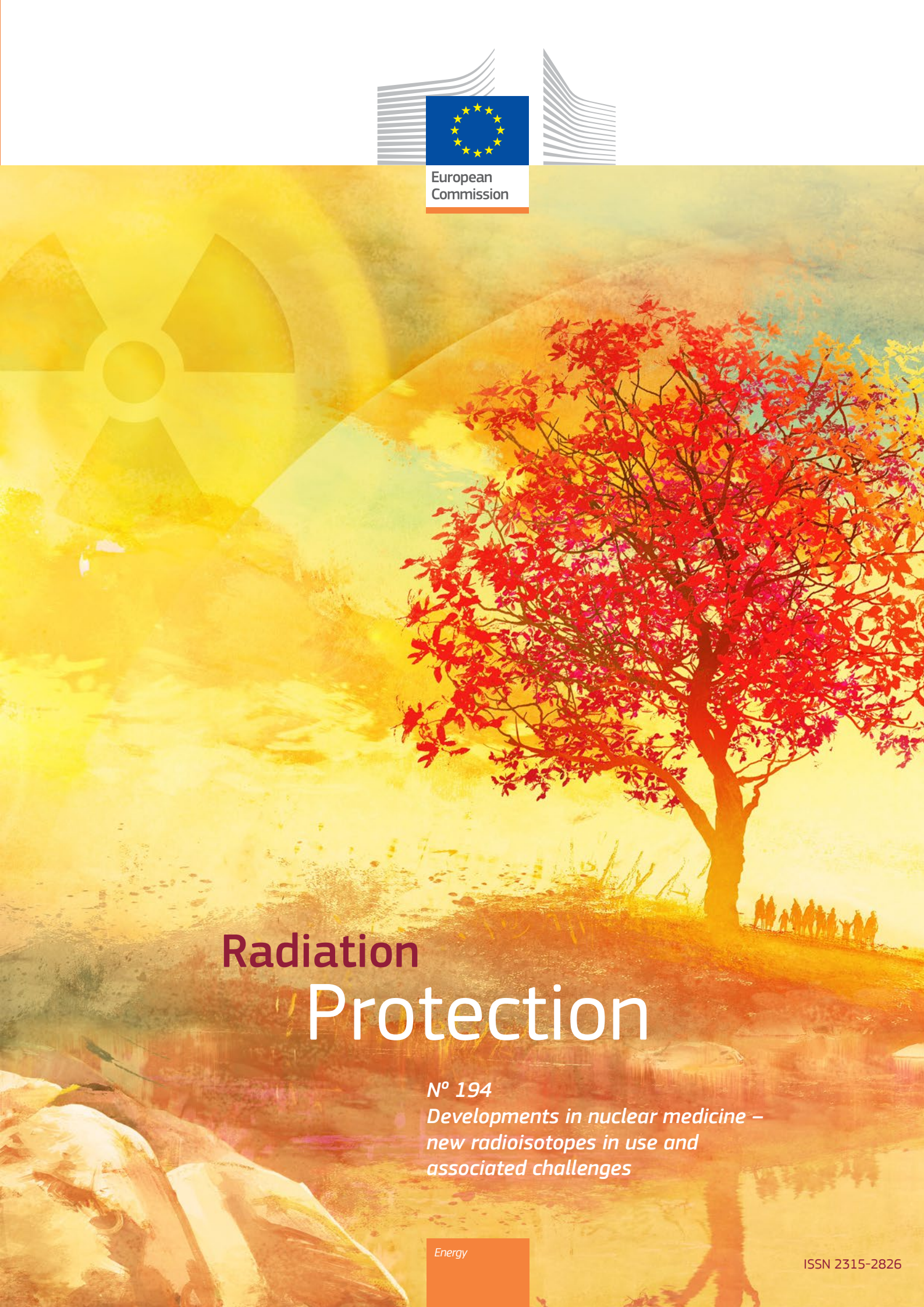

Radiation Protection

Nº 194

Developments in nuclear medicine – new radioisotopes in use and associated challenges

Energy

ISSN 2315-2826

Luxembourg: Publications Office of the European Union, 2020

Print	ISBN 978-92-76-27009-6	ISSN 1681-6803	doi:10.2833/522008	MJ-AX-20-003-EN-C
PDF	ISBN 978-92-76-27010-2	ISSN 2315-2826	doi:10.2833/905722	MJ-AX-20-003-EN-N

EUROPEAN COMMISSION

RADIATION PROTECTION N° 194

EU Scientific Seminar November 2019

Developments in nuclear medicine – new radioisotopes in use and associated challenges

Proceedings of a scientific seminar held in Luxembourg on 13 November 2019

Working Party on Research Implications on Health and Safety Standards of the Article 31 Group of Experts

Directorate-General for Energy

Directorate D — Nuclear Energy, Safety and ITER

Unit D3 — Radiation Protection and Nuclear Safety

2020

Foreword

Luxembourg, October 2020

The European Commission organises every year, in cooperation with the Group of Experts referred to in Article 31 of the Euratom Treaty, a Scientific Seminar on emerging issues in Radiation Protection – generally addressing new research findings with potential policy and/or regulatory implications. Leading scientists are invited to present the status of scientific knowledge in the selected topic. Based on the outcome of the Scientific Seminar, the Group of Experts referred to in Article 31 of the Euratom Treaty may recommend research, regulatory or legislative initiatives. The European Commission takes into account the conclusions of the Experts when setting up its radiation protection programme. The Experts' conclusions are valuable input to the process of reviewing and potentially revising European radiation protection legislation and may assist in the implementation of Council Directive 2013/59/Euratom (Basic Safety Standards Directive).

In November 2019, the EU Scientific Seminar covered the issue *Developments in nuclear medicine – new radioisotopes in use and associated challenges*. Internationally renowned scientists presented:

- Radionuclide therapy in nuclear medicine – developments and challenges
- Production of radiopharmaceuticals –regulatory issues
- Dosimetry and dosimetric tools in radionuclide therapy, including results of a European survey
- Radiation protection issues in radionuclide therapy – workers (medical staff), third persons, waste management
- Evaluation of risks of radionuclide therapy.

The presentations were followed by a round table discussion, in which the speakers and additional invited experts discussed potential *policy implications and research needs*.

The Group of Experts discussed this information and drew conclusions that are relevant for consideration by the European Commission and other international bodies.

Contents

Radionuclide therapy in nuclear medicine – developments and challenges

Michael Lassmann[1]

Klinik und Poliklinik für Nuklearmedizin, Universitätsklinikum Würzburg, Würzburg, Germany

1 Introduction

Until mid-2000, the majority of radionuclide therapies comprised the treatment of benign and malignant thyroid diseases with radioiodine (*1,2*) or the treatment of neuroblastoma with [^{131}I]I-mIBG (*3*). In recent years, more and more new radiopharmaceuticals for radionuclide therapies obtained marketing authorization or are in several stages of clinical trials. Examples are Xofigo® ([^{223}Ra]Ra-dichloride (*4*)), Lutathera® ([^{177}Lu]Lu-Oxodotreotid, [^{177}Lu]Lu-DOTATATE (*5*)) and [^{177}Lu]Lu-PSMA-617 ("Vision Trial", EudraCT Number: 2018-000459-41 (*6*)).

Therapies in nuclear medicine comprise either metabolically active radiopharmaceuticals such as radioiodine, specifically binding radiopharmaceuticals (compounds that address specific antigens or receptors) or locoregional therapies (e.g. microspheres instilled locally for the treatment of liver cancer). A summary of the most important and established treatments with marketing authorizations (except [^{177}Lu]Lu-PSMA-ligands) is given in Table 1.

2 Developments

The activities administered to patients are in the range of 1-10 GBq for beta emitters such as ^{177}Lu and 5-10 MBq for alpha emitters such as ^{223}Ra with a half-life of the radionuclide in the range of several days. Table 2 provides an overview of the main radionuclides used for therapies and their respective physical properties.

[1] Corresponding author: Michael Lassmann, Klinik und Poliklinik für Nuklearmedizin, Universitätsklinikum Würzburg, Oberdürrbacher Str. 6, D-97080 Würzburg, Germany, Lassmann_m@ukw.de

	Radionuclide / radio-pharmaceutical	Treatment	Reference
Metabolically active radiopharmaceuticals	[^{131}I]NaI	Benign/Malignant thyroid disease	(*1,2*)
	[^{223}Ra]$RaCl_2$ (Xofigo®)	Bone pain of prostate cancer bone metastases	(*4*)
Specifically binding radiopharmaceuticals	**Compounds addressing specific antigens or receptors**		
	[^{131}I]mIBG	Neuroblastoma	(*3*)
	[^{177}Lu]Lu-DOTATATE (Lutathera®)	Neuroendocrine Tumours	(*5*)
	[^{177}Lu]Lu-PSMA-ligands [^{225}Ac]Lu-PSMA-ligands	Prostate cancer metastases	(*6*)
	Antibodies		
	[^{90}Y]Y-ibritumomab tiuxetan (Zevalin®)	Lymphoma	(*7*)
Locoregional therapies			
	Selective internal radiotherapy		
	^{90}Y-microspheres (glass or resin)	Liver diseases	(*8*)
	Radiosynovectomy		
	[^{169}Er]Er-citrate [^{90}Y]Y-silicate/citrate [^{186}Re]Re-sulphide	Pain palliation of joints	(*9*)

Table 1: *Therapy Modalities*

Radionuclide	Half-life (h)	β_{max} (MeV)	γ (keV) for imaging	Max. range (mm)
^{131}I	192.6	0.61	364	2.0
^{90}Y*	64.0	2.28	-	12
^{177}Lu	159.5	0.50	208	1.5
^{223}Ra	274.3	5.87 (α) ≈ 28 (α)**	81/84/95/ 144/154/269**	0.05

* β^+-Emitter (Positron Branching Ratio: $31.9*10^{-6}$)

** including progeny

Table 2: *Properties of the most frequently used radionuclides in radionuclide therapies (nuclear data taken from http://www.lnhb.fr/nuclear-data/nuclear-data-table/)*

Radiopharmaceuticals are administered either as a one-time administration with the option of later retreatment or in several repeated cycles. The dosing often follows a fixed activity scheme, possibly corrected for body weight. Dosimetry-based treatment planning or post-therapy absorbed dose verification, although in principle required by the Basic Safety Standards Directive of the European Union (*10*) which states that radiotherapeutic procedures (which includes targeted radionuclide therapies) should be both planned and verified, is often not performed rigorously.

In the near future, new therapeutic radiopharmaceuticals such as ^{225}Ac- (*11*) or ^{177}Lu-labelled PSMA-compounds (*12,13*), ^{90}Y- or ^{177}Lu-labelled CXCR4 antagonists (*14*), ^{177}Lu-labelled somatostatin antagonists (*15*), or ^{177}Lu labelled anti-CD37 radioimmunoconjugates (*16*) will be introduced in clinical practice. In contrast e.g. to radioiodine therapy of differentiated thyroid cancer, it is highly likely that most of these therapies will need a patient-specifically tailoring of the activities to administer such that the absorbed dose limits for normal organs and tissues are considered while achieving high absorbed doses to the treatment target.

3 Challenges

Radionuclide therapy is not just radioactive chemotherapy, as it is, in many cases, possible to quantify the biodistribution of the compound by quantitative imaging. It is also not directly comparable to external beam therapy due to the spatial and temporal variability of the biodistribution of the radiopharmaceutical. In addition, dose-rate effects, DNA-damage repair and variable biology within a tumour play a major role. As the main treatment effect is caused by ionizing radiation, and, very often, the radiopharmaceutical is administered systemically, the potential treatment-associated radiation risk for patients is both deterministic (in target organs and lesions) and stochastic (in non-targeted tissue).

Consequently, there are several challenges for radionuclide therapies that should be addressed on a European level.

3.1 Standardization of quantitative Imaging

For [^{18}F]-fluorodeoxyglucose (FDG), EARL[2] initiated an accreditation program in order to support imaging sites, which perform FDG-PET/CT oncology examinations, in meeting the requirements indicated in the European Association of Nuclear Medicine (EANM) imaging guideline which aims at providing a minimum standard for the acquisition and interpretation of PET and PET/CT scans with FDG. This accreditation ensures similar performance of PET/CT systems within a multicenter setting by harmonizing acquisition and processing of PET/CT scans.

[2] EANM Research Ltd

For SPECT/CT Zimmerman et al. (*17*) could show, in an international multicenter calibration and standardization trial by using calibrated ^{133}Ba sources, that SPECT/CT systems showed better reproducibility and better accuracy compared to planar imaging. The results for SPECT/CTs were almost operator-independent. Wevrett et al. (*18*) reported on an inter-comparison of quantitative imaging of ^{177}Lu in European hospitals using a simple geometry (a 'shell sphere' consisting of two isolated concentric spheres allowing the creation of a 'core' filled with a high activity concentration, surrounded by a less-active 'background' shell). The authors conclude that further research into the sources of uncertainty should be performed in order to fully determine a realistic uncertainty budget.

Siemens Healthineers recently introduced the use of a NIST-traceable calibration source (^{75}Se) with a 3 % uncertainty (99 % confidence level) for radionuclides emitting photons with energies between 150 and 250 keV (^{123}I, ^{111}In, ^{177}Lu) to ensure standardization of quantitative SPECT/CT (see https://www.healthcare.siemens.de/molecular-imaging/xspect/xspect-technology/features). Using this calibration method Tran-Gia et al. (*19*) showed that a quantification accuracy of < 2 % could be achieved.

Further efforts for standardizing SPECT/CT calibration have been undertaken in the joint European Metrology Research Project (EMRP) MRTdosimetry (www.mrtdosimetry.eu) which ended May 2019. Main goals of the project were to improve the accuracy and metrological traceability in the calculation of dose from time-sequences of quantitative imaging measurements and to determine uncertainties in relation to the full MRT dose measurement chain from a primary standard to a range of commercial and non-commercial dosimetry calculation platforms. The final publishable report of project is available at http://mrtdosimetry-empir.eu/wp-content/uploads/2019/08/15HLT06_Publishable_Report_M36_Final.pdf.

Another European project, "MEDIRAD"[3] (http://www.medirad-project.eu/), which started in 2017, develops and implements in one of the work packages the tools necessary to establish, for the first time in a multicenter setting, the range of absorbed doses delivered to healthy organs to thyroid cancer patients undergoing thyroid ablation. The technical part of the project comprises standardization of quantitative imaging as well as centralized dosimetry reading.

The results of these joint European efforts emphasize the necessity to define a standardized and reproducible calibration across sites for SPECT/CT quantitative imaging as a prerequisite for dosimetry in multicenter trials.

[3] MEDIRAD stands for Implications of Medical Low Dose Radiation Exposure

3.2 Foster research efforts in dosimetry methodologies and radiobiology

As mentioned above, MEDIRAD is one of the projects that address the impact of low dose radiation exposure from ^{131}I radioiodine ablation of thyroid cancer in order to

- Establish the range of absorbed doses to healthy organs
- Determine a threshold absorbed dose for successful ablation
- Assess the relation between patient biokinetics, success of thyroid ablation and acute to mid-term toxicity
- Assess optimal methods for internal dosimetry to be applied practically in a large scale European multicenter setting.

In addition, the role of radiobiology to examine the impact of radioresistance, low and continuous absorbed dose rates, and heterogeneity of uptake at either a cellular, microscopic or macroscopic scale needs investigation for radionuclide therapies (*20*).

The EURATOM work programme call NFRP-2019-2020-13, for which the European Alliance for Medical Radiation Protection Research (EURAMED) submitted a proposal[4], addresses the roadmap to future research efforts in these areas. The overarching objective of EURAMED when addressing this call is to generate a European consensus on research needs and their priorities in medical radiation application and corresponding radiation protection to optimize the use of ionizing radiation in medicine and thereby improve its benefit to Europe's patients. The aim is to base this consensus on an integrative approach, bringing together the existing medical radiation protection research platform (EURAMED) as well as the other radiation protection research platforms in Europe, the research community in the health and digitization areas in Europe as well as the relevant industries, suppliers, healthcare professionals, professional and scientific organizations, and regulatory bodies. This objective will be addressed within a central document called "strategic research agenda", a roadmap interlinked with the overarching roadmap of the European radiation protection platforms as currently under development and other general roadmaps within the health sector, and a document showing the interlinks with the different research fields and contributing platforms and networks.

3.3 Implement dosimetry early in early stages of clinical trials (phase I/II)

In addition, early stages of clinical trials (phase I/II) should implement rigorously patient-specific dosimetry for improving safety and efficacy of new therapies for an improved assessment of patient dosing in later phases or for obtaining marketing authorization. For example, the posologies issued by regulatory agencies for recently authorized

[4] The proposal for the 3-year EURAMED rocc-n-roll project was accepted and the project started on 1 September 2020 (https://cordis.europa.eu/project/id/899995).

radiopharmaceuticals such as Lutathera® or Xofigo® provide only very general data on dosimetry (see Table 3). More regulatory clarifications and guidelines will be needed to achieve this goal.

Organ	**Organ absorbed dose (mGy/MBq) (n=20)**	
	Mean	SD
Kidneys	**0.65**	**0.29**
Red Bone Marrow	**0.03**	**0.03**
Spleen	0.85	0.80
Liver	0.49	0.62
Urinary Bladder Wall	0.45	0.18
Osteogenic Cells	0.15	0.27
Breasts	0.03	0.01
Ovaries (n=9)	0.03	0.01
Testes (n=11)	0.03	0.02

Table 3: *Example of dosimetry data for some organs (organs-at-risk are denoted in bold) provided by the European Medicines Agency (EMA) in Table 12 of the posology for Lutathera®*[5]

3.4 Balance accuracy vs. efforts for clinical dosimetry

A document published by the EANM Internal Dosimetry Task Force[6] provides some examples for an approach to achieve sufficient accuracy versus staff efforts for treatment planning and peri-therapeutic verification of the absorbed doses. One of the conclusions of the report is that "in almost all therapeutic procedures considered, the ability to perform image-based patient-specific dosimetry has been demonstrated. This allows verification of the absorbed doses delivered to tumours, target volumes and healthy organs. Patient-specific treatment planning is also feasible in all cases, either from tracer studies with the therapeutic radionuclide, with surrogate imaging radionuclides as 'companion diagnostics', or within an 'adaptive planning' strategy in the case of multiple administrations."[3]

Today, the prescription of many therapeutic radiopharmaceuticals is based on fixed activities, in some cases modified by body weight or body surface area. Therefore, the report's conclusions need to be balanced against the missing clinical evidence for the superiority of prospective therapy prescription on basis of patient-specific dosimetry. Additionally, dosimetry-guided treatment is, for most therapeutic compounds, not in line

[5] https://www.ema.europa.eu/en/documents/product-information/lutathera-epar-product-information_en.pdf, accessed on 10-Nov-2019

[6] Analysis of Potential and Prospects for Treatment Planning in Preparation of the Implementation of the European Council Directive 2013/59, accessible at https://www.eanm.org/publications/idtf-report/

with the instructions for use recommended by EMA with the consequence that the posology would need to be modified and complemented in order to comply with the Basic Safety Standards Directive of the European Union (see also chapter 3.3).

3.5 Availability of radionuclides

The need for investments for improving the availability of diagnostic radionuclides is addressed in conclusion 10 of the SAMIRA project (Final report, Contract ENER/17/NUCL/SI2.755660[7]):

"Medical Radioisotopes: Security of Supply: Research reactor based ^{99}Mo production will remain necessary to fulfil European and global demand until 2030. Significant decline in demand is not foreseen until 2030. A supply situation without a new dedicated research reactor in Europe – PALLAS being the most likely candidate – would not lead to European self-sufficiency and could create shortages at the global scale."

For the availability of radionuclides for therapy, the JRC/2019/OP/3311 call for tender ("Study on Sustainable and Resilient Supply of Medical Radioisotopes in the EU– SMER 2), a study on the EU market of medical radionuclides, focusing on the therapy field, was published in October 2019 by the European Commission.

3.6 Access to treatment in all European countries

Throughout the European Union there is an imbalance concerning the opportunities to perform radionuclide therapies as, in some countries, there is a lack of trained staff (physicians, medical physics experts, radiochemists) and a lack of adequate treatment facilities. In addition, reimbursement or additional financial means for some of the more costly procedures are not guaranteed in some countries.

3.7 Waste management of long-lived impurities in therapeutic radionuclides

Some of the therapy radionuclides contain long-lived impurities due to their production process. Examples are:

- Lutathera®: At time of production a maximum of 0.05 % ^{177m}Lu (half-life: 161 days)
- Xofigo®: At time of production a maximum of: 0.004 % ^{227}Ac (half-life: 21.8 years) and 0.5 % ^{227}Th (half-life: 18.7 days)[8]

[7] https://op.europa.eu/en/publication-detail/-/publication/6ae3e9cd-2e7a-11e9-8d04-01aa75ed71a1

[8] http://www.verwaltungsvorschriften-im-internet.de/BMUB-RSII3-20151218-SF-A002.htm

In many countries, the rules for the disposal of these impurities vary according to local rules and legislation. The respective bodies of the EU (European Medicines Agency -EMA- or the European Commission) should provide recommendations how to handle these wastes, based on international recommendations.

4 Summary and conclusion

Radionuclide therapy is not just chemotherapy as it is possible to quantify the biodistribution of the compound. It is also not directly comparable to external beam therapy due to the highly spatial and temporal variability of the biodistribution of the radiopharmaceutical. Dosimetry should be performed to comply with the Basic Safety Standards Directive and for generating robust data on safety and efficacy of radionuclide therapies. For this purpose, further standardization of dosimetry methods in radionuclide therapies is needed.

Dosimetry and treatment planning in radionuclide therapies should surpass a simple assessment of the absorbed doses; it should also take major biological effects such as DNA damage and repair mechanisms or the influence of the number and frequency of treatment cycles or of the pharmaceutical itself on biokinetics in normal organs and tissues and tumours into account. Treatment planning in nuclear medicine should always consider – if technically possible – **the safety and the efficacy** of a particular treatment. Further efforts should be promoted that lead to best patient care and that may minimize avoidable short- and long-term toxicity.

The requirements for obtaining marketing authorization for new drugs should be raised such that sufficient dosimetry data from early clinical trials will be made available. Further research efforts are needed, in agreement with the EURAMED Strategic Research Agenda (SRA) and the results of the support action NFRP-2019-2020-13, to elucidate the role of biodistribution studies, dosimetry and radiobiology in radionuclide therapies.

5 References

1. Luster M, Clarke SE, Dietlein M, et al. Guidelines for radioiodine therapy of differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging.* 2008;35:1941-1959.

2. Stokkel MP, Handkiewicz Junak D, Lassmann M, Dietlein M, Luster M. EANM procedure guidelines for therapy of benign thyroid disease. *Eur J Nucl Med Mol Imaging.* 2010;37:2218-2228.

3. Giammarile F, Chiti A, Lassmann M, Brans B, Flux G. EANM procedure guidelines for 131I-meta-iodobenzylguanidine (131I-mIBG) therapy. *Eur J Nucl Med Mol Imaging.* 2008;35:1039-1047.

4. Poeppel TD, Handkiewicz-Junak D, Andreeff M, et al. EANM guideline for radionuclide therapy with radium-223 of metastatic castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging.* 2018;45:824-845.

5. Bodei L, Mueller-Brand J, Baum RP, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. *Eur J Nucl Med Mol Imaging.* 2013;40:800-816.

6. Kratochwil C, Fendler WP, Eiber M, et al. EANM procedure guidelines for radionuclide therapy with (177)Lu-labelled PSMA-ligands ((177)Lu-PSMA-RLT). *Eur J Nucl Med Mol Imaging.* 2019.

7. Tennvall J, Fischer M, Bischof Delaloye A, et al. EANM procedure guideline for radio-immunotherapy for B-cell lymphoma with 90Y-radiolabelled ibritumomab tiuxetan (Zevalin). *Eur J Nucl Med Mol Imaging.* 2007;34:616-622.

8. Giammarile F, Bodei L, Chiesa C, et al. EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds. *Eur J Nucl Med Mol Imaging.* 2011;38:1393-1406.

9. Clunie G, Fischer M, Eanm. EANM procedure guidelines for radiosynovectomy. *Eur J Nucl Med Mol Imaging.* 2003;30:BP12-16.

10. Council of the European Union. Council Directive 2013/59/Euratom 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. *OJ of the EU.* 2014;L13:1-73.

11. Kratochwil C, Bruchertseifer F, Giesel FL, et al. ^{225}Ac-PSMA-617 for PSMA-Targeted alpha-Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer. *J Nucl Med.* 2016;57:1941-1944.

12. Kratochwil C, Giesel FL, Stefanova M, et al. PSMA-Targeted Radionuclide Therapy of Metastatic Castration-Resistant Prostate Cancer with ^{177}Lu-Labeled PSMA-617. *J Nucl Med.* 2016;57:1170-1176.

13. Weineisen M, Schottelius M, Simecek J, et al. ^{68}Ga- and ^{177}Lu-Labeled PSMA I&T: Optimization of a PSMA-Targeted Theranostic Concept and First Proof-of-Concept Human Studies. *J Nucl Med.* 2015;56:1169-1176.

14. Herrmann K, Schottelius M, Lapa C, et al. First-in-Human Experience of CXCR4-Directed Endoradiotherapy with ^{177}Lu- and ^{90}Y-Labeled Pentixather in Advanced-Stage Multiple Myeloma with Extensive Intra- and Extramedullary Disease. *J Nucl Med.* 2016;57:248-251.

15. Wild D, Fani M, Fischer R, et al. Comparison of somatostatin receptor agonist and antagonist for peptide receptor radionuclide therapy: a pilot study. *J Nucl Med.* 2014;55:1248-1252.

16. Blakkisrud J, Holtedahl JE, Londalen A, et al. Biodistribution and dosimetry results from a phase 1 trial of ^{177}Lu-lilotomab satetraxetan antibody-radionuclide conjugate therapy. *J Nucl Med.* 2017.

17. Zimmerman BE, Grosev D, Buvat I, et al. Multi-centre evaluation of accuracy and reproducibility of planar and SPECT image quantification: An IAEA phantom study. *Z Med Phys.* 2017;27:98-112.

18. Wevrett J, Fenwick A, Scuffham J, et al. Inter-comparison of quantitative imaging of lutetium-177 (^{177}Lu) in European hospitals. *EJNMMI Physics.* 2018;5:17.

19. Tran-Gia J, Lassmann M. Characterization of Noise and Resolution for Quantitative ^{177}Lu SPECT/CT with xSPECT Quant. *J Nucl Med.* 2019;60:50-59.

20. Terry SYA, Nonnekens J, Aerts A, et al. Call to arms: need for radiobiology in molecular radionuclide therapy. *Eur J Nucl Med Mol Imaging.* 2019;46:1588-1590.

Production of radiopharmaceuticals – regulatory issues

Oliver Neels

German Cancer Research Center (dkfz), Division of Radiopharmaceutical Chemistry, Heidelberg, Germany

1 Introduction

Radiopharmaceuticals have been used in nuclear medicine for many decades for diagnostic and therapeutic purposes. Briefly, radionuclides for medical purpose are obtained from nuclear reactors, cyclotrons, particle accelerators or radionuclide generators and are used directly or in most cases subsequently attached to e.g. small molecules, peptides or antibodies for the manufacturing of radiopharmaceuticals. The concept of theranostics as part of a personalized medicine approach has led to a renaissance of Nuclear Medicine in the last years using diagnostic nuclear imaging agents like PET or SPECT radiotracers to guide therapy [1]. In consequence, numerous radiopharmaceuticals either for diagnostic purposes or endoradiotherapies are currently used in clinical trials or have received marketing authorization, e.g. [^{68}Ga]Ga-PSMA-11, Axumin®, SomaKit TOC®, Lutathera® or [^{177}Lu]Lu-PSMA-617.

2 Background

The manufacturing of radiopharmaceuticals as medicinal products holding marketing authorization or used in clinical trials within the EU is regulated in Directives 2001/83/EC [2], 2001/20/EC [3] and 2003/94/EC [4]. These requirements are further outlined in specific EU and European Medicines Agency (EMA) guidelines [5]. Examples are the EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines and its annexes [6]. The necessity of GMP and its excessive requirements for radiopharmaceuticals led to a significant decrease in clinical trials after aforementioned directives came into force [7]. Regulation EU 536/2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC has come into force in April 2014 [8]. The radiopharmaceutical community in Europe is currently facing regulatory issues based on Directive 2001/83/EC and regulation EU 536/2014 which are described in this paper.

3 Impact on radiopharmaceuticals - Directive 2001/83/EC

Within Directive 2001/83/EC a marketing authorization according to Article 6 is required for medicinal products when placed on the market. This includes not only radiopharmaceuticals, radionuclide generators, kits and industrially prepared radiopharmaceuticals but also radionuclide precursor radiopharmaceuticals. Directive 2001/83/EC defines:

1. a *medicinal product* as "(a) any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or (b) any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis",
2. a *radiopharmaceutical* as "any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose",
3. a *radionuclide generator* as "any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical",
4. a *kit* as "any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration",
5. a *radionuclide precursor* as "any other radionuclide produced for the radio-labelling of another substance prior to administration"

while the term "*radionuclide precursor radiopharmaceutical*" is not defined.

Promising radionuclides like ^{225}Ac or the Terbium quadruplet ($^{149/152/155/161}$Tb) are made available, being produced or developed with high financial support of the EU in highly specialized research institutions [9],[10]. Nevertheless, these isotopes can, according to abovementioned Article 6, either only be distributed for routine clinical use when a marketing authorization is granted or the medicinal product is used for research and development trials. The same applies for well-established radionuclides like ^{18}F, which cannot be supplied routinely to university hospitals or research institutions with a well-equipped state-of-the-art radiopharmacy fulfilling all GMP requirements but without on-site cyclotron, if no marketing authorization has been granted for the supplier of ^{18}F. Depending on the use of a radionuclide precursor and the method of radiolabelling, the radionuclide precursor could be described either as radionuclide precursor *starting material* (a radionuclide precursor that is to be used in a radiochemical synthesis that is followed by one or more purification steps) or radionuclide precursor *radiopharmaceutical* (a licensed radionuclide precursor that that can be added to a licensed kit for radiopharmaceutical preparations) [11]. Nevertheless, definitions for both are missing within the Directive. An update on the definition of radionuclide precursor and/or radionuclide precursor radiopharmaceutical within Directive 2001/83/EC is, therefore, needed.

4 Impact on radiopharmaceuticals - Regulation EU 536/2014

Regulation EU 536/2014 has come into force on 16th April 2014 but has not yet come into application for several years due to technical difficulties with the development of the IT systems [12]. The current start of the systems is postponed to 2020. The goal of this regulation is to strengthen harmonization in the (electronic) submission process, transparency, higher safety standards and a general facilitation of clinical trials within the Member States.

Generally, in accordance with Article 61 of the regulation, manufacturing of investigational medicinal products (IMPs) require a manufacturing authorization. Radiopharmaceuticals used as diagnostic IMP are excluded in Article 61 paragraph 5 where "this process is carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such process, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State", but according to Article 61 paragraph 6 Member States "shall make the processes set out in paragraph 5 subject to appropriate and proportionate requirements to ensure subject safety and reliability and robustness…".

Article 63 describes the application of manufacturing practice for IMPs to "ensure the quality of such medicinal products in order to safeguard the safety of the subject and the reliability and robustness of clinical data generated in the clinical trial ('good manufacturing practice')" but excludes explicitly IMPs mentioned in article 61 paragraph 5 (radiopharmaceuticals used as diagnostic IMP).

As a conclusion, regulation EU 536/2014 facilitates the use of diagnostic radiopharmaceuticals in clinical trials and describes requirements to ensure subject safety, reliability and robustness of clinical data to be fulfilled by the EU Member States. These facilitations should be interpreted consistently in all Member States to achieve overall aim of harmonization.

5 Conclusions

A clear clarification or re-definition of the terms *radionuclide precursor* and *radionuclide precursor radiopharmaceutical* is necessary within Directive 2001/83/EC to assure the production and the availability for patient care of e.g. novel ^{18}F based radiopharmaceuticals at centres/hospitals without on-site cyclotron. In addition, regulation 536/2014 supposed to facilitate clinical trials with radiopharmaceuticals (still not operational, yet) should be interpreted in all Member States in the same way.

6 References

[1]. Langbein T, Weber WA, Eiber M (2019) Future of Theranostics: An Outlook on Precision Oncology in Nuclear Medicine, J Nucl Med 60:13S-19S doi: 10.2967/jnumed.118.220566

[2]. The European Parliament and the Council of the European Union. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use. Off J Eur Communities. 2001:L311/67–128 https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02001L0083-20190128&from=EN.

[3]. The European Parliament and the Council of the European Union. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Off J Eur Communities. 2001:L121/34-44 https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32001L0020&from=EN.

[4]. The European Parliament and the Council of the European Union. Directive 2003/94/EC of the European Parliament and of the Council of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. Off J Eur Union. 2003:L262/22-26 https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32003L0094&from=EN.

[5]. Lange R, ter Heine R, Decristoforo C et al. (2015), Untangling the web of European regulations for the preparation of unlicensed radiopharmaceuticals: a concise overview and practical guidance for a risk-based approach, J Nucl Med Comm 36(5):414-22. doi: 10.1097/MNM.0000000000000276.

[6]. European Commission. EudraLex The Rules Governing Medicinal Products in the European Union: EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines. https://ec.europa.eu/health/documents/eudralex/vol-4/

[7]. European Commission. Q&A: New rules for clinical trials conducted in the EU. 2014 https://ec.europa.eu/commission/presscorner/detail/en/MEMO_14_254

[8]. The European Parliament and the Council of the European Union. Regulation 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Off J Eur Union. 2014:L158/1–76 https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02014R0536-20140527&from=EN.

[9]. European Commission. Medicis-Promed (H2020 contract # 642889 Medicis-Promed) www.cern.ch/medicis-promed

[10]. IAEA and European Commission. Report on Joint IAEA-JRC Workshop "Supply of Actinium-225". 2018 http://www-naweb.iaea.org/napc/iachem/working_materials/Report_Workshop%20on%20Supply%20of%20Ac-225_IAEA_JRC_October2018.pdf

[11]. Neels O, Patt M, Decristoforo C (2019), Radionuclides: medicinal products or rather starting materials?, EJNMMI Radiopharmacy and Chemistry (4:22). doi: 10.1186/s41181-019-0074-3

[12]. European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation

Dosimetry and dosimetric tools in radionuclide therapy, including results from a European survey

Katarina Sjögreen Gleisner[9]

Medical Radiation Physics, Lund University, Sweden

1 Introduction

Radionuclide therapy refers to medical procedures in which radioactive drugs are administered with therapeutic intention. The therapeutic mechanisms involve the induction of damage to cellular targets, such as the DNA, by irradiation with ionizing radiation. In most radionuclide therapies, the radioactive drug is administered intravenously and the delivery thus driven by a combination of physiological and molecular mechanisms. This approach is particularly suited for therapy of disseminated disease and radionuclide therapy thus forms a complement to other radiotherapy modalities, such as external beam radiotherapy and brachytherapy, which are mainly used for the treatment of localized disease.

The absorbed doses delivered by internally distributed radioactive substances are estimated by means of internal dosimetry calculations. Parameters that enter such calculations are the activity distribution in the body and its redistribution over time, the transport of radiation energy, and the mass of the tissues in which the energy is absorbed. The formalism for internal dosimetry calculations has been described in documents developed by the major radiation protection organizations, such as the International Commission on Radiation Units and Measurements[10], the International Commission on Radiological Protection[11], and the International Atomic Energy Agency[12], while clinical guidelines have been developed within the framework of the European Association of Nuclear Medicine[13]. Much of the fundamental framework has been developed by the committee on Medical Internal Radiation Dose (MIRD) of the Society of Nuclear Medicine and Molecular Imaging[14], with the first pamphlet published in 1968 [1].

[9] Corresponding author: Katarina Sjögreen Gleisner, Medical Radiation Physics, Lund University, Barngatan 4, S-22185 Lund, Sweden, Email: katarina.sjogreen_gleisner@med.lu.se

[10] ICRU https://icru.org/

[11] ICRP http://www.icrp.org/

[12] IAEA https://www.iaea.org/

[13] EANM https://www.eanm.org/

[14] MIRD http://www.snmmi.org/ClinicalPractice/content.aspx?ItemNumber=4212

Internal dosimetry calculations are routinely performed for purposes of radiation protection, for instance at the introduction of a new radiopharmaceutical with a diagnostic or therapeutic application. The formalism for internal dosimetry is applicable also to radionuclide therapy patients. However, there is an important distinction, which in turn has consequences for how the parameters in the dosimetry calculation are estimated. In radiation protection, involving comparably low absorbed doses (< 100 mGy), the purpose of dosimetry is to calculate radiological quantities related to the risk of cancer induction, such as the effective dose e.g., applicable to populations. In this case, the absorbed doses are calculated for a reference person, as represented by a standardized computational phantom, and are taken to represent all patients that undergo a particular medical procedure. In radionuclide therapy, involving absorbed doses of between one and tenths, or even hundreds of gray, the primary purpose of dosimetry is to evaluate the risk for deterministic tissue reactions and the probability of disease control for an individual patient. Thus, the absorbed doses must be calculated for the individual, including patient-specific estimates of the activity accumulation in relevant tissues and the masses of the tissues in which the radiation energy is absorbed. Although, at present, the evidence for radiobiological dose-effect relationships in radionuclide therapy is limited, it is clear that the absorbed doses delivered are at such levels that the radiobiological effects of primary concern are deterministic tissue reactions and that absorbed doses need to be considered individually [2].

1.1 Radionuclides used in radionuclide therapy

Radionuclides used for therapeutic purposes emit particle radiation, such as electrons from β-decay or alpha particles. Compared to diagnostic applications, most radionuclides used for therapy has a long half-life, in the order of days, in order to match the pharmacokinetic turnover rate of the molecule used for disease targeting. In addition to particle emission the radionuclides often also emit gamma radiation, thus allowing for measurement using gamma-camera imaging (planar or SPECT/CT). In a few cases positron-emitting radionuclides are used, thus enabling PET/CT imaging. The traditionally used, and still most common radionuclide is ^{131}I which disintegrates by β^- decay and has a half-life of 8.0 days [3]. In addition to beta-particles, gamma photons are also emitted with a principal emission of 364 keV. A radionuclide more recently introduced into the clinic is ^{177}Lu, also a β^- emitter with a half-life of 6.6 days. ^{177}Lu emits gamma radiation of 208 keV and 113 keV and is very suitable for gamma camera imaging. ^{90}Y is an almost pure β^- emitter with a half-life of 2.7 days, which is currently mainly used for microsphere treatments in the liver. Although ^{90}Y lacks the emission of gamma photons, the bremsstrahlung emitted during slowing down of electrons can be measured with a gamma camera, and it was rather recently discovered that owing to the low, yet measurable branching for β^+ emission, ^{90}Y can also be measured by PET/CT [4]. The first alpha-emitting radionuclide introduced for systemic radionuclide therapy is ^{223}Ra with a half-life of 11.4 days. Although ^{223}Ra emits gamma-photons, the low amount of activity administered combined with a modest gamma yield make gamma-camera imaging

challenging, but several groups have used an energy window over the characteristic X-rays produced in the collimator with successful imaging as a result [5]. Other beta-emitting radionuclides used for clinical radionuclide therapy include for instance ^{32}P, ^{89}Sr, ^{153}Sm, ^{166}Ho, ^{169}Er, ^{186}Re, and ^{188}Re, and within clinical trials the alpha-emitters ^{225}Ac, ^{227}Th and ^{212}Bi.

1.2 Formalism for absorbed-dose estimation

Following the notations of the MIRD Pamphlet No. 21 [6] the mean absorbed dose $D(r_T)$ to a target region r_T is calculated according to

$$D(r_T) = \sum_{r_s} \tilde{A}(r_s) \cdot S(r_T \leftarrow r_S), \tag{1}$$

where $\tilde{A}(r_s)$ is the time-integrated activity, i.e. the total number of decays occurring in r_S, and $S(r_T \leftarrow r_S)$ is the S value, representing the mean absorbed dose given to target tissue r_T per unit of time-integrated activity. The factor $\tilde{A}(r_s)$ is obtained as the time integral of the activity $A(r_s, t)$ from the time of administration to a time T when then exposure ends, following

$$\tilde{A}(r_s) = \int_0^T A(r_s, t)\, \mathrm{d}t, \tag{2}$$

where usually the time T is set to infinity. The calculation of $\tilde{A}(r_s)$ from measured activities $A(r_s, t)$ can be made using numeric integration, or by fit of a time-activity curve to $A(r_s, t)$ and then integrate analytically based on the fit parameters of this curve. The factor $S(r_T \leftarrow r_S)$ is defined according to

$$S(r_T \leftarrow r_S) = \frac{1}{M(r_T)} \sum_i E_i \cdot Y_i \cdot \phi(r_T \leftarrow r_S,\, E_i) \tag{3}$$

where E_i and Y_i represent the energy emitted and the corresponding yield, as obtained from reference radionuclide data[15]. The absorbed fraction ϕ is a geometry- and radionuclide-specific factor that describes the fraction of radiation energy emitted within the source tissue r_S that is absorbed in a target tissue r_T. The factor M represents the mass of the target region r_T for which the absorbed dose is calculated. For cases where the target-region mass

[15] Laboratoire National Henri Bequerel http://www.nucleide.org/DDEP_WG/DDEPdata.htm or Brookhaven National Laboratory https://www.nndc.bnl.gov/mird/

or the geometry change during the exposure the factors M and ϕ are time-dependent, thus rendering also the S value to be time dependent.

The S values are specific for each radionuclide and source-target combination, and are calculated by means of Monte-Carlo calculations. Precompiled S values for a human-like geometry were made available in the 1970ties and were based on analytically defined shapes with dimensions taken from the reference man, and assumed uniform distribution of activity in source regions. These have later been developed and complemented, and the most commonly used set of S values are probably still those made available in the software Olinda v.1 [7]. During the last 20 years, more realistic human-like geometries have been developed, in voxelized, or more flexible nurbs-based representations. In 2016 the ICRP published specific absorbed fractions for updated voxelized phantoms [8], available in a computer program called IDAC-Dose2.1 [9].

In many organs, the kinetic energy of charged particles is nearly fully absorbed in the region where it is emitted. The factor ϕ in Equation 3 is then very near, or equal to unity and the S value is governed by the mass of the target region $M(r_T)$. In order to make the S value patient-specific a mass-scaling needs to be applied, of the reference model organ mass $M_{ref}(r_T)$ to the patient organ mass $M_{pat}(r_T)$. For charged particle radiation this mass-scaling follows from

$$S(r_T \leftarrow r_S)_{pat} = \frac{M_{ref}(r_T)}{M_{pat}(r_T)} \cdot S(r_T \leftarrow r_S)_{ref}, \qquad (4)$$

meaning that the organ mass for the particular patient needs to be estimated, and is often made by anatomic imaging such as CT. Other means to make the S values patient specific are to perform Monte Carlo energy transport calculations directly on the voxel geometry obtained from quantitative SPECT/CT imaging. Depending on the range of the emitted radiation in comparison to the voxel dimensions, and the spatial resolution of the imaging system, such voxel-based calculations can be simplified for alpha- and beta particles. The assumption of local-energy deposition, i.e. that the particle energy is fully absorbed in the same voxel as where it was emitted, can often be made with negligible loss of accuracy. The photon contribution to the absorbed dose may still need to be estimated by use of an S value or patient-specific Monte Carlo calculations.

The other factor that needs to be estimated patient-specifically is the time-integrated activity (Equation 1) which, in turn, requires repeated measurements of the activity residing in different organs and tissues at different times (Equation 2). Thus, in order to arrive at patient-specific estimates of the absorbed doses, two parameters need to be estimated for the individual patient; the activity as a function of time, and the mass of the tissue in which the radiation energy is absorbed. The number of activity measurements to perform is intimately related to the pharmacokinetics of the radiopharmaceutical, and in order to

appropriately capture the entire washout phase repeated measurements over several days are often required.

2 Metrological techniques used for dosimetry

2.1 The activity meter as a reference instrument

The activity meter, sometimes called dose calibrator, can be considered as a reference instrument in radionuclide therapy. It is used for determination of the activity administered to patients, and generally also for calibration of the instruments used for both radiochemistry and dosimetry. Thus, the activity meter is the instrument that provides the connection between the activities and absorbed doses measured at each individual centre, to the SI-derived quantities activity and absorbed dose.

Activity meters are typically constructed as well-shaped ionization chambers filled with highly pressurized inert gases. When a radioactive source is placed in the well chamber the gas is ionized, thus inducing a current that ideally is linearly related to the source activity. The chamber response, i.e. the current induced per amount of activity in the source, depends strongly on the emission spectrum of the particular radionuclide. In addition, the response may be sensitive to the source geometry, i.e. whether it is a vial or a syringe, the source volume, and in some cases the rate of exposure, i.e. the amount of activity. Thus, the calibration factor for the activity meter needs to be determined for each radionuclide and each measurement situation. The traceability to a standard laboratory needs to be established for at least one reference geometry, by purchasing a source along with a certificate that states the source activity and how traceability of the activity measurement is assured. Cross-calibration to other geometries can then be made, starting from this reference calibration factor.

Even if traceable calibration is available for a standard source used for constancy checks, such as ^{137}Cs, this does not imply that activity measurements are traceable for other, therapeutic radionuclides such as ^{131}I, ^{177}Lu, or ^{90}Y. Moreover, considering the high absorbed doses given in radionuclide therapy even a small fractional deviation in the calibration factor may result in a considerable difference in the absorbed doses given. Of concern, it was noted by the Bureau International des Poids et Mesures (BIPM) that a standard of the Becquerel is not available in all European countries[16] .

2.2 Techniques for in-vivo activity measurements and dosimetry

The choice of measurement technique for a particular kind of radionuclide therapy largely depends on the emission spectrum of the radionuclide, the tissue that is considered to be at

[16] https://www.bipm.org/utils/en/pdf/BIPM-services-ionizing-radiation.pdf

risk and for which dosimetry is needed, and the practical possibilities for performing repeated measurements after administration.

2.2.1 Dosimetry of the whole body and thyroid based on probe activity measurements

Whole-body dosimetry has been found useful in particular for therapies using ^{131}I-labelled radiopharmaceuticals. The high yield of photon emission for ^{131}I results in an exposure of the whole body, including the radiosensitive bone marrow. In some applications the whole-body absorbed dose has thus successfully been used as a surrogate of bone marrow absorbed dose [10]. In this case, measurement of the whole-body activity can be made using probe detectors, such as scintillation detectors or survey meters. The factor for converting from the meter reading to activity is commonly determined by making a first measurement shortly after the administration, before the patient has voided, and normalizing this reading to the administered activity. The mass $M_{pat}(r_T)$ in Equation 4 is then taken as the patient weight.

Probe-based measurements are also used for dosimetry in benign thyroid disease [11]. As [^{131}I]NaI is accumulated in the thyroid, with little or no activity in nearby surrounding tissues, the count rate detected in a scintillation detector placed at a well-defined distance from the patient neck can be considered to originate from activity in the thyroid. The conversion from the detected count rate to activity is usually accomplished by a measurement of activity in a phantom, constructed to represent the depth and geometry of the thyroid in the neck. The mass $M_{pat}(r_T)$ in Equation 4 is obtained from separate measurements using ultrasound, or ^{99m}Tc-pertechnetate gamma-camera imaging.

2.2.2 Dosimetry of the bone marrow based on activity measurement of blood

Dosimetry based on blood samples has been applied for estimating the absorbed dose to bone marrow, either as a surrogate measure using the blood absorbed dose, or by calculation of the fraction of the plasma activity that enters the interstitial space of the red marrow [12-14]. Measurement of low activity concentrations such as those in plasma or blood are preferentially made using a spectroscopic well scintillation detector.

2.2.3 Image-based dosimetry for organs and tumours

For internal organs such as kidney, liver, lungs, and for tumours, image-based dosimetry is preferred. Many of the radionuclides used in radionuclide therapy, such as ^{131}I and ^{177}Lu, are well suited for gamma-camera imaging as they emit photons in the energy range where the sensitivity of clinical cameras is sufficiently high and collimators are available. Owing to the lack of gamma-emission, imaging of ^{90}Y is more challenging with standard gamma-camera techniques, although the bremsstrahlung emitted at the beta-particle interactions can be used when advanced correction methods are available. Owing to the small emission of positrons in the ^{90}Y decay PET/CT has become the method used in most centres.

While gamma cameras may be used for dosimetry both in planar and tomographic SPECT/CT mode, PET/CT always produce tomographic images. Planar scintigraphy has the drawback in that the activity distribution is only resolved in two dimensions, while the depth dimension is unresolved. Thus, activity residing in tissues that overlap each other in the projection image cannot be separated. An advantage with whole-body scintigraphy is however that the whole body can be covered with a reasonably short imaging duration, which is useful for radionuclide therapies where the whole body needs to be monitored. Tomographic imaging by SPECT/CT or PET/CT has the advantage of providing three-dimensional images, which when overlaid on the anatomic images from CT, yield a solid basis for accurate dosimetry.

For quantitative SPECT/CT and PET/CT imaging, a key element for the image formation is the tomographic reconstruction. The acquired raw data consist of counts in a set of two-dimensional angular projections, acquired over at least 180 degrees. Each data bin in the projections represents the camera response to photons that are emitted from the internal activity distribution and are transmitted along the line of response for the particular bin position. By tomographic reconstruction, the three-dimensional distribution of the activity concentration in different positions in the patient is calculated. Ideally, the response represented in each data bin would be proportional to the line integral of the number of radioactive decays occurring in positions along the line of response during the image acquisition. However, due to physical effects such as photon attenuation and scatter, and for some radionuclides collimator-septal penetration, this is not the case. So, in order to make the reconstructed images quantitatively accurate, corrections for these physical effects are required. Contemporary imaging systems use iterative tomographic reconstruction methods that embed corrections for attenuation and scatter. The CT image is then used to estimate the distribution of the attenuating properties of the tissues in the patient, and for some methods also the tissue scattering properties.

An additional intrinsic limitation for nuclear-medicine imaging devices is the limited spatial resolution that modulates high-frequency components of the signal, thus producing blurry images in which the counts are spread over a volume larger than the real volume and information about small details and sharp edges is lost. This effect, the partial-volume effect (PVE), can to some extent be mitigated by incorporation of resolution modelling and compensation in the iterative reconstruction, thus producing somewhat less blurry images. However, even when resolution modelling is included in the reconstruction it is not possible to completely recover all spatial details that are lost due to limited resolution. For quantitative imaging, the application of a post-reconstruction correction factor is then needed, termed the partial-volume correction.

Ideally, when all compensations embedded in the iterative reconstruction are accurate, the image values in the reconstructed image represent the counts that would have been recorded if the activity distribution were located in air (or vacuum). In order to convert from counts to activity a calibration factor needs to be applied. To analyse the counts in a

particular organ or tissue (a source region), volumes-of-interest (VOIs) are delineated in the image, either manually or by some semi-automatic segmentation method. The factor for PVE correction is usually applied after the volumes-of-interest have been delineated in the image. Thus, the expression for obtaining the activity from a reconstructed image becomes

$$A(r_S) = \frac{C_{VOI}}{\tau} \cdot \frac{1}{\epsilon} \cdot \frac{1}{p_{VOI}} \quad (5)$$

where C_{VOI} are the reconstructed counts in a VOI, τ is the acquisition time interval in unit of seconds, ϵ is the calibration factor in unit of counts-per-second per MBq. The factor p_{VOI} is the correction factor for PVE, which takes values between zero and one depending on the object volume, shape, and internal activity distribution. The method for determination of the calibration factor ϵ is standardized for PET/CT and is determined from a reconstructed image of a PET/CT study of a cylindrical phantom with a uniform activity solution. For SPECT/CT the calibration method is currently not standardized and has been approached in different ways, either by calibration of the planar-image projections, by the assumption that the tomographic reconstruction accurately propagates the detected counts from the projections to the reconstructed image, or by a method similar to that for PET/CT. Initiatives are currently taken to standardize also quantitative SPECT/CT calibration. In a cross-European project led by the European metrology institutes, the latter method was deemed to be the most clinically feasible[17].

Image based dosimetry forms a complex measurement chain, and it was not until recently that studies of the combined uncertainty were published, approached by analytical or Monte Carlo-based propagation methods [15, 16].

2.2.4 Examples of the application of image based dosimetry

The radiopharmaceutical [^{177}Lu]Lu-DOTA-TATE has now obtained marketing authorization by the European Medicines Agency for the treatment of unresectable or metastatic, progressive, well differentiated somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours. Another expanding radiopharmaceutical currently in clinical trial is [^{177}Lu]Lu-PSMA-617 for the treatment of metastatic castration-resistant prostate cancer. Both [^{177}Lu]Lu-DOTA-TATE and [^{177}Lu]Lu-PSMA-617 are given as multi-cycle treatments. Principal organs at risk are considered to be the kidneys and bone marrow, and for [^{177}Lu]Lu-PSMA-617 also the salivary glands. For [^{177}Lu]Lu-DOTA-TATE observations of absorbed-dose related incidence of bone marrow toxicity and tumour effects have been reported [17, 18] as well as long-term hematologic effects [19]. The pharmacokinetics of small molecules such as peptides is governed by a comparably initial fast extravasation followed by an active uptake in tissues expressing the target protein. The absorbed dose to lesions and normal organs following administration can be performed using serial quantitative SPECT/CT imaging, or a

[17] http://mrtdosimetry-empir.eu/

combination of SPECT/CT and serial planar imaging. The timing of imaging sessions should be adopted to cover the time interval of the active uptake, which delivers the major part of the absorbed dose, and acquisitions are typically made at 1 d, 2d – 3d, and preferably a later time point at approximately 1 week [20]. The SPECT/CT images are processed according to procedures outlined above and the activity in source regions quantified according to Equation 5. For organs, the patient-specific mass in Equation 4 is estimated by delineation in the CT image, whereas for tumours the most common approach is to apply S values valid for a sphere with a volume corresponding to the particular lesion volume. For solid organs, the time-integration (Equation 2) is typically made by assuming mono-exponential washout, whereas for bone-marrow, a bi-exponential plasma curve has been assumed.

Radioembolization using ^{90}Y-microspheres is used for the treatment for unresectable liver cancers. The administration route differs from those above, in that the ^{90}Y-microspheres are delivered locally into the arterial hepatic vasculature. The selection principle between healthy liver and tumour tissue is based on the different routes of blood supply to these tissues. There is an increasing amount of evidence for dose-effect relationships, both for normal liver parenchyma and different tumour types such as hepatocellular carcinoma, neuroendocrine tumour metastases, and colorectal cancer metastases, see [21] for a recent review. The measurement technique used for quantification of the ^{90}Y activity in normal liver and tumours is based on either bremsstrahlung SPECT/CT or PET/CT. Owing to the local deposition of the ^{90}Y-microspheres and the permanent entrapment, the calibration from the reconstructed count rate into activity can be made by measuring the total counts in the liver, and dividing by administered activity. Moreover, the dose-rate pattern is completely governed by the ^{90}Y physical decay, and one single image acquisition is sufficient to determine time-integrated activity. The mass of the target regions is preferably estimated based on contrast-enhanced CT, combined with the SPECT/CT or PET/CT image of the ^{90}Y distribution.

3 European survey

The Internal Dosimetry Task Force (IDTF) was formed within the European Association of Nuclear Medicine (EANM) to address aspects of Council Directive 2013/59/Euratom specifically concerned with dosimetry for radionuclide therapy. Within the work of this task force, it was noted that the extent and practice of dosimetry implementation in Europe is poorly mapped, and an electronic survey was undertaken. Details of the survey results were reported in [22]. In addition, the IDTF produced a report with the aim to examine the potential for personalised, dosimetry-based treatment planning and verification of the

absorbed dose delivered, available at the EANM web site[18]. A summary of this report was also published [23].

The survey explicitly considered 18 different kinds of radionuclide therapies (Table 1), as well as other therapies, given in 2015. From the 208 responding centres, spread across 26 countries, the total number of therapies was reported to 42,853. The number of responding centres were estimated to represent approximately 20 % of the total number of centres that offer radionuclide therapy. The most frequently given therapies were [^{131}I]NaI for benign thyroid diseases (34 %), [^{131}I]NaI for thyroid remnant ablation of adults (26 %), [^{131}I]NaI for thyroid cancer therapy for adults (11 %) and [^{223}Ra]$RaCl_2$ (Xofigo®) for bone metastases (10 %). The most frequent implementation of dosimetry was for tumours in the liver with ^{90}Y-microspheres, [^{131}I]mIBG for neuroblastoma, and [^{131}I]NaI for benign thyroid diseases. However, when looking at the percentage of responses that stated that dosimetry was included on an always/majority basis, the median over all treatments was only 36 %. Most concerning was perhaps that for 32 % of the therapies given, responders stated that a medical physicist was never or rarely involved (average over all treatments). Without the involvement of a medical physicist, the likelihood that dosimetry will be implemented is probably low.

As concluded in the discussions within the IDTF, and as judged by the responses, there were sometimes difficulties related to the terminology used within the field. For instance, for radionuclide therapies given in a planned sequence of cycles, the word “treatment” may indicate each cycle or the sequence of cycles. On the question on the involvement of a medical physicist, the term “involved”, which is also used in the Directive 2013/59/Euratom, would need specification. Moreover, in a radiotherapy modality that uses pharmaceuticals for its delivery the word “dose” can be used in different ways, and the use of the correct name of the SI-derived quantity absorbed dose is of importance. Of note and with possible serious implications, during response analysis it became evident that some responders did not understand the difference between a “dose” (in grams or millilitres) and an absorbed dose (in gray).

[18] https://www.eanm.org/publications/idtf-report/

Therapy type	Percent of treatments
[^{131}I]NaI for benign thyroid diseases	34
[^{131}I]NaI for thyroid remnant ablation of adults	26
[^{131}I]NaI for thyroid remnant ablation of children and young adults	0.43
[^{131}I]NaI for thyroid cancer therapy for adults	11
[^{131}I]NaI for thyroid cancer therapy for children and young adults	0.37
[^{131}I]mIBG for neuroblastoma	0.26
[^{131}I]mIBG for adult neuroendocrine tumours	0.24
^{177}Lu-somatostatin analogues for neuroendocrine tumours	5.6
^{90}Y-somatostatin analogues for neuroendocrine tumours	4.5
^{177}Lu-PSMA therapy of castration resistant prostate cancer	0.85
^{90}Y-resin microspheres (SIR-Spheres®) for intra-arterial treatments in the liver	2.8
^{90}Y-glass microspheres (TheraSphere®) for intra-arterial treatments in the liver	0.92
Radiation synovectomy using ^{90}Y-, ^{186}Re- or ^{169}Er-colloids	2.2
[^{153}Sm]EDTMP (Quadramet®) for bone metastases	0.59
[^{89}Sr]$SrCl_2$ (Metastron®) for bone metastases	0.10
[^{223}Ra]$RaCl_2$ (Xofigo®) for bone metastases	10
^{32}P-Sodium-Orthophosphate for myeloproliferative disease	0.32
[^{90}Y]Y-ibritumomab-tiuxetan (Zevalin®) for B-cell lymphoma	0.10

Table 1. *Radionuclide therapies explicitly considered in the survey, and the percentage of the respective treatment given, with respect to all reported treatments*

4 Summary and conclusions

Radionuclide therapy covers a range of indications, and probably has its largest benefit in the possibility to treat metastasized disease. In many kinds of radionuclide therapy, it is feasible to undertake dosimetry for the individual patient. The applied measurement techniques span from ordinary detector probes to SPECT/CT or PET/CT tomographic imaging, and may consider the whole body, blood, or specific tissues such as kidneys, liver, bone marrow, and tumours. The choice of technique in a particular situation largely depends on the emission spectrum of the radionuclide, and which tissue is considered to be at risk and for which dosimetry is needed. Irrespective of the metrological technique used, there is a need for accurate activity measurements of both the amount injected to patients, and for calibration of the instruments used for in-vivo activity quantification and dosimetry.

Traceable measurements of the activity of therapeutic radionuclides then need to be established, which currently is not the case in all European centres. Radionuclide therapy is multi-disciplinary and requires the engagement of different medical specialties. In order to implement dosimetry, medical physicists need to be closely involved. Although the implementation of dosimetry has been the slowest to develop among radiotherapy modalities, the data and evidence of study dose-effect relationships in radionuclide therapy is gathering from research-oriented clinical centres [2]. Yet, the absorbed doses delivered, and their relation to the risks of toxicity and the probability of treatment effects, are poorly understood. Had dosimetry been implemented to a greater extent, it would provide a foundation for a better understanding of the radiation risks involved and, likely, an improved optimization.

5 References

[1] R. Loeevinger and M. Berman, A schema for absorbed-dose calculations for biologically-distributed radionuclides, *J Nucl Med,* pp. Suppl 1:9-14, Feb 1968.

[2] L. Strigari, M. Konijnenberg, C. Chiesa, M. Bardies, Y. Du, K. S. Gleisner, M. Lassmann, and G. Flux, The evidence base for the use of internal dosimetry in the clinical practice of molecular radiotherapy, *Eur J Nucl Med Mol Imaging,* vol. 41, no. 10, pp. 1976-88, Oct 2014.

[3] C. V. Bé M, Duileu C, Kellett M, Mougeot X, Arinc A, Chechev V, Kuzmenko N, Kibédi T, Luca A, Nichols A. Table of Radionuclides [Online].

[4] R. Lhommel, L. van Elmbt, P. Goffette, M. Van den Eynde, F. Jamar, S. Pauwels, and S. Walrand, Feasibility of 90Y TOF PET-based dosimetry in liver metastasis therapy using SIR-Spheres, (in eng), *Eur J Nucl Med Mol Imaging,* vol. 37, no. 9, pp. 1654-62, Aug 2010.

[5] C. Hindorf, S. Chittenden, A. K. Aksnes, C. Parker, and G. D. Flux, Quantitative imaging of 223Ra-chloride (Alpharadin) for targeted alpha-emitting radionuclide therapy of bone metastases, *Nucl Med Commun,* vol. 33, no. 7, pp. 726-32, Jul 2012.

[6] W. E. Bolch, K. F. Eckerman, G. Sgouros, and S. R. Thomas, MIRD pamphlet No. 21: a generalized schema for radiopharmaceutical dosimetry--standardization of nomenclature, (in eng), *J Nucl Med,* vol. 50, no. 3, pp. 477-84, Mar 2009.

[7] M. G. Stabin, R. B. Sparks, and E. Crowe, OLINDA/EXM: the second-generation personal computer software for internal dose assessment in nuclear medicine, *J.Nucl.Med.,* vol. 46, no. 6, pp. 1023-1027, 2005.

[8] ICRP, ICRP Publication 133. The ICRP computational framework for internal dose assessment for reference adults: specific absorbed fractions, *Ann ICRP,* vol. 45, no. 2, p. 74, 2016.

[9] M. Andersson, L. Johansson, D. Minarik, S. Mattsson, and S. Leide-Svegborn, An internal radiation dosimetry computer program, IDAC 2.0, for estimation of patient doses from radiopharmaceuticals, *Radiat Prot Dosimetry,* vol. 162, no. 3, pp. 299-305, Dec 2014.

[10] S. E. Buckley, S. J. Chittenden, F. H. Saran, S. T. Meller, and G. D. Flux, Whole-body dosimetry for individualized treatment planning of 131I-MIBG radionuclide therapy for neuroblastoma, (in eng), *J Nucl Med,* vol. 50, no. 9, pp. 1518-24, Sep 2009.

[11] H. Hanscheid, C. Canzi, W. Eschner, G. Flux, M. Luster, L. Strigari, and M. Lassmann, EANM Dosimetry Committee Series on Standard Operational Procedures for Pre-Therapeutic Dosimetry II. Dosimetry prior to radioiodine therapy of benign thyroid diseases, *Eur J Nucl Med Mol Imaging,* Apr 11 2013.

[12] M. Lassmann, H. Hanscheid, C. Chiesa, C. Hindorf, G. Flux, M. Luster, and E. D. Committee, EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry I: blood and bone marrow dosimetry in differentiated thyroid cancer therapy, *Eur J Nucl Med Mol Imaging,* vol. 35, no. 7, pp. 1405-12, Jul 2008.

[13] G. Sgouros, Bone marrow dosimetry for radioimmunotherapy: theoretical considerations, *J Nucl Med,* vol. 34, no. 4, pp. 689-694, 1993.

[14] C. Hindorf, G. Glatting, C. Chiesa, O. Linden, and G. Flux, EANM Dosimetry Committee guidelines for bone marrow and whole-body dosimetry, (in eng), *Eur J Nucl Med Mol Imaging,* vol. 37, no. 6, pp. 1238-50, Jun 2010.

[15] J. I. Gear, M. G. Cox, J. Gustafsson, K. S. Gleisner, I. Murray, G. Glatting, M. Konijnenberg, and G. D. Flux, EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations, *Eur J Nucl Med Mol Imaging,* Sep 14 2018.

[16] J. Gustafsson, G. Brolin, M. Cox, M. Ljungberg, L. Johansson, and K. S. Gleisner, Uncertainty propagation for SPECT/CT-based renal dosimetry in (177)Lu peptide receptor radionuclide therapy, *Phys Med Biol,* vol. 60, no. 21, pp. 8329-46, Nov 7 2015.

[17] L. Hagmarker, J. Svensson, T. Ryden, M. van Essen, A. Sundlov, K. Sjogreen Gleisner, P. Gjertsson, and P. Bernhardt, Bone marrow absorbed doses and correlations with hematological response during (177)Lu-DOTATATE treatments are influenced by

image-based dosimetry method and presence of skeletal metastases, *J Nucl Med,* Mar 22 2019.

[18] E. Ilan, M. Sandstrom, C. Wassberg, A. Sundin, U. Garske-Roman, B. Eriksson, D. Granberg, and M. Lubberink, Dose response of pancreatic neuroendocrine tumors treated with peptide receptor radionuclide therapy using 177Lu-DOTATATE, *J Nucl Med,* vol. 56, no. 2, pp. 177-82, Feb 2015.

[19] H. Bergsma, K. van Lom, M. Raaijmakers, M. Konijnenberg, B. Kam, J. J. M. Teunissen, W. W. de Herder, E. P. Krenning, and D. J. Kwekkeboom, Persistent Hematologic Dysfunction after Peptide Receptor Radionuclide Therapy with (177)Lu-DOTATATE: Incidence, Course, and Predicting Factors in Patients with Gastroenteropancreatic Neuroendocrine Tumors, *J Nucl Med,* vol. 59, no. 3, pp. 452-458, Mar 2018.

[20] A. Sundlov, K. Sjogreen-Gleisner, J. Svensson, M. Ljungberg, T. Olsson, P. Bernhardt, and J. Tennvall, Individualised 177Lu-DOTATATE treatment of neuroendocrine tumours based on kidney dosimetry, *Eur J Nucl Med Mol Imaging,* Mar 22 2017.

[21] R. Bastiaannet, S. C. Kappadath, B. Kunnen, A. Braat, M. Lam, and H. de Jong, The physics of radioembolization, *EJNMMI Phys,* vol. 5, no. 1, p. 22, Nov 2 2018.

[22] K. Sjogreen Gleisner, E. Spezi, P. Solny, P. M. Gabina, F. Cicone, C. Stokke, C. Chiesa, M. Paphiti, B. Brans, M. Sandstrom, J. Tipping, M. Konijnenberg, and G. Flux, Variations in the practice of molecular radiotherapy and implementation of dosimetry: results from a European survey, *EJNMMI Phys,* vol. 4, no. 1, p. 28, Dec 4 2017.

[23] C. Stokke, P. M. Gabina, P. Solny, F. Cicone, M. Sandstrom, K. S. Gleisner, C. Chiesa, E. Spezi, M. Paphiti, M. Konijnenberg, M. Aldridge, J. Tipping, M. Wissmeyer, B. Brans, K. Bacher, C. Kobe, and G. Flux, Dosimetry-based treatment planning for molecular radiotherapy: a summary of the 2017 report from the Internal Dosimetry Task Force, *EJNMMI Phys,* vol. 4, no. 1, p. 27, Nov 21 2017.

Radiation protection issues in radionuclide therapy – workers (medical staff), third persons, waste management

Ritva Bly

Radiation and Nuclear Safety Authority (STUK), Helsinki, Finland

Summary

Radionuclide therapies for treatment of diseases is common practice worldwide, while new radionuclides create new challenges for radiation protection. Many guidelines are still applicable for implementing dose constraints, using appropriate calibrated instruments for dose rate and contaminations measurements and following good practices of waste management.

Special caution and considerations are needed to prevent annual dose limits to be exceeded in some situations with new radionuclide therapies. In fractionated therapies, dose constraints should be set considering anticipated repetition of the treatment. In handling of alpha emitters all contamination pathways need to be considered and training of workers is essential both to prevent contamination and to detect and measure contaminations. Waste management is an issue if there are radionuclides of long half-lives considering also possible impurities. In case there is a need for cremation after a radionuclide therapy with alpha emitters, it may be necessary to wait even several months prior to cremation.

1 Introduction

There is a clear trend towards increased therapeutic applications in modern nuclear medicine worldwide according to UNSCEAR [1]. New radionuclide therapies include either beta or alpha emitters and typically there is also gamma radiation of several energies. Radiation protection of these beta emitters have similarities with well guided radiation protection for ^{131}I, but there are new challenges with new radionuclide therapies.

There are three main international guidelines for radiation protection of workers and third persons in connection with the radionuclide therapies: the EU Radiation Protection 97 “Radiation Protection following Iodine-131 therapy (exposures due to out-patients or discharged in-patients)” [2], the ICRP Publication 94 “Release of patients after therapy with unsealed radionuclides” [3] and the IAEA Safety Report Series No. 63: “Release of Patients After Radionuclide Therapy” [4] that was prepared together with the ICRP Committee 3

members. These guidelines were published more than ten years ago and thus do not cover radiation protection for the latest radionuclide therapies. However, these guidelines are well established, and the radiation protection principles and methodology can still be applied in many cases especially in radionuclide therapies involving beta and gamma radiation.

In this paper, some general guidelines for radiation protection are reviewed and detailed considerations for radiation protection of some important radionuclides for radionuclide therapies are discussed.

2 General guidelines

2.1 Dose limits and dose constraints

Dose limits are issued in the Council Directive 2013/59/EURATOM (Basic Safety Standards Directive, BSS Directive) [5]. A dose constraint is defined in the BSS Directive to mean a constraint set as a prospective upper bound of individual doses, used to define the range of options considered in the process of optimization for a given radiation source in a planned exposure situation. The establishment of dose constraints is required in Article 6 for occupational, public and medical exposure of carers and comforters and volunteers participating in medical or biomedical research. In Article 56.3 for each medical or biomedical research project involving medical exposure dose constraints are required for individuals for whom no direct medical benefit is expected from exposure; and in Article 56.5 for exposure of carers and comforters, where appropriate.

Typically used dose constraints for the exposure of carers and comforters are 3 or 5 mSv, however for persons over 60-year-old dose constraints up to 15 mSv have been used in Europe [2]. The dose to children visiting patients who have ingested radioactive materials should be constrained to be less than 1 mSv [2]. The situation concerning dose constraints for young and very young children is complicated by the fact that they may not be able to give informed consent to be involved.

There is a new challenge with fractionated therapies. Typically, dose constraints for workers and the public are set on the basis that dose from one source would be 1/3 of the annual dose limit. Especially, for the members of the public the dose constraint is set per episode, but new therapies are given often in few fractions that should be considered in setting dose constraints. Moreover, dose constraints for carers and comforters should be set considering the fractionation of the treatment when radiation protection measures for the first fraction are planned.

One more issue is the cremation after a radionuclide therapy with alpha emitters. It may be necessary to wait even several months before the calculated dose to a representative person is below a public dose limit or a dose constraint. It may not be known to another hospital or

third persons that the deceased person has recently had a radionuclide therapy. For that reason, it is recommended to provide a patient after a radionuclide therapy a credit card sized document of the relevant details of the treatment to be carried along during a pre-specified time period [4, 6].

2.2 Dose rate measurements and instrument calibration

Most of the radionuclides used in therapy emit beta particles, which have low tissue penetration. Often, they also emit Auger electrons, gamma rays and/or characteristic X-rays. New radionuclide therapies may also emit alpha particles.

Radiation protection of workers and third persons is often based on dose rate measurements. The BSS Directive [5] requires in Article 34 undertakings to seek advice from the radiation protection expert on regular calibration of measuring instruments and regular checking that they are serviceable and correctly used. In Article 68, the undertakings are required to check the effectiveness and maintenance of equipment in the acceptance of them and ensure the regular calibration of measuring instruments. In the metrology system, a calibration should always be traceable to a primary standard.

The uncertainty of the calibration should be stated in the calibration certificate. In the use of meters measurement situations are typically different from the calibration conditions and that causes additional uncertainty to the measurements. Differences can be for example in the energy range to be measured compared to the calibration, level of the dose rate and the measurement geometry. As a rule of thumb, the uncertainty of the measurement is three times of the uncertainty of the calibration. For example, if the uncertainty of the calibration is 5 % then the uncertainty of the measurement can be assessed to be of 15 %. Thus, a reading of 30 µSv/h in the measurement instrument means in fact a result in the range of 25-35 µSv/h. An uncertainty even higher than 15 %, even up to 60 %, can sometimes be acceptable in dose rate measurements. The uncertainty increases when the measured dose rate is near the background level. The uncertainty should be considered if dose rate measurements are used for comparing to dose constraints or dose limits.

2.3 Contamination pathways and measurement of contamination in radionuclide therapy

In the handling of unsealed sources, there is always a risk of contamination. Moreover, excretory pathways for radionuclides administered in therapy may also lead to contamination. These pathways include urine, faeces, saliva, sweat, lachrymal fluid and breast milk. There are differences in clearance rates between radiopharmaceuticals but also for the same radiopharmaceutical in different patients. A common rule of thumb is to assume that no more than one millionth of the activity being handled will become an intake to an individual working with the material. The risk of contamination with radionuclides is generally low but not negligible. Usually, for adult relatives of the patient, the internal dose due to ^{131}I contamination is less than 10 % of the external dose [4].

It has been calculated that the effective dose, from air contamination, for carers and comforters of cancer patients treated on an outpatient basis with ^{131}I could be up to 6.5 mSv and could, thus, exceed the 1 mSv public annual dose limit [7]. However, the dose limit does not apply to comforters and carers, but a dose constraint should be applied as discussed in paragraph 2.1 above. Furthermore, after three days of hospitalization, the risk of exceeding the dose limit for the public in this way at home is typically eliminated. After hospitalization, contamination measurements at the patient's room are essential measures to verify radiation safety of workers and third persons.

In Article 68 of the BSS Directive [5], the undertakings are required to accept into service adequate equipment and procedures for measuring and assessing exposure of members of the public and radioactive contamination of the environment. Adequate equipment is equipment that is suitable for measuring the required quantity for the radiation quality (beta and/or alpha radiation) at the relevant energy range and useable in the measurement conditions. A display of pulse count rate should not be mixed with the display of dose rate.

The equipment must detect at least such small activities that are on the level of contamination limits. If there are several radionuclides in the area or object to be measured and the equipment cannot distinguish between them, it is not possible to verify which radionuclide or radiation has been measured.

Common equipment for the detection of beta radiation are Geiger-Müller (G-M) detectors with a thin window (typically the thickness is about 2 mg/cm^2), plastic scintillation detectors and proportional counters. Some dual alpha and beta contamination probes can separate alpha and beta radiation and display the results on two different channels [8].

The alpha contamination can be measured directly with a measurement equipment or indirectly using a wipe test. The window of a measurement equipment should be very thin (about 1 mg/cm^2). Typical detectors are of zinc sulfide, a dual probe with zinc sulfide and a plastic scintillation detector and a Geiger-Müller detector with a mica-window. However, the G-M detector cannot distinguish between radiation qualities. The detector should be positioned at a maximum distance of 1 cm from the measured area/object and should be moved slowly over the area/object to be measured. The area of the detector window should be large enough to ensure minimum detection limits lower than the contamination limits [8].

2.4 Waste management

The waste management in nuclear medicine should follow the general principles and good practices for radioactive waste management. The generating of waste should be minimized, the waste should be segregated, packages should be labelled, and the waste should be stored for decaying. Typically, the radioactive waste should be stored for a minimum period of about 10 half-lives when after decay only 0.1 % of the initial activity remains. The exemption and clearance values of the BSS Directive [5] should be applied.

Some countries require short-term storage of hospital waste (usually urine only) containing radionuclides from hospitalized therapy patients until the activity has reached a particular level. However, ICRP states that radionuclides released into modern sewage systems are likely to result in doses to sewer workers and the public that are well below public annual dose limits [3].

There is a challenge in the waste management of a few new radionuclide therapies due to some radionuclides with long half-lives. These radionuclides may exist as impurities because of the manufacturing process. New ways of producing these radionuclides have been developed to remove this problem, however end users may not be aware of the origin of the radionuclide.

3 Detailed guidelines for radionuclide therapies with various radionuclides

3.1 Beta particle therapies

In use of pure beta particle emitters, with their lower tissue penetration, there is no exposure to workers, the public or third persons through external radiation in therapies. Concern for the radiation safety of carers and comforters, workers, third persons and the public is primarily related to the handing of radionuclides and patient's excreta and body fluids.

Guidelines are also available for radiation protection in a situation when the patient dies in the period immediately following therapy. Special consideration may need to be given to the autopsy or the treatment of the corpse. Corpse activity limits are suggested by IAEA for ^{32}P, ^{89}Sr, ^{90}Y, ^{131}I and ^{198}Au [4].

Phosphorus-32

Phosphorus-32 is in the form of sodium phosphate. The half-life is 14.3 d. An example of intracavitary therapy is ^{32}P chromic phosphate for treatment of malignancies of the pleural and peritoneal cavities and intra-articular administration for synovectomy. Phosphorus-32 is also used to treat polycythaemia.

Urinary excretion in the 48 hours following administration is significant, which requires care. Phosphorus-32 can migrate through the skin and is difficult to remove if contamination occurs. Toilet practices should follow those for ^{131}I therapy of benign thyroid disease. Advice for emergencies is as for ^{131}I therapy of benign thyroid disease [4].

Strontium-89

Strontium-89 is in the form of strontium chloride. The half-life is 50.5 d. ^{89}Sr treatment is used for bone metastases. Urinary excretion of unbound material occurs in the 48 hours following administration. The main issue in radiation protection is urinary excretion. When conducted on an outpatient basis, the patient should be kept in hospital until at least one or two post-administration bladder voidings occur. Special arrangements may be required for incontinent patients. Toilet practices, as well as practices for cutlery, crockery, laundry and advice for emergencies, are as for ^{131}I therapy of benign thyroid disease [4].

Yttrium-90

Yttrium-90 has a half-life of 2.7 d. Y-90 SIRT (Selective Internal Radiation Therapy) therapy is a treatment for cancers and tumours that are located within the liver. The aim of this treatment is to reduce tumour size in inoperable tumours or decrease the number of lesions in the liver. Microspheres are of glass or resin and their diameter is 20-60 micrometers. Also, ^{90}Y colloid is used for radiation synovectomy. Excretion of ^{90}Y is minimal to none. No special precautions need to be taken by patients and families other than for emergencies. The low level of external radiation, and short half-life means that post-discharge safety issues do not normally arise. Advice for emergencies is as for ^{131}I therapy of benign thyroid disease [4].

3.2 Beta particle therapies with gamma radiation

Iodine-131

Iodine-131 is a beta and gamma emitter and average gamma energy is 364 keV. The half-life is 8.0 d. Iodine-131 sodium iodide is commonly used for hyperthyroidism or thyroid cancer. There are also other therapies such as ^{131}I MIBG (meta-iodobenzylguanidine) and ^{131}I labelled lipiodol therapies. Iodine-131 therapies are performed with either the patient hospitalized or as an outpatient only. Safety issues for carers and comforters, workers, third persons and the public arise with either approach. The potential risks are from both external irradiation and contamination. Radioiodine is excreted primarily via the kidneys, and, consequently, the patient should be encouraged to drink water freely to assist clearance. The next most significant pathway is via the salivary glands. This will manifest itself in contamination of eating and drinking utensils, as well as pillow coverings. Lesser pathways for contamination occur in sweat and faeces. Breast milk can contain significant amounts of radioiodine. It is best, if measurements cannot be made, to assume that contamination is present in all pathways.

Guidelines for releasing patients after ^{131}I therapy are given for example by EC [2], ICRP [3] and IAEA [4] including guidelines for radioiodine patients to restrict dose to 1 mSv in co-workers and family, travel time for thyroid cancer patients to restrict public dose to 1 mSv and period during which pregnancy should be avoided following radionuclide therapy.

Samarium-153

Samarium-153 is in the form of EDTMP (ethylene-diamine-tetra-methylene-phosphonate). ^{153}Sm is used for radiation synovectomy. The half-life of ^{153}Sm is 1.9 d and it is a beta and gamma emitter. The gamma emission from ^{153}Sm is not a major concern, because it does not give rise to high dose rate. The main issue is urinary excretion.

Urinary excretion of unbound material occurs in the 48 hours immediately following administration. When conducted on an outpatient basis, the patient should be kept in the hospital until at least one or two post-administration bladder voidings occur. Special arrangements may be required for incontinent patients. No special radiation safety precautions are required. However, based on ICRP advice, some practitioners suggest that pregnant women and children should remain at arm's length for two days. Toilet practices, as well as practices with cutlery, crockery and laundry, are as for ^{131}I therapy of benign thyroid disease for the first few days. Advice for emergencies is as for ^{131}I therapy of benign thyroid disease [4].

Holmium-166

Holmium-166 is a beta and gamma emitter. The half-life of ^{166}Ho is 26.8 h. The energy and intensity of the 81 keV gamma line are suitable for SPECT imaging. Due to magnetic susceptibility, dosimetry is possible using MRI. Holmium-166 is produced via neutron activation either directly from ^{165}Ho (high purity) or from ^{164}Dy with two neutrons (^{166}Dy/^{166}Ho generator) – impurities are negligible from radiation protection point of view.

Examples of treatments are: ^{166}Ho-microspheres (QuiremSpheres®) for intra-arterial treatment in the liver, ^{166}Ho-RE (other than QuiremSpeheres®) for intra-arterial treatment in the liver, ^{166}Ho-microspheres (HoMS) for recurrences of head and neck squamous cell carcinoma, ^{166}Ho-chitosan for hepatocellular carcinoma (HCC) and [^{166}Ho]Ho-DOTMP for bone metastases.

For radiation protection, guidelines for ^{131}I can be applied considering faster decaying of ^{166}Ho. Over 75–80 % of the administered activity is excreted via urine within 24 hours of injection. Advice for emergencies is as for I-131 therapy of benign thyroid disease [4].

Lutetium-177

Lutetium-177 emits beta particles of 490 keV and gamma radiation of 113 keV (6 %) and 208 keV (10 %). Lutetium-177 may be produced in two different ways, directly and indirectly. In using the direct production route there is also ^{177m}Lu as impurity. It has a long half-life (160 d) and is a beta and gamma emitter, so waste management is needed. The other way is an indirect production route, in which there is a complicated radiochemical separation procedure. For radiation safety reasons, it is important to know about the production route [9].

Lutetium-177 PSMA (Prostate-Specific Membrane Antigen) therapy is treatment that is increasingly being used for people with advanced prostate cancer. In Lu-177-PSMA therapy patients are typically treated with an activity of 7400 MBq. Dose rate of the patient after the injection is quite high (48 µSv/h). After 5 h the dose rate decreases below 30 µSv/h at 1 m distance and exposure of the caregivers remains below 5 mSv (Table 1) [10].

Hospitalization is needed for 5 hours and instructions for the patient are needed to avoid other persons in a similar way than in ^{131}I treatments. To keep dose to the public in acceptable levels might require hospitalization (isolation) of the patient depending of the unavoidable contacts to the public [11].

Time after infusion (hours)	0 m (µSv/h)	0.25 m (µSv/h)	0.50 m (µSv/h)	1.00 m (µSv/h)	2.00 m (µSv/h)
0	536 ± 89	297 ± 68	137 ± 28	48 ± 13	24 ± 7
1	468 ± 71	245 ± 54	118 ± 18	38 ± 7	21 ± 6
2	299 ± 62	198 ± 32	94 ± 15	33 ± 9	17 ± 6
4	180 ± 41	123 ± 27	62 ± 14	23 ± 6	11 ± 4
6	162 ± 36	91 ± 18	44 ± 11	15 ± 4	8 ± 3
18	118 ± 32	69 ± 16	33 ± 8	11 ± 3	5 ± 1
24	105 ± 27	31 ± 6	21 ± 6	7 ± 2	3 ± 1
48	63 ± 16	21 ± 5	11 ± 3	5 ± 1	1 ± 0.3
120	11 ± 3	4 ± 1	3 ± 0.8	1 ± 0.2	0.3 ± 0.1

Table 1. *Dose rate of patients (µSv/h) treated with 7400 MBq ^{177}Lu-PSMA at different distances and time marks [10]*

When a patient is released immediately after administration of the labelled somatostatin analogue (7400 MBq), the cumulative dose to which the general public is exposed is estimated to be in the range from 1.00 to 8.81 [mSv/course of treatment]. In such an event, the cumulative dose might exceed 1 mSv per year. For that reason hospitalization is needed for 1 day, if the dose constraint for public is 0.3 mSv. Children aged 2-5 years remain in average 13 days in a hospital [12]. There is no consensus yet available about post-discharge issues. Advice for emergencies is as for ^{131}I therapy of benign thyroid disease [4].

Lutetium-177 therapies may be repeated or fractionated in few weeks period. Radiation protection recommendations are typically per one fraction, however dose limits are for one

year. If the therapy is planned to be given in fractions, radiation protection should also be optimized and fractionation should be taken into account for example in setting dose constraints to workers and the public so that doses from one source would not exceed 1/3 of the annual dose limit.

Rhenium-188

Rhenium-188 emits high-energy beta particles with an average energy of 784 keV and a maximum energy of 2.12 MeV, sufficient to penetrate and destroy targeted abnormal tissues. In addition, the low-abundant gamma emission of 155 keV (15 %) is efficient for imaging and for dosimetric calculations. Moreover, the highly reproducible on-demand availability of ^{188}Re from the ^{188}W/^{188}Re generator system permits installation in hospital-based or central radiopharmacies for availability of no-carrier-added (NCA) ^{188}Re. Rhenium-188 and ^{99m}Tc exhibit similar chemical properties and represent a “theranostic pair” [13]. Examples of ^{188}Re treatments are ^{188}Re (Rhenium-SCT®) for non-melanoma skin cancer and Re-188-HEDP for painful bone metastases. The half-life of ^{188}Re is 17 h.

Urinary excretion of unbound material occurs in the early period following administration. When conducted on an outpatient basis, the patient should be kept in hospital until at least one or two post-administration bladder voidings occur. Special arrangements may be required for incontinent patients. Toilet practices, as well as practices with cutlery, crockery and laundry, are as above for ^{131}I therapy of benign thyroid disease until the contamination risk is negligible. Advice for emergencies is as above for ^{131}I therapy of benign thyroid disease [4].

3.3 Alpha particle therapies

With a short particle range and high linear energy transfer, alpha-emitting radionuclides demonstrate high cell-killing efficiencies. Targeted alpha-therapy relies on the significant differential targeting properties of a molecular vector in delivering the lethal alpha-payload to cells expressing higher target concentrations. Consequently, alpha-emitting radionuclides have been conjugated to a wide range of biomolecules, antibodies, peptides, small-molecule inhibitors, and nanocarriers. Numerous alpha-conjugates showing promising preclinical outcomes are now being evaluated in clinical trials or salvage therapy studies [14].

Because an alpha particle of at least 7.5 MeV is required to penetrate the protective skin layer (0.07 mm thick), pure alpha-emitters do not constitute an external radiation hazard. However, inhaled and ingested alpha particles are of concern. Proper handling of alpha-emitters is radionuclide-dependent, and each progeny must be considered because periodicity changes with decay [14]. Contamination measurements are discussed above in the paragraph 2.3.

Actinium-225

Actinium-225 in emitting alpha particles. The half-life is 10 d. It has a short-lived daughter nuclide ^{213}Bi ($T_{1/2}$ = 46 min) that is an alpha and beta emitter. Production of ^{225}Ac can be based on radiochemical extraction from ^{229}Th sources or accelerator driven processes. An important advantage of the proton irradiation of ^{226}Ra targets in a cyclotron is that no other long-lived actinium isotopes such as ^{227}Ac ($T_{1/2}$ = 21.8 y) are co-produced, and chemical purification of the irradiated targets yields ^{225}Ac of high isotopic purity. Waste management of ^{227}Ac has to be considered if that exists as impurity because of the long half-life.

Thorium-227

Thorium-227 is an alpha emitter and it has ^{223}Ra as a daughter radionuclide. The half-live of ^{227}Th is 19 d and of ^{223}Ra 11 d. Thorium is considered as nuclear material, but in practice, only ^{232}Th is of interest in that respect. Clinical trials are going on in a few European countries and examples of treatments are: ^{227}Th-conjugate CD22 positive non-Hodgkin lymphoma, ^{227}Th-antibody for ovarian cancer and mesothelioma and ^{227}Th-PSMA antibody for metastatic castration-resistant prostate cancer.

There are no international guidelines available for radiation protection in a situation when the patient dies in the period immediately following ^{227}Th therapy. Special consideration may need to be given prior to the autopsy or the treatment of the corpse. In Finland, a case study showed that even 4.5 months waiting time is needed before cremation.

4 Conclusions

The most parts of the existing guidelines for radiation protection are still applicable and should be followed. Radiation protection of beta emitters have similarities with well-guided radiation protection for ^{131}I, but new radionuclides have also created new challenges.

Typically, dose constraints for workers and the public are set per episode on the basis that it would be 1/3 of the annual dose limit. Especially, for the members of the public the dose constraint is set per episode, but new therapies are often given in few fractions and that should be considered in setting dose constraints. Moreover, dose constraints for carers and comforters should be set considering the fractionation of the treatment when radiation protection measures for the first fraction are planned.

Another challenge for radiation protection is alpha emitters. Especially inhaled and ingested alpha emitters used in radiotherapy may easily cause an exposure that exceeds a dose limit. Handling of these radionuclides in the daily work needs special attention and training of workers is essential. Contamination measurements of alpha emitters on the level of detection threshold is also challenging and needs measurement equipment that are suitable for the purpose.

Waste management has also a challenge of some radionuclides with long half-lives. Such radionuclides may exist as impurities because of the manufacturing process. New ways of producing these radionuclides have been developed to remove this problem; however, end users may not be aware of the origin of the radionuclide.

One more issue is the cremation after a radionuclide therapy with alpha emitters. It may be necessary to wait even several months before the calculated dose to a representative person is below a public dose limit or a dose constraint. It may not be known to another hospital or third persons that the deceased person has recently had a radionuclide therapy. For that reason, it is recommended to provide the patient after a radionuclide therapy a credit card sized document of the relevant details of the treatment to be carried along during a pre-specified time period.

5 References

[1] UNITED NATIONS SCIENTIFIC COMMITTEE ON THE EFFECTS OF ATOMIC RADIATION, Sources and Effects of Ionizing Radiation, UNSCEAR 2008 Report to the General Assembly with Scientific Annexes, Volume 1, United Nations, New York (2010)

[2] EUROPEAN COMMISSION, Radiation Protection Following Iodine-131 Therapy (Exposures due to Out-patients or Discharged In-patients), Radiation Protection 97, European Commission, Luxembourg (1998)

[3] INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION (ICRP), Release of Patients After Therapy with Unsealed Radionuclides, Publication 94, Elsevier, Oxford (2004)

[4] INTERNATIONAL ATOMIC ENERGY AGENCY (IAEA), Release of Patients after Radionuclide Therapy, with contributions from the International Commission on Radiological Protection, Safety Report Series No. 63, International Atomic Energy Agency, Vienna (2009).

[5] EUROPEAN COMMISSION. 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. Official Journal of the European Communities No L 13, Volume 57, 17 January 2014.

[6] HEADS OF THE EUROPEAN RADIOLOGICAL PROTECTION COMPETENT AUTHORITIES (HERCA). https://www.herca.org/docstats/HERCA_Patient_release_Card.pdf

[7] Wellner, U., et al., The exposure of relatives to patients of a nuclear medicine ward after radioiodine therapy by inhalation of ^{131}I in their home, Nuklearmedizin 37 (1998) 113–119.

[8] INTERNATIONAL ATOMIC ENERGY AGENCY, Monitoring for Compliance with Exemption and Clearance Levels, Safety Report Series No. 67, International Atomic Energy Agency, Vienna (2012).

[9] Dash, A., et al.: Production of ^{177}Lu for Targeted Radionuclide Therapy: Available Options. Nucl Med Mol Imaging (2015) 49:85-107.

[10] Demir, M., et al.: Evaluation of radiation safety in ^{177}Lu-PSMA therapy and development of outpatient treatment protocol. Journal of Radiological Protection 36.2 (2016): 269-278.

[11] Kurth, J., et al.: External radiation exposure, excretion, and effective half-life in ^{177}Lu-PSMA-targeted therapies. EJNMMI research 8.1 (2018): 32.

[12] Levart D. et al.: Radiation precautions for inpatient and outpatient ^{177}Lu DOTATATE peptide receptor radionuclide therapy of neuroendocrine tumours. EJNMMI Physics (2019) 6:7.

[13] Lepareur, N., et al.: Rhenium-188 Labelled Radiopharmaceuticals: Current Clinical Applications in Oncology and Promising Perspectives. Front Med (Lausanne). 2019; 6: 132.

[14] Poty, S., et al.: α-Emitters for Radiotherapy: From Basic Radiochemistry to Clinical Studies—Part 1. J Nucl Med. (2018) 59(6): 878-884.

Evaluation of risks of radionuclide therapy

Mark Konijnenberg

Department of Radiology and Nuclear Medicine, Erasmus MC, Rotterdam, The Netherlands

1 Introduction

Radionuclide therapies form an extraordinary branch within the radiotherapy family. It offers the possibility to image and treat disease in a targeted manner through its metabolic function and ionizing radiation action. It is therefore capable of treating disseminated disease, like metastasized forms of cancer. The imaging possibilities by gamma emission of either the therapeutic drug itself or by a diagnostic companion drug targeting the same disease enables to actually see and also quantify what is treated. This theranostic principle (combining therapy and diagnostics) is a great asset to radionuclide therapy. By using the imaging and the dosimetry possibilities, radionuclide therapies can be made truly patient-specific. It is by this capacity the molecular form of image guided conformal radiotherapy, instead of a complex linear accelerator array of beams a sophisticated molecule will lead to the patient-specific irradiation.

Recent market authorizations for targeted radionuclide therapies were evaluated as form of pharmaceutical therapies rather than radiotherapies. Following the traditional way, these radionuclide therapies are prescribed on a fixed activity dosing scheme, comparable to a chemotherapy. The prescribed amount of activity (sometimes adjusted for body weight or surface area) is based on the maximum tolerable activity derived from investigational clinical trials. In most cases, this leads to a therapy without or just a limited amount of adverse events. The lack of serious toxicity by these therapies is considered to be their great advantage, it can be however argued that the therapy was actually delivered at a sub-optimal level. The current way of determining a safe amount of activity to be administered leads to a drug prescription based on responses by the most radiation sensitive patient cohort.

Patient-specific therapy planning could lead to higher responses, but unlike other forms of radiotherapy, patient dosimetry is hardly performed in the routine clinical practice of radionuclide therapy which leads to a lack of knowledge on the dose-effect relations for radiation-induced damage in radionuclide therapies. Slowly evidence is gathered on dose-effect curves for radionuclide therapy applications. For instance, renal damage after therapy with ^{90}Y labelled peptides showed a comparable steep sigmoid shaped curve with absorbed

dose to the kidneys as was known from experience with external radiation exposure. The threshold for late renal damage shifted by almost 10 Gy going from external to internal radiation. Radiobiology explains this shift by the large difference in dose rate.

The knowledge of the radiobiology for internal exposures by radionuclide therapy is minimal and in most cases derived from external beam radiation exposure knowledge. Research into the radiobiology of radionuclide therapy and its internal exposure needs to be intensified. This knowledge is needed to change from the fixed activity dosing to a dosimetry based treatment planning. As an increasing number of patients is treated with radionuclide therapies, concerns are raised on their late effects, such as induction of secondary cancers in off-target tissues. Optimizing the therapy according to a safe and effective therapeutic window may lead to a lower and justifiable off-target absorbed dose.

Article 56 on optimization of medical exposure in Council Directive 2013/59/Euratom states that in radiotherapy "*exposures of target volumes shall be individually planned and their delivery appropriately verified*" (*1*). Radionuclide therapy does not form an exception to the radiotherapy definition, however in practice it does, as almost all radiopharmaceuticals are prescribed according to fixed activity. Verification of the absorbed doses delivered will help to gain more knowledge on dose-effect relations in radionuclide therapies. Investigational clinical trials need to be designed in a different manner, dose-escalation steps should be based on both activity and absorbed dose, either to organs at risk (phase 1) and to target volumes (phase 2 and 3) in order to follow the optimization principle (Article 56) and enable the requirement for a patient specific prescription to be followed in radionuclide therapy.

2 Chemotherapy or molecular radiotherapy

The first radionuclide therapy ^{131}I NaI was developed in the 1940s as a therapy of thyroid disorders and carcinoma. Initially, ^{131}I NaI was prescribed on basis of the absorbed dose either to the thyroid (*2*) in the case of benign thyroid disease or to a maximum tolerable absorbed dose to the bone marrow (*3*). This dosimetry based approach has increasingly been replaced by empirically derived fixed activities which was proven to be effective and safe in the majority of patients. In the clinical guidelines for ^{131}I NaI therapies, individual dosimetry-based prescription is only advised in patients < 45 years of age (*4*) in the case of benign thyroid disease. Activities for treatment of thyroid cancer with ^{131}I NaI are generally empirically determined depending on disease state and patient age (*5*).

New therapeutic radiopharmaceuticals have been approved for market authorisation based on comparable fixed activity dose prescription schemes. Radium-223 chloride has shown to be successful in delivering a median prolongation of 3 months in life expectancy in comparison to a placebo drug in end-stage patients with skeletal metastases of prostate cancer (*6*). This was a remarkable finding for an alpha-particle emitting radionuclide therapy

that was intended to be a palliative agent. The market approval for (^{223}Ra) Xofigo was issued on the basis of activity per kg body weight at 55 kBq/kg given in 6 therapy cycles, resembling the prescription of a chemotherapy drug (*7*).

Clinical trial to study the combination of Xofigo with the most effective chemotherapy in metastatic prostate cancer Abiraterone did not show any synergetic effect. Abiraterone alone led to a comparable median survival benefit of 4 months (*8*). In combination with Xofigo however it led to an almost 3-fold increase of bone fractures (29 % vs. 11 %) (*9*). Combination of both therapies are therefore contraindicated in all patients, whereas individual dosing of the radionuclide therapy (^{223}Ra Xofigo) could hypothetically help to identify the patients at largest risk of developing skeletal events. Personalisation of this therapy is complex, due to the low amount of activity administered and the gamma-ray emission spectrum, but is possible when using in combination with its theranostic companion drugs ^{99m}Tc HDP or ^{18}F NaF (*10, 11*). Compartmental modelling of the skeletal uptake may help to identify patients with high uptake, merely by using one quantitative SPECT together with various probe-based whole body measurements (*12*). This procedure might be of value for patient selection and for therapy planning.

The second radiopharmaceutical therapy drug that recently received market authorisation was ^{177}Lu-DOTA-tyr^3-octreotate or Lutathera (*13*). This drug has proven to be a very successful therapy against metastatic neuroendocrine tumours with increase in survival of more than 10 months (*14*). The market authorisation for Lutathera was granted by EMA in 2017 with a fixed activity prescription of 7.4 GBq given in 4 therapy cycles. Yet again, a radiopharmaceutical therapy drug being administered as if it is a form of chemotherapy instead of radiotherapy.

Personalised radionuclide therapies can be achieved by using dosimetry as guidance. Many arguments have been raised against the use of dosimetry to guide routine radionuclide therapy; the most important objections are listed in Table 1, together with possible solutions.

Most of the objections in establishing personalised prescription are based on the belief that fixed activities lead to good outcomes in ^{131}I Iodine therapies and most radionuclide therapies do not lead to severe radiation-induced adverse events. Performing dosimetry assessments in a cancer patient in late stage of the disease can be very demanding, as in most protocols 3 imaging time points are foreseen which can form a burden for patients. Still this discomfort is minor in comparison to the 30-40 daily sessions with 2 Gy fractions external beam radiotherapy patients have to undergo although the radiotherapy patients are generally in better condition. Attempts are made to provide indications of the absorbed doses delivered based on a single imaging time-point together with prior knowledge on average clearance patterns from the target region (*15*). Arguments against dosimetry-based prescription are the lack of established dosimetry methods, large uncertainties in the absorbed doses obtained and consequently unclear dose-response models. This leads to

treatment protocols for radionuclide therapies without even verification of the individual patient's absorbed doses delivered (see SPCs as authorized by the EMA for Xofigo (*7*) and for Lutathera (*13*).

Objections to individualised therapy	Solutions
Time and resource consuming	Reimbursement for dosimetry studies
Inconvenient for the patient	Keep it practical and relevant
On-site expertise needed	Medical physics expert support mandatory
No established dosimetry method	Benchmarks for dosimetry software
Unclear dose-response models	Focussed radiobiology research in MRT
Large uncertainties in absorbed dose	Improve accuracy in dosimetry process
Safe activity from clinical trials / experience	Dose response model guided clinical trials
One size fits all is more convenient	Sub-optimal patient care is not acceptable

Table 1. *Arguments against dosimetry guided radionuclide therapy and possible solutions*

An important barrier in establishing routine clinical dosimetry for radionuclide therapy is the absence of reimbursement schemes all over Europe. This leads to the "catch-22" situation where paradoxically hardly any evidence for the added value of dosimetry guided therapy is being gained and therefore reimbursement is not financed. Furthermore, a shortage of expertise is encountered, despite the almost 80 years of experience in radionuclide therapy (*16*). In the European Association of Nuclear Medicine (EANM) survey on the clinical practice of molecular radiotherapy in Europe it was found that in 32 % of the centres performing radionuclide therapies a medical physicist is never or in minor number of cases involved (*17*).

Clinical trials for radionuclide therapies should be organized in a different manner than the traditional pharmaceutical approach, absorbed doses to target volumes and organs at risk should be considered as individual parameter for efficacy and toxicity. This would really exploit the patient-specificity radionuclide therapies can offer and lead to a true image guided theranostic conformal radiotherapy. The main question is therefore whether targeted radionuclide therapies can be considered to be a member in the family of radiotherapy treatments or a form of chemotherapy.

3 Therapeutic windows in radiotherapy

An important concept in optimization of radiotherapy is formed by the therapeutic window; the range in absorbed doses that leads to a maximized cure probability at a minimal probability for radiation induced toxicity. Both the Tumour Control Probability (TCP) and the Normal Tissue Complication Probability (NTCP) follow a Poisson statistics function with its typical sigmoid shape shown in Figure 1. The absorbed dose in the target volume describes both the TCP and the NTCP in external beam radiotherapy through the exposure of organs at risk within the irradiation field range. Treatment planning in external beam radiotherapy is based on trying to optimize the Probability of Uncomplicated Cure (PUC) which is defined as PUC = TCP x (1-NTCP).

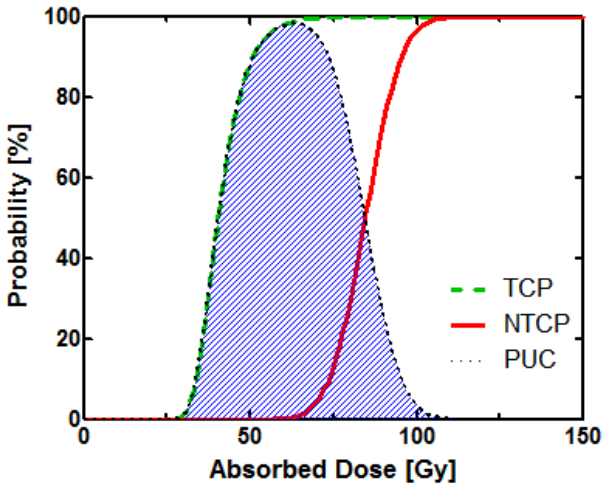

Figure 1. *Concept of therapeutic window for external beam radiotherapy, indicating the region between a curative absorbed dose (indicated by the Tumour Control Probability TCP) and the absorbed dose threshold that leads to toxicity (Normal Tissue Complication Probability NTCP) in the normal organ at risk within the radiotherapy exposure field. The Probability of Uncomplicated Cure (PUC) can be optimized by different angles and intensities of incoming ionizing radiation beams.*

Optimization of radionuclide therapy can follow the same concept of trying to obtain a favourable PUC, albeit that the active manipulation of incoming beams is replaced by the targeting vector molecule possibly combined with additional agents to influence the pharmacokinetics in normal organs, like e.g. amino acids to reduce kidney uptake of radiolabelled peptides. The absorbed dose to the organs at risk are not directly linked to the absorbed dose to the tumour lesions and instead of one graph indicating both TCP and NTCP two separate graphs are needed (Figure 2).

Another difference with radiotherapy is that the target volume in radionuclide therapy consists of a multitude of tumour metastases with a non-uniform dose distribution. Together with a much lower accuracy in the dosimetry this has led to the conception that the large uncertainties of 20 % and higher obscure the ability to observe dose-effect relations in radionuclide therapies. Causes for the non-uniformity of the dose distributions lie mostly in variation in blood perfusion through the tumour lesions, differences in receptor expression between tumour cells and specific targeting through trapping of the radionuclides in the microvasculature feeding tumour lesions.

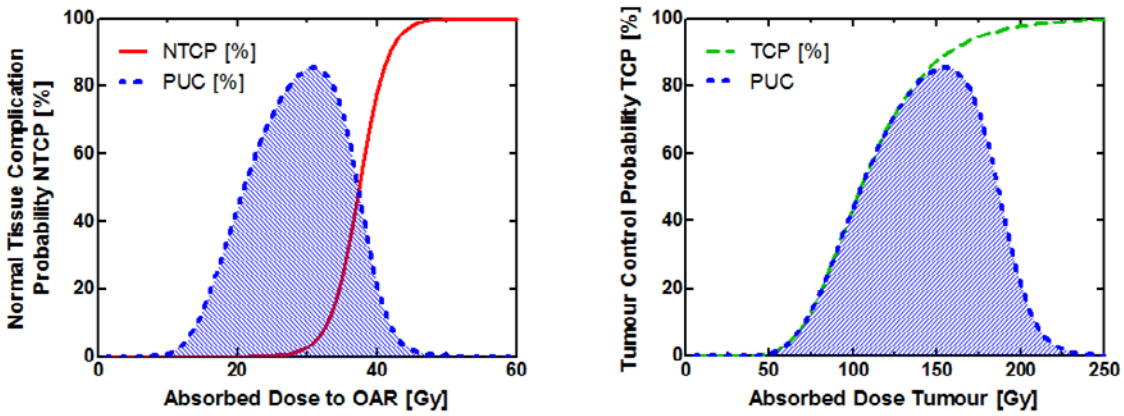

Figure 2. *Therapeutic window concept for radionuclide therapies, with curves defined in figure 1. The absorbed dose to the tumour and the absorbed dose to the organ at risk (OAR) are not necessarily linked and are highly patient-specific. Optimization of the PUC is reached by tailoring the administered activity to the patient in combination with interventions to reduce uptake in OAR or enhance the radiation effects in the tumour.*

4 Evidence for dose-effect relations MRT

Despite the low accuracy in absorbed doses for radionuclide therapies, several of these therapies have shown distinct dose-relationships for both toxicity as for tumour control. In a literature review, we analysed the results of 79 clinical studies that led to some dose response model (*18*). The majority of the evidence was considered to be of low to moderate clinical relevance as the set-up of the clinical studies was mostly of anecdotal nature together with less well-defined end-points. A clear lack of randomized studies was identified that are focussed on survival and possible symptom-free survival. The majority of the studies were using either ^{131}I or ^{90}Y.

The most impressive dose-response relations were obtained with ^{90}Y-DOTA-octreotide. In a phase 1 trial for this radiopharmaceutical, the dose escalation was partly in escalating activity and partly by limiting the absorbed dose to the kidneys at a maximum of 27 Gy (*19*).

The dosimetry for ^{90}Y is not straightforward as it is a pure beta-emitter and in this study the positron-emitter ^{86}Y was used to determine the pharmacokinetics and dosimetry. Longer follow-up of a sub-group within the total patient population included led to the observation that the patients with higher absorbed doses to the kidneys had a higher probability of a large reduction in kidney function (*20*). Not only the cumulative absorbed dose to the kidneys was a predictive factor for end-stage toxicity, but also the number of therapy cycles that were used to reach 27 Gy, comparable to the situation of fractionated radiotherapy. The total dose of 27 Gy was based on the standard kidney weight of 150 g per (male) kidney according to the MIRD dosimetry phantom. In reality, the patients showed a large variance in kidney volume, as determined from CT-images, and patients with kidney weights below the standard weight were more likely to suffer from end-stage renal disease.

5 Radiobiology for molecular radiotherapy, unknown territory

The knowledge of the radiobiology for internal exposures by radionuclide therapy is minimal and in most cases derived from external beam radiation exposure knowledge. Research into the radiobiology of radionuclide therapy and its internal exposure needs to be intensified. This knowledge is needed to change from the fixed activity dosing to a dosimetry based treatment planning. As increasing number of patients are treated with radionuclide therapies, concerns are raised on their late effects, such as induction of secondary cancers in off-target tissues. Optimizing the therapy according to a safe and effective therapeutic window may lead to a lower and justifiable off-target absorbed dose. The experience with renal toxicity after ^{90}Y-DOTA-octreotide therapy led to the introduction of radiobiology in the field for radionuclide dosimetry. The Biological Effective Dose (BED) concept was used to account for the low dose rates and exponential decay pattern in radionuclide therapies in MIRD pamphlet 20 (*21*)**.** It is based on the linear quadratic model, an established radiobiology model in external beam radiotherapy and brachytherapy, and BED is a helpful tool in comparing absorbed doses by radionuclide therapy to doses given in 2 Gy fractionated radiotherapy. The radiobiology for ionizing radiation events by radionuclide therapy is very different from the situation in conventional external beam radiotherapy. Not only the dose rate is different (a factor 100-1000 lower and following exponential decay) also the absorbed dose distribution is highly non-uniform. Molecular uptake patterns define the absorbed dose distributions by variable expression of target receptors in target volumes or organs at risk. In most radionuclide therapies, the target volume consists of multiple regions with for instance metastasized cancer. An iso-effective dose representation is needed to take both the non-uniform dose distribution, the range in tissue and the LET character of the radiation particles into account. Again, external beam exposures are taken into account as reference with uniform dose distributions in the target volume. The Equivalent Uniform Dose (EUD) model is generally being proposed to make a link between non-uniform dose distributions in radionuclide therapy and homogeneous dose

distributions. Research is needed to determine the microdosimetry of radiation tracks from specific molecular targeted cancer cells and to identify the appropriate macrodosimetry model.

Radionuclide therapy administration neglecting the underlying radiobiology may lead to toxicity or sub-optimal therapy. The first example comes again from the radiopeptide therapies against neuroendocrine tumours. A phase II trial was performed with ^{90}Y-DOTA-octreotide administered in 2 or more treatment cycles at 3.7 GBq ^{90}Y /m^2 body surface (*22*). Not only did this dosing neglect the threshold absorbed dose for kidney toxicity, but also the activity per treatment cycle was increased by a factor 1.3 - 1.6 compared to the average dosing per cycle of 4.4 GBq used in the phase 1 study. The activity per treatment cycle was found to form a considerable risk factor in the study by Barone (*20*). The phase II study resulted in a devastating 9 % (102 out of 1109 patients) level of very severe radiation induced toxicity (grade 4: permanent dialysis and grade 5: death).

Negligence of the dosimetry lead to failure in a large phase III trial, comparing the efficacy of ^{90}Y resin microspheres in combination with the standard FOLFOX chemotherapy and FOLFOX alone in patients with liver metastases from colorectal cancer (*23*). The dosing of ^{90}Y resin spheres was based on an empirical formula for the amount of activity, which is the most widely used prescription method for this therapy (*24*):

$$A\left[GBq\ ^{90}Y\right] = BSA[m^2] - 0.2 + \left(\frac{\%\ tumour\ involvement}{100}\right)$$

with BSA the patient's body surface area (in m^2) and the % tumour involvement the percentage of the total liver volume that is taken up by tumour metastatic lesions. Both the overall survival as the progression free survival did not lead to an indication that therapy with ^{90}Y resin microspheres leads to better outcome, despite the large number of patients considered (550 patients in each treatment arm). The SARAH trial also failed to prove better survival for liver cancer (HCC) patients, a phase III study to compare ^{90}Y resin microspheres prescribed according to the BSA method and standard care: sorafenib chemotherapy (*25*). Therapy with ^{90}Y resin microspheres did lead to less adverse events and improved quality of life. Evidence for improved survival in ^{90}Y microsphere therapy has been indicated for tumour absorbed doses exceeding 205 Gy with ^{90}Y glass microspheres in HCC tumours (*26*). Consensus has been reached among experts to recommend the use of dosimetry based prescription methods for ^{90}Y glass microspheres (*27*).

The amount of evidence showing the benefits of dosimetry-based prescription methods has surprisingly not led to an increase in dosimetry driven clinical trials for radionuclide therapy. For instance, the Vision trial that is currently including prostate cancer patients for therapy of their metastatic disease with ^{177}Lu-PSMA (Prostate Specific Membrane Antigen) excludes all dosimetry, even the verification post therapy (*28*). Fixed activities of 7.4 GBq ^{177}Lu-PSMA are being used in multiple therapy cycles, without any knowledge on the individual patients' dosimetry, reminiscent of the clinical trial with ^{90}Y-DOTA-octreotide (*22*). Apparently, the

lessons learned have not led to different protocols 10 years later. It will not be possible to determine either any threshold value in absorbed dose that prevents inadvertent radiation induced toxicity or a minimum absorbed tumour dose necessary for an efficacious therapy.

6 Conflicting legislation radiation protection and medicine approval

Procedures for dosimetry-guided radionuclide therapies have been proposed by the EANM internal dosimetry task force, showing its feasibility based on clinical experience (*29*). The capacity to vary the prescribed amount of activity is however limited by the maximum amount of activity indicated in the package insert for the radiopharmaceutical. Optimal therapy using a dose according to the dosimetry assessment exceeding the maximum tolerable activity would fall in an experimental therapy setting, which would severely reduce its application. This dilemma has been raised by the EANM dosimetry committee, indicating the impossibility to adhere at the same time to the optimisation principle in the Council Directive 2013/59/Euratom and the posology set out in the EMA market authorisations for current radionuclide therapies (*30*). In order to change the way radionuclide therapies are prescribed it will be necessary to reconsider the methods to prove its therapeutic potential. Personalized treatment planning methods should be part of the market registration process for radionuclide therapies, enabling its placement within the realm of radiotherapies instead of chemotherapy.

7 Risks of radionuclide therapy

Many new radionuclide therapies have been successfully developed or are currently being tested for metastatic cancers. These, mainly European driven, efforts are leading to spectacular results in various types of metastasized cancer, which would have no real options for therapy otherwise. Adverse events with radionuclide therapies are in general minimal, mostly observed after the use of the longer-ranged beta-emitters like ^{90}Y. Dosimetry has proven to be of great value in reducing the risk for late renal damage after ^{90}Y-DOTA-octreotide. The risks for radiation induced deterministic damage with the other types of radionuclide therapy are minimal, mostly related to bone marrow toxicity. This could possibly change when the prescription base is changed to reach the maximum tolerable absorbed dose, or the as high as safely administrable (AHASA) concept (*31*). Knowledge on safe threshold doses and its interpatient variance is available for conventional therapies, but needs to be researched in new radionuclide therapy applications. It is of great importance that the absorbed dose delivered is verified after unconventional radionuclide therapies to help building the expertise. Clinical trial protocols for radionuclide therapies should include patient-specific dosimetry as an essential prerequisite. Preferably, clinical trials should use dosimetry as prospective treatment planning tool.

8 References

1. Council of the European Union. COUNCIL DIRECTIVE 2013/59/EURATOM of 5 December 2013. https://ec.europa.eu/energy/sites/ener/files/documents/CELEX-32013L0059-EN-TXT.pdf.

2. Marinelli LD, Quimby EH, Hine GJ. Dosage determination with radioactive isotopes; practical considerations in therapy and protection. *Am J Roentgenol Radium Ther.* 1948;59:260-281.

3. Maxon HR, Thomas SR, Hertzberg VS, et al. Relation between effective radiation dose and outcome of radioiodine therapy for thyroid cancer. *N Engl J Med.* 1983;309:937-941.

4. Stokkel MP, Handkiewicz Junak D, Lassmann M, Dietlein M, Luster M. EANM procedure guidelines for therapy of benign thyroid disease. *Eur J Nucl Med Mol Imaging.* 2010;37:2218-2228.

5. Luster M, Clarke SE, Dietlein M, et al. Guidelines for radioiodine therapy of differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging.* 2008;35:1941-1959.

6. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369:213-223.

7. EMA EMA. Xofigo, radium Ra223 dichloride. https://www.ema.europa.eu/en/medicines/human/EPAR/xofigo.

8. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol.* 2012;13:983-992.

9. Smith M, Parker C, Saad F, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2019;20:408-419.

10. Pacilio M, Ventroni G, De Vincentis G, et al. Dosimetry of bone metastases in targeted radionuclide therapy with alpha-emitting (223)Ra-dichloride. *Eur J Nucl Med Mol Imaging.* 2016;43:21-33.

11. Murray I, Chittenden SJ, Denis-Bacelar AM, et al. The potential of (223)Ra and (18)F-fluoride imaging to predict bone lesion response to treatment with (223)Ra-dichloride in castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging.* 2017;44:1832-1844.

12. Taprogge J, Murray I, Gear J, Chittenden SJ, Parker CC, Flux GD. Compartmental Model for (223)Ra-Dichloride in Patients With Metastatic Bone Disease From Castration-Resistant Prostate Cancer. *Int J Radiat Oncol Biol Phys.* 2019;105:884-892.

13. EMA EMA. Lutathera, lutetium (177Lu) oxodotreotide. https://www.ema.europa.eu/en/medicines/human/EPAR/lutathera.

14. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med.* 2017;376:125-135.

15. Hanscheid H, Lapa C, Buck AK, Lassmann M, Werner RA. Dose Mapping After Endoradiotherapy with (177)Lu-DOTATATE/DOTATOC by a Single Measurement After 4 Days. *J Nucl Med.* 2018;59:75-81.

16. Flux GD, Verburg FA, Chiesa C, et al. Comparison of Empiric Versus Dosimetry-Guided Radioiodine Therapy: The Devil Is in the Details. *J Nucl Med.* 2017;58:862.

17. Sjogreen Gleisner K, Spezi E, Solny P, et al. Variations in the practice of molecular radiotherapy and implementation of dosimetry: results from a European survey. *EJNMMI Phys.* 2017;4:28.

18. Strigari L, Konijnenberg M, Chiesa C, et al. The evidence base for the use of internal dosimetry in the clinical practice of molecular radiotherapy. *Eur J Nucl Med Mol Imaging.* 2014;41:1976-1988.

19. Jamar F, Barone R, Mathieu I, et al. 86Y-DOTA0)-D-Phe1-Tyr3-octreotide (SMT487)--a phase 1 clinical study: pharmacokinetics, biodistribution and renal protective effect of different regimens of amino acid co-infusion. *Eur J Nucl Med Mol Imaging.* 2003;30:510-518.

20. Barone R, Borson-Chazot F, Valkema R, et al. Patient-specific dosimetry in predicting renal toxicity with (90)Y-DOTATOC: relevance of kidney volume and dose rate in finding a dose-effect relationship. *J Nucl Med.* 2005;46 Suppl 1:99S-106S.

21. Wessels BW, Konijnenberg MW, Dale RG, et al. MIRD pamphlet No. 20: the effect of model assumptions on kidney dosimetry and response--implications for radionuclide therapy. *J Nucl Med.* 2008;49:1884-1899.

22. Imhof A, Brunner P, Marincek N, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [^{90}Y-DOTA]-TOC in metastasized neuroendocrine cancers. *J Clin Oncol.* 2011;29:2416-2423.

23. Wasan HS, Gibbs P, Sharma NK, et al. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. *Lancet Oncol.* 2017;18:1159-1171.

24. Limited SM. Product information SIR-Spheres® Microspheres (Yttrium-90 Microspheres). https://www.sirtex.com/media/155127/pi-ec-12.pdf.

25. Vilgrain V, Pereira H, Assenat E, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol.* 2017;18:1624-1636.

26. Garin E, Rolland Y, Edeline J, et al. Personalized dosimetry with intensification using 90Y-loaded glass microsphere radioembolization induces prolonged overall survival in hepatocellular carcinoma patients with portal vein thrombosis. *J Nucl Med.* 2015;56:339-346.

27. Salem R, Padia SA, Lam M, et al. Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. *Eur J Nucl Med Mol Imaging.* 2019;46:1695-1704.

28. Register ECT. VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ^{177}LU-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC). https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-000459-41/GB.

29. Stokke C, Gabina PM, Solny P, et al. Dosimetry-based treatment planning for molecular radiotherapy: a summary of the 2017 report from the Internal Dosimetry Task Force. *EJNMMI Phys.* 2017;4:27.

30. Chiesa C, Sjogreen Gleisner K, Flux G, et al. The conflict between treatment optimization and registration of radiopharmaceuticals with fixed activity posology in oncological nuclear medicine therapy. *Eur J Nucl Med Mol Imaging.* 2017;44:1783-1786.

31. Verburg FA, Biko J, Diessl S, et al. I-131 activities as high as safely administrable (AHASA) for the treatment of children and adolescents with advanced differentiated thyroid cancer. *J Clin Endocrinol Metab.* 2011;96:E1268-1271.

Summary

Prepared by Dr. Laurence Lebaron-Jacobs

on behalf of the

Working Party "Research Implications on Health and Safety Standards" (WP RIHSS) of the Group of Experts referred to in Article 31 of the Euratom Treaty[19]

1 Introduction

This chapter provides the rationale of EU Scientific Seminars, summarises the individual presentations, and the roundtable discussion on policy implications and research needs of this year's Scientific Seminar on "Developments in nuclear medicine – new radioisotopes in use and associated challenges". It takes into account the discussions that took place during the seminar and during the subsequent meeting of the Article 31 Group of Experts, although it is not intended to report in an exhaustive manner all the opinions that were expressed. These proceedings have been submitted for comments to the lecturers and round-table participants, as far as their contributions were concerned.

2 The Article 31 Group of Experts and the rationale of the scientific seminars

The Article 31 Group of Experts is a group of independent scientific experts referred to in Article 31 of the Euratom Treaty, which assists the European Commission in the preparation of the Euratom Basic Safety Standards for the protection of the health of workers and members of the public against the dangers arising from ionizing radiation. This Group of Experts has to give priority to the protection of health, to the safety and to the development of the best available operational radiation protection. To this end, the Group of Experts is committed to proactively scanning new or emerging issues in science and technology, and

[19] The Scientific Seminar was chaired by G. O' Reilly. L. Lebaron-Jacobs was acting as rapporteur. In addition, the following members of the Working Party on Research Implications on Health and Safety Standards of the Article 31 Group of Experts contributed to the preparation of this overview: H. Janžekovič F. Bochicchio, R. Huiskamp, P. Krajewski, and P. Smeesters. They were assisted by F. Tzika and S. Mundigl from the European Commission.

ongoing developments in the area of radiation protection and informing the European Commission on potential policy implications.

In this context, a Scientific Seminar is devoted every year to emerging issues in Radiation Protection – generally addressing new research findings with potential policy and/or regulatory implications. Following suggestions from the Working Party Research Implications on Health and Safety Standards (WP RIHSS), the Article 31 Group of Experts selects the topic of the seminar. After selection of the topic and approval of the programme by the Article 31 Group of Experts, the WP RIHSS deals with the preparation and the follow up of the seminar[20]. Leading scientists are invited to present the status of scientific knowledge in the selected topic. Additional experts, identified by members of the Article 31 Group of Experts from their own country, take part in the seminars and act as peer reviewers. The Commission convenes these seminars in conjunction with a meeting of the Article 31 Group of Experts to allow the Group to discuss potential implications of the presented scientific results. Based on the outcome of the Scientific Seminar, the Article 31 Group of Experts may recommend research, regulatory or legislative initiatives. The Experts' conclusions are valuable input to the setting up of the European Commission's radiation protection programme, and to the process of reviewing and potentially revising European radiation protection legislation.

3 Key highlights of the presentations at the Scientific Seminar on developments in nuclear medicine – new radioisotopes in use and associated challenges

Patrick Smeesters – Objectives of the seminar and introduction to the topic

There are important developments in nuclear medicine. Particularly, over the last few years, radionuclide therapy or molecular radiotherapy (MRT) has strengthened the therapeutic arsenal. Many new radiopharmaceuticals are produced or are in the pipeline. The associated issues that have to be addressed include radiation protection issues, dosimetry, training of new groups of workers, and, last but not least, knowledge about possible short- and long term MRT-induced effects. This is all the more important as there is a lot of new evidence about radiation-induced effects that could have large consequences in the field of radiation protection. These effects are qualified as potential "game-changers" in the European research strategic agenda and include non-cancer effects at low and moderate cumulative doses (neurocognitive, circulatory ...), epigenetic effects (embryo, foetus ...) and individual radiosensitivity, with the age at exposure (children) holding a special role throughout these issues.

[20] This Scientific Seminar was prepared in collaboration with the Working Party on Medical Exposure in particular with contributions from G. O'Reilly and S. Nazarenko.

Article 56 of Council Directive 2013/59/Euratom – the European BSS Directive – requires that: *"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*". This includes radionuclide therapy. However, a European Survey on radionuclide therapies administered in 2015 showed that there are serious needs to increase the implementation of individual dose planning and post-treatment verification as well as the systematic involvement of medical physicists who are not involved in a very large number of centres.

The aim of this seminar is to identify and highlight the current issues and to suggest possible ways forward.

Michael Lassmann – Radionuclide therapy in nuclear medicine – developments and challenges

Over the last few years, radionuclide therapy has strengthened the therapeutic arsenal. Radionuclide therapy is developed according to the disease and the target organ to be treated.

In radionuclide therapies, different influencing variables have to be considered: administered activity, physical and chemical properties of the radiopharmaceutical, spatial variability of the biodistribution, organ considered as source of irradiation or target or both, biological uptake and excretion, DNA damage and repair.

There are different therapy modalities: metabolically active radiopharmaceuticals (radioiodine therapy (I) of benign or malignant thyroid diseases), specifically binding radiopharmaceuticals such as compounds addressing specific antigens or receptors (Dotatate or Dotatoc (Lutathera®, ^{177}Lu) for neuroendocrine tumour treatment) or antibodies (^{177}Lu, ^{90}Y Zevalin® for lymphoma treatment), and locoregional therapies (selective internal radiotherapy (^{90}Y, ^{166}Ho) for the treatment of liver metastases).

The implementation of these treatments has raised a number of challenges:

1. The availability of radionuclides: the conclusions of SAMIRA (European Study on Medical, Industrial and Research Applications of Nuclear and Radiation Technology) show that a supply situation without a new dedicated research reactor in Europe would not lead to European self-sufficiency and could create shortages at the global scale;
2. The access to treatment in all countries due to the lack of trained staff (physicians, physicists, radiochemists), adequate facilities for treatment and of reimbursement issues;
3. The excessive requirement for manufacturing of radiopharmaceuticals;

4. The standardization of quantitative imaging: the Board of the European Association of Nuclear Medicine (EANM) launched EANM Research Ltd (EARL) as an initiative to promote multicentre nuclear medicine and research. EARL has set up the EARL FDG-PET/CT accreditation programme to help imaging sites, which perform FDG-PET/CT oncology examinations, meet the standard requirements indicated in the EANM imaging guideline. Standardized quantitative imaging for therapeutically applied radiopharmaceuticals and improvements in the accuracy and metrological traceability in the calculation of absorbed dose and by determining uncertainties will further support the use of dosimetry in molecular radiotherapy (MRT).
5. The balance between sufficient accuracy and efforts for clinical dosimetry. Article 56.1 of Council Directive 2013/59 Euratom on optimisation, emphasizes that exposures of target volumes to radiopharmaceuticals shall be individually planned and their delivery appropriately verified taking into account that doses to non-targeted volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure. The EANM's Internal Dosimetry Task Force has published examples of balance between sufficient accuracy and efforts for treatment planning/ dose verification, and demonstrated the feasibility of patient-specific image-based dosimetry, treatment planning and dose verification in almost all considered therapeutic procedures. This report's conclusions need to be balanced against the missing clinical evidence for the superiority of prospective therapy prescription on basis of patient-specific dosimetry and the instructions for use recommended by EMA that are, in many cases, not in line with the Basic Safety Standards Directive.
6. Research efforts have to be developed in dosimetry methodologies and radiobiology. MEDIRAD is a 4 year EC Horizon 2020 funded project (2017 – 2021) aiming to increase knowledge of health effects of diagnostic and therapeutic medical radiation procedures, to improve recording and estimation of doses and to develop evidence based policies. EURAMED rocc-n-roll (EURopeAn MEDical application and Radiation prOteCtion Concept: strategic research agenda aNd ROadmap interLinking to heaLth and digitisation aspects) aims to propose an integrated and coordinated European approach to research and innovation in medical applications of ionising radiation and related radiation protection based on stakeholder consensus and existing activities in the field.
7. Implement dosimetry in early stages of clinical trials (phase I/II). The requirements for obtaining marketing authorization for new drugs should be strengthened so that sufficient dosimetry data from early clinical trials will be made available.
8. According to local rules and legislation, the waste management of therapeutical radiopharmaceuticals varies throughout the EU. The European Medicines Agency (EMA) or the European Commission should provide recommendations.

Oliver Neels – Production and regulation of radiopharmaceuticals – radiation protection issues

The European Directive 2001/83/EC provides a regulatory basis for the use of radiopharmaceuticals. In this Directive, a radionuclide precursor is defined as any other radionuclide produced for the radiolabelling of another substance prior to administration. The definition of a radionuclide precursor varies according to its use and the method of radiolabelling used: it is either a radionuclide precursor "starting material" or a radionuclide precursor "radiopharmaceutical". These terms are not defined in Directive 2001/83/EC. A radiopharmaceutical is defined as any medicinal product that contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose. Consequently, to assure the production and the availability of radiopharmaceuticals for patient care at centres/hospitals, we need to clarify or clearly define the terms 'radionuclide precursor' and 'radionuclide precursor radiopharmaceutical'.

Regulation 536/2014 on clinical trials on medicinal products for human use (repealing Directive 2001/20/EC) has been established aiming at more harmonization in the submission process, transparency and higher safety standards of clinical trials. However, Regulation 536/2014 has not yet come into application since 2014 since the timing of this depends on the development of a fully functional EU clinical trials portal and database, which will be confirmed by an independent audit. The Regulation becomes applicable six months after the European Commission publishes a notice of this confirmation. Due to technical difficulties, the completion of the IT systems is postponed to 2020. According to Article 61 of the regulation, manufacturing of investigational medicinal products (IMPs) requires an authorization, but therapeutic radiopharmaceuticals when used as diagnostic IMP are excluded from authorisation.

Katarina Sjögreen Gleisner – Dosimetry and dosimetric tools in radionuclide therapy, including results of the European survey

Dosimetric tools have been developed to assess absorbed doses to patients exposed to radionuclides. The primary objective is to understand the risks of deterministic tissue reactions and the probability of disease control for the individual patient. There are software available for calculation of the absorbed dose to estimate the radiation risk for diagnostic examinations in nuclear medicine at hospitals. One such example is IDAC-Dose2.1 that was developed based on the ICRP specific absorbed fractions and computational framework of internal dose assessment given for reference adults in ICRP Publication 133. For radionuclide therapy, patient-specific dosimetry is required. In this case, instead of using standard S values (representing the mean absorbed doses given to target tissues per unit of time-integrated activity) and assuming standard physiology, the organ mass for the particular patient needs to be estimated, as does the time-integrated activity.

Some radionuclide therapies are dosimetry-guided:

1. Probe activity measurements are used as part of ^{131}I-NaI treatment planning of benign thyroid diseases;
2. Probe activity measurements or whole-body scintigraphy for neuroblastoma treatment planning with ^{131}I-mIBG to take into account the radiosensitive bone marrow;
3. Blood and bone marrow dosimetry rely on whole-body measurements and blood sampling shortly after the first radiopharmaceutical administration is used for ^{131}I-NaI treatment planning of thyroid cancer.

Metrological techniques are used for measurement of the activity administered to patients in radionuclide therapy: an activity meter is used as accurate reference instrument as it can calibrate instruments used for dosimetry too. Traceability to standard laboratories in activity measurements is needed for therapeutic radionuclides such as ^{131}I, ^{177}Lu, or ^{90}Y.

Dosimetry can be based on quantitative tomographic imaging. An accurate tomographic reconstruction is carried out using a single calibration factor to convert from count rate to activity for all image values. A number of examples of image based dosimetry were given, such as dosimetry for multi-cycle treatments, using [^{177}Lu]Lu-DOTA-TATE or [^{177}Lu]Lu-PSMA-617, and dosimetry for radioembolization using ^{90}Y-microspheres.

In the end, the choice of measurement technique in the framework of a specific radionuclide therapy largely depends on the emission spectrum of the radionuclide, the radiosensitivity of tissues and the need of dosimetry, as well as the practical possibilities for performing repeated measurements after administration.

A European survey on the extent and practice of dosimetry implementation of radionuclide therapy procedures was carried out in 2016. The conclusions show that dosimetry is indeed feasible for many kinds of radionuclide therapy, but the implementation of dosimetry is low. Moreover, medical physicists need to be involved to entrench the understanding of absorbed dose concept and the value of dosimetry.

Ritva Bly - Radiation protection issues in radionuclide therapy – workers (medical staff), third persons, waste management

In terms of radiation protection, there is a lack of information on new radionuclide therapies. Comprehensive European guidelines exist only for ^{131}I-therapy. Specific radiation protection training needs to be developed for new groups of medical professionals involved in radionuclide therapies. Waste management of radionuclide treatments is a challenge with a special focus on patient's excreta. After having been treated with a radionuclide, a patient must be considered as a radioactive source. So, what about the protection of carers and

comforters? Criteria for the release of a patient after radionuclide therapy to another ward/department or for the cremation of a patient remain challenges to be solved.

In nuclear medicine, radionuclides can be used as pharmaceuticals when there is a marketing authorization by the European Medicines Agency (EMA), and when a CE marking applicable for a medical device has been affixed to a product. Is this enough? Can a radiation protection authority authorize a practice without comprehensive quality certification of a radiopharmaceutical? Calibration of a medical device containing a radionuclide is not clearly framed due to uncertainties. It is also not framed for measurements under the detection limit. Besides, monographs of the pharmacopeia are not always available when treatments start: for example, a monograph to liquid ^{177}Lu exists, but not yet for ^{177}Lu-PSMA. In that respect, a general requirement on quality assurance must apply on radionuclide therapies with the help of Medical Agencies to be highlighted.

Patients with advanced prostate cancer are candidates for ^{177}Lu PSMA (Prostate-Specific Membrane Antigen) therapy. Its increased use creates radiation protection problems. Lutetium-177 emits beta particles and gamma radiation. Its production route has to be specified and taken into consideration when addressing radiation protection issues. By direct route of production, the product contains also ^{177m}Lu, an impurity that is a beta and gamma emitter with a long half-life (160 d) and therefore requires appropriate waste management. The indirect production route of ^{177}Lu involves a complicated radiochemical separation procedure. Consequently, the release of a patient treated with ^{177}Lu PSMA is not recommended immediately after its administration. If a patient is immediately released after administration of ^{177}Lu somatostatin analogues (^{177}Lu-DOTA-TATE), it can lead to the exposure of members of the public (cumulative dose: 1.00 to 8.81 mSv/course of treatment*).* In addition, ^{177}Lu therapies may be repeated or fractionated over several weeks. However, Directive 2013/59/Euratom and national legislation set annual dose limits for workers and for members of the public. For new therapies, appropriate dose constraints for workers and the public need to be developed taking account of the fact that these therapies are often administered in multiple fractions.

The alpha-emitter ^{225}Ac has a short half-life (10 d). The best route to produce ^{225}Ac is proton irradiation of ^{226}Ra targets in a cyclotron as it avoids the generation of long-lived impurities such as the actinium isotope ^{227}Ac (half-life 21.8 y). Other production routes resulting in the generation of the long-lived impurities, such as ^{227}Ac, require a more complex radioactive waste management.

Rhenium-188, a high-energy beta and gamma-emitter, can be used as labelled radiopharmaceutical or included in a medical device for treatment of non-melanoma skin cancer. In case of such a treatment, an outpatient should be kept in hospital to allow for sufficient bladder voiding. As regards incontinent patients, special arrangements need to be considered.

ICRP 94 made recommendations on release of patients after therapy with radionuclides: "*Radionuclides released into modern sewage systems are likely to result in doses to sewer workers and the public that are well below public dose limits*." These treatments produce hospital waste containing radionuclides that have to be short term stored until the activity has decayed to a defined level. Long-lived radionuclides, produced as impurities during the manufacturing process, create waste management challenges for some of the new radionuclide therapies. Consequently, new production routes have been developed to overcome this problem.

In case of decease of a patient after treatment with radionuclides, release criteria have to be defined to establish the date of his autopsy, burial or cremation, considering the radionuclides decay.

In conclusion, European guidelines are needed proposing dose constraints, taking into account fractionation of new radiopharmaceutical treatments, re-evaluation of waste management strategies considering new challenges such as long-lived radionuclides and patients' household waste.

Even if harmonization between all European countries is difficult, the goal is to increase understanding of requirements and recommendations. At present, HERCA is collecting data on existing national guidelines concerning local rules, patient release criteria after new radionuclide therapies, and cremation.

Mark Konijnenberg - Evaluation of risks of radionuclide therapy

Theranostics combining diagnostics and treatment of disseminated diseases, as metastasized forms of cancer, with radionuclides in a targeted manner makes it possible to view and quantify what is treated. In addition, radionuclide therapies or molecular radiotherapy (MRT) coupling imaging and dosimetry are patient-specific.

New therapeutic radiopharmaceuticals have received market authorisation based on comparable fixed prescription schemes of activity dose. For example, (^{223}Ra) Xofigo is prescribed as a chemotherapy drug. A clinical trial on combined use of Xofigo and Abiraterone (the most effective chemotherapy in metastatic prostate cancer) did not show any synergetic effect, but in contrast, led to an almost three-fold increase of bone fractures. Combination of both therapies are therefore contraindicated in all patients, whereas individual dosing of the radionuclide therapy (^{223}Ra Xofigo), by compartmental modelling of the skeletal uptake, could help to identify patients with high uptake and thus at largest risk of developing skeletal events allowing patient selection and therapy planning. A recent market authorisation was received for ^{177}Lu-DOTA-tyr^{3}-octreotate or Lutathera with a fixed activity prescription. This treatment increasing survival of more than 10 months is indicated

in case of metastatic neuroendocrine tumours, but it is administered as if it was a form of chemotherapy instead of radiotherapy.

The absence of radionuclide therapy reimbursement in Europe is a barrier for establishing routine clinical dosimetry. Moreover, many centres performing radionuclide therapies have no or not enough medical physicists. When organising clinical trials for radionuclide therapies, efficacy and toxicity should be separately considered in terms of absorbed doses to target volumes and organs at risk. In addition, although the absorbed dose to the organs at risk is not directly linked to the absorbed dose to the tumour lesions the analysis has to be done according to probabilities: Normal Tissue Complication Probability and Tumour Control Probability. Consequently, according to specificities of each patient treated by radiopharmaceuticals an image guided theranostic conformal radiotherapy could be developed. The remaining question is whether radionuclide therapies can be considered as radiotherapy treatment or as a sort of chemotherapy.

Almost all radiopharmaceuticals are prescribed according to fixed activity: does one activity for MRT fit all patients? With the safe amount of activity to administer determined based on responses by the most radiation sensitive patient cohort, it can be argued that the therapy may be delivered at a sub-optimal level. At the moment, MRT dosimetry does not have an established method to be used in routine clinical practice, so internal dosimetry is needed for radionuclide therapies, since we know that there is 20 % uncertainty in the measured absorbed dose. For example, a study showed ^{90}Y-DOTATOC effectiveness in treatment of neuro-endocrine patients but dosimetry is unknown: 13 % of patients have severe hematologic toxicity and 9 % very severe renal toxicity. In addition, a case report with no dosimetric information, has shown visual deficit due to optic nerve damage possibly caused by ^{177}Lu-PSMA-617 treatment in patients with metastatic castrate-resistant prostate cancer. The amount of evidence showing the benefits of dosimetry-based prescription methods has surprisingly not led to an increase in dosimetry driven clinical trials for radionuclide therapy. At the moment, even in large clinical trials on metastatic castration resistent prostate cancer patients, no dosimetry, or post-therapy verification, is being carried out. Fixed activities ^{177}Lu-PSMA are being used in multiple therapy cycles, without any individual dosimetry. As protocols have not been modified since 10 years, there is no indication about the absorbed dose that could prevent radio-induced toxicity or define an efficient minimum absorbed tumour dose. Dosimetry based prescription methods for ^{90}Y glass microspheres have been recommended by experts.

The EANM dosimetry committee has raised the issue that, in some cases, optimisation according to the Council Directive 2013/59/Euratom would lead to prescribing activities that exceed the posology of current radionuclide therapies according to the EMA market authorisations. That would fall in an experimental therapy setting, thus reducing the application of the radiopharmaceutical. As radiopharmaceuticals are administered as a form

of chemotherapy, the methods to prove their therapeutic effectiveness have to be reconsidered in order to change the way of their prescription.

Late effects, such as induction of secondary cancers in non-targeted tissues, have to be considered due to the increase of patients treated with radionuclide therapies. A safe and effective therapeutic window would be a means to optimise radionuclide therapies by limiting off-target absorbed dose.

Investigational clinical trials need to be designed in a way that dose-escalation steps be based on both activity and absorbed dose, to organs at risk and to target volumes, in order to ensure that both the optimization principle and the requirement for a patient specific prescription are followed in radionuclide therapy.

Radionuclide therapies lack knowledge on the dose-effect relations in terms of radiation-induced damages in contrast to other forms of radiotherapy. Radiobiology for MRT is unknown. The knowledge of the radiobiology for internal exposures is in most cases derived from external beam radiation exposure knowledge. Dose rate effects with MRT have to be considered because MRT induces prolonged irradiation. In addition, DNA damage repair process during dose delivery, lower limit in dose rate and RBE (Relative Biological Effectiveness) of high LET (Linear Energy Transfer) particles have to be taken into account to analyse radio-induced damages. Absorbed dose distributions are non-uniform with radionuclide therapies using short-ranged particle emitters. Ionisation can induce secondary biological effects such as cellular adaptive response or DNA-misrepair leading to secondary effects by ‘‘danger’’ signals from irradiated to non-irradiated cells, leading to off-target effects. Research into the radiobiology of radionuclide therapy and its internal exposures needs to be intensified.

Research in microdosimetry should be developed to analyse the impact of radiation track length and ionisation density on specific targeted cancer cells and to identify the appropriate macrodosimetry model by taking into account the non-uniform dose distribution, the range in tissue and the LET character of the radiation particles.

In conclusion, should MRT be considered as radioactive chemotherapy or molecular radiotherapy? To improve care of patients treated by MRT and increase their survival an individual dosimetry based treatment planning has to be established and standardised. Prospective clinical trials for drug development should be guided by dosimetry considering adaptive dose response models and comparing dosimetry and activity.

4 Summary of the roundtable discussion: policy implications and research needs

Maria Del Rosario Perez (WHO), Miroslav Pinak (IAEA), speakers, representatives from DG ENER and DG SANTE, Geraldine O'Reilly (Moderator)

The representative of WHO presented the WHO views on research needs in some areas of nuclear medicine and policy implications related to radiation protection (RP). After setting the scene from a public health perspective addressing the UN sustainable development goals (SDGs) she highlighted the role of nuclear medicine in the management of non-communicable diseases and the need to ensure access to quality health-care services towards the achievement of universal health coverage (UHC). She gave as examples some key areas in terms of RP challenges such as: (i) the development, the production, the supply and the use of diagnostic, therapeutic, and theranostic radioisotopes and radiopharmaceuticals; (ii) the design, manufacturing, commercialization, procurement, and operation of nuclear medicine equipment and instrumentation; (iii) the radiopharmacy facility designs and infrastructures; (iv) the education, training, certification, accreditation, and licensing of health workers; (v) the methodology for dose and health risk assessment of patients, comforters, workers and public; (vi) the development, update and implementation of standards, norms and regulations; and (vii) the identification of research, gaps and the implementation of a strategic research agenda.

There is a need for skilled health workforce such as nuclear medicine physicians, technologists, radiologists and radiographers specialised in hybrid imaging, medical physics experts, biomedical engineers, radiopharmacists, and radiochemists.

Research challenges in nuclear medicine include long-term risks from low-dose internal exposure in adults and especially in children, internal dosimetry considering methodology, tools and protocols, evidence generation considering preclinical evaluation, clinical trials, research partnerships, quality assurance, and ethical issues.

Instruments exist such as the international Basic Safety Standards and supporting safety guides, Council Directive 2013/59/Euratom – the European BSS Directive – and related guidance, guidance from the EMA and local agencies, international Pharmacopea, Good Manufacturing Practices (WHO, IAEA, EC), WHO Lists of Priority Medical Devices. However, more instruments are needed because some issues remain.

The representative of IAEA pointed out that the increasing number of patients benefiting of nuclear medicine procedures around the world has raised the need to avoid any related accidental radiation exposure. Incidents can happen during the preparation of radiopharmaceuticals, during the management of radioactive materials, and during the procedure on the patient. IAEA has proposed to include radionuclide therapy in SAFRON,

Safety in Radiation Oncology, an anonymous reporting and learning system of radiotherapy incidents and near misses, designed to support the sharing of safety-related information.

A new safety guide (IAEA SSG-46) on nuclear medicine was published in 2018. It provides recommendations on radiation protection in nuclear medicine. However, there is a need for new guides. This need in nuclear medicine has clearly been mentioned in the Bonn Call for Action[21] (Action N° 5).

In the discussion that followed, the experts noted that a closer collaboration between radiation protection experts and practitioners using radionuclides has to be developed, an assessment of the level of dosimetry is needed according to radiotherapy procedures, and research funds lack in the fields of radiobiology, dosimetry, and treatment optimisation. Randomised clinical trials using radiopharmaceuticals are needed for better treatment outcomes. Radiosensitive patients, such as children, raise the issues on the selection of patients who had benefits from radionuclide therapies, and on dosimetry (absorbed dose).

The experts repeated that there is a lack in medical physicists, and radiation protection training in the field of nuclear medicine. According to the BSS Directive, medical professionals have to be aware of the concept of dose. Moreover, the experts noted that medical physicists should have a more prominent role in treatment planning using radiopharmaceuticals. The BSS Directive states in Article 58(d) that *"in standardised therapeutical nuclear medicine practices as well as in radiodiagnostic and interventional radiology practices, involving high doses as referred to in point (c) of Article 61(1), a medical physics expert shall be involved"*. It further states in Article 83.2 that *"depending on the medical radiological practice, the medical physics expert takes responsibility for dosimetry, including physical measurements for evaluation of the dose delivered to the patient and other individuals subject to medical exposure"*.

Lack of financial resources and limited access to treatment (new radioisotopes are very expensive) remain two issues that could be solved by using a more holistic approach and not on a country by country basis. More solidarity is needed to progress with, for example, a greater involvement of the pharmaceutical industry that should consider the benefit of each treatment and not only the application of standards. There is a dysfunction between what is needed and what is implemented in national regulation. Again, training is essential to apply standards, but also to understand the concepts of dosimetry.

[21] https://www.iaea.org/sites/default/files/17/12/bonn-call-for-action.pdf

Conclusions[22]

Article 56 of Council Directive 2013/59/Euratom – the European BSS Directive – requires that: *"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*". However, a European Survey on radionuclide therapies administered in 2015 showed that there are needs to increase the implementation of individual dose planning and post-treatment verification as well as the systematic involvement of medical physicists who are not involved in a very large number of centres. The reasons for these issues are a lack of financial resources, high costs, lack of infrastructures, lack of dosimetry tools, lack of training of multidisciplinary staff, and reimbursement issues. In radionuclide therapy, dosimetry and treatment planning should be performed in order to comply with the BSS Directive and also for generating robust data on safety and efficacy of radionuclide therapies. In addition, a radiation safety culture in molecular radiotherapy has to be developed.

The requirements for obtaining marketing authorization for new radiopharmaceuticals should be strengthened to entail sufficient dosimetry data from early clinical trials in order to limit uncertainties. Standardisation is not correctly applied, so detailed guidelines are needed. Personalized treatment planning methods should be part of the market registration process for radionuclide therapies, enabling their placement within the realm of radiotherapies instead of chemotherapy.

Drug prescription according to a maximum safe amount of activity, based on responses by the most radiation sensitive patient cohort, may lead to sub-optimal therapies. On the other side, an optimal therapy, using a dose according to the dosimetry assessment exceeding the maximum tolerable activity, would fall in an experimental therapy setting thus reducing its application. Investigational clinical trials need to be designed considering radionuclide therapies' efficacy and toxicity in terms of activity and absorbed doses to target volumes and organs at risk with a view to follow the optimization principle and the requirement for a patient specific prescription.

Optimising the radionuclide therapy by establishing a safe and effective therapeutic window, considering also late effects such as induction of secondary cancers in off-target tissues, may lead to a lower and justifiable off-target absorbed dose.

[22] These conclusions were prepared by: L. Lebaron-Jacobs, G. O'Reilly, H. Janžekovič F. Bochicchio, R. Huiskamp, P. Krajewski, and P. Smeesters. They were assisted by F. Tzika and S. Mundigl from the European Commission.

Ambiguities in legislation whether radionuclide therapies can be considered as radiotherapy treatment or as chemotherapy result in a lack of appropriate dosimetry.

The rapid development of molecular radiotherapy with many new radiopharmaceuticals being produced requires to have a closer look to emerging radiation protection issues related to these therapies and to discuss how these issues can best be resolved. For new therapies, appropriate dose constraints for workers and the public need to be developed taking account of the fact that these therapies are often administered in multiple fractions. In addition, there are justification issues with the exposure of workers and members of the public, the risk of contaminations, existence of impurities, use of new alpha-emitters. In addition, specific radiation protection training has to be developed for new groups of medical professionals involved in nuclear medicine. Gathering of radiation protection data (including dosimetric, epidemiological, operational radiation protection experience) could help in establishing guidelines for all radiopharmaceuticals taking into account exposed carers and comforters, release criteria, dose constraints, access to other departments, waste management, deceased patients, and pregnancy.

Long-term effects due to the use of radiopharmaceuticals have been highlighted: toxicity on kidneys or salivary glands, hematologic diseases and second primary cancer. However, there is a lack of knowledge notwithstanding new evidence about radiation-induced non-cancer effects (brain...), dose-effect relations for tumours and non-targeted tissues. Finally, research in radiobiology for molecular radiotherapy needs to be intensified.

Limited access to these therapies due to their high cost raise the importance to discuss ethical aspects of molecular radiotherapy. An individual appropriate dosimetry is necessary to reduce toxicity of radionuclide therapies and to improve quality of life balancing toxicity versus survival. The fixed maximum tolerable activity dosing should be replaced by dosimetry based patient-specific treatment planning.

As a global conclusion, this seminar has highlighted the necessity of making serious progress in the implementation of Article 56 of the European BSS Directive throughout the EU, in particular in radionuclide therapy. This has various policy implications (marketing authorization process, infrastructures, equipment, development of dosimetry tools, training, costs and resources), as well as significant radiation protection implications (need of much more data and guidance). Important research needs have also been highlighted, particularly regarding long-term risks from low-dose internal exposure in adults and especially in children.

Getting in touch with the EU

In person
All over the European Union there are hundreds of Europe Direct information centres. You can find the address of the centre nearest you at: https://europa.eu/european-union/contact_en

On the phone or by email
Europe Direct is a service that answers your questions about the European Union. You can contact this service:
– by freephone: 00 800 6 7 8 9 10 11 (certain operators may charge for these calls),
– at the following standard number: +32 22999696 or
– by email via: https://europa.eu/european-union/contact_en

Finding information about the EU

Online
Information about the European Union in all the official languages of the EU is available on the Europa website at: https://europa.eu/european-union/index_en

EU publications
You can download or order free and priced EU publications at: https://publications.europa.eu/en/publications. Multiple copies of free publications may be obtained by contacting Europe Direct or your local information centre (see https://europa.eu/european-union/contact_en).
EU law and related documents
For access to legal information from the EU, including all EU law since 1952 in all the official language versions, go to EUR-Lex at: http://eur-lex.europa.eu

Open data from the EU
The EU Open Data Portal (http://data.europa.eu/euodp/en) provides access to datasets from the EU. Data can be downloaded and reused for free, for both commercial and non-commercial purposes.

MJ-AX-20-003-EN-N

Publications Office
of the European Union

ISBN 978-92-76-27010-2