The Diagnosis, Dosimetry, Therapy Approach in Neuroendocrine Tumors

Effective Clinical Dosimetry in Neuroendocrine Tumors

Marta Cremonesi
marta.cremonesi@ieo.it
Educational Objective

Understand the theoretical and practical aspects of clinical dosimetry in the field of Peptide Radionuclide Receptor Therapy (PRRT)

**Dosimetry** has the purpose to derive information able...

to improve therapy designs

- which radionuclide?
- more appropriate therapy schedules?
- effect of inhomogeneous activity/dose distribution?
- radiobiological models?
Most Used Radiopeptides for PRRT

characteristics already well known…

<table>
<thead>
<tr>
<th>Peptide</th>
<th>$E_{\beta_{\text{max}}}$</th>
<th>$R_{\text{max,}\beta}$</th>
<th>$R_{\text{mean}}$</th>
<th>$T_{1/2 \text{phys}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>90Y-DOTATOC</td>
<td>2.3 MeV</td>
<td>~ 11 mm</td>
<td>~ 4 mm</td>
<td>64 h</td>
</tr>
<tr>
<td>177Lu-DOTATATE</td>
<td>0.5 MeV</td>
<td>~ 2 mm</td>
<td></td>
<td>6.7 d</td>
</tr>
</tbody>
</table>

90Y-DOTATOC

$[^{90}\text{Y-DO} \text{T} \text{A}^0 \text{-} \text{Yr}^3 \text{-}]$-octreotide

177Lu-DOTATATE

$[^{177}\text{Lu-DO} \text{T} \text{A}^0 \text{-} \text{Yr}^3 \text{-}]$-octreotate

...others: Lanreotide, 90Y-DOTATATE, ...

Bremstrahlung, →
Cross-fire: tumor irradiation

Bremstrahlung, images...

Less cross-fire

Imaging !!!

imaging/ therapy with the same complex
To simulate $^{177}$Lu-PRRT...

Dosimetry can be done with the same complex before and during treatment as well, enriching the response evaluation of $^{177}$Lu-PRRT.

Uptake variation in tumor & organs with cycles can be observed, deriving useful information for the patient.
How to simulate $^{90}\text{Y}-\text{PRRT}$?

To avoid the well known difficulties of Bremstrahulng imaging →

$^{111}\text{In}$ imaging

(the most practical solution)

$^{111}\text{In}$ has similar chemical behaviour to $^{90}\text{Y}$...

$^{111}\text{In}$-pentreotide (Octreoscan)

Its use is recommended for patient recruitment only, not for practical dosimetry.

Different peptides lead to different chemical behaviour.

$^{111}\text{In}$-derivatives

$T_{\text{phys}}$ close to $^{90}\text{Y}$, compatible with $T_{\text{biol}}$ peptide

SPECT resolution

The same compound used for PRRT labeled with $^{111}\text{In}$ is a good surrogate for dosimetry purposes

$^{111}\text{In}$ chemical behaviour vs $^{90}\text{Y}$ similar or identical?
The same compound for PRRT labeled with $^{86}$Y: chemical structure totally preserved. To simulate $^{90}$Y-PRRT...

- Behaviour identical to $^{90}$Y;
- PET resolution
- High energy $\gamma$ rays prompt

Without appropriate corrections, false activity in bone marrow

$E_{\text{max}}$: 1.2, 1.5, 2.0; $E_{\text{g}}$: 0.6, 1.1, 1.2, 1.9 MeV

$^{68}$Ga imaging: too low $T_{\text{phys}}$ (68 min)

$^{68}$Ga imaging as compared to peptide $T_{\text{biol}}$

- Low $T_{\text{phys}}$ (14.7 h)
- Low abundance
- Late information lost!

$^{86}$Y imaging

S. M. Qaim ECPM 2005

Cremonesi, et al. QJNM 2010
However... Bremsstrahlung imaging... work in progress

**SPECT-CT**
Quantitative Analysis of $^{90}$Y Bremsstrahlung SPECT-CT Images for Application to 3D Patient-Specific Dosimetry

**SPECT-CT**
Evaluation of quantitative $^{90}$Y SPECT based on experimental phantom studies

**PET-CT: TOF**
Feasibility of $^{90}$Y TOF PET-based dosimetry in liver metastasis therapy using SIR-Spheres
Lhommel, et al. EJNMMI 2010 Apr 27. [Epub ahead of print]

**WB + CT**
Evaluation of quantitative planar $^{90}$Y bremsstrahlung whole-body imaging

$^{90}$Y-imaging is most promising; it might become the future standard approach
What’s well known from dosimetry in PRRT
Typical pharmacokinetics of peptides:

fast

Prevalent elimination through the urine:
- Not negligible absorbed dose to
  u. bladder...& Kidney involved

Relatively low RM dose expected

\[
\frac{A_{\text{RM}}}{m_{\text{RM}}} = \frac{A_{\text{blood}}}{m_{\text{blood}}}
\]

Model experimentally proven in LuDOTATATE*

Typical biokinetics of peptides: imaging

A(t) for all source organs: → mean dose / dose distribution

**Methods:**

* Transmission scan (attenuation correction)

* Serial scintigraphic images WB, SPECT
  - multiple window acquisition → scatter correction
  - absolute/relative calibration → quantification

* CT for organ mass determination

**major source organs:**

- spleen, kidneys, liver, (testes)
- TB, u.bladder, RM...

**Time schedule for data collection?**

1) **biexponential trend**, most often
   → at least 4-5 points..

2) **Kidneys** are critical organs
   → plan SPECT, especially in pts at risk

3) **Late information** might consistently influence the results

   good imaging @: 0, 3-4 h, 16-24 h, 2 d, 3-4 d
Greater impact on $^{177}\text{Lu}$-peptide vs. $^{90}\text{Y}$-peptide dose results (e.g. $\Delta = 40\%$ vs. $10\%$)

The impact increases when evaluating the BED (Biological Effective Dose)
Doses per unit Activity in PRRT

mean values, essential characteristics

KIDNEYS are the critical organs, despite the renal uptake reduction reduction of 25% - 65%

relatively low dose to RED MARROW (RM)

large variability in tumour doses

Typically, for cumulative 11 GBq of $^{90}$Y-peptides

- Kidneys 27 Gy with protection
- RM 0.4 Gy

### 90Y- & 177Lu-PRRT schemes commonly applied

Many different rationales from groups

Injected activities, number of cycles, time intervals between cycles

<table>
<thead>
<tr>
<th></th>
<th>90Y-PRRT</th>
<th></th>
<th>177Lu-PRRT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n. of</td>
<td>A/cycle</td>
<td>A tot</td>
<td>n. of</td>
<td>A/cycle</td>
</tr>
<tr>
<td>cycles</td>
<td></td>
<td></td>
<td>cycles</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.925-1.85-2.78-3.7 GBq/m²</td>
<td>up to 32 GBq</td>
<td>6-9</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>1.11-2.59 GBq</td>
<td></td>
<td>6-9</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>2.96-5.55 GBq</td>
<td></td>
<td>6-9</td>
<td>4-7</td>
</tr>
<tr>
<td>≥ 4</td>
<td>3.9-8.9 GBq/m²</td>
<td>6.1 ± 1.3 GBq/m²</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.85 GBq</td>
<td>7.4 GBq</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

All these are empirical schemes, mostly based on standard activities and “clinical sensitivity”

However, in PRRT, dosimetry evaluations have been seriously taken into account to plan therapy, after some first serious side effects. This has allowed to improve information for future therapies.

Cremonesi et al. QJNM 2010
Meaning of mean doses among patients

To optimise risks vs. benefits balance, TREATMENTS NEED TO BE PERSONALISED
Some more questions
177Lu or 90Y? vs. DOTA-peptide

From previous experimental data:
Tumor/kidney dose ratio is not always in favour of the same radionuclide

 Benefit/risk balance needs to be established for each patient

However, it was noticed an advantageous ratio for:
177Lu in case of smaller tumors,
90Y for bigger tumors

the answer: it depends…

Tumors

Kidneys
**Dosimetry**

- **90Y-DOTA-peptide** → for big lesions
- **177Lu-DOTA-peptide** → for small lesions

Dose factors $S$

**Dose factor $S_t (Lu) / S_t (Y)$**

- **177Lu** - Tumor efficacy
- **90Y**

**Morphology, receptors...**

- other essential factors influencing:
  - Receptor density
  - Vascularity
  - Kinetics
  - Specific Radiosensitivity
  - Tumour dimension

**Uniformity?**

- Small $T$: probably more uniform
- Big $T$: ...anarchy

Cross fire properties could compensate non uniformity...
Uniformity?

- Where and how much?
  - dosimetry at the voxel level, dose volume histograms (DVH)

- Can it affect response / toxicity?

- How to be taken into account?

- Is it possible to lower it? Is it worthwhile?
  - radiobiological models and experiments
  - BED (and BEDVH) and EUD concepts may be most useful tools

Still open questions, work in progress...
...from activity to dose distribution

Activity distribution

Dose distribution at the voxel level

Voxel source

$D_{(\text{voxel}, k)} = A_{\phi} \sum_h \tau_{\text{voxel}, h} \cdot S_{(\text{voxel}, k \rightarrow \text{voxel}, h)}$

Voxel dosimetry

feasible

Anatomical data - CT

direct MC simulations

still very demanding...

Dose %

Vol %


IEO
Istituto Europeo di Oncologia

...etc

work in progress ...
A new tool available for voxel dosimetry

Literature (MIRD 17) provides S-factors for voxel dimensions not specifically corresponding to the ones used by nuclear medicine equipments. Specific calculations require MC simulation.

S-voxel factors now available on line for several voxel sides and radionuclides

www.df.unibo.it/medphys
(link: Research → Voxel Dosimetry...)

2.33, 3, 4, 4.42, 4.8, 5, 6, 6.8, 9.28 mm

at moment

90Y, 177Lu, +
89Sr, 131I, 153Sm, 186Re, 188Re

M.Pacilio, N.Lanconelli, S.LoMeo, L.Torres, M.Coca Perez, F.Botta, M.Cremonesi, A.Di Dia, M.Ferrari

mpacilio@scamilloforlanini.rm.it
nico.lanconelli@unibo.it
francesca.botta@ieo.it
The activity distribution and radionuclide may hardly influence the kidney safety.

The radiobiological model would indicate different renal burden: uniform vs. non uniform vs. $^{90}$Y vs. $^{177}$Lu.

---

Cremonesi et al. abstr EANM 2009
Non uniformity in Tumors

dose distribution in tumoral and surrounding normal tissues?

Monte Carlo simulations

Mean dose representativity:
→ very radionuclide dependent
→ hardly influenced by activity distribution

90Y cross-fire can play against non uniformity in tumours...

177Lu

higher UNIFORMITY inside
inside: dose = mean dose

90Y

higher dose in the core
edge: dose < mean dose

Hp: uniform activities in spheres for equal mean doses

Botta F et al. EJNMMI 2008, 35(2):S201
Efficacy of PRRT has been proven (>25% O.R.)

Tumor reduction vs. dose: correlation?...tendency

- Tumour dimension/structure
- Activity distribution
- Radiosensitivity

Radiobiological studies are warranted

Pauwels et al. JNM 2005, 1872-80
correlations with side effects?
radiation nephropathy

**Effect**

- dose rate
- radiosensitivity
- repair capacity
- repopulation
- clinical data...

**BED in kidneys**

**BED**

- Biological Effective Dose

**RADIOBIOLOGY**

cumulative with cycles

and possible different schemes

**NTCP curves for RT & PRRT**

NTCP = Normal Tissue Complication Probability

Wessels et al JNM 2008, 1884-99
Pts with high kidney absorbed doses and no renal toxicity received the activity fractionated in a high number of cycles and over a longer period.

Radiobiological prediction/interpretation of clinical results:

BED (Dxn) > n \times BED (D)

\[ \Delta \text{BED (Gy)} \]

KIDNEY - dose tot (Gy)

BED sparing (Gy)

6 cy
4 cy
3 cy
2 cy

\[ \Delta \text{BED (Gy)} \]

0 10 20 30 40 50

Multiple cycles allow renal cell sparing.

Bodei et al. EJNMMI 2008 1847-56
Cremonesi et al. QJNM 2010
1. Red Marrow toxicity - side effects

- Clinical data
  - $^{90}$Y-DOTATOC - mild but progressive depletion of RM resources
  - $^{177}$Lu-DOTATATE - lower RM toxicity, usually
  → cumulative effect with cycles lowering tolerability

Bodei et al. EJNMMI 2008, 1847-56.

2. Activity concentration in RM aspirates identical to that in blood
   - No significant binding of the radiopeptides to RM stem cells
   - No correlation between RM doses and change in PLT

Forrer et al. EJNMMI 2009, 1138-46.

more studies are needed...
Men sterility - side effects

177Lu-DOTATATE

\[ \text{dose to the testes:} \]
\[ 0.16 \text{ Gy/GBq} \]
\[ \rightarrow 0.6 - 1.2 \text{ Gy / cycle} \]

These doses are consistent with the effects observed...

sterility thresholds, ICRP 60

<table>
<thead>
<tr>
<th></th>
<th>men</th>
<th>women</th>
</tr>
</thead>
<tbody>
<tr>
<td>temporary</td>
<td>0.2 Gy</td>
<td>2.5 - 6.0 Gy</td>
</tr>
<tr>
<td>permanent</td>
<td>3.5 - 6.0 Gy</td>
<td>6.0 Gy</td>
</tr>
</tbody>
</table>

These doses are consistent with the effects observed...

alteration of clinical parameters

permanent men sterility after each cycle of therapy
in men only; reversible

Kwekkeboom DJ al. J Clin Oncol Invest 2005
The clue

Multidisciplinarity

New (pre)Clinical studies

Improved dosimetry accuracy

Further optimized therapy designs
Thank you!
Still in too many countries, scientific contributes are hold back because of governments, putting funds and resources far from real progress, research, medical care…

Also in favour of science, dictatorships, declared or not, should not exist

Galileo Galilei
This project, born under the guidance of the oncologist Umberto Veronesi, aims to create a great movement for peace led by the scientific and cultural communities.

Main goals:
- A widespread culture for peace
- The progressive reduction of military expenses in favour of greater investments in research & development (education, health policies, social emergencies, etc...)

So far, 21 Nobel Laureates and important personalities from science and culture have joined this movement. Kathleen Kennedy Townsend is the vice-president.

The Science for Peace project schedules an annual World Conference in order to discuss and propose concrete solutions of peace. The 2nd edition will take place in Milan (Italy) on November 18th and 19th 2010.

www.fondazioneveronesi.it