REVIEW

Heterogeneity of absorbed dose distribution in kidney tissues and dose–response modelling of nephrotoxicity in radiopharmaceutical therapy with beta-particle emitters: A review

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Abstract

Absorbed dose heterogeneity in kidney tissues is an important issue in radiopharmaceutical therapy. The effect of absorbed dose heterogeneity in nephrotoxicity is, however, not fully understood yet, which hampers the implementation of treatment optimization by obscuring the interpretation of clinical response data and the selection of optimal treatment options. Although some dosimetry methods have been developed for kidney dosimetry to the level of microscopic renal substructures, the clinical assessment of the microscopic distribution of radiopharmaceuticals in kidney tissues currently remains a challenge. This restricts the anatomical resolution of clinical dosimetry, which hinders a thorough clinical investigation of the impact of absorbed dose heterogeneity. The potential of absorbed dose–response modelling to support individual treatment optimization in radiopharmaceutical therapy is recognized and gaining attraction. However, biophysical modelling is currently underexplored for the kidney, where particular modelling challenges arise from the convolution of a complex functional organization of renal tissues with the function-mediated dose distribution of radiopharmaceuticals. This article reviews and discusses the heterogeneity of absorbed dose distribution in kidney tissues and the absorbed dose–response modelling of nephrotoxicity in radiopharmaceutical therapy. The review focuses mainly on the peptide receptor radionuclide therapy with beta-particle emitting somatostatin analogues, for which the scientific literature reflects over two decades of clinical experience. Additionally, detailed research perspectives are proposed to address various identified challenges to progress in this field.

Keywords: Absorbed dose heterogeneity; Radiopharmaceutical therapy; Kidney dosimetry; Dose–response modelling; Normal tissue complication probability (NTCP); Biophysical modelling

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Introduction

In radiopharmaceutical therapy, the kidneys are often a major organ at risk (OAR) and can be a dose-limiting organ due to radiation-induced nephrotoxicity [1,2]. The distribution of activity is usually not uniform in kidney tissues due to differential uptake of radiopharmaceutical along distinctive nephron substructures. This is influenced by aspects such as the molecular weight, charge, and molecular conformation of the radioligand, as well as the expression of target receptors in kidney tissues [2,3]. Radioligands based on relatively small (< 30 kDa) molecules, such as radiolabelled peptides and small antibody fragments, are easily filtered by the nephron glomerulus, resulting in rapid clearance from blood circulation and passage to the nephron tubules. Once in the glomerular filtrate, small radioligands can be reabsorbed and temporarily trapped in the proximal tubule cells of the renal cortex and of the outer stripe of the renal outer medulla [3–6]. Additionally, the functioning of distinct types of nephrons can impact the distribution of radiopharmaceuticals in the kidneys [7]. This heterogeneous distribution of radiopharmaceuticals can lead to a corresponding heterogeneous distribution of absorbed dose across renal tissue regions [6–8], and even among the distinct substructures within them [9,10], particularly for radionuclides emitting charged-particle radiation with short penetration range in tissues like alpha particles and low- to medium-energy electrons.

Differences in the sub-organ spatial and temporal absorbed dose distributions of radiopharmaceuticals in the kidneys increase the difficulty of determining accurate absorbed dose–effect relationships for nephrotoxicity useful for predicting the clinical response of different radiopharmaceutical therapy settings. In peptide receptor radionuclide therapy (PRRT), for example, the microscopic absorbed dose distribution in human kidneys is thought to contribute to the seemingly lower occurrence of nephrotoxicity of ^{177}Lu-labelled somatostatin analogues when compared with similar ^{90}Y-labelled peptides [7,11]. The glomeruli are sometimes thought to be the absorbed dose-limiting substructure of the kidney in radiopharmaceutical therapy labelled with some beta- emitters [12–15]. Yet, loss of proximal tubules has been associated with long-term nephrotoxicity in mice with either beta or alpha particle emitting radioligands [8,16]. Biophysical models to predict clinical endpoints of tissue toxicity based on absorbed dose and radiobiological considerations are highly desired to support the implementation of individual treatment evaluation and planning in radiopharmaceutical therapy [17,18]. Models for estimating normal tissue complication probability (NTCP) developed for conventional external beam radiotherapy (EBRT) could be considered for radiopharmaceutical therapy, where adaptations are required to account for differences between modalities in the temporal and spatial characteristics of radiation delivery [19,20].

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This article reviews the heterogeneity of absorbed dose distribution in kidney tissues and the absorbed dose–response modelling of nephrotoxicity in radiopharmaceutical therapy. First, some fundamental methods used for radiation dosimetry in nuclear medicine and mathematical modelling of the radiobiological effects of radiotherapy are summarized. An overview of computational models of the human kidney and its substructures, which allow radiation dosimetry of heterogeneous radionuclide distributions at sub-organ level, is presented. Next, the heterogeneity of absorbed dose distribution in kidney tissues in PRRT with beta-particle emitting somatostatin analogues is reviewed. The focus is mainly on radiopeptides [^{90}Y-DOTA^0,Tyr^3]-octreotide (^{90}Y-DOTA-TOC) and [^{177}Lu-DOTA^0,Tyr^3]-octreotate (^{177}Lu-DOTA-TATE), for which the scientific literature reflects over two decades of clinical experience [21–23]. This is followed by a review of models for estimating NTCP for nephrotoxicity in radiopharmaceutical therapy. Finally, the topics addressed in the literature review are discussed and detailed research perspectives to address various identified challenges to progress in this field are proposed, in line with the strategic research agendas of the European Radiation Dosimetry Group (EURADOS) (https://eurados.sckcen.be/) [24], the Multidisciplinary European Low Dose Initiative (MELODI) (https://melodi-online.eu/) [25], and the European Alliance for Medical Radiation Protection Research (EURAMED) (https://www.euramed.eu/) [26].

Radiopharmaceutical dosimetry

The internal dosimetry methodology developed by the Medical Internal Radiation Dose (MIRD) Committee and the International Commission on Radiological Protection (ICRP) is commonly used to assess the absorbed dose from the administration of radiopharmaceuticals in nuclear medicine [27]. The basic formalism can be expressed in a time-independent manner as:

$$D(r_T) = \sum_{rS} \tilde{A}(r_S) \cdot S(r_T \leftarrow r_S) \quad (1)$$

where $D(r_T)$ is the mean absorbed dose to target region r_T delivered by the cumulated activity in all source regions; $\tilde{A}(r_S)$ is the time-integrated activity in source region r_S; and $S(r_T \leftarrow r_S)$ is the radionuclide-specific absorbed dose rate per unit of activity in target region r_T delivered by source region r_S (often referred to as S value). $\tilde{A}$ denotes the total number of radioactive decays (determined by integrating the time–activity curve from time 0 to infinity) occurring within an organ or a tissue region accumulating the radiopharmaceutical. $\tilde{A}$ can be estimated by quantitative imaging at several time points after the administration of the radiopharmaceutical. This may result in an assessment of organ level, sub-organ level, or voxel-specific pharmacokinetics [28,29].

S values depend on several parameters, including the type, energy, and abundance of the decay radiation emissions, the distance between the point of emission of the radiation and the target tissue (which depends on the source–target tissue geometry), the material composition and density along the path between source and target, and the mass and composition of the target tissue. S values are calculated for a specific radionuclide using specific reference computational anatomical models or for a voxel geometry using radiation transport simulations [30,31]. Such anatomical models consist of compartments which mimic the geometry, the elemental composition and the density of tissues in the human body [32–36]. For S value calculations, radioactivity (and dose deposition) is assumed to be uniformly distributed throughout a source (or target) compartment. Therefore, a phantom model may consist of multiple compartments, each corresponding to a different source and/or target tissue or cellular region, to allow the consideration of heterogeneous distributions of radiopharmaceuticals among the represented anatomical regions.

Computational models for dosimetry in kidney tissues at sub-organ level

A few computational models of the human kidney or its substructures are available in the literature which allow absorbed dose estimates of radionuclide distributed at the sub-organ level based on the MIRD dosimetry formalism [9,10,32,37,38].

Already in the late 60's, Snyder and Ford [37] and then McAfee [38] published two independent computational models of the kidney consisting of three regions representing the renal cortex, medulla, and inner renal regions (pelvis and papilla). The cortex and medulla were modelled as two concentric ellipsoidal shells. In the phantom model of Snyder and Ford, the medulla region was further delimited by 32 circular cones representing medullary pyramids, and the intramedullary space between the pyramids was apportioned to the cortex region. These models, however, were not widely used in nuclear medicine dosimetry, likely because dose estimates were reported only for two radionuclides (^{197}Hg and ^{203}Hg). Also, time-dependent activity biodistribution information at the sub-kidney level was still very limited in the few decades following the publication of the models.

A few decades after the introduction of Snyder's and McAfee's models, the MIRD committee published in pamphlet No. 19 a set of six age-dependent multiregional models of the kidney (Figure 1A) [32]. The MIRD19 models are defined using simple mathematical surfaces (so-called

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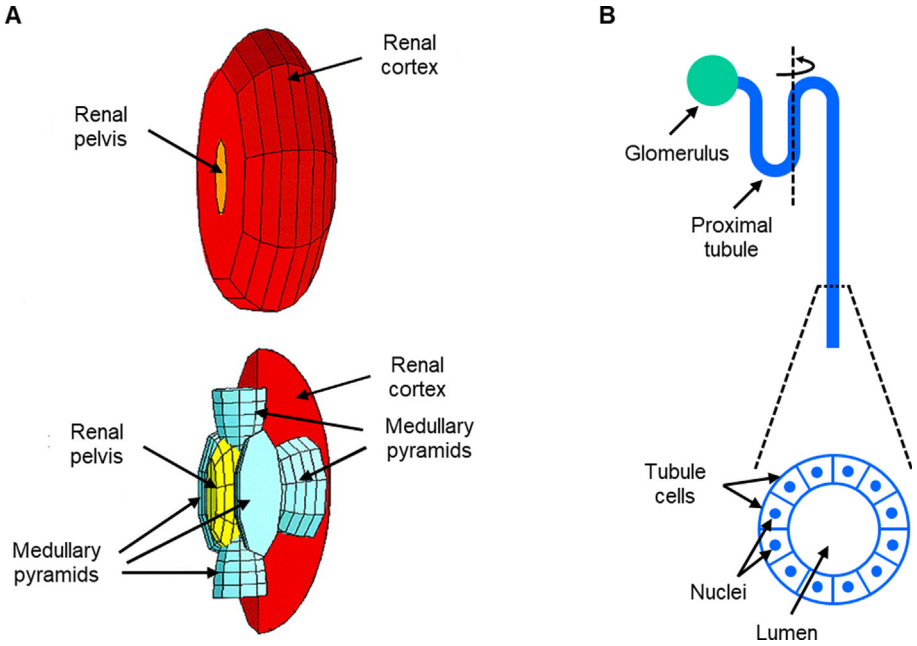

Figure 1. Examples of computational models for internal dosimetry of human kidney tissues at sub-organ level. **A**: 3D representation of kidney model of MIRD pamphlet No. 19 (figure adapted from [32]). **B**: 2D representation of a nephron model [9].

stylized models), which delimit four anatomical regions: renal cortex, medullary pyramids, papilla, and renal pelvis (Figure 1A). Absorbed fractions of energy emitted and *S* values were reported for each kidney region as a source (and/or target) for 26 electron and photon-emitting diagnostic and therapeutic radionuclides. Full utilization of the models requires serial imaging of the kidneys with regions of interest assigned to at least the renal cortex and medulla. In another study, Konijnenberg et al. [7] implemented the MIRD19 model as a lattice of 3-mm wide cubic voxels. Each voxel of the cortex region consisted of two compartments (a cylinder of 1.7-mm diameter in the centre and a surrounding region), allowing the authors to model a cortical uptake with a streaky pattern relatively similar to that observed in kidney autoradiographs with a radiolabelled peptide [4].

Going more in detail into the anatomical structures of the kidney, Hobbs et al. [9] described a nephron- and cellular-based kidney dosimetry methodology for alpha-particle radiopharmaceutical therapy. The macro-to-micro model-based methodology assigns kidney time-integrated activity information to microscopic-level kidney substructures of a nephron model. According to Hobbs et al., the glomerulus and the proximal tubule of kidney nephrons are expected to receive the highest absorbed doses from alpha particles in radiopharmaceutical therapy; therefore, they are likely to absorb a dose close to the limiting dose for nephrotoxicity. Thus, their nephron model considered only those two nephron parts. The nephron was modelled using simple mathematical shapes (i.e., a stylized model) (Figure 1B). Two versions of the nephron model were presented, one for a human nephron, and a scaled version for a murine nephron. *S* values were reported for the glomerulus and three sub-compartments of the tubule for a range of alpha emitters of clinical interest and their progeny. Although the model was meant for dosimetry of alpha particle emitters in their work, it may also be used for dosimetry of other relevant short penetration-range particles, such as low energy electrons [39]. Another study [10] presented a complete model of a nephron, consisting of six compartments corresponding to different parts of the glomerular corpuscle and tubules. The model of Jabari et al. appears to be a more realistic representation of a human nephron (in their study, however, Jabari et al. do not report what kind of data was used to derive their model). In their study *S* values were reported for ^{111}In, ^{99m}Tc, ^{177}Lu, ^{225}Ac, and ^{212}Bi, for radioactivity located in the glomerulus or in the proximal tubule.

Mathematical modelling of radiobiological effects

Linear quadratic model

The linear quadratic (LQ) model is commonly used to describe the relationship between the probability of survival of cells and the delivered dose of ionizing radiation [40]. For

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protracted exposures, like in radiopharmaceutical therapy, the fraction of surviving cells (*SF*) is related to the total physical absorbed dose (*D*), the radiosensitivity of a specific type of cells (represented by the constants α and β), and the Lea-Catcheside factor *G:*

$$SF(D) = e^{-\alpha D - G\beta D^2} \tag{2}$$

The generalized Lea-Catcheside factor *G* for a time-dependent absorbed dose rate ($\dot{D}(t)$) is given as [41]:

$$G = \frac{2}{D^2}\int_0^{\infty} \dot{D}(t)dt \int_0^{t} e^{-\mu(t-t')}\dot{D}(t')dt' \tag{3}$$

Radiobiological parameters α and β correspond to the lethal and sub-lethal damages to the DNA relative to the absorbed dose and dose-rate, respectively; and μ is the exponential repair rate constant (with half-life $T_{\mu} = \ln(2)/\mu$) that quantifies the repair rate of sub-lethal damage. These parameters are derived experimentally from preclinical *in vitro* studies using specific cell lines or from *in vivo* experiments on rodents. The second integration over the time parameter *t*' in Equation (3) refers to the exponential repair of a first sub-lethal event. The first integral term expresses the second sub-lethal event that can combine with the first event remaining after repair to produce a lethal lesion. As opposed to a single lethal event, sub-lethal damage is dependent on the dose rate. This is characteristic of irradiations with low linear energy transfer radiation, such as beta particles and photons. For acute exposures, like most EBRT exposures, *G* equals to 1. The total absorbed dose *D* may be given in *n* fractions of absorbed dose *d* (i.e., $D = n{\cdot}d$), to enable damage repair between fractions to reduce toxicity effects in major OARs.

Other versions of the LQ have been proposed which consider additional factors to account for the effect of other radiobiological phenomena, such as repopulation of cells during treatment (cell loss factor) and the decreased radiosensitivity of hypoxic cells (oxygen enhancement ratio) [42,43].

Biologically effective dose, BED

In EBRT and, more recently radiopharmaceutical therapy, the LQ model has been used to predict clinical endpoints of tumour control probability (TCP) and NTCP [44,45]. The underlying assumption is that the macroscopic tissue response is driven by the death of some cell population(s), and that the magnitude of the biological effect is directly related to the fraction of surviving cells (*SF*).

The LQ model in Equation (2) implies that a given cumulative absorbed dose can result in different surviving fractions when delivered at different dose rates (or dose fractionation schemes). This variation led to the introduction of the concept of biologically effective dose (BED) to compare the effect of the same cumulative absorbed dose for different tissues and time–irradiation schemes [46,47]. The BED is defined as the cumulative absorbed dose in a target volume (VOI) that is required to cause a given surviving fraction if the dose would be delivered in infinitesimally small doses per fraction or, equivalently, at very low absorbed dose rates. This means that the dose-rate dependency of cell kill (corresponding to the non-linear term D^2 in the exponential in Equation (2)) is incorporated into the definition of BED.

$$SF_{\dot{D}(t)\to 0} = SF_{\dot{D}(t)} \tag{4}$$

Using the LQ model of Equation (2) it follows that:

$$e^{-\alpha BED} = e^{-\alpha D\left(1+\frac{GD}{\alpha/\beta}\right)} \tag{5}$$

By solving the previous equation for the BED, the following is obtained:

$$BED = D\left(1 + \frac{GD}{\alpha/\beta}\right) \tag{6}$$

The expression in parenthesis in Equation (6) is known as the relative effectiveness per unit absorbed dose (*RE*) and is specific for the type of exposure. Thus, the BED can be rewritten as:

$$BED = D \cdot RE \tag{7}$$

In radiopharmaceutical therapy, absorbed dose rate often follows (or is assumed to follow) an exponential decrease as a function of time. Dale [48] demonstrated that in such case, for a complete decay of the source, *RE* becomes:

$$RE = 1 + \left[\frac{D\lambda_{eff}}{(\alpha/\beta)(\lambda_{eff}+\mu)}\right] \tag{8}$$

Where λ_{eff} is the effective clearance rate given by the sum of the physical decay and the biological clearance rates.

Equivalent uniform dose, EUD

The concept of an equivalent uniform dose (EUD) was introduced by Niemierko [49] with the aim of facilitating the comparison of alternative treatment plans for which the absorbed dose in tissue is not uniformly distributed. The EUD for tumours is defined as the biologically equivalent absorbed dose that, if given uniformly, will lead to the same cell kill in the tumour volume as the actual heterogeneous absorbed dose distribution. The radiobiological formulations of the EUD are based on cell survival estimations using a radiobiological model [49,50]. Later, based on the empirical power law for partial uniform irradiation of tissue [51], Niemierko presented a semi-phenomenological formulation (Equation (9)), sometimes referred to as the generalized EUD, to apply to normal tissues [52]:

$$gEUD = \left(\sum_i v_i D_i^a\right)^{1/a} \tag{9}$$

where v_i is the sub-volume with absorbed dose D_i. The sub-volume may correspond with, for example, bins of a dose–volume histogram (DVH). Volume-effect parameter a is a model parameter which depends on the tissue and the irradiation characteristics. Values of a (or a similar parameter) can be derived by fitting to EBRT clinical data [51–56].

Important to note, the generalized EUD formulation in Equation (9) and other formulations of the EUD are based upon the assumption that tissue function is uniform and independent across tissue sub-volumes v_i, i.e., the tissue is assumed to have a purely parallel-like architecture.

Although the EUD was originally proposed in the context of EBRT treatment planning, it can also be applied in radiopharmaceutical therapy. For that, instead of the generalized EUD (Equation (9)), a radiobiological formulation based on the LQ model accounting for dose rate effects is of interest to consider the biological effect of protracted exposures and tissue specific radiosensitivity [50].

For a volume of interest consisting of N sub-volumes (e.g., voxels, or cells, for a multicellular analysis) receiving different absorbed doses D_i, the surviving fraction becomes:

$$SF = \frac{\sum_{i=1}^{N} SF_i}{N} \tag{10}$$

The EUD is the absorbed dose, which, when uniformly distributed in a target volume, would result in the same biological effect as the absorbed dose from a non-uniform irradiation. Therefore, considering biological effect as a matter of cell survival:

$$SF_{heterogeneity} = SF_{uniformity} \tag{11}$$

Using the LQ model of Equation (2) it follows that:

$$e^{-\alpha EUD-\beta EUD^2} = \frac{\sum_{i=1}^{N} e^{-\alpha D_i-\beta D_i^2}}{N} \tag{12}$$

By solving the previous equation for the EUD, the following radiobiological formulation of the EUD is obtained [50]:

$$EUD = \frac{1}{2\beta}\left(-\alpha + \sqrt{\alpha^2 - 4\beta \cdot ln\left(\frac{\sum_{i=1}^{N} e^{-\alpha D_i-\beta D_i^2}}{N}\right)}\right) \tag{13}$$

Other radiobiological formulations of the EUD have been proposed, for example, using a linear model for cell survival [49].

Normal tissue complication probability, NTCP

The complication probability for normal tissues is used in treatment planning as a tool to differentiate between the potential effect of alternative treatment plans. NTCP models are prediction models used in radiotherapy to estimate the risk of radiation-induced complications in normal tissues. These models aim to translate radiation absorbed dose distributions, in combination with tissue, treatment and even patient characteristics, into a predicted probability that a complication will occur.

The absorbed dose dependence of NTCP can be described mathematically by sigmoid functions, which may or not be coupled to a radiobiological model. NTCP models can be classified into empirical and phenomenological models. Empirical models are based on curve fitting of clinical absorbed dose–response data [54], such as that compiled by Emami et al. and the QUANTEC initiative for normal tissues based on general clinical experience in EBRT [55–58]. An empirical model commonly used in EBRT is the 3-parameter (TD_{50}, m and n) Lyman-Kutcher-Burman (LKB) model [53,54,59]:

$$NTCP_{LKB}(u) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{u} e^{-x^2/2} dx \tag{14}$$

with:

$$u = \frac{D - TD_{50}(V)}{m \cdot TD_{50}(V)} \tag{15}$$

and:

$$TD_{50}(V) = TD_{50}(1) \cdot V^{-n} \tag{16}$$

This model assumes a normal distribution of complication as a function of absorbed dose around a mean value, the TD_{50}, corresponding to the uniform absorbed dose given to a tissue volume fraction V that would result in a 50% complication probability. Parameter m denotes the slope of the NTCP curve at TD_{50}. Parameter n accounts for the effect of partial irradiations (often called volume effects) assuming a power-law relationship [51,53]. Thus, alike the generalized EUD (Equation (9)), a DVH-reduction scheme can be used to associate a heterogeneous absorbed dose pattern with a uniform one inducing the same toxicity. For bilateral whole-kidney external-beam irradiation, Emami et al. and the QUANTEC initiative found that an absorbed dose of 18 and 28 Gy, when delivered in fractions of approximately 2 Gy, corresponded to respectively a 5% and 50% probability of nephropathy within 5 years (corresponding to $TD_{5,5}$ and $TD_{50,5}$ in the LKB model) [55–58]. By fitting to the data of Emami et al. for partial uniform external-beam irradiations of an organ [57], Burman et al. found an n parameter value of 0.70 for the kidney [54]. Other sigmoid functions can be used to fit (the same) clinical absorbed dose–response data, which can result in significantly different NTCP estimations, particularly in the tail regions of the sigmoid curve [60,61].

The model parameters of purely empirical approaches depend on the fitting function and are not necessarily representative of radiobiological phenomena. Yet, it is possible to couple an empirical NTCP formulation with a radiobiological model, resulting in a semi-empirical NTCP model. By

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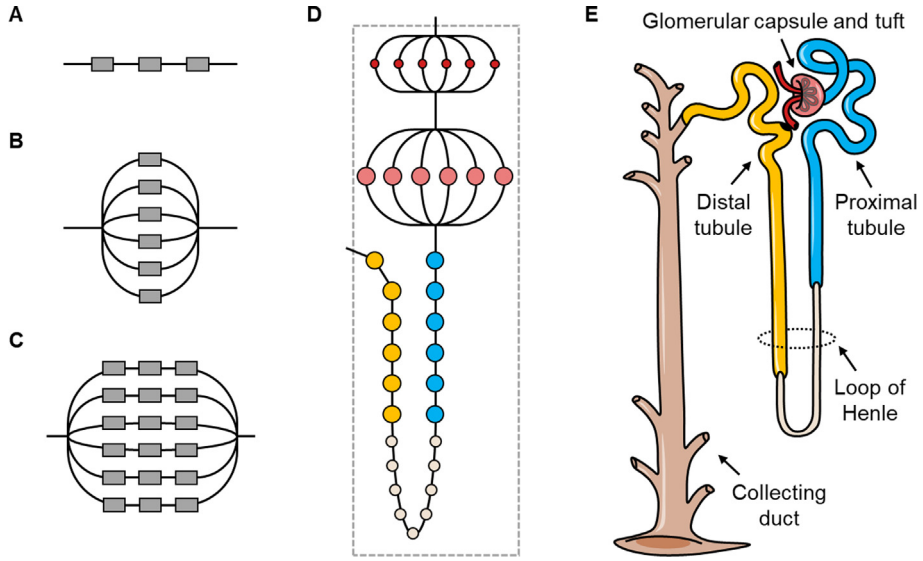

Figure 2. Schematic examples of tissue organization structures: a serial string of sub-units (rectangular symbols) (**A**), a parallel structure of sub-units (**B**), and a combined parallel-serial structure of sub-units (**C**) [66]. An example (**D**) of the parallel-serial model applied to the nephron (**E**), the structural and functional sub-unit of the kidney. The parallel structure is the capillary system inside the glomerular capsule, serially followed by the capsule itself and the tubules.

using a dosimetric quantity adjusted by a radiobiological model (e.g., the BED based on the LQ model), empirical NTCP models may be extended to account for the time-related effects of irradiation, such as cellular repair and repopulation between irradiation fractions or during protracted irradiations [12,62,63].

The fact that organ tissues consist of different cell types, which may have distinctive function, spatial organization, radiosensitivity and capacity to repopulate, has led to the consideration of organ architecture to explain and describe the absorbed dose response of normal tissues, particularly in case of partial or non-uniform irradiations. An organ may be considered a collection of independent functional subunits (FSUs) [64,65]. The FSU is a tissue subcomponent which contributes independently to overall organ function, and whose loss results in an incremental loss of function. The impact of partial and non-uniform irradiations depends on the organization of FSUs in tissue, which may be serial, parallel or a combination thereof (Figure 2A–C). In a serial architecture (e.g., spinal cord, oesophagus, colon), the inactivation of a single FSU is sufficient to damage the organ, whereas in a parallel architecture (e.g., lungs, liver), organ injury occurs only if all (or a critical number of) FSUs are inactivated.

Similarly, the organization of substructures and cells within an FSU (parallel, serial, or a cross-link; Figure 2D) may also be considered to analyse the response of more complex tissue structures, such as kidney tissues [66]. The FSU of the kidney is the nephron. Each human kidney contains several hundred thousand nephrons organized in parallel. Yet, the substructures of a nephron (the glomerular tuft and capsule, and the distinct segments of the tubule, cf. Figure 2E) have a predominant serial organization [66].

Phenomenological expressions of NTCP are based on postulates of organ architecture and cell (or FSU) survival estimations based on a radiobiological model, typically the LQ model. In such NTCP models, absorbed dose heterogeneity is considered by dividing the organ into sub-volumes containing FSUs and estimating the response probability independently in each sub-volume using a radiobiological model. How the estimated local responses are then compounded into a whole organ response metric depends on the assumptions considered for tissue architecture and radiobiological characteristics. Some underlying assumptions of phenomenological models are that the stochastic killing of FSUs upon exposure to ionizing radiation follows a binomial probability distribution of absorbed dose, and that the radiation response of FSUs is statistically independent (*i.e.*, the inactivation of a FSU does not influence the survival or killing of another FSU, and the location of FSUs within the organ or sub-volume is irrelevant). Moreover, FSUs are assumed to be small enough so that the absorbed dose in an FSU is effectively homogeneous.

Examples of phenomenological models relevant for the kidney are the parallel quantal model [67], the relative seriality model [66], the critical element model [68], and the model proposed by Yorke et al. [69]. The mathematical formulations are specific to the NTCP model (for that, the reader is referred

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to the literature previously cited and the review by D'Andrea et al. [19]. Model parameters usually have a (radio)biological basis (e.g., parameters used in the LQ model, number of FSUs, number of cells per FSU) or a phenomenological basis (e.g., parameters describing tissue and FSU architecture, the critical number of active FSUs required for an organ to function, etc.). Some of these NTCP models assume that a certain fraction of the kidney's FSUs need to be eradicated for severe renal injury to occur [67–69]. The relative seriality model introduces a parameter to account for organs with a cross-linked serial-parallel architecture [66]. Inter-individual variability in model parameters may as well be considered in the formulation of NTCP, to account for differences between the individual response and the population-averaged response [67,70].

However, the widely used NTCP models suffer from indeterminacies due to the heterogeneity of volume definitions (e.g., tissue function, hollow organs), discrepancies in the definition of tissue volumes, heterogeneity in the data quality, and differences in radiobiological assumptions for the model development (e.g., tissue radiosensitivity, tissue recovery, cellular repopulation, cell migration or even bystander effects, etc.) [18,19,44,71–75]. For example, in PRRT with ^{90}Y-DOTA-TOC, the consideration of patient-specific kidney tissue volumes and modelling of dose rate and fractionation effects were found to be essential for finding an absorbed dose–response relationship of kidney toxicity [14]. In EBRT, clinical data argue against the presumed uniform distribution of function and radiobiological properties even in normal tissues typically considered as having parallel architecture [75,76]. Also, tissues with a diminished functional capacity (due to, e.g., patient pre-existent clinical conditions, effect of previous therapies, etc.) may be associated with an increased radiosensitivity which can affect how an organ responds to irradiation [71,72,75,77].

Heterogeneity of absorbed dose distribution in radiopharmaceutical therapy with ^{177}Lu- and ^{90}Y-radiolabelled somatostatin analogues

PRRT with ^{177}Lu- and ^{90}Y-radiolabelled somatostatin analogues is an established, well-tolerated, and effective radiopharmaceutical therapy for neuroendocrine tumours [78,21–23]. The kidney is, however, a major OAR and is generally considered an absorbed dose-limiting organ [14,77,79]. Consequently, patient-specific kidney dosimetry is increasingly being used clinically as a tool for PRRT treatment planning, evaluation, and optimization.

Despite the relatively early evidence on the heterogeneous distribution of radiolabelled peptides in human kidneys [4], little literature exists so far on the absorbed dose distribution in kidney tissues of PRRT and its influence in clinical nephrotoxicity. Most kidney absorbed doses reported in the literature for ^{177}Lu- and ^{90}Y-radiolabelled peptides are calculated using S values determined with single-region kidney or sphere models [80,81], which suppose the assumption of a uniform distribution of radioactivity and absorbed dose throughout kidney tissues [11,15,77,82–84]. Mean absorbed doses to kidneys, based on voxel-based dosimetry methods and patient-specific activity distributions in kidney tissues derived with planar or single-photon emission computed tomography (SPECT) imaging, have also been reported [85–88]. Except for the work by Baechler et al. [87], however, these studies did not report any quantitative analysis on the heterogeneity of the sub-kidney dose distribution.

Most studies considering absorbed dose heterogeneity in the kidneys perform dosimetry at a regional (i.e., intermediate) level, based on the multiregional model of MIRD19 [13,14,32,89]. For compounds that are concentrated in the proximal tubules (such as radiolabelled somatostatin analogues), the radionuclide may be considered to be localized primarily in the renal cortex region for dosimetry at an intermediate level. MIRD pamphlet No. 19 showed that, for a ^{90}Y activity fully localized in the cortex compartment, the absorbed dose to the cortex would be about 1.3 times that of the single-region model, whereas the medullary absorbed dose would be less than 30% of that same single-region dose value [32]. Similar results were obtained with ^{131}I, a radionuclide with a beta-particle emission spectrum similar to that of ^{177}Lu. Other investigators have performed dosimetry of kidney tissue regions, using the MIRD19 model, to estimate biological kidney response (cf. next section) [13,14,89]. More detailed kidney absorbed dose estimations at sub-organ level have been performed by Konijnenberg et al. and Baechler et al. [7,12,87], as described below.

Aiming to establish a feasible image-based patient-specific dosimetry approach for PRRT, Baechler et al. [87] calculated mean absorbed doses and DVHs of the renal cortex and the medulla for PRRT with ^{90}Y, ^{177}Lu, and ^{111}In, using a voxel-based approach based on direct Monte Carlo absorbed dose calculations and the activity distributions of serial SPECT images of ^{111}In-DTPA-octreotide. Kidney absorbed dose heterogeneity, expressed in terms of the cortex-to-medulla dose ratio, was considerable and was more pronounced for ^{177}Lu (2.26) and ^{90}Y (1.95), than for ^{111}In (1.35). The DVHs indicated that the portion of the cortex receiving a high absorbed dose is larger for the ^{177}Lu distribution than for ^{90}Y. Yet, the difference in DVHs was not so marked, particularly when comparing ^{177}Lu and ^{90}Y, as would be expected from the considerable difference in tissue penetration range of their beta particles (maximum range of 12 mm for ^{90}Y, against 2.1 mm for ^{177}Lu). Although not explicitly addressed in the study, this was presumably related to the use of a rather large voxel size (4.5 mm width)

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for absorbed dose calculations and the poor spatial resolution of the SPECT images (typically 7-15 mm [90]) relative to the range of ^{177}Lu and ^{90}Y beta particles.

Going towards a more detailed and more realistic representation of the activity distribution of radiopeptides in kidney tissues, Konijnenberg et al. [7] investigated the impact of the heterogeneity of radionuclide distribution in kidney tissues reported by De Jong et al. [4] for ^{111}In-DTPA-octreotide. Absorbed dose distributions in the kidneys were calculated for PRRT with ^{90}Y-, ^{177}Lu-, and ^{111}In-radiolabelled somatostatin analogues. Two dosimetry methods based on direct Monte Carlo radiation transport simulations were used for analysing absorbed dose heterogeneity. In the first method, autoradiography data were used in a 2D model of the kidney tissue sections. In the second method, a voxel lattice was implemented inside the cortex region of the MIRD19 kidney model to generate a 3D representation of the streaky uptake pattern seen in the autoradiographs. Using isodose curves and DVHs, the authors showed that the heterogeneous activity distribution considerably affects the absorbed dose distribution, generating regions within the kidney and within the cortex with significantly lower and higher doses than the average kidney absorbed dose. This effect of absorbed dose heterogeneity is much more pronounced for ^{177}Lu than for ^{90}Y, which results in more averaging of doses inside the kidney regions. Konijnenberg et al. concluded that for high-energy beta emitters, such as ^{90}Y, a reasonably accurate kidney dosimetry for radionuclide therapy can be achieved using the MIRD19 kidney model. In contrast, low-energy beta emitters, such as ^{177}Lu, and Auger-electron emitters, such as ^{111}In, produce absorbed dose distributions in the kidneys that are very dependent on the activity distribution pattern in the kidney and even within the renal cortex. This limits the appropriateness of the MIRD19 model and imposes a need for using voxel-based dosimetry and DVHs analysis. Unfortunately, the quality of histological images used to analyse the autoradiography data were not sufficient to enable activity quantification and absorbed dose estimation at the level of nephron substructures (e.g., glomeruli, proximal tubules).

Kidney absorbed dose–response modelling in radiopharmaceutical therapy

In radiopharmaceutical therapy, absorbed dose heterogeneity in kidneys results from gradients of radiopharmaceutical uptake across the nephron substructures. Collectively, specific nephron substructures constitute specific renal tissues: the renal cortex and distinct medullary regions. For analysing and estimating nephrotoxicity in radiopharmaceutical therapy, distinct renal tissue regions may be considered, like nephron substructures, having a serial architecture. This reasoning has led some to assume that renal dysfunction will occur if any renal tissue region is severely damaged [13,91]. The renal cortex is often assumed to be the absorbed dose-limiting target for nephrotoxicity in radiopharmaceutical therapy because this tissue region contains the glomeruli, which are key for renal function, and because of the high absorbed doses expected in this tissue due to the high uptake of some radiopharmaceuticals in the proximal tubules [13,14,89]. Thus, the renal cortex is the main dosimetry target of studies on kidney response modelling addressing absorbed dose heterogeneity on a tissue region level.

Several investigators applied absorbed dose–response modelling in PRRT, some with considerations of dose heterogeneity in kidney tissues, to investigate the absorbed dose dependence of clinical toxicity data or in a theoretical approach to estimate nephrotoxicity [89,91,12–14]. The LQ model-based BED is often used to model the biological effect of distinct time–irradiation patterns between radiopharmaceutical therapy schemes and between radiotherapy modalities [12,14,15,77,91]. In PRRT with ^{90}Y-DOTA-TOC, the analysis of the absorbed dose dependence of nephrotoxicity data in terms of the kidney BED has shown to be valuable in improving the agreement with dose–toxicity data from EBRT [12,14,92]. The same approach, however, has shown limited usefulness in predicting the nephrotoxicity in PRRT with ^{177}Lu-labelled radiopeptides, for which the clinical occurrence of nephrotoxicity seems to be lower than that expected from dose–toxicity data of EBRT and PRRT with ^{90}Y-labelled peptides [11,92]. Based on that, it was suggested that the microscopic absorbed dose distribution needs to be considered for analysing the nephrotoxicity in PRRT with low- to medium-energy electrons and beta particles [7,8]. Compared with the rather low-energy betas of ^{177}Lu (133 keV, on average), the higher-energy betas of ^{90}Y (933 keV), when emitted from the proximal tubules, are more likely to cross-irradiate distant glomeruli, which would presumably lead to a higher risk of nephrotoxicity. Currently, however, very little scientific literature exists on the consideration of heterogeneous absorbed dose distributions within specific renal tissue regions (such as the cortex) in the modelling of kidney response in radiopharmaceutical therapy.

Barone et al. [14] calculated patient-specific absorbed doses in the renal cortex for ^{90}Y-DOTA-TOC based on positron emission tomography (PET) imaging activity data of ^{86}Y-DOTA-TOC and the MIRD19 kidney model. Barone et al. found that ^{90}Y-DOTA-TOC renal absorbed dose estimates were primarily influenced by the sub-kidney regional distribution of the radionuclide, the size of the target organ (i.e., the kidney), and the absorbed dose rate. Accounting for patient-specific kidney volume and the effect of dose rate through the BED estimation was critical for finding a clear absorbed dose–effect relationship.

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Just a few studies attempted to estimate the probability of kidney toxicity in radiopharmaceutical therapy [12,13,91], based on cell (or FSU) survival estimations using the LQ model or on the LKB NTCP model coupled with radiobiological dosimetry, as summarized further below. Absorbed dose heterogeneity was considered at a regional tissue level (renal cortex/medulla) [13,91], or at a sub-regional tissue level (within the cortex) [91], thus without discriminating distinct nephron substructures within a tissue region. Similarly, the serial organization of kidney tissues is sometimes considered between the renal cortex and medulla, thus only on a regional tissue level [13,91]. On the other hand, phenomenological NTCP models of the kidney proposed in EBRT do not appear to be directly implemented in radiopharmaceutical therapy.

Based on the LKB model with kidney absorbed dose thresholds proposed in fractionated EBRT [57], and on an expression of the BED accounting for the protracted and fractionated irradiation of PRRT, Konijnenberg [12] calculated NTCP curves for nephropathy for ^{90}Y-DOTA-TOC and predicted an increase in the tolerance absorbed dose in PRRT with respect to EBRT, in agreement with clinical absorbed dose–response data reported later by Barone et al. [14]. A large uncertainty in the tolerance absorbed doses estimated for PRRT was reported by Konijnenberg, due to the large variability in the radiobiological parameters of the LQ model. Additionally, absorbed dose heterogeneity in the renal cortex was demonstrated with DVHs, using Monte Carlo calculations and a lattice-based version of the MIRD19 kidney model with ^{90}Y uniformly distributed in the kidney or in the cortex region. To account for the biological effect of the heterogeneous cortex absorbed dose distributions, the effective volume method (a DVH-reduction method proposed for whole organs in the context of EBRT, [59]) was considered. However, the application of such method in radiopharmaceutical therapy was ultimately deemed speculative because the method assumes a uniform distribution of biological function in renal tissues.

In Wessels et al. [13], the MIRD committee calculated self-irradiation absorbed doses to the renal cortex and medulla for several electron-emitting radionuclides using the MIRD19 kidney model, for several examples of radiopharmaceutical uptake and clearance in the kidney. Using the LQ model to estimate FSU survival, Wessels et al. computed regionally based surviving fractions for the cortex and medulla and investigated the predicted effect of dose rate and absorbed dose distribution on a regional tissue level (cortex-to-medulla self-dose ratio). Since the radiobiological parameters required for the LQ model were not available in the experimental literature for distinct kidney tissues, Wessels et al. used hypothetical region-specific values, based on the radiosensitivity parameters for the whole kidney for EBRT [93], and on the assumption that the glomeruli (corresponding to the renal cortex region in the dosimetry model) are the most radiosensitive biological target of the kidney. Moreover, Wessels et al. assumed a serial architecture between the cortex and the medulla, a parallel architecture within these regions, and that organ and tissue region failure occurs when more than 75% of the FSUs are inactivated. Their analysis indicated that higher dose rates from short-lived radionuclides or increased localization of radiopharmaceuticals in radiosensitive sub-kidney regions can potentially lead to greater whole-organ toxicity.

A more detailed analysis of dose heterogeneity was performed by Sarnelli et al. [91], who investigated the use of absorbed dose–response modelling to estimate kidney toxicity for different treatment schedules of PRRT with ^{177}Lu- and ^{90}Y-DOTA-TATE and various dosimetry considerations. Response modelling was performed for 12 patients, based on mean kidney absorbed doses determined from patient-specific time–activity data, and on reference DVHs of both homogeneous and heterogeneous activity distributions in the kidney and in the cortex. For the heterogeneous sources, DVHs reported by Konijnenberg et al. [7] and Wessels et al. [13] were considered, after being rescaled to match the patient-specific mean kidney absorbed dose. NTCP was estimated based on the LKB model (including DVH reduction) and BED estimations based on the LQ model for the whole kidney. LKB model parameter values (TD_{50}, m and n) derived from EBRT were used [54,57], as these parameters were not available for radiopharmaceutical therapy. Additionally, for the whole kidney and the cortex, the response was modelled in terms of surviving fraction using a radiobiological expression of the EUD (referred to as EUBED) based on the LQ model. The same assumptions about tissue radiosensitivity and architecture and organ failure made by Wessels et al. [13] (previously mentioned) were followed.

Sarnelli et al. [91] found that a heterogeneous activity distribution in the kidney results in lower estimated toxicity, and this effect was more pronounced for the less uniform absorbed dose distribution resulting from ^{177}Lu (compared with ^{90}Y). The same effect was observed when considering the response of the cortex only. The estimated surviving fraction was lower in the cortex than in the whole kidney, which Sarnelli et al. expected from the specific DVHs and higher assumed radiosensitivity considered for the cortex. Those results highlight the importance of considering the absorbed dose distribution within the kidney (and the cortex) in the estimation of toxicity. Although a higher NTCP was found for the treatment schedules of ^{90}Y than for those of ^{177}Lu, which may be considered to qualitatively agree with some clinical observations [94,95], a thorough quantitative comparison with clinical PRRT data was beyond the scope of the study. Sarnelli et al. highlighted that more experimental data of different radiopharmaceutical therapies would be

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required to evaluate the predictive power of their response modelling methods and underlying assumptions. A limitation in their analyses was the lack of patient-specific information on the microscopic radiopharmaceutical absorbed dose distribution in kidney tissues. Nonetheless, their study demonstrated the potential applicability of absorbed dose–response modelling for treatment evaluation in radiopharmaceutical therapy.

Discussion and research perspectives

The establishment of absorbed dose–effect relationships based on clinical experience and supported by biophysical modelling promises a basis for individual treatment optimization in radiopharmaceutical therapy, as it facilitates the prediction of collateral toxicity and therapeutic efficacy, and it enables comparison of competing treatment options [17,18,92]. An aspect that complicates the establishment of accurate absorbed dose–effect relationships of nephrotoxicity is the heterogeneous distribution of absorbed dose in kidney tissues. In radiopharmaceutical therapy, the absorbed dose distribution affects kidney response, is dependent on the patient-specific radiopharmaceutical biodistribution, and can be difficult to assess accurately on an individual basis with current clinical imaging techniques. This precludes a direct translation of clinical absorbed dose–response relationships between radiotherapy modalities and between radiopharmaceuticals with distinctive spatial dose distributions, as appears to be the case between ^{90}Y- and ^{177}Lu-labelled somatostatin analogues used in PRRT. While the effect of dose rate and fractionation in kidney response seems to be accounted for by the LQ model using a radiobiological dose quantity, the impact of kidney absorbed dose heterogeneity in kidney response is still an open and underexplored topic in radiopharmaceutical therapy and even in EBRT [96].

The investigation of sound absorbed dose–response relationships requires knowledge on the biological targets affecting organ response and accurate assessment of the radiation absorbed dose delivered to them, which requires knowing the spatial and temporal distribution of radiopharmaceuticals in tissues and appropriate dosimetry methods. Despite more than two decades of clinical experience of PRRT with ^{177}Lu- and ^{90}Y-labelled somatostatin analogues, the amount of quantitative clinical data on the absorbed dose distribution in kidney tissues is still rather scarce. Although some anatomical models are available for kidney dosimetry to the level of some nephron substructures, the clinical assessment of the microscopic distribution of radiopharmaceuticals in kidney tissues remains a challenge which limits the anatomical resolution of clinical dosimetry. It has been shown that in PRRT the impact of absorbed dose heterogeneity in kidney response has been analysed mainly at a regional tissue level, with dosimetry estimations and response modelling focusing on the renal cortex. This approach is driven by the assumption that this region might reach the limiting absorbed dose for nephrotoxicity and by the difficulty to assess sub-regional (microscopic) kidney-tissue activity and absorbed dose distributions. Yet, the distribution of absorbed dose, biological function, and radiobiological characteristics are not (or might not be) uniform throughout the renal cortex, which leads one to a priori anticipate a limited value of regional tissue-level approaches to unravel the impact of any dose heterogeneity. Whether nephrotoxicity is driven by a renal tissue region, or by the collective of a nephron substructure, or by a more complex interplay of local responses of distinct substructures, is currently unknown. This indicates a need to investigate the absorbed dose dependences of distinct renal tissues and even of distinct nephron substructures and their role in nephrotoxicity, which implies a need of quantitative radiobiological research and detailed dosimetry accounting for the heterogeneous distribution of radiopharmaceuticals in renal tissues. Although the developments achieved and the experience gained in biological response modelling in EBRT over the last four decades offer an advanced reference for radiopharmaceutical therapy, in the latter biophysical modelling of normal tissue response is at an earlier stage of development and it requires investigation of methods to account for the effect of heterogeneous absorbed dose distributions for the kidneys.

Below we discuss further some challenges and propose detailed research directions, in line with the strategic research agendas of EURADOS, MELODI and EURAMED [24–26], concerning the assessment and the impact of the heterogeneous absorbed dose distribution in kidney tissues resulting from radiopharmaceuticals in nephrotoxicity and its consideration in biophysical kidney response modelling.

Radiopharmaceutical biodistribution

Methods that allow to quantify the detailed activity distribution of radiopharmaceuticals within tissue over time are required to evaluate the absorbed dose distribution of radiopharmaceutical therapy. Biodistribution investigations in human tissues require the use of *in vivo* methods, particularly for non-blood normal tissues, such as SPECT and PET, which are used in clinical biodistribution studies of radiopharmaceutical therapy [28,97]. However, quantitative SPECT imaging of therapeutic radionuclides can be a challenge because their suitability for imaging (yield of suitable photon emissions) is secondary compared to their therapeutic properties [90]. Furthermore, the trade-off between detection sensitivity and spatial resolution in SPECT imaging or the effects of detector width and the posi-

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tron range in PET imaging, limit the spatial resolution of emission tomography to a few millimetres. This restricts the capability to resolve heterogeneous radionuclide distributions at a lower dimension scale, e.g. in the micrometre scale [90]. Therefore, emission tomography techniques have been used to derive the biodistribution of theranostic radiopharmaceuticals mainly at the organ level, and occasionally at the level of some main organ tissue regions, such as the renal cortex and the medulla for the kidneys [87,98].

To overcome the above-mentioned limitation, complementary methods may be used to derive time-dependent radiopharmaceutical distribution at the level of relevant tissues or even substructures, like nephron substructures for kidneys. Physiologically based pharmacokinetic (PBPK) models with specific compartments dedicated to relevant tissue substructures could be useful for computing the time-dependent microscopic distribution of radiopharmaceuticals in human tissues [99,100]. Such biokinetic models can be developed, calibrated, refined, and validated using experimental data from biodistribution studies in animals and humans [101,102]. Another approach for estimating human microscopic time-integrated activity (TIA) data consists in allocating human tissue macroscopic TIA data (measurable *in vivo*) to microscopic human tissue substructures based on microscopic TIA data derived from an animal model and reference anatomical and physiological data of the human and the animal tissue. Such kind of methodology has been proposed for small-scale human kidney dosimetry [9]. While clinical imaging tools with the higher spatial resolution are developed, preclinical studies will continue to play a key role in the investigation of microscopic distribution of radiopharmaceuticals in animal tissues [103]. Indeed, pharmacokinetic distribution in sub-organ and microscale can be obtained in preclinical models thanks to the possibility to perform high-resolution imaging *ex vivo* on dissected tissues using quantitative autoradiography or even mass spectrometry techniques [6,104–107]. Further research on methods to translate animal biodistribution data to humans is therefore of interest in radiopharmaceutical therapy [108,109].

Absorbed dose distribution

The level of dosimetric detail required to unravel the nephrotoxicity of different radiopharmaceuticals still needs to be understood. Starting with sub-organ dosimetry estimations at an intermediate level might be a good starting point, yet for some radionuclides small-scale dosimetry at the level of microscopic renal substructures might be required [6,7,9]. For the potentially highly heterogeneous absorbed dose distributions resulting from low- to medium-energy electron and beta-particle emitting radiopharmaceuticals, a question that needs to be addressed is the role of local damage to specific nephron substructures in nephrotoxicity. This becomes of greater importance given the increasing interest in radiopharmaceutical therapy with alpha particles, which deposit their energy closely to the point of emission and are highly cytotoxic due to their high linear energy transfer [110]. While the latter is a good characteristic for more localized and potent irradiation of malignant cells, it might be adverse for specific substructures of the kidney with substantial radiopharmaceutical retention [16].

More detailed anatomical phantoms of human tissues will be useful to investigate the heterogeneous absorbed dose distribution at the millimetre and microscopic scale, particularly in tissue substructures that can be dose-limiting in radiopharmaceutical therapy, such as those with high radiosensitivity or receiving high absorbed doses or with a key role in organ function. Such phantoms may be customized further to represent better a variety of patient anatomical characteristics relevant to dosimetry and radiobiological modelling of nephrotoxicity.

Currently no kidney model includes the outer stripe of the outer medulla as a separate compartment, even though this tissue consists of proximal tubules, where there can be significant retention of fast-clearing relatively small radioligands [6,8]. The level of detail might be increased further to account for the 3D arrangement of distinct types of nephrons and their substructures, to investigate the contribution of the absorbed dose-related damage to these compartments to the kidney absorbed dose–response. Furthermore, anatomical variability could encompass factors such as the size of the kidney and renal tissues, the number of nephrons in the kidney, the size of nephrons and their substructures, etc. [111]. Some of these anatomical characteristics are correlated with patient age and clinical patient-specific (renal) conditions which have been identified as risk factors for nephrotoxicity in PRRT with radiolabelled peptides [2,77].

Because of the difficulty of assessing radiopharmaceutical distribution at the microscopic scale in human tissues *in vivo*, absorbed dose heterogeneity at the sub-millimetre and the microscopic scale and its impact on a biological response need to be investigated in animal models. Therefore, improved activity quantification and dosimetry methods are also required for the animal murine models typically used in radiopharmaceutical therapy investigations [6,74,112]. Similarly, as for human kidneys, 3D models of murine kidney tissues with more compartments and with an improved anatomical realism would be helpful to investigate the role of damage to distinct renal substructures associated with a heterogeneous dose distribution in kidney response [6,8]. This information can be particularly relevant to evaluate and compare the nephrotoxicity risk associated with different radioligands being preclinically tested, and to evaluate the effectiveness of renoprotective strategies for kidney tissues in treatment optimization [2,113]. More

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realistic absorbed dose estimates of mouse kidney tissues will support the preclinical investigation of absorbed dose–response relationships of specific kidney tissues resulting from novel radiotheranostic agents [8,13]. Such insight, together with prior understanding of dose–response relationships in humans, can be useful in the design of first-in-human trials of novel radioligands, by informing about potential toxicities due to the predicted absorbed dose distribution in human kidney tissues [103]. The more detailed models obtained in preclinical settings may be adapted and integrated into anatomical models for human sub-tissue dosimetry.

More clinical sub-organ detailed dosimetry data of kidney tissues is required to investigate the role of absorbed dose heterogeneity in the response of radiopharmaceutical therapy. A more widespread clinical implementation of DVH will be helpful to quantitatively describe and analyse the absorbed dose distribution of radiopharmaceutical therapy within whole organs and within main organ regions. Contrary to EBRT, the potential of DVH information in predicting the response of radiopharmaceutical therapy still needs to be thoroughly investigated for kidney tissues. This requires substantial amount of patient-specific detailed dosimetry data based on quantitative imaging and clinical response data of the kidney encompassing different levels of toxicity, from many patients and for defined radiopharmaceutical therapy settings with distinct absorbed dose distributions. The exploitation of emission tomography imaging in quantifying the activity distribution of radiopharmaceuticals in the patient is recommended [45,114]. Estimation of DVHs at the level of cortex region is feasible with current state-of-the-art SPECT and PET imaging capabilities [87]. However, it should be investigated if, with the increasing use of theranostic approaches [115,116], DVHs at kidney and regional cortex level based on activity distributions derived with SPECT or PET can be helpful in the analysis of the tissue response from radiopharmaceutical therapy.

Nonetheless, the spatial resolution of clinical voxel-level absorbed dose estimates based on emission tomography data is likely to limit the effectiveness of DVHs in resolving the influence of heterogeneous microscopic dose distributions on the response to radiopharmaceutical therapy [29,45,90]. One voxel might encompass several tissue substructures, which might differ not only in the actual absorbed dose received, but also in radiobiological characteristics and functional role in the organ. For the kidneys, this can be the case for cortical glomeruli and different segments of the tubules. Thus, the dose at the voxel level might not necessarily be a good predictor of the radiation-induced damage to the tissues that the voxel encompasses nor of the biological response that this damage entails. This is complicated further by the potentially high uncertainties in voxel-level absorbed dose estimates based on SPECT and PET imaging [90,98]. Indeed, the accuracy of emission tomography voxel-level activity data (and, thus, of voxel absorbed-doses) can be highly influenced by several factors, including partial volume effects (PVE) resulting from the limited spatial resolution of the imaging system, image reconstruction settings, photon counting statistics, image post-processing, etc. [29,98]. PVE, in particular, can lead to a potentially high underestimation of the activities in the renal cortex [98]. Furthermore, accurate estimation of voxel-level time-integrated pharmacokinetic data is challenging, as this requires accurate registration, at the voxel level, of the time series of SPECT (or PET) images. All this can lead to high uncertainties in the modelling of the effect of kidney absorbed dose heterogeneity using DVHs of the kidney or the cortex. Therefore, complementary small-scale dosimetry estimates, such as those based on macro-to-micro methods, sub-organ biokinetic modelling and detailed computational phantoms, might nevertheless be required to unravel accurate absorbed dose–response relationships of therapies with different heterogeneous microscopic absorbed dose distributions.

Absorbed dose–response modelling

The potential of biophysical modelling to support individual treatment optimization has been recognized in radiopharmaceutical therapy and there is interest in further developing this field to predict the risk of radiation-induced nephrotoxicity [13,18,45,91,117]. Compared with EBRT, absorbed dose–response modelling in radiopharmaceutical therapy is at an earlier stage of development, particularly when it concerns the response of normal tissues. The amount of scientific literature on response modelling for the kidneys is still scarce, indicating a vast opportunity for research. Models to estimate NTCP of the kidney developed in the context of EBRT might be of interest for radiopharmaceutical therapy. However, any direct translation would require prior thorough testing and validation, and most likely also adaptations to account for differences in the irradiation nature of these modalities [20]. The underlying assumptions of a model would need validation, particularly those relating to considerations of tissue architecture at different anatomical levels used for estimating the effect of heterogeneous absorbed dose distribution.

While partial kidney irradiation in EBRT usually implies the irradiation of a fraction of hundreds of thousands nephrons of the kidney, in radiopharmaceutical therapy implies a differential irradiation of a whole collective of distinct nephron substructures, each of which has distinct (radio)biologic characteristics. Therefore, modelling of the biological response of heterogeneous irradiations of kidney tissues in terms of a parameter of the whole kidney, which does not account for the specificities of different kidney tissues, might not be accurate for the irradiations with radio-

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pharmaceuticals. This indicates a need to evaluate the relevance and accuracy of the volume effect parameters of the LKB model (n) and the generalized EUD of the whole kidney (a) derived from EBRT in radiopharmaceutical therapy, which implies evaluating the assumption of parallel tissue organization throughout kidney tissues [55].

Alternatively, the consideration of a serial dependence between renal tissue regions seems more reasonable for the tissue function-mediated absorbed dose distribution of radiopharmaceutical therapy [13]. Yet, the range of validity of kidney response modelling in terms of toxicity to the whole renal cortex, without discrimination of the absorbed dose–effect of distinct nephron substructures, remains to be determined. DVHs of the renal cortex might not resolve a potentially different kidney response resulting from distinct irradiation of specific nephron substructures. Therefore, (complementary) absorbed dose–response modelling methods to integrate small-scale dosimetry and radiobiological considerations at the level of nephron substructures also deserve attention and research [7,9,110]. Similarly, it remains to be investigated whether the concept of critical functional reserve is valid, or even relevant, for the absorbed dose distribution of radiopharmaceuticals, either at the kidney level (like considered for EBRT [68]), or at regional tissue level (like considered for radiopharmaceutical therapy [13,91]), or at the level of specific nephron substructures.

Concerning the type of NTCP model, phenomenological models based on quantitative radiobiology approaches incorporating organ architecture offer a potential to more realistically model radiation-induced response [70,118]. Their high level of modelling complexity promises a wider range of applicability in terms of irradiation conditions and biological target characteristics, which would facilitate comparative analyses of competing treatment options. That complexity, however, also hinders their integration in clinical practice, as clinical data with which to effectively parametrize the radiobiological, organizational, and spatial absorbed dose dependencies driving organ response is currently insufficient [67,70,72,96]. On the other hand, the mathematical restraint of empirical models facilitates clinical assimilation, as experienced with the LKB model in the field of EBRT [55,119]. This comes, however, at the expense of a narrower range of applicability and little biophysical meaning in model parameters, which might obscure model translation between distinct applications and dampen constructive (bottom-up) model development [75].

Even when considering an empirical NTCP model as a basis, radiobiological considerations can be helpful to extend the applicability of a model to other irradiation conditions and tissues [91,120]. A quantitative understanding of the underlying cellular and tissue radiobiology of kidney irradiations with therapeutic radiopharmaceuticals will be essential to further develop absorbed dose–response modelling methods appropriate for the irradiation conditions of radiopharmaceutical therapy [74,114,117]. Radiobiological models that account for time-dependent dose rate and cellular repair will be preferred for nephrotoxicity modelling, as these have been shown to significantly improve the correlation with absorbed dose between radiopharmaceuticals, therapy schedules, and EBRT [13,14,91]. The importance in kidney response of other (radio)biological phenomena, such as cellular repopulation, cell migration, radiation-induced immune response or even bystander effects, remains to be examined for radiopharmaceutical therapy [44,73,74]. Furthermore, as in any model, knowledge on the model parameter values is essential for an accurate model result. NTCP and radiobiological dose calculations based on the LQ model typically assume a uniform cellular radiosensitivity and repair capacity throughout the kidney, based on experimental toxicity data derived from external photon-beam irradiations of the entire organ [93]. The investigation of the role of different renal substructures requires, however, knowing the radiobiological model parameters of the different relevant cell populations of the kidney [13]. Such data is, however, currently lacking in the experimental literature.

More clinical absorbed dose and toxicity data will be needed to further develop absorbed dose–response modelling of nephrotoxicity in radiopharmaceutical therapy, as that is the basis for fitting an accurate mathematical function in empirical models and for validation of model assumptions and characterization of model parameters in phenomenological models [74]. The typically low-to-mild incidence of severe nephrotoxicity in radiopharmaceutical therapy poses a challenge to achieve this, in addition to the scarcity of dosimetry data for which the physical details of the non-uniform irradiation are documented [1,92]. Although this situation might improve with the growing number of controlled clinical trials being performed considering activity escalation based on imaging-based patient-specific dosimetry [114], data on moderate-to-high kidney complication needed to derive an accurate function of NTCP will likely remain scarce because such clinical trials are designed to avoid severe nephrotoxicity. Moreover, kidneys might not be the only OAR in radiopharmaceutical therapy, thus, other tissues, typically bone marrow, might be absorbed dose limiting [20,92]. There is a need to identify early biological markers of toxicity that can be used in patients as surrogates of late radiation effects with the aim of gaining a lead time in assessing toxicity, but in particular of improving statistical power by increasing the occurrence of events [71,74]. Barone et al. found an absorbed dose–effect relationship for renal failure [14]. The endpoint was an annual reduction in creatinine clearance of >20%, as not all patients developed G3 (moderate) or G4 (severe) nephrotoxicity. Indeed, the kidney is an organ with a slow cellular turnover, and radiation-induced renal toxicity can manifest many years

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after exposure. Other (and more reliable) molecular biomarkers, such as urinary kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), Cystatin-C (CysC) and urinary clusterin (CLU), have been proposed as endpoints of early kidney injury [121]. Relevant biomarkers may be used to investigate the absorbed dose dependence of acute kidney injury and the value of this in predicting late renal toxicity.

Albeit the relevance of clinical data, preclinical studies on animal models will be needed to provide complementary data difficult or impossible to derive in a clinical setting. Knowledge on the radiobiological basis of kidney response may be best obtained in animal systems, where a controlled, systematic study of the microscopic activity and absorbed dose distribution, diverse biological endpoints of local tissue toxicities, and clinically relevant endpoints of kidney response is possible [6,8]. While a direct extrapolation from mice to humans might be impossible, object lessons and parallelism between reasonably selected applications will remain to be invaluable for the further development of radiopharmaceutical therapy, including the testing and improvement of tissue absorbed dose–response models [74,103].

Finally, due to the increasing power of computers and artificial intelligence-based algorithms able to learn, reason, and build the "digital twin" of a patient, in the next future, the digital twin technology is expected to boost the capacity to describe the kidney radiobiological features and assess the impact of radiopharmaceuticals treatments as for other medicine specialties [122].

Conclusion

Absorbed dose heterogeneity in kidney tissues is an important issue in radiopharmaceutical therapy. The effect of dose heterogeneity in nephrotoxicity is, however, not fully understood yet, which hampers the implementation of treatment optimization by obscuring the interpretation of clinical response data and the selection of optimal treatment options. Although some dosimetry methods have been developed for kidney dosimetry to the level of microscopic renal substructures, the clinical assessment of the microscopic distribution of radiopharmaceuticals remains a challenge which restricts the anatomical resolution of clinical dosimetry and, therefore, hinders a thorough clinical investigation of the impact of dose heterogeneity.

To address several important challenges in this field, future research efforts should focus on several topics, including: a more widespread clinical implementation DVH analyses of the kidney based on patient-specific imaging-based dosimetry, the preclinical investigation of the absorbed dose–response and the radiobiological role in nephrotoxicity of different renal substructures, the development of more detailed and more realistic anatomical dosimetry models of kidney tissues, and the investigation of macro-to-micro methodologies for estimating the pharmacokinetics in the kidney and its sub-compartments.

The potential of absorbed dose–response modelling to support individual treatment optimization in radiopharmaceutical therapy is recognized and gaining attraction in the field. However, it is currently underexplored for the kidney, where particular modelling challenges arise from the convolution of a complex functional organization of renal tissues with the function-mediated absorbed dose distribution of radiopharmaceuticals. The development of biophysical modelling in radiopharmaceutical therapy should benefit from the experience gained in EBRT, but should not be limited to it, as there are significant differences in the temporal and spatial characteristics of dose delivery between these modalities. The scarcity of detailed clinical absorbed dose–toxicity data of the kidney is a major challenge for evaluating and testing NTCP models, which might improve as more controlled clinical studies considering patient-specific dosimetry are performed. Complementary preclinical investigations on animal models with accurate data on the microscopic distribution of radiopharmaceuticals in kidney substructures, sound dosimetry, and quantitative radiobiology will remain essential for developing and testing improved biophysical models suitable for radiopharmaceutical therapy.

Ethical approval

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CSV: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. MA: Investigation, Writing – original draft, Writing – review & editing. CBC: Writing – original draft, Writing – review & editing. WBL: Writing – original draft, Writing – review & editing. BM: Conceptualization, Writing – review & editing. PC: Supervision, Writing – review & editing. LaS: Conceptualization, Supervision, Writing – review & editing. LiS: Writing – review & editing.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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