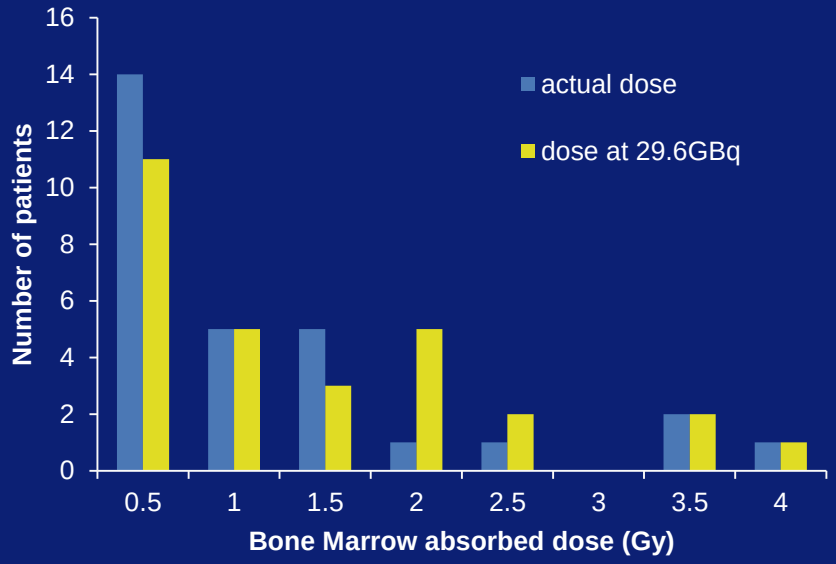
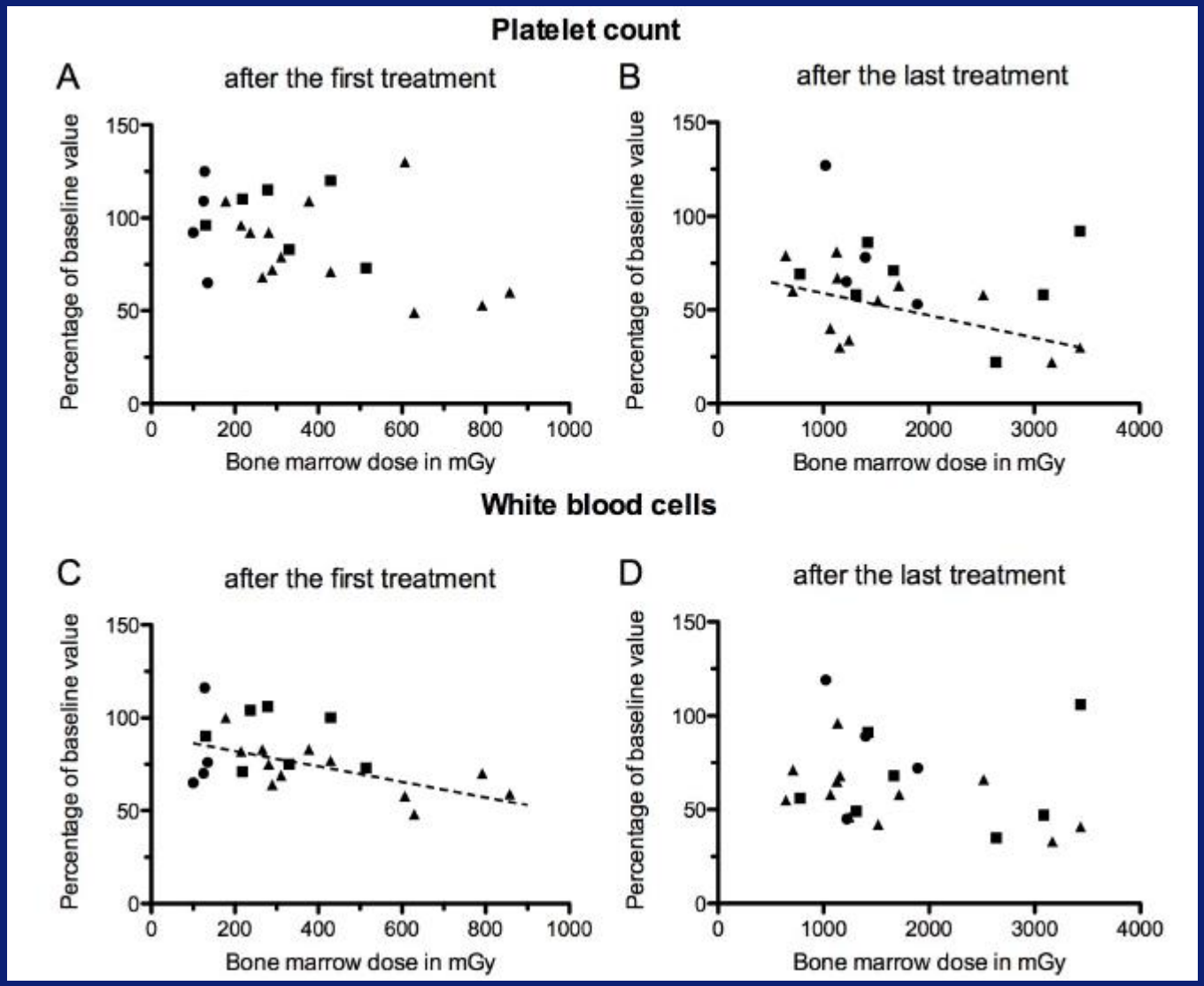
Bone Marrow dosimetry for ^{177}Lu-DOTA-octreotate (N=29)

- Absorbed dose in red marrow:
  - 34% by self-dose (blood)
  - 50% by total body (1 - urine)
  - 14% by organs (γ-camera)
- No correlation between dose and platelet decrease after 3.7 GBq
- Cumulative red marrow dose
  - 0.66 Gy (0.1 – 4.1 Gy)
  - 5 patients (17%) > 2 Gy
- Dose for fixed dosing 29.6 GBq
  - 1.5 ± 1.1 Gy
  - 9 patients (31%) > 2 Gy





Some correlation with bone marrow dose



Platelet:

R^2 =0.35

White blood cells:

R^2 = 0.49

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Risk factors for hematologic toxicity after ^{177}Lu PRRT

Variable	Step-forward Coefficient	Step-forward p-value	Step-backward Coefficient	Step-backward p-value
Any toxicity (Hb/PLT/WBC)				
Cockcroft*	-0,160	0,028	-0,150	0,044
Bonemetastasis	1,055	0,017	0,912	0,056
WBC < 4.0 at baseline*	1,828	0,005	1,741	0,011
Tumoruptake on Octreoscan ≥ Kidneys	0,867	0,051	1,055	0,023
Previous radiotherapy	-		1,225	0,074
Previous chemotherapy	-		-1,171	0,161
Hemoglobin				
Age > 70 years*	1,698	0,045	1,860	0,039
Extensive tumor mass*	2,551	0,002	2,570	0,003
Previous radiotherapy	-		2,165	0,036
Platelets				
Cockcroft*	-0,022	0,010	-0,025	0,008
Bonemetastasis	1,268	0,009	-	
WBC < 4.0 at baseline	1,731	0,016	1,565	0,196
Extensive tumor mass	-		1,174	0,024
Previous radiotherapy	-		1,392	0,055
Previous chemotherapy	-		-1,604	0,144
White Blood Cells				
Age > 70 years			1,161	0,062
WBC < 4.0 at baseline*	2,436	0,001	2,531	0,000
Tumoruptake on Octreoscan > Kidneys*	1,321	0,022	1,549	0,010
Previous radiotherapy	1,363	0,068	-	

Logistic regression analysis of grade 3+4 toxicity in 34 out of 320 patients

- Kidney function
- WBC count
- Tumour uptake
- Bone mets

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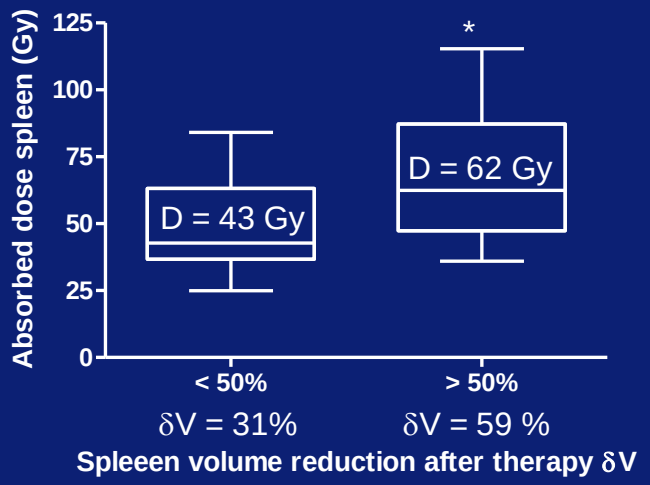
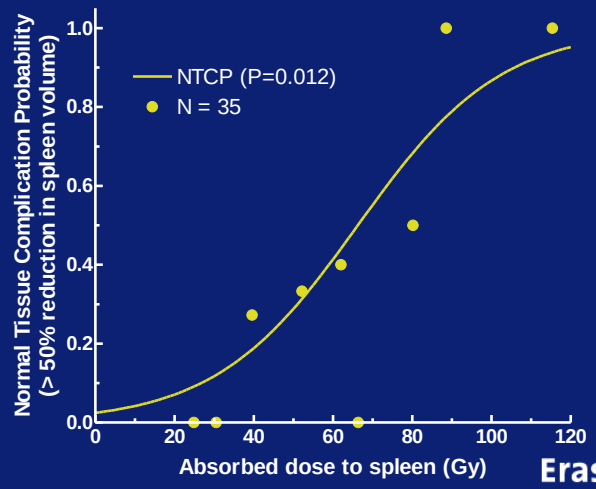
Spleen dosimetry for 44GBq ^{177}Lu-DOTA-octreotate (N=35)

- Absorbed dose spleen after retreatment 52 Gy (25 – 115)
- **25%** volume reduction after Tx1
- **35%** volume reduction after Tx2
- **NTCP** model for serious reduction in spleen volume
  - Threshold at **TD_5 = 13 Gy** and 50% at **TD_{50} = 66 Gy**
- **No clinical signs for malfunctioning spleen**
  - **Lymphocytes drop**





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Do you think that the dosimetry you are doing could be incorporated in MRT treatment planning on individual patients and be used for personalised treatments?

Bone marrow dosimetry

- Image based
- Additional early time-point
  - Voiding (AA – infusion)
- Functional imaging of individual red marrow

Kidney dosimetry

- Spect/CT + planar combination
- Volume correction
- Dose escalation study to determine actual dose limit
- Derive α/β, repair $T_{1/2}$ and BED, specific for ^{177}Lu

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Conclusie dosimetry for ^{177}Lu-DOTA-octreotate PRRT

- With fixed dosing scheme (4 × 7.4 GBq) with amino-acids
  - Absorbed dose of 21 ± 7 Gy to the kidneys
  - Hardly cases of renal toxicity
  - No difference in toxicity dosimetry and no-dosimetry
- Heamatological toxicity (10%) seems more a problem
  - No correlation between Red Marrow dose and toxicity
- **The therapy might be sub-optimal.....**
  - **Dosimetry based treatment planning based on image-derived bone marrow (and kidney) dosimetry**

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Thank You!

Acknowledgements

Erasmus MC Rotterdam

- Dik Kwekkeboom
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- Wouter van der Zwan
- Roelf Valkema
- Eric Krenning

…and the patients
treated with PRRT

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