NUCLEAR MEDICINE EUROPE
the industry association

Dosimetry in context of Therapeutic Radiopharmaceuticals

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What are therapeutic radiopharmaceuticals (tRPs)?

tRPs are medicinal products which contain one or more radionuclides and are used for therapeutic purposes, mostly in oncology. They are administered systemically and can therefore reach metastatic tumours throughout the body. tRPs can be radioligand therapies (RLTs, where the radionuclide is bound to a ligand) or radionuclides on their own (e.g. Sodium Iodine-131). tRPs are by nature different to other treatment modalities using ionizing radiation.

Locally administered ionizing radiation

The radiation dose delivered externally by medical equipment (**External Beam Radiation Therapy, EBRT**) or internally through medical devices (**Brachytherapy / Selective Internal Radiation Therapy, SIRT**) can be tightly controlled in space, time and intensity. The organs-at-risk depend on the location of the tumour that is to be irradiated in the individual patient.

Systemically administered ionizing radiation

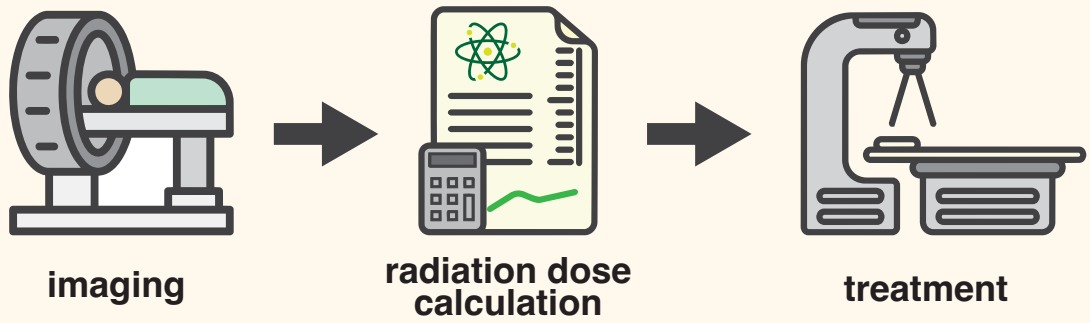
The **absorbed dose (AD)** of radiation delivered by a tRP depends on the systemic distribution throughout the body based on the properties of the molecule and patient-specific kinetics in tissue. In the case of RLTs, the ligand directs the distribution of the isotope. The organs-at-risk are therefore dependent on the tRP but independent of the location of the tumour. Thus, for a particular ligand, the pattern of organs at risk will be similar across patient populations and the AD depend on molecule distribution and kinetics.

What is dosimetry?

Dosimetry is the measurement and calculation of ionising radiation delivered to human tissue (organs, lesion, tissues or total body). It is commonly used to improve medical outcomes while minimizing exposure to normal tissue or the probability for toxicity. It involves different procedures in different applications:

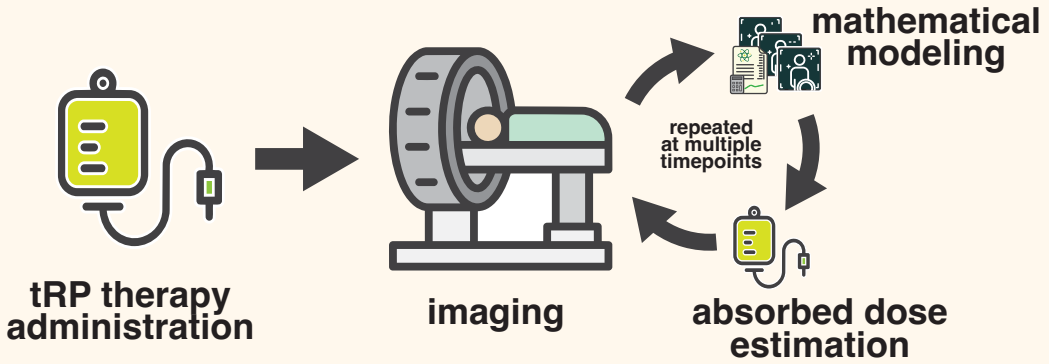
• In dosimetry for EBRT and brachytherapy the necessary radiation is calculated and applied externally/locally with high precision based on prior imaging of the region surrounding the primary tumour.

Dosimetry for external beam radiation and brachytherapy



• In contrast, dosimetry for tRPs involves imaging of the patient **usually at multiple timepoints** after treatment administration to estimate the AD in the tumour and other organs. It is worth noting that internal dosimetry for tRPs depends on tRP biodistribution, as well as being radionuclide-dependent. Each radionuclide has distinct decay characteristics (with potential daughter redistribution and organ uptake) and emits specific radiation types and energies, shaping the spatial AD distribution. Owing to challenging decay characteristics, image-based dosimetry is currently restricted to research settings for some radionuclides (mainly alpha-emitting e.g. Lead-212, Radium-223 and Actinium-225) and is not established in clinical practice.

Internal dosimetry



Divergent opinion on the role of dosimetry in tRP across the Nuclear Medicine community

Divergent opinions[1,2,3] across Nuclear Medicine specialists exist on how tRPs could be made more personalised. Some experts consider standardized activity dosing to risk under- or overtreating individual patients, and that dosimetry should be systematically performed in clinical practice at an individual level, de facto using the AD as a surrogate endpoint for determining efficacy and safety.

Other experts argue that AD is not a clear surrogate endpoint (i.e. substitute for a clinical endpoint) for efficacy and safety in tRPs; therefore, they suggest alternative approaches such as standardized dosing (whereby the benefit/risk profile is proved in clinical trials at a target patient population level) is more appropriate.

What is the role of the Nuclear Medicine Industry regarding dosimetry in tRPs?

The nuclear medicine industry contributes to the advancement of tRPs in many ways, including (but not limited to):

- developing highly sensitive scanners to support the increasingly diverse range of radionuclides used in tRPs,
- accelerating harmonisation and validation of dosimetry methodologies,
- developing and manufacturing tRPs with well-defined specific activity,
- generating evidence in robust clinical trials.

High quality dosimetry and clinical outcomes data supporting investigation of exposure-response relationships for different tRPs will characterise more appropriate exposure thresholds for this modality and reduce reliance on EBRT thresholds. All of this ultimately will drive better patient outcomes.

Risks of excessively stringent dosimetry requirements for tRPs

The Basic Safety Standards Directive (Directive 2013/59/EC Euratom) broadly requires individual treatment planning according to exposure to organ and tumour (Euratom Art 56.1) for all therapeutic uses of ionizing radiation. While the application of Article 56.1 is straightforward for local administrations of ionizing radiation, it is far more complex for systemically administered tRPs.

There is presently a lack of harmonised, validated methodology for dosimetry and insufficient evidence demonstrating that dosimetry-guided dosing clearly provides tangible benefits for the patient in terms of clinically meaningful improvements of safety or efficacy. While recognising that the situation is not identical for all tRPs, there are far-reaching practical implications for compulsory dosimetry in routine clinical practice such as:

- additional procedures for patients
- delayed access
- logistical/ regulatory complexity for healthcare systems

Nuclear Medicine Europe recommendations

Dosimetry is an important and valuable tool to guide optimal dosage finding during early development for tRPs. An integrated approach centred around benefit/risk considerations in specific disease settings, based on dosimetry, preliminary safety and efficacy, and exposure-response relationship should be pursued in early clinical trials. Further data needs to be collected in a structured manner to clarify its potential clinical impact.

- While Nuclear Medicine Europe recognises there are circumstances where there can be benefit from individual dosimetry-guided dosing, it should not be compulsory in all patients in large, late-stage clinical trials or routine clinical practice with approved tRPs while there is no harmonized, validated methodology and evidence of a clear clinical benefit.

- The current EU regulatory framework for radiopharmaceuticals is overly complex and fragmented[4,5,6,7]. Fast innovation in the field requires adaptations to recognise the specificities of tRPs. The medicines legislation (Directive 2001/83/EC / Regulation(EC) No 726/2004) and the Basic Safety Standards Directive (Directive 2013/59/EC Euratom) should function coherently to allow for sustainable, science-driven development of tRPs whilst safeguarding patient access, safety and quality of care.

- As a complex, multidisciplinary field, with great potential for patients, all involved stakeholders, including treatment developers/ industry must be engaged in multistakeholder dialogue to ensure evolving tRP guidelines are both fit for purpose and future proof.

References

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Glossary of Terms

AD : Absorbed Dose
EBRT : External Beam Radiation Therapy
RLT : Radioligand Therapy
SIRT : Selective Internal Radiation Therapy
tRP : Therapeutic Radiopharmaceutical