Personalized dosimetry in diagnostic and therapeutic nuclear medicine

IAEA Conference on Radiation Protection in Medicine: Achieving Change in Practice

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Article 56 (Optimisation)

For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified, taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.

Article 4 (Definitions) – 81

“radiotherapeutic” means pertaining to radiotherapy, including nuclear medicine for therapeutic purposes.

The directive thus asks for dosimetry In Therapeutic Nuclear Medicine, as is routinely implemented in radiotherapy, using external beam or brachytherapy sources.
INTERNAL DOSIMETRY TO SUPPORT THE RADIONUCLIDE THERAPY

NET

131I-MIBG, 90Y-, 177Lu-peptides (PRRT)

Bone Pain
89Sr, 32P, 153Sm-EDTMP, 188Re-HEDP, 90Y-HEDP, 223Ra

Thyroid Diseases

131I

Hepatic Tumors
Selective Internal Radiotherapy (SIRT)
90Y-microspheres

Lymphomas (NHL)
90Y-Zevalin

Bone Pain

89Sr, 32P, 153Sm-EDTMP, 188Re-HEDP, 90Y-HEDP, 223Ra

Thyroid Diseases

131I

Hepatic Tumors
Selective Internal Radiotherapy (SIRT)
90Y-microspheres

Lymphomas (NHL)
90Y-Zevalin
Iodine therapy of advanced differentiated thyroid cancer (DTC)

Context

About 15% of patients with high-risk DTC have a significantly reduced life expectancy as many do not respond sufficiently to $^{131}$I therapy to prevent recurrence and progression of DTC, or even death.

In patients with advanced DTC, the scientific debate is not about a “low”, a “lower” or “no” $^{131}$I activity, but instead about a “high” or a “higher” $^{131}$I activity.

$^{131}$I activity selection strategies

- **Empirical activity selection**, 3,700, 5,550 7,400 or 11.000 MBq.
  - absorbed doses delivered to lesions per unit of administered activity can range widely

- **Lesion dosimetry.** The activity to be administered is determined after a pretherapeutic dosimetric assessment (either with $^{124}$I or $^{131}$I) to calculate the minimal activity required to achieve an effective absorbed dose (ALARA)
The maximum tolerable absorbed dose approach in NM therapy

*Exposures of target volumes shall be individually planned*

In NM therapy we have patients or situations where the absorbed dose to the target volume cannot be calculated or reliably predicted for technical or practical reasons:

- metastatic lesions may not be measurable
- There may be too many lesions with different uptake
- The molecule used in the tumour pre-treatment dosimetry may have limited power to predict the absorbed dose of the therapeutic agent during treatment

*Absorbed doses to non-target volumes and tissues*

The next best alternative is to base therapy planning on the maximum tolerable absorbed dose (MTAD) to nontarget organs or tissues (AHASA as high as safely attainable).

The AHASA approach has been endorsed by the European Association of Nuclear Medicine in its procedural guidelines.
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<th>Study</th>
<th>Summary</th>
<th>Journal</th>
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<td>Lee JJ et al</td>
<td>Maximal safe dose of $^{131}$I after failure of standard fixed dose therapy in patients with differentiated thyroid carcinoma</td>
<td>Ann Nucl Med. 2008</td>
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<tr>
<td>Klubo-Gwiedzinska J et al</td>
<td>Efficacy of dosimetric versus empiric prescribed activity of $^{131}$I for therapy of differentiated thyroid cancer.</td>
<td>J Clin Endocrinol Metab. 2011</td>
</tr>
<tr>
<td>De Andreis D et al</td>
<td>Comparison of Empiric Versus Whole-Body/-Blood Clearance Dosimetry-Based Approach to Radioactive Iodine Treatment in Patients with Metastases from Differentiated Thyroid Cancer</td>
<td>J Nucl Med 2017</td>
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</table>
Maximal safe dose of $^{131}$I after failure of standard fixed dose therapy in patients with differentiated thyroid carcinoma

Forty-seven differentiated thyroid carcinoma patients with non-responsive residual disease despite repetitive fixed activity $^{31}$I therapy

MTAD to deliver a maximum of 2 Gy to blood

The mean calculated activity was 12.5 ± 2.1 GBq (339.6 ± 57.5 mCi).

- 7 (14.9%) complete remission
- 15 (31.9%) partial remission
- 19 (40.4%) stable disease
- 6 (12.8%) disease progression

The MTAD provides an effective means of treatment in patients who failed to respond adequately to conventional fixed activity therapy.

Efficacy of dosimetric versus empiric prescribed activity of $^{131}$I for therapy of differentiated thyroid cancer.

Retrospective- Eighty-seven differentiated thyroid carcinoma patients. 43 treated with Dosimetric and 44 with empiric approach to predict $^{131}$I therapy activity.

Although PFS was not significantly different between the D-Rx and E-Rx groups ($P=0.34$), the Kaplan-Meier curves show a trend toward longer PFS in patients treated with D-Rx.

Higher efficacy of D-Rx with a similar safety profile compared to E-Rx supports the rationale for employing individually prescribed activity in high-risk patients with DTC.

Klubo-Gwiezdzinska J et al J Clin Endocrinol Metab 2011
Comparison of Empiric Versus Whole-Body/-Blood Clearance Dosimetry-Based Approach to Radioactive Iodine Treatment in Patients with Metastases from Differentiated Thyroid Cancer.

Retrospective -352 differentiated thyroid carcinoma patients. 121 treated with Dosimetric (MSKCC) and 231 with empiric approach (GR) to predict $^{131}$I therapy activity.

Routine use of WB/BC dosimetry without lesional dosimetry provided no Overall Survival advantage when compared with empiric fixed activity in the management of thyroid cancer patients with distant metastases.

*De Andreis D et al J Nucl Med 2017*
Comparison of Empiric Versus Whole-Body/-Blood Clearance Dosimetry-Based Approach to Radioactive Iodine Treatment in Patients with Metastases from Differentiated Thyroid Cancer.

The patients treated with dosimetry were
1. much older (a median of 10 years)
2. had a much greater extent of distant metastatic disease.

*Each of these factors separately would be sufficient to cause a significant difference in DTC-specific survival in favour of the fixed activity group*

An alternative possible explanation for the lack of a significant difference in prognosis in spite of a considerable bias against the AHASA activity group, is of the efficacy of AHASA $^{131}$I therapy.

De Andreis D et al J Nucl Med 2017

Flux G et al J Nucl Med 2017
# Dose–Response relationship in DTC

**Table 4** Studies showing dose–effect relationships for $^{131}$I (NaI) therapy against DTC

<table>
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<th>Reference</th>
<th>No. of patients</th>
<th>Endpoint</th>
<th>Threshold dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>[13]</td>
<td>50</td>
<td>Ablation</td>
<td>300 Gy (remnant)</td>
</tr>
<tr>
<td>[13]</td>
<td>26</td>
<td>Response</td>
<td>80 Gy (metastases)</td>
</tr>
<tr>
<td>[14]</td>
<td>23</td>
<td>Ablation</td>
<td>49 Gy (remnant)</td>
</tr>
<tr>
<td>[15]</td>
<td>449</td>
<td>Ablation</td>
<td>0.35 Gy (blood)</td>
</tr>
<tr>
<td>[16]</td>
<td>122</td>
<td>Complications</td>
<td>2 Gy (blood)</td>
</tr>
<tr>
<td>[17]</td>
<td>198</td>
<td>Toxicity grade 3 or more</td>
<td>2 Gy (blood)</td>
</tr>
<tr>
<td>[18]</td>
<td>17</td>
<td>Toxicity grade 3 or more</td>
<td>1.7 Gy (blood)</td>
</tr>
</tbody>
</table>
The MTAD approach - Evidences

The aim of blood and bone marrow dosimetry for $^{131}$I therapy is ensure that higher levels of activity can be administered safely:
- There is no greater toxicity with the AHASA approach.

This method provides indications of best outcome, in contrast to the fixed activity approach, although a clinical study with the highest level of evidence (phase III randomized) has never been pursued.

The controversy in the interpretation of the available material illustrates the need for prospective, randomized, controlled studies comparing dosimetry-based $^{131}$I therapy and conventional fixed-activity based strategies

Until results are available, the available evidence is viewed in a light more favourable to MTAD based $^{131}$I therapy
**90Y-microsphere SIRT**

Normal liver tissue receives about 75% of the blood by the portal vein.

Liver tumors (>20mm) receive approximately 80-100% of blood from the hepatic artery.

90Y Microspheres are directly administered to the liver tumors through the hepatic artery under angiographic guidance.

They are permanently lodged in microcapillaries.

A pre treatment **simulation is performed with** 99mTc-MAA to check for gastrointestinal shunt (absolute contraindication to treatment) and to evaluate lung shunt.

Simulation session can be used for dosimetric treatment planning.
90Y PET vs 99mTc MAA SPECT ABSORBED DOSE IN LIVER

99mTc MAA SPECT scatter correction implemented
90Y PET automatically coregistered to 99mTc MAA SPECT
VOIs of SPECT automatically applied to 90Y PET (crucial choice)

Parenchyma

Lesions

Bland-Altman plot for parenchyma dose (90Y - 99mTc)

Bland-Altman plot for lesions (90Y - 99mTc)

Limit of agreement = ± 30% of TD20 limit

Limit of agreement = ± 57% of TCP50

Predictivity is weaker on lesions. Planning is based mainly on parenchyma limit

Courtesy of C. Chiesa
BASAL

Patient with **Portal Vein Thrombosis (PVT)**

6 months expectancy of life without actions

9 months with standard of care (sorafenib)

12 MONTHS AFTER SIRT

Patient No Evidence of Disease

He survived 59 months

and died for cirrhosis

**SIRT CAN SAVE LIFE**

Courtesy of C. Chiesa

**SIRT CAN KILL (SELDOM)**

**LIVER DECOMPENSATION**

Mazzaferro et al Hepatology 2013
The European SARAH Study with 467 patients showed that compared with standard treatment of sorafenib, local treatment of advanced or inoperable Hepatocellular Carcinoma (HCC) with SIR-Spheres® $^{90}$Y resin microspheres:

- did not lead to a significant improvement in overall survival
- the tumour response (complete or partial response) was significantly higher in the SIRT group than in the sorafenib group.
- significantly reduced the frequency and severity of side effects
- was significantly better tolerated
- was associated with a significantly better Quality of Life

Vilgrain V Lancet Oncol 2016
The Asian SIRveNIB Study, with 360-patients, showed that compared with the standard treatment of sorafenib, local treatment of advanced or inoperable Hepatocellular Carcinoma (HCC) with SIR-Spheres® \(^{90}\text{Y}\) resin microspheres:

- did not show a significant improvement in overall survival
- had a significantly reduced frequency and severity of adverse events
- was significantly better tolerated
- significantly improved PFS and TTP, overall and in the liver, in the treated population

**Remarks on both studies**

- Comparison of PFS was done on Intention to treat Basis
  - Many patients (~30%) were not submitted to the planned treatment
- No individual dosimetry was performed in both studies
Tumor Absorbed Dose – Response relationship in HCC

In terms of the impact of tumour absorbed dose in HCC, the results were concordant and a response relationship and tumour threshold absorbed doses were clearly identified. Tumour absorbed dose has also been found to influence survival.

Table 1 Studies with MAA based tumor dose evaluation in HCC

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Dosimetry</td>
<td>resin</td>
<td>resin</td>
<td>resin</td>
<td>glass</td>
<td>MIRD with BEDs</td>
<td>MIRD</td>
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<tr>
<td>Nb patients</td>
<td>19</td>
<td>71</td>
<td>10</td>
<td>52</td>
<td>36</td>
<td>71</td>
</tr>
<tr>
<td>Nb lesions</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>65</td>
<td>58</td>
<td>NA</td>
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<tr>
<td>Lesion size (cm)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>5.6</td>
<td>7.1</td>
<td>7.1</td>
</tr>
<tr>
<td>Prior therapy (%)</td>
<td>NA</td>
<td>NA</td>
<td>Yes (50)</td>
<td>Yes (28.9)</td>
<td>Yes (42)</td>
<td>Yes (51)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>S (NA)</td>
<td>S (15.5)</td>
<td>S (13.8)</td>
<td>S (22.5)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CE (NA)</td>
<td>CE (0)</td>
<td>CE (25)</td>
<td>CE (18.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other (NA)</td>
<td>Other (13.4)</td>
<td>Other (2.7)</td>
<td>Other (32.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No (50)</td>
<td>No (71.1)</td>
<td>No (58)</td>
<td>No (49)</td>
</tr>
<tr>
<td>Number of radioembolization (%)</td>
<td>NA</td>
<td>1 (77.9)</td>
<td>1 (100)</td>
<td>1 (89.6)</td>
<td>1 (61)</td>
<td>1 (69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 to 5 (22.1)</td>
<td>2 (10.4)</td>
<td>2 (39)</td>
<td>2 (31)</td>
<td></td>
</tr>
<tr>
<td>Response Evaluation</td>
<td>RECIST1.1</td>
<td>WHO</td>
<td>RECIST1.1</td>
<td>EASL</td>
<td>EASL</td>
<td>EASL</td>
</tr>
<tr>
<td>Time of evaluation</td>
<td>6 w</td>
<td>NA</td>
<td>NA</td>
<td>3 m</td>
<td>3 m</td>
<td>3 m</td>
</tr>
<tr>
<td>Dose/response relationship threshold dose (Gy)</td>
<td>NA</td>
<td>YES</td>
<td>Probably b</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Impact on survival</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>257</td>
<td>205</td>
<td>205</td>
</tr>
</tbody>
</table>

a Only a visual evaluation of MMA was done
b All lesion with a TD>91 Gy responded but all evaluated lesions were responding

Nb = number, NA = non available, S = surgery, CE = chemoeombolization, w = week, m = months

Planning method indicated in the device leaflet (legally mandatory)

Resin microspheres:

a) tumor involvement (abandoned)

b) \( A = (\text{Body Surface Area} - 0.2) \times \frac{\text{tumor volume}}{\text{liver volume}} \)

c) Tumor - non tumor absorbed dose (fully dosimetric, good, but seldom used)

Glass microspheres (roughly dosimetric):

\( A = \frac{\text{Absorbed dose to lobe} \times \text{Lobe mass}}{50} \)

80 Gy < Absorbed dose to lobe < 150 Gy

- No biological clearance
- Physical halflife 64.24 h
- One \(^{99m}\text{Tc MAA SPECT scan is enough}
- \( D = \frac{A}{\lambda} \quad S = 1.443 \ T_{1/2} \ A <E> / M \)
- \( D[\text{Gy}] = 49.7 \ A[\text{GBq}] / \text{mass[kg]} \)
Peptide-receptor radionuclide therapy with $^{177}$Lu-DOTATATE in Neuroendocrine Tumours

In the therapy of neuroendocrine tumours with radiolabelled somatostatin analogues, the radiopeptide DOTATATE labelled with $^{177}$Lu is going to be registered.

The observed clinical results indicate a net increase in overall survival compared with the nonlabelled somatostatin analogues (NETTER-1 study).

The administration schedule (posology) proposed in the registration study (7.4 GBq four times) may be a matter of concern if viewed from the perspective of optimization.
Peptide-receptor radionuclide therapy with $^{177}$Lu-DOTATATE in Neuroendocrine Tumours

In the ongoing ILUMINET clinical study based on $^{177}$Lu-DOTATATE, the number of cycles is tailored to the absorbed dose to the kidneys in the individual patient (cumulative BED to the kidneys of 27(±2) Gy), and in an interim analysis the number of delivered cycles was found to vary between three and eight.

The decline in renal function was moderate, with no grade 3-4 toxicity observed so far.

*Sundlöv A EJNM 2017*
Absorbed dose–effect relationships for radiopeptide therapy of NET

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Radionuclide</th>
<th>Carrier</th>
<th>Endpoint</th>
<th>Threshold dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>[31]</td>
<td>13</td>
<td>$^{90}$Y</td>
<td>DOTA-octreotide</td>
<td>&gt;20 % lesion shrinkage</td>
<td>230 Gy (tumour)</td>
</tr>
<tr>
<td>[33, 35]</td>
<td>18+25</td>
<td>$^{90}$Y</td>
<td>DOTA-octreotide</td>
<td>&gt;20 % decline per year in creatinine clearance</td>
<td>35 Gy BED (kidneys) ED$_{50}$: 44 Gy BED (kidneys)</td>
</tr>
<tr>
<td>[32]</td>
<td>9</td>
<td>$^{90}$Y</td>
<td>DOTA-octreotide</td>
<td>50 % reduction in PLT</td>
<td>2 GY (BM)</td>
</tr>
<tr>
<td>[34]</td>
<td>23/5</td>
<td>$^{90}$Y/$^{177}$Lu</td>
<td>DOTA-octreotide, DOTA-octreotate</td>
<td>Creatinine toxicity more than grade 1</td>
<td>28 Gy BED (kidney risk factors), 40 Gy BED (no kidney risk factors)</td>
</tr>
</tbody>
</table>

Strigari L et al EJNM Mol Im 2014
Shape and promote a strategic research agenda for radiation protection in medicine

“Promote research to improve methods for organ dose assessment, including patient dosimetry when using unsealed radioactive sources”

- What results have been achieved and changes in practice implemented?
- What can be done further and how to proceed in terms of strategies and action for better implementation of the Bonn Call for Action

BONN CALL FOR ACTION
10 Actions to Improve Radiation Protection in Medicine in the Next Decade
Conclusions I

Based on National Cancer Institute guideline definition, the studies on absorbed dose–effect relationships in Therapeutic Nuclear medicine had a moderate or low rate of clinical relevance due to the limited number of studies investigating overall survival and absorbed dose.

Nevertheless, the evidence strongly implies a correlation between the absorbed doses delivered and the response and toxicity, indicating that dosimetry-based personalized treatments would improve outcome and increase survival.

Strigari L et al EJNM Mol Im 2014
Conclusions II

“...therapeutic radiopharmaceuticals exert their biological response primarily by the deterministic effect of radiation.”

“The hypothesis that the level of activity administered has a greater impact on treatment outcome than the subsequent bio distribution, the radiation delivery and the absorbed dose is ignoring the results of decades of radiation research on biological systems.”

“Any studies demonstrating apparent safety in spite of empirical or semi-empirical methods only leads to the logical conclusion that these methods have a conservative tendency to undertreat, sacrificing efficacy for safety.”

“The modern era of personalized medicine demands the measurement of patient-specific biophysical parameters to individualize treatment so as to maximize the desired effect while minimizing toxicity”
Shape and promote a strategic research agenda for radiation protection in medicine

“Strengthen manufacturers’ role in contributing to the overall safety regime”

What challenges were not seen before, but are visible now, and how should they be dealt with?

**BONN CALL FOR ACTION**

10 Actions to Improve Radiation Protection in Medicine in the Next Decade
Conclusions III

When regulatory agencies accept radiopharmaceutical posology based only on fixed administrations:

- fixed activities and a fixed number of cycles (177Lu DOTATATE),
- a fixed activity per body mass (223Ra),

Therapists may be prevented from basing their prescriptions on the individual patient absorbed dose to comply with the package insert.

Package inserts containing only non dosimetric posology force therapists into conflict with article 56 of the BSS.

The package insert of any radioactive agent for therapy should indicate, in parallel with conventional posology, a dosimetry-based administration undertaken under the full responsibility of the therapy team.
Dosimetry in diagnostic Nuclear Medicine

Diagnostic examinations represents about 90% of the Nuclear Medicine procedures.

To date, the estimated radiation-absorbed dose to organs and tissues in “reference” patients undergoing diagnostic examinations in nuclear medicine is derived via calculations based on models of the human body and the biokinetic behaviour of the radiopharmaceutical, including:

- Anatomical and physiological reference values
- Phantom
- Specific Absorption Fractions
- Nuclear decay data
- Effective dose calculations
<table>
<thead>
<tr>
<th>Software</th>
<th>Occupational and environmental exposures</th>
<th>Patients</th>
<th>Anatomical and Physiological reference values</th>
<th>Phantom</th>
<th>Specific Absorption Fraction</th>
<th>Nuclear decay data</th>
<th>Effective Dose calculations</th>
</tr>
</thead>
</table>
Shape and promote a strategic research agenda for radiation protection in medicine

“Promote research to improve methods for organ dose assessment, including patient dosimetry when using unsealed radioactive sources”

- Have any tools/text-material/training material (cost-free) been developed by organizations since the Bonn Call for Action was launched, that will help in its’ implementation?

**BONN CALL FOR ACTION**

10 Actions to Improve Radiation Protection in Medicine in the Next Decade
IDAC-Dose2.1 is created for diagnostic nuclear medicine reference dosimetry based on standardised anatomical and biokinetic models for patients.

IDAC-Dose2.1, was developed based on the International Commission on Radiological Protection (ICRP)-specific absorbed fractions and computational framework of internal dose assessment given for reference adults in ICRP Publication 133. The program uses the radionuclide decay database of ICRP Publication 107, the voxel phantoms defined in ICRP 110 and considers 83 different source regions irradiating 47 target tissues, defining the effective dose as presented in ICRP Publications 60 and 103.

IDAC-Dose2.1 has a sub-module for absorbed dose calculations in spherical structures of different volumes and composition; this sub-module is intended for absorbed dose estimates in radiopharmaceutical therapy.
Internal Dose Assessed by Computer” (IDAC-Dose) program has been used by ICRP to tabulate dose coefficients for reference adults patients undergoing examinations with radiopharmaceuticals in nuclear medicine.

The ICRP Task Group on “Radiation dose to patients in diagnostic nuclear medicine” has issued several publications on the absorbed dose to reference adult patients from different clinically used diagnostic radiopharmaceuticals using the IDAC-Dose1.0 program.

- Radiation dose to patients from radiopharmaceuticals. Publication 53. 1988
- Radiation dose to patients from radiopharmaceuticals: (addendum 2 to ICRP publication 53). Publication 80. 1998
- Radiation dose to patients from radiopharmaceuticals. Addendum 3 to ICRP publication 53. Publication 106. 2008
- Radiation Dose to Patients from Radiopharmaceuticals. A compendium of current information related to frequently used substances. ICRP publication 128. 2015.
ICRP 103 is very hard to be implemented in Nuclear Medicine “Real Life”

- They recommend to separate male and female absorbed dose calculations, but this can’t be done for existing radiopharmaceuticals, as published pharmacokinetics are not separated for male and female. Therefore using different phantoms for absorbed dose calculation BUT using the same pharmacokinetics will mathematically end up in a higher absorbed dose to women... Possibly leading to incorrect comments like women are more sensitive to radiation, as their absorbed dose is higher for the same radiopharmaceutical...

- Even if they computed « correctly » the absorbed dose for male and female, the ICRP 103 recommendations do not consider a gender specific radiation weighting factor... And by the way no age-specific weighting factor either, which would probably be the most important thing to implement...
Conclusions

- This is a transition time, as at the moment the ICRP 103 can’t be implemented in nuclear medicine practice...

- Dosimetry for the reference adults patients using the framework of ICRP 60 is still the most feasible (unique) option.

- “Personalized” dosimetry would require the insertion of data measured on patients regarding the cumulated activity, which seems neither feasible nor appropriate.