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Towards Routine Clinical Use of Dosimetry in [^{177}Lu]Lu-PSMA Prostate Cancer Radionuclide Therapy: Current Efforts and Future Perspectives

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In light of widely expanding personalized medicine applications and their impact on clinical outcomes, it is naturally befitting to explore all the dimensional aspects of personalized radionuclide therapy (RNT). Adoption of absorbed radiation dose into clinical practice in the field of RNT has been hampered by difficulties such as evidence of dose-effect correlation, technical requirements in quantitative imaging of the radiopharmaceutical, heterogeneity of methods between not only centers, but also across software, hardware and radionuclides used. Additionally, standardized agreed upon definition of outcome measures is being debated whether it be solely related to toxicity, quality of life, survival or other measures. Many clinical RNT activity administrations are still based on empirical/fixed activities, or scaled based on parameters such as body surface area. Although still challenging, a tremendous amount of progress has been made to facilitate routine clinical dosimetry with discussions regarding standardization, harmonization and automated processing techniques. This has also been aided by the development and FDA approval of several companion diagnostics allowing within the theranostic paradigm not only a crude qualitative predictive biomarker but also an objective dosimetry based predictive therapeutic biomarker. This work aims to review the literature of [^{177}Lu]Lu-PSMA RNT, focusing on clinical trials and studies, with the goal to summarize the range of dosimetry techniques and the range of doses calculated to organs and tissues of interest from these techniques. A dosimetry method for [^{177}Lu]Lu-PSMA RNT should be reliable, reproducible and encompassing the knowledge gained from all clinical trials evaluating it. Its translation into clinical routine practice can be achieved with the confirmation that dose calculation represents good clinical efficacy and low treatment-related toxicity. Finally, some future perspectives on the future of [^{177}Lu]Lu-PSMA RNT are made, especially in the rapidly emerging field of artificial intelligence (AI), where deep learning may be able to play a large role in the simplification of dosimetry calculations to aid in their clinical adoption.

Keywords: dosimetry, 177 lu, PSMA, prostate, cancer

INTRODUCTION

Prostate cancer (PC) is currently the most prevalent malignancy and the second most frequent cause of cancer mortality in adult men worldwide [1]. It is expected that the incidence and mortality will increase by approximately 57 and 64%, respectively, from the years 2020–2040 [2]. Latest statistics, provided by the National Institutes of Health (NIH), predict approximately 268,490 new diagnoses and 34,500 deaths in the United States in 2022 [3].

As the disease progresses, systemic chemotherapeutic options for metastatic castration-resistant PC (mCRPC) patients involve docetaxel and cabazitaxel as first and second line agents, respectively. Patients failing chemotherapy, eligibility (i.e. due to contraindications) and whose cancers become advanced or aggressive may be managed with prostatectomy, radiation therapy or androgen deprivation therapy. 10–20% of PC patients, experience disease progression into CRPC within 5 years of follow up, following surgical or medical castration (i.e., androgen deprivation) [4]. According to the Prostate Cancer Working Group 2 criteria, CRPC is defined as PC with any progression occurring in the presence of castrate-level testosterone levels, and may present itself as a continuous rise in prostate-specific antigen (PSA) serum levels, or progression in known sites of disease or with new metastases [5]. 90% of CRPC patients develop bone metastases causing significant morbidity, such as pain, pathologic fractures and bone marrow failure [6].

Early radioligand imaging for PC relied mainly on monoclonal antibodies. The murine (mAb) 7E11 and the humanized mAb hJ591 developed in the 90s showed some drawbacks such as long circulation half-life, low signal to noise ratio and poor target tissue uptake [7]. The 7E11 was developed as a theranostic agent, with [^{111}In]In-7E11 (ProstaScint) as the diagnostic radiopharmaceutical (itself with poor positive predictive value), to potentially be used with SPECT imaging and [^{90}Y]Y-7E11 as its therapeutic counterpart. However, when [^{90}Y]Y-7E11 showed high myelotoxic effects and the hJ591 showed overall poor sensitivity as a SPECT imaging agent, both stopped in development [8, 9]. At the same time, radiolabelled J591 mAb, as [^{89}Zr]Zr-hJ591, was investigated for PET/CT imaging with its therapeutic counterpart being [^{177}Lu]Lu-hJ591 [9, 10].

More recently in the clinical space, the FDA has in 2020 and 2021 approved two diagnostic imaging agents [^{68}Ga]Ga-PSMA-11 [11], and [^{18}F]F-DCFPyL [Pylarify] [12]. Both agents work by imaging the prostate-specific-membrane-antigen (PSMA) protein, which is often found in large amounts on prostate cancer cells and is associated with biologic aggressiveness. Upon the development of small molecule PSMA peptide inhibitors, studies have shown them to be a superior alternative to antibody-based imaging agents [13]. The key parameters in mind when these agents were under development, was to ensure high PSMA affinity and rapid blood clearance and excretion [7].

Multi-center prospective trials have demonstrated the sensitivity of these PET radiotracers for identifying small sites of metastatic disease which has a significant impact on the selection of treatment options. In the context of theranostics (i.e. imaging radioisotope surrogates for therapeutic radioisotopes) these two agents offer a potential paradigm to deliver predictive therapeutic dosimetry. This is of great importance especially in lieu of the recent 2022 FDA approval of [^{177}Lu]Lu-PSMA as a therapeutic option in mCRPC patients.

^{177}Lu is a beta emitter with $t_{1/2}$ = 6.7 days, E_{β}^{-}(av) = 134 keV, E_{β}^{-}(max) = 496 keV, D_{av} = 0.6 mm, D_{max} = 1.6 mm and emits several accompanying photons of 208 keV (11%) and 113 keV (6.4%), which can be used for pre and post-treatment diagnostic evaluation and dosimetry purposes via imaging with a gamma camera [^{177}Lu]Lu-PSMA-617 is currently only used on the basis of individual therapeutic trials in some European countries [14], in addition to its anticipated use in the United States as it becomes readily available [15]. As with all types of radiation therapy, the goal of [^{177}Lu]Lu-PSMA radionuclide therapy (RNT) is to achieve the highest therapeutic efficacy by delivering maximum absorbed dose into the tumor lesions while sparing healthy tissues. In order to achieve a desired radiation absorbed dose (minimum dose for maximum efficacy) and to estimate the absorbed dose after administration of the radiopharmaceutical, accurate dosimetry is needed pre- and post-treatment [16]. Dosimetry has played a critical role in the development of [^{177}Lu]Lu-PSMA RNT, yet due to the difficulty of adopting dosimetry in routine clinical practice, it was not integrated into large, randomized studies initially [17]. Although dosimetry helped initially estimate the absorbed doses to healthy tissues and tumor lesions, it was not until wider utilization in phase 1 and 2 clinical trials that better knowledge of toxicities was gained [17]. The recently published European Association of Nuclear Medicine (EANM) procedure guidelines for [^{177}Lu]Lu-PSMA RNT are good practice standards to follow in line with national and international legal or regulatory provisions [18]. The aim of these guidelines is to identify the appropriate candidates for therapy, provide a protocol consensus to aid when performing the treatment, summarize potential toxicities, safety considerations and efficacy data, and describe the value of dosimetry in the optimization of therapy and its necessity to be carried out when the treatment to be given differs from the approved protocol [19]. These guidelines are similar to those published on ^{90}Y microspheres [20] [^{131}I]I-MIBG [21] [^{131}I]I-NaI [22], and [^{177}Lu]Lu-DOTATATE [23], summarizing the views of the EANM/Medical Internal Radiation Dose (MIRD) Committees for therapy optimization. Additional guidance has also been provided by EANM RNT dosimetry committee recommendations [24].

The purpose of this review on ^{177}Lu-PSMA RNT dosimetry is to give a brief overview on imaging-based dosimetry methods, and primarily to provide a summary on the ^{177}Lu-PSMA clinical trials that have been carried out or are ongoing, and the results of dosimetry from these trials. In this context, we present current efforts and highlight future perspectives on this matter.

IMAGING-BASED DOSIMETRY

To ensure that the radiation doses to organs at risk (OAR), (i.e. kidneys, salivary and lacrimal glands) in ^{177}Lu-PSMA RNT is

minimized, accurate determination of the activity of ^{177}Lu within a defined volume is required and, hence, imaging-based dosimetry can fulfil this purpose [23]. The collection of fully quantitative data is an important step in accurate dosimetry calculations, as issues may arise with efficacy or adverse side effects with inaccurate calibrations for quantitative dosimetry [25].

Imaging-based dosimetry involves the patients being imaged at different time points, which allows for the rate of activity accumulation and depletion in each organ to be determined post-administration. To increase the accuracy of the dose estimates, the number of imaging time points acquired can be increased, however this is to be balanced against many logistical issues such as the patients' willingness to be scanned over many days, scanner availability and cost with potential insurance/chargeback issues. Studies have been performed into the optimal timepoints for imaging in PSMA therapy, with a recent simulation study demonstrating that four timepoint imaging showed similar results as with three timepoints, and that a total imaging time of 96 h was feasible [26].

There are two main imaging-based dosimetry methods commonly used: dosimetry performed with 2D planar scintigraphy and 3D imaging using single-photon emission computed tomography (SPECT) or positron emission tomography (PET), or a combination of both methods using dual modality with CT [27]. The hybrid 2D and 3D SPECT/CT methods allows for the gathering of half-life information from planar images as well as 3D image derived local uptake distribution. The 2D planar data-based absorbed dose estimates approach has long been the method of choice for its ease of use and thorough documentation [28]. In this case the well-recognized MIRD dosimetry schema has been implemented through a range of commercial and freely available software solutions such as OLINDA (https://www.hermesmedicalsolutions.com/organdosimetry/) and OpenDose (https://www.opendose.org/). The shift from using planar imaging alone to tomographic imaging, or a combination of both, has provided an increase in the accuracy of activity quantification for dosimetry [29]. As an example, a comparison of 2D planar-based, 3D SPECT/CT-based, and hybrid dosimetry that combines 2D and 3D data demonstrated high agreement between the absorbed doses of normal organs using 3D and hybrid dosimetry for normal organs (median up to 4.0%) [30]. However, substantial differences (median up to 10.9%) were reported when 2D and 3D dosimetry approaches were compared. Hybrid dosimetry was found to have high accuracy when estimating the absorbed dose, relative to 3D dosimetry for all organs of interest. Despite the potential accuracy of 3D dosimetry, it is important to note however, that evaluation of SPECT/CT reconstruction techniques are vital in ensuring accurate dosimetry quantification. Recent work demonstrated pitfalls using different reconstruction schemes of a kidney cortex/medulla phantom, noting that large differences from the true organ distribution can be obtained, and demonstrated a potential remedy by using a partial volume correction technique [31].

When quantitative SPECT is fully utilized, attenuation and scatter correction are required, but also corrections for dead time and distant-dependent detector blurring, which degrade image quality. The wide range of correction techniques found for SPECT makes the optimization process challenging. Also, with small organs such as the salivary/lacrimal glands, and inherently due to a lower spatial resolution, partial volume effects may be challenging and recovery coefficient corrections may be needed. ^{177}Lu isotope specific guidelines for quantitative ^{177}Lu SPECT (not specific for prostate PSMA) imaging are available in the MIRD pamphlet [16]. Examples of application of this quantitative ^{177}Lu SPECT methodology in a physical phantom using a 20% energy window for photopeaks of 113 keV, 208 keV and a combination of both demonstrated a quantification error up to 40% for the 113 keV energy window only, <3.2% for the 208 keV window only and 14% error for a combination of windows [23].

Although not relevant for ^{177}Lu imaging, Bremsstrahlung (continuous X-ray spectrum) imaging for certain theranostic isotopes that emit no or low-yield gamma rays (i.e. ^{90}Y and ^{89}Sr) may be employed, however the quantification of Bremsstrahlung imaging remains challenging [32].

METHODS OF DOSIMETRY CALCULATION

To date, there are several dosimetry techniques available, with the MIRD schema (developed by the MIRD Committee of the Society of Nuclear Medicine and Molecular Imaging (SNMMI)) being the most incorporated technique for radiolabelled PSMA [33,34,35]. The schema was developed as a means to estimate the average absorbed radiation doses of radiopharmaceuticals to patients' organs, tissues, voxels and cellular compartments [36,37], via the computation of time-activity curves, which then allow for the calculation of the cumulative radioactivity in a volume of interest [38,39]. It can be implemented using "S-values" (absorbed dose rate per unit activity) that are determined using Monte Carlo (MC) simulations for different isotopes [40,41,42]. Limitations of S-value calculations are based on assumptions such as homogenous distribution of radioactivity within organs and standardized organ masses [43,44]. Due to its relative simplicity, quick algorithms that require 2D imaging, and the use of average organ characteristics, S-value dosimetry has been used in routine clinical settings and represents a minimum standard of dosimetry computation [35,45,46,47,48]. Additionally, in the past S-values used in dosimetric analysis have been used as a reference for new dosimetry methodologies [49,50,51].

Further accuracy in dosimetry calculations can be achieved using direct MC simulations of radiation transport. MC simulations involve input parameters that initiate an iterative statistical process, resulting in voxel-level absorbed dose calculations being carried out through estimating interactions of particles [43]. They can account for inhomogeneous radioactivity distribution and secondary particles, and allow for simulation in patient-specific organ and lesion geometries [44,45]. However, due to its computational and operational resources and expertise required to implement a simulation,

MC simulation is used more so in research settings and can be considered a *de facto* reference standard due to the high level of accuracy that can be achieved.

In analogy with the MIRD formalism, MIRD pamphlet no.17 (1999) [39], provides voxel-based dosimetry using voxel S-values (VSV). Using MC simulations, VSV are calculated for specific isotopes and voxel dimensions [52,53]. Consequently a kernel matrix is used to estimate the mean absorbed dose for each voxel, whereby each voxel is a uniform source and each nearby voxel is a target ([54], [39]). This, as a result, generates a voxel-by-voxel dose map [56]. Although different MC codes may provide variances in dose estimates within a few percent, this is not a large enough margin to be considered relevant in a clinical setting [51],[44], [58]. The VSV method is particularly advantageous for its ability to handle inhomogeneous radioactivity distributions [54]. **Figure 1** demonstrates a comparison of VSV, direct MC technique and a deep learning technique for dose rate calculation on images of the same patient.

The local energy deposition method is yet another technique that is applied in dosimetry calculations, proposed to simplify the application of VSV for beta emitters. In this method, the assumption is that all of the energy is absorbed in the voxel of origin. It is primarily used for alpha and beta particles or auger electrons and not gamma emitters or secondary photons because of their longer range in tissue [59].

Various studies have demonstrated the use of simplified dosimetry calculation methodologies for potential clinical adaptation. Recent work reported on two simplified [^{177}Lu]Lu-PSMA-617 dosimetry schemes for organs at risk, whereby one method simplified image acquisition and the other, dose calculation [60]. The simplified schemes were found to be feasible and showed potential for simplification in future works, and were both consistent with their reference method for cumulative absorbed dose. Mix et al. attempted to simplify dosimetry by using intratherapeutically acquired SPECT/CT scans to determine the kidney dose per cycle, noting that extrapolation of individual data from dosimetry of the first treatment cycle was highly predictive of the cumulative kidney dose at the end of treatment [61]. Other work similarly reported on the ability to approximate the [^{177}Lu]Lu-DOTATATE absorbed doses to abdominal organs and lesions from a single time point measurement of the abdominal activity distribution [62]. The study found that a single measurement by SPECT/CT 4 days after the administration can be used to estimate the doses absorbed efficiently. A recent simulation study also looked at optimal sampling schedules for renal and tumor dosimetry for [^{177}Lu]Lu-PSMA RNT. The study demonstrated that a timepoint at 192 h was necessary, and improvements in accuracy and precision could be achieved with careful selection of timepoints [63].

CLINICAL TRIALS

Since the beginning of 2021, the results of two large, randomized, controlled clinical trials, the TheraP [64] and VISION [65] trials, have been published showing promising clinical outcomes. Consequently, the international phase 3 VISION trial (NCT03511664) led to the Food and Drug Administration (FDA) granting breakthrough designation to [^{177}Lu]Lu-PSMA RNT, eventually leading to its final approval in March 2022 [66]. Results reported on the overall survival (OS) and radiographic progression-free survival (rPFS) of [^{177}Lu]Lu-PSMA RNT plus protocol-permitted standard of care (SOC) in 831 prostate cancer patients, with a sub-dosimetry study aimed at estimating the absorbed dose in organs at risk. For the dosimetry study, a separate cohort of 29 patients from four centers received 7.4 GBq of [^{177}Lu]Lu-PSMA-617 per cycle in addition to SOC every 6 weeks for a maximum of 6 cycles. Whole body scintigraphy scans and SPECT/CT scans after the first administration of the RNT, as well as blood and urine samples were collected. The radiation absorbed doses per unit activity were found to be the highest in the lacrimal glands (mean 2.1 Gy/GBq) and the salivary glands (mean 0.63 Gy/GBq) [67].

The TheraP multicenter, randomized phase 2 trial (NCT03392428) reported on prostate-specific antigen (PSA) response of 201 patients receiving 6–8.5 GBq of [^{177}Lu]Lu-PSMA-617 every 6 weeks for up to 6 cycles. Similarly, large clinical trials are underway such as UpFrontPSMA [68], PSMAfore [69], PSMAddition [70], and ENZA-p [71] that have not specifically included imaging-based dosimetric related outcomes. They have instead focused attention on endpoints such as efficacy, safety and toxicity, which may have been improved by looking at dosimetry implications. There are currently four phase 1 and 2 clinical trials underway with radiation dosimetry of [^{177}Lu]Lu-PSMA in humans as an endpoint, as summarized in **Table 1**. A further study (NCT03042468) demonstrated that in a phase 1 dose-escalation cohort patients received 7.4–22 GBq and in phase 2 the patients received a 22.2 GBq dose, a maximum tolerable dose of 22.2 GBq of [^{177}Lu]Lu-PSMA-617 is safe for a fractionated cycle [72].

Also under investigation is a trial of 43 patients (NCT03454750), who were administered 3.7–5.5 GBq of [^{177}Lu]Lu-PSMA-617, four times at 8-weeks intervals [73]. Dosimetry was carried out using the MIRD formalism (OLINDA/EXM software) in 30.2% of the patients (n = 13), low grade hematological (with the exception of two patients showing G3), salivary gland and renal toxicity was reported, concluding that [^{177}Lu]Lu-PSMA-617 is safe and salivary gland uptake may be reduced by co-administration of polyglutamate tablets.

TUMOR LESION DOSIMETRY

Recent work has shown high tumor doses for skeletal, lymph node, and liver metastases [74], and in some (prospective) studies for lung metastases as well [75] in patients administered with [^{177}Lu]Lu-PSMA-617. Radiation dosimetry demonstrated high tumor absorbed doses, as shown in **Table 2**, and low exposure to OAR. Similarly, with [^{177}Lu]Lu-PSMA-I&T, two studies reported on the absorbed doses to tumor lesions [88,89]. The studies found the highest absorbed doses in bone, lymph node, liver and lung tumor lesions [^{177}Lu]Lu-

TABLE 1 | Summary of ongoing clinical trials for 177Lu-PSMA RNT.

Clinical Trial Identifier	Study Title	Phases	Primary Objective
NCT03874884	177Lu-PSMA-617 Therapy and Olaparib in Patients With Metastatic Castration Resistant Prostate Cancer	1	Evaluate the safety and tolerability of olaparib in combination with 177Lu-PSMA-617
NCT03042468	Phase I Dose-escalation Study of Fractionated 177Lu-PSMA-617 for Progressive Metastatic CRPC	1,2	Find the highest dose level of 177Lu-PSMA-617 that can be given without severe side effects
NCT03490838	177Lu-PSMA-R2 in Patients With PSMA Positive Progressive, Metastatic, Castration Resistant Prostate Cancer	1,2	The first phase will determine the recommended 177Lu-PSMA-R2 dose. The second phase will study the preliminary activity of repeated treatments administered, with continued assessments of the safety and quality of life of the RNT.
NCT04430192	Dosimetry, Safety and Potential Benefit of 177Lu-PSMA-617 Prior to Prostatectomy	1,2	Evaluate the dosimetry, efficacy and toxicity of Lu-PSMA-617
NCT03454750	Radiometabolic Therapy (RMT) With 177Lu PSMA 617 in Advanced Castration Resistant Prostate Cancer (CRPC)	2	Evaluate the efficacy and toxicity of 177Lu-PSMA-617

TABLE 2 | Tumor absorbed doses after 177Lu-PSMA RNT.

Radiopharmaceutical	Study	References	No. of Patients	Organ/Target	Mean Absorbed Dose (Gy/GBq)	PET/CT or SPECT/CT	Dosimetry Calculation Method
	1	Paganelli et al[73]	14	Skeletal	4.70	SPECT	Planar
				Nodal	3.64		
	2	Maffey-Steffan et al[76]	32	Skeletal	4.01 ± 2.64	SPECT	Planar
				Lymph node	3.12 ± 2.07		
				Liver	2.97 ± 1.38		
	3	Scarpa et al. [77]	10	Skeletal	3.4 ± 1.9	SPECT	Planar w/blood sampling
				Lymph node	2.6 ± 0.4		
				Liver	2.4 ± 0.8		
	4	Violet et al. [78]	30	Skeletal	5.28 ± 2.46	SPECT	Blood sampling
				Nodal	3.91 ± 3.93		
	5	Zhang et al. [79]	14	Tumor	13.75 ± 31.59	SPECT	Planar
	6	Delker et al. [80]	5	Bone	5.3 ± 3.7	SPECT	Planar
			3	Lymph node	4.2 ± 5.3		
			1	Soft tissue	2.1 ± 0.8		
	7	Kratochwil et al[81]	4	Tumor	6.1–22.8	SPECT, PET	—
	8	Sarnelli et al[82]	9	Liver	0.16 ± 0.15	SPECT	Planar w/blood sampling
	9	Peters et al[83]	10	Tumor	3.25 ± 3.19	SPECT	—
	10	Völter et al[84]	30	Skeletal	4.7 ± 3.9	SPECT	—
				Nodal	7.7 ± 9.7		
	11	Yadav et al[85]	26	Tumor	10.95 ± 18.01	—	Planar w/blood sampling
	12	Fendler et al[86]	30	Tumor	6.1 ± 4.9	—	—
	13	Rosar et al[87]	24	Skeletal	1.42 ± 0.99	SPECT	Planar
177Lu-PSMA-I&T	14	Barna et al[88]	22	Bone	4.38	SPECT	Voxel-wise
				Lymph node	5.47		
				Liver	4.95		
	15	Okamoto et al. [89]	18	Bone	3.4 ± 2.7	PET	Planar
				Lymph node	3.2 ± 2.2		
				Liver	1.2 ± 0.67		
				Lung	1.75 ± 0.92		

PSMA-I&T was noted to achieve high tumor to background ratios of the mean absorbed doses [90,91].

NORMAL ORGAN AND TISSUE DOSIMETRY

Various studies have reported on absorbed doses to normal organs and tissues [74,75,76,77,89,92], as is shown in **Table 3**. Many retrospective and prospective studies, concluded that the organs with the highest absorbed doses were the kidneys and salivary glands [81,85,87,93,94]. Additional studies have also reported that the maximum cumulative doses to the kidneys and salivary glands were the highest [78,85,94] and the lacrimal glands possibly representing the dose-limiting organs [95]; they concluded that the doses did not exceed the commonly applied dose constraints for the kidney (23 Gy [96]) and salivary glands (45 Gy [93]) [97,98]. When the kidney

TABLE 3 | Normal organ absorbed doses after 177Lu-PSMA RNT.

Radiopharmaceutical	Study	References	No. of Patients	Organ/Target	Mean Absorbed Dose (Gy/GBq)	PET/CT or SPECT/CT	Dosimetry Calculation Method
	1	Paganelli et al[73]	14	Lacrimal glands	2.26	SPECT	Planar
				Parotid glands	0.65		
				Submandibular glands	0.59		
				Kidneys	0.42		
	2	Maffey-Steffan et al[76]	32	Kidneys	0.771 ± 0.564	SPECT	Planar
				Lacrimal glands	0.845 ± 0.505		
				Parotid glands	0.534 ± 0.217		
				Submandibular	0.455 ± 0.171		
	3	Scarpa et al[77]	10	Parotid glands	0.561 ± 0.248	SPECT	Planar
				Submandibular glands	0.498 ± 0.146		
				Lacrimal glands	1.006 ± 0.690		
				Kidneys	0.600 ± 0.362		
	4	Violet et al[78]	30	Kidneys	0.39 ± 0.15	SPECT	Blood sampling
				Submandibular glands	0.44 ± 0.36		
				Parotid glands	0.58 ± 0.43		
				Bone marrow	0.11 ± 0.10		
	5	Zhang et al[79]	14	Kidneys	0.81 ± 0.32	SPECT	Planar
				Whole body	0.058 ± 0.027		
	6	Delker et al[80]	5	Left kidney	0.60 ± 0.19	SPECT	Planar
				Right kidney	0.61 ± 0.16		
				Salivary glands	1.41 ± 0.53		
				Liver	0.11 ± 0.06		
	7	Kratochwil et al[81]	4	Kidneys	0.75	SPECT	Planar, w/blood sampling
				Red marrow	0.03		
				Salivary glands	1.4		
	8	Sarnelli et al[82]	9	Parotid glands	0.81 ± 0.74	SPECT	Planar
				Kidneys	0.67 ± 0.27		
				Liver	0.16 ± 0.15		
				Whole body	0.049 ± 0.031		
	9	Peters et al[83]	10	Salivary glands	0.39 ± 0.17	SPECT	—
				Kidneys	0.49 ± 0.11		
				Liver	0.09 ± 0.01		
	10	Yadav et al[85]	26	Salivary glands	1.24 ± 0.26	—	Planar w/blood sampling
				Kidneys	0.99 ± 0.31		
				Liver	0.36 ± 0.10		
				Urinary bladder	0.243 ± 0.09		
	11	Fendler et al[86]	30	Left kidney	0.5 ± 0.3	—	—
				Right Kidney	0.6 ± 0.2		
				Liver	0.1 ± 0.1		
				Spleen	0.1 ± 0.1		
			10	Salivary glands	1.0 ± 0.6		
	12	Rosar et al[87]	24	Kidneys	0.54 ± 0.28	SPECT	Planar
				Parotid gland	0.81 ± 0.34		
				Submandibular gland	0.72 ± 0.39		
				Liver	0.10 ± 0.05		
	13	Gosewisch et al. (92)	5	Bone marrow	0.108	3D	Planar w/blood sampling
	14	Kabasakal et al[93]	7	Parotid glands	1.17 ± 0.31	—	Planar w/blood sampling
				Kidneys	0.88 ± 0.40		
				Liver	0.28 ± 0.09		
				Total body	0.061 ± 0.026		
	15	Kabasakal et al. [94]	7	Parotid glands	1.90 ± 1.19	SPECT	Planar
				Kidneys	0.82 ± 0.25		
				Liver	0.17 ± 0.09		
				Bone marrow	0.030 ± 0.008		
	16	Hohnberg et al[95]	9	Kidneys	0.525 ± 0.173	—	Planar
				Salivary glands	0.721 ± 0.142		
				Lacrimal glands	2.82 ± 0.76		

(Continued on following page)

TABLE 3 | (*Continued*) Normal organ absorbed doses after 177Lu-PSMA RNT.

Radiopharmaceutical	Study	References	No. of Patients	Organ/Target	Mean Absorbed Dose (Gy/GBq)	PET/CT or SPECT/CT	Dosimetry Calculation Method
				Whole body	0.0630 ± 0.0229		
	17	Ozkan et al[99]	10	Kidneys	0.70 ± 0.24	—	—
				Parotid glands	1.34 ± 0.78		
				Submandibular glands	0.94 ± 0.45		
				Lacrimal glands	2.28 ± 1.29		
	18	Gosewisch et al. [100]	10	Bone marrow	0.012	SPECT	—
	19	Mix et al [61]	59	Kidneys	0.67 ± 0.24	SPECT	—
	20	Privé et al. [101]	10	Salivary glands	0.39 ± 0.17	SPECT	Blood sampling
				Kidneys	0.49 ± 0.11		
				Liver	0.09 ± 0.01		
177Lu-PSMA-I&T	21	Barna et al[88]	22	Parotid glands	0.77	SPECT	Voxel-wise
				Kidneys	0.71		
				Liver	0.27		
	22	Okamoto et al[89]	18	Liver	0.72 ± 0.21	SPECT, PET	Planar
				Submandibular glands	0.64 ± 0.40		
				Lacrimal glands	3.8 ± 1.4		
				Whole body	0.06 ± 0.03		

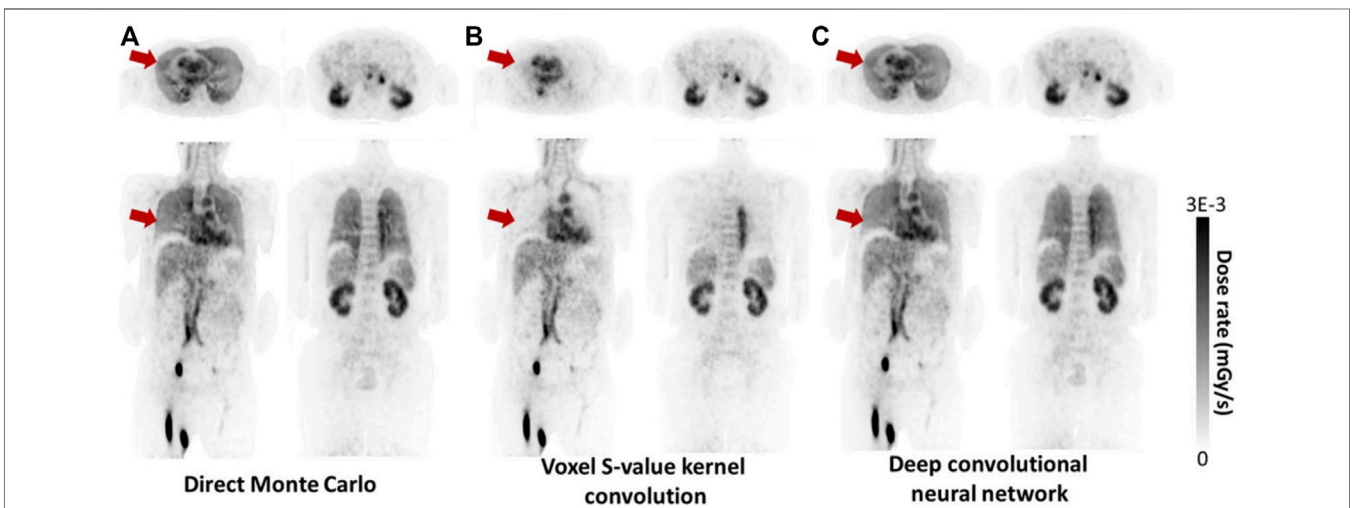

FIGURE 1 | Example of dose rate maps produced by direct MC simulation (considered ground truth), voxel S-value convolution and a deep convolutional neural network (CNN). The CNN approach generates dose rate maps similar to MC, and better agreement in certain areas such as lungs compared to VSV, as highlighted by the red arrows (With copyright permission - [146]).

doses were above the International Commission on Radiological Commission (ICRP) critical dose limits however, they were observed to not cause clinical complications due to nephrotoxicity [99].

PREDICTIVE DOSIMETRY

Many works have reported on pretherapeutic [^{68}Ga]Ga-PSMA-617 PET possibly serving to indicate the dosimetry of [^{177}Lu]Lu-PSMA-617. One such study by Wang et al. [74] reported on a high correlation between the standard uptake value (SUV) of tumor lesions in [^{68}Ga]Ga-PSMA-617 PET and those in [^{177}Lu]Lu-PSMA-617. Maffey-Steffan et al. [76] studied the ^{68}Ga/^{177}Lu-theranostic concept in PSMA-targeting of mCRPC patients. The study concluded that while whole body scintigraphy allows for accurate follow up of patients treated with [^{177}Lu]Lu-PSMA-617 [^{68}Ga]Ga-PSMA-11 PET/CT is recommended to be performed for both patient selection and final response assessment.

The use of [^{68}Ga]Ga-PSMA-11 PET/CT for an absorbed estimation of [^{177}Lu]Lu-PSMA RNT has not yet been evaluated extensively in literature. However, a recent study compared predicted absorbed doses to actual delivered doses; it did so through the use of [^{177}Lu]Lu-PSMA SPECT imaging data to determine population tissue effective half-times and estimate dosimetry using a single time point pretherapeutic [^{68}Ga]Ga-PSMA PET [102]. The PET/SPECT absorbed dose ratios were 1.01 ± 0.21 for the kidneys, 1.10 ± 0.15 for the liver, 1.20 ± 0.34 for the submandibular glands, and 1.11 ± 0.29 for the parotid glands. As for the lesion kinetics, a larger range was reported with a PET/SPECT absorbed dose ratio of 1.3 ± 0.7 (range: 0.4–2.7), possibly due to the difficulty in calculating the SPECT absorbed dose for small structures. This raises the increased probability of larger uncertainties for the calculations associated with these small volumes [103,104]. Predictive dosimetry has also been shown to be improved by obtaining continuous tracer distribution data 1 h post [^{68}Ga]Ga-PSMA administration using PET imaging [105], however would likely suffer from complex acquisition logistics.

DISCUSSION & FUTURE PERSPECTIVES

Seeing the results of both retrospective and prospective studies, the dosimetry of [^{177}Lu]Lu-PSMA RNT played a pivotal role in its FDA approval and hence its use in clinical practice. We project that the current ongoing clinical trials will bring more light to the dosimetry of [^{177}Lu]Lu-PSMA, in hopes of optimizing its use so its clinical feasibility will be expanded. There are various studies that have investigated "cocktail therapy" (a combination of drugs used to treat a certain condition) [106], while others explored [^{177}Lu]Lu-PSMA RNT post-exhaustion of standard treatment options. However, there are studies yet to evaluate the optimal sequencing of treatment of options.

Recently, alpha-based RNT has proven to be a promising therapeutic option in mCRPC patients with tumors refractory to beta RNT [107]. Clinical studies with alpha emitters such as ^{213}Bi have suggested that contrary to beta-emitters RNT, patients do not develop resistance to alpha emitter therapy [108]. By lessening the localized dose pattern with higher energy beta electrons to achieve uniformity [109], or chelating PSMA molecules with radioisotopes, such as alpha emitters, capable of causing greater DNA damage through high LET emission [110], radiation dose delivery may be optimized. While 223RaCl is the first and only alpha emitting radioligand currently FDA and European Medicines Agency (EMA) approved for mCRPC with bone metastases with no known extra-skeletal metastases [111,112,113], radionuclides such as ^{149}Tb, ^{211}At, ^{213}Bi, ^{212}Pb/^{212}Bi, ^{227}Th, and ^{225}Ac are being evaluated for their use in PSMA RNT preclinical and clinical studies [114,115,116,117,118]. The dosimetry of the latter three radionuclides for RNT in prostate cancer patients is being investigated with both PSMA and other chelators [119,120,121,122,123,124,125,126,127].

While encouraging results are being documented, some studies have reported on irreversible toxicities associated with alpha emitting PSMA agents. The shorter tissue range of alpha radiation has shown beneficial in targeting tumor cells that have penetrated bone marrow with a relatively lower toxicity when compared to beta emitters [110]. However, a high rate of irreversible xerostomia was reported as the dose-limiting toxicity upon exceeding 100 kBq/kg per cycle, thus leading to the use of ^{225}Ac-PSMA therapy only for salvage therapy [107,110]. Similarly, irreversible grade 2 + neutropenia was observed in the use of 50kBq/kg of ^{223}Ra in prostate cancer patients [128].

Artificial Intelligence in RNT

The field of diagnostic imaging has seen a huge increase in the use of AI in almost all aspects of the clinical patient pathway. For Nuclear Imaging, this has led to AI developments in patient positioning, attenuation and scatter correction [129], low-count image reconstruction techniques [130,131], event positioning in monolithic crystals [132] and various postprocessing applications. In external beam radiotherapy, AI has been investigated for radiation dose calculations such as optimization of treatment plan quality/uniformity with a reduction of planning time [133], prediction of human operator behavior in the treatment planning process of prostate IMRT [134] and automated organ at risk and lesion segmentation [135,136]. Although technically very similar, lesion segmentation has proven to be more challenging when compared to organ segmentation, due to the possible variability in the location, size and shape of lesions leading to unusual pathophysiology that may be unseen by AI training algorithms. Clinical tools from major vendors are available for automated/semi-automated segmentations with varying degrees of success in oncological cases. To improve efficiency and standardization, U-Net architecture using AI-based algortihms has shown promise [137,138,139]. A full review on AI developments in EBRT treatment planning and segmentation is reported by Wang et al [140].

Similarly, explorations are also underway to incorporate AI into RNT dosimetry, primarily where MC simulations are used as a reference standard. Recent work has used a deep neural network (DNN) to extend single S-value kernels to specific S-value kernels corresponding to patient-specific anatomy to construct 3D dose maps of [^{18}F]FDG distribution [141]. Using training data of density maps (via CT images) and reference voxel wise S-values (generated using Monte Carlo simulations), whole-body dose maps can be constructed like the standard voxel-based MIRD scheme. The growth in the importance of mandatory regulation for each test that will be put to routine use in clinical practice, with the latest regulatory papers undergoing certification to prove reproducibility is expected [142,143]. Perhaps more studies are needed to address the challenges of how these AI ML models will join clinical practice to predict PC using histopathological or imaging methods for diagnosis [144].

Similar work aimed at incorporating dosimetry calculations into clinical practice with less computational effort used a U-net architecture with full MC simulation as a reference to predict individual absorbed dose distributions with inputs of CT (density maps) and dose maps (estimated using MIRD calculations, whole

organ S-values and time activity data) [145]. This work examined the predictions of 26 ^{177}Lu-PSMA datasets (4 timepoint imaging), and their resulting method outperformed the standard MIRD DVK dose calculation method in terms of dose deviation. Similar work using data also trained from MC ground truth to predict a 3D dose rate map evaluated their method on 10 datasets of [^{68}Ga] Ga-NOTA-RGD [146]. Their CNN-based dose rate map agreed with the ground truth with voxel dose rate errors of 2.54 ± 2.09%. Although their work demonstrates a proof of principle of learning dose estimates, and the ability to significantly reduce dosimetry calculation time while retaining accuracy of MC simulations, the cohort of these 2 studies are small. Similarly, many AI methods are limited by small cohort studies. Therefore, the collaborations between various clinical centers will be necessary for more generalizable models and accurate training data.

Such advances in AI dosimetry methods in diagnostic imaging, histopathology, and genomics offers the possibility for the delivery of personalized, precision medicine. Current work performed is remains difficult to standardize in terms of quantification, dosimetry calculation technique and analysis but offers good insight into the true potential of dosimetry in predicting toxicity and outcomes. The use of AI is promising and has the potential to truly deliver predictive dosimetry.

AUTHOR CONTRIBUTIONS

All authors, RA, MD, OB and JD, contributed to the drafting of the manuscript and have approved the final manuscript.

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