MetroMRT

Metrology for Molecular Radiotherapy

MetroMRT 3rd Workshop

Clinical implementation of dosimetry for molecular radiotherapy

NPL 20-21 April 2015

Dosimetry experience at IEO, Milan

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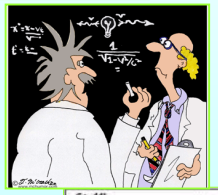

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MULTIDICIPLINARITY

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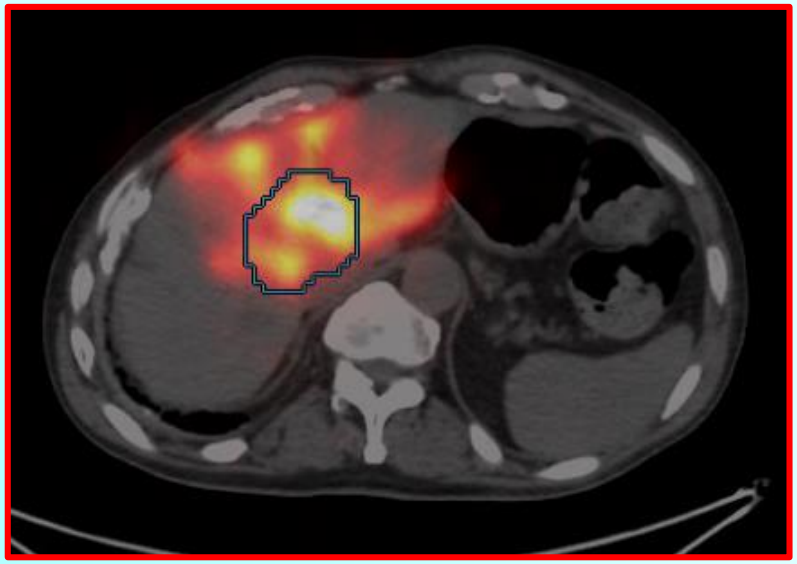
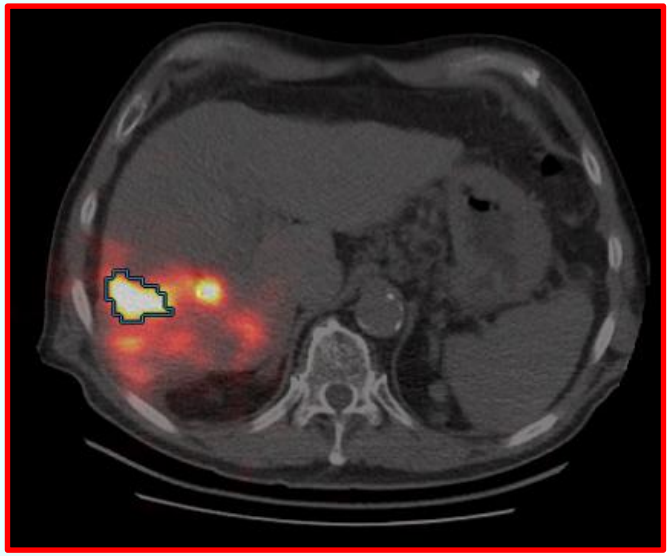
Our experience…..

MRT procedure	Dosimetry data used for	Dosimetry method
^{90}Y- MoAbs (3 step)- 1995	- Research - safety	Planar images Mean doses
^{90}Y- and ^{177}Lu- PRRT- 1997	-Research - kidney/red marrow safety	Planar images Mean doses
High Activity Zevalin – 2000	- Red marrow safety before transplantation -Safety	Planar images Mean doses
IART (^{90}Y-biotin) +EBRT in breast cancer – 2004	To combine MRT+EBRT	Planar images + 1 SPECT Mean doses+DVH+ BED
SIRTEX ^{90}Y - resin microspheres – 2007	To determine the activity to be injected	SPECT/CT DVH + BED etc….
NETTER-1 study (AAA) - dosimetry central lab - 2014	To demonstrate that dosimetry is not mandatory 	Planar images + 1-2 SPECT/CT Mean doses + kidneys BED +……work in progress

SIRT- how are dosimetric data used ?

- Patients undergo dosimetry
- Dosimetry is used to determine the ^{90}Y activity to be injected in patient
- The activity is established considering healthy liver (HL) EUBED < 40Gy
- The actual activity injected relies on single patient “viability”, as resin microspheres clug up vessels





SIRT - Dosimetric procedure

- ~ 74 MBq ^{99m}Tc-MAA to simulate therapy – 1 SPECT/CT (no biologial removal)

  @ the end of interventional radiological procedure

- Radiopaque marker in CTs and SPECT for SPECT /CT fusion
  CT low dose for AC + CT with contrast medium

- SPECT
  120 projections (15 s each), 128x218,

  OSEM, 8 iterations, 6 subsets, no filter

  Scatter correction: energy window subtraction

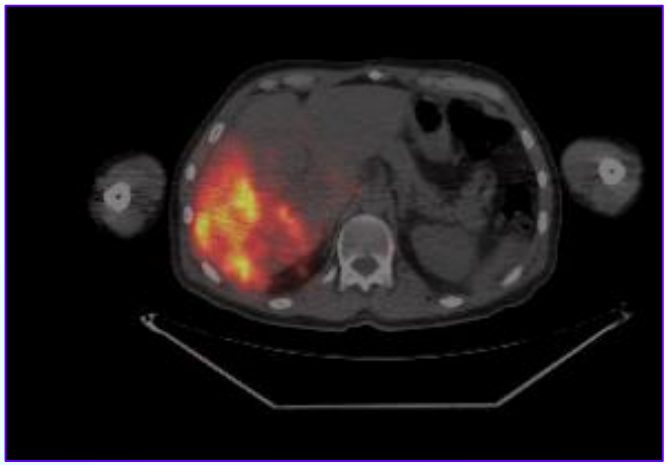
  Attenuation correction (GEHC Xeleris 3.1)

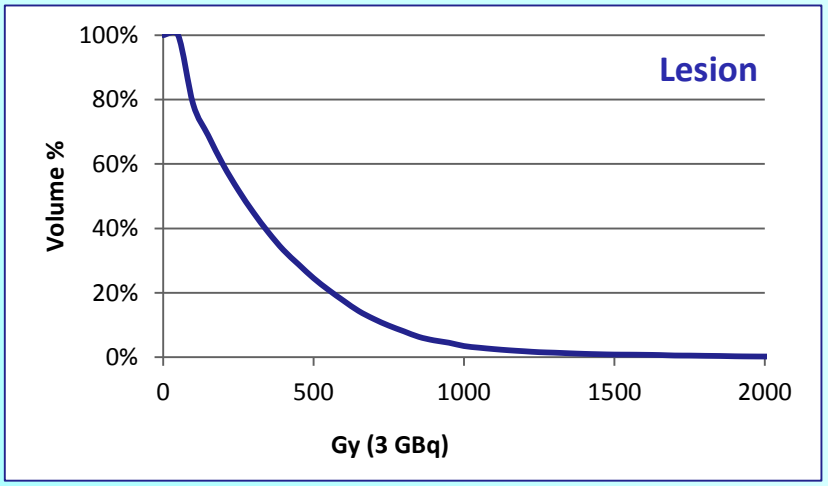
- Target volumes manual delineation on contrast CT (Lesions - healthy liver)

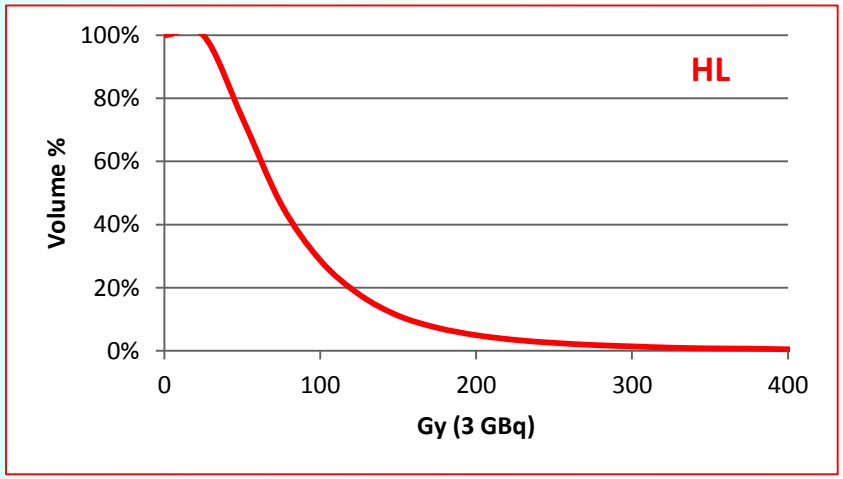
- Voxel dosimetry
  convolution (MATLAB ® support); S-voxel matrix (7x7x7) by MC simulation (Penelope) to obtain for HL and lesions DVHs and radiobiological parameters

SIRT- how the results are presented

P.G. (3 feb 15)	1 GBq	2 GBq	3 GBq
Mean dose HL (Gy)	21	43	64
EUBED HL (Gy)	8	14	18
Survival fraction HL	87%	79%	75%
Mean dose lesion (Gy)	100	200	300







SIRT – How do calibrate the measurements?

We use relative calibration

SIRT – What type of accuracy validation measurements have you done?

NONE!

SIRT – Can you estimate the uncertainty in your dose measurements?

Accuracy influenced by:

Activity measurement
in dose calibrator

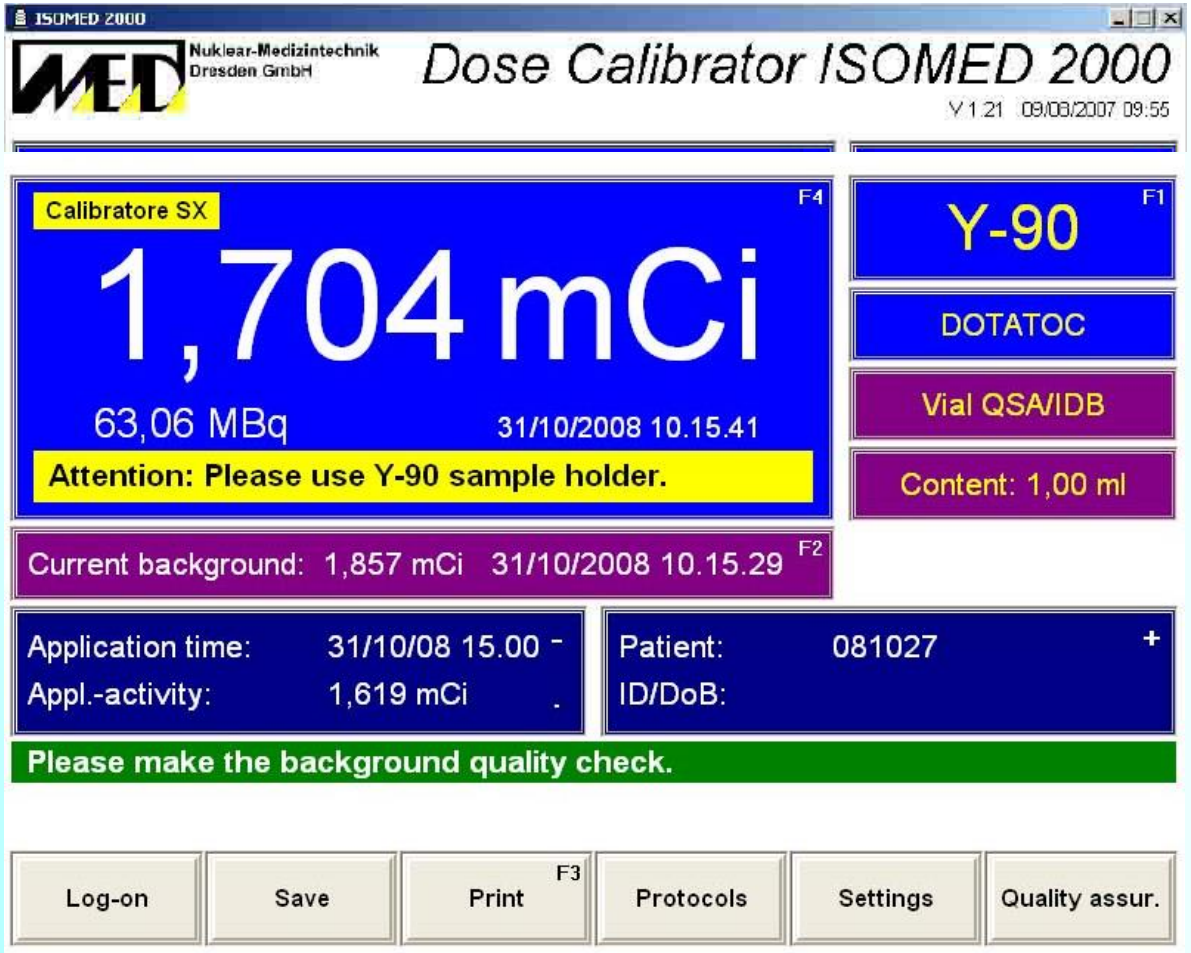
Image quality

- isotope
- actual resolution
- image reconstruction
- image corrections
- image noise
- …….

Radiobiological parameters

…….

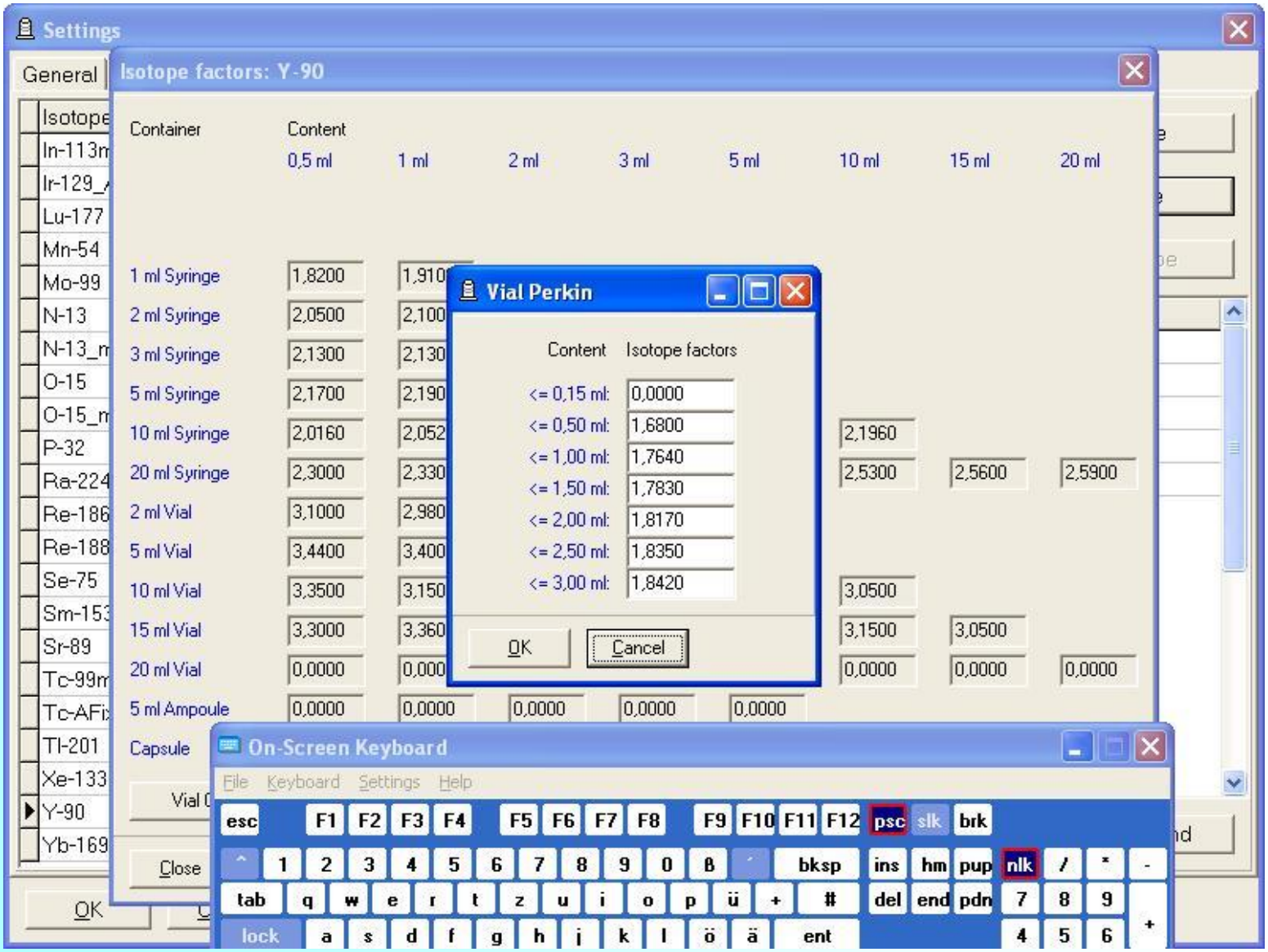
Dose Calibrator



Geometry

Volume

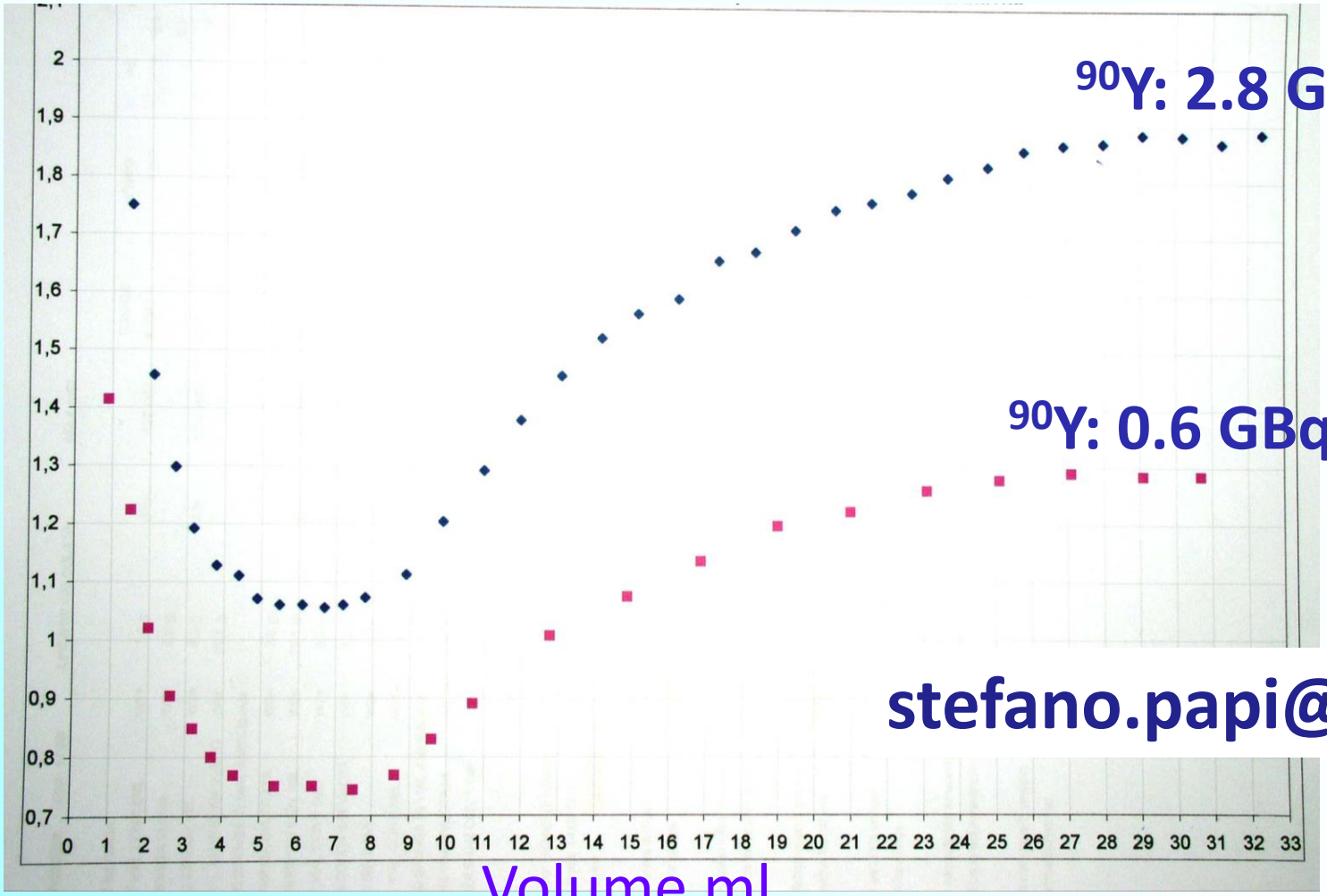
For each volume and geometry an appropriate factor……



Attention…. with an old calibrator….

The **calibration factors** were depending from geometry,

volume (not in a linear way) and …. **RANGE OF ACTIVITIES**!!!!



^{90}Y: 2.8 GBq

^{90}Y: 0.6 GBq

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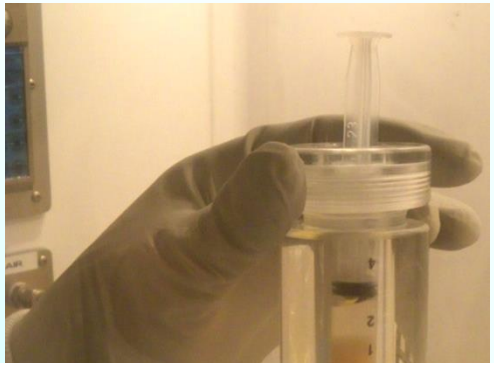
Attention ….. Spheres collapse……



Product: SIR-Spheres Yttrium-90 microspheres.

Manufacture Date: Sunday, 22 Feb 2015

Radionuclide: Yttrium-90

Nominal Activity: 3 GBq +/- 10% at 23:00 on calibration date

Calibration Date: Tuesday, 24 Feb 2015

About image quality/corrections……

Work in progress…….

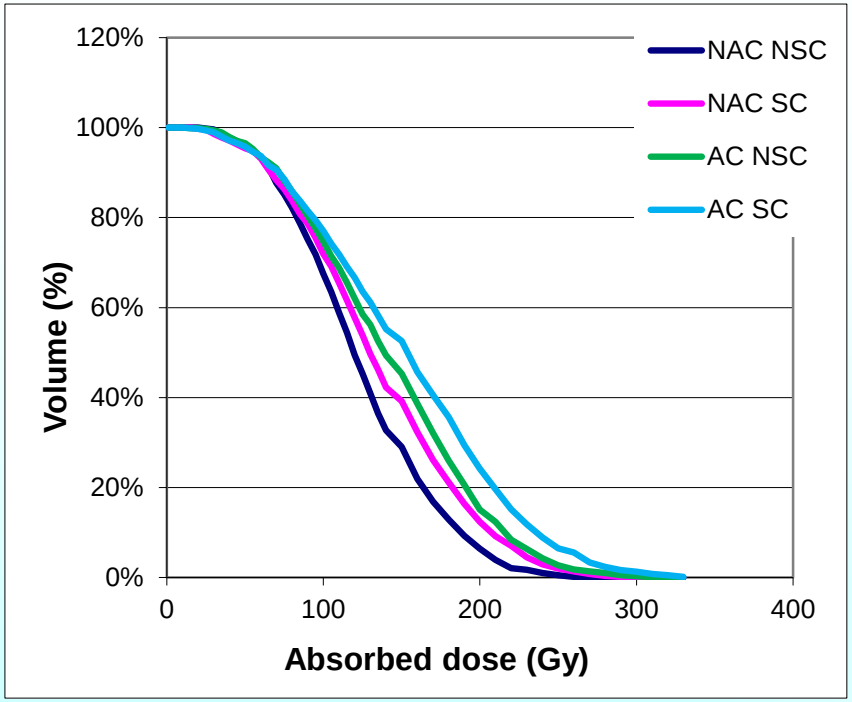
QSPECT with ^{99m}Tc: impact of scatter and attenuation corrections in the prospective dosimetry for SIRT

Massimiliano Pacilio, Marta Cremonesi, Carlo Chiesa, Mahila Ferrari, Francesca Botta, Leda Lorenzon, Michael Ljungberg

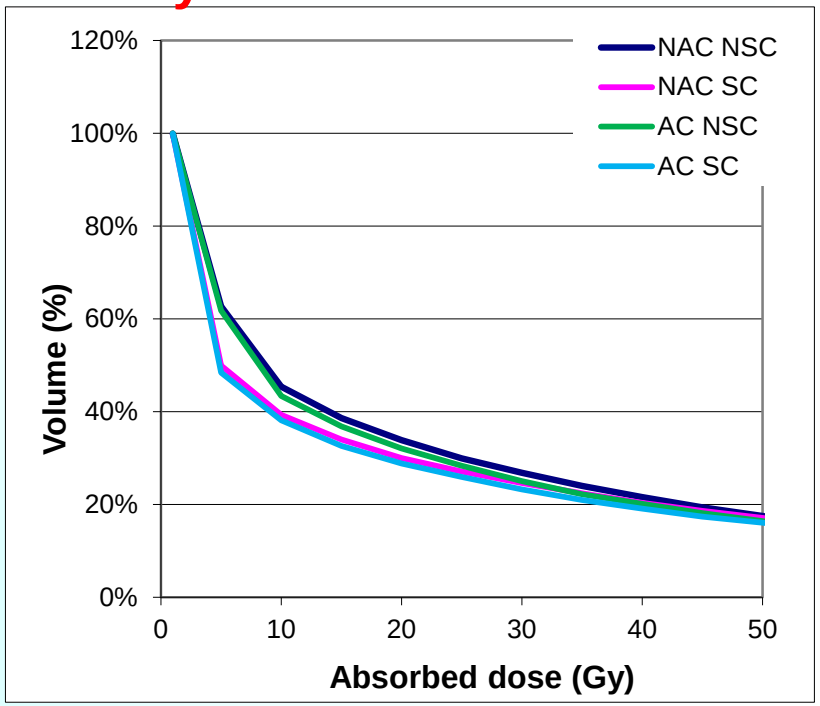
To compare the patient dose images obtained from different methods of reconstruction (with and without corrections) for simulated patients (SIMIND) and clinical cases, including different scatter correction, resolution and noise of the images, relative and absolute calibration…..

Liver metastasis lesion

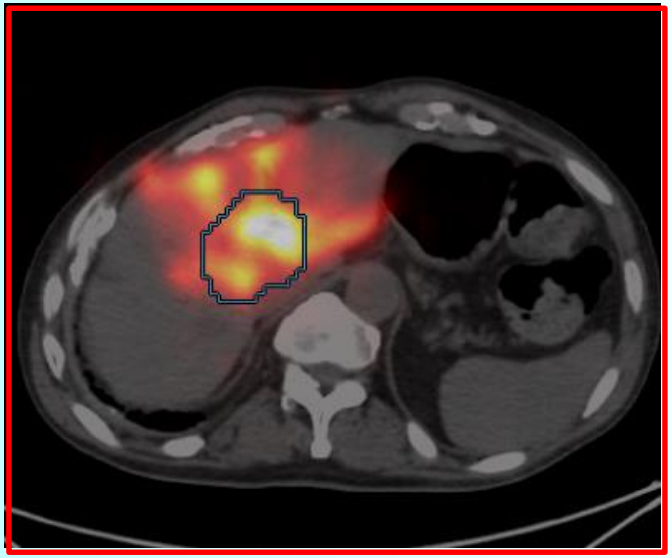
Pt 6_CG, 80 kg, lesion 100 g, healthy liver involved 825g , total liver 1825 g



Healthy liver



delta%	NAC NSC	AC NSC	NAC SC
D mean	-19%	-7%	-12%
D20	-22%	-9%	-14%
D70	-16%	-5%	-10%
D90	-7%	1%	-8%



delta%	NAC NSC	AC NSC	NAC SC
D mean	8%	3%	5%
D20	19%	9%	12%
D90	910%	1067%	-85%

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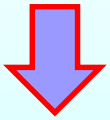
SIRT - Do you think that the dosimetry you are doing could be incorporated in MRT treatment planning on individual patients and be used for personalised treatments?

YES!

- It's easy and no time consuming
- Useful for the management of the patient
- Also local deposition can be considered without compromising the results

^{177}Lu-DOTATATE- how are dosimetric data used ?

AAA is conducting a dosimetry sub-study within the Phase III clinical trial, with the primary objective to correlate whole body and organ radiation dosimetry results with findings of the Erasmus Medical Center Phase I/II study



……. four treatments of 7.4 GBq of ^{177}Lu-DOTA0-Tyr3-Octreotate

can be safely given without the need for individualized dosimetry assessments…….

……a planned treatment will be withheld if the resulting cumulative bone marrow radiation dose exceeds 3.7 Gy, or if the cumulative kidney radiation dose is determined to exceed 38 Gy of Biologically Effective Dose (BED)

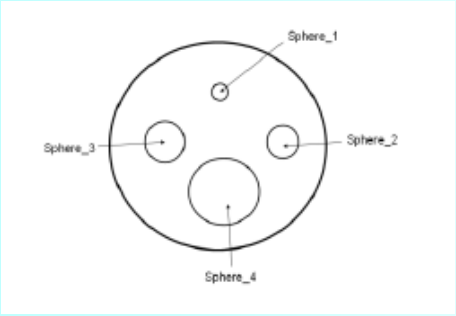
^{177}Lu-DOTATATE - Dosimetric procedure -1

Dosimetry based on:

- **planar whole body** imaging (WB; anterior and posterior views), in combination with transmission data
- **SPECT** scans in the upper abdomen (to include the kidneys, liver, and spleen)
- **blood and urine analysis** of radioactivity

calibration data:

- attenuation coefficient for gamma camera
- calibration with a ^{177}Lu reference source for gamma counter
- SPECT of a phantom

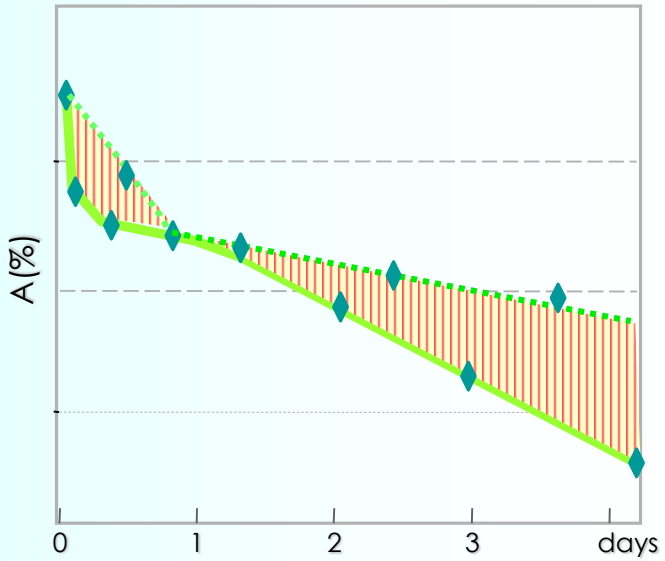


2B - Acquisition of the emission images	
Acquisition parameters	*Suggested*
Peak energy	15% at 208 keV
Supplemental energy windows for scatter correction (to be set as separate image from the 208 peak image)	4% at 189 keV + 4% at 229 keV
collimator	MEGP
WB speed (continuous)	10 cm/min
WB matrix	256 x 1024
WB body contouring	if possible
SPECT matrix	128x128
SPECT setting	60 frames, 45 s /frame Zoom 1
SPECT body contouring	if possible
SPECT attenuation correction	CT
SPECT reconstruction	iterative reconstruction specifying the number of iterations and subsets (e.g. 8 iter. and 6 sub. recommended) possibly with attenuation and scatter correction)

2C - Acquired images with reference to **Lutathera infusion No. ① ② ③ ④**		
Image	*Date and time*	*Duration (min)*
Transmission scan *blank* with flood source of Co-57 (**without** patient)		
Transmission scan with flood source of Co-57 (**with** patient)		
WB 1 h		
WB 4-6 h		
WB 16-24 h		
WB 40-48 h		
WB 60-72h		
WB 156-168 h (optional)		
SPECT 24 h		
SPECT 48 h		
CT		—

^{177}Lu-DOTATATE - Dosimetric procedure - 2

- ^{177}Lu radioactivity in the organs (relative calibration): the **conjugate-view technique** is applied to ant and post images after **background, scatter, attenuation, and physical decay corrections**
- Counts are normalized at the first image, scanning the patient with **100%** of the injected activity **subtracted** by the percent of injected activity **eliminated in the urine before the first image acquisition**
- The number of decays (NDs) per unit injected activity is calculated from **multiexponential fits** to the time–activity curves
- **Absorbed doses** to target organs are calculated by entering the ND values for all the source organs in the **OLINDA/EXM** software and adjusting the doses reported by the software for individual weight and organ masses
- **Kidney BED** is also evaluated



^{177}Lu-DOTATATE - how the results are presented

DOSIMETRY REPORT			
pt identification code	-		
date and time of administration	1-Oct-14		
Activity administered (GBq)	7.455		
Radiopharmaceutical	177Lu-DOTATATE		
		per cycle (7.4 GBq)	4 cycles x 7.4 GBq
Absorbed dose to	absorbed doses per unit activity	absorbed doses in the cycle	cumulative absorbed doses in 4 cycles
TARGET ORGANS	Gy/GBq	Gy	Gy
Kidneys	0.90	6.69	27
Liver	0.53	3.92	15.7
Red Marrow	0.05	0.39	1.6
Spleen			
Urin Bladder Wall			
Total Body			
Other organs			
TUMORS			
Lesion 1			
Lesion 2			
Lesion 3			

The patient receives to the kidneys an absorbed dose of 0.9 Gy/GBq, within the standard values found in the literature of 0.9±0.3 Gy/GBq (Zaknun et al. EJNMMI 2013;40:800-816). The cumulative kidney BED is 31 Gy in four cycles, which is witin the limit BED of 40 Gy for patients without risk factors.

The abosorbed dose to the red marrow is 0.05 Gy/GBq, within the standard values found in the literature of 0.04±0.02 Gy/GBq (Zaknun et al. EJNMMI 2013;40:800-816). The cumulative absorbed dose is of 1.6 Gy in four cycles, which is below the limit considered as safe (2-3 Gy).

There are no special comments regarding the other organs

	Kidney absorbed dose/cycle	Kidney BED/cycle
	Gy	Gy
cy1	0.90	7.6
cy 2 -4	0.90	7.7
cumulative Gy (4 cycles x 7.4 GBq)	**3.6**	**31**

^{177}Lu-DOTATATE – How do calibrate the measurements?

We use relative calibration, in WB planar dosimetry.

We are attempiting to perform 3D dosimetry with SPECT, but we have some problems with absolute calibration and SPECTs alignment

^{177}Lu-DOTATATE – What type of accuracy validation measurements have you done?

NONE!

^{177}Lu-DOTATATE – Can you estimate the uncertainty in your dose measurements?

Some key points for accuracy are:

- **biokinetics**
- **actual masses**
- **dose distribution**
- **biodistribution among cycles**
- **..... much more....** 2D/3D imaging
  Kidney models
  response evaluation
  radiobiological parameters.....

biokinetics

Kidney Dosimetry in ^{177}Lu and ^{90}Y Peptide Receptor Radionuclide Therapy: Influence of Image Timing, Time-Activity Integration Method, and Risk Factors

Hindawi Publishing Corporation
BioMed Research International
Volume 2013, Article ID 935351, 12 pages
http://dx.doi.org/10.1155/2013/935351

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NDs were derived for ^{177}Lu- & ^{90}Y-peptides by:
(i) **trapezoidal+ physical-decay** after experimental data (←commercial software);
(ii) **trapezoidal+ biological-decay** after the last 2 points;
(iii) **bi-exp** fit;
(iv) **mono-exp** fit.

→ **4 and 64h notably impact the dose estimate**

→ **inappropriate** model(i), overestimating ND(^{177}Lu) **up to 3-fold** vs. (iii)

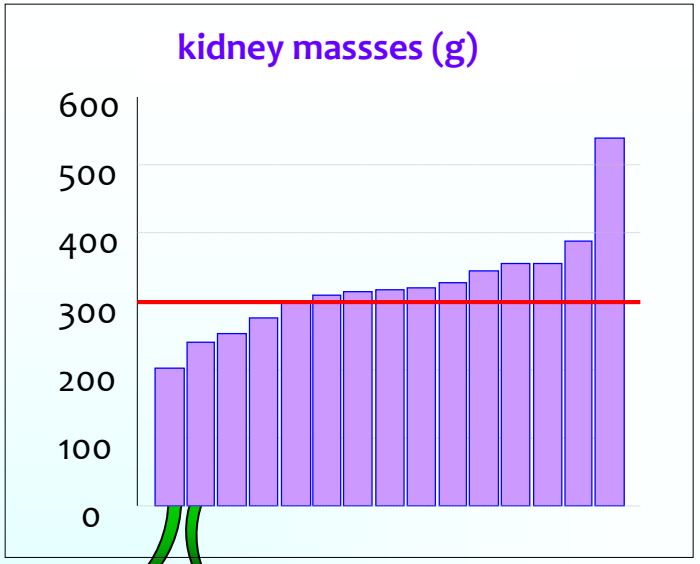
→ **Model (ii) underestimates vs.(iii / iv)**

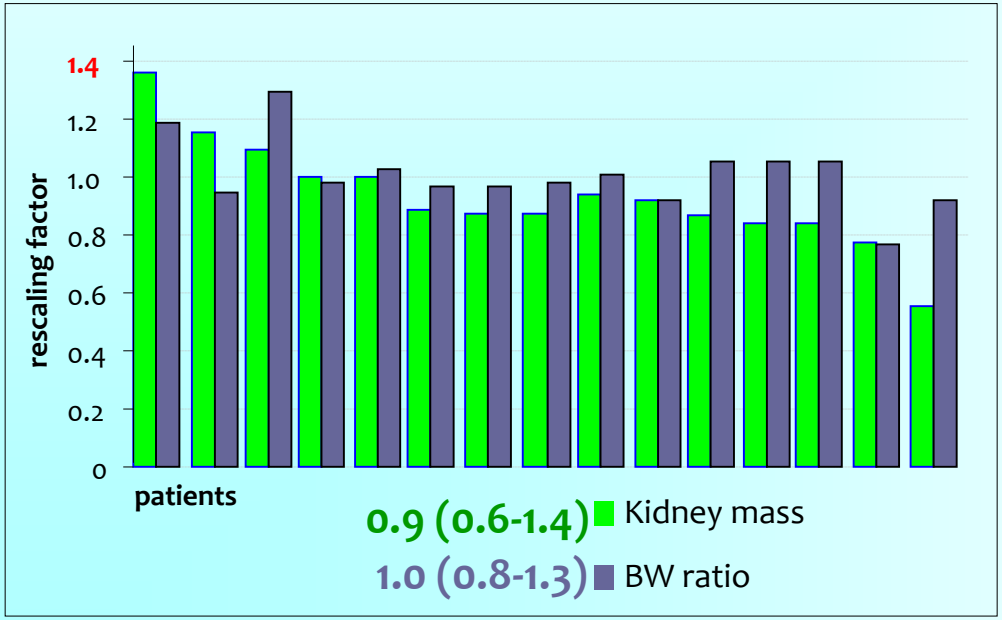
→ differences biexp - monoexp: 8% (-50,+72)%.

Kinetic models strongly impact dose estimates
ND_{TAIL} is major influencing
Bi-exp model better reflects the metabolic behaviour

actual masses

For a group of 15 patients, comparing the actual mass of the kidneys vs. the standard values of 300 g (male) and 275 g (female) …

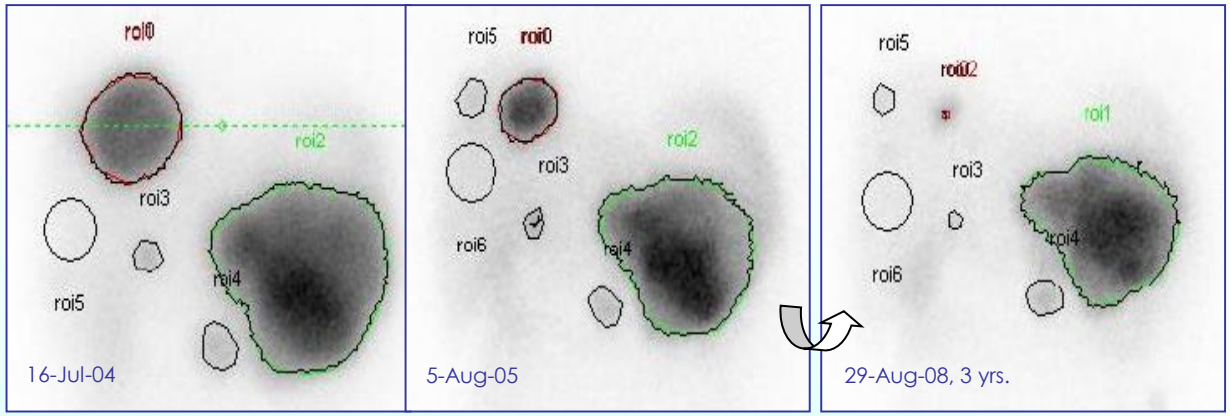




dose rescaling factor based on patient specific mass of kidneys or BW

Up to 40% error

average dose is not enough



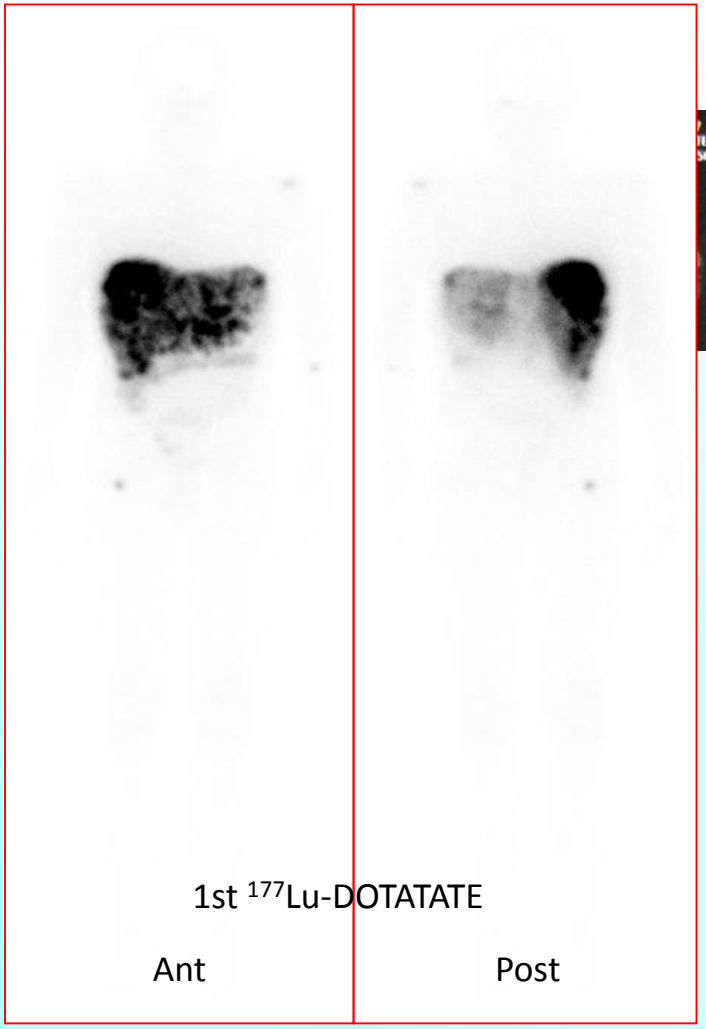
Bodei, J Endocrinol Invest 2009,360-9

	L Liver	L Pancreas
mass (g)	200	1150
A% (24h)	4%	25%
dose (Gy)	**95**	**90**
Response	**CR**	**SD/MR**

- Activity/dose distribution
- Non uniformity due to receptor density
- Tumour dimension
- Radiosensitivity (growth pattern, DNA repair capacity)

biodistribution can vary with cycles

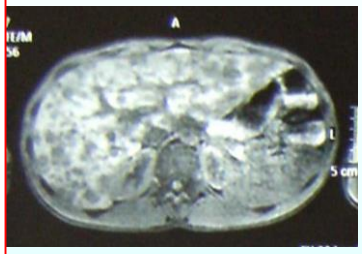
Diffuse liver and bone mets from a pancreatic NETG2



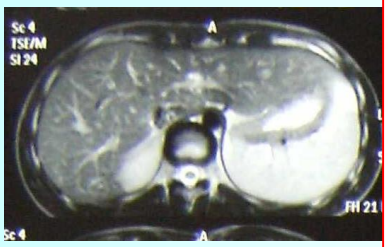
1st ^{177}Lu-DOTATATE

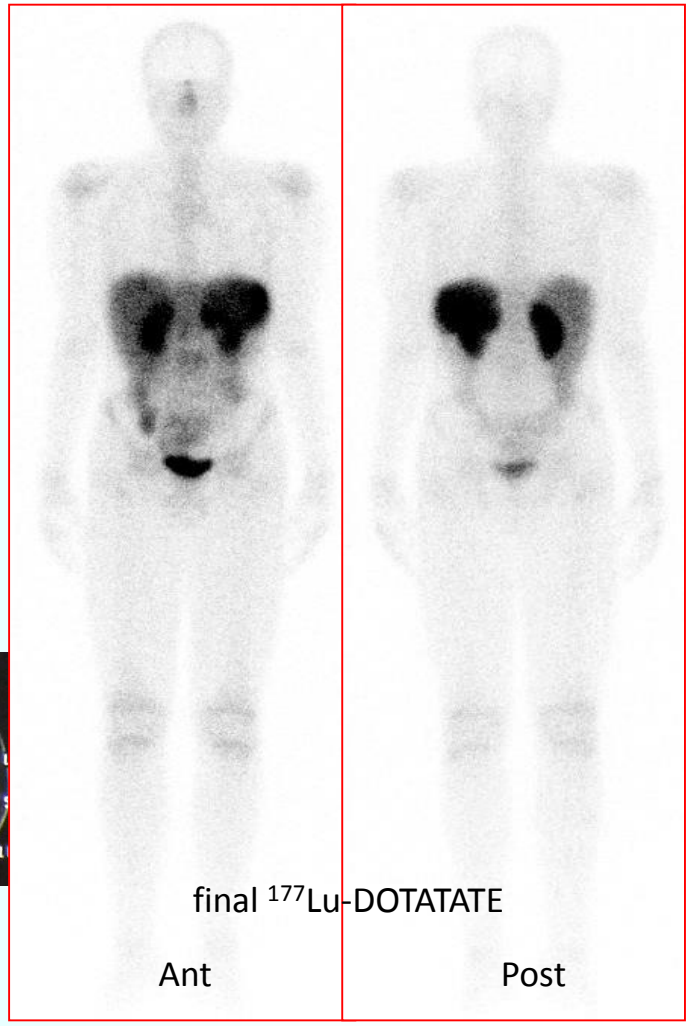
Ant Post

basal MRI



final MRI





final ^{177}Lu-DOTATATE

Ant Post

Uptake in tumour & organs can vary with cycles, especially in case of large burden

^{177}Lu-DOTATATE - 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?

What should not be done

-To **avoid dosimetry just because apparently time consuming/expensive**

- To **perform "bad" dosimetry, i.e.**:
  - not collecting the essential data useful for future refinements
  - not giving the method specifics for dosimetry
- To **derive hasty conclusions without specifying how dosimetry was made**
- To **forget the concept of OPTIMIZATION**

^{177}Lu-DOTATATE - 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?

What should be done

More than ever, dosimetry should be done, as accurate as possible and providing, in any case, all the specifications, and refinements :

- revise and analyse possible ways to reduce inaccuracies
- focus efforts on the implementation of methods improving dosimetry results

answers will be derived ar

clinical results improved

Thank you!