# Dosimetry with $^{177}$Lu-DOTATATE in clinical routine

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**Nuclear Medecine Department**

# Start of the story …


« First treatment with $^{177}$Lu-DOTATATE :
I really want to know, at least, the absorbed dose to the kidneys .
No stress, it is planned for next month. Thanks !»


# Start of the story …

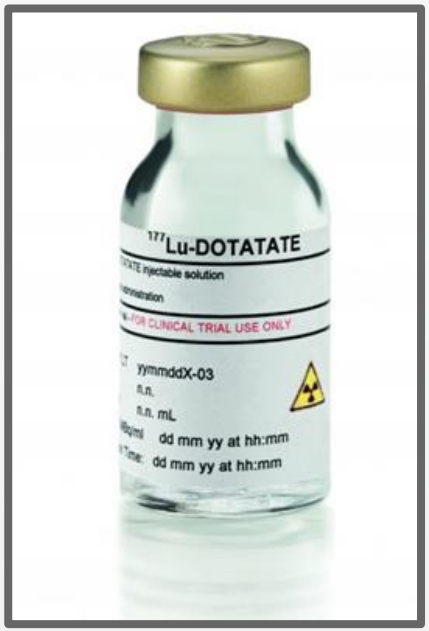
***$^{177}$Lu-DOTATATE***

**T=6,647 jours**

**Traitement des tumeurs neuroendocrines gastro-entéro-pancréatiques bien différenciées de l'intestin moyen à l'état métastatique ou inopérable**

**Surexpression de récepteurs à la somatostatine**

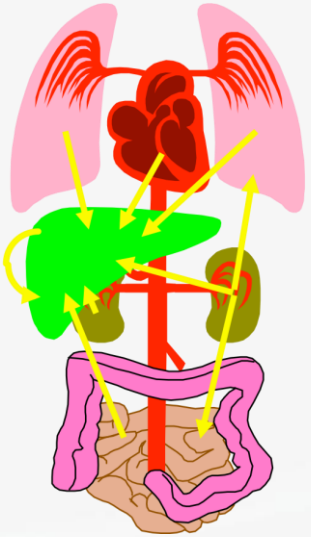
| Type d'émission | Energie (keV) | Probabilité d'émission (%) |
|---|---|---|
| Particules **β**-<br><br>***Thérapie*** | 498,30 | 79,30 |
| Rayonnements **γ**<br>- Principaux pics<br><br>***Imagerie post traitement et imagerie pour la dosimétrie*** | 208,37<br>112,95 | 10,40<br>6,20 |



# Absorbed dose determination

***Mean absorbed dose (Gy)***

*to an organ of interest*



$$\overline{D}_k = \sum_h \tilde{A}_h \times S_{(k \leftarrow h)}$$

| Gy | MBq.h | Gy/(MBq.h) |
|---|---|---|
| ***Mean absorbed dose*** *in target k from source h* | ***Cumulated activity*** *Total number of decays in source h* | ***S factor*** *Absorbed dose in target k per decay in source h* |

**BIOLOGICAL COMPONENT** ***(pharmacokinetics)***

**PHYSICAL COMPONENT** ***(calculation)***

*By courtesy of Dr Manuel Bardiès*

# Absorbed dose determination

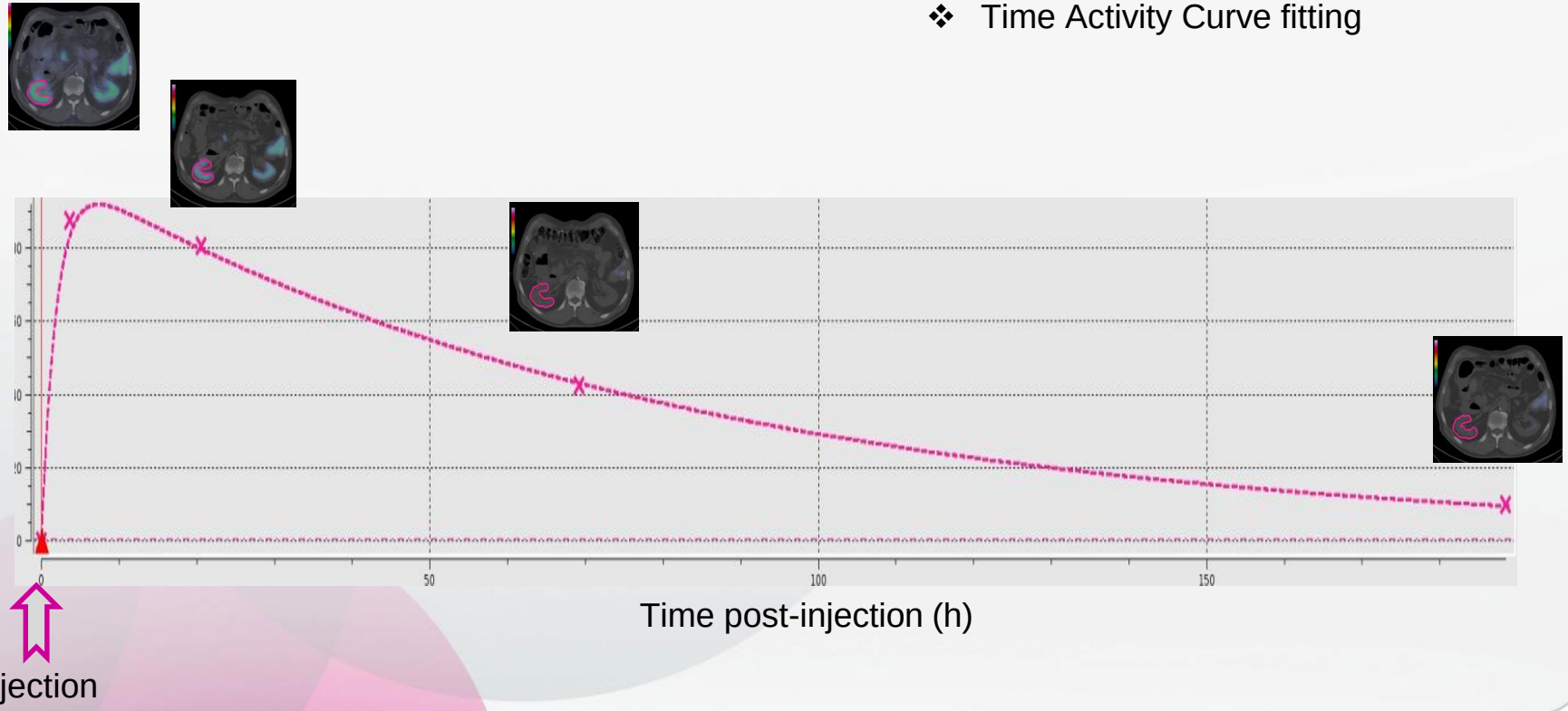
## BIOLOGICAL COMPONENT

***Cumulated Activity in MBq.h***

*Total number of decays in a segmented organ during the exploration time period*

Spatial and temporal distribution of the radiopharmaceutical

- Quantitative imaging
- Time Activity Curve fitting



# Absorbed dose determination

## PHYSICAL COMPONENT

How much of the energy emitted by the radioactive source is absorbed in organs of interest ?

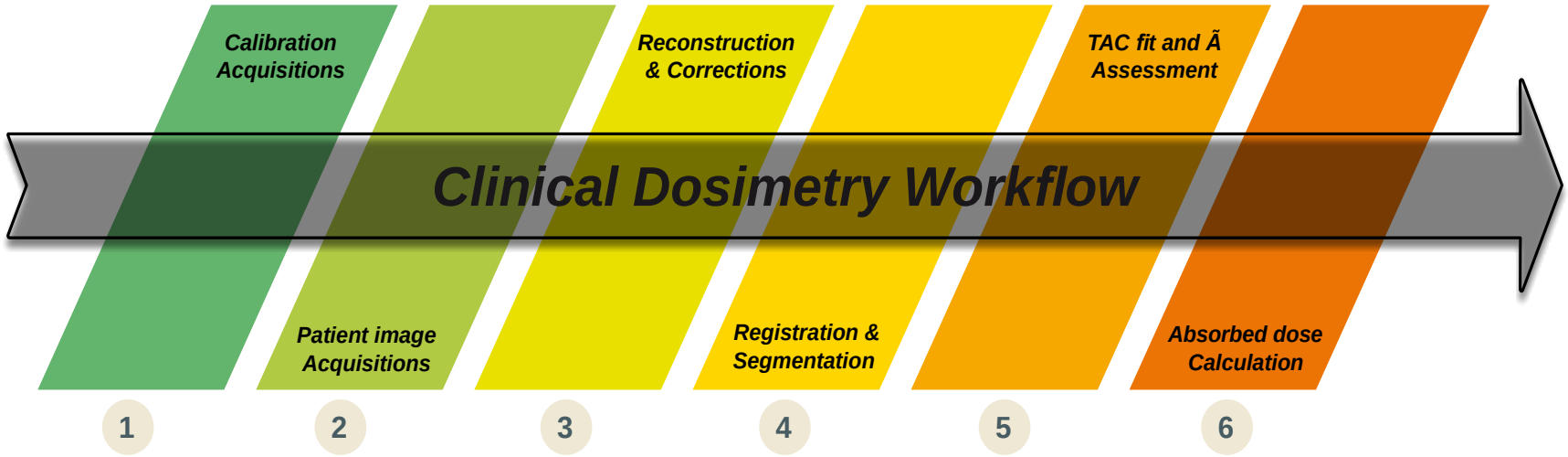
**Depends on :**

- Type and energy of radiation emitted from the radionuclide
- Shape, size and mass of the source and target organs
- Distance and type of material between the source and target organs

**Determined by :**

Calculation algorithms : Local deposition method (LDM), convolution of Voxel Dose Kernels (DK), full radiation transport modelling with Monte Carlo codes

# Dosimetry workflow



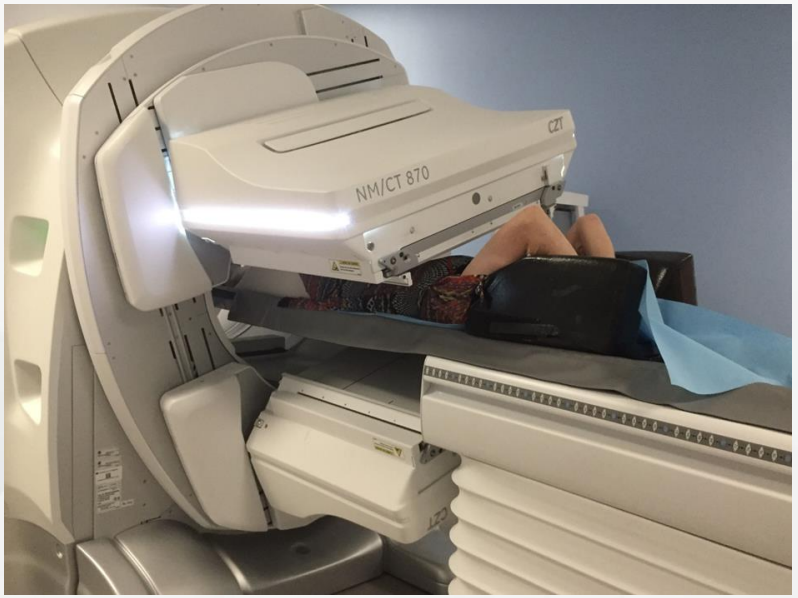

*E Mora-Ramirez et al. Med. Phys. (2020)*

# Calibration process

- **Equipment**

**SPECT/CT Discovery NM/CT 670 (GE)**
*Medium-Energy General Purpose collimator*
*3/8-in NaI(Tl) crystal thickness*
*Bright Speed 16 CT*

**SPECT/CT Discovery 870 CZT (GE)**
*Medium-Energy collimator MEHRS*
*130 CZT modules 39.4x39.4x7.25mm*
*Optima CT540*



# Calibration process

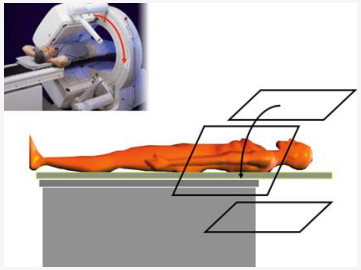
- **Correction maps creation for $^{177}$Lu: energy and uniformity**

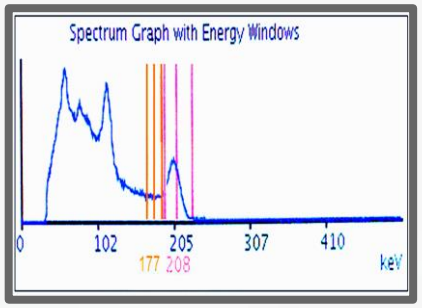
*L Santoro et al. EJNMMI Res. (2018)*

- **Acquisition imaging protocol implementation**

*(MIRD Pamphlet 26 )*

**3D SPECT/CT imaging protocol**






| Collimator | Emission Window | Scatter Window | Matrix (pixel) | Number of Projections | Time per projection (s/p) | Angle projections (°) | Acquisition duration (min) | Auto-Contour |
|---|---|---|---|---|---|---|---|---|
| MEGP | 208 keV _20% | 177 keV 10% | 128×128 | 60 | 45 | 6 | 22.5 | *Body Contour* |

- **Reconstruction parameters**

**Volumetrix MI**
**Xeleris Software (GE)**

| Reconstruction method | Corrections | Number of iterations | Number of subsets |
|---|---|---|---|
| OSEM | AC + SC + RR | 6 | 10 |

# Calibration process

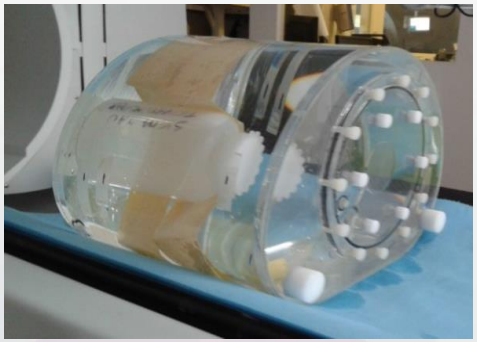
- **Calibration factor (CF) => Conversion Counts –> MBq**

$$CF = \frac{C \text{ (number of counts)}}{A_{t\,acq} \text{ (MBq)} \times T_{acq} \text{ (s)}}$$

Decay activity corrected at $t_{acq}$

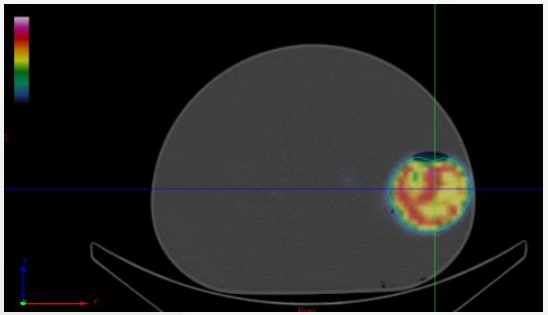
Acquisition duration

**A (MBq)**



500 mL bottle
273 ± 15 MBq of $^{177}$Lu

**C (number of counts)**



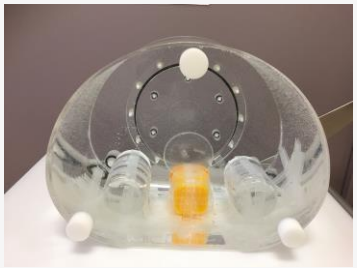
Isocontour representing a volume of 500 mL automatically segmented on the nuclear medicine image

**SPECT/CT Imaging and reconstruction with clinical protocol**

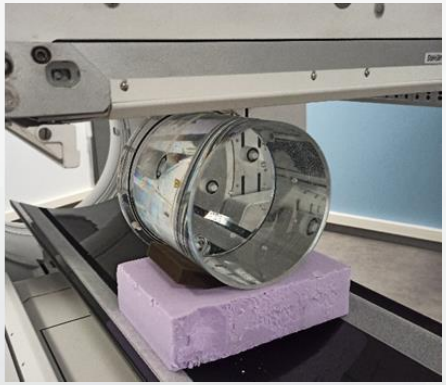
# Calibration process

- **Calibration factor (CF) => Conversion Counts –> MBq**

**A (MBq)**

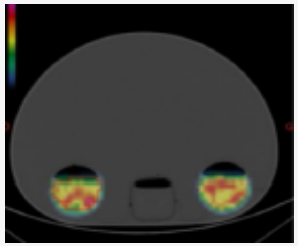


2 bottles of 250 mL filled with
200 mL of 82.2 ± 4.1 MBq of $^{177}$Lu

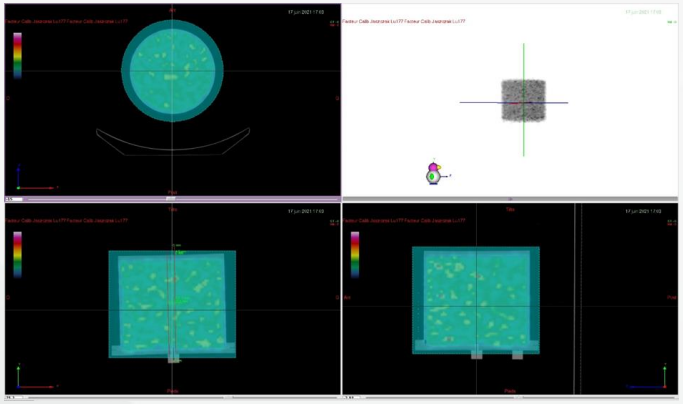


Jaszczak fantom without insert
625 MBq of $^{177}$Lu

**C (number of counts)**



Isocontour representing a volume of 200 mL automatically segmented on the nuclear medicine image



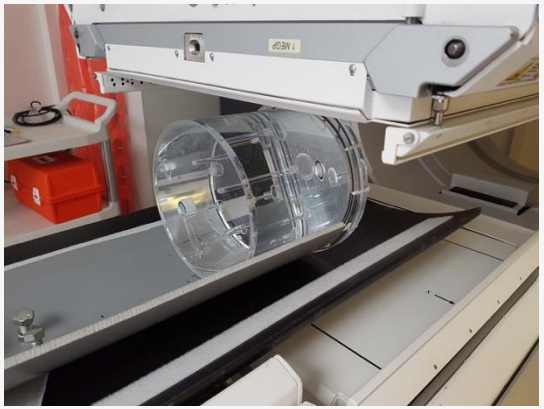
VOI higher than the phantom

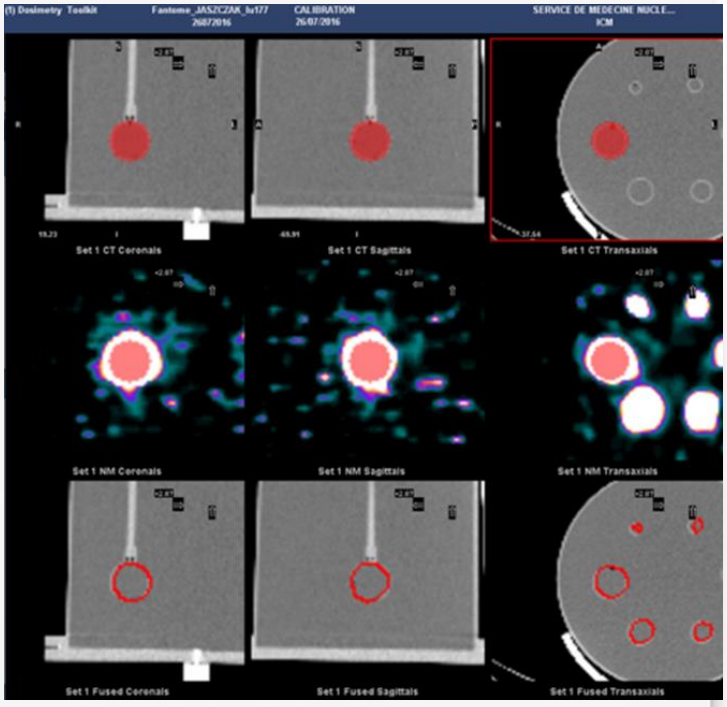
***MRTDosimetry _J Tran-Gia and M Lassmann***

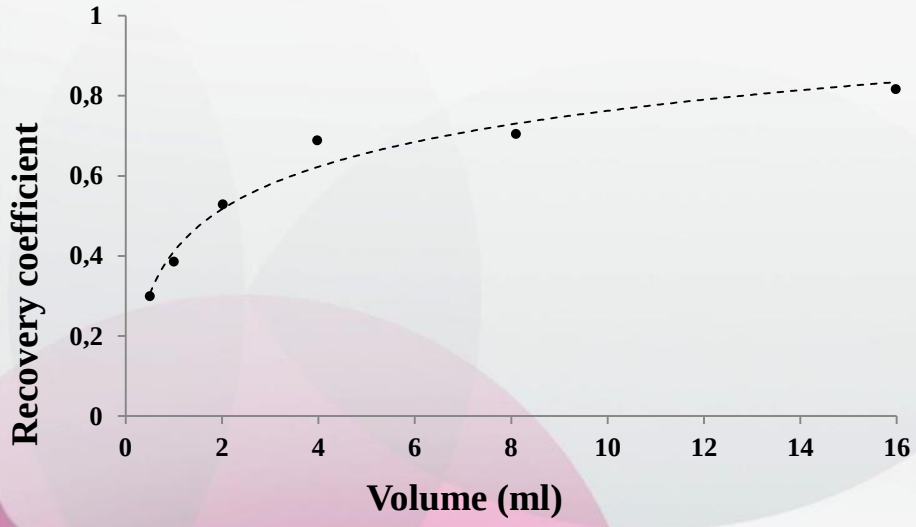
**SPECT/CT Imaging and reconstruction with clinical protocol**

# Calibration process

- **Recovery coefficients => Partial Volume Effect correction**



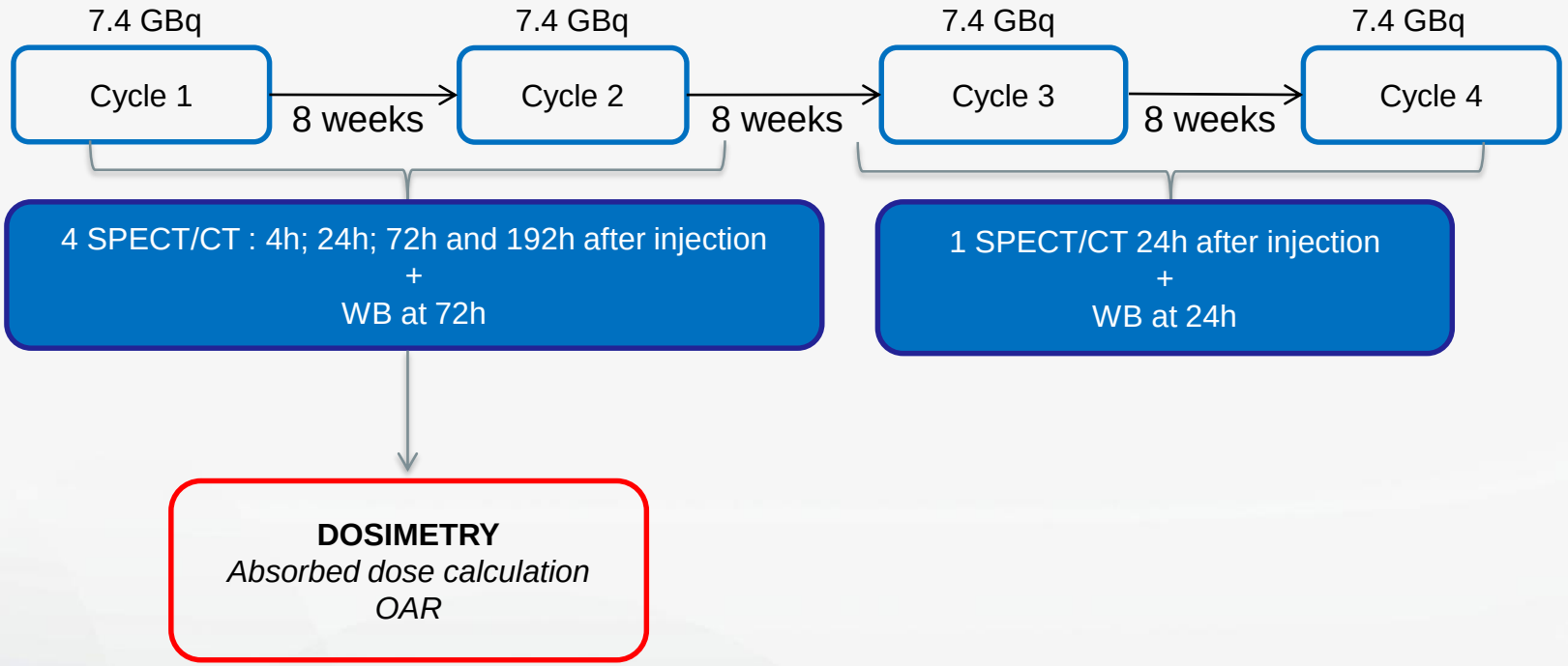



$$RC_i = \frac{A_{SPECT/CT\ (Vi)}}{A_{(Vi)\ measured\ (dose\ calibrator)}}$$

# Dosimetry workflow

## *Dosimetry imaging protocol*




D0 : SPECT/CT (4h) - CT Optimized Dose (better image quality)
D1 : SPECT/CT (24h) - CT Low Dose
D3 : SPECT/CT (72h) - CT Low Dose
D8 : SPECT/CT (192h) - CT Low Dose

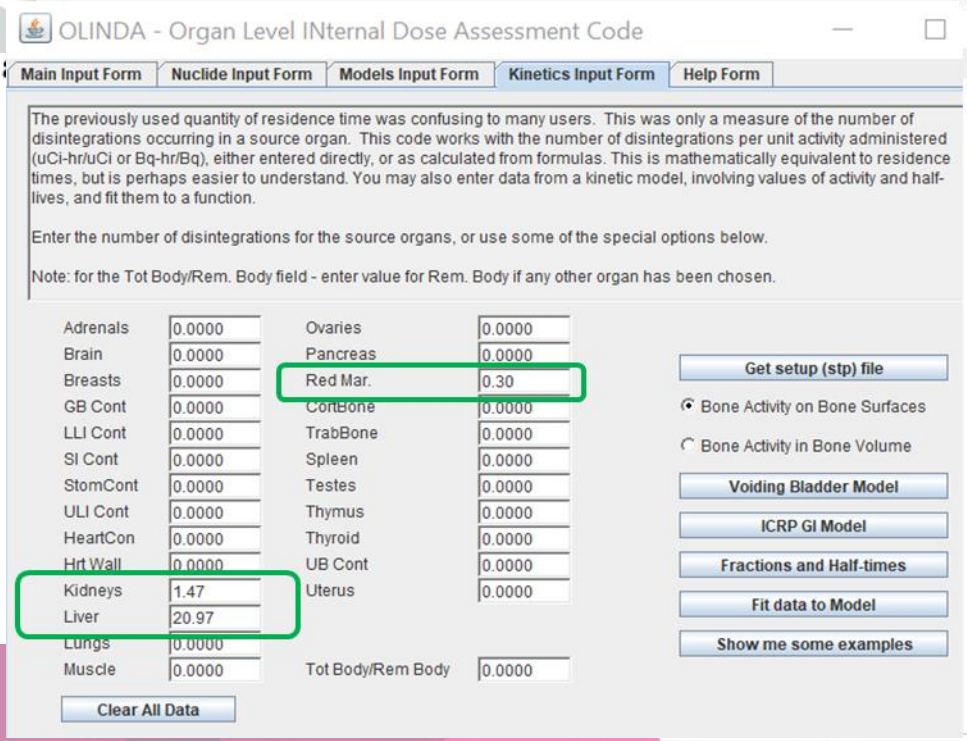
**Reproducible patient set up with immobilization devices**

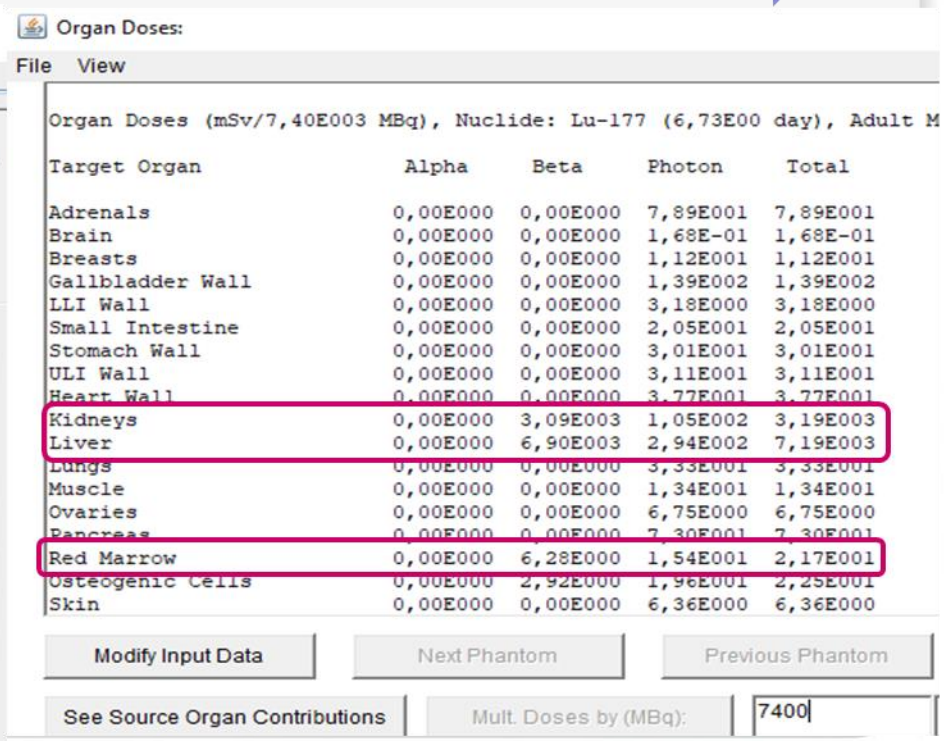
# Dosimetry workflow

Reconstruction → Registration → Segmentation → Time activity curve fitting Ã evaluation → Absorbed dose calculation

« Preparation for DTK » (GE) → DOSIMETRY TOOLKIT (GE) → TIAC (h) → OLINDA/EXM® V1.0 → AD (Gy)

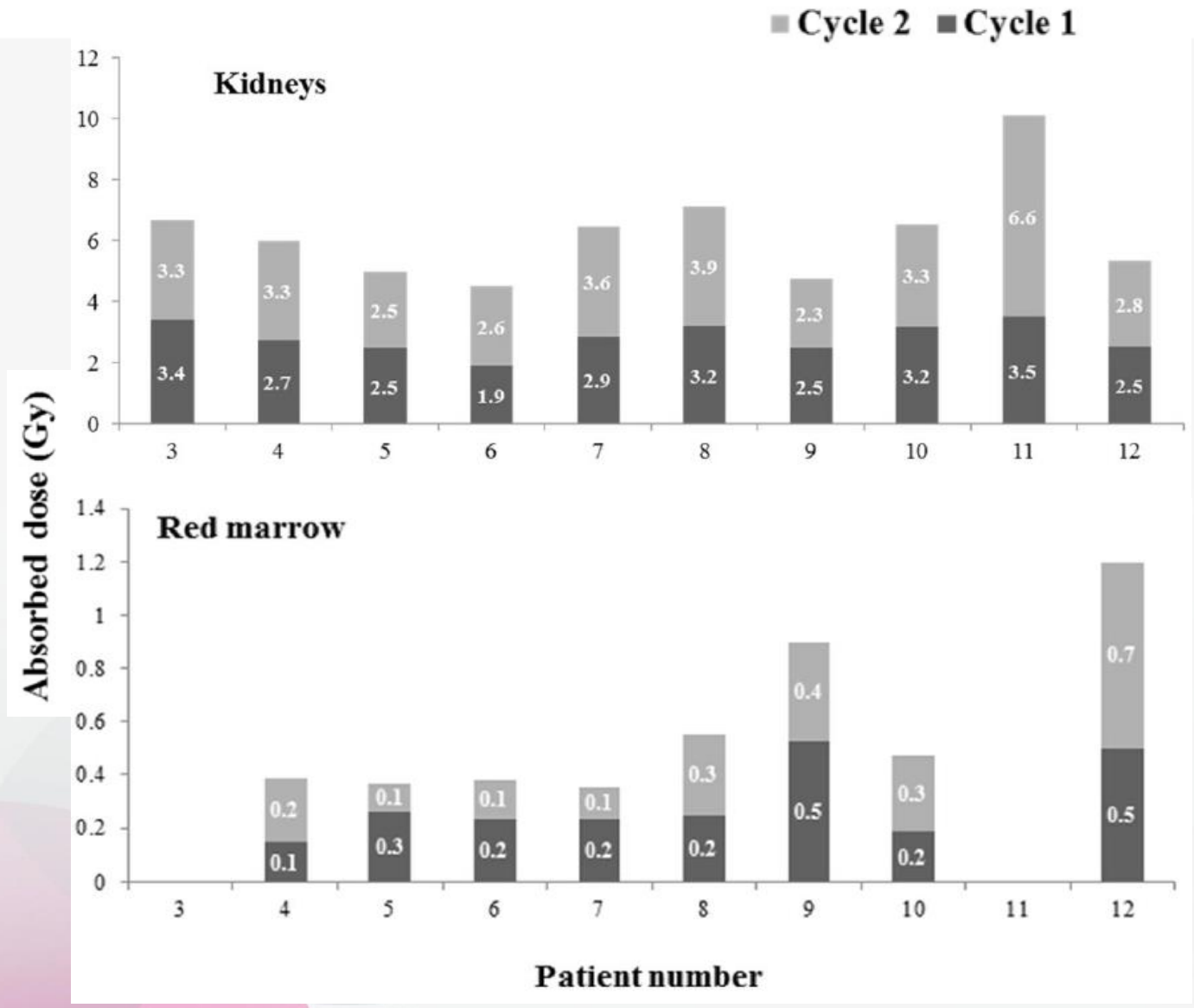
TIAC, time integrated activity coefficient; DTK, Dosimetry Toolkit; AD, absorbed dose



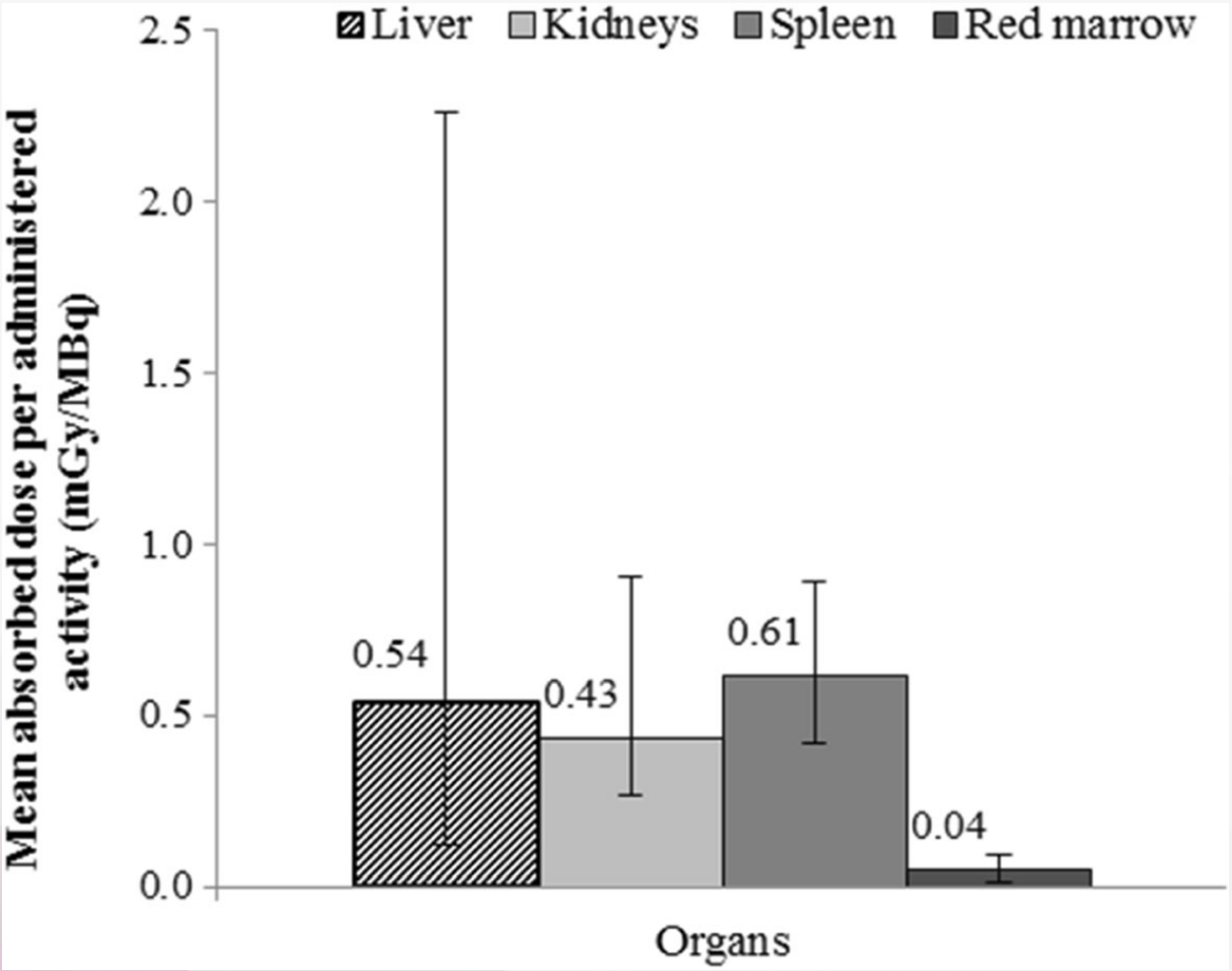
# Dosimetry workflow

**12 patients**
**22 dosimétries**

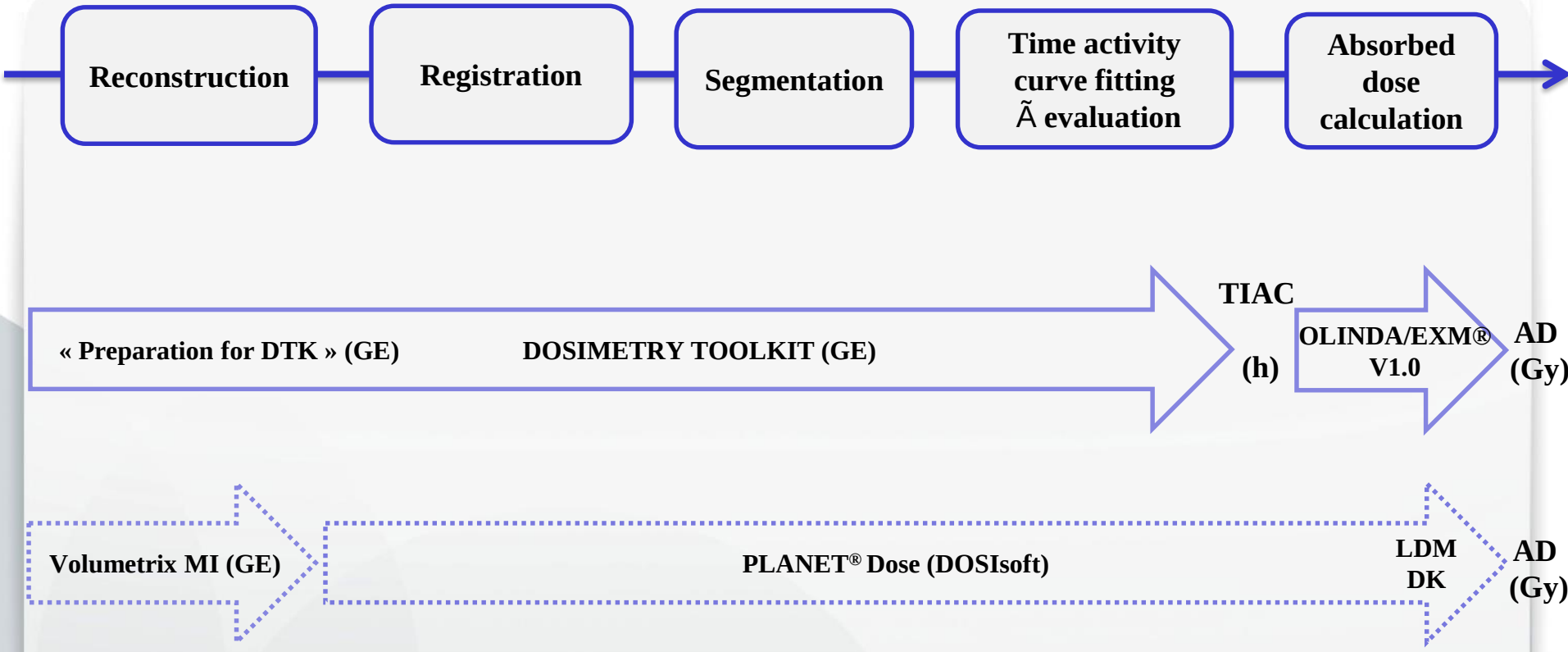


# Dosimetry workflow

**12 patients**
**22 dosimétries**



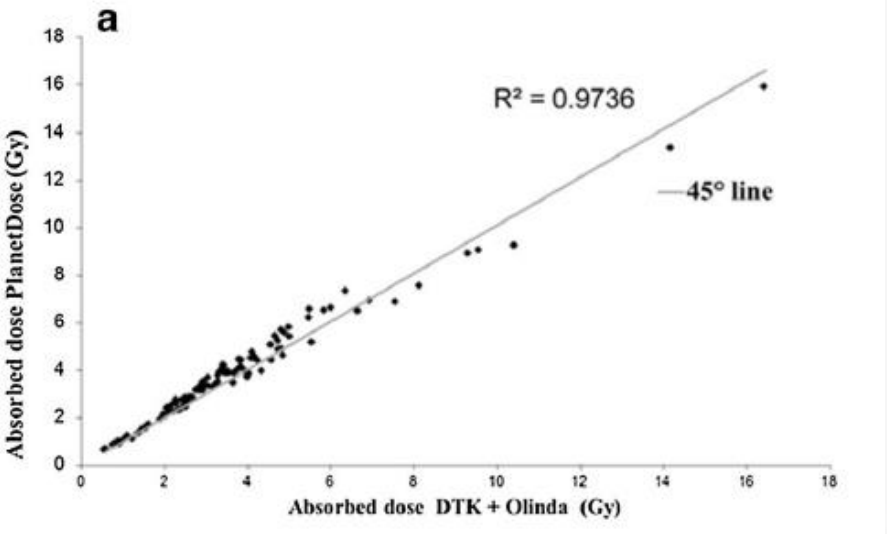
# Dosimetry workflow

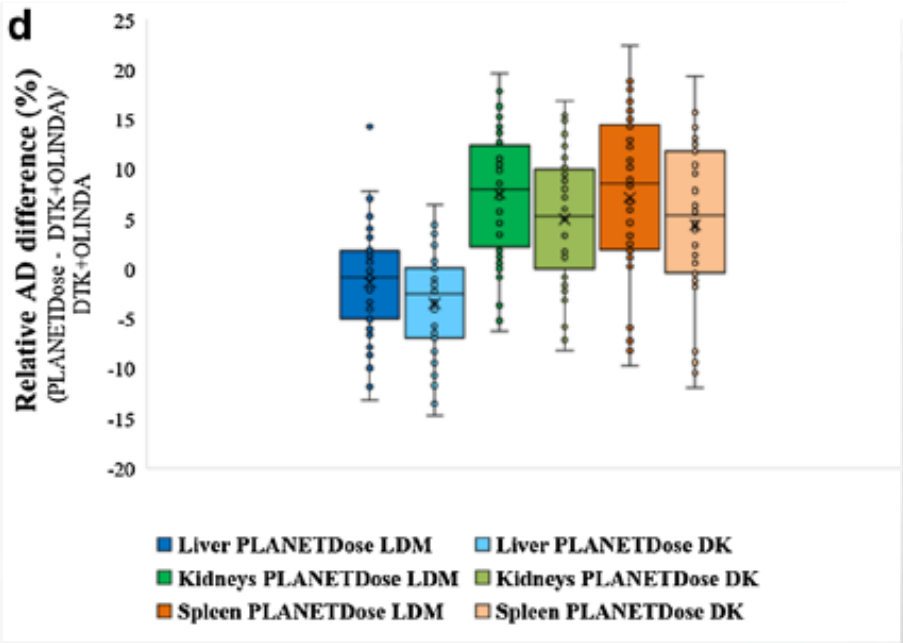



TIAC, time integrated activity coefficient; DTK, Dosimetry Toolkit; AD, absorbed dose; LDM, local deposition method; DK, dose kernel

# Dosimetry workflow

**21 patients**
**40 dosimétries**



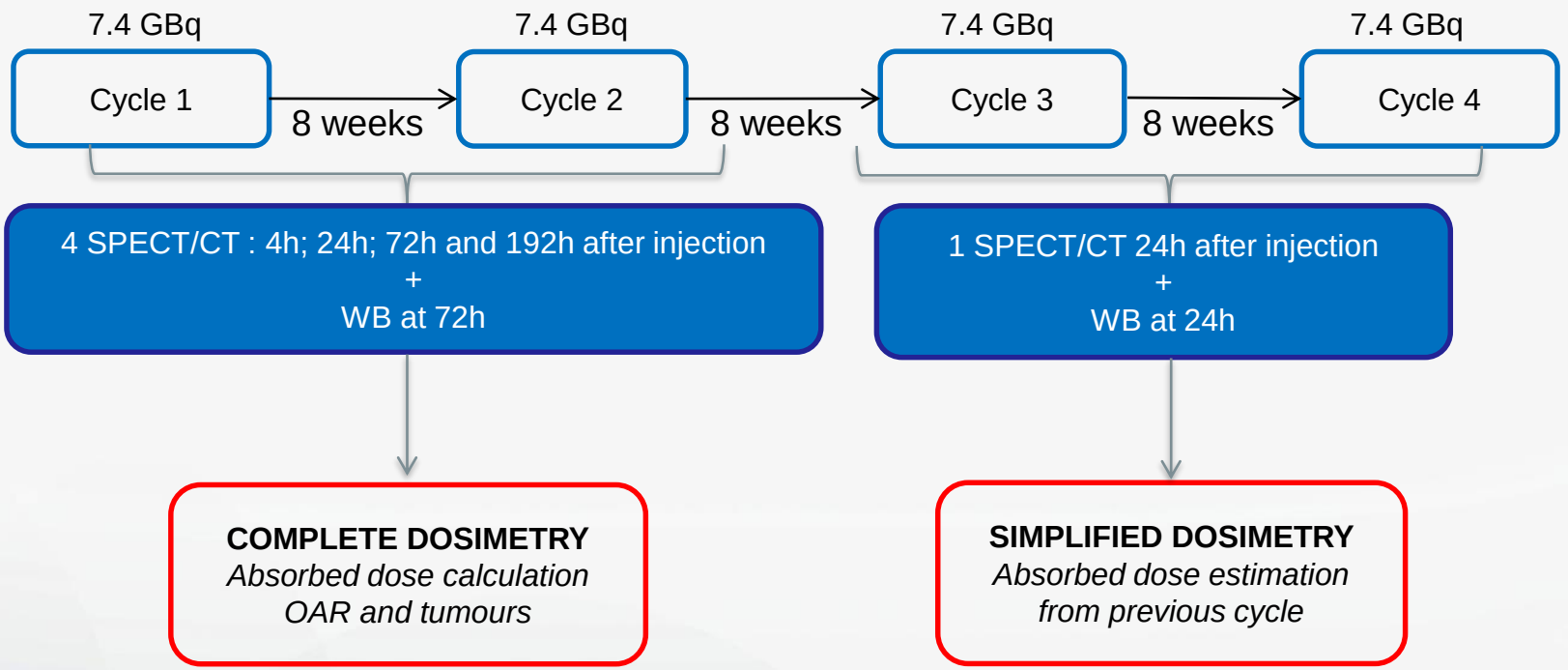




| ORGANS | Mass (g) | | TIAC (h) | | Absorbed dose (Gy) | | |
|---|---|---|---|---|---|---|---|
| | DTK + OLINDA/EXM® V1.0 | PLANET®Dose | DTK + OLINDA/ EXM® V1.0 | PLANET® Dose | DTK + OLINDA/ EXM® V1.0 | PLANET®Dose | |
| | | | | | | LDM | DK |
| Liver | 2141.6 ± 1213.3 | 2191.7 ± 1205 | 14.9 ± 24.1 | 15.1 ± 24.2 | 3.40 ± 3.9 | 3.27 ± 3.7 | 3.21 ± 3.6 |
| Kidneys | 478.3 ± 111.4 | 461.5 ± 108.3 | 2.2 ± 0.7 | 2.4 ± 0.8 | 3.01 ± 0.9 | 3.23 ± 0.9 | 3.16 ± 0.9 |
| Spleen | 290.4 ± 181.3 | 281.7 ± 178.5 | 2.0 ± 1.5 | 2.0 ± 1.4 | 4.15 ± 1 | 4.45 ± 1.2 | 4.36 ± 1.2 |

*L Santoro et al.*
*EJNMMI Res. (2021)*

# Dosimetry workflow

## *Dosimetry imaging protocol*



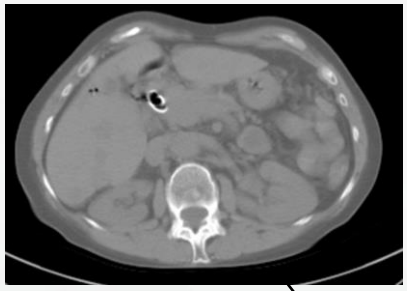

D0 : SPECT/CT (4h) - CT Optimized Dose (better image quality)
D1 : SPECT/CT (24h) - CT Low Dose
D3 : SPECT/CT (72h) - CT Low Dose
D8 : SPECT/CT (192h) - CT Low Dose

**Reproducible patient set up with immobilization devices**

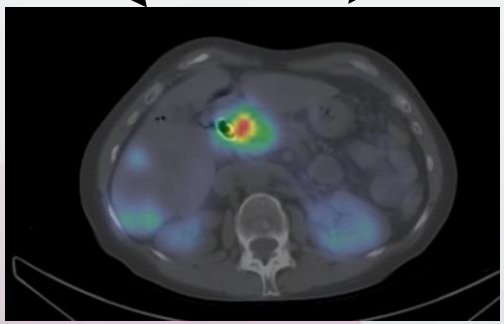
# Dosimetry workflow

**Reconstruction** → **Registration** → **Segmentation** → **Time activity curve fitting Ã evaluation** → **Absorbed dose calculation**

CT



NM

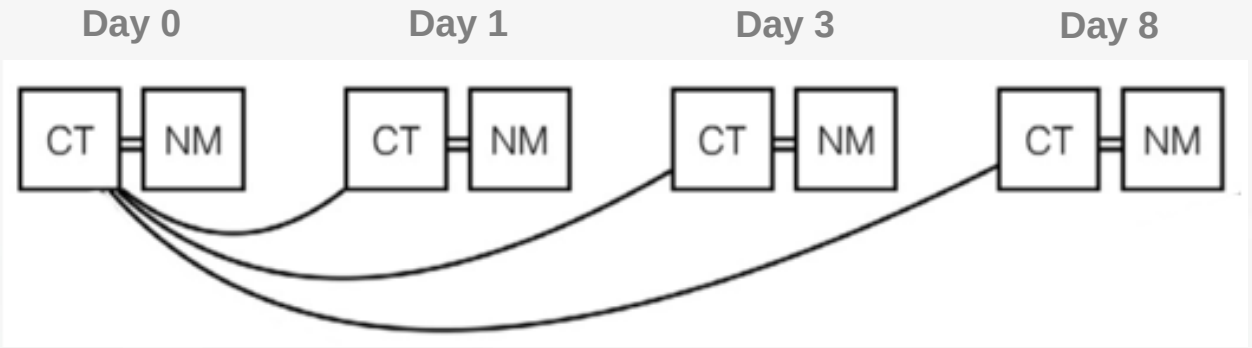


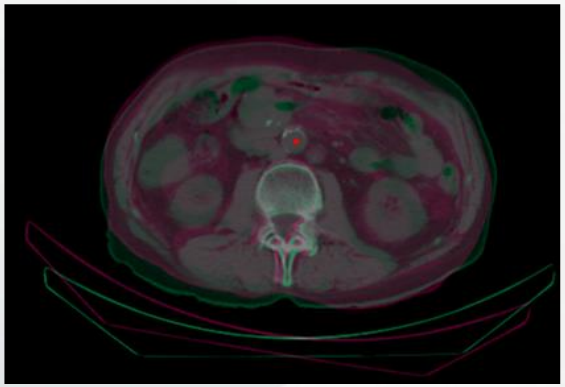
**Volumetrix MI**
**Xeleris Software (GE)**

| Reconstruction method | Corrections | Number of iterations | Number of subsets |
|---|---|---|---|
| OSEM | AC + SC + RR | 6 | 10 |

# Dosimetry workflow

Reconstruction → **Registration** → Segmentation → Time activity curve fitting Ã evaluation → Absorbed dose calculation



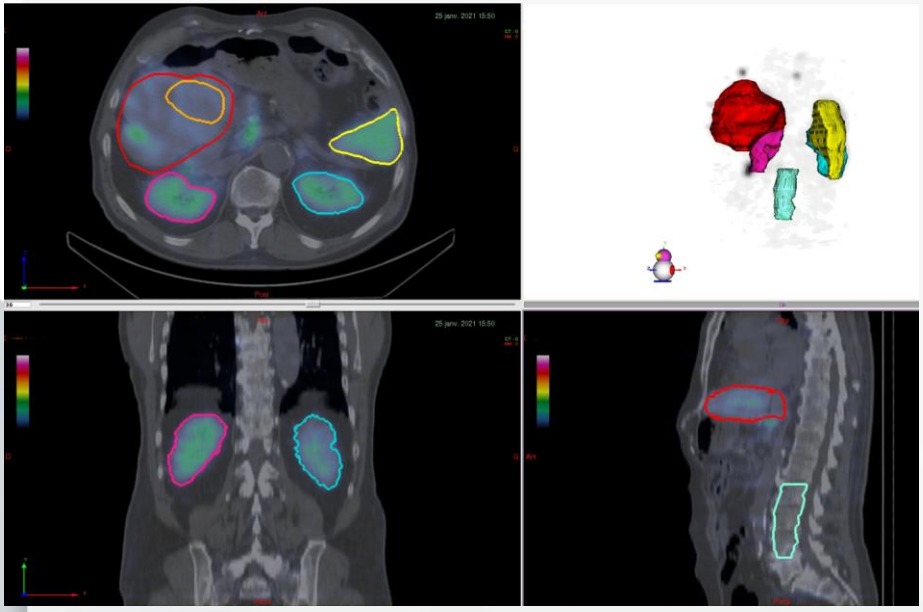



**Rigid Registration**
**Reference = CT (4h)**

**PLANET® Dose (DOSIsoft)**

# Dosimetry workflow

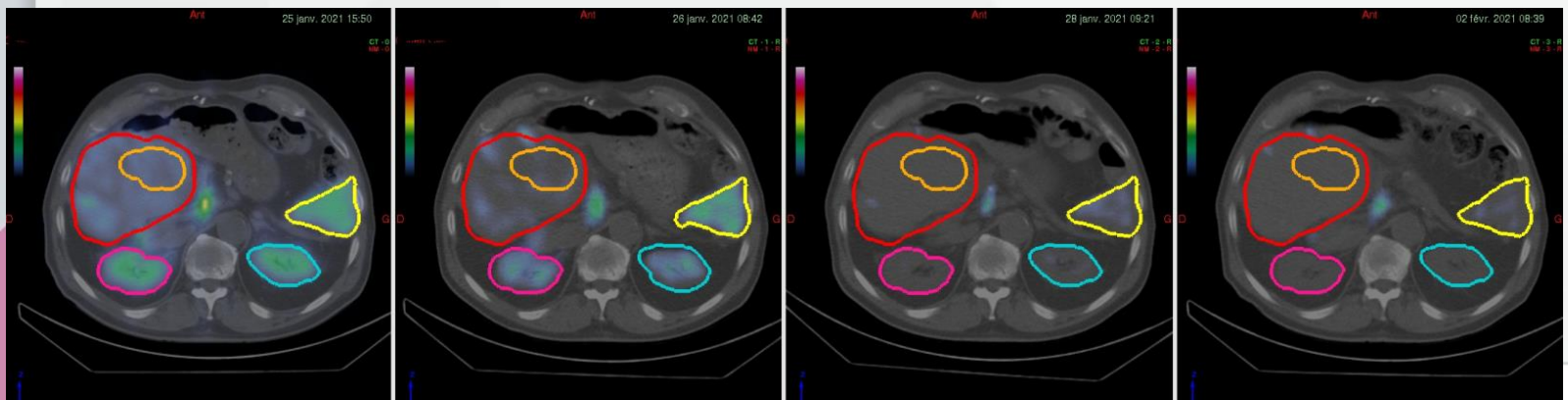
Reconstruction → Registration → **Segmentation** → Time activity curve fitting Ã evaluation → Absorbed dose calculation



**OAR** segmented on the first CT (D0)

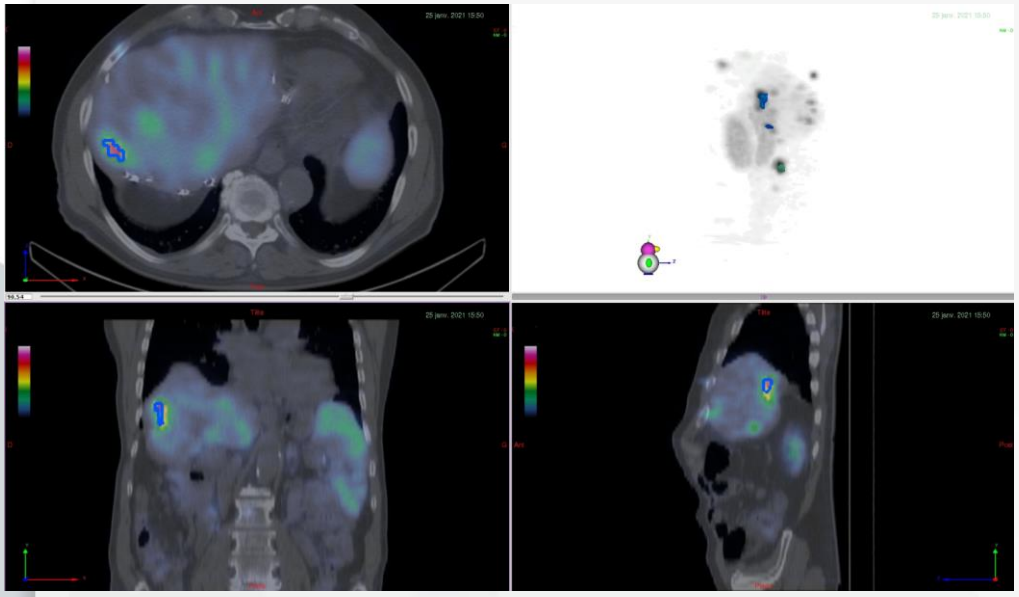
*Liver, healthy liver, right kidney, left kidney, spleen, Bone marrow of L2,L3,L4*

OAR Copied to other time points by rigid propagaton and manually corrected on each time point CT



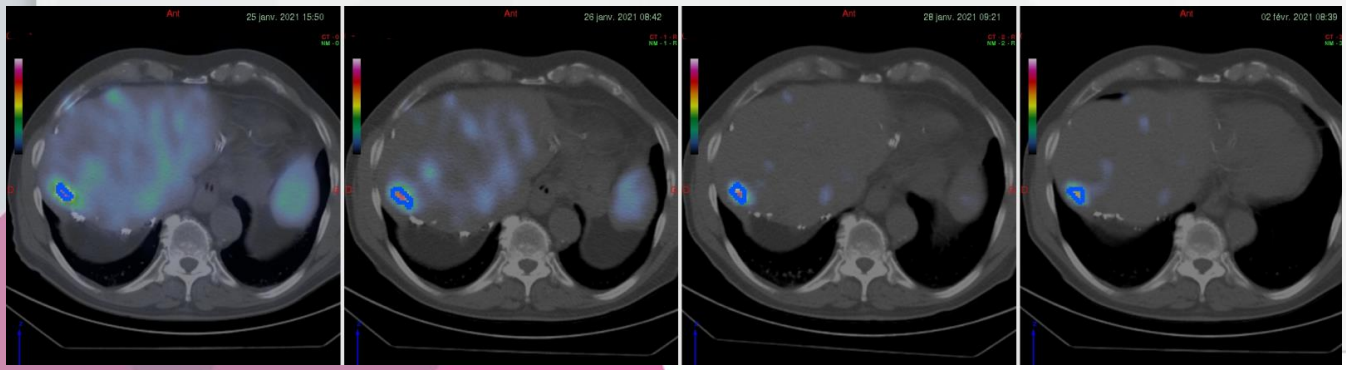
# Dosimetry workflow

Reconstruction → Registration → **Segmentation** → Time activity curve fitting Ã evaluation → Absorbed dose calculation



**Lesions** segmented on NM images at each time point

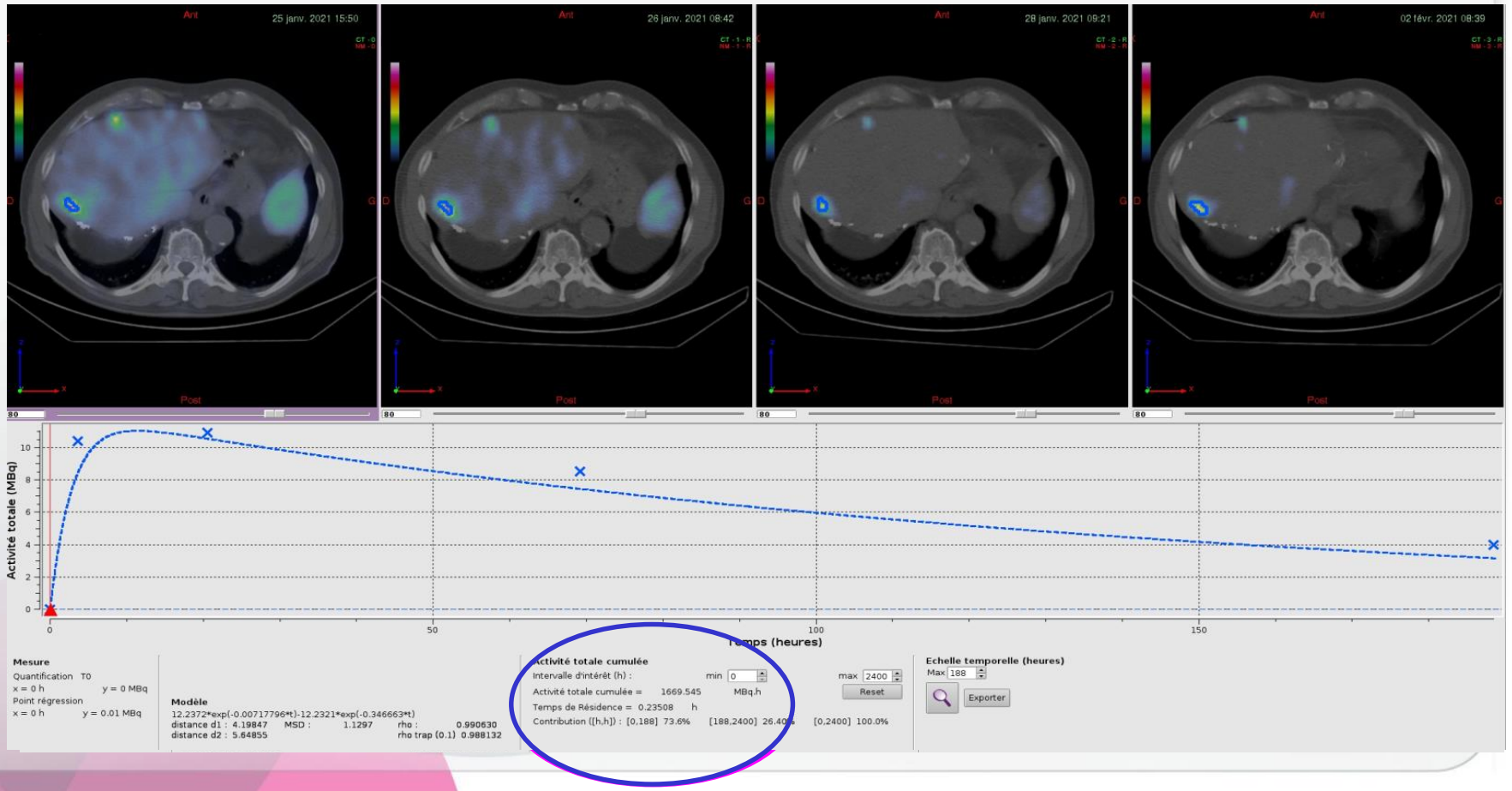
Isocontour representing a volume determined from the CT baseline (before treatment)



# Dosimetry workflow

Reconstruction → Registration → Segmentation → **Time activity curve fitting Ã evaluation** → Absorbed dose calculation

- Selection of the **time activity curve fitting function**

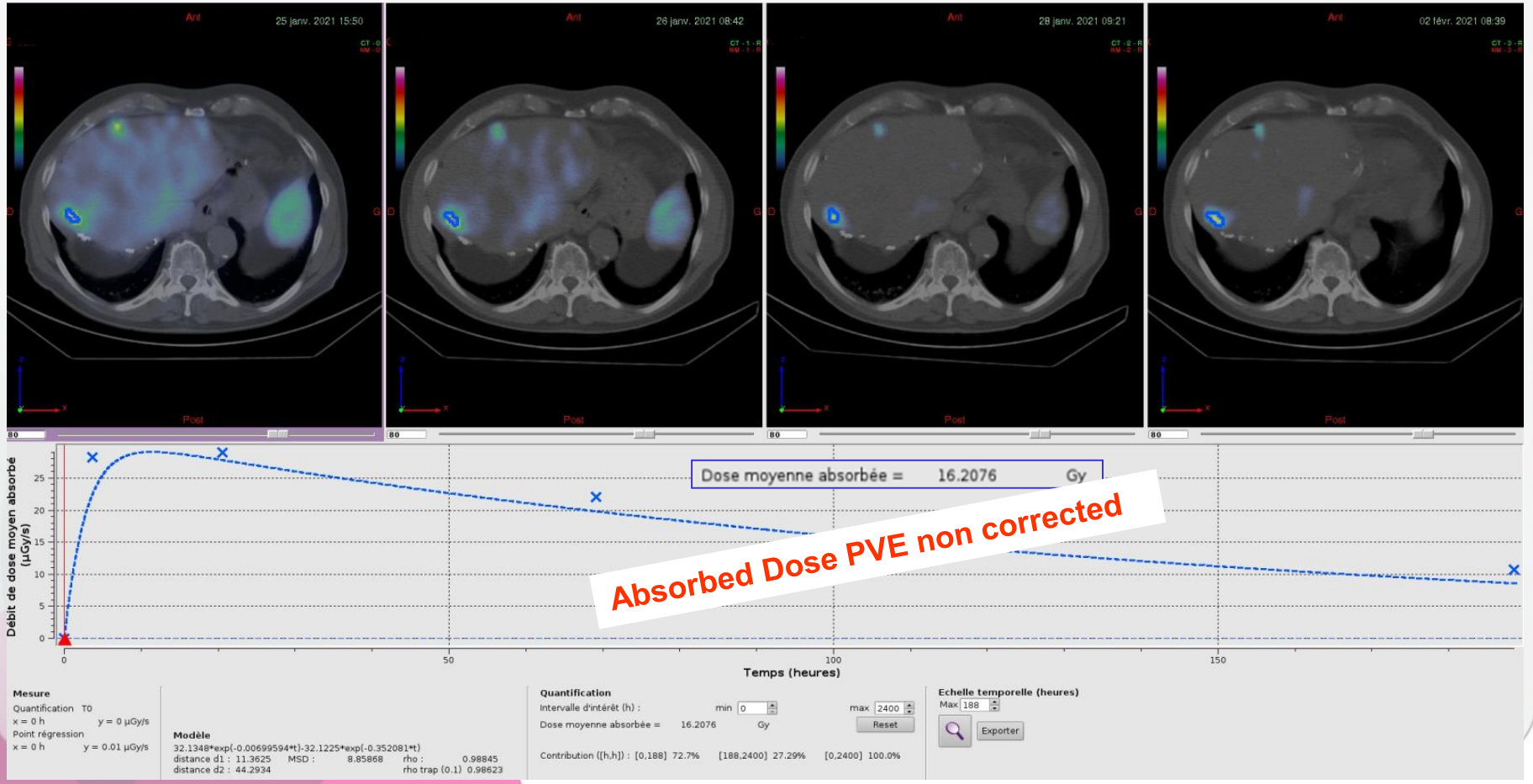


# Dosimetry workflow

Institut régional du Cancer Montpellier | Val d'Aurelle

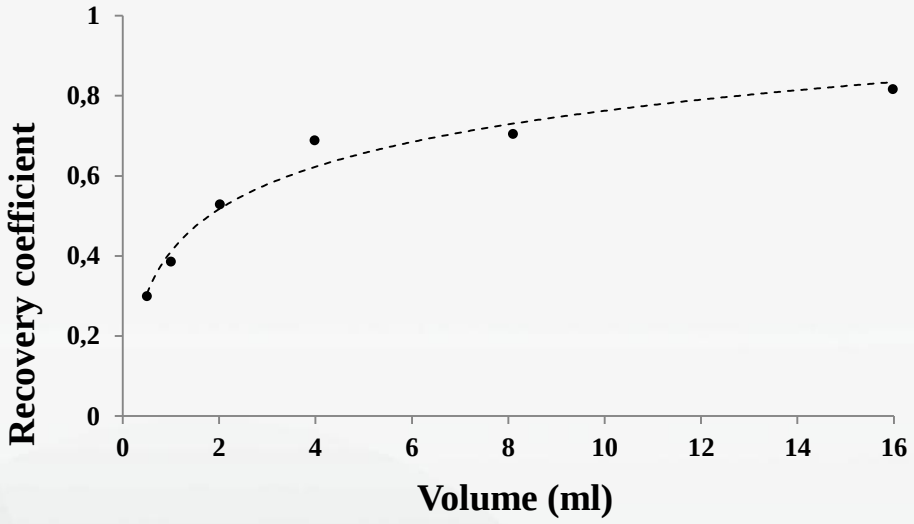
**Reconstruction** → **Registration** → **Segmentation** → **Time activity curve fitting Ã evaluation** → **Absorbed dose calculation**

- Absorbed dose calculation **by Local Deposition Method** and **density correction**



# Dosimetry workflow

Reconstruction → Registration → Segmentation → Time activity curve fitting Ã evaluation → Absorbed dose calculation




| | VOL CT BASELINE | VOLUME (cc) MOYEN | DOSE PLANET (Gy) | CR | DOSE CORRIGEE CR (Gy) |
|---|---|---|---|---|---|
| LESION 1 : HEP SEG IV | 8.5 | 8.62 | 16.2076 | 0.74 | **21.9** |
| LESION 2 : GG COELIAQUE | 2.28 | 2.45 | 14.6563 | 0.55 | **26.8** |
| LESION 3 : GG MESENTERIQUE | 4.05 | 4.12 | 24.7756 | 0.63 | **39.5** |

# Dosimetry workflow

## Fiche Dosimétrique Patient Après traitement au LUTATHERA

| | |
|---|---|
| Nom | |
| Prénom | |
| ID Patient | |
| Date de naissance | XX/XX/XXXX |
| Taille (cm) | 190 |
| Poids (Kg) | 86 |

Traitement n° : 2
Cure n° : 1
Date de la cure : 25/01/202

*Traitement :*

| | MBq | Heure |
|---|---|---|
| Activité du flacon (mesure) | 7263.95 | 10:00 |
| Activité résiduelle (mesure) | 107.6 | 12:20 |
| Activité réellement injectée au patient | **7101.6** | **11:44** |

*Imagerie:*

Discovery CZT 870 NUMERIQUE (GE)

▪ Date et heure des examens d'imagerie :

| | | | |
|---|---|---|---|
| SPECT/CT 1: | 25/01/20 à | 15:24:00 | J0 |
| SPECT/CT 2: | 26/01/20 à | 8:46:00 | J1 |
| SPECT/CT 3: | 27/01/20 à | 9:00:00 | J3 |
| SPECT/CT 4: | 03/02/20 à | 10:07:00 | J8 |

*Données de reconstruction :*

| | |
|---|---|
| *Application utilisée (Qvols ; Vols for_ ; Préparation for DTK ; _) :* | Qvolumetrix MI |
| Nombre itérations : | 6 |
| Nombre de sous-ensemble : | 10 |
| Filtre : | Gauss 0.25 |

*Logiciel et outils d'analyse dosimétrique:*

➢ *PLANET Dose (Dosisoft)*

▪ Facteur Calibration FC = **67 (analogique)** Bq/coup

▪ Modèle d'ajustement :

| *Organe:* | *Modèle d'ajustement :* | *Origine:* |
|---|---|---|
| Foie | Bi-exponentiel | Origine |
| Foie sain | Bi-exponentiel | Origine |
| Rein droit | Bi-exponentiel | Origine |
| Rein gauche | Bi-exponentiel | Origine |
| Rate | Bi-exponentiel | Origine |
| MO de L2L3L4 | Bi-exponentiel | Origine |
| **Lésion1** | Bi-exponentiel | Origine |
| **Lésion2** | Bi-exponentiel | Origine |
| **Lésion3** | Bi-exponentiel | Origine |

▪ Méthode de calcul : **Dépôt Local (LDM)**

▪ Correction de densité : **Correction de densité**

## Fiche Dosimétrique Patient Après traitement au LUTATHERA

| | |
|---|---|
| Nom | 0 |
| Prénom | 0 |
| ID Patient | 0 |
| Date de naissance | XX/XX/XXXX |
| Taille (cm) | 190 |
| Poids (Kg) | 86 |

Traitement n° : 2
Cure n° : 1
Date de la cure : 25/01/2021

| | | |
|---|---|---|
| Activité réellement injectée au patient (MBq) | 7101.6 | 11:44 |

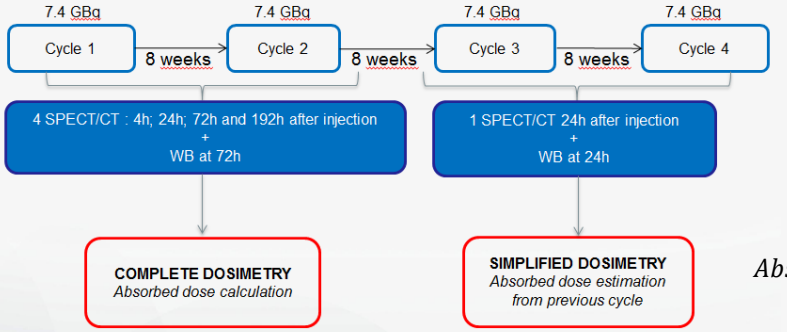
| Organes sains | Dose absorbée (Gy) |
|---|---|
| Foie total | 2.4 |
| Foie sain | 1.5 |
| Rein droit | 3.0 |
| Rein gauche | 2.8 |
| Rate | 5.1 |
| Moelle osseuse hématopoïétique à partir de L2, L3 et L4 | 0.45 |

| Lésions | Dose absorbée en Gy |
|---|---|
| LESION 1 : HEP SEG IV | 21.9 |
| LESION 2 : GG COELIAQUE | 26.8 |
| LESION 3 : GG MESENTERIQUE | 39.5 |

MEDECIN NUCLEAIRE : Dr Deshayes

PHYSICIEN : Lore Santoro

# Dosimetry workflow




$$\textbf{Treatment Cumulated AD} = \textbf{AD cycle 1} + \textbf{AD cycle 2} + \textbf{AD cycle 3} + \textbf{AD cycle 4}$$

$$Absorbed\ Dose\ C3/C4 = AD\ cycle\ 2 \times \frac{Nb\ counts\ SPECT\ D1\ cycle\ 3/4}{Nb\ counts\ SPECT\ D1\ cycle\ 2} \times \frac{Volume\ cycle\ 2}{Volume\ cycle\ 3/4}$$

***Ilan et al. JNM. 2015***

## Patient Dosimetric Report after LUTATHERA treatment

Mean Absorbed Dose (Gy)

| | CYCLE 1 | CYCLE 2 | CYCLE 3 | CYCLE 4 | Total absorbed dose (Gy) |
|---|---|---|---|---|---|
| Liver | 1.7 | 1.8 | 1.70 | 1.80 | 7.0 |
| Healthy liver | 1.3 | 1.4 | 1.30 | 1.60 | 5.6 |
| Right kidney | 2.6 | 2.9 | 2.90 | 2.50 | 10.9 |
| Left kidney | 2.7 | 3.0 | 2.60 | 2.60 | 10.9 |
| Spleen | 4.7 | 7.3 | 6.70 | 7.80 | 26.5 |
| Bone marrow (from L2, L3 et L4) | 0.20 | 0.25 | 0.30 | 0.28 | 1.03 |
| LESION Hepatic Dome: | 24.9 | 26.9 | 33.0 | 30.0 | 114.8 |
| LESION Hepatic Segment III : | 20.5 | 25.4 | 32.1 | 28.8 | 106.8 |
| LESION Jonction Hepatic Seg V/I : | 25.7 | 21.9 | 25.2 | 20.3 | 93.1 |

# Dosimetry implemented… And so ?

- The dosimetry analysis is requested by the physician
(low renal function, multi-focal bone involvement, retreatment…)

- Previous dosimetry results requested by the physician when re-treatment

- Since May 2016 : > 40 patients benefited from a dosimetry analysis

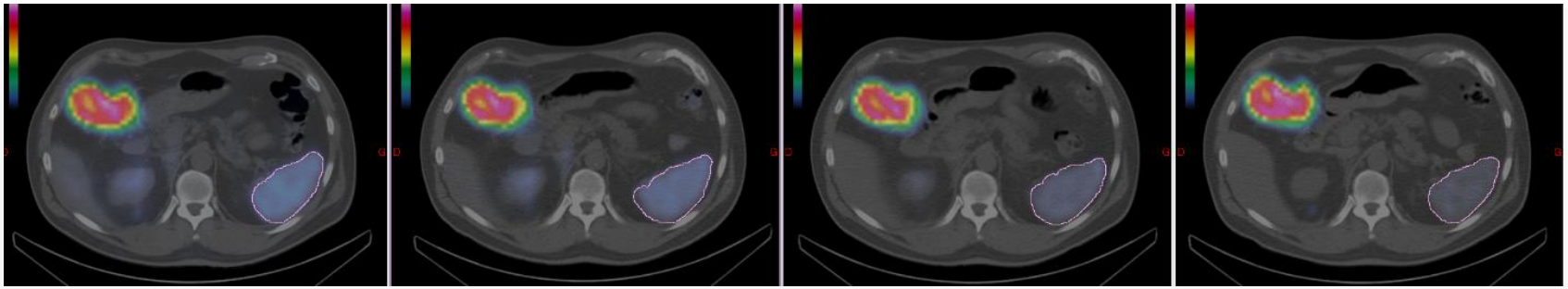
  - > 80 complete dosimetry analyses realized (cycle 1 and 2)
  - > 80 simplified dosimetry analyses realized (cycle 3 and 4)

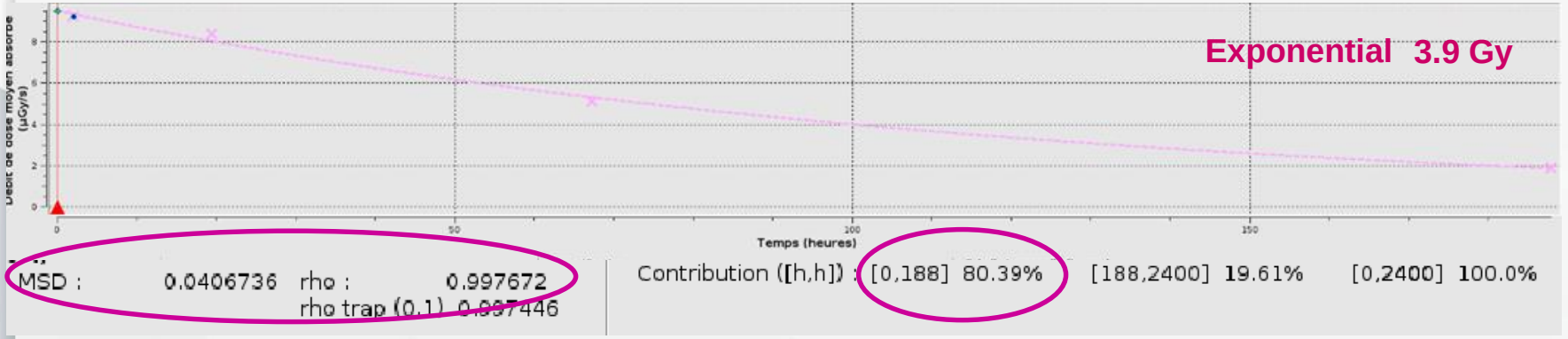
- Collection and analysis of all dosimetric data (OAR and tumours) in order to establish the correlation with clinical outcome (disease control and toxicities).

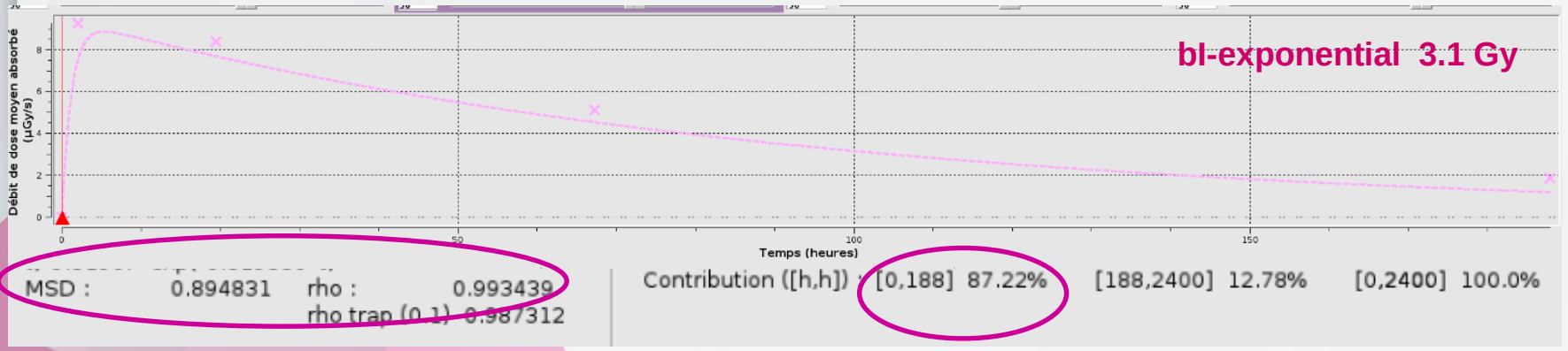
# ??? Remaining Question ???

## *Fitting curve*

- **HOW TO CHOOSE THE BEST FITTING CURVE ?**



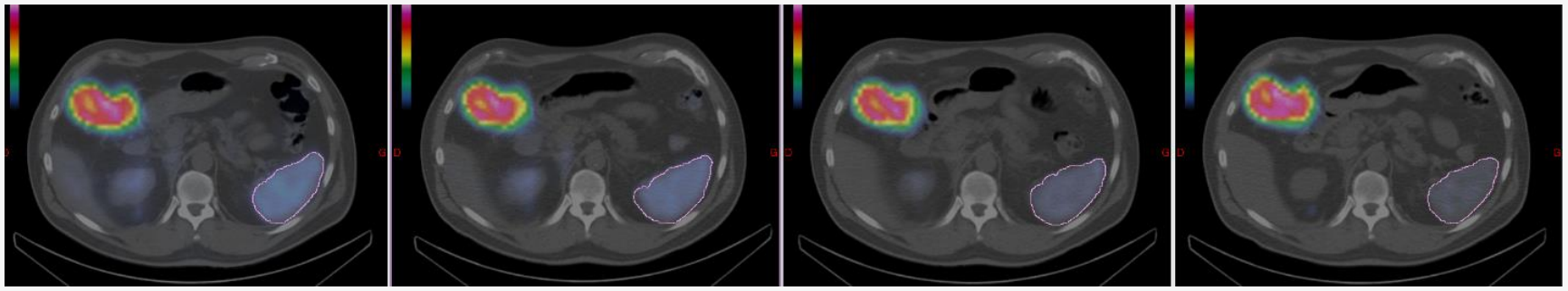


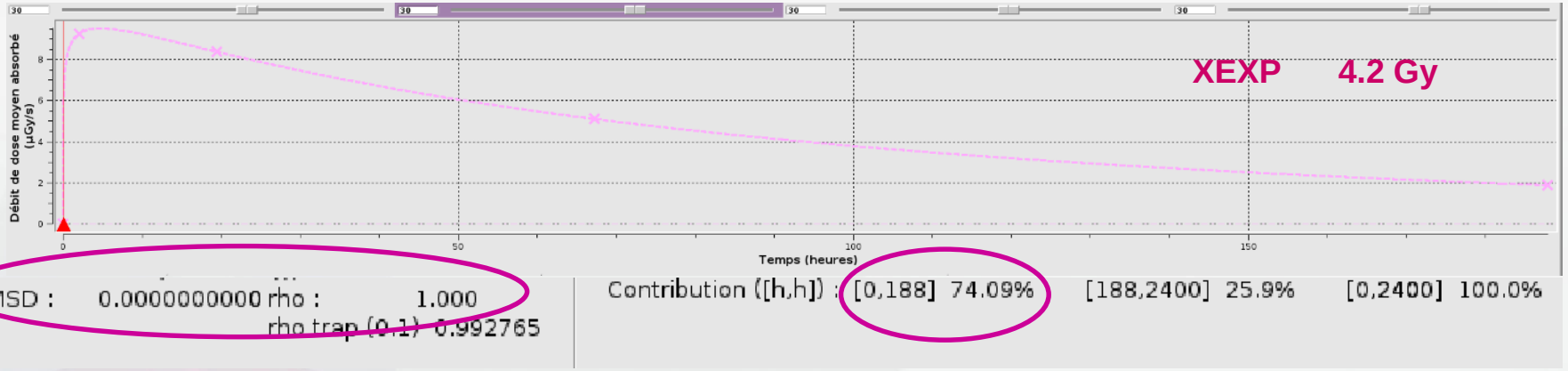



# ??? Remaining Question ???

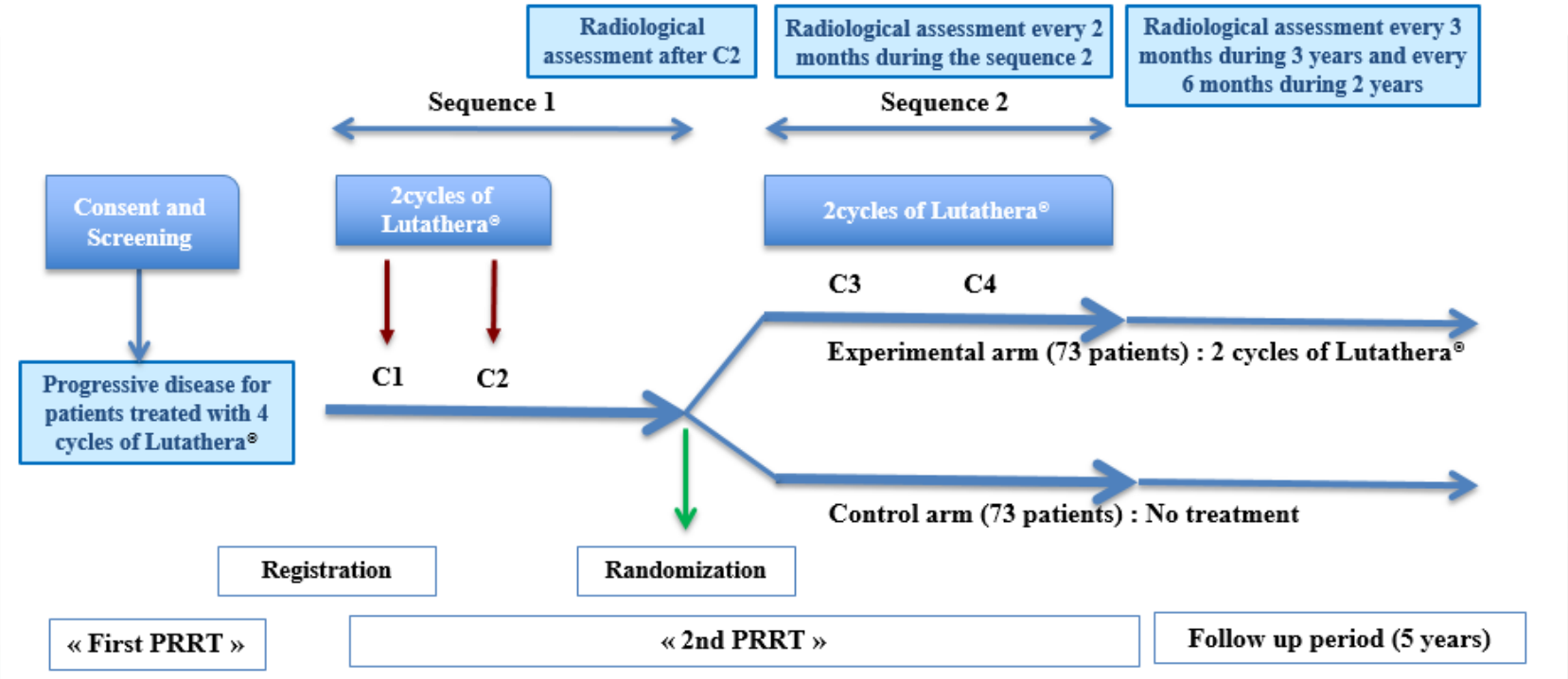
## *Fitting curve*

- **HOW TO CHOOSE THE BEST FITTING CURVE ?**





# The story goes on : PHRC RELUTH




**Primary objective :**

To evaluate the efficacy of two additional cycles of Lutathera® (one injection every two months), compared to active surveillance during 6 months in patients already retreated with two cycles.

**Ancillary Study :**

This ancillary dosimetric study will collect data from various centers who already performed dosimetry for [177Lu]Lu-DOTA-TATE PRRT. It will help answering scientific questions specific to molecular radiotherapy clinical dosimetry.

The exploratory objective of the ancillary study is to generate dosimetric data from patients treated with Lutathera® and establish the correlation with clinical outcome (disease control and toxicities).

# Conclusion

Strong collaboration between physicists and physicians allows $^{177}$Lu-based PRRT **dosimetry in clinical routine**

- **Technologists**
- **Radiopharmacists**
- **Physicist residents**
- **Radiations protection experts**
- **Patients**

For:

- Personalization of patient's follow-up & (re)treatment
- Better understanding of underlying mechanisms (radiobiology)

Further developments still expected :

- AI
- Less time points ?
- TAC fitting
- Standardisation
- Bone marrow dosimetry optimization

Institut régional du Cancer
Montpellier | Val d'Aurelle

# Merci de votre attention