EANM Dosimetry guidelines

Compliance to individual treatment planning in Molecular RadioTherapy

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EANM Dosimetry Committee

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EANM Dosimetry Committee Guidelines for Molecular RadioTherapy

- EANM DC series on standard operational procedures for pre-therapeutic dosimetry:
  - Blood and bone marrow dosimetry in differentiated thyroid cancer therapy (2008)
  - Dosimetry prior to Radioiodine Therapy of Benign Thyroid Diseases (2013)
  - A unified methodology for pre- and post-therapy dosimetry of liver primary and secondary lesions treated with $^{90}$Y microspheres (in preparation, 2019)
- EANM DC guidelines for bone marrow and whole-body dosimetry (2010)
- EANM DC guidance: good practice of clinical dosimetry reporting (2010)
- EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations (2018)

https://www.eanm.org/publications/guidelines/dosimetry/
# EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry
## I: blood and bone marrow dosimetry in differentiated thyroid cancer therapy

**Table 1** Timelines of measurements

<table>
<thead>
<tr>
<th>Time</th>
<th>Task</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Quality control, preparation of $^{131}$I standard and tracer activity, micturition (just before administration)</td>
<td>“Preparation of $^{131}$I standard and tracer activity” section</td>
</tr>
<tr>
<td></td>
<td>Administration of $^{131}$I tracer activity</td>
<td>“Blood sampling” section</td>
</tr>
<tr>
<td></td>
<td>Avoid micturition or defecation</td>
<td>“Pre-therapeutic quantification of whole-body retention” section</td>
</tr>
<tr>
<td>10 min (i.v. admin.); 2 h (oral admin)</td>
<td>Measurement of whole-body activity, blood sampling (2 ml)</td>
<td>“Blood sampling” section “Pre-therapeutic quantification of whole-body retention” section</td>
</tr>
<tr>
<td>6 h</td>
<td>Micturition (just before whole-body measurements), measurement of whole-body activity, blood sampling (2 ml)</td>
<td>“Blood sampling” section “Pre-therapeutic quantification of whole-body retention” section</td>
</tr>
<tr>
<td>24 h</td>
<td>Micturition (just before whole-body measurements), measurement of whole-body activity, blood sampling (2 ml)</td>
<td>“Blood sampling” section “Pre-therapeutic quantification of whole-body retention” section</td>
</tr>
<tr>
<td>96 h</td>
<td>Micturition (just before whole-body measurements), measurement of whole-body activity, blood sampling (2 ml)</td>
<td>“Blood sampling” section “Pre-therapeutic quantification of whole-body retention” section</td>
</tr>
<tr>
<td>144 h</td>
<td>Blood sampling (2 ml) optional: measurement of whole-body activity</td>
<td>“Blood sampling” section “Absorbed dose calculation” section</td>
</tr>
<tr>
<td></td>
<td>Evaluation of blood absorbed dose and therapeutic activity</td>
<td>“Blood sampling” section “Absorbed dose calculation” section</td>
</tr>
</tbody>
</table>

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EANM Dosimetry Committee Series on Standard Operational Procedures for Pre-Therapeutic Dosimetry II. Dosimetry prior to radioiodine therapy of benign thyroid diseases

Potential sources of error

- Errors in target volume determination
- Inappropriate attenuation correction (no or inadequate phantom)
- Contamination of the phantom
- Incorrect distance between the detector and the patient or phantom
- Deviation of the individual target tissue depth from the calibration depth
- Inappropriate centring of the probe over the phantom or the target tissue (target tissue partially outside the probe’s FoV)
- Instability of the electronics of the measuring device, especially if quality control is inadequate
- Variation in background count rate (e.g. from radiation emitted by other patients) for the different uptake measurements
- Reduced or delayed absorption due to recent food intake
- Recent administration of another radionuclide
- Unfavourable choice of timing of the uptake measurements

\[ A_{\alpha}[\text{MBq}] = \frac{1}{E} \cdot \frac{M[g] \cdot D[Gy] \cdot k_B[d^{-1}] \cdot k_T[d^{-1}]}{k_i[d^{-1}]} \]  

\[ RIU(t) = \frac{k_i}{k_B - k_T} \cdot (e^{-k_B t} - e^{-k_T t}) \]

\[ \int_{t=0}^{\infty} R IU(t) \cdot dt = \frac{k_i}{k_B \cdot k_T} \]

Fig. 2 Fit of Eq. 4 (solid line) to measurements (circles) of the fractional target mass uptake RIU(t). The residence time (area under the curve) is \( k_i \cdot k_B^{-1} \cdot k_T^{-1} \)

Fig. 3 Determination of the residence time in the target tissue based on two measurements of the fractional uptake 2 and 6 days after activity administration. The factor 0.97 accounts for the area between the monoexponential decay function (dashed line) and the actual uptake function in the phase of accumulation (solid line)
A UNIFIED METHODOLOGY FOR 
PRE- AND POST-THERAPY DOSIMETRY OF 
LIVER PRIMARY AND SECONDARY LESIONS 
TREATED WITH \(^{90}\)Y MICROSPHERES

Carlo Chiesa\(^1\), Katarina Sjogreen-Gleisner\(^2\), Stephan Walrand\(^3\), Lidia Strigari\(^4\), Glenn Flux\(^5\), Caroline Stokke\(^6\), Pablo Minguez Gabina\(^7\), Peter Bernhardt\(^8\), and Mark Konijnenberg\(^9\)

<table>
<thead>
<tr>
<th>Total intended (^{90})Y activity (GBq)</th>
<th>2.03</th>
<th>2.71</th>
<th>2.91</th>
<th>3.12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraction of residual activity in vial (hypothetical)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>LSFplanar (NAC)</td>
<td>0.028</td>
<td>0.028</td>
<td>0.028</td>
<td>0.028</td>
</tr>
<tr>
<td>Lung absorbed dose NAC (Gy)</td>
<td>2.8</td>
<td>3.8</td>
<td>4.0</td>
<td>4.3</td>
</tr>
<tr>
<td>LSF* (AC approximated)</td>
<td>0.010</td>
<td>0.010</td>
<td>0.010</td>
<td>0.010</td>
</tr>
<tr>
<td>Activity in liver (GBq)</td>
<td>2.03</td>
<td>2.68</td>
<td>2.88</td>
<td>3.07</td>
</tr>
<tr>
<td>Lesion VII segm. Mean dose (Gy)</td>
<td>243</td>
<td>324</td>
<td>347</td>
<td>373</td>
</tr>
</tbody>
</table>

| Mass (g) | 297 |
| Lesion VII segm. Viable portion Mean dose (Gy) | 329 | 439 | 470 | 505 |
| Mass (g) | 170 |
| Perfused region mean dose (Gy) | 66 | 88 | 94 | 101 |
| Mass (g) | 432 |

SPECT lung counts estimated from mean 2.7 attenuation correction factor 1.000 229,948
EANM Dosimetry Committee guidelines & related reports

• The evidence base for the use of internal dosimetry in the clinical practice of molecular radiotherapy. L Strigari et al., Eur J Nucl Med Mol Im 2014

• Internal Dosimetry Task Force (EANM member initiative, 2014-2017)
  • Dosimetry-based treatment planning for molecular radiotherapy: a summary of the 2017 report from the IDTF. C Stokke et al. EJNMMI Phys. 2017
  • Resource implications of dosimetry in molecular radiotherapy (P Minguez et al., under evaluation)

EANM guidelines on radionuclide therapy

• EANM guideline for radionuclide therapy with radium-223 of metastatic castration-resistant prostate cancer (2018)
• The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours (2013)
• EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds (2011)
• EANM procedure guidelines for therapy of benign thyroid disease (2010)
• EANM procedure guidelines for $^{131}$I-meta-iodobenzylguanidine ($^{131}$I-mIBG) therapy (2008)
EANM Guidelines in preparation

• Dosimetry Committee:
  • Dosimetry for $^{131}$I mIBG treatment of neuroendocrine tumours
  • Guideline on SOP for $^{177}$Lu Dosimetry (PSMA and peptides)
  • Guidelines for alpha-particle emitter dosimetry ($^{223}$Ra, $^{225}$Ac and ...)

• Oncology and Theranostic Committee:
  • EANM procedure guidelines for radionuclide therapy with $^{177}$Lu-labeled PSMA-ligands ($^{177}$Lu-PSMA-RLT)
MRT
Conventional therapy posology
- 7400 MBq
- 55 kBq/kg
- Per BSA
- Cohort dosimetry

MRT
Personalized Therapy posology
- Patient-specific dosimetry proc.
- NTCP tolerance
- TCP efficacy

BSS 2013/59 EU directive:
..exposures of target volumes shall be individually planned..

From fixed activities to Personalized treatments in radiation therapy: lost in translation?
Project plan for guidance to adhere to the optimisation paragraph in MRT according to the basis safety standards directive 2013/59/Euratom

• The level of compliance may vary considerably, depending on accuracy, radiotoxicity as well as clinical end-points.

• These levels need to be defined together with the constraints in which situation they can be considered to be acceptable.

• Consensus should be obtained on minimum acceptable levels for each radionuclide therapy.
Probability of Uncomplicated cure: \[ PUC = TCP \times (1 - NTCP) \]

Optimisation principle in EBRT and MRT

a. External Beam RT absorbed dose defined by linac m.u.
b. MRT absorbed dose to normal organ, kinetics & physiology
c. MRT absorbed dose to tumour, specific targeting
Project plan for guidance to adhere to the optimisation paragraph in MRT according to the basis safety standards directive 2013/59/Euratom

• Prospective Patient-Specific Dosimetry compliance levels:
  • Level 0: patient-cohort average dosimetry and activity administered.
  • Level 1: 1-time point activity assessment by quantitative WB imaging using patient-averaged clearance kinetics, phantom based S-values and activity adm.
  • Level 2: multiple time-point activity assessments by hybrid quantitative WB and SPECT imaging, phantom based S-values and activity administered.
  • Level 3: full 4D dosimetry assessment by multiple quantitative SPECT-CT / PET-CT imaging reporting voxelised dose distributions and activity administered.
  • Level 4: level3 together with multi-compartment PK analysis
What is the current level of PPSD compliance in MRT (part 1)?

<table>
<thead>
<tr>
<th>MRT aim</th>
<th>Posology</th>
<th>Target dose</th>
<th>OAR dose</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain palliation</td>
<td>150 MBq $^{89}$SrCl$_2$ 37 MBq/kg $^{153}$Sm EDTMP</td>
<td>9 - 92 Gy 3 - 60 Gy</td>
<td>Red BM: 1.65 Gy Red BM: 3.9 Gy</td>
<td></td>
</tr>
<tr>
<td>Treatment of sclerotic metastases</td>
<td>55 kBq/kg $^{223}$RaCl$_2$ (6 cycles)</td>
<td>9 – 59 Gy</td>
<td>Red BM: 0.2 – 1.9 Gy</td>
<td>Bone fractures</td>
</tr>
<tr>
<td>Radiosynoviorthesis</td>
<td>20-40 MBq $^{169}$Er citrate 180-200 MBq $^{90}$Y citrate</td>
<td>Unknown 92 Gy (100 g)</td>
<td>Unknown Lymph nodes: 10 Gy</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Benign thyroid disease</td>
<td>3.7-11.1 MBq/mL $^{131}$I or fixed 370-740 MBq $^{131}$I NaI</td>
<td>300-400 Gy (N) 120-150 Gy (G)</td>
<td>not usually required</td>
<td>radiation thyroiditis, sialadenitis and gastritis</td>
</tr>
<tr>
<td>Differentiated thyroid carc. (DTC)</td>
<td>1.11 - 7.4 GBq $^{131}$I NaI, depending disease stage</td>
<td>49 – 300 Gy (R) 40 – 80 Gy (M)</td>
<td>Blood: &lt; 2 Gy Lung: &lt; 3 GBq @ 48h</td>
<td>Above + pneumonitis and myelosuppression</td>
</tr>
<tr>
<td>Malignant Neural Crest Tumors</td>
<td>444 MBq/kg $^{131}$ImIBG (NB) 3.7-18.5GBq $^{131}$ImIBG (NE)</td>
<td>5 – 300 Gy</td>
<td>Whole body: 2 Gy</td>
<td>Myelosuppression Hypothyroidism</td>
</tr>
</tbody>
</table>

Level 0 - 1

https://www.nucmed-guide.app/#!/startscreen
What is the current level of PPSD compliance in MRT (part 2) ?

<table>
<thead>
<tr>
<th>MRT aim</th>
<th>Posology</th>
<th>Target dose</th>
<th>OAR dose</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroendocrine tumours</td>
<td>4 x 7.4 GBq $^{177}$Lu-peptide 4x1.85-3.7 GBq/m² $^{90}$Y DT</td>
<td>10 – 340 Gy</td>
<td>kidney:1-14 Gy/cycle kidney:4-16 Gy/cycle</td>
<td>Myelosuppression Radiation nephritis g4-5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not reported</td>
<td>kidney:4-16 Gy/cycle</td>
<td></td>
</tr>
<tr>
<td>Primary &amp; secondary hepatic malignancy</td>
<td>120 Gy to liver $^{90}$Y microspheres</td>
<td>100-1000 Gy</td>
<td>Liver: 20-120 Gy Lung: 0 – 30 Gy</td>
<td>Liver failure (gr 4-5) pneumonitis</td>
</tr>
<tr>
<td>RIT for non-Hodgkin Lymphoma</td>
<td>11-14 MBq $^{90}$Y-ibritumomab tiuxetan</td>
<td>5.8 – 67 Gy</td>
<td>Red BM: 2.2 ± 0.7 Gy Lymph nodes: 10 Gy</td>
<td>Myelosuppression Infection</td>
</tr>
<tr>
<td>PSMA-Targeted Internal RT prostate</td>
<td>2-9 GBq/(m²) $^{177}$Lu-PSMA per cycle</td>
<td>7 - 30 Gy</td>
<td>Sal glands: 13 Gy Kidney: 5-9 Gy Red BM: 0.1-0.4 Gy</td>
<td>Xerostomia, hematotoxicity</td>
</tr>
</tbody>
</table>

Level 0 - 1

Level 2

https://www.nucmed-guide.app/#!/startscreen
How can we come to a higher level of compliance?

- Dosimetry mandatory in all clinical trials for MRT
- Ask the therapy question: palliation or cure?
- Identify the dose limiting organ
- Evaluate resources needed to perform dosimetry
  - Balance clinical benefit and resource investments
Dosimetry for $^{177}$Lu-DOTA-tyr$^3$-octreotate therapy

- Dosimetry assessments
  - Kidneys
  - Tumour lesions
  - Bone marrow (maybe)

T = 0  T=1 day  T=4 days  T=7 days
Dose-effect relation for late occurring kidney toxicity after $^{90}$Y-DOTATOC therapy

MIRD pamphlet 20, 2008

- Only patient-specific kidney dose shows correlation
- Linear Quadratic model: 
  \[ p(\text{survival}) = \exp(-\alpha D - \beta D^2) = \exp(-\alpha \text{BED}) \]
- Biologically Effective Dose explains shift from XRT curve

\[
\text{BED} = D \left( 1 + \frac{T_{repair}}{T_{eff}+T_{repair}} \times \frac{D}{N} \times \frac{\beta}{\alpha} \right)
\]
Nephrotoxicity observed at Erasmus MC after 4 x 7.4 GBq $^{177}$Lu-DOTA-Octreotate


Erasmus MC
- 323 patients
- 228 dose < 23 Gy
- 191 ≥ 1 y f.u.
Subacute haematotoxicity after PRRT with $^{177}$Lu-DOTA-octreotate: prognostic factors, incidence and course

Hendrik Bergama $^1$ - Mark W. Konijnencberg $^1$ - Boen I. R. Kam $^1$ - Jaap J. M. Teunissen $^1$ -
Peter P. Kooij $^1$ - Wouter W. de Herder $^2$ - Gaston J. H. Franssen $^3$ -
Casper H. J. van Eijck $^3$ - Eric P. Krenning $^1$ - Dik J. Kwakkeboom $^1$

Fig. 2 Venn diagram of haematological toxicity (grade 3/4) in 34 out of 320 patients treated with a median cumulative dose of 29.6 GBq $^{177}$Lu-DOTATATE

Some correlation with bone marrow dose (11% >grade 3)
Persistent Hematologic Dysfunction after Peptide Receptor Radionuclide Therapy with $^{177}$Lu-DOTATATE: Incidence, Course, and Predicting Factors in Patients with Gastroenteropancreatic Neuroendocrine Tumors

Hendrik Bergsmal, Kirsten van Lom2, Marc H.G.P. Raaijmakers2, M. Konijnenberg1, B.L. Boen L.R. Kam1, Jaap J.M. Teunissen1, Wouter W. de Herder3, Eric P. Krenning1, and Dik J. Kwekkeboom1

FIGURE 3. Expected number of patients with hematopoietic neoplasms and type, based on data from The Netherlands Cancer Registry, as well as observed number of patients (of 274 GEP NET patients) with PHD after PRRT with $^{177}$Lu-DOTATATE, including 8 patients with hematopoietic neoplasms and 3 with BM failure. Red = MDS; orange = AML; yellow = MPN + MDS/MPN; green = BM failure.

FIGURE 5. Comparison of PHD and cumulative dose to BM. (A) Cumulative estimated BM dose in 11 patients with PHD (including 5 AML/MDS ○ and 6 other diagnosis ● patients) and 263 patients without PHD. (B) Marrow dose in 3 patients with AML/MDS ○ and 28 patients without AML/MDS. Data for dosimetry analysis in subgroup of 807 patients were adopted from Bodei et al. (8). Whiskers represent minimum and maximum estimated BM dose in grays. Height of box shows interquartile range, and horizontal line in box is median estimated BM dose in grays.
Dose Response of Pancreatic Neuroendocrine Tumors Treated with Peptide Receptor Radionuclide Therapy Using $^{177}$Lu-DOTATATE

Ezgi Iilan$^{1,2}$, Mattias Sandström$^{1,2}$, Cecilia Wassberg$^{1,3}$, Anders Sundin$^{1,3}$, Ulrike Garske–Román$^{1,3}$, Barbro Eriksson$^{4}$, Dan Granberg$^{4}$, and Mark Lubberink$^{1,2}$

DOI: 10.2967/jnumed.114.148437

Practical Dosimetry of Peptide Receptor Radionuclide Therapy with $^{90}$Y-Labeled Somatostatin Analogs


Tumour doses $> 150 \sim 200$ Gy
Variation in absorbed dose values at 4 x 7.4 GBq

- Absorbed dose
- Kidneys:
  - $4 \times (6 \pm 2)$ Gy
- Bone marrow:
  - $4 \times (0.5 \pm 0.1)$ Gy
- Tumour
  - $4 \times 50$ (10 - 120) Gy

M. Cremonesi et al. EJNMMI 2018
Proceed with fixed activity (4 x 7.4 GBq) or treat to the maximum tolerated dose?

- Proceed with 7.4 GBq $^{177}$Lu cycles
- Until the kidneys BED = 40 Gy
- Dosimetry based on combined planar WB and SPECT/CT

**ILUMINET—trial design**

**Step 1**
- Patient population
  - mNET
  - G1-2
  - PD
- 177Lu 7.4 GBq
- 177Lu 7.4 GBq
- 177Lu 7.4 GBq

**Step 2**
- BED: 40 ± 2 Gy
- 177Lu 7.4 GBq
- 177Lu 7.4 GBq
- STOP

- Age
- Previous therapy
- Adverse event
- Still PD

**BED:** 27 ± 2 Gy

GO if:
- Kidneys ok
- Bone marrow ok
- No PD
- No toxicities

Sundlöv et al. EJNMMI Physics (2018) 5:12
Dosimetry guided therapy:

- 23 Gy to the kidneys
  - \( \leq 4 \times 7.4 \text{ GBq} \) \( ^{177}\text{Lu} \) DOTAstate in 102 patients
- 5-9 \( \times 7.4 \text{ GBq} \) \( ^{177}\text{Lu} \) (N=98)
- Overall median survival
  - 54 months (reached 23 Gy)
  - 25 months (< 23 Gy)

Prospective observational study of \( ^{177}\text{Lu}-\text{DOTA-occteate} \) therapy in 200 patients with advanced metastasized neuroendocrine tumours (NETs): feasibility and impact of a dosimetry-guided study protocol on outcome and toxicity

Unbeknown to Garvoc-Roman 1-7, Mattias Sandström 2, Karasyna Frosi Oron 1, Lars Lundin 2, Per Hellman 1, Staffan Welin 1, Silvia Johansson 1, Tanweer Khan 1, Hans Lundqvist 1, Barbro Eriksson 1, Anders Sundin 1, Dan Granberg 1
Salvage therapy (repeat 7.4 GBq):

- $4 \times 7.4$ GBq $^{177}$Lu DOTAtate
- $2 \times 7.4$ GBq $^{177}$Lu (N=168)
- $2 \times 7.4$ GBq $^{177}$Lu (N=13)

Cumulative 26-61 GBq

Overall median survival

- GEPNET: 81 m vs. 51 m (control)
- Midgut NET: 77 m vs. 51 m (control)
- Pancreas NET: Not significant
Comparisons in overall survival (don’t tell the statistician)

• Netter-1 study (N=229)  
  (J. Strosberg et al., NEJM 2017)  
  • > 30 months vs 20 months (control)

• Dosimetry guided protocol (N=200)  
  (Uppsala, U. Garske et al. 2018)  
  • 54 months (23 Gy) vs 25 months (<23)

• Repeat 7.4 GBq “blindly” (N=267)  
  (Rotterdam, W vd Zwan et al. 2019)  
  • 81 months (repeat) vs 51 months (4)
The maximum benefit from dosimetry guidance in PRRT?

- Select the non-responders to fixed dosing schemes 4 x 7.4 GBq:
  - Pancreatic NET
  - Non-responders according to PPQ genetic NET test (L. Bodei et al. EJNMMI (2018) 45:1155–1169)
  - Wait for the overwhelming results from the Illuminet trials
Compliance to individual treatment planning in Molecular RadioTherapy?

- Is actually hardly routinely being performed
- EANM is providing the SOPs to aid therapy and dosimetry
- Definition of levels in compliance to patient-specific dosimetry
  - Selection of patients and relevant efficacy as well as toxicity end-points
- How about the bone marrow dosimetry?
Acknowledgements

The EANM dos com

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• Pablo MinguezGabina

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