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Modernizing dosimetry documentation to address the challenge of standardization

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Nuclear imaging and therapy are defined by the integration of radiopharmaceuticals and patient biological 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 utilization of radiopharmaceuticals. The foreseeable expansion of our field will be driven in part by RD. The establishment of new radiopharmaceuticals rely on RD in their development. The establishment of strategies for personal tailoring of radiotherapies will be based on with RD. If we take a moment to reflect of decades of digital innovation that has 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 RD literature begins to emerge.

RD exists in the form of numbers/data, and the integrity with which they are derived and presented is of principle importance. Deriving RD is largely a physics-based endeavor and is accomplished using image/data analysis and dose deposition modelling. 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 region(s) 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 publication of RD estimates should include the associated biodistribution characterizations used to create them. This biodistribution summary should provide accounting for 100% of the activity modeled in the presented dosimetry calculations - i.e., 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 supplementary data portions of published articles.

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, biological dose) as well as varying biological functions measured with varying protocols and affected by varying properties of isotopes.

There are few generalized error estimates for internal dosimetry that can be found in literature. We have seen efforts to characterize the dependability of our RD data, reported with uncertainty values between 10%-100% or more (*2-4*). This ambiguity has consequences as it has left the interpretation of dosimetry to individual preferences, interests, and intuitions – thereby creating a situation conducive to disagreement of the implications of RD studies. The confusion has impeded consensus, and the field has largely not moved beyond simplistic treatment protocols, standard radionuclide therapies are carried out at fixed or clinically-individualized (e.g. body weight, BSA, clinical features) activity levels. The field could benefit from a greater understanding or 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 within regulations.

Imaging RD is commonly published in 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 trace 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 modelling assumptions and different software (*6*). A change in practice towards more robust biodistribution documentation could ensure that RD estimates are reproducible by linking them to source study data, rather than the version of dose software they are created with.

RD documentation in therapy

Dosimetry in radionuclide therapy is employed under the premise that we may be able to correlate high-quality RD with healthy and disease tissue response, thereby enabling patient-specific optimization of therapeutic treatment. Our challenge is to establish dependable correlations, the quality of which will impact 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 existing literature provides enough supporting evidence that spending time and resources on routine RD calculation in therapeutic procedures is justified and we should treat the administration of radiopharmaceuticals in a similar manner 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, issues of uncertainty, standardization, and biological complexities have not been adequately addressed, and we should treat the administration of radiopharmaceuticals like 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, where 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, if standardization across the field is lacking, this 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.

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, histopathological and genomic characteristics implicated in the tissue response to the radiation. Accurate, reproducible RD will play a central role in this. Also, it is prudent that we have in place a strategy for reporting cases where 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 similar manner to work that has been presented in previous decades. However, the modern digital landscape is bringing us new opportunities for enhancing our imaging related practices (*11*).

It is increasingly recognized that data is a resource (*12*), and when it is digitized and stored it can be used to support advanced data analysis strategies and innovative methods of utilization. We have also seen ideas develop in the scientific community around data sharing that are beginning to transform the scientific landscape (*13*). We are no longer limited to physical journal pages to share information. We now have well developed online architecture that allows journals, institutions, and research groups to archive and make available scientific data to accompany research studies (see Kesner, et al. (*11*), Table 2). 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(*14*).

Summary

RD is an important area of nuclear medicine and its advances have the potential to impact imaging and radiotherapy treatment development and application protocols. In this letter, we present a case for treating biodistribution measurements as a valuable part of dosimetry work that is worthy of robust documentation. Biodistribution data is already collected in every dosimetry case, and its standard documentation may help us understand the value and limitations of our RD, identify errors, resolve discrepancies, and enable the reproducibility of results. Ultimately it 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

The authors have no conflicts of interest to disclose.

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