Internal Dosimetry in Nuclear Medicine: Challenges and Opportunities

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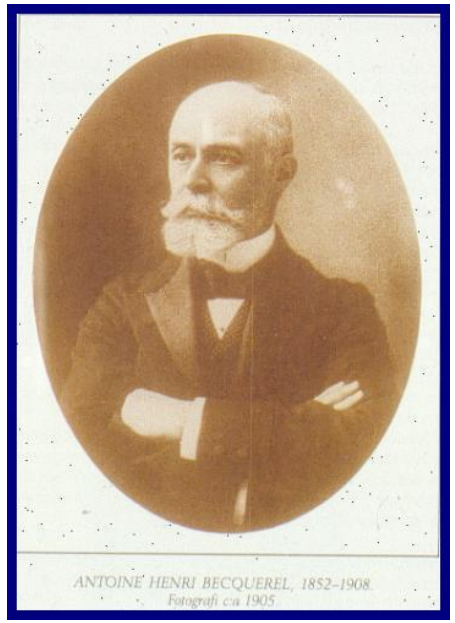
History

- Soon after the initial discovery of radioactivity by Henri Becquerel in 1896 and of Radium by Marie and Pierre Curie in 1898, the exciting opportunities offered by this strange phenomenon were exploited.
- Despite no understanding of the true biological effects of radiation, commercialization for its supposed health benefits were readily encouraged.
- First Molecular radiotherapy introduced in the 1930 s, the field is now rapidly expanding with many new agents for a growing number of indications.
- Internal radionuclide radiation dosimetry specifically deals with the deposition of radiation energy in tissue due to a radionuclide within the body.
- However, unlike external radiation dose (which can often be measured), internal radiation dose must be calculated

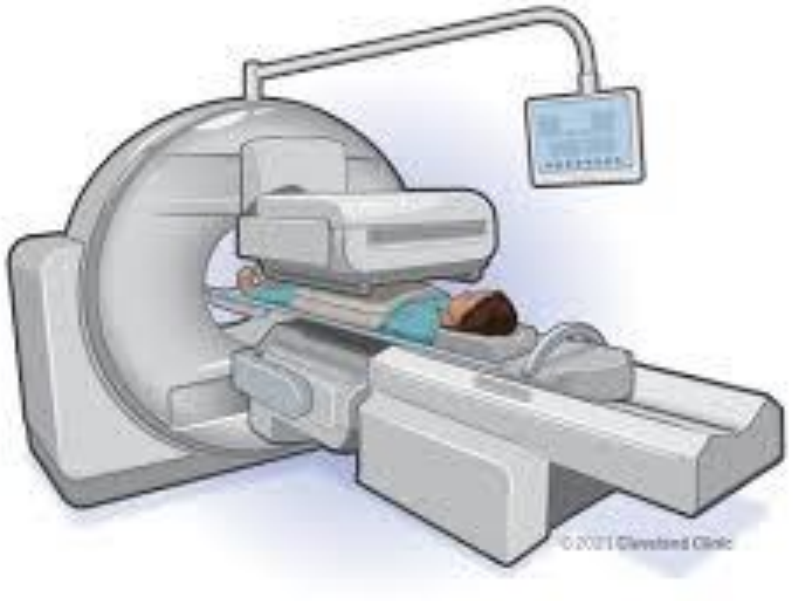


Radiopharmaceutical Administration

- The approved radiopharmaceuticals are administered to patients using a fixed activity (MBq) or activity per unit body weight (MBq/kg) approach, with few exceptions.
- For diagnostic radiopharmaceuticals, this is reasonable and safe; misadministrations occur, but doses to any individual organ are not likely to exceed 50 mSv, and effective doses are low.
- In therapeutic applications, however, our goal is to maximize the radiation dose to malignant tissues while sparing as much as possible the dose to normal, healthy tissues.
- This can only be accomplished by characterizing the uptake and clearance of activity in the various tissues of the body, which requires quantitative analysis of the results.
- Patients are generally receiving suboptimal therapy, compared to patients receiving external beam therapy for cancer, for whom, careful radiation therapy plans are made on a patient-specific basis every day.

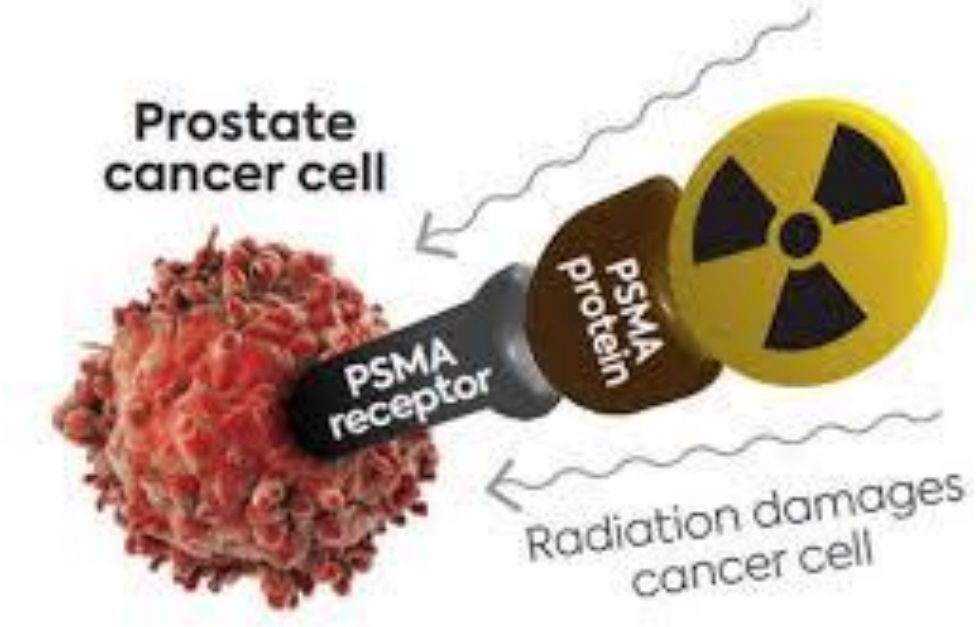
Dosimetry in Diagnostic

- For diagnostic radiopharmaceuticals, dosimetry is generally based on standard, anatomic models and average human or, oftentimes, animal kinetic (i.e., time–activity) data.
- May deviate rather significantly from the actual normal organ doses for individual patients
- Accuracy in Diagnostics: +/- say 20%
- Such dose estimates are useful for
  - first-order assessment of the relatively low stochastic risk associated with diagnostic agents
  - Dosimetric intercomparison of different radiopharmaceuticals
  - Imaging procedures intercomparison to minimize patient doses.



Dosimetry in Therapy

- At a time that many alternative treatments are emerging, including targeted therapies, immune- and gene-therapies,
- Molecular radiotherapy: capacity to image the biodistribution and to calculate the radiation absorbed doses delivered on a patient-specific basis,
- In radionuclide therapy with escalating administered activities and associated normal-tissue doses, serious radiation injury can ensue
- Accuracy in therapy: better than +/- 5% (like external radiation therapy)
- With the ongoing development of new radiopharmaceuticals and the increasing therapeutic application of such agents, internal dosimetry in nuclear medicine continue to evolve—from population-average and organ-level to patient-specific and localized (or voxel level) dose estimation.



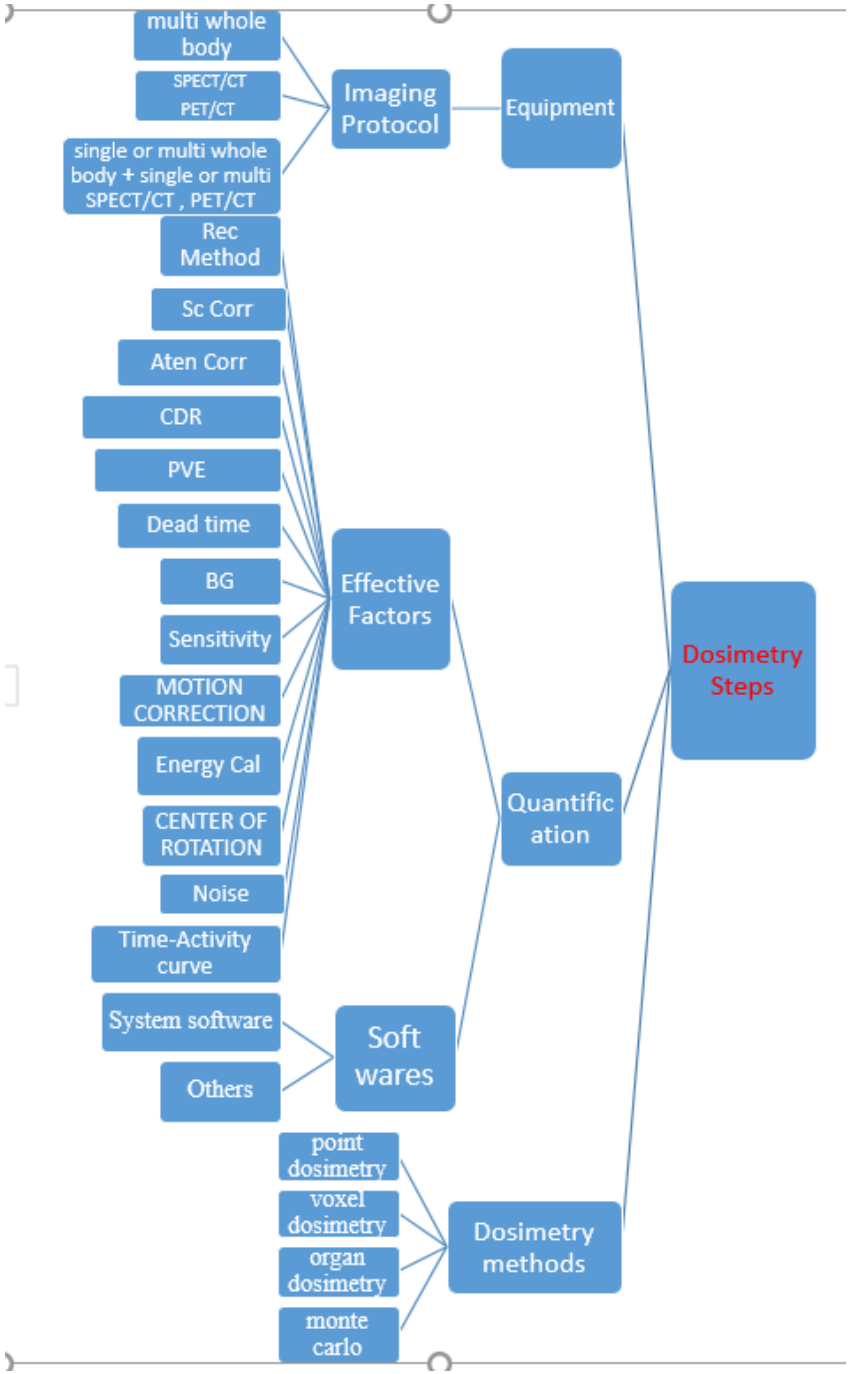
MIRD Dose calculations

$$\overline{D}_{(Target \leftarrow Source)} = \tilde{A}_{Source} \cdot S_{(Target \leftarrow Source)}$$

- In MIRD Equation: all the biology is combined in the time-integrated activity (Ã) , and all the physics in the S value,
- The S values are, of course, radionuclide- and anatomic model–specific, as
  - the energies and frequencies per decay (E_i and Y_i), respectively of emitted radiations depend on the radionuclide,
  - the absorbed fractions (ϕ) depend on the anatomic model (i.e., the sizes, shapes, and separations of the organs) as well as the radionuclide and its emitted radiations.
- Conceptually, the S value is equivalent to the absorbed dose to target region per decay of the radionuclide in source region.

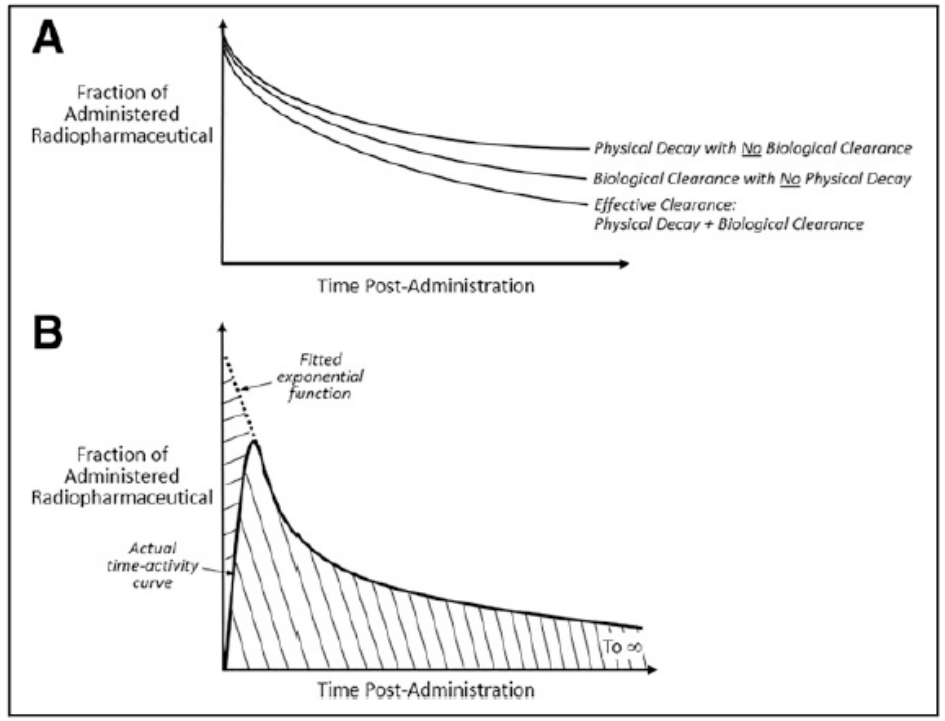
Practical Dose calculations

- **Protocols**
  - Type of equipment/measurements
  - Image quantification (corrections performed; attenuation, scatter, dead time, reconstruction parameters for SPECT or PET, background subtraction)
  - Time points on time-activity curves
  - Bladder voiding interval
  - Dose computation model
  - Number of participant in the study
- The major contributor to uncertainty in absorbed dose estimations is
  - ***the activity quantification and how frequently the measurements can be done***



Time Activity Data

- Each radiopharmaceutical is, of course, characterized by its own time-dependent biodistribution and this varies not only across different species but also among different subjects of the same species.
- The biology-related aspects of internal are thus particularly challenging.
- Initial human absorbed dose estimates for new radiopharmaceuticals are derived from animal biodistribution studies, typically in mice or rats.
- Once organ and total-body time–activity data have been measured, either preclinically in an animal model or clinically for an individual patient, these data must be reduced to time-integrated activities.
- This is generally accomplished by fitting a mathematic function to these data
- Integrating piecewise by the trapezoidal rule



(A) Idealized exponentially decreasing time–activity curves illustrating relationship among physical, biologic, and effective half-times in tissue or organ for administered radiopharmaceutical. (B) Actual time–activity curve will be more complex

Time Activity Curves

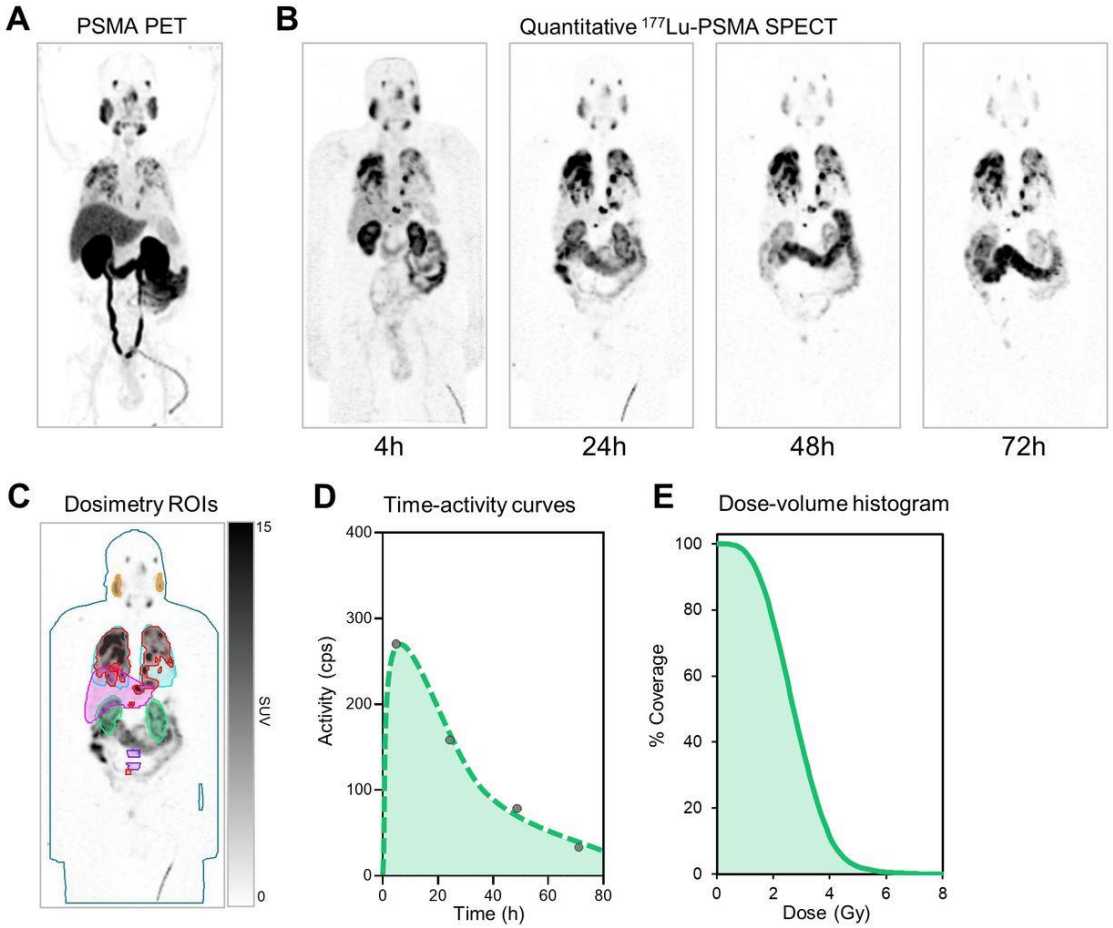
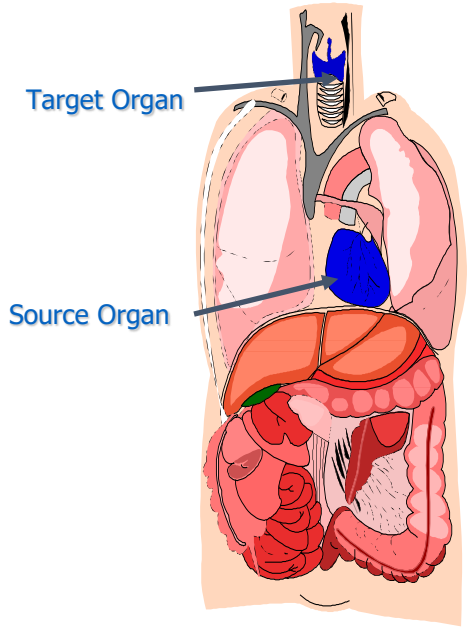
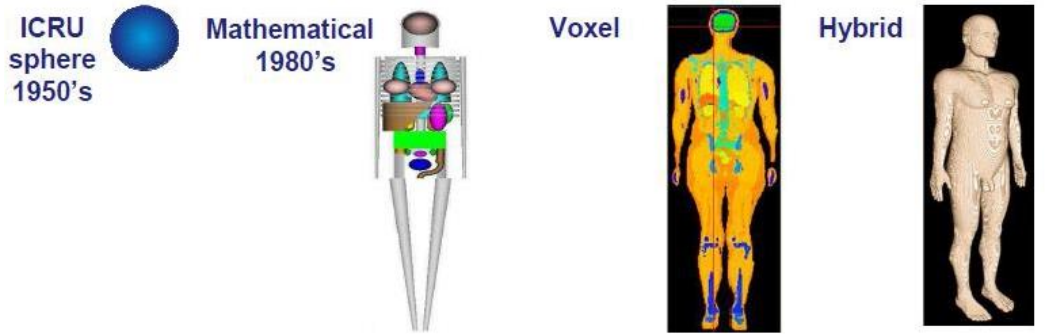


Figure 1. Representative patient dosimetry example. **A.** Pre-therapy PSMA PET. **B.** Multi-timepoint quantitative ^{177}Lu SPECT MIPs at 4h, 24h, 48h, and 72h after administration of cycle 1. **C.** Normal organ and tumor volumes displayed on the 24h SPECT MIP. **D.** Representative time-activity curve for kidney uptake. **E.** Dose-volume histogram for the kidneys.

S Values And Anatomic Models

- S values and related quantities depend on the particular radionuclide and anatomic model.
- The relevant radionuclide decay data are available in any number of authoritative sources, such as the MIRD radionuclide data and and ICRP publication 107.
- Derivation of S values, on the other hand, is a challenging computational task.
- Ideally, S values would be computed by Monte Carlo radiation-transport simulations using segmented organs in whole-body CT or MR images of each individual patient.
- More commonly, organ-level dosimetry is performed using precomputed tables of radionuclide S values for source-organ/target-organ pairs selected from a series of anatomic computerized phantoms of age-dependent average individuals.
- Differences in body size and contour and internal organ anatomy between a reference phantom and an individual patient can potentially introduce sizable errors in estimates of mean organ doses to the patient.





Adaptation of the MIRD Schema to Patient-Specific and Tumor Dosimetry

- patient-specific S values can be computed by Monte Carlo radiation-transport simulations or other computational means using segmented organs in whole-body CT or MR images of each individual patient to yield patient-specific S values.
- Alternatively, various mathematic formulas may be applied to estimate, approximately, patient-specific organ S values from those of reference anatomic models.
- An individual's self-dose S value for a particular organ may be obtained from the respective reference-phantom S value by scaling by the ratio of the phantom-to-individual organ mass (assuming the individual's organ masses have been measured by, for example, CT or MRI).
- MIRDcalc and IDAC also supports approximate tumor dosimetry by calculating the self-dose to a sphere from time-integrated activity uniformly distributed within the sphere.
- MIRDcalc allows user selection not only of the spheric and nonspheric volumes but also of composition (i.e., the relative amounts of bone and soft-tissue composing the tumor).

European Federation of Organisations for Medical Physics (EFOMP) policy statement NO. 19: Dosimetry in nuclear medicine therapy – Molecular radiotherapy - 2023

- It is well established that fixed activity administrations (, often in multiples of 100 mCi) to all patients deliver a wide range of absorbed doses to tissues-at-risk and to tumours, raising the risk of under- and over-treatments.
- The benefit of patient-specific dosimetry has been demonstrated in reports on relationships between the absorbed dose and toxicity of normal tissues or disease control.
- The implementation of radiation dosimetry into routine clinical practice faces a number of pressing challenges that, if addressed, will introduce unprecedented opportunities for cancer treatment.
- 1- Collection of evidence to inform treatments
  - Few patients are treated with molecular radiotherapy in comparison with non-radioactive drug treatments or external beam radiotherapy. An understanding of treatment effectiveness and risks, and their dependence on patient-specific baseline characteristics and prognostic biomarkers, is hampered by limited data regarding the absorbed doses delivered and treatment outcomes.
- 2- Service and research infrastructure
  - Further developments within molecular radiotherapy require resourcing for service and research infrastructure. This is particularly relevant to medical physics which suffers wide variations in staffing levels throughout Europe and minimal research funding.
- 3. Training and education
  - Training programs in molecular radiotherapy, including patient imaging, dosimetry and radiobiology, vary widely throughout Europe and between disciplines.
- 4- Investigator-initiated clinical trials
  - Currently, many industry developed radiotherapeutic drugs are introduced in the clinic without protocols for patient imaging or dosimetry.

Future implementation of molecular radiotherapy

- Clinical implementation of molecular radiotherapy relies on shared roles and responsibilities between the Medical Physics Expert (MPE) and the medical practitioner (MD).
- As for any radiotherapeutic modality the MPE should be responsible for treatment planning based on individualised patient dosimetry, metrological monitoring, and verification of the absorbed doses delivered.
- The MD prescribes treatment according to the projected absorbed dose distribution, with account taken of patient specific information that may include baseline characteristics and treatment history.

Schematic, generic example of how roles and responsibilities in dosimetry-guided molecular radiotherapy can be shared.

Step	Role and responsibility
i	The MD declares intention to treat and identifies the target tissues and tissues-at-risk.
ii	The MPE presents to the MD a range of activities to administer that are likely to yield a corresponding range of absorbed doses delivered to tissues-at-risk and/or target tissues.
iii	The MD decides whether treatment will be given.
iv	The MD specifies the maximum permissible absorbed doses to be delivered to tissues-at-risk and/or the aimed absorbed doses to be delivered to target tissues, taking account of relevant patient-specific parameters, clinical risk factors and treatment intent. The MPE gives advice on matters such as relevant tissues-at-risk and tolerance absorbed doses, as well as the absorbed doses that may be effective for treatment.
v	The MPE has responsibility for instruments and protocols used for measurement of the prescribed activity, patient dosimetry data (including e.g. quantitative imaging), data analyses and dosimetry calculations.
vi	Following administration, the MPE conducts the metrological monitoring of the biodistribution of the radiotherapeutic agent and verifies the absorbed doses delivered to target tissues and tissues-at-risk. The data on absorbed doses are recorded in the patient information system and should be traceable to (signed by) an individual MPE and MD. This information may then inform a further treatment cycle or retreatment.

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