Title

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Journal

Journal of Nuclear Medicine, 62(8)

ISSN

0161-5505

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Publication Date

2021-08-01

DOI

10.2967/jnumed.120.255547

Peer reviewed

Overview of the First NRG Oncology–National Cancer Institute Workshop on Dosimetry of Systemic Radiopharmaceutical Therapy

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In 2018, the National Cancer Institute and NRG Oncology partnered for the first time to host a joint workshop on systemic radiopharmaceutical therapy (RPT) to specifically address dosimetry issues and strategies for future clinical trials. The workshop focused on current dosimetric approaches for clinical trials, strategies under development that would optimize dose reporting, and future desired or optimized approaches for novel emerging radionuclides and carriers in development. In this article, we review the main approaches that are applied clinically to calculate the absorbed dose. These include absorbed doses calculated over a variety of spatial scales, including whole body, organ, suborgan, and voxel, the last 3 of which are achievable within the MIRD schema (S value) and can be calculated with analytic methods or Monte Carlo methods, the latter in most circumstances. This article will also contrast currently available methods and tools with those used in the past, to propose a pathway whereby dosimetry helps the field by optimizing the biologic effect of the treatment and trial design in the drug approval process to reduce financial and logistical costs. We also briefly discuss the dosimetric equivalent of biomarkers to help bring a precision medicine approach to RPT implementation when merited by evidence collected during early-phase trial investigations. Advances in the methodology and related tools have made dosimetry the optimum biomarker for RPT.

Key Words: radiopharmaceutical therapy (RPT); targeted radionuclide therapy (TRT); dosimetry; microdosimetry; cellular dosimetry; MIRD

J Nucl Med 2021; 62:1133–1139
DOI: 10.2967/jnumed.120.255547

In 2018, the National Cancer Institute (NCI), NRG Oncology (the acronym NRG is derived from the names of the 3 parental groups: the National Surgical Adjuvant Breast and Bowel Project, the Radiation Therapy Oncology Group, and the Gynecologic Oncology Group (1)), and the Imaging and Radiation Oncology Core partnered for the first time to host a joint workshop on systemic radiopharmaceutical therapy (RPT) to address dosimetry issues and strategies for future clinical trials that might be supported by the NCI National Clinical Trials Network or other related entities (Fig. 1). The workshop discussed current dosimetric approaches for clinical trials, dosimetric strategies under development that would optimize dose reporting, and future desired or optimum approaches for novel emerging radioisotopes and carriers in development. These 3 points have been discussed separately in articles by St. James et al. (2) and Divgi et al. (3). This article summarizes the workshop, whose agenda in presented in Appendix A.

RPT is available to patients in the United States in many forms, thanks to developments in the production of α- and β-emitting radionuclides, informed by γ- or PET emissions, along with developments in pharmaceutical targeting. The term *RPT* is being adopted to encompass a variety of radionuclide therapies, also called targeted radionuclide therapies. Examples of RPT or targeted radionuclide therapies include thyroid or thyroid cancer ablation with the administration of ^{131}I, treatment of liver cancer with ^{90}Y-microspheres, and treatment of bony metastases with $^{223}RaCl_2$ (4–6). In addition to several available Food and Drug Administration (FDA)–approved RPTs, others are in clinical trials.

RPTs are often prescribed by administered activity, normalized or not to body weight or surface area and not always accompanied by image-based absorbed radiation dose prediction or dose verification. This lack of standardization often results in uncertainties in the

Received Aug. 18, 2020; revision accepted Nov. 20, 2021.
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Published online December 4, 2020.

FIGURE 1. Attendees and speakers.

reporting of the resulting absorbed dose delivered to tumor volumes and normal organs, including organs at risk, given individual patient pharmacokinetics. For conventional radiation therapy (e.g., external-beam radiation therapy and brachytherapy), uncertainties of 7% in the absorbed dose have been shown to impact the tumor control probability and the normal-tissue complication probabilities (7). The uncertainties are likely far more prominent in RPT because of the limited accuracy and precision of quantitative imaging methods, available pharmacokinetic models, and dosimetry methods at many treatment facilities. Because of the unique characteristics of each treatment, methods tailored to each RPT approach (e.g., α-emitters vs. β-emitters) need to be developed and integrated into early-phase clinical trials to improve the quality of these clinical trials and, ultimately, benefit patients.

In this article, we review the main approaches that are applied clinically to calculate the absorbed dose. These include absorbed doses calculated over a variety of spatial scales, such as whole body, organ, suborgan, and voxel, the last 3 of which are achievable within the MIRD schema. The mean absorbed dose per unit time-integrated activity (S value) can be calculated with analytic methods or Monte Carlo methods, the latter being more accurate in most circumstances. Because the accuracy of the predicted absorbed dose strongly depends on the method and underlying assumptions, we discuss simplifications made in each approach. Emerging and promising image-based dosimetry methods for personalized dosimetry are also discussed.

RPT delivers radiation to targeted cells and to normal organs. In this regard, it is analogous to radiotherapy. The experience of external-beam radiotherapy led to a well-established understanding of the impact of radiation on organs and tumor tissue, critical for assessing potential efficacy and toxicity and ruling out futility. That this knowledge has not been broadly applied to RPT trials, which in many instances adopted the largely empiric paradigm of chemotherapy instead, may contribute to some less-than-optimal outcomes with some of the early implementations of RPT. The limited dosimetry experience of the last several decades understandably led many practitioners to conclude that dosimetry was financially and logistically costly, was inconvenient for patients, and had a minimal effect on patient outcome. Application of state-of-the-art imaging and dosimetry methods in clinical trials could change this perspective by enabling a better selection of responders, shorter absorbed-dose escalation phases, an earlier termination of ineffective therapies, and better insight into the reasons for success and failure.

Within years of the invention of CT in the early 1970s, CT data were adopted to provide anatomic input for the 3-dimensional (3D) treatment-planning process in external-beam radiotherapy. This development led to patient-specific treatment planning that significantly improved treatment efficacy by increasing tumor control and reducing toxicities in patients. Because RPT was developed much more recently, it is perhaps 50 years behind external-beam radiotherapy regarding routinely deployed patient-specific treatment planning in the clinic. The formerly FDA-approved therapeutic for non-Hodgkin lymphoma, ^{131}I-tositumomab (Bexxar; GlaxoSmithKline), used a dosimetric whole-body scan of 185 MBq of ^{131}I to calculate total-body dosimetry (as a surrogate for absorbed radiation dose to the marrow) (8). This treatment showed

considerable efficacy, and the treatment was prescribed as a patient-specific 65- to 75-cGy total-body dose, accounting for the considerable patient-to-patient dosimetric variability (4). Absorbed dose response and dose–toxicity relationships were observed, however, supporting the importance of patient-specific dosimetry (9). Although effective, this product was not commercially successful (10,11).

In addition, some patient-specific dosimetry methods using anatomic and functional imaging were developed as early as the late 1980s (12). These dosimetry methods can be classified into several categories: local energy deposition, voxel kernel convolution using voxel-level S values based on the MIRD formalism, point kernel convolution, and direct Monte Carlo radiation transport (13–15). Each of these methods has its own advantages and limitations with regard to accuracy and computational efficiency. More recently, some of these methods have been implemented in commercial software products (available from DOSIsoft, MIM Software Inc. [molecular radiotherapy automated segmentation], and Hermes Medical Solutions). Currently, these products are approved in the United States only for posttreatment use, but some are being used for pretreatment dosimetry in Europe and elsewhere.

The workshop gave an overview of current patient-dosimetry methods and discussed current barriers that impede routine clinical implementation of patient-specific dosimetry. And perhaps more relevant to this workshop, we attempted to identify specific actions that should be taken to address these barriers. These actions include streamlining the dosimetry workflow, generating accurate radiobiology parameters, developing standards relevant to radionuclide metrology, establishing patient-specific procedures for quality assurance and quality control, and expanding educational and training opportunities for physicists and physicians.

RPT with associated companion diagnostics is the embodiment of precision medicine. Companion diagnostics should improve patient response rates through better patient selection for therapy and should optimize the therapeutic ratio. Many gaps in knowledge must be filled before this vision becomes a reality. First, the radiobiology of systemically administered radionuclides must be studied further to better understand the effects of a given absorbed dose on normal-tissue tolerance. Ideally, this understanding of the biologic effects of radiation could extend to predictors of patients whose disease or normal tissues are sensitive or resistant to radiation. Although particularly keen for α-particle emitters, this need remains unmet for β-particle emitters as well. When companion diagnostic agents are not chemically identical to the therapeutic agents, we need to better understand the reliability of estimates that are derived from the biodistribution of one and applied to the other. Finally, once validated, these techniques must be made straightforward for the end user. If these goals were achieved, RPT could dramatically increase opportunities for precise and personalized therapies for a wide variety of diseases.

CURRENT METHODS AND CHALLENGES

Establishing Good Dosimetry Practices for RPT

In external-beam radiotherapy, the required dosimetry provides useful predictions on both normal-organ toxicities and the effectiveness of tumor control that can guide treatment planning. In contrast, many current RPT regimens do not use predictive dosimetry in determining the optimal administered activity. Recent developments in imaging instrumentation, quantitative reconstruction, image analysis, and absorbed dose estimation have made high-quality dosimetry feasible, at least in the context of clinical trials. Implementing state-of-the-art practices that provide more accurate dosimetry requires attention to detail and the use of harmonized and verified methodologies.

The first requirement for high-quality RPT dosimetry is selection of the appropriate imaging modality. Although conventional and straightforward planar imaging can estimate whole-body activity and organ activity, it requires careful adjustments for attenuation, scatter, background activity, and organ thickness and overlap. Proper compensation for all these factors is challenging and requires information from 3D imaging modalities. With the wide availability of SPECT/CT systems and the development of quantitative reconstruction methods, SPECT/CT imaging can provide superior accuracy, especially for small objects in the presence of overlying activity. Although quantitative reconstruction methods for therapeutic radionuclides such as ^{177}Lu are commercially available, methods specific to some other more challenging radionuclides, such as ^{90}Y, are typically not. Selection of an appropriate collimator and energy windows is also critical, especially for therapeutic radionuclides, for which the emission spectrum is often complex and includes single or paired high-energy photons or a continuous spectrum, as is the case for bremsstrahlung imaging. Even with state-of-the-art quantification methods, careful calibration to convert image counts to activity units (e.g., Bq/mL) is necessary (16). An essential ingredient is standards-traceable activity measurements. For imaging calibration, the impact of this can often be reduced, but standards traceability is necessary for measuring therapeutic activities.

A second requirement is selection of an appropriate number of imaging time points that can lead to robust and quantitative pharmacokinetic models. Careful consideration of the pharmacokinetics of the RPT agent and the decay properties of the therapeutic radionuclide is required. Typically, data from at least 3 time points are needed when attempting to fit the kinetics with a multiexponential distribution as performed in OLINDA/EXM (8,17), though there has been recent work to reduce this requirement for certain types of RPT clearance kinetics.

Image processing, including the definition of normal tissue and tumor volumes of interest in the case of 3D images, and registration of images from multiple time points, is of paramount importance for developing robust and quantitative pharmacokinetic models. The manual definition of volumes of interest that requires the user to contour 2-dimensional regions of interest on each slice is tedious but remains the most common method (18). Semiautomatic methods, such as atlas-based and machine learning–based segmentation, show promise for reducing the tedium and associated cost of volume-of-interest definition. For fully 3D dosimetry, registration across time points of activity images or absorbed dose maps should aim at achieving voxel-level precision, which is challenging because of patient motion between scans. Even for organ-level dosimetry, registration across time points can reduce the effort required in volume-of-interest definition. State-of-the-art 3D deformable registration is available commercially and is highly effective with anatomic images.

Selection of appropriate methods for estimating absorbed dose from the activity distributions is also critical (19). 3D methods provide better estimates when patient anatomy deviates substantially from standard phantoms and when tumor dosimetry is required. 3D dosimetry recently became available commercially and is associated with dose metrics superior to the average organ-absorbed dose, such as dose–volume histograms. Dose metrics specifically developed for RPT that account for radiobiologic factors and microscale dosimetry should provide more robust predictions of toxicity

and response, especially for α-particle emitters, for which the spatiotemporal distribution dictates the tumor response and normal-tissue toxicity.

Finally, an essential practice of good dosimetry is a standardized and complete reporting of the methods and parameters used in estimating the absorbed dose to enable replication of the results at other centers and in other practice settings (20).

Clinical Dosimetry Methods for RPT

There is growing use of 3D image–based dosimetry to support RPT treatment planning instead of using fixed fractions, empiric adjustment, patient body weight, or single organ dose values. New 3D methods provide the desired precision and accuracy to optimize treatment with clinically used RPT such as radioimmunotherapy, peptide receptor radionuclide therapy, or microsphere therapy with isotopes such as ^{131}I, ^{90}Y, ^{177}Lu, ^{153}Sm, and ^{223}Ra.

Dosimetry based on imaging is increasingly used for ^{131}I, an isotope that for 75 years has been applied worldwide in patients with residual thyroid cancer or avid metastatic tumors, in contrast to a traditional approach focused on respecting a whole-body dose threshold of 200 cGy (vs. the 75-cGy whole-body dose for Bexxar) (9). Image-based studies such as ^{124}I PET/CT, ^{123}I SPECT/CT, and ^{131}I SPECT/CT with tracer quantities have demonstrated a relationship between lesion-absorbed dose and tumor response, leading to a greater focus on individual lesion dosimetry and uncovering the vast absorbed-dose heterogeneity. Challenges with ^{124}I image–based dosimetry include the imperfect nature of ^{124}I as a positron emitter, the need for costly whole-body PET, and coincident high-energy photons that impact quantification accuracy. Needed corrections are gradually being introduced in clinical software. Despite these challenges, the existence of isotopes that can be imaged creates unique opportunities for ^{131}I dosimetry.

Therapeutic applications with ^{90}Y microspheres and ^{90}Y-labeled antibodies (e.g., ibritumomab tiuxetan) and peptides (e.g., DOTATOC) have sparked growing interest in quantitative imaging and dosimetry of ^{90}Y. Direct imaging of the β-emitter ^{90}Y can be done via SPECT or PET but is complex because of the need for specialized reconstruction techniques (e.g., sophisticated scatter estimation in SPECT, the inclusion of time-of-flight information in PET). Pretreatment imaging typically includes ^{99m}Tc-labeled macroaggregated albumen for radioembolization (also called selective internal radiation therapy) and ^{111}In-labeled antibodies or peptides, but the images are currently not used to predict the absorbed dose distribution. Despite reports of discrepancies between the ^{99m}Tc-macroaggregated albumen particles and ^{90}Y-microsphere distributions, some other studies have demonstrated that dosimetry-guided treatment is feasible in radioembolization. Dosimetry-guided treatment planning has also been demonstrated in ^{90}Y-DOTATOC therapy using a single time to estimate the total integrated activity and absorbed dose to within 10% accuracy (21). Several software vendors have started to offer specific toolboxes recently cleared by the FDA (e.g., SurePlan LiverY90 [MIM Software Inc.], selective internal radiation therapy [Hermes Medical Solutions], and PLANET Dose [DOSIsoft]) based on voxel dosimetry.

Recently, radioembolization of hepatic malignancies using ^{166}Ho-labeled microspheres has become commercially available and is clinically used in Europe. ^{166}Ho is attractive for therapy applications as it emits high-energy β-particles and a low-energy γ-ray suitable for imaging. The advantage over ^{90}Y microspheres is that the same microspheres can be used for pretherapy imaging without the need to use a surrogate such as ^{99m}Tc-macroaggregated albumen. Furthermore, the paramagnetic properties and high density of ^{166}Ho enable visualization by MR and CT imaging (22).

There is recent interest in the β- and γ-emitter ^{177}Lu for imaging and dosimetry due to the FDA approval of ^{177}Lu-DOTATATE (Lutathera; Advanced Accelerator Applications) peptide receptor radionuclide therapy for treatment of metastatic gastroenteropancreatic neuroendocrine tumor and the use of ^{177}Lu-prostate-specific membrane antigen radioligand therapy for metastatic prostate cancer (23). Both these therapies are administered in 4 consecutive cycles with a fixed administration of 7.4 GBq/cycle (22,24). SPECT-based dosimetry could be used for absorbed dose verification after each cycle, using ^{177}Lu photon emissions, following guidelines published in a MIRD/European Association of Nuclear Medicine joint pamphlet (25). A commercial toolbox for quantitative ^{177}Lu SPECT/CT received FDA clearance in 2019 (SurePlan MRT; MIM Software Inc.). Important points that need to be addressed and are still at the research stage include the reduction of time points needed to capture the ^{177}Lu biodistribution to single-time-point imaging, use of absorbed dose to predict response and establish a dose–effect relationship, and dose-based optimization of the number of cycles to maximize efficacy while keeping toxicity (in particular the kidney and bone marrow) at an acceptable level.

^{153}Sm-ethylenediamine tetramethylene is a β-particle–emitting radiopharmaceutical used as a palliative agent for painful bone metastases, licensed by Lantheus as Quadramet. It is a calcium mimetic that rapidly localizes to areas of new bone growth and calcium uptake. ^{153}Sm emits a 103-keV photon, which is suitable for imaging and pretherapeutic planning. The accuracy of imaging quantification compares with that of standard radiopharmaceuticals (e.g., ^{111}In and ^{131}I). The dose-limiting organ is the bone marrow, with an established maximum tolerated dose of 39.5 MBq/kg based on preclinical studies (26).

^{223}Ra-dichloride (Xofigo; Bayer) has reemerged as a bone-seeking α-emitting radionuclide to target metastatic bone disease in patients with castration-resistant prostate cancer. On the basis of the high energy and radiotoxicity of the α-emissions of ^{223}Ra, low activities (55 kBq/kg) that can be safely administered yield proven therapeutic benefits. The low photon fluence at these activities presents considerable challenges for quantitative imaging but has allowed the biodistribution of radium and its daughters to be studied successfully in patients. The rapid clearance of ^{223}Ra from the blood pool, and the favorable short half-lives of the first 2 daughters, possibly mitigates their radiotoxicity, which remains contained within the bone or the gut contents, the dominant sites of radionuclide accretion.

RPT DOSIMETRY METHODS UNDER DEVELOPMENT

Optimizing Imaging Time Points

Quantitative dosimetry for RPT relies on the ability to measure the spatiotemporal activity distribution in the different organs of interest to accurately calculate the time-integrated activity and total absorbed dose. Because of the variability of organ clearance time, and the potential interpatient variability, it is impractical to perform imaging at all the necessary time points. Medical centers are investigating the potential of measurements at limited time points or at a single time point for estimating the critical organ dose and thus the maximum safe administered activity (21).

Challenges with α-Dosimetry

Recent developments in new radionuclides focus on α-emitters, such as ^{212}Pb, ^{225}Ac, ^{213}Bi, ^{211}At, and ^{227}Th (27(–30). Dosimetry

challenges associated with these isotopes were discussed during the workshop and are briefly summarized below.

^{212}Pb. Regarding ^{212}Pb, direct imaging is difficult because of the emission of a high-energy γ-ray; however, the emission of a 279-keV photon associated with the decay of ^{203}Pb can serve as an imaging surrogate. ^{203}Pb-DOTATOC and ^{212}Pb-DOTATOC constitute a theranostic pair investigated to treat neuroendocrine tumors, metastatic melanoma, and pediatric cancers.

^{225}Ac. After an initial demonstration of the clinical efficacy of ^{225}Ac, oncology clinical trials have been hindered because of the lack of availability of ^{225}Ac. Methods to image the activities of ^{225}Ac and its daughters are needed to develop robust, quantitative dosimetry translatable to clinical use. Preclinical studies assessing clearance from organs and tumors with heterogeneous target expression and perfusion are also needed to better understand the pharmacokinetics and dosimetry of ^{225}Ac compounds at the microscale. Since ^{225}Ac-specific emissions are not easily imaged in clinically relevant modalities, surrogate imaging tracers are needed.

^{213}Bi. ^{213}Bi is the first α-particle–emitting radionuclide to be used in a clinical trial of α-particle radioimmunotherapy, ^{213}Bi has been applied to clinical studies of glioblastoma and melanoma patients and to leukemia studies that initiated the development of imaging and dosimetry methodology. Its short 46-min half-life provides practical and logistical challenges for therapy.

^{211}At. Regarding ^{211}At, 2 clinical trials have been performed, one for the treatment of recurrent brain tumors and the other for the treatment of intraperitoneal ovarian cancer. Multiscale dosimetry methods have been developed, with their use depending on the quality of the pharmacokinetic data and biologic and clinical endpoints. Current research includes binary theranostic agents based on a combination of PET/SPECT and α-particle–emitting therapeutic radionuclides using nuclear nanotechnologies, such as intrinsic radioactive nanoparticles.

^{227}Th. ^{227}Th therapies include ^{227}Th-ethylenediamine tetramethylene for bone metastases, the radioimmunoconjugate ^{227}Th-rituximab for the treatment of CD20+ lymphoma, and ^{227}Th-trastuzumab for the treatment of human epidermal growth factor receptor 2–expressing ovarian cancer. The possibilities of both γ-camera imaging and 3D SPECT imaging of patients treated with ^{227}Th-labeled monoclonal antibodies have been reported.

Multiscale Dosimetry Methods

The dosimetric quantity traditionally reported in RPT is the mean organ- or tumor-absorbed doses estimated under the assumption of a uniform activity distribution within a target region. Variations due to actual nonuniform absorbed dose and dose-rate distributions can be significant and motivated the development of voxel-level dosimetry for both treatment planning and response evaluation (31,32). Challenges in voxelized dosimetry include the relatively large voxel size due to the finite spatial resolution of PET and SPECT (4–15 mm), which reduces its ability to capture the heterogeneity of dose distributions, especially at the microscopic level. This limitation is particularly crucial for α-particles that travel a short distance (50–100 μm) and require an assessment of their distribution at a resolution that is not clinically achievable without resorting to biopsy samples and autoradiography techniques. The high linear-energy transfer of α-particles yields a very dense pattern of energy deposition that leads to enhanced and dose-rate–independent biologic effects per absorbed dose when compared with low–linear-energy-transfer radiations such as β-emitters or external-beam radiotherapy. This problem can be potentially addressed using physiologically based voxel tissue models (i.e., cell level) such as MIRDcell, which are needed for cellular- and multicellular-level dosimetry (33). Accordingly, understanding the implication of normal-organ or tumor dosimetry from an α-emitter requires knowledge of the relative biological effectiveness (34).

The relative biological effectiveness is defined as the ratio of the absorbed dose deposited by a low–linear-energy-transfer particle emitter to high–linear-energy-transfer particle emitters required to reach a given biologic endpoint. The assessment of the relative biological effectiveness from α-particle–emitting therapeutics is complex because of nonuniform activity uptake within the cellular and extracellular components and because of variable radiosensitivity, depending on the location of the site of emission within the cell. For example, autoradiography data from normal and tumor tissues have shown that cell populations take up widely different amounts of radioactivity. Recent progress in quantifying nonuniform uptake of radiopharmaceuticals at the cellular level may potentially be used to optimize treatments based on measurements of variable uptake among circulating tumor cells. Innovative approaches that combine a priori biologic behavior, preclinical, and human studies are needed to calculate the absorbed dose and translate it into likely biologic response.

FUTURE OPPORTUNITIES

The rationale for improving and optimizing dosimetry in radionuclide therapy has become a critical area for investigation to improve oncologic patient care, guiding clinical trial design to reduce financial and logistical costs in drug approval. This article has contrasted emerging methods and traditional tools to propose a pathway whereby dosimetry can advance the RPT field by optimizing biologically based therapy and clinical trial design for drug approval. We also briefly discussed the concept of the dosimetric equivalent of biomarkers to introduce a precision medicine approach to RPT implementation—when merited by evidence collected during early-phase trials. A precision-medicine philosophy will ultimately improve patient response rates by improving the selection of patients and therapies.

Furthermore, there was a discussion of the dosimetric equivalent of biomarkers to help bring a precision medicine approach to RPT implementation—when merited by evidence collected during early-phase trials. Chemotherapy and targeted biologic therapy, in particular, are increasingly focused on identifying genetic and epigenetic markers of tumor susceptibility to help select and stratify patients more likely to benefit from the treatment. Advances in the methodology and related tools have made dosimetry the ideal biomarker for RPT.

Such goals rely on the development of improved companion diagnostics, more accurate absorbed dose models and calculations specific to the emitter (i.e., β or α), and a more advanced and robust understanding of the radiobiology that should be integrated into early-phase clinical trials. Because the accuracy of the absorbed dose strongly depends on the method and underlying assumptions, we discussed simplifications made to each approach, with the intent of soon improving the emerging image-based dosimetry methods for personalized dosimetry and of guiding the quality assurance of RPT dosimetry for clinical trials. These discussions may be presented at a follow-up NRG Oncology–NCI workshop on dosimetry of systemic RPT.

DISCLOSURE

NRG Oncology is funded in part by grants 2U24CA180803-06 (Imaging and Radiation Oncology Core) and 2U10CA180868-06

(NRG Oncology) from the NIH. Other grants that were supportive of this workshop include R01 EB022075 from the NIBIB, R01CA240706 from the NCI (principal investigator, Yuni K. Dewaraja), and P30 CA008748 from the NCI Cancer Center (support to John Humm from Memorial Sloan Kettering). No other potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

We gratefully acknowledge the NIH for providing accommodations for the workshop in Bethesda, MD. The contributors include all listed coauthors. The organizing committee comprises Jacek Capala, Ying Xiao, and Jeff Buschbaum. We thank Bonnie Clarke (Society of Nuclear Medicine and Molecular Imaging, Reston, Virginia) for her assistance with this workshop.

APPENDIX A. WORKSHOP AGENDA

Day 1: April 19, 2018

8:00 AM: Opening remarks—C. Norman Coleman, Bhadrasain (Vik) Vikram, and Jacek Capala

8:15 AM: Current status of targeted radionuclide therapy (TRT)—Sara St. James and Bonnie Clarke

Approved treatments and clinical trials:

9:00 AM: Currently applied TRT dosimetry methods—Stanley Benedict and Emilie Roncali

Advantages and limitations of methods used in clinical practice:

9:45 AM: Available TRT dosimetry methods/approaches—Bryan Bednarz and George Sgouros

New methods that are ready for clinical application, the advantage over methods currently used in the clinic, how they might improve the clinical outcome, and the reasons they are not used:

10:45 AM: TRT dosimetry methods under development—Yuni Dewaraja, Wesley Bloch, and R. Howell

The advantage over methods that have been already developed, how they might further improve clinical outcome, and what the simplest possible methods are to reduce the stress of going through additional procedures before already very difficult TRT:

11:30 AM: Desired RPT dosimetry methods/approaches—Daniel Pryma and Richard Wahl

A visionary presentation of a clinician's wish list and expected improvements in outcome:

1:30 PM: Panel discussion—Pat Zanzonico, Ying Xiao, Stanley Benedict, and George Sgouros

Barriers to introduction of robust radiation dosimetry methods to TRT, the best strategy to overcome them and demonstrate that dosimetry for TRT will improve patient care, and the design of relevant clinical trials:

3:15 PM: Good dosimetry practices: Eric Frey

Dosimetry needs and methods for TRT using …

4:00 PM: ^{131}I—Steve Larson and Joe Grudzinski

4:30 PM: ^{90}Y—Yuni Dewaraja, Emilie Roncali, and Mark Madsen

5:00 PM: ^{177}Lu—Yuni Dewaraja and Eric Frey

5:30 PM: ^{153}Sm—Robert Hobbs

Day 2: April 20, 2018

8:00 AM: α-emitter–specific dosimetry issues (overview)—George Sgouros

Dosimetry needs and methods for TRT using …

8:30 AM: ^{223}Ra—John Humm

9:00 AM: ^{212}Pb—Michael Ghaly and Mark Madsen

9:30 AM: ^{225}Ac—Saed Mirzadeh and David Morse

10:30 AM: ^{213}Bi—George Sgouros

11:00 AM: ^{211}At—Gamal Akabani

11:30 AM: ^{227}Th—Wesley Bloch

12:00 PM: Meeting summary and discussion of the resulting publications—Jacek Capala and Stanley Benedict

REFERENCES

1. Home page. NRG Oncology website. https://www.nrgoncology.org/. Accessed March 11, 2021.
2. St. James S, Bednarz B, Benedict S, et al.. Current status of radiopharmaceutical therapy. *Int J Radiat Oncol Biol Phys*. 2021;109:891–901.
3. Divgi C, Carrasquillo JA, Meredith R, et al.. Overcoming barriers to radiopharmaceutical therapy (RPT): an overview from the NRG-NCI working group on dosimetry of radionuclide therapy. *Int J Radiat Oncol Biol Phys*. 2020;109:905–912.
4. Kaminski MS, Zelenetz AD, Press OW, et al.. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. *J Clin Oncol*. 2001;19:3918–3928.
5. Houle S, Yip TK, Shepherd FA, et al.. Hepatocellular carcinoma: pilot trial of treatment with Y-90 microspheres. *Radiology*. 1989;172:857–860.
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. Ibbott GS, Followill DS, Molineu HA, Lowenstein JR, Alvarez PE, Roll JE. Challenges in credentialing institutions and participants in advanced technology multi-institutional clinical trials. *Int J Radiat Oncol Biol Phys*. 2008;71(suppl):S71–S75.
8. Wahl RL, Kroll S, Zasadny KR. Patient-specific whole-body dosimetry: principles and a simplified method for clinical implementation. *J Nucl Med*. 1998;39(suppl):14S–20S.
9. Dewaraja YK, Schipper MJ, Shen J, et al.. Tumor-absorbed dose predicts progression-free survival following 131I-tositumomab radioimmunotherapy. *J Nucl Med*. 2014;55:1047–1053.
10. Kaminski MS, Tuck M, Estes J, et al.. 131I-tositumomab therapy as initial treatment for follicular lymphoma. *N Engl J Med*. 2005;352:441–449.
11. Wahl RL. The clinical importance of dosimetry in radioimmunotherapy with tositumomab and iodine I 131 tositumomab. *Semin Oncol*. 2003;30:31–38.
12. Sgouros G, Barest G, Thekkumthala J, et al.. Treatment planning for internal radionuclide therapy: three-dimensional dosimetry for nonuniformly distributed radionuclides. *J Nucl Med*. 1990;31:1884–1891.
13. Papadimitroulas P, Loudos G, Nikiforidis GC, Kagadis GC. A dose point kernel database using gate Monte Carlo simulation toolkit for nuclear medicine applications: comparison with other Monte Carlo codes. *Med Phys*. 2012;39:5238–5247.
14. Lee MS, Kim JH, Paeng JC, et al.. Whole-body voxel-based personalized dosimetry: the multiple voxel S-value approach for heterogeneous media with nonuniform activity distributions. *J Nucl Med*. 2018;59:1133–1139.
15. Dieudonné A, Hobbs RF, Bolch WE, Sgouros G, Gardin I. Fine-resolution voxel s values for constructing absorbed dose distributions at variable voxel size. *J Nucl Med*. 2010;51:1600–1607.
16. Dewaraja YK, Frey EC, Sgouros G, et al.. MIRD pamphlet no. 23: quantitative SPECT for patient-specific 3-dimensional dosimetry in internal radionuclide therapy. *J Nucl Med*. 2012;53:1310–1325.
17. Stabin MG, Sparks RB, Crowe E. OLINDA/EXM: the second-generation personal computer software for internal dose assessment in nuclear medicine. *J Nucl Med*. 2005;46:1023–1027.
18. Vicente EM, Lodge MA, Rowe SP, Wahl RL, Frey EC. Simplifying volumes-of-interest (VOIs) definition in quantitative SPECT: beyond manual definition of 3D whole-organ VOIs. *Med Phys*. 2017;44:1707–1717.
19. Grimes J, Celler A. Comparison of internal dose estimates obtained using organ-level, voxel S value, and Monte Carlo techniques. *Med Phys*. 2014;41:092501.

20. Lassmann M, Chiesa C, Flux G, Bardies M; EANM Dosimetry Committee. EANM Dosimetry Committee guidance document: good practice of clinical dosimetry reporting. *Eur J Nucl Med Mol Imaging*. 2011;38:192–200.
21. Madsen MT, Menda Y, O'Dorisio TM, O'Dorisio MS. Technical note: single time point dose estimate for exponential clearance. *Med Phys*. 2018;45:2318–2324.
22. Kwekkeboom DJ, de Herder WW, Kam BL, et al.. Treatment with the radiolabeled somatostatin analog [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate: toxicity, efficacy, and survival. *J Clin Oncol*. 2008;26:2124–2130.
23. Rinscheid A, Kletting P, Eiber M, Beer AJ, Glatting G. Technical note: optimal sampling schedules for kidney dosimetry based on the hybrid planar/SPECT method in ^{177}Lu-PSMA therapy. *Med Phys*. 2019;46:5861–5866.
24. Ling X, Latoche JD, Choy CJ, et al.. Preclinical dosimetry, imaging, and targeted radionuclide therapy studies of Lu-177-labeled albumin-binding, PSMA-targeted CTT1403. *Mol Imaging Biol*. 2020;22:274–284.
25. Ljungberg M, Celler A, Konijnenberg MW, Eckerman KF, Dewaraja YK, Sjögreen-Gleisner K. MIRD pamphlet no. 26: joint EANM/MIRD guidelines for quantitative ^{177}Lu SPECT applied for dosimetry of radiopharmaceutical therapy. *J Nucl Med*. 2016;57:151–162.
26. Quadramet [package insert]. Lantheus Medical Imaging, Inc.; 2017.
27. Washiyama K, Amano R, Sasaki J, et al.. ^{227}Th-EDTMP: a potential therapeutic agent for bone metastasis. *Nucl Med Biol*. 2004;31:901–908.
28. Kratochwil C, Giesel FL, Bruchertseifer F, et al.. ^{213}Bi-DOTATOC receptor-targeted alpha-radionuclide therapy induces remission in neuroendocrine tumours refractory to beta radiation: a first-in-human experience. *Eur J Nucl Med Mol Imaging*. 2014; 41:2106–2119.
29. Dos Santos JC, Schäfer M, Bauder-Wüst U, et al.. Development and dosimetry of ^{203}Pb/^{212}Pb-labelled PSMA ligands: bringing "the lead" into PSMA-targeted alpha therapy? *Eur J Nucl Med Mol Imaging*. 2019;46:1081–1091.
30. Teze D, Sergentu DC, Kalichuk V, et al.. Targeted radionuclide therapy with astatine-211: oxidative dehalogenation of astatobenzoate conjugates. *Sci Rep*. 2017;7:2579.
31. Bolch WE, Bouchet LG, Robertson JS, et al.. MIRD pamphlet no. 17: the dosimetry of nonuniform activity distributions—radionuclide S values at the voxel level. *J Nucl Med*. 1999;40(suppl):11S–36S.
32. Howell RW, Goddu SM, Rao DV. Application of the linear-quadratic model to radioimmunotherapy: further support for the advantage of longer-lived radionuclides. *J Nucl Med*. 1994;35:1861–1869.
33. Vaziri B, Wu H, Dhawan AP, Du P, Howell RW; SNMMI MIRD Committee. MIRD pamphlet no. 25: MIRDcell V2.0 software tool for dosimetric analysis of biologic response of multicellular populations. *J Nucl Med*. 2014;55:1557–1564.
34. Hobbs RF, Howell RW, Song H, Baechler S, Sgouros G. Redefining relative biological effectiveness in the context of the EQDX formalism: implications for alpha-particle emitter therapy. *Radiat Res*. 2014;181:90–98.