Personalized Nuclear Medicine Imaging and Radionuclide Therapy

Medical Physics Perspectives

prof. dr. Kristof Baete, medical physicist

Nuclear Medicine, University Hospitals Leuven, Belgium

Nuclear Medicine and Molecular Imaging, Dept. of Imaging and Pathology,

KU Leuven, Belgium

kristof.baete@uzleuven.be

Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH

20th EAN workshop, AGES, Vienna, 2 – 4 October 2023

Why personalized or individually planned?

Official Journal
of the European Union

English edition

A "directive" sets out a goal that EU countries must achieve

COUNCIL DIRECTIVE 2013/59/EURATOM

of 5 December 2013

laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom

Article 56

Optimisation

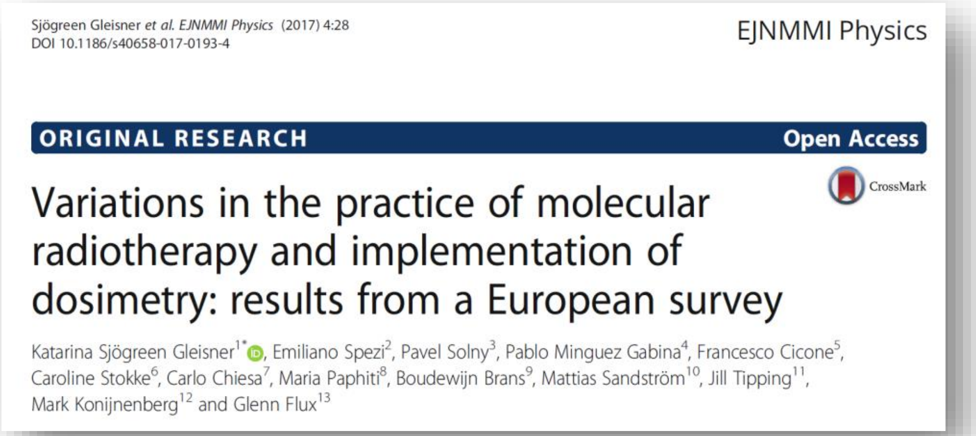
For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended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

(81) "radiotherapeutic" means pertaining to radiotherapy, including nuclear medicine for therapeutic purposes;

Hitchcock, A. (1960). Psycho. Paramount Pictures.

What has been the effect of the Directive

- There was a response by the NM community
- Initiatives by EANM dosimetry committee
  - Internal Dosimetry Task Force
  - explore the Potential and Prospects
- European survey
  - wide variation of MRT practice, including medical physics expert involvement and implementation of dosimetry-guided treatments



Sjögreen Gleisner *et al. EJNMMI Physics* (2017) 4:28
DOI 10.1186/s40658-017-0193-4

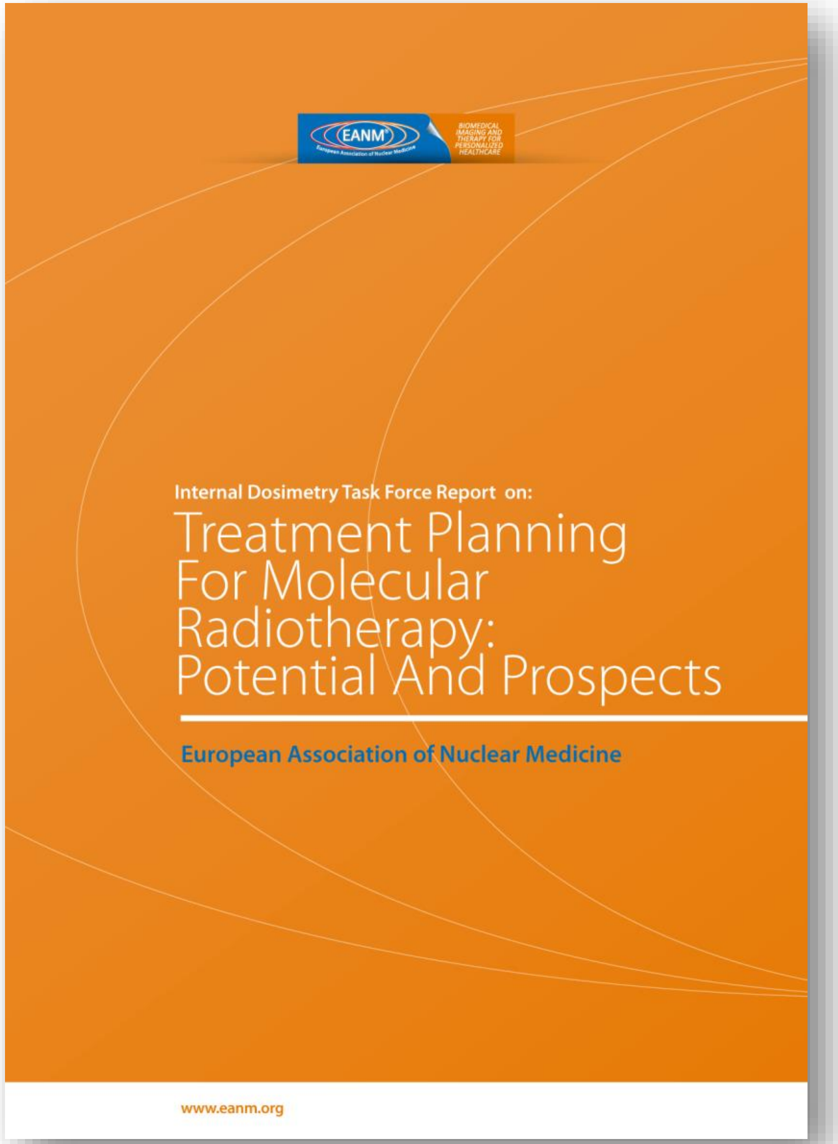
EJNMMI Physics

ORIGINAL RESEARCH Open Access

CrossMark

Variations in the practice of molecular radiotherapy and implementation of dosimetry: results from a European survey

Katarina Sjögreen Gleisner[1*], Emiliano Spezi[2], Pavel Solny[3], Pablo Minguez Gabina[4], Francesco Cicone[5], Caroline Stokke[6], Carlo Chiesa[7], Maria Paphiti[8], Boudewijn Brans[9], Mattias Sandström[10], Jill Tipping[11], Mark Konijnenberg[12] and Glenn Flux[13]



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What has been the effect of the Directive

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Eur J Nucl Med Mol Imaging (2017) 44:1783–1786
DOI 10.1007/s00259-017-3707-3

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Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-017-3820-3

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Eur J Nucl Med Mol Imaging (2018) 45:152–154
https://doi.org/10.1007/s00259-017-3859-1

LETTER TO THE EDITOR

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REVIEW **Open Access**

Huizing *et al. EJNMMI Research* (2018) 8:89
https://doi.org/10.1186/s13550-018-0443-z

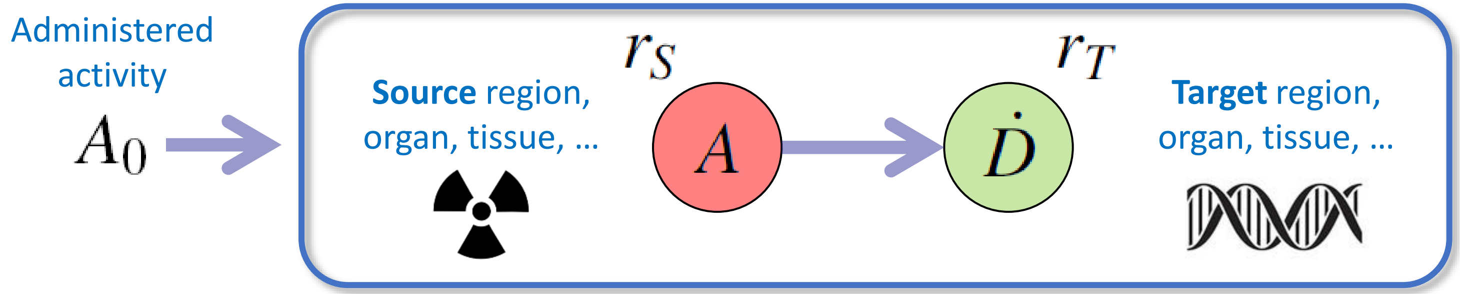
Dosimetry methods and clinical applications in peptide receptor radionuclide therapy for neuroendocrine tumours: a literature review

Conclusion: Clinical dosimetry in PRRT is feasible and can result in improved treatment outcomes. Current clinical dosimetry studies focus on safety and apply non-voxel-based dosimetry methods. Personalised treatment using sophisticated dosimetry methods to assess tumour and normal tissue uptake in clinical trials is the next step towards routine dosimetry in PRRT for NET.

Medical Physics challenges in Theranostics

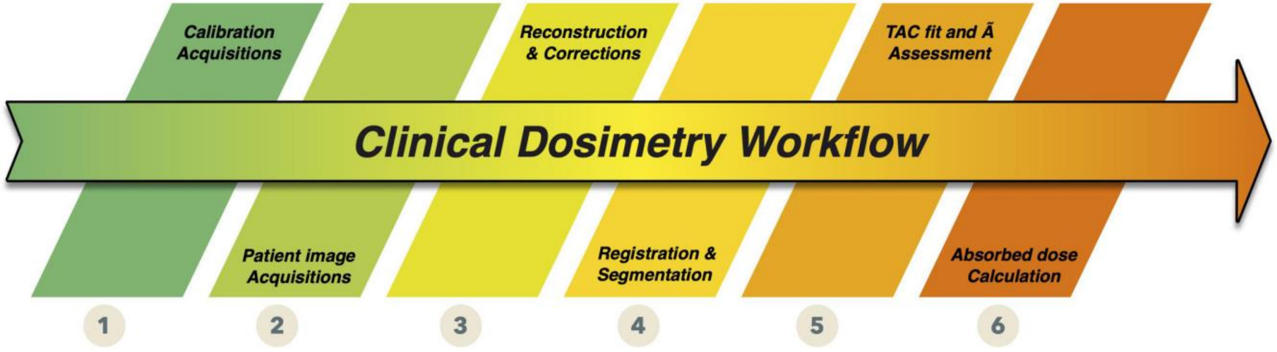
- Aim: the absorbed dose to a target region

$$\dot{D}(t) \propto A(t)$$



$$D(r_T) = \int_0^{T_D} \dot{D}(r_T, t)dt$$

- NM instrumentation can help with the relative or absolute quantification of
  - administered activity A_0
  - activity conc. in samples (Bq/ml)
  - detection rate as a surrogate for activity

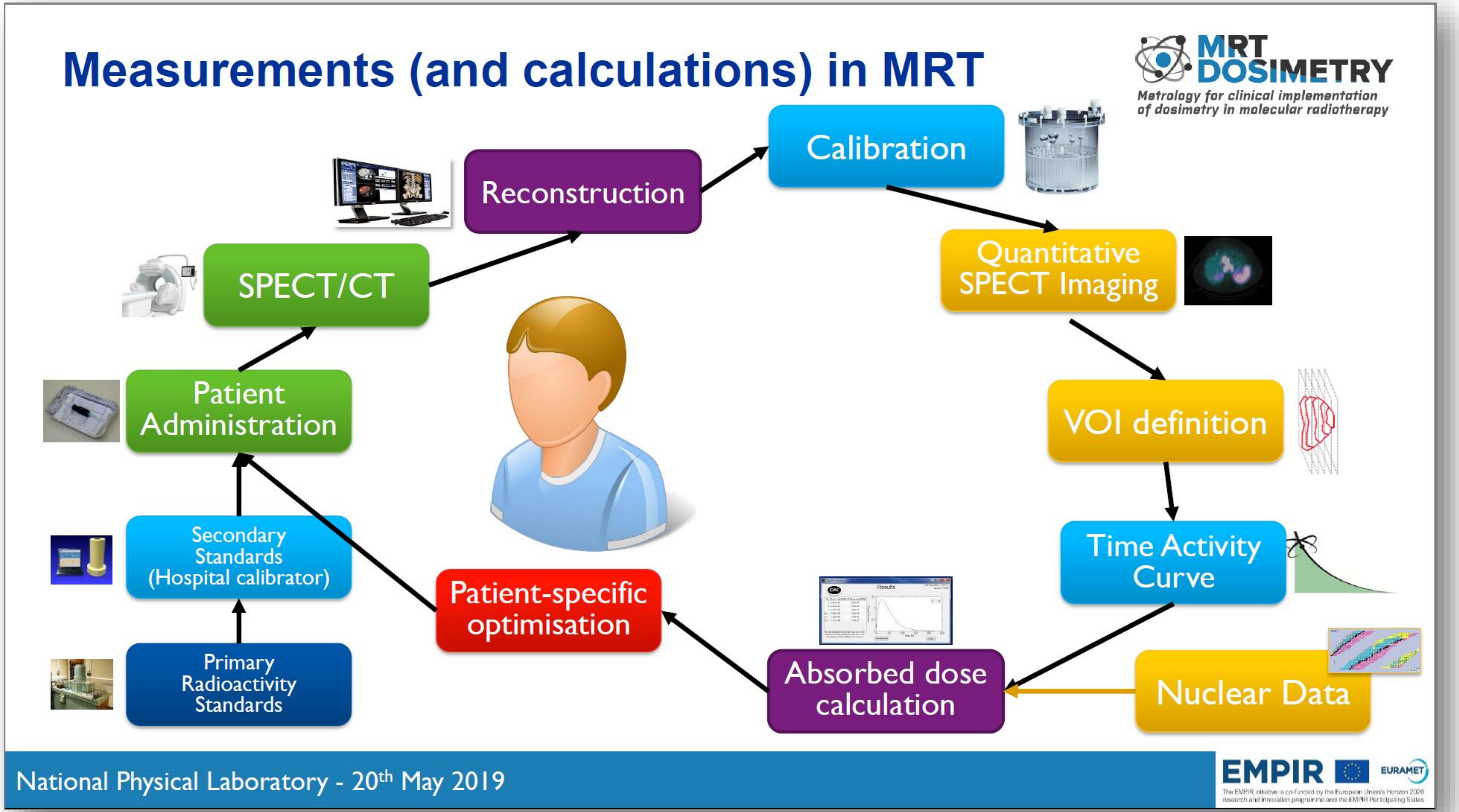


- Follow-up of these quantities over time

Erick Mora-Ramirez *et al.*, Med Phys 47 (9), Sept 2020

Establishing a clinical dosimetry workflow

- Andrew Robinson (NPL), 4th scientific workshop for stakeholders (2019)



EURAMET

MetroMRT
Metrology for Molecular Radiotherapy

MRT DOSIMETRY
Metrology for clinical implementation of dosimetry in molecular radiotherapy

“The translation process requires good preparation and time alignment”

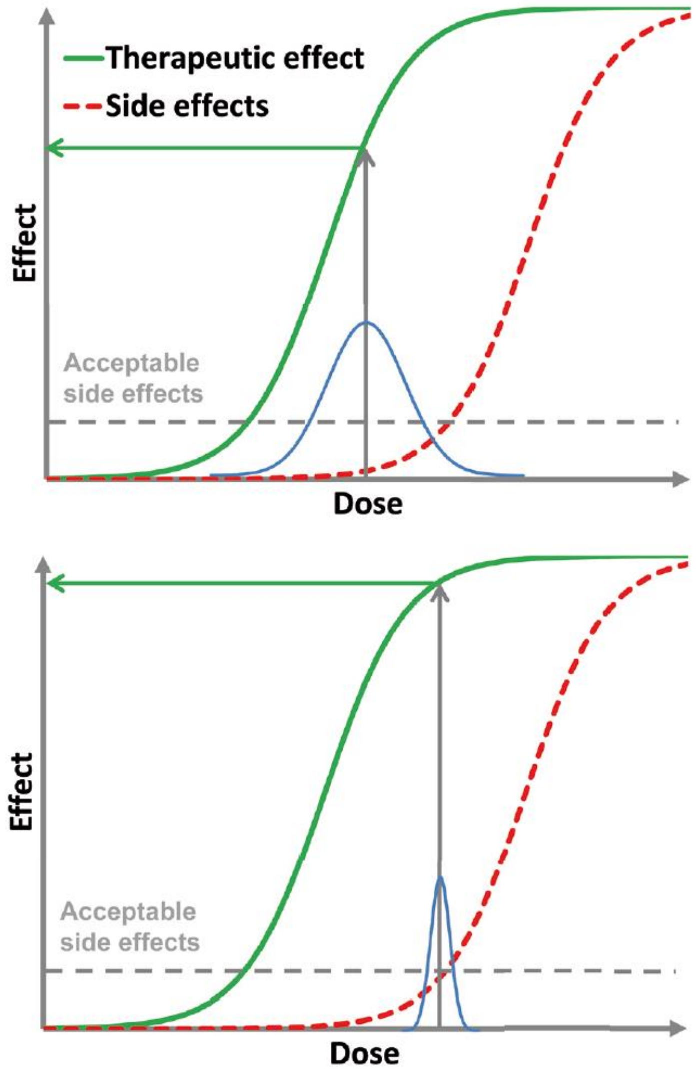
Dosimetry challenges and objectives

- Enormous technological evolution in healthcare

- NM evolves very rapidly – requires advanced QA & QC
  - MI and RNT are becoming very sophisticated disciplines
  - Theranostics – trend towards personalized medicine
  - Quest for the dose-effect relationship

- One wants to be sure about what is being measured
  - Measurement uncertainty influences decision making
  - Standardization is important for comparison of results

- Quantification and advanced dosimetry tools

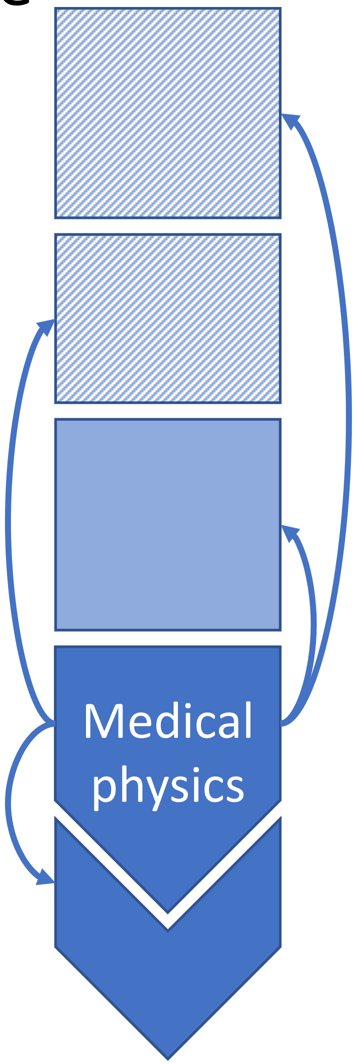


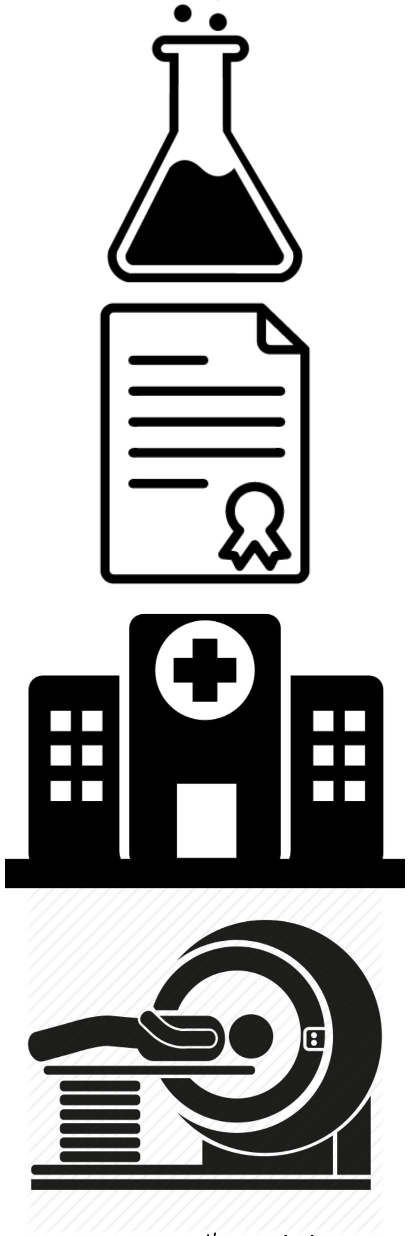
"Nuclear Physics for Medicine", NuPECC, 2014

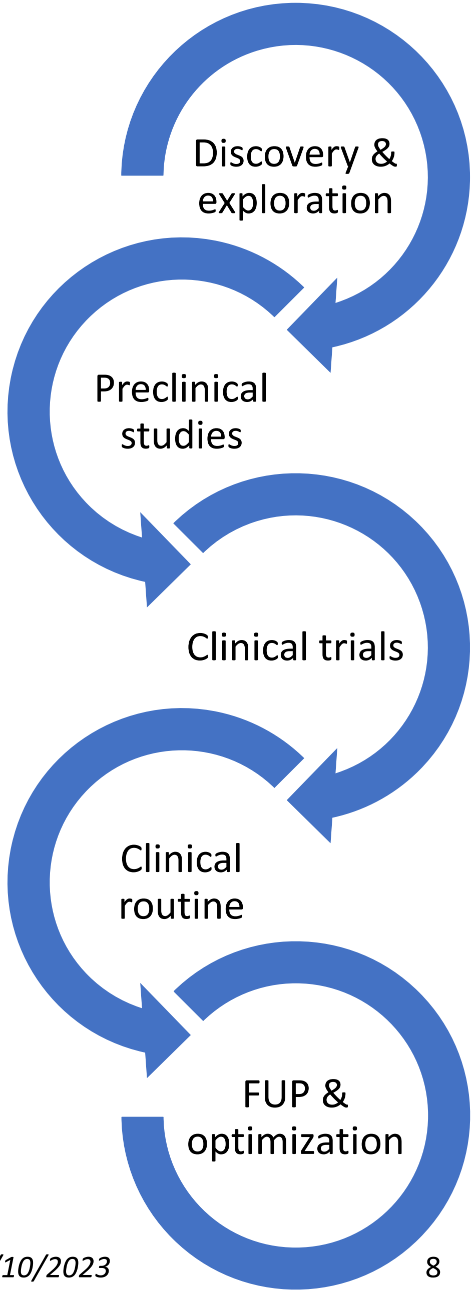
Nuclear Physics European Collaboration Committee

Roadmap to clinical applications

- Early discovery and exploration phase
  - nuclear physics & radiochemistry
  - radiopharmacy
- Preclinical studies
  - models, safety, translation
- Clinical trials
  - safety, efficacy, dosage
  - effectiveness, response & comparison
- Clinical routine
  - protocols and procedures
- Follow-up and optimization phase
  - quality assurance & control
  - patient-specific precision medicine

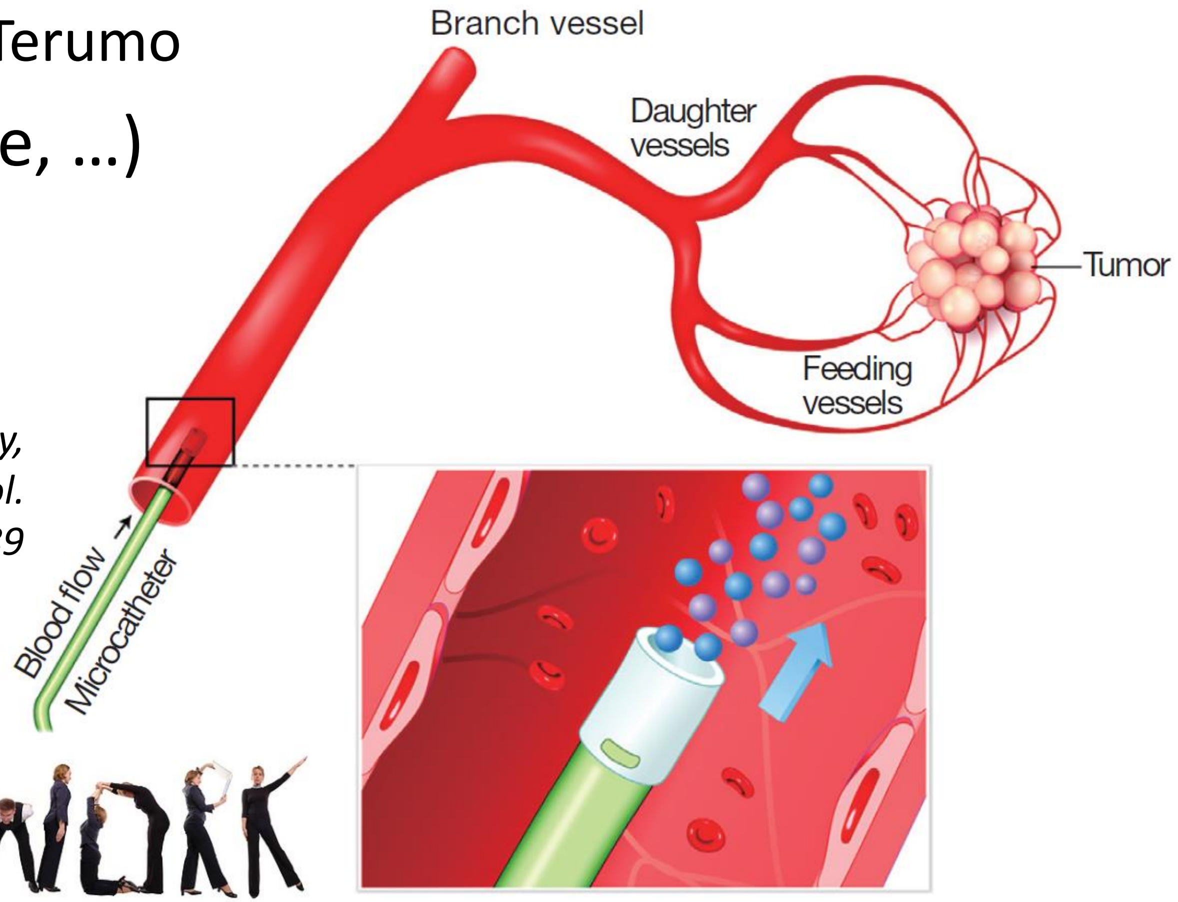






Selective Internal Radiation Therapy (SIRT)

- SIRT portfolio @ UZ Leuven
  - ^{90}Y – SIR-Spheres – Sirtex Medical
  - ^{90}Y – TheraSphere – BTG, Boston Scientific
  - ^{166}Ho – QuiremSpheres – Quirem Medical, Terumo
- liver tumors (HCC, ICC, metastatic disease, …)
- a multi-disciplinary approach
  - NM, oncology, interventional radiology
  - nursing units
  - NM technologists
  - radiopharmacy
  - medical imaging research
  - medical physics experts
  - radiation protection



Kennedy, J Gastrointest Oncol. 2014;5(3):178-189

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SIRT planning – activity prescription

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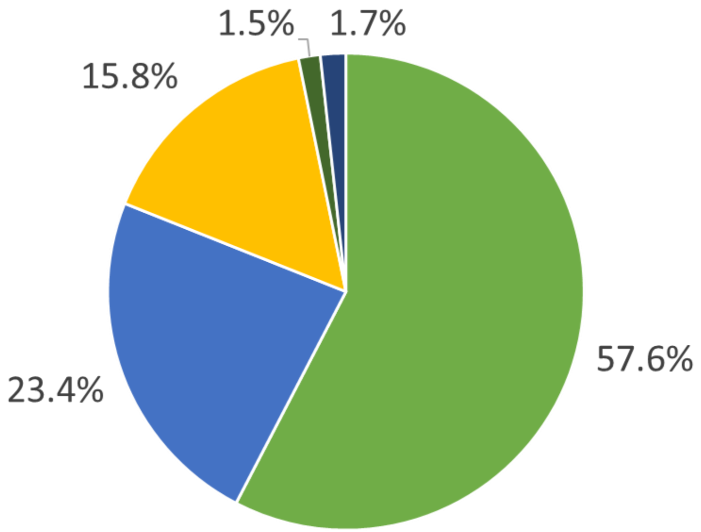
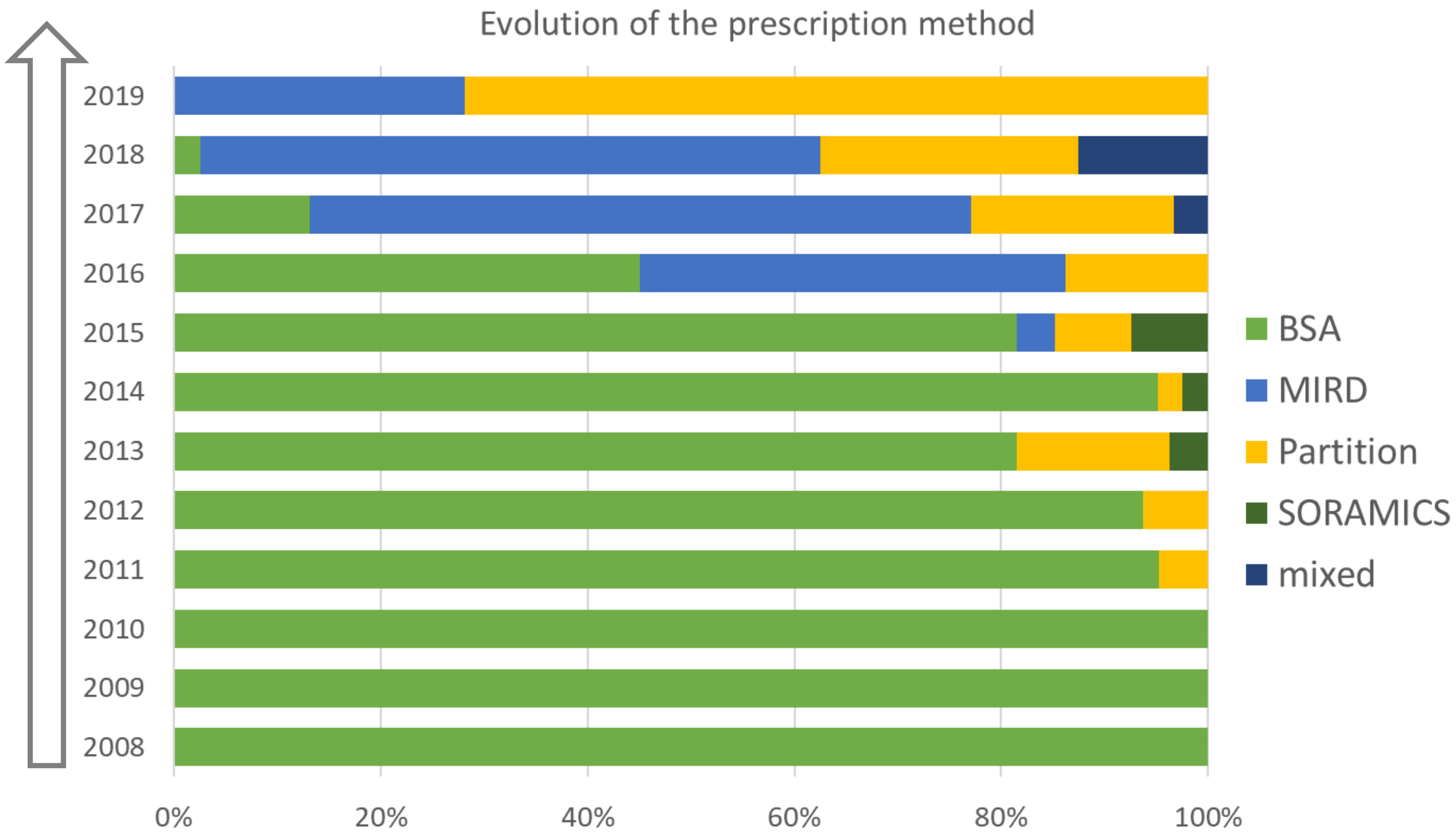
- Different dosimetry methods
  - body-surface area (BSA)
  - modified BSA method
  - SIRFLOX lookup tables
  - MIRD scheme
  - partition method
  - voxel based dosimetry





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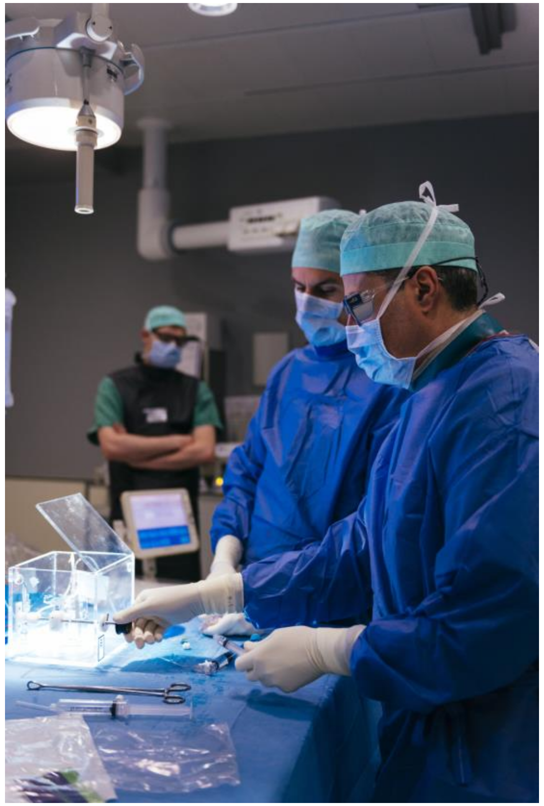
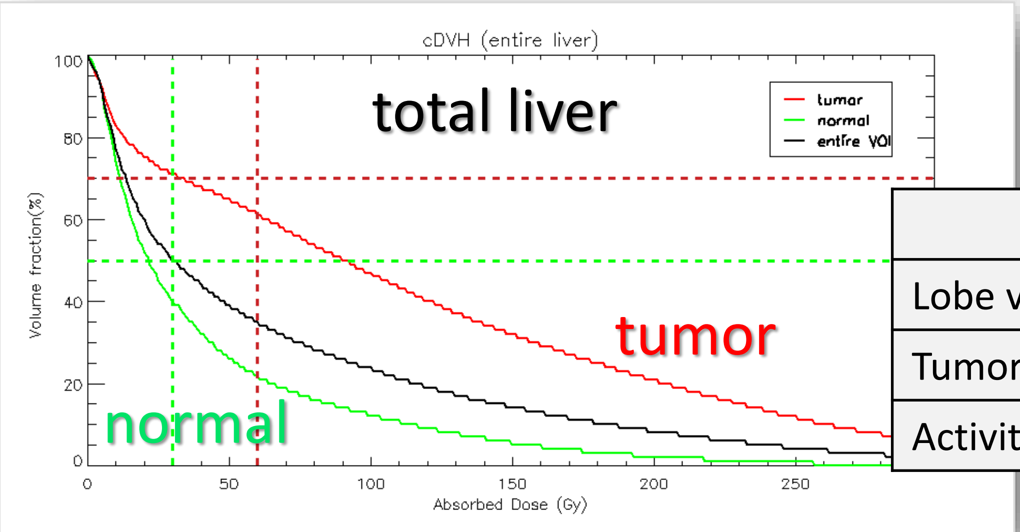
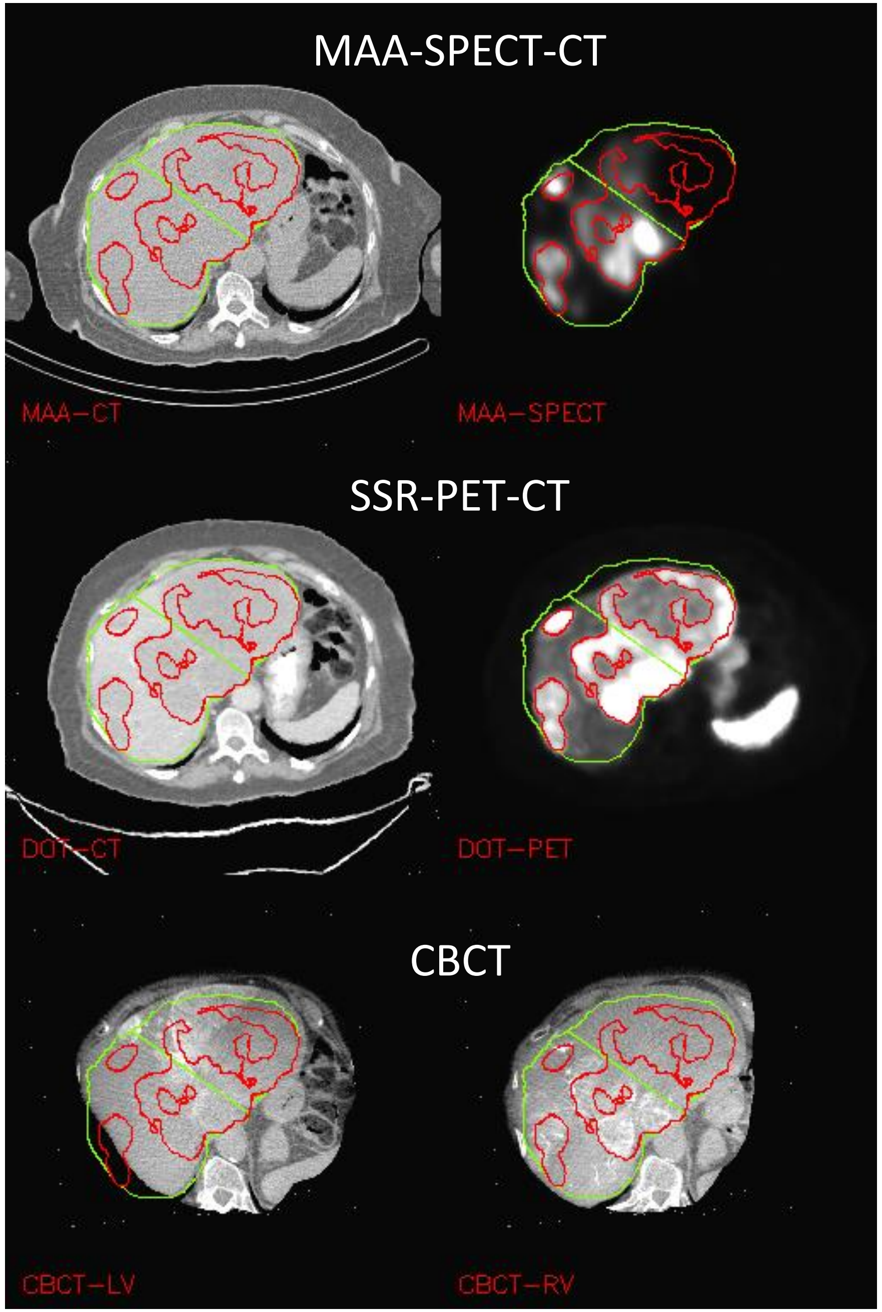
SIRT in clinical practice

- treatment simulation
- registration, segmentation
- method selection & dose estimate
  - dose volume analysis
  - criteria verification (target / non-target)
- performing treatment
- treatment verification

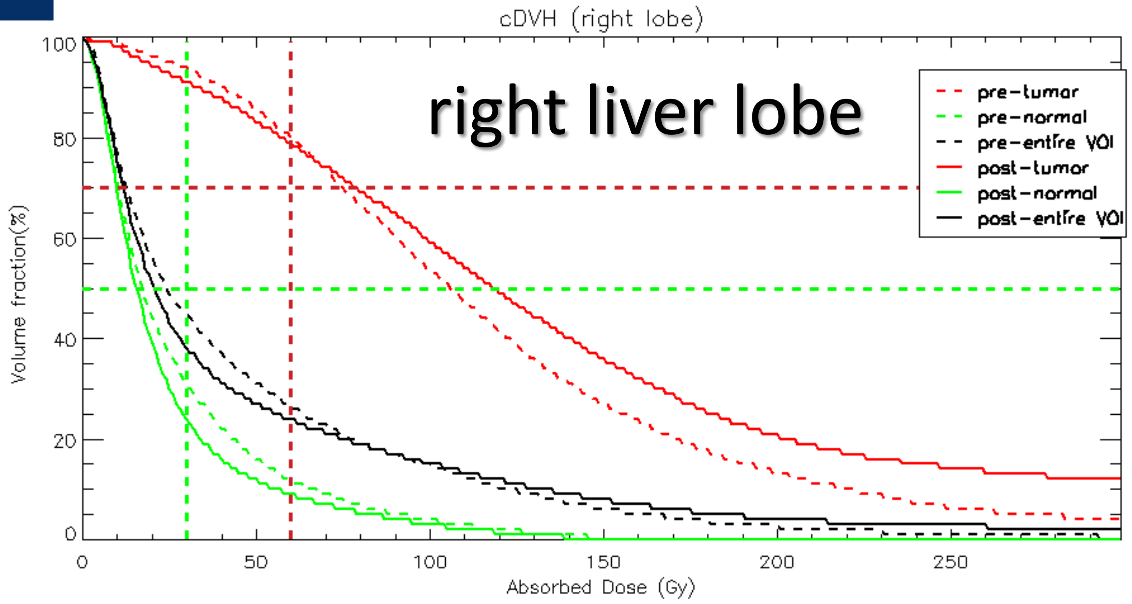


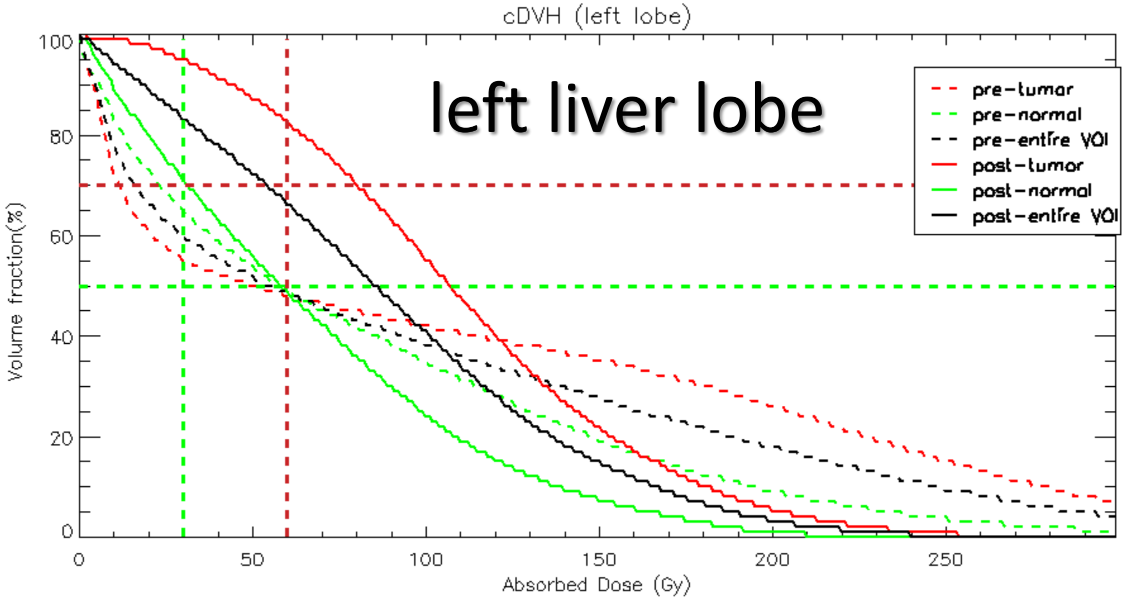


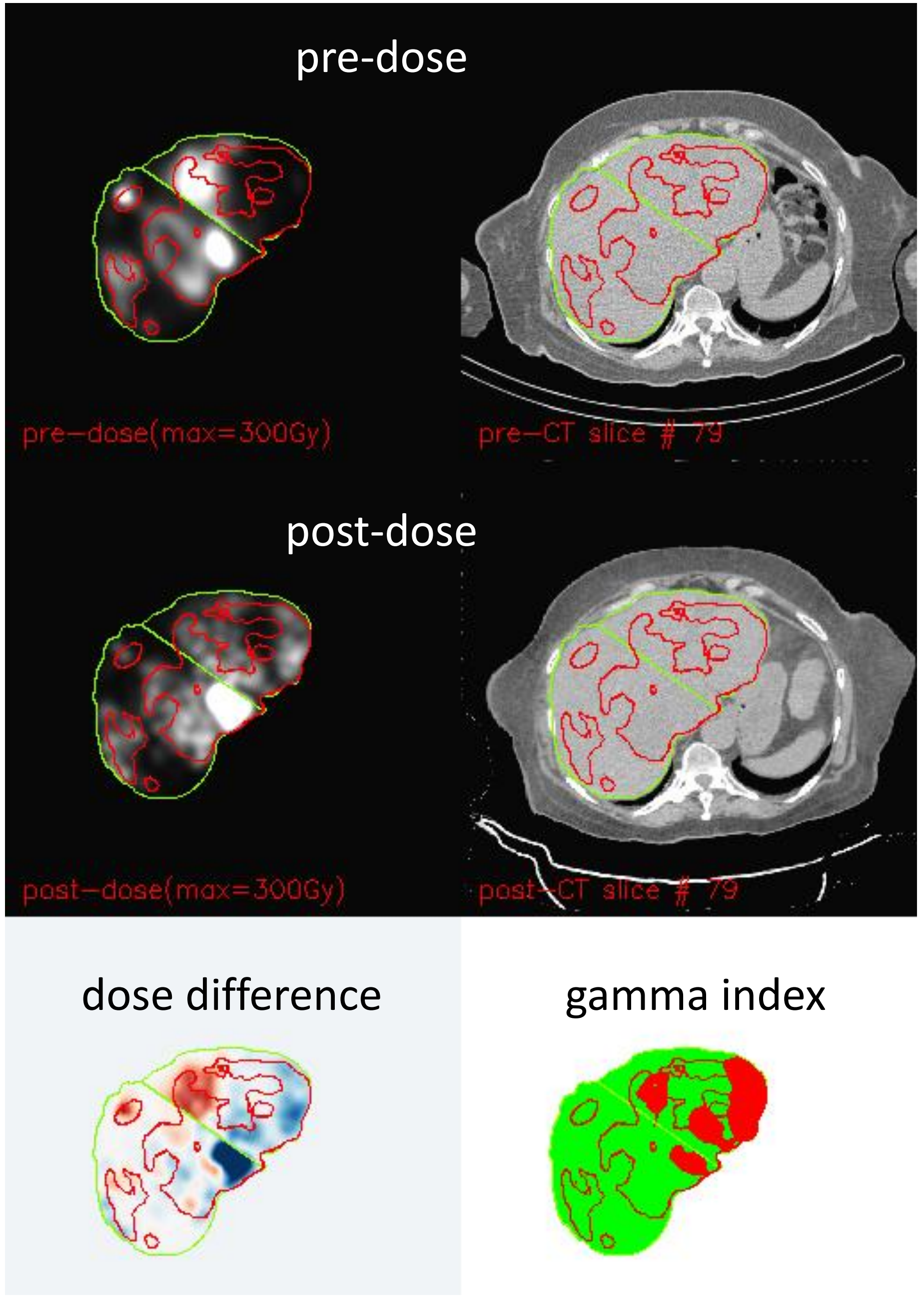
	Right	Left
Lobe volume	1494 cm^3	890 cm^3
Tumor volume	622 cm^3	759 cm^3
Activity	1557 MBq	928 MBq



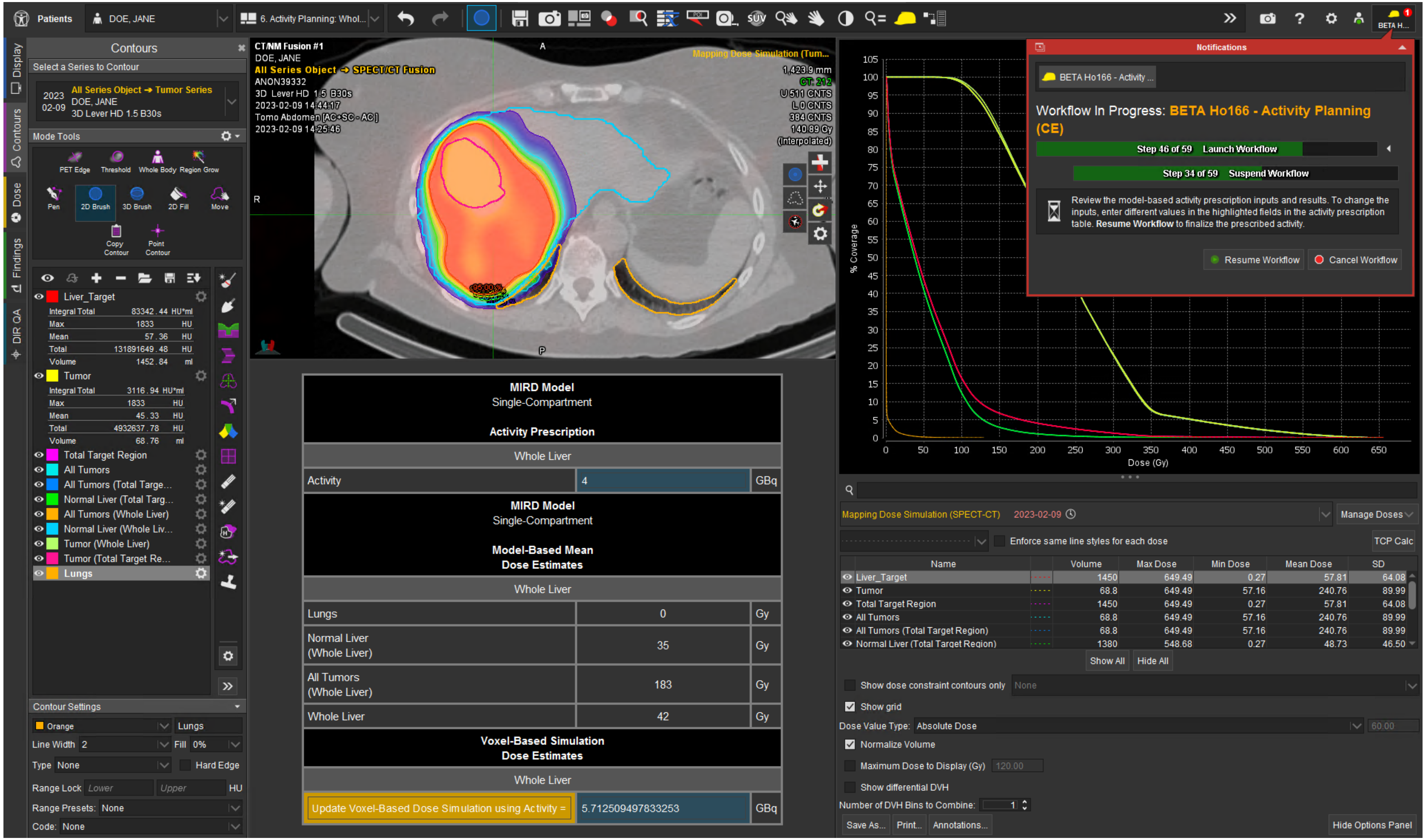
Treatment Verification





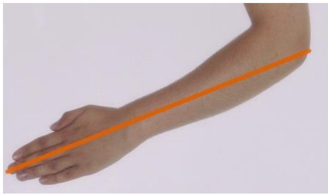


Treatment planning & verification



Calibration requires standardization

- The challenge of standardization is not new
  - ell (ulna) – cubit (forearm)

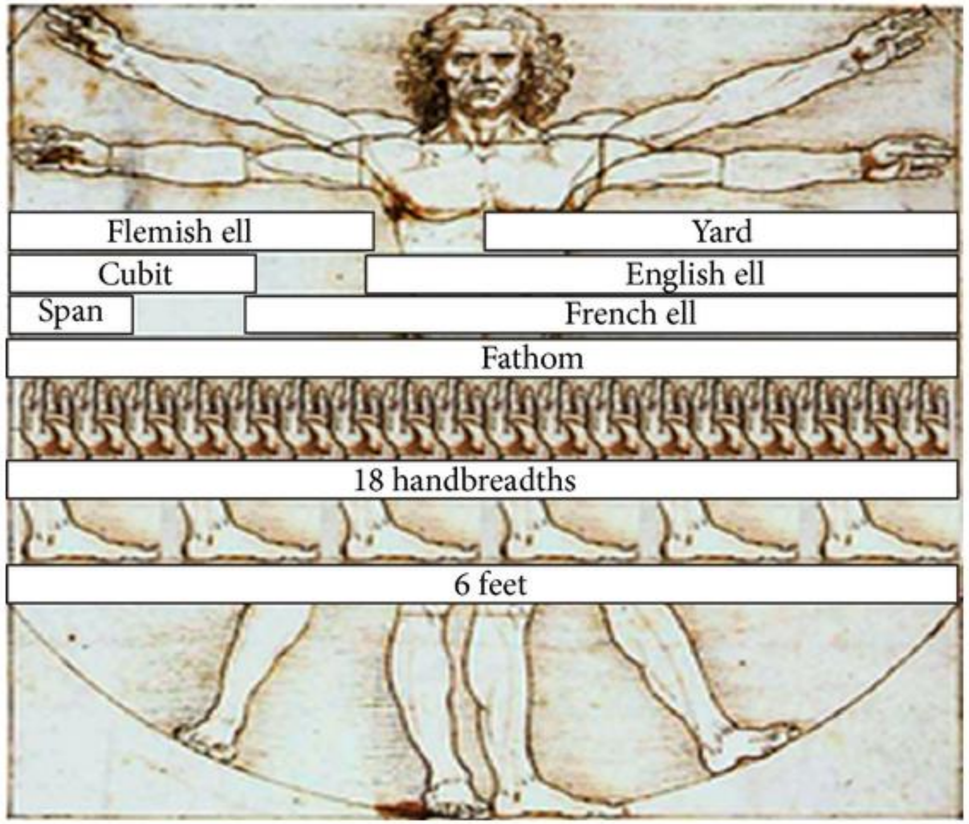


- Nuclear data, e.g. half-life, …
  - branching ratio for positron emission of Y-90 in PET acquisition software (2022)
    - device A : 32 × 10^{-6}
    - device B : 34 × 10^{-6}

Branching ratio

Bq <–> e^+

- Imaging standards (e.g. DICOM, ISO-12052)
  - time references & decay correction
- It looks like … there's much more need for standardization, even <u>before</u> calibration



Mark H. Stone, "The Cubit: A History and Measurement Commentary", *Journal of Anthropology*, vol. 2014, 489757, 11 pp, 2014.

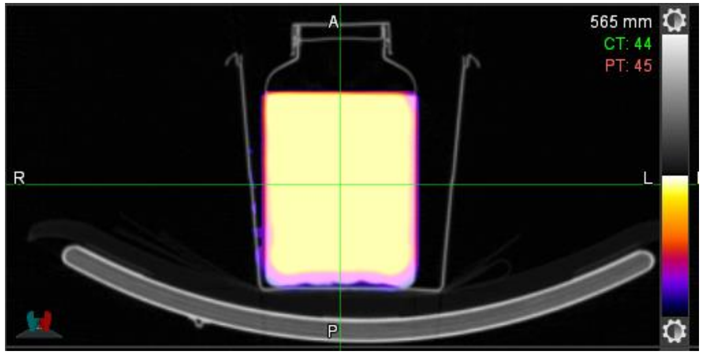
Bureau International des Poids et Mesures

OIML Organisation Internationale de Métrologie Légale
International Organization of Legal Metrology

20 May 2023
www.worldmetrologyday.org

Nuclear Medicine Equipment Standards

- A quantified and traceable measure using an NM instrument
  - numerical value – relative or absolute measure
  - physical quantity – (SI) unit of measurement
- Nuclear medicine (NM) instruments
  - radionuclide calibrator or activity meter (Bq)
  - gamma counter samples (Bq/ml)
  - SPECT phantom (cps/voxel)
  - quantitative PET/CT or SPECT/CT (Bq/ml)
- Calibration step
  - conversion between units
- Verification and follow-up
  - QA & QC



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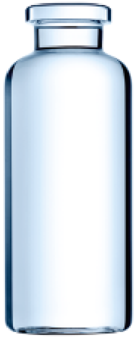
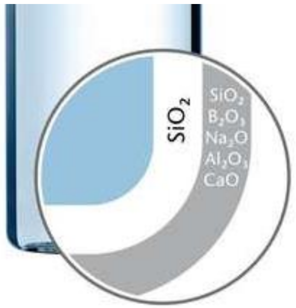
Standardization challenges

- Crossing the valley of death – translational research
  - global : regulatory – radiological protection – medicines agencies
  - local : health physics – radiopharmacy – clinical environment

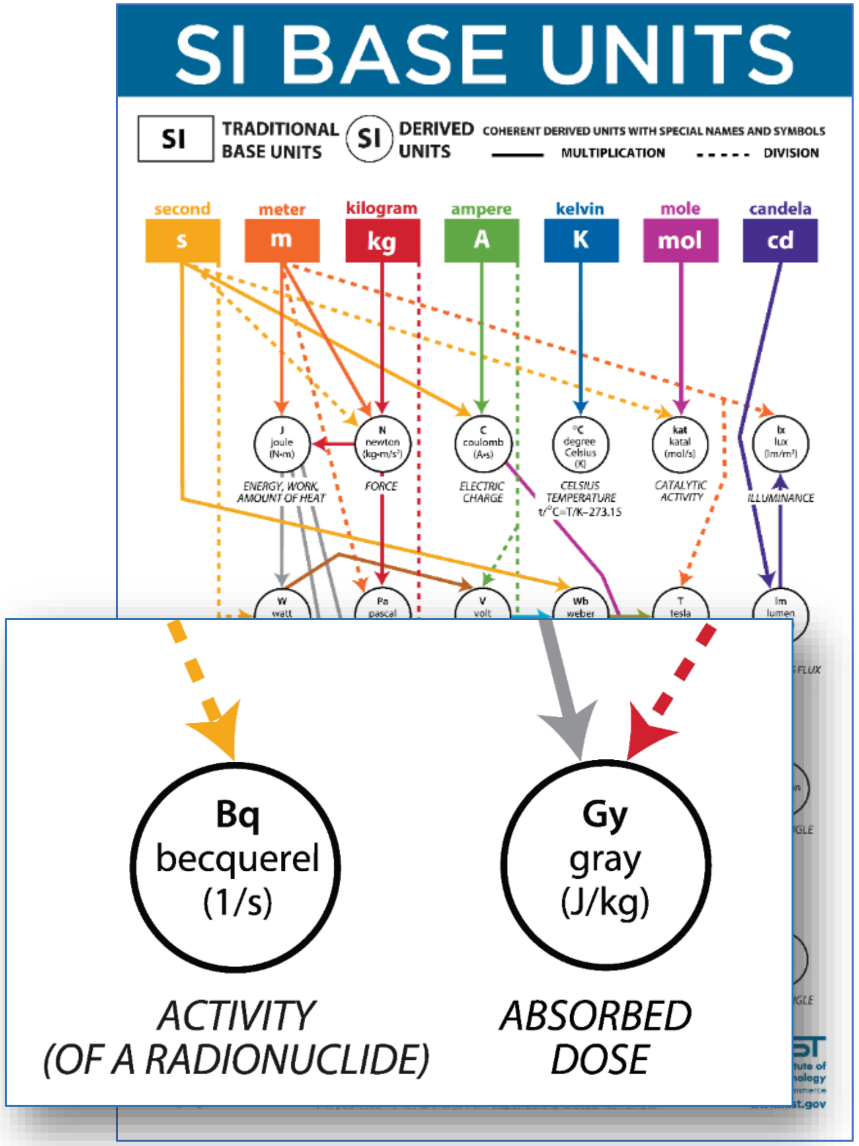
- Closing gaps between radiopharmacy and medical physics
  - use of standardised recipients : V-vial, 10R Type 1+ Schott vial, …

- Approach manufacturers
- Approach suppliers
- Approach EMA





Butler, D. Translational research: Crossing the valley of death. Nature 453, 840–842 (2008)

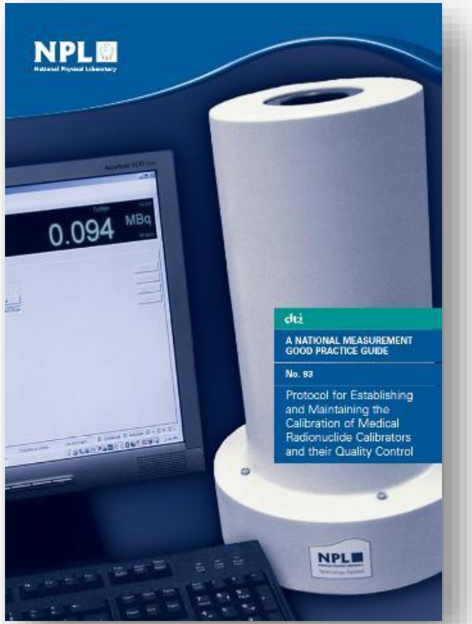


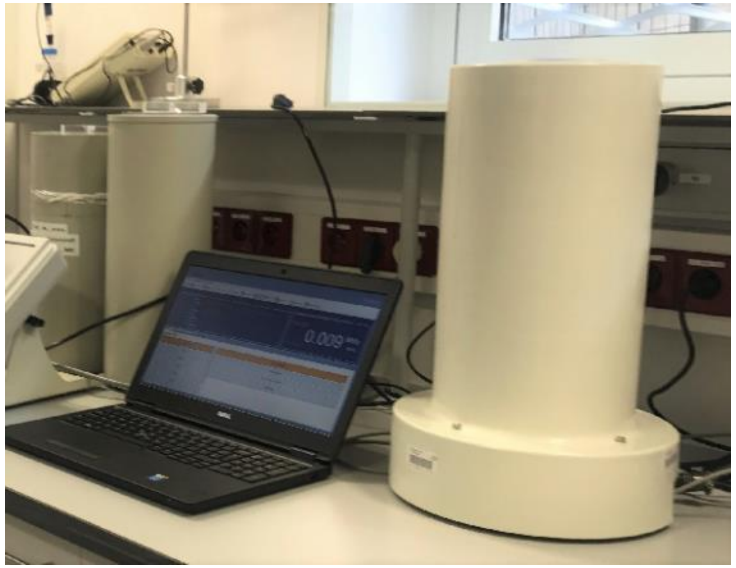
Special Publication (NIST SP) – 1247
https://doi.org/10.6028/NIST.SP.1247

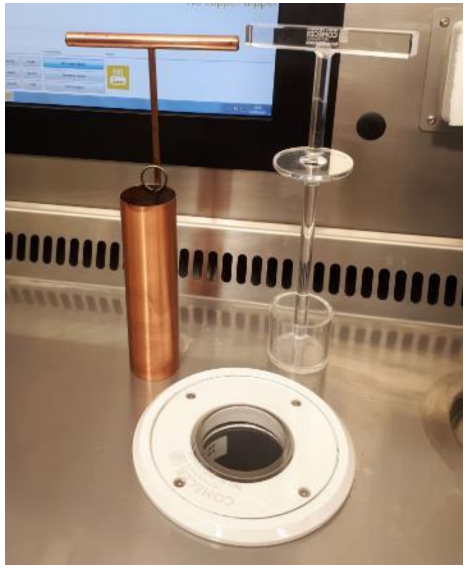
NIST National Institute of Standards and Technology

Calibration

- The "calibration" problem is typically not intercepted by standard quality assurance measures
- This can lead to significant inaccuracies with the determination of the activity of a radiopharmaceutical
- More advanced quality control measures are therefore urgently required → medical physics experts
- Theranostics: quantitative imaging for radionuclide therapy and personalized dosimetry are based on this







World Health Organization

IAEA

TRS-374 – Calibration of Dosimeters Used in Radiotherapy (IAEA, 1994)

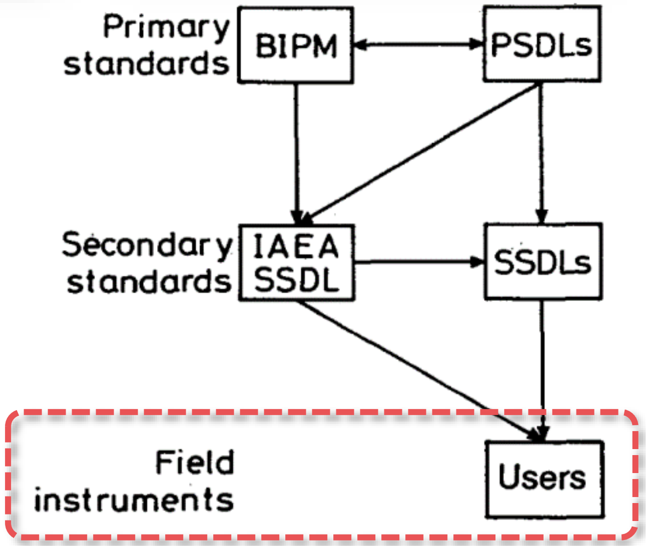
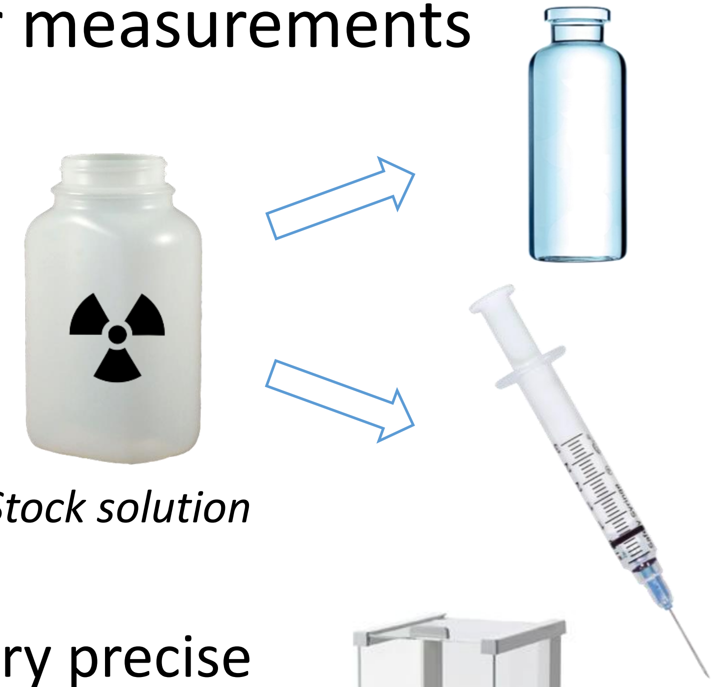


FIG. 1. The international measurement system.

Traceability of radionuclide calibrators

- Intercomparison and accuracy of radionuclide calibrator measurements
  - stock solution with an activity concentration (Bq/ml)
  - 2 recipients: syringe & vial – gravimetrical dispensing
  - measurements in a number of Belgian NM departments



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Physica Medica

journal homepage: www.elsevier.com/locate/ejmp

ELSEVIER

Original paper

Intercomparison of ^{99m}Tc, ^{18}F and ^{111}In activity measurements with radionuclide calibrators in Belgian hospitals

Clarita Saldarriaga Vargas[a,*], Sunay Rodríguez Pérez[a], Kristof Baete[b,c], Stefaan Pommé[d], Jan Paepen[d], Raf Van Ammel[d], Lara Struelens[a]

[a] Belgian Nuclear Research Centre (SCK·CEN), Boeretang 200, 2400 Mol, Belgium
[b] UZ Leuven, Department of Nuclear Medicine, Herestraat 49, 3000 Leuven, Belgium
[c] KU Leuven, Department of Imaging and Pathology, Herestraat 49, 3000 Leuven, Belgium
[d] European Commission, Joint Research Centre (JRC), Directorate for Nuclear Safety and Security, Retieseweg 111, 2440 Geel, Belgium

Physica Medica 45 (2018) 134–142

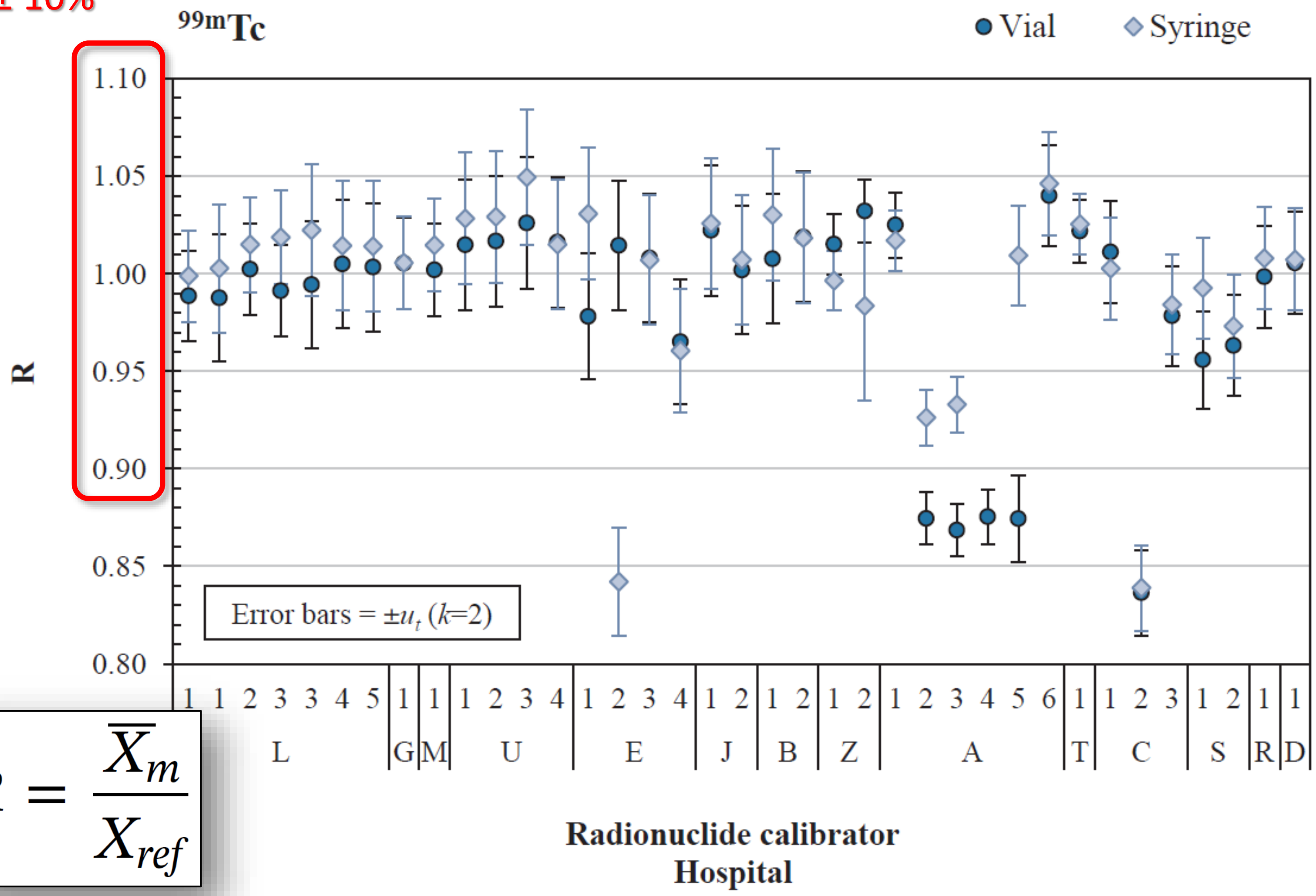
- Additionally, very precise activity concentration measurements in a reference radionuclide laboratory and a nuclear research center :

sck cen
Belgian Nuclear Research Centre

irmm
Institute for Reference Materials and Measurements

Intercomparison using Tc-99m

± 10%



$$R = \frac{\overline{X}_m}{X_{ref}}$$

Physica Medica 45 (2018) 134–142

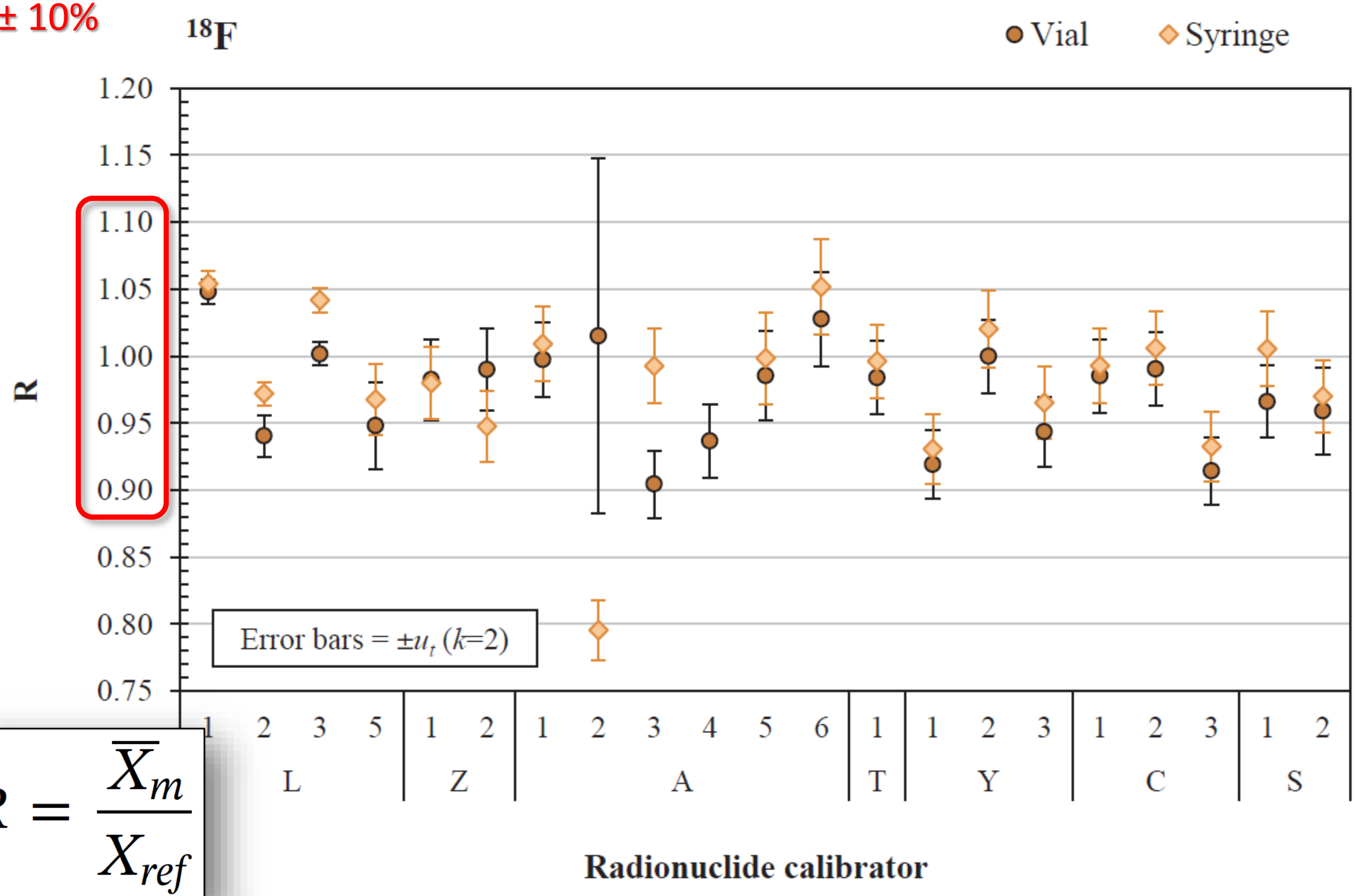
- suspension level for accuracy deviation > 5% for > 100 keV (RP-162, EC 2012 & NPL 2006)

European Commission

NPL National Physical Laboratory

Intercomparison using F-18

± 10%



$$R = \frac{\overline{X}_m}{X_{ref}}$$

Physica Medica 45 (2018) 134–142

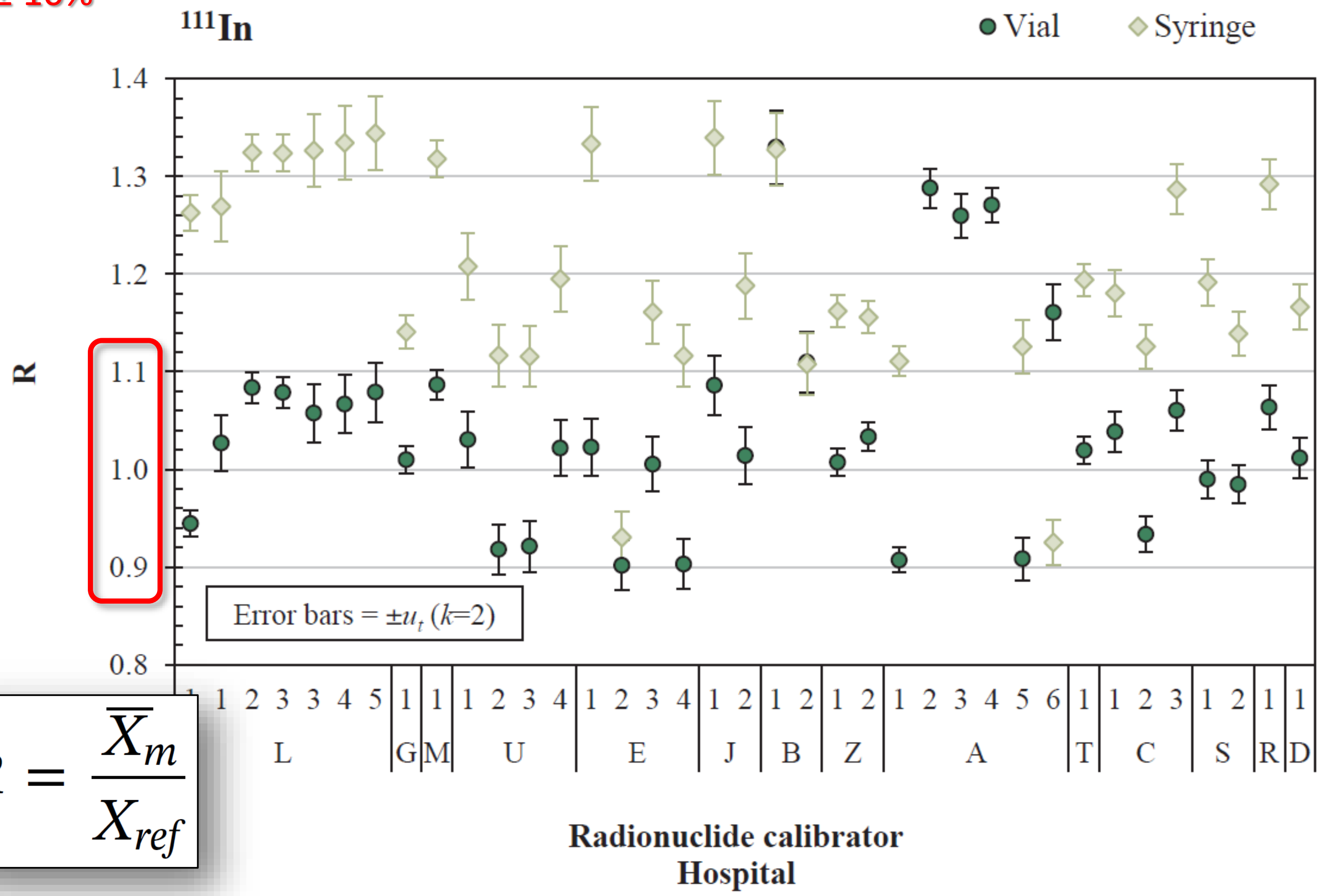
- Involvement of a "Fidelis", secondary standard radionuclide calibrator

southern scientific

sck cen Belgian Nuclear Research Centre

Intercomparison using In-111

± 10%



$$R = \frac{\overline{X}_m}{X_{ref}}$$

Physica Medica 45 (2018) 134–142

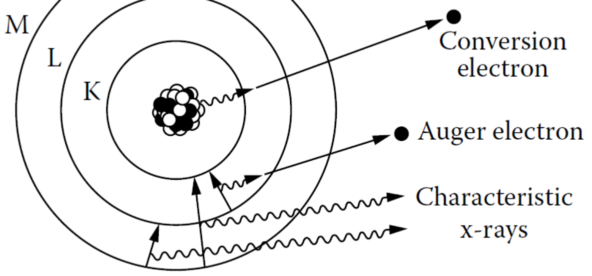


TABLE 3. Nuclear Data for ^{111}In

Principal radiation	E_i (keV)*	n_i	Equilibrium dose constant, Δ_i (rad g μCi^{-1} h^{-1})	Equilibrium dose constant, Δ_i (Gy kg Bq^{-1} s^{-1})
Auger electron	2.7	0.98	5.68E−03	4.27E−16
	19.3	0.156	6.41E−03	4.82E−16
Conversion electron	144.6	0.078	2.40E−02	1.80E−15
	167.3	0.0106	3.78E−03	2.84E−16
	170.5	0.00203	7.37E−04	5.54E−17
	171.2	0.000424	1.55E−04	1.16E−17
	218.7	0.0493	2.30E−02	1.73E−15
	241.4	0.00785	4.04E−03	3.03E−16
	244.6	0.00151	7.87E−04	5.91E−17
	245.3	0.000301	1.57E−04	1.18E−17
x-ray	3.1	0.069	4.60E−04	3.46E−17
	23	0.235	1.15E−02	8.64E−16
	23.2	0.443	2.19E−02	1.64E−15
	26.1	0.145	8.06E−03	6.06E−16
γ	171.3	0.902	3.29E−01	2.47E−14
	245.4	0.94	4.91E−01	3.69E−14

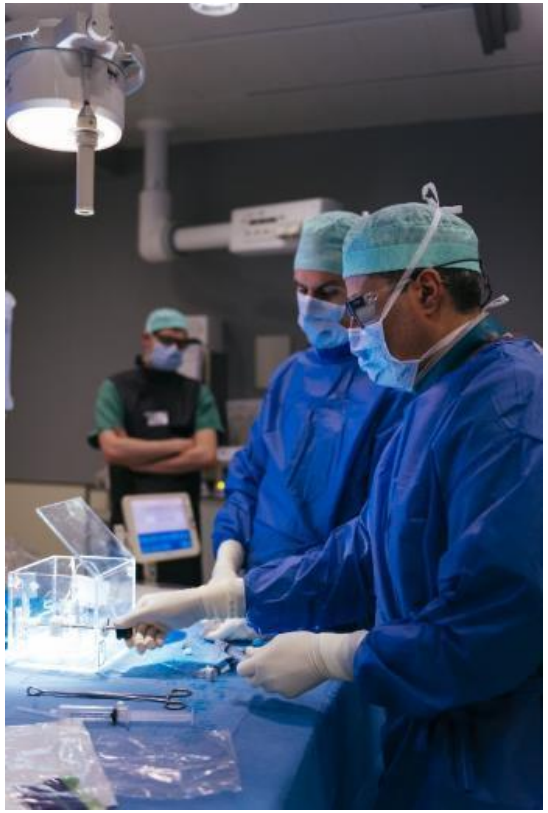
*Average electron energies.

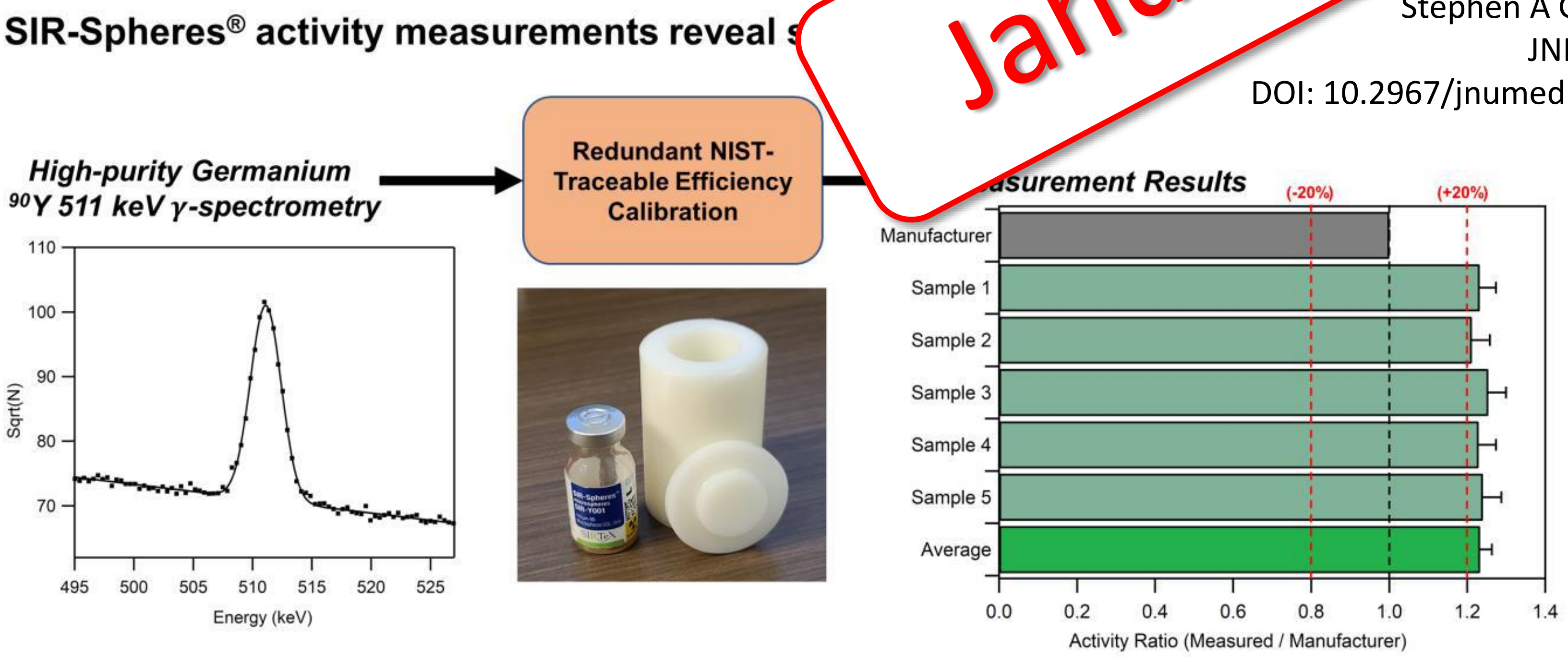
E_i = mean energy per particle or photon; n_i = mean number of particles or photons per nuclear transition; Δ_i = mean energy emitted per nuclear transition.

^{111}In has the following properties: physical half-life, 67.3 h; decay constant, 0.0103 h^{-1}; and decay mode, electron capture.

Accuracy of activity for ^{90}Y-SIRT

- SIRT = selective internal radiation therapy of liver cancer
- gamma spectrometry reveals that the ^{90}Y primary SIR-Spheres® activity calibration appears to be a significant underestimate of true activity: 1.233 ± 0.030





January 2022

Stephen A Graves, *et al.*
JNM, Jan 2022,
DOI: 10.2967/jnumed.121.262650

Accuracy of activity for ^{90}Y-SIRT

Silvano Gnesin, *et al.*
JNM, No…22,
DOI: 10.2967/jnume…8

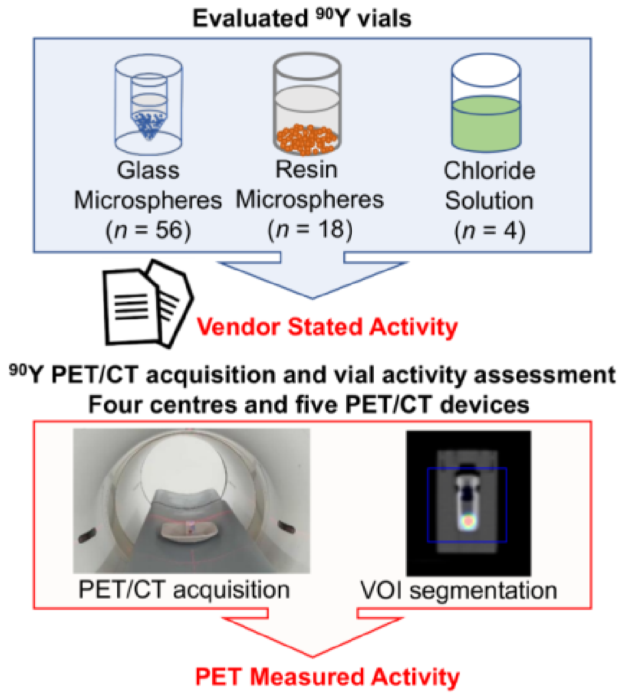
November 2022

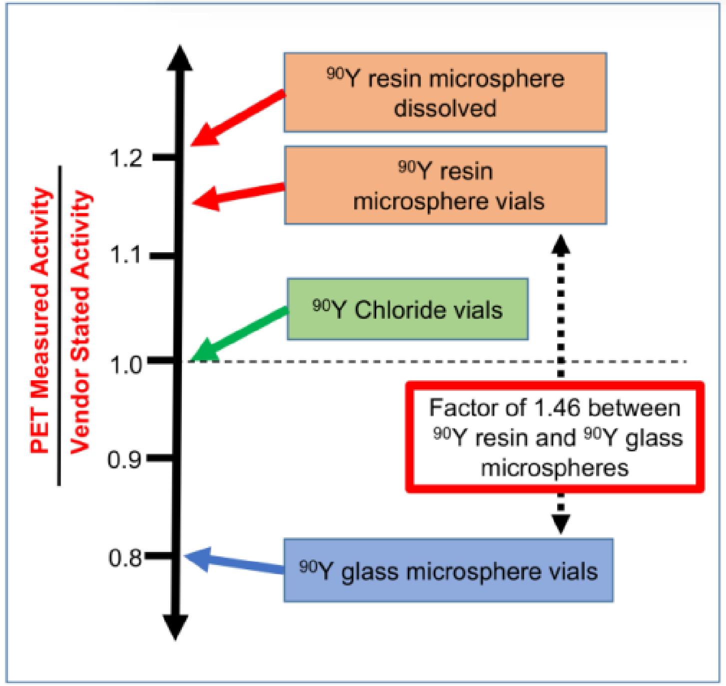
- confirmation of previous study and observations

Title: A multicenter study on observed discrepancies between vendor-stated an… ^{90}Y activities for both glass and resin microsphere devices

Authors: Silvano Gnesin*, Justin K. Mikell*, Maurizio Conti… Thiago V. M. Lima, Yuni K. Dewaraja.

Graphical Abstract





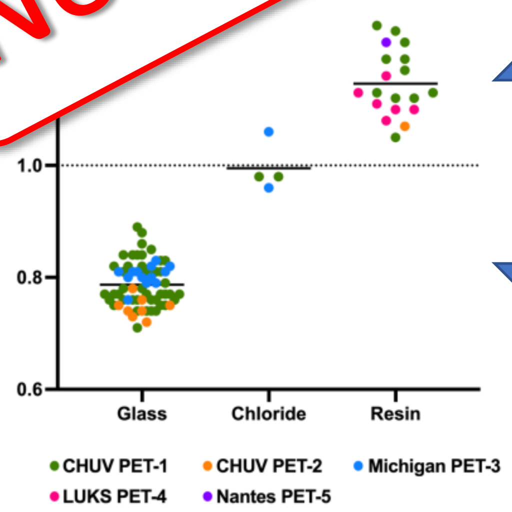


Figure 1. Distribution of A_{PET}/A_{M} ratios for the four vial products tested in this study (i.e ^{90}Y-labeled glass microspheres, ^{90}Y-Chloride solution, ^{90}Y-labeled resin microspheres and ^{90}Y-labeled liquefied resin).

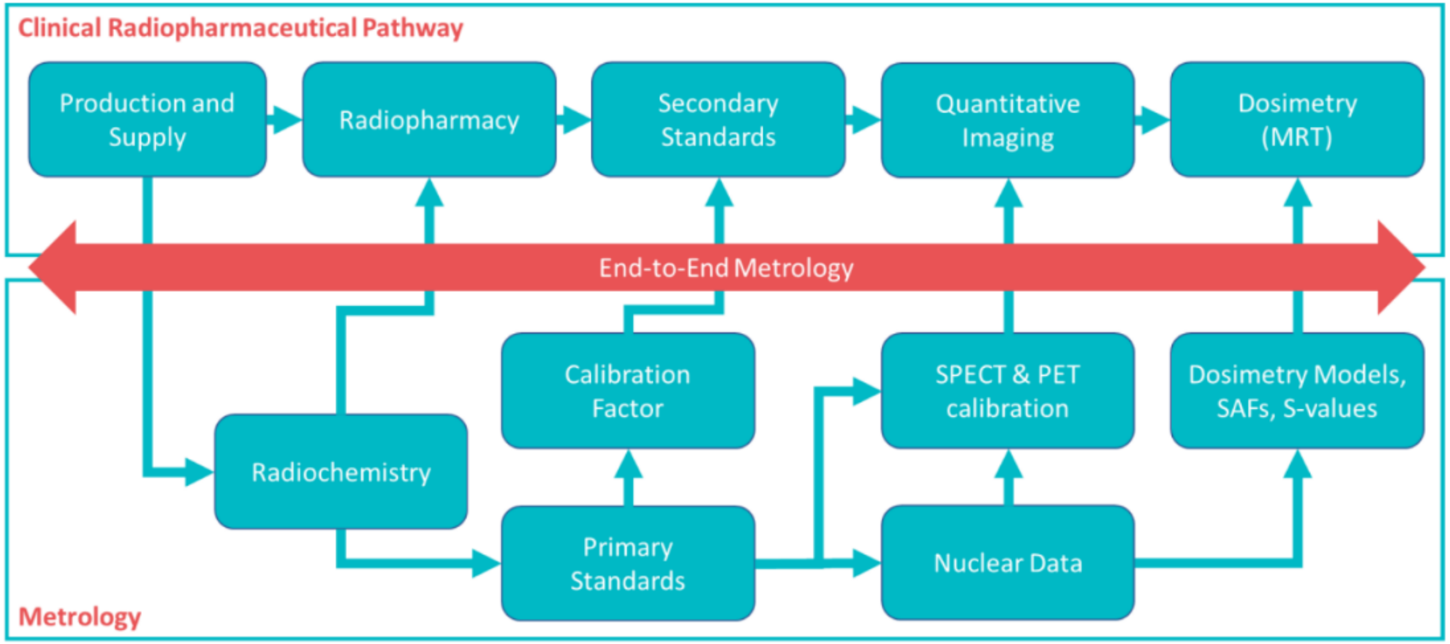
Δ ~ 50%

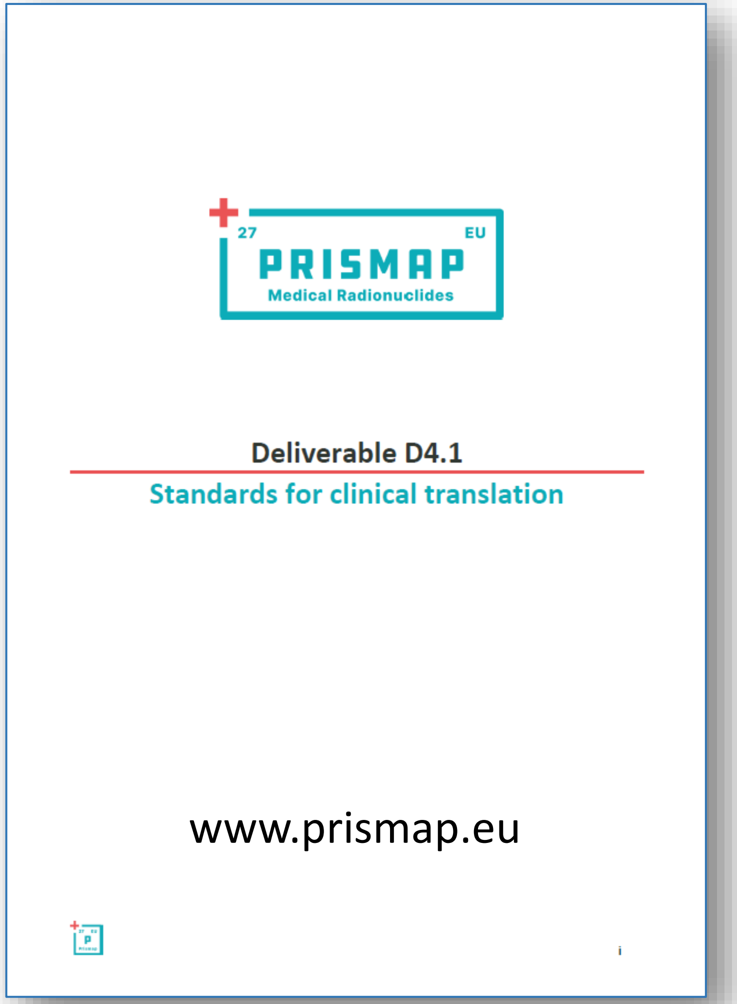
significant uncertainty for therapy

Traceable calibration of all instrumentation

- PRISMAP recommends the implementation of
  - an end-to-end metrology methodology, and
  - the involvement of medical physics experts (MPE)

for the standardization and harmonization of novel radiopharmaceuticals for imaging and therapy





Deliverable D4.1

Standards for clinical translation

www.prismap.eu

Clemens Decristoforo, et al. (2022). https://doi.org/10.5281/zenodo.6599181

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Dosimetry in radionuclide therapy: the clinical role of measuring radiation dose

Courtney Lawhn-Heath, Thomas A Hope, Juana Martinez, Edward K Fung, Jaehoon Shin, Youngho Seo, Robert R Flavell

THE LANCET Oncology

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- "Health-care infrastructure poses another key challenge in the implementation of radionuclide therapy dosimetry."
- "… scarcity of insurance reimbursement codes for physics and dosimetry …"
- "… new scanners to accommodate the increased volume, increasing technologist staffing to perform the imaging studies, and increasing physician and medical physicist staffing to perform the image analysis that is necessary to establish the amount of activity or number of cycles that can be administered."
- "Importantly, increased equipment and staffing outlays are difficult to justify in the absence of assured insurance reimbursement, emphasizing the need for advocacy for coverage of dosimetry."

Some take-home messages

- Align Medical Physics expertise with the translation process
- There are so many practicalities to prepare for – keep this in mind
- One day, these preparations will become important for the further steps in theranostics and clinical applications
- A lot of problems have been investigated, however, solutions are not always easily applicable into the clinical environment
- Inform authorities at the respective levels about the need for cooperation and sufficient involvement of medical physics teams
- A solid quality assurance framework that supports and monitors the clinical translation process
- Early involvement of experts
- Integration of expertise

Editorial

The research versus clinical service role of medical physics

Thomas Bortfeld [a], Alberto Torresin [b], Claudio Fiorino [c,*], Pedro Andreo [d], Giovanna Gagliardi [e], Robert Jeraj [f], Ludvig P. Muren [g], Marta Paiusco [h], David Thwaites [i], Tommy Knöös [j,k]

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kristof.baete@uzleuven.be
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