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Overview of the First NRG-NCI Workshop on Dosimetry of Systemic Radiopharmaceutical Therapy (RPT)

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Abstract

In 2018, the National Cancer Institute (NCI) and the NRG Oncology partnered for the first time to host a joint Workshop on Systemic Radiopharmaceutical Therapy (RPT) to specifically address issues and strategies of dosimetry for future clinical trials. The workshop focused on (1) current dosimetric approaches for clinical trials, (2) strategies under development that would provide optimal dose reporting, and (3) future desired/optimized approaches for the new and novel emerging radionuclides and carriers in development. In this proceedings, 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, sub-organ, and voxel, the latter three all achievable within the Medical Internal Radiation Dose (MIRD) schema (S-value) can be calculated with analytic methods or Monte Carlo methods, the latter in most circumstances. This proceeding 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 biological 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.

Keywords:

Radiopharmaceutical Therapy (RPT), Targeted radionuclide Therapy (TRT), Dosimetry, Microdosimetry, Cellular dosimetry, Medical Internal Radiation Dose (MIRD), S-value, Monte Carlo and analytical methods, Biokinetics

1 Introduction

In 2018, the National Cancer Institute (NCI), NRG Oncology™ (*1*), and IROC (Imaging and Radiation Oncology Core) partnered for the first time to host a joint Workshop on Systemic Radiopharmaceutical Therapy (RPT) to address issues and strategies of dosimetry for future clinical trials that might be supported by NCI National Clinical Trial Network or other related entities (Figure 1). The workshop discussed (1) current dosimetric approaches for clinical trials, (2) dosimetric strategies under development that would provide optimal dose reporting, and (3) future desired/optimum approaches for new and novel emerging radioisotopes and carriers in development (Table 1). These three points are discussed separately in articles by St. James et al. and by Divgi et al. (*2,3*) This editorial presents a summary of the workshop.

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 gamma 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 (TRT). Examples of RPT or TRT 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 FDA approved radiopharmaceutical therapies, there are additional ones in clinical trials.

Radiopharmaceutical therapies are often prescribed by administered activity, normalized or not to body weight or surface area and not always accompanied by image-based radiation absorbed dose prediction nor dose verification. This often results in uncertainties in the reporting of the resulting absorbed dose delivered to the tumor volumes and the normal organs including organs at risk given individual patient pharmacokinetics. For conventional radiation therapy (e.g. external beam radiation therapy, 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, due to the limited accuracy and precision of quantitative imaging methods and

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. beta 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 proceeding, 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, sub-organ, and voxel, the latter three achievable within the Medical Internal Radiation Dose (MIRD) schema. The mean absorbed dose per unit time-integrated activity (S value) can be calculated with analytical 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 as well as to normal organs. In this regard, it is analogous to radiotherapy. The experience of external-beam radiotherapy (EBRT) led to a well-established understanding of the impact of radiation on organs and tumor tissue, critical for assessing potential efficacy, toxicity and ruling out futility. That this knowledge has not been broadly applied to RPT trials, which in many instances adopted the largely empirical 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, 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 could provide better insight into the reasons for success and failure.

Within years of the invention of computerized tomography (CT) in the early 1970s, CT data was adopted to provide anatomical input for the three-dimensional treatment planning process in EBRT. This development led to patient-specific treatment planning that significantly improved treatment efficacy by increasing tumor control and reducing toxicities in patients. Due to its much more recent development, RPT is perhaps 50 years behind EBRT regarding routinely deployed patient-specific treatment planning in the clinic. The formerly FDA-approved therapeutic for non-Hodgkin lymphoma, ^{131}I tositumomab therapeutic regimen (Bexxar®), used a dosimetric whole body scan of 185 MBq of ^{131}I to calculate total body dosimetry (as a surrogate for marrow radiation absorbed dose)(*8*). This treatment showed considerable efficacy and the treatment was prescribed as a patient specific 65-75 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*). While effective, this was not a commercially successful product (*10,11*).

In addition, some patient-specific dosimetry methods using anatomical 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 commercially available software products (DosiSoft, MIM MRT, Hermes Medical Solutions). Currently, these products are only approved

for post-treatment use in the US, but some are being used for pre-treatment 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 quality-assurance and quality-control procedures, and finally 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 optimize the therapeutic ratio. Many gaps in knowledge must be filled before this vision becomes a reality. First and foremost, the radiobiology of systemically administered radionuclides must be studied further to obtain a more accurate understanding of the effects of a given absorbed dose on normal tissue tolerance. Ideally, this understanding of the biological effects of radiation could extend to predictors of patients whose disease and/or normal tissues are sensitive or resistant to radiation. While this need is particularly keen for α-particle emitters, it remains an unmet need for β-particle emitters as well. When companion diagnostics are not chemically identical to the therapeutic, we need a better understanding of the reliability of estimates 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 patients with a wide variety of diseases.

2 Current methods and challenges

2.1 Establishing good dosimetry practices for RPT

In EBRT, the required dosimetry provides useful predictions of 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 methods 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 the selection of the appropriate imaging modality. While conventional and straightforward planar imaging can estimate whole body activity and organ activity estimates, it requires careful compensation for attenuation, scatter correction, background activity and adjustments for 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. While 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. The selection of appropriate collimator and energy windows is also critical, especially for therapeutic radionuclides where 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 (*17*). 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 the 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 three time points are needed when attempting to fit the kinetics with a multiexponential distribution as carried out in OLINDA/EXM (*8,18*), 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 (VOIs) 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 VOIs that requires the user to contour 2D regions-of-interest (ROIs) on each slice is tedious but remains the most common method (*19*). Semi-automatic methods, such as atlas-based and machine learning-based segmentation, show promise for reducing the tedium and associated cost of VOI definition. For fully 3D dosimetry, registration across timepoints of activity images or absorbed dose maps should aim at achieving voxel-level precision, which is challenging due to patient motion between scans. Even for organ-level dosimetry, registration across timepoints can reduce the effort required in VOI definition. State-of-the-art 3D deformable registration is available commercially and highly effective with anatomical images.

The selection of methods for estimating absorbed dose from the activity distributions is also critical (*20*). 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 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 radiobiological factors and micro-scale dosimetry should provide more robust predictions of toxicity and response, especially for α particle emitters where 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 (*21*).

2.2 Clinical dosimetry methods for RPT

There is a growing use of 3D image-based dosimetry to support RPT treatment planning instead of using fixed fractions, empirical 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 (PRRT), 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 used in patients with residual thyroid cancer or avid metastatic tumors for 75 years worldwide, 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 positron emission tomography PET/CT, ^{123}I single photon emission computed tomography 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 its imperfect nature 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 a growing interest in quantitative imaging and dosimetry of ^{90}Y. Direct imaging of the beta emitter ^{90}Y can be done via SPECT or PET. Still, it is complex due to the need for specialized reconstruction techniques (e.g. sophisticated scatter estimation in SPECT,

the inclusion of time-of-flight information in PET). Pre-treatment imaging typically includes ^{99m}Tc labeled MAA for radioembolization (also called SIRT, for selective internal radiation therapy) and ^{111}In labeled antibodies/peptides but the images are currently not used to predict the absorbed dose distribution. Despite reports of discrepancies between the ^{99m}Tc MAA particles and ^{90}Y microspheres 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 (*22*). Several software vendors have started to offer specific toolboxes recently cleared by the FDA (e.g., MIM SurePlanLiverY90, Hermes Medical Solutions SIRT, Dosisoft PLANET® Dose) based on voxel dosimetry.

Recently, the radioembolization of hepatic malignancies using ^{166}Ho labelled microspheres has become commercially available and is clinically used in Europe. ^{166}Ho is attractive for therapy applications as it emits high-energy beta particles and a low-energy gamma-ray suitable for imaging. The advantage over ^{90}Y microspheres is that the same microspheres can be used for pre-therapy imaging without the need to use a surrogate like ^{99m}Tc-macroaggregated albumen (MAA). Furthermore, the paramagnetic properties and high density of ^{166}Ho enable visualization by magnetic resonance (MR) and CT imaging (*23*)

There is recent interest in the beta/gamma emitter ^{177}Lu imaging and dosimetry due to the FDA approval of ^{177}Lu-DOTATATE (Lutathera) peptide receptor radionuclide therapy (PRRT) for treatment of metastatic gastroenteropancreatic neuroendocrine tumor (gNET) and the use of ^{177}Lu prostate-specific membrane antigen (PSMA) radioligand therapy for metastatic prostate cancer (*24*). Both these therapies are administered in 4 consecutive cycles with a fixed administration of 7.4 GBq/cycle (*23,25*). SPECT-based dosimetry could be used for absorbed dose verification after each cycle, using ^{177}Lu photon emissions, following guidelines published in a MIRD/EANM joint pamphlet(*26*). A commercial toolbox for quantitative ^{177}Lu SPECT/CT received FDA clearance in 2019 (MIM SurePlanMRT). Important points that need to be addressed and that are still at the research stage include the reduction of time points needed

to capture the ^{177}Lu biodistribution to a 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 (^{153}Sm EDT-MP) is a beta 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 pre-therapeutic treatment planning. Imaging quantification accuracy compares to that of standard radiopharmaceuticals (e.g. ^{111}In, ^{131}I). The dose-limiting organ is the bone marrow, with an established maximum tolerated dose (MTD) of 39.5 MBq/kg based on preclinical studies (*27*).

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

3 RPT Dosimetry Methods under Development

3.1 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 limited to single time point measurements for estimating the critical organ dose and thus the maximum safe administered activity (*22*).

3.2 Challenges with for α dosimetry

Recent developments in new radionuclides focus on α emitters, such as ^{212}Pb, ^{225}Ac, ^{213}Bi, ^{211}At, and ^{227}Th (*28-31*). Dosimetry challenges associated with these isotopes were discussed within the Workshop Dosimetry Needs and Methods Section and are briefly summarized below:

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

- ^{225}Ac. After an initial demonstration of its clinical efficacy, 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 the 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. It 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 leukemia studies which initiated the development of imaging and dosimetry methodology. Its short 46 minute half life provides practical and logistical challenges for therapy.

- ^{211}At. Two clinical trials have been carried out for the treatment of recurrent brain tumors and the treatment of intraperitoneal ovarian cancer. Multiscale dosimetry methods have been developed, which are used depending on the quality of the pharmacokinetic data and biological and clinical endpoints. Current research includes binary theranostic agents based on a combination of a PET/SPECT and α particle-emitting therapeutic radionuclides using nuclear nanotechnologies, such as intrinsic radioactive nanoparticles.

- ^{227}Th. Thorium-227 therapies include ^{227}Th EDTMP for bone metastases, the radioimmunoconjugate ^{227}Th-rituximab for the treatment of CD20+ lymphoma, and ^{227}Th-trastuzumab for the treatment of HER2-expressing ovarian cancer. Possibilities of both gamma camera imaging and 3D SPECT imaging of patients treated with ^{227}Th labeled monoclonal antibodies have been reported.

3.3 Multi-scale 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 (*32,33*). Challenges in voxelized dosimetry include the relatively large voxel size due to the finite spatial resolution of PET and SPECT (4 – 15 mm) that 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 (LET) of α particles yields a very dense pattern of energy deposition that leads to enhanced and dose-rate independent biological effects per absorbed dose when compared to low LET radiations such as beta 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 (*34*). Accordingly, understanding the implication of normal organ or tumor dosimetry from an α emitter requires knowledge of the relative biological effectiveness (RBE) (*35*).

The relative biological effectiveness (RBE) is defined as the ratio of the absorbed dose deposited by a low LET to high-LET particle emitters required to reach a given biological end-point. The assessment of the RBE values from α-particle emitting therapeutics is complex due to nonuniform activity uptake within the cellular and extracellular components, and variable radiosensitivity depending on the location of the site of emission within the cell. For example, it has been observed from autoradiography data from normal and tumor tissues that cell populations uptake 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 uptakes among circulating tumor cells. Innovative approaches that combine *a priori* biological behavior, preclinical, and human studies, are needed to calculate the absorbed dose and translate it into likely biological response.

4 **Future Opportunities:**

The rationale for improving and optimizing dosimetry in radionuclide therapy has become a critical area for investigation needed to improve oncologic patient care, guiding clinical trial design to reduce financial and logistical costs in drug approval. This proceeding 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. beta or α), 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 in each approach with the intent that emerging image-based dosimetry methods for personalized dosimetry are improved in the near future and to guide quality assurance of RPT dosimetry for clinical trials. These discussions may be presented at a follow up NRG-NCI Workshop on Dosimetry of Systemic Radiopharmaceutical Therapy (RPT).

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FIGURE 1:

PHOTO of ATTENDEES and SPEAKERS

TABLE 1: Agenda

NCI Workshop on Dosimetry of Systemic Targeted Radiopharmaceutical Therapy (RPT)
NIH Campus/Rockville, MD, April 19-20, 2018
Day 1: April 19, 2018

8:00 am **Opening Remarks**
C. Norman Coleman, Bhadrasain (Vik) Vikram, Jacek Capala

- Presentations and Discussions

8:15 am **Current Status of TRT, *Sara St. James & Bonnie Clarke***

- Approved treatments and Clinical trials

9:00 am **Currently Applied TRT Dosimetry Methods: *Stanley Benedict & Emilie Roncali***

- Advantages and limitations of methods used in clinical practice

9:45 am **Available TRT Dosimetry Methods/Approaches: *Bryan Bednarz & George Sgouros***

- New methods that are ready for clinical application
- The advantage over the methods currently used in the clinic
- How they might improve the clinical outcome?
- The reasons they are not used

10:45 am: TRT Dosimetry Methods under Development: *Yuni Dewaraja, Wesley Bloch, R. Howell*

- The advantage over the methods that have been already developed
- How they might further improve the clinical outcome?
- What are the simplest possible methods to reduce the stress of going through additional procedures before already very difficult TRT?

11:30 am **Desired RPT Dosimetry Methods/Approaches: *Daniel Pryma & Richard Wahl***

- A visionary presentation of a clinician's wish list
- Expected improvements of the outcome

1:30 pm **Panel Discussion: *Pat Zanzonico, Ying Xiao, Stanley Benedict, George Sgouros***

- What are barriers to introduction of robust radiation dosimetry methods to TRT?
- What is the best strategy to overcome them and demonstrate that dosimetry for TRT will improve patient care?
- 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 & Joe Grudzinski***
4:30 pm **^{90}Y:** ***Yuni Dewaraja, Emilie Roncali, Mark Madsen***
5:00 pm **^{177}Lu:** ***Yuni Dewaraja & Eric Frey***
5:30 pm **^{153}Sm:** ***Robert Hobbs***

Day 2: April 20, 2018

8:00 am **Alpha emitters-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 & Mark Madsen***
9:30 am **^{225}Ac:** ***Saed Mirzadeh & 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 & Stanley Benedict