Dosimetry of patients injected with tracers Ga-68, Zr-89 and Lu-177
What is NM speciality?

- Imaging radiology
  - Physics
  - Diagnostic
  - Treatment assessment

- Clinical pathology
  - Biological marker
  - Diagnostic
  - Treatment assessment

- Radiotherapy
  - Physics
  - Radiobiology

- Chemotherapy
  - Pharmacology
  - Biology

⇒ Multidisciplinary 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

Monoclonal Antibody

Chelate

Malignant B-cell

CD20 antigen

TOX

$^{89}$Zr or $^{90}$Y

Imaging

Therapy

In-111 Ga-68

Lu-177 Y-90

(Tyr$^3$)-octreotate
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,...)
68Ga diagnostic short half-live

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

- 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

\[(x, E_0) = \frac{E}{E_0}\]

Absorbed fraction by mass

\[(x, E_0) = \frac{(x, E_0)}{dm}\]

Mean absorbed dose Gy [J/Kg]

\[\bar{D} = \frac{E}{dm} = \frac{(x, E_0)}{dm} E_0 = (x, E_0) E_0\]
Dose in a volume

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

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

\[ D(t)_{(k \leftarrow h)} = A_h(t) \cdot E_0 \cdot \Phi(k \leftarrow h) \]

- 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
  - \( E_i \) its energy
  - \( n_i \) the number of particles of type i emitted per transition
- \( \Delta_i \) is the mean energy per transition for radiation i in J/(Bq.s), and \( \Delta \) the total energy per transition

\[ \Delta_i = k \cdot n_i \cdot E_i \quad \quad \Delta = \sum \Delta_i = K \sum n_i E_i \]

- the dose rate is the sum of all radiation types

\[ D(t)_{(k \leftarrow h)} = K \cdot A_h(t) \cdot \sum n_i E_i \cdot \Phi_i(k \leftarrow h) \]
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

\[ D_{(k \leftarrow h)} = \tilde{A}_h \cdot S_{(k \leftarrow h)} \]
S-factor

\[ D = A_0 \tau S \]

- 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
Gamma counter

+• Energy spectrum
  • Geometry non-dependent
  ⇒ Montecarlo simulation

–• Small counting range
  • Non convenient
  • Closed geometry
SPECT/CT

+

- Energy spectrum
- Open geometry
- Collimators
- No vendor calibration
- Low resolution
Partial volume effect

\[ RC = \frac{\text{activity}_{\text{measured}}}{\text{activity}_{\text{injected}}} \]
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

- 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?)

$\Rightarrow$ 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 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
Immuno Dosimetry: Zr89 to Y90

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

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

<table>
<thead>
<tr>
<th>Organ</th>
<th>Disintegrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidneys</td>
<td>1.30E000 MBq-h/MBq or uCi-h/uCi</td>
</tr>
<tr>
<td>Liver</td>
<td>7.76E000 MBq-h/MBq or uCi-h/uCi</td>
</tr>
<tr>
<td>Lungs</td>
<td>4.15E000 MBq-h/MBq or uCi-h/uCi</td>
</tr>
<tr>
<td>Spleen</td>
<td>9.68E-01 MBq-h/MBq or uCi-h/uCi</td>
</tr>
<tr>
<td>Remainder</td>
<td>4.85E001 MBq-h/MBq or uCi-h/uCi</td>
</tr>
</tbody>
</table>

Organ Doses (mSv/MBq), Nuclide: Y-90 (6.41E01 hr), Adult Male

Calculated: 06.26.2012 at 03:57:23 CEST

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Alpha</th>
<th>Beta</th>
<th>Photon</th>
<th>Total</th>
<th>EDE Cont.</th>
<th>ED Cont.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidneys</td>
<td>0.00E000</td>
<td>2.29E000</td>
<td>0.00E000</td>
<td>2.29E000</td>
<td>1.37E-01</td>
<td>5.72E-03</td>
</tr>
<tr>
<td>Liver</td>
<td>0.00E000</td>
<td>2.19E000</td>
<td>0.00E000</td>
<td>2.19E000</td>
<td>1.31E-01</td>
<td>1.09E-01</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.00E000</td>
<td>2.24E000</td>
<td>0.00E000</td>
<td>2.24E000</td>
<td>2.68E-01</td>
<td>2.68E-01</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.00E000</td>
<td>2.76E000</td>
<td>0.00E000</td>
<td>2.76E000</td>
<td>1.66E-01</td>
<td>6.91E-02</td>
</tr>
<tr>
<td>Urinary Bladder Wall</td>
<td>0.00E000</td>
<td>3.55E-01</td>
<td>0.00E000</td>
<td>3.55E-01</td>
<td>0.00E000</td>
<td>1.77E-02</td>
</tr>
</tbody>
</table>

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
Tracer: which octreotide for diagnostic?
Tracer: which octreotide for diagnostic?

![Graph showing absorbed dose for various organs with 68Ga-DOTATATE and 68Ga-DOTATOC compared.]

<table>
<thead>
<tr>
<th>Organ</th>
<th>68Ga-DOTATATE*</th>
<th>68Ga-DOTATOC (12)</th>
<th>68Ga-DOTANOC (13)</th>
<th>111In-DTPA-octreotide (19)</th>
<th>18F-FDG (20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidneys (mSv/MBq)</td>
<td>9.2E−02</td>
<td>2.2E−01</td>
<td>8.97E−02</td>
<td>4.5E−01</td>
<td>1.7E−02</td>
</tr>
<tr>
<td>Liver (mSv/MBq)</td>
<td>4.50E−02</td>
<td>7.4E−02</td>
<td>3.38E−02</td>
<td>7.0E−02</td>
<td>2.1E−02</td>
</tr>
<tr>
<td>Spleen (mSv/MBq)</td>
<td>2.82E−01</td>
<td>2.4E−01</td>
<td>7.25E−02</td>
<td>3.2E−01</td>
<td>1.1E−02</td>
</tr>
<tr>
<td>Urinary bladder wall (mSv/MBq)</td>
<td>1.25E−01</td>
<td>7.0E−02</td>
<td>8.36E−02</td>
<td>1.8E−01</td>
<td>1.3E−01</td>
</tr>
<tr>
<td>ED (mSv/MBq)</td>
<td>2.57E−02</td>
<td>2.3E−02</td>
<td>1.67E−02</td>
<td>8.0E−02</td>
<td>1.9E−02</td>
</tr>
</tbody>
</table>

Typical IA

<table>
<thead>
<tr>
<th>MBq</th>
<th>185</th>
<th>185</th>
<th>185</th>
<th>74</th>
<th>370</th>
</tr>
</thead>
<tbody>
<tr>
<td>mCi</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Estimated ED per scan (mSv)</td>
<td>4.8</td>
<td>4.3</td>
<td>3.1</td>
<td>5.9</td>
<td>7.0</td>
</tr>
</tbody>
</table>
Tracer: which octreotide for therapy?

Figure 4. Normalized uptake of different types of metastases and pancreatic primary tumors.

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).

Results of Individual Patient Dosimetry in Peptide Receptor Radionuclide Therapy with $^{177}$Lu DOTA-TATE and $^{177}$Lu DOTA-NOC Christiane Wehrmann
Which Marker for therapy?

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

- **Y90**
  - Beta-emitter
  - Half-life = 2.7 days
Conclusion

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