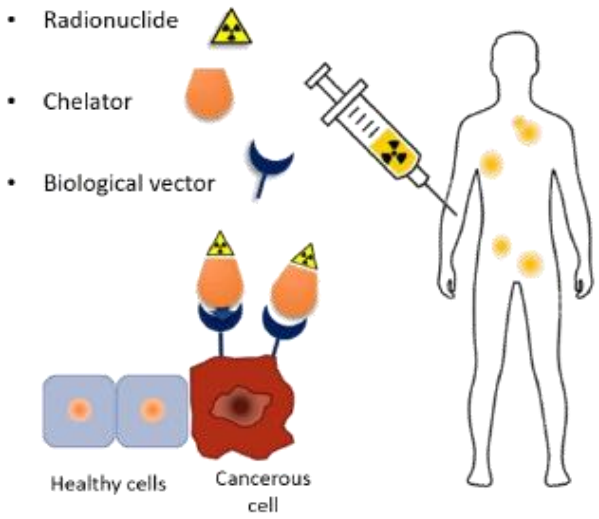
3D voxel-based dosimetry for an extravasation case

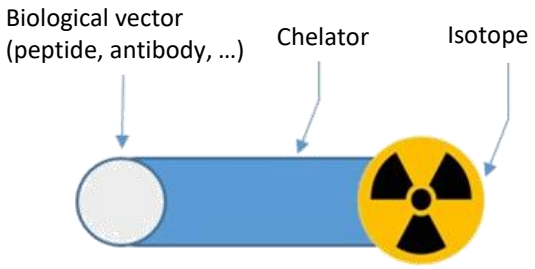
Introduction

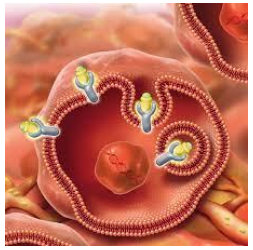
Nuclear Medicine

Cancer = 9.7 million deaths / 20 millions new cases (WHO, 2022)



Choice of biological vector and isotope → Binding isotope with biological vector → Injection of radiopharma-ceutical → Tumor fixation → Biological elimination of the drug

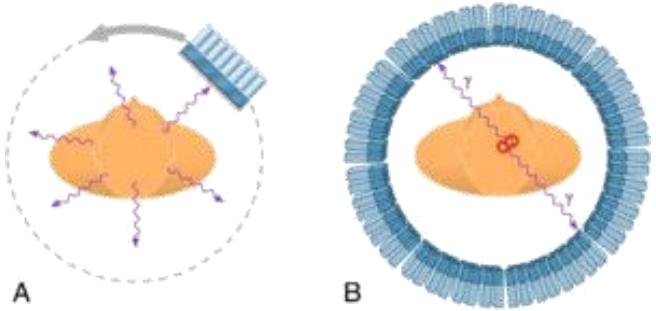




https://www.afmps.be/sites/default/files/content/RMA/L/Lutathera/lutathera_patient_fr.pdf

Choice of isotope:

- γ / β^+ emitter = imaging
- **Auger / β^- / α emitter = therapy**
  - ➢ **Molecular Radiotherapy (MRT)**



SPECT PET

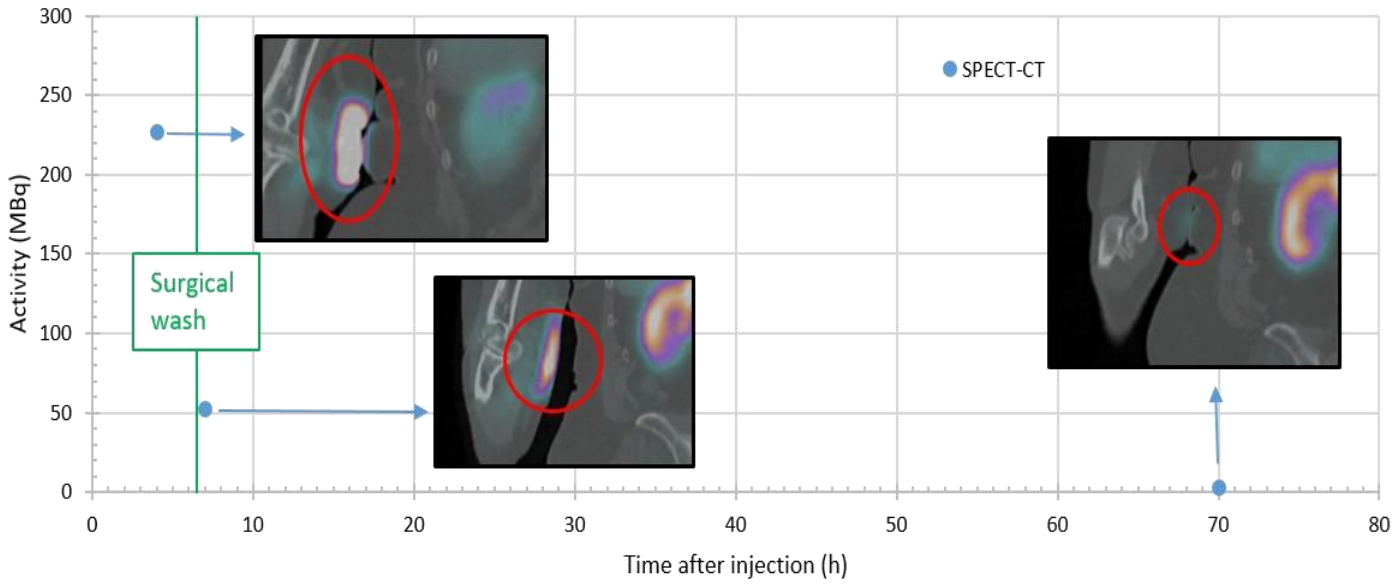
https://www.cnp-mn.fr/les-fondamentaux-chapitre-5-medecine-nucleaire/

Dosimetry and biological assessment

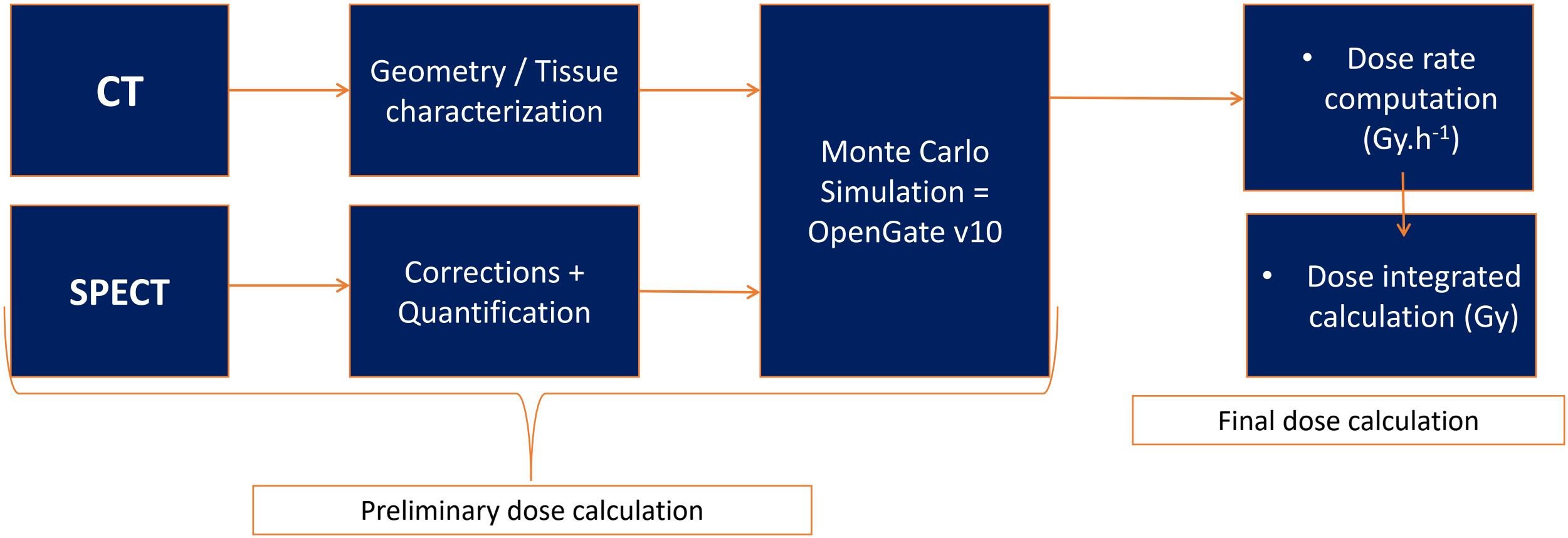
Extravasation case

Clinical Context

- Injection of 6.9 GBq of ^{177}Lu-DOTATATE for neuroendocrine tumors
- Extravasation = passing out of a vessel into surrounding tissues:
  - Detected 15 min after injection
  - Activity estimated as 2.7 GBq (40 %)
- Clinical follow-up:
  - SPECT-CT acquisition at 4h, 7h, 70h
  - Surgical washing performed at 6.5h
- Clinical following of side effects



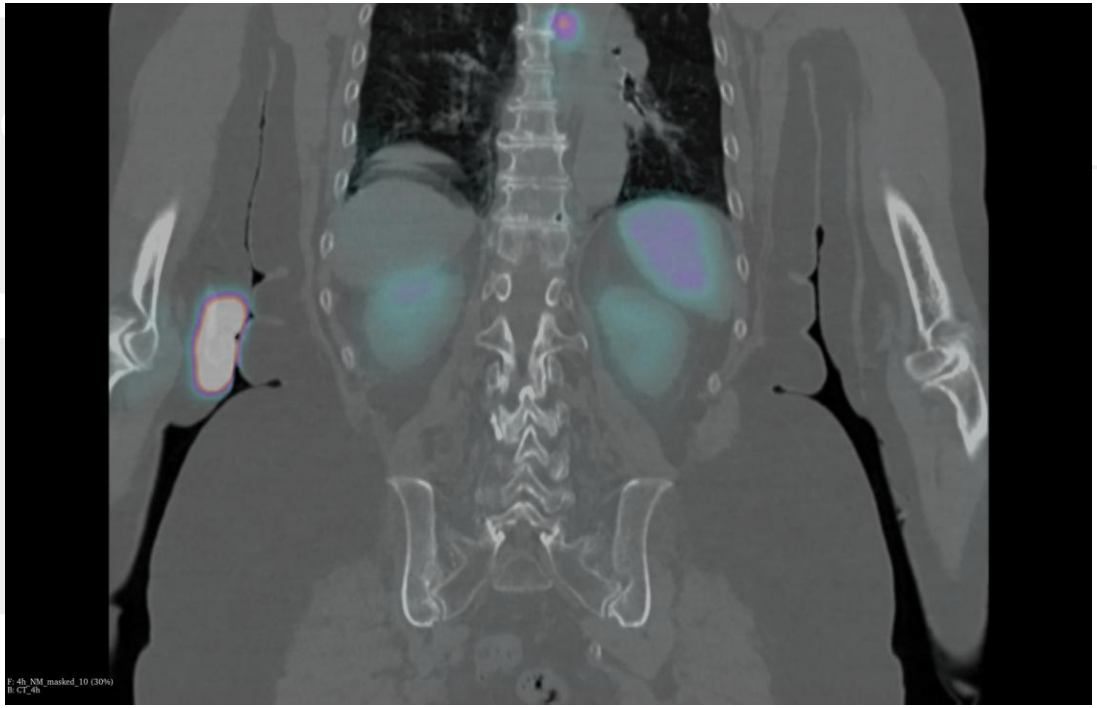
3D voxel-based dosimetry



3D voxel-based dosimetry

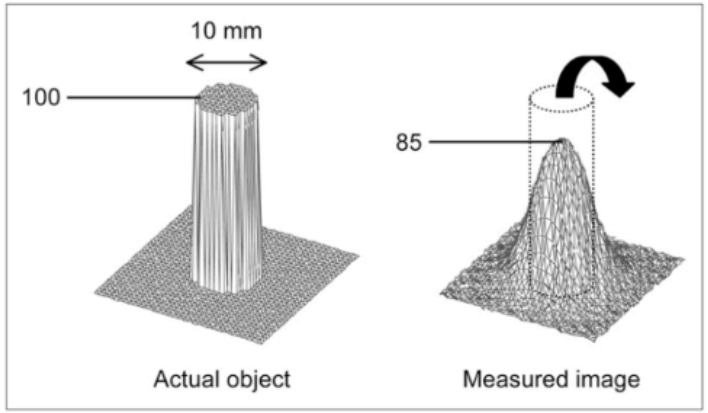
CT

SPECT



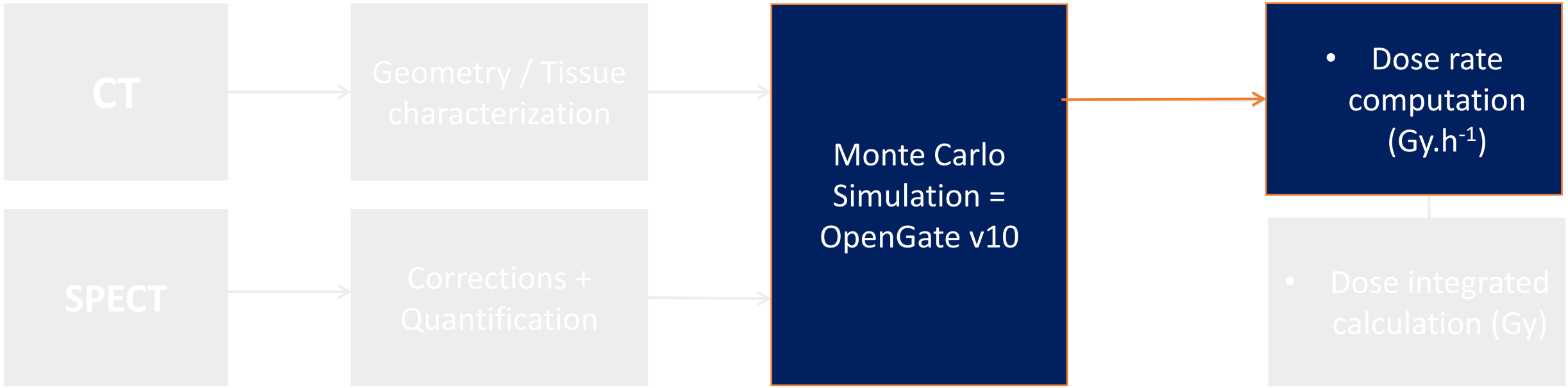
- Dose rate computation ($Gy.h^{-1}$)
- Dose integrated calculation (Gy)

- Corrections + Quantification for SPECT:
  - Partial Volume Effect (PVE) corrected by Point Spread Function (PSF) deconvolve
  - SPECT registered to CT coordinates
  - Calibration factor determined in filled phantom of known activity and after thresholding 10%



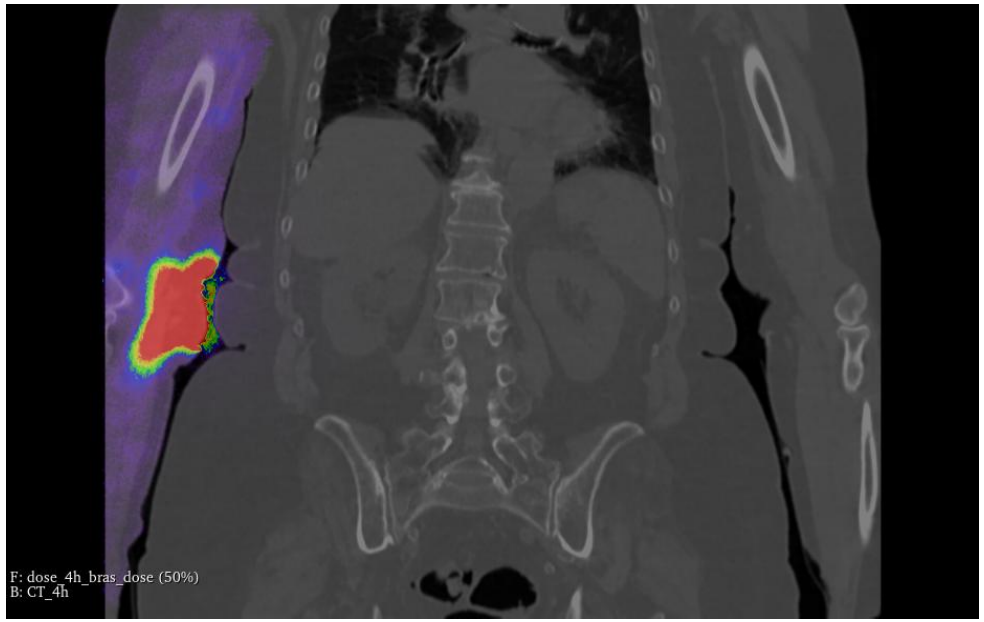
http://jnm.snmjournals.org/cgi/doi/10.2967/jnumed.106.035774

3D voxel-based dosimetry



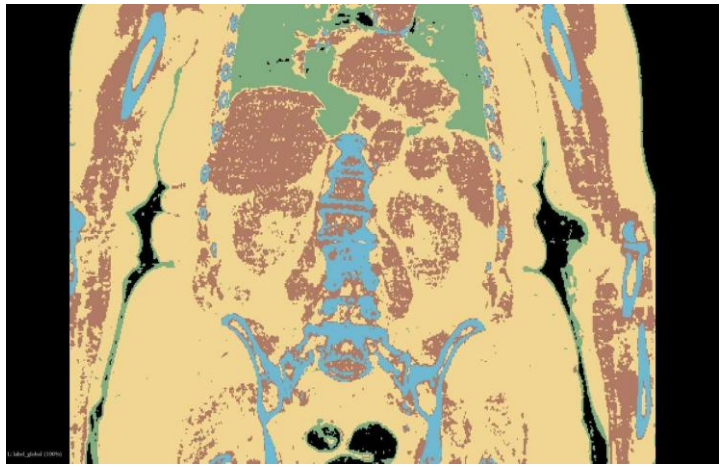
- Monte Carlo simulations:
  - Geometry = CT at 4h/7h (i.e. before and after surgical washing)
  - Sources = SPECT at **4h**/**7h** (constant biodistribution hypothesis)
  - QGSP_BIC_EMZ physic list
  - Multithreading (8 threads) for time calculation improvement
  - 10^8 ^{177}Lu decays within the arm for lower uncertainties
  - DoseActor for dose per voxel computation

3D voxel-based dosimetry



Dose map

Uncertainties below 10%



Tissues segmentation

Dose distribution

- Dose rescale to total number of decays:
  - $D = \frac{D_{MC}}{N_{sim}} \times \tilde{A}$, with $\tilde{A} = \int_{t_0}^{t} A_0 e^{-\lambda t'} dt'$
- **D_{max} = (40,61 ± 1,34) Gy** before surgical washing | **D_{max} = (3,76 ± 0,17) Gy** after surgical washing
  - 91,53% dose deposited before surgical washing
- Dose deposition in adipose tissue
- Threshold necrosis = 25 Gy according to Barré et al, 2013 → $V_{>25Gy}$ = 2.84 mL

Isodose lines fused to CT: from 5 Gy to 30 Gy.

Biological model

- EQD2 = dose equivalent if therapy was made by External Beam Radiotherapy (EBRT)
- D → BED_{MRT} | Same biologicals effects : $BED_{MRT} = BED_{EBRT}$ → EQD2
  - Use MIRD Pamphlet n°20
- **$EQD2_{max}$ = 220.14 Gy**
- Threshold 62 Gy = EBRT → $V_{>62Gy}$ = 5.05 mL

BUT NO NECROSIS OBSERVED (8 months follow-up)

EQD2 Isodose lines fused to CT: from 40 Gy to 62 Gy.

Limits of the model

Limits of the model

- Spatial resolution of SPECT Images despite PVE correction:
    - Overestimated Volume
    - Underestimated Dose
- Conditions of estimation of the toxicity threshold and parameters of MIRD Pamphlet n°20:
    - Interventional radiology / EBRT
    - Higher dose rate
    - Cutaneous tissues (highly sensitive)
- Applicable to MRT-β^- but not MRT-α

Conclusion and Outlook

Conclusion and outlook

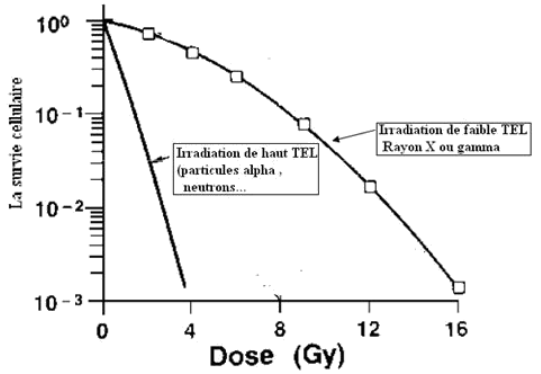
- Use of 3D dose distribution in clinical case:
  - Dose per voxel = isodose lines
  - Assess more precisely dose distribution rather than MIRD protocol
  - Spatial resolution / PVE limitations in SPECT
- Possible to convolve dose distribution with biological effect model:
  - Toxicity threshold have to be reconsidered
  - Only available for MRT-β^-
- Improvement of the biological model for MRT-α

Thank you for your attention

Question ?

MIRD Pamphlet n°20

- $BED = \frac{-\ln(SF)}{\alpha}$
  - SF = Survical fraction
  - α = number of lethal events (Gy^{-1})
  - β = number of sub-lethal events (Gy^{-2})



https://www.researchgate.net/figure/Figure-215-Courbes-de-survie-exponentielle-et-avec-epaulement_fig10_45229821

- MIRD Pamphlet n°20 :

$$BED = \frac{R_0}{\lambda_{eff}} C \left(1 + \frac{2R_0\lambda_{eff}}{(\mu - \lambda_{eff})\left(\alpha/\beta\right)} \cdot \frac{A - B}{C} \right)$$

- $A = \frac{1-e^{-2\lambda_{eff}t}}{2\lambda_{eff}}$
- $B = \frac{1-e^{-(\mu+\lambda_{eff})t}}{\mu+\lambda_{eff}}$
- $C = 1 - e^{-\lambda_{eff}t}$

- BED for EBRT with 2 Gy / fraction:

$$BED = \frac{D}{1 + \frac{2}{(\alpha/\beta)}}$$

Limits of the biological model

- Spatial resolution of SPECT Images despite PVE correction:
  - Overestimated Volume
  - Underestimated Dose
- Conditions of estimation of the toxicity threshold (Barré et al., 2013):
  - Interventional radiology
  - Delivery in a single irradiation/fraction (higher dose rate)
  - Large exposure area
  - Cutaneous tissues (highly sensitive) (NB: no available data for other tissues)
- Parameters of the biological model:
  - α/β = determined from measurement in EBRT
  - μ = determined from measurement in EBRT

  } Cutaneous tissues (Paper of Dale et al. 1999)
- Applicable to MRT-β^- but not MRT-alpha

Outlook

- Application of the workflow to preclinical studies
- Microdosimetric experiments -> quantify biologic effect with α irradiation