Targeted radionuclide therapy (TRT) is recognized as an effective means for treating a variety of cancers (1), ranging from conventional $^{131}$I-radioiodine for differential thyroid carcinoma (DTC), $^{223}$Ra-Dichloride for bone metastasis of castration-resistant prostate cancer (CRPC), $^{90}$Y microspheres for hepatic cancers, to newly EMA (Europe) and FDA (USA) approved $^{177}$Lu-DOTATATE Peptide Receptor Radionuclide Therapy (PRRT) for neuroendocrine tumors. Furthermore, several other therapeutic agents including $^{177}$Lu-PSMA for prostate cancers and alpha-particle emitters for treating different cancers are in clinical trial or are being developed and evaluated (2). Personalized treatment planning can ensure TRT efficacy while avoiding potential toxicity to critical organs by considering patient-specific pharmacokinetics. Sequential radionuclide imaging following a pre-therapy tracer administration can serve as a non-invasive tool for predicting the radiation absorbed doses delivered to tumor and critical organs by the therapy. In the case of therapies administered over multiple cycles, such as $^{177}$Lu-DOTATATE, imaging-based dosimetry after one cycle can be used to predict the absorbed doses that will be delivered by subsequent cycles for consideration of potential dosage adjustment. Quantitative emission computed tomography (ECT), i.e., single photon emission computed tomography (SPECT) and positron emission tomography (PET), provides 3-dimensional (3D) activity distributions for voxel-level dosimetry, which is of increasing research and commercial interest in TRT (3,4). Sequential ECT images can be directly converted to dose-rate maps or a time integrated activity (TIA) map, which can then be converted to an absorbed dose map.

Conventional corrections for diagnostic agents in ECT include uniformity, scatter, attenuation, detector response and sometimes partial volume effect. Depth dependent collimator-detector response correction is important for SPECT as well as correction of random coincidences for PET. For therapeutic radionuclides used in TRT, besides the conventional corrections, special attention should be placed on down scatter and collimator penetration for SPECT (5); multi-energy window selection and scatter correction for Bremsstrahlung imaging; prompt gamma emission and increased positron range for PET as their decay schemes are usually complex and associated with high energy positrons/photons emissions, even for their imaging surrogates. Partial volume correction is also important for all imaging modalities in TRT generally. Instead of the organ/lesion-level partial volume correction using recovery coefficients, the need for voxel-level correction has been recognized and solutions are being investigated (6,7). With appropriate modelling, quantitative accuracy can reach >90% for PET (8), SPECT (9) and Bremsstrahlung imaging (10). Clinically, state-of-the-art spatial resolutions of 6–8 mm (11) or even <3 mm (12) for dedicated organs in SPECT, 4–6 mm in PET (13) have been reported. Considering the travelling
distance for common beta (1.5–19 mm) and alpha particles (0.016–0.075 mm) (14) associated with TRT agents, the spatial resolution and thus resolvable voxel size would need to be further improved to reduce the uncertainties in dose estimation at the voxel-level (6,15). Techniques such as time-of-flight PET, point spread function modelling, solid-state detectors, digital ECT using silicon photomultiplier tubes with photon counting capability have demonstrated improved quantitative imaging performance and hold promise for improving TRT voxel-based dosimetry. Novel collimators designs are possible ways to improve SPECT and Bremsstrahlung imaging (16). For example, pinhole collimators are shown to reduce collimator penetration for I-123 imaging (17). However, factors such as field-of-view and sensitivity would need to be considered when designing collimators as acquisition time is important for patient throughput in clinical TRT practice. Besides, respiratory motion degrades image quality particularly near the lung-liver interface. Therefore, it may impact the quantitative accuracy and dosimetric estimation for post-therapy $^{90}$Y PET/Bremsstrahlung imaging and pre-therapy $^{99m}$Tc-macro aggregated albumin (MAA) SPECT for treatment planning of microsphere radioembolization in hepatic cancers. Respiratory gating via external tracking devices (18,19) as well as fully data-driven approaches (20) can be used to alleviate this problem in SPECT (21) and PET (22). New initiatives for imaging instrumentation dedicated for TRT are underway (23).

Usually patients are imaged at multiple time points for TRT dosimetry to obtain the time activity curves (TAC) for critical organs and tumors. Accurate alignment between these sequential images is of much importance for 3D dosimetry (24). Multiple research groups have performed voxel-level spatial alignment for dosimetry (25,26). Our group at University of Macau has demonstrated that voxel-based non-rigid registration from sequential SPECT is feasible to enhance the 3D absorbed dose estimations and cumulative dose volume histograms (27). The integrated CT or MRI images can be used to further improve the precision of sequential ECT image registration and segmentation (28), while registration between ECT and CT/MRI at the same time point is also important to avoid errors from misaligned attenuation maps and volumes-of-interest defined on the anatomical image that are applied to ECT images (29). Repeated CT scans paired with the corresponding sequential ECTs are nevertheless not in routine practice due to the concern of increased radiation exposure and a single CT is usually acquired. Some groups rely on SPECT/CT at a single time point coupled with planar whole body imaging to estimate pharmacokinetics (30). If multiple SPECT/CTs are performed, the CT exposure can be minimized by reducing the tube current substantially at all but one imaging time points, or by the “virtual CT” method proposed by our group (31). On the other hand, $^{90}$Y microsphere imaging is a relatively simplified TRT application as only 1 imaging time point is generally needed. The microspheres are assumed to be trapped in the microcapillaries with only physical decay afterwards, thus multi-time point imaging and registration are not performed. Furthermore, because $^{90}$Y is an almost pure beta emitter, reasonably accurate voxel-based dosimetry can be performed assuming local energy deposition without the need to consider photon-transport. However, imaging of $^{90}$Y is complex as it relies on SPECT imaging of Bremsstrahlung photons and PET imaging of annihilated photons from a very low positron branching ratio. Specialized reconstruction methods including methods based on Monte Carlo simulations (10,32,33) and neural networks (34,35) have been proposed to address the challenges of $^{90}$Y imaging. The use of PET/MR could be beneficial for the radioembolization application particularly due to the superior soft tissue contrast provided by MR for tumor segmentation in the liver (36). Automatic and reliable segmentation methods would be desirable to alleviate the processing time and inter/intra operator inconsistency (37) especially for applications with many organs of interest and multiple imaging sessions.

Curve fitting is usually used to obtain the TACs from multiple time point imaging data and is generally considered to be more accurate than numerical integration for estimating TIA. Mono- or multi-exponential models are typically employed depending on number of imaging time points and the tracer pharmacokinetics, while best fit can be obtained from certain criteria testing and minimizing the errors as compared to the measurements (38,39). Recently proposed approaches for approximating TIA based on single time point $^{177}$Lu-PSMA (40), $^{177}$Lu-DOTATATE (41) and $^{90}$Y-DOTATOC (42) imaging data would greatly enhance the clinical feasibility of personalized dosimetry considering limited reimbursement, patient compliance and clinical resources. However, selection of an optimal imaging time point for different
organs of interest, tumors and tracers is critical and this method may not be suitable for outlier patients with unique pharmacokinetics.

The gold standard for converting TIA maps to voxel-level absorbed dose maps (or activity maps to dose-rate maps) is based on Monte Carlo simulations (MCS) (43-45) with inputs of TIA (or activity) maps and CT-based density maps. The long computational time impedes its implementation in the clinic. An efficient alternate is to use dose point kernel (DPK)/voxel-S-value (VSV) method for dose conversion. This method is based on kernels of different voxel sizes, isotopes and media generated by MCS while many of them are tabulated in the literature (46). Its accuracy is shown to be comparable to full MCS in soft tissues generally, but substantial deviations have been shown at the lung-liver interface for 90Y microspheres (47) or lungs for 177Lu applications (48), even when tissues-specific kernels were assigned (49). New dose kernels to address the tissue heterogeneity problem are being developed (50). Lately, deep learning methods have been proposed to generate 3D absorbed dose maps or dose rate maps directly from TIA or activity maps with high accuracy and speed, using convolutional neural network (CNN) (51,52) or deep neural network (DNN) (53). Although the training process based on ECT/CT images paired with their MCS generated absorbed dose maps for specific TRT agents can be time consuming, this process is performed only one time in general. Prior to clinical use of these new methods, sufficient data are required for the training/testing process to establish generalizability.

There are other exciting ongoing developments in TRT dosimetry. While dosimetry is currently mostly performed on beta and gamma emitters, alpha particles hold promise for TRT due to their high linear energy transfer (LET) for killing cancer cells in a short range while sparing normal tissues. Microdosimetry is more suitable for alpha particles and is being investigated by several groups (54,55), yet its standard imaging protocols are to be established (56). Besides, as precise voxel-based dosimetry would require a dedicated physicist or research personnel which may not be available in many clinics, a robust one-stop internal dosimetry software package for image registration, segmentation, curve fitting, dose conversion and 3D dose analysis such as isodose contours and dose volume histograms would be paramount for practical clinical implementation of TRT dosimetry. Various research (57-63) and commercial (64-66) internal dosimetry software is now available, with enhanced functions being developed. Figure 1 shows an example of voxel-level dosimetry based on multiple SPECT/CT imaging sessions for a patient undergoing 177Lu-DOTATATE PRRT using the Dose Planning Method (DPM) Monte Carlo software (67). Some programs (62,63) are integrated with models to estimate radiobiologic dose-metrics such as biological effective dose (BED) and equivalent uniform dose (EUD), although the values of model parameters, such as lesion/normal-tissue radiosensitivity, are not yet well established. Besides, as voxel-based calculation for aforementioned dosimetric operations, e.g., registration, curve fitting and segmentation can be computational demanding, deep learning or GPU-based computation can be feasible options to accelerate the voxel-based dose estimation process. After all, development and testing of new dosimetric methods require access to clinical patient images. Currently, University of Michigan is establishing a data-sharing repository of anonymized patient PET/CT and SPECT/CT imaging datasets for various therapeutic agents (68). Access to such data is expected to facilitate research in TRT dosimetry and multi-institutional collaborations among researchers or even clinicians since post-therapy imaging data are still not typically acquired at most clinics.

Albeit there have been ongoing debates regarding the necessities of personalized (69) and voxel-based dosimetry (70), most agree that one-dose-fits-all is not the best way to treat patients as dose escalation or reduction is necessary for efficacious and safe treatment of some patients. Voxel-based method provides more accurate and complete dosimetric information such as heterogeneous absorbed dose distribution within the same organ as compared to the conventional mean absorbed dose method. This information is particularly useful for organs with substructures such as cortex and medulla in kidneys. With standardized dosimetric methodologies, reliable software, advance imaging technologies more available to reduce the dosimetric uncertainties and demand on clinical resources, voxel-based dosimetry is becoming feasible for routine clinical practice in various TRT applications. More systematic studies are warranted to demonstrate the absorbed dose-effect relationships and potential improvement in clinical outcome for “confident” personalized voxel-based dosimetry.
Acknowledgments

Funding: The authors would like to acknowledge research funding from University of Macau (MYRG2017-00060-FST) and the National Institutes of Health, USA (R01CA240706 and R01EB022075). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, Quantitative Imaging in Medicine and Surgery. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/qims-20-1006). Dr. GSPM serves as an unpaid editorial board member of Quantitative Imaging in Medicine and Surgery; she reports that she has a China software copyright registration for an internal dosimetry software (BIGDOSE). Dr. YKD reports personal fees from MIM Software, Inc., USA, outside the submitted work.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.
References


31. Li T, Mok GS. Virtual CT for reducing CT dose in targeted radionuclide therapy dosimetry. Med Phys 2018;45:5138-44.


Cite this article as: Mok GSP, Dewaraja YK. Recent advances in voxel-based targeted radionuclide therapy dosimetry. Quant Imaging Med Surg 2021;11(2):483-489. doi: 10.21037/qims-20-1006