Modern Radiopharmaceutical Dosimetry Should Include Robust Biodistribution Reporting

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Radiopharmaceutical dosimetry is an important area of nuclear medicine, and its advances have the potential to affect imaging and radiotherapy development and application protocols. Dosimetry is a computationally intensive, assumption-based process, and not all dosimetry is created equal. In this brief communication, we present biodistribution measurements as a valuable part of radiopharmaceutical dosimetry that is worthy of robust documentation. Biodistribution data are routinely collected in every dosimetry case and are integral to the subsequent dosimetry calculations. Standard documentation of these data may help us understand the value and limitations of our dosimetry estimates, identify errors, resolve discrepancies, and enable the reproducibility of results. We may also recognize that the modern digital landscape provides both opportunity and motivation to usher in the evolution of standards in our field. Ultimately, these steps may improve the current generally poor acceptance of dosimetry procedures by clinicians.

Key Words: radionuclide dosimetry; internal dosimetry; biodistribution; reporting

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Nuclear imaging and therapy are defined by the integration of radiopharmaceuticals and patient biologic systems. Radiopharmaceutical dosimetry (RD) describes the interaction between the energy deposition associated with a radiopharmaceutical's emissions and the patient's body and helps to guide optimal clinical use of radiopharmaceuticals. The foreseeable expansion of our field will be driven in part by RD. The establishment of new radiopharmaceuticals relies on RD in their development. The establishment of strategies for personal tailoring of radiotherapies will be based on RD. If we take a moment to reflect on the decades of digital innovation that has modernized our field, and continues to modernize our field, particularly with respect to information-sharing capacities, we can find that a justification for updating our documentation practices in the RD literature begins to emerge.

RD exists in the form of numbers and data, and the integrity with which they are derived and presented is of principal importance. Deriving RD is largely a physics-based endeavor and is accomplished using image analysis, data analysis, and dose deposition modeling. What makes RD unique among other medical uses of radiation in medicine is that the source, an administered radiopharmaceutical, is distributed throughout the body across both spatial and temporal domains along with the regions of dosimetric interest. The process of determining the source biodistribution of a radionuclide is fundamental to the associated estimation of dosimetry. Methods for acquiring biodistribution estimates involve many steps and assumptions that can vary significantly for different tracers, protocols, and across centers. Current standards for documenting and reporting biodistribution measurements in dosimetry-related studies do not exist.

A PROPOSAL FOR A NEW RD PUBLICATION STANDARD

Our proposal is that all thorough reporting of RD estimates should include the associated biodistribution characterizations used to create them. The biodistribution summary should account for 100% of the activity modeled in the presented dosimetry calculations—that is, time-integrated activity coefficients for all patients involved in the respective study, which include organ uptake, remainder-of-body uptake, and assumed waste. The information can be in the form of a table, or more thorough templated data (*1*), and distributed in the body, appendix, or supplemental data portions of published articles. Justification of this standard is presented in the following text.

QUANTITATIVE UNCERTAINTIES IN RD

A proper understanding of the error associated with RD is fundamental to its efficacious use. The discussion of error in RD is complicated by the different types of error measurements (accuracy, precision, uncertainty, and trueness) and dosimetry measures (absorbed dose, effective dose, biologic dose) as well as varying biologic functions measured with varying protocols and affected by varying properties of isotopes.

Few generalized error estimates for internal dosimetry can be found in the literature. We have seen efforts to characterize the dependability of our RD data, reported with uncertainty values of 10%–100% or more (*2–4*). This ambiguity has consequences because it has left the interpretation of dosimetry to individual preferences, interests, and intuitions, thereby creating a situation conducive to disagreement on the implications of RD studies. The confusion has impeded consensus, and the field of radiopharmaceutical therapy has largely not moved beyond simplistic treatment protocols, with standard radionuclide therapies being performed at fixed or clinically individualized (e.g., body weight, body surface area, and clinical features) activity levels. The field

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could benefit from a greater understanding of the error associated with our RD measurements.

RD DOCUMENTATION IN IMAGING

Dosimetry for imaging radiopharmaceuticals is usually used to understand population average and stochastic risks. However, accurate and reproducible dosimetry is important because tracer dose can vary significantly across radiopharmaceuticals (*5*), and understanding relative risk is an important concept for ensuring optimized imaging and maintaining safe compliance with regulations.

Imaging RD is commonly published in the contemporary literature. Protocols and descriptions of protocols vary widely across publications. The inclusion of biodistribution details is not routine, and when included, the format of presentation also varies. If and when there are differences between similar studies, it can be difficult or impossible to understand these differences.

Another consideration is that S values, tissue-weighting factors, radiation-weighting factors, and other assumptions used to calculate dose can change over time with different modeling assumptions and different software (*6*). A change in practice toward more robust biodistribution documentation could ensure that RD estimates are reproducible by linking them to source study data rather than to the version of dose software with which they are created.

RD DOCUMENTATION IN THERAPY

Dosimetry in radionuclide therapy is used under the premise that we may be able to correlate high-quality RD with healthy-tissue and diseased-tissue response, thereby enabling patient-specific optimization of treatment. Our challenge is to establish dependable correlations, the quality of which will affect the efficacy of our efforts. It is widely agreed that prospective, randomized clinical trials would be the gold standard for establishing the value of dosimetry in therapies (*7,8*); however, these trials are hardly feasible, as they are resource-intensive for patients, personnel, and machinery occupancy and thus have yet to come to fruition.

It has been argued that the existing literature provides enough supporting evidence that spending time and resources on routine RD calculation in therapeutic procedures is justified and that we should treat the administration of radiopharmaceuticals in a manner similar to external-beam radiotherapy and personalize treatments based on standardized absorbed dose estimations (*9*). Alternatively, we have seen counter narratives arguing that basing treatment on dosimetry is premature; that issues of uncertainty, standardization, and biologic complexities have not been adequately addressed; and that we should treat the administration of radiopharmaceuticals as we do other pharmaceuticals, administered with a fixed dose until standardized and proven individually predictive outcomes using RD are established (*8*). The two positions are not mutually exclusive. It is notable that much of the cited work demonstrating the positive potential of RD comes from single-center studies, in which methods, personnel, and equipment do not need to be explicitly characterized and documented to be reproduced. A recent review of the evidence base for the use of dosimetry in radionuclide therapies identified this dependence on single-center studies as a shortcoming of our literature (*10*). Overall, a lack of standardization across the field can obfuscate true dose–response relationships in our literature and cause confusion in the field. The juxtaposition of high-precision dosimetry in single-center studies and concerns over the adequacy of our evidence base suggest an opportunity to bridge the gap between the different views with improved standardization, which can be supported with improved documentation.

With respect to advancing radiopharmaceutical therapeutics, emphasis should be placed on generating specific organ tolerability thresholds for each treatment, improving tumor and organ modeling, and integrating RD estimates with other tumor- and patient-specific clinical, histopathologic, and genomic characteristics implicated in the tissue response to the radiation. Accurate, reproducible RD will play a central role in this goal. Also, it is prudent to have a strategy for reporting cases in which tissue complications arise from exposure to radiation. These cases are invaluable for refining our optimization models, and their robust documentation will be important for their accurate interpretation.

MODERN AND FUTURE PERSPECTIVES ON IMPROVING RD DOCUMENTATION

Our field is largely working within a legacy (20th century) infrastructure. Contemporary RD studies are performed and published in a manner similar to work that has been presented in previous decades. However, the modern digital landscape is bringing us new opportunities for enhancing our clinical practices (*11*). New tools are now coming out that integrate error propagation into RD calculations and support more robust RD documentation (REFX). We are also seeing new and accessible innovations around phantom models, Monte Carlo/voxel-level dosimetry, and small-scale/cellular-level dosimetry (*12*).

Our understanding of data is also evolving. It is increasingly recognized that data are a resource (*13*), and when they are digitized and stored they can be used to support advanced data analysis strategies and innovative methods of use. In the scientific community, we have also seen the development of data-sharing ideas that are beginning to transform the scientific landscape (*14*). We are no longer limited to physical journal pages to share information. We now have a well-developed online architecture that allows journals, institutions, and research groups to archive and make available scientific data to accompany research studies (Table 2 in Kesner et al. (*11*)). Furthermore, beyond the newly available architecture for data sharing, we have also seen growing recognition that the sharing of source data is good scientific practice (*15*).

SUMMARY

RD is an important area of nuclear medicine, and its advances have the potential to affect imaging and radiotherapy developments and application protocols. Presently, our field utilizes RD without documenting unprocessed measurements and without performing uncertainty characterization on the data we share. In this brief communication, we present a case for updating our practice to treat biodistribution measurements as a valuable part of dosimetry work and therefore worthy of robust documentation. Biodistribution data are already collected in every dosimetry case, and standard documentation of these data may help us understand the value and limitations of our RD, identify errors, resolve discrepancies, and enable the reproducibility of results. Ultimately modernizing documentation may improve the current generally poor acceptance of dosimetry procedures by clinicians. We are now at an opportune time when changing our reporting practices

is practical and can lay the groundwork for a more robust and dynamic field in the coming decades.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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