EVALUATION OF RISKS OF RADIONUCLIDE THERAPY

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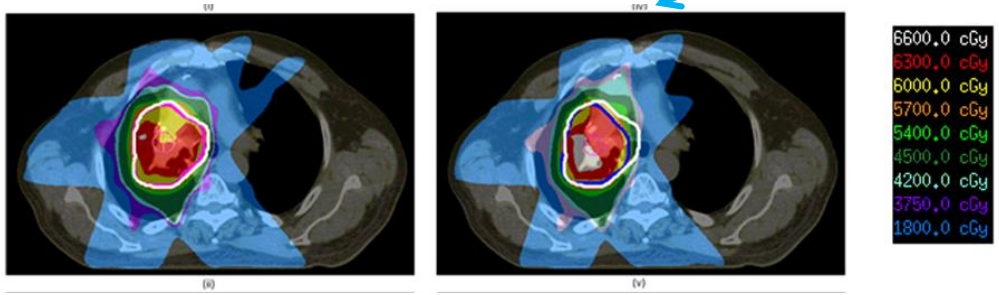
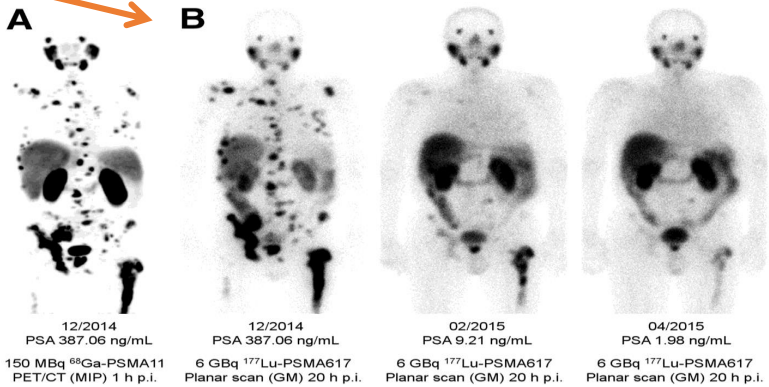
Radionuclide therapy, or molecular radiotherapy

- Image guided patient specific IMRT / molecular conformal radiotherapy





- What you see is what you treat ...
  … and quantify
  ... and verify

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^{177}Lu-DOTA-Octreotate (lutathera) neuro-endocrine tumour therapy

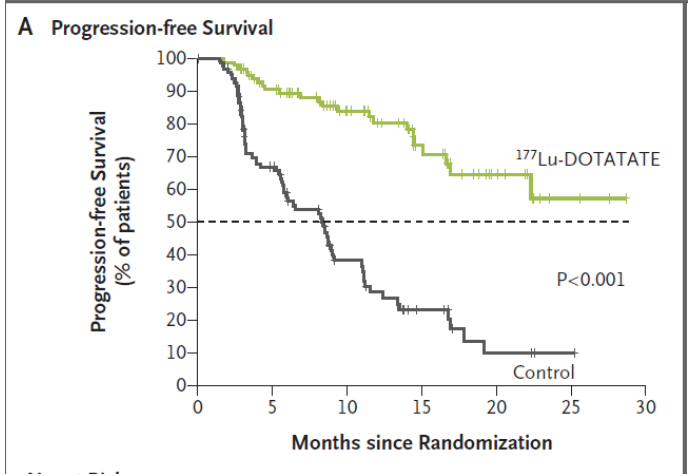
- Netter-1 phase III study results (N=229) at
  - **4 x 7.4 GB ^{177}Lu-DOTA-octreotate**
    - **Somatostatin receptor targeted therapy**
    - **Low-energy beta-particle emitter ($T_{1/2}$ 6.5 d)**
  - 79% Risk reduction
    - in disease progression or death

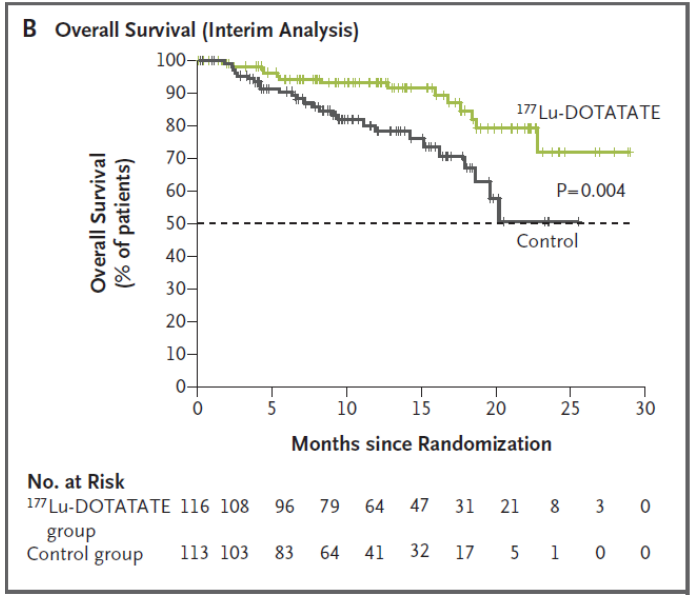
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*





^{223}Ra (Xofigo) Therapy for metastasized prostate cancer

- α-particle emitter with $T_{1/2}$ = 11.4 days
- Bone-seeking calcium-mimetic
- 6 x 55 kBq/kg at 4 weeks interval
  - 3 months increase in survival
  - No Serious Adverse Events

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 18, 2013 VOL. 369 NO. 3

Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fosså, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø.S. Bruland, and O. Sartor, for the ALSYMPCA Investigators*

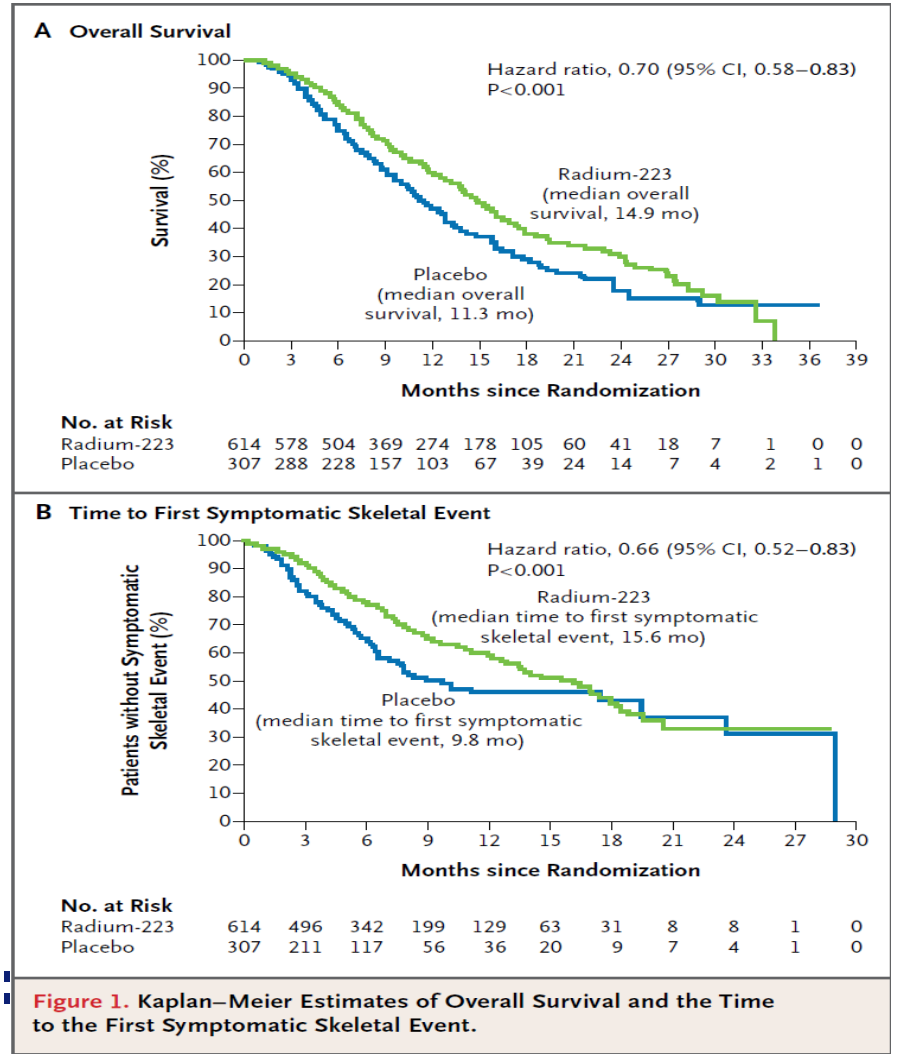


Figure 1. Kaplan–Meier Estimates of Overall Survival and the Time to the First Symptomatic Skeletal Event.

Chemotherapy against prostate cancer

- 4 months increase in survival
- Combination of ^{223}Ra and Abiraterone
  - Increase in bone fractures (29% vs 11%)

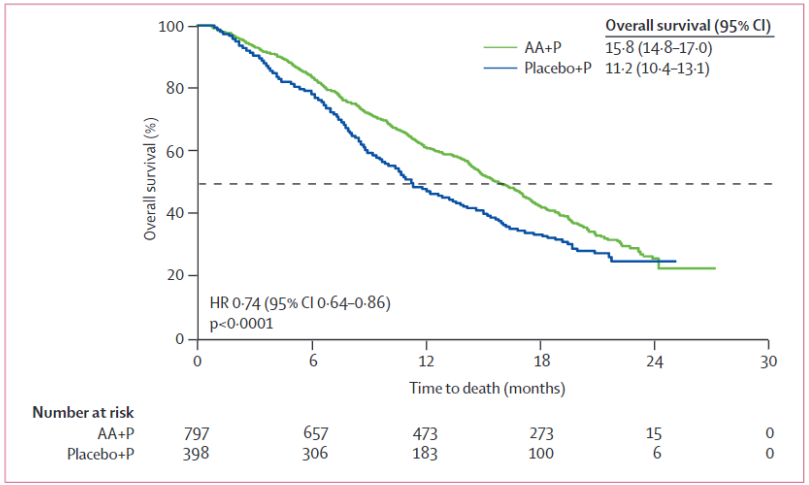


Figure 2: **Overall survival**
HR=hazard ratio. AA=abiraterone acetate. P=prednisone.

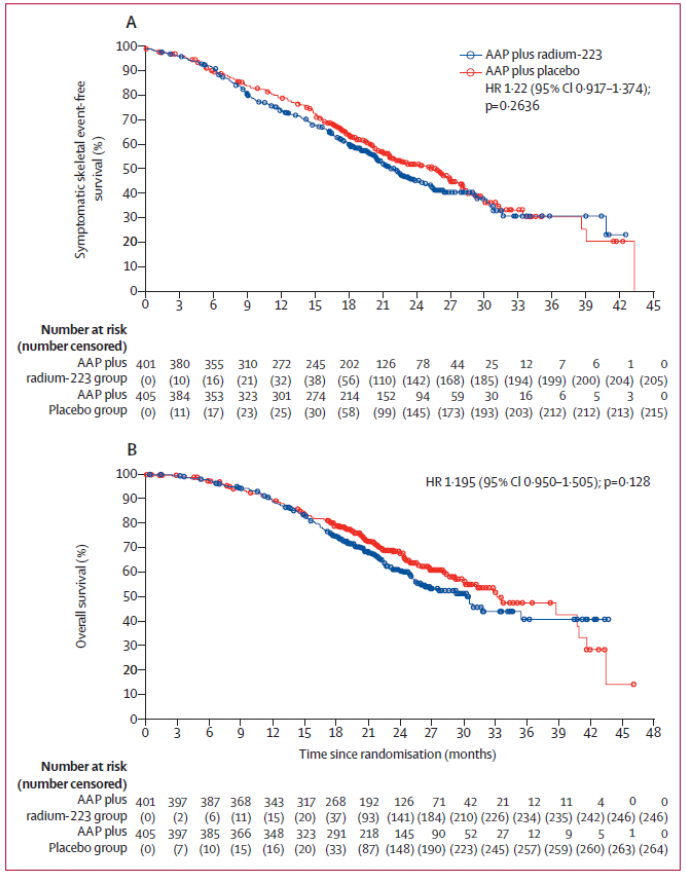


Figure 2: **Kaplan-Meier estimates of symptomatic skeletal event-free survival (A) and overall survival (B) in the intention-to-treat population**

K Fizazi et al., Lancet Oncol 2012; 13: 983–92

M Smith et al., Lancet Oncol 2019; 20: 408–19

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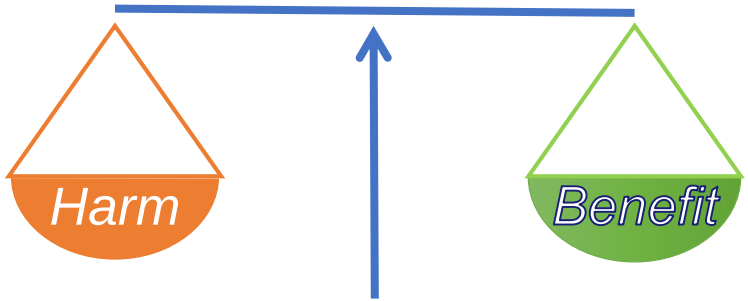
Chemotherapy or molecular radiotherapy?

- Bone pain palliation therapy **6 × 55 kBq/kg** $^{223}RaCl_2$ (Xofigo)
- Peptide Receptor Radionuclide Therapy neuroendocrine tumours: **4 × 7.4 GBq** ^{177}Lu-DOTA-octreotate (Lutathera)

Why still the use of fixed activity dosing schemes?



One activity for MRT fits all patients?

Arguments against clinical dosimetry

1. Time and resource consuming
2. Costly, no reimbursement
3. Inconvenient for the patient
4. On-site expertise needed
5. No established method
6. Unclear dose-response models
7. Large uncertainties in absorbed dose
8. Safe activity from clinical trials / experience
9. One size fits all is so convenient

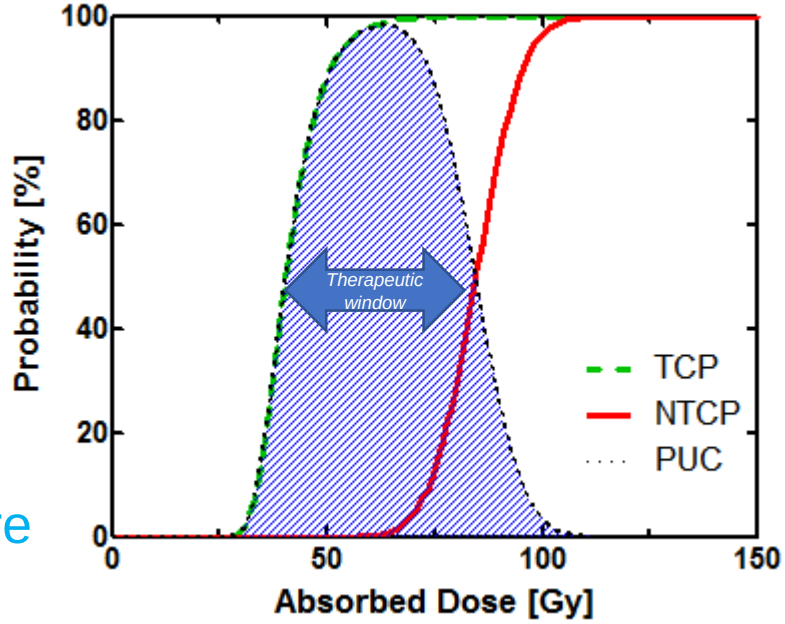
Solutions for routine clinical dosimetry

1. Keep it practical and relevant
2. Reimbursement for dosimetry
3. Minimize number of patient-scan times
4. Medical physics expert support manditory
5. Benchmarks for dosimetry software
6. Focussed radiobiology research in MRT
7. Improve accuracy in dosimetry process
8. Dose response model guided clinical trials
9. Sub-optimal patient care is not acceptable

Therapeutic window External Beam Radiotherapy

Therapeutic window between

- Harm NTCP
  - Normal Tissue Complication Probability
- Benefit TCP
  - Tumour Control Probability
- Optimal benefit and harm PUC
  - Probability for Uncomplicated Cure



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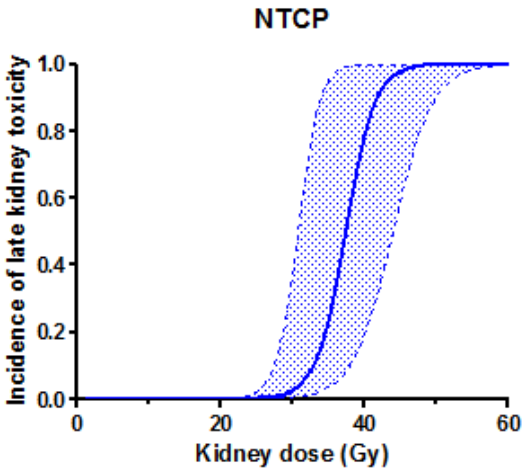
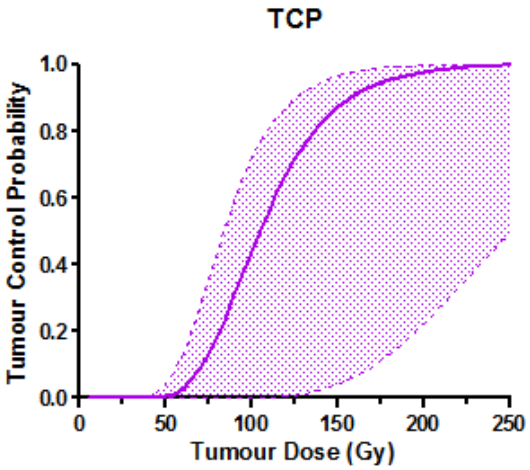
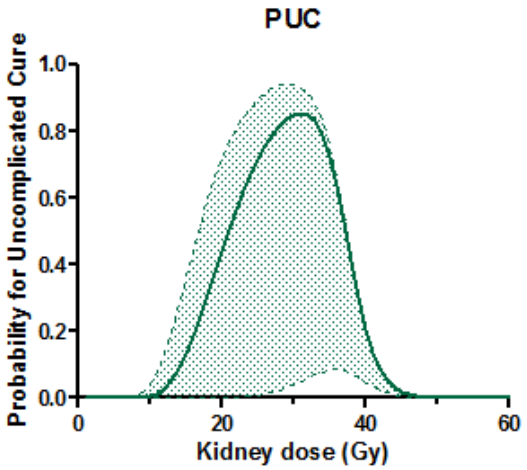
Therapeutic window example in Targeted Radionuclide Therapy







Organ at Risk: Kidneys

Dose ratio Tumour/Kidney : 5

Therapy at maximum tolerable kidney dose

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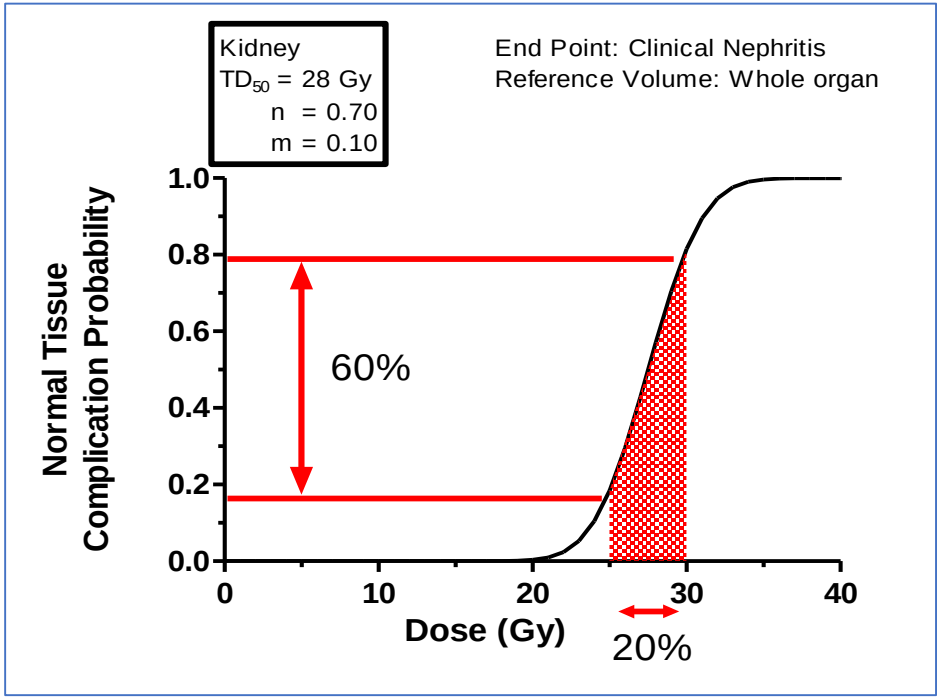
Propagation of absorbed dose uncertainty into effect



- Absorbed dose OAR (kidney):
  - D = 27.5 ± 2.5 Gy
- Uncertainty in risk is amplified by steep NTCP curve
- ***20% uncertainty in radionuclide therapy absorbed dose***
- ***Dose-effect relation ?***

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Eur J Nucl Med Mol Imaging (2014) 41:1976–1988
DOI 10.1007/s00259-014-2824-5

REVIEW ARTICLE

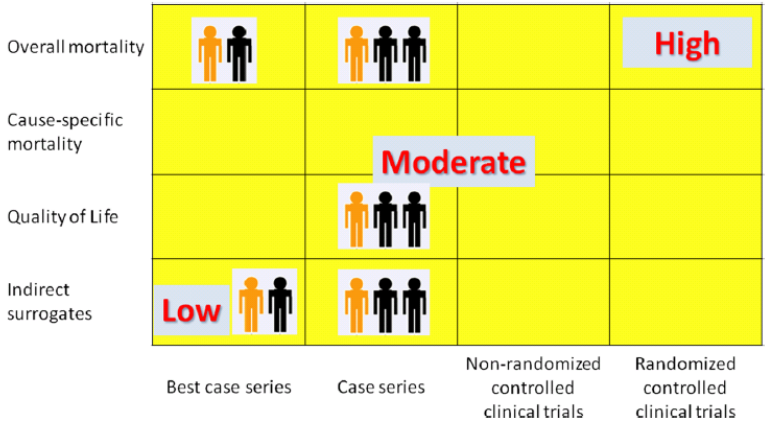
Evidence for dose-effect relations MRT

The evidence base for the use of internal dosimetry in the clinical practice of molecular radiotherapy

Lidia Strigari · Mark Konijnenberg · Carlo Chiesa · Manuel Bardies · Yong Du · Katarina Sjögreen Gleisner · Michael Lassmann · Glenn Flux

Table 2 Percentage of the 79 studies including dosimetry investigating various endpoints

Endpoint	Percentage of papers reporting the endpoint
Overall survival	28
Cancer-specific survival	4
Quality of life	1
Surrogate endpoints	94
Toxicity	71
Response to therapy	71



- More dose-effect relations than anticipated
- Prospective trials are mandatory to derive NTCP and TCP dose-effect relations

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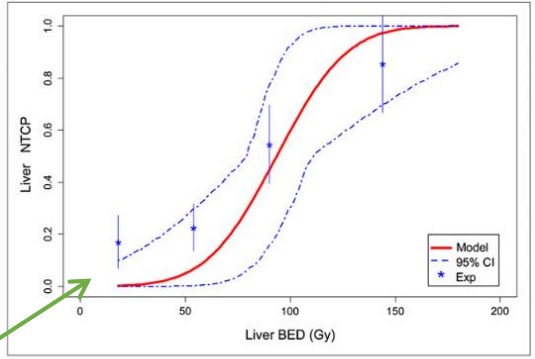
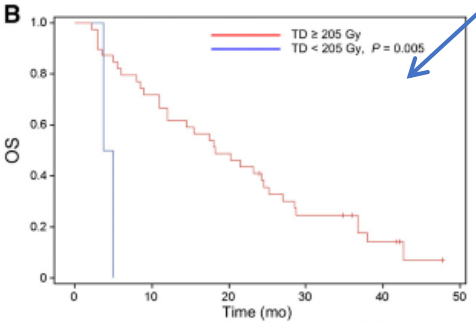
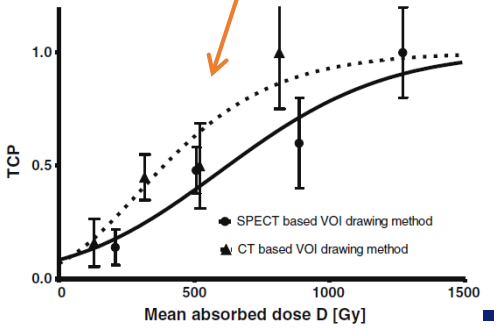
Dose-effect relations in ^{90}Y therapy of (metastatic) liver cancer

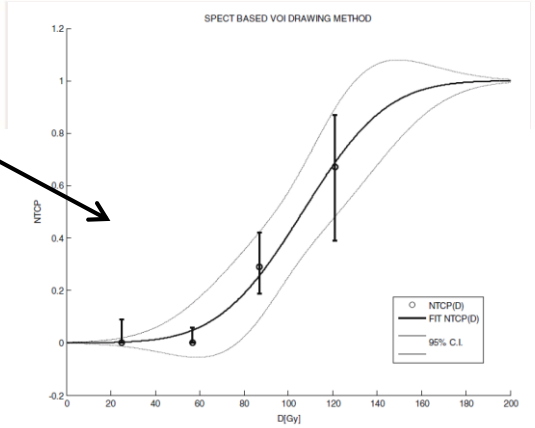
Table 9 Studies showing dose–effect relationships for intraarterial therapy of liver cancer using radiolabelled microspheres

Reference	No. of patients	Radionuclide	Carrier	Endpoint	Threshold dose
[47]	71	^{90}Y	Ivalon microspheres	PR (>50 % reduction), pneumonitis	225 Gy (lesion), 30/50 Gy (lung)
[48]	36	^{90}Y	Glass microspheres	Response (PR+CR)	205 Gy (lesion)
[49]	185	^{188}Re	Lipiodol	OS	30 Gy (tumour)
[50]	12	^{90}Y	Resin microspheres	Metabolic FDG response>50 %	260 Gy (tumour)
[51]	8	^{90}Y	Resin microspheres	Metabolic FDG response >50 %	46 Gy (tumour)
[52]	52	^{90}Y	Glass microspheres	EASL density response (PR+CR)	500 Gy (lesion)
[53]	73	^{90}Y	Resin microspheres	50% TCP (PR+CR) 5 %≥G2 liver toxicity	150 Gy (tumour), 50 Gy BED (liver)
[54]	45	^{90}Y	Resin microspheres	REILD	40 Gy (liver)
[55]	52	^{90}Y	Glass microspheres	Tumour density reduction, liver decompensation	200 Gy (tumour), >60 Gy to the parenchyma
[56]	15	^{166}Ho	Polylactic acid microspheres	G3 liver and blood toxicity	80 Gy (liver)









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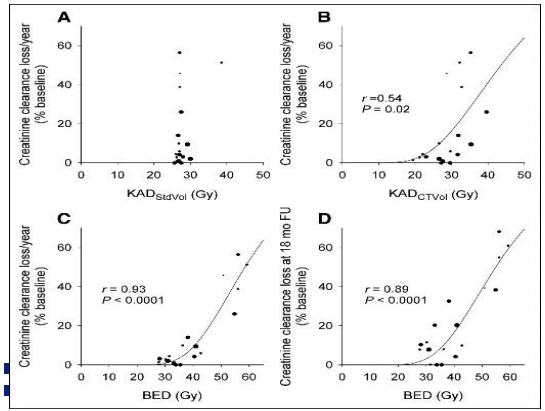
Dose-effect relations in peptide receptor radionuclide therapy PRRT

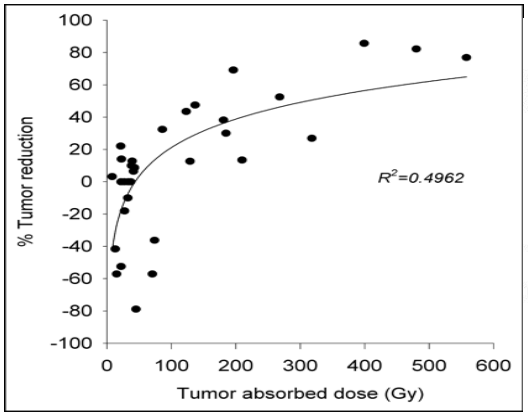
Table 7 Studies showing dose–effect relationships for radiopeptide therapy of NET

Reference	No. of patients	Radionuclide	Carrier	Endpoint	Threshold dose
[31]	13	^{90}Y	DOTA-octreotide	>20 % lesion shrinkage	230 Gy (tumour)
[33, 35]	18+25	^{90}Y	DOTA-octreotide	>20 % decline per year in creatinine clearance	35 Gy BED (kidneys) ED_{50}: 44 Gy BED (kidneys)
[32]	9	^{90}Y	DOTA-octreotide	50 % reduction in PLT	2 Gy (BM)
[34]	23/5	^{90}Y/^{177}Lu	DOTA-octreotide, DOTA-octreotate	Creatinine toxicity more than grade 1	28 Gy BED (kidney risk factors), 40 Gy BED (no kidney risk factors)

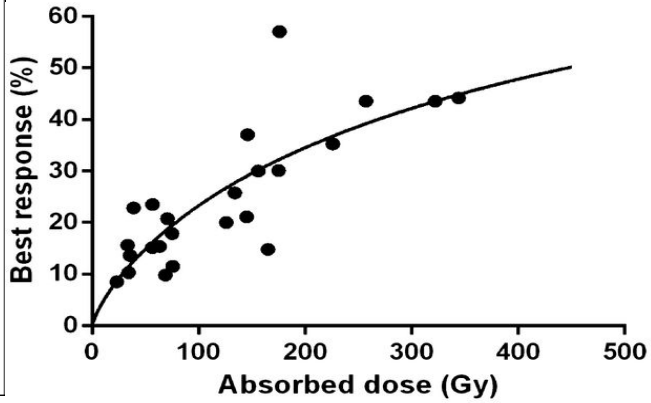
Renal toxicity
^{90}Y-DOTA-octreotide



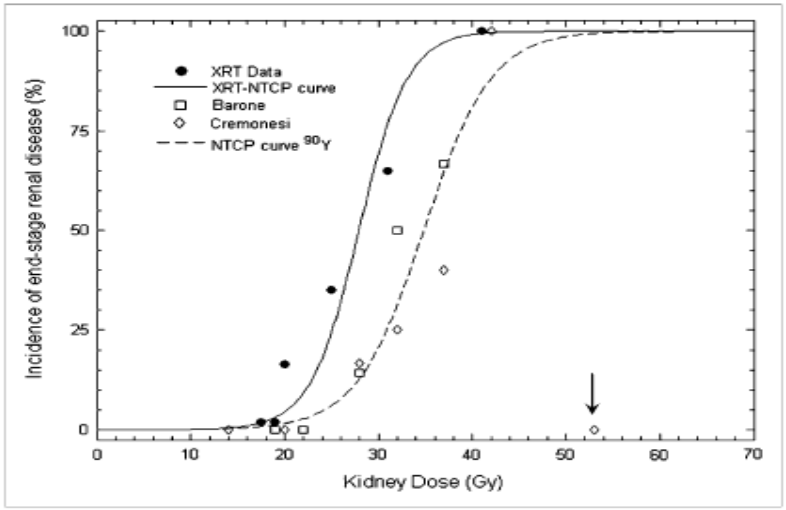
Tumour size reduction
^{90}Y-DOTA-octreotide

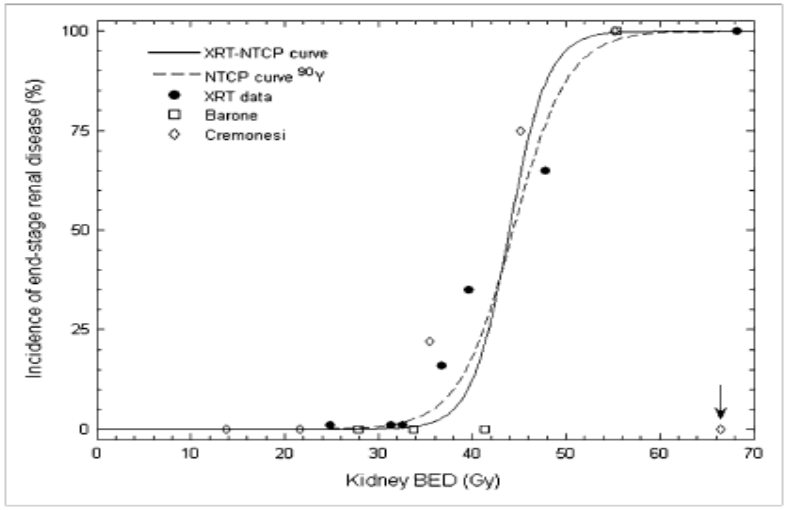


Tumour size reduction
^{177}Lu-DOTA-octreotate



Dose-effect relation for late occurring kidney toxicity after ^{90}Y-DOTATOC therapy





- Only patient-specific kidney dose shows correlation with toxicity
- Radiobiology explains shift from XRT curve, dose-rate effect

B. Wessels et al., MIRD pamphlet 20, J Nucl Med (2008) 49: 1884-1899

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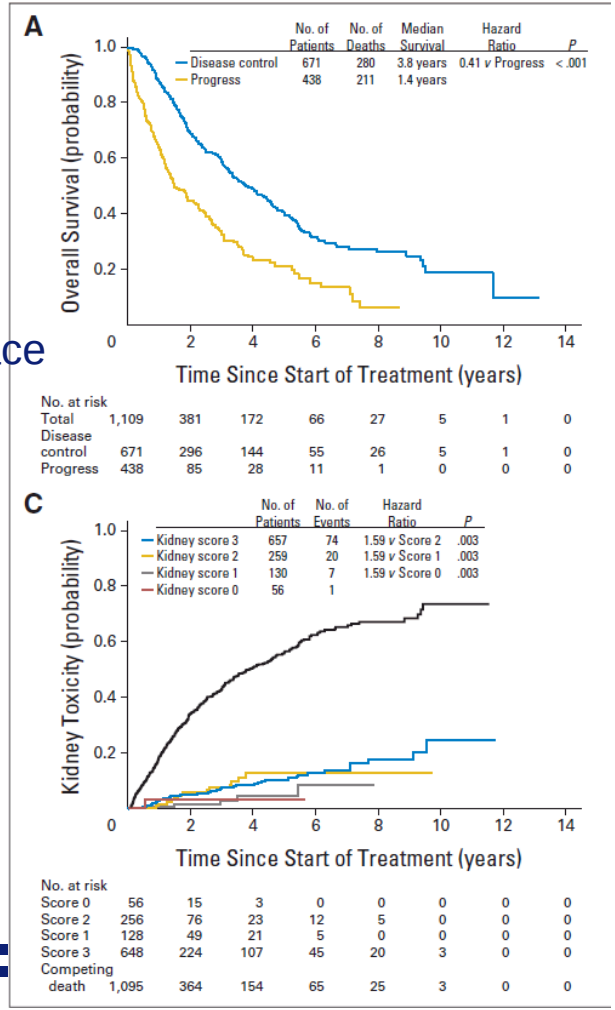
Phase 2 trial ^{90}Y DOTATOC

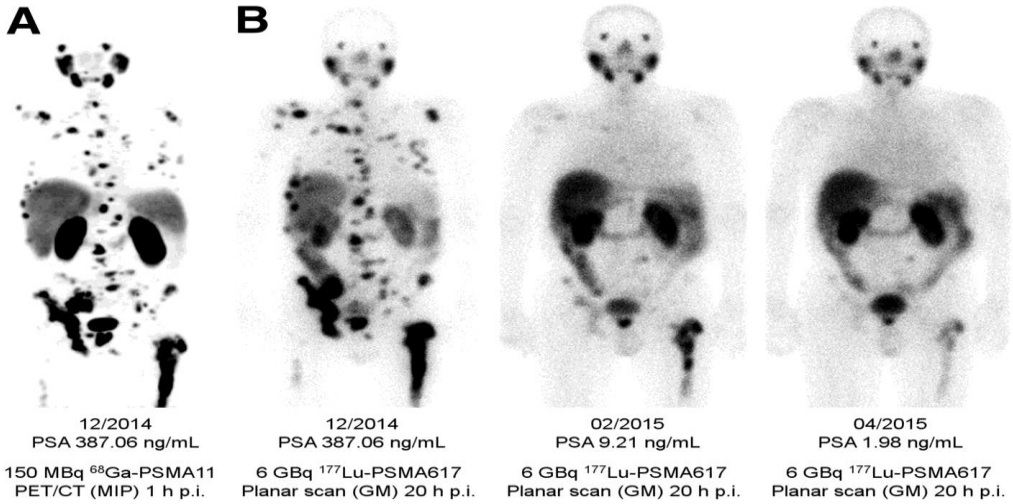
- 1109 Neuro-endocrine patients included
- Multiple cycles activity dosing 3.7 GBq ^{90}Y /m^2 body surface
- **Dosimetry unknown**
- Efficacy
  - 671 (61%) patients showed clinical response
  - Median survival 95 months
- Toxicity
  - 142 (13%) severe (grade 3/4) hematologic toxicity
  - **102 (9%) very severe (grade 4/5) renal toxicity**



A. Imhof et al., J Clin Oncol (2011) 29: 2416-2423

Study of ^{177}Lu-PSMA-617 In Metastatic Castrate-Resistant Prostate Cancer (VISION trial)

- 750 Prostate cancer patients
  - 500: 4 – 6 × 7.4 GBq ^{177}Lu-PSMA-617
  - 250: Best standard of care
- **No dosimetry**
- Study started 23 May 2018
- Estimated end date August 2020



ClinicalTrials.gov Identifier: NCT03511664

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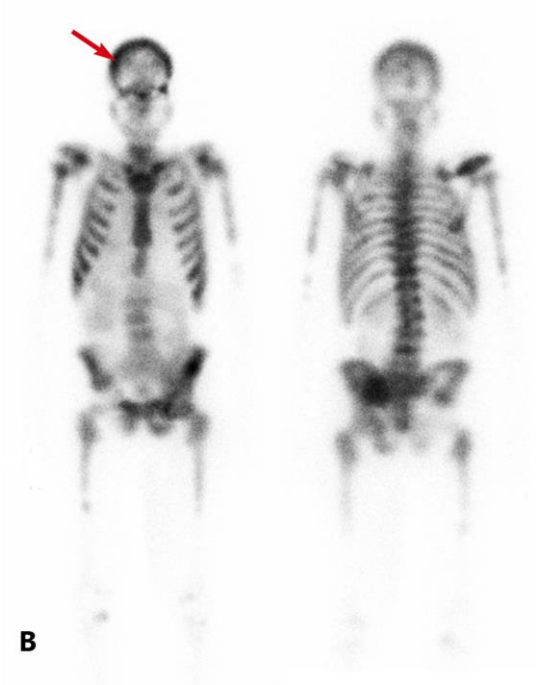
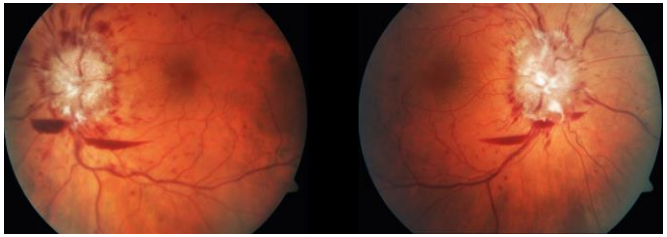
Case report
Visual deficit possibly caused by lutetium-177 PSMA treatment

A



B



- ***Optic nerve damage***
- **2 x 6 GBq ^{177}Lu-PSMA**
- ***Dosimetry unknown***
  - ***Optic nerve***
  - ***Lacrimal gland***

van Kalmthout L, et al. BMJ Case Rep 2018

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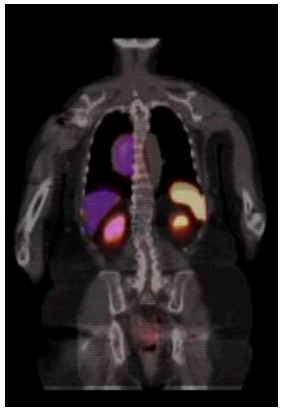
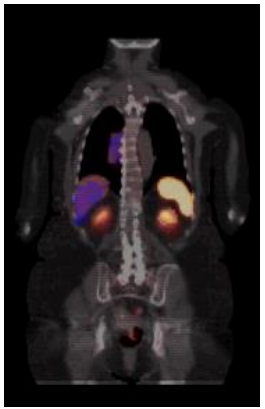
Dosimetry based decision on further therapy with ^{177}Lu-DOTA-octreotate

- Tumour ^{68}Ga-DOTA-octreotate positive PET
- Large tumour (120 cm^3) in thorax
- Proceed therapy 4 cycles of 7.4 GBq ^{177}Lu-DOTA-octreotate?

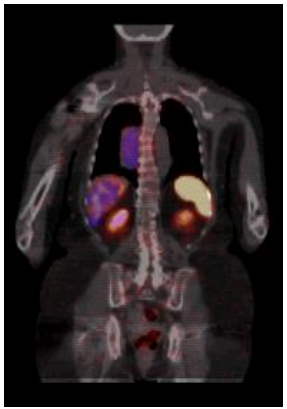
^{68}Ga PET/CT



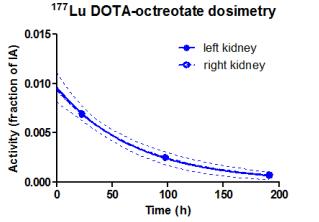
^{177}Lu SPECT/CT at 23 h



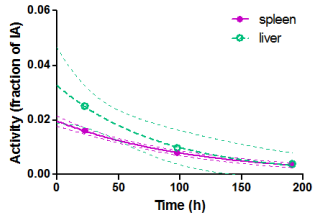
^{177}Lu SPECT/CT at 98 h

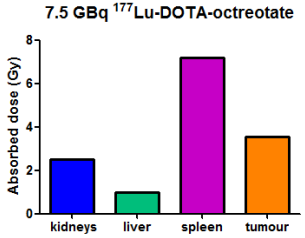


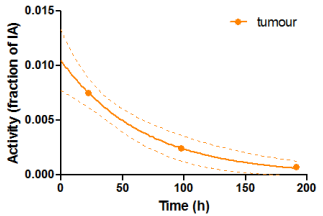
^{177}Lu SPECT/CT at 192 h



Tumour volume 120 ml

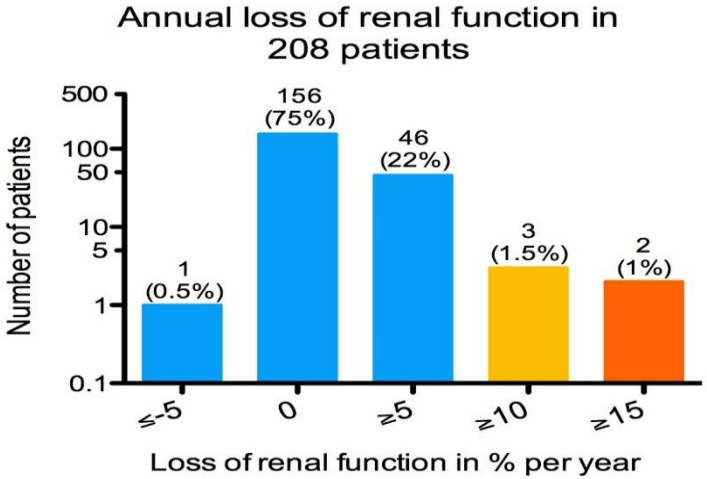




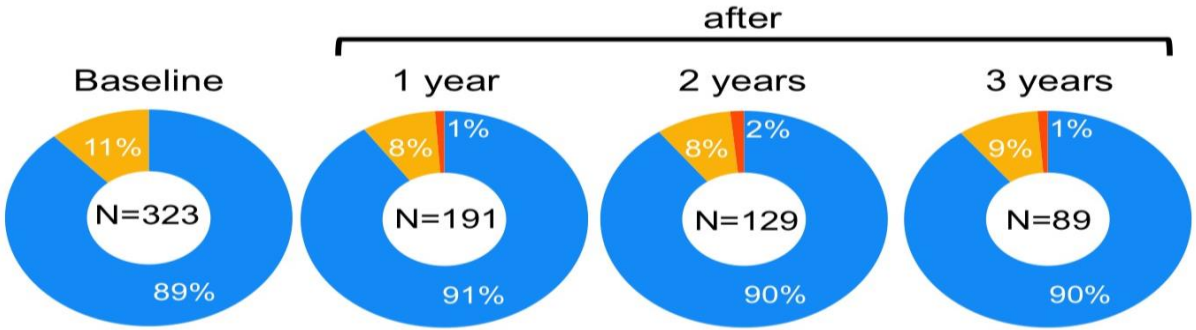


Tumour dose 3.5 Gy

How about nephrotoxicity after ^{177}Lu-DOTA-Octreotate?



- 323 patients *4 x 7.4 GBq*
- 228 patients with dose < 23 Gy
- Mean kidney absorbed dose
  - 20 ± 5 Gy (5 – 38)
- 191 ≥ 1 y follow-up



H Bergsma et al., Eur J Nucl Med Mol Imaging (2016) 43:1802–1811

Grade 1: ≥60 ml/min, Grade 2: 59-30 ml/min, Grade 3: 29-15 ml/min

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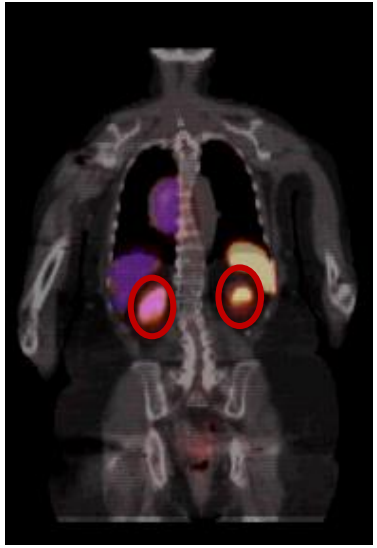
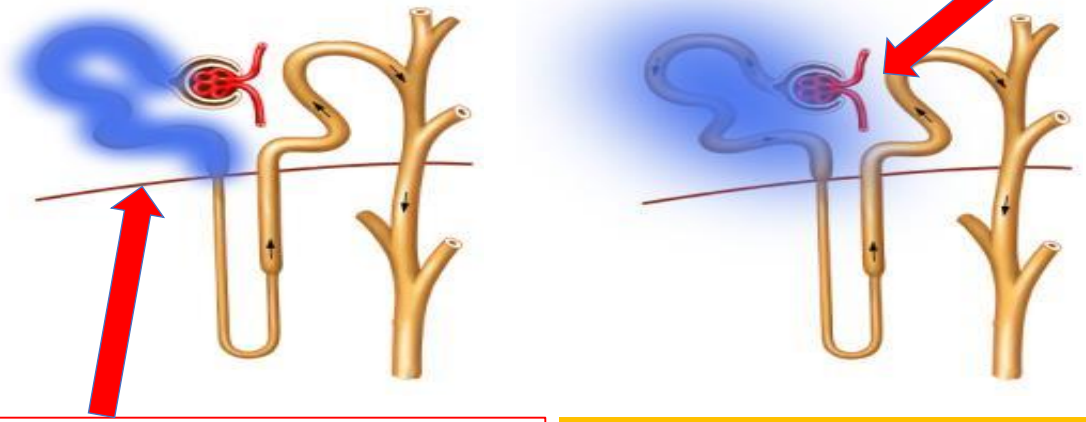
Kidneys – nephron uptake in proximal tubuli



^{177}Lu
R_{max} = 2 mm

^{90}Y
R_{max} = 11 mm



1. Glomerulus
Critical element

2. Tubular reabsorption of peptide

R_{max} = max range in tissue

Kidneys: Dose-limiting organ with ^{90}Y Peptide not with ^{177}Lu

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

Subacute hematologic toxicity

- in 34 / 320 (11%) patients
- Slight correlation with bone marrow dose

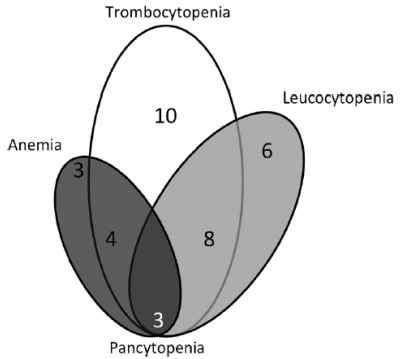

Fig. 2 Venn diagram of haematological toxicity (grade 3/4) in 34 out of 320 patients treated with a median cumulative dose of 29.6 GBq ^{177}Lu-DOTATATE

H. Bergsma et al., EJNMMI (2016) 43: 453-463

Persistant hematologic toxicity (leukemia / MDS)

- in 11 / 274 (4%) patients
- No correlation with bone marrow dose

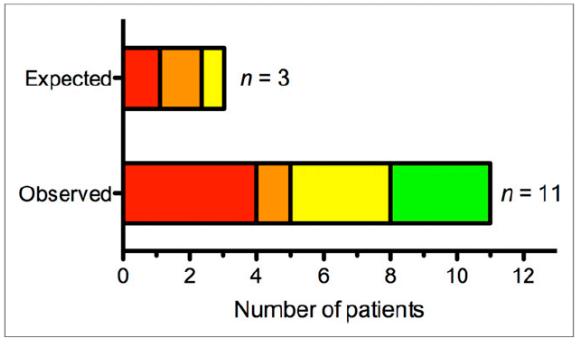

FIGURE 3. Expected number of patients with hematopoietic neoplasms and type, based on data from The Netherlands Cancer Registry, as well as observed number of patients (of 274 GEP NET patients) with PHD after PRRT with ^{177}Lu-DOTATATE, including 8 patients with hematopoietic neoplasms and 3 with BM failure. Red = MDS; orange = AML; yellow = MPN + MDS/MPN; green = BM failure.

H. Bergsma et al., J Nucl Med (2018) 59: 452-458

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Radiobiology for normal tissue and tumour dose response models

- External beam
- Brachytherapy

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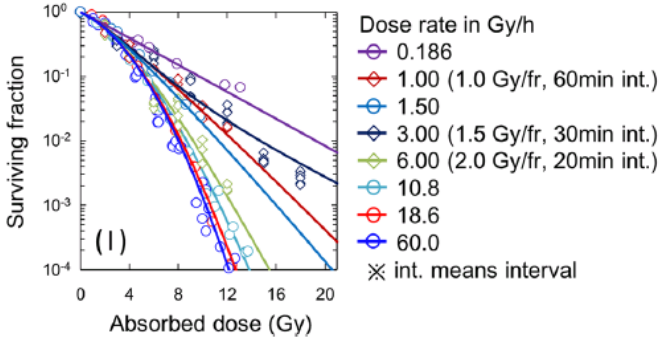
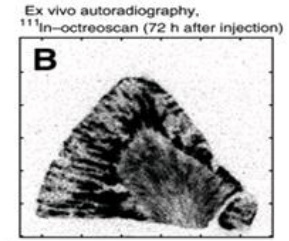
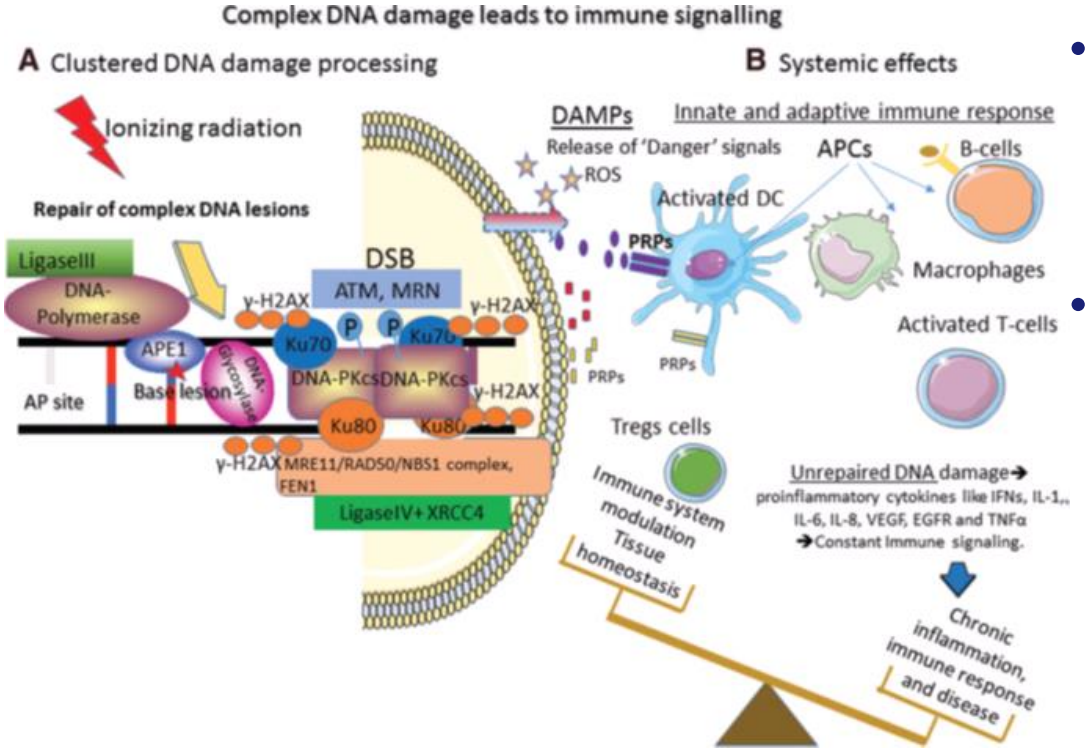
Radiobiology for molecular radiotherapy, unknown territory

- Dose rate effects (MRT: 0.5 – 0.01 Gy/h)
  - Prolonged irradiation with MRT
  - DNA damage repair process during dose delivery
  - Biologically Effective Dose LQ model
  - Lower limit in dose rate
  - RBE by high LET (α)
- Non-uniform absorbed dose distributions
  - Physiologically defined activity distribution
  - Short-ranged particle emitters (α: 10-50 μm, β: 0.01-10 mm)
  - Effective Uniform Dose model
  - Change in radiation response architecture
- Secondary biological effects induced by ionisation
  - Cellular adaptive response
  - DNA-mis repair leading to secondary effects





Radiobiology has more to offer...



- Cell damage by direct and indirect ionizing radiation effect in DNA, lipids, and proteins.
- Secondary cell damage by "danger" signals from irradiated to nonirradiated cells, leading to off-target effects (immune response).

J.P. Pouget et al., Antioxid. Redox Signal. 2018

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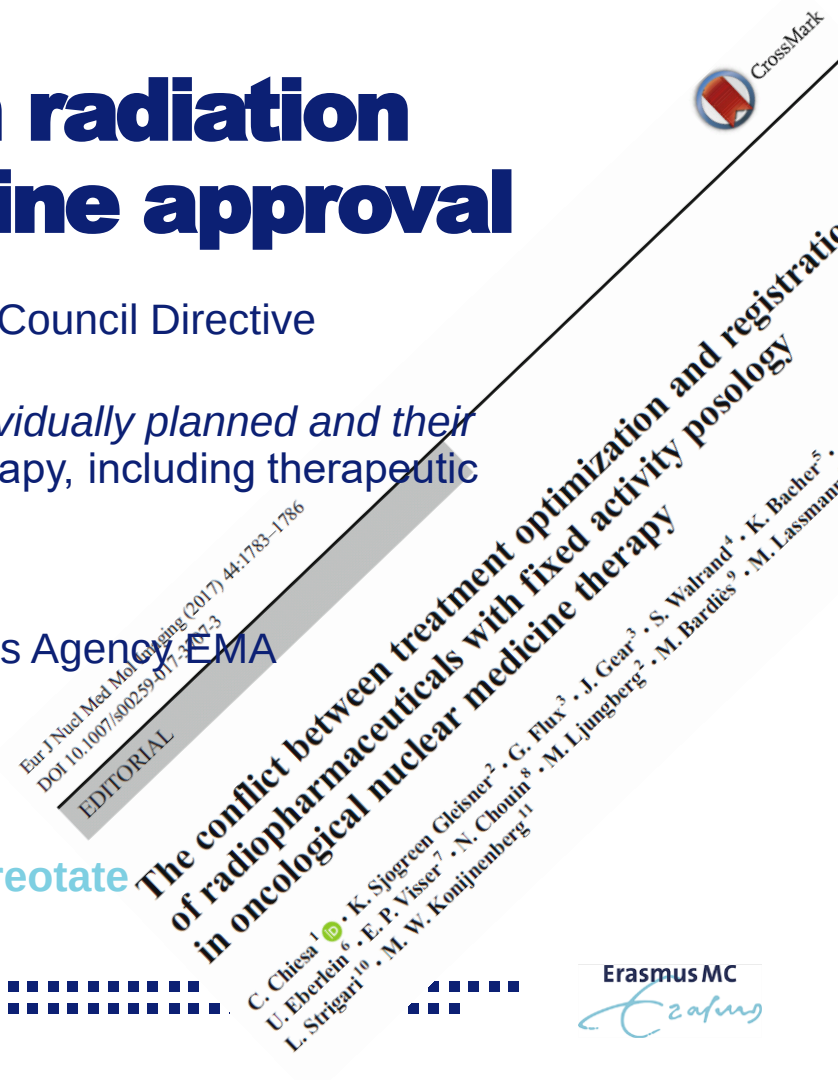
Conflicting legislation radiation protection and medicine approval

- Article 56 optimization of medical exposure in Council Directive 2013/59/Euratom
  - "*exposures of target volumes shall be individually planned and their delivery appropriately verified*" in radiotherapy, including therapeutic nuclear medicine.

- Market autorisation by the European Medicines Agency EMA
  - 13 November 2013:
  - **Xofigo - 6 x 55 kBq/kg ^{223}Ra**
  - 15 January 2018:
  - **Lutathera - 4 x 7.4 GBq ^{177}Lu DOTA-octreotate**



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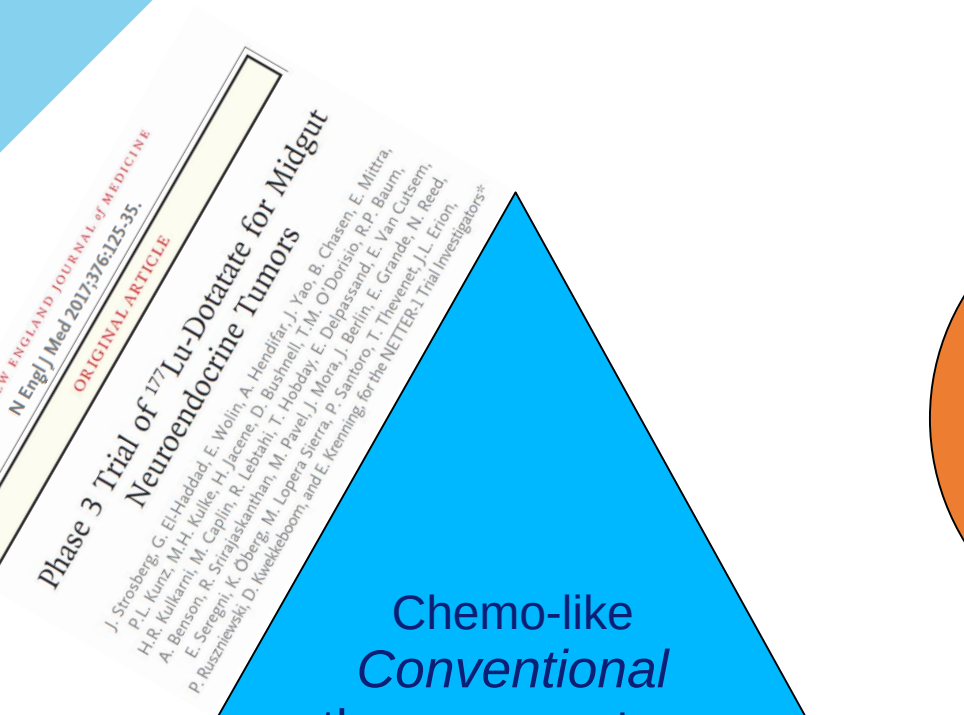

Chemo-like
Conventional
therapy posology

- *7400 MBq*
- Per BW
- *Per BSA*
- Cohort dosimetry

BSS 2013/59
EU directive:
..exposures of target volumes shall be individually planned..

MRT
Personalized
therapy posology

- *Patient-specific dosimetry*
- to tolerance (NTCP)
- *Optimal efficacy*

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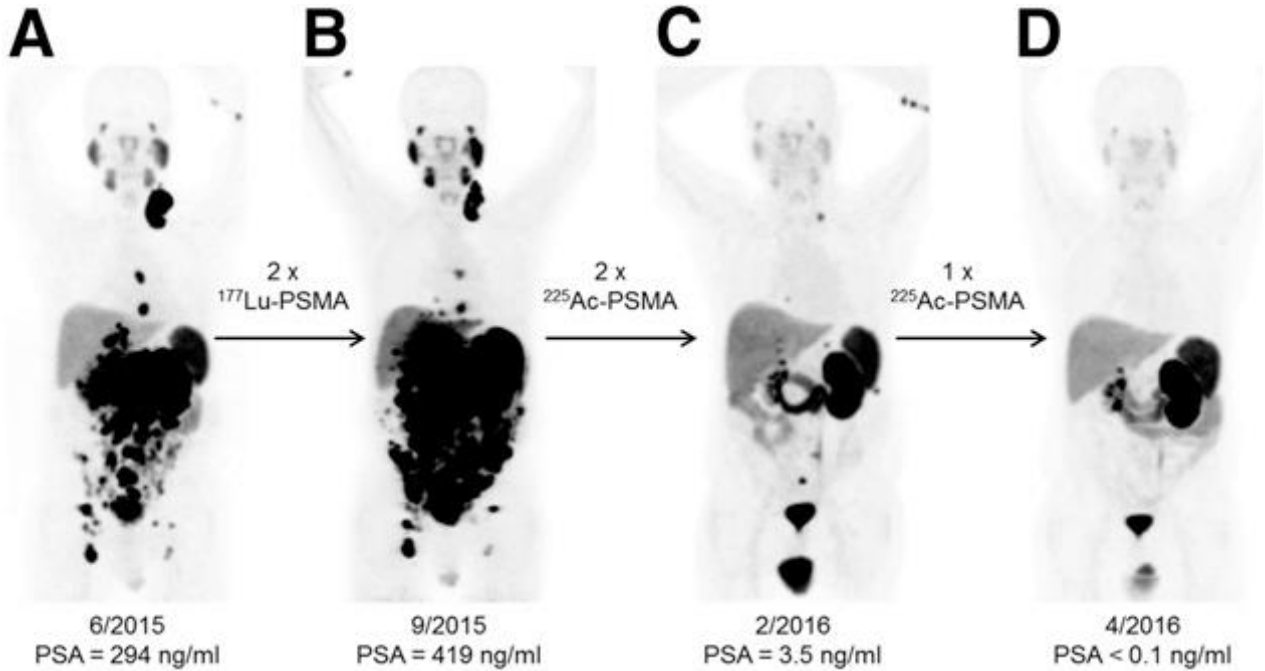
Alpha-particle therapy with ^{225}Ac-PSMA

Use of high LET-radiation with α-particle emitters

- Impressive results with ^{225}Ac PSMA in patients
- Salivary gland damage
- Dosimetry ?



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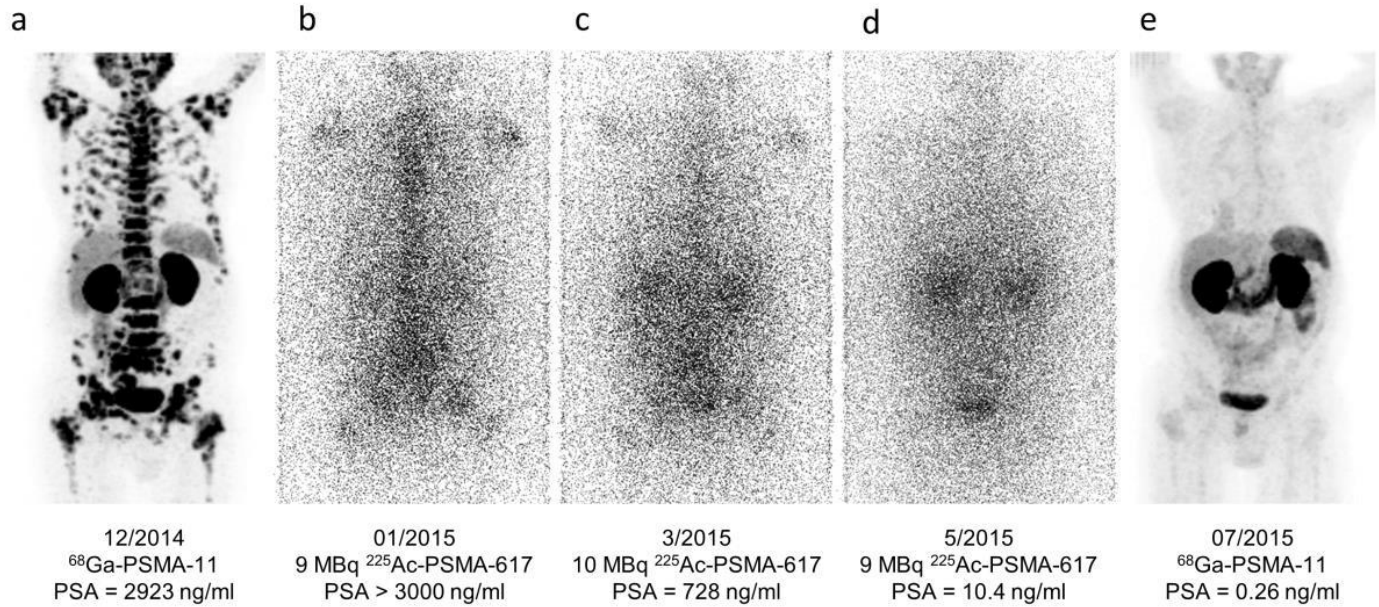
Kratochwil et al., J Nucl Med 2016; 57:1941–1944

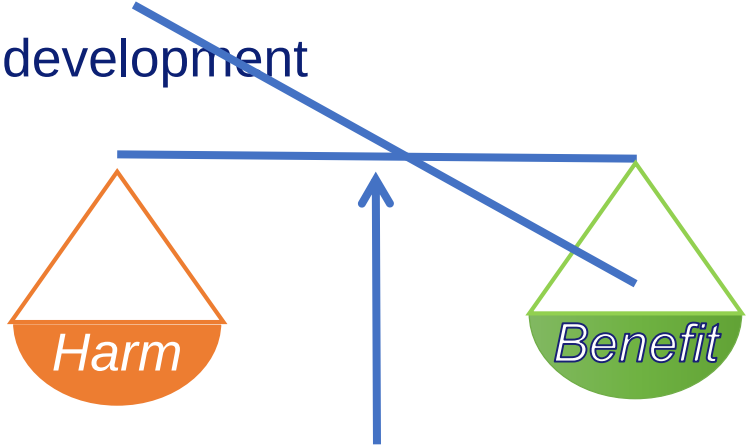
Post-therapy imaging ^{225}Ac PSMA



Kratochwil et al., J Nucl Med 2017; 58:1624–1631

Does individual dosimetry based treatment planning for MRT improve patient care?

- It is hardly routinely being performed
  - Radioactive chemotherapy or molecular radiotherapy?
  - Follow package insert or apply patient specific therapy?
- Standardisation of dosimetry methods is needed
- Dosimetry guided clinical trials for drug development
  - Adaptive dose response models
- Prospective clinical trials needed
  - Comparing dosimetry and activity
  - Increase in survival?



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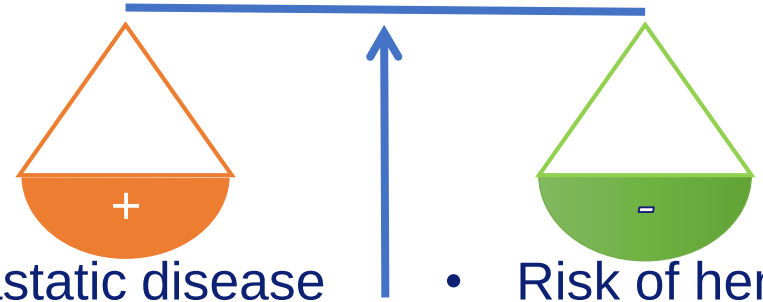
Risks of radionuclide therapy



- Cure of metastatic disease
- See what you treat
- Option for patient-specificity
- Many new developments

- Risk of hematologic toxicity
- Risk of renal / salivary damage
- Need for radiobiology
- Difficulty in detecting α-emitters

Molecular radiotherapy: patient care you can see and personalize

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Open for your opinion and discussion …