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Comparative Study of Dosimetry Methodology and Software Tools for Personalized Radionuclide Therapy: Review Article

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Abstract

Purpose: *The aim of this review article is to collate the detailed insight of different dosimetry methodology and non-commercial /commercial dosimetry software tools, along with clinical study explored by specific authors, published in recent peer-review journals. The present work is segmented in three sections: i) Literature review of various dosimetry methodologies to evaluate absorbed dose in personalized radionuclide/ radiopharmaceutical therapy. ii) Technical as well as comparative information related to commercial dosimetry software tools used in radiopharmaceutical therapy (RPT). iii) Clinical review to compile the data of patient study for patient-specific dosimetry in internal radionuclide therapy.* ***Methods:*** *Our study is based on latest available articles, to compile the information of upcoming dataset of newer methods to calculate absorbed dose, quantitative comparison of non-commercial / commercially available dosimetry software tools and recent study on patients who were clinically studied for targeted radionuclide therapy. To integrate the software based dosimetry tools in clinical routine; our department is planning to purchase few dosimetry software, henceforth a detailed survey is performed for recent articles published between 2018-2021 and other articles related to our work.* ***Results:*** *The analysis of current review is categorized in three sections: i) Literature review for different calculation techniques for assessment of personalized internal radionuclide therapy, detail information of traditional and modern methods to calculate absorbed dose were gathered. With new updated dosimetry evaluation methods; more accurate, personalized and fast calculations are possible in clinical practice. ii) Technical review on different non-commercial / commercial software tools used in clinical routine, gives the first hand information of advantages and limitations of different software. The comparative study of different software is a step to achieve successes in performing the clinical practice for patient specific internal radionuclide therapy in our department. iii) Clinical review of the data, of patient study performed by various authors selected in our work gives the guideline to set the protocol to perform radionuclide therapy in clinical routine.* ***Conclusions:*** *The objective of the present review is to compare the results generated by different non-commercial / commercial dosimetry software toolkits. The objectives of this work is not to provide the ranking or to recommend a given dosimetry methodology or software tools. However, encouraging results obtained in terms of absorbed doses were generally consistent between the different software toolkits. In absorbed dose calculations along with the harmonization process of different dosimetry methods and software tools, there are critical steps that should be deeply investigated on real cases based on voxel level or organ level calculations. The study provides the information of the most adequate computation technique and the methodology for the clinical or research application. Finally the outcome of the*

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present study includes classification of various techniques mostly practiced in clinical routine, ranging from the less advance to personalized and the most accurate.

Keywords: Radiopharmaceutical Therapy (RPT), Personalized Radionuclide Therapy, Dosimetry software, Dosimetry methodology

INTRODUCTION

The current era demands for the growth of personalized medicine in order to customize care and optimize cancer patient response to therapy. Improved understanding of genetic and molecular characteristics of cancerous cells has opened the door to creating selective biological vehicles designed to bind specifically to malignant tissue. Often, these tissue-specific agents can be paired with radioactive elements to create powerful diagnostic and therapeutic tools [1]. In early 2010, a New England Journal of Medicine Perspective shared a vision of "steering patients to the right drugs at the right dose at the right time" [2]. Thus cancer treatment using targeted radionuclide's offers two levels of personalized medicine- (i) The "right drug" is achieved by selecting the appropriate radiopharmaceutical based on the specificity of cancer cell biology and receptor expression, (ii) The "right dose" is administered by individualized treatment planning through the use of a tracer amount for pre-assessment of uptake and retention. Therefore, personalized dosimetry in radionuclide therapy is a right need at right time for individual patient treatment. Radionuclide therapy [3] based on patient-specific internal dosimetry, aims to deliver desired radiation dose to the tumor/cancer, while maintaining radiation dose to organs at risk, below threshold levels to minimize adverse effects. Measurements are usually performed by molecular imaging tools, more specifically planar and SPECT (Single Photon Emission Computed Tomography) imaging or combined with PET (Positron Emission Tomography)/ CT (Computed Tomography).

In current clinical practice, patient dose monitoring is commonly based on the Medical Internal Radiation Dose Committee (MIRD) formalism [4]. The traditional MIRD technique is based on organ-level dosimetry using time-integrated activity and radionuclide S-values, which represents the mean absorbed dose to a target organ per radioactive decay in a source organ. Voxel-level MIRD schema is defined as a 3D voxel matrix representing the mean absorbed dose to a target voxel per unit activity in a source voxel embedded in an infinite homogeneous medium using Monte Carlo (MC) simulations for calculating S-values. Full MC simulations methodology is at present the gold standard for dose calculation in clinical setting due to accurate estimation of whole-body dose map [5, 6]. The MC simulation method takes into account the non-uniform activity distribution and heterogeneity of patient-specific anatomical features. Accurate patient-specific dosimetry is becoming a must, taking advantage of advances in targeted radionuclide therapy and theranostic imaging [7]. In personalized dosimetry, the Monte Carlo Simulation method [8] is considered the most robust method in which radiation transport and interactions of particles with matter are simulated in 3D. Yet, this approach is not employed in clinical routine procedures due to the heavy computational burden, the procedure time, cost and the constraints imposed on patients and imaging devices [9]. Recent exploration of deep learning approach employed for radiation dose estimation has emerged as a promising technique in the area of computer vision and image processing, exhibiting superior performance over conventional methods in medical image analysis in SPECT/CT and PET/CT imaging, including attenuation and scatter correction [10, 11, 12], low-count image reconstruction [13, 14, 15], and automated image segmentation [16, 17].

In the last decades Radiopharmaceutical Therapy (RPT) [18] approach produced very encouraging results in treatment especially for neuroendocrine tumors (NET), which make use of somatostatin analogues labeled with ^{177}Lu(Lutetium) [19]. Despite the general demand for a more individualized treatment based on pre-therapeutic dosimetry study in NET, dosimetry is not conducted always in the clinical routine; instead 'one-size-fits-all' treatment approach is most frequently applied [20]. This is

mostly because dosimetry is often considered time consuming, expensive and sometimes inaccurate due to lack of standardization and harmonization. At present a standard procedure for calculating the absorbed dose is not well defined for all kind of radionuclide therapy. In the last few years, dosimetry with multiple 3D imaging for Peptide Receptor Radionuclide Therapy (PRRT) has been officially released [21]. The PRRT optimization can be based on the evaluation of absorbed doses delivered to critical organs, such as kidneys and red or active bone marrow [22, 23, 24]. Different approaches to clinical dosimetry have been proposed, based on whole body (WB) planar images [25], SPECT/CT images [26, 27] and hybrid methods by combining WB planar images with one or two SPECT/CT scans [28]. The activity administered in pediatric patients [29] is also optimized by considering the anatomical and physiological characteristics of each patient [4, 30].

With the rise in number of applications in Targeted Radionuclide Therapy (TRT), to ensure effective treatment, patient-specific internal dosimetry is increasingly important [31]. Moreover, assessment of 3D absorbed dose distribution is of high clinical value as low dose regions might lead to potential lesion recurrence while high dose regions could cause necrosis in tissues. For effective dose conversion, dose-point kernel (DPK) convolution [32], voxel S-value (VSV) convolution [33] and Monte Carlo simulation (MCS) based methods [34] are developed to convert the voxelized activity to the 3D absorbed dose rate. Various groups have developed their own methodology using the tools available, according to their own organizational possibilities [35, 36, 37] and also specific dosimetry software programs have been developed [38–41].

The availability of commercial software tools eases the implementation of dosimetry in clinical routine. However their performance in the different steps of dosimetry (i.e. calibration procedure, image acquisition, reconstruction, registration, segmentation tools, time integrated activity fitting and absorbed dose calculation) needs to be evaluated [42]. OLINDA/EXM is the first commercial dosimetry software based on MIRD technique, is widely used for PRRT dosimetry. OLINDA/EXM version 1.1 [43] has been used for decades; recently a new updated commercial version of OLINDA/EXM version 2 [44] is also available. Other commercially available dosimetry software are VoxelMed2.0 software [45] which provides good calculation accuracy and easy applicability in clinical practice using voxel S-value dosimetry based on dose kernel convolution, were as RAYDOSE software [46] works on MC simulation techniques are considered to be most accurate approach for dose estimation. Few more commercial dosimetry software developed recently are STRATOS [45], VIDA [47], HERMES [48] and PLANET [49].

Thanks to recent advances in targeted radionuclide therapy and theranostics [50–54], the accurate patient-specific voxel-scale internal dosimetry is rapidly growing. At present standardization and harmonization of the calculation systems are important. Therefore, it is essential to compare the various results obtained with the most advanced existing non-commercial / commercial software and other less advanced methods still used worldwide. In this context, the main objective of the present work is to compare different modalities along with software tools for patient-specific absorbed dose calculation, to know the advantages and the limitations and also to provide detailed information for the most accurate computation technique and methodology to be practiced in clinical routine.

METHODS

To integrate the software based dosimetry tools in clinical routine; our department is planning to use commercial dosimetry software, henceforth a detailed survey is performed for recent articles published between 2018-2021 and other articles related to our work. The overall goal of the review article is to compile the information of upcoming dataset of new methodologies to calculate absorbed dose, quantitative comparison of non-commercial / commercially available dosimetry software tools and recent study of patients who were clinically treated by targeted radionuclide therapy. The present work is segmented in three sections:

a. Literature review of various dosimetry methodologies to evaluate absorbed dose in Personalized Radionuclide Therapy (PRT).

b. Technical as well as comparative information related to non-commercial / commercial dosimetry software tools used in Radiopharmaceutical Therapy (RPT).
c. Clinical review to compile the data of patient study done by various authors for patient specific dosimetry in internal radionuclide therapy.

LITERATURE REVIEW: VARIOUS DOSIMETRY EVALUATION METHOD

The purpose of dosimetry in radionuclide therapy is to ensure sufficient adsorbed dose into the lesions by estimation of the absorbed radiation dose after administration of radiopharmaceutical. To calculate absorbed dose, different methodologies are in practice. This literature review gives the brief insight of various dosimetry evaluation techniques: (1) Organ level S-value method, (2) Voxel level S-value method, (3) Local energy deposition, (4) Full Monte Carlo simulation, (5) Deep Neural Network method and (6) Specific absorbed dose rate method.

Organ Level S Value Method (MIRD)

Organ level dosimetry is based on the Medical Internal Radiation Dose (MIRD) formalism, developed by the Society of Nuclear Medicine (SNM), was originally designed to estimate average radiation doses to patients that received radiopharmaceuticals [55], based on absorbed fraction dosimetry. The MIRD formalism is performed using S-values, which is mean absorbed dose in the target volume per unit cumulative radioactivity in the source. For S-values, homogeneous distribution of radioactivity within organs and standardized organ mass are assumed [56, 57], as described in MIRD pamphlet no. 5 and 11. Initially, standardized organs with fixed dimensions and spheres of different volumes were used to represent tumors, for dosimetry analysis while assuming infinite homogeneous media with soft tissue density. Later MIRD/ICRP (International Commission on Radiological Protection) voxel-based anthropomorphic phantoms were specified for male, female and children of different ages to calculate S-value [58]. S-value is dependent on source-to-target distance, tissue density, target mass and the radionuclide emission pattern. S-values have been evaluated for specific tissues and for various radiopharmaceuticals using MC simulations technique [59]. Patient-specific organ masses are derived from diagnostic imaging, adjustments for position, tissue in-homogeneity and shape of organs. S-value dosimetry is accessible for clinical use due to estimate activity distributions and the use of average organ characteristics [60]. MIRD based Organ level dosimetry has become the standard dosimetry method for radiopharmaceutical studies, treatment safety monitoring [61] and for new dosimetry methodologies [62]. For absorbed dose calculation, S-value dosimetry is clinically practiced due to relatively simple and quick algorithms of required sequential 2D imaging but cross-fire dose is not taken into consideration and tumor/cancer lesions are assumed to be spherical [63].

Voxel Level S-Value Method (VSV)

The voxel S-value approach considers activity distribution on the voxel level and calculates the corresponding voxelized dose distribution [64]. Voxel-level dosimetry is based on dose voxel kernel (DVK) convolution. MIRD pamphlet no. 17 provides [4] voxel-based dosimetry in analogy with the MIRD formalism using voxel S-values (VSV). VSV are specified for specific isotopes and voxel dimensions, calculated using MC simulations technique [65]. Each voxel is considered an individual uniform source and neighboring voxels as uniform targets [66]. Mean absorbed dose calculations per voxel are performed using a dose voxel kernel matrix, resulting in a voxel-by-voxel dose map. The limitations of the voxel S-value technique are that, they are calculated for a source material of uniform density and tissue in-homogeneities are not taken in account [3]. However, the advantage of using the voxel S value approach is that it makes 3D dose calculations simple and fast.

Local Energy Deposition (LED)

In local energy deposition method for dosimetry calculations, all energy is assumed to be absorbed in the voxel of origin. This theory holds true for certain α and β-particles or auger electrons but does not apply for γ-emissions or secondary photons due to the longer penetration depth. However, if one

is primarily interested in assessing certain parts of the radionuclide emission pattern, then this method is fairly accurate for a quick analysis in toxicity studies [67].

Full Monte Carlo Simulation (MCS)

Monte Carlo techniques use the known physics of photon and particle interactions with matter to simulate radiation transport. Reconstructed SPECT images provide quantitative information about the activity distribution and radioactive emissions can be simulated and propagated through a computerized patient model to determine the 3D dose distribution [3]. The computerized model can be constructed based on a CT image set of the patient and the method is thus able to take into account patient-specific source and target organ geometries and tissue in-homogeneities. Quantitative 3D imaging techniques like PET/CT and SPECT/CT visualize non-uniformities within organs and tumors. Monte Carlo (MC) simulation is the most robust method for dose estimation but its use may be quite complicated and it requires very long computation times. Monte Carlo codes commonly used for radiotherapy and nuclear medicine applications include the electron gamma shower (EGS) code [68], MCNP [69], PENELOPE [70] and the GEANT4 code [71]. In personalized dosimetry, MC simulation is still considered the most accurate technique and the reference standard for research application.

Deep Neural Network Method (DNN)

A novel method to perform whole-body personalized organ-level dosimetry taking into account the heterogeneity of activity distribution, non-uniformity of surrounding medium and patient-specific anatomy using deep learning algorithms [72]. This method extended the voxel-scale MIRD approach from single S-value kernel to specific S-value kernels corresponding to patient-specific anatomy to construct 3D dose maps using hybrid emission/transmission image sets. In this context, Deep Neural Network (DNN) predicts the distribution of deposited energy, representing specific S-values, from a single source in the center of a 3D kernel composed of human body geometry. The training dataset consists of density maps obtained from CT images and the reference voxel wise S-values generated using Monte Carlo simulations. Accordingly, specific S-value kernels are calculated and whole-body dose activity maps are constructed in a manner analogous to the voxel-based MIRD formalism. Yet, this approach is not employed in clinical routine procedures owing to the heavy computational burden.

Specific Absorbed Dose Rate Method (SADR)

The SADR "specific absorbed dose rate" is a unique quantitative metric that uses realistic Monte Carlo (MC) simulations and computational pediatric models which is specific to a particular organ [73]. It is defined as the absorbed dose rate in an organ when the biodistribution of radioactivity over the whole body is considered. Initially, a validation procedure is applied that calculates specific absorbed fractions (SAFs). The GATE Monte Carlo toolkit using the Geant4 simulation toolkit (v9.5) code was used to calculate absorbed doses per organ. The SADRs provide the instantaneous absorbed dose rate in a target organ from the activity of all organs throughout the body based on a specific biodistribution. A brief insight of various dosimetry evaluation techniques is shown in Table 1.

TECHNICAL REVIEW: DIFFERENT DOSIMETRY SOFTWARE TO CALCULATE ADSORBED DOSE

Numerous commercial software tools have become available for dosimetry evaluations in clinical settings. Some software toolkits have or aim for FDA/EMA approval or CE marking for use in the clinical environment. OLINDA/EXM v1.0 [43] is probably the most established and well-known software that allows the computation of absorbed doses. OLINDA/ EXM v1.0 developed by the RADAR (Radiation Dose Assessment Resource) group was one of the first registered tools and commercialized by Hermes Medical Solutions (OLINDA/EXM v2.0, Stockholm, Sweden) [44]. Other recently CE-marked commercial software is PLANET Dose (DOSIsoft, Chachan, France).

Table 1. Comparative literature review analysis of different dosimetry methodologies for absorbed dose estimation in radionuclide therapy.

Specifications	Organ level S value method (MIRD)	Voxel level S value method (VSV)	Local energy deposition (LED)	Full Monte Carlo simulation (MCS)	Deep Neural Network method (DNN)	Specific absorbed dose rate method (SADR)
Presumption	Organ level dosimetry, Homogeneous energy distribution with fixed dimension and spheres of different volume representing organs/ tumour, Infinite Homogeneous density	Voxel level dosimetry, Homogeneous energy distribution within voxel, Uniform and infinite Homogeneous density	Low range charge particles, Energy absorbed within voxel size	Particle energy simulation by CT density image volume, Patient specific SPECT/CT & PET/CT as input data	Whole-body personalized organ-level dosimetry, Includes heterogeneity of activity distribution, non-uniformity of surrounding medium and patient-specific anatomy by CT	Unique quantification metric, Specific absorbed dose per organ accounting patient specific CT data, Activity assigned homogeneously in each ROI
Advantages	Clinically accepted due to simple and quick algorithms, commonly used as standard dosimetry method	Method better than organ level, Applicable in clinical routine due to accuracy	Simple voxel level method, Limited accuracy	Most accurate as Gold standard dosimetry method, Cross-fire dose and tissue density heterogeneities are included	Robust/ accurate method for molecular imaging, personalized whole-body activity map data-set, deep learning algorithm, minimal risk of over fitting	Creates time-distribution organ dose rate curve, 3D image of deposited energy with specified voxel resolution, Large data base of SADR for patient-specific classification
Limitations	Phantom base fix analysis, Not for tissue and density heterogeneities, No cross-fire dose assumption	Phantom base fix analysis, Not for tissue and density heterogeneities, No cross-fire dose assumption	Not possible with photons or γ radiations	Complex & long calculation, Time consuming	For diagnostic purpose only, long preparation time for data-set, requires study with different radioisotopes and data-set mapping	Pediatric patient model only, Long and tine taking calculation, Requires more study on all age group patients
Clinical utility	Dosemetry with electrons e^-, β particles and photons or γ radiations, MCS organ S value calculation for fixed organ size and radioisotope specific, PET/CT and SPECT/CT scans	Dosemetry with electrons e^-, β particles and photons or γ radiations, MCS point-dose kernel voxel S value calculation for fixed voxel size and radioisotope specific, PET/CT and SPECT/CT scans	Dosimetry with α and β particles, PET/CT scans	Advised for personalized dosimetry with specific software, Calculation of organ and voxel S values	Advance & upcoming personalized dosimetry, Specific S-value kernel corresponding to patient-specific anatomy to construct 3D dose map	Application in using both photon and electron emitters, Mean activity within each organ as function of time based on radiopharmaceutical biodistribution for dosimetry

Software	OLINDA/EXM, Dosimetry Toolkit(DTK), Hybrid dosimetry module(HDM)	STRATOS, PLANET Onco Dose (PDOSE), SurePlan-MRT, VoxelMed, BIGDOSE	PLANET Onco Dose(PDOSE)	RAYDOSE, GATE Monte Carlo Simulation	GATE Monte Carlo Simulation-Geant4 v9.5 code	Geant4 MC toolkit
Reference	[74], [75],[76]	[74], [75], [3], [76]	[75], [3]	[47], [75], [3], [76]	[72]	[73]

In the technical review all aspects of various software toolkits available for dosimetry calculation in radionuclide therapy are accounted, as well as the comparative study is performed on work done by various authors published in peer-review journals. *Mora-Ramirez et al.* [77] quantitatively compared five commercial dosimetric software platforms- the Dosimetry Toolkit (DTK) software [78], the Hybrid Dosimetry Module (HDM), the STRATOS software, the PLANET Onco Dose (PDOSE) and SurePlan MRT. *Huizing et al.* [79] performed segmentation, TAC fitting and dosimetric analysis using hybrid viewer dosimetry module together with OLINDA/EXM v2.1 and PLANET Dose v3.1.2. *Santoro et al.* [80] compared a commercial dosimetry workstation PLANET Dose, the Dosimetry Toolkit and OLINDA/EXM v1.0, for quantification of the absorbed dose in organs at risk after peptide receptor radionuclide therapy. *Finocchiaro et al.* [76] Studied the performances of three systems for dosimetry in PRRT that use different techniques for absorbed dose calculation by comparison of organ-level dosimetry using OLINDA v1.1, voxel-level dose kernel convolution with VoxelMed v2.0 and Monte Carlo simulations on radiation transport based on the Geant4 MC toolkit. *Li et al.* [41] developed comprehensive 3D dosimetric software-BIGDOSE, with new features of image registration and virtual CT for patient-specific dosimetry.

The aim of this technical review is to assess the importance of the choice of the most adequate calculation modality, providing detailed information about the choice of the computational tool. The technical specifications of following software tools are studied: 1) OLINDA/EXM, 2) Dosimetry Toolkit (DTK), 3) Hybrid dosimetry module (HDM), 4) STRATOS, 5) PLANET Onco Dose (PDOSE), 6) SurePlan MRT, 7) VoxelMed, 8) BIGDOSE, 9) GATE Monte Carlo Simulation and 10) RAYDOSE.

OLINDA/EXM

OLINDA v1.1 [43] is an organ-level (OL) dosimetry software based on the MIRD methodology [81] for internal dose estimation. Absorbed doses to organs and to lesions can be calculated by using different models in the software: human/ phantom models. OLINDA sphere model (commonly used to calculate doses to lesions) is used to generate the results for the inserts placed in the Geometrical phantom and for the dummy lesion housed in the anthropomorphic phantom. Doses are scaled using the true patient weight and organ masses. The S-values based on standard phantoms are not patient-specific. OLINDA/EXM can make first-order adjustments for patient-specific organ masses if these are known, but not for the shapes and relative positions of organs, which varies from patient to patient. Tumor doses are approximated by OLINDA/EXM using pre-calculated absorbed fractions to spheres of different sizes filled with uniform activity. These spheres are treated as isolated objects, so cross-dose to or from other tumors or organs is not accounted for.

Dosimetry Toolkit (DTK)

Dosimetry Toolkit (DTK) from GE (Version 3.0423) is an application of the Xeleris software (GE Healthcare) [78]. For clinical dosimetry, different scenarios are available: whole-body, hybrid or multi-SPECT/CT and a procedure based on planar acquisition is also recommended by GE Healthcare. It includes two steps: the first, "Preparation for Dosimetry Toolkit", is used for the reconstruction of SPECT/CT raw data and registration (manual or automatic) of the CT or planar whole body scans. The second, "Dosimetry Toolkit" (DTK), is used to segment the different organs, create the time activity curves fitted by a mono-exponential function.

Hybrid Dosimetry Module (HDM)

Hybrid Dosimetry Module (HDM) from HERMES (Version 1.0) allows the reconstruction of imported raw data using Hybrid Recon-Oncology version-1.3-Dicom (HROD). HDM can accommodate a minimum of three serial anterior–posterior WBs or three WBs and one SPECT (or SPECT/CT) or three serial SPECT (or SPECT/CT) scans. Manual and automatic registration and segmentation can be performed. Fitting can be done using mono-exponential or bi-exponential functions [82].

STRATOS from Phillips

STRATOS is part of the *IMALYTICS* (Imalytics 3.2, Rev 6289(64)) research workstation. It uses reconstructed 3D SPECT/CT data. Manual and automatic registration and segmentation can be performed. Time-integrated activities (TIA) are calculated at the voxel-level (VL) using the trapezoidal integration, after the last time-point and a mono-exponential function assuming only physical decay. Voxel-based absorbed dose calculation is performed by convolution of dose voxel kernels (DVK) and thereby generating absorbed dose-volume histograms (DVHs).

PLANET Onco Dose (PDOSE)

PDOSE from DOSIsoft (version 3.1.1) was initially developed for the dosimetry of radioactive ^{90}Y microspheres for the treatment of liver cancers [83]. PDOSE only accepts reconstructed SPECT/CT (3D) datasets in DICOM format. Registration and segmentation can be performed (manual or automatic) and the software estimates mean time-integrated activity (TIA) in regions-of-interest (ROI). Fitting can be done using a range of approaches: the trapezoidal method, "X"-exponential, mono-exponential, bi- or tri-exponential fits (currently eight fitting models are available).The mean absorbed doses can be calculated using either the local energy deposition [84] or convolution of DVK [85, 86]. Fitting/integration of activity/absorbed dose rate can also be performed at the voxel level.

SurePlan MRT

SurePlan MRT from MIM (Version 6.9.3) allows the reconstruction of imported raw data and works using different work flows, allowing the user to work with 3D or hybrid datasets [87]. Manual and automatic registration (rigid or elastic) and segmentation can be performed using different tools. Fitting can be done using different approaches: the trapezoidal (including tail extrapolation), mono-exponential or bi-exponential fit and there is an automatic option to choose the best-fitting option per volume-of-interest (VOI) [88]. It allows voxel-based time-activity curve (TAC) fitting and integration and estimates mean absorbed dose in VOI by convolution of DVK.

VoxelMed Version 2.0

VoxelMed is in-house software for dose calculation developed at Azienda USL-IRCCS research hospital (Reggio Emilia, Italy). It is developed in the MATLAB programming and designed on the CERR platform and includes a graphical user interface (GUI). It performs on voxel-level dosimetry, based on the MIRD guidelines[4] and provides the user with the time-integrated activity (TIA) at VOI level, which can be used for dosimetry with OLINDA v1.1 both for organs and lesions. To calculate the number of disintegrations VoxelMed integrates the time-activity curve (TAC) with the trapezoidal method in the time interval between the first and the last acquisition. Time-integrated activity is calculated in each voxel or in the whole organ depending on the modality of dose calculation.

BIGDOSE

BIGDOSE includes a portable wizard based graphical user interface (GUI) written in Python [41]. It consists of six module: (i) input of sequential ECT/ CT/ vCT (virtual CT) images, (ii) ECT or CT-based segmentation, (iii) whole-body or organ-based ECT or CT registration, (iv) curve fitting of TACs and voxel-based integration to obtain cumulative activity, (v) dose conversion via convolution with VSV kernels and (vi) 3D dose analysis. ECT is taken from single photon emission computed tomography (SPECT) and positron emission tomography (PET). The vCT method, which required

only a single CT acquisition and vCTs at other time point could be generate by non-rigid image registration, provides comparable registration accuracy of sequential CT scans [89]. The 3D dose analysis includes organ absorbed dose information, dose map, dose contour and cumulative dose volume histogram (CDVH) for the organ-of-interest.

GATE Monte Carlo Simulation

Monte Carlo (MC) simulation is based on an iterative statistical process to estimate random pathways and interactions of particles in three dimensions, allowing for voxel-level absorbed dose estimations [90]. Numerous input parameters are required for an accurate simulation, including scattering and absorption behavior, medium characteristics and the number of simulated primary particles. In general, MC simulations are quite extensive taking tissue penetration depth, energy loss, bremsstrahlung photons and cross-fire dose into account [91]. The cross-fire dose refers to irradiation of a structure by its surroundings and is especially relevant for isotopes with γ-emission due to the longer path length through tissue compared to β and α-particles or auger electrons. The main advantages of MC simulations are the capability to account for an inhomogeneous radioactivity distribution, induction of secondary particles (often γ-radiation), transitions between tissue types, and patient specific organ and lesion geometries [92]. Modern quantitative imaging techniques (PET/CT and SPECT/CT) are used as input for MC simulations and provide information on anatomical geometry, tissue densities, heterogeneities and (non-uniform) distribution patterns. Full MC simulations are not recommended for routine clinical use due to complex calculations and relative long computational times [66, 93, 94]. Different MC simulator toolkits are nowadays available. *Papadimitroulas et al.* [73] calculated the absorbed dose, based on the Geant4 (GEometry ANd Tracking) Application for Tomographic Emission (GATE) MC toolkit [95, 96] using the Geant4 simulation toolkit (v9.5) code [97]. Full MC simulations are regarded as the gold standard approach.

RAYDOSE

RAYDOSE is a software package developed at Cardiff University (School of Engineering, Cardiff University, UK) and designed to carry out 3D patient-specific image based dosimetry for PRRT. It provides personalized 3D dose map performing Monte Carlo simulations on radiation transport based on the Geant4 MC toolkit (CERN, Switzerland). Geant4 is the state-of-the-art package for the simulation of the transport of particles through matter [98]. It also generates voxel-level dose maps using anatomical and physiological data taken from morphologic and functional images [46, 47]. To obtain the time-activity curve, it allows different fitting modalities: mono-exponential, linear uptake plus mono-exponential or the trapezoidal method, for the whole organ activities in the VOI. For absorbed dose calculation, Monte Carlo (MC) techniques provide the most accurate estimate.

The compiled technical dataset of each software as discussed in the review article is shown in Table 2.

CLINICAL REVIEW: FOR RADIONUCLIDE THERAPY

In the present work we have compared the clinical study done by eight authors, recently published in peer-review journals, to collate the real-time information of dosimetry calculation for radionuclide therapy patients in clinical practice.

Clinical study 1: Akhavanallaf et al. [72] acquired whole-body unenhanced CT images for 24 patients. For evaluation of the model, hybrid PET/CT image sets consisting of a low-dose CT scan and dynamic whole body PET scans were employed. The hybrid PET/CT image sets were acquired on a Siemens Biographic mCT scanner using a dynamic scanning protocol at 13-time points, after intravenous injection of ^{18}F-FDG [99, 100]. PET scanning was conducted using continuous bed motion scan at ever increasing time intervals.

Clinical study 2: Finocchiaro et al. [76] performed the PRRT trial on 100 patients. The clinical trial designed in such a way that every patient had to be sequentially administered with either ^{177}Lu

labelled adiopeptides (^{177}Lu-DOTATOC) or ^{90}Y labelled radiopeptides (^{90}Y-DOTATOC), up to a maximum of 5 infusions (or cycles). Each patient underwent 5 SPECT/CT scans at 1, 4, 24, 44, 72 h post injections. According to the trial design, clinical absorbed doses for ^{177}Lu and ^{90}Y labelled radiopeptides for liver, spleen and kidneys were calculated. Each organ was manually contoured and absorbed doses were calculated in compliance with the MIRD scheme [101] at organ-level (OL) from images.

Table 2. Technical review data: Comparative analyses of different dosimetry software tools used for evaluation of absorbed dose in radionuclide therapy.

S.N.	Software	Specification & Version(v)	Ref.	Dosimetry method	Calibration Factor (CF)	TIAC Fitting Exponential function	Absorbed Dose calculation
1	OLINDA/EXM	Hermes (v1.0), (v2.0)	[77] [75] [76]	Organ level	MBq/counts	Mono, bi, trapezoidal	Organ S-value
2	Dosimetry Toolkit (DTK)	GE Healthcare (v3.0423) Xeleris software	[77] [80]	Organ level	MBq/counts	Mono	Organ S-value
3	Hybrid dosimetry module (HDM)	HERMES- (v1.0)	[77] [79]	Organ level	MBq/counts	Mono, bi, trapezoidal	Organ S-value
4	STRATOS	Phillips (Imalytics 3.2, Rev 6289(64))	[77]	Dose Voxel kernels (DVK)	Bq/counts	Mono, trapezoidal	Voxel S-value
5	PLANET Onco Dose (PDOSE)	DOSIsoft (v3.1.1), (v3.1.2)	[77] [79] [80]	DVK & Local energy deposition (LED)	Bq/counts	Mono, bi, tri, X trapezoidal (8 fittings)	Voxel S-value
6	SurePlan- MRT	MIM (v 6.9.3)	[77]	DVK	MBq/counts	Mono, bi, trapezoidal	Voxel S-value
7	VoxelMed	MATLAB (GUI) version 2.0	[76]	Organ/voxel level	MBq/counts	Mono, bi, trapezoidal	Voxel S-value
8	BIGDOSE	GUI written in Python	[41]	DVK	Bq/counts	Mono, bi, trapezoidal	Voxel S-value using vCT
9	GATE Monte Carlo Simulation	Deep learning algorithms & Geant4 v9.5 code	[72] [73]	Deep Neural Network (DNN) & SADR	-	Voxel wise TIAC over 13-time point dynamic	Special S-value kernels
10	RAYDOSE	Geant4 MC toolkit	[76]	3D patient-specific image based	-	Mono, trapezoidal	Voxel-level dose maps using anatomical & physiological image data

Clinical study 3: Papadimitroulas et al. [73] proposed a method for the SADR calculation employed clinically derived biodistributions from pediatric scintigraphy studies. The data of 5 pediatric patients (age 7-17 yr) were used to extract the biodistributions of commonly used radiopharmaceuticals. Manual region of interest (ROI) segmentation was applied to the whole-body planar images at four or five different times after radiopharmaceutical administration to extract the time activity curves of the organs of interest. The scans were acquired at 4, 24, and 48 h (^{123}I-mIBG); 4, 24, 48, and 72 h (^{131}I-NaI); and 2, 4, and 24 h (^{99m}Tc-MDP and ^{153}Sm-EDTMP).

Clinical study 4: Grimes & Celler [74] did the study on 6 patients (3 males and 3 females), injected with 800–1000 MBq of ^{99m}Tc hydrazinonicotinamide-Tyr3-octreotide. For each patient, a series of 3-4 whole body planar scans were acquired over a period of 24 h following injection. In addition, a single SPECT/CT scan was acquired approximately 3 h after injection. A hybrid planar/SPECT imaging

protocol was used to estimate ^{99m}Tc time-integrated activity coefficients (TIACs) for kidneys, liver, spleen, and tumors. The TIACs were used as input for OLINDA/EXM for organ-level (OL) dose calculation and voxel-level (VL) dosimetry was performed using the voxel S value method and Monte Carlo simulation.

Clinical study 5: Mora-Ramirez et al. [77] performed dosimetry using DTK on two patients (one male, one female) for the first two cycles, on selected organs; liver, spleen, and kidneys. Clinical data were obtained from patients treated with ^{177}Lu-DOTATATE. [52] For each cycle, patients were administered approximately 7400 MBq.

Clinical study 6: Huizing et al. [79] proposed the study that includes ten consecutive patients treated with ^{177}Lu-DOTATATE, with sufficient uptake (> liver) on ^{68}Ga-DOTATATE PET/CT. The PRRT protocol included four cycles of 7.4 GBq ^{177}Lu-DOTATATE administered in 10-week intervals.

Clinical study 7: Santoro et al. [80] conducted the study on 21 patients (5 women and 16 men; age 41-82 years) with neuroendocrine tumor and treated with ^{177}Lu-[DOTA0, Tyr3]-octreotate of 7.4 GBq activity (four infusions in total) injected every 8 weeks. SPECT/CT images were acquired at 4 h, 24 h, 72 h and 192 h after infusion.

Clinical study 8: *Li et al.* [41**]** evaluated the clinical feasibility of BIGDOSE software, with one patient of neuroendocrine tumors injected with ^{111}In-DTPAOC. Three-time point SPECT/CT scans were obtained at 24, 48, and 72 hours post-injection of 222 MBq ^{111}In-DTPAOC for ^{90}Y-DOTAOC dosimetry. Target organs: liver, kidneys and spleen, were segmented out from the CT images at all time points, with organ-based registration for dose analysis. Two patients with ^{90}Y microsphere embolization were used to demonstrate the clinical effectiveness of the software. The comparative study of each clinical case study is shown in Table 3.

RESULT ANALYSIS OF ABSORBED DOSE EVALUATION FROM VARIOUS METHODS AND SOFTWARE

The comparative result of each clinical case study for dosimetry in radionuclide therapy as discussed by authors in the recently published articles is expressed in brief.

In clinical study1 by *Akhavanallaf et al.* [72] predicted specific voxel S-value kernels exhibited good agreement with the MC-based kernels. This approach relies on the assumption that most absorbed doses are contributed by self-absorption and dose estimation errors are commonly observed at the boundaries of heterogeneous media. In clinical study2 by *Finocchiaro et al*. [76] pointed out the absorbed doses calculated with VoxelMed and RAYDOSE were highly correlated and better agreement was obtained between Dose kernel convolution and Monte Carlo simulations results. In clinical study3 by *Papadimitroulas et al.* [73] found that the absorbed dose discrepancies of approximately 10-150% between the SADR methodology and OLINDA for two different radiopharmaceuticals. The absorbed doses from SADR and from individualized S-values in the same pediatric model differed approximately 1–50%. They proposed the SADR method, which accounts for the biodistribution of the radiopharmaceutical over time as well as the patient's specific anatomy as an alternative method for calculating internal radionuclide organ absorbed doses. In addition to considering the differences in the organ masses and the patient's anatomy the dosimetric results of pediatric patients in this study are within the range. In clinical study4 by *Grimes & Celler* [74] concluded that the S-values for all investigated radionuclide's used by OLINDA/EXM and the corresponding patient-specific S-values calculated by Monte Carlo agreed within 2.3% on average for self irradiation and differed by as much as 105% for cross-organ irradiation. Total organ doses calculated by OLINDA/EXM and the voxel S-value technique agreed with Monte Carlo results within approximately ± 7%. Comparison of the Monte Carlo and voxel S-value dose distributions showed that each method produced similar dose volume histograms, agreeing within ± 3% on average.

Table 3. Clinical review data: Patient case study done by different Authors for dosimetry in radionuclide therapy.

Clinical study	Article/Ref.	No. of patients	Radio-isotope	Dosimetry method	Imaging Tool	Scan time points	Software	ROI
1	*Akhavanallaf et.al.* [72]	24	^{18}F-FDG	DNN	Hybrid PET/CT	13 (dynamic scan)	MCS, OLINDA/EXM	Brain, heart, kidney, liver, lungs, spleen, bone, bladder
2	*Finocchiaro et.al.* [76]	100	^{177}Lu-DOTATOC, ^{90}Y-DOTATOC	OL, VL, MC	SPECT/CT	1,4,24, 44,72h	OLINDA1.1, VoxelMed2.0, RAYDOSE	Kidney, spleen, liver
3	*Papadimitroulas et.al.* [73]	5(pediatric 7-17 yr)	^{99m}TcMDP, ^{123}I-mIBG, ^{131}I-NaI, ^{153}Sm-EDTMP	SADR	SPECT/CT	4-5 scan as per radio-pharmaceuticals	MCS-GATE-Geant4 v9.5, OLINDA/EXM v1.1	Whole body(21 main organs)
4	*Grimes & Celler* [74]	6	^{99m}Tc-HTO	OL, VL, MC	Hybrid SPECT/ CT	3-4 WB planar scan/ 24h, 1 SPECT/ CT-3h	OLINDA/EXM, MCS	Kidney, spleen, liver
5	*Mora-Ramirez et.al.* [77]	2	^{177}Lu	OL,VL	SPECT/CT	4,24,72, 192h	OLINDA/EXM v1.0/ 2.0, DTK, HDM, STRATOS, PDOSE, MRT	Kidney, spleen, liver
6	*Huizing et.al.* [79]	10	^{177}Lu-DOTA-TATE	OL, Vl	Hybrid SPECT/CT	0.5,4,24, 72h	OLINDA/ EXM v2.1, PDOSE v3.1.2	NET(Neuroendocrine tumour)
7	*Santoro et.al.* [80]	21	^{177}Lu-DOTA-TATE	OL, VL	SPECT/CT	4,24,72,192h	DTK, PDOSE, OLINDA/EXM v1.0	Kidney, spleen, liver
8	*Li et.al.* [41]	3	^{111}In - DTPAOC & ^{90}Y-DOTAOC	OL, VL, MC	SPECT/CT	24, 48, 72 h	BIGDOSE, MCS-GATE-v6.1, OLINDA/EXM v1.1	Kidney, spleen, liver

In general, good agreement was found between total organ doses calculated using OLINDA/EXM, Voxel S-values and Monte Carlo for all analyzed isotopes. However, more detailed analysis of these results clearly indicates that patient anatomy had a large impact on cross-organ S-values. In clinical study5 by *Mora-Ramirez et al*. [77] resulted that the majority of organ mass estimates varied by <9.5% between all commercial dosimetric software platforms. Relative standard deviations in mean absorbed doses were slightly higher compared with those observed for TIAC but remained of the same order of magnitude between all commercial dosimetry software platforms. In clinical study6 by *Huizing et al.* [79] indicated that the mono-exponential fits showed the most comparable correlation between the measured and fitted data between OLINDA/EXM and PLANET DOSE software. Bi-exponential fits resulted in lower correlations and agreement values. In clinical study7 by *Santoro et al*. [80] explored that the difference of 2.2% was obtained between the absorbed doses to organs at risk calculated with Local Deposition Method and Dose voxel-Kernel convolution on PLANET Dose software. In clinical study8 by *Li et al.* [41] concluded that when compared with OLINDA/EXM, large improvement could be observed in absorbed dose estimation in the target organs by BIGDOSE. There are certain limitations that it only considers absorbed dose for beta particle and assumes absorbed dose contributions from organs other than the target organs are negligible.

The results of comparative study of various dosimetry methodologies to calculate the absorbed dose in the lesions with different non-commercial / commercial software tools provide a wide spectrum of information and guideline to set the protocol to practice patient-specific radionuclide therapy in clinical routine.

DISCUSSION

The objective of the present study is to compare the results generated by different non-commercial / commercial dosimetry software toolkits. However, encouraging results obtained in terms of absorbed doses were generally consistent between dosimetry software tools. The objectives of this work was not to provide the ranking or to recommend a given dosimetry methodology or software tool. While comparing different methodologies and software for absorbed dose calculation based on clinical studies done by various authors, observed the advantages and limitations of each study. *Akhavanallaf et al.* [72] proposed a unified methodology for patient-specific whole-body voxel wise internal dosimetry using deep learning algorithms that exhibited comparable performance to the direct Monte Carlo approach. They only provided a model for ^{18}F, which can be extendable to all types of radionuclides /radiotracers in future focusing on the current methodology to generate whole-body voxel wise dose maps in few minutes to serve as Monte Carlo-based datasets. *Finocchiaro et al*. [76] suggested that voxel-level techniques for dosimetry calculation are potentially more accurate and personalized than organ-level methods. In particular, a voxel-convolution method provides good results in a short time of calculation, while Monte Carlo based computation is considered the most accurate and require very powerful computers to run fast for a possible use in clinics. The Monte Carlo simulation modality seems to be more accurate than voxel-convolution methods. *Papadimitroulas et al.* [73] standardized a method for more personalized internal radionuclide dosimetry in pediatric NM applications. The ultimate goal in future is to create a database of SADRs that can be used to match patients to the best anatomical model in the database according to characteristics such as weight, height, age, gender and CT information, thereby providing more accurate patient-specific organ absorbed doses for a specific examination. The SADR dataset could be extended to a variety of pediatric models for variety of radiopharmaceutical used in pediatric applications. *Grimes & Celler* [74] showed that the comparison of voxelized dose calculated by Monte Carlo and the voxel S-value technique, the 3D dose distributions produced by the respective methods are nearly identical. In general, good agreement was found between total organ doses calculated using OLINDA/EXM, Voxel S-values and Monte Carlo for sample isotopes.

The 3D dose distribution calculated time by the voxel S-value method was approximately 1 h but by Monte Carlo simulation was about 30 h. *Mora-Ramirez et al*. [77] concluded that the flowchart of each toolkit was different, which complicates the comparison exercise and recommended the features that should be desirable for a dosimetry software platform: i) Specific workflows to improve the user-friendliness of dosimetry software toolkits. ii) Central processing of data acquired by import/export features for processing data from absorbed dose maps. iii) images/data to be acquired using the relevant protocol. iv) A "calibration module" should be available. v) A modular approach of step-by-step processing with checkpoints to perform a dosimetry study. vi) The history of the processes performed should be traceable. vii) The output format should be standardized and well documented. This gives the framework for future research. *Huizing et al.* [79] showed that there are slight differences in outcomes achieved by different software systems as there are differences in methodology. Final outcome also depends on pharmacological behavior of the radiopharmaceutical, acquisition time and protocol. *Santoro et al*. [80] validated the use of PLANET Dose software in clinical routine for patient-specific dosimetry, to evaluate the absorbed dose-response for targeted radionuclide therapy (TRT) and proposed that this software is user-friendly, with wide range of tools for segmentation and the time for dosimetry analysis is reduced. *Li et al.* [41] introduced BIGDOSE software that provides a one-stop platform for voxel-based dose estimation with high accuracy, incorporating 3D personalized imaging with the availability of both organ-based and whole-body registrations. It is a promising tool to streamline the current clinical TRT dosimetric practice for treatment planning and post-therapy dose verification. The comparative study in this review article provides the information of the most adequate computation technique and the methodology for the clinical or research application. The outcome of the present study includes classification of various techniques mostly practiced worldwide in clinical routine, ranging from the less advance to personalized and the most accurate.

CONCLUSION

We finally conclude that OLINDA/EXM is still the most popular main stream organ-based dosimetric software in the clinic but there is raise in the demand of 3D voxel-based personalized dosimetry. Full Monte Carlo simulations are regarded as the gold standard approach. For absorbed dose calculation, Monte Carlo (MC) techniques provide the most accurate estimate. The non-commercial software provides a full customization of the procedure, yet the calculations are tricky. The commercial systems for a 3D workflow can be safer for the user and easier to use but the proper customization may be difficult for the user. Following the results of the present work, authors concluded that in dosimetry calculations and in the harmonization process of different dosimetry software there are critical steps that may be summarized as: contouring of volumes of interest; matrices of S-values and type of convolution used to calculate absorbed doses; calculation over the whole field or on a restricted region of the 3D image; time activity curve fitting and integral from the first to the last image time point; time activity curve extrapolated from the last time point to infinity; time required for calculations; degree of personalization of the technique. The use of different settings may provide very different results; all these steps should be deeply investigated on real cases before implementing a new non-commercial or commercial dosimetry software system, based on voxel level or on organ level calculations. However, the growing availability of user-friendly clinical dosimetry software solutions are promising in order to further develop and optimize targeted radionuclide therapy.

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Conflicts of Interest

The authors have no relevant conflicts of interest to disclose.

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