IAEA activities in the field of dosimetry for Radiopharmaceutical Therapy

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European Workshop on Quantitative Imaging for Molecular Radiotherapy: Metrology for Clinical Practice, 5-6 April 2017, Vienna
(c) For therapeutic medical exposures, absorbed doses to the tissues or organs for individual patients, as determined to be relevant by the radiological medical practitioner.

(d) For therapeutic radiological procedures with unsealed sources, typical absorbed doses to patients.
Roles & responsibilities

✓ Roles and responsibilities of a CQMP in specialties of medical physics
✓ Harmonization of education and clinical training worldwide
CQMPs in nuclear medicine contribute to the implementation and optimization of clinical procedures for diagnosis and treatment utilizing radionuclides. They have responsibilities [...] for the planning of therapeutic applications [...]
Academic education and clinical training

Guidance for the establishment of a postgraduate academic education programme in medical physics

Clinical training guide for medical physicists specialising in Nuclear Medicine
MODULE 6 – RADIOACTIVITY MEASUREMENTS AND INTERNAL DOSIMETRY

Sub-module 6.1: Use of traceable standards for radioactivity measurements
Sub-module 6.2: Formalism and application of internal dosimetry
Sub-module 6.3: Radiation dose from diagnostic nuclear medicine radiopharmaceuticals
Sub-module 6.4: Quantitative nuclear medicine imaging
Sub-module 6.5: Patient-specific dosimetry

MODULE 8 – RADIONUCLIDE THERAPY USING UNSEALED SOURCES

Sub-module 8.1: Understanding the Principles of Radionuclide Therapy
Sub-module 8.2: Facility Design for Radionuclide Therapy
Sub-module 8.3: Treatment Procedure
Sub-module 8.4: Selection of Radiopharmaceuticals for Nuclear Medicine Therapy
Sub-module 8.5: Dosimetry for Radionuclide Therapeutic Procedure
Sub-module 8.6: Radiation safety precautions for therapy using unsealed radionuclide sources
Medical Physics staffing requirements

Guidelines for Medical Physics staffing requirements in diagnostic imaging and radionuclide therapy

<table>
<thead>
<tr>
<th>Input variable (per year)</th>
<th>Weighting factor (FTE)</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedures with no image data per 100 patients</td>
<td>0.001</td>
<td>Such as blood sampling, thyroid uptake, sentinel lymph node mapping</td>
</tr>
<tr>
<td>Imaging procedures per 100 procedures</td>
<td>0.004</td>
<td>Imaging procedures including planar, SPECT/(CT), PET/CT</td>
</tr>
<tr>
<td><strong>Outpatient radionuclide therapy (e.g. $^{131}$I Thyrotoxicosis) per 100 procedures</strong></td>
<td>0.05</td>
<td>For patient dosimetry and radiation safety</td>
</tr>
<tr>
<td><strong>Inpatient radionuclide therapy (e.g. $^{131}$I for thyroid carcinoma) per procedure</strong></td>
<td>0.001</td>
<td>For patient dosimetry and radiation safety</td>
</tr>
<tr>
<td><strong>Complex radionuclide therapy (e.g. $^{131}$I mIBG, $^{177}$Lu, $^{90}$Y) per procedure</strong></td>
<td>0.005</td>
<td>For patient dosimetry and radiation safety</td>
</tr>
<tr>
<td>Risk assessment in pregnant or breast feeding patients (per calculation)</td>
<td>0.002</td>
<td>This includes dose assessment and reporting of results</td>
</tr>
</tbody>
</table>
Procedures for quantification of nuclear medicine images and for internal dosimetry

I. Buvat  
E. Frey  
A. Green  
M. Ljungberg
✓ Physical effects that degrade image quality and affect the accuracy of quantification
✓ Methods to compensate for them in
  - Planar
  - SPECT
  - PET
Education & Training

Training courses

e-Learning material

humanhealth.iaea.org

Publications
Joint ICTP-IAEA Workshop on Internal Dosimetry for Medical Physicists Specializing in Nuclear Medicine
Trieste - November 21-25, 2016
Support of AAPM and EFOMP
1 week, 6 lecturers
236 aspiring participants

38 selected participants from 24 countries
22 Students ICTP MSc in Medical Physics

The workshop provided participants with a comprehensive review of the basics and recent developments in the fields of nuclear medicine image quantification and internal dosimetry.
Coordinated Research Projects

Involve participants from different countries into state of the art scientific research and create scientific networks
CRP on Quantitative NM imaging

Objectives:
• investigate image quantification capabilities
• assess the need for:
  − training
  − standardized protocols
• develop and test quantitative imaging methods
• assess the achievable accuracy of absolute activity quantitation with SPECT and planar imaging

Multi-centre evaluation of accuracy and reproducibility of planar and SPECT image quantification: An IAEA phantom study

Brian E. Zimmerman¹, Darko Grošev², Irène Buvat³, Marco A. Coca Pérez⁴, Eric C. Frey⁵, Alan Green⁶, Anchali Krisanachinda⁷, Michael Lassmann⁸, Michael Ljungberg⁹, Lorena Pozzo¹⁰, Kamila Afroj Quadir¹¹, Mariella A. Terán Gretter¹², Johann Van Staden¹³, Gian Luca Poli¹⁴

http://dx.doi.org/10.1016/j.zemedi.2016.03.008
# $^{133}\text{Ba}$ sources

$^{133}\text{Ba}$ as a surrogate of $^{131}\text{I}$

<table>
<thead>
<tr>
<th></th>
<th>$^{133}\text{Ba}$</th>
<th>$^{131}\text{I}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{1/2}$</td>
<td>10.5 y</td>
<td>8 d</td>
</tr>
<tr>
<td>$E_{\gamma}$ (keV)</td>
<td>356 (62%)</td>
<td>364 (81.5%)</td>
</tr>
<tr>
<td></td>
<td>302 (18%)</td>
<td>637 (7.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>723 (1.8%)</td>
</tr>
</tbody>
</table>

- **TEW scatter compensation**
- **Septal penetration**
133Ba sources

✓ Sources fabricated and calibrated by NIST
✓ Standard uncertainty on the activity:
  ➢ 1.43% (A, B and C) and 1.74% (D)
✓ Low activity (dead-time not an issue)
✓ No background activity
✓ Height: 3.8 cm

<table>
<thead>
<tr>
<th>Source</th>
<th>$\phi_{\text{internal}}$ (cm)</th>
<th>V (cm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.794</td>
<td>2</td>
</tr>
<tr>
<td>B</td>
<td>1.27</td>
<td>4</td>
</tr>
<tr>
<td>C</td>
<td>1.43</td>
<td>6</td>
</tr>
<tr>
<td>D</td>
<td>2.86</td>
<td>23</td>
</tr>
</tbody>
</table>
$^{133}$Ba international comparison

$^{133}$Ba sources, Jaszczak phantom
- Planar
- SPECT(Chang-AC)
- SPECT/CT

- **Trial 1:** quantify activity with local protocol
  - New guidelines and harmonized protocol

- **Trial 2:** use new guidelines and protocol
  - Comparison of Trial 1 vs Trial 2

- *Centralized Data Analysis (CDA)*
R = \frac{A_{\text{meas}}}{A_{\text{NIST}}}

SPECT (Chang/AC)

Planar

SPECT/CT
Transmission study for AC

Conjugate view

Planar

SPECT (Chang-AC)

SPECT/CT
**\(^{133}\text{Ba} \text{ international comparison}**

- **Absolute quantification** of simple objects with no background
  - > 6 % for planar imaging and SPECT\(\text{(Chang-AC)}\)
  - < 2 % for SPECT/CT

- Planar, CDA: good results, but simple geometry

- Chang’s method for attenuation correction is critical

- **SPECT/CT provided best results:** more standardized and less subject to errors

- Need for **standardized protocols and training**
NEW CRP: Dosimetry in Radiopharmaceutical Therapy for Personalized Patient Treatment (E23005)

Objective:
Enhance, through research, the capabilities of Member States to incorporate dosimetry in RPT practice

Expected Results:
• Harmonized dosimetric protocols and methodologies in RPT
• Tools, suitable for training or information on dosimetry for RPT (such as slide sets, web pages, web based modules, pamphlets and posters), freely available through the IAEA websites
Two main steps involved in dosimetry:

1. Generate biodistribution
2. Extrapolate dosimetry

Template to support summary reporting of tracer biodistribution within a patient

Radiotracer BiDistribution Template

http://bitly.com/IAEA-RABIT

Courtesy of A. Kesner
Overview of internal dosimetry protocols

Data Collection

Biodistribution
Summary

Radiation Dose
Calculations

Dose Reporting

Biodistribution summary is common point in dosimetry calculations and protocols.
This step can be robustly encapsulated in the IAEA Radiotracer Biodistribution Template
The template allows user to enter data into organized category blocks:

- **SID**: Subject ID
- **SPE**: Species (e.g., human, mouse, ...)
- **GEN**: Sex (M/F)
- **HEI**: Height (cm)
- **WEI**: Weight (kg)
- **PBV**: Projected whole body blood volume (ml)
- **ISO**: Isotope (e.g., F-18, Lu-177,...)
- **RPH**: Radiopharmaceutical (e.g., FDG, DOTATOC, ...)
- **DAQ**: Date of administration (YYYYMMDD)
- **TAQ**: Time of administration (HHMM)
- **ACT**: Net injected activity (MBq)
- **SOF**: Software used for image analysis
- **IOA**: Institution of acquisition
- **COA**: City of acquisition
- **INI**: Author initials (optional)
- **EMA**: Inquiry contact email (optional)

The technical details explain and define the units presented in Section D measurements data:

- **MSM**: Main measurement modality (PET = 1, uPET = 2, SPECT = 3, uSPECT = 4, Probe = 5, Blood = 6, Urine = 7, Planar = 8, SPECT-planar hybrid = 9, other hybrid = 10, other = 11)
- **BMS**: Blood measurement modality (Main modality = 1, well counter = 2, other = 3)
- **BMU**: Blood measurement units (mCi = 1, MBq = 2, counts = 3) [MBq PREFERRED]
- **AMU**: VOI/ROI measurement units (mCi = 1, MBq = 2, counts = 3) [MBq PREFERRED]
- **MET**: Organ VOI/ROI drawing method (whole organ = 1, small ROI = 2)
- **TPU**: Time point units (minutes = 1, hours = 2, days = 3) [hours PREFERRED]
- **VOU**: Volume units (mm^3 = 1, cm^3 = 2, mm^2 = 3, cm^2 = 4) [cm^3 PREFERRED]
- **MCL**: Method of calibration (system = 1, standard source in FOV = 2, assay [post sacrifice] = 3, other = 4)
- **ACA**: Attenuation correction applied (transmission/CT = 1, lookup table = 2, global fixed = 3, none = 4)
- **GMA**: Geometric mean applied (AP planar) (yes = 1, no = 2, n/a = -1)
- **DCA**: Decay correction applied (injection time = 1, imaging start time = 2, other = 3, none = 4)
- **PVC**: Scatter correction applied (DEW = 1, TEW = 2, iter recon = 3, none = 4)
- **SCA**: Partial volume correction applied (yes = 1, no = 2)
- **WCC**: Well Counter Calibration Factor (please use CPS/MBq)
- **PCF**: Probe Calibration Factor (please use CPS/MBq)
- **SCF**: Planar/SPECT Calibration Factor (please use Counts/MBq)
- **TIA**: Time int. act. coef (hr (res time) = 1, # dis = 2, % total (#dis_organ/#dis) = 3) ['hr' PREFERRED]
IAEA RaBiT

✓ Freely available organ-level biodistribution template to standardize data organization and reporting

✓ To document biodistribution measurements in an organized manner

✓ Shared for easy dissemination of work/results

✓ To create databases that can be analyzed / reprocessed

✓ To support development of dosimetry software tools
Dosimetry in radionuclide therapy

✓ Gaps in education and training of medical physicists on methods for patient-specific dosimetry
✓ Need for standard methods for calibrating or implementing MRT dosimetry in the clinic

10 consultants met in November 2015 to discuss the current status of internal dosimetry and assess the need, feasibility, purpose and possible content of a publication on dosimetry in radionuclide therapy

• AAPM, EANM, EFOMP, MIRD-SNMMI, NPL
• IAEA: Accessibility & international impact
Dosimetry in radionuclide therapy

- Main publication describing the principles common to all radiopharmaceutical therapies
- Series of practical disease-specific reports
# Table of contents

1. Introduction  
2. Physics  
3. Metrology  
4. Radiobiology  
5. Equipment and tools  
6. Clinical implementation - clinical trials  
7. Radiopharmaceutical treatment modalities  
8. Concluding/summary
A. Introduction

B. Periodic procedures to assure safe treatment and accurate dosimetry
   1) Required **equipment**
   2) **Calibration** (including “dose calibrator”)
   3) Measurement, validation and uncertainty assessment
   4) QA/QC procedures

C. **Patient procedures** to assure safe treatment and accurate dosimetry
   1) Measurement procedures
   2) Equipment setup
   3) QA/QC procedures during patient treatment
   4) Measurement **time-points**
   5) Analysis procedures – **curve fitting and integration**
   6) **Volumetry**
   7) Absorbed dose coefficient calculation
   8) Typical **Uncertainty** Table (TUT)
   9) Data worksheet (to be filled in by tech and physicist)
   10) **Treatment plan**
   11) Pitfalls/tricks of the trade
   12) Patient Dosimetry Record (PDR)
   13) Examples
Reports

Radioiodine therapy
- Thyroid benign
- Carcinoma

Microsphere therapy
- Glass
- Resin
- Holmium polylactic acid

Radiopeptide therapy
- Beta-emitter-labeled
- Alpha-emitter-labeled

mIBG

Radioimmunotherapy
Small molecules

Alpha emitters
- At-211 (IP administration)
- Pb-212/Bi-212
- Ra-223 (Xofigo)
- Ac-225
- Bi-213
- Sm-153
- Sr-89
- Re-188
- Polycythemia vera
- P-32 pleural effusion
- Radiosynovectomy
Thank you
IAEA Safety Standards hierarchy

Safety Fundamentals

- Fundamental safety objectives and principles for protecting people and environment
  - *moral obligation*

Safety Requirements

- Requirements that must be met to ensure safety
  - *legal obligations, "shall"*

Safety Guides

- Recommended ways of meeting the requirements, "should"
Safety Guide on Medical Uses

✓ Medical exposure
✓ Occupational exposure
✓ Public exposure

Safety Guide on Radiation Protection and Safety in Medical Uses of Ionizing Radiation

Radiation Protection and Safety in Medical Uses of Ionizing Radiation

IAEA SAFETY STANDARDS
for protecting people and the environment

Proposed Joint Report

DRAFT SAFETY GUIDE
IAEA

Draft revision 2
STI/PUB.1 Second edition of the draft publication by IAEA

IAEA International Atomic Energy Agency
Dosimetry of patients – radiopharmaceutical therapy procedures

4.211. GSR Part 3 [3], para. 3.168 requires nuclear medicine facilities to determine typical absorbed doses to patients for their therapeutic radiological procedures. Methodologies for the determination of doses from therapy radiopharmaceuticals are explained in detail in Refs [259, 261, 277, 279 – 282, 292 – 298].

4.212. Radiopharmaceutical toxicity in therapeutic nuclear medicine is dependent upon the absorbed dose to critical organs (e.g. to the haematopoietic system) and the efficacy of the treatment is related to the absorbed dose received by target tissues. In current clinical practice, the nuclear medicine therapeutic treatment is usually delivered on the basis of an administered activity prescription, in some cases with adjustments made for body mass or surface area. Ideally, a pre-treatment calculation of the absorbed doses received by organs at risk and target tissues would allow for an accurate prediction of toxicity and efficacy of the treatment. The dosimetry calculations performed in this context should take into account individual patient pharmacokinetics and anatomy.
Other publications

Nuclear Medicine Resources Manual
Ver 2.0 - Guide for decision makers

IAEA HUMAN HEALTH SERIES
No. 33
Quality Management Audits in Nuclear Medicine Practices
Second Edition

IAEA International Atomic Energy Agency
To provide advice to the IAEA on the current status of patient-specific dosimetry, as well as identifying any gaps that should be addressed.

- Available software
- Uncertainty analysis
- Paucity of dose-response data
- Shortage of qualified medical physicists to support dosimetry
To provide advice to the IAEA on the current status of patient-specific dosimetry, as well as identifying any gaps that should be addressed.

- Available software
- Uncertainty analysis
- Paucity of dose-response data
- Shortage of qualified medical physicists to support dosimetry
- Education and training of medical physicists
- Standardization of methods
Optimization of protection and safety

**Requirement 38** - Optimization of protection and safety for each medical exposures

**Dosimetry of patients**

3.167. Registrants and licensees shall ensure that dosimetry of patients is performed and documented by or under the supervision of a medical physicist, using calibrated dosimeters and following internationally accepted or nationally accepted protocols, including dosimetry to determine the following:
RaBiT specifications

- **Structured format file** that can be used to store specific (organ level) radio-pharmaceutical biodistribution measurements plus metadata

- Distributed in two file types .xlsx or .csv. The Excel version is available for users to enter data in a color formatted sheet (easier for organization), but the competed distribution data should be saved/distributed in the .csv format

- The .csv files are simple in structure, and can be used for automated code
Attenuation coefficient

\[ \mu_{\text{eff}} \text{ or } \mu_{\text{narrow}} ? \]

\[ \text{Measure of } \mu_{\text{eff}} \]

\[ \text{AF} = \frac{C_{\text{transmission}}}{C_{\text{blank}}} = e^{-\mu \cdot T} \]

Planar - Transmission ACF - \( \mu_{\text{narrow}} \)

- Site 1
- Site 2
- Site 3
- Site 4

\[ y = 1.002e^{-0.101x} \]
\[ R^2 = 0.996 \]
Attenuation coefficient

.source-phantom distance

$\mu_{\text{eff}} \rightarrow \mu_{\text{narrow}}$
Energy windows

TEW scatter compensation in trial 2:

- Peak 356 keV 15%
- Lower scatter 321 keV 5%
- Upper scatter 403 keV 10%
Transmission study

$^{133}\text{Ba}$ sources in the phantom

$^{133}\text{Ba}$ downscatter in $^{57}\text{Co}$ window
Participants and equipment

Trained **Medical Physicist** with experience in quantitative imaging

- Bangladesh
- Brazil
- Croatia
- Cuba
- Germany
- South Africa
- Thailand
- USA
- Uruguay

**Scanners**

- ✓ Siemens E.Cam (1)
- ✓ Mediso Nucline (2)
- ✓ Siemens Symbia (6)
- ✓ GE Infinia Hawkeye (1)

**SPECT**

**SPECT/CT**
Trial 1 - Local protocol

Tasks:
✓ Develop local protocol
✓ Quantify the activities in the 4 $^{133}$Ba sources
✓ 3 scans for each modality
✓ Second smallest source used for calibration
✓ Fixed acquisition time
  Planar: 10 min
  SPECT: 60 min

Training:
➢ IAEA Human Health Reports No. 9
Trial 2 - Planar protocol

✓ High energy collimator
✓ Matrix size 128x128
✓ TEW scatter compensation

- Energy windows
  - Peak: 356 keV, 15%
  - Lower scatter: 321 keV, 5%
  - Upper scatter: 403 keV, 10%

✓ Attenuation correction: $\mu(^{133}\text{Ba}) = 0.111 \text{ cm}^{-1}$
✓ ROIs drawn manually to include majority of counts
Trial 2 - SPECT Protocol

✓ Matrix size: 128x128
✓ Step and shoot, autocontour
✓ ~3 degrees/step
✓ TEW scatter compensation
✓ OSEM, 50 updates
✓ No post reconstruction filter
✓ SPECT(Chang-AC)
  ✓ Zero-th order Chang-AC
  ✓ VOIs to be drawn to include the majority of counts without overlap
✓ SPECT/CT
  ✓ CT-AC
  ✓ VOI drawn to fit CT image of source and dilated 1cm without overlap
Results - Trial 1, planar

2 outliers @ \( R=3.19 \) and \( R=1.54 \)

Underestimation of the activity \( \sim 15 \% \)

Range: 0.53 - 1.04
✓ One centre did not apply attenuation correction
✓ Overestimation of the activity ~10 %
✓ Highest variability
Results - Trial 1, SPECT/CT

✓ Overestimation of the activity by about 10 %
✓ Overall best results
✓ no outliers
✓ Range: 0.85 - 1.27
Results – Trial 2

<table>
<thead>
<tr>
<th>Method</th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>CDA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Median</td>
<td>Mean</td>
</tr>
<tr>
<td>Planar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjugate View AC</td>
<td>0.84(12)</td>
<td>0.86(7)</td>
<td>0.91(14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPECT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chang-AC</td>
<td>1.09(21)</td>
<td>1.10(10)</td>
<td>1.18(39)</td>
</tr>
<tr>
<td>CT-AC</td>
<td>1.08(13)</td>
<td>1.12(6)</td>
<td>1.06(8)</td>
</tr>
</tbody>
</table>

Planar

➢ No clear evidence of improved performance
➢ 2 outliers @ R=0.35 and 1.38
➢ Range: 0.68-1.19 (compared to 0.53-1.04)

SPECT/Chang

➢ No clear evidence of improved performance

SPECT/CT

➢ Slight improvement
## Results – CDA

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</table>

- **Overall improvement** in the quantitative accuracy when the same procedure is applied to all the data by a single analyst
- **No outliers**
- **Reduced variability**