The Abdus Salam
International Centre for Theoretical Physics

International Atomic Energy Agency

Joint ICTP-IAEA Advanced School on Internal Dosimetry

Trieste, 12 - 16 April 2010

Dosimetry in radiopeptide treatments with somatostatin analogues

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Dosimetry in PRRT:

what for ?

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Dosimetry has the purpose to address…

- **Which peptide?**
- **Which radionuclide?**
- **Inhomogeneous activity/dose distribution?**
- **How to improve dosimetry accuracy?**
- **Radiobiological models ?**
- **Therapy schedules?**

***goal*: to improve trial designs**

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Data collection for dose estimates

- **Pharmacokinetics**

  blood clearance → radiation impact on bone marrow, (TB)

  excretion rate → radiation impact on u.bladder, kidneys, (TB)

- **Biodistribution vs. time**

  planar, SPECT imaging

- **Normal organ and tumour masses**

  CT, NMR

Most Used Radiopeptides for PRRT

characteristics already well known…

$E_{\beta\ max}$	2.3 MeV
$R_{max,\beta}$	~ 11 mm
R_{mean}	~ 4 mm
$T_{1/2\ phys}$	64 h

^{90}Y

^{90}Y-DOTATOC

[^{90}Y-DOTA^{0}-Tyr^{3}]-octreotide

Bremstrahlung, →
Cross-fire

Bremstrahlung,
images....

$E_{\beta max}$	0.5 MeV
E_{γ}	0.11, 0.21 MeV
$R_{max,\beta}$	~ 2 mm
$T_{1/2\ phys}$	6.7 d

^{177}Lu

^{177}Lu-DOTATATE

[^{177}Lu-DOTA^{0}-Tyr^{3}]-octreotate

Less cross-fire

Imaging !!!

imaging/ therapy with the same complex

…others: **Lanreotide, ^{90}Y-DOTATATE, Octreoscan©…**

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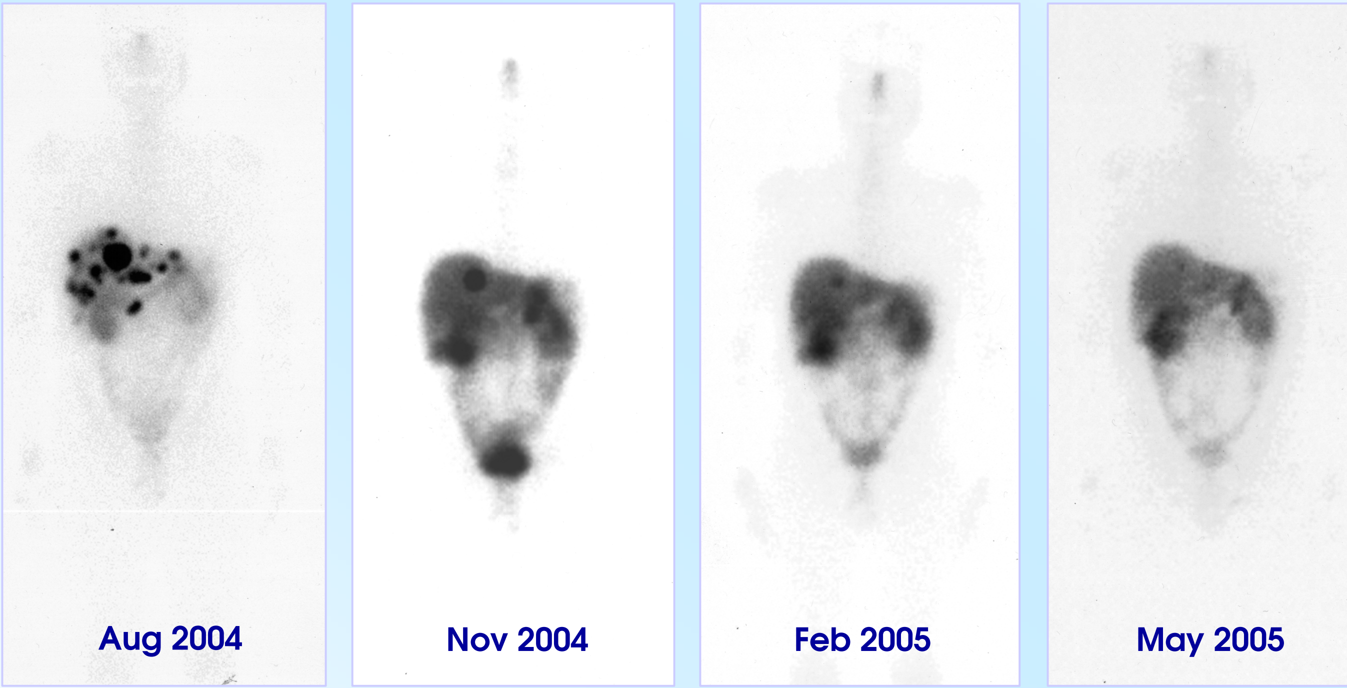
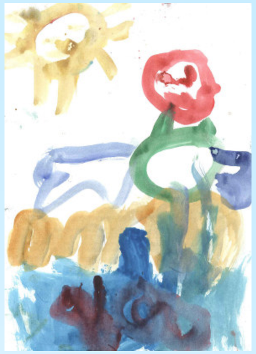
To simulate ^{177}Lu-PRRT…

imaging ^{177}Lu γ, β^{-}

physical characteristics enable imaging/ therapy with the same complex enriching the response evaluation of ^{177}Lu-PRRT



Uptake variation in tumour & organs with cycles can also be evaluated
Limited tumour bulky represents a favourable prognostic factor



How to simulate

^{90}Y-PRRT ?

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How to simulate ^{90}Y-PRRT …?

imaging ^{111}In

To avoid the well known difficulties of Bremstrahulng imaging: alternative methods…

most practical solutions

Bremstrahulng

^{111}In-pentetreotide (Octreoscan)

Its use is recommended for patients recruitment only, not for practical dosimetry.

Different peptides lead to different chemical behaviour.

.. doses to kidneys, spleen overestimated; doses to tumour free liver underestimated.

^{111}In-derivative

The same compound used for PRRT labelled with ^{111}In is a good surrogate for dosimetry purposes

gamma emission; T_{phys} close to ^{90}Y, compatible with peptide T_{biol}

SPECT resolution

^{111}In has similar chemical behaviour to ^{90}Y…

Similar or identical ?

To simulate ^{90}Y-PRRT…

imaging ^{86}Y γ, β^+

^{86}Y-derivative

Eur J Nucl Med (2003) 30:354–361

The same compound for PRRT labelled with ^{86}Y: chemical structure totally preserved!

Gold standard for dosimetry purposes?

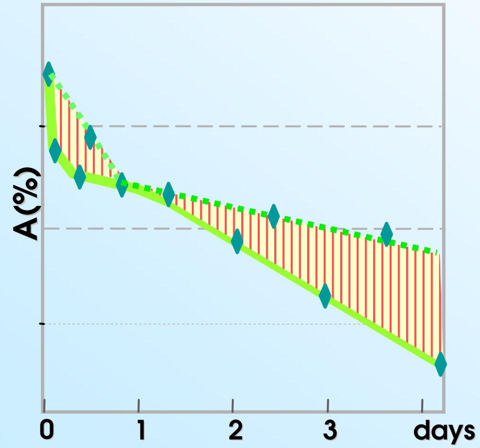
behaviour identical to ^{90}Y; PET resolution

as compared to peptide T_{biol},

T_{phys} (14.7 h) low

Low abundance

→ late information lost!

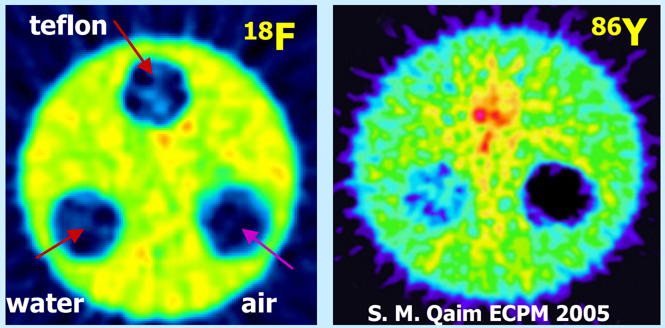


Scarse availability

High energy γ rays

prompt

false activity in bone marrow if no appropriate corrections



E_{max} 1.2, 1.5, 2.0; E_{γ} 0.6, 1.1, 1.2, 1.9MeV

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^{90}Y-Bremsstrahlung difficulties…

To avoid the "well known" difficulties of Bremsstrahulng imaging, quantification…

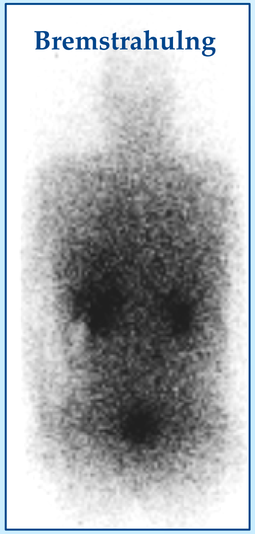
…alternatives give adantages and drawbacks

^{111}In-pentetreotide (Octreoscan®)

^{86}Y-derivatives

^{111}In-derivatives

^{68}Ga-derivatives



However…

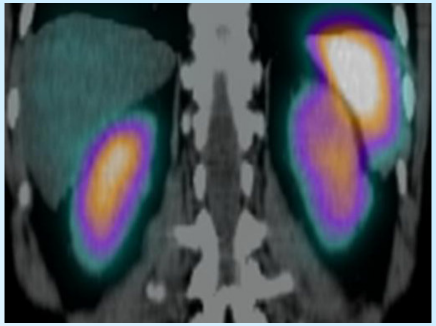
is "this" Bremsstrahlung present or almost past ?

Helish, et al. EJNMMI 2004;1386-92.

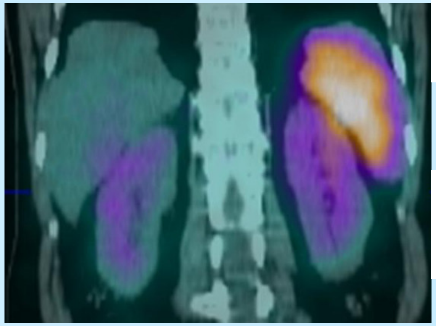
Cremonesi, et al. QJNM 2010

Bremsstrahlung imaging: work in progress

SPECT-CT



Octreoscan® - 185 MBq



^{90}Y-DOTATATE - 1.7 GBq

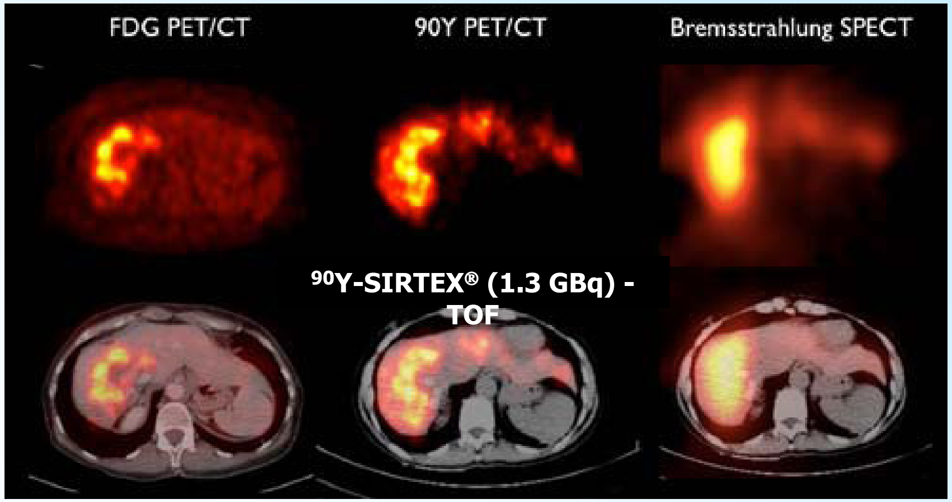
Quantitative Analysis of ^{90}Y Bremsstrahlung SPECT-CT Images for Application to 3D Patient-Specific Dosimetry

Fabbri, et al. Cancer Bioth. Radiopharm 2009, 145-54.

SPECT/CT ^{90}Y-Bremsstrahlung images for dosimetry during therapy

Fabbri, et al. Ecancermedicalscience,2008. 2, n.106.
ww.ecancermedicalscience.com/tv

PET-CT



Yttrium-90 TOF PET scan demonstrates high-resolution biodistribution after liver SIRT

Lhommel, et al. EJNMMI 2009:1696

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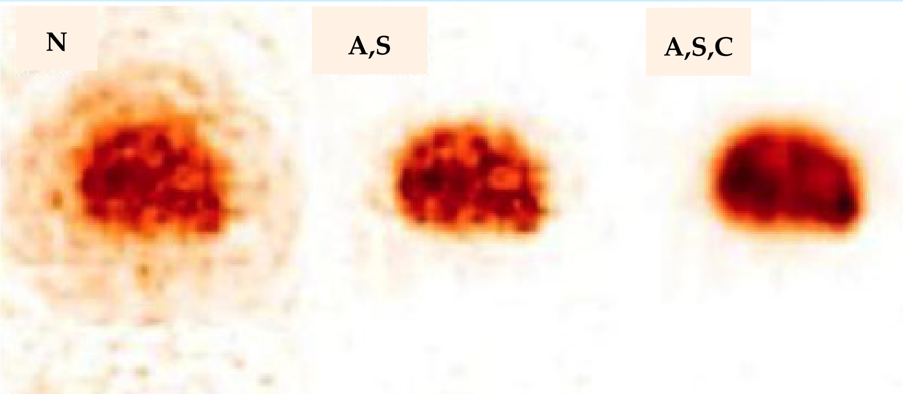
…further processing Bremsstrahlung images

Lund University, Sweden

Evaluation of quantitative ^{90}Y SPECT based on experimental phantom studies

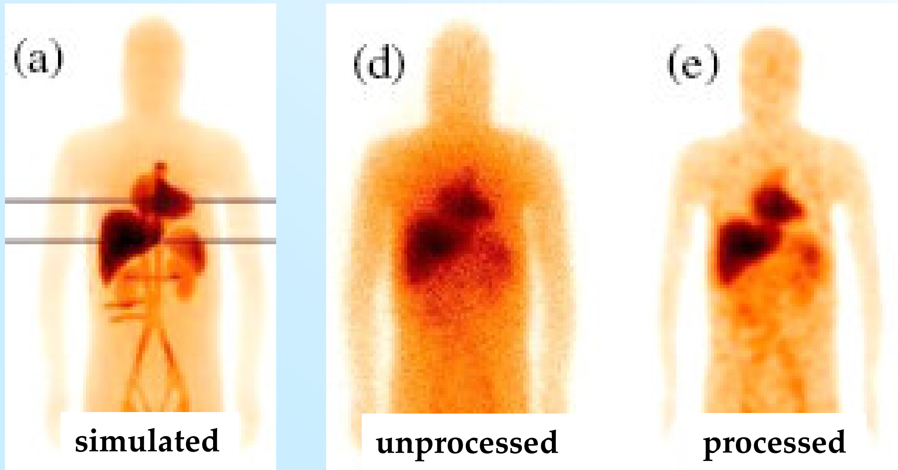
Minarik et al. Phys Med Biol 2008, 5689-5703



N:not corrected; A:attenuation, S:scatter, C:ollimator corrected

Evaluation of quantitative planar ^{90}Y bremsstrahlung whole-body imaging

Minarik, et al. Phys Med Biol 2009, 5873-5883.



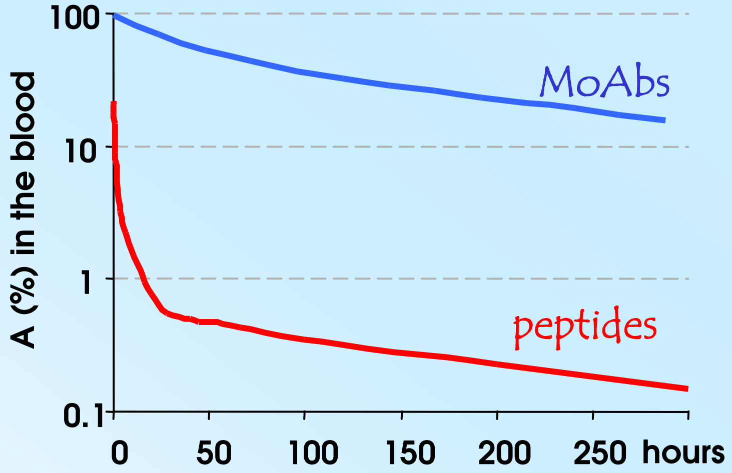
→ "It is possible to omit ^{111}In- for imaging during therapy"

^{90}Y-imaging is most promising and might become the future standard approach

What's well known

Typical blood clearance of peptides

Blood clearance - biological curve



relatively low RM dose predicted

^{90}Y → $ND_{peptides}$ ~ 0.2 h

^{90}Y → ND_{MoAbs} ~ 2.5 h

A_{blood} ⇨ $A_{red\ marrow}$

ND_{blood} ⇨ ND_{RM}

accepted model:

$$A_{RM} = f \times \frac{m_{RM}}{m_{blood}} \times A_{blood}$$

peptides f ~ 1

(MoAbs f ~ 0.3)

Forrer F, et al.

Eur J Nucl Med Mol Imaging. 2009

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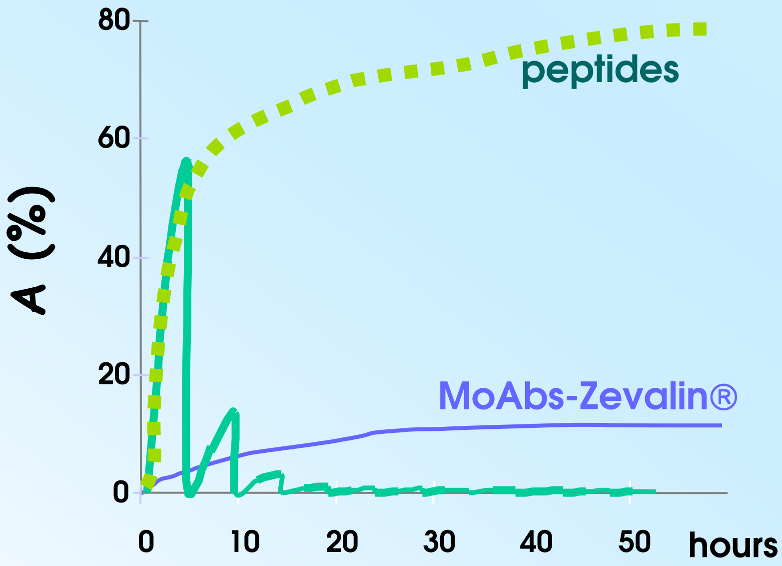
Typical elimination of peptides

Urine collection



% A cumulative elimination

% A in the urinary bladder

(u. bladder dynamic model MIRD 14)

fast and prevalent elimination

trhough the urine:

➔ not negligible absorbed dose to U. bladder

➔ KIDNEY…

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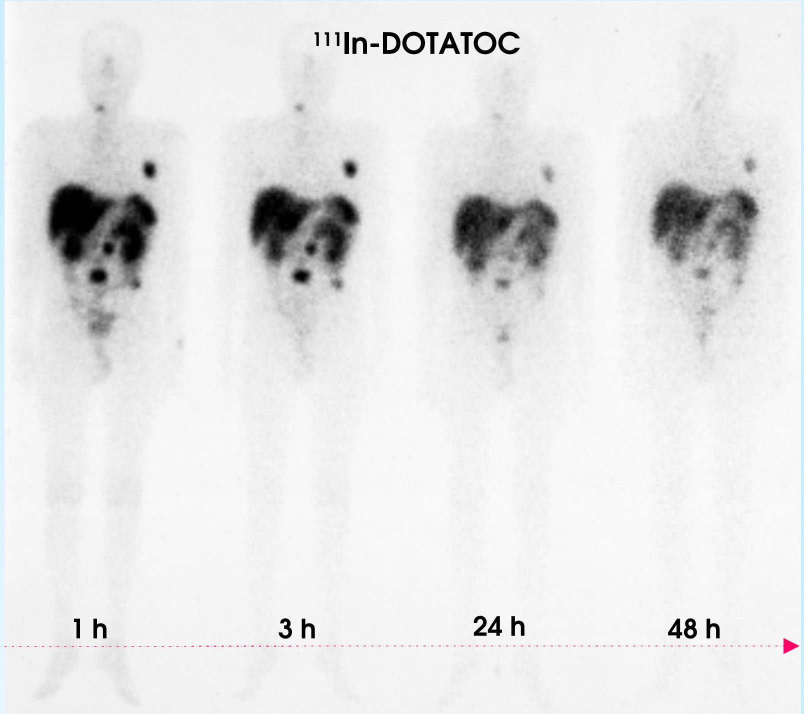
Typical biokinetics of peptides



Major source organs:

spleen, kidneys, liver, (testes)
+
TB, u.bladder, RM…

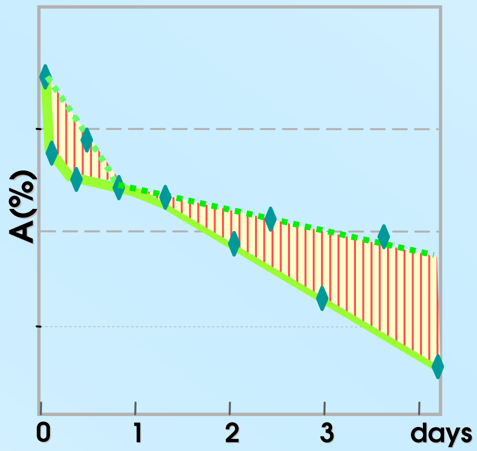
METHODS:

- Trasmission scan for attenuation correction
- Serial scintigraphic images WB, SPECT
- CT for mass determination

A(t) for all source organs:

↓

mean dose /dose distribution



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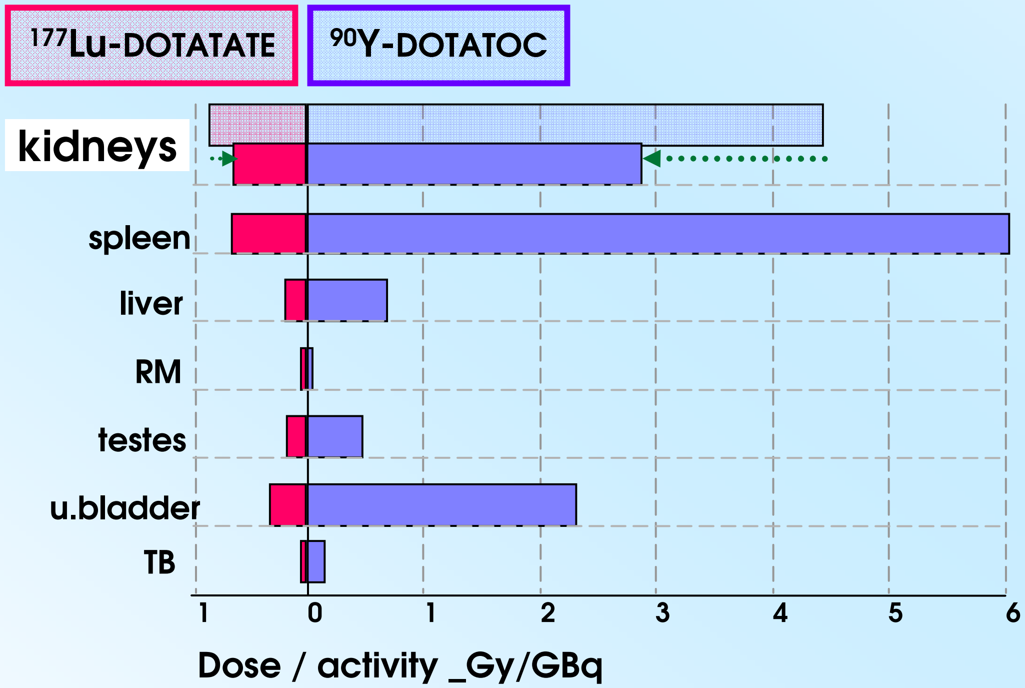
Mean Doses / Activity

major characteristics



Tumours (2-42) (0.6-56) Gy/GBq

for both radiopeptides:

← **KIDNEYS are the critical organs, despite the renal uptake reduction**

reduction of 25% - 65%

← **relatively low dose to RED MARROW (RM)**

← **large variability in tumour doses**

Typically, for cumulative activity of 11 GBq

Kidneys	27 Gy	with protection
RM	0.4 Gy	

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Cremonesi et al. QJNM 2010

^{90}Y- & ^{177}Lu-PRRT schemes commonly applied

Injected activities, number of cycles, time interval between cycles

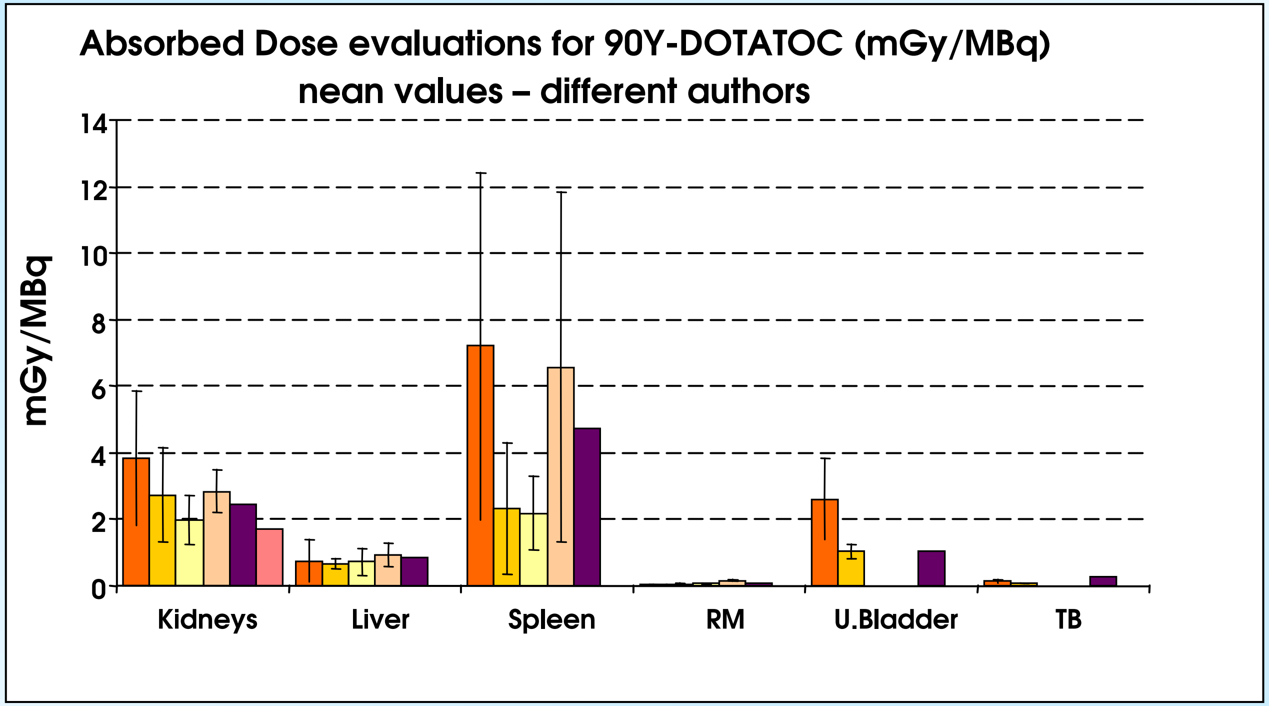
^{90}Y-PRRT				^{177}Lu-PRRT			
n. of cycles	**A/cycle**	**A tot**	**Time interval (weeks)**	**n.of cycles**	**A/cycle**	**A tot**	**Time interval (weeks)**
4	0.925-1.85-2.78-3.7 GBq/m^2	up to 32 GBq	6-9	4	3.7-7.4 GBq	22.2-29.6 GBq	6-10
3	1.11-2.59 GBq		6-9	4	5.2-7.4 GBq	22.2-29.6 GBq	8-12
2	2.96-5.55 GBq		6-9	4-7	3.7-5.2 GBq		8-12
$\geq$ 4		3.9-8.9 GBq/m^2 6.1 $\pm$ 1.3 GBq/m^2	6				
4	1.85 GBq	7.4 GBq	6				

All these are empirical schemes, mostly based on standard activities

However, in PRRT, dosimetry evaluations have been seriously taken into account to plan therapy, due to some first serious side effects .This has allowed to improve information for future therapies.

Cremonesi et al. QJNM 2010

Meaning of mean doses among patients



?

To optimise risks vs. benefits balance,

TREATMENTS NEED TO BE PERSONALISED

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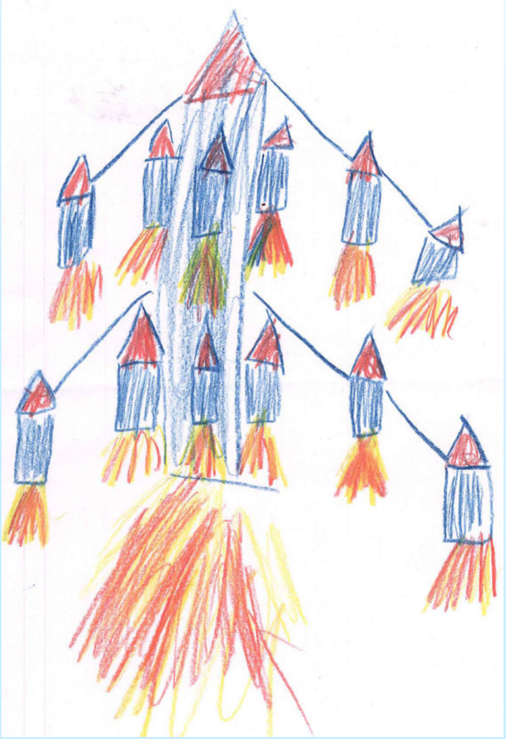
What's new ?

improvements

open questions

future aims



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1. Which peptide?

dosimetry providing information

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DOTATOC or DOTATATE ?

Esser et al. EJNMMI 2006, 1346-51

comparing τ residence times of ^{177}Lu-peptides

	Tumour			Kidney			Spleen		
	DOTATOC	DOTATATE	TATE:TOC	DOTATOC	DOTATATE	TATE:TOC	DOTATOC	DOTATATE	TATE:TOC
Mean±SEM	0.36±0.16	0.60±0.25	2.1	0.37±0.03	0.51±0.06	1.4	0.89±0.22	1.31±0.34	1.5
P value		0.016			0.016			0.016	

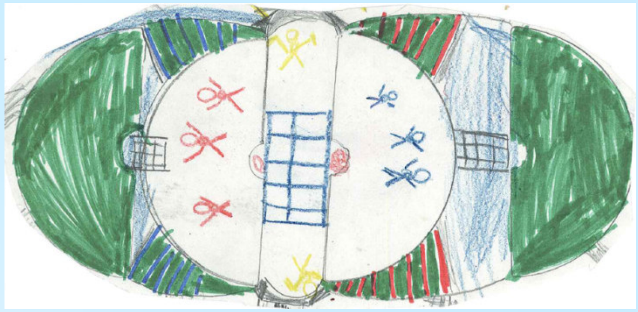
Bodei et al. J Endocrinol Invest 2008, 360-9

- τ for DOTATATE → higher tumor doses but also higher renal doses
- due to the higher tumor dose, ^{177}Lu appears more beneficial to label DOTATATE
- in view of higher renal dose, ^{90}Y appears more convenient to label DOTATOC

1. Which peptide ?

2. ^{177}Lu or ^{90}Y ?

dosimetry providing information



^{177}Lu vs. ^{90}Y -peptides ?

From previuos experimental data:

Tumor/kidney dose ratio is not always in favour of the same radionuclide

⇩

Benefit/risk balance needs to be established for each patient

^{177}Lu- **vs.** ^{90}Y- **DOTA-peptide**

However, it was noticed an advantageous ratio for Lu in case of smaller tumours, for Y for bigger tumours

the answer: it depends!…

Tumours **Kidneys**

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^{177}Lu vs. ^{90}Y?

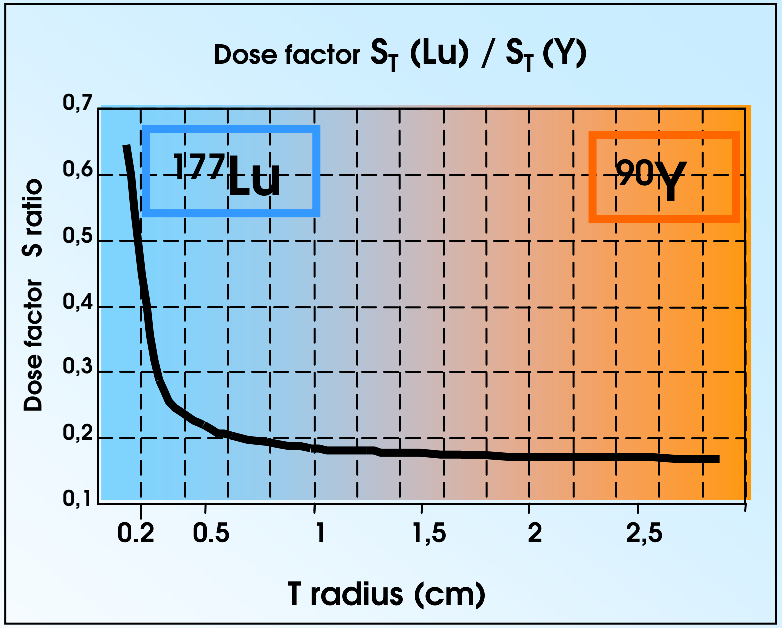
Tumours

Dosimetry

^{90}Y-DOTA-peptide → for big lesions

^{177}Lu-DOTA-peptide → for small lesions

Dose factors S



+

Morfology, receptors…

other essential factors influencing:

- Receptor density
- Vascularity
- Kinetics
- Specific Radiosensitivity
- Tumour dimension

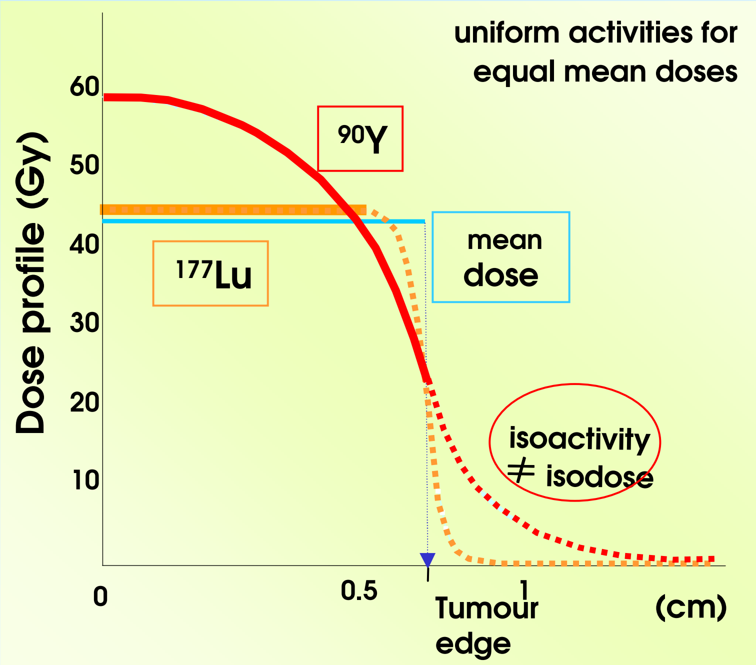
Uniformity ?

Small T: probably more uniform

Big T: …anarchy

Cross fire properties could compensate non uniformity…

Cross-fire contribution ?



^{90}Y **higher dose in the core**
edge: dose < mean dose

^{177}Lu **higher UNIFORMITY inside**
inside: dose ≈ mean dose

Mean dose representativity…

…very radionuclide dependent

… hardly influenced by activity distribution

^{90}Y cross-fire can be a trump card to be played against non uniformity in tumours…

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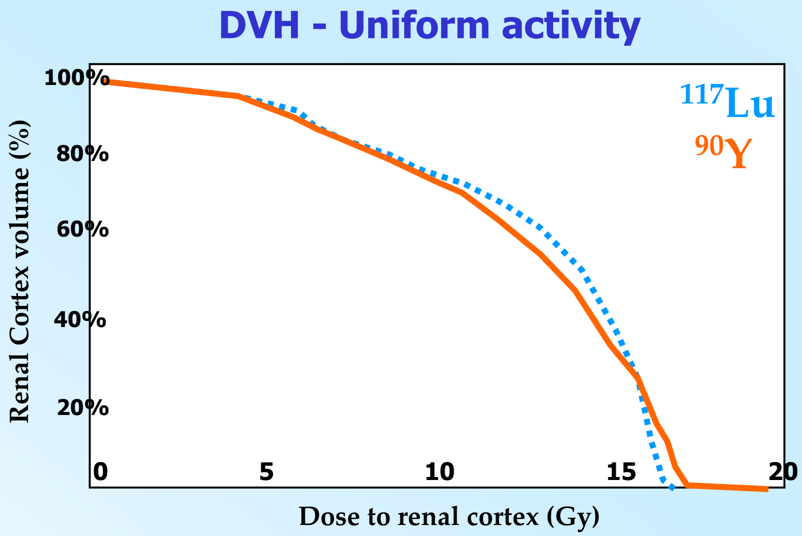
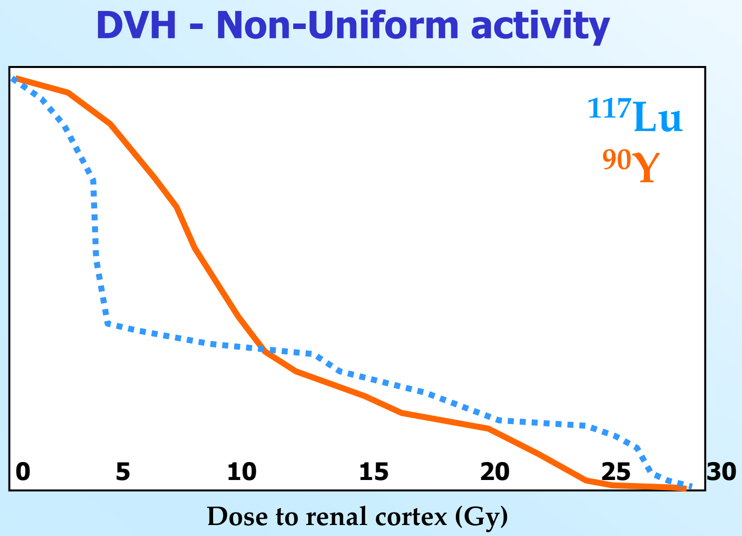
Botta F et al. EJNMMI 2008, 35(2):S201

^{177}Lu vs. ^{90}Y?

Kidneys

Also in kidneys the choice of the radionuclide can make the difference for the kidney safety; this is strictly related to dose distribution





The model would indicate

renal burden

- **non uniformity < uniformity**
- **non uniformity: ^{177}Lu < ^{90}Y**

???

To be verified

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Konijnenberg et al. J Nucl Med 2007;134-42
Wessels et al. J Nucl Med 2008;1884-99
Cremonesi et al. EANM 2009

1. which peptide ?

2. ^{177}Lu or ^{90}Y ?

3. dose distribution ?

advances in dosimetry

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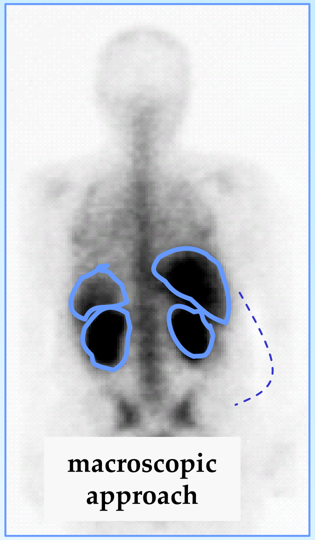
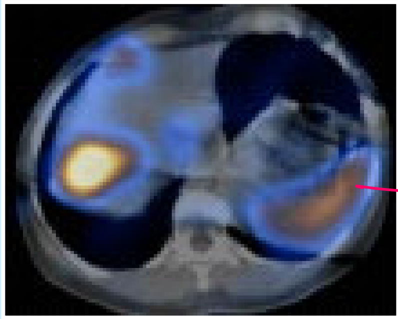
looking for activity distribution…

To improve accuracy, looking for a specific activity and dose distribution analysis:

Standard dosimetry → Voxel dosimetry

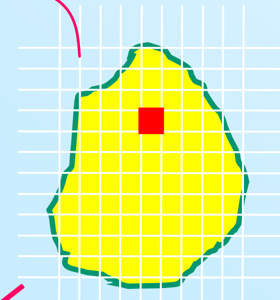


mean doses



MIRD formalism

using S values at voxel level



$$D_{(voxelk)} = A_o \cdot \Sigma_h \tau_{voxel,h} \cdot S_{(voxelk \leftarrow voxelh)}$$

dose distribution at voxel level

MIRD 17. Bolch, et al. JNM 1999;11S-36S.

A new tool available for voxel dosimetry

Literature provides S-factors for voxel dimensions not specifically corresponding to the ones used by nuclear medicine equipments. A specific calculation requires Monte Carlo simulation.

S-voxel factors now available on line for several voxel sides and radionuclides

just a click…

www.df.unibo.it/medphys

(link: Research → Voxel Dosimetry…)

2.33, 3, 4, 4.42, 4.8,
5, 6, 6.8, 9.28 mm ←------ *at moment* ------→ ^{90}Y, ^{177}Lu, + ^{89}Sr, ^{131}I, ^{153}Sm, ^{186}Re, ^{188}Re

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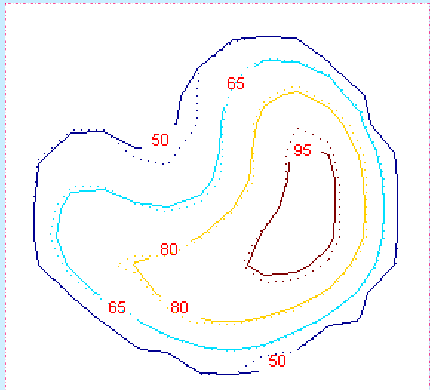
...towards dosimetry distribution

still too demanding ...

Activity distribution



Anatomical data - CT

direct MC simulations

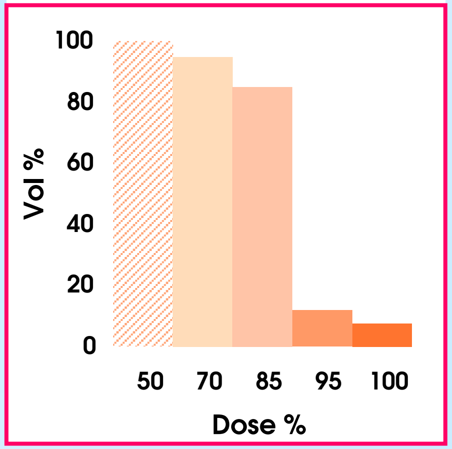
Svoxel

Voxel dosimetry

feasible

Dose distribution at the voxel level

DVH ...



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work in progress ...

Uniformity ?

- **Where ?**
- **How much?**
- **Can it affect response / toxicity?**
- **How to be included in radiobiological models?**
- **Is it possible to lower it ?   Is it worthwhile?**

These are still open questions in PRRT… work in progress…

→ the BED and EUD concepts, the Dose and BED volume hystograms represent most useful tools

radiobiological model equations

The following equations from the LQ model were applied to kidney and tumour doses for the different therapy schemes and the two radiopeptides

Biological-Effective-Doses(BED)

Kidneys

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

Tumour (including repopulation)

$$BED = D + \beta/\alpha \cdot \frac{T_{1/2rep}}{T_{1/2rep} + T_{1/2eff}} \cdot D^2 - \ln 2 \cdot \frac{\Delta T}{\alpha \cdot T_{av}}$$

Surviving-Fraction curves (SF%)

$$SF = \exp(-\alpha\ BED)$$

or, to consider in detail the variation of dose vs. time (D_t):

$$SF(D_t) = \exp(-\alpha D_t - g(t) \cdot \beta \cdot D_t)$$

$g(t) = A\ (1 - E_t + F_t)/H_t$

$A = \lambda_e/(\lambda_e + \mu)$; $E_t = 2 \cdot \lambda_e/(\lambda_e - \mu) \cdot \exp(-(\lambda_e + \mu) \cdot t)$;

$F_t = (\lambda_e + \mu)/(\lambda_e - \mu) \cdot \exp(-2\lambda_e \cdot t)$; $H_t = (1 - \exp(-\lambda_e \cdot t)^2)$

radiobiological parameters**

Kidneys		Tumours	
T_{repair}	2 h	T_{av}	10, 30, 60 days
α/β	2.5 Gy	α/β	10 Gy
α_{cortex}	0.06 Gy^{-1}	α_{tum}	0.3 Gy^{-1}

→ *clonogenic doubling time*

Bouchet et al. MIRD19 JNM 2003 1113-47

Dale Phys Med Biol 1996 1871-84.

Wessels et al. MIRD20 JNM2008 1884-99

1. which peptide ?
2. ^{177}Lu or ^{90}Y ?
3. dose distribution ?

4. Any Correlation ?

Radiobiological Models vs. Clinical Outcomes

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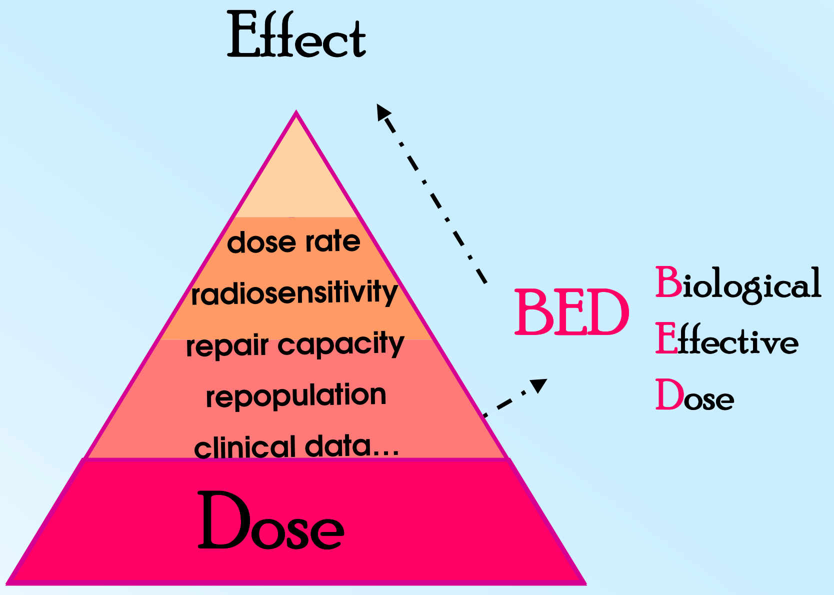
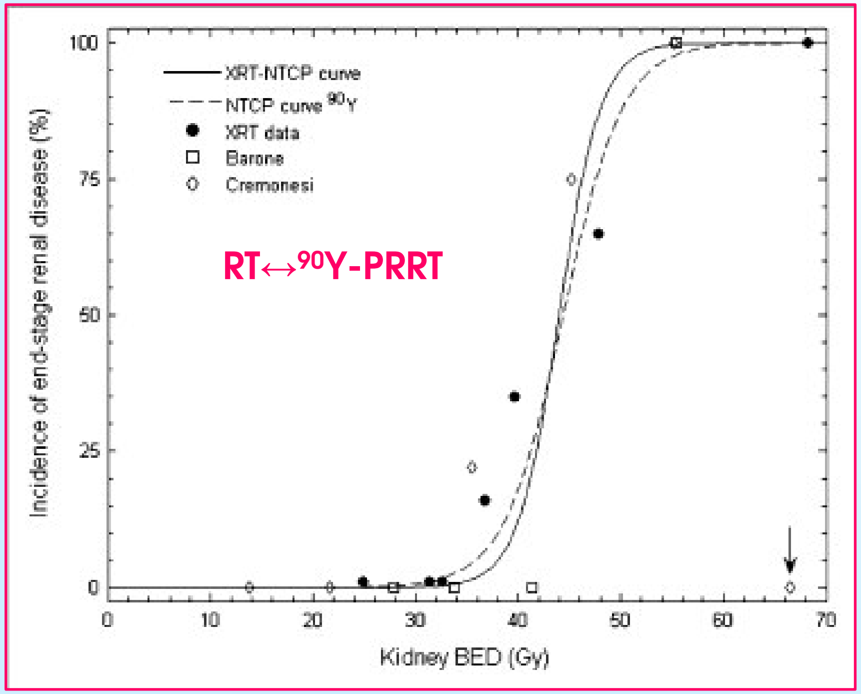
radiation nephropathy

any correlation?



RADIOBIOLOGY

BED in kidneys



unique NTCP curve for RT & PRRT

NTCP = Normal Tissue Complication Probability

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Wessels et al JNM 2008, 1884-99

cycles for safety

clinical results

Bodei L. et al.
EJNMMI 2008 1847-56

Pts with high absorbed doses and no toxicity received the activity fractionated in a high number of cycles and over a longer period

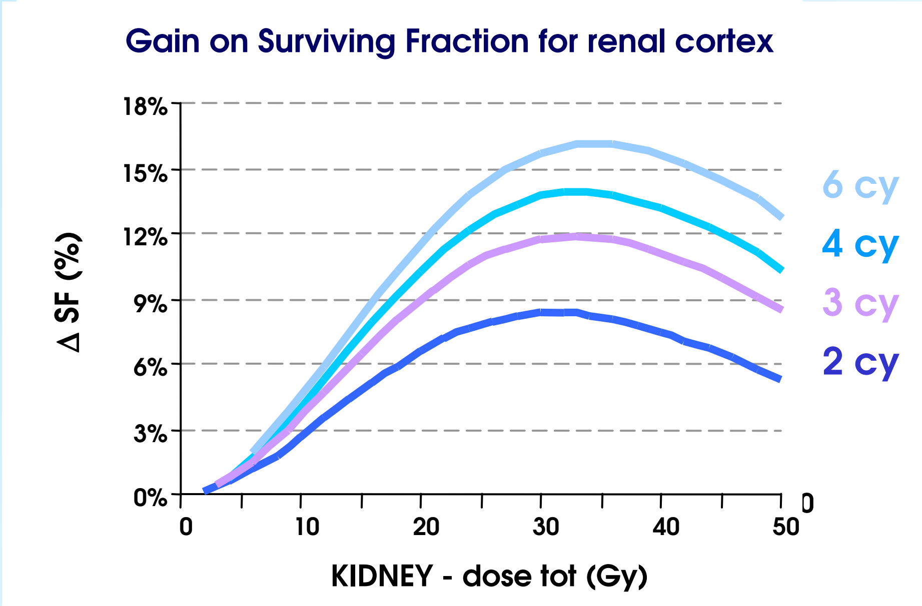
radiobiological model prediction/interpretation **BED (d×n) > n×BED (d)**

↑ fractionation:

2 options

lower IA/cycle
less damage
similar response

higher A_{tot},
same damage
improved response



Multicycles allow a renal cell sparing up to ~ 15%

Kidneys: side effects

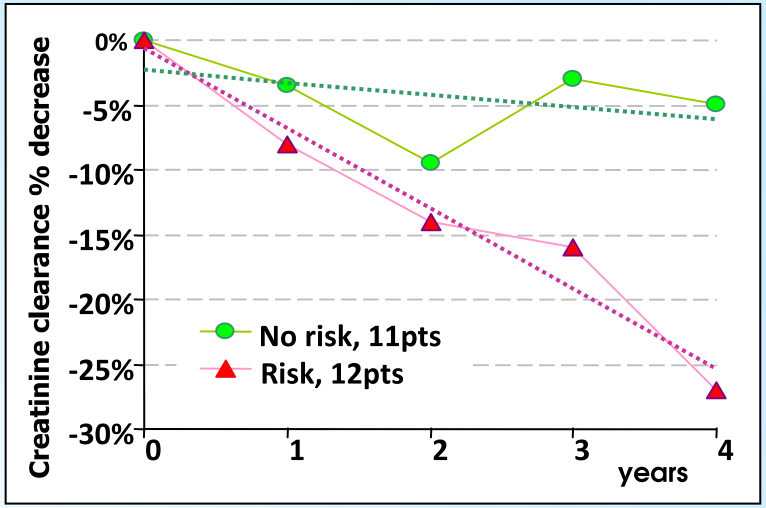
any further correlation?

renal toxicity remains the major concern

Renal toxicity

clinical results →

- sparing effects are obtained with fractionated PRRT
- PRRT is reasonably safe up to a BED ~ 40 Gy to kidneys, cumulatively
- risk factors (hypertension, diabetes) lower the tolerability (threshold BED ~ 28 Gy) and the recovery of renal parameters



in pts with risk factors →

lower initial renal function

(i.e. PRRT starts with SF_K<100%)

Bodei et al.
EJNMMI 2008,1847-56.

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Red Marrow - side effects

no correlation...yet

RM toxicity

Long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE: the role of associated risk factors

Bodei et al. EJNMMI 2008,1847-56.

^{90}Y-DOTATOC - mild but progressive depletion of RM resources

^{177}Lu-DOTATATE - lower RM toxicity, usually

Bone marrow dosimetry in peptide receptor radionuclide therapy with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate

Forrer et al. EJNMMI 2009, 1138-46.

Activity concentration in RM aspirates identical to that in blood No significant binding of the radiopeptides to RM stem cells.

No correlation between RM doses and change in platelets

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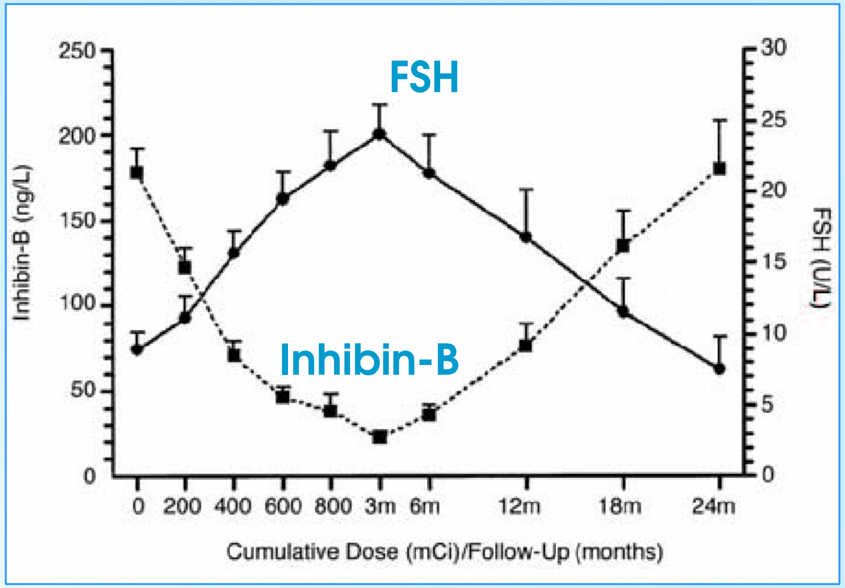
Men sterility - side effects

consistence

^{177}Lu-DOTATATE



Kwekkeboom DJ al. J Clin Oncol Invest 2005

- **alteration**
- **reversible**

dose to the testes:

0.16 Gy/GBq

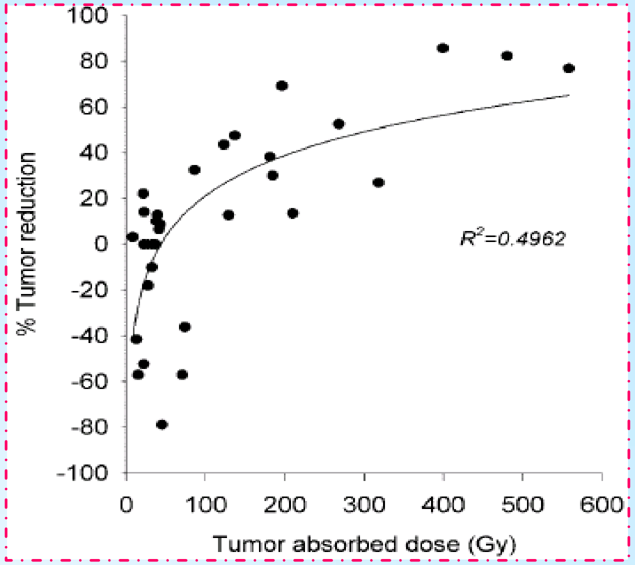
→ **0.6 - 1.2 Gy / cycle**

These doses are consistent with the effects observed...

sterility thresholds, ICRP 60	
men	
temporary	0.2 Gy
permanent	3.5 - 6.0 Gy
women	
permanent	2.5 - 6.0 Gy

Efficacy

a correlation?



Efficacy of PRRT has been proven (>25% O.R.)

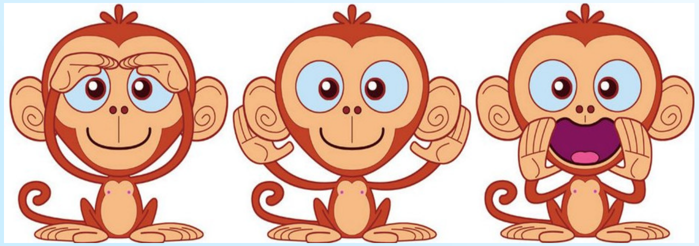
correlation?…tendency

- **Tumour dimension**
- **Radiosensitivity** tumour grading, DNA repair capacity
- **Activity distribution** concentration, $T_{1/2\ eff}$ → dose rate, dose

Radiobiological studies are warrented

Bodei et al. J Endocrinol Invest 2009,360-9 Pauwels et al. JNM 2005, 1872-80 Murray.Ca.Bioth.Radioph 2007,1-23

Future directions

The clue: 

Multidisciplinarity

Improvements on data accuracy

(pre)Clinical studies

Optimised Trial Design

a personal message, out of the rules

The beauty of science is freedom and innovation. Mostly, out of "the rules".

Still in too many countries, scientific contributes are hold back because of governments putting funds and resources far from real progress, research, medical care…

There are also many countries offering today an example of what willing people can do, once relieved from a totalitarism

In favour of science, dictatorships should not exist

Galileo Galilei

Medicine Nuclear Department

IEO Istituto Europeo di Oncologia

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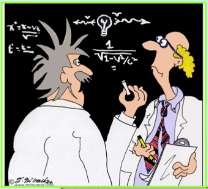

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Thank you !