Radionuclide therapy in nuclear medicine – developments and challenges

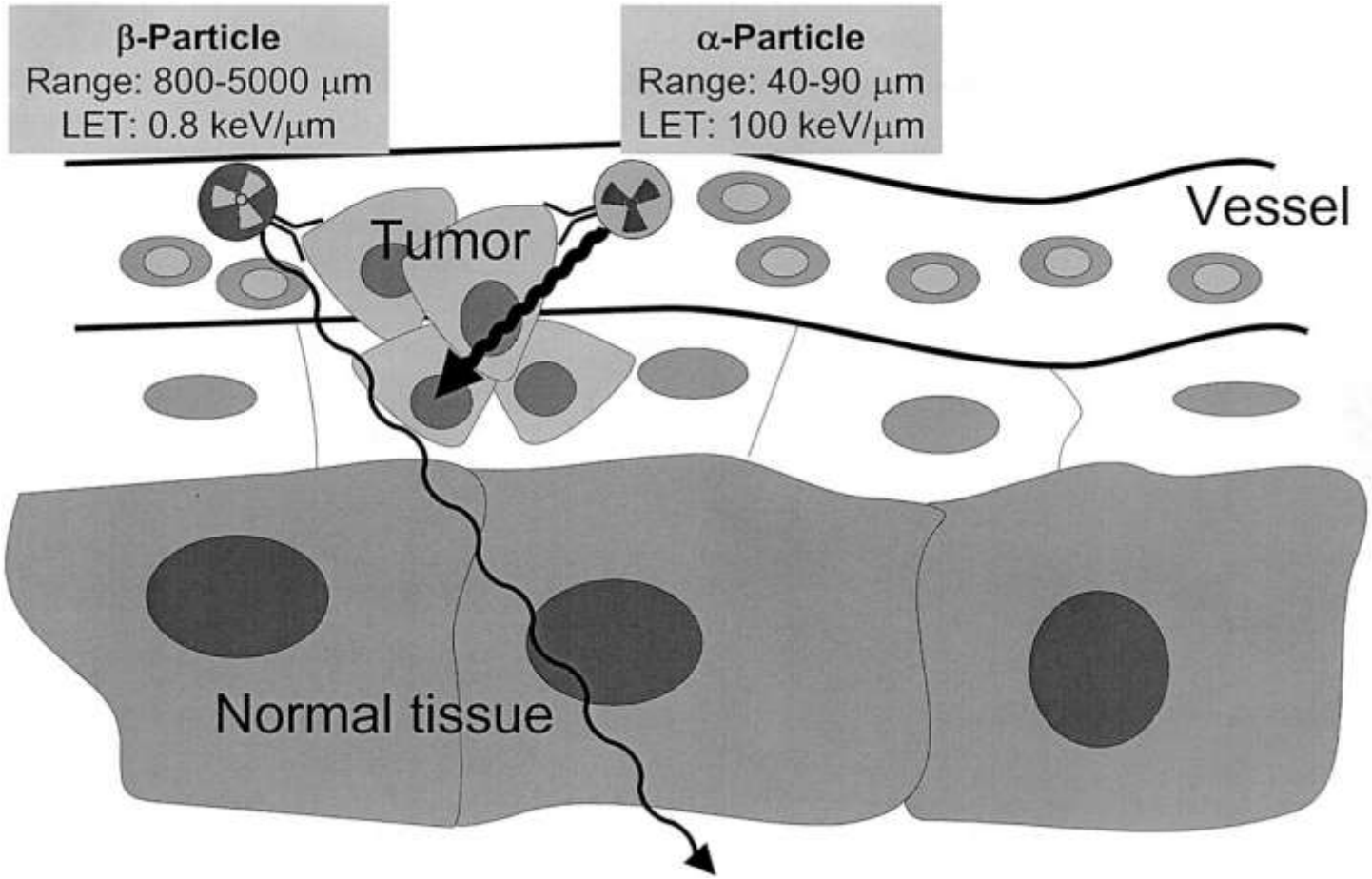
M Lassmann

Klinik und Poliklinik für Nuklearmedizin
Direktor: Prof. Dr. A. Buck

Contents

- Introduction
- Developments in Radionuclide Therapies
- Challenges
- Conclusion and Outlook

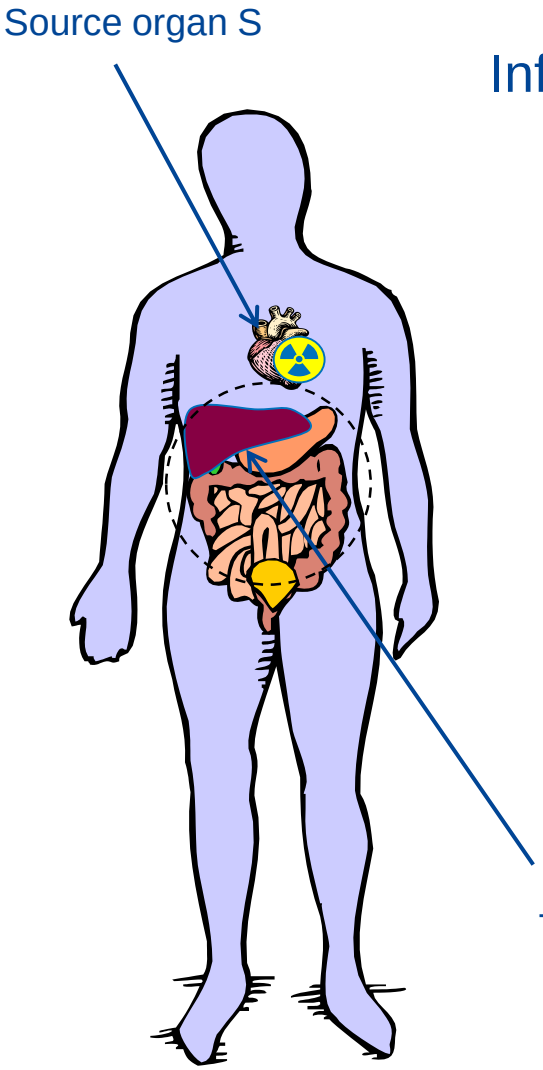
Targeted Therapy – Basic Principles



Nuclear Medicine Diagnostics and Therapy

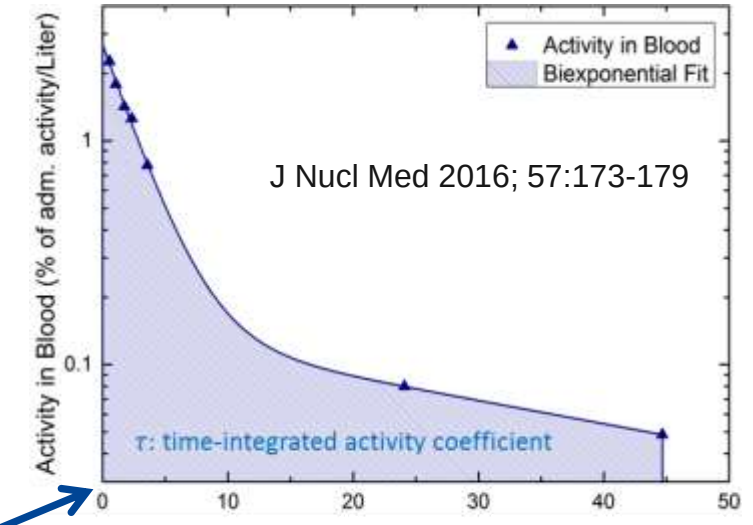
Diagnostics	Therapy
Low activities ~<1GBq, short-lived nuclides, γ/β^+ emitters	High activities: ~>1GBq for Beta-Emitters, 5-10 MBq for Alpha Emitters long-lived nuclides, α/β^- emitters
Stochastic risk	Deterministic damage and stochastic risk
Model-based dosimetry in a representative group of volunteers or patients	Patient-specific dosimetry
Optimize image quality	Maximize tumor absorbed doses
Minimizing radiation-associated risk	Minimize the absorbed doses to the organs-at-risk

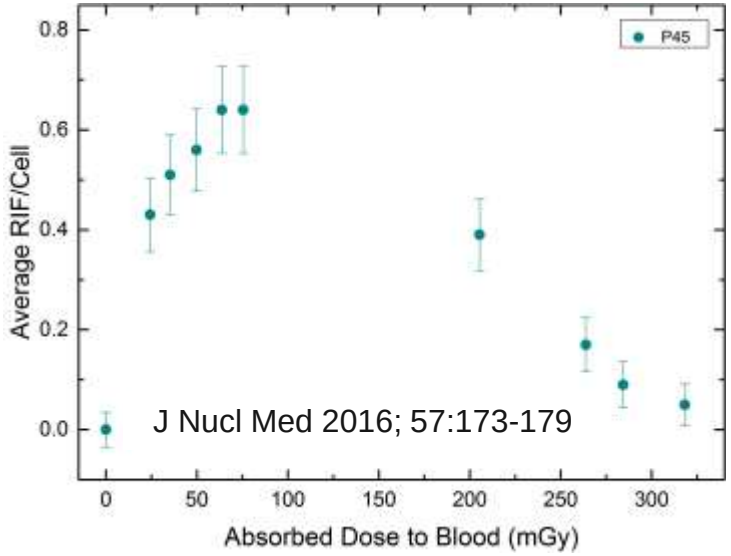
Special Challenges in Nuclear Medicine Therapy



Influencing variables in radionuclide therapies:

- Administered activity
- Physical and chemical properties of the radiopharmaceutical
- Spatial variability of the biodistribution
- Sources that irradiate targets
- Biological uptake and excretion
- DNA damage and Repair





Contents

- Introduction
- Developments in Radionuclide Therapies
- Challenges
- Conclusion and Outlook

Most Important Radionuclides used for Therapy

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

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

** incl. progeny

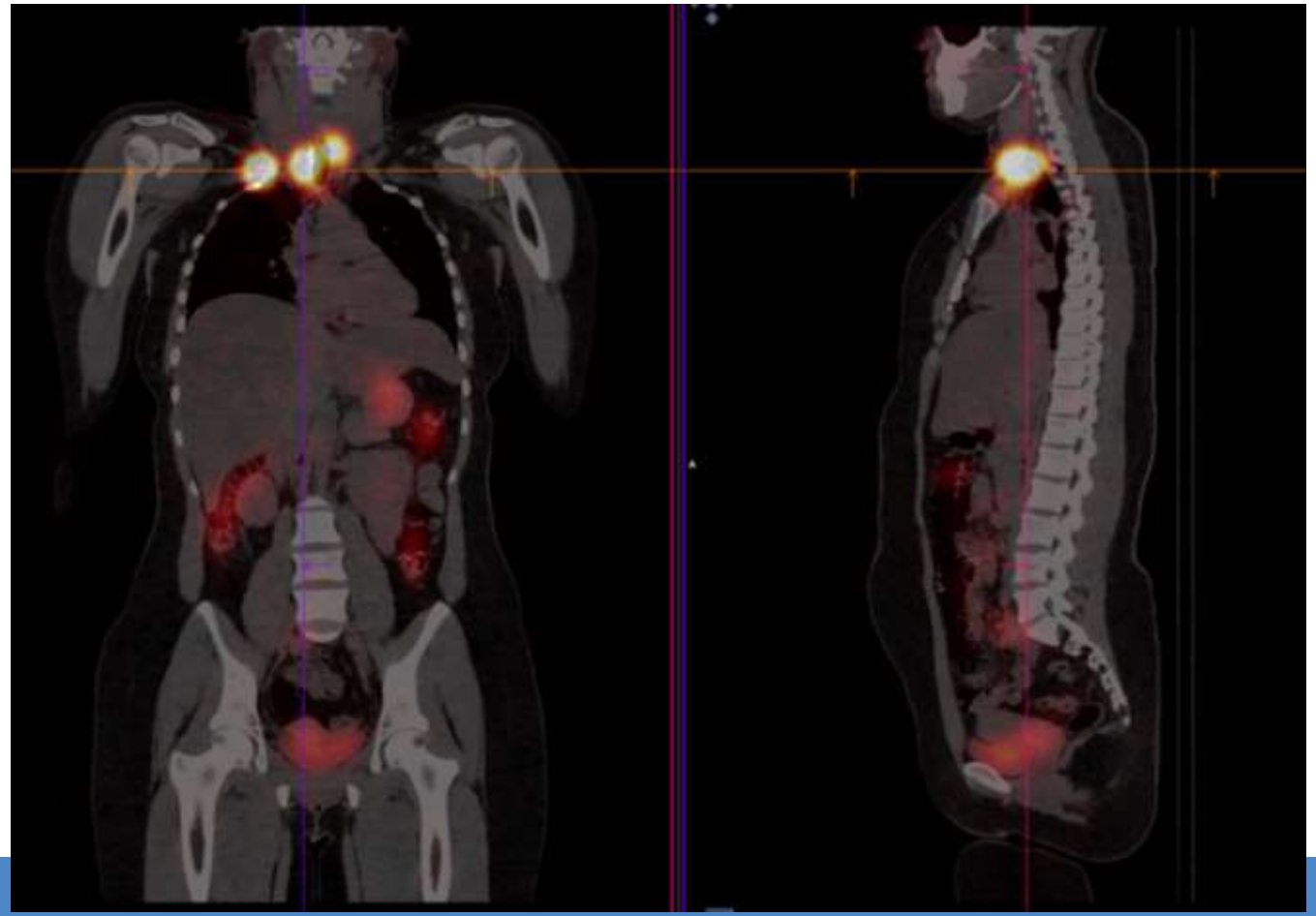
Data taken from http://www.lnhb.fr/nuclear-data/nuclear-data-table/

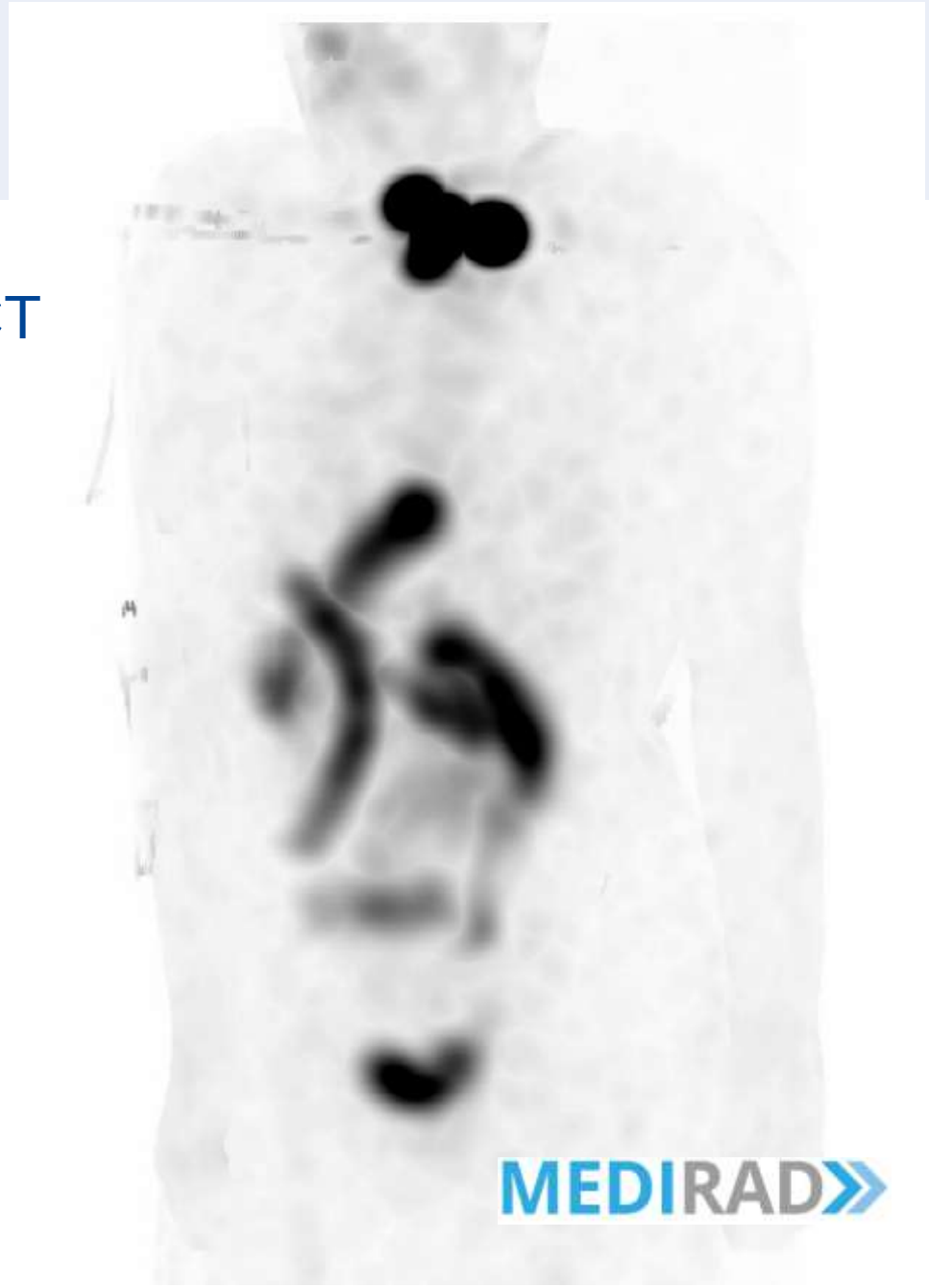
Therapy Modalities

- Metabolically active radiopharmaceuticals
  - Radioiodine Therapy of Thyroid Diseases (benign/malignant, I-131)
  - Bone Pain Palliative Treatment of Bone Metastases (Xofigo®, Ra-223)
- Specifically binding radiopharmaceuticals
  - Compounds addressing specific antigens or receptors
    - Dotatate or Dotatoc (Lutathera®, Lu-177), Neuroendocrine Tumor Treatment
    - MiBG (I-131), Neuroblastoma Treatment
    - PSMA-labelling ligands (Phase 3 “Vision Trial”, Lu-177), Prostate Cancer Metastases Treatment
  - Antibodies (Lu-177, Y-90 Zevalin®), Lymphoma Treatment
- Locoregional therapies
  - Selective Internal radiotherapy (Y-90, Ho-166)*, Treatment of Liver Metastases
  - Radiosynoviorthesis (Er-169, Re-188, Y-90), Pain Treatment in Arthritis Patients

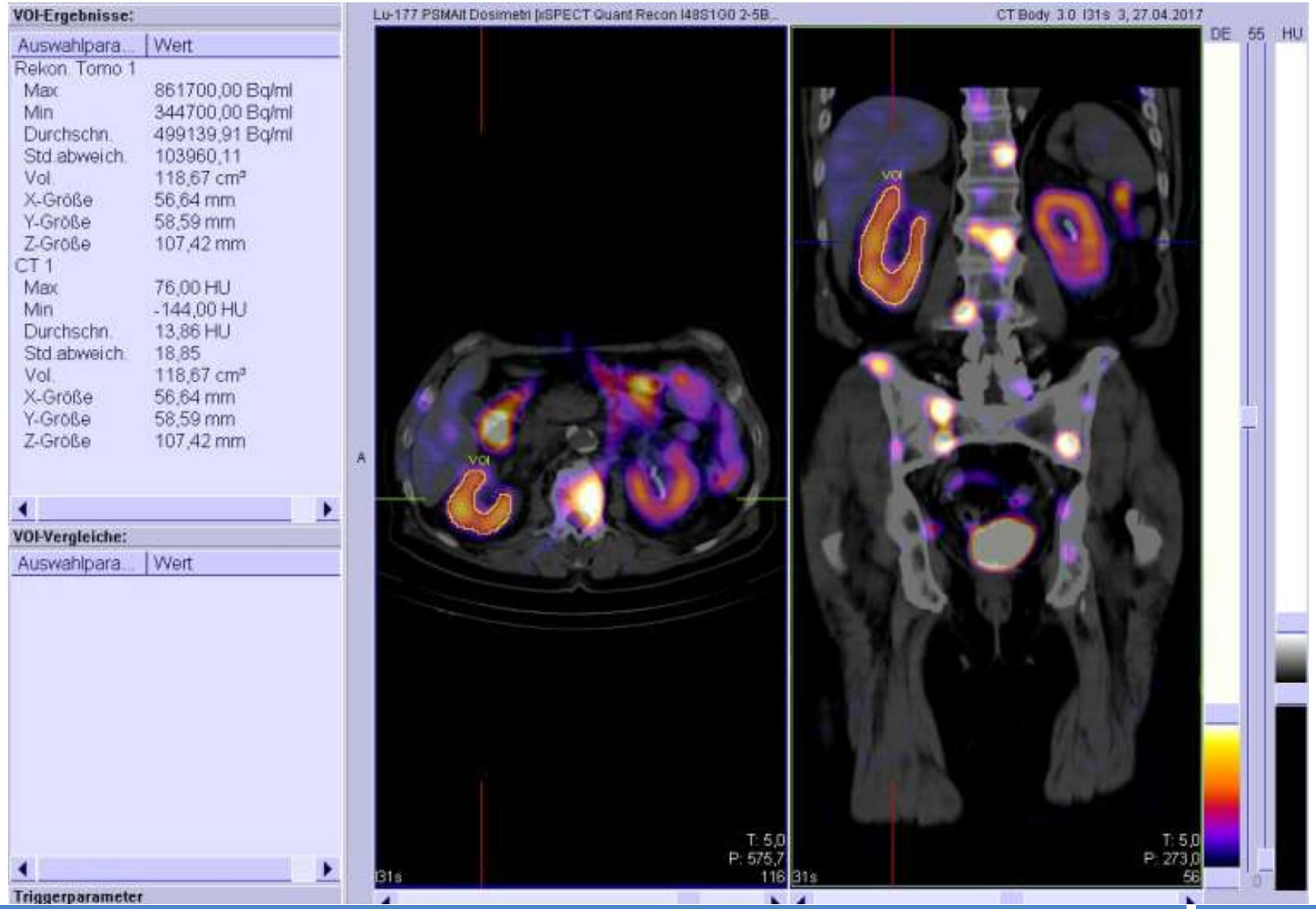
Radioiodine Therapy of Thyroid Cancer

48h SPECT/CT





The Treatment of Prostate Cancer with Lu-177-PSMA



Alpha emitting isotopes for potential therapeutic applications in nuclear medicine

Radionuclide	Half-Life	Max. Particle Energy*
At-211	7.2 hrs	6.0 MeV
Bi-213	46 min	6.0 MeV
Ra-223	11.4 days	5.8 MeV
Ac-225	10.0 days	5.9 MeV

* without progeny

Contents

- Introduction
- Developments in Radionuclide Therapies
- Challenges
- Conclusion and Outlook

Challenges in Radionuclide Therapies

- Availability of Radionuclides

SAMIRA

European Study on Medical, Industrial and Research Applications of Nuclear and Radiation Technology

Final Report Available at:

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

Conclusion 10:

Medical Radioisotopes: Security of Supply:

Research reactor based Mo-99 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.

Challenges in Radionuclide Therapies

- Availability of Radionuclides
- Access to treatment in all countries

  - Lack of trained staff (Physicians, Physicists, Radiochemists)
  - Lack of Adequate Facilities for Treatment
  - Reimbursement Issues

Challenges in Radionuclide Therapies

- Availability of Radionuclides
- Access to treatment in all countries
- Excessive requirements for manufacturing of radiopharmaceuticals (Dr. Neels)

Challenges in Radionuclide Therapies

- Availability of Radionuclides
- Access to treatment in all countries
- Excessive requirement for manufacturing of radiopharmaceuticals (Dr. Neels)
- Standardization of quantitative imaging (EANM/EARL)

EARL · EANM Forschungs GmbH / EANM Research Ltd. · Schmalzhofgasse 26· 1060 Vienna, Austria
Tel: +43-(0)1-890 44 27 · Fax: +43-(0)1-890 44 27-9 · E-mail: earl@eanm.org · URL: http://earl.eanm.org
Austrian Registry of Corporations: FN 291161d · VAT-ID No. in Austria: ATU 63436026

FDG PET/CT Accreditation

RESEARCH 4 LIFE©
an EANM initiative

EARL initiated this accreditation programme in order to support imaging sites, which perform FDG-PET/CT oncology examinations, in meeting the requirements indicated in the EANM imaging guideline.

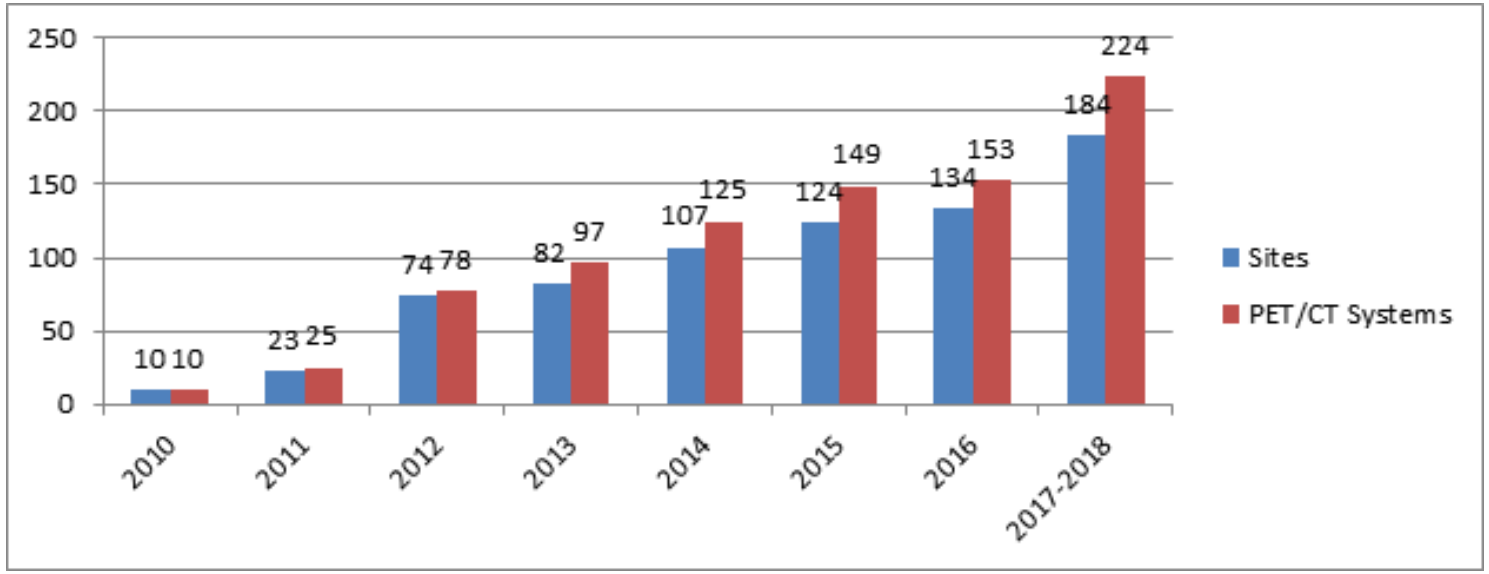
- aims at providing a minimum standard for the acquisition and interpretation of PET and PET/CT scans with [^{18}F]-fluorodeoxyglucose (FDG).
- goal is to enhance the quality standard of PET/CT investigations for both daily use and for multicentre studies
- PET/CT accreditation ensures similar performance of PET/CT systems within a multicentre setting by harmonising acquisition and processing of PET/CT scans.
- Accredited PET/CT centres of excellence can compare, exchange and combine FDG-PET/CT findings, including SUV values, since data are collected and processed in a standardised manner.

EARL · EANM Forschungs GmbH / EANM Research Ltd. · Schmalzhofgasse 26· 1060 Vienna, Austria
Tel: +43-(0)1-890 44 27 · Fax: +43-(0)1-890 44 27-9 · E-mail: earl@eanm.org · URL: http://earl.eanm.org
Austrian Registry of Corporations: FN 291161d · VAT-ID No. in Austria: ATU 63436026

FDG PET/CT Accreditation

RESEARCH 4 LIFE©
an EANM initiative

GROWTH OF EARL since first established

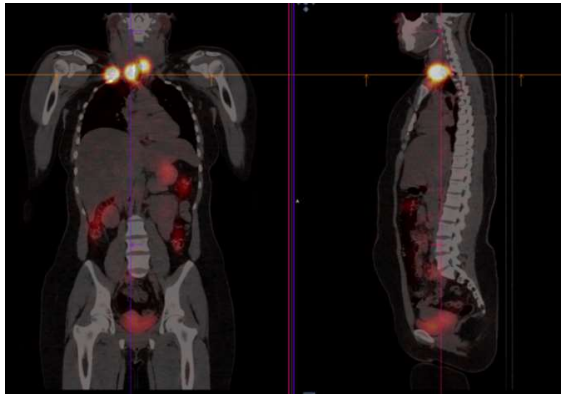


EARL · EANM Forschungs GmbH / EANM Research Ltd. · Schmalzhofgasse 26· 1060 Vienna, Austria
Tel: +43-(0)1-890 44 27 · Fax: +43-(0)1-890 44 27-9 · E-mail: earl@eanm.org · URL: http://earl.eanm.org
Austrian Registry of Corporations: FN 291161d · VAT-ID No. in Austria: ATU 63436026

Progress in Quantitative Imaging - SPECT/CT

Integrated CT:

- Morphologic correlation
- Measurement of the attenuation map
- Scatter correction by using triple window techniques
- Quantitative analysis



MRTDosimetry

15HLT06 MRTDosimetry
MRT DOSIMETRY
Metrology for clinical implementation of dosimetry in molecular radiotherapy

June 2016 - May 2019

MRTDosimetry

15HLT06 MRTDosimetry
MRT DOSIMETRY
Metrology for clinical implementation of dosimetry in molecular radiotherapy

Main goals:

- To improve the accuracy and metrological traceability in the calculation of absorbed dose from time-sequences of quantitative imaging measurements

- 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.

June 2016 - May 2019

Final publishable report: http://mrtdosimetry-empir.eu/wp-content/uploads/2019/08/15HLT06_Publishable_Report_M36_Final.pdf

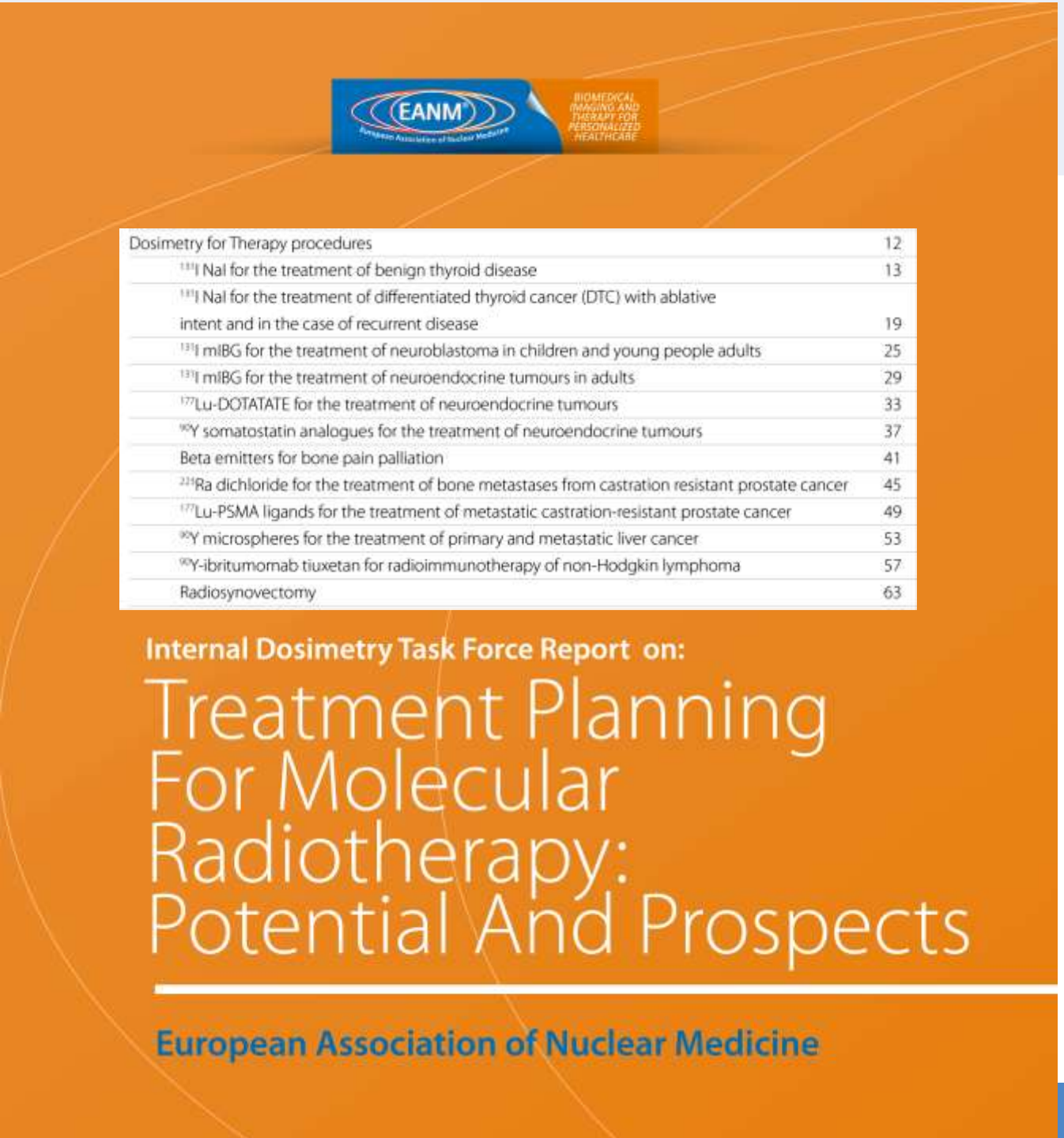
Challenges in Radionuclide Therapies

- Availability of Radionuclides
- Access to treatment in all countries
- Excessive requirement for manufacturing of radiopharmaceuticals - Dr. Neels
- Standardization of quantitative Imaging (EANM/EARL)
- Balance accuracy vs. efforts for clinical dosimetry (EANM) – Dr. Sjögreen-Gleisner

Council directive 2013/59 Euratom

Article 56 Optimisation

- ‘For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.’
- The term ‘radiotherapeutic’ is specifically defined as ‘including nuclear medicine for therapeutic purposes’ (Definition 81).



Analysis of Potential and Prospects for Treatment Planning in Preparation of the Implementation of the European Council Directive 2013/59

Available at:
https://www.eanm.org/publications/idtf-report/

Challenges in Radionuclide Therapies

- Availability of Radionuclides
- Access to treatment in all countries
- Excessive requirement for manufacturing of radiopharmaceuticals - Dr. Neels
- Standardization of quantitative Imaging (EANM/EARL)
- Balance accuracy vs. efforts for clinical dosimetry (EANM) – Dr. Sjögreen-Gleisner
- Foster research efforts in dosimetry methodologies and radiobiology (EU)

MEDIRAD

4 year EC Horizon 2020 funded project (2017 – 2021)

- Increase knowledge of health effects of diagnostic and therapeutic medical radiation procedures.
- Improve recording and estimation of doses.
- Develop evidence based policies.

WP3 Impact of low dose radiation exposure from ^{131}I radioiodine ablation of thyroid cancer

- Establish range of absorbed doses to healthy organs.
- Determine 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 multicentre setting.

MEDIRAD – WP3

- Multicenter, international, prospective observational study.

- 100 adults with differentiated thyroid carcinoma post-total thyroidectomy will be recruited across four centres:
  - UMR & UKW (Germany)
  - INSERM & IUCT (France)
  - RMH (UK)

- 1.1 - 3.7 GBq ^{131}I
  - Mode of TSH stimulation at clinician discretion

The Role of Radiobiology

“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 is under investigation, and will expand if dosimetry data are made available to compare with outcomes.”

LETTER TO THE EDITOR

From fixed activities to personalized treatments in radionuclide therapy: lost in translation?

G. D. Flux[1] · K. Sjogreen Gleisner[2] · C. Chiesa[3] · M. Lassmann[4] · N. Chouin[5,6] · J. Gear[1] · M. Bardiès[7] · S. Walrand[8] · K. Bacher[9] · U. Eberlein[3] · M. Ljungberg[2] · L. Strigari[10] · E. Visser[11] · M. W. Konijnenberg[12]

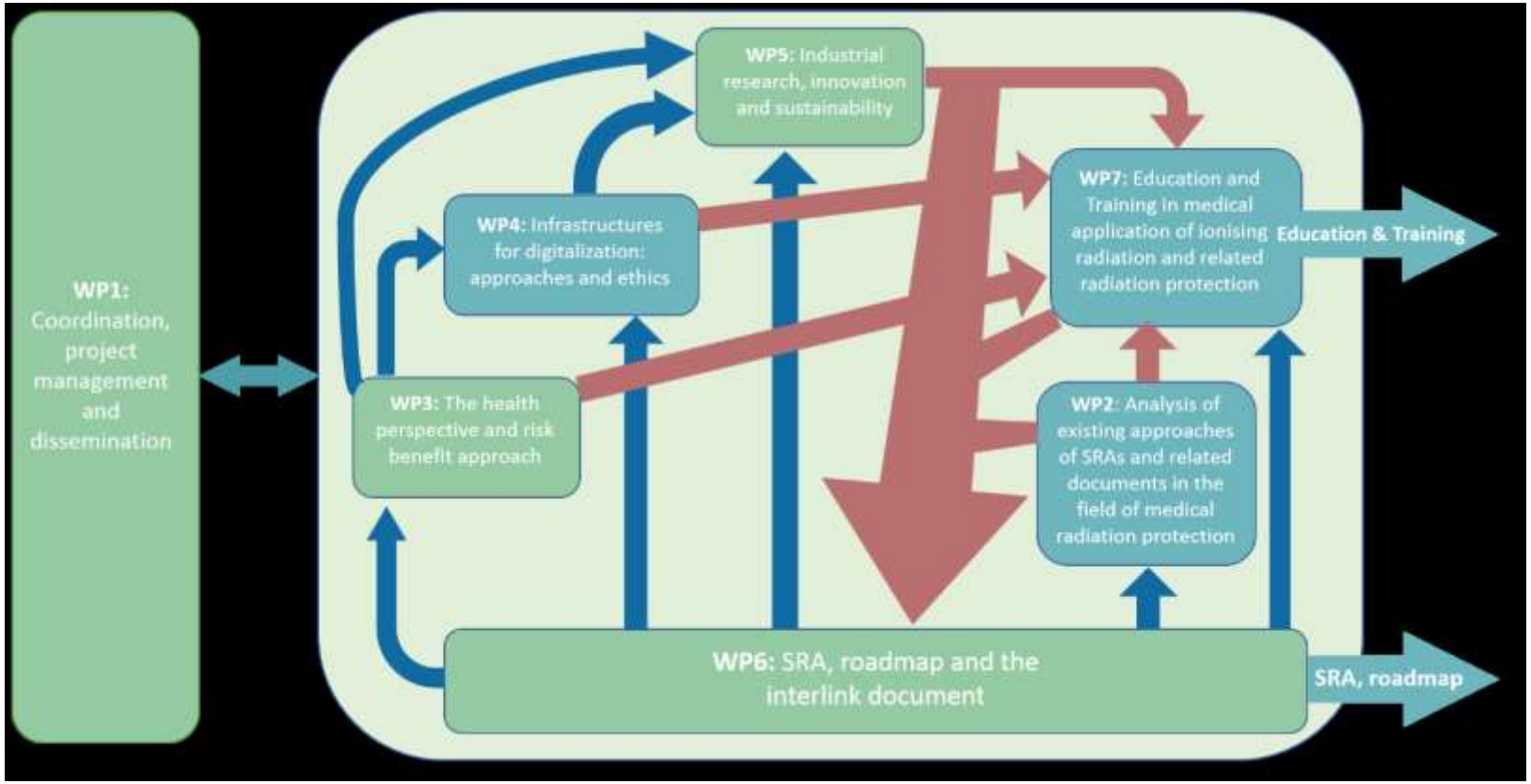
Research agenda and Roadmap

Horizon 2020 Call: NFRP-2019-2020 (Nuclear Fission and Radiation Protection Research)

Topic: NFRP-2019-2020-13

Proposal Title:

EURope**A**n **MED**ical application and Radiation p**rO**te**C**tion Concept: strategic research agenda a**N**d **RO**admap inter**L**inking to hea**L**th and digitisation aspects



Acronym:

EURAMED rocc-n-roll

Submitted for EURAMED by EIBIR

Challenges in Radionuclide Therapies

- Availability of Radionuclides
- Access to treatment in all countries
- Excessive requirement for manufacturing of radiopharmaceuticals - Dr. Neels
- Standardization of quantitative Imaging (EANM/EARL)
- Balance accuracy vs. efforts for clinical dosimetry (EANM) – Dr. Sjögreen-Gleisner
- Foster research efforts in dosimetry methodologies and radiobiology (EU)- NFRP-13
- Implement dosimetry in early stages of clinical trials (phase I/II) (EU)

Council directive 2013/59 Euratom

Article 56 Optimisation

- ‘For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.’
- The term ‘radiotherapeutic’ is specifically defined as ‘including nuclear medicine for therapeutic purposes’ (Definition 81).

EMA Posology – Most Recent Examples (1/2)

Ra-223 XOFIGO

The dose regimen of Xofigo is an activity of 55 kBq per kg body weight, given at 4 week intervals for 6 injections.

Safety and efficacy beyond 6 injections with Xofigo have not been studied.

28/09/2018 Xofigo - EMEA/H/C/002653 - A20/1459/C/2653/0028

Xofigo : EPAR - Product Information (PDF/375.94 KB) (updated)

First published: 28/11/2013

Last updated: 11/10/2018

EMA Posology – Most Recent Examples (2/2)

Lu-177 LUTATHERA

The recommended treatment regimen of Lutathera in adults consists of 4 infusions of 7,400 MBq each. The recommended interval between each administration is 8 weeks which could be extended up to 16 weeks in case of dose modifying toxicity

- 21/03/2018 Lutathera - EMEA/H/C/004123 - IAIN/0003
- Lutathera : EPAR - Product Information (PDF/794.29 KB)
- First published: 17/01/2018
- Last updated: 11/04/2018

https://www.ema.europa.eu/en/documents/product-information/lutathera-epar-product-information_en.pdf

EMA Posology – Most Recent Examples (2/2)

Lu-177 LUTATHERA

The recommended treatment r ns of 7,400 MBq each. The recommended /hich could be extended up to 16 weeks in ca

- –21/03/2018 Lutathera - E
- –Lutathera : EPAR - Prod
- –First published: 17/01/2(
- –Last updated: 11/04/201

https://www.ema.europa.eu/en/do ct-information_en.pdf

Table 12. Absorbed dose estimates for lutetium (^{177}Lu) oxodotreotide from NETTER-1 phase III study (Olinda output)

Organ	Organ absorbed dose (mGy/MBq) (n = 20)	
	Mean	SD
Adrenals	0.04	0.02
Brain	0.03	0.02
Breasts	0.03	0.01
Gallbladder Wall	0.04	0.02
Lower Large Intestine Wall	0.03	0.02
Small Intestine	0.03	0.02
Stomach Wall	0.03	0.02
Upper Large Intestine Wall	0.03	0.02
Heart Wall	0.03	0.02
Kidneys	0.65	0.29
Liver	0.49	0.62
Lungs	0.03	0.01
Muscle	0.03	0.02
Ovaries**	0.03	0.01
Pancreas	0.04	0.02
Red Marrow	0.03	0.03
Osteogenic Cells	0.15	0.27
Skin	0.03	0.01
Spleen	0.85	0.80
Testes*	0.03	0.02
Thymus	0.03	0.02
Thyroid	0.03	0.02
Urinary Bladder Wall	0.45	0.18
Uterus**	0.03	0.01
Total Body	0.05	0.03

*n=11 (male patients only)
**n=9 (female patients only)

Challenges in Radionuclide Therapies

- Availability of Radionuclides
- Access to treatment in all countries
- Excessive requirement for manufacturing of radiopharmaceuticals - Dr. Neels
- Standardization of quantitative Imaging (EANM/EARL)
- Balance accuracy vs. efforts for clinical dosimetry (EANM) – Dr. Sjögreen-Gleisner
- Foster research efforts in dosimetry methodologies and radiobiology (EU)- NFRP-13
- Implement dosimetry in early stages of clinical trials (phase I/II) (EU)
- Waste management of long-lived impurities in therapeutic radionuclides

Waste management

- Long-Lived Impurities (Examples)
  - 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 L: 21.8 Years)

    0.5 % ^{227}Th (Half-Life L: 18.7 Days)

Contents

- Introduction
- Developments in Radionuclide Therapies
- Challenges
- Conclusion and Outlook

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 EU directive and in order to generate robust data on safety and efficacy. Examples are provided by the EANM IDTF Report

- Further standardization of dosimetry methods in Nuclear Medicine is needed. There is, presently, more expertise in Europe than in other parts of the worlds

Summary and Conclusion

- Radionuclide therapy is highly interdisciplinary. All 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 SRA, to elucidate the role of biodistribution studies, dosimetry and radiobiology in radionuclide therapies
- The waste management of therapeutically uses radiopharmaceuticals should be unified throughout the EU

Thank you!

Contact: Lassmann_M@ukw.de