Dosimetry of patients injected with tracers Ga-68, Zr-89 and Lu-177

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What is NM speciality?

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Imaging radiology

- Physics
- Diagnostic
- Treatment assessment

Clinical pathology

- Biological marker
- Diagnostic
- Treatment assessment

Nuclear Medicine

Radiotherapy

- Physics
- Radiobiology

Chemotherapy

- Pharmacology
- Biology

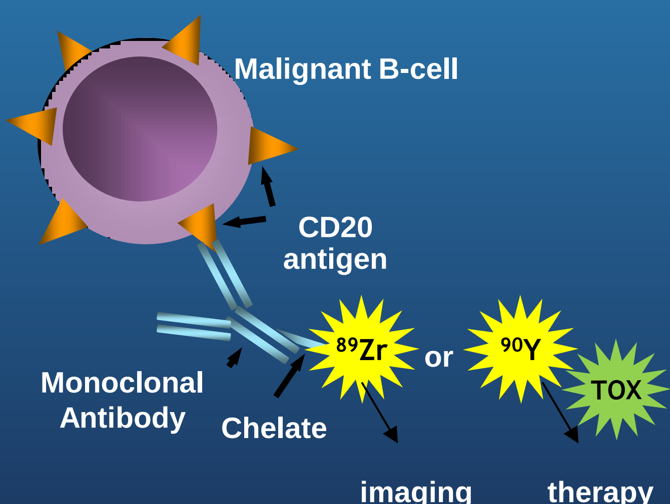
$\Rightarrow$ Multidisciplanary approach

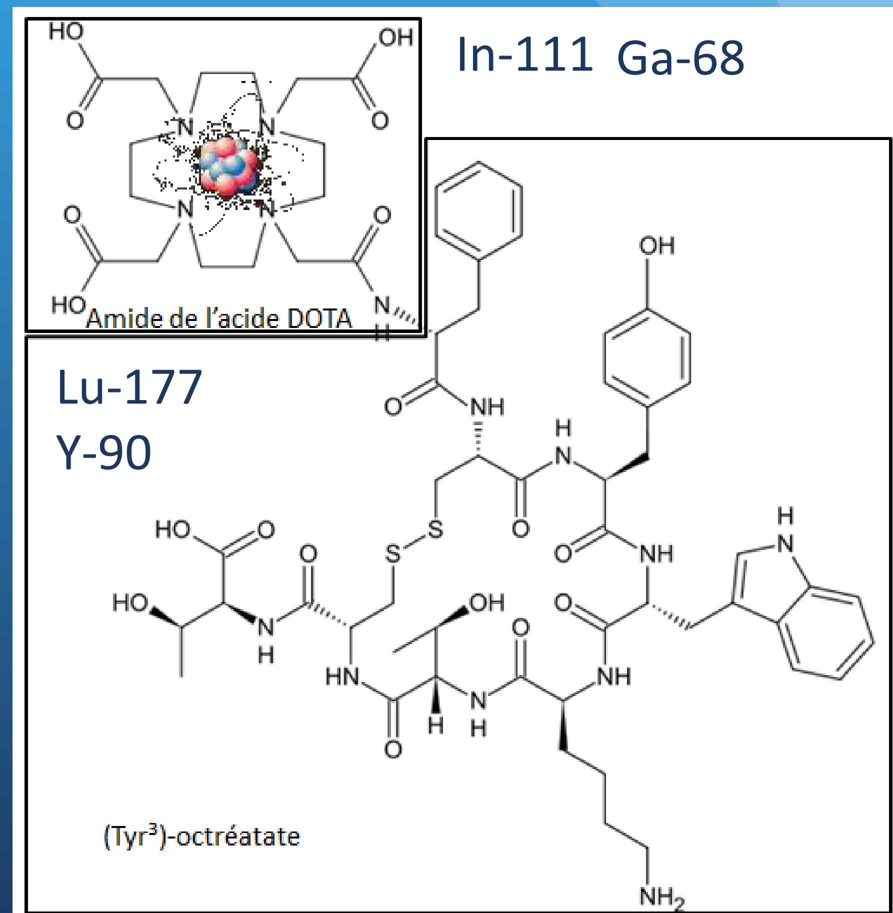
Plan

- What is a radiopharmaceutical and how to choose it
- An introduction to a dedicated dosimetry, the MIRD formalism and the pharmacokinetics
- Which equipment used in NM are required (radionuclide calibrator, gamma counter and gamma camera)
- A Presentation of some practical examples with Zr89 labelled to antibodies and octreotide labelled with Ga68 or Lu177

Radiopharmacology

- Pharmaceuticals labelled to a radionuclide
  - Hormone
    - peptide
  - Antibody
    - rituximab





Physical properties

- Physical half lives
  - Short ≈ hours
    - => Diagnostic
  - Long ≈ days
    - => Diagnostic for long biological half-lives
    - => Therapeutics
- Types of emissions
  - Gamma
  - Beta
  - Alpha
- Energies of emissions
- Intensities of emissions
- Chemical properties (binding, mass,…)

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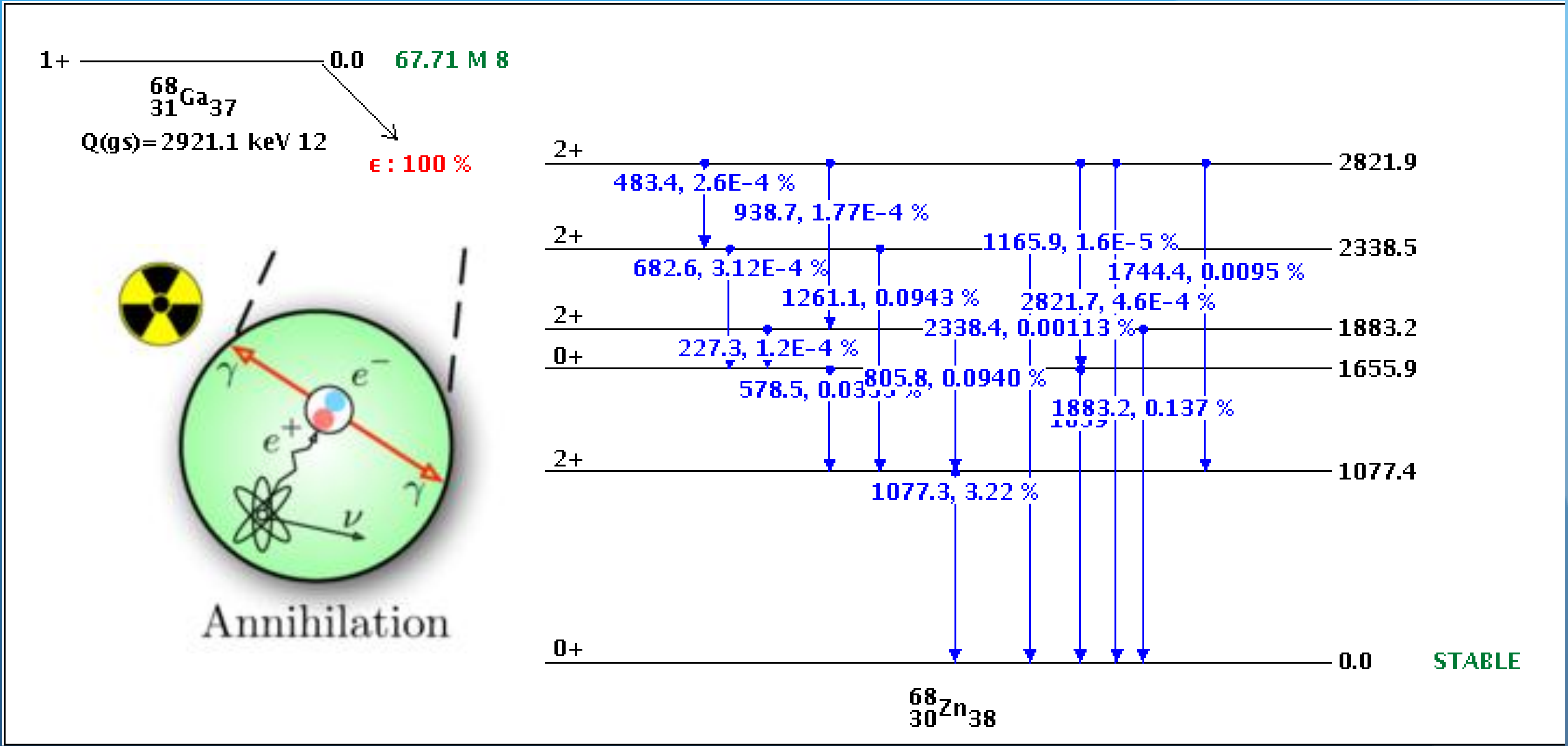
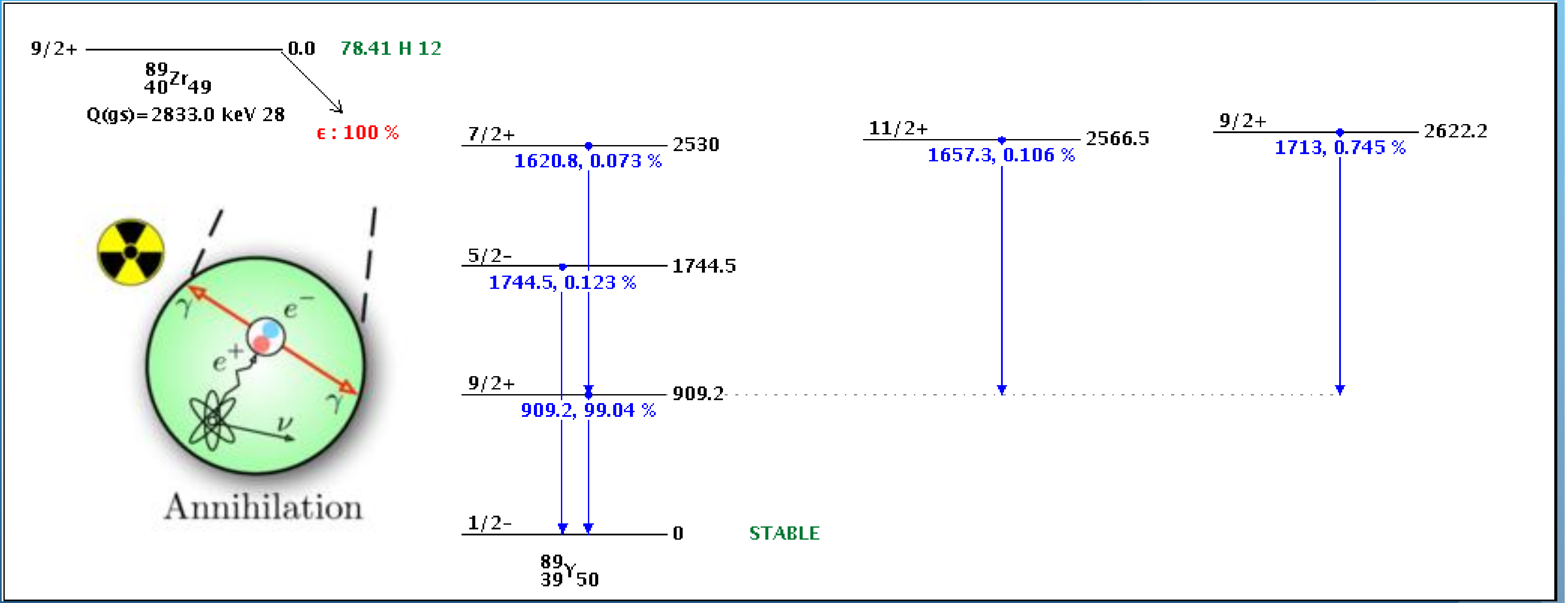
68Ga diagnostic short half-live



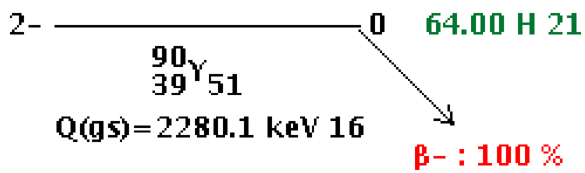
- Electron capture or beta + emissions (88%)
- 2 gamma after annihilation of beta +
- TVL = 17 mm Pb

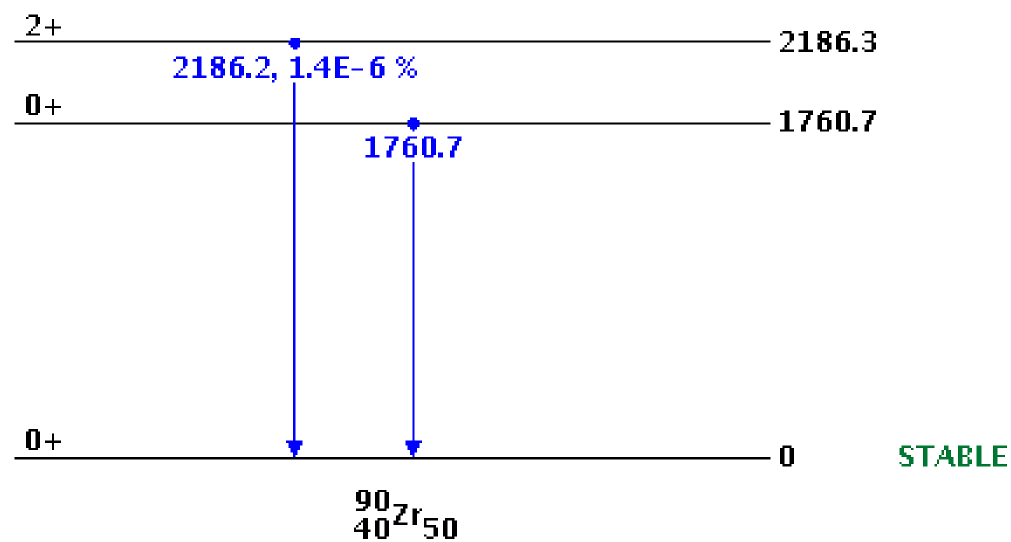
89Zr diagnostic long half-live



- Electron capture or beta + emissions (23%)
- 2 gamma after annihilation of beta +
- TVL = 32 mm Pb

90Y therapeutic



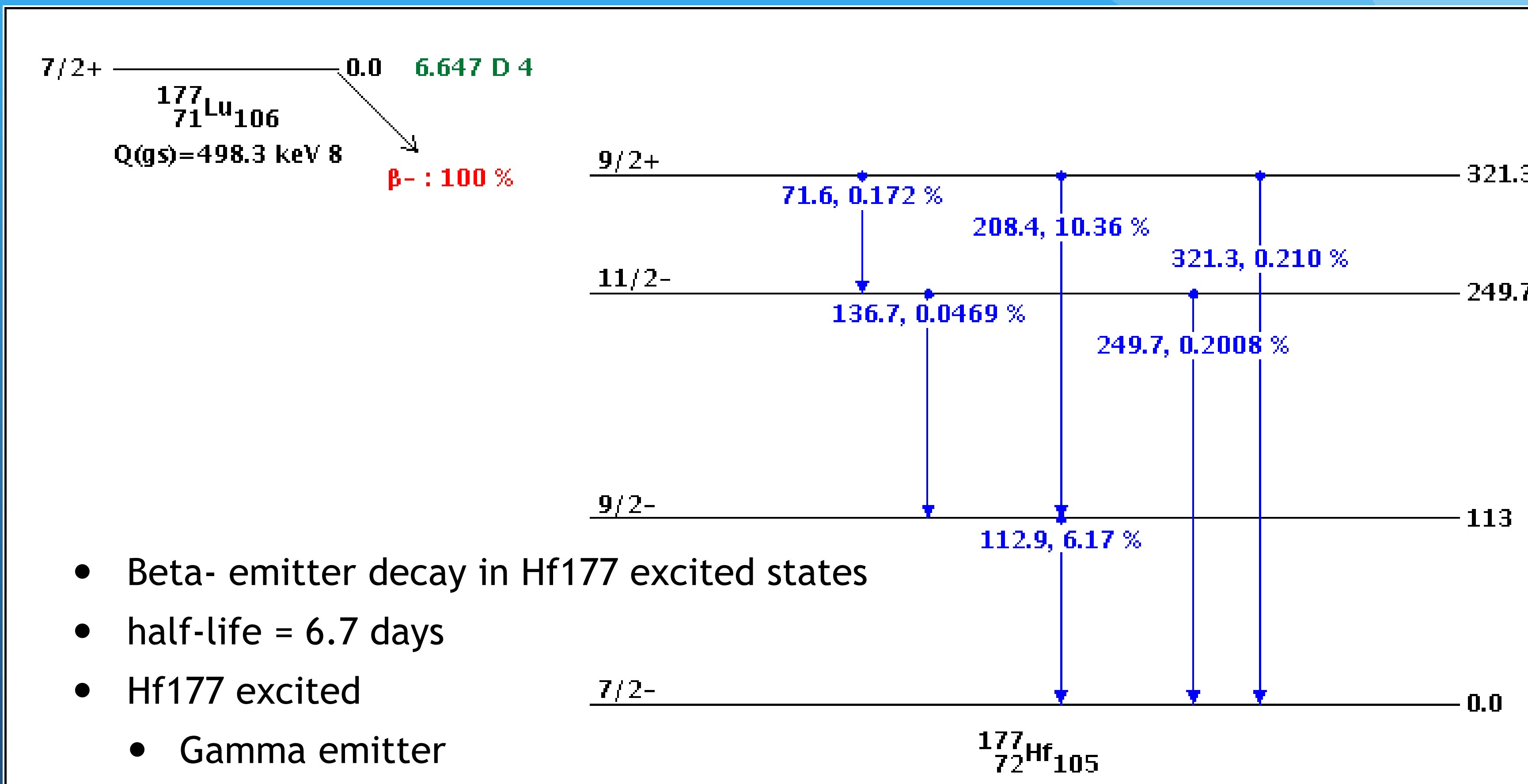


- Beta- emitter
- half-life = 2.7 days
  - 90Zr 0+ could make a pair production => beta+ emission

Maximum Range of Beta in Air: 9 m

Maximum Range of Beta in Water: 11 mm

177Lu therapeutic



- Beta- emitter decay in Hf177 excited states
- half-life = 6.7 days
- Hf177 excited
  - Gamma emitter

    113 & 208 keV
  - Half-life < nanosecond
- TVL = 2.1 mm Pb

Committee on Medical Internal Radiation Dose (MIRD)

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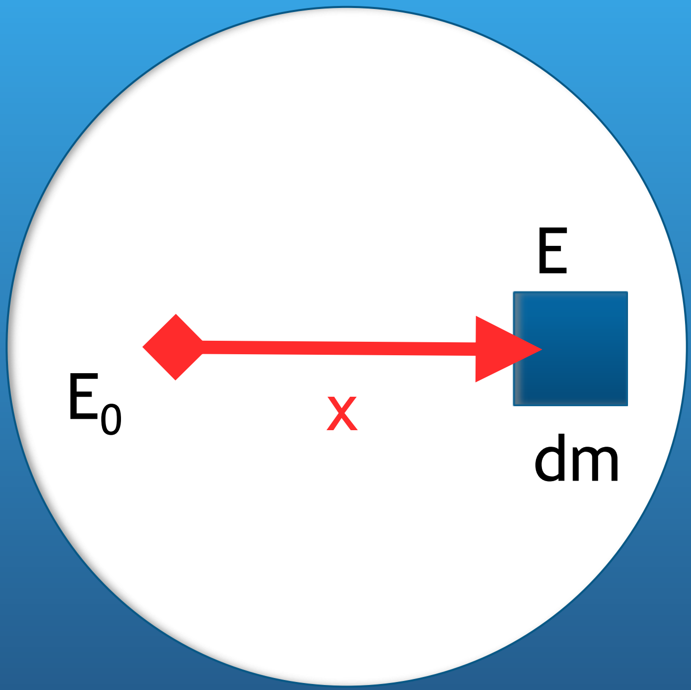
- Radiation dosimetry provides the fundamental quantities used for radiation protection, risk assessment, and treatment planning.
- The MIRD Committee develops standard methods, models, assumptions, and mathematical schema for assessing internal radiation doses from administered radiopharmaceuticals.
- The virtue of the MIRD approach is that it systematically reduces complex dosimetric analyses to methods that are relatively simple to use, including software tools for experimental and clinical use.

The MIRD Formalism



Absorbed fraction

$$f\left(x,E_0\right)=\frac{E}{E_0}$$

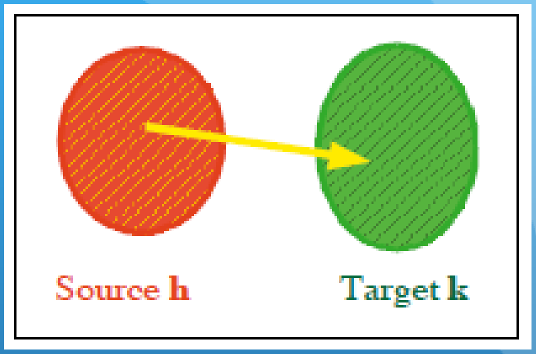
Absorbed fraction by mass

$$F\left(x,E_0\right)=\frac{f\left(x,E_0\right)}{dm}$$

Mean absorbed dose Gy [J/Kg]

$$\bar{D}=\frac{E}{dm}=\frac{f\left(x,E_0\right)\cdot E_0}{dm}=F\left(x,E_0\right)\cdot E_0$$

Dose in a volume

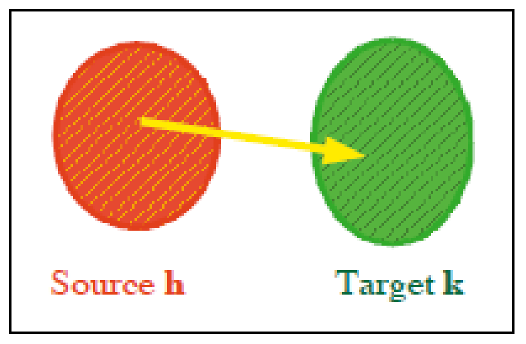


$$D\,(k \leftarrow h) = \frac{E}{m_k} = \frac{\varphi(k \leftarrow h)\,E_0}{m_k} = \Phi(k \leftarrow h)\,E_0$$

- D = mean dose in target volume
- if radiations are non-penetrating
  - $\varphi_i(k \leftarrow h) = 0 \quad \text{if } k \neq h \quad \rightarrow \quad D\,(k \leftarrow k) = \dfrac{E_0}{m_k}$
  - $\varphi_i(k \leftarrow h) = 1 \quad \text{if } k = h \quad \rightarrow \quad D\,(k \leftarrow h) = 0$

Radionuclides

$$\dot{D}(t)_{(k \leftarrow h)} = A_h(t)\, E_0\, \Phi(k \leftarrow h)$$



- mean dose rate in target k at time t for source h with one type of radiation of energy E0
- if i is a specific type of particle with
  - Ei its energy
  - ni the number of particles of type i emitted per transition

  → Δi is the mean energy per transition for radiation i in J/(Bq.s), and Δ the total energy per transition

$$\Delta_i = k\, n_i\, E_i \qquad \Delta = \sum \Delta_i = K \sum n_i\, E_i$$

- the dose rate is the sum of all radiation types

$$\dot{D}(t)_{(k \leftarrow h)} = K\, A_h(t) \sum n_i\, E_i\, \Phi_i\,(k \leftarrow h)$$

Residence time

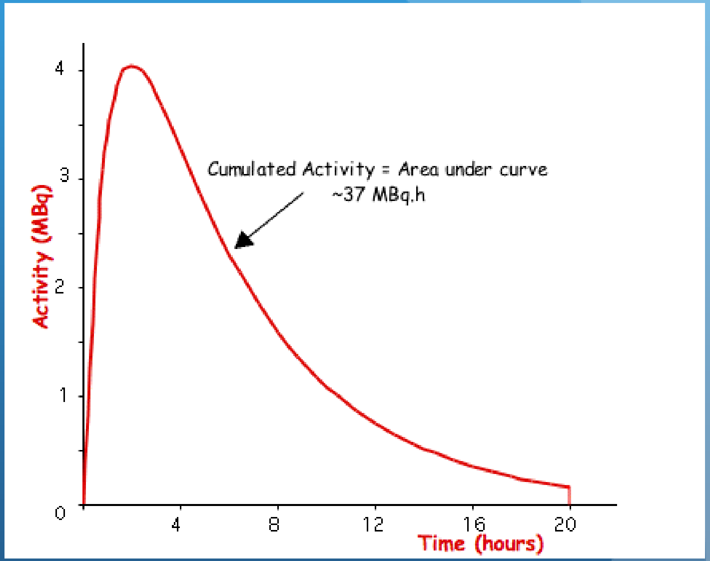
$$D_{(k \leftarrow h)} = \int_{t_1}^{t_2} \dot{D}(t)_{(k \leftarrow h)}\, dt = K\, \tilde{A}_h \sum n_i E_i\, \Phi_i\, (k \leftarrow h)$$

- $\tilde{A}_h$ is the cumulated activity

$$\tilde{A}_h = \int A_h(t)\, dt$$

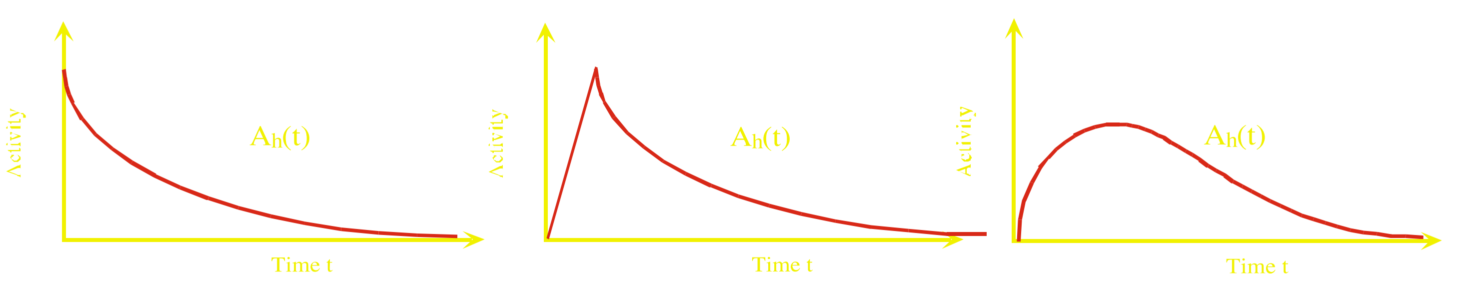
$\tilde{A}_h$ = total number of transitions in source h

calculated from biological data (graphically or numerically)



- Residence time is different for each organ-source (diff pharmacokinetics)

$$\tau_h = \frac{\tilde{A}_h}{A_0}$$



MIRD fundamental equation

$$D_{(k \leftarrow h)} = K \tilde{A}_h \sum n_i E_i \, \Phi_i (k \leftarrow h)$$

- the factors independent of time are included in the S-factor :

$$S_{(k \leftarrow h)} = K \sum n_i E_i \, \Phi_i (k \leftarrow h)$$

- MIRD simplified equation

$$D_{(k \leftarrow h)} = \tilde{A}_h . S_{(k \leftarrow h)}$$

S-factor

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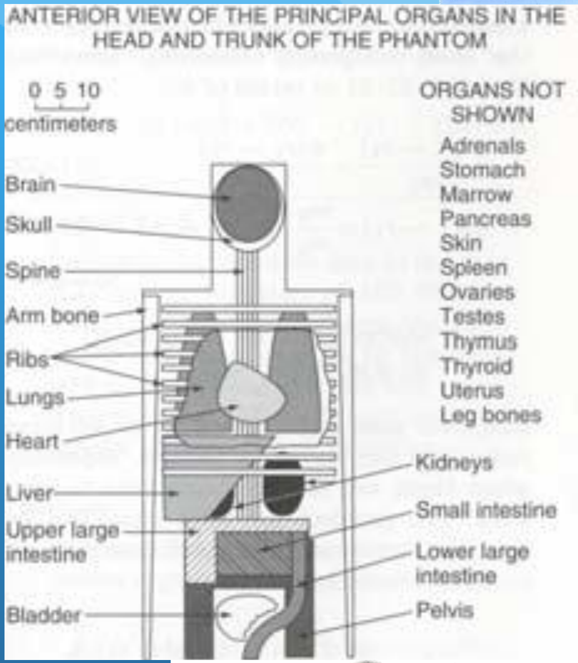
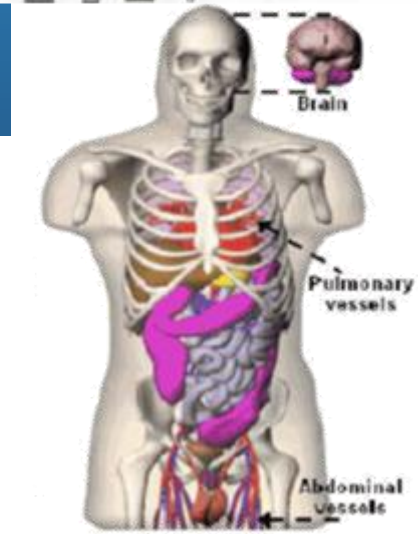
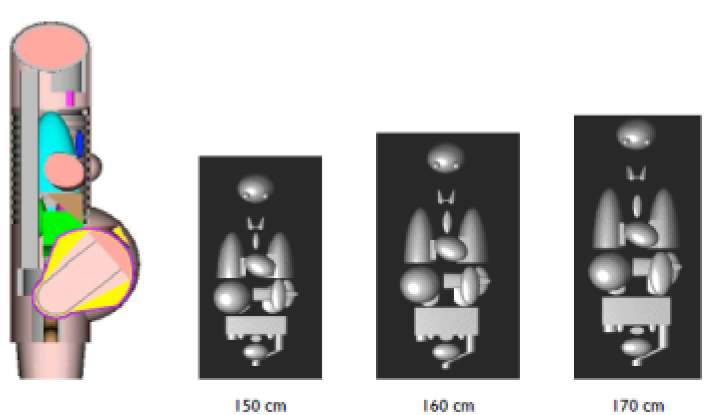
$$D = A_0 \tau S$$

- to obtain a dose from an initial activity one must know
  - the residence time
  - the S-factor for the specific geometry
- S-factors calculated using phantoms
  - mathematical : simplified
  - voxelized : from CT or MR data
- calculation methods
  - analytical
  - Monte Carlo







Quantification

Material

- Radionuclide or dose calibrator with a well-established conversion factor for the specific radionuclide and for the acquisition parameters used in routine (container geometry, position in the radionuclide calibrator, liquid volume,…)
- Gamma counter with a well-established conversion factor for specific radionuclide and for the counting parameters used in routine (activity range, volume of liquid, standard vial …)
- Gamma camera SPECT-CT with a well-established conversion factor for specific radionuclide and for the acquisition parameters used in routine (type of collimator, energy window, activity range,…)
- Imaging processing software (fusion tool, delineation)
- Dosimetry software : Olinda software (provided by MIRD committee)

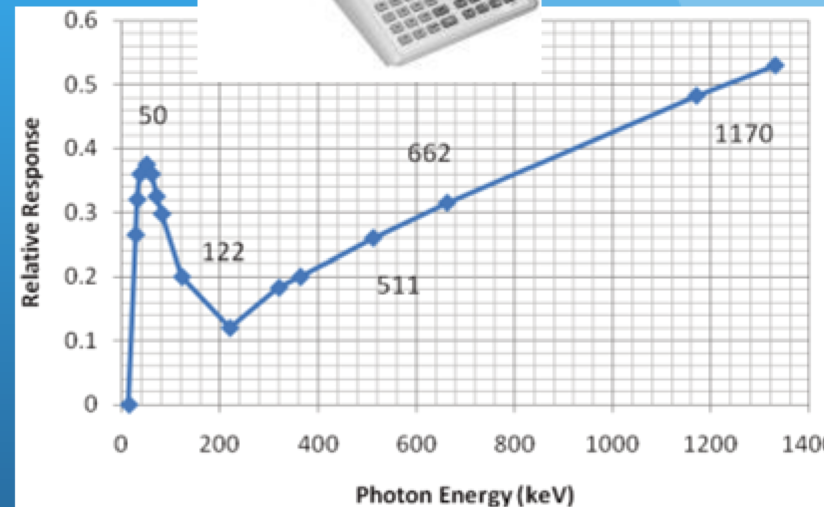
Radionuclide calibrator

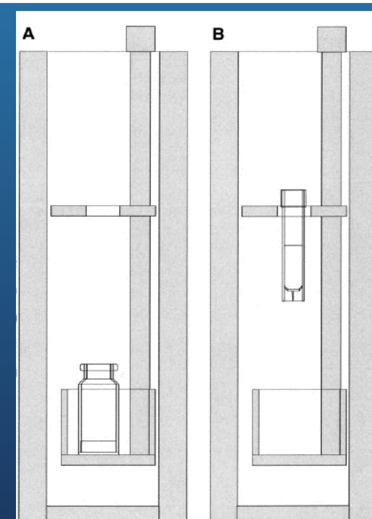
+

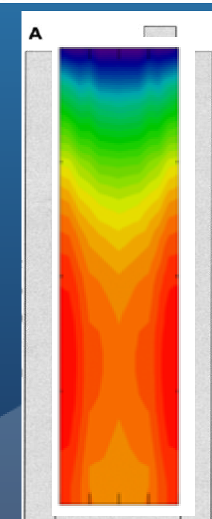
- Wide energy range
- Wide counting range
- Convenient open geometry

-

- No energy spectrum
- Geometry dependent
- Calibration with a limited set of radionuclides and geometries







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Gamma counter

+

- Energy spectrum
- Geometry non-dependent

⇒ Montecarlo simulation

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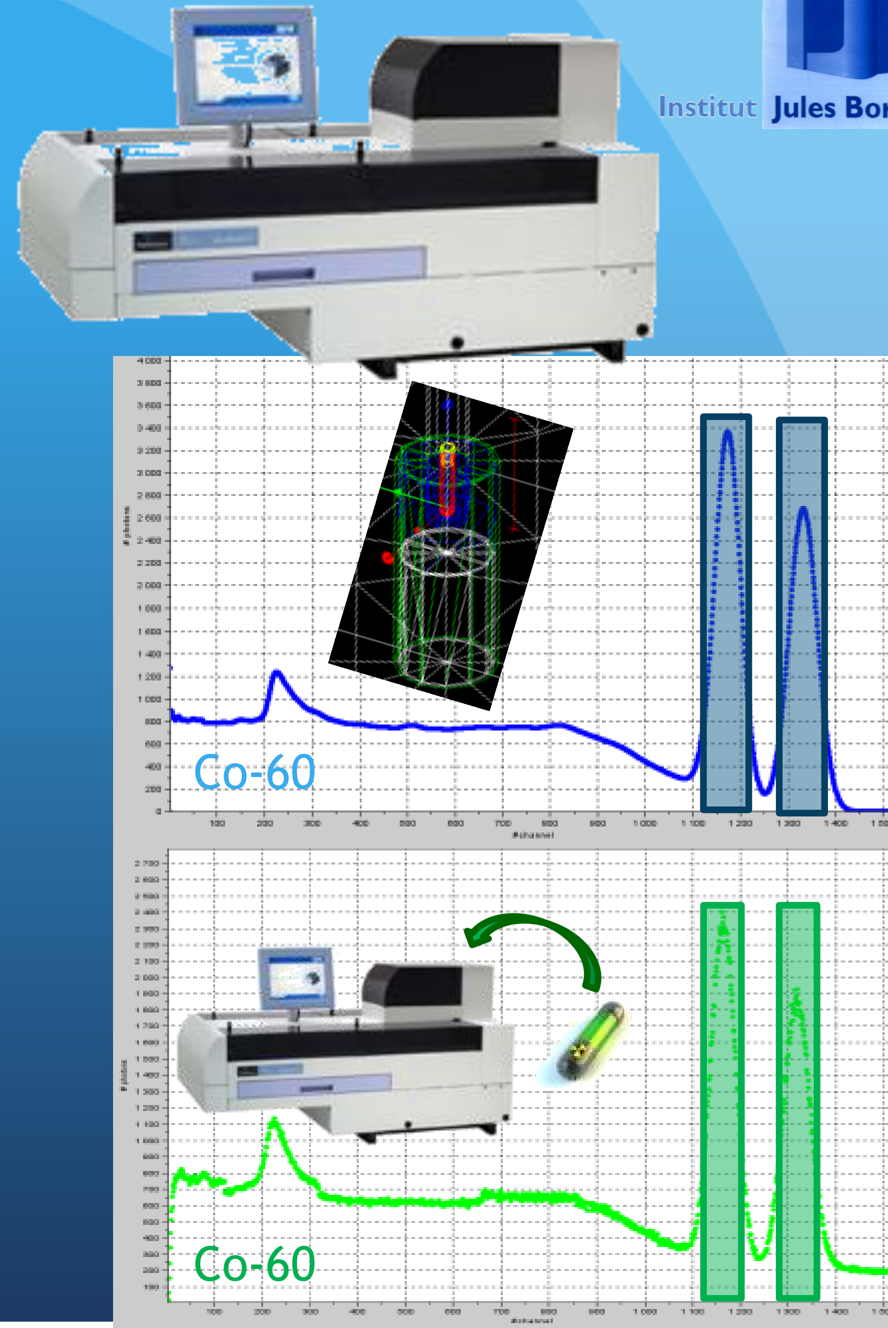
- Small counting range
- Non convenient
- Closed geometry



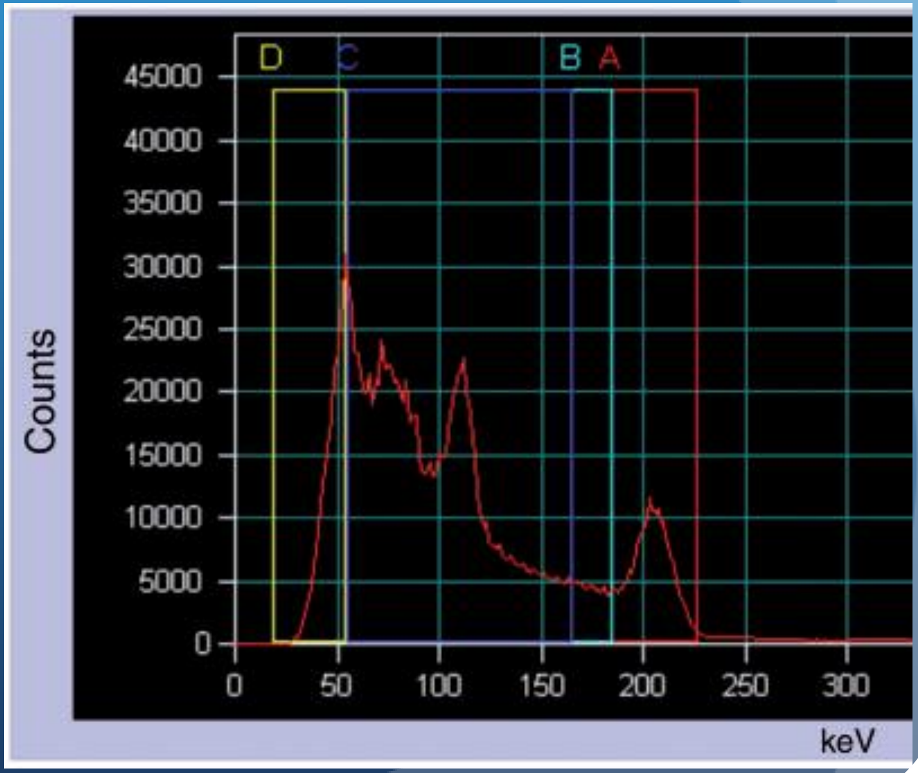
SPECT/CT

+

- Energy spectrum
- Open geometry

–

- Collimators
- No vendor calibration
- Low resolution



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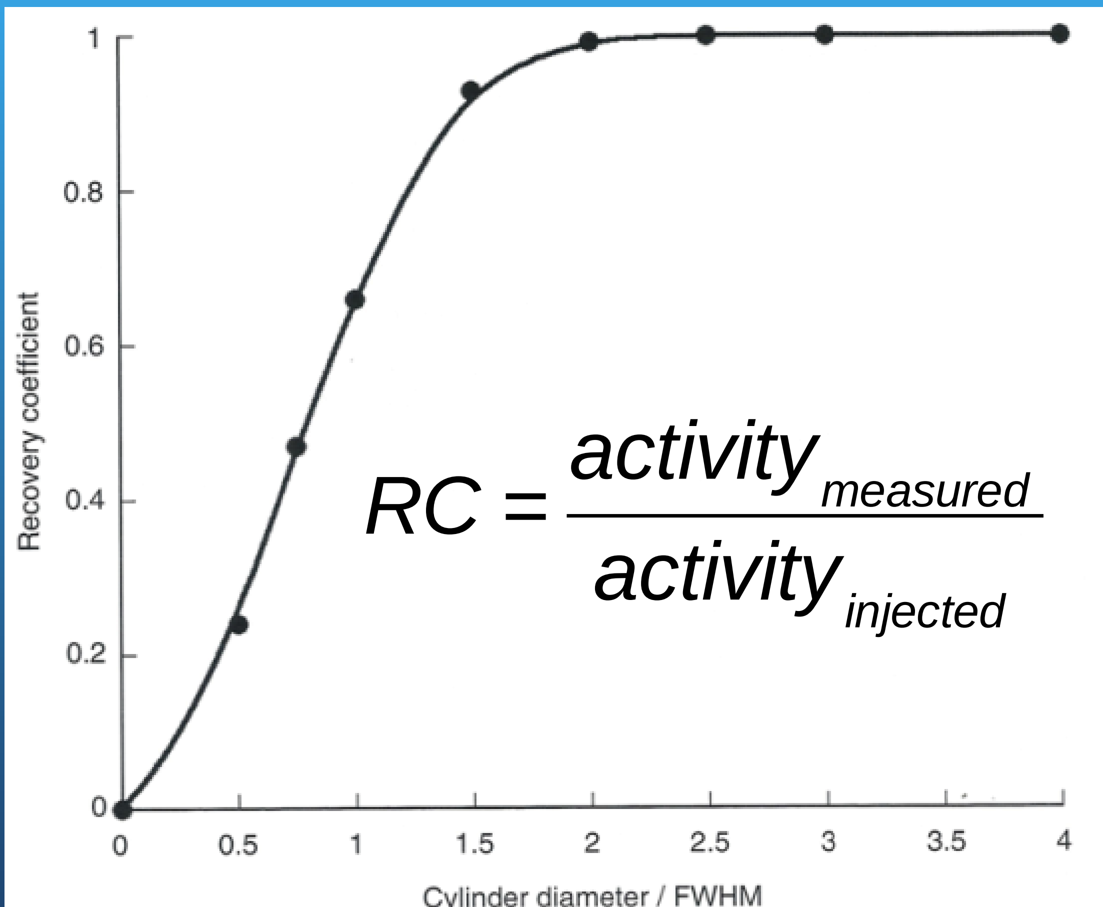
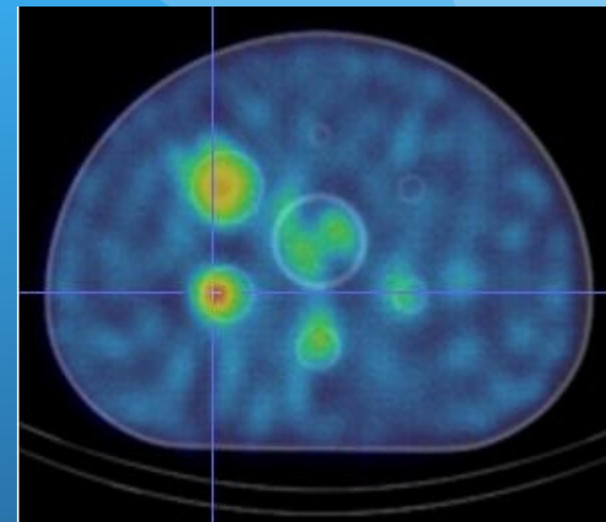
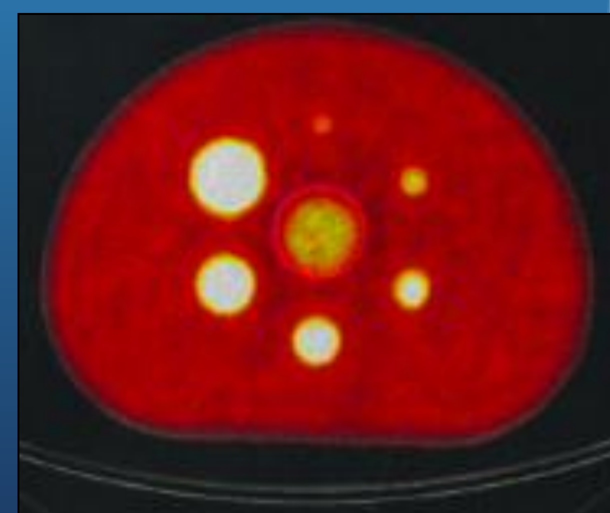
Partial volume effect



$$RC = \frac{activity_{measured}}{activity_{injected}}$$





S.R Cherry and J.A Sorenson. Phelps M.E. Physics in Nuclear Medicine. 3rd ed. Philadelphia. Saunders., 2003.

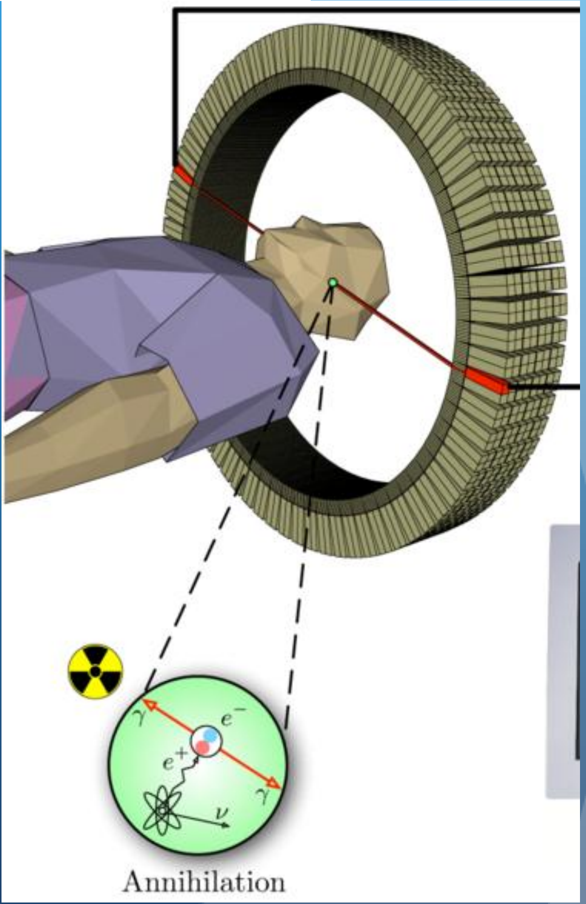
PET/CT

+

- High resolution
- High sensitivity
- Calibrated for positron counting
- Self collimation
- Time of flight

–

- Irradiate the patient and the worker
- Equipment and radionuclide expensive



Processing software

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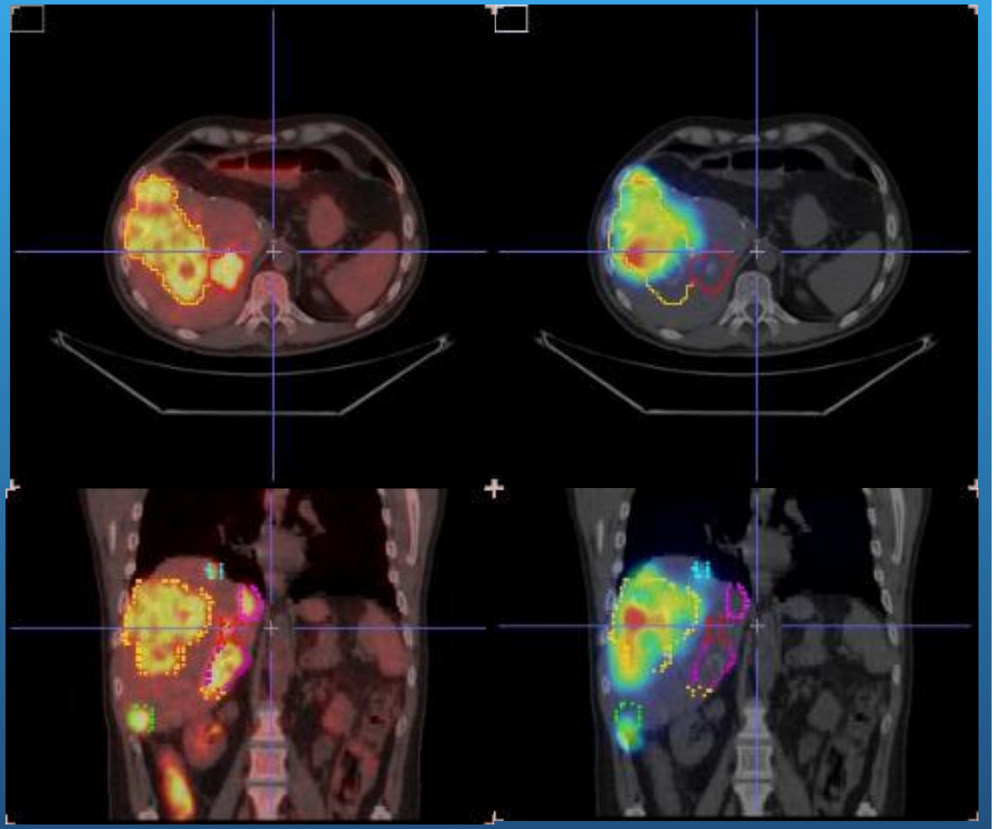
- Fusion
  - Different modalities
- Contouring
  - Different modalities
- Conversion & correction
  - Counts to activities or dose
  - Partial volume effect
- Exporting
  - Statistic
  - contouring



Dosimetry software: olinda

- Choose the isotope and phantom to determine S-factor
- Insert the residence time calculated with the statistics obtained (which integration?)

=> the dose table

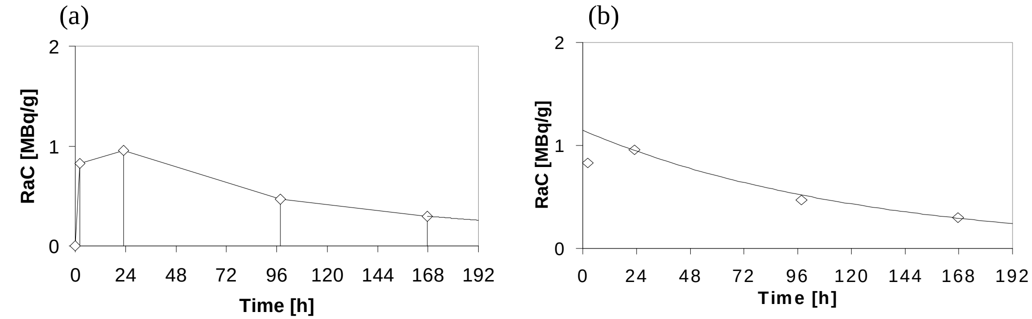
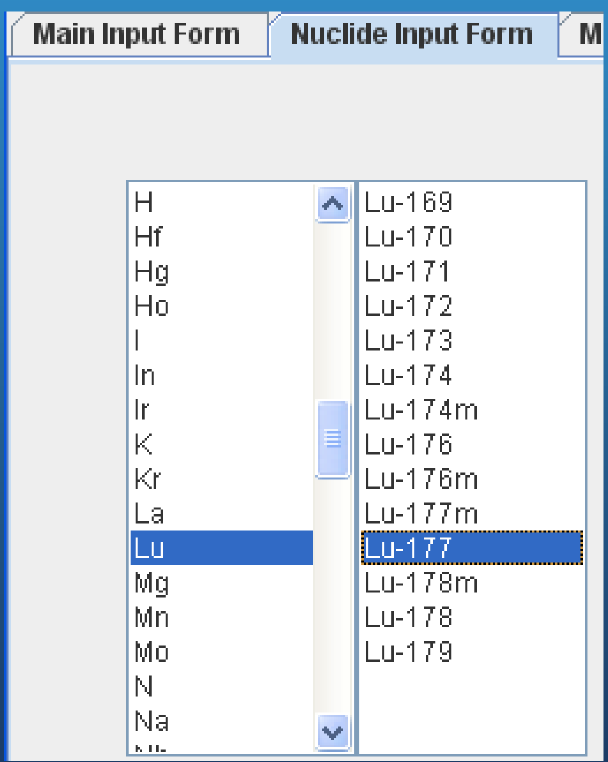
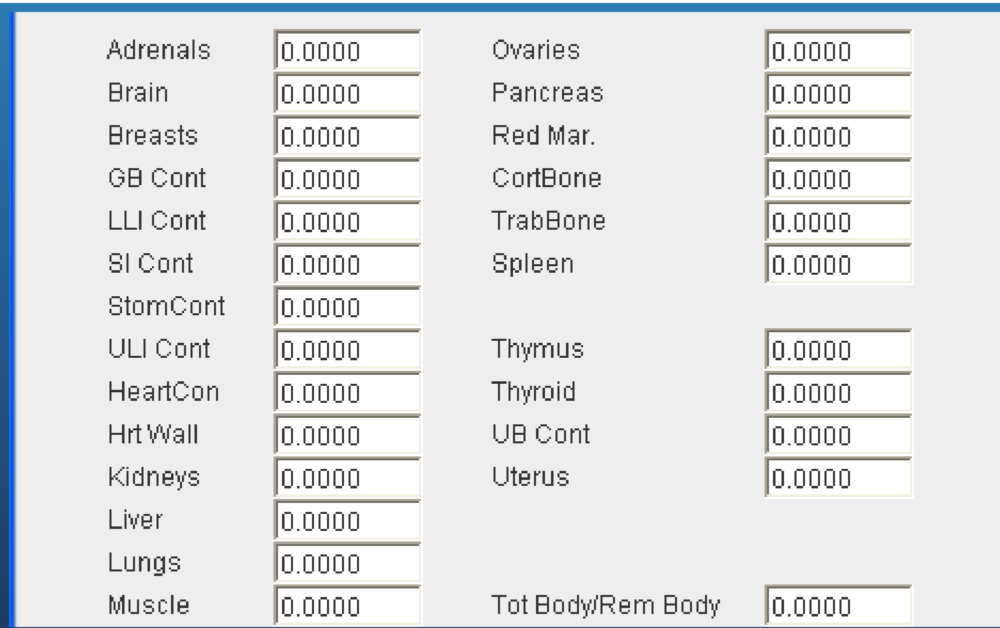


Figure 6: Typical kidney clearance curve integrated with the trapezoid method (a) or exponential fit method (b) in a patient treated with ^{177}Lu-octreotate.

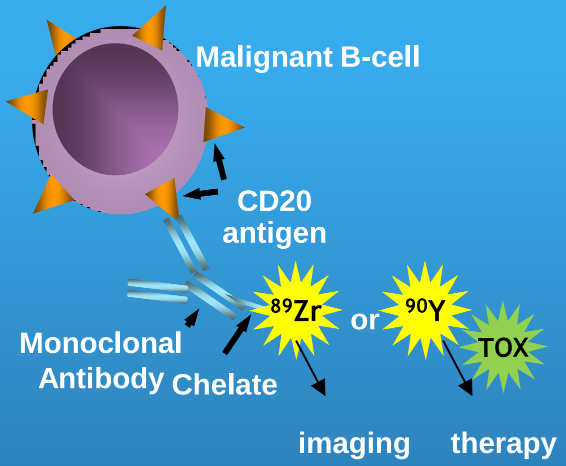




Quality Assurance

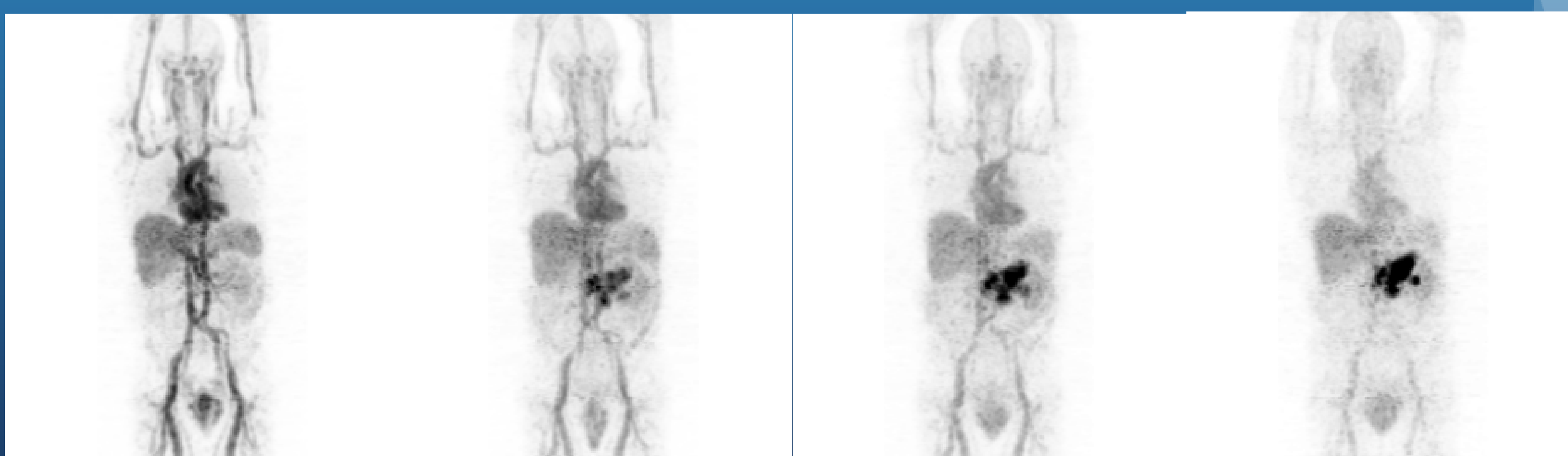
- Standard Procedure :
  - to optimize the reproducibility of the measurements
- Quality control of the equipment
  - to keep the calibrations
  - to evaluate systematic and stochastic errors
  - to evaluate the derives

Immuno-PET/CT



- Immuno-PET/CT combines the high sensitivity of PET/CT with the specificity of the chimeric monoclonal antibody (mAb) for the antigen expressed on the surface of cancer cells.
- Zirconium-89 is a positron emitter with a half-life of 78.4 hours, which is compatible with the time needed for intact mAb to achieve optimal tumour-to-background ratios.
- Antibody half life in blood 2-4 day

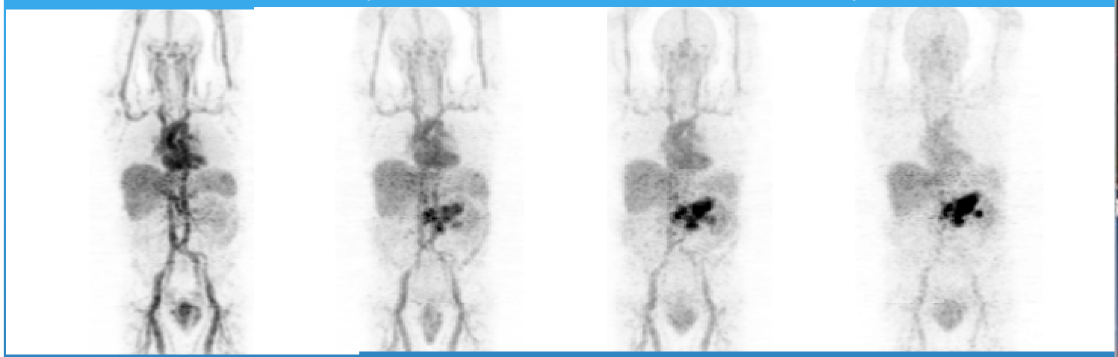
^{89}Zr-rituximab Immuno-PET/CT



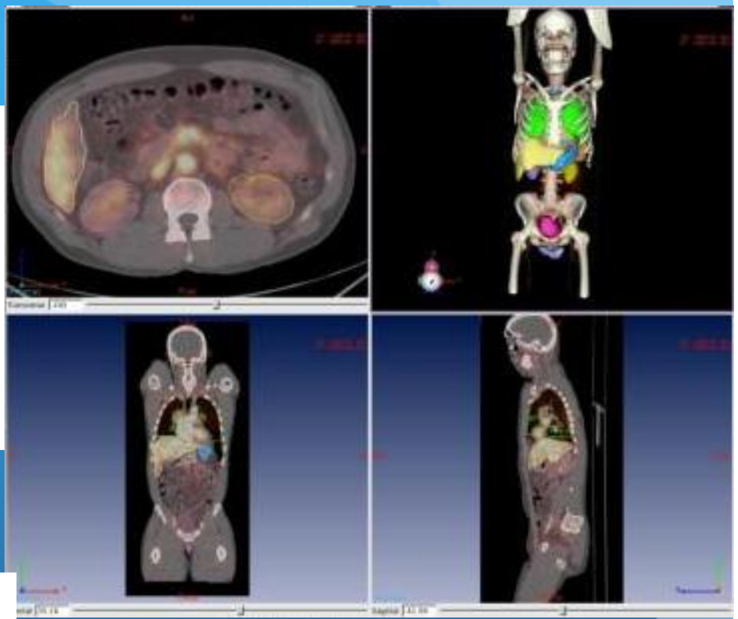
1 hour p.i. | 1 day p.i. | 3 days p.i. | 6 days p.i.

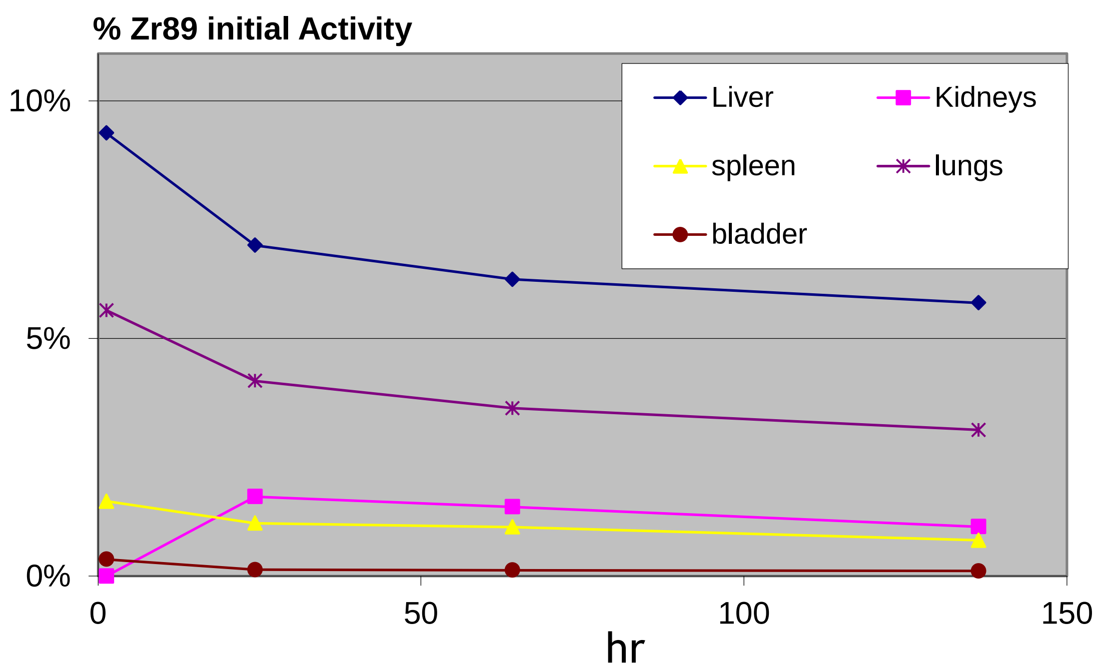
Immuno Dosimetry : Zr89 to Y90

^{89}Zr-rituximab Immuno-PET/CT
Antibody half life in blood 2-4 day



1 hour p.i. | 1 day p.i. | 3 days p.i. | 6 days p.i.





- % Zr89 is converted in % Y90 in function of her decay
- The Number of Y90 decay is the AUC + Y90 decay for the time remaining

Immuno Dosimetry : Olinda 1.0

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Number of Disintegrations in Source Organs:

Kidneys	1,30E000	MBq-h/MBq or uCi-h/uCi
Liver	7,76E000	MBq-h/MBq or uCi-h/uCi
Lungs	4,15E000	MBq-h/MBq or uCi-h/uCi
Spleen	9,68E-01	MBq-h/MBq or uCi-h/uCi
Remainder	4,85E001	MBq-h/MBq or uCi-h/uCi

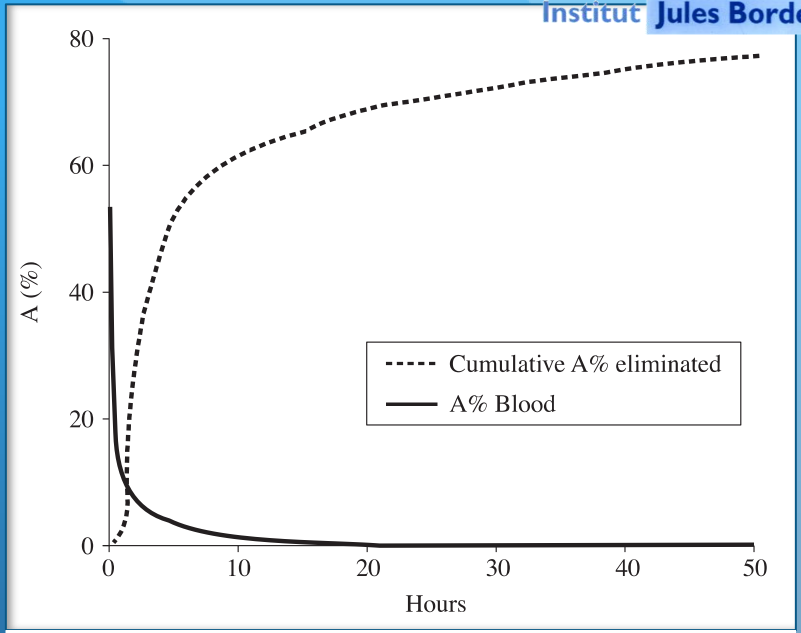
Organ Doses (mSv/MBq), Nuclide: Y-90 (6,41E01 hr), Adult Male

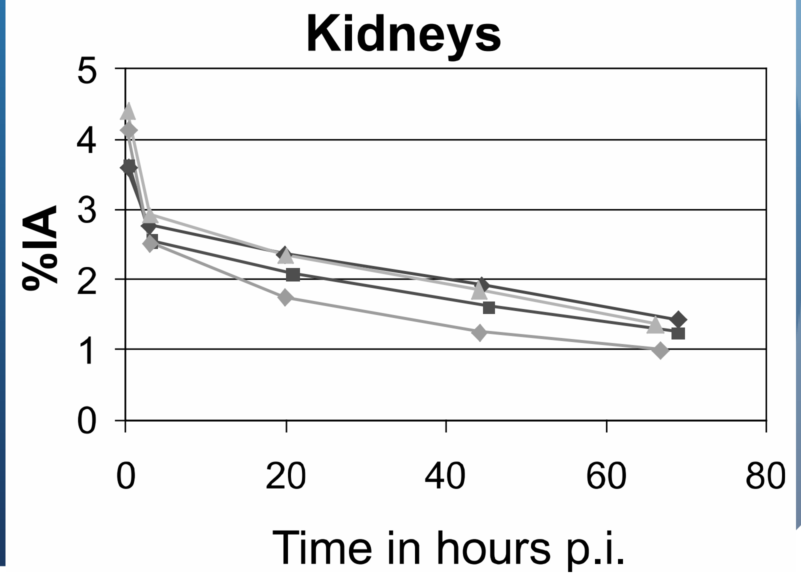
Calculated: 06.26.2012 at 03:57:23 CEST

Target Organ	Alpha	Beta	Photon	Total	EDE Cont.	ED Cont.
Kidneys	0,00E000	2,29E000	0,00E000	2,29E000	1,37E-01	5,72E-03
Liver	0,00E000	2,19E000	0,00E000	2,19E000	1,31E-01	1,09E-01
Lungs	0,00E000	2,24E000	0,00E000	2,24E000	2,68E-01	2,68E-01
Spleen	0,00E000	2,76E000	0,00E000	2,76E000	1,66E-01	6,91E-02
Urinary Bladder Wall	0,00E000	3,55E-01	0,00E000	3,55E-01	0,00E000	1,77E-02
Effective Dose Equivalent (mSv/MBq)					1,11E000	
Effective Dose (mSv/MBq)						8,54E-01

Tracer: Octreotide

- Somatostatine analog
- Binds on over-expressed receptors of neuroendocrine tumor
- Half-life in blood = 2 hours
- Uptake in kidneys, half-life depending on kidney function of the patient





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Tracer: which octreotide for diagnostic?

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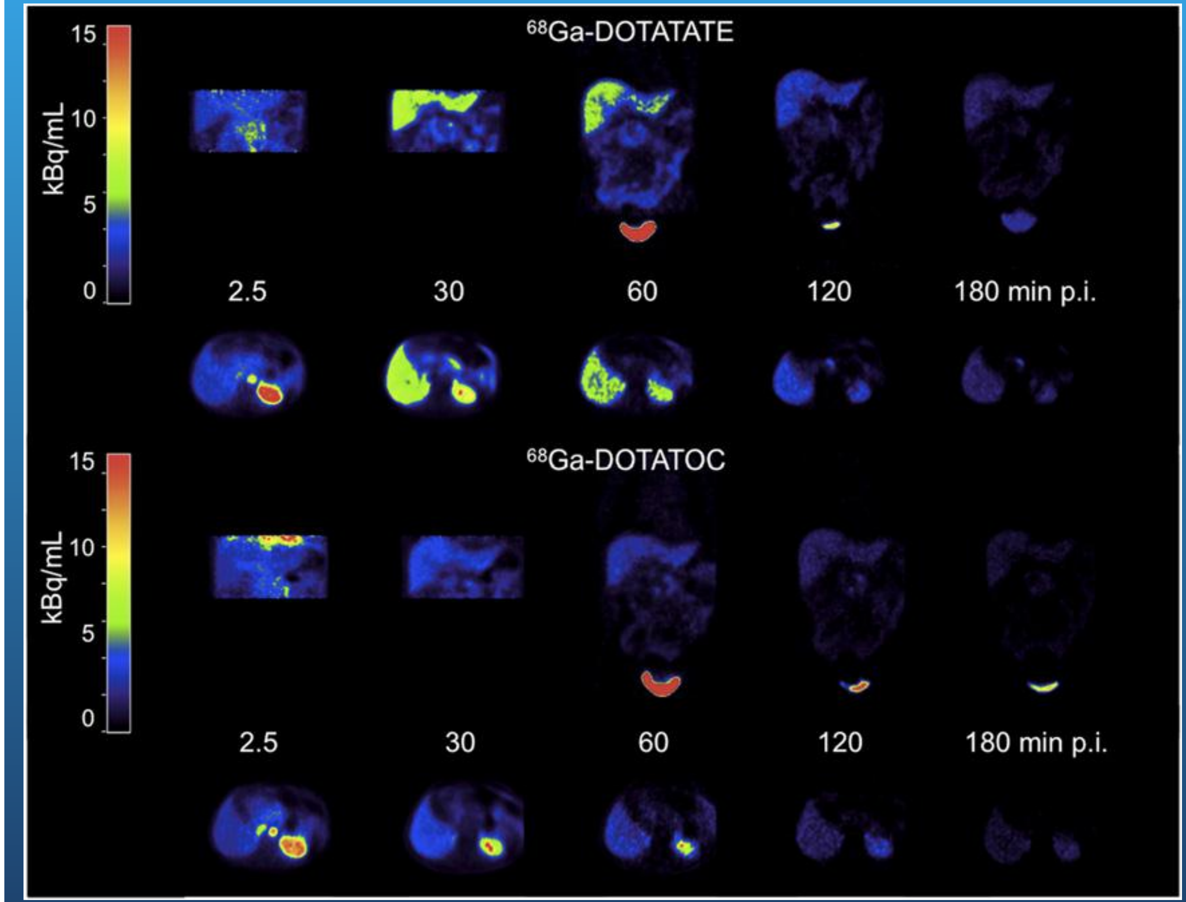

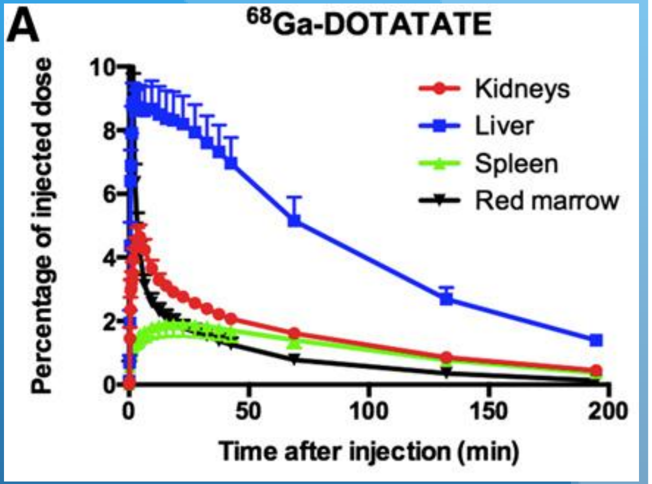

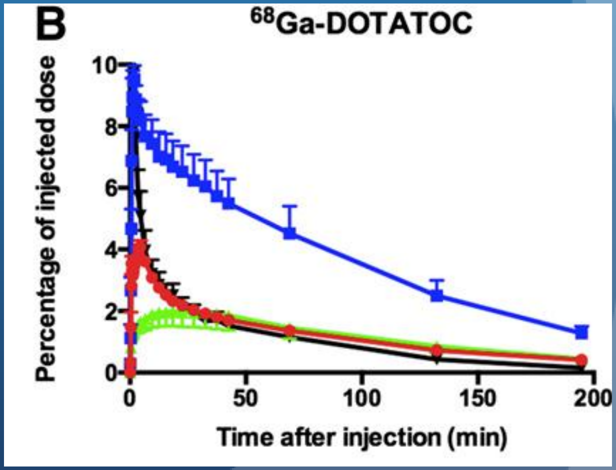

DOSIMETRY OF 68GA-DOTATOC AND 68GA-DOTATATE • Sandströ̈m et al.

Tracer: which octreotate for diagnostic?

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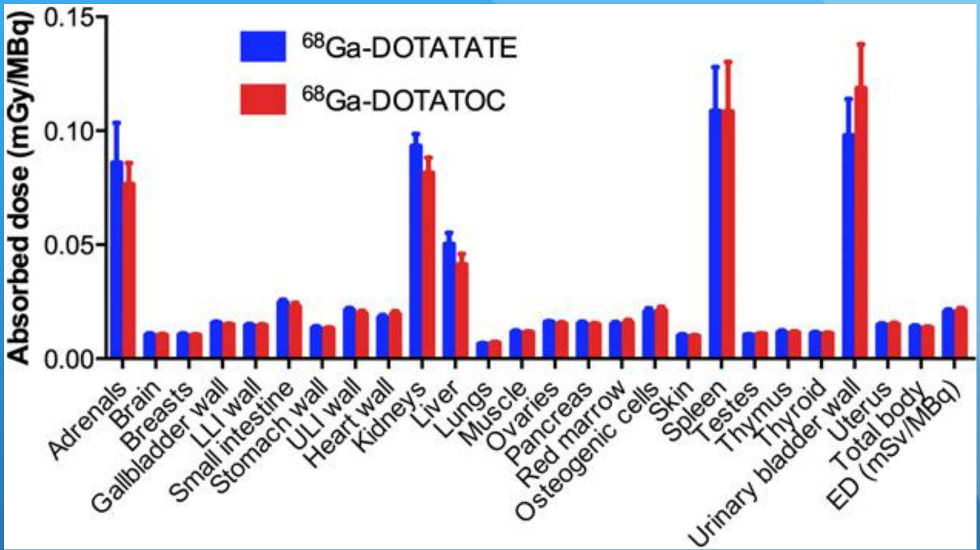

Selected Organ Dose and ED for Discussed Radiopharmaceuticals

Organ	^{68}Ga-DOTATATE*	^{68}Ga-DOTATOC (*12*)	^{68}Ga-DOTANOC (*13*)	^{111}In-DTPA-octreotide (*19*)	^{18}F-FDG (*20*)
Kidneys (mSv/MBq)	9.21E−02	2.2E−01	8.97E−02	4.5E−01	1.7E−02
Liver (mSv/MBq)	4.50E−02	7.4E−02	3.38E−02	7.0E−02	2.1E−02
Spleen (mSv/MBq)	2.82E−01	2.4E−01	7.25E−02	3.2E−01	1.1E−02
Urinary bladder wall (mSv/MBq)	1.25E−01	7.0E−02	8.36E−02	1.8E−01	1.3E−01
ED (mSv/MBq)	2.57E−02	2.3E−02	1.67E−02	8.0E−02	1.9E−02
Typical IA					
MBq	185	185	185	74	370
mCi	5	5	5	2	10
Estimated ED per scan (mSv)	4.8	4.3	3.1	5.9	7.0

68GA-DOTATATE HUMAN DOSIMETRY • Walker et al. JNM • Vol. 54 • No. 6 • June 2013

Tracer: wich octreotide for therapy?

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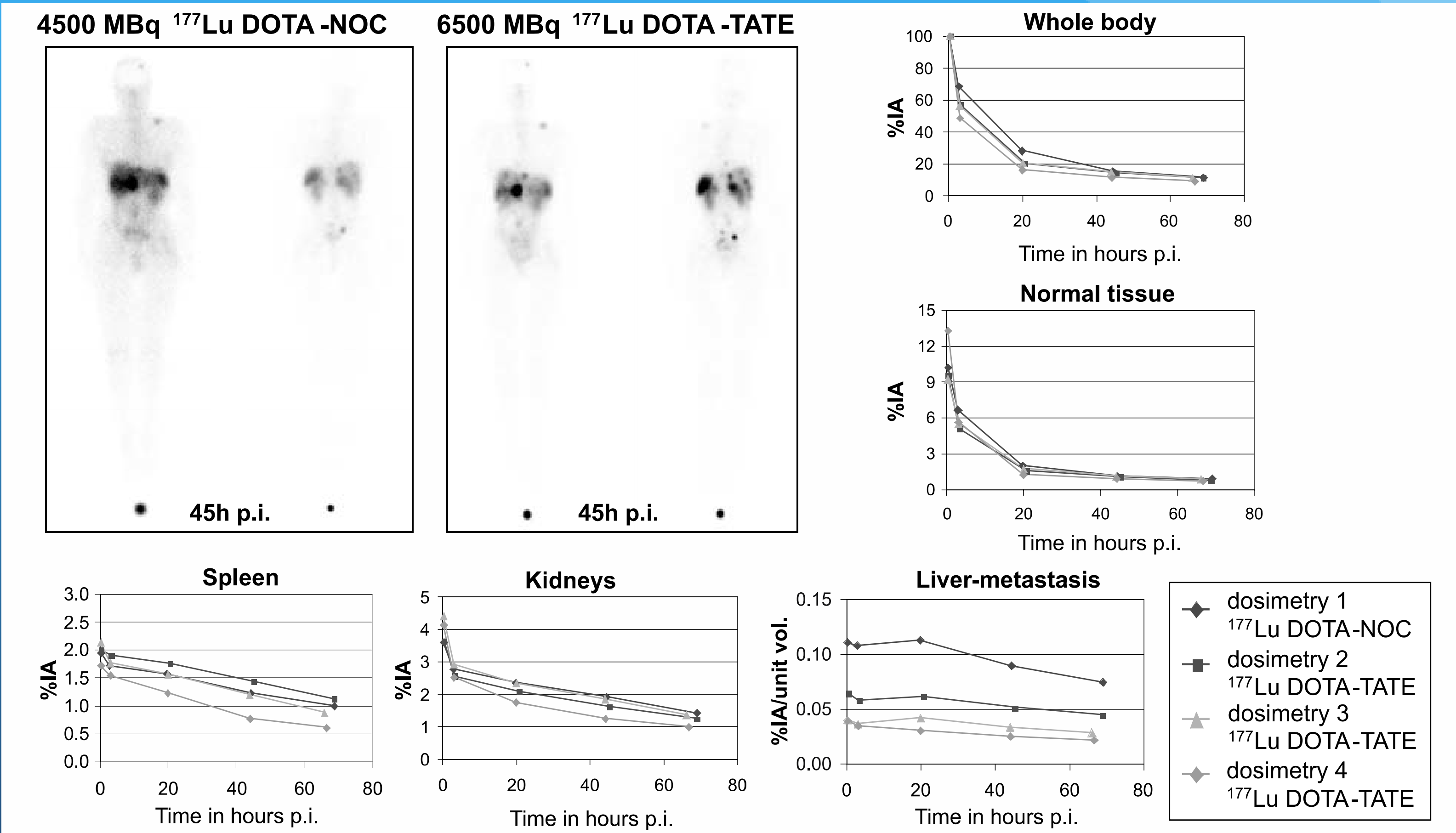

Figure 5. Peptide receptor radionuclide therapy using ^{177}Lu DOTA-TATE and ^{177}Lu DOTA-NOC in the same patient (scans are scaled to the maximum pixel of both scans).

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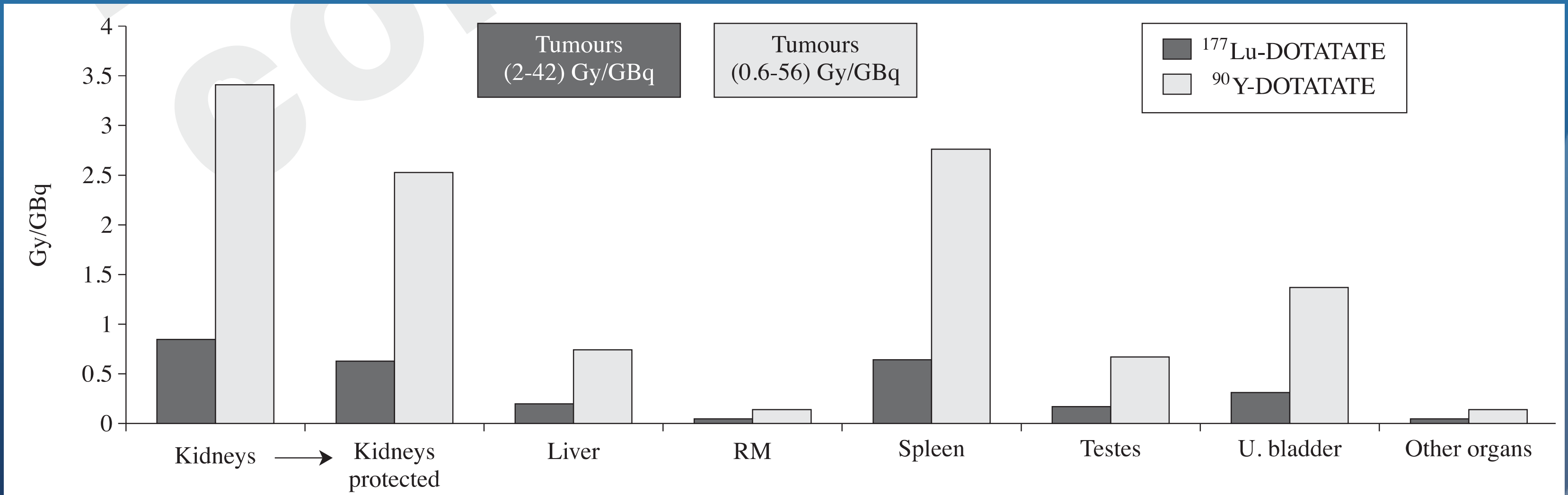
Which Marker for therapy ?

- Y90
  - Beta- emitter
  - half-life = 2.7 days
- Lu177
  - Beta- emitter decay in Hf177 excited states
  - half-life = 6.7 days
  - Hf177 excited
    - Gamma emitter 113 & 208 keV
    - Half-life < nanosecond



Dosimetry for treatment with radiolabelled somatostatin analogues. A review. Q J NUCL MED MOL IMAGING 2010;54:37-51

Conclusion

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- Patient Specific internal dosimetry in NM is achievable
- With systematic and stochastic errors
- We need robust and reproducible multisciplanary methodology that allow :
  - to estimate stochastic errors
  - to correct systematic errors (even retrospectively)