The Relevance of Dosimetry in Precision Medicine

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The aim of this review is to provide an overview of the most recent technologic developments in state-of-the-art equipment and tools for dosimetry in radionuclide therapies. This includes, but is not restricted to, calibration methods for imaging systems. In addition, a summary of new developments that consider the influence of small-scale dosimetry and of biologic effects on radionuclide therapies is given. Finally, the current limitations of patient-specific dosimetry such as bone-marrow dosimetry or dosimetry of α-emitters are discussed.

Key Words: dosimetry; SPECT/CT; calibration; absorbed dose calculation; radiobiology

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A recent letter to the editor of the European Journal of Nuclear Medicine and Molecular Imaging stated that "in any scientific field concerned with biological effects of radiation, whether for therapy or radiation protection purposes, the effects of radiation on tissue are primarily dependent on the well-established measure absorbed dose" (*1*). In addition, the basic safety standards directive of the European Union (*2*) states that radiotherapeutic procedures (which include targeted radionuclide therapies) should be both planned and verified. Consequently, great efforts are needed to assess absorbed doses in cells, tissues, and organs as a prerequisite for treatment planning and for verification of the absorbed doses. These efforts include but are not restricted to quantitative imaging with SPECT or PET, with or without CT (*3*). A comprehensive overview on the use of theranostic imaging for therapy planning for radioiodine therapy of differentiated thyroid cancer and peptide receptor radionuclide therapy (PRRT) was provided in a recent review article by Eberlein et al. (*4*). However, dosimetry and treatment planning in radionuclide therapies should surpass simple assessment of absorbed doses and also take into account major biologic 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 tissues and tumors. Treatment planning in nuclear medicine should always consider—if technically possible—the safety and the efficacy of a particular treatment.

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Consequently, the aim of this review is to provide an overview of the most recent developments in mathematical and physical methods to increase the accuracy of activity quantifications and absorbed dose calculations in radionuclide therapies. In addition, a summary of new developments that consider the influence of biologic effects on targeted radionuclide therapies will be given. It is not the aim of this review to familiarize the reader with a stepwise approach on how to perform dosimetry.

BASIC PRINCIPLES OF DOSIMETRY IN RADIONUCLIDE THERAPY

Patient-specific treatment planning and dosimetry include but are not restricted to the following steps:

- the individual (quantitative) measurement of biokinetics in the patient;
- integration of the respective time–activity curves;
- subsequent calculation of the expected absorbed dose relying on the physical properties of the radionuclide and the measured biokinetics (*5–8*);
- inclusion of model-based predictions of toxicity, for example, for the kidneys (*9*);
- patient-specific prediction of the activities at which absorbed dose limits will be reached for organs at risk, denoting the onset of deterministic biologic effects such as early or late kidney damage or bone marrow toxicity (*5*,*10*,*11*);
- and, if technically feasible, determination of whether the tumor absorbed doses are sufficient to induce a significant therapeutic effect.

A mandatory prerequisite for quantitative imaging is a traceable calibration of the respective imaging system, including strategies for overcoming partial-volume effects in small structures. Overall, patient-specific dosimetry and treatment planning of radiolabeled substances are essential both for the safety of a treatment and for establishing absorbed dose–response relationships (*5,12,13*).

THE EVIDENCE BASE FOR INTERNAL DOSIMETRY

There is sufficient and constantly increasing evidence that treatment outcome correlates with the absorbed doses delivered to tumors and to healthy organs. The findings up to 2014 are summarized in a review article by Strigari et al. for several treatments involving radionuclides, such as radioiodine therapy of benign and malignant thyroid diseases or PRRT of neuroendocrine tumors (*13*). In recent years, more publications appeared that provided additional evidence for a dose–response relationship in patient treatments. To name a few examples, for the treatment of differentiated thyroid cancer, there are 3 recent reports describing treatment-related dose–effect relationships based on pretherapeutic ^{124}I imaging (*14–16*). For radioimmunotherapies with a novel ^{177}Lu-labeled compound addressing the CD-37 antigen, Blakkisrud

et al. succeeded in establishing a correlation between the hematologic toxicity and absorbed dose to the bone marrow (*17*).

Overall, the evidence that dosimetry results correlate with patient safety or efficacy is growing constantly. This fact is linked to improvements in technologies for image quantification in nuclear medicine.

NEW DEVELOPMENTS IN MATHEMATICAL AND PHYSICAL METHODS FOR DOSIMETRY

Image Quantification

Quantitative imaging is a major part of today's dosimetry and treatment planning workflow. Tomographic methods permit the determination of the activity distribution in a patient at given time points.

PET/CT systems have been used for treatment planning of radionuclide therapies mainly with the radionuclide ^{124}I (*14–16*). Quantification using this radionuclide is, however, hampered by the presence of a prompt γ-emission that could potentially lead to false coincidences. Some manufacturers have a built-in prompt γ-correction, which, for ^{124}I, leads to acceptable image quantification (*18*). Other nuclides that could potentially be used for pretherapeutic PET-based dose planning are ^{44}Sc, ^{68}Ga, and ^{86}Y (*19*).

For posttherapeutic dosimetry, imaging of ^{90}Y is proposed after selective internal radiation therapy. The best results are achieved by using systems that include time-of-flight image reconstructions (*20*).

Modern SPECT/CT systems offer the opportunity for generating patient-specific attenuation maps through CT imaging. Attenuation and scatter corrections can be performed on the projection images, on the reconstructed images, or as part of an iterative reconstruction method (*3*).

Detailed radionuclide-specific recommendations for the use of SPECT and SPECT/CT systems in general, and in particular for ^{131}I and ^{177}Lu, are provided by MIRD pamphlets 23, 24, and 26 (*21–23*). Recommendations for the setup of PET/CT systems for ^{90}Y PET used for selective internal radiation treatment of liver disease are provided by Willowson et al. (*20*).

Despite these efforts to provide the users with a comprehensive overview on how to perform quantitative imaging for dosimetry, some questions still need to be addressed. One of them is how best to perform SPECT/CT calibration and quantification, as there is still no general recommendation.

An overview of the most recently applied methods for SPECT/CT quantification with therapeutically used radionuclides, different phantom geometries, volumes, camera vendors, reconstruction methods, and the related accuracies has been provided by Tran-Gia et al. (*24*). Table 1 shows only publications with reported accuracies of less than 10% (*25–32*).

NOTEWORTHY

- Improvements in quantification of SPECT/CT images reduce uncertainties in absorbed dose calculations.
- There are still limitations concerning bone marrow dosimetry and dosimetry for therapies with α-emitters.
- Pharmacokinetic modeling is about to become an important tool for predicting radiopharmaceutical-related effects.
- For radionuclide therapies, the role of radiobiology in conjunction with dosimetry at a cellular, microscopic, or macroscopic scale needs to be strengthened.

In an international multicenter calibration and standardization trial, Zimmerman et al. (*25*) found by using calibrated ^{133}Ba sources that SPECT/CT systems showed better reproducibility and better accuracy than planar imaging. The results for SPECT/CT were almost operator-independent.

Wevrett et al. (*33*) reported on an intercomparison of quantitative imaging of ^{177}Lu in European hospitals using a simple geometry (a shell sphere consisting of 2 isolated concentric spheres allowing the creation of a core filled with a high activity concentration surrounded by a less active background shell). In that study, corrections for partial-volume effects, dead time, or background concentration were not fully incorporated. The authors found an uncertainty of about 20% for the inner sphere and about 83% for the outer section. They concluded that the sources of uncertainty should be further researched 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 (https://www.healthcare.siemens.de/molecular-imaging/xspect/xspect-technology/features#). Using this calibration method, Tran-Gia et al. (*26*) showed that a quantification accuracy of less than 2% could be achieved.

Further efforts at standardizing SPECT/CT calibration are presently being undertaken in the joint European project MRT Dosimetry (http://mrtdosimetry-empir.eu/). Results are expected to be made available by the end of 2019.

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

Volume-of-Interest (VOI) Delineation

Once the imaging system is calibrated, VOIs need to be drawn to quantify the activity in larger objects. Despite efforts in recent years to provide reproducible operator-independent VOI drawing methods (*34–36*), a gold standard has yet to be established. Many centers today still rely on operator-dependent manual VOI drawing for image quantification.

Developing a reliable and reproducible method for VOI drawing is also of interest for correcting for partial-volume effects. Presently one method for compensation is, for example, enlarging the VOI around small objects beyond the boundaries of the object, as this might partially account for count losses due to spill-out caused by the limited spatial resolution of the SPECT/CT systems. Another method for partial-volume correction is to derive correction factors by quantifying the activity in CT-based VOIs of spheric objects of varying sizes and to derive correction factors based on the activity in a large object. This method works well for spheres; however, nonspheric objects such as the kidneys might need different partial-volume-error correction factors as has been shown by Robinson et al. (*37*) and Tran-Gia et al. (*38*).

Determining Optimal Time Points

Because dosimetry and treatment planning require quantitative imaging at more than only one time point, the question of the optimal time points for scanning patients still needs to be addressed. General recommendations are provided in MIRD pamphlet 16 (*39*).

Two recent publications suggested reducing the number of scans needed for dosimetry. Maaß et al. (*40*) looked into whether the accuracy of treatment planning in PRRT is dependent on the

TABLE 1
Calibration Methods and Accuracy for Quantitative SPECT Radionuclides Emitting Photons with Energies of More Than 200 keV

Author	Radionuclide	Phantom geometry	Volume	System	Reconstruction	Reported accuracy
Tran-Gia et al. (*26*)	^{177}Lu	Cylinder	6.8 L	Siemens	Manufacturer	1.2%
Beauregard et al. (*27*)	^{177}Lu	Cylinder	1.75–2.5 L	Siemens	In-house	~5.6%
D'Arienzo et al. (*28*)	^{177}Lu	Cylinder	4.2 L	Philips	Manufacturer	3.7% and −11.6% (2 systems)
de Nijs et al. (*29*)	^{177}Lu	Sphere	26.5 mL	Philips	Manufacturer	~6.6%
Uribe et al. (*30*)	^{177}Lu	Spheres/bottles	113–199 mL	Siemens	In-house	<5% (objects > 100 mL)
van Gils et al. (*31*)	^{131}I	Large thorax		Siemens	In-house	1%
Koral et al. (*32*)	^{131}I	Sphere	7 and 135 mL	Marconi	In-house	1%–24% (volume-dependent)
Zimmermann et al. (*25*)	^{133}Ba	4 cylinders	2–23 mL	Siemens/GE	Manufacturer	~10%

Siemens = Siemens Healthineers; Philips = Philips Healthcare; GE = GE Healthcare; Marconi = Marconi Medical.

sampling schedule. When using a priori information from a physiologically based pharmacokinetic model combined with Bayesian information about physiologically based pharmacokinetic model parameter distribution, the administered activity could be determined with acceptable accuracy using only 2 time points (4 h and 2 d) and thus allow a considerable reduction of needed data for individual dosimetry. Hänscheid et al. (*41*) suggested that a single quantitative 3-dimensional image might be sufficient to provide values for absorbed doses for PRRT with an accuracy of 10%–15%. However, the results of both studies need to be confirmed in larger patient cohorts.

Integration of the Time–Activity Curve and Dose Calculations

Once the quantitative data have been obtained, the time–activity curves need to be integrated to obtain the time-integrated activity coefficients. The influence of temporal sampling on the results of this integration process has been studied by Guerriero et al. (*42*). The authors concluded that data should be collected until 100 h after injection for ^{177}Lu therapies and 70 h for ^{90}Y therapies. If data collection is stopped earlier, the extrapolation to infinity becomes less accurate, thus influencing the calculation of the time-integrated activity coefficient strongly. Kletting et al. (*43*) provided a software solution for integrating time–activity curves that includes error propagation and criteria for choosing the optimal fit functions by providing several additional parameters and criteria for the selection.

For the actual dosimetry calculation in radionuclide therapies, appropriate absorbed dose rates per unit activity values (S values) either on an organ scale or voxel-based are applied. Organ-based S values provide mean absorbed doses to whole organs or tissues. The most accurate S values are, at present, provided by Monte Carlo calculations. However, only one publication benchmarked the differences in 3-dimensional dose distributions due to the calculation method of voxel-based S values, showing that the major uncertainty for 3-dimensional dosimetry on clinical SPECT or SPECT/CT images is caused by image blurring and not by differences among the voxel S value calculation methods (*44*).

Gustafsson et al. (*45*) established a computer model assessing dosimetry-related uncertainties such as γ-camera calibration, selection of imaging time points, generation of mass-density maps from CT, SPECT image reconstruction, VOI delineation, partial-volume effects, calculation of absorbed-dose rates, curve fitting, and integration to obtain absorbed dose and biological effective dose (BED). As a result, the authors estimated the importance of different sources of uncertainty. They concluded that the compensation for partial-volume effects via a recovery coefficient and the γ-camera calibration have the largest impact on the uncertainties.

Ideally, commercially available treatment planning systems for radionuclide therapies should cover all the aforementioned aspects. Presently, commercial software solutions for dosimetry are marketed by Hermes (Hermes Hybrid Dosimetry), Mirada (Simplicit^{90}Y), Philips Medical Systems (Stratos), PLANET Dose (DOSIsoft), ABX-CRO Advanced Pharmaceutical Services (QDOSE), and GE Healthcare (Dosimetrix). Only a few of these systems include image reconstruction software for quantitative SPECT or SPECT/CT. Most of the codes rely on adequately quantified images. Some of the companies already obtained a CE (Conformité Européene, or European Conformity) marketing authorization for their software for the purpose of selective internal radiation therapy (Hermes, Mirada, and DOSIsoft).

Because there are no benchmarking tests available for dosimetry software used in radionuclide therapies, efforts are undertaken to produce reference dosimetry data with Monte Carlo simulation software (*46*). At present, these tests are used in only a few specialized centers. Consequently, the currently available commercial software solutions used for treatment planning need to be carefully evaluated as to whether they suit the respective purpose.

Finally yet importantly, the question remains how best to report the results of a dosimetry study for treatment planning. The European Association of Nuclear Medicine provided some general recommendations on what should be reported and how it should be reported (*8*). Because the information needed for dosimetry in radionuclide therapy goes beyond providing dose maps in the same format as for external-beam therapy, the first efforts undertaken by Kesner et al. were to provide a template for reporting a full set of parameters for absorbed dose calculations (*47*).

Biology-Driven Improvements

Another important aspect that takes the individuality of patients into account is the use of pharmacokinetic modeling for predicting absorbed doses or the influence of coadministered nonradioactive compounds. Kletting et al. (*48,49*) have successfully initiated this approach and have applied this method to PRRTs and to prostate-specific membrane antigen (PSMA) therapies with ^{177}Lu. For targeted radionuclides using α-particles, compartment modeling is currently the only method for quantifying the influence of the progeny on absorbed doses (*50*). However, no data on the prospective application of patient-specific pharmacokinetic models have been published.

To further refine absorbed dose calculations with the purpose of including biologic effects such as cell killing and survival, Dale et al. modified the linear-quadratic model, originally developed for radiation oncology, in such a way that it can be applied to radionuclide therapy (*10*). For kidney dosimetry, the effect of model assumptions on response and the respective implications for radionuclide therapy are compiled in MIRD pamphlet 20 (*9*). Gustafsson et al. further extended this specific kidney model to better describe the effect of normal-tissue damage repair (*51,52*). The only available dose–response curves, which are based on BED calculations and agree with external-beam therapy, have been provided for kidney toxicity after PRRT with ^{90}Y-labeled DOTA compounds (*9*). For other radionuclides and organs, with the exception of selective internal radiation treatment, no BED-related organ dose–response data have been published, most likely because of the low toxicity of most of the treatments today with ^{131}I or ^{177}Lu.

A combination of both methods—pharmacokinetic modeling and radiobiology—was applied to ^{177}Lu-labeled PSMA peptides in a simulation study (*53*) suggesting that in patients with large, PSMA-positive tumor volumes, higher activities and peptide amounts could safely be administered to maximize tumor BEDs without exceeding the tolerable BED for the organs at risk.

Because ionizing radiation causes DNA damage in normal organs and tissue, it is of great interest to study how this damage is being repaired in patients after radionuclide therapies and, in particular, the relationship to the absorbed doses in normal organs and tissues. Several publications combined patient-specific dosimetry with a quantification of the DNA damage associated with radionuclide therapies (*54–57*). The authors of these studies showed that the DNA damage in leukocytes after radioiodine therapy for differentiated thyroid cancer and PRRT was associated with the absorbed dose only in the first hours after therapy and was effectively repaired a few days after administration of the radiopharmaceutical. Presently, efforts are under way to extend this method to targeted α-therapies (*58*).

Current Limitations

The clinical implementation of patient-specific dosimetry currently faces several challenges, despite the technical advances and the increase in knowledge about radiobiology and radiation biology.

Methods for bone marrow dosimetry, although compiled in a comprehensive guideline by the dosimetry committee of the European Association of Nuclear Medicine (*7*), are still not mature enough to provide robust estimates for absorbed doses to the bone marrow. There have been some promising efforts to correlate the absorbed dose to the bone marrow by imaging methods; however, most have been restricted to a few patients in clinical trials (*13,17,59*). Further efforts to include MRI in this process have been undertaken but have not yet been introduced to the clinic (*60,61*).

The gap between organ and tissue dosimetry might be closed by applying small-scale dosimetry models combined with clinical patient biokinetics and compartment modeling. This closure could potentially serve as a bridge between organ and tissue dosimetry and in the interpretation of intrinsic geometric variation and its uncertainties in absorbed dose. An example of this approach in a pretherapy clinical study with ^{111}In-ibritumomab tiuxetan was given by Meerkhan et al. (*62*). The authors focused on the dosimetry for the testicle and presented significant differences in the absorbed dose to the radiosensitive germ cells depending on the location of the radioactive source region and geometry variations of the seminiferous tubule (*62*). Further research is needed in this area for establishing dose–response relationships.

Dosimetry of α-particle emitters for radionuclide therapy based on quantitative imaging still remains a challenge because of the much lower activities that are being administered in comparison to therapies with β-emitters. Efforts have been undertaken to quantify images for dosimetric purposes after therapies with ^{223}Ra-dichloride; however, the errors in quantitative imaging still remain substantial (*63–65*). To further promote dosimetry in treatments with α-particles, methods need to be developed that combine imaging and other patient-specific information such as activity in blood samples as input for tailored pharmacokinetic modeling.

Clinical practice will soon see the introduction of new therapeutic radiopharmaceuticals such as ^{225}Ac- or ^{177}Lu-labeled PSMA compounds (*66–68*), ^{90}Y- or ^{177}Lu-labeled chemokine receptor 4 antagonists (*69*), ^{177}Lu-labeled somatostatin antagonists (*70*), and ^{177}Lu-labeled anti-CD37 radioimmunoconjugates (*71*). In contrast to radioiodine therapy of differentiated thyroid cancer, for example, it is highly likely that most of these therapies will need patient-specific tailoring of the administered activity such that the absorbed dose limits for normal organs and tissues are considered while achieving high absorbed doses to the treatment target.

CONCLUSION

Prescriptions in radionuclide therapy have been based mostly on a fixed amount of activity for all patients. It is unfortunate that there still have been no randomized controlled trials to evaluate the respective benefits of dosimetry-based versus fixed-activity approaches. However, in the era of precision medicine, the absence of evidence from clinical trials should not hinder the development of dosimetry-based prescriptions and certainly does not justify the absence of posttreatment verification of the absorbed doses delivered, as this verification provides patient-specific information without changing patient management.

The role of radiobiology and radiation biology in examining the impact of radioresistance, low and continuous absorbed dose rates, and heterogeneity of uptake at a cellular, microscopic, or macroscopic scale is under investigation. Dosimetry data will help to expand this field if they are compared with outcomes. We believe that this research field should be strengthened to fully develop the theranostic advantage of radionuclide therapy.

Overall, dosimetry in the era of precision medicine needs fruitful collaborations between different medical specialties in nuclear medicine, oncology, and medical physics. If we succeed in establishing these collaborations, we can foresee a bright future for radionuclide therapy.

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